Scientific Report
October 2008 - August 2011

Max Planck Institute for Dynamics of Complex Technical Systems

MAX-PLANCK-GESELLSCHAFT

MAX-PLANCK-INSTITUT
FÜR DYNAMIK KOMPLEXER
TECHNISCHER SYSTEME
MAGDEBURG

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Frequently Used Abbreviations

Research Groups headed by MPI Directors

BPE	Bioprocess Engineering
CSC	Computational Methods in Systems and Control Theory
PCF	Physical and Chemical Foundations of Process Engineering
PSE	Process Systems Engineering
SBI	Systems Biology (until 5/2011)

Research Groups headed by External Scientific Members

PSD	Process Synthesis and Dynamics
SCT	Systems and Control Theory

Max Planck Research Groups headed by Senior Scientists

ARB	Analysis and Redesign of Biological Networks
ESB	Experimental Systems Biology
MSD	Molecular Simulations and Design
PoES	Otto Hahn Group Portable Energy Systems

Others

AiF	Working Party of Industrial Research Associations
AvH	Alexander von Humboldt Foundation
BMBF	Federal Ministry of Education and Research
BMWi	Federal Ministry of Economy
CDS	Center for Dynamic Systems: Biosystems Engineering (Magdeburg)
CPTS	Chemistry, Physics and Technology Section of MPG
DAAD	German Academic Exchange Service
DFG	German Science Foundation
FEIT	Faculty of Electrical Engineering and Information Technology
FHG	Fraunhofer Society
FMA	Faculty of Mathematics
FME	Faculty of Medicine
FNW	Faculty of Natural Sciences
FVST	Faculty of Process and Systems Engineering
IMPRS	International Max Planck Research School
LSA	German Federal State of Saxony-Anhalt
MaCS	Magdeburg Center for Systems Biology
MPG	Max Planck Society (Max-Planck-Gesellschaft)
MPI	Max Planck Institute for Dynamics of Complex Technical Systems
OvGU	Otto von Guericke University Magdeburg
Pro3	Competence Network on Process Engineering Pro3
SAB	Scientific Advisory Board

Max Planck Institute for Dynamics of Complex Technical Systems Magdeburg

Overview

by the Managing Director Udo Reichl

Group leaders (left to right): J. Raisch, A. Seidel-Morgenstern, A. Kienle, U. Reichl, M. Stein, P. Benner, S. Klamt, K. Sundmacher (not shown: U. Krewer)

1 Present Status

In the following the developments and the highlights of the research groups of the Max Planck Institute for Dynamics of Complex Technical Systems (MPI) covering the time period between the last report (October 2008) and July 2011 are described. More detailed information concerning specific research highlights, related research of other researchers and ideas regarding future directions of the MPI groups are addressed in the corresponding subchapters. Previous evaluations of the MPI by the Scientific Advisory Board (SAB) took place in June 2003, in December 2005, and in February 2009.

With the appointment of Prof. Peter Benner as a new director at the MPI heading the department System Theoretical Fundamentals of Process and Bioprocess Engineering, the board of directors consists of four active Scientific Members of the Max Planck Society (MPG). Professors Kai Sundmacher (Department for Process Engineering, PSE group), Udo Reichl (Department for Systems and Signal Oriented Bioprocess Engineering, BPE group), and Andreas Seidel-Morgenstern (Department for Physical and Chemical Foundations of Process Engineering, PCF group) are also full professors at the OvGU (Faculty of Process and Systems Engineering, FVST). In early 2011, Prof. Benner was awarded honorary professor at the OvGU (Faculty of Mathematics, FMA). As a consequence, all directors of the MPI are linked closely to the Faculties of the OvGU (FMA, FVST). Before becoming emeritus end of May 2011, the founding director of the MPI, Prof. Ernst Dieter Gilles, was provisional head of the Department for System Theoretical Fundamentals of Process and Bioprocess Engineering.

In addition to the groups led by the four active department heads, there are the following research groups at the MPI: the Process Synthesis and Process Dynamics (PSD) group headed by Prof. Achim Kienle (full professor at the OvGU; Faculty of Electrical Engineering and Information Technology, FEIT); the Systems and Control Theory (SCT) group headed by Prof. Jörg Raisch (full professor at the Technische Universität Berlin, TUB), and the Systems Biology (SBI) group, which was restructured after the leave of Prof. Gilles in June 2011 (see below). Both, Prof. Kienle and Prof. Raisch are External Scientific Members of the MPI. The Molecular Network Analysis (MNA) group headed by Prof. Wolfgang Marwan was transferred to the OvGU as Department of Regulatory Biology of the Institute of Biology as agreed upon in the collaboration contract of MPG/OvGU with the establishment of his group. Since January 2009, the MNA group is completely funded by the OvGU.

In addition to the seven groups already mentioned, there are currently three Max Planck Research Groups. In 2008, the Otto Hahn Group Portable Energy Systems (PoES) headed by Jun.-Prof. Ulrike Krewer (Junior Professorship since 2009, OvGU) was established. Jun.-Prof. Krewer's PoES group is an independent Max Planck Research Group funded by central funds of the MPG. In addition, the Analysis and Redesign of Biological Networks (ARB) group headed by Dr. Steffen Klamt, and the Molecular Simulations and Design (MSD) group headed by Dr. Matthias Stein were established in 2009 and 2010, respectively. The ARB and the MSD groups are connected to research activities of the BPE and the PCF group headed by Prof. Reichl and Prof. Seidel-Morgenstern, respectively. In 2008, the activities of the Population Dynamics (PDY) Group of Dr. Heiko Briesen at the MPI were discontinued after his appointment as leader of the Chair for Process Systems Engineering at the Technische Universität München. In addition, the following chairs have been accepted by former members of the MPI: Dr. Soumik Banerjee (assistant professor, Washington State University), Dr.-Ing. Martin Elsner (full professor, Georg-Simon-Ohm University of Applied Sciences, Nürnberg), Dr.-Ing. Hannsjörg Freund (full professor, Friedrich-Alexander

Universität Erlangen-Nürnberg), Dr.-Ing. habil. Peter Heidebrecht (temporary professorship, Brandenburgisch Technische Universität Cottbus), Dr.-Ing. habil. Malte Kaspereit (full professor, Friedrich-Alexander Universität Erlangen-Nürnberg), Dr.-Ing. habil. Andreas Kremling (full professor, Technische Universität München), Dr. habil. Heike Lorenz (apl. Prof., OvGU), Dr. Thomas Sauter (full professor, University of Luxembourg), Dr.-Ing. Michael Mangold (apl. Prof., OvGU), Dr. Jörg Stelling (full professor, ETH Zürich), Dr. habil. Klaus Peter Zeyer (full professor, University of Applied Sciences, München). Current offers for a professorship: Hartmut Grammel (Biberach University of Applied Sciences), Jun.-Prof. Ulrike Krewer (Technische Universität Braunschweig).

Over the last years the number of Ph.D. students, postdoctoral scientists, visiting scientists, and members of the technical staff has further increased. As of July 2011, the total number of staff employed at the MPI was 235 (see Fig. 1).

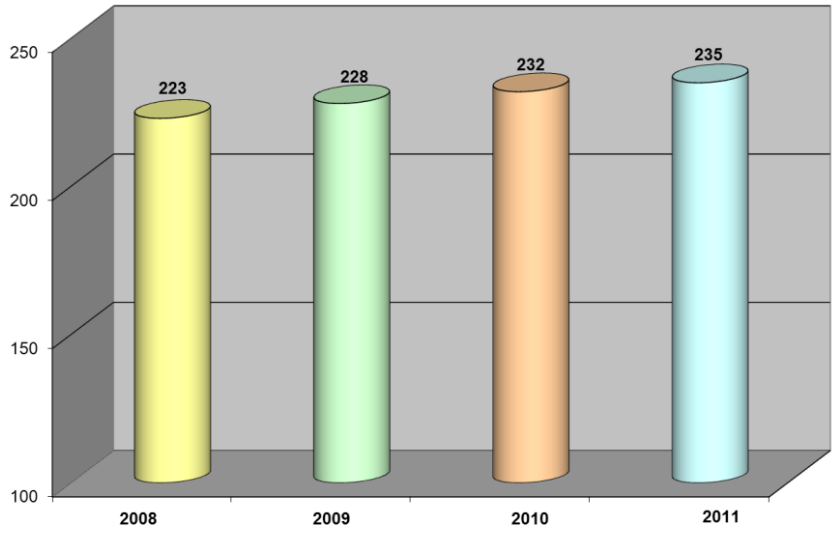

Fig. **1:** Development of the total number of MPI staff between 2008 and 2011 (as of July 31).

2 Important Developments in the Period of this Report

In 2011 the President of the MPG thanked Prof. Blossey (Lille Cedex), Prof. Santamaria (Zaragoza), Prof. Keith Scott (Newcastle-upon-Tyne), and Prof. Morbidelli (Zürich) for their substantial and valuable support given over the last three to six years to the MPI as SAB members. The appointment of Prof. Antsaklis was extended for one more evaluation period to guarantee consistency of evaluations. Furthermore, the terms of Prof. Noll, Prof. Carrondo, Prof. Doherty, and Prof. Strohrmann were extended. Invitations to become new SAB members were accepted by Prof. Belfort (Troy), Prof. Leugering (Erlangen), Prof. Srienc (Minneapolis), Prof. Stimming (Garching), Prof. Stolten (Jülich), and Prof. Styring (Uppsala).
During its last visit the SAB addressed various issues considered of key importance for the future of the MPI, i.e. the identification of an excellent candidate for the vacant directorship after the retirement of Prof. Gilles. As mentioned already above, Prof. Benner was identified as the ideal candidate for this position during a search colloquium “Mathematical Methods to Analyze Complex Technical and Biological Systems” in December 2008. He was appointed as a new director at the MPI heading the department System Theoretical Fundamentals of

Process and Bioprocess Engineering in 2010. As a result, systems theory and computational methods will continue to play a central role as an integrating factor for the research activities of the MPI. Prof. Benner's research interests focus on highly efficient computational methods and numerical algorithms for the analysis, reduction and simulation of large-scale dynamical process models. The main interest lies is in the derivation, analysis, and implementation of numerical algorithms. A particular emphasis is the use of system-theoretic concepts for model reduction and control of dynamical systems as well as the application of new numerical methods to control systems described by ordinary or partial differential(-algebraic) equations. So far, a broad range of engineering applications has been treated, ranging from circuit simulation involving large-scale and hierarchical network structures over micro-electrical-mechanical systems (MEMS), computational electromagnetics, and Hartree-Fock models in computational chemistry to flexible multibody systems and machine tool models. Research of his group also has already outreached to model reduction for biochemical reaction networks and most recently to dynamical models for neuron formation and, together with the PCP group, to chromatographic processes.

Besides the installation of a new director, the future of research activities concerning systems biology approaches was considered by the SAB of crucial importance. With the establishment of the ARB group of Dr. Klamt in early 2009 a first step towards the stabilization of research activities regarding the modeling of large biological networks has been achieved. Furthermore, the close connection between experimental work and theoretical studies will continue as an integral part of the institute's activities in systems biology research. Therefore, a new group Experimental Systems Biology (ESB) headed by Dr. Katja Bettenbrock and Dr. Hartmut Grammel has been established in 2011. Both scientists have been members of the hitherto existing SBI group, and were assigned to the newly founded centralized research unit ESB together with substantial support regarding laboratory technicians and consumables. Research of the ESB group will continue on third party-funded projects raised in previous years. In addition, new challenging topics will be taken up in close collaboration with other MPI research groups. Examples include projects on energy harvesting by coupling biohydrogen production with fuel cells (with PoES group), co-cultivation of microalgae and photosynthetic bacteria (with PSE group), microbial production, purification and application of racemases (with PCF group), and enzymatic systems for CO_2 utilization (with PSE group). The remaining activities regarding the theoretical projects of the SBI group (third party funding) and future projects are coordinated by Dr. Klamt. The research activities of the new MSD group are directed towards improving our understanding of complex phenomena in chemistry and biology.

Since the installation of the MSD group in July 2010, several projects were initiated to establish an understanding at the molecular level of processes in chemical (together with the PCF group) and biological engineering (with the BPE group). The computational results and concepts are evaluated and applied on an interdisciplinary basis with strong experimental partners in the institute.

The SAB also encouraged the Scientific Members of the MPI to prepare a Vision 2015+ paper which should look towards mid-term goals and defines targets, where greater technological breakthroughs might be achievable. The final version of this paper was submitted to the President of the MPG, Prof. Gruss, and the head of the SAB, Prof. Antsaklis, in early 2010. Briefly, besides the central role of systems theory, all research groups agreed on the continuation of existing research projects considered very successful, but also on starting new activities in the analysis, synthesis and control of chemical and biological process systems. In particular, the planned integration of the theoretical and

experimental methodologies of process engineering and systems biology should allow pushing the institute into a unique position of highest international visibility in the innovative field of biosystems engineering. Further details are addressed in the reports of the individual groups.
To support the ambitious goals, several measures concerning the existing B.sc./M.sc. degree program Biosystems Engineering at the OvGU were undertaken: 1) an increase in the number of students getting access to this degree program (from 50 to 60), 2) application for additional funding by the OvGU for a scientific coordinator, tutors, and consumables to further improve the quality of teaching and laboratory courses, 3) an internationally accepted accreditation of degree program (granted by the ASIIN e.V. in July 2011), 4) the appointment of Prof. Fred Schaper as head of the new Department of Systems Biology (Faculty of Natural Sciences, OvGU), and 5) steps towards an extension of the IMPRS towards new applications including bioelectrochemical systems and networks, cellular biosystems, and synthetic biosystems. Measures taken at the OvGU were only possible by completion of the long-promised new building for the Faculty of Process and Systems Engineering in early 2011. Since then, research activities of the OvGU Professors Marwan, Reichl, Seidel-Morgenstern and Sundmacher have been transferred into new laboratories, releasing laboratory capacity at the MPI, thus eliminating a serious obstacle for further growth in the past. In addition, the construction of a second building concerning research activities dedicated towards systems biology in the context of the Magdeburg Center for Systems Biology (MaCS) and the Center for Dynamic Systems: Biosystems Engineering (CDS) was approved by the German Federal State of Saxony-Anhalt (LSA) in 2010. Therefore, additional research capacities (laboratories and office space) will be available in early 2013.

To intensify the discussions with experts from industry, a series of workshops has been started. In October 2010, the BPE group coordinated the establishment of the first workshop of the European Network on Viral Vaccine Processes (ENVVP) in Frankfurt am Main. The main goal of these workshops is to establish a platform for scientists and engineers from basic and applied research, R&D, vaccine manufacturing, regulatory authorities, charity and foundations to discuss current status and future developments related to viral vaccine production processes. The first meeting has attracted about 50 scientists, the majority from industry. A second meeting was scheduled for October 2011. Moreover, in May 2011, a series of Max Planck Industrial Workshops has been started. In this first meeting, the focus was on tandem presentations covering chemical engineering, computational methods, and tools for the analysis and control of complex biological and chemical systems. This workshop was attended by 76 participants from industry and academia.

3 Concept and Organization of Research

The research activities of the institute are focused on challenging problems in chemical process engineering, bioprocess engineering, process systems engineering, systems biology, and systems theory. This objective does not only require the development and application of process engineering and systems engineering approaches but also the establishment of new computational methods and advances in systems theory. As the interdisciplinary character of the MPI implies a structure that does not allow for strictly separated departments, various research groups have been established. Currently, there are nine research groups and a centralized research unit for experimental systems biology (see Fig. 2).

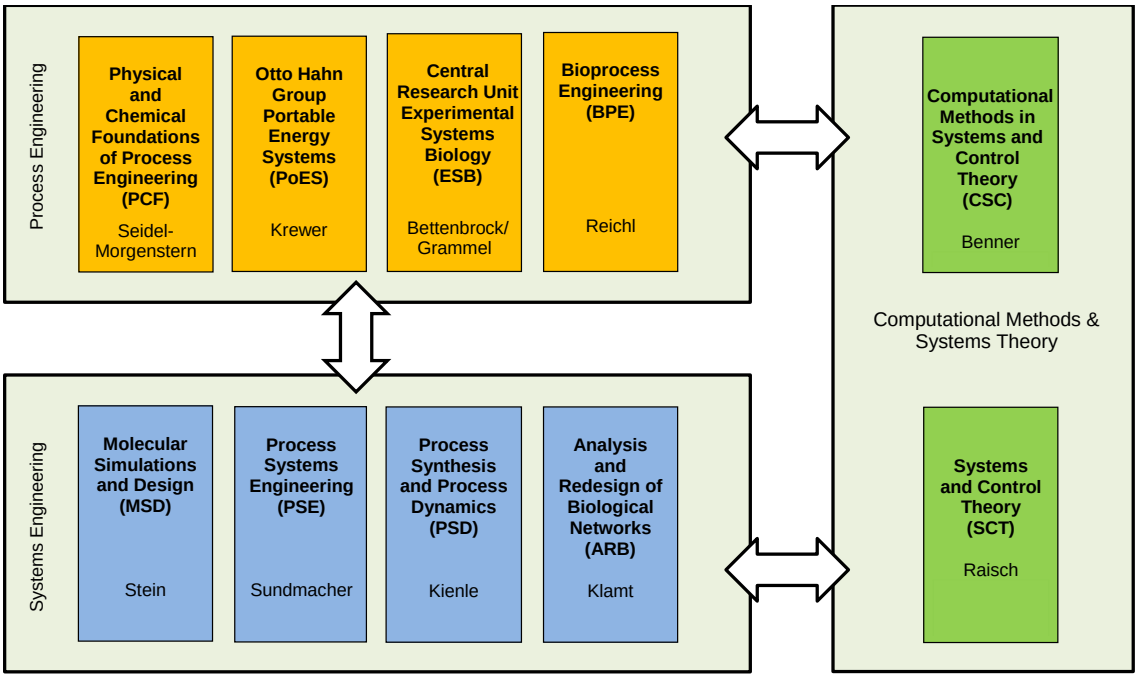

Fig. 2: Group structure of the MPI.

Applications cover the synthesis, analysis and control of chemical reactors and energy conversion processes, separation processes, the collection of thermodynamic and kinetic data, the control, design and optimization of Micro-Electro-Mechanical Systems (MEMS), integrated circuits (ICs) and machine tools, the design and optimization of bioprocesses, biomedical applications, and the analysis of molecular networks in biological systems. All research topics share a common theme: they use modeling approaches and tools provided by systems science, so that systems science remains the important integrating factor in the institute.

To strengthen interdisciplinary cooperation, researchers from different groups are working closely together. As in the previous years, the main focus was on biological and physico-chemical processes and systems. With the establishment of Prof. Benner's CSC group, applications in electrical engineering complement the range of research topics, and systems theoretical and computational methods continue to play an essential role in the institute's research activities. An overview is given in Tab. 1.

Tab. 1: Overview on fields of applications and system categories investigated by the MPI

System Categories / Systems & Process Engineering	Networks	Hierarchical Structures	Population Balance Systems	Integrated Processes	Hybrid and Discrete Events	Nonlinear Dynamic Systems
Biological	**9**[1] ARB; BPE; ESB; MSD; PoES; PSD; PSE; SBI; SCT	**4** BPE; ESB; PSE; SBI	**3** BPE; PSD; PSE	**3** BPE; PCF; PSE	**1** PCF	**6** ARB; CSC; PSD; PSE; SBI; SCT
Physico-Chemical	**5** MSD; PCF; PoES; PSD; PSE	**3** PoES; PSE; SCT	**4** PCF; PSD; PSE; SCT	**6** BPE; PCF; PoES; PSD; PSE; SCT	**5** MSD; PCF; PSD; PSE; SCT	**6** CSC; PCF; PoES; PSD; PSE; SCT
Electrical / Electrochemical	**1** CSC	**2** CSC; SCT		**2** PoES; PSE	**1** SCT	**4** CSC; PoES; PSD; PSE
Systems Theoretical & Computational Methods	**6** ARB; CSC; MSD; PSD; SBI; SCT	**2** CSC; SCT	**3** PSD; PSE; SCT	**2** PSD; SCT	**2** MSD; SCT	**5** ARB; CSC; PSD; SBI; SCT

1) Number of MPI groups involved

Scientists from several disciplines share their particular point of view and methods in the examination of a certain research topic. Interdisciplinary collaborations of the MPI manifest in two respects.

(i) Methods from several System Categories are used to examine one application in Systems & Process Engineering from different perspectives. For example, for analysis and design of Biological Systems, the characterization of signal transduction networks regarding interactions, hierarchical structures and nonlinear dynamics plays a crucial role. Similar approaches enable the design and optimization of Bioprocesses. Here, analysis of cell growth and product formation in a bioreactor is supported by use of population balances to investigate, for example, the impact of changes in cultivation conditions on the distribution of producing and non-producing cells and therefore final yields. In addition, metabolic network analysis is a standard tool to analyze basic properties of the large metabolic networks of producer cell lines and to identify possible pathways towards optimization of product yields.

(ii) Tools from the same System Category are often employed to deal with problems arising in different fields of applications in Systems & Process Engineering. For the analysis and control of crystallization processes, for example, the use of Population Balances is of central importance. The same applies to the analysis of precipitation processes to produce fine powders and pigments or to the characterization of the progress of virus propagation in population of cells.

Finally, to cope with the enormous complexity of the investigated systems and to establish efficient methods for dealing with the corresponding problems, the development of new systems theoretical and computational methods is required.

As summarized in Table 1, main research activities are directed towards modeling approaches for biological networks (9 research groups), systems theoretical and computational methods for network analysis (6 research groups), and the analysis, design and optimization of integrated physico-chemical processes (6 research groups). Significant work is also dedicated towards the improvement of our understanding of the nonlinear dynamics of biological/physico-chemical systems and processes as well as on the use of modeling approaches for physico-chemical systems and processes (at least 5 research groups). As in the previous reports a short description of the focus of the various system categories considering engineering and theoretical aspects is given below.

Networks

Networks describe the structure of systems, i.e. they capture the topology spanned by the components and their interactions. Accordingly, techniques of network theory aim at identifying and characterizing essential properties of a system from its structural representation. For example, the structure of a given reaction network may exclude bistable behavior irrespective of the parameters used. Network-theoretical methods are ubiquitously employed at the MPI for modeling and optimization of complex processes in physico-chemical/biochemical engineering and systems biology as well as for IC and MEMS design. One important concept from network theory is modularization where process models are subdivided into elementary modeling units. These modules, once they are sufficiently characterized and parametrized, can conveniently be combined (and re-used) when setting up complex models. Modular modeling is an integral part of software tools developed at the MPI (ProMoT and Diana) facilitating the convenient setup and simulation of different systems such as membrane reactors, fuel cells or cellular signaling networks. Methods of network theory play also a particular role in Systems Biology where biological systems can often only be analyzed from their underlying network structure because quantitative details are usually unknown. *CellNetAnalyzer* is a software package developed at the MPI providing various algorithms for analyzing structure and function of biochemical reaction networks.
The methods and tools developed in the field of network theory provide a common infrastructure for systems and process engineering actively used by several MPI groups as well as by the international scientific community.

Hierarchical Structures

In many areas of technology, process complexity has increased tremendously over the last few years, often defying the use of traditional synthesis and control methods. Hierarchical approaches are a possible solution to this dilemma. They rely on decomposing the overall problem into sub-problems and reassembling their solutions in a hierarchical structure. Sub-problems are solved using process models of different abstraction levels: higher-level, long-term decisions are taken on the basis of a ‘coarse' model of the overall process; whereas lower-level, short-term decisions stem from detailed models of individual process units. Although this is an extremely intuitive philosophy, a systematic and mathematically sound strategy only exists in its rudimentary forms. The essential objective within the described project area is the further development of this strategy in order to increase practical applicability, and to apply available results to solve challenging large-scale problems in practice.

Population Balance Systems

Populations of similar objects are frequently characterized by a distribution of certain properties. Typical examples of technical relevance are solid particles, emulsion droplets, molecules or cells in stirred tank reactors. Some important properties required for the characterization of these objects are, for example, their size and shape, their chain length, moisture content or age. In populations of several objects these characteristics are not identical. The corresponding distribution functions change frequently with time and often also depend on the local positions of the objects. For several important processes, a quantitative understanding of systems with distributed properties is of essential importance, e.g. for comminution or precipitation processes to produce fine powders and pigments (as drug

components or dyes), for crystallization processes to purify and isolate dissolved components, for the formation of colloidal suspensions or for the drying of solid particles, for characterization of growth and product formation of populations of cells.
Although there are significant differences between the processes mentioned above, population balance models allow for the description of the dynamics of distributions of the different specific properties in a unified manner. Successful applications comprise the modeling of various aspects of crystallization and precipitation processes as well as cellular production processes. Challenges in the field comprise adequate description of the kinetic processes in a multidimensional space of internal coordinates, identification of unknown kinetic parameters, optimal design of experiments, coupling with non-ideal flow fields, efficient simulation strategies, nonlinear model reduction and control.

Integrated Processes

In the chemical industry and in biotechnology, the conversion of substances and purification of the desired products is usually carried out either in (i) multifunctional units or in (ii) closely linked unit operations.

(i) The integration of unit operations in multifunctional units very often gives rise to synergetic effects which can be technically exploited. Possible advantages of process integration are e.g. higher productivity, higher selectivity, reduced energy consumption, improved operational safety and improved ecological harmlessness by avoidance of auxiliary agents and chemical wastes. Due to the interaction of several process steps in one apparatus, the steady-state and dynamic operational behavior of an integrated process unit can be much more complex than the behavior of a single unit. Therefore, suitable methods for the design and control of integrated processes have to be developed and applied, ensuring optimal and safe operation of the considered integrated process

(ii) Complex technical processes routinely consist of several individual sub-processes interacting in tandem. Numerous examples are found in bio/chemical engineering where the analysis, design and optimization of such processes require not only a detailed understanding of the structural and dynamic properties of the individual sub-processes but also a thorough characterization of the interaction of all subunits. Complexity further increases when the behavior of the coupled overall process cannot be correctly predicted through dependence upon previous knowledge of the individual units, particularly when a qualitatively new behavior emerges from the coupling.

The foremost objectives of the research within both application fields are the development of new design concepts, the investigation of their efficiency, and the enhancement of availability for technical application. For these reasons, experimental tools and theoretical methods are intimately combined. In addition, mini-plant technologies are used in the institute's experimental investigations to guarantee the applicability of new processes at industrial scale.

Hybrid and Discrete Event Systems

For many purposes, especially in the context of control systems analysis and design, both the process under consideration and the specifications to be met can be adequately modeled by discrete event or hybrid systems. A discrete event system (DES) describes the occurrence of certain selected events, for example the crossing of well-defined threshold values by temperature or pressure variables. If only the temporal order of events is important, a *logical discrete event system* is an appropriate choice. *Logical DES* can be

formulated as (finite) automata, formal languages, Petri nets etc. If additional time information, other than ordering, is important for judging the correct functioning of the respective process, *timed DES* must be used. Examples are timed automata, timed Petri nets, and the so-called Max-plus-algebra. A model containing both discrete event components and continuous dynamics with nontrivial interaction is called hybrid. Hybrid models are ubiquitous in modern control systems, where discrete control functions influence, and are influenced by, continuous plant and controller dynamics.

Nonlinear Dynamics

In the realm of nonlinear dynamics the whole is greater than or might even become very different from the sum of its parts leading to the emergence of novel and coherent structures or patterns. Such emergent entities have their own peculiar way of interacting, maybe on a higher level of description. For instance the molecules of chemistry emerge from nonlinear interactions on the atomic level that provide structures for proteins (and ribonucleic acids) of biochemistry and so on. The nonlinear interactions within a description level and the nonlinear interconnections of various such levels result in a whole which may (or may not) offer a hierarchical network structure. The choice of suitable order parameters and appropriate scaling is of utmost importance for the understanding (analysis, design and optimization) for each level and for the whole system.
For continuous processes, nonlinear dynamics addresses these choices in models given in terms of ordinary or partial differential equations, or differential-algebraic equations or population balance equations allowing tuning or control actions, often after state estimation/parameter identification.
At the MPI, nonlinear dynamics occur in the study of large scale systems like biochemical reaction networks or electrical circuits as well as in the analysis and design of smaller systems like the subunits/motifs arising in a modularization approach. Intensive work is dedicated to reliable model reduction techniques and semi-global approximation methods. Hereby, the interdisciplinary cooperation within the MPI has proven to be a fruitful basis for a successful development and implementation of such reduction strategies. The results, often non-local, for the reduced systems are then validated (numerically and experimentally). Other important questions in nonlinear dynamics, like stability, bifurcation and sensitivity analysis and robustness margins are studied for various challenging application examples.

4 Publications

A complete list of publications submitted by the research groups will be finalized in December 2011 as a supplement to this report. A summary of the general development of MPI publications from 1998 until June 2011 is provided below.
Fig. 3 shows the distribution of journal articles, conference contributions, Ph.D. theses and book contributions over the past 13 years.

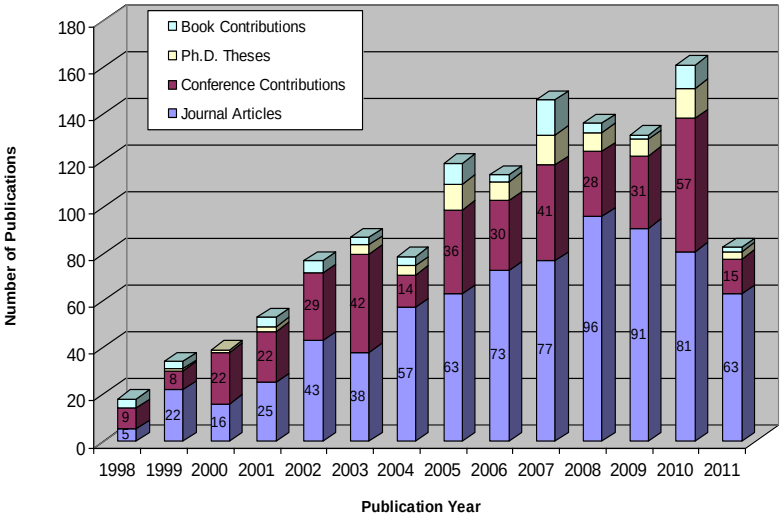

Fig. 3: Development of the number of published journal articles, conference contributions, Ph.D. theses and book contributions during the period 1998 - June 2011.

The publications within the natural sciences disciplines are predominantly journal articles. Therefore, these areas of research are covered well by the Science Citation Index (SCI), offered by Thomson Scientific (the former Institute for Scientific Information, ISI) and several other hosts. To ensure coherence, the data presented here are exclusively based on the SCI accessible under the Web of Science (WoS), the search platform provided by Thomson/ISI.
At the date of the search (July 26, 2011), a total of 695 journal articles have been published with at least one author assigned to the MPI address.
Fig. 4 shows the number of citations per year (not cumulative) of MPI-authored journal articles published since 1998 as a function of the publication year of the citation. As the number of MPI papers since 1998 and the number of citations accumulate with time, the impact steadily increases. The slope of such a curve is a significant indicator of the research impact of a corresponding research institute. The graph reveals that the number of papers citing MPI papers has increased continuously.

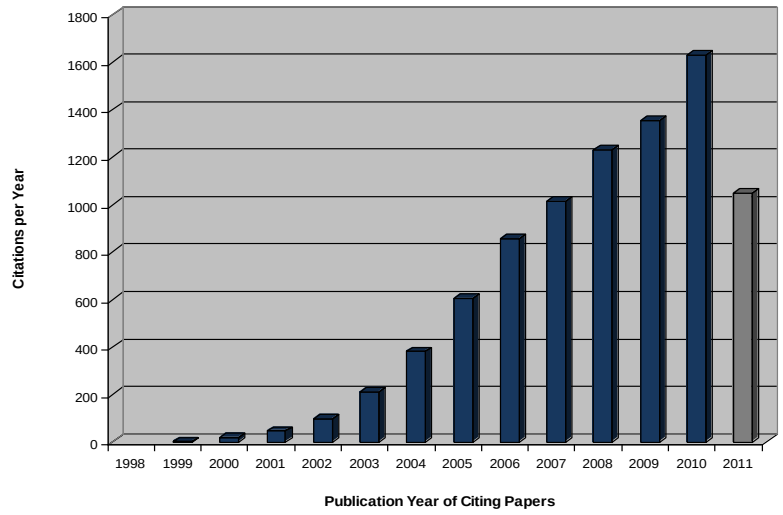

Fig. 4: Time-dependent impact of MPI papers, expressed as number of citations per year.

When analyzing Fig. 4, it should be noted that a) the present impact of MPI journal articles is to a large extent caused by the delayed citations of earlier articles published at the beginning of the time period analyzed here and b) self-citations are included. The latter cannot easily be excluded under WoS at present. The running average of the impact of papers within the first years after their publication may be consulted to check the impact tendency of a research institute.

Fig. 5 shows the time-dependent number of citations per MPI paper within the year of publication and the following two years. In this way, the impact of papers out of different publication years is comparable with each other because all publications accumulate their citations within the same time period.

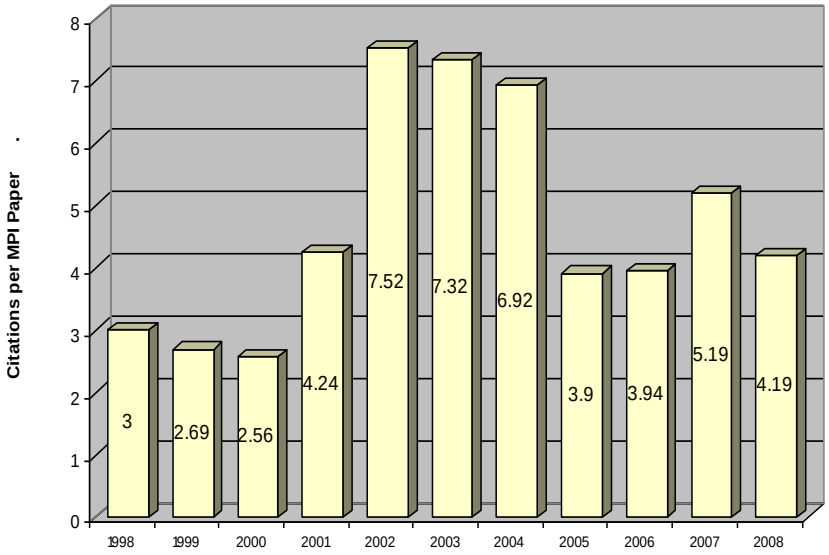

Fig. 5: Running average of impact of MPI papers within the first 2 - 3 years after publication.

The large variation of the average citation rate given in Fig. 5 may be caused primarily by the relative small sample size of MPI papers per year, in particular before 2005. The average number since 2000 is roughly 5 citing papers per MPI paper within the time frame of the first 2.5 years since the publication. This compares rather well to the average number of around 4 citations per paper in the same time frame quoted in the ISI Essential Science Indicators (ESI-2009) for chemistry and physics disciplines.

In addition, a Relative Citation Rate (C-index) is defined as the relative impact index of an actor (institution, country, etc.) in a given period of time and within a given frame of reference (e.g. world) proportional to the actor's expected impact index for the same period and within the same frame of reference. For a given actor, the relative citation rate shows whether the actor is cited more or less than the average of the journal in which the actor's publications appear. By this, the citation rate of a research institute can be compared with the world wide average citation rate based on the same journals, document types, and publication years. Hereby, $C > 1$ means above average and $C < 1$ below average. The C-index of the MPI is currently 1.23 (time period 2002 – 2008; source: National Citation Report for Germany, updated NCR data are currently not available). This indicates that articles of the MPI in this field enjoyed a significantly greater visibility than all articles published in the same journals, taken as a whole. The evaluated 421 articles revealed 3621 citations, i. e. on average they were cited 8.60 times.

5 Scientific and Technical Staff

In the following a collection of statistical data is given which quantifies the number of MPI scientists as well as the number of technical staff involved. As of July, 2011, a total of 235 people were employed by the MPI (see Fig. 1). As illustrated in Fig. 6, the largest fraction of our staff consists of students working towards a Ph.D. degree. They form about one third of the overall workforce (37%). Another 18% of our workforce consists of senior and postdoctoral scientists.
The scientific staff is supported by student research assistants (19% of workforce). These undergraduates do their work at the MPI while studying at the OvGU. The research work at MPI is an important additional experience for their education and allows the identification of the students most capable of pursuing Ph.D. studies after graduation.

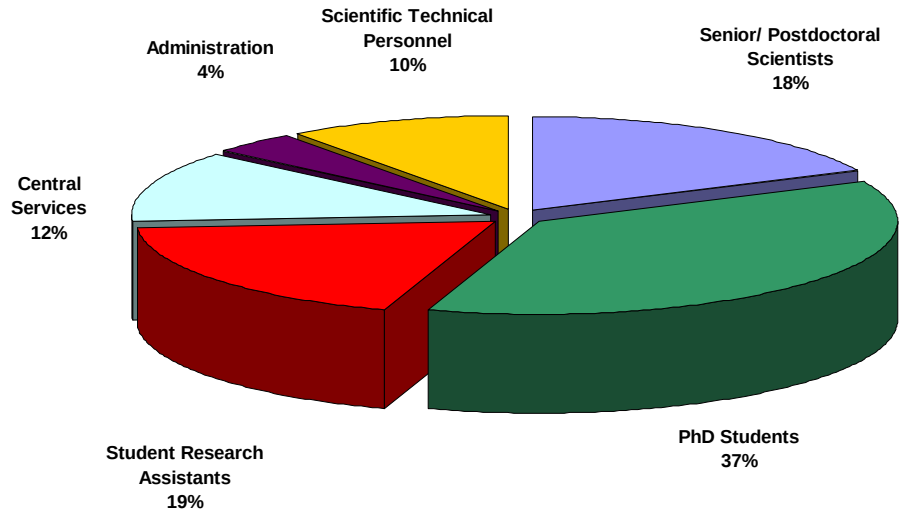

Fig. 6: Composition of MPI personnel as of July 31, 2011.

In order to prepare and perform experimental work in the institute's chemical and biological laboratories, the scientists are supported by laboratory technicians and engineers (10%). Moreover, 12% of the MPI staff represents central services such as the library, secretarial services, public relations, computer services, the mechanical workshop, the electrical workshop, the service for our bench-scale hall and the MPI house keeping service. Last but not least, the MPI has an administrative staff which is responsible for project budgeting, collecting offers for and purchasing of technical equipment, etc. This staff makes up 4% of the total number of employees.
Since 2008 the total number of employees has increased only marginally by 9%. However, with the appointment of Prof. Benner and the reallocation of research activities into the new building at the OvGU a further increase is anticipated for the next years.
The age distribution of the employees is displayed in Fig. 7. At present about 46% of the institute's staff are less than 30 years old. Only about 6% of the workforce is aged 50 and older.
The age distribution of all scientists is shown in Fig. 8, which specifies also the fraction of permanent and temporary employment in 5-year age groups. As of July 31, 2011, there were 129 scientists employed at the MPI, 43 of them senior and postdoctoral scientists and 86 of

them Ph.D. students. Of these scientists, 70% are 35 years old or younger, which again reflects a very young scientific workforce at our institute. At present, in addition to the directors, only 12 scientists hold permanent positions, reflecting the general employment policy of the Max Planck Society.

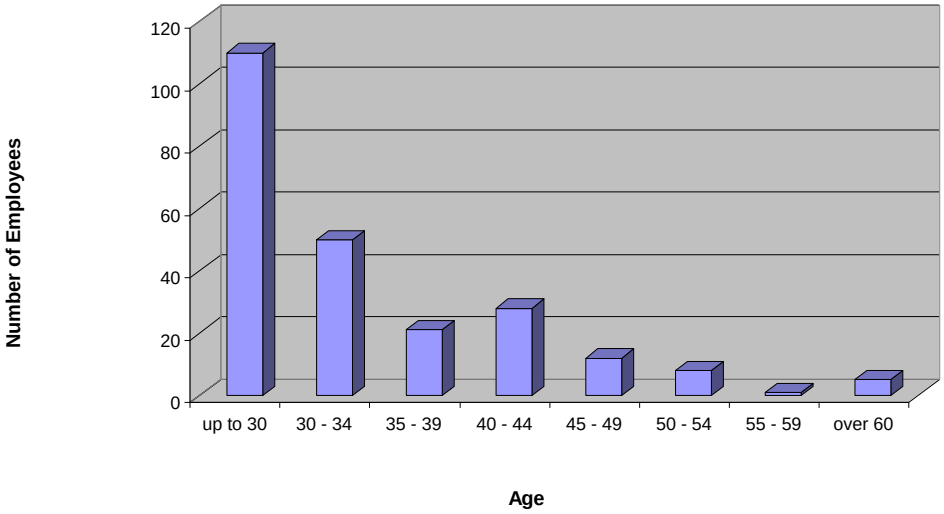

Fig. 7: Age distribution of all MPI employees as of July 31, 2011.

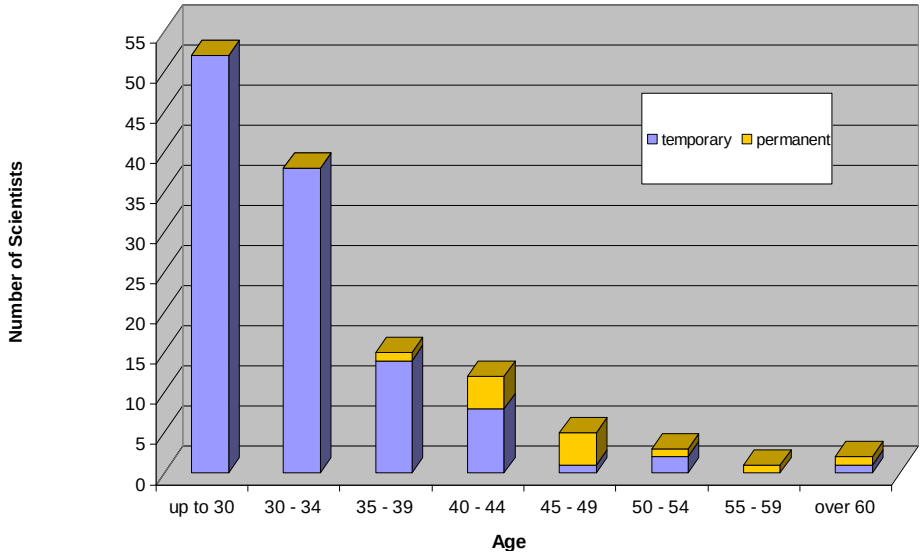

Fig. 8: Age distribution of MPI scientists divided into permanent and temporary employments as of July 31, 2011.

The distribution of our scientific coworkers according to gender is shown in Fig. 9. The percentage of female scientists is about 26% and 41% for senior scientists and Ph.D. students, respectively. As in the previous years, we have a higher proportion of female employees than normally encountered in engineering sciences in Germany.

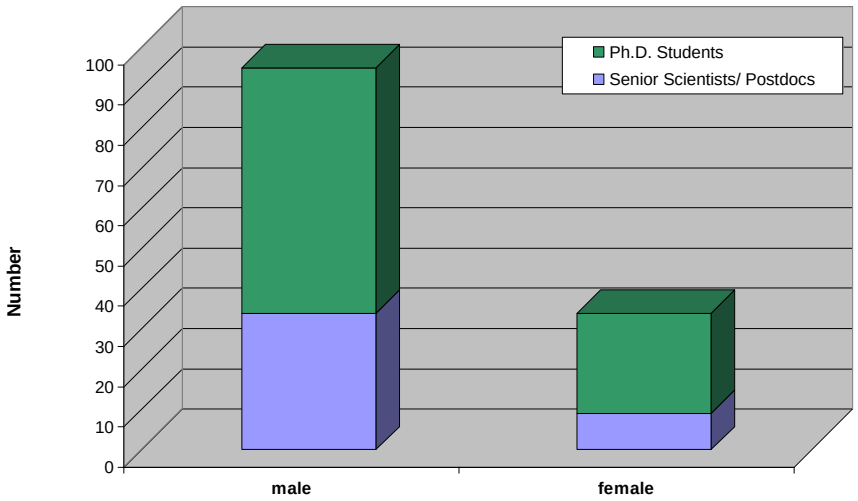

Fig. 9: Gender distribution of scientists as of July 31, 2011.

As pointed out above, the graduate students represent about one-third of the total MPI staff and two-thirds of scientific coworkers. Most of them are registered at the OvGU and are seeking a Ph.D. degree in the FVST, FEIT or FNW. Ph.D. students in the SCT group are registered at TUB and work towards a degree in the Department of Electrical Engineering and Computer Science. Compared to the period covered by the previous status report, the number of Ph.D. students in the MPI has further increased.
Over the last years the fraction of students coming from abroad was in the range between 30 and 43 percent, which clearly shows that the institute is very attractive to students from international schools (Fig. 10).
The MPI has established close working relationships with a large number of short-term visiting scientists, as reflected by Fig. 11, which illustrates the distribution of these visitors with respect to their home countries.

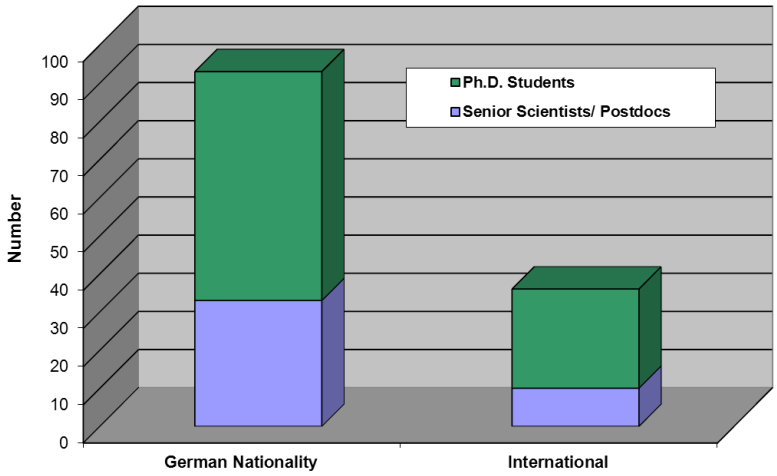

Fig. 10: Number of Ph.D. students as of July 31, 2011 from abroad and from Germany.

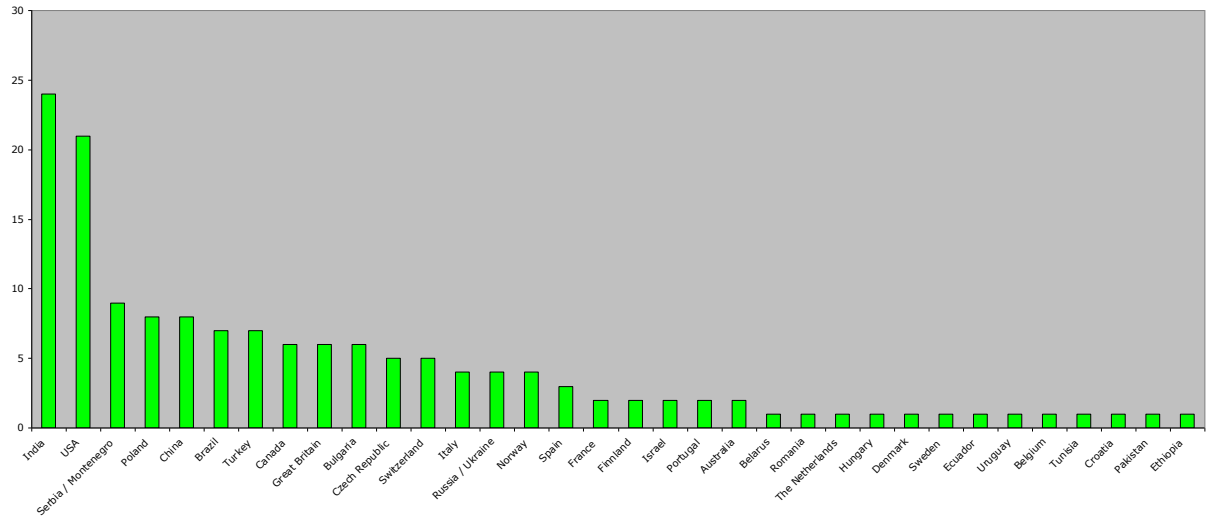

Fig. 11: Number of visits by international scientists from 2008 - July 2011 (with a stay of at least two days).

Among the visitors are a) guest professors, who stay for several months to work directly within one of the research groups, b) scientific visitors, who give courses and talks during a stay of several days, and c) experts from industry who come to exchange ideas on common research projects.
From 2008 to July 2011, a total of 102 German scientists and 150 guest scientists from abroad visited our institute. Among the international guests, 24 came from India, 21 from the US, and 105 from other countries.

6 Cooperation with OvGU Magdeburg and Teaching Activities

As outlined in Section 1, all four directors of the MPI, one external scientific member (Prof. A. Kienle) and three Max Planck Research Group leaders (Dr. Klamt, Jun.-Prof. Krewer, Dr. Stein) are directly involved in teaching activities at various Faculties of the OvGU (FEIT, FMA, FVST). In addition, teaching at the OvGU (FVST, FEIT) is supported by Prof. Dietrich Flockerzi, apl. Prof. Heike Lorenz, apl. Prof. Michael Mangold, and various other senior scientists of the MPI. The activities comprise specialized lectures, mandatory lectures and laboratory courses as well as supervision of diploma, bachelor and master theses. Details are given in the corresponding research group reports. In addition, Ph.D. students from the MPI participate as assistants for lectures and laboratory courses at the OvGU.
All above-mentioned colleagues have been also closely involved in the process of transforming the former diploma curricula at the OvGU into new consecutive bachelor and master curricula (Bologna Process) and the accreditation of the bachelor and master degree programs by the ASIIN e.V. (February and June, 2011). All FVST programs have been positively evaluated, and accreditation was granted for all programs in July 2011.
At present the MPI is involved directly in the following diploma (phasing out), bachelor and master degree programs of the OvGU: (FVST), Biosystems Engineering, Chemical and Process Engineering, Environmental and Energy Process Engineering, Molecular and Structural Product Design, Safety and Danger Prevention, Sustainable Energy Systems

(starting October 2011); (FEIT), Systems Engineering and Cybernetics; (FMA), Mathematics, Industrial Mathematics, Computer Mathematics.
In addition to our teaching activities at the OvGU, the MPI invests a considerable amount of energy to directly approach students from high schools of the Federal State of Saxony-Anhalt and partially also from all over Germany to encourage them to consider studying engineering sciences or natural sciences. On a regular basis, each spring and each fall, the MPI offers one-week laboratory courses for interested students from high schools in Saxony-Anhalt. These courses are conducted by our Ph.D. students. Additional laboratory courses are offered within the program Women in Science together with the OvGU and on an individual basis. Finally, the MPI continues to maintain successful direct partnerships with several regional high schools.

7 IMPRS Magdeburg

In 1999, the Max Planck Society started to found International Max Planck Research Schools (IMPRS), after a general agreement with the Association of Universities and Other Education Institutions in Germany (*Hochschulrektorenkonferenz*, HRK). At present, more than 60 IMPRS are offering highly qualified doctoral students from all over the world possibilities to work in a close cooperation between (at least) one Max Planck Institute and a German university. A structured curriculum generally complements the excellent research conditions.

A proposal for the establishment of an *IMPRS for Analysis, Design and Optimization in Chemical and Biochemical Process Engineering* was submitted in June 2006 to the Max Planck Society, and a general agreement was signed between the MPI Magdeburg and the Ministry of Education (*Kultusministerium*) of the Federal State of Saxony-Anhalt regarding the financial support of the IMPRS via the OvGU. In October 2007, the first ten students from four continents started their doctoral projects at the IMPRS Magdeburg.

Thirteen research groups are involved in the IMPRS currently, seven of them from the MPI and six from the OvGU. The latter are members of the faculties for the Natural Sciences, Mathematics, Electrical Engineering and Information Technology, and Process and Systems Engineering.

The funding of the IMPRS (approx. 5 million EUR for 6 years) allows supporting of up to 25 doctoral students at a time. Emphasis is on mathematical and systems aspects, both theoretical and applied; experimental set-ups are added for validation. The goals include:

- to identify system structures,
- to investigate process behavior
- to design technical processes for specific tasks
- to characterize challenging technical processes experimentally, and
- to solve mathematical problems related to these technical applications.

As of July 2011, the first candidates have already successfully defended their theses, and 42 doctoral students are currently enrolled. The fact that 15 students are being supported via external resources (budget resources and third party funding at MPI/OvGU) documents the attractiveness of the program. With 22 (52 %) of the students from a non-German background representing 14 nations the IMPRS is a truly international school.

The current students come from the bio/chemical engineering sciences as well as from mathematics, computer science and biology. Thus, additional benefits result for individual students by having the opportunity to meet students at the IMPRS from other disciplines that apply similar modeling tools or theoretical concepts.

Fig. 12: IMPRS students and supervisors during the annual workshop in Eisenach in March 2011

8 Important Joint Research Projects

Many research projects are being pursued jointly between MPI research groups and external partners from academia as well as industrial institutions. Some important larger projects are listed below:

- A major joint research project was started in January 2007 by the MPI together with two institutes of the Fraunhofer Society (IFF in Magdeburg, IKTS in Dresden). The research was focused on integrated process systems for converting biomass to electricity in fuel cells (ProBio). The project was funded for three years by MPG and FhG with the MPI being the ProBio coordinator.
- Between June 2008 and May 2011, a project was funded for three years started within the 7th Framework Program of the European Union. Partners of six countries studied various pathways to produce pure enantiomers. The MPI was coordinating this so-called INTENANT project (INTegrated synthesis and purification of single ENANTiomers).

There are further several DFG projects carried out with partners at other universities:

- Optimal control-based feedback stabilization in multi-field flow problems, a cooperation with FAU Erlangen-Nürnberg (Prof. E. Bäusch) within the DFG Priority Programm 1253: Optimization with Partial Differential Equations.
- SFB Transregio 63: Integrated Chemical Processes in Liquid Multiphase Systems (PSE, PCF and PSD groups in cooperation with TU Berlin, TU Dortmund, and OvGU Magdeburg).
- Restructuring of colloidal aggregates in a shear field, a cooperation with RWTH

Aachen (Prof. M. Behr) within the DFG Priority Program 1272 Colloidal Engineering.
- Coupling membrane separation and crystallization for enantioseparation, a cooperation of the PCF group with RWTH Aachen (Prof. K. Leonhardt) and Technische Universität Karlsruhe (Prof. W. Schaber), cooperative DFG project PAK 281.
- Coupled preferential crystallization (PCF group with J. Raisch, TUB), cooperative DFG project PAK 226.

Close cooperation between MPI research groups and university groups are established in the framework of several joint projects supported significantly by the Federal Ministry of Education and Research (BMBF):

- FORSYS-Center MaCS**:** Systems analysis of signaling and regulatory networks: from basic principles to complex cellular interactions (one of four national centers, Partner: OvGU)
- BMBF joint project Simulation of particle populations in complex flow fields (SimPaTurS, Partners: OvGU, MPI, University of Saarland, MPI for Mathematics in the Sciences)
- FORSYS-Partner: Dynamics and regulation of the metabolic balance in *E. coli* (Partners: University of Osnabrück, University of Jena, Helmholtz Center for Infection Research Braunschweig)
- FORSYS-Partner Syslogics (Partners: Technische Universität Hamburg-Harburg, University of Bielefeld, University of Saarland, Leibniz Universität Hanover, Helmholtz Center for Infection Research Braunschweig, Probiogen AG Berlin)
- FORSYS-Partner: Development of a photosynthetic bacterium, *Rhodospirillum rubrum* for superexpression of industrially relevant carotenoids using a systems approach (Partner: University of Stuttgart)
- “Virtual Liver” Competence Network: BMBF project with more than 70 national partners
- SUMO & SUMO2: An integrative multi-level systems biological approach to understanding bacterial responses to oxygen (University of Stuttgart, University of Sheffield, University of Amsterdam, University of Edinburgh)
- P-SysMO: Systems analysis of process-induced stresses: towards a quantum increase in performance of *Pseudomonas putida* as the cell factory of choice white biotechnology (18 partners from Germany, UK and Spain)
- SyreNe: BMBF joint project SyreNe: Mathematics for innovations in industry and provision of services regarding system reduction in IC Design in nanoelektronics (Partners: Universität Hamburg, TU Braunschweig, TUB, TU Chemnitz, Fraunhofer ITWM Kaiserslautern, Qimonda München, Infineon Neubiberg, NEC Laboratories Europe Sankt Augustin)
- MoreSim4Nano: Research network within the BMBF funded program Mathematics for Innovations in Industry and Services: Model reduction for fast simulation of new semiconductor structures for nanotechnology and microsystems technology (9 partners from academia and industry from Germany)
- BMBF joint project: Model based methods for the optimal design of stimulus experiments and dynamic analysis of signal transduction (MODEXA), Partners: OvGU, MPI, CT computing
- BMBF joint project CO2RRECT: CO2 reaction using regenerative energies and

catalytic technologies (Partners: BTS, Bayer Materials, RWE, Siemens, Leibniz Institute for Catalysis, Fritz Haber Institute Berlin, MPI Magdeburg, RWTH Aachen, U Bochum, TH Darmstadt, TU Dortmund, TU Dresden, Karlsruhe Institute of Technology, U Stuttgart)

The research center for Dynamic Systems (CDS) was established in 2007 in close cooperation between the MPI and OvGU. It is funded by the Federal State of Saxony Anhalt within its excellence program. For the next five years a new concept with focus on Biosystems Engineering was proposed, which is currently evaluated. The Federal State of Saxony-Anhalt also funded the junior research group NEWE (Networks of Electrochemical Energy Converters, 2008 – 2010) which was a joint activity of the MPI together with the OvGU and the Fraunhofer Institute (IFF) in Magdeburg.
Finally, the MPI continues to be a member of the German Competence Network on Process Engineering (*Kompetenznetz Verfahrenstechnik Pro3*), which was initiated in February 2000 together with the Universities of Stuttgart and Karlsruhe and several companies (e.g. BASF and Degussa) and has been growing since then.

9 International Collaborations

Collaboration of the MPI with foreign partner institutions and groups has increased significantly during the period covered by this report. As one highlight, a Max Planck Partner group has been established for the period 2010-21014 at the East China University of Science and Technology (ECUST) in Shanghai/China. The group is headed by Prof. Zhiwen Qi, a former senior scientist of the PSE group. The following table summarizes the most important academic partner institutions and fields of cooperation.

Tab. 2: Current international collaborations of the MPI

Name of project	**Partner institution**
HYCON2: Highly-complex and networked control systems	The project consists of 23 partner institutions from the following countries: Italy (7), France (4), Germany (4), The Netherlands (3), Spain (2), Sweden (2) and Switzerland.
EU-HYCON - Hybrid Control: Taming Heterogeneity and Complexity of Networked embedded systems	The project consists of 19 partner institutions from the following countries: France (3), Sweden (3), Italy (4), Switzerland, The Netherlands (3), Spain, Belgium, the UK and Northern Ireland (2).
DISC - Distributed Supervisory Control of complex plants	The project consists of 6 partner institutions from the following countries: the Netherlands, Belgium, Spain, Czech Republic, Italy and France.
Ion and solute homeostasis in enteric bacteria: an integrated view generated from the interface of modeling and biological experimentation	The project consists of 3 partner institutions from the following countries: The Netherlands, Spain and Great Britain.

Controlled Functional Electrical Stimulation (FES) in the rehabilitation of stroke patients and patients with spinal cord injuries	The project consists of 3 partner institutions from the following countries: Italy and the UK and Northern Ireland (2).
SUMO2: Systems understanding of Microbial Oxygen-Dependent and Independent Catabolism	The project consists of 3 partner institutions from the following countries: Great Britain (2) and The Netherlands.
SUMO: An integrative multi-level systems biological approach to understanding bacterial responses to oxygen	The project consists of 3 partner institutions from the following countries: Great Britain (2) and the Netherlands.
America	
Cell retention for suspension cells in vaccine production processes	BRI-NRC, Bioprocess Center, Animal Cell Technology, Dr. Kamen
Optimal design of experiments for the identification of gas-solid-reaction kinetics	Carnegie Mellon University, Prof. Biegler
Simulation of glyphosate aerial spray drift	Escuela Politécnica Nacional, Quito, Ecuador, Prof. Mena
Development and optimization of a biotechnological process to produce factor VIII for the treatment of Haemophilia A	Federal University of Rio de Janeiro, Brazil, Prof. dos Reis Castilho
Parameter estimation for preferential crystallization and control of SMB processes	Georgia Institute of Technology, Atlanta, Prof. Kawajiri
Analyzing high-throughput data of the EGFR/ErbB signaling network	Harvard Medical School, Prof. Sorger
Efficient preconditioners in the reduced basis method	Harvard School of Engineering and Applied Sciences, Dr. Knezevic
Model reduction for parametric PDEs	Massachusetts Institute of Technology (MIT), Prof. Willcox
Redox phenomena in photosynthetic bacteria	Ohio State University, Prof. Tabita
Multidimensional population balances for faceted crystals	Purdue University, Prof. Ramkrishna
Cybernetic modeling of cellular systems	Purdue University, Prof. Ramkrishna
Model reduction for nonlinear and parametric systems	Rice University, Prof. Sorensen
Modeling of transport & reaction in Direct Methanol Fuel Cells	University of Delaware, Prof. Advani

Biomimetic chemistry	University of Illinois, Prof. Rauchfuss
Gas-expanded liquids as solvents for chemical reactions	University of Kansas, Prof. Subramaniam
Structure-preserving methods for Hamiltonian eigenproblems with applications to control	University of Kansas, Prof. Xu
Interpolatory model reduction for parametric systems	Virginia Tech University, Prof. Beattie & Prof. Gugercin
Australia	
Hierarchical control theory	Melbourne University, Prof. Davoren
Belgium	
Control of advanced chromatographic processes	Université Mons, Prof. Wouwer
Bulgaria	
Characterization of the impact of gene regulatory elements on segregational plasmid instability and modeling of fermentation processes for production of recombinant proteins	Bulgarian Academy of Science, Prof. Mironova
Segregation instability of expression plasmids carrying the human interferon gamma gene in *E. coli*	Bulgarian Academy of Science, Prof. Nacheva
China	
Computer aided design of solvents for chemical processes	East China University of Science and Technology, Prof. Qi
Reaction engineering in membrane reactors	Dalian Institute of Technology, Prof. Yang
Control system design for fuel cells	Tongji University, Prof. Zhou
Croatia	
Damping optimization in vibrational systems	University of Osijek, Prof. Truhar
Czech Republic	
Mass transport in porous media	Academy of Sciences of the Czech Republic, Dr. Uchytil
Water Electrolysis using Solid Polymer Electrolytes	Institute of Chemical Technology Prague, Prof. Bouzek

Finland	
Advanced operating modes for reactive chromatography	Lappeenranta University of Technology, Prof. Sainio
France	
Hierarchical abstraction-based control of timed discrete event systems	University D'Angers, Prof. Hardouin
Control of HTS systems in a dioid framework	University D'Angers, Prof. Hardouin
Crystallization of enantiomers	Université de Rouen, Prof. Coquerel
Numerical linear algebra in non-Euclidian geometries	Université du Littoral Côte d'Opale in Calais, Prof. Salam
Greece	
Analyzing high-throughput data of signaling networks by means of logical models	NTU Athens, Dr. Alexopoulos
India	
Chromatographic separation of biomolecules Membrane reactors	Indian Institute of Technology, Prof. Jayaraman & Prof. Pushpavanam
Multiphase reaction processes, process intensification	Indian Institute of Technology, Prof. Nigam
Biofuel production using green algae	Indian Institute of Technology Prof. Sharma
Microreaction systems for nitration reactions	NCL Punai, Prof. Kulkarni
Italy	
Reactor optimization for methane partial oxidation based on detailed microkinetics	Politecnico di Milano, Prof. Maestri
Modeling of heat transport in structured catalyst supports	Politecnico di Milano, Prof. Tronconi
Theoretical and bioinorganic chemistry	University of Milano-Bicocca, Prof. de Gioia
Norway	
Optimization of direct Methanol Fuel Cell systems	SINTEF, Dr. Zenith
Poland	
Evaluation and comparison of diastereomeric and preferential crystallization for pharma-ceutically active compounds; separation effects in chromatographic columns	Rzeszów University of Technology, Prof. Antos

Portugal	
Use of MDCK suspension cells for production of canine adenovirus	IBET, Ph.D. Corodinha
Quantitative and qualitative membrane-proteome-analysis of *Pseudomonas putida*	University of Minho, Prof. Santos
Romania	
Structure-preserving algorithms in computational control	National Institute for Research & Development in Informatics, Prof. Sima
Serbia	
Evaluation of periodic processes	University of Belgrade, Prof. Petkovska
Nonlinear Frequency Response Analysis (NFRA) of electrochemical systems	University of Belgrade, Prof. Petkovska
Spain	
PSYSMO - Systems Analysis of Process-induced stresses: Towards a quantum increase in performance of the cell factory *Pseudomonas putida*	Centro Nacional de Biotecnología CSIC, Madrid, Prof. de Lorenzo
Catalytic reactions in membrane reactors	Universidad de Oviedo, Prof. Díez
Multicore and multi-GPU computing	Universidad Jaume I, Dr. Remon
Sweden	
Electrocatalytic oxidation of sugars at enzyme-modified electrodes	University of Malmö, Prof. Ruzgas, Dr. Shleev
Bioinorganic chemistry and catalysis	University of Uppsala, Dr. Ott
Switzerland	
Theory of minimal cut sets in metabolic networks	ETH Zürich, Dr. Haus
Spin-spin interactions	ETH Zürich, Prof. Reiher
Structure-preserving algorithms for eigenproblems and tensor calculations	EPF Lausanne, Prof. Kressner
Continuous chromatographic separation	ETH Zürich, Prof. Mazzotti
The Netherlands	
Impact of influenza virus infection on central metabolism	Delft University of Technology, Dr. Wahl
Spin-orbit coupling operators	Free University Amsterdam, Dr. van Lenthe
High throughput glycan analysis for glycosylation pattern screening	Leiden University Medical Center (LUMC), Prof. Wuhrer

Ukraine	
Computational methods and tools for nonlinear analysis of chemical processes	Technical University Donetsk, Prof. Svatnyj
United Kingdom	
Identification of signaling pathways by means of logical models Development and application of a new approach for the setup of domain-oriented models for signal transduction	EBI Hinxton, Dr. Saez-Rodriguez
Preconditioning for PDE-constrained optimization and Cahn-Hilliard equations	University of Oxford, Dr. Wathen
Protein film electrochemistry	University of Oxford, Prof. Armstrong
Alkaline Direct Methanol Fuel Cell	University of Newcastle, Prof. Scott & Dr. Yu
EraSysBio: Project TBHOSTNET: modeling the interactions between MTB bacillus and human macrophages	University of Surrey, Prof. Kierzek
Others	
Proteomic analysis of a cell culture-based rabies vaccine production process: Influence of cell growth conditions and virus-host cell interactions	Pasteur Institute of Tunisia, Prof. Kallel
Mixed crystal formation in chiral systems	St. Petersburg State University, Prof. Glikin

10 Workshops and Symposia

Within the period covered by this report, the MPI played an active role in organizing national and international meetings. Our research groups have organized several symposia, workshops and seminars with participants from all over the world:

- Max Planck Colloquium on Mathematical Methods to Analyze Complex Technical and Biological Systems, Magdeburg, December 1-2, 2008, Organization: PCF group
- 2nd Workshop - internal retreat of the IMPRS Magdeburg, Tangermünde, March 19-20, 2009, Organization: IMPRS/BPE group
- 1st Summer School of the IMPRS Magdeburg, The Theory of Process Engineering, Magdeburg, September 28 - October 2, 2009, Organization: IMPRS/BPE group
- DECHEMA Regional Colloquium Poröse Materialien in der Verfahrenstechnik, Magdeburg, November 19, 2009, Organization: PCF group
- Annual Meeting of the Board „Crystallization of the GVC, Magdeburg, March 11-12, 2010, Organization: PCF group
- 3rd Workshop - internal retreat of the IMPRS Magdeburg, Alexisbad, Selketal, Harz mountains, March 25-26, 2010, Organization: IMPRS/BPE group

- 2nd Ph.D. students´ seminar crystallization, Magdeburg, July 19, 2010, Organization: PCF group
- WODES 10th International Workshop on Discrete Event Systems, Berlin, August 30-September 1, 2010, Organization: SCT group
- 4th International Conference on Population Balance Modeling PBM2010, Berlin, September 15-17, 2010, Organization: PCF & PSE group
- ENVVP 1st Workshop European Network on Viral Vaccine Processes, Frankfurt/Main, October 14-15, 2010, Organization: BPE group
- CSC Welcome Colloquium, Magdeburg, November 4-5, 2010, Organization: CSC group
- ACIDS Symposium, Symposium on Analysis & Control of Infinite-Dimensional Systems in the Engineering Sciences, Magdeburg, November 18-19, 2010, Organization: CSC/SCT/PSD/PSE groups
- Workshop: Model Reduction for Complex Dynamical Systems, Berlin, December 2-4, 2010, Organization: CSC group
- MOR2011: Workshop on Model Order Reduction in Optimization and Control with PDEs, Berlin, January 26-28, 2011, Organization: CSC group
- DECHEMA Colloquium „Tunable Solvents in Chemical Process Engineering, Magdeburg, February 10, 2011, Organization: PSE group
- 7th Ph.D. students´ seminar Chromatographische Trennprozesse, Wernigerode, March 20-22, 2011, Organization: PCF group
- 4th Workshop - internal retreat of the IMPRS Magdeburg, Eisenach, March 28-29, 2011, Organization: IMPRS/BPE group
- Workshop „Simulation, Identifizierung und Optimierung nichtlinearer mechanischer Systeme, Magdeburg, March 30, 2011, Organization: CSC group
- 1st Max Planck Industrial Workshop – Bridging the gap between basic research and industrial application, Magdeburg, May 6, 2011, Organization: CSC/PSD/PSE/SCT groups
- INTENANT Workshop on Efficient Production of Enantiomers, Berlin, May 12-13, 2011, Organization: PCF group
- 1-Day Symposium on Eigenvalues, Model Order Reduction and Trust Regions, Reno, NV, USA, June 11, 2011, Organization: CSC group
- CSC-Aachen Workshop on parametric model order reduction, Magdeburg, July 5, 2011, Organization: CSC group

Not specifically mentioned are numerous additional activities of scientists from the MPI in various program committees of international conferences and workshops.

11 Summary and Outlook

The present board of MPI directors consists of four Scientific Members of the MPG active in the areas of systems theoretical fundamentals (Prof. Benner), chemical engineering (Prof. Seidel-Morgenstern), process systems engineering (Prof. Sundmacher), and bioprocess engineering (Prof. Reichl). With Prof. Gilles' retirement in May 2011, research activities in systems biology continue with the Analysis and Redesign of Biological Networks group (ARB, Dr. Klamt) and the experimental facility for systems biology (ESB, Dr. Bettenbrock and Dr. Grammel). As in the previous years, the institute's integrating research field of systems science is actively pursued by the members of the SCT (Prof. J. Raisch, Control) and the

PSD group (Prof. Kienle, Process Synthesis and Dynamics). In addition, the Otto Hahn Group Portable Energy Systems (Jun.-Prof. Krewer) and the newly established Max Planck Research Group Molecular Simulations and Design (Dr. Stein) strengthen the MPI's research activities in the field of chemical engineering and computational chemistry and biology, respectively.

Compared to the last evaluation period, the output of publications of the MPI has stabilized at a high level. To a certain degree this reflects the moderate increase in the number of scientists for the time span considered. With the total number of publications rising steadily, the impact of MPI papers, expressed as number of citations per year further increased. Also, judged by a C-index of 1.23, the institute's visibility is clearly above the average of research institutions active in the corresponding field. Furthermore, the number of international collaborations and invitations for our scientists to present results at international conferences, and the number of workshops and conferences organized directly by MPI co-workers has increased again. With 22%, the level of third party funding was kept at a high level in 2011, compared to the average level of other MPIs.

As in the previous years teaching activities will remain a focus of collaboration with the different departments of the OvGU. With successful accreditation of the Bachelor and Master degree programs in chemical engineering of the FVST and FMA in 2011, and the recent introduction of related degree programs, e.g. Sustainable Energy Systems, the number of students is expected to stabilize at the current level. Finally, based on a successful evaluation of the activities of the International Max Planck Research School, teaching as well as Ph.D. training will continue to be a solid basis for attracting excellent students to the MPI research activities.

Within the period covered by this report the staff of the MPI grew moderately. However, with the completion of the new building of the Institute of Process Engineering at the OvGU and the corresponding relocation of research activities of the university chairs of Profs. Marwan, Seidel-Morgenstern, Sundmacher, and Reichl in March 2011, the initiation of new challenging research activities will be possible.

On the one hand, the scope of topics covered will be broadened by Prof. Benner's group focusing on theoretical approaches such as model reduction, optimization of large-scale systems, parallel algorithms, robust stabilization and control of distributed systems. In addition, the expertise of the MPI will be extended towards highly challenging applications in electrical engineering, i.e. applications in IC and MEMS design, which require coupling of different physical field equations. Moreover, the CSC group is setting up a high-performance computing (HPC) environment at the MPI, including the computer cluster "otto", which offers a completely new perspective on the scope of numerical simulations. Clearly, the use of these new HPC opportunities will stimulate fruitful interaction among all groups concerning software engineering and parallelization aspects and initiate new algorithmic developments.

On the other hand, further efforts towards achieving a unique position of highest international visibility in the innovative field of biosystems engineering will be made. Nearly all research groups of the MPI are involved in this initiative, and they have already started a number of very promising joint research projects focusing on various challenging aspects of biosystems. Examples include:

- the model-based analysis and design of advanced separation processes for complex mixtures of biologicals (PCF, BPE, PSE, CSC groups),
- the use of molecular modeling approaches for design of dedicated separation processes (MSD, PCF, BPE groups),
- the development and validation of a thermodynamically consistent model for biogas

generation via anaerobic digestion (PSE, BPE, CSC groups),

- the investigation of enzymes as catalysts for racemization (PCF, ESB groups),
- the synthesis of new microbial communities for the production of energy carriers (PSE, ESB groups),
- the development of bioelectrochemical systems for energy and material conversion (PSE, ESB groups),
- the establishment of efficient methods for parameter identification and optimal experimental design of biological systems (PSD, PSE, BPE groups),
- the use of methods from control engineering and network theory for the understanding, and, in the long term, the manipulation and reprogramming of the metabolic pathways in *E. coli* and other microorganisms (SCT, ARB, ESB, PSD, PSE groups).

Finally, for continuation of the successful research collaborations between the MPI and the OvGU, a joint proposal has been prepared and submitted to the Federal State of Saxony-Anhalt in July 2011 for achieving the extension of the funding of the "Center for Dynamic Systems (CDS): Biosystems Engineering" in the period 2012 - 2015. The proposal is focused on the research field Biosystems Engineering, and thus perfectly fits into the MPI's mid- and long-term research strategy. The most important research areas addressed in the CDS proposal are: (1) cellular reprogramming, (2) signal transduction processes, (3) heterogeneity and variance in multi-cellular systems, (4) merging qualitative and quantitative data from biosystems, (5) novel biotechnological processes for biologicals and chemicals production as well as energy conversion.

As part of the CDS proposal mentioned above, five new research professorships are to be funded by the Federal State of Saxony-Anhalt and to be established at different departments of OvGU (FVST: Synthesis of biofuels, FEIT: Theory of complex networks, FMA: Mathematical methods for biological systems, FNW: Biophysics of dynamical systems, FME: Translational research on inflammation processes). To complement this initiative, the MPI will establish two new research groups (bioelectrochemistry, numerical methods for dynamic systems) in addition to the existing ARB and MSD groups. Furthermore, the institute - supported by OvGU and the Federal State of Saxony-Anhalt - is planning to apply for funding of two other Max Planck Research Groups (cellular biosystems, synthetic biosystems) from the Strategic Innovation Fund of the MPS President. If approved and successfully implemented, the CDS will become a central hub for joint research activities of MPI and OvGU groups. On this basis, Magdeburg has the potential to become a top research place of highest international visibility in the area of Biosystems Engineering.

Research Group:

Physical and Chemical Foundations of Process Engineering (PCF)

Prof. Dr.-Ing. Andreas Seidel-Morgenstern

This report covers the period from October 2008 to August 2011

1 Introduction

The main focus of the research of the Physical and Chemical Foundations of Process Engineering (PCF) group is the development of innovative processes for the separation of mixtures exploiting mainly selective crystallization, chromatography and membranes. In order to study these processes, systematic experimental and theoretical investigations are undertaken with different model systems and also with industrially relevant compounds.

Despite tremendous progress achieved in separation science, there are several generic problems which continue to cause difficulties and require innovative and efficient methods. One important problem is related to the separation of very similar molecules, e.g. isomers. Hereby often the concentrations of the “contaminants” are in the same order as the target component concentrations, and frequently only a relative small number of components is present. Another difficult problem consists in isolating a target component with high purity from complex mixtures containing a large number of other components. Hereby the target compounds are often present only in low concentrations.

In the last three years, the work of the PCF group has been concentrated in particular on studying separation processes capable of separating extremely similar molecules as e.g. enantiomers. Highlights were the development of various new crystallization-based generic approaches capable of successfully isolating chiral molecules that can form racemic compounds and the first demonstration of a continuous multi-column chromatographic separation process, which has the potential to isolate efficiently any component present in a complex mixture.

A major European project devoted to study the *int*egrated synthesis and purification of single *enanti*omers (INTENANT) was coordinated between 2008 and 2011 by the PCF group. A consortium of 11 partners from 6 countries successfully investigated various innovative ways to combine the approaches developed by synthesis chemists and separation scientists traditionally in a segregated manner. Further contributions to the development of improved concepts for the provision of pure enantiomers were made by the PCF group in two other larger projects founded by the German Science Foundation. The parallel operation of two connected enantioselective crystallization processes was investigated in cooperation with the group of Prof. Raisch at the Technical University Berlin. Together with the RWTH in Aachen and the Karlsruhe Institute of Technology (KIT) a new approach was tested for the first time based on using liquid supported chiral membranes for enrichment coupled with subsequent preferential crystallization.

Besides investigating difficult separations and developing innovative resolution processes the PCF group also investigated new concepts to carry out chemical reactions. Inspired by the success of multi-column chromatography the focus was set on analyzing periodically operated reactor cascades. Of ongoing interest were investigations of the combination of reactions with chromatographic and membrane separations in order to improve conversion and selectivity with respect to certain target components. Regarding research on membrane reactors, a corresponding major project of the MPI and the OvGU was supported by the German Science Foundation and formally finalized in 2008. The results achieved and more recently acquired findings were summarized in a book in 2010 [1].

Many thermodynamic and kinetic parameters must be known in order to reach a quantitative understanding and to predict the processes investigated. Due to the fact that there are typically deficits regarding the availability of these data, the activities of the PCF group continue to focus on developing and validating suitable experimental methods. Efforts are

also permanently made to develop appropriate mathematical models, capable of describing the processes of interest, and reliable numerical techniques to solve the model equations.
Since January 2009 members of the PCF group have published more than 70 research papers in international scientific journals and filed 3 patents. In this period 12 Ph.D. projects were successfully completed by members of the PCF group and the joint OvGU group.
Motivated also by the recommendations of the SAB given during the last MPI evaluation, the PCF group intensified activities to acquire deeper insight into the processes investigated by applying molecular simulation methods. After an intensive search Dr. Matthias Stein was identified as the Head of the new Junior Research Group “Molecular Simulations and Design”. Since 2010 this group brings new interesting projects into the institute and contributes efficiently to different projects of the PCF and other MPI research groups.
Cooperation of the PCF group with various international partners remained intensive and successful. In addition to the INTENANT network new international collaborations were initiated, e.g. with Georgia Tech (Prof. Kawajiri), University of New Brunswick (Prof. Eic) and St. Petersburg University (Prof. Glikin).
Within Germany the long established cooperation with Prof. Tallarek (University Marburg) in the field of exploring equilibrium and transport phenomena in porous media and chromatographic columns continued to be fruitful. A new collaboration was initiated with Prof. Seeberger (MPI of Colloids and Interfaces, Potsdam-Golm) devoted to combine continuously carried out reaction processes with immediate continuous chromatographic product separations.
Several projects were performed together with other groups at the MPI. Within the INTENANT project there was a close collaboration with the PSD group (A. Kienle). Further examples for successful internal cooperations are the joint analysis of new types of simulated moving bed processes (with the PSD group, A. Kienle, and the SCT group, J. Raisch), the investigation of chromatographic techniques in the downstream processing of biomolecules (with the BPE group, U. Reichl), the analysis of multi-phase reaction processes (with the PCE group, K. Sundmacher), the development of mathematical methods to predict multi-component adsorption equilibria (with the SCT group, D. Flockerzi). Recently new MPI cooperation projects were initiated. They are related to apply model reduction techniques to study periodic processes (together with P. Benner, CSC group) and to incorporate racemization reactions of enantiomers in order to increase the yield in chiral separation processes (together with K. Bettenbrock, ESB group). The latter project is part of the activities of the PCF group to focus in future stronger on investigating reaction and separation processes in biological systems.
In 2010 the PCF group organized a Dechema-Colloquium “Porous Media in Chemical Engineering” at the MPI and was strongly involved in the organization of the 4th International Conference on Population Balance Modelling (PBM2010) in Berlin. In 2011 the public final workshop of the INTENANT project in Berlin was organized by the PCF group. Members of the group were actively involved in the organization of several national and international conferences (e.g. International Symposium on Preparative and Industrial Chromatography and Allied Techniques – SPICA, Fundamentals of Adsorption – FOA, International Workshop on Industrial Crystallization – BIWIC, International Symposium on Industrial Crystallization – ISIC).
During the period of this report Dr. Heike Lorenz was appointed as Adjunct Professor (apl. Prof.) by the Faculty of Process and Systems Engineering of OvGU. In September 2011

Dr. Martin Peter Elsner started his work as Professor for Physical Chemistry at the University of Applied Sciences in Nuremberg.

2 Members of the Research Group

Tab. 1: Members of the Physical and Chemical Foundations of Process Engineering Group

	Research Topics	**Group Member**
Head		
Prof. A. Seidel-Morgenstern		since 1998
Senior Researcher		
apl. Prof. H. Lorenz	Crystallization, phase equilibria	since 10/1998
Postdocs		
Dr. J. W. Lee	Chromatography, continuous processes	since 12/2009
Dr. G. Levilain	Crystallization, process concepts	since 09/2010
Dr. S. Melnikov	Molecular modeling	since 04/2008
Dr. M. P. Elsner	Crystallization, modeling and process concepts	01/2003 – 08/2011
Dr. J. v. Langermann	Synthesis and purification of enantiomers	07/2008 – 05/2011
Dr. S. Qamar	Numerical methods, separation processes	02/2009 – 01/2011
Dr. E. Rapp	Chromatography and mass spectrometry	02/2003 –02/2008
Ph.D. Students		
M.Sc. D. Binev	Crystallization, continuous process variants	since 01/2010
Dipl.-Ing. (FH) M. Eicke	Crystallization, coupling crystallizers	since 06/2008
M.Sc. K. Gałan	Crystallization, continuous process variants	since 01/2010
M. Sc. K. Gao	Membrane reactors	since 10/2010
Dipl.-Ing. Z. Horváth	Continuous reaction and separation	since 01/2009
Dipl.-Ing. (FH) L. Klukas	Membranes separation and crystallization	since 08/2008
M.Sc. T. Le Minh	Quantifying solubility	since 04/2008
M.Sc. C. Martínez Cristancho	Chromatography, isolation of biomolecules	since 02/2009
Dipl.-Ing. J. Nowak	Chromatography, ternary mixtures	since 03/2007
M.Sc. L. Alvarado Perea	Catalysis, preparation of novel catalysts	since 01/2010
M.Sc. H. O. Rubiera Landa	Selective adsorption in fixed-beds	since 10/2009
M.Sc. V. S. Sistla	Crystallization of diastereomers	since 05/2008
Dipl.-Chem. D. Stoltenberg	Separation on functionalized surfaces	since 06/2008
Dipl.-Ing. E. Temmel	Crystallization, continuous process variants	since 07/2010
Dipl.-Phys. V. Baranau	Temperature fields in membrane reactors	11/2009 – 04/2010
Dipl.-Ing. F. Czapla	Crystallization, role of additives	04/2005 – 06/2009
M.Sc. A. Damtew	Chromatography, mobile phase gradients	01/2007 – 05/2010
Dipl.-Ing. M. Ilić	Adsorption, multi-component equilibria	02/2004 – 12/2008
Dipl.-Ing. A. Marković	Transport in porous media	01/2007 – 09/2009
M.Sc. S. Palani	Chromatographic separation of biomolecules	10/2007 – 10/2009

M.Sc. K. Petruševska-Seebach	Enantioseparation and racemization	07/2006 – 10/2009
Dipl.-Ing. (FH) D. Polenske	Crystallization, entrainment effects	03/2004 – 04/2009
M.Sc. B. Sreedhar	Separation using solid phase gradients	03/2007 – 01/2011
Dipl.-Ing. V. Zahn	Periodic operation of chemical reactors	01/2007 – 08/2011
Technical Staff		
Dr. T. Wolff	Laboratory assistant: preparation of catalysts	since 11/2001
J. Protzmann	Engineer: plant design, safety, maintenance	since 01/2002
J. Kaufmann	Laboratory assistant: analysis	since 02/1999
L. Borchert	Laboratory assistant: analysis	since 02/2005
M. Uxa	Laboratory trainee	since 09/2009
J. Wilke	Laboratory assistant: reaction engineering	01/2008 – 06/2009
S. Leuchtenberg	Laboratory trainee	09/2005 – 02/2009
Administrative Staff		
A. Raasch	Secretary	since 07/2002
M. Bratz	Secretary Coordinator of EU project “Intenant”)	02/2007 – 01/2009 07/2009 – 08/2011
S. Eckart	Coordinator of EU project “Intenant”)	05/2008 – 07/2009
Guests		
In the period of this report several guests joined the research of the PCF group, e.g. Dr. Y. Kawajiri (now Georgia Tech, Atlanta), Prof. M. Eic (University of New Brunswick, Fredericton), Prof. M. Petkovska (University of Belgrade), Prof. G. Jayaraman (Indian Institute of Technology, Chennai), Prof S. Qamar (COMSATS Institute of Information Technology, Islamabad), Prof. D. Antos (Rzeszów University of Technology).		
“Chemical Process Engineering” group at OvGU (below *)		
Senior Researcher: Dr.-Ing. C. Hamel *Ph.D. Students:* Dipl.-Ing. J. Markert, Dipl.-Ing. T. Lehmann, M.Sc. T. H. Duc, Dipl.-Ing. H. Haida, M.Sc. S. Javeed (with Prof. Warnecke, OvGU/Faculty of Mathematics), Dipl.-Ing. L. Gueorguieva (until 12/2010), M.Sc. S. Tulashie (until 07/2010), Dipl.-Ing. H. Kaemmerer (until 09/2010) *Technical and Administrative Staff:* M. Chrobog, J. Wilke, N. Ziebell		

3 Survey of Research Projects

There are research projects related to the two separation processes studied intensively in the PCF group, i.e. crystallization and chromatography, projects devoted to study coupled separation processes and projects which focus on the development of novel reactor concepts. The research done in these four fields contributes in different ways to the MPI project areas described in the general introduction of this report.

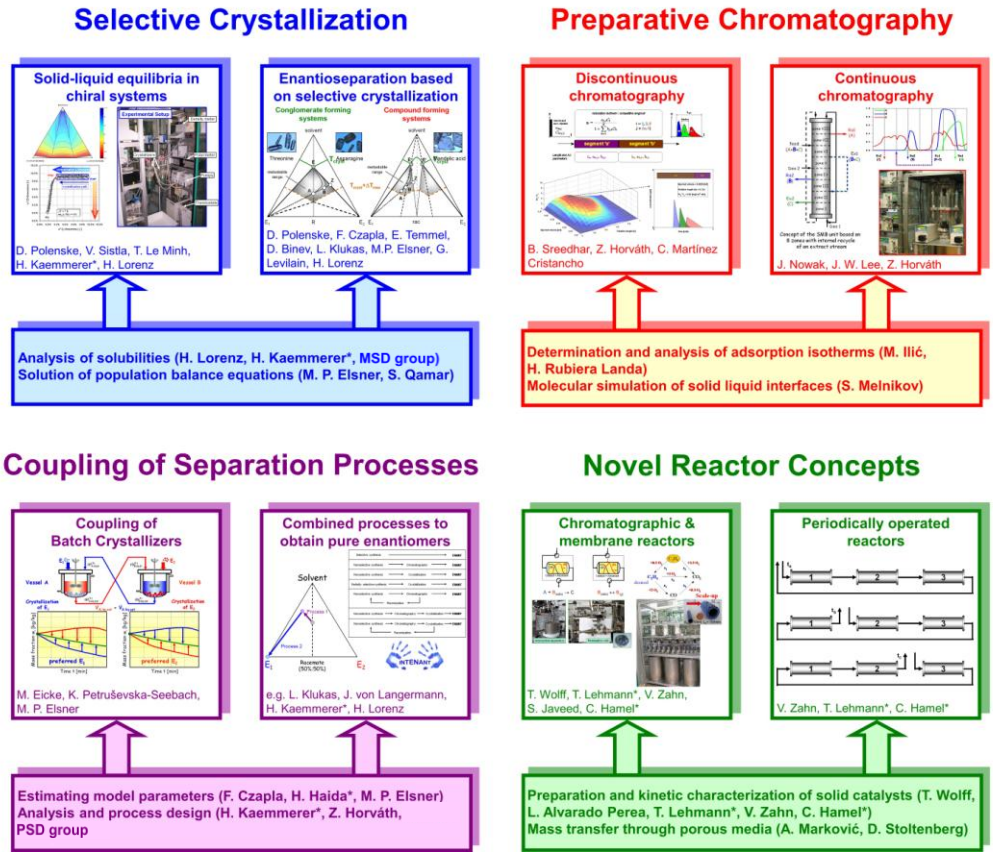

Fig. 1: Survey of research projects of the PCF group.

Tab. 2: Research projects of the PCF group

Project group "Selective Crystallization"	The goal of the projects is to better understand, design and optimize crystallization-based separation processes aiming at isolating pure components from mixtures, in particular enantiomers. Research is devoted to acquire at first a profound knowledge of the underlying thermodynamic equilibria. Based on an accompanying process modeling various promising new crystallization techniques are under investigation, both for model systems and industrially relevant compounds.			
Subprojects	**Scientists**	**Funding**	**Start**	**Partners**
Solid-liquid equilibria in chiral systems	H. Lorenz D. Polenske T. Le Minh V. Sistla H. Kaemmerer* H. Haida*	MPI	2001	U. Manchester Prof. Davey St. Petersburg U. Prof. Glikin Univ. Rouen Prof. Coquerel MPI MSD

Solution of population balance equations	M.P. Elsner S. Qamar	IMPRS MPI	2005	OvGU Prof. Warnecke
Enantioselective crystallization	H. Lorenz M.P. Elsner F. Czapla D. Polenske M. Eicke G. Levilain	EU MPI	2005	Univ. Rouen Prof. Coquerel ETH Zurich Prof. Mazzotti
Continuous crystallization processes	H. Lorenz M. P. Elsner K. Galan D. Binev E. Temmel	MPI	2008	OvGU Prof. Thévenin
Problems inspired by industry	H. Lorenz T. Le Minh E. Temmel H. Kaemmerer*	Industry	2008 2010 2011	AstraZeneca Bayer Tech. Serv. MOLISA Uhde Südzucker Hapila GmbH

Project group "Preparative Chromatography"	The goal of these projects is to better understand, design and optimize chromatographic separation processes with preparative purposes. Considered are both discontinuous and continuous processes with single columns or innovative multi-column arrangements. An important basis for the process development is the thorough quantification of the underlying specific multi-component distribution equilibria.			
Subprojects	**Scientists**	**Funding**	**Start**	**Partners**
Determination and analysis of adsorption isotherms	M. Ilić H. Rubiera	Solvay Foundat. MPI	2005	Univ. Belgrade Prof. Petkovska MPI SCT
Molecular simulation of liquid-solid-interfaces	S. Melnikov H. Kaemmerer*	MPI	2008	Univ. Marburg Prof. Tallarek MPI MSD
Improved modes for batch and SMB chromatography	B. Sreedhar Z. Horváth J. W. Lee	IMPRS MPI	2007	Georgia Tech Prof. Kawajiri MPI SCT, PSD
Chromatographic resolution of biomolecules	C. Martínez Cristancho S. Palani L. Gueorguieva*	DFG DAAD MPI	2008	IIT Madras Prof. Jayaraman TU Braunschweig Jun.-Prof. Franco-Lara MPI BPE
Chromatographic separation of ternary or "quasi-ternary" mixtures	J. Nowak	EU DFG MPI	2005	Univ. Rzeszów Prof. Antos ETH Zurich Prof. Mazzotti MPI BPE

Project group "Coupling of Separation Processes"	There is large potential in efficiently coupling different types of separation processes in order to improve access to pure compounds. The objective of this project is to understand, design and optimize different process combinations. Main focus is set on separation processes aiming to provide pure enantiomers. Hereby essentially chromatography, crystallization and membrane separation are considered as suitable separation processes.

Subprojects	Scientists	Funding	Start	Partners
INTegrated synthesis and purification of single ENANTiomers (INTENANT project)	J. v. Langermann H. Lorenz S. Sistla T. Le Minh H. Kaemmerer*	EU	2008 (-2011)	ETH Zürich Univ. Rouen Univ. Toulouse Univ. Manchester Polytechn. Milano Univ. Stockholm AstraZeneca Bayer Techn. Serv. Molisa GmbH Dechema MPI PSD
Coupling batch crystallizers	G. Ziomek M. Eicke M. P. Elsner	DFG MPI	2008	TU Berlin Prof. Raisch
Membrane separation coupled with crystallization	L. Klukas H. Lorenz	DFG	2008	Univ. Karlsruhe Prof. Schaber RWTH Aachen Prof. Leonhard

Project group „Novel Reactor Concepts"	A main focus of these projects is to better understand, design and optimize novel processes combining chemical reaction with selective transport and distribution processes. This requires projects devoted to understand the specific sub-processes individually as well as projects which investigate aspects specific for process combinations.			
Subprojects	**Scientists**	**Funding**	**Start**	**Partners**
Preparation and kinetic characterization of solid catalysts	T. Wolff V. Zahn C. Hamel* T. Lehmann*	MPI	2003	OvGU Prof. Weiß
Mass and heat transfer in porous media	A. Marković D. Stoltenberg	DFG OvGU MPI	2005	Univ. Leipzig Prof. Enke Czech Ac. Sci. Dr. Uchytil OvGU Prof. Tsotsas
Solution of fixed-bed reactor model equations	S. Javeed S. Qamar	MPI	2009	OvGU Profs. Warnecke MPI CSC
Periodically operated cascades of fixed-bed reactors	V. Zahn C. Hamel*	DAAD MPI	2007	Univ. Belgrade Dr. Petkovska MPI PSD, SCT
Novel reactor concepts for multi-phase reactions	J. Markert* C. Hamel*	DFG (TR-SFB) OvGU	2010	TU Berlin Profs. Schomäcker, Enders, Kraume Univ. Dortmund Profs. Behr, Gorak, Sadowski MPI PCE, PSD
Dosing concepts using tubular membrane reactors	V. Zahn C. Hamel*	DFG DAAD MPI	2002 (-2008)	IIT Madras Prof. Pushpavanam Univ. Oviedo Prof. Diez OvGU several groups MPI PCE, PSD
Analysis of chromatographic reactors	S. Javeed S. Qamar	MPI Vietn. Gov.	2008	U. Lappeenranta Prof. Sainio

				Univ. Hanoi Dr. Tien Vu
Combining continuous reactor operation with continuous chromato-graphic separation	Z. Horváth	MPI	2011	MPI for Colloids and Interfaces Prof. Seeberger
Combining enantiosepa-ration with enzymatic racemization	M. P. Elsner K. Petruš.-Seebach J. v. Langermann G. Levilain	Helmholtz Society MPI	2007	Novartis Dr. Lütz MPI^{ESB}

4 Research Highlights

In the last years the research of the PCF group has been focused on investigating possibilities to carry out extremely difficult separations. Probably the most challenging task in this field is the separation of two enantiomers. Enantiomers are molecules which possess a chiral center and behave like image and mirror-image. Recent evaluations of the ways capable of carrying out enantioseparation clearly reveal severe limitations of the currently available techniques [R1-R3].

By choosing the difficult field of enantioseparation several high risk but also high potential projects were carried out. Hereby the PCF group concentrates its actual investigations in particular on understanding, developing and applying crystallization-based techniques and preparative chromatography using chiral stationary phases. These two techniques appear to be particularly promising to provide efficient resolution processes. Systematic research in these fields will probably also contribute to develop techniques, which could be applied to solve other separation problems, e.g. in the area of biotechnology.

4.1 Selective Crystallization

Information about thermodynamic equilibria is the basis for understanding and designing crystallization processes. A classical overview with emphasis on chiral systems was given in [R4]. There are two main types of chiral systems: conglomerates and racemic compound-forming systems. Enantiomers of chiral organic molecules that crystallize as conglomerates are simpler to separate but, unfortunately, less frequent. The more frequent and more challenging problem is to separate the enantiomers of racemic compound-forming systems. There are the following clear deficits and obstacles, which hinder the development of reliable and productive enantioselective crystallization processes and which are tackled by the PCF group:

a) For chiral systems there is a lack of both accurate experimental thermodynamic data (in particular solid-liquid equilibria) and reliable theoretical prediction methods,
b) There is a lack of reliable, productive and robust process concepts capable to carry out crystallization based enantioseparations, in particular for racemic compound-forming systems.

a) Solid-liquid equilibria

In the period of this report the PCF group investigated systematically more than 40 ternary or pseudo-ternary phase diagrams (solvent and two enantiomers, eventually plus additives,

resolving agents or impurities). Hereby, the main focus was set on systems characterized by one or several of the following frequently encountered complicated features:

- Racemic compound-forming systems and systems allowing for the formation of solid solutions,
- Systems with very high or very low eutectic compositions (close to the pure enantiomers or the compounds).

Ternary phase equilibria were systematically studied for various systems in order to identify specific properties that facilitate the selective crystallization of pure enantiomers. In [2] and [3] are described examples of complex phase equilibria determined, including interpretations and first attempts of quantification. Recent results of analyzing a chiral system which exhibits in a wide range miscibility in the solid state are illustrated in Fig. 2.

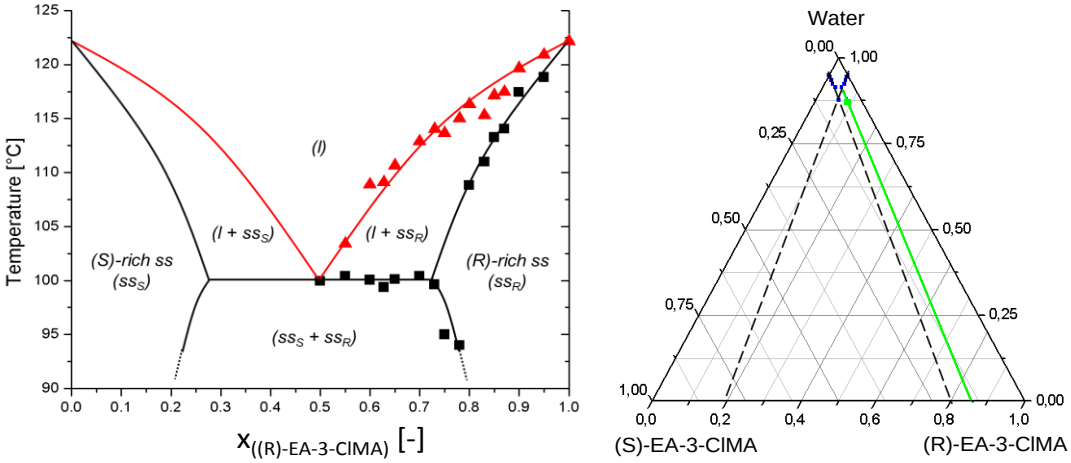

Fig. 2: Binary melt phase diagram (left) and ternary solubility phase diagram (right) of the (R)- and (S)-ethanolamine salt of 3-chloromandelic acid (EA-3-ClMA). The system turned out to belong to the conglomerate type of chiral systems exhibiting partial miscibility at solid state. The boundaries of miscibility are found at mol fractions of 0.2 and 0.8, respectively [3].

To optimize the so-called “classical resolution”, which applies chiral resolving agents and which is still the most frequently used crystallization technique at industrial scale [R3], the underlying phase equilibria were determined, e.g. for the amino acid serine [4] (Fig. 3).

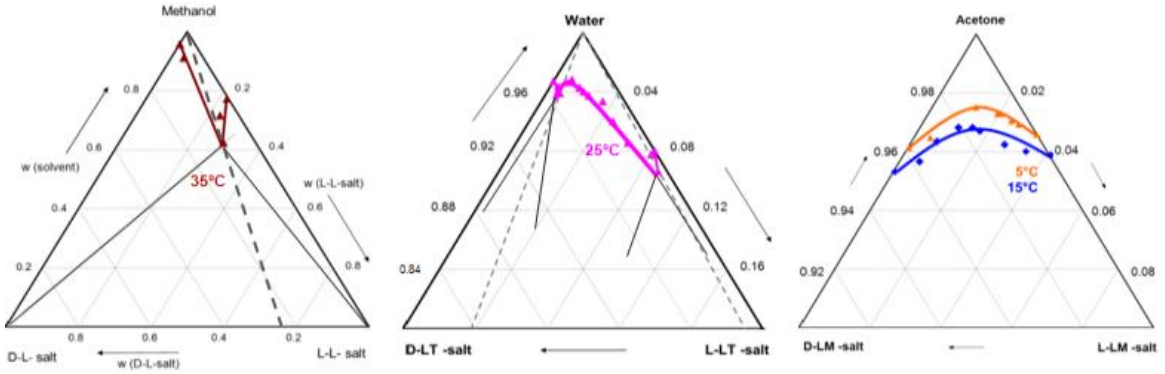

Fig. 3: Ternary solubility phase diagrams of the diastereomeric salts of serine with 2,3-dibenzoyl-L-tartaric acid, L-tartaric acid and L-mandelic acid as resolving agents in different solvents (from left to the right). It can be seen that the phase behavior of the salts obtained is completely different. Actually, with the three resolving agents used, three particular types of systems result, as there are a simple eutectic (left), the formation of an intermediate compound (double salt, middle) and complete miscibility in the solid state (mixed crystals, right) [4].

An up to now hardly considered possible shift of the eutectic composition with temperature or solvent type and composition was found for several interesting chiral compounds [e.g. 5,6] . A not yet published example is given in Fig. 4.

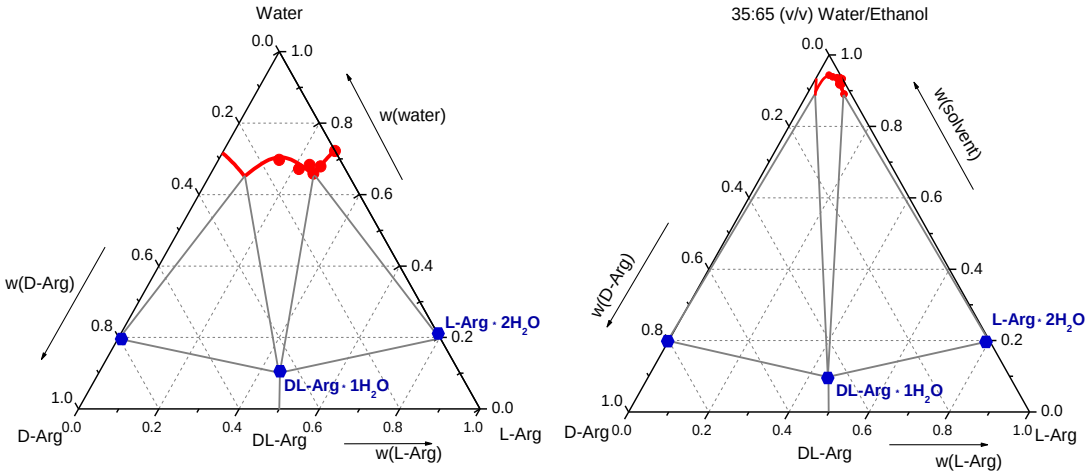

Fig. 4: Ternary solubility phase diagrams of the amino acid arginine (Arg) in water (left) and a water/ethanol mixture (right) at 45°C. Depending on the solvent and temperature used, the eutectic composition in the chiral system changes; under the conditions given in the figure it shifts from 75 mol.-% in water to 84 mol.-% in the water/ethanol mixture. Further, the solubility ratio of the enantiomer to the racemic compound inverts: in the water/ethanol mixture the solubility of the enantiomer exceeds that of the racemic compound, in water it falls below it. In presence of water both the enantiomer and the racemic compound of arginine form different hydrates. Additionally to the forms shown, at low temperatures a dihydrate of DL-Arg occurs.

In order to apply most suitable solvents, own synthesis activities were carried out in the PCF group. Task-specific solvents were produced, which allow for enantioselective recognition of the mandelic acid enantiomers in solution and support enantioseparation or even facilitate racemate resolution [7].

Currently available approaches to describe solid-liquid equilibria quantitatively are summarized e.g. in [R5] and [R6]. There are still severe limitations to apply these concepts to describe chiral systems and improvements are needed to generate reliable predictions. Own first activities based on applying the COSMO-RS method [6] could be recently extended and improved originating from a first successful cooperation with the MSD group [8].

b) New process concepts for selective crystallization

The already applied concepts of chiral resolution using crystallization have been recently reviewed in [R7]. Based on the identified deficits we focus our research efforts on the following three challenging but in case of success very promising concepts:

- preferential crystallization for racemic compound-forming systems,
- exploiting shifts of the eutectic composition in the chiral systems,
- continuous crystallization processes.

Preferential crystallization is a well-established technique to resolve conglomerates [R7]. However, there is not much work done and knowledge available regarding application of this concept to the larger class of racemic compound-forming systems. One possibility, developed and first demonstrated in our group, is a new process option, which allows us to apply preferential crystallization to process close-to-eutectic enriched solutions. The feasibility and potential of a related cyclic separation concept, providing consecutively the

desired pure enantiomer and the racemic compound, could be shown successfully for chiral mandelic acid as a model system (Fig.5, left).

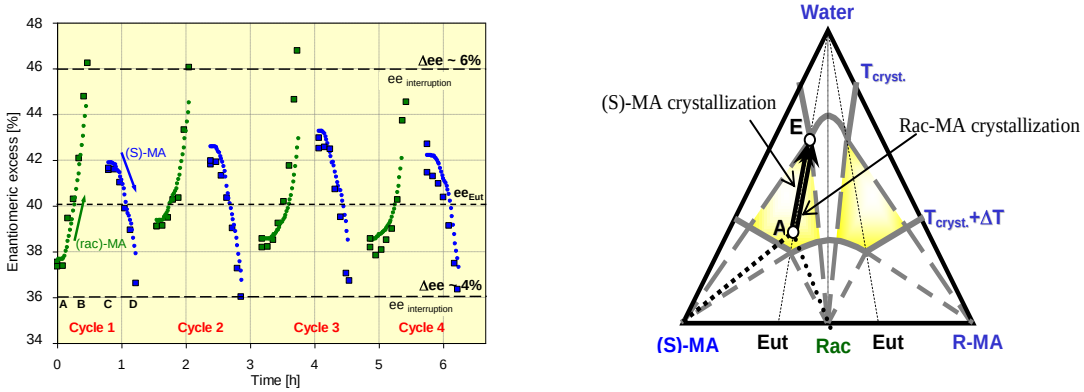

Fig. 5: left: Profiles of the enantiomeric excess for four consecutive separation cycles in auto-seeded polythermal preferential crystallization of mandelic acid (MA) [9]; right: Crystallization pathways of simultaneous preferential crystallization for MA [10,11].

A patented extension of the concept uses a combination of entrainment and simultaneous preferential crystallization in two coupled reactors [10]. A schematic illustration of the crystallization pathways is shown in Fig. 5 (right).

The possible highly efficient exploitation of the shift of the eutectic point in a two-step crystallization process could be demonstrated first for methionine [5] and then, within the INTENANT project, for the pharmaceutically relevant compound bicalutamide [6,12]. The derived approach allows a separation independent of the initial enantiomeric enrichment in the solution and, thus, facilitates the provision of the desired enantiomer even for rather small initial asymmetries. As a result of this research another patent was filed [13].

Continuous crystallization processes are applied in large scale for simple purifications of inorganic molecules [R8]. The PCF group recently started intensive efforts to develop dedicated continuous crystallization processes for the separation of enantiomers exploiting three different principles. First promising results could already be achieved by applying a self-made fluidized bed crystallizer for preferential crystallization which is connected with a permanent seed provision realized by crushing small amounts of product crystals in an ultrasound field [14].

Finally it should be mentioned that in cooperation with the OvGU reliable numerical methods could be developed which are capable of efficiently solving mathematical models for different types of selective crystallization processes. The model equations are generally non-conservative weakly hyperbolic systems of PDEs which pose major difficulties to analytical and numerical investigations. Several high resolution flux-limiting finite volume and finite element schemes and discontinuous Galerkin methods were successfully tested and implemented [e.g. 15-17].

Altogether the results of the various PCF projects belonging to the “Selective crystallization” project group were published in more than 30 papers since 2009.

4.2 Preparative Chromatography

The significant progress achieved in the last years in the field of preparative chromatography was recently summarized in [R9]. There are still large deficits in applying this powerful separation technique to process more complex feed mixtures. In the last two years the focus

of the PCF group shifted from applying chromatography to solve binary chiral separation problems [R10-R12] to the development of methods capable of resolving multi-component mixtures. In particular in the area of downstream processing of biomolecules (which was recommended by the Scientific Advisory Board as a very suitable field of internal MPI cooperation between the BPE, PSE and PCF groups), chromatography is a very powerful technology of even increasing importance [R13], that still needs to be better understood and further developed. In particular the understanding of the underlying thermodynamic equilibria and the development of new types of continuous operating modes are main fields of research in the PCF group.

a) Adsorption equilibria

Several contributions were made by the PCF group to improve or develop methods capable of accurately measuring equilibrium isotherms for single component and mixture adsorption. As a quite complex but accurate new method the frequency response analysis was validated successfully. It is based on analyzing the column outlets after periodic input concentration fluctuations [18].

A challenging problem is the reliable description of competitive adsorption isotherms. These functions are the most essential information which should be provided to design and optimize separation processes based on selective adsorption. Although real systems can deviate from the ideal state, thermodynamically consistent competitive isotherms predicted by the Ideal Adsorbed Solution (IAS) theory [R14] are very useful in simulating, designing and optimizing adsorption processes. Together with the SCT group a new and very flexible competitive adsorption isotherm model was derived for binary mixtures [19], capable of processing single component isotherms which are second order truncations of higher order equilibrium models. The suggested thermodynamically consistent and widely applicable model can be recommended as a flexible tool for efficient simulations of fixed-bed dynamics. We further provided a generalized concept to solve the equations of the IAS-theory for mixtures with an arbitrary number of components characterized by general single component adsorption isotherm behavior. The new approach is based on transforming the nonlinear algebraic system of IAS-theory equations into a simple decoupled system of corresponding ordinary differential equations [20].

In chromatographic processes often mixtures of solvents are used as mobile phases. Within narrow pores these mixtures might “demix” and the local solvent composition must be known in order to understand chromatographic retention. To elucidate the separation mechanism active in hydrophilic liquid chromatography (HILIC) a first molecular scale description of the processes in a nano-size solid-liquid interface was made together with Prof. Tallarek (Univ. Marburg) using Molecular Dynamics (MD) simulation. The equilibration of the water/acetonitrile mixtures between cylindrical bare silica nano-pores and two adjoining bulk reservoirs was simulated. Different water/acetonitrile mixture compositions in silica pores of two diameters (3 nm and 9 nm) have been studied. The 3-nm pore is the lower edge of the pore size distribution of HILIC chromatographic supports and 9-nm pore is the main pore size (Fig. 6). The computationally demanding task required large scale parallel calculations. Computational facilities of Rechenzentrum Garching (Germany) and the new computational cluster at the MPI (“Otto”) have been intensively used. Composition, structure and mobility of water/acetonitrile mixtures inside bare silica nano-pores have been determined. The simulation results are in good agreement with experimental excess adsorption isotherms and

corroborate previous guesses about the water-rich stagnant layer at the silica surface. An important observation is that the mixture compositions within the pore noticeably differ from that in the bulk reservoirs. The obtained results promote our understanding of solvent partitioning and mobility inside bare silica nano-pores [21].

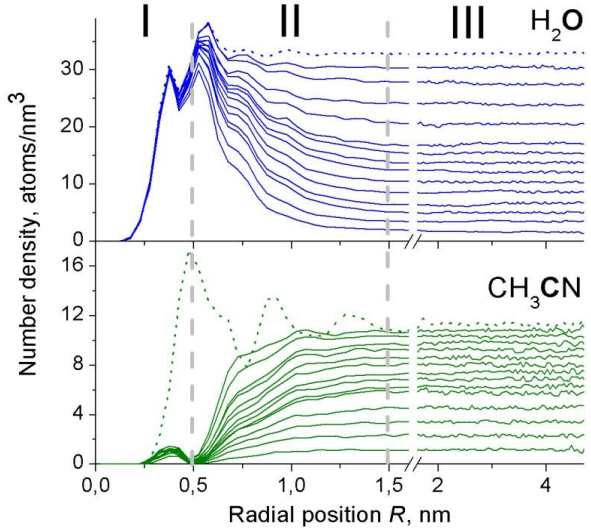

Fig. 6: Radial density profiles of water oxygen (blue color) and the central carbon atom of acetonitrile (green color). Dashed curves designate pure component cases, solid ones are mixture cases (05/95, 10/90, 15/85, 20/80, 25/75, 30/70, 35/65, 40/60, 45/55, 50/50, 60/40, 70/30, 80/20, 90/10 v/v water/acetonitrile from the bottom upward for water, and from the top downward for acetonitrile). Three distinct regions of density profiles are separated by grey vertical lines and denoted by I, II and III [21].

b) New chromatographic process concepts

In the last years several new promising chromatographic resolution concepts were suggested, validated and optimized in the PCF group. Examples are the joint application of segments filled with different stationary phases (“solid gradients”) [22] and the application of a new fractionation and feed-back counter-current process (patented as “FF-SMB”, [23]). The latter process was analyzed in detail together with the SCT group and promising ranges of applicability were identified [24,25]. The identification of arrangements of several columns was studied in a systematic manner together with the PSD group [26].

Major efforts were made in the last years in order to continuously split a feed stream into three fractions, which allows solving very general separation problems and is consequently the subject of intensive international research [e.g. R15, R16]. Our original approach is based on developing an 8-zone SMB separation unit. As shown in Fig. 7 (left), the ternary feed mixture is split into one stream containing either the most or the least retained component and another, which contains the two other compounds, including the target [27]. This stream is then internally fed back and used as feed in a second sub-unit, which then separates the target from the remaining contaminant. Recently several first successful experimental runs aiming to separate and purify cyclohexanone (C6) out of a model ternary mixture of three cycloketones have been realized (Fig. 7, right, [28]). This result received recently the poster award at the leading international meeting on preparative chromatography (PREP) in Boston [28].

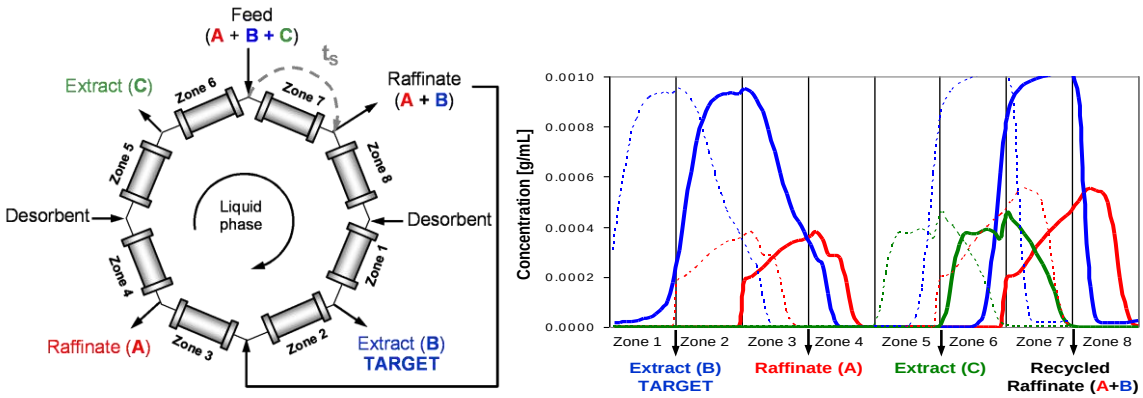

Fig. 7: left: Schematic structure of an integrated 8-zone SMB unit with internal recycle of raffinate stream; right: Internal concentration profiles of the components to be separated at the beginning and at the end of the switching interval [28]

Such complicated processes as described above are still very difficult to apply in the field of processing complex feed mixtures of biomolecules originating from fermentation processes. Here simpler open-loop processes are attractive. In a collaboration with the IIT in Chennai the enzyme streptokinase was isolated continuously from a cell lysate using gradient hydrophobic interaction chromatography (HIC) using a flexible three column set up described in [29]. This general principle was recently applied successfully together with the BPE group in order to isolate a virus from a mixture containing in addition host cell proteins and DNA [30]. A complementary project with the Technical University of Braunschweig focuses on applying a similar open-loop three-zone two-step solvent-gradient SMB-process using immobilized metal affinity chromatography to isolate an antibody fragment from a broth (Fig. 8) [31].

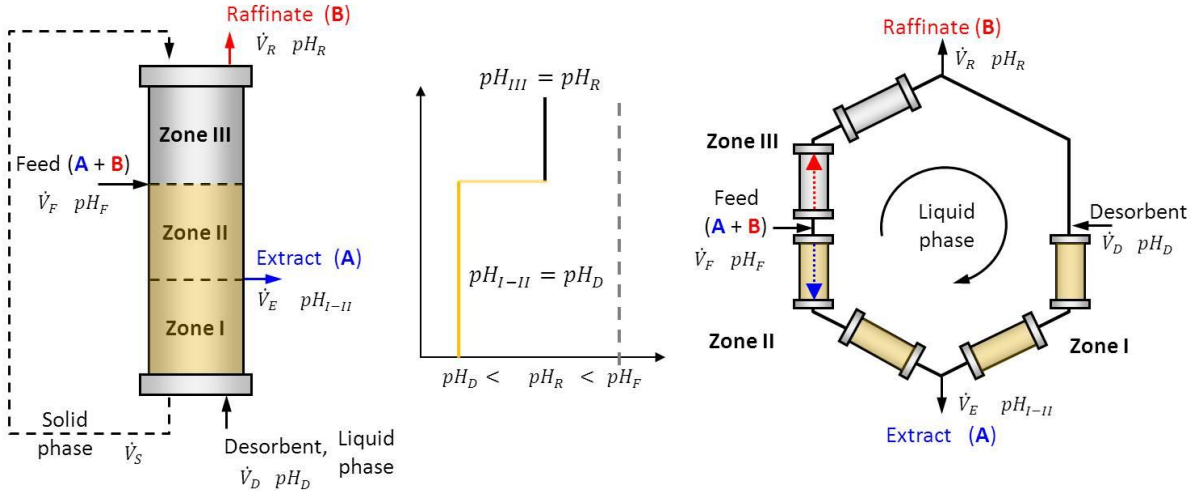

Fig. 8: Principle of open-loop three-zone two-step solvent-gradient True Moving Bed (TMB, left) and corresponding Simulated Moving Bed (SMB, right) for the purification of biomolecules [29, 31].

Since 2009 the PCF group has published more than 15 papers summarizing results acquired during research in the field of “Preparative Chromatography”.

4.3 Coupled Separation Processes

The application of several separation processes sequentially has been state of the art for a long time [32]. However, this is not yet true regarding a systematic development and joint optimization of selecting and using complementary separation principles. In the area of chiral separation just a few efforts were reported [e.g. R17, 33].

a) INTENANT project

The basic idea of the mentioned INTENANT project (INTegrated synthesis and purification of single ENANTiomers) was to efficiently combine the potential of the two rivaling approaches, namely the development of a) enantioselective synthesis methods and b) physical methods aiming to separate efficiently mixtures of the two enantiomers. The main goals of INTENANT were to demonstrate the potential of such a new combined approach for several relevant target compounds, to develop tools capable of evaluating innovative process schemes and to quantify their potential. To achieve these ambitious goals the INTENANT project was suggested by a consortium consisting of 7 European academic institutions, 3 industrial partners and a research coordination society. The whole project generated up to now more than 40 publications and 3 patents. The results were presented in a public workshop “Integrated Chemical Synthesis and Product Purification” (May 12 – 13, 2011, Berlin) organized by the PCF group. Fig. 9 illustrates the concept developed and validated for the pharmaceutically relevant component bicalutamide. The optimized coupled process is based on initial chromatographic enrichment and two subsequent crystallization processes exploiting finally an anti-solvent [6, 12].

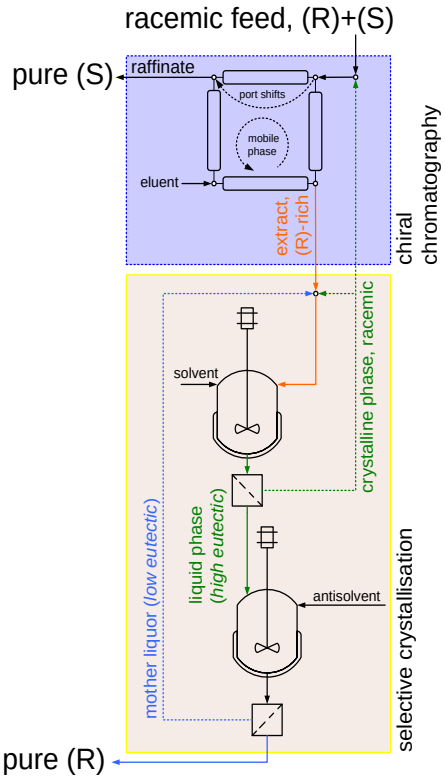

Fig. 9: Process scheme to separate the enantiomers of bicalutamide developed and validated within the INTENANT project. The distomer (S) leaves the chromatographic unit at high enantiomeric purity, while the extract is enriched by the eutomer (R) (~90%). This enriched fraction is split in a first crystallization step into a solid fraction of racemic composition and a liquid fraction of >97% purity. The liquid fraction is further purified to >99.99% enantiomeric purity in a second crystallization step. The internal recycling of mother liquor (dashed blue line) improves the overall process yield [6, 12].

Other and even more challenging examples were studied intensively, considering the incorporation of a racemization step and a feedback loop [34].

Altogether the just finished INTENANT project is regarded as a large success by all partners involved and also by the European Commission. It provides ongoing inspiration for further projects in the area of efficiently combining different separation processes.

b) Coupled crystallizers

In comparison to the classical simple isothermal batch-wise crystallization, a configuration exploiting coupled crystallizers (Fig. 10) was found to be a very promising concept to separate enantiomers of conglomerate forming systems [35, 36]. Hereby, in two separated tanks each enantiomer is being crystallized under exactly the same conditions (except for the initially introduced different types of seeds of the preferred p-enantiomer) and crystal-free mother liquor is continuously exchanged between these two tanks. Assuming absolute process symmetry between both tanks, the advantage of the coupled mode in comparison to the simple batch preferential crystallization (PC) is obvious: by coupling both tanks via the liquid phase the supersaturation of the preferred (p) enantiomer increases whereas conversely that of the counter (c) enantiomer decreases at the same time in each of both tanks. Coherently, the crystallization rate and therefore the yield of p-crystals being harvested at the same batch time are promoted. Moreover, the delay or even suppression of the nucleation of the c-enantiomer facilitates the handling and control of the process which is reflected by throughout higher purities of the p-product. The effect of mimicking a “racemization” by exchanging the fluid phases allows a favorable manipulation of the concentration profiles in order to enhance the process performance in case of conglomerates. A comprehensive and systematic experimental investigation of PC performed in an isothermal coupled mode was carried out and the results were compared with the standard isothermal single-batch process for aqueous threonine solutions [36].

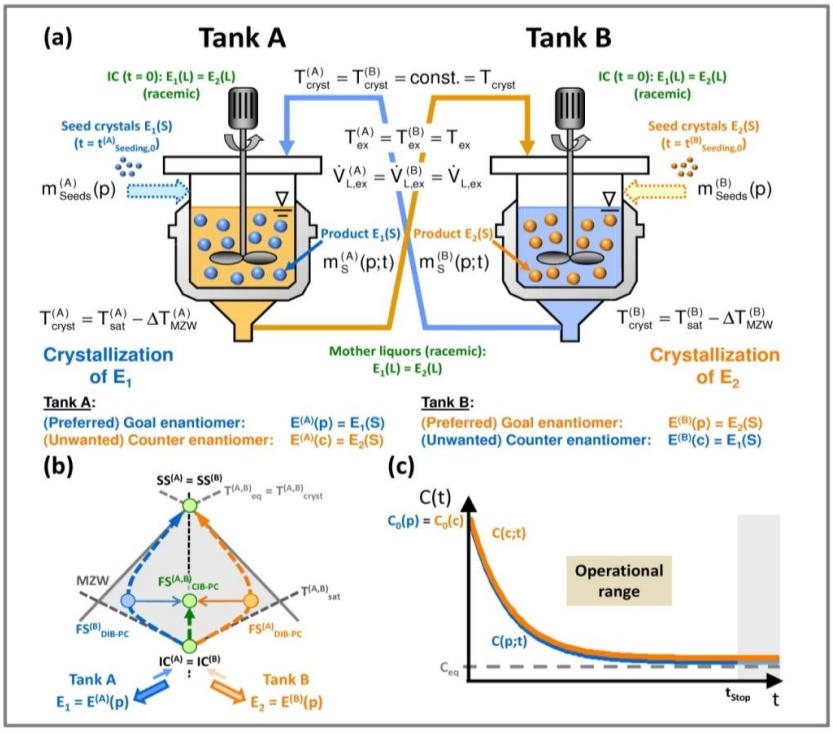

Fig. 10: Principle of coupled isothermal preferential crystallization. (a) Concept of arrangement. (b) Trajectories in both tanks. (c) Typical concentration curves for both enantiomers in each tank [35, 36].

In co-operation with the SCT group and funded by the DFG currently concepts to control the two coupled crystallizers in order to maintain symmetry are under investigation. First results are summarized in [37]. Further work is devoted to explore the possibility of using the approach to separate a pure enantiomer and the corresponding compound for a racemic compound-forming system.

c) Coupling membrane separation with crystallization

Another attractive and challenging concept is based on exploiting the potential of membrane technology to provide enantiomerically enriched solutions which could be subsequently processed by preferential crystallization. In a DFG funded co-operation with RWTH Aachen und Karlsruhe Institute of Technology the general applicability of this concept was demonstrated successfully for the first time for the racemic compound-forming mandelic acid system characterized by a critical eutectic composition of 40% [38]. The trajectories of the new pertraction process (R→P) coupled sequentially with a two-step preferential crystallization process (first around point A to further enrich the liquid phase up to 40%, then around point B to deliver the pure product) is illustrated in Fig. 11.

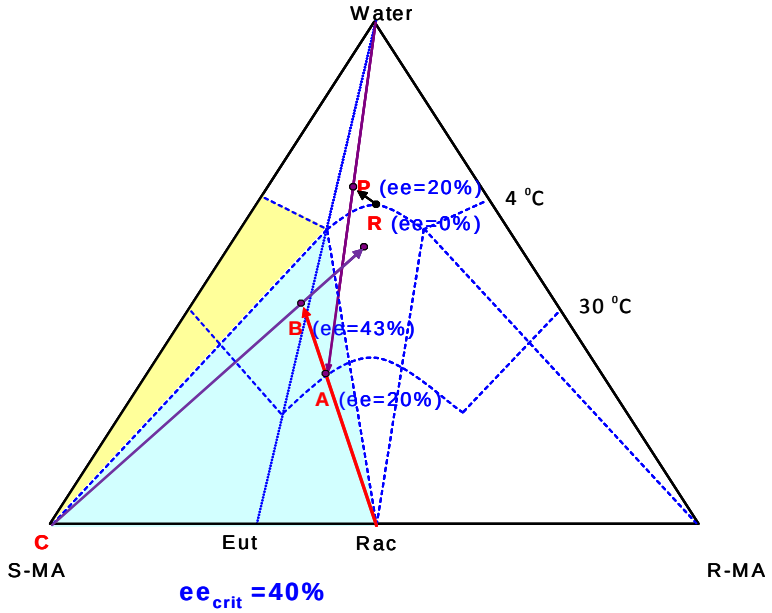

Fig. 11: Principle of coupling membrane enrichment by pertraction (R→P) and subsequent preferential two-step crystallization in order to obtain the pure S-enantiomer of mandelic acid (MA) [38]

4.4 Novel Reactor Concepts

In chemical reaction engineering there is tremendous interest in developing new reactor concepts capable of tackling permanent key problems related to reaction reversibilities and limited selectivities and/or yields in reaction networks. A comprehensive overview about current developments was given at the last ISCRE-Congress [R18].

The PCF group concentrates current research in particular on promising types of membrane reactors and chromatographic reactors and on exploiting the potential of forced periodic reactor operation.

a) Dosing concepts to enhance selectivities and yields

In order to understand and exploit the potential of porous membranes to distribute reactants in an optimal manner into reactive spaces, an understanding of the occurring mass transfer is mandatory. Systematic work led to a validated predictive model for gas transport through promising new micro- and mesoporous glass membranes allowing for selective gas transport [39, 40].

To study attractive gas dosing concepts a systematic analysis was undertaken together with Prof. Diez (Oviedo) and Prof. Tsotsas (OvGU) in order to evaluate the potential of delivering controlled amounts of oxygen through ceramic membranes into a fluidized bed reactor to improve butane oxidation to maleic anhydride [41].

The extensive work performed in the PCF, PSE and PSD groups at the MPI together with various groups at the OvGU led last year to the publication of a book [1], which highlights the potential of the membrane reactor concept but also addresses limitations regarding practical application.

b) Periodic reactor operation exploiting multi-column simulated moving bed concepts

Periodic operation is known to possess the potential to enhance the reactor performance as it offers more degrees of freedom to be exploited for specific objectives and exhibits different phenomena compared to classical steady state processes. A project of the PCF group was concerned with a new heat integrated reactor concept offering an energy efficient way to conduct important reactions as total oxidations of VOCs or equilibrium limited exothermic reactions in catalytic fixed-bed reactors. The idea is based on applying a cascade of fixed-bed units, in which the first segment is shifted to the end periodically after a specific time. Temperature fronts of exothermic reactors can be captured in this way and thermal energy accumulation allows for ignited reactor operation at high temperatures while introducing the feed at ambient conditions [R19, R20]. Such operation resembles a simulated moving bed process, which is well known in the separation science community (Fig. 12, left).

In cooperation with the PSD group (M. Mangold) a theoretical framework was developed consisting of two model approaches. The first one is a hybrid, discrete event dynamic model to simulate the dynamic operation directly. A reduced model based on the limiting case of a very large number of segments was developed to approximate the reactor states. In theoretical studies the agreement was evidenced successfully. Specifically, it was shown that bifurcation phenomena of both models show compatible results which motivated a thorough nonlinear analysis of the reduced model (Fig. 12, right). Software tools developed by the PSD group (Promot/Diana) capable of analyzing higher order singularities could be successfully exploited [42, 43]. In a further study a reliable control concept was identified and a method for parameterization was developed [44]. Finally, an experimental setup was built to demonstrate the reactor operation and to validate the dynamic models and the concept developed. Proper disturbance rejection via permanently adjusted switching times could be achieved. Recent work focused on studying the reactor behavior for mixtures in the feed gas. Advanced control in collaboration with the SCT group (J. Raisch) and model reduction techniques in collaboration with the CSC group (P. Benner) are under development. It is expected that this promising reactor concept can be developed in future to apply it in other areas, e.g. for carrying out efficiently reversible exothermal reactions.

The project was complemented by activities devoted to evaluate theoretically with Prof. Petkovska (Belgrade) the potential of periodic reactor operation exploiting nonlinear frequency analysis [45] and to quantify in more detail thermal effects occurring in cascades of fixed-bed reactors in co-operation with Prof. Sainio (Lappeenranta) [46].

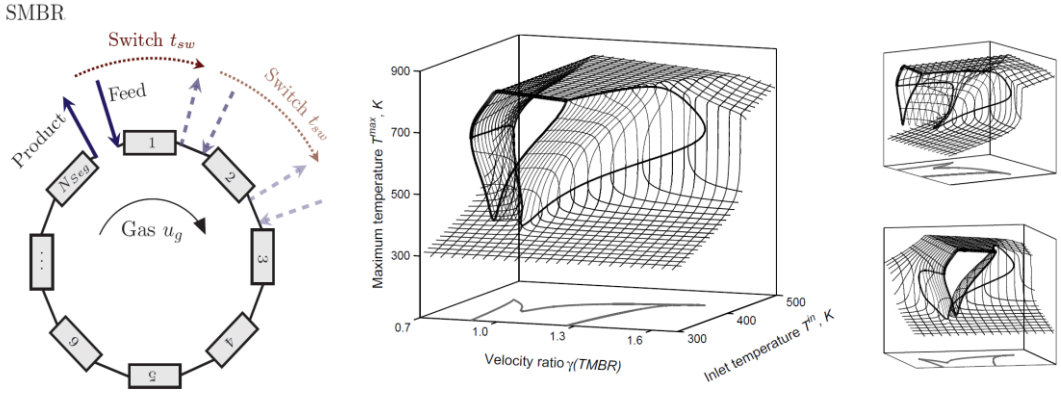

Fig. 12: left: Schematic representation of the periodically operated adiabatic heat integrated reactor cascade; right: Calculated reactor operation for the example of propylene oxidation illustrating multi-stability [42-44].

c) Continuous reaction chromatography

The area of combining reaction processes and chromatographic separation appears to be very promising in several directions and is of large interest for the PCF group.

At the beginning of 2011 a project was started with the Max Planck Institute for Colloids and Interfaces (Golm, Prof. Seeberger) in which in a continuous addition-elimination reaction is carried out. The product stream contains a target product A and two by-products B and C. The PCF group already successfully developed a batch chromatographic separation method using a tetrahydrofuran-water 40:60 mixture as a mobile phase and reverse phase silica gel as a stationary phase and started recently to design an SMB process capable of performing a continuous product separation from the effluent stream coming directly from the reactor. First tests of combining the two processes at the MPI in Magdeburg are currently underway.

A field, where the coupling of reaction and separation appears to be extremely promising, is racemization combined with enantioseparation to supply pure target enantiomers at 100% yield. First successful demonstrations could be provided for resolving the enantiomers of asparagine [47-49] and chlorothalidone [R21]. For the future the development and application of new enzymes carrying out racemization reactions for specific chiral molecules is planned together with the ESB group (K. Bettenbrock) as outlined in the “Vision 2015+” paper of the MPI.

5 Selected Teaching Activities, PhD Projects and Habilitations

Lectures of Prof. A. Seidel-Morgenstern (at OvGU)

Chemical Reaction Engineering (summer terms, German and English)
Safety in Chemical Reactions (winter terms, English)
Adsorption and Heterogeneous Catalysis (winter terms, German)
Numerical Methods in Chemical Process Engineering (summer terms, German)
Chemical Process Technology (summer terms, German)

Lectures of apl. Prof. H. Lorenz (at OvGU)

Chemical Process Technology (summer terms, German)
Technical Chemistry (summer terms, English)

Lectures of Dr. M. P. Elsner (at OvGU)

Technical Crystallization (summer terms, English; winter terms, German)
Integrated Innovative Reactor Concepts (summer and winter terms, German)
Numerical Tools for Technical and Chemical Problems (winter terms, German)

Ph.D. projects defended at OvGU between October 2008 and August 2011

Tab. 3: Ph.D. theses supervised by A. Seidel-Morgenstern (*Ph.D. students at the OvGU group; [1]IMPRS; [2]Ph.D. student at Indian Institute of Technology Madras, jointly supervised with Prof. G. Jayaraman)

L. C. Keßler	Enhancing the Potential of Simulated Moving Bed Chromatography	02/2009
A. Marković	Experimental and theoretical analysis of the mass transport through porous glass membranes with different pore diameters	08/2009
F. Czapla	Modeling of polythermal preferential crystallization	03/2010
A. Damtew Hamza	Analysis of the potential of nonlinear solvent gradients in preparative chromatography	06/2010
Á. Tóta*	Experimentelle und simulationsbasierte Studien der mehrstufig verteilten Eduktzufuhr in Festbett- und Festbettmembranreaktoren	06/2010
K. Gedicke*	Gradient Injection in Preparative Chromatography – Exploitation of Sample Solvents Different than the Mobile Phase	07/2010
S. K. Tulashie	The Potential of Chiral Solvents in Enantioselective Crystallization	07/2010
D. Polenske	Bewertung des Potentials der Bevorzugten Kristallisation zur Enantiomerentrennung	08/2010
L. Gueorguieva*	Einfluss der Lösungsmittelzusammensetzung auf Adsorptionsgleichgewichte und den Verlauf chromatographischer Trennungen	12/2010
B. Sreedhar[1]	Preparative Chromatographic Separation of Ternary Mixtures – Analysis of Fractionation Times and Novel Concepts	12/2010
S. Palani[2]	Recombinant Protein Purification Using Gradient Assisted Simulated Moving Bed Chromatography	12/2010
G. Ziomek	Evaluation of different operation modes for chromatographic and crystallization processes	08/2011

6 Selected Memberships, Appointments, Awards

Andreas Seidel-Morgenstern

since 2002 Scientific member of MPG and Director of the Max Planck Institute for Dynamics of Complex Technical Systems in Magdeburg

2005 – 2006	Dean of the Faculty of Process and Systems Engineering of OvGU
since 2006	German member of the Working Party “Chemical Reaction Engineering” of the European Federation of Chemical Engineers
since 2006	Member of Board of Trustees of Ernest Solvay Foundation, Hanover
2007 – 2008	Managing Director of the Max Planck Institute for Dynamics of Complex Technical Systems in Magdeburg
2008	Honorary Doctorate of Lappeenranta University of Technology (Finland)
since 2008	Elected member of the Commission of the Senate of the German Science Foundation (DFG) for Collaborative Research Units (SFB)
since 2010	Member of Board of Directors of International Adsorption Society (IAS)
since 2010	Member of Berlin-Brandenburg Academy of Sciences and Humanities

Heike Lorenz

since 2004	Appointed member of Board of “Crystallization” of Society of Process Engineering and Chemical Engineering (GVC), Düsseldorf
2008	“Applied Research Award” of the Federal State of Saxony-Anhalt
since 2009	Elected Chairwoman of Board “Crystallization” of Society of Process Engineering and Chemical Engineering (GVC), Düsseldorf
since 2010	Elected Member of the Scientific Council of the Max Planck Society (Chemistry, Physics and Technology Section)
since 2010	Adjunct Professor at OvGU

7 Future Directions

The PCF group will continue to focus strongly on the challenging and industrially important field of enantioseparation and expand in the future its activities into the wide field of isolating and purifying biomolecules.

In enantioselective crystallization the research work of the PCF group will concentrate on two directions. Up to now crystallization of enantiomers is predominantly carried out batch-wise. The PCF group will develop and validate new process options exploiting more productive concepts based on continuous enantioselective crystallization. The insight acquired already from existing possibilities to crystallize selectively chiral compounds of the compound-forming type will trigger in future the development of new adjusted process combinations based on optimized enrichment steps prior to crystallization. It is also planned to investigate the not sufficiently understood chiral systems which can form solid solutions. Another example of a high risk research goal is devoted to completely resolve mixtures of chiral molecules which contain several chiral centers.

Chiral membranes could offer attractive alternative possibilities to separate racemic mixtures in a continuous manner. Earlier attempts of developing such membranes focused on achieving a complete resolution and were not successful. The basic idea behind our approach will be to restrict the requirements for the membrane separation and to use it primarily for enrichment purposes in combination with a second separation technique. Thus, the chances to develop sufficiently selective membranes should improve. It is expected that

these investigations can profit from expertise acquired earlier in the PCF group during studies of mass transfer processes in other types of membranes. The successful incorporation of chiral membranes into integrated enantioselective separation processes is seen as a challenging long term goal of considerable relevance for several industries.

Preparative chromatography is known to be a powerful selective separation process and will remain a field of activity for the PCF group. However, the focus will shift from applying it to chiral separation to resolve more complex mixtures. In particular in the area of downstream processing of biomolecules, chromatography is seen as a very important technology, which still needs to be better understood and further developed. In addition to the development, identification and usage of highly selective stationary phases, in particular new types of operating modes based on recycling and continuous countercurrent principles and optimized combined applications of several chromatographic modes offer a large potential to solve challenging separation problems.

To support and further strengthen a planned stronger orientation of the PCF group to study also biological systems and, thus, also to further intensify the cooperation with the BPE and the ESB groups in the MPI, a new field of activity will be started in the group. Based on preliminary successful results acquired in the recently finished European project “INTENANT”, the PCF group will investigate the incorporation of racemization steps into the chain of enantioselective separation processes. Racemization is an efficient transformation of the “unwanted” enantiomer into racemic mixtures, which allows efficient applications of recycling concepts and thus, overall process improvements. Hereby, in particular the application of enzymatic racemization using racemases is very promising. However, the provision of such biocatalysts is currently in its very infancy and represents a challenging task. To contribute to the development and provision of active racemases to the PCF group, heterologous expression of selected racemases in Escherichia coli and subsequent purification are planned by the ESB group. Using these racemases the PCF group will develop and optimize in cooperation with the PSD group new and highly efficient reactive separation processes.

The rapidly developing theoretical methods of “Molecular Modeling” will be increasingly applied in the PCF group to support the solution of the separation problems mentioned. Major areas of future research in this field will be the prediction of thermodynamic and kinetic parameters, the critical evaluation of the potential of the available methods and their optimal application in order to support the design of dedicated separation processes.

In summary, the PCF group has the overall long term goal to develop new options to separate very similar components from each other and to resolve complex mixtures.

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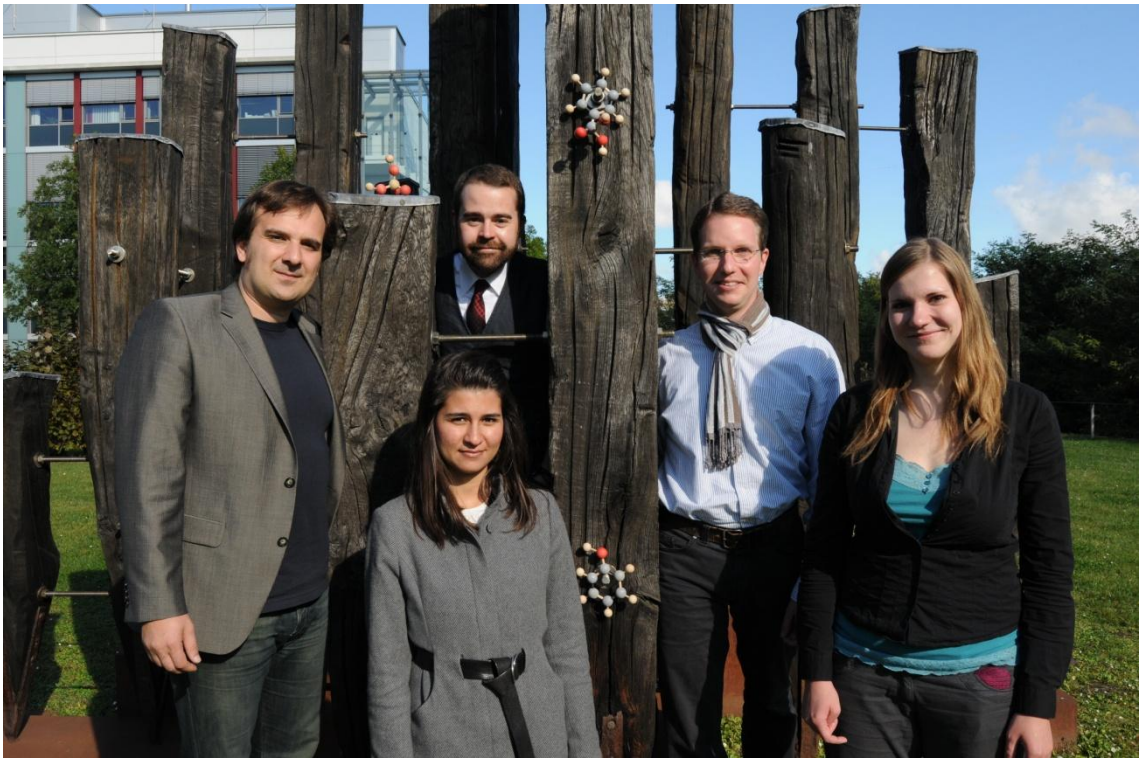
Research Group:

Molecular Simulations and Design (MSD)

Dr. Matthias Stein, M.Sc.



This report covers the period from July 2010 to August 2011.

1 Introduction

The Molecular Simulations and Design Group started its work at the MPI Magdeburg with the appointment of Dr. Matthias Stein as a Junior Research Group Leader (W2) in July 2010. Matthias Stein moved from the Heidelberg Institute for Theoretical Studies (HITS; a private research institution supported by the Klaus Tschira Foundation) to Magdeburg.

The time period to cover in this report is just from July 2010 to July 2011. Thus, it must be regarded as a start-up phase. The explicit molecular simulations and quantum chemical calculations by members of the MSD group are very demanding in terms of hard- and software requirements. A Linux cluster with 16 compute nodes and 24 cores each was approved by the "Beratenden Ausschuss für EDV-Anlagen in der MPG (BAR)" in June 2010, installed and put into operation in October 2010 but only became fully operational in April 2011. Since then it can be used to perform detailed and in-depth molecular simulations at atomic resolution.

The main research areas of the MSD group are *Chiral Separation*, *Enzymatic Catalysis*, *Biomimetic Systems* and *Molecular Systems Biology*.

In the *Chiral Separation* project Dr. Ronald Zinke, a theoretical physicist from the OvGU, investigates the rationalization of separation of racemic mixtures in close interaction and collaboration with the PCF group of Professor Seidel-Morgenstern by means of computer simulations. In the *Enzymatic Catalysis* project protein structural modeling and elucidation of enzymatic reaction mechanism, with an emphasis on hydrogen converting enzymes, are performed. External partners (HU Berlin, FU Berlin, Oxford University, MPI Muelheim) each contribute their individual expertise to the success of this project. The properties and mechanisms of synthetic *Biomimetic Systems* are investigated in international collaborations with universities in Illinois, Uppsala and MPI Muelheim. *Molecular Systems Biology* investigates the protein-protein and protein-small molecule interactions and kinetics in networks (both metabolic and signaling) and is the topic of research in collaboration with HITS GmbH, MPI for Cell Biology and Genetics Dresden and MPI for Biology of Ageing Cologne.

Further collaborations within the MPI Magdeburg that were initiated or have started in 2011 are the computational peptide-based ligand design for human influenza HA1 virus (co-supervising PhD student Anja Serve from the BPE group of Professor Reichl), rhodium catalyst design for hydroformulation reactions (with Professor Seidel-Morgenstern, PCF), and the Excellence Initiative of the Bundesland Saxony-Anhalt "Dynamic Systems in Biomedicine and Process Technology Research Center".

2 Members of the Research Group

	Research Topics	**Membership**
Head of Group		
Dr. Matthias Stein	Chiral solubility, hydrogen converting enzymes, bioinformatics, protein structural modeling, molecular dynamics and Brownian dynamics, quantum chemistry, catalysis, calculation of spectroscopic observables, molecular systems biology.	since 07/2010

Postdocs		
Dr. R. Zinke	Chiral molecules in solution	since 07/2010
Ph.D. Students		
Samira Yazdi	Molecular systems biology of signal transduction	From 09/2011

3 Survey of Research Projects

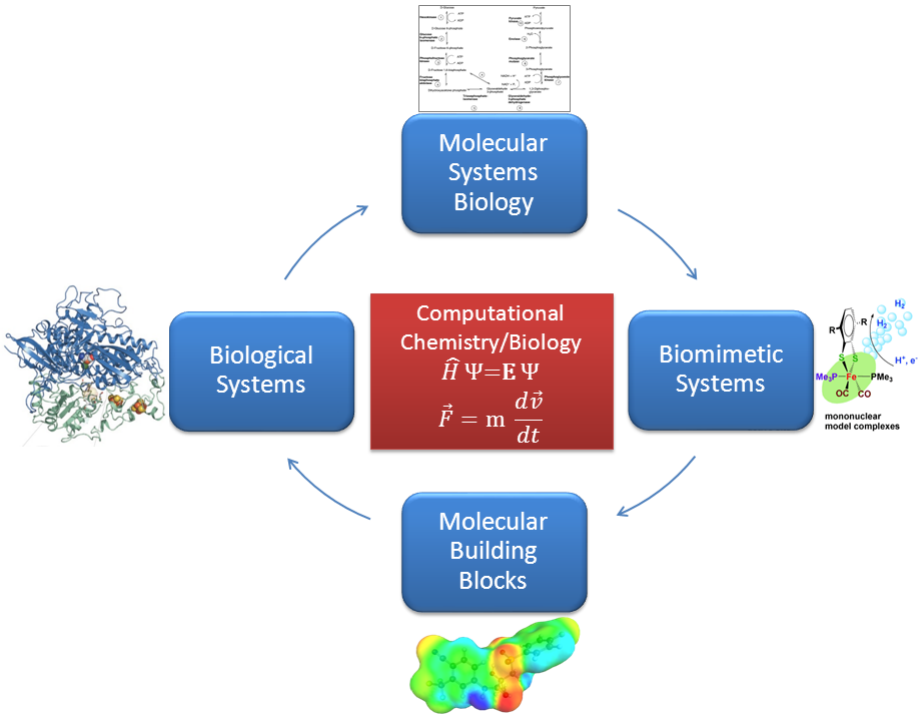


Fig.1: Research areas of the MSD group.

Intra- and intermolecular interactions are the focus of research of the MSD group. Which forces hold molecules and proteins together and how do they steer and enforce second partner binding? By means of computer simulations, efficient simulation techniques for investigating the energetics and dynamic behavior are developed and applied to large and complex chemical and biological systems.

With the beginning of activities at the Max Planck Institute in Magdeburg in July 2010, new scientific collaborations were initiated. With Professor Seidel-Morgenstern, the computational prediction of solubility of chiral molecules in order to design an enantioselective separation process has started. The MSD group has strong scientific collaborations within Germany and also internationally in the area of molecular systems biology, characterization of hydrogen converting enzymes and biomimetic systems.

Project: **Research Group Molecular Simulations and Design** Head of Group: Dr. Stein	This group brings in new aspects of simulation in atomistic and molecular detail. At different levels of representations, detailed insight into complex chemical and biological processes can be gained on a multiscale level. The group supports existing research at the MPI (crystallization, catalysis) and also pursues their own projects.

Subprojects	Scientists	Funded by	Period	Partners
Chiral Separation	Zinke	MPI	Since 07/2010	MPI Magdeburg, PCF Group
Enzymatic Catalysis	Stein	MPI	Since 07/2010	Humboldt University Berlin (Prof. Friedrich), University of Oxford (Prof. Armstrong), MPI for Bioinorganic Chemistry (Prof. Lubitz)
Biomimetic Systems	Stein	MPI	Since 07/2010	University of Uppsala (Dr. Ott), University of Illinois (Prof. Rauchfuss), Max Planck Institute for Bioinorganic Chemistry Muelheim (Prof. Lubitz)
Molecular Systems Biology	Stein	MPI	Since 07/2010	HITS GmbH (Dr. Wade), MPI for Cell Biology and Genetics Dresden (Prof. Zerial), MPI for Biology of Ageing Cologne (Dr. Habermann)

4 Research Highlights

The following gives an overview of research activities initiated at the MPI in Magdeburg (Chiral Molecules in Solution) and ongoing research (Biological Energy Conversion and Biomimetics). The latter research areas fit perfectly into the profile of the MPI.

4.1 Chiral Molecules in Solution

Knowledge of the solubility and the activity coefficients of chiral molecules is a pre-requisite for the design of a separation process. There are several approaches to predict the solubility of chemical compounds in solution, e.g. group contribution methods UNIFAC [R1] or 3D-QSAR, see for example [R2]. The Conductor-like Screening Model (COSMO) is an implicit solvation model in which the solute is embedded in a dielectricum. COSMO-RS is an extension to calculate the mesoscale properties of the solute in presence of an arbitrary solvent [R3]. There are very similar other implementations of COSMO-type solvation thermodynamics, see for example [R4].

The separation of enantiomers from solution very often requires a two-step process. In the first step, an initial enantiomeric enrichment is obtained from HPLC with a chiral stationary phase. In the second step, an anti-solvent is added and enantioselective crystallization is

performed. Knowledge of the solubility of complex chemical and pharmaceutical compounds is an essential pre-requisite for the successful design of such a separation process.

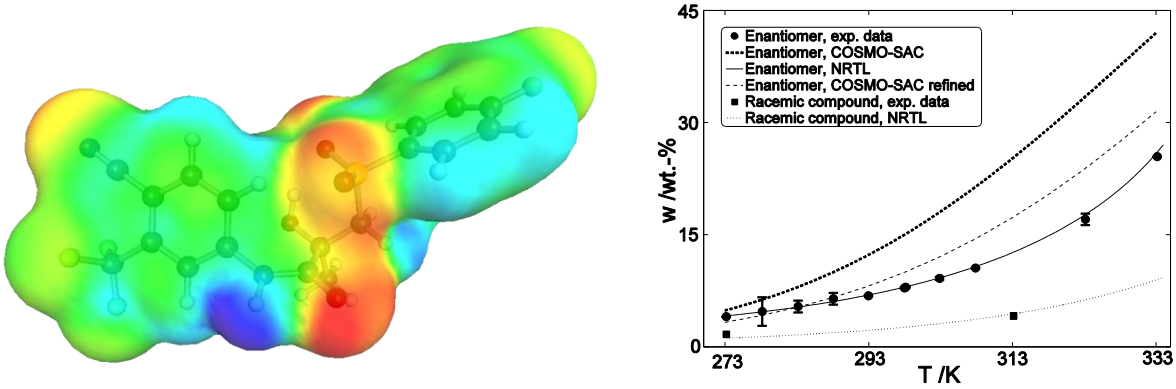


Fig. 1 Screening charge density surface σ on the molecular surface of bicalutamide (**left**). Temperature-dependence of solubility of bicalutamide in water-methanol mixtures. Comparison of different COSMO implementations, NRTL model and experimental data (**right**).

We used COSMO-RS and different other COSMO implementations to screen for suitable anti-solvents and to calculate the temperature-dependence of the solubility of the chiral pharmaceutical chiral compound bicalutamide in the chosen binary solvent. **Figure 1** shows the screening charge density surface σ of bicalutamide mapped on its molecular surface and a comparison of the calculated and experimentally determined solubility in a water/methanol mixture [1, 2].

4.2 Biological Energy Conversion

Hydrogenases are enzymes which catalyze the heterolytic splitting of molecular hydrogen (H_2) into protons and electrons or the reverse reaction, the production of molecular hydrogen. According to the composition of their active site, they have been classified as [NiFe]-, [FeFe]- or [Fe]-hydrogenases [R5]. Most of the [NiFe]-hydrogenases are very sensitive to oxygen. The oxygen tolerance of some subfamily of [NiFe]-hydrogenases, however, has been the issue of in-depth scientific research. Modifications of the gas access channel to block O_2 access to the active site [R6-R7], and alterations of the active site itself were discussed, see discussion in [R8] .

4.2.1 Oxygen-Tolerant Hydrogenases Possess Identical Active Site

By a combination of electron paramagnetic resonance (EPR), infrared (IR), X-ray absorption spectroscopy (XAS) and Density Functional Theory (DFT) calculations, we were able to show that the active site composition of the O_2-tolerant membrane-bound hydrogenase (MBH) from *Ralstonia eutropha* H16 is identical to that of the standard hydrogenase from *Desulfovibrio gigas* in the Ni-B and Ni-C states and some of the diamagnetic states. Only some oxidized cysteine amino acid modifications in a non-activating state could be detected [3]. It was suggested that the oxygen tolerance of the MBH might originate from alterations of the Fe-S centers in the small subunit.

4.2.2 Discovery and Characterization of a New Type of [FeS]-Cluster

A bioinformatics analysis of oxygen-tolerant hydrogenases revealed the existence of two additional cysteine amino acids in the small subunit of [NiFe]-hydrogenases [4]. In standard hydrogenases these positions are occupied by glycines. From comparative protein structural modeling it became apparent that those cysteine amino acid residues are in spatial proximity to the proximal [4Fe4S]-cluster and may even interact with it (see **Figure 2**). The coordination of a cubane iron-sulfur cluster by six cysteine residues within bonding distance is novel and occurs only in this subgroup of [NiFe]-hydrogenases. Site-directed mutagenesis experiments with the MBH from *R. eutropha* of either one at a time or both additional cysteines simultaneously to a standard glycine re-introduced the oxygen sensitivity of the active site. Cysteine Cys_{120} had a more pronounced effect on the hydrogen oxidation capability of the MBH than Cys_{19}. The proximal FeS cluster in MBH displays an unusual redox behavior with two redox transitions at +160 mV and -60 mV. Standard [4Fe-4S] clusters undergo only one redox transition from the 3+ to 2+ state at about +300 to +500 mV. It can be speculated that this unusual redox properties of the proximal cluster exert some protective function on the active site at a distance of 10 Å. The role of two additional cysteine residues in the extension of the redox capability of a conventional [4Fe-4S] center is an intriguing question and the focus of current research activity of the MSD group in collaboration with other groups.

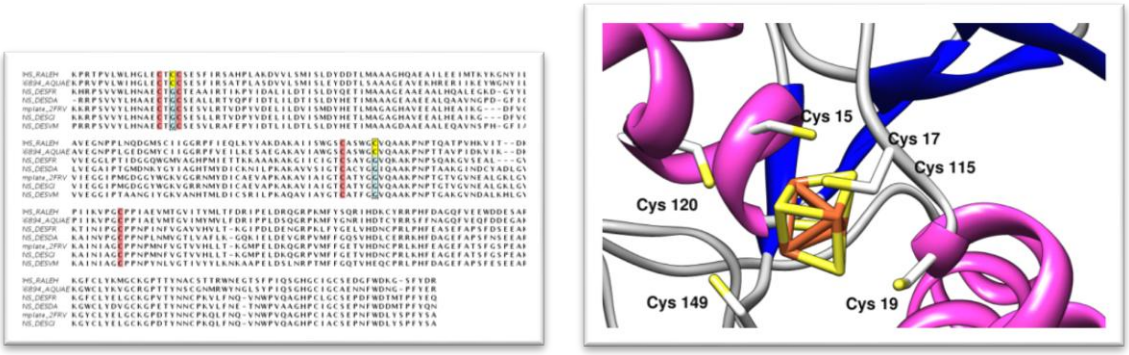


Fig. 2: Left: Multiple sequence alignment of the small subunit of standard and oxygen-tolerant [NiFe]-hydrogenases. **Right:** The oxygen-tolerant [NiFe]-hydrogenases possess two extra cysteines which are in binding distance to the proximal [FeS]-cluster and may influence its redox properties.

4.3 Small Molecules Mimicking Nature

Design principles can be extracted from biological systems after many experiments and with lots of experience only. For [FeFe]-hydrogenases some open questions still remain regarding the atomic composition of the active site cofactors and mechanistic details. Chemical syntheses afforded the creation of small molecules that either mimic the active site composition or the enzyme's activity [R9].

In [FeFe]-hydrogenases, the active site (termed 'H-cluster') consists of a cubane [4Fe-4S]-cluster that is linked to a binuclear FeFe cluster via one cysteine residue. The binuclear FeFe is made up of two Fe atoms, two inorganic carbon monoxide ligands, two cyanide ligands and a bidentate ligand bridging the transition metal atoms. The bridging ligand is a three-membered carbon chain. Either a propanedithiolate (pdt), an oxadithiolate or an azadithiolate are possible. The difference between those could neither be obtained from protein X-ray

crystallography [R10] nor from a quantum chemical based refinement [R11]. Recently, ^{14}N-HYSCORE experiments of the oxidized form H_{ox} of the [FeFe]-hydrogenase revealed quadrupole interactions from two distinct nitrogen atoms in the vicinity of the H-cluster but a definite assignment could not be made [R12].

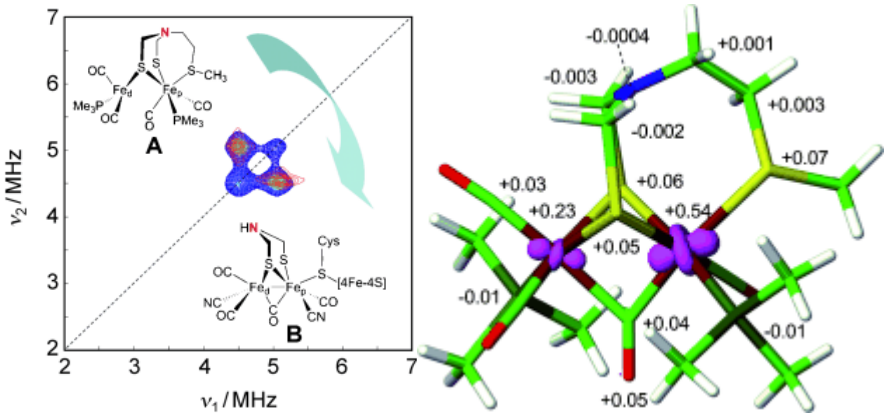


Fig. 3: Left: Convincing evidence for the presence of a nitrogen atom in the dithiolate bridge of the active site of [FeFe] hydrogenases (**B**) is provided by a spectroscopic, electrochemical, and theoretical study of a well-characterized structural mimic of the [FeFe] hydrogenase subcluster (picture: 14N matched-HYSCORE spectrum of the model compound **A**). **Right:** Calculated spin density distribution and atomic spin densities of complex **A.**

Figure 3 shows the ^{14}N matched HYSCORE spectra of a mixed-valence Fe(I)Fe(0) structural mimic of the binuclear FeFe hydrogenase active site. The complex only contains *ONE* nitrogen atom in an azadithiolate bridging position. The calculated g-tensor principal values, IR spectra, ^{31}P, ^{1}H/^{2}H and ^{14}N/^{15}N hyperfine and quadrupole coupling constants, where applicable, helped to elucidate the electronic structure of a spin-delocalized system with the majority of the unpaired spin density residing on the Fe_d atom. The similarity of the nuclear quadrupole coupling constant and the asymmetry parameter, η, in the complex and in the H_{ox} state of the enzyme unequivocally allowed the assignment of a weakly hydrogen-bound azadiothiolate in the enzymatic systems [5]. Acting as an intermediate base and proton acceptor the nitrogen atom in the bridging ligand has a significant role as a proton relay in the enzymatic mechanism.

4.3.1 Reactive Mimics of Enzymatic Activity

In the ‘H-cluster’ the Fe atom distal to the [4Fe4S]-cubane (Fe_d) is regarded as the site of protonation and H_2 release. A structural mimic of the coordination sphere of the Fe_d is shown in **Figure 4**. The Fe(II) is octahedrally coordinated by two trimethylphosphine ligands (which are very often used as electronic mimics of inorganic cyanide ligands), two carbon dioxide ligands and one bidentate benzene-1,2-dithiolate ligand.

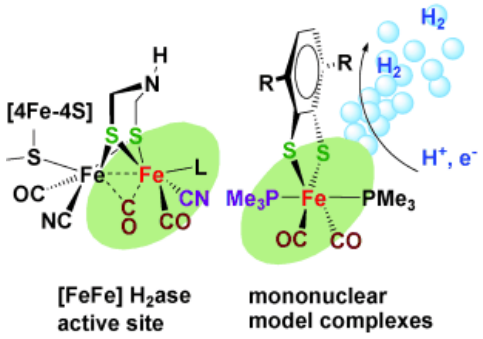


Fig. 4: Details of the composition of the active site of [FeFe] hydrogenase and a mononuclear model complex. Structural similarities in the coordination sphere are highlighted in green.

Initial protonation occurs at one of the sulfur atoms [6]. The first electrochemical reduction leads to an Fe(I) complex and spontaneous breaking of one Fe—S bond. This opens a coordination site at the central atom. Details of the reaction mechanism can be seen in **Figure 5**. The observation of two catalytic peaks with distinct turnover rates indicates that formation of H_2 from the same acid can proceed via two pathways with two different rate-limiting steps. The mechanism at first wave is a sequential CECEC sequence of chemical and electrochemical steps, in which **1H** allows for further reduction at a similar potential. The second catalytic peak at -1.7 V is attributed to a CEECC mechanism that involves the doubly reduced intermediate **1H**$^-$ at more negative potential. For Fe(0) (**1H**$^-$), the hydride formation is kinetically favored.

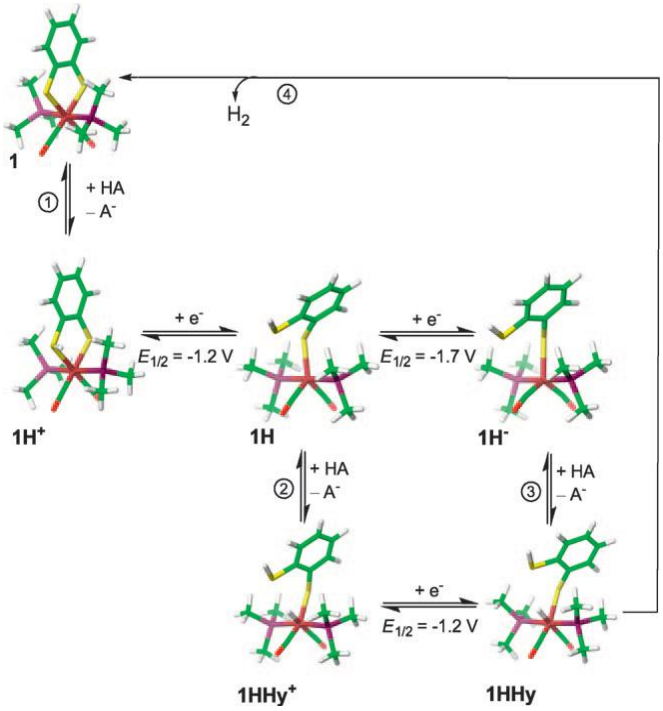


Fig. 5: Mechanistic proposal for the catalytic formation of hydrogen from the acid HA with DFT-optimized structures of proposed intermediates.

5 Selected Teaching Activities, PhD Projects and Habilitations

Dr. Matthias Stein considers teaching as an important objective also of a researcher at an MPI. Teaching activities at the Otto-von-Guericke University Magdeburg will start in the winter term 2011/2012. Dr. Matthias Stein will offer a combined course (lecture and hands-on

practical work) entitled **Molecular Modeling/Computational Biology and Chemistry** (taught in English) for students of the Master courses CEE, MPSD and BSYT.
As to scientific outreach, the work by the MSD group made it onto the first page of the local newspaper Magdeburger Volksstimme on 12th April 2011 presenting the newly established MSD group and reporting about the publication in Angewandte Chemie.
The MSD group members were very active in preparing activities for the general public during the **Night of Science** on 28th May 2011. In particular children were encouraged to assemble molecules from colored wooden balls and sticks representing atoms and bonds. About 200 children and adults built various molecules with great enthusiasm and commitment. Adults were given an introduction into computer-aided drug design and virtual screening. A general lecture on computer-aided drug design was given.

6 Selected Memberships, Appointments, Awards

1996 - 1999 Chemiefonds-Stipendium (scholarship) by Chemical Industry Funds
2001 Schering Prize for PhD Thesis
2002 Marie-Curie Individual Fellowship
2005 Fondation Fourmentin-Guilbert Travelling Grant
2006 EML Award for best scientific presentation
2008 Wenner-Gren-Foundation Young Investigator Grant
2010 EML/HITS Award for best scientific presentation
Since 07/2010 Research Group Leader (W2) at MPI

7 Future Directions

After an initial start-up phase in 2010/2011, the MSD group will continue to grow and expand its research activities. Further research projects will deal with the generation of possible molecular crystal structures and the crystallisation process of chiral molecules. The prediction and accurate energetic ranking of possible crystal structures for chiral molecules that are of relevance for the chemical and pharmaceutical companies will be performed. In particular, the calculation of different crystal forms (polymorphs) and the variability of the molecular composition of solid solution in molecular crystals will be considered. Also, the formation and stereoselective binding in diastereomeric complexes will be investigated. An international cooperation between the MSD group and Prof. Sarah Price (University College London) was approved by the Max Planck Society in Munich and UCL and is about to begin in October 2011.
The molecular systems biology work will be extended to consider signal transduction pathways. The interplay between posttranslational modifications of proteins, receptor recognition and signal transduction will be investigated on a multiscale and multirepresentation level in collaboration with experimental partners at the faculty of medicine at the OvGU (Prof. Naumann).
Small molecule converting enzymes, in particular hydrogen, and the evaluation of the potential of molecular catalysts to perform a similar function are an on-going research topic of the MSD activities.

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8.1 Own References

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Research Group:

Process Systems Engineering (PSE)

Prof. Dr.-Ing. K. Sundmacher

This report covers the period from October 2008 to August 2011.

1 Group Introduction

Technical systems of ever increasing complexity change our environment to a dramatic extent. Research on these systems is ultimately triggered by the key question: How can the Earth's resources be better utilized in the future?

Vision

In the past decades, continuous progress in increasing the productivity, selectivity and sustainability of chemical and biotechnological production processes has been made. Nevertheless, in order to cope with the challenges of the future, breakthroughs in process systems engineering are necessary to find "dream processes" for synthesizing chemicals and transforming energy, to enable the transition from fossil fuels and petrochemical feedstocks to renewable materials and energy, to close carbon dioxide cycles, to enhance efficiency significantly, and to incorporate new functionality in materials and products [1].

For this purpose, new scientifically founded process engineering approaches need to be developed, able to deal with the inherent multi-level structure of production systems (see Fig. 1). Very efficient process systems might be designable if engineers succeed to consider all hierarchical levels involved in a process system simultaneously, i.e. from the molecular level up to the plant level [84-87]. But a multi-level design strategy will be successful only if the underlying sub-models are validated by use of reliable experimental data obtained at different levels of the process hierarchy. Experimental data are an indispensable element required to discriminate between rival models and to identify model parameters with small uncertainties. Hence, only by closely combining mathematical process models and experimental data, an advanced quantitative understanding of complex process systems can be attained for opening new paths to translate fundamental science into practical solutions.

Furthermore, due to unique features such as specificity, adaptivity or reproduction, biological parts (enzymes, organelles, cells, cellular communities) are expected to play an important role in the future chemical production and energy conversion systems. In other words, the future "tool box" of process engineers should not only contain chemical and physical "screw drivers", but also biological devices. Establishing these devices as engineering tools might become reality if process systems engineering principles can be successfully combined with upcoming synthetic biology approaches [66].

Mission

This vision forms the background for the group's research strategy formulated in the "Vision 2015+" paper of the institute. In accordance with the statements made in that paper, our group closely combines mathematical modeling of complex production processes with theoretical methods for process analysis, design and optimization as well as with experimental validation techniques. As confirmed by the SAB in their 2009 report, understanding and modeling the dynamics of complex process systems is the core competency of the group. Thus, we have continued to expand our competency in this direction by integrating new theoretical concepts and challenging process examples including chemical production systems, energy conversion systems, and more recently also biological production and conversion systems. In order to reflect the fact that we are investigating complex chemical as well as biological systems, the group's name "Physical and Chemical Process Engineering" was modified to "Process Systems Engineering" (PSE group).

2 Members of the Research Group

Since 2001, Kai Sundmacher, in his function as Director of the MPI department for Process Engineering, has guided the research activities of the PSE group and his university group at the Otto-von-Guericke University Magdeburg (OvGU). In coordinating these activities, he is supported by six team leaders (5 from MPI, 1 from OvGU; see Table 1).

Tab. 1: Members of the Process Systems Engineering Group

	Research Topics / Responsibilities	**Membership**
Head of PSE Group		
Prof. Dr.-Ing. K. Sundmacher	Theoretical and experimental methods for modeling, analysis and design of chemical production systems, energy conversion systems and biosystems	since 10/1998
Project Coordinators & Team Leaders		
Dr.-Ing. H. Freund	Chemical production systems, catalytic reactors, (modeling, analysis, design, optimization)	since 09/2005
Dr.-Ing. R. Hanke-Rauschenbach	Energy conversion systems, PEM fuel cells, water electrolysis, biogas production (modeling, analysis)	since 11/2001
Dr.-Ing. P. Heidebrecht	Energy conversion systems, high-temperature fuel cells, reforming, bioseparation (modeling, design)	since 09/2005
Dr. techn. L. Rihko-Struckmann	Energy conversion systems, energy storage, biofuel production (experiments, analysis)	since 01/2001
Dr.-Ing. T. Vidaković-Koch	Enzymatic fuel cells, electrolysis, electroanalytical methods (experiments, analysis)	since 10/2011
Postdocs		
Dr. S. Banerjee	Molecular dynamics simulation of crystal growth	08/2008 - 10/2009
Dr. P. Datta	Mixed oxides for cyclic water gas shift processes	since 11/2008
Dr. A. Katariya	Simulation of coupled reactive distillation processes	12/2006 - 11/2009
Dr. R. Kumar	Miniplant experiments on olefin hydration by reactive distillation using reactive entrainers	10/2006 - 03/2010
Dr. P. Malladi	Modeling of affinity membrane adsorbers	09/2008 - 08/2010
Dr. V. Panić	Frequency response of electrochemical processes	09/2009 - 09/2010
Dr. S. Thotla	Entrainer based reactive divided wall columns	07/2008 - 09/2010
Ph.D. Students		
R. Ahamed	Process design for the indirect hydration of C_6 olefins	since 11/2006
C. Borchert	Modeling of crystal shape distribution dynamics	07/2007 - 10/2011
Q. N. Do Thi	Model-based analysis of an enzymatic fuel cell	since 11/2010
M. Fachet	Dynamic metabolic analysis of green microalgae	since 07/2011
M. Fricke	Emulsion-assisted precipitation processes	11/2005 - 06/2011
B. Hartono	Model-based design of biomass-fed fuel cell systems	since 10/2008
C. Hertel	Analysis of a cyclic water gas shift reactor	since 04/2007
I. Ivanov	Development of a direct glucose enzymatic fuel cell	since 01/2007

G. Ji	Model-based control of PEM fuel cell systems	09/2009 - 08/2011
T. Kadyk	Nonlinear frequency response analysis of the PEMFC	07/2011 - 09/2011
F. Karst	Methodology for combined catalyst and reactor design	since 09/2009
S. Kirsch	Nonlinear dynamics of PEM fuel cells fed with H_2/CO	since 11/2008
K. McBride	Computer-aided molecular design of solvents	since 09/2011
C. Oettel	Electrochemical water gas shift membrane reactor	07/2007 - 06/2011
A. Peschel	Model-based design of optimal chemical reactors	since 11/2007
S. Piewek	Advanced modeling of gas diffusion electrodes	since 08/2008
S. Pirwitz	Dynamics of photosynthetic microbial communities	since 10/2011
S. Rollié	Aggregation processes in particle and cell populations	05/2006 - 02/2011
A. Sommer	Conceptual design of fuel cell based CHP systems	since 12/2008
M. Varnicić	Experimental analysis of an enzymatic fuel cell	since 03/2011
W. Wang	Modeling of affinity-based membrane adsorbers	since 09/2010
K. Ye	Modeling of gas-expanded liquid systems	since 09/2008
A. Zinser	Energetic evaluation of energy conversion processes	since 01/2011
Visiting Researchers		
Prof. D. K. Sharma (IIT Delhi, India)	Green microalgae: metabolism, synthetic communities	01/2011 - 12/2011
Prof. Z. Qi (ECUST, China)	Innovative solvent systems for chemical processes	several visits of 1-2 weeks
Prof. S. Zhou (U Tongji, China)	Dynamics and control of electrochemical processes	several visits of 3-4 weeks
Dr. K. Eichhorn (NUST, Norway)	Nonlinear dynamics of fuel cells	06/2010 - 09/2010
Enrico Bianchi (Politech. Milano, Italy)	Heat transport in structured catalyst supports	06/2011 - 10/2011
Kshipra Gautam (IIT Delhi, India)	Analysis of metabolic networks of green microalgae	06/2011 - 12/2011
Technical Staff		
M. Ikert	Lab assistant: electrochemistry, analytics	since 05/2006
S. Nickel	Lab assistant: bioanalytics, cell cultures	since 05/2011
T. Schröder	Lab engineer: design, operation, safety, maintenance	since 01/2002
P. Siegmund	Lab engineer: design, operation, safety, maintenance	since 02/2003
B. Stein	Lab assistant: physical & chemical analytics	since 10/2001
Members of the Process Systems Engineering Group at OvGU		
Team Leader: Dr. A. Voigt Postdocs: Dr. V. Becker, Dr. J. Diaz-Ochoa, Dr. E. van der Zalm Ph.D. Students: B. Bensmann, A. Bornhöft, H. Eisenschmidt, A. El-Sibai, R. Flassig, M. Fricke, B. Hentschel, I. Gonzalez-Martinez, T. Heidig, T. Kadyk, R. Lemoine, C. Oettel, M. Pfafferodt, C. Steyer Visiting Scientist: Dr. P. Kazempoor (University of Tarbiat-Modares, Iran) Lab Assistant: E. Felsch		

3 Survey of Research Projects

As illustrated in Figure 1, the PSE group is active in three research areas, namely chemical production systems, energy conversion systems, and biological production and conversion systems. The group members working on these projects, the funding sources, and the collaborations with external and internal partners are listed in Table 2. Selected research highlights from these projects are presented in section 4 of this group report.

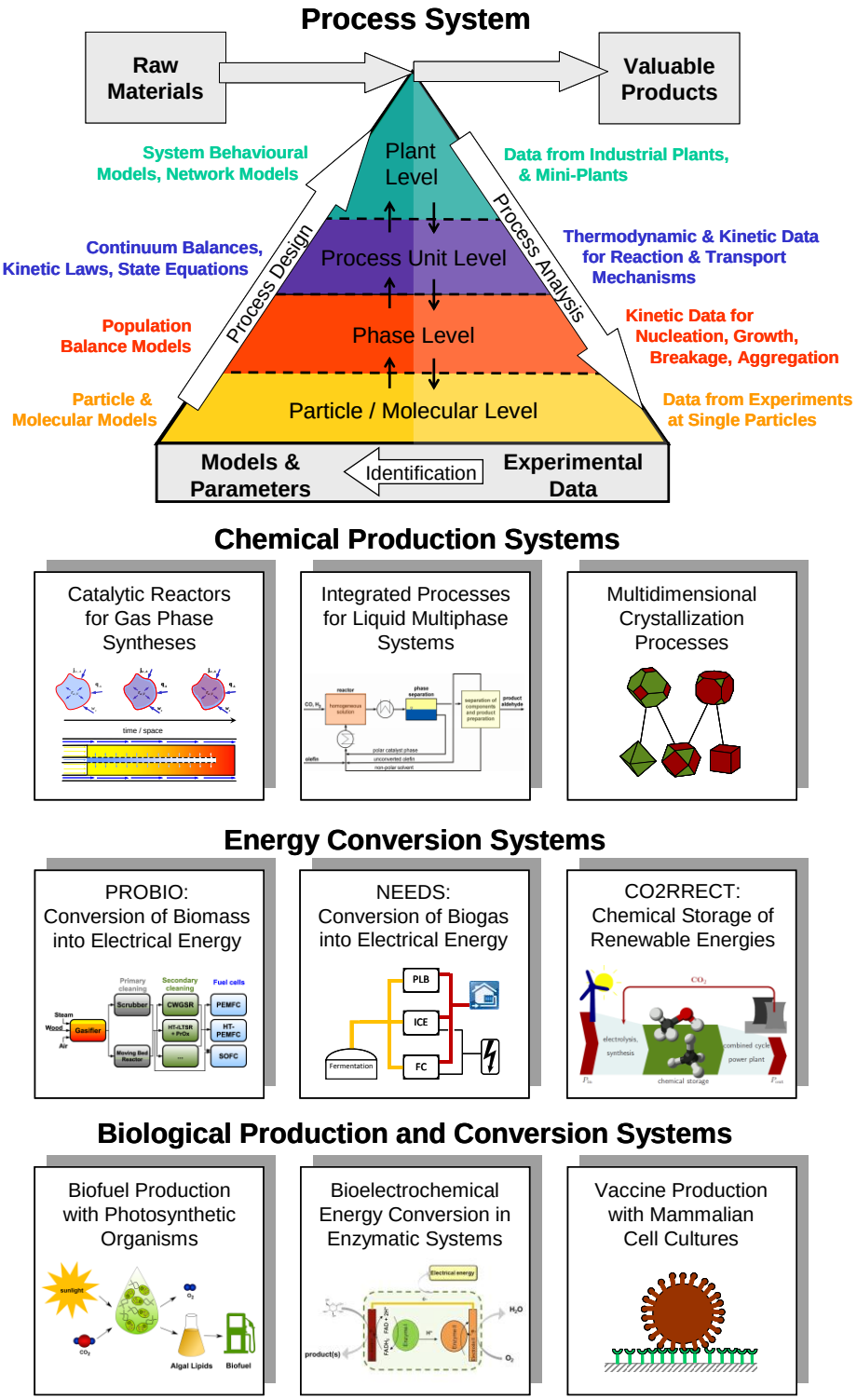

Fig. 1: Survey of research areas and projects of the PSE group.

3.1 Chemical Production Systems

The PSE group has continued to develop their "Elementary process functions (EPF) methodology" as a general framework for process analysis and design. Our long-term vision is to overcome the classical "unit operations concept" in order to attain technological breakthroughs in the efficient transformation of chemical and biological substances, under consideration of all involved hierarchical process levels. For this purpose, new computational methods have been established and integrated into our research projects, e.g. advanced numerical algorithms for dynamic optimization, advanced thermodynamic state equations, methods for the kinetic modeling of complex reaction networks, and quantum chemical methods for solvent design.

In our research area "Chemical Production Systems", the EPF methodology has been successfully applied to the optimal design of catalytic reactors for gas phase syntheses, partly in close collaboration with several industrial partners. Currently, we are working on the extension towards integrated processes for liquid multiphase systems. In that project, the key idea is to control the physical-chemical properties of solvents in a desired manner via adjustment of operating parameters and/or via purposeful design of the molecular solvent structure. Combining the optimization of both operating parameters and molecular parameters within a coherent design framework is the main direction of impact of this ambitious project. Currently, thermo-regulated solvent mixtures, gas-expanded liquids, and ionic liquids are included in our research program.

On the mid-term we will extend the EPF methodology also to disperse systems, particularly for the purpose of optimal design of production processes for crystals with well-defined size and morphology. As a major prerequisite for this project, we are currently working on the modeling of crystal morphology evolution by means of multidimensional population balances, on the model-based identification of face-specific growth kinetics using advanced imaging techniques, and also on the shape control of crystals via temperature manipulation.

3.2 Energy Conversion Systems

In our research area "Energy Conversion Systems", we are currently working on three projects aiming at the efficient conversion or storage of renewable energies (biomass, wind, solar). The first project, PROBIO, is dealing with integrated process systems for biomass conversion into electrical energy using fuel cells. The main goal is to identify energy-optimal process routes out of a huge number of rival variants. Besides classical units for reaction and separation steps, the PSE group is thoroughly investigating novel reactor concepts, namely a periodically operated water gas shift reactor, an electrochemical membrane reactor for performing the water gas shift reaction, and an electrochemical membrane reactor for preferential oxidation of carbon monoxide.

The second energy-related project, NEEDS, is focused on the production and conversion of biogas using high- or low-temperature fuel cells. This activity is aiming at the quantitative understanding, optimization and control of the behavior of the whole power generation system. For this purpose, the PSE group has developed steady state and dynamic models for Molten Carbonate Fuel Cell stacks and Proton Exchange Membrane Fuel Cells. Regarding the anaerobic fermentation process, so far it is not possible to predict and fully control the behavior of biogas production plants, due to fluctuations of the feed com-

position and complex behavior of the microbial communities acting along the biomass digestion pathway. For this reason, the PSE group is intending to formulate and validate an advanced anaerobic digestion model, as the major prerequisite for the derivation of model-based process control strategies.

The third research project within the research area “Energy Conversion Systems”, CO2RRECT, is focused on the chemical storage of renewable energies by use of carbon dioxide. It is based on the idea to produce hydrogen from wind or solar energy via high-pressure water electrolysis and to convert this energy carrier by reaction with carbon dioxide (from coal- or biomass fed power plants) into more easily storable compounds like methane, methanol or formic acid. On demand, these storage compounds could be either used for the production of chemicals or re-converted into electrical energy. The research activities of the PSE group aim at the systematic analysis of whole energy conversion chains, and at understanding the dynamics of water electrolysis processes operated with fluctuating electrical energy input.

3.3 Biological Production and Conversion Systems

As outlined above, biological systems feature special properties which make them very attractive for chemicals production and energy conversion. Thus, the PSE group has intensified existing and started new research activities in the area “Biological Production and Conversion Systems”. Currently, three challenging process examples are investigated as briefly described in the following:

First, the PSE group has started a new interdisciplinary research project located at the interface between process systems engineering and systems biology. It is aiming at the production of biofuels using photosynthetic organisms. In particular, green microalgae are unicellular organisms able to convert solar energy into lipids and other valuable compounds. The goal of this project is to analyze and control the steady state and dynamic behavior of the underlying metabolic networks. Experimental investigations are closely combined with kinetic network modeling for model discrimination and parameter identification.

The second project is focused on bioelectrochemical energy conversion from glucose into electricity using enzymatic fuel cells. These cells are biomimetic devices equipped with electrodes at which enzymes are used as catalysts. Our research activities in this project aim at the development, experimental characterization, and model-based analysis of these very interesting devices. In particular, we try to understand the complex dynamic interactions of the underlying reaction and transport mechanisms. For this purpose, advanced electroanalytical techniques are currently being developed.

The third biosystems engineering project is dealing with virus production in mammalian cells. It is a complex process consisting of several difficult production steps. The focus of the PSE group’s research is on the stochastic simulation of cellular infection dynamics, the population balance modeling of cellular aggregation processes and the modeling of the downstream virus separation via membrane affinity adsorption. Our long-term goal is to create a scientific basis for the rational design of up- and downstream units in such biotechnological processes.

Tab. 2: Survey of research projects of the PSE group (* Members of the OvGU group)

Research Area: Chemical Production Systems

Project: **Catalytic Reactors for Gas Phase Syntheses** **Coordinator:** Dr. Freund	**Abstract:** The novel reactor design methodology developed in this project aims at the identification and technical realization of optimal reaction routes. A fluid element is tracked over the reaction time on an abstract level and its state is optimally adjusted at any time. Thereby, at the early design stage no constraints owing to predefined apparatus specific limitations are narrowing the solution space. **Publications:** [1], [2], [33], [63], [82], [84-87]			
Subprojects	**Researchers**	**Funding**	**Period**	**Partners**
Design of chemical reactors by dynamic optimization	Peschel	IMPRS, MPI	since 11/2007	Companies BASF, Evonik
Methodology for combined catalyst and reactor design	Karst, El-Sibai*	IMPRS, DFG	since 09/2009	Prof. Maestri (Politechnico Milano)
Analysis of reaction and transport processes in catalytic foams	Heidig*, Bianchi	OvGU, MPI	since 05/2011	Prof. Tronconi (Politechnico Milano)

Project: **Integrated Chemical Processes for Liquid Multiphase Systems** **Coordinator:** Dr. Freund	**Abstract:** This project focuses on the systematic analysis of process intensification options on all levels of the process hierarchy (molecules, phases, process units, plant). In particular, innovative solvent systems for industrially relevant liquid multiphase processes are investigated (ionic liquids, multicomponent solvent mixtures, gas-expanded liquids). **Publications:** [8], [18], [19], [25], [41], [44], [51], [52], [69], [79], [80], [91], [93]			
Subprojects	**Researchers**	**Funding**	**Period**	**Partners**
Molecular design of solvents	McBride	MPI	since 09/2011	MPI Partner Group: Prof. Qi (ECUST, Shanghai)
Modeling of gas-expanded liquids for conceptual process design	Ye	IMPRS	since 09/2008	Prof. Subramaniam (Kansas University)
Optimal reactor design for liquid multiphase systems	Hentschel*, Peschel	DFG, IMPRS, MPI	since 01/2010	SFB Transregio 63 (TU Berlin, TU Dortmund, OvGU), Prof. Nigam (IIT Delhi)
Reactor-separator networks	Ahamed, Katariya, Kumar, Thotla	Industry, MPI	since 10/2006	Prof. Mahajani (IIT Bombay), Company DSM

Project: **Multidimensional Crystallization Processes** **Coordinator:** Dr. Voigt*	**Abstract:** The dynamic behavior of reactive and non-reactive crystallization processes is investigated by means of population balance equations with focus on multidimensional particle distributions in terms of internal as well as external coordinates. In particular, the control of crystal shape evolution is an important goal. **Publications:** [4-6], [9], [13], [21], [24], [32], [39], [43], [46], [59], [60], [72], [74], [76-78], [81], [90]			
Subprojects	**Researchers**	**Funding**	**Period**	**Partners**
Crystal shape evolution by population balance modeling	Borchert	MPI	since 07/2007	Prof. Ramkrishna (Purdue University)
Shape control of crystals by growth-dissolution cycles	Eisenschmidt	MPI, OvGU	since 04/2011	Dr. Bajcinca (SCT)
Size control of crystals via emulsion-assisted precipitation	Fricke*	MPI, OvGU, Industry	since 09/2006	Companies BASF, Klüber Lubrication
Numerical simulation of multidimensional population balance systems	Borchert	BMBF, MPI	since 04/2006	Prof. John (U Saarland), Prof. Hackbusch (MPI Math. Sciences) Prof. Tobiska (OvGU), Prof. Flockerzi (SCT)

Research Area: Energy Conversion Systems

Project: **PROBIO – Conversion of Biomass into Electrical Energy** **Coordinators:** Dr. Heidebrecht, Dr. Rihko-Struckmann	**Abstract:** In this project, integrated processes for the production of electrical energy from solid biomass using fuel cells are developed. Research activities include the model-based conceptual design of the whole energy conversion chain and the investigation of novel reactor concepts for hydrogen purification (CWGSR, EWGSR, ECPrOx). **Publications:** [3], [14], [16], [17], [20], [31], [34], [36], [38], [45], [50], [53], [64], [67], [68], [70], [73], [75]			
Subprojects	**Researchers**	**Funding**	**Period**	**Partners**
Conceptual design of biomass-fed energy systems	Hartono, Hertel	MPG/FhG	since 04/2007	Fraunhofer Institutes (IFF/Magdeburg, IKTS/Dresden)
CWGSR: Cyclic water gas shift reactor for H_2 purification	Hertel, Datta	MPG/FhG, MPI	since 11/2003	Physics Department of OvGU
Determination of gas-solid reaction kinetics via nonlinear TPR experiments	Heidebrecht	DAAD, MPI	since 02/2008	Prof. Biegler (Carnegie Mellon Uni.)
EWGSR: Electrochemical reactor for water gas shift reaction	Oettel*	MPG/FhG, MPI, OvGU	since 07/2007	Company Fumatech
ECPrOx: Electrochemical reactor for preferential oxidation of CO	Kirsch	IMPRS, MPG/FhG, MPI	since 09/2006	Prof. Krischer (TU München), Prof. Flockerzi (SCT)

Project: **NEEDS – Conversion of Biogas into Electrical Energy** **Coordinators:** Dr. Hanke-Rauschenbach, Dr. Heidebrecht	**Abstract:** This project deals with process systems for the production of biogas followed by its energetic conversion in high- or low-temperature fuel cells. Research activities include the model-based system design, the optimization of the steady-state behavior and the investigation of the nonlinear dynamics of individual process units. **Publications:** [10], [12], [22], [30], [37], [40], [47], [48], [54], [58], [61], [71], [83], [88], [89], [94]			
Subprojects	**Researchers**	**Funding**	**Period**	**Partners**
Design of fuel cell power systems by nonlinear programming	Sommer	NIP	since 12/2008	Company Dalkia Energy Systems
Dynamics, analysis and control of anaerobic digestion processes for biogas production	Bornhöft*	LSA, OvGU	since 09/2009	Prof. Reichl (BPE), Prof. Benner (CSC)
Hierarchical modeling of Molten Carbonate Fuel Cells (MCFC)	Piewek, Pfafferodt*	DFG, MTU, MPI, OvGU	since 08/2008	Company MTU Onsite Energy
Dynamics, analysis and control of PEM Fuel Cells (PEMFC)	Ji, Kadyk*, Lemoine*	MPI, LSA	since 03/2006	Prof. Zhou (U Tongji), Prof. Mangold (PSD)

Project: **CO2RRECT – Chemical Storage of Renewable Energies** **Coordinator:** Dr. Rihko-Struckmann	**Abstract:** In this new project, different options for the chemical storage of renewable energies are analyzed theoretically. Thereby, the feasibility to use captured CO_2 as a C-source is explored. Because of the fluctuating character of renewable energies, the dynamic behavior of water electrolysis for hydrogen production is investigated in detail. **Publication:** [35]			
Subprojects	**Researchers**	**Funding**	**Period**	**Partners**
Energy systems analysis	Zinser	BMBF	since 10/2010	BTS, Bayer Mat., RWE Siemens, Leibniz Inst. Rostock, Fritz Haber Inst., KIT, U Bochum, RWTH Aachen, TU Dortmund, TU Dresden, U Stuttgart, TH Darmstadt
High-pressure water electrolysis: Experiments and modeling	Bensmann*	OvGU	since 07/2010	Prof. Bouzek (ICT Prague)

Research Area: Biological Production and Conversion Systems

Project: **Biofuel Production with Photosynthetic Organisms** **Coordinator:** Dr. Rihko-Struckmann	**Abstract:** Green microalgae are very interesting photosynthetic unicellular organisms able to convert solar energy into lipids and other valuable compounds. The goal of this project is to analyze and control the steady state and dynamic behavior of the underlying biochemical networks. Experimental investigations are closely combined with intra- and inter-cellular modeling, population balance modeling, model discrimination and parameter identification. **Publications:** [11], [23], [27], [29], [65], [66], [92]			
Subprojects	**Researchers**	**Funding**	**Period**	**Partners**
Experimental analysis of metabolic networks in microalgae	Fachet, Gautam, Sharma	MPI	since 01/2011	Dr. Grammel (ESB), Dr. Giavalisco (MPI Molecular Plant Physiology, Golm)
Experimental analysis of photo-synthetic energy conversion	van der Zalm*	BMBF	Since 02/2011	Dr. Schüttler (MPI Molecular Plant Physiology, Golm)
Dynamic-kinetic modeling and optimal design of experiments for analysis of biological networks	Flassig*	BMBF	since 09/2009	Dr. Klamt (ARB), Prof. Mangold (PSD), Company CiT
Flow cytometry analysis and population balance modeling of particle / cell populations	Rollié	MPI, CDS	since 09/2006	Prof. Naumann (OvGU) Prof. Reichl (BPE), Prof. Briesen (TUM)
Analysis and design of microbial communities for biofuel production	Pirwitz	MPI	since 10/2011	Dr. Grammel (ESB)

Project: **Bioelectrochemical Energy Conversion with Enzymatic Systems** **Coordinator:** Dr. Vidaković-Koch	**Abstract:** Enzymatic fuel cells are biomimetic devices able to convert chemicals directly into electrical energy. Enzymes are employed as catalysts. In this project we are aiming at the development, experimental characterization and model-based analysis of enzymatic fuel cells. Frequency response analysis techniques are used to understand the underlying reaction and transport processes. **Publications:** [7], [15], [26], [28], [42], [55-57], [62]			
Subprojects	**Researchers**	**Funding**	**Period**	**Partners**
Development & characterization of a glucose enzymatic fuel cell	Ivanov, Varnicić	MPI	since 01/2007	Prof. Shleev (U Malmö), Dr. Grammel (ESB)
Dynamic analysis of bioelectrochemical systems	Do Thi, Panić	IMPRS, MPI	since 09/2009	Prof. Petkovska (U Belgrade)

Project: **Vaccine Production with Mammalian Cell Cultures** **Coordinator:** Dr. Voigt*	**Abstract:** Virus production with mammalian cells is a complex process consisting of many production steps. In this project we are aiming at the quantitative description of the cellular infection dynamics and of the downstream virus separation via membrane affinity adsorption. For this purpose, multidimensional population balance models are developed and validated with experimental data. **Publication:** [49]			
Subprojects	**Researchers**	**Funding**	**Period**	**Partners**
Dynamics of virus replication by Monte Carlo simulation	Diaz*	CDS, OvGU, MPI	since 09/2006	Prof. Reichl (BPE), Prof. Kienle (PSD), Prof. Briesen (TUM)
Modeling of membrane affinity adsorption for virus separation	Malladi, Wang	MPI, IMPRS	since 09/2008	Prof. Reichl, Dr. Wolff, (BPE), Prof. Seidel-Morgenstern (PCF)

4 Research Highlights

4.1 Chemical Production Systems

4.1.1 Elementary Process Functions: Design Methodology for Integrated Chemical Processes

As a long-term goal, the PSE group works on the development of a rigorous, model-based methodology for the design of efficient chemical processes that exploit the full potential of innovative process intensification options. In the chemical and process engineering community, process intensification is currently considered as an example-driven approach where in many cases the measures to perform the process improvements have been found incidentally or as an empirical result of a series of experimental studies. Despite recent efforts to classify process intensification into systematic categories (e.g. [R1-R3]), it can be concluded that there is currently neither a theoretical basis nor are there scientific guidelines for process intensification available that can be generalized and thus help to identify process intensification options when analyzing a chemical process as to its efficiency.

These shortcomings were the motivation for the PSE group to develop a novel flux-oriented approach which decomposes a chemical production system into elementary process functions [1]. Instead of choosing the apparatus a priori and optimizing the free parameters of the chosen setup, the apparatus design is the final result that is derived from the optimal flux profiles as to approximate the same. This allows for an extended and more fundamental perspective on the process and its intensification options. Following this new concept, a chemical process can be decomposed into a multi-scale structure of four hierarchical levels, ranging from the molecular level up to the plant level (see Figure 1). At each of these process levels, process intensification options can be analyzed and evaluated [84-87]. As examples, single phase systems as well as multiphase systems were investigated.

In the time period covered by this report, the main focus of the aforementioned concept of elementary process functions was on the development of a design methodology for innovative multifunctional reactor concepts [33], [63], [69], [79]. The key idea of this novel approach is to track a fluid element on an abstract level on its way through the – not yet specified – reactor and to optimize the fluxes along its way. The outer fluxes are adjusted, and the reaction fluxes are scaled to meet the optimal reaction conditions at every point along the reaction coordinate, which we define as the optimal route in the thermodynamic state space. To design a technical reactor based on this idea, a three-step approach is developed leading to a technical approximation of the optimal route by an appropriate reactor design. The methodological approach is illustrated in Figure 2.

On the first design level, the optimal route in state space is calculated by solving a dynamic optimization problem with unlimited outer fluxes and – as far as meaningful – scaled reaction fluxes as optimization variables. The reaction kinetics are given by the chosen catalyst, but the reaction fluxes can be optimized in a certain range by scaling the catalyst densities along the reaction coordinate. Only system inherent limitations such as a maximum catalyst temperature and thermodynamic relations are taken into account, but no limitations arising from choosing a predefined apparatus are considered. That way, the solution space can be very efficiently screened to investigate the best reaction route in state space. The solution of this optimal control problem corresponds to the maximum possible performance of the reaction system. As a benchmark, technical reference reactors are optimized with regard

to the free design parameters to quantify the potential of intensified cases. It is important to evaluate the potential of the different concepts to decide how to guide ongoing engineering work already at the early design stage. The results of the first optimization level determine whether it is worthwhile to develop a new type of reactor or whether the parameter optimization of standard reactors is already close to the optimum of the reaction system.

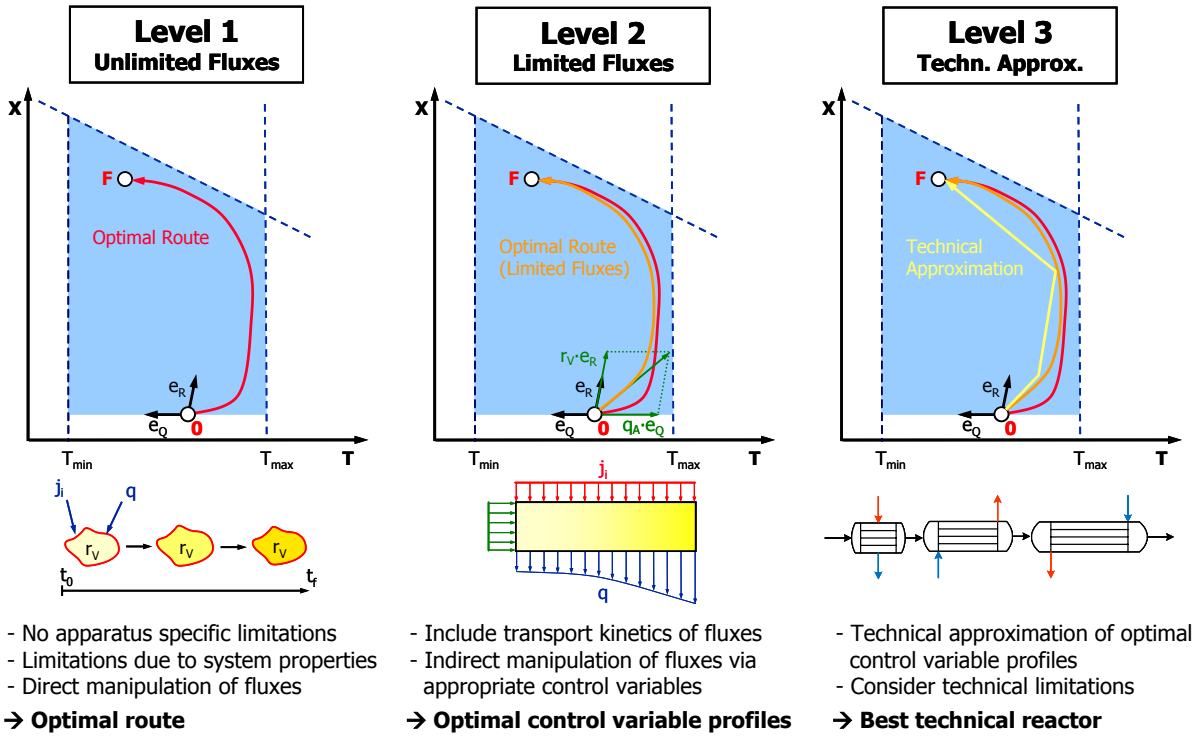

Fig. 2: Illustration of the methodological approach: From the optimal trajectory to the technical reactor.

In contrast to the first design level where the fluxes are directly optimized, on the second design level flux limitations are considered by including the transport kinetics of each flux. For this purpose, specific terms of the transport kinetics are optimized in order to identify the best suited control variables to achieve the desired fluxes. The optimal profiles of certain variables of the transport kinetics, which can be controlled by the reactor design (e.g. specific surfaces), are calculated. Owing to the limitation of the fluxes, the optimal route can in general not be realized anymore and hence the state space trajectory of level 2 differs from the optimal trajectory of level 1. The losses due to limited mass and energy transport can be quantified by comparing the difference in the objective between the first and the second level. As a result of level 2, a detailed catalog of requirements for the optimal technical reactor can be derived. Different control variables, transport mechanisms, options to provide the catalyst, and channel geometries giving rise to specific exchange areas for heat and mass are compared, and the best combination is determined.

On the basis of the profiles of the best suited control variables, an optimal technical reactor is derived on the third design level. Several possible technical approximations of the control variable profiles may exist since the transformation from control variable profiles to the reactor design is not unique. In case the number of possible technical approximations is large, the comparison of the different technical approximations can preferably be performed in two steps in order to reduce the computational effort significantly. In a first step, all technical approximations are calculated using simple models. The difference in the objective func-

tion value between the technical approximation and the ideal control profiles of level 2 quantifies the losses due to non-idealities in the technical realization of the control variable profiles. In a second step, the most promising reactor concept is further investigated using more detailed reactor models, e.g., a two-dimensional reactor model. This allows for the quantification of the losses arising from the non-ideal flow field, radial gradients, and dispersion effects.

To sum up, the advantage of this approach is that, at the early design stage, no constraints owing to predefined apparatus specific limitations are narrowing the solution space. That way it is possible to quantify the maximum potential of the reaction system and to finally derive an innovative reactor design based on the optimal flux profiles.

The novel concept has been successfully applied to heterogeneously catalyzed gas phase reaction systems, e.g., SO_2 oxidation [33] and ethylene oxide production [63]. The latter process was investigated within a bilateral research project together with the company BASF. Here, the task was to design an optimal reactor under consideration of the recycle streams within the overall process, i.e. an optimal reactor from a process point of view. For this, it is essential to consider the interaction of the reactor and the downstream processing since the recycle streams will affect the optimal reactor design and operating conditions. With our developed methodology, the optimization of “stand-alone” reactors as well as reactors with consideration of recycles taking the overall downstream process into account (i.e. the entire flowsheet model) is possible. Figure 3 shows the flowsheet of the considered oxygen based ethylene oxide production process. To quantitatively compare all possibilities regarding the integration of different fluxes for obtaining the desired flux profiles on level 1, a systematic decision structure is applied. The impact of different integration concepts on the operating costs is illustrated in Figure 4, where a significant cost reduction potential has been identified.

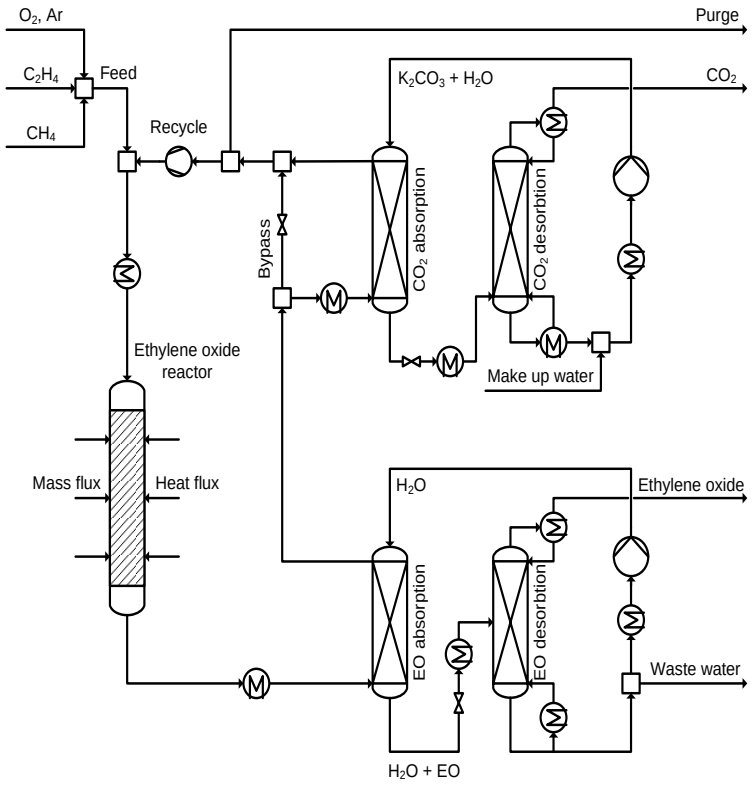

Fig. 3: Ethylene oxide production: Process flowsheet.

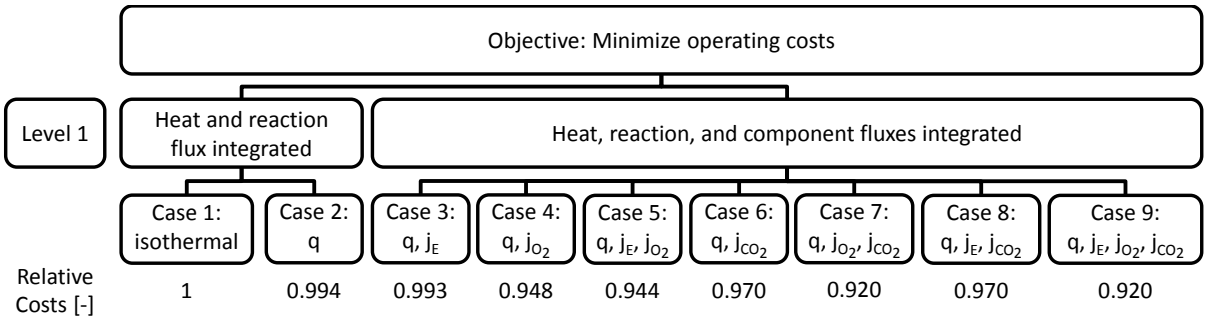

Fig. 4: Ethylene oxide production: screening of intensification concepts and impact on running expenses.

The examples discussed so far deal with single phase systems, which were the starting point in the development of our methodology. However, we have recently extended our approach such that also multiphase systems can be accounted for. This involves higher complexity in the model with regard to the appropriate description of the thermodynamic phase behavior as well as transport processes between the phases. In our optimization approach, we focus on the reactive phase and consider the remaining phases as “service phases” that provide optimal fluxes, e.g., supply the reactive phase with reactants or extract products.

As one example for a complex catalytic multiphase reaction system, the hydroformylation of long chain alkenes in innovative solvent systems is currently investigated within the DFG funded collaborative research center SFB/TR 63 in close collaboration with partners from TU Berlin and TU Dortmund. Using the methodology described before, a novel reactor setup was derived ([69], [79]) for a given reaction system from literature [R4]. Here, a selectivity increase of 11.7% was obtained by simultaneous optimization of the heat flux profile and the dosing profiles of 1-octene, hydrogen, carbon monoxide. The results of the dynamic optimization reveal that both the space time yield and the selectivity of the hydroformylation process depend strongly on the intensity of gas-liquid mass transfer. The optimal design variable profiles and (k_La)-value can be approximated by a reactor set-up with static mixers, advanced cooling, and discrete 1-octene dosing (see Figure 5).

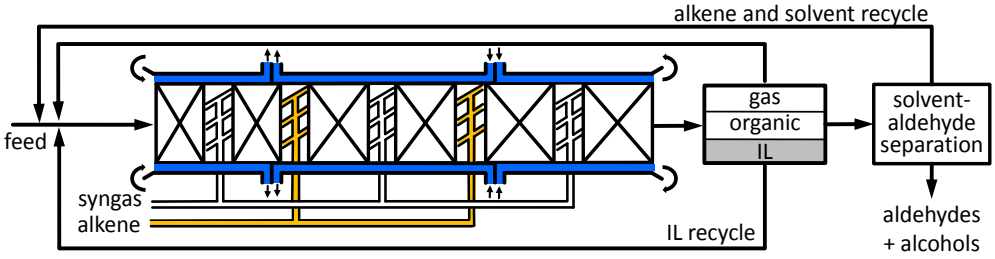

Fig. 5: Optimized reactor set-up for the hydroformylation of long chain alkenes.

4.1.2 Modeling and Observation of Crystal Shape Evolution

The availability of the adequate crystal shape is of importance where ever crystals are used, for example in catalysis, photocatalysis, solar cells, optical applications, pharmaceuticals or biomedical systems. Therefore, the focus of research for large-scale crystal production aims ever more at controlling not only the crystal size but also the shape [R5]. Crystal shape is the result of the kinetic processes of growth and/or dissolution. That is, the harvesting of crystals from crystallizers yields kinetically rather than thermodynamically controlled shapes. Hence,

the command over the growth mechanism is the key to shape control. This is customarily achieved by chemical means, i.e. by the usage of additives or by changing the solvent. In the same manner impurities can inadvertently shift the shape in an undesired way. Recent developed concepts to combine cycles of growth and dissolution aim at expanding the attainable region of crystal morphologies which avoids the application of additives or different solvents [R6]. Supersaturation control is yet another method for systems which exhibit a clear dependency of the relative growth rate between different facets on the level of supersaturation [R7, R8].

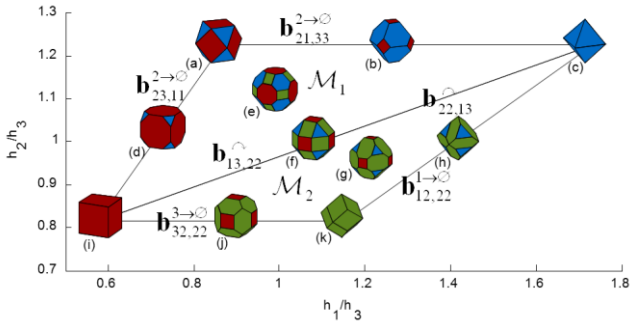

Fig. 6: State space partitioning of a cubic crystal.

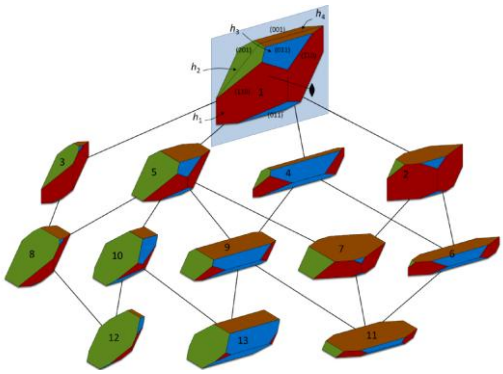

Fig. 7: Qualitatively different morphologies of paracetamol with four faces.

Since in mass crystallizers not only a single crystal is grown but a whole crystal population whose individuals vary in size and shape, it is necessary to reflect this property distribution and its dynamics in a model. Population balances are an adequate basis to incorporate detailed models for phenomena influencing a property distribution. These mechanisms are generally nucleation, growth, aggregation and breakage. As for instance Doherty and coworkers pointed out, crystallographic faces can appear and disappear during the growth evolution of a crystal shape [R9]. From a system-theoretical point of view this qualitative change can be interpreted as a switch in dynamical dimensions because a face not present on the crystal surface must not any longer be tracked by a dynamical coordinate. Hence, in the fully dimensional state space, manifolds exist on which less complex shapes – i.e., shapes with fewer faces – exist. An example is shown in Figure 6 for the case of a cubic crystal with the crystallographic forms {001}, {011} and {111} [72]. It can be seen that the shapes resulting from state vectors $\mathbf{h}^T = (h_1, h_2, h_3)$ in different domains look qualitatively different. Shapes which lack certain crystallographic forms exist on lower-dimensional linear manifolds in the state space. This state space structure can be unfolded for arbitrarily complex convex 3D polyhedra with an automated analysis algorithm [72]. A slightly more complex case is depicted in Figure 7 for the pharmaceutical substance paracetamol. Shown are the thirteen qualitatively different shapes which can be formed from the included four different crystallographic forms [72].

For the formulation of a population balance model, the specially structured state space requires the evaluation of the fluxes between different morphological dimensions of possibly different dimensionality [76]. For a continuous crystallizer operated in steady state mode, subject to nucleation and growth only, all crystals follow the same trajectory through the multidimensional state space if all nuclei have the same shape and growth rate dispersion can be neglected. In this case, the multivariate population balance model can be reduced to a 1D population balance with crystal age as the property coordinate and a dynamical single crystal model in terms of the residence time [4]. Assumptions about the symmetry are an

essential supposition to confine the geometrical state space to a manageable number of dimensions. If, however, symmetry cannot be assumed, the shapes deviating from ideal symmetry are assigned to lower symmetry classes while keeping the dimensionality of dynamical variables constant [32]. With respect to optimal control, the multivariate character of the shape distribution evolution equations poses challenging problems which have been addressed with regard to unconventional process control through cycles of growth and dissolution [77-78], [81] as for instance discussed by Doherty and coworkers [R9].

The measurement of shape distributions is – compared to size distribution quantification – far less developed since true 3D sensors capable of resolving spatial structures involving tomography and laser scanning microscopy require an expensive sample preparation. Current research activities aim at imaging the crystal suspension with flow-through microscopes [R10]. The so acquired images can be analyzed with regard to classical shape descriptors of the projected crystals from which multivariate feature distributions can be estimated [43]. On the other hand the contours of the projection can be employed to estimate the state of the 3D object, i.e., the crystal shape [59]. With the help of this single particle technique the geometrical state distribution can be measured for a whole population (see Figure 8) over time and kinetic parameters for the growth process can be estimated [59].

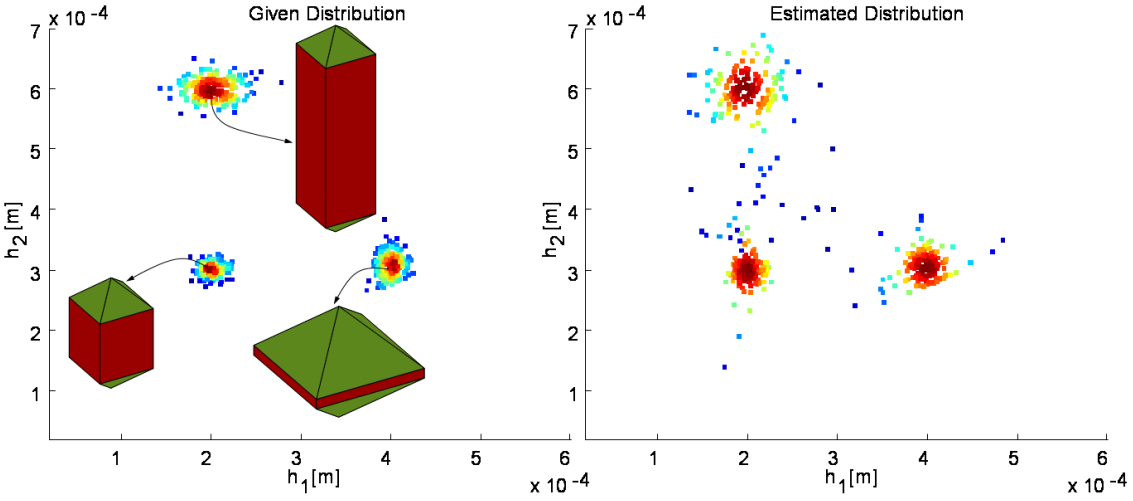

Fig. 8: Crystal population photographed from random perspectives: in-silico (left), re-estimated (right).

From the preceding explanations it can be concluded that the work of the PSE group in the area of crystallization is mainly concerned with the formulation, analysis and identification of process-level modeling tools which allow the incorporation of shape information. In the three different focus areas we underpin our activities through joint projects with colleagues having a special expertise. For model formulation, a long-term partnership with Prof. Ramkrishna's group at Purdue University has been established. Analysis and numerical techniques were worked out from a control-theoretical point of view with the SCT group ([39], [46, [77-78], [81]), and from a mathematical perspective with the groups of Prof. John (Weierstrass Institute Berlin), Prof. Tobiska (OvGU) and Prof. Hackbusch (MPI for Mathematics in the Sciences, Leipzig) within the BMBF funded joint research project "SimPaTurS" [5]. For the experimental identification of the crystal shape dynamics, we have recently started a collaboration with the PCF group.

4.2 Energy Conversion Systems

4.2.1 Model-based Process Design for Conversion of Biomass into Electricity

If produced sustainably, biomass is a CO_2-neutral energy carrier. A technically feasible and efficient process option for the conversion of biomass into electrical energy is the thermo-chemical gasification and the subsequent electrochemical oxidation of the product gas in fuel cells. With regard to the design of stationary fuel cell power plants based on biomass, only a few studies exist which focus on specific designs (e.g. [R11-R12]). To the best of our knowledge, no systematic investigation of optimal process design has been carried out so far. Thus, the computer aided design of such plants was the focus of the PSE group in the framework of PROBIO, a joint research project performed with partners from the Fraunhofer Institutes IFF in Magdeburg (Prof. Schenk) and IKTS in Dresden (Prof. Michaelis).

A fuel cell power plant fed with biomass comprises several stages, including the fuel conversion into a gas mixture, primary gas cleaning (removal of tar, dust, and sulfur), secondary gas cleaning (reduction of CO content), electrochemical conversion in fuel cells, and final combustion of the spent fuel gas. Each of these steps can be realized in different process units. This leads to a multitude of possible plant designs which can only be explored systematically by a computer aided approach. For this purpose, a library of unit models has been developed in close collaboration with our project partners. Then, this library was used to implement a Mixed Integer Nonlinear Program (MINLP) based on a superstructure describing the process design problem. This MINLP problem was first solved by systematic optimization of all (more than 3000) system variants [34].

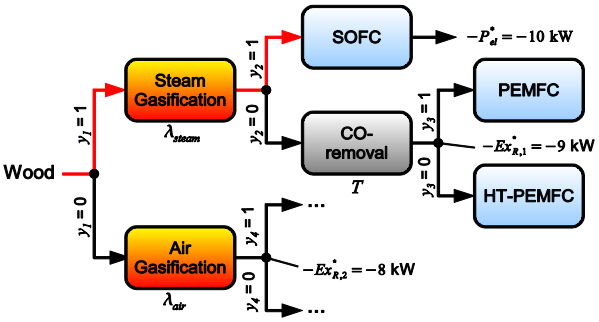

Fig. 9: Binary superstructure representing the MINLP. Exergy analyses are performed at each node and used to dismiss inefficient branches.

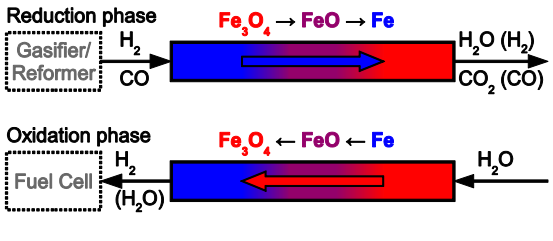

Fig. 10: Principle of the Cyclic Water Gas Shift Reactor (CWGSR), one of the reactor concepts investigated in detail in the research project PROBIO.

In order to reduce the high computational effort, the PSE group has very recently developed a new algorithm especially tailored for the solution of MINLP problems for energy systems design [75]. Based on the classical methodology of Branch & Bound algorithms [R13], an exergy analysis has been performed at every node of a discrete decision tree, as illustrated in Figure 9. This analysis delivers an upper bound for the objective function value of the respective branch of the tree and thus replaces the conventional relaxed NLP problem, which otherwise needs to be solved at every node at a significantly higher computational expense. This upper bound allows dismissing whole branches of suboptimal solutions, thus reducing the computational time needed to solve the design problem by about two thirds. Moreover, the reduction of the subproblems' dimensions helps to avoid multiple optima, leading to more reliable convergence of the method.

For the energetic utilization of biomass, the purification of the gas is the most critical part of the whole system. In addition to well established units such as shift reactors or pressure swing adsorption steps, we have investigated novel integrated reaction-separation processes which have the potential to significantly increase the overall efficiency, as already demonstrated in the PROBIO project. One of the new process units that are being developed by the PSE group is the Cyclic Water Gas Shift Reactor (CWGSR). It is a tubular reactor filled with a fixed bed of iron oxide particles operated at 600 to 800°C, which are periodically reduced by the effluent purified stream of the gasification reactor, and thereafter are oxidized by steam (see Figure 10). The hydrogen gas produced during the oxidation phase is free of carbon monoxide and can thus be used to feed low temperature PEM fuel cells. The CWGSR has been described earlier as “steam iron process” in the literature (e.g. [R14]) or as a chemical looping system (e.g. [R15]). But a detailed model-based analysis and design of this periodically operated reactor has never been carried out.

Based on conceptual studies of the dynamic reactor behavior ([17], [R16]), a detailed process design study is currently being conducted. As suitable fixed bed material, the PSE group has synthesized a new oxide mixture consisting of iron oxide mixed with $CeZrO_2$. The latter component increases the material’s long-term stability, oxygen capacity and catalytic activity. In addition, we have shown that the addition of molybdenum leads to a significant improvement of the mixed oxide material properties [50].

For the purpose of model-based process design, the gas-solid reaction kinetics have been investigated by means of thermogravimetric analysis (TGA) and temperature programmed reduction (TPR) experiments, and suitable rate expressions have been identified. As part of these kinetic studies, the optimal design of nonlinear TPR experiments has been elaborated in collaboration with Prof. Biegler (CMU, Pittsburgh). In particular, it was shown that TPR experiments with non-constant temperature gradients can lead to a significantly improved accuracy of the estimated parameters. Moreover, by application of nonlinear TPR one can better discriminate competing kinetic models [53].

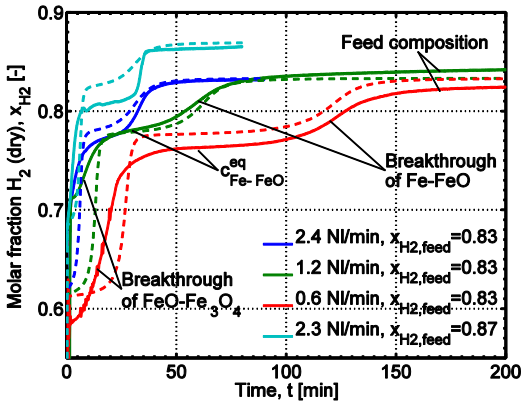

Fig. 11: CWGSR breakthrough behavior during fixed bed reduction with pure hydrogen. Solid lines: experimental response, dashed lines: simulated response.

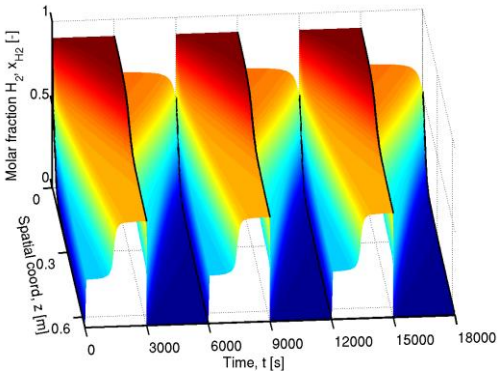

Fig. 12: Simulated CWGSR behavior: hydrogen concentration during three repeated reduction/oxidation cycles, illustrating the moving reaction zones.

Based on the identified reaction kinetics, a dynamic CWGSR model has been developed which was subsequently validated by miniplant experiments in the institute’s pilot plant hall (Figure 11, [68]). These experiments have confirmed that the reactor behavior is dominated by the movement and breakthrough of reaction zones. The process model is capable of simulating transient profiles of gas composition, gas velocities and temperatures

in the CWGSR under cyclic operating conditions. As an example, Figure 12 shows the simulated mole fraction of hydrogen over three repeated cycles [89].

Besides the CWGSR, two novel membrane reactor concepts have been investigated. The first reactor is capable of efficiently performing the electrochemical preferential oxidation of carbon monoxide (ECPrOx: described in detail in section 4.2.2 of this group report), while the second allows the production and purification of hydrogen by the electrochemical water gas-shift reaction (EWGSR, [70]). Current research activities include the proof of concept, the identification of essential operating and design parameters, as well as the quantitative analysis of the steady state and dynamic operating behavior of the two membrane reactors.

In the aforementioned system design problem, short-cut models of the just mentioned novel process units (CWGSR, ECPrOx, EWGSR) have been included. The solution of the corresponding MINLP problem is a power plant combining a high-temperature and a low-temperature fuel cell, arranged in parallel configuration. The CWGSR acts as gas separator providing a stream of pure hydrogen feed for a PEMFC (Polymer Electrolyte Membrane Fuel Cell) and a second stream of carbon monoxide / hydrogen gas for an SOFC (Solid Oxide Fuel Cell). This power plant is able to yield electrical energy at a high electrical efficiency of about 46%. Alternatively, it can provide a wide spectrum of possible products such as electrical base and peak power, high and low graded heat and high-purity hydrogen [34].

4.2.2 Nonlinear Dynamics of PEM Fuel Cells

Polymer Electrolyte Membrane Fuel Cells (PEMFC) allow the direct conversion of hydrogen or other fuels into electricity at high efficiency. Challenges and directions for future research on PEM fuel cells are described in our recent review article [36]. Thus, PEMFC have been a focus of research activities within our project area “Energy Conversion Systems”.

First, within the Project “Conversion of Biomass into Electrical Energy” (see section 4.2.1), the PEMFC is utilized as an apparatus for deep CO removal from reformate gas via electrochemical preferential oxidation (ECPrOx reactor). This system shows strongly nonlinear operating behavior, such as autonomous potential oscillations and intriguing spatiotemporal patterns. The oscillatory behavior facilitates the selective oxidation of CO. Here, the activities of the PSE group aim at the fundamental understanding of the reactor’s nonlinear behavior and its possible technical exploitation.

Second, within the Project “Conversion of Biogas into Electrical Energy”, PEMFCs are considered as the terminal process unit for the conversion of hydrogen rich gases into electrical energy. The meaningful design and the efficient operation of such systems require a comprehensive understanding of their steady-state and transient behavior. Special attention needs to be paid when nonlinear operating behavior occurs. The fuel cell literature of the last decade contains various relevant experimental reports and theoretical predictions. Among them are several observations of bistabilities, e.g. [R17, R18], and oscillations, e.g. [R20]. So far, these studies are isolated and have not been put into an overall context. Thus, the efforts of the PSE group aim at the development of a unifying prototype model which allows the understanding, classification and prediction of nonlinear phenomena in fuel cells.

Nonlinear operating behavior of PEM fuel cells: A prototype model

Within the period covered by this report, the relevant studies on nonlinear phenomena observed in fuel cells were carefully reviewed by our group [54] and set in context with the concept of negative differential resistance, originally proposed for the classification of nonlineari-

ties occurring during electrochemical reactions at single electrodes [R22]. According to this concept, nonlinear operating behavior, such as bistability or oscillations, can be traced back to a branch of the system's current-voltage-curve, exhibiting a Negative Differential Resistance (NDR). Two different types of such an NDR-branch can be distinguished: an N-type and an S-type, both with different technical properties (see Figure 13).

With the help of a prototype model [54], based on the NDR concept and developed together with the PSD group (Prof. Mangold), qualitative explanations for the majority of nonlinear effects in fuel cells can now be given. Furthermore, the prototype model allows for the identification of three main classes of system properties leading to an NDR-branch [54]. The first class of phenomena originates from the ion transport through the electrolyte material. In order to create a negative differential resistance, a state-dependent electrolyte resistance is required. Clear examples for such a behavior can be found in PEM fuel cells operated under reduced feed stream humidification at constant flow rate (e.g. [R17], [R29]), as well as in high-temperature fuel cells (e.g. [R19]). Bistable current-voltage-curves of the S-type have been observed or predicted under such conditions.

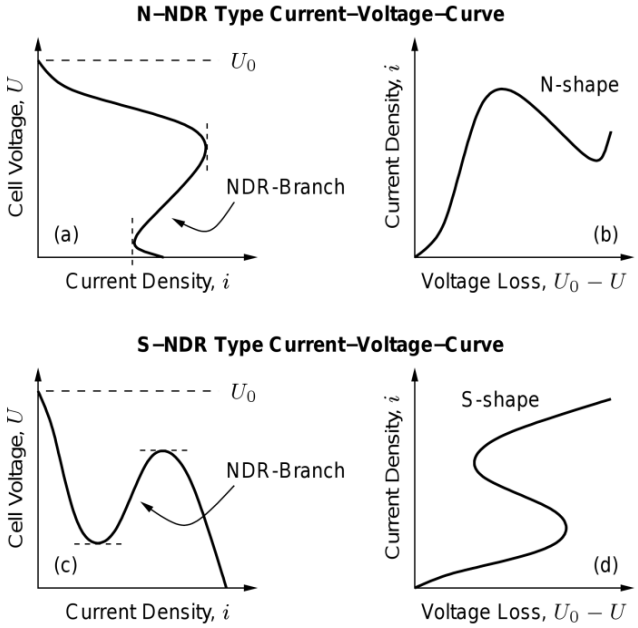

Fig. 13: Qualitative sketch of (a) N-NDR and (c) S-NDR type current-voltage-curves (NDR = Negative Differential Resistance). The representations given in (b) and (d) plot the current density as function of the voltage loss, U_0−U, which is the driving force to be "invested" to draw the corresponding current. An N-type NDR-branch ends in two vertical tangents in the current-voltage phase plane. Systems possessing such an NDR-branch can exhibit bistability under galvanostatic control, but not under potentiostatic control. An S-type NDR-branch ends in two horizontal tangents in the current-voltage-phase-plane. Such systems can exhibit bistability under potentiostatic control, but not under galvanostatic conditions.

The second class of phenomena originates from nonlinear electrochemical surface kinetics at one of the electrodes of the fuel cell. In order to create a negative differential resistance, a potential-dependent transport step is required. PEM fuel cells exposed to H_2/CO-mixtures give a clear example for this class (e.g. [R20]). Here, the surface coverage of hydrogen, which is the reactant of the main Faradaic reaction at the anode, is influenced at elevated electrode potentials by the dissociation of water towards the catalyst surface. As a consequence an N-type NDR-branch is formed, which is hidden under steady-state conditions by the electro-oxidation of CO. Due to an interaction of the fast N-NDR system with the slower dynamics of the CO, oscillations occur under galvanostatic control.

A third class of phenomena was identified, which originates from nonlinearities other than ion transport in the membrane or electrochemical surface kinetics. So far, one example for this last class exists in the relevant literature. The self-inhibition of the transport of product water within the porous structures of a PEM fuel cell was found to lead to bistability [R29], [40]. As the oxygen transport towards the cathode catalyst layer gets affected by the presence of the product water, this non-electrochemical nonlinearity projects an N-type NDR-branch into the current-voltage curve of the cell.

As a further outcome of the analysis of our prototype model, we are able to formulate new hypotheses to explain some of the experimental findings published by other groups. An interesting example are studies published by Vayenas and his co-workers on a bistability observed in PEM fuel cells operated at low H_2 partial pressure (e.g. [R18]). The experimental proof of the antithesis, already being formulated, is subject of our ongoing research work.

Oscillations and spatiotemporal pattern formation in PEMFC fuel cells during electrochemical preferential oxidation (ECPrOx) of CO from H_2/CO-mixtures

In 2002, Zhang and Datta [R20] reported a systematic investigation of potential oscillations in a PEM fuel cell fed with H_2/CO mixtures. The reason for the oscillatory behavior is a cyclic interplay of a mass storage, represented by the CO surface coverage, θ_{CO}, and a charge storage, represented by the anode overpotential, η_a [16]. In a couple of subsequent articles this initial finding was discussed by several authors in two different application directions (see [64] for a brief recent survey): First, as a strategy to increase the CO tolerance of PEM fuel cells as an alternative to other techniques, such as air bleed (e.g. [R23]), current pulsing (e.g. [R24]) or advanced anode electrocatalysts (e.g. [R25]), and second, as a concept for deep CO removal from reformate gas (so-called ECPrOx = Electrochemical Preferential Oxidation) as an alternative to the conventional preferential oxidation (PrOx).

Recent work of the PSE group was dedicated to the second application direction. The main advantage of ECPrOx, in comparison to PrOx, is the fact that non-selectively oxidized hydrogen is converted into electrical energy instead of being burned. The design of an ECPrOx reactor is identical to a PEM fuel cell, but it is equipped with a PtRu anode. The difference between the two units is the desired operation mode. While in the fuel cell a high conversion of the whole H_2/CO mixture is desired, the goal in an ECPrOx reactor is the full conversion of CO without oxidizing hydrogen. In an early paper, Datta and co-workers [R26] gave a proof of principle of the ECPrOx concept. A bundle of our own studies was dedicated to the analysis and the design of cascades of several ECPrOx reactors [R31], [3], [16], [64].

Our studies were aiming at a mechanistic understanding of the system's complex nonlinear behavior. In two initial papers, the behavior of a spatially distributed model formulation was analyzed in detail [31], [38]. For this purpose a lumped model of the system [R20] was extended to consider variations along the gas channel. Complex spatiotemporal patterns have been predicted for a wide range of technically relevant operating conditions (see Figure 14). The experimental proof is subject of ongoing work. To explain the observed behavior, the system can be understood as a cluster of coupled oscillators. Dynamic modeling reveals that spatiotemporal pattern formation can be caused by global coupling as well as by migration coupling, and it depends on the electrolyte's conductivity. Furthermore, the system features coupling by means of the anode gas channel dynamics. Depending on the characteristic time for the CO transport in the channel, two limiting cases exist. In the first case, for large feed flow rates, the channel dynamics is fast and plays a secondary role. The

spatial profile of the channel CO mole fraction does not change in time significantly. It basically determines the intrinsic oscillation frequency of each of the oscillators. Depending on the electrolyte conductivity, coupling/synchronization or decoupling can be observed. In the second case, for small feed flow rates, the channel dynamics dominates the oscillatory behavior of the system and leads to more complex behavior. The spatiotemporal evolution of the CO surface coverage is governed by shock waves traveling through the channel. Depending on the fraction of covered cell area and on the electrolyte conductivity, a series of subsequent pre-ignitions during each main oscillation period can be observed. They manifest themselves in characteristic patterns in the cell voltage, which have recently been observed experimentally by Varela and co-workers [R27].

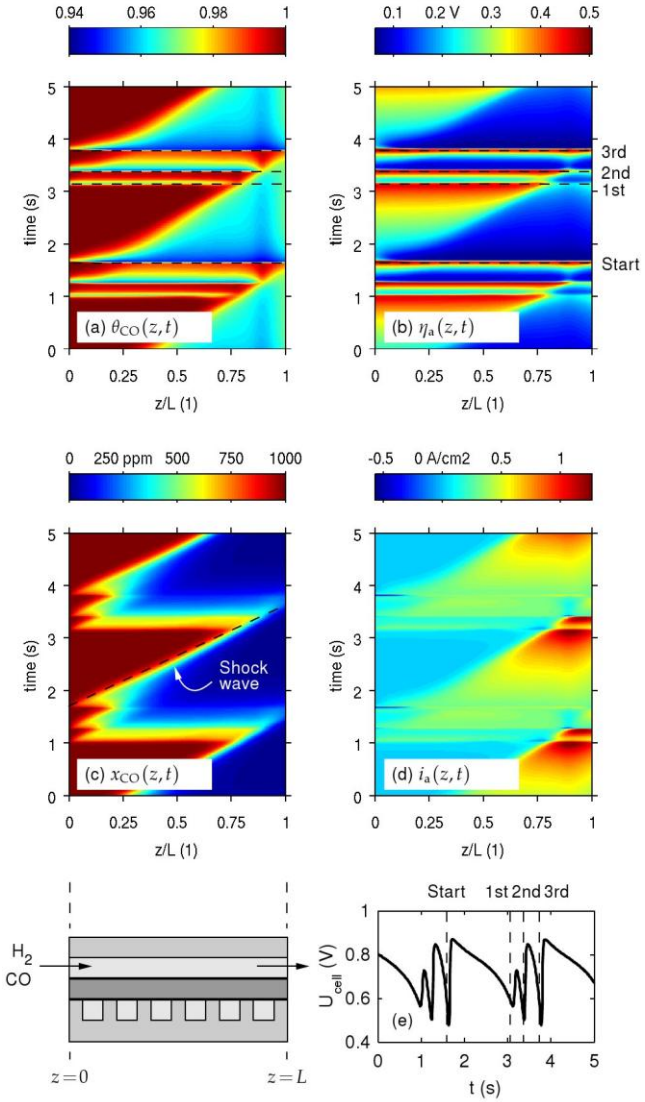

Fig. 14: Oscillatory behavior of the system in case of strong influence of the channel dynamics: (a)-(d) spatio-temporal evolution of the CO surface coverage θ_{CO}, the anode overvoltage η_a, the channel CO mole fraction x_{CO} and the local anodic current density i_a; (e) temporal evolution of the cell voltage U_{cell}.

A very recent effort, undertaken in collaboration with the group of Krischer (TU München) and the SCT group (Prof. Flockerzi), aims at the correct classification of the underlying oscillator. In an initial paper, Zhang et al. [R28] identified an HN-NDR oscillator. Our own theoretical and experimental study [67] revealed the presence of an S-NDR instability, coexisting with the HN-NDR oscillator.

4.3 Biological Production and Conversion Systems

4.3.1 Dynamics of Cellular Populations

In biotechnology often fermentation processes based on populations of living cells are used to transform raw materials into valuable products. From the system-theoretical point of view, the control of these processes is a very challenging task. Cell populations represent dynamic systems which are distributed not only with respect to the external (i.e. spatial) coordinates, but also with respect to the internal coordinates, e.g. the concentrations of intra-cellular metabolites. Population balances are a suitable modelling concept to describe the behaviour of such complex systems. But, to be able to use population balance models for the quantitative description of cellular systems, one has to know the kinetics of the underlying mechanisms on the single cell level.

Due to the fact that kinetic rate expressions derived from single cell experiments may not be valid in multi-cellular systems, we decided to identify the kinetic parameters from experimental population dynamic data. For this purpose we used flow cytometry in collaboration with the BPE group, because this measuring technique, by use of fluorescence markers, is able to yield multidimensional property distributions. Due to the fact that experiments with biological systems are often difficult to reproduce, in preliminary studies we investigated the aggregation kinetics in binary and ternary physical particle mixtures, consisting of polystyrene particles (PS, d = 1.998 µm, ζ = −88 mV) and melamine-formaldehyde particles (MF, d = 366 nm, ζ = +38 mV), the latter being labelled with Rhodamine B or FITC [R32], [27].

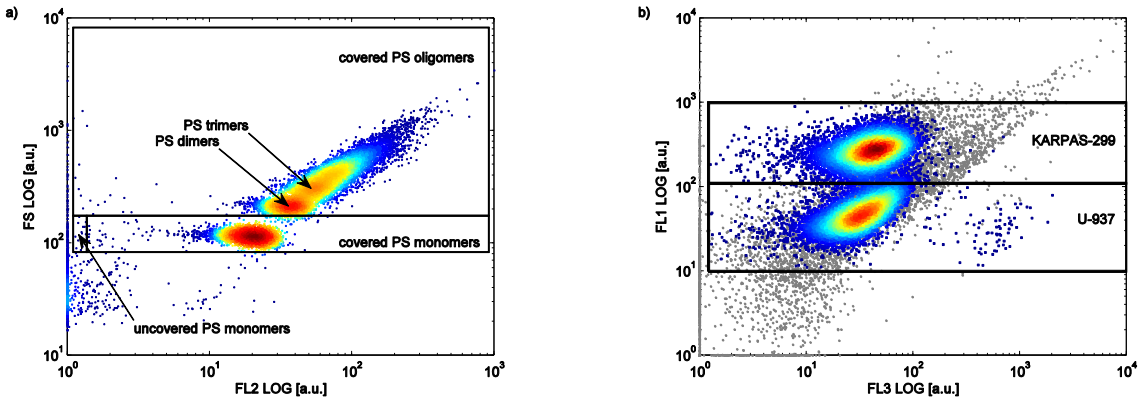

Fig. 15: Number density colored 2D distribution plots with indicated gates. a) Aggregation in binary particle system, b) CD13 aggregation to KARPAS-299 and U-937 cells. Cell debris is shown in grey color.

For a biological model system, we investigated the aggregation of monoclonal CD13 antibodies, labelled with phycoerythrin, to a cellular mixture of human U-937 cells (d = 13.8 µm, ζ = −11.9 mV) and KARPAS-299 cells fluorescently labelled with H-110 (d = 14.1 µm, ζ = −12.6 mV). Experiments with IgG1 antibodies were used as an isotope control [23]. Samples were immediately diluted and cooled, inhibiting further aggregation during the subsequent washing procedure to remove excess antibody, before being analyzed in the flow cytometer. By appropriate gating, viable monomeric cells could be separated from dead cells and debris. For the analysis of multi-dimensional distributions of cluster composition, an Epics XL flow cytometer (Beckman-Coulter, USA), equipped with a 488 nm Argon laser, was

used. Experimentally obtained distributions for the particle and the cellular system are presented in Figure 15.

The cell aggregation dynamics was simulated with a property-discrete population balance equation [11], [23], [92]. The state-space was spanned by the absolute number of particles constituting a certain aggregate. In the case of the particle system, the number of PS particles and the number of MF-RhB particles are the discrete property coordinates. The discrete state-space grid was adaptively reduced by a semi-heuristic approach [11], [92]. The aggregation rate was modelled by means of suitable kernels [R33] which account for Brownian particle motion and interparticle forces in terms of the DLVO theory. Aggregation between CD13, KARPAS-299 cells and U-937 cells was simulated similarly to particle aggregation. Specific biological interactions were modelled by heterogeneously distributed receptor surface patches with superimposed non-DLVO interaction potentials [23], [92].

In binary mixtures of differently sized and oppositely charged PS and MF-RhB particles, aggregation proceeds in an electrostatically mediated two-step process. First, PS particles are covered by the smaller MF-RhB particles. Upon sufficient surface heterogeneity, bridging events become more likely and the clusters can aggregate into more complex structures. Applying the kernel concept proposed by Moncho-Jorda et al. for patchy-particles [R33] under consideration of DLVO interaction potentials in bivariate physically discrete population balance simulations, we found that complex aggregates containing more than one PS particle only form at intermediate mixing ratios (MF−RhB : PS = 20 : 1) [11]. Simulation results are compared to flow cytometric data in Figure 16a. By appropriate gating, we were able to determine the CD13 aggregation separately for each cell type (see Figure 15b).

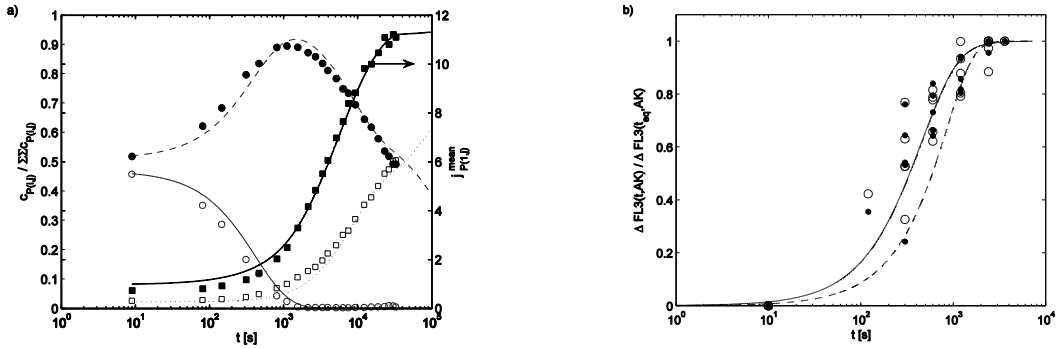

Fig. 16: Simulated aggregation dynamics (lines) versus experimental data (symbols): a) binary 20:1 particle system for uncovered PS monomers (○, −), covered PS monomers (●, - - -) and their coverage (■, −) as well as PS oligomers (□, …), and b) the ternary mixture of CD13 antibody, KARPAS-299 (●, −) and U-937 (○, −−) cells.

Experiments with the cellular system showed that U-937 cells bind more CD13 antibodies than KARPAS-299 cells. The difference in binding extent was not as pronounced as expected. Since an absolute quantification of receptor numbers by flow cytometry remains difficult, aggregation dynamics can be compared to simulation results on a relative basis only. As illustrated in Figure 16b, the aggregation dynamics of CD13 to both cell types can be simulated quite well. During receptor coverage, the distribution of adsorbed CD13 per cell broadens considerably. After saturation only unspecific aggregation persists and a quasi-equilibrium state, featuring a narrow distribution, is obtained. Despite a high CD13-to-cell ratio and purely attractive CD13-receptor potentials, preferential antibody aggregation to cellular targets remains a rate-limited process due to the low receptor surface coverage.

Experimental deviations are mainly attributed to varying expression levels of CD13 receptors on the cell surfaces.

The just described results are an important methodological prerequisite for the new research project "Biofuel Production using Photosynthetic Organisms" (see section 7.3). In that project flow cytometry is planned to be combined with population balance modeling in order to understand and control the dynamic behavior of cellular populations.

4.3.2 Bioelectrochemical Energy Conversion in Enzymatic Fuel Cells

Enzymatic fuel cells (EFC) are biomimetic devices which convert chemical energy directly into electrical energy by employing enzymes as biocatalysts at the electrodes. The basic working principle of EFC mimics effectively the cellular respiration of living cells. Similar to cellular respiration, glucose (or another energy-rich metabolite) is supplied to the system as an electron donor, while oxygen plays the role of the final electron acceptor. Usually the fuel is only partially oxidized. E.g., if glucose oxidase (GOx) is used as the anode catalyst, gluco-lactone, which is hydrolyzed further to gluconic acid, will be the main oxidation product [15]. Thus, EFC can be considered as co-generation systems supplying electrical energy as well as valuable chemicals.

a) b)

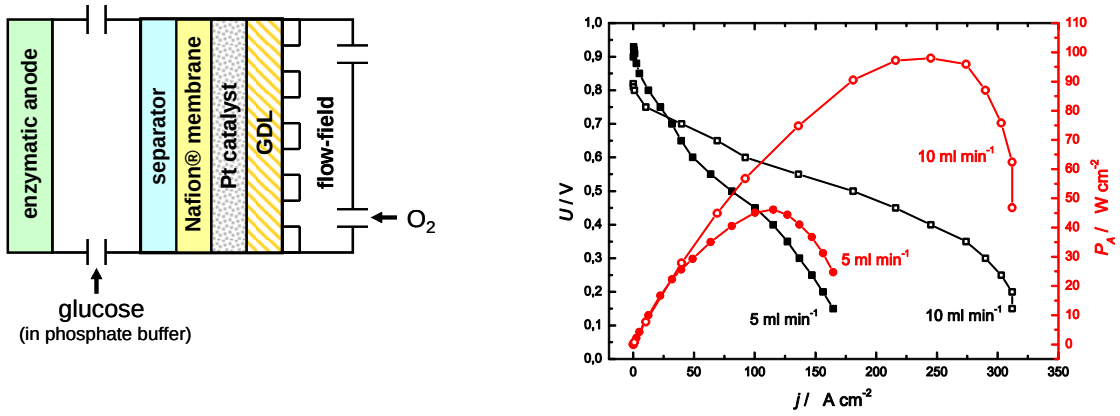

Fig. 17: a) Schematic presentation of the developed hybrid enzymatic fuel cell; b) polarization (black squares) and power curves (red circles) of the hybrid fuel cell at glucose flow rates of 5 ml min^{-1} (full symbols) and 10 ml min^{-1} (open symbols). Conditions: anode operated at 5 mM glucose in 0.1 M phosphate buffer, pH 7.2, 37 °C, N_2 atmosphere; cathode operated at 500 ml min^{-1} dry oxygen [55].

Very first publications on EFC date back to the 1960s, but strongly intensified research has been started during the last decade. The recent progress in this field regarding experimental and modelling efforts has been reviewed thoroughly by our group [26]. Due to low performance and stability, EFC are still far from practical application. When designing biomimetic energy conversion systems based on redox enzymes, the following points have to be considered: 1) enzyme immobilization; 2) contact between enzyme and electrode surface; 3) enzyme kinetics; 4) enzyme electrode architecture and, 5) integration of electrodes into the overall system [55]. The first three aspects have been extensively studied in the past, mainly in the framework of the development of amperometric biosensors (see e.g. [R34-R35]). This resulted in a number of preparation methods for biosensor enzymatic electrodes. But these methods cannot be transferred directly to EFC without modification, as we have shown recently in collaboration with colleagues from the University of Malmö [42]. By syste-

matic screening of enzymatic electrode preparation methods we have identified the salt tetrathiafulvalene-tetracyanoquinodimethane (TTF-TCNQ) as a promising charge transfer complex for the enzyme GOx [55]. To the best of our knowledge, we are the first group to demonstrate the functionality of TTF-TCNQ as charge transfer complex in a hybrid enzymatic glucose-oxygen fuel cell whose configuration is illustrated in Figure 17a.

With an optimized anode structure, a limiting current density of nearly 400 μA cm^{-2} was achieved in 5 mM glucose solution. The EFC exhibited unexpectedly high OCV values (up to 0.99 V), which were tentatively ascribed to different pH conditions at the anode and the cathode. OCV was influenced by glucose crossover and was decreasing with an increase of glucose concentration or flow rate. Although the performance of the fuel cell is limited by the enzymatic anode, the long-term stability of the fuel cell is mainly influenced by the Pt cathode, while the enzymatic anode has higher stability. The fuel cell delivered power densities up to 120 μW cm^{-2} in 5 mM glucose solution (see Figure 17b). These performance data are quite encouraging. Nevertheless, for real world applications, e.g., in implantable power devices, the performance and stability of EFC must be improved further. For this purpose a detailed understanding of the underlying enzymatic reaction mechanism, which is coupled to the charge and mass transport within the catalyst layer, is indispensable.

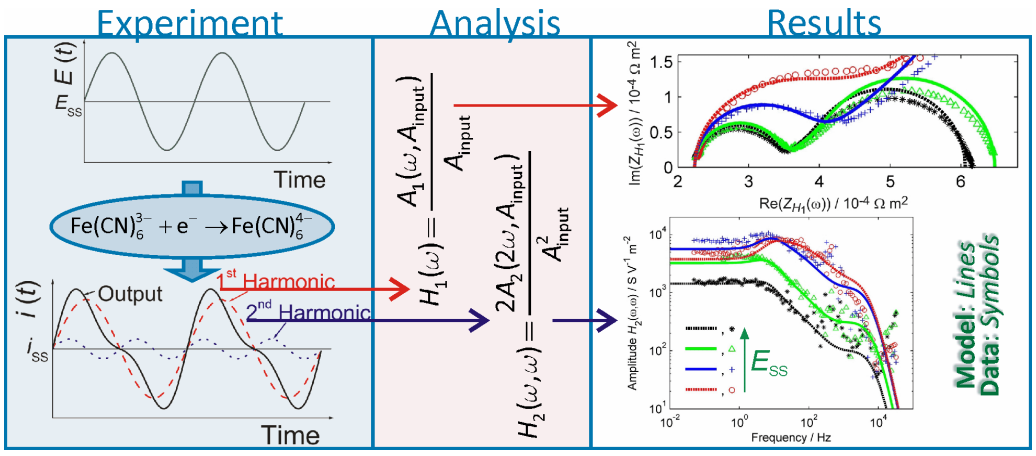

Fig. 18: Schematic illustration of the working principle of Nonlinear Frequency Response Analysis (NFRA) [57].

The kinetics of electrochemical glucose oxidation in the presence of charge transfer complexes has been studied by several groups (e.g. [R36-R38]), but the mechanism is still subject of controversial discussions. In our opinion, advanced electroanalytical techniques must be applied in order to discriminate between competing mechanistic hypotheses, such as Nonlinear Frequency Response Analysis (NFRA). While in classical Electrochemical Impedance Spectroscopy (EIS) input signals with small amplitudes are used, NFRA applies harmonic perturbations of larger amplitudes. Thereby, one obtains higher-order system responses which contain valuable information about the system's nonlinearities [56]. The PSE group, in close collaboration with Prof. Petkovska (University of Belgrade), has applied the NFRA technique successfully for the investigation of the ferrocyanide oxidation kinetics [57] and for discrimination of competing kinetic models of the electrochemical methanol oxidation [28]. Furthermore, we have investigated NFRA as a diagnostic tool for dehydration, flooding, and CO poisoning in PEM fuel cells [10], [47], [71]. In the next step, we are planning to use NFRA for the identification of the mechanism and the kinetics of the enzymatically catalyzed electrochemical oxidation of glucose.

5 Selected Teaching Activities, PhD Projects and Habilitations

5.1 Teaching Activities at OvGU

- B.Sc. Course Simulation Technology (Voigt*)
- B.Sc. Course Process Dynamics (Voigt*, Sundmacher)
- B.Sc. Course Process Optimization (Heidebrecht)
- M.Sc. Course Process Systems Engineering (Freund, Hanke-Rauschenbach)
- M.Sc. Course Process Simulation (Freund)
- M.Sc. Course Experimental Design and Parameter Estimation (Sundmacher)
- M.Sc. Course Population Balance Systems (Voigt*)
- M.Sc. Course Molecular Modeling (Voigt*)
- M.Sc. Course Fuel Cell Engineering (Hanke-Rauschenbach, Heidebrecht)
- M.Sc. Course Electrochemical Process Engineering (Vidaković-Koch)
- M.Sc. Course Biofuels: Sustainable Production and Utilization (Rihko-Struckmann)
- M.Sc. Course Advanced Process Systems Engineering (Sundmacher)

5.2 Additional Teaching Activities

Two times a year the PSE group coordinates a one-week laboratory course for up to 30 high school students from all over Germany where they get the chance to work under scientific guidance on chemical, biological, and systems engineering problems in the MPI labs. Furthermore, members of the PSE group continued the NaT-working project (NaT: Natural and Engineering Sciences; jointly started with Bosch Foundation) together with the Systems Theory Group of OvGU (Prof. Findeisen). In addition, members of the PSE group supervised student teams of OvGU in the German ChemCar competition, a joint initiative of DECHEMA and ProcessNet. Finally, several high school students worked on selected research projects under the guidance of PSE group members as part of their high school program (BELL).

5.3 Supervision of Ph.D. Theses

Currently, Prof. Sundmacher acts as supervisor of 30 PhD students (see Table 1) planning to submit their theses to the Faculty of Process & Systems Engineering of OvGU. For each student a PhD Advisory Committee (PAC) has been defined, in adoption of the regulations established in the IMPRS. The supervisor, the adviser (one of the team leaders given in Table 1), and – if required – a third member (professor of OvGU or of an external university or a scientist from another MPI group) form the PAC. The status of all PhD projects is reported to the PAC on a quarterly basis. Based on this supervision concept, five PhD students have successfully finished their projects in the period covered by this report (B. Niemann [90], M. Chalakova [91], S. Rollié [92], F. Steyer [93], M. Pfafferodt [94]). Another five theses are close to submission (C. Borchert, B. Hartono, I. Ivanov, T. Kadyk, A. Peschel).

5.4 Habilitation Projects

Dr.-Ing. R. Hanke-Rauschenbach	Analysis, design and operation of electrochemical energy converters	in preparation
Dr.-Ing. P. Heidebrecht	Model hierarchies for chemical process design	finished in 2011, [89]
Dr. techn. L. Rihko-Struckmann	Development and analysis of catalytic processes for the production of biofuels	in preparation
Dr.-Ing. T. Vidaković-Koch	Kinetics of electrochemical processes for energy and material conversion	in preparation

6 Selected Memberships, Appointments, Awards

Dr. S. Banerjee

2011 Offer for Assistant Professorship at Washington State University (accepted)

B. Bensmann

09-12/2010 DAAD Scholarship, Research stay, ICTP Prague/Czech Republic

C. Borchert

06/2009 Best Lecture Award “ESCAPE Conference”, Cracow, Poland

Dr. H. Freund

since 2010 Chair of AIChE Proc. Dev. Division Area Process Intensification
2010 Hanns-Hofmann Award of the ProcessNet Division Reaction Engineering
2011 Erlangen Excellence in Engineering of Advanced Materials Award
2011 Offer for W2 Professorship at University of Erlangen-Nuremberg (accepted)

Dr. R. Hanke-Rauschenbach

2009 Otto Hahn Medal of the Max Planck Society

Dr. P. Heidebrecht

since 2011 Guest Professor for Process Systems Engineering at BTU Cottbus
2011 Habilitation at OvGU, Venia Legendi: Process Systems Engineering

F. Karst

2009 Faculty Award of OvGU Magdeburg

S. Piewek

12/2008 Volkswagen Woman Driving Award, Wolfsburg, Germany

Dr. L. Rihko-Struckmann

2009-2011 EU Evaluator for FP7-PEOPLE-2009/2010/2011-IEF-IIF-IOF (Marie Curie)
2009 Evaluator for DESMI, Republic of Cyprus & European Reg. Develop. Fund
2010 Evaluator for Estonian Science Foundation

Dr. T. Vidaković-Koch

since 2011 Theme Editor in Bioelectrochemistry and Fuel Cells in the open access “Journal of Electrochemistry Science and Engineering”

K. Sundmacher

since 1999 Full Professor for Process Systems Engineering at OvGU
since 2001 Director of the MPI Department for Process Engineering
since 2003 Executive Editor of “Chemical Engineering Science”
since 2006 Member of Selection Committee of the German Scholarship Foundation
since 2006 Ed. Advisory Board of Ullmann’s Encyclopedia of Industrial Chemistry
2007-2010 Chair of GAFOE (German-American Frontiers of Engineering Symposia)
2009 Dr. Meyer Struckmann Award 2008, BTU Cottbus
2009 Einstein Professorship, Chinese Academy of Sciences (CAS)
2009-2010 Managing Director of MPI
since 2010 Vice Chair of the DFG Collaborative Research Center SFB/Transregio 63 “InPrompt”, established at TU Berlin, TU Dortmund and OvGU
since 2010 Spokesman of “Center for Dynamic Systems” established at OvGU
since 2010 Guest Professor, East China University of Science & Technology, Shanghai

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7.1 Selected Publications of the PSE Group (2008-2011)

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[8] *Radulescu, G., J. Gangadwala, N. Paraschiv, A. Kienle and K. Sundmacher:* Computers & Chemical Engineering **33**, 590-597 (2009)

[9] *Steyer, C. and K. Sundmacher:* Journal of Crystal Growth **311**, 2702-2708 (2009)

[10] *Kadyk, T., R. Hanke-Rauschenbach and K. Sundmacher:* Journal of Electroanalytical Chemistry **630**, 19-27 (2009)

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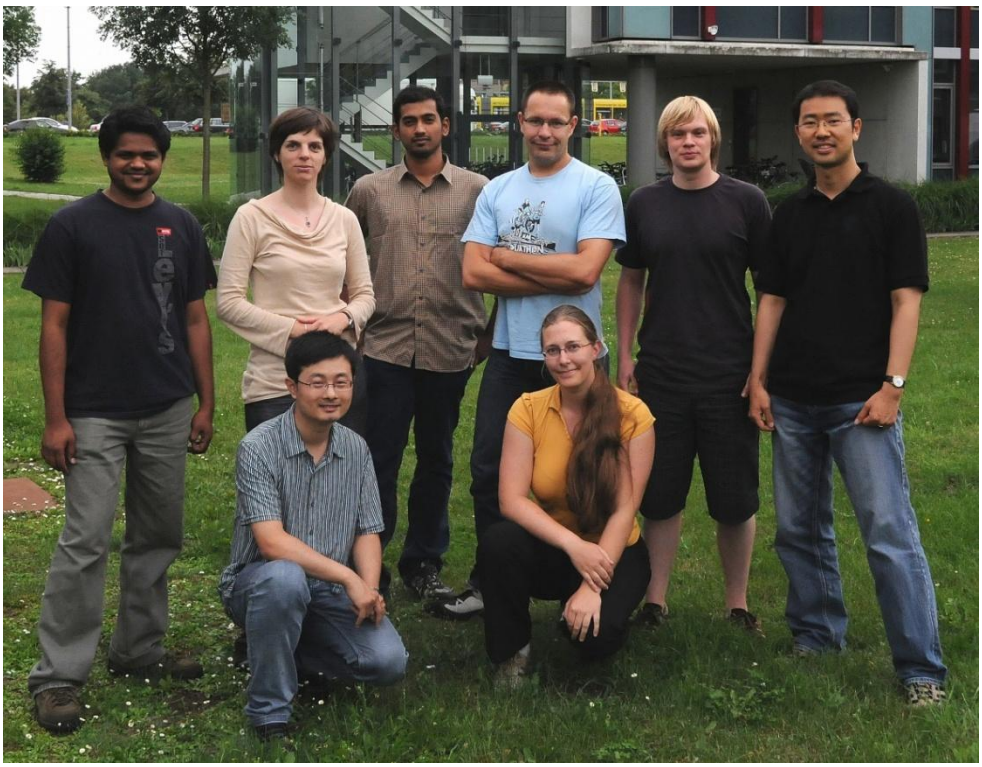
(Please note that this is not a complete list of publications.)

Research Group:

Otto Hahn Group Portable Energy Systems (PoES)

Jun.-Prof. Dr.-Ing. Ulrike Krewer



This report covers the period from October 2008 to August 2011.

1 Introduction

The Otto Hahn Group Portable Energy Systems (PoES) is an independent research group supported by centralized funds of the Max Planck Society. The head of the group, Ulrike Krewer, also hold a Juniorprofessorship (equivalent to assistant professorship) at OvGU until January 2012; the group members at MPI and OvGU collaborate closely on their research topics. All projects of the group deal with the analysis, the optimal design and the operation of portable electrical energy systems like fuel cells and batteries. As a distinction from most other groups in the portable energy systems field, the PoES group focuses on generating in-depth knowledge on the processes occurring and interacting with each other in energy systems and on limitations and stability issues of the systems by combining rigorous model-based analysis and experimental validation. The gained knowledge is subsequently used to develop improved energy system concepts or operating modes. Although the processes within the contemplated energy systems differ, all are open systems with matter and heat being exchanged with the environment. As such they show a certain dependence on environmental conditions which may lead to malfunctions and even instability during operation; such limitations are a central research topic of the group.

The group's current research projects are *Small Fuel Cell Systems, Alkaline Electrochemical Cells,* and *Analysis and Diagnosis of Fuel Cell State*. In the *Small Fuel Cell Systems* project, the media management of fuel cell systems is investigated at various hierarchical levels. Studies of complete systems are complemented by detailed investigations on key system components and their stabilizing effect in the system. Joint research with the MPI's research groups has been conducted on energy harvesting (ESB group: Dr. Grammel) as a part of the institute's *Vision 2015+* initiative and on hybrid control for energy systems (SCT group). The *Alkaline Electrochemical Cells* project investigates promising and potentially low-cost alkaline fuel cells and batteries for which there is a lack in quantitative understanding of the processes occurring inside the cells. The studies analyze, quantify and mitigate the performance-limiting processes and the cells' sensitivities to environmental conditions. External partners (Univ. Newcastle, UC Irvine, MLU Halle-Wittenberg, Karl-Winnacker-Institute) participate in the project with their expertise on cell material. Finally, the project *Analysis and Diagnosis of Fuel Cell State* uses the knowledge on fuel cell processes and their dynamics for diagnostic purposes on the fuel cell state during operation. The developed methods deliver important information for the control of fuel cell systems and help to reduce the number of external sensors. Collaborations with the PSE group in this field have led to several research papers already [1-3].

During the period covered by this report, the PoES group has grown from 2 members to 7, has published 15 peer-reviewed research papers (additional 3 papers under review process) including 3 invited reviews [1,3,4] and presented their research at more than 20 occasions at international scientific conferences.

2 Members of the Research Group

Since 2008, Ulrike Krewer is leading the research activities of the PoES group at the MPI. The activities are supported by team members that are located at the OvGU, where she has been Juniorprofessor for Portable Energy Systems from 2009 to 2011. In addition, numerous international and local undergraduate students assist in the group's research.

	Research Topics	Membership
Head of Group		
Jun.-Prof. Dr.-Ing. U. Krewer	Analysis, diagnosis and optimization of electrochemical energy systems	Since 01/2008
Postdocs		
Dr. Q. Mao	Diagnosis and energy harvesting with fuel cells	Since 03/2009
Dr.-Ing. F. Zenith	Analysis and optimization of portable direct methanol fuel cell systems	04/2008-04/2010
Ph.D. Students		
M. Kraus	Micro-structured gas-liquid separators for direct methanol fuel cell systems	Since 12/2008
P.S. Khadke	Analysis and optimization of electrodes for alkaline direct methanol fuel cells	Since 11/2009
C. Weinzierl	Model-based analysis of alkaline direct methanol fuel cells	Since 02/2010
Visiting Scientists		
Dr. S. Arisetty	Delaware University, USA: Modeling of transport and reaction in fuel cells	10/2008-02/2009
Dr. V. Kulshrestha	Centre for Non-conventional Energy Resources, India: Membranes for gas-liquid separation	10/2009-11/2009
V.V. Nair	UC Irvine, USA: Pd catalyst for alkaline direct methanol fuel cells	07/2011-09/2011
Group at OvGU: Portable Energy Systems		
Ph.D. Students: D. Schröder, Y. Na		

3 Survey of Research Projects

Small Fuel Cell Systems

	This project deals with the systematic design and optimization of small fuel cell systems by employing model-based and experimental analysis techniques. Of particular interest is the influence of environmental conditions on the system and the interaction between components and system; both of which may lead to instability or low efficiency of a system.				
Subprojects	**Scientists**	**Funded by**	**Period**	**Publi-cations**	**Partners**
Analysis and optimization of portable direct methanol fuel cell systems	Zenith, Na, Krewer	DFG, MPG	Since 04/2008	[4-16]	SINTEF (Dr. Zenith), Tongji University (Prof. Zhou), SCT group
Micro-structured gas-liquid separators for direct methanol fuel cell systems	Kraus	MPG	Since 12/2008	[11,17-20]	Karlsruhe Institute of Technol. (Prof. Dittmeyer), OvGU (Profs. Metzger, Schmidt), Centre for Non-conventional Energy Resources (Dr. Kulshrestha)
Energy harvesting using fuel cell and *R. rubrum*	Mao, Krewer	MPG	Since 11/2010	Study thesis	ESB group (Dr. Grammel)

Alkaline Electrochemical Cells

	Fuel cells and batteries employing alkaline electrolytes are systematically analyzed and optimized to identify and improve the processes limiting the cells' performance. Focus is on the model-based and experimental analysis of interaction of transport and reaction processes and on the effect of environmental conditions on cell stability.

Subprojects	Scientists	Funded by	Period	Publi-cations	Partners
Analysis of processes in alkaline direct methanol fuel cells	Weinzierl, Krewer	MPG	Since 02/2010	[21-24]	Univ. Newcastle (Dr. Yu), H_2 Institute of Appl. Technol. (Dr. Ruffmann)
Analysis and optimization of electrodes for alkaline direct methanol fuel cells	Khadke, Nair	MPG, MPI	Since 11/2009	[24-26]	UC Irvine (Prof. Mumm), Univ. Halle-Wittenberg (Prof. Bron)
Model-based analysis of processes in secondary Zn-air batteries	Schröder	Fed. State of Saxony Anhalt	Since 07/2010	[27]	Karl Winnacker Institute (Dr. Drillet)

Analysis and Diagnosis of Fuel Cell State

	Fuel cells based on proton exchange membranes, especially direct methanol fuel cells, are analyzed with regard to the processes that govern their behavior and limit their performance. Focus is on model-based analysis of the processes inside the fuel cells and on determining the fuel cells' state, e.g. the methanol concentration level, during operation by using dynamic methods.				
Subprojects	**Scientists**	**Funded by**	**Period**	**Publi-cations**	**Partners**
Dynamic methods for fuel cell state diagnosis	Mao, Krewer	Humboldt, MPG	Since 03/2009	[1-3,28-30,38]	Research Center Jülich (Dr. Mergel), PSE group
Modeling of transport and reaction in direct methanol fuel cells	Arisetty, Krewer	MPG	10/2008 - 05/2009	[31-33]	Univ. Delaware (Prof. Advani)
Influence of adsorption processes in the high temperature PEMFC	(Krewer)	-	01/2009-12/2010	[34,35,39]	Volkswagen AG

4 Research Highlights

The following section presents selected research highlights from the above listed projects.

4.1 Direct Methanol Fuel Cell Systems

Portable energy systems need to supply off-grid electrical energy at all kinds of environments; they are complex and, often, open systems and thereby vulnerable to changes in external conditions [4]. Direct methanol fuel cell (DMFC) systems are no exception: the energy, methanol and oxygen balances can be easily stabilized [5,7], whereas the water level is prone to instability [5,6,R1]. Water management is problematic in active systems [R1,5], which employ power consuming components such as pumps, as well as in passive systems, which rely on forces like natural convection for reactant management [R2]. A significant effort on how to mitigate water loss has been done for passive systems [R2], but only little attention was paid on active systems. The PoES group has systematically evaluated such systems (Fig. 1, left) by model-based analysis and showed that feedback control allows stabilizing the water level at certain, but not all operating and environmental conditions. Important influencing factors on the stable operating range are environmental temperature and humidity (Fig. 1, middle), air flow rate and efficiency of heat exchanger (Fig. 1, right). Design and operating point of the fuel cell were identified to be of minor importance

[6]. The usage of micro separators in DMFC systems enables a switch from feedback to feedforward (sensorless) water level control by releasing excess water through its capillaries [11]. R&D on DMFC systems focused on applied development of prototypes with few notable exceptions [R3-4]. Apart from the stability investigations, the effort of the PoES group has therefore been to generate more fundamental knowledge on DMFC systems and the correlation between design and performance. The design of fuel cell systems was found to have negligible effect on system stability but a stronger effect on fuel and system efficiency, on the minimum size of system components, hence, system size, and on the complexity of the system's behavior. Increased process integration by joining the anode and cathode exit streams reduces the system size due to a decrease in maximum heat exchanger duty, but it is strongly detrimental to fuel and system efficiency, as in the integrated design the cathode's exhaust gas is saturated with methanol from the anode exit [15].

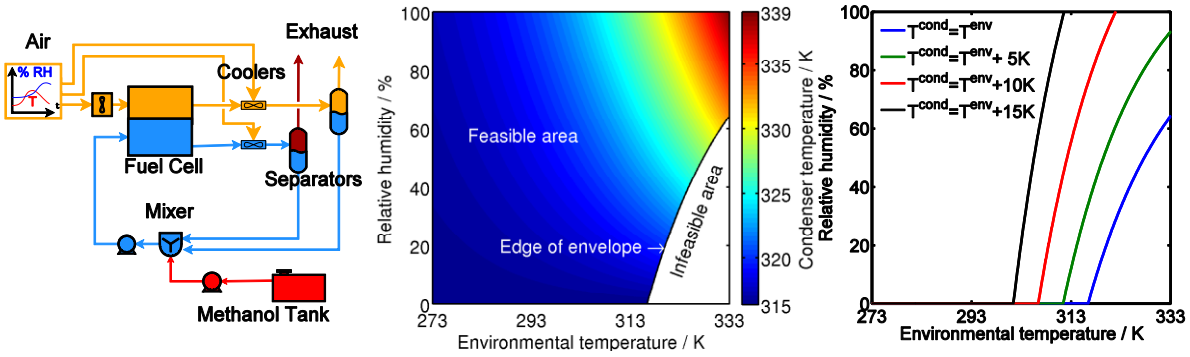


Fig. 1: Reference DMFC system (left), and feasibility range for stable operation depending on environmental conditions (middle) and heat exchanger capacity (right).

Usage of DMFC systems as a portable power source requires them to operate independently of orientation in the gravity field; this is challenging for the built-in gas/liquid (g/l) separators, which separate and recycle water from the exhaust gas streams. Micro separators enable designing capillary forces to dominate over gravity forces; hence, they may be suitable for DMFC systems. While micro-sized reactors, heat exchangers and mixers have been widely studied, there is lack of and demand for research on micro separators [R5]. Existing studies on g/l micro separation focus on a separator's application and proof of functionality at system level [R6]. The PoES group's target is to generate in-depth knowledge on g/l micro separators at various hierarchical levels: Model-based and experimental studies on the component level elucidate the governing and limiting processes and the influence of design, operating and environmental conditions on performance [11,17]; the studies on the system level show the interaction between separator and system, such as the effect of the separator on a system's stability, performance and dynamic behavior [11]. Two different separator concepts have been applied: irregular structures as found in porous membranes [17] and machined micro channels [11,19]. For both, modification of surface properties allowed a separation of either gas or liquid from the main stream (Fig. 2, left). Any of these separator designs can achieve complete separation independent of orientation [20] (Fig. 2, right).

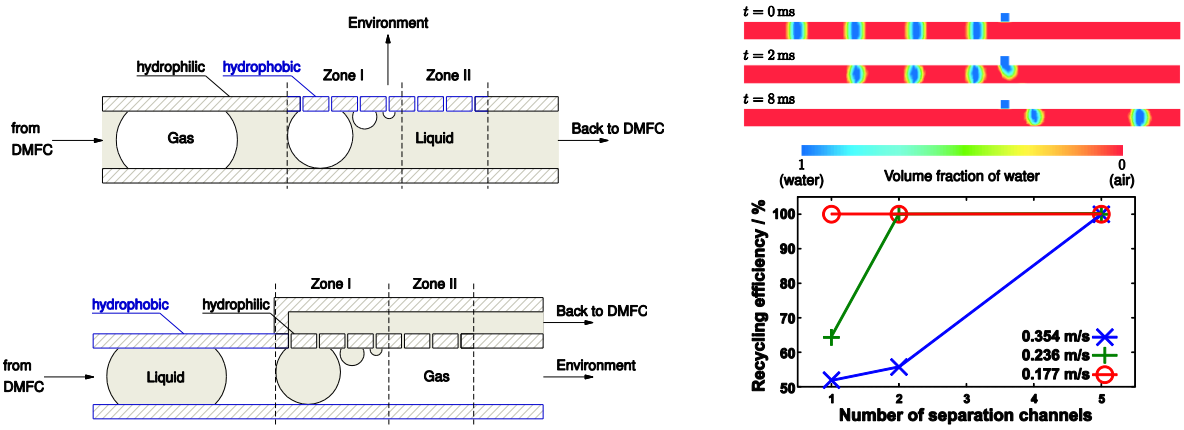


Fig. 2: Capillary-based g/l and l/g micro separators (left), and simulation of a single channel separation and separator scale-up (right).

4.2 Energy Harvesting using Fuel Cell and *R. rubrum*

As a contribution to the *Vision 2015+* of the MPI, the PoES and the ESB-group (Dr. Grammel) recently started a joint project on coupling hydrogen producing bacteria with small fuel cell systems for energy harvesting. Energy harvesting is a concept for generating off-grid power from low energy density streams that are of little interest for large-scale power production; it is seen as a suitable way to use the small hydrogen stream generated presently by *Rhodospirillum rubrum:* the bacteria convert natural sugars into H_2, which is then converted to electricity using a PEMFC. Few studies exist on coupling other types of H_2-producing bacteria with fuel cells [R7]; the attractiveness of using *R. Rubrum* as the hydrogen generator in a small fuel cell system lies in the extensive knowledge of the functioning of the species, which enables the engineering of a stabilized, miniaturized system with flexible nutrition. The proof of concept has been demonstrated: For several hours, ca. 50% of the generated H_2 could be converted into electricity.

4.3 Alkaline Direct Methanol Fuel Cells

Alkaline electrochemical cells with air electrodes, such as the alkaline DMFC (ADMFC) and the zinc-air secondary battery, are promising and low-cost portable electricity suppliers. ADMFCs have attracted wide attention in recent years as new material developments have led to a notable, though not yet satisfying increase in performance [21,R8]. Reasonably active and stable Pt-free catalysts may be used when operating in alkaline electrolyte. As liquid alkaline electrolytes form precipitates by reaction with CO_2, they are replaced by OH^- conducting polymers. A notable lack of understanding the performance-limiting processes in ADMFC and the dependence of stable operation on environmental and operating parameters motivates the PoES group to contribute to these issues. The ADMFC is systematically analyzed on various hierarchical levels by means of simulation and experiment. On both, cell and electrode level, stability and performance limitations have been identified. While the methanol, oxygen, and heat balances of the ADMFC are stable, maintaining a stable water level in ADMFCs is challenging: water is produced at the anode, a location with water already in excess, whereas it is needed as reactant at the gas-fed, hence dry, cathode.

The systematic experimental quantification of the diffusion and drag processes of methanol and water in given membrane material enables the PoES group detailed modeling and analysis of the fuel cell with a realistic parameter set.

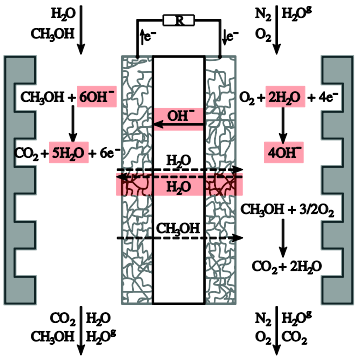


Fig. 3: Processes occurring in the ADMFC.

On the electrode level, the demand for high performance requires the ADMFC's solid electrolyte to form a maximum three-phase boundary area with catalyst and the pores that supply reactants. High performance in ADMFCs is presently only achieved by adding liquid electrolyte into the methanol stream [R9-10], which is not feasible for real applications due to carbonate precipitation. In current studies, the potential losses of an ADMFC without liquid electrolyte as well as the processes limiting the performance of the ADMFC are analyzed.

4.4 Diagnosis of Fuel Cell State

Significant knowledge of the processes that affect the performance of methanol or hydrogen fuelled PEMFC has already been gained. In addition, a large variety of complex apparatuses which employ spectroscopic or other methods enable the monitoring of the state of lab-based fuel cells [R11-12]. As such apparatuses are often not portable, expensive, or sensitive to external disturbances, they usually cannot be integrated as components into portable systems. Temperature and humidity sensors can be used to control the state of H_2 fuelled PEMFC (PSD and PES groups, [R13]). If MEA parameters of DMFCs are known and constant, even feed-forward (sensorless) control can be applied to adjust the methanol concentration at the inlet of DMFCs [7]. In many cases, e.g. during start-up or due to dynamic operation or fast environmental changes, fuel cells can have an undefined state and run into critical conditions with non-ideal supply of reactants. The need for additional sensing of the fuel cell state can be satisfied by analysis and interpretation of the dynamic behavior of the fuel cell itself. Fuel cells fed with C-containing fuels are known to have a pronounced dynamic response to changes in current which is caused by the anode oxidation kinetics [1]. In DMFCs, the predominantly nonlinear dynamic response [3,36] decreases monotonously in intensity with decreasing methanol concentration. This has been proven for step changes in current, where the cell voltage overshoots the new steady state value for some seconds (Fig. 6, top) [30,36]. This has also been demonstrated for sinusoidal current changes of large amplitude, where the total harmonic distortion (THD) of the cell voltage response is evaluated (Fig. 6, bottom): the THD contains the sum of the contributions from higher frequency responses and is sensitive to methanol concentration in a certain frequency range [2]. The observed correlation between dynamic fuel cell behavior and inlet concentration

enables the use of both methods for sensorless detection of the methanol concentration level in DMFC systems. The current step change method was also calibrated for its use at various operating conditions and for stacks [30]. Simulation studies on the dynamics of various anode kinetic models [36,38] support the three-step methanol oxidation mechanism developed previously [37]. Besides methanol concentration, the effect of oxygen concentration and status of cathode flooding on the dynamics of the cell is also quantified [29].

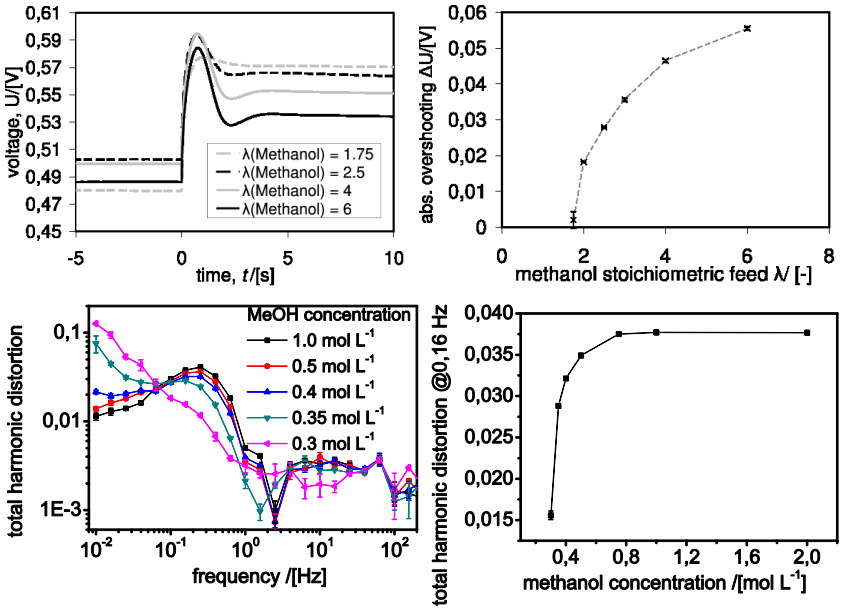


Fig. 4: Dynamic methods for sensing methanol concentration with DMFC: voltage response to a current step (top) and to a sinusoidal deflection (bottom). Calibration curves are given on the right side.

5 Selected Teaching Activities and Ph.D. Projects

5.1 Teaching Activities at OvGU

- Course on Modeling and Analysis of Energy Systems (English language)
- Course on Portable and Autonomous Energy Systems

In addition, U. Krewer developed and organized a new, interdisciplinary M.Sc. course on Sustainable Energy Systems at the OvGU; the first students started their studies in the winter semester 2011/12.

5.2 Supervision of Ph.D. Theses

The following Ph.D. students are working on their Ph.D. thesis (*: OvGU employees):
P.S. Khadke, M. Kraus, Y. Na*, D. Schröder*, C. Weinzierl.
Their topics are given in the tables in sections 2 and 3.
In addition, U. Krewer served as supervisor for several diploma, master, bachelor and internship projects and was a member of external and internal doctoral committees.

6 Selected Memberships, Appointments, Awards

Ulrike Krewer

2006 Award for best PhD thesis 2006 at OvGU
2006 Gold medal at the Samsung SDI Paper Award 2006

2007 Otto Hahn Medal 2007, Max Planck Society
Since 2008 W2 Head of Otto Hahn Group Portable Energy Systems
Since 2009 Junior Professor for Portable Energy Systems at OvGU
2010 Award Wissenschaft Interaktiv 2010
2010 Award for Fundamental Research of the Federal State of Saxony-Anhalt
Since 2010 Selected member of AcademiaNet
Since 2010 Member of board of International Max Planck Research School
Since 2011 Member of editorial board of Journal of Electrochemical Science and Engineering
2011 Offer of a W3-Professorship (Chair) for Systems of Energy and Process Engineering at the Technische Universität Braunschweig (accepted)
2011 Offer of a W3-Professorship (Chair) for Energy Processes and Systems at the Otto-von-Guericke-University Magdeburg (declined)

7 Future Directions

In the next years, research within the three established projects *Small Fuel Cell Systems*, *Alkaline Electrochemical Cells*, *Analysis and Diagnosis of Fuel Cell State* is to be intensified. The activities will be continued at the Technische Universität Braunschweig after the scheduled end of the PoES group in January 2013.

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Research Group:

Process Synthesis and Dynamics (PSD)

Prof. Dr.-Ing. Achim Kienle

This report covers the period from October 2008 to August 2011.

1 Introduction

The Process Synthesis and Dynamics (PSD) group is headed by Achim Kienle, who is an external scientific member of the MPI. He also holds a professorial position at the Otto von Guericke University. MPI and university group are closely collaborating.
The PSD group develops methods and tools for synthesis, analysis and control of complex process systems. It combines physical chemical insight with theoretical concepts from systems and control as well as applied mathematics. Process insight guides the way to suitable problem formulations and feasible as well as efficient solution strategies. If possible with reasonable effort, theoretical concepts are validated experimentally. With its approach the PSD helps to bridge the gap between theory and application.
An overview of the research projects is given in Fig. 1.

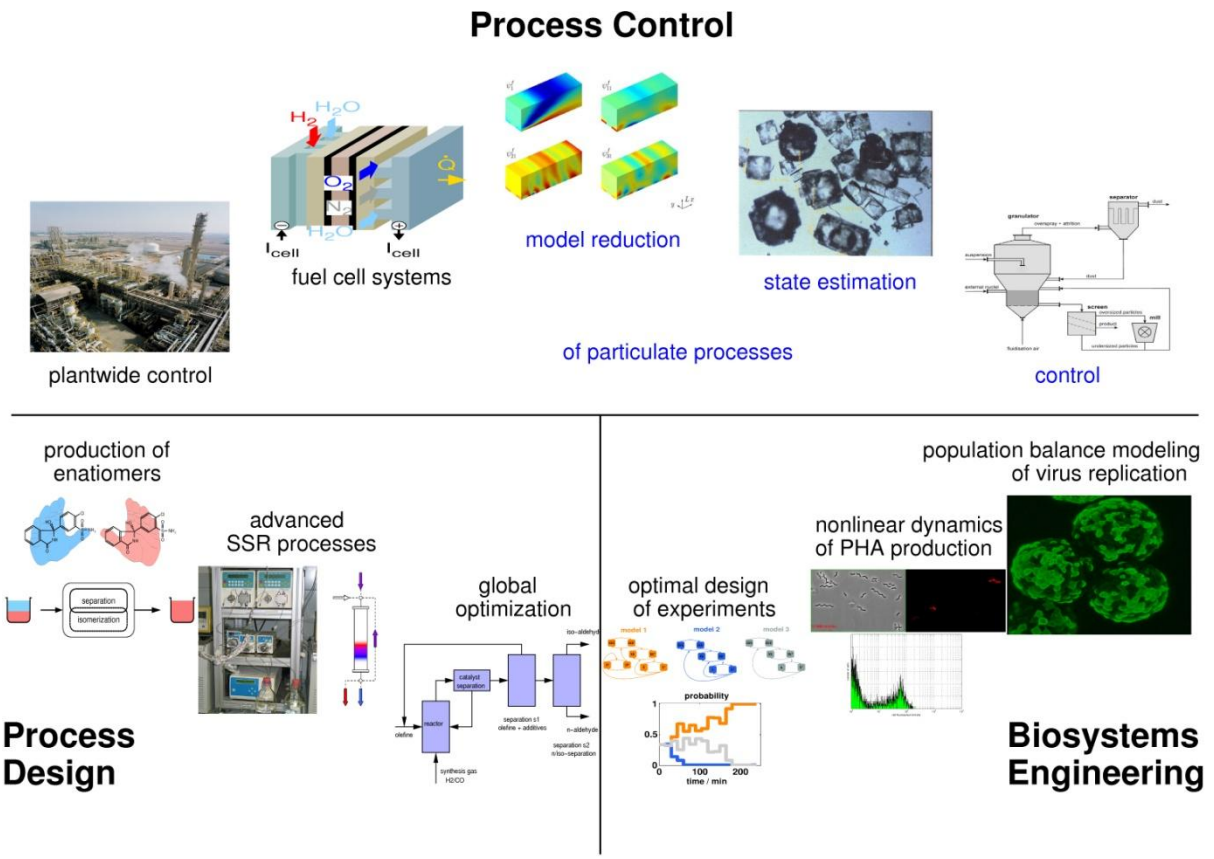

Fig. 1: Overview of research projects of the PSD group

Process control has developed as a major field of research in the PSD group during the last years. New methodologies have been introduced in the areas of nonlinear model reduction for particulate processes with nonideal flow fields, model based measurement and control of particulate processes, the synthesis of robust plantwide control strategies and nonlinear model based control of various types of fuel cell systems. In the field of particulate processes, besides crystallization, fluidized-bed spray granulation processes are considered, which also play an important role in process industries. Control of these processes, however, is difficult and has hardly been studied.

Main activities in the field of *process design* have been centered around the successful European IntEnant project. IntEnant aims at improved production of enantiomers through clever combination of reaction and separation steps. In this project, the PSD group provided computational methods for a systematic design of promising process candidates. Objectives and constraints arising in practice were defined by industrial partners. Concepts were validated successfully for industrial application examples. Independently, a new integrated simulated moving bed process was proposed and feasibility was demonstrated experimentally. Advanced steady state recycling was studied as an attractive alternative to more established batch and simulated moving bed chromatography. For that, novel design approaches were introduced and also validated experimentally. In addition, there is an ongoing activity towards global optimization of integrated processes in cooperation with the Weismantel group at ETH Zürich within the joint research project Transregio SFB 63, which involves about 15 other partners from TU Berlin, TU Dortmund and OvGU.

Biosystems engineering has been identified as a research area of common interest at the Max Planck Institute and the Otto von Guericke University. The joint research center for Dynamics of Complex Systems is currently being restructured in this direction with Prof. Kienle being one of the main coordinators. In addition the PSD group is also involved in the Magdeburg Center for Systems Biology. Important contributions of the PSD group to biosystems engineering lie in the fields of novel methods for optimal experimental design, nonlinear dynamics, and multidimensional population balance modeling. Synthesis of biopolymers was identified as an interesting field of application.

Major fields of cooperation with the other groups at MPI are integrated processes for the production of pure enantiomers together with the PCF group, nonlinear dynamics and modeling of fuel cell systems together with the PSE group, population balance modeling of virus replication in vaccine production processes together with the BPE group and selected mathematical aspects together with Dietrich Flockerzi from the SCT group.

During the period of this report, the PSD group has generated 37 articles, which have been published in international scientific journals or are in press. Further, 5 PhD projects and 2 Habilitation projects were finished. The researchers, who have finished their Habilitation during the period of this report, Klaus Peter Zeyer and Malte Kaspereit have received full professor positions at German universities. In recognition of his scientific achievements Michael Mangold was appointed ‘außerplanmäßiger Professor’ of the Department of Electrical Engineering and Information Technology at the Otto von Guericke University Magdeburg. The group has received several awards for its scientific work. A detailed list is given in section 6 of this report.

2 Members of the Research Group

Head of the group:
Prof. Dr.-Ing. Dr.h.c. A. Kienle, Professor at OvGU, and external scientific member of the MPI

Secretary (part-time working):
Carolyn Mangold

Senior researchers:

- Michael Mangold (MPI, permanent)
- Malte Kaspereit (EU, until 08/2011)

PhD students and Postdocs:

- Robert Dürr (IMPRS, since 05/2010)
- André Franz (MPI, since 01/2008)
- Javier García Palacios (IMPRS, until 02/2011)
- Markus Grötsch (BMBF, until 04/2009)
- Mykhaylo Krasnyk (BMBF, until 06/2010, visiting scientist 03/2011 - 08/2011)
- Ganesh Paramasivan (IMPRS, until 07/2011)
- René Schenkendorf (BMBF, since 01/03/2007)
- Subramaniam Swernath (IMPRS, since 08/2008)

Researchers at OvGU:

- Ilknur Disli (BMBF/MaCS)
- Christian Kunde (OvGU, DFG)
- Thomas Müller (CDS)
- Stefan Palis (OvGU)
- Steffen Sommer (OvGU)

Sources of funding:

- MPI - Max Planck Institute
- IMPRS - International Max Planck Research School
- BMBF - Federal Ministry of Education and Research
- EU - European Commission
- CDS - Research Center for Dynamic Systems
- DFG – German Science Fundation (Deutsche Forschungsgemeinschaft)

Moreover, the PSD group received input from several guest scientists including Prof. Ramkrishna (Purdue University), Prof. Vande Wouwer (University of Mons), Prof. Svjatnyj (TU Donezk), Prof. Kulkarni (NCL Punai), Prof. Sainio (TU Lappeenranta, Finland) and was hosting a number of Master and Ph.D. students from the U.S., Switzerland, India, and Ukraine with funding from MPI, DAAD, the European Commission and the PRO3 competence network for chemical engineering.

3 Survey of Research Projects

3.1 Process Control

Project:	**Synthesis of plantwide control strategies**
Abstract:	A methodology for synthesizing plantwide control strategies for chemical processes is developed using methods from mixed integer dynamic optimization. Special focus is on highly integrated nonlinear chemical processes which are difficult to control and on robustness of the developed control schemes. Publications: [34, 35, 36, 37].
Researcher:	G. Paramasivan
Period:	since 2008
Funding:	IMPRS
Partners:	-

Project:	**Model based control of fuel cell systems**
Abstract:	Innovative control strategies for different types of fuel cell systems are developed. Multiphase behavior, nonlinearity and spatial distribution for systems with larger electrode area are explicitly taken into account. Publications: [7, 17, 18, 21, 23].
Researcher:	M. Grötsch, C. Kunde, M. Mangold
Period:	since 2007
Funding:	BMBF, MPI
Partners:	Volkswagen, Fraunhofer IZM, PSE

Project:	**Control oriented models for particulate processes**
Abstract:	The interaction of crystal formation and fluid dynamics is considered. The project's objectives are the development of reduced models for process control purposes. Publications: [13, 14, 15, 16].
Researcher:	M. Krasnyk, M. Mangold
Period:	since 2007
Funding:	BMBF, MPI
Partners:	Partners of SimPaTurS project

Project:	**State estimation of particulate processes**
Abstract:	State estimators are developed for the online reconstruction of particle property distributions like particle size distributions from available integral or distributed measurement information, like chord length distributions obtained from FBRM measurements. Publications: [2, 19, 20, 22].
Researcher:	M. Mangold
Period:	since 2006
Funding:	BMBF, MPI
Partners:	Partners of SimPaTurS project

Project:	**Control of particulate processes**
Abstract:	The project aims at stabilization of continuous particulate processes by feedback control. Besides crystallization main focus is on fluidized bed spray granulation processes. Besides established methods for finite dimensional linear systems also new Lyapunov based approaches for the present class of infinite dimensional nonlinear systems are explored. Publications: [29, 30, 31, 32, 33].
Researcher:	S. Palis
Period:	since 2008
Funding:	OvGU, MPI
Partners:	Prof. Tsotsas at OvGU, Prof. Heinrich at TU Hamburg Harburg

3.2 Process Design

Project:	**Integrated processes for the production of enantiomers**
Abstract:	Enantiomers are isomers of extreme relevance in the production of pharmaceuticals and fine chemicals. The production of pure enantiomers can be improved in various ways by a clever combination of reaction and separation steps. This project aims at developing methods and tools for systematically identifying improved process combinations and proposing new integrated processes. Publications: [8, 9, 26, 27, 28, 47].
Subproject:	Synthesis of combined processes
Researcher:	S. Swernath, M. Kaspereit
Period:	since 2008
Funding:	EU
Partners:	12 partners from European academia and industries
Subproject:	Synthesis of new integrated process for the production of pure enantiomers
Researcher:	J. García Palacios, M. Kaspereit
Period:	since 2006
Funding:	IMPRS
Partners:	-

Project:	**Advanced steady state recycling chromatography**
Abstract:	Steady state recycling chromatography is an attractive alternative to conventional batch or simulated moving bed chromatography. However, its full potential has not yet been exploited due to a lack of proper design tools. Publications: [10, 39, 44].
Researcher:	M. Kaspereit
Period:	since 2008
Funding:	MPI, DAAD
Partners:	Prof. Sainio (TU Lappeenranta, Finland)

Project:	**Global optimization of integrated multiphase systems**
Abstract:	Global optimization strategies based on convex relaxations are developed in cooperation with the Weismantel group from ETH Zurich. This requires suitable model formulations, the subsequent analysis of their structural properties and suitable optimization strategies. Publications: [1], article in preparation.
Researcher:	C. Kunde
Period:	since 2010
Funding:	OvGU, DFG SFB-TR 63
Partners:	Prof. Weismantel (ETH Zurich), partners of SFB-TR 63

3.3 Biosystems Engineering

Project:	**Optimal Experimental Design for Structure and Parameter Identification**
Abstract:	Strategies for parameter identification and optimal experimental design of biochemical systems are developed. Focus is on methods for high order nonlinear systems with a large number of parameters. Structural identifiability criteria and global sensitivity indices are used to determine the most important model parameters. Sigma points and monomial cubature rules prove to be efficient methods to evaluate covariances, parameter confidence intervals and experimental design criteria. Publications: [40, 41, 42, 43].
Researchers:	R. Schenkendorf, M. Mangold
Period:	since 2007
Funding:	BMBF
Partners:	Partners of the MODEXA project

Project:	**Virus replication during vaccine production**
Abstract:	Population balance modeling of virus replication during vaccine production in mammalian cell cultures is considered. To gain a better understanding of the underlying biological processes focus has shifted to multidisperse and multidimensional approaches. Major challenges are appropriate model formulations, and parameter identification from integral and distributed measurement information obtained from flow cytometry. Recent publications: [24], article in preparation.
Researchers:	T. Müller, R. Dürr
Period:	since 2007
Funding:	CDS, IMPRS
Partners:	BPE

Project:	**Nonlinear Dynamics of PHA production in micro-organisms**
Abstract:	In this project the effect of regulation on nonlinear behavior of continuous cell cultures is studied experimentally and theoretically. As an interesting field of application the production of biopolymers (PHA) in micro-organisms was identified. Publications: [3, 5, 6].
Researchers:	A. Franz
Period:	since 2008
Funding:	MPI, BMBF
Partners:	Prof. Ramkrishna/ Purdue University, Dr. Grammel from ESB

4 Research Highlights

In the following research highlights are given for selected projects from section 3.

4.1 Synthesis of plantwide control strategies using mixed integer optimization

Problem statement and state of the art

In chemical process control, frequently decentralized linear controllers are used, because of their ease of implementation and handling in practice. The design of such control system involves the selection of a suitable control structure and controller parameters. This is usually done sequentially by first fixing the control structure, often using linear interaction measures and sensitivities, and then tuning the control parameters (e.g. [R21]). This approach is simple and intuitive, but often leads to suboptimal solutions. Further, hard constraints on the process dynamics cannot be taken into account.

In contrast to this, our work focuses on an algorithmic approach to overcome these limitations. Mixed integer optimization is used to determine the optimal control structure and controller parameters simultaneously. Process dynamics is included explicitly into the constraints using rigorous nonlinear dynamic process models, which leads to mixed-integer dynamic optimization (MIDO) problems. Compared to previous work (see e.g. [R42] and references therein) special focus is on robustness and on highly nonlinear integrated chemical processes, which are difficult to control.

Results of this project

In the present work, different problem formulations and solution strategies were explored and compared with each other and with established heuristic design methods. Besides deterministic [34, 35] also extended stochastic problem formulations [36] were proposed to account for robustness. In the stochastic approach, disturbances are modeled by multivariate probability distributions. An analogous approach can be applied for parametric model uncertainty. The resulting objective function is a weighted sum of the expectation and the variance of process performance. It was shown that expectation and variance can be evaluated accurately and efficiently by means of monomial cubatures, which convert the stochastic optimization problem into a deterministic one. Further, it was shown that the resulting deterministic MIDO problems can be solved efficiently with a sequential approach using Generalized Benders decomposition.

First, the methods were applied to inferential control of reactive distillation columns as a challenging class of problems, which has received a lot of attention in recent literature [34, 35, 36]. Process examples range from established idealized benchmark problems to highly nonideal methyl acetate production as a real world application example. In all cases, significant improvement over existing heuristic control strategies was achieved with our approach. Most convincing results were obtained for a ternary reactive distillation column with inert. Based on a heuristic approach it was claimed in the literature [R21] that inferential control of this type of process is not possible. In contrast to this, a robust inferential control scheme with good performance was identified for this process in a systematic way with our algorithmic approach [37, 38].
Finally, application of the developed methods was also demonstrated for a complex multi column plant for the production of dimethyl carbonate [R11, 38].

4.2 Model based control of fuel cell systems

Problem statement
Fuel cells are nonlinear multiphase systems. Nonlinear effects become important when a fuel cell must undergo strong load changes. Multiphase effects are crucial for low temperature fuel cells, where liquid water or even ice may form inside the cell stack and impedes transport of gaseous reactants. For efficient fuel cell operation, control schemes are required that can cope with nonlinearities and phase changes. This includes the need for available control oriented fuel cell models.

State of the art
The majority of publications on control of fuel cells use linear control algorithms based on perfectly mixed one-phase fuel cell models [R15, R19, R30, R43]. Only a few authors take spatial dependencies into account when designing controllers, e.g. [R24, R25], where linear control algorithms are used.

Results of this project
A control oriented three-phase model for the freeze start of PEM fuel cells in automotive applications was developed in [23]. The model is able to describe the complete start-up process from freezing ambient temperatures up to nominal operation conditions and agrees well with experimental data. The interaction between nonlinear fuel cell dynamics and DC-DC converters is studied in [7]. The approach of combining a detailed fuel cell model and a detailed converter model is novel, as it combines contributions from chemical and electrical engineering. In [17] a nonlinear controller for a miniature fuel cell stack is developed that is able to bring the stack from arbitrary initial conditions to a desired temperature and humidity by manipulating the cathode air fan. The problem of fast load changes in PEM fuel cells with spatial distribution is considered in [18, 21]. A passivity based controller in combination with a nonlinear observer was proposed in order to prevent flooding or drying-out of the fuel cell. The latter results obtained the best presentation award at the annual meeting of the control engineers in Boppard/Germany in 2009.

4.3 State estimation of particulate processes

Problem statement

Measuring particle size distributions online is desirable for monitoring and controlling many chemical production processes. A direct measurement of size distributions is not possible in most cases. Often only integral quantities of a particle distribution like average size or total particle mass can be measured online, especially if the particles are small (nano-meter scale). Even if distributed measurement information is available, e.g. from a FBRM (focus beam reflectance measurement) sensor, calculating the size distribution from the measurements may lead to an ill-posed problem. In this project, state estimation techniques are studied as a method to reconstruct particle size distributions online. Parts of the results were obtained within the joint research project SimPaTurS funded by BMBF.

State of the art

In the case of FBRM measurements, detailed sensor models have been published over the last years [R34, R12, R14], so the correlation between a given particle population and the resulting measured chord length distribution seems to be well understood. On the other hand, many studies show that the inverse problem, i.e. the reconstruction of a size distribution from a chord length distribution is ill-posed and numerically unreliable. Various static methods have been proposed to solve the inversion problem [R12, R41, R20], but these are either computationally very expensive or sensitive against non-spherical particle shapes.

Results of this project

Nonlinear state estimation methods in combination with distributed process models were considered for two cases. In the first case, detailed process models with nucleation and growth kinetics are available, whereas the measurements provide only information on the average particle size. Structural observability could be shown for these processes [2]. Unscented Kalman filters [22, 2] and moving horizon estimators [22] were tested successfully for a crystallization and a granulation process. In the second case, FBRM provides detailed measurement information, while the process model used for state estimation is rudimentary and parameter free. An Extended Kalman Filter is found to be able to overcome the problem of non-spherical particles and to estimate the particle growth rate as an additional benefit [19, 20]. A presentation of the latter results achieved the best poster award on the 4th International Conference on Population Balance Modeling PBM2010.

4.4 Control oriented models for particulate processes in complex fluid flows

Problem statement

Often, the evolution of particle populations is strongly affected by the flow conditions in the fluid phase (aggregation, breakage, attrition etc.). Detailed first principle models, which describe the interaction between particle population and fluid flow accurately, are distributed in several external (space) and internal (property) coordinates and are computationally very demanding. For process design as well as advanced process control, models of low system order are required that can be solved in real time but nevertheless capture the nonlinear properties of the system.

State of the art

The design of controllers for particulate processes is usually based on models with strongly simplifying assumptions for the fluid flow, like perfect mixing or compartment approaches, e.g. [R6, R7, R13]. The resulting uncertainties in the model prediction have to be compensated by robustness properties of the controllers, at the price of slower performance of the closed loop system. Proper Orthogonal Decomposition (POD) has become popular as a model reduction method for flow systems described by the Navier Stokes equations [R18, R28, R39], but has hardly been used so far for flow systems with solid particles. One of the additional difficulties in particle system lies in the more complicated nonlinear terms, in contrast to simple quadratic nonlinearities in Navier Stokes equations. The most widely used way to reduced population balance systems is the method of moments with its generalizations [R22]. The drawback of this method is that the reduced model only describes the leading moments of a property distribution, but not the distribution itself.

Results of this project

In this project, which is a part of the joint research project SimPaTurS, reduced models of a urea crystallizer have been derived starting from a reference model with two external and one internal coordinate and using POD. Empirical eigenfunctions are generated from snapshot solutions of the reference model; the nonlinear reduced model equations follow from applying Galerkin's method of weighted residuals [14, 15]. The biggest challenge of the model reduction in this case consists in the efficient treatment of nonlinear terms during runtime of the reduced model. The best points interpolation method suggested by Nguyen et al. [R27] for parameterized functions has been applied here successfully [13]. As a result, one obtains a reduction of 3-4 orders of magnitude in system order as well as computation time [16].

4.5 Integrated processes for the production of enantiomers

Problem statement

Enantiomers are stereoisomers of extreme pharmaceutical relevance. They have identical physico-chemical properties in achiral environments, but differ frequently in their physiological effects. Therefore, typically only one of the two enantiomers is desired as a product. Classical chemical synthesis is an attractive option, but delivers only a 50:50 mixture of both enantiomers. This requires a subsequent separation to obtain the desired form. The overall yield of such an approach is limited to 50 %, which represents a major economical drawback, since enantiomers can be rather expensive. To overcome this limitation, separation processes can be combined with chemical racemization in various ways. In this project, the PSD group develops methods and tools for a systematic design of promising process candidates.

State of the art

Current process development in pharmaceutical industries largely relies on conventional separation processes. Process design focuses on individual unit operations and complete separation. A systematic evaluation and optimization of process combinations and integrated reaction separation processes is not performed. Simulated moving bed (SMB) chromatography-crystallization is the only process combination investigated in detail [11, R1]. Altogether, a significant economic potential is left unexploited.

Very few attempts were made to develop integrated SMB processes for producing a single isomer. Hashimoto et al. proposed to use side reactors for sugar isomerization [R10]. Later in [R5, R4] an internal, thermal racemization was suggested. However, the proposed concepts focus on producing the stronger adsorbing component at limited purity and do not perform a generic process development.

Results of this project

A part of the work was performed in the successful collaborative European research project IntEnant. A three-step approach was established for developing improved process combinations for the production of pure enantiomers. In the first step, qualitative criteria, like feasibility of racemization and fundamental physico-chemical properties, are applied to identify promising process candidates. In the second step, shortcut methods are applied to design single and combined processes. This facilitates evaluating the performance and narrowing down the number of candidates. The shortcuts are based on simplified models and often employ mathematical concepts from equilibrium theory [R32]. In addition to existing shortcut methods [R23, 11, 12] also new methods were developed for various types of processes [9]. In the final step, the remaining candidate(s) are subjected to a rigorous, detailed numerical optimization to identify optimal process configurations and operating conditions. The approach was applied to various industrial and model systems [9, 8, 47] The generated concepts are capable of achieving a yield of 100 % and a superior performance in comparison to the conventional approach. Successful validation for relevant pharmaceutical compounds was performed in collaboration with an industrial partner.

A second research direction was the development of new reactive simulated moving bed (SMB) processes with an internal racemization reaction. First concepts were presented during the last evaluation of the MPI. Using numerical optimization of various process options based on a simplified true moving bed model, it was shown that a spatial distribution of the racemization reaction is essential and can be very beneficial compared to side-reactor or reactor-separator-recycle concepts [26]. Using equilibrium theory, analytical expressions could be derived to explain and quantify the effects [26, 25]. Results were confirmed with a more detailed SMB model [28]. With the SMB model additional effects, due to cyclic column switching can be studied. The most promising process candidate identified in this study was a new three-zone system that confines the racemization reaction to a single zone. The concept is applicable to both the weaker and the stronger adsorbing enantiomer as target product. The concept was successfully validated experimentally for a model system [27]. The results demonstrate that this process is indeed capable of producing a single enantiomer with almost 100 % purity and 100 % yield from racemic mixtures.

4.6 Advanced steady-state recycling processes

Problem statement

Steady state recycling (SSR) is an advanced mode of operation for single column chromatographic processes. It allows for larger injection volumes compared to conventional batch chromatography [R2]. This results in only partially resolved elution profiles. These are fractionated such that the sufficiently pure leading and trailing parts are collected as products. The remaining unresolved fraction is mixed with a certain amount of fresh feed and then re-injected. After several cycles the process attains a periodic steady state. Despite its simplicity it achieves a superior performance and is of interest in various industries, including

pharmaceutical [R9] and biotechnological applications. In this project design methods and new concepts for a further performance enhancement were developed.

State of the art
The main challenge in applying an SSR process is its design. So far this could be performed only empirically or based on extensive simulation studies [R37]. An analytical approach proposed in [R2] is only valid for total separation with negligible dispersion and Langmuir adsorption isotherms.

Results of this project
In a first step, the previous theoretical design approach in [R2] was extended to arbitrary purity requirements [39]. This allows an a priori prediction of the required fractionation times as well as of the steady state itself without requiring dynamic process simulation. In a second step, a design method was proposed for more realistic conditions with significant dispersion due to mass transfer resistances and axial dispersion and general favorable adsorption isotherms [10]. The second method is based on experimental chromatograms only. It requires neither the knowledge of adsorption isotherm parameters, nor a process model. The method was successfully validated for an experimental model system [10].
Another direction of research is devoted to the development of advanced SSR processes that perform a solvent removal step in the recycle in order to overcome the dilution of the re-injected mixture. A detailed theoretical analysis was performed on the basis of equilibrium theory. The results reveal that different operational windows exist, depending on the specific position where the solvent removal is performed [44]. During the 13th Symposium on Preparative and Industrial Chromatography and Allied Techniques, (SPICA) in Stockholm, Sweden, 2010, this work was awarded with the best poster award.

4.7 Methods for model identification and optimal experimental design

Problem statement
Models of chemical and biological processes typically contain a large number of unknown parameters that have to be identified from experimental data. Especially for biological systems, experiments are time consuming and expensive, hence there is a strong need to design experiments in such a way that a maximum amount of information with respect to model identification may be retrieved from them. This project focuses on new methods for identification of chemical and biological models that can cope with the typical challenges of this class of models like strong nonlinearities, high number of unknown parameters, and small number of measurement data. The methods are tested with models of signal transduction cascades of genotoxic stress within the joint research project MODEXA funded by BMBF.

State of the art
To determine theoretical or practical identifiability of a model as a first step of a model identification process is challenging for nonlinear systems [R26]. Methods of differential algebra are able to determine identifiability of moderately complex systems [R35], but fail for large scale systems or are only able to estimate local probabilities of non-identifiability [R38]. In order to keep the model identification effort low, one is interested in focusing the identification on those parameters the model is most sensitive against. Methods for global

sensitivities exist [R40, R33], but are computationally very demanding, especially for higher order models. More efficient methods for computing global sensitivities are highly desirable. Traditional methods of optimal experimental design usually rely on design criteria based on the Fisher information matrix and the underlying linear theory [R3, R8, 4, 48]. It is well-known that the application of this theory to nonlinear systems may strongly underestimate the confidence intervals of the identified parameters. As an alternative to the Fisher information matrix, the sigma point method was introduced to optimal experimental design in this project [40] as described in the previous report.

Results of this project
The sigma point method for optimal experimental design (OED) was extended and applied to more challenging model examples. The sigma point method permits more general cost functions for OED than the traditional A-, D-, and E-criteria. By this generalization it becomes possible to design experiments that identify models with optimal predictive qualities (minimal confidence intervals of the model states), instead of just designing experiments that minimize the confidence intervals of the model parameters, which makes an important difference especially for nonlinear systems [41]. Further the sigma point method could be successfully applied to OED for model discrimination [42]. An efficient method to compute first order Sobol sensitivity indices is presented in [43]. The method exploits sigma points and monomial cubature rules and results in a considerable speed-up compared to conventional Monte Carlo approaches. Methods of structural observability in combination with a parameter free model representation were used to determine structural identifiability in [43]. Although providing only necessary identifiability conditions, these methods turn out to be highly efficient also for high order systems.

4.8 Nonlinear dynamics of PHA production in micro-organisms

Problem statement
In this project the effect of intracellular regulation on nonlinear dynamics of polyhydroxyalkanoate (PHA) formation in micro-organisms is studied experimentally and theoretically. PHA’s are biopolymers, which are synthesized by many micro-organisms under unbalanced growth conditions as an internal carbon and energy storage material. PHAs have attracted a lot of interest, since they are biocompatible, biodegradable and can be produced from renewable resources. The objective of this project is to contribute to a better understanding of the underlying dynamic processes and their interactions. In the longer term, this may guide the way to improved processes and improved products.

State of the art
PHA production in particular in Ralstonia eutropha has been studied extensively in the past (see e.g. [R31]). Nonlinear dynamics, however, has hardly been considered. Only in a recent publication the existence of multiple steady states in continuous cell cultures was discussed theoretically [R29]. However, the underlying model was rather simple and no experimental evidence was given.

Results of this project
In a first step, the focus was on poly(beta-hydroxybutyrate) (PHB) formation in Ralstonia eutropha with different substrates. For fructose and acetate substrates, a homogeneous

population of cells was observed. To account for regulatory processes, which are important during PHB formation and subsequent degradation, mathematical models with different degree of detail were constructed from metabolic flux analysis in a systematic way using a cybernetic approach. In the cybernetic approach optimal regulation in view of available resources is assumed. The models show good agreement with independent experimental data over a wide range of operating conditions. A subsequent analysis revealed that the window with multiple steady states predicted by these models is rather small [5] compared to the theoretical predictions in [R29].
Different patterns of behavior were observed for the facultative photosynthetic bacterium Rhodospirillum rubrum on acetate. Using flow cytometry segregation of cells into subpopulations with high and low PHB content, respectively, was observed and interpreted as the signature of bistability on the single cell level. Potential biological mechanisms are currently identified with a model based approach. Population balance modeling is applied to reproduce the distributions measured with flow cytometry.
It is a well-known fact that Ralstonia eutropha H16 cannot grow on glucose as the sole carbon source. However, we recently observed that it can "adapt" in surprisingly short time to grow with glucose when incubated in glucose-rich media. No mutagenic treatment [R36, R16] or longwinded cultivation processes [R17] are required in contrast to previous reports of glucose-utilizing mutants. The findings were confirmed by independent experiments conducted at University of Göttingen (Bowien, personal communication). Molecular mechanisms are further investigated in cooperation with Hartmut Grammel from the ESB group [6].

5 Teaching Activities, Ph.D. and Habilitation Projects

Besides teaching fundamentals in Systems Theory and Control Engineering for a large number of students from Chemical, Mechanical, and Electrical Engineering, the group is heavily involved in specialized studies in Engineering Cybernetics and Biosystems Engineering, which have provided excellent students doing their PhD at MPI.

Teaching activities of A. Kienle at OvGU

- Signals and Systems (winter semester, 3h/week)
- Control Engineering (summer semester, 3h/week)
- Nonlinear Process Dynamics (summer semester, 3h/week)
- Process Systems Modeling (winter semester 2009, 3h/week will be replaced in 2011 by a new course on Dynamics of Distributed Parameter Systems)
- Systems Identification (summer semester, 3h/week)
- Mathematical Modeling of Physiological Systems (winter semester, 2h/week)

The course Chemical Process Control initially given by A. Kienle is now being taught by S. Sommer and I. Disli (summer semester, 4h/week).
M. Mangold is giving a course on State Estimation (summer semester, 4h/week).
M. Kaspereit was giving a course on Industrial Chromatography (summer semester, 4h/week).

Habilitation projects finished during the period covered by this report:

- K. P. Zeyer. Nonlinear phenomena in reaction and separation processes. Defended in January 2009
- M. Kaspereit. Optimal Synthesis and Design of Advanced Chromatographic Process Concepts. In cooperation with PCF group. Defended in May 2011

PhD projects finished during the period covered by this report:

- M. Fütterer. On Design and Control of Simulated Moving Bed Processes. Defended April 2010
- M. Grötsch. Modeling, Analysis and Control of PEM Fuel Cell Systems. Defended November 2010
- J. García Palacios. Synthesis of Integrated Chemical Processes for the Production of Single Enantiomers. Defended November 2011
- G. Paramasivan. Synthesis of Plantwide Control Strategies using Mixed Integer Optimization. Submitted
- S. Schwarzkopf. Echtzeitfähige optimierungsbasierte Regelung von Stofftrennprozessen. Submitted

There are currently 7 PhD projects in progress. 3 at OvGU and 4 at MPI.
Besides, 5 - 10 Diploma and Master Projects per year are supervised by the PSD group.

6 Offers, Appointments and Awards

- 2009 Michael Mangold received the best presentation award for his contribution "Passivity based control of fuel cell systems" at the annual meeting of the control engineers in Boppard/Germany.

- 2010 Mykhaylo Krasnyk received the Otto Hahn Medal of the Max Planck Society for his PhD Thesis "DIANA - An object-oriented tool for nonlinear analysis of chemical processes"

- 2010 Together with his cooperation partners from Lappeenranta University of Technology/Finland Malte Kaspereit received the best poster award at the International Symposium on Preparative and Industrial Chromatography and Allied Techniques (SPICA) 2010 in Stockholm/Sweden for the joint contribution "Solvent removal in steady state recycling chromatography"

- 2010 Michael Mangold received the best poster award at the 4th International Conference on Population Balance Modeling (PBM) 2010 in Berlin/Germany for his contribution "Reconstruction of particle size distributions from FBRM measurements - yet another solution to a well-known ill-posed problem"

- 2010 Achim Kienle was approved as co-coordinator of the research center "Dynamic Systems" at the Otto von Guericke University Magdeburg

- 2010 Malte Kaspereit received the young professor talent award (Hochschullehrer-Nachwuchspreis) of DECHEMA

- 2010 Michael Mangold received an offer of a full professorship position (W2) at Beuth University of Applied Sciences in Berlin (rejected)

- 2010 Malte Kaspereit received an offer of a full professorship position (W2) at Friedrich Alexander University of Erlangen-Nuremberg (accepted, start in September 2011)

- 2011 In recognition of his scientific achievements Michael Mangold was appointed 'außerplanmäßiger Professor' of the Department of Electrical Engineering and Information Technology at the Otto von Guericke University Magdeburg

- 2011 In recognition of his scientific achievements Achim Kienle received an honorary doctorate from the National Technical University of Donezk/Ukraine

- 2011 Markus Grötsch received the award for the best PhD thesis of the Department of Electrical Engineering and Information Technology of the Otto von Guericke University Magdeburg in 2010

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Research Group:

Computational Methods in Systems and Control Theory (CSC)

Prof. Dr. Peter Benner

This report covers the period from April 2010 to August 2011.

1 Introduction

The research group “Computational Methods in Systems and Control Theory (CSC)“ was established on April 1, 2010, when Peter Benner took up his position as director at the MPI. For the first 5 months, until August 31, 2010, this was his secondary employment, while he still held a full-time position as full professor for “Mathematics in Industry and Technology (MiIT)“ at Chemnitz University of Technology (CUT). The position at CUT became secondary when he started full-time at the MPI on September 1, 2010. The initial 5 months at the MPI were therefore mainly used for the administrative set-up of the group, hiring on all levels (scientific and technical staff, secretary), and planning the distribution of projects between the remaining CUT group (1 Senior Researcher, 2 Post Docs, 2 Ph.D. students) and the new CSC group at the MPI. Since September 1, 2010, the CSC group has grown to currently 20 members (as of August 31, 2011), with an expected hiring of 5-8 more researchers (Post Docs and Ph.D. students) until spring of 2012. This required the definition of a new hierarchical structure of the group and a formation of research teams as described later in the “Survey of Research Projects“.

Another main challenge of the first year at the MPI was and still is the initiation of links to the other research groups at the institute as well as to other scientific entities in Magdeburg. Regarding internal collaborations, numerous discussions about possible cooperation took place, leading already to the definition of 2 research projects, one with the PCF group on reduced-basis methods for chromatographic processes, the other with the PSE (formerly PCP) group on nonlinear model reduction for dynamical models of biogas reactors. An important link to all those groups within the MPI using high-performance computing (HPC) techniques has been the initiation of the Linux compute cluster project **otto**, which is managed by CSC and, at this point, provides the highest computing power in LSA[1]. Moreover, Peter Benner joined the board of the IMPRS, 2 CSC Ph.D. students became associated and two IMPRS positions will be available for CSC students. Also, Peter Benner joined the LSA Center of Excellence “Dynamical Systems“ (CDS), and presented the CSC group's research areas there in a welcome colloquium on February 8, 2011.

With respect to external collaborations, the CSC group has established connections to the Department of Mathematics (FMA) of OvGU via teaching activities (see the corresponding section), the honorary professorship of Peter Benner (since January 24, 2011) as well as initiating first research projects (with L. Tobiska and F. Schieweck, “Divergence-free finite elements in PDE-constrained optimization of flow problems“, a DFG proposal is planned). Further contacts have been established with the Fraunhofer IFF (so far, 2 meetings took place, including a half-day workshop, where CSC and IFF members presented their current research). Also, CSC is participating in the set-up of a Neuroengineering platform in Magdeburg.

The research of the CSC group focuses mainly on computational methods for control systems, with an emphasis on advanced techniques from Numerical Linear Algebra (NLA) and HPC. On the methodological side, the derivation and analysis of new NLA algorithms and their implementation in mathematical and HPC software, with a focus on applications to dynamical and high-dimensional systems, are at the core of many research projects. The main research areas are **model order reduction** (**MOR**, aka dimension reduction or system

[1] To the best of our knowledge and as far as performance data is publicly available.

approximation), stabilization and control of dynamical systems summarized as **Computer-Aided Control Systems Design (CACSD)** and **Scientific Computing**. The dynamics of the systems under consideration are usually described by systems of ordinary or partial differential (-algebraic) equations (ODEs/PDEs/DAEs). In the past at CUT, we have mainly developed MOR methods for linear systems, including second-order systems arising frequently in vibrational and flexible multi-body systems. The research area "MOR for Mechanical Systems" is still one of the active research areas of the group, but mainly conducted at CUT. Current and future topics in **MOR** are in particular parameter-preserving methods for design and optimization as well as for uncertainty quantification (i.e., for systems with stochastic parameters), and nonlinear MOR methods based on (quadratic-) bilinearization of nonlinear terms. The latter two areas also play a major role in successful application of MOR for micro- and nano-electronic systems (see, e.g., the BMBF thematic networks SyreNe[2] (2007-2010) which particularly tackled MOR methods for VLSI design, i.e., very large electronic networks organized in hierarchical structures, and MoreSim4Nano[3] (2010-2013), both coordinated by Peter Benner) as well as in the future cooperations within the institute. Here, the application of MOR in biochemical networks, systems biology, chemical process engineering and biosystems technology will be the main focus. It is important to note that we develop MOR methods on the level of ODEs/DAEs often resulting from physical problems via black box modeling tools, but also directly approaching the problem on the PDE level, if access to the original PDE model equations is possible (which is, unfortunately, often not the case in engineering applications).

In **CACSD**, open- and closed-loop control of PDEs are investigated. Topics include preconditioning of optimality (KKT/saddle point) systems arising in open-loop control and numerical approximation of infinite-dimensional feedback as well as the associated Riccati operators via advanced NLA algorithms for matrix equations (closed-loop control). Nonlinear PDE control systems have been tackled via extending model predictive control techniques (MPC) to infinite-dimensional systems and by allowing time-varying linearizations. Other CACSD topics considered are robust control ("H_∞ control") and numerical algorithms for descriptor systems, i.e., systems with constrained dynamics (DAEs).

In the area of **Scientific Computing**, the primary focus in the recent past has been on the development of parallel numerical algorithms for distributed memory computing. Several software libraries for CACSD and MOR have been released. These activities are continued at the MPI on a much higher level by setting up and managing **otto** and deriving new algorithms for the hybrid distributed/shared memory multi-core cluster architecture of **otto**. By providing this platform also to the other research groups at the MPI, we also expect a fruitful interaction on developing algorithms on this computing platform for their application areas. With the emergence of (multi-)GPUs, i.e., graphics processors as available nowadays in every desktop computer, for numerical computations, we have also started to investigate efficient and reliable algorithms for these architectures. These often require hybrid multi-core/multi-GPU algorithms due to limited memory access of GPUs and the communication overhead resulting from the data movement if all computations would be performed on the GPU.

[2] www.syrene.org
[3] www.moresim4nano.org

A main issue in all the project areas is the efficient exploitation of structures, resulting from the given physical model. Often encountered are hierarchical structures as in integrated circuit (IC)/VLSI design and apparent in matrices resulting from the discretization of non-local operators. Other issues are certain symmetries, often resulting from physics, e.g., Hamiltonian and symplectic structures underlying many dynamical processes. We strive to develop algorithms that preserve and make use of these structures as much as possible, thereby often gaining reliability and efficiency. Also, network structures so far have played a major role in our research in IC and MEMS design, where the realizability of a reduced-order model as a network with the same properties as the original model is an important topic. We expect this to become also a crucial issue in the internal collaborations at the MPI.

2 Members of the Research Group

Tab. 1 Members of the Computational Methods in Systems and Control Theory Group

	Research Topics	**Membership**
Head of Group		
Prof. P. Benner	Numerical Linear Algebra; Model Reduction and System Approximation; Nonlinear Equations, in particular Algebraic Riccati Equations; Robust Stabilization of Linear and Nonlinear Systems; Control of Instationary PDEs; Mathematical Software; High Performance / Multicore / GPU Computing	since 04/2010
Secretaries		
J. Holzmann		since 07/2010
R. Wagner		since 04/2010
Postdocs		
Dr. U. Baur	Parametric Model Reduction; Hierarchical Matrices	since 07/2011
Dr. L. Feng	Parametric Model Reduction; Recycling Methods for Linear and Nonlinear Systems	since 08/2010
Dr. J. Saak	Mathematical Software; Optimal Control of PDEs	since 09/2010
Dr. M. Stoll	PDE-constrained Optimization; Preconditioning of Linear Systems	since 10/2010
Ph.D. Students		
T. Breiten	Nonlinear Model Reduction; Bilinear Control Systems	since 09/2010
M. Heß	Reduced Basis Method for Maxwell Equations	since 01/2011
P. Kürschner	Numerical Methods for Nonlinear Eigenvalue Problems.	since 01/2011
T. Mach	Eigenvalue Algorithms for Hierarchical Matrices and Tensors	since 10/2010
A. Schneider	Model Reduction for Linear Multi-Port Systems in IC Design	since 11/2010
J. Schneider	Uncertainty Quantification for EM Problems	since 01/2011
M. Monir Uddin	Matrix Equations Solvers for DAE Systems	since 08/2011
M. Voigt	Computational Methods for Robust Control	since 08/2010

Technical Staff		
M. Köhler	High-Performance Computing	since 01/2011
External Ph.D. Students		
A. Bruns	Model Reduction of Fluid Dynamical Systems	since 06/2011
Planned Recruitments		
Y. Zhang	Reduced Basis Model Reduction	09/2011
S. Grundel	Splines and NURBS for Response Surfaces	10/2011
J. Denißen	Dynamical Systems in Systems Biology	09/2011
N. Lang	Model Reduction & Inverse Problems for Thermo-Mechanical Systems	09/2011
M. Sahadet Hossain	Periodic Control Systems	10/2011
K. Ahuja	Recycling-Krylov-Subspaces	01/2012
A. Agwu Onwunta	Numerical Methods for Stochastic Partial Differential Equations	01/2012
Visiting Scientists		
Dr. T. Damm	TU Kaiserslautern: Stochastic Model Reduction	07/2010
Z. Tomljanović	J. J. Strossmayer University of Osijek, Croatia: Damping Optimization in Vibrational Systems	08/2010 - 09/2010
Dr. A. Remón Gómez	Universidad Jaume I, Castelló de la Plana, Spain: Multicore and multi-GPU computing	10/2010 - 12/2010
Dr. H. Mena	Escuela Politécnica Nacional, Quito, Ecuador: Simulation of Glyphosate Aerial Spray Drift	10/2010 - 12/2010
P. Ezzatti	Universidad de la Republica, Montevideo, Uruguay: Multicore and Multi-GPU Computing	11/2010 - 12/2010
Prof. M. Nakhla	Carleton University, Ottawa, Canada: Model-Order Reduction of High-Speed Interconnect Networks	12/2010
Dr. J. Rommes	NXP Semiconductors, Eindhoven, Netherlands: Model Reduction, Large-Scale Numerical Linear Algebra	12/2010
Dr. H. Mena	Escuela Politécnica Nacional, Quito, Ecuador: Simulation of Glyphosate Aerial Spray Drift	01/2011 - 02/2011
Prof. T. Reis	TU Hamburg-Harburg: Model Reduction for Networks	03/2011
Dr. M. Freitag	University of Bath, UK: Efficient Solution of Eigenvalue Problems; Inverse Problems	05/2011
Dr. D. Knezevic	MIT / Harvard, USA: Efficient Preconditioners in the Reduced Basis Method	05/2011
Prof. D. Kressner	ETH Zürich/ EPF Lausanne, Switzerland: Structure-preserv-ing Algorithms for Eigenproblems and Tensor Calculations	05/2011
P. Goyal	IIT Madras, India: Realization of the adaptive moment-matching scheme for LTI systems in MATLAB	05/2011 - 07/2011
S. Panda	DAAD student from IIT Kharagpur, India: Terminal Reduc. for LTI Systems using the TermMerg Approach	05/2011 - 07/2011

Dr. V. Sima	National Institute for Research & Development in Informatics, Bucharest, Romania: Structure-preserving Algorithms in Computational Control	06/2011 - 07/2011
F. Nuray Yilmaz	Gazi University, Turkey: PDE-Constrained Optimization	07/2011
Dr. H. Mena	Escuela Politécnica Nacional, Quito, Ecuador: Simulation of Glyphosate Aerial Spray Drift	07/2011 - 08/2011
Group at TU Chemnitz: Mathematics in Industry and Technology		
Ph.D. students: P. Losse, H. Weichelt, M. Sahadat Hossain; Postdoc: Dr. U. Baur (until 06/2011), Dr. S. Hein (until 09/2011), Dr. R. Schneider, Senior Researcher: Dr. M. Pester		

3 Survey of Research Projects

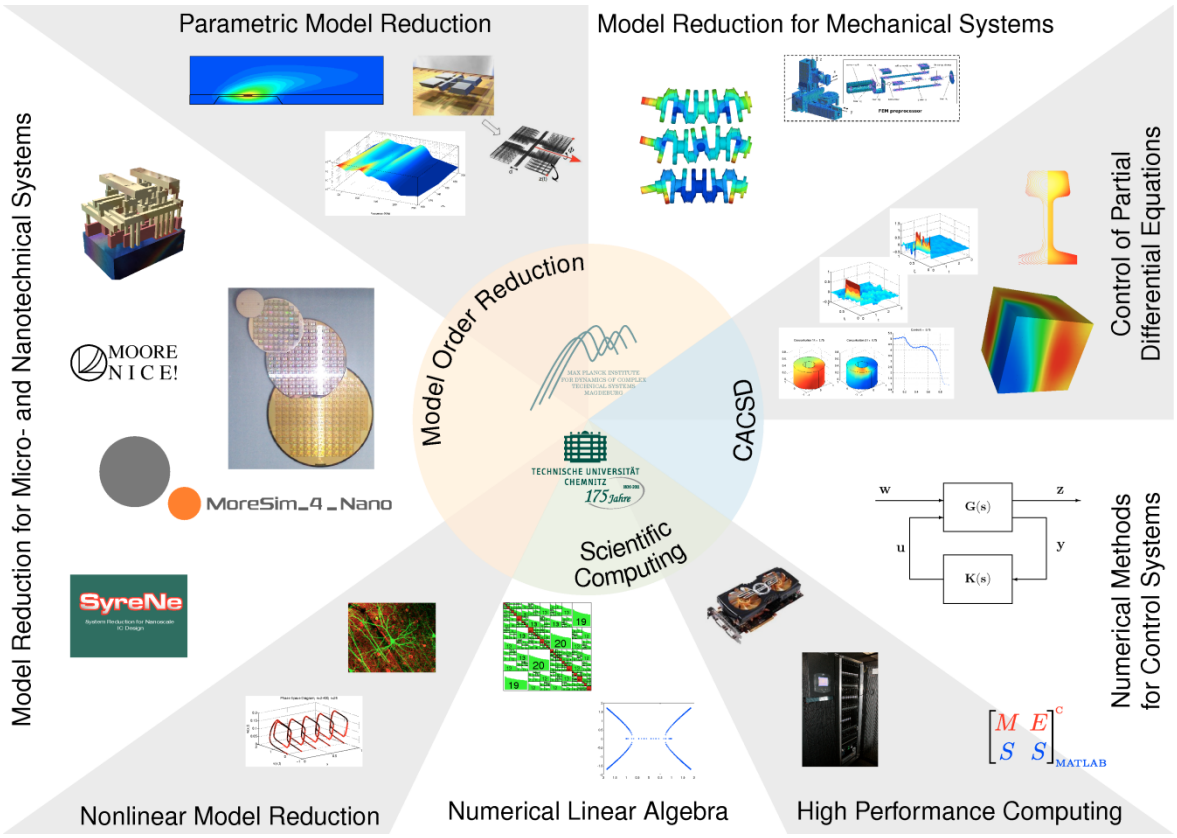

Fig. 1: Research activities of the CSC group

3.1 Model Order Reduction

Tab. 2 Research Activities MOR

Model Reduction for Micro- and Nanoelectronic Systems Coordinator: Prof. Dr. P. Benner	In this research area different model order reduction methods for the design of micro- and nanoscale integrated circuits and systems are developed. Special requirements are the consideration of linear systems with many input and output terminals, the analysis of the electromagnetic influence described by Maxwell's equations using uncertainty quantification and the treatment of nonlinear models.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Operational Model Order Reduction for Nanoscale IC Electronics	Dr. M. Striebel	EU	02/07 - 01/10	U. Antwerp Eindhoven UT NXPSemiconduct
System Reduction for Nanoscale IC Design (SyreNe): Reduced Representation of Power Grid Models	A. Schneider T. Mach Dr. U. Baur M. Sahadet Hossain	BMBF	07/07 – 12/10	TU Braunschweig TU Berlin U. Hamburg Fraunhofer Inst. NEC Europe Qimonda AG Infineon AG
Model Reduction for Fast Simulation of New Semiconductor Structures for Nanotechnology and Microsystems Technology (MoreSim4Nano), MOR Methods for Analysis of The Electro-magnetic Influence on Semicon-ductors with Parametric Uncertainties	J. Schneider	BMBF	Since 10/10	TU Braunschweig TU Berlin TU Darmstadt U. Hamburg Fraunhofer ITWM Infineon AG MunEDA GmbH X-FAB AG CST AG
Reduced Basis Methods for Electromagnetic Problems	M. Hess	MPI	Since 01/11	

Parametric Model Reduction Coordinator: Dr. L. Feng	We develop new methods for parameter-preserving model reduction, which are based on interpolation as well as hybrid techniques using system-theoretic approaches together with partial interpolation. These approaches efficiently reduce the large dimension of parameter-dependent systems as they arise in several application areas, e.g. in microsystems technology.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Model Reduction for Bilinear Systems	T. Breiten	MPI	Since 01/10	U. Bayreuth (Prof. Damm) Virginia Tech (Prof. Gugercin, Prof. Beattie)
Interpolatory Methods for Parametric Model Reduction	P. Benner	MPI Virginia Tech	Since 02/09	Virginia Tech (Prof. Gugercin, Prof. Beattie) MIT (Prof. Willcox)
Automatische, Parameter-erhaltende Modellreduktion für Mikrosystem-technische Anwendungen (MST-Param-KOMPAKT)	Dr. U. Baur Dr. L. Feng	DFG	10/06 – 06/10	TU Freiburg (Prof. Korvink)
Parametrical MOR for Structure-Fluid-Coupling	A. Bruns	Bosch	Since 06/11	Robert Bosch AG (Stuttgart)

Model Reduction for Mechanical Systems Coordinator: Dr. J. Saak	Structural models of mechanical systems usually appear in the form of second order ODEs. Most MOR approaches rewrite these into first order form and thus derive first order reduced order models (ROMs). Here we focus on the exploitation of the second order structure and the generation of second order ROMs.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Integrated Simulation of the System "Machine Tool - Actuation - Stock Removal Process" based on Model Order Reduction of the Structural FEM Model	Dr. J. Saak	DFG MPI iwb CUT	01/07 – 12/08 Since 01/09	TU Braunschweig TU Munich (iwb)
FVV Pilot Study - Modern Model Reduction Methods for Elastic Components in the Simulation of Flexible Multi-Body Systems	P. Kürschner Dr. J.Saak	FVV	01/10 – 03/11	Forschungs-vereinigung Verbrennungs-kraftmaschinen, U. Stuttgart (ITM) U. Kassel (IMK)
Model Order Reduction for Thermo-elastic Assembly Group Models	Dr. J. Saak	DFG (TR 96)	Since 07/11	TU Dresden RWTH Aachen

Model Reduction of Nonlinear Systems Coordinator: Prof. Dr. P. Benner	On the one hand, we investigate the application of snapshot-based methods (POD, RB) for application in highly nonlinear systems in process engineering applications. On the other hand, we develop a new methodology which is not snapshot-based and thus free of selecting training inputs. The reduced-order models will therefore be applicable under a wider range of operation conditions.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
MOR by Rewriting to (Quadratic-) Bilinear System Order Reduction	T. Breiten	MPI	Since 01/11	
Reduced Basis Methods for Chromatographic Processes	Dr. L. Feng	MPI	Since 04/11	MPI (Prof. Seidel-Morgenstern, S. Li)
Dynamic, Analysis and Control of Anaerobic Digestions Processes for Biogas Production	T. Breiten	MPI	11/10	MPI (Prof. Sundmacher, Dr. R. Hanke-Rauschenbach, A. Bornhöft)

3.2 Computer Aided Control Systems Design

Tab. 3 Research Activities CACSD

Control of Partial Differential Equations Coordinator: Dr. M. Stoll	Our team focuses on the numerical aspects of optimal control problems with PDE constraints. We concentrate on the efficient solution of the underlying matrix equations in the form of linear saddle point systems or matrix Riccati equations.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
All-at-Once Solution of Periodic Optimal Control Problems	Dr. M. Stoll	MPI	Since 05/10	U. Oxford (Prof. Wathen) UBC Vancouver (Dr. Rees)
Solution of Inverse Heat Conduction using LQR Techniques	Dr. J. Saak	MPI	Since 11/10	Fraunhofer IWU (Chemnitz)
Simulation of the Glyphosate Aerial Spray Drift at the Ecuador-Colombia border	Dr. J. Saak N. Lang	SENACYT EPN Quito	Since 07/09	EPN Quito (Prof. Mena)

Numerical Solution of Optimal Control Problems with Instationary Diffusion-Convection and Diffusion-Reaction Equations	Dr. S. Hein Dr. J. Saak	DFG	01/06 – 09/10	
Optimal Control-Based Feedback Stabilization in Multi-Field Flow Problems	H. Weichelt	DFG SPP253	10/06 – 06/13	U. Erlangen-Nürnberg (Prof. Bänsch)

Numerical Methods for Control Systems Coordinator : Prof. Dr. P. Benner	This research topic mainly deals with numerical algorithms for robust control and stabilization of descriptor systems. One focus is the construction of (sub-)optimal H-infinity controllers or the computation of system norms by using spectral information of certain structured matrix pencils. Another important point is the development of efficient and robust software to solve these problems.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Numerical Algorithms for Generalized Eigenvalue Problems of Even Structure with Application in Robust Control of Descriptor Systems	P. Losse M. Voigt	DFG MPI	09/06 – 09/10 Since 08/10	TU Berlin (Prof. Mehrmann) U. Kansas (Prof. Xu)
Development of the Systems and Control Library SLICOT	M. Voigt	SynOptio	Since 02/11	ICI Bucharest (Dr. Sima)

3.3 Scientific Computing

Tab. 4 Research Activities Scientific Computing

Numerical (Multi-)Linear Algebra Coordinator: Dr. M. Stoll	We study linear and nonlinear eigenvalue problems with special structures arising in control, boundary element methods, or molecular dynamics. Moreover, we investigate the solution of special linear systems of equations arising in PDE control and MOR algorithms.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Efficient Solution and Preconditioning of linear systems	Dr. M. Stoll	MPI	Since 10/11	U. Oxford (Prof. Wathen) U. Harvard (Dr. Knezevic)
Algorithms for Rank and Tensor Structured Matrices	T. Mach	MPI State Sachsen	Since 02/08	
Large Scale Matrix Equations	M. Köhler Dr. J. Saak	MPI	Since 08/11	U. of Osijek (Prof. Truhar)
Large Scale and Nonlinear Eigenvalue Problems	P. Kürschner P. Benner	MPI Université du Littoral Côte d'Opale	Since 08/11 Since 06/10	U. Eindhoven (Prof. Hochstenbach) U. du Littoral Côte d'Opale (Prof. Salam)

High Performance Computing Coordinator : Dr. J. Saak	We investigate the parallel solution of the numerical problems related to the projects of the research group. The applications range from shared memory parallelization on modern multi-core CPU workstations and graphics processors to massively parallel approaches employing the new Linux Cluster **otto** of the Institute.

Subprojects	Scientists	Funded by	Period	Partners
Development of Parallel Software Libraries (M.E.S.S.)	Prof. P. Benner, M. Köhler, Dr. J. Saak	MPI	10/07	EPN Quito (Prof. Mena)
Multicore and (Multi-)GPU Computing	Prof. P. Benner, M. Köhler Dr. J. Saak	MPI	Since 12/09	U. Jaume I (UJI) (Dr. Remón, Prof. Quintana-Ortí); U. Montevideo (Dr. Ezzatti)
Linux Cluster **otto**	M. Köhler Dr. J. Saak	MPI	Since 05/2010	

4 Research Highlights

4.1 Model Order Reduction for Nano- and Microelectronics

The work done within the project “Reduced Representation of Power Grid Models” was part of a highly connected research network “System Reduction for Nanoscale IC Design (SyreNe) funded by the German Federal Ministry of Education and Research (BMBF). The project partners as well as the research connections can be found in Fig. 2. Additionally, three industrial partners, namely Infineon Technologies AG, Qimonda AG, and NEC Europe Ltd. were involved.

Due to on-going development, see Fig. 3, the feature “structure size” of integrated circuits (ICs) decreases while, at the same time, the number of included elements increases. Linear systems arise in many of applications regarding micro- and nano-electronics, e.g., in mathematical modelling of RLC networks via modified nodal analysis. There are well investigated systems which appear during the decoupling of the linear parts of a VLSI Chip,

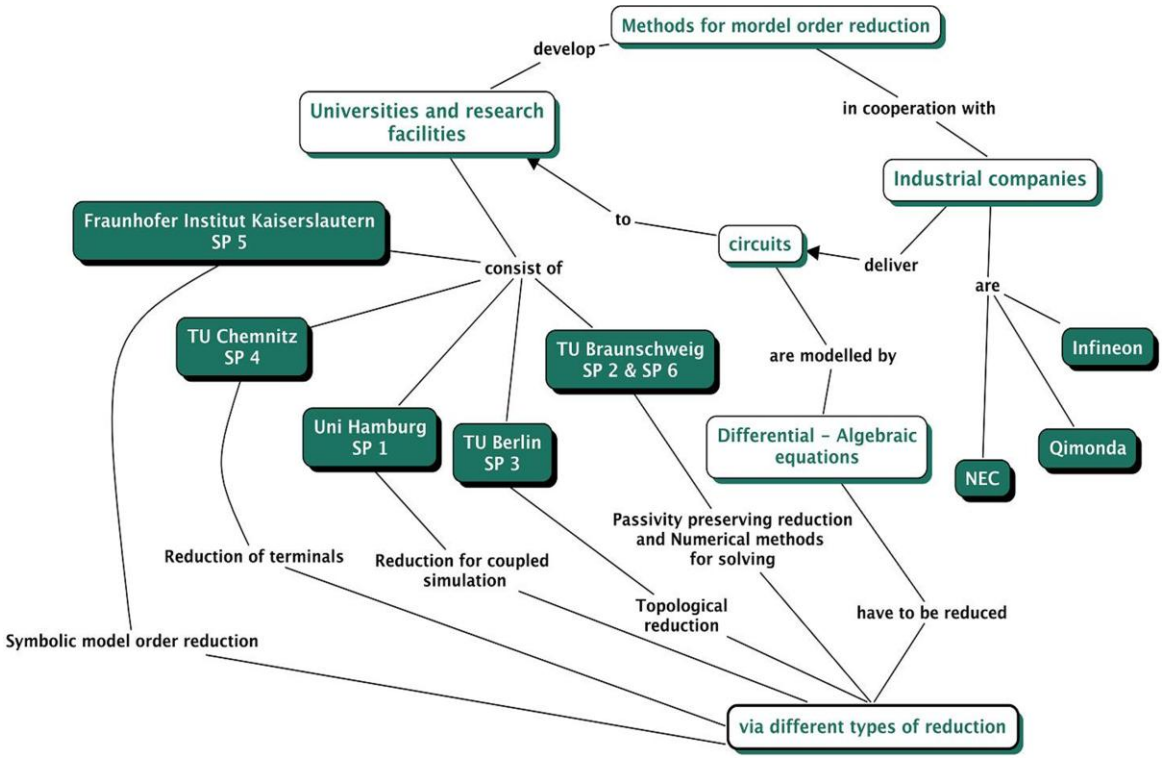

Fig. 2: SyreNe – Schematic Overview

the modelling of conducting paths and pins or during the linearization about an expansion point. In contrast to these systems, e.g., power grids or time synchronization networks cause considerable problems during the simulation. There, nearly every element of the circuit plays the role of an input or an output pin (terminal), such that the reduction of the system order with known approaches becomes numerically very complicated, often impossible. The sub-project “Reduced Representation of Power Grid Models” dealt with these special systems to create new algorithms for their terminal and order reduction and consequently for their faster solution. For the future, it is expected that this approach will also turn out in other project areas, such as in MOR methods for flexible multibody systems, where a high number of inputs/outputs arise due to coupling structures.

The main goal of our subproject is to approximate the original input-output behavior during the simulation by applying operators which map the systems matrices to those of a virtual terminal reduced system. It turned out that the ESVDMOR approach [R4, R7] is the method to be preferred. Hence, the ESVDMOR algorithm was implemented. Thereby, significant potential for numerical improvement potential was detected. Modifications that increase the numerical efficiency are described in [22]. For example, the computation of the operators needs the knowledge of the moments of the transfer function. These moments are used to define ansatz matrices which reveal, after a singular value decomposition (SVD), the significance of the terminals. Due to the use of a truncated SVD and a modern implementation, this step could be reduced to an iterative process of sparse matrix vector multiplication which is much faster than the former approach. The order reduction of the virtual system is based on the balanced truncation approach which provides an error bound [R8]. With the help of this error bound we are able to estimate the approximation error of the whole reduction a priori [24]. Also the preservation of important system properties like passivity, stability and other properties could be proven within the project [23]. More information including a full list of talks and publications as well as information about the other involved research topics and groups is available at **http://www.syrene.org.**

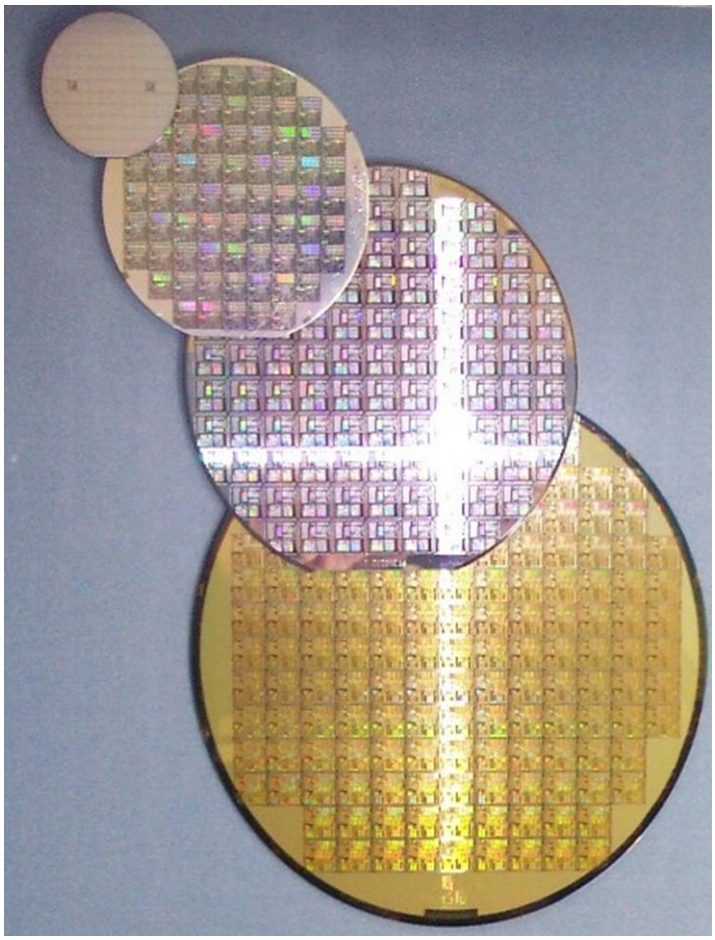

Fig. 3: Development of Wafers from 2" to 8” (Source: Wikipedia)

As sequel to SyreNe, the research network Model Reduction for Fast Simulation of New Semiconductor Structures for Nanotechnology and Microsystems Technology (MoreSim4Nano), which is also funded by the BMBF, started in October 2010. One of the key aspects of this project is the analysis of the influence of the surrounding electromagnetic (EM) field on the semiconductor structures. Besides that the variations of the feature structure size, caused by inaccuracies of the resolution during the lithography, are considered as parametric uncertainties. In the context of this project, we study the use of (spectral) collocation methods for uncertainty quantification as well as reduced-basis methods for EM fields with stochastic parameters.

4.2 Parametric Model Reduction

Model order reduction techniques are of fundamental importance for simulation, optimization and design of large-scale systems arising in many application areas, as described, e.g., in Section 4.1. These techniques can tremendously shorten computational times for transient and harmonic analysis. However, design cycles often involve parameter modifications. Standard model reduction techniques cannot be applied if the system incorporates time-varying matrices or parameters which should remain in the reduced model. Thus, we work on the development of parameter-preserving model reduction methods. Some of these methods can then also be used for model reduction of time-varying systems. The first approach is a coupling of the balanced truncation method for model order reduction of (deterministic) linear, time-invariant systems with interpolation methods. The approach is quite flexible in allowing the use of numerous interpolation techniques like polynomial, Hermite, rational, sinc, and spline interpolation [2, 3]. This approach was taken up by other research groups to investigate alternative methods for interpolating reduced-order models [see R9, R1].

For systems including more than one parameter, the problem of finding a reduced-order interpolating function over the whole parameter space is much more involved. This is due to the exponentially growing number of interpolation points for higher dimensional parameter spaces. This leads to a high computational complexity because balanced truncation must be applied many times. Furthermore, the order of the reduced-order system grows exponentially as well. Our strategy for an effective and representative choice of parameter points in higher dimensional parameter spaces is inspired by the use of sparse grids. This approach is based on a hierarchical basis and a sparse tensor product construction [R12, R13]. Significantly fewer interpolation points are needed for obtaining a similar accuracy as with interpolation in a full grid space. A coupling of balanced truncation with piecewise polynomial interpolation using sparse grid points is described in [2].

The computed reduced-order systems are accurate and allow a significant reduction of the computational time in numerical simulations. For instance, the evaluation of the reduced-order transfer function of a micro anemometer with three parameters on a grid over the whole parameter space takes 15 seconds as compared to 91.46 hours for computing the full-order transfer function on all grid points.

Furthermore, we have introduced a general projection framework for structure-preserving model reduction of parametric systems. That is, the reduced-order model has the same parameter-affine structure as the original system, parameters are preserved as symbolic quantities of the describing system matrices. The projection operators are derived using rational interpolation and are computed using rational Krylov subspaces. We proved Hermite interpolation properties with respect to the frequency variable and all parameters for the

obtained reduced-order model. The model reduction capabilities of this approach are illustrated by several numerical examples from technological applications in [1, 6, 37, 38].

4.3 Control of Partial Differential Equations

The solution of partial differential equations has been in the focus of numerical analysis for many decades as many processes in engineering and science are described by a PDE or by systems of PDEs. In the past, the solution of the PDE, i.e., forward problem, has been at the heart of many research projects. Recently with advances in algorithms and computing technology, the solution of so-called optimal control problems with respect to PDE constraints has become increasingly popular [R10]. The goal in this field is to find the parameters/setup for a particular PDE or systems of PDEs such that an objective function is minimized. The CSC group focuses on two categories of optimal control problems.

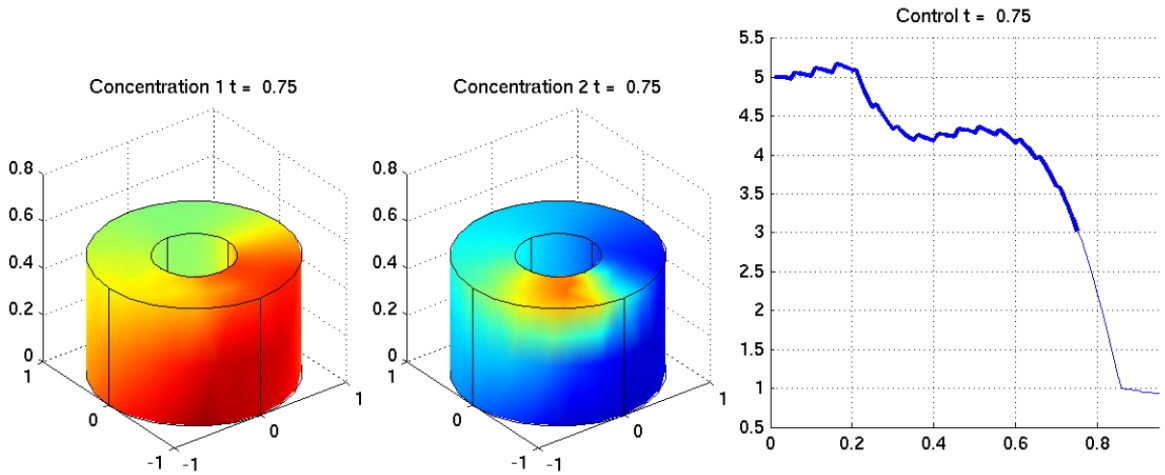

Fig. 4: LQG control of a diffusion-reaction process

Open loop Control and Efficient Solution of Linear Saddle Point Systems

The first category is the so-called open loop control problem where the system input is computed purely on the basis of a-priori knowledge. Here, we focus on the efficient solution of the optimization problem with state-of-the-art numerical techniques. The task of solving optimal control problems is challenging as most realistic problems are posed in three dimensions and the discretization, often done with finite elements, results in many degrees of freedom [R3]. At the heart of the problem typically lies the solution of the first order optimality conditions or Karush–Kuhn–Tucker (KKT) conditions and the corresponding linear system in saddle point form. For realistic scenarios it is not possible to use techniques based on factorizations to solve this problem. Hence iterative Krylov subspace solvers have to be employed. These are usually only feasible if some form of preconditioning is applied; a technique that solves a modified, simpler problem. We derived preconditioners that take the structure of the KKT system and the underlying infinite-dimensional problem into account. For steady [29, 28, 35, 33] and unsteady [31, 34, 32] problems we constructed efficient approximations to the Schur-complement of the saddle point problem, which involves the forward and the adjoint discretized PDE. In the case of unsteady problems we showed that multilevel techniques approximating only one matrix provide sufficient approximations for the Schur-complement and that independence with respect to the mesh-parameter is given. For a variety of problems, such as the (time-periodic) heat equation [31] or the unsteady Stokes

equation [34], we illustrated that only crude approximations to the discretized PDE suffice to obtain accurate results to the optimal control problem.

Closed Loop Control and Solution of Large Scale Matrix Equations

The second category of control problems studied within the research group is the one of regulator problems. These problems are described by the minimization of an objective function over a possibly infinite time horizon incorporating a feedback loop, i.e., the incorporation of certain output (observed quantities) of the current system behavior into the control input. Again, one is interested in the minimization of a functional subject to unsteady, possibly nonlinear, PDEs. In general the PDEs are rewritten as an infinite dimensional evolution equation [R2, R6], or Cauchy problem. In the case of a linear PDE the optimization problem can then be posed as a linear quadratic regulator (LQR) problem that we solve via a system theoretic approach leading to algebraic or differential Riccati equations [30]. For nonlinear PDEs this approach must be embedded in a model predictive control (MPC) scheme [25], where local linearizations around working points (or working trajectories) are employed. In any case after semi-discretization using the method of lines, a very large system of ordinary differential equations (ODEs) and related very large matrix equations are obtained. Our special focus in these approaches has been to prove the numerical feasibility of such matrix equation based approaches in the PDE context.
Examples that were analyzed by the research group include the heat equation [15] and time-dependent diffusion-advection-reaction systems [25, 16, 17, 18]. Within the DFG Special Priority Program “Optimization with Partial Differential Equations” (SPP1253), we consider the solution of a stabilization problem of the above type, with the constraint given by the linearized Navier-Stokes equation. The method of lines discretization leads to a differential algebraic equation (DAE). We again were able to follow the LQR approach and computed feedback boundary control employing the solution of a certain projected algebraic Riccati equation [4, 36]. For the Burgers equation and a nonlinear diffusion-advection-reaction (see Fig. 4) system we incorporated stochastic uncertainties within the feedback loop and showed that by application of an additional filter Riccati equation, i.e. by applying linear quadratic Gaussian (LQG) design [25, 16, 17, 18], we are able to handle the case of white noise on the measured quantities and initial conditions for the system state efficiently.

4.4 High Performance Computing

The area of high performance computing has become an increasingly important field of research during recent years. On the one hand, the growing demand for computational power can no longer be made up for by simply increasing the CPU speed for standard workstations. Thus more and more researchers need to perform computations on supercomputers. On the other hand, the introduction of multicore processors has opened up a new field of research regarding parallel computations on desktop computers [R5]. Many ideas that have been developed on shared memory supercomputers must be adapted to the special properties and capabilities of multicore machines. Moreover, these ideas must be transferred back to supercomputers where single computation nodes in a large network are also equipped with multicore CPUs. This generates hybrid parallel machines that require a new way of thought. Besides these developments modern graphics adaptors carry processor units (GPUs) that are especially powerful vector operations. With these being the central tool in linear algebra, GPUs become especially attractive for linear algebraic operations [R11].

The programming model of the GPUs is very different from the ideas used on multicore and massively parallel machines, such that new types of abstractions must be developed to make these devices accessible for a broad range of application scientists.

Fig. 5 A view on some of **otto'**s components: Cooling rack (left), some computation nodes (upper right) and storage (lower right)

The research conducted in our group is threefold. We investigate distributed memory algorithms and implementations on our Linux cluster **otto**. On single nodes of **otto**, as well as on the various workstations, we adapt our solvers to the special shared memory setup of modern multicore CPUs. In collaboration with researchers at UJI Castellón (Spain) and Universidad de la Republica Uruguay, Montevideo (Uruguay), we develop GPU versions of our solvers for large scale matrix equations.

Distributed Memory Computing on otto

At CUT we have (together with our collaboraters at UJI) developed the PLiC (Parallel library in Control) family of solvers for several problems in control and model reduction of large and possibly densely populated systems. These solvers apply methods especially attractive to massive parallelism. Development and testing has been performed using the CUT Linux cluster CHiC, as well as the different HPC resources available at UJI. In order to continue our work at the MPI we initiated the setup of **otto** which will be fully operational as of July 2011.
Researchers at the MPI can now access 16 AMD based nodes and 56 Intel based nodes equipped with 24 and 12 cores each, summing up to 1080 cores total. The cores share 96GB (AMD) and 48GB (Intel) of main memory on each node, thus giving a grand total of 4.2TB of

random access memory. For storing the results a redundant network file system with 28TB of space is installed. The peak performance of **otto** is more than 10TFlops which makes it one of the most powerful computational resources in LSA. For future extension the inclusion of special GPU-based nodes is planned.
Otto is not a restricted resource for the CSC group only, but is provided as the central resource for computations to all groups at the MPI. One of our main tasks in this project will therefore be to provide the mathematical and computer scientific knowledge to researchers from the other groups; as well as providing guidance for parallelizing simulations from the various application areas of the institute's research groups.

Shared Memory Solution of Large Scale Matrix Equations with M.E.S.S.

A strong research interest in the group is the numerical solution of matrix equations of Lyapunov or Riccati type. These equations are equally important in the balancing-based model order reduction and linear quadratic optimal control approaches for partial differential equation systems. We developed a software package M.E.S.S.[4] for such equations, which includes algorithms based on the low rank version of the alternating directions implicit (ADI) iteration [20, 30, 21, 19]. There the most costly part is the solution of certain shifted linear systems of equations. Having achieved very good results with our solvers in MATLAB for single core systems [30], we started porting the algorithms to a C language library exploiting the capabilities of multicore CPUs in the solution of these shifted linear systems [27]. Some of our ideas have also been transferred to interpolatory model reduction methods where similar shifted systems arise [26].

GPU and Multi-GPU Computing

Matrix sign-function based solvers for Lyapunov and Riccati equations are a class of solvers especially attractive for the massively parallel solution of matrix equations. These have been used in the PLiC family mentioned earlier. Recently we have been able to port some of these solvers also to the special CUDA C-language dialect used for the programming of Nvidia GPUs. With the introduction of the recent Fermi class of GPUs that are able to perform double precision computations in reasonable time, this has allowed our solvers to become a competitive alternative to standard CPU based computations. The main drawback of these implementations as compared to massively parallel versions is the very limited amount of memory that can be addressed on current GPU boards. Therefore hybrid versions using distributed memory ideas to divide the computations into blocks that can be handled by a single GPU and thus generating a multi-GPU solver constitute ongoing research [7, 8, 9, 10,11, 12, 13, 14].

5 Selected Teaching Activities and PhD Projects

Tab. 5 Teaching activities (summer term 2010, winter term 2010/2011)

Title of lecture /Seminar / Exercise Course	Place	Lecturer
Numerical Linear Algebra for Eigenvalue Problems	OvGU	P. Benner
Geometric Numerical Integration	CUT	P. Benner

[4] http://svncsc.mpi-magdeburg.mpg.de/trac/messtrac/

Differential-Algebraic Equations	CUT	P. Benner
Applied Linear Algebra	CUT	P. Benner
Numerical Linear Algebra (Exercices)	OvGU	P. Kürschner
Mathematics I – Elementary Course for Engineering Economics, BG and SPTE	OvGU	P. Kürschner M. Voigt

Tab. 6 Finished PhD Projects (since 04/2010)

Title	**Group Member**	**finished**
Dimension Reduction for Damping Optimization of Vibrating Systems	Z. Tomljanovic U. Zagreb	05/2011
Model Reduction for Time-Varying Descriptor Systems	M.-S. Hossain MiIT (CUT)	09/2011
The H_∞ Optimal Control Problem for Descriptor Systems	P. Losse MiIT (CUT)	11/2011

Tab. 7 Finished Diplom/Master theses

Title	**Group Member**	**finished**
L_∞-Norm Computation for Descriptor Systems	M. Voigt (CUT)	07/2010
Two-Sided Eigenvalue Algorithms for Modal Approximation	P. Kürschner (CUT)	07/2010
Feedback Stabilization of Unsteady, Incompressible Flow Problems via a Riccati Approach	H. Weichelt (CUT)	12/2010
H_2 Model Order Reduction – Algorithms, Implementation, Comparison	M. Köhler (CUT)	12/2010
Model Reduction for Piezo-Mechanical Systems Using Balanced Truncation	M. Uddin (KTH Stockholm)	04/2011
Solution on an Inverse Heat Conduction Problem as a Linear Quadratic Regulator Problem	N. Lang (CUT)	09/2011
Exponential Symplectic Integrators for Hamiltonian Systems	S. Meister (CUT)	09/2011

6 Selected Memberships, Appointments, Editorships, Workshop Organization

Memberships in Scientific Organizations

P. Benner:

- Deutsche Mathematiker-Vereinigung (DMV) (German Mathematical Society)
- Gesellschaft für angewandte Mathematik und Mechanik (GAMM) (International Association for Applied Mathematics and Mechanics)
    - GAMM Activity Group “Applied and Numerical Linear Algebra” (chair since 01/2009)
    - GAMM Activity Group “Dynamical Systems and Control Theory”
    - GAMM Activity Group “Optimization with Partial Differential Equations”
- Society for Industrial and Applied Mathematics (SIAM)
    - SIAM Activity Group on “Linear Algebra”
    - SIAM Activity Group on “Computational Science and Engineering”

- European Mathematical Society (EMS)
- GMA Activity Group 1.30 “Modeling, Identification and Simulation in Automation Technology”
- NICONET e. V. (Society for Developing Control and Systems Software, in particular SLICOT; chair since 07/2006)

J. Saak:

- Gesellschaft für angewandte Mathematik und Mechanik (GAMM) (International Association for Applied Mathematics and Mechanics)
    - GAMM Activity Group “Applied and Numerical Linear Algebra”
    - GAMM Activity Group “Optimization with Partial Differential Equations”

M. Stoll:

- Gesellschaft für angewandte Mathematik und Mechanik (GAMM) (International Association for Applied Mathematics and Mechanics)
    - GAMM Activity Group “Applied and Numerical Linear Algebra”
    - GAMM Activity Group “Optimization with Partial Differential Equations”
- Society for Industrial and Applied Mathematics (SIAM)
    - SIAM Activity Group on “Computational Science and Engineering”

Editorships

P. Benner

- Associate Editor of SIAM *Journal on Matrix Analysis and Applications*
- Member of the Editorial Board of *Numerical Linear Algebra with Applications*
- Guest Editor *of Linear Algebra and its Applications*

Appointments

P. Benner

- Guest Professorship at Université du Littoral Côte d'Opale, Calais (France) (2010/2011)
- Honorary Professor at the Faculty of Mathematics of the OvGU Magdeburg (since 01/2011)
- Elected member of the Managing Board of the GAMM (since 01/2011)

Conference and Workshop Organization

P. Benner

- 17th International Linear Algebra Society Conference (ILAS), August 2011, Braunschweig, Germany
- CSC-Aachen Workshop on Parametric Model Order Reduction, July 2011, Magdeburg, Germany
- 1-day Symposium on Eigenvalues, Model Order Reduction and Trust Regions in celebration of Danny Sorensen's 65th birthday, June 2011, Reno, USA
- 1st Max Planck Industrial Workshop – Bridging the gap between basic research and industrial application, May 2011, Magdeburg, Germany
- Workshop on Simulation, Identification and Optimization of Nonlinear Mechanical Systems, Magdeburg, March 2011, Magdeburg, Germany

- Workshop on Model Order Reduction in Optimization and Control with PDEs, January 2011, Berlin, Germany
- Workshop on Model Reduction for Complex Dynamical Systems, December 2010, Berlin, Germany
- ACIDS – Symposium on Analysis & Control of Infinite-Dimensional Systems, November 2010, Magdeburg, Germany

7 Future Directions

In silicio design and optimization as well as real-time control applications require the ability to simulate the forward model of a physical process very quickly. In particular, if a model contains various parameters, and parameter studies or design optimization are to be carried out, the model will often be evaluated a thousand, a million times or even more. The *curse of dimensionality* describes the fact that if facing a *d*-dimensional parameter space, discretized using a uniform grid with N points in each direction, a full parameter study will require $n=N^d$ evaluations, that is, we observe an exponential growth in the computational cost. It is therefore our challenge to overcome this curse of dimensionality. Our research in the recent past on fast NLA/HPC algorithms, including effective preconditioners, fast matrix equations and eigenproblem solvers as well as integrators for certain classes of ODEs, can be seen as an effort to accelerate each individual forward simulation. MOR, in particular parametric MOR (PMOR), has become an important tool in Computer-Aided Engineering (CAE) as it often yields a very significant reduction of the simulation times for the evaluation of a dynamical system at a given parameter configuration. The example from MEMS design (three-parametric micro-fluid sensor/anemometer model) reported in the PMOR section demonstrates acceleration factors of 20,000 and more can easily be achieved using modern PMOR techniques. It should be noted that achieving such an acceleration simply by expecting a further increase in computing power would require to wait either for more than 30 years (in a free interpretation of Moore's law, computing power of CPUs doubles every 2 years) or to employ supercomputers within the top range – the latter option is not feasible in daily engineering practice. Of course, using current multi-core/-GPU computing facilities in combination with PMOR and employing HPC algorithms, one can gain further improvements in computational speed. (It should also be noted that the computation of reduced-order models itself should be adequately fast and requires efficient NLA and HPC techniques!)
Nevertheless, PMOR and HPC alone are not able to break the curse of dimensionality as the number of evaluations in a uniformly sampled parameter space will still grow exponentially. Even if each individual evaluation becomes much faster, this will not be sufficient for systems with parameter spaces of dimension larger than 10 or even in the hundreds as occurring frequently in process engineering, systems biology and the emerging biosystems technology applications which will be the focus of the MPI in the future. Thus, one major challenge we are faced with is to combine PMOR and HPC techniques with other techniques that allow the reduction of the number of evaluations to become ideally linear in *d* (for some small integer *k*, $d\log(d)^k$ would be sufficient in most cases as well). One possibility to be explored further is sparse grid interpolation, which we have already combined with PMOR in [2, 3]. This topic will be targeted in collaboration with Michael Griebel, director of the Fraunhofer SCAI in St. Augustin. A joint Ph.D. project on using sparse grid PMOR for PDEs will start October 2011. As the topic of PMOR for multi-parametric process models is a topic in several departments

at SCAI, we hope to establish a long-lasting and fruitful collaboration between the two institutes, leading also to future joint research proposals. We also expect that the mathematical foundations laid in this area will be important to establish PMOR as a relevant simulation technique in biosystems engineering where the number of parameters is often of the same order as the number of states. This will in the future particularly be pursued in cooperation with the other research groups at the MPI as well as the CDS.

A rather new approach to break the curse of dimensionality is the use of hierarchical matrix and tensor structures. Currently, we are researching the problem of computing eigenvalues of non-local linear operators employing hierarchical matrices and tensors. But as already observed in the context of stochastic differential equations, hierarchical tensor techniques can also be used for an efficient discretization that allows a cheap evaluation when exploring the full probability space, e.g., in the context of uncertainty quantification. So far, these techniques are mostly developed by mathematicians and applied to academic examples. It is therefore our ultimate goal to combine ideas from tensor computations, particularly based on the hierarchical tensor format developed by Grasedyck, Hackbusch and co-workers as well as tensor trains recently suggested by Tyrtyshnikov and Oseledets, with sparse grid and PMOR ideas to derive simulation methods for parametric dynamical systems free of the curse of dimensionality.

Another interdisciplinary topic ubiquitous at the MPI is nonlinear MOR. The nonlinear MOR methods, developed in the CSC group, are quite effective for homogeneous nonlinearities (i.e., all or most state variables occur in the same nonlinear expression, e.g., α/xi_3 for all $i=1,...,n$ if x_i are the state variables) as encountered if the large-scale system to be reduced arises from the semidiscretization of a PDE. On the other hand, nonlinearities in biochemical networks and systems biology are often heterogeneous, i.e., the state variables appear in different nonlinear expressions due to the underlying modeling of the reaction and interaction mechanisms. MOR techniques used in this context are often physically motivated (e.g., neglecting fast reactions) or apply sophisticated techniques from nonlinear dynamics. The latter methods can often be considered as projection onto nonlinear manifolds, using for instance the *Center Manifold Theorem* or approximations based on inertial manifolds. These methods are applied analytically, and are therefore rather difficult to employ if the state-space dimension grows. Some attempts at using (approximate) inertial manifolds which allow for numerical computation also exist. In any case, the compression rates achieved by manifold methods so far are often far from those obtained by linear MOR techniques. In the future, we would like to use our expertise in efficient numerical algorithms to define hybrid algorithms that make use of the interpolatory approaches we have been developing in combination with nonlinear manifolds. That is, the main idea will be to develop a scheme that uses interpolation data provided on a suitable nonlinear manifold, thereby employing the good nonlinear approximation quality of approximate inertial manifold methods with the high compression rates achievable by interpolation methods. In this context it will be important to combine PMOR ideas with nonlinear MOR. A technique for parametric MOR of PDEs that is currently booming is the reduced-basis method (RBM). We would like to further develop this method in the direction of applications in process engineering (as in the chromatography application we are working on currently with the PCF group) and biosystems technology. Cooperation on the solid mathematical foundation will in particular be based on a networking initiative among the CSC group, the research groups of Martin Grepl and Karen Veroy at RWTH Aachen, and David Knezevic's group at Harvard University. Also, some ideas of

cooperation on RB methods and greedy sampling ideas will be explored with Bernard Haasdonk's junior research group within the Center of Excellence „SimTech“ at the University of Stuttgart.

An important challenge for many of the dynamical processes studied at the MPI is their efficient control. Often, the mathematical models of these systems consist of coupled field equations, such as reactive and diffusive processes in a fluid at varying temperatures (due to their endothermic or exothermic nature). A natural goal is thus to derive open- and closed-loop control mechanisms for these coupled systems. So far, this is mostly achieved by a full discretization, and solving the resulting nonlinear program using software like IPOPT. Current research, e.g., within the DFG Priority Program 1253 “Optimization with PDEs“, shows that this strategy is often not optimal. There is substantial evidence that deriving the optimality system on the continuous level of the field equations often yields better control strategies with a much better ratio of optimization versus simulation time. We will thus continue our efforts to derive efficient numerical methods for solving optimality systems as required in open-loop control. Moreover, we will also investigate feedback control mechanisms for coupled PDE systems for stabilizing trajectories, which are perturbed off the optimized (open-loop) path.

Last but not least, we have just started to introduce HPC at the MPI. With the installation of **otto**, whose finalization is expected for fall 2011, the simulation capacities at the MPI are raised to a completely new level. The CSC group, in particular the HPC team, will serve as a partner to all research groups within the MPI to exploit these new opportunities. We expect that the necessity of new or at least adapted algorithms for the hybrid distributed/shared memory multi-core cluster architecture of **otto** will lead to numerous joint research efforts with these groups. Also, our activities in the direction of developing software libraries for NLA computations on (multi-)GPUs will offer yet another cornucopia of HPC possibilities which we hope will find ample applications at the MPI and elsewhere.

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(Please not that this is not a complete list of publications.)

Research Group:

Systems and Control Theory (SCT)

Prof. Dr.-Ing. Jörg Raisch

This report covers the period from October 2008 to August 2011.

1 Introduction

The Systems and Control Theory Group cooperates closely with the Control Systems Group ("Fachgebiet Regelungssysteme") at Technische Universität (TU) Berlin. Both groups are headed by Jörg Raisch, who holds a full time (W3) professorial position at TU Berlin, and was also appointed by the Max Planck Society as an external scientific member (Auswärtiges wissenschaftliches Mitglied) of the Max Planck Institute for Dynamics of Complex Technical Systems.

Both groups' research interests are – not surprisingly – in the area of Systems and Control Theory (SCT). SCT has been recognized as a research area in its own right for several decades. Roughly speaking, its subject is the analysis and synthesis of dynamical systems, in particular the design of control systems. As a result, SCT provides an array of analysis and synthesis methods and tools which have been successfully applied to solve a great number of application problems. Additionally, it has served as a bridge between a variety of application areas, e. g., chemical engineering, mechanical and manufacturing engineering, economics, biology, etc. By translating specific application problems into a mathematical framework, SCT provides a common language that allows scientists and engineers with extremely diverse technical backgrounds to communicate with each other. SCT therefore has the potential to generate considerable synergy effects.

This general perspective of SCT is reflected in our research interests. We address both challenging problems from the "core domain" of SCT and – in cooperation with other research groups from the MPI and elsewhere – problems from a number of application areas. In this way, we hope both to contribute to advancing SCT as a subject and, at the same time, to help increase interaction between the diverse research fields at the MPI and to strengthen interdisciplinary research at the TU Berlin. In practice, both groups operate as a single team, with frequent joint meetings and seminars. Most of our projects involve members of both groups.

2 Members of the Research Group

As of July 30, 2011, the SCT group at the MPI Magdeburg consists of the following members:

Head of Group: Jörg Raisch (head of SCT group since March 1998, Professor at TU Berlin since Feb. 2006, Professor at OvGU Magdeburg from Sep. 2000 to Feb. 2006, and External Scientific Member of the MPI since Feb. 2002)

Senior Researcher: Dietrich Flockerzi (joined SCT 10/2003)

PhD students and Postdocs: Naim Bajcinca (since 03/2008), Katharina Holstein (since 11/2008), Yashar Kouhi (since 07/2008), Suzhou Li (since 10/2006), Dongfeng Luo (since 12/2007), Christian Schmuck (since 03/2010)

Secretary: Janine Holzmann (since 02/2004, working part time (25%) for SCT group)

As of July 30, 2011, the Control Systems Group at the TU Berlin consists of the following members:

Professor: Jörg Raisch (since 02/2006)

Senior Researcher: Thomas Schauer (since 03/2006)

PhD students and Postdocs: Adolfo Anta (since 09/2010), Olivier Bilenne (since 02/2009), Ivo Boblan (since 05/2009), Thomas Brunsch (since 09/2008), Darina Goldin (since 09/2009), Shaban Guma (since 04/2008), Anne-Kathrin Hess (since 03/2010), Steffen Hofmann (since 06/2008), Christian Klauer (since 03/2010), Holger Nahrstaedt (since 11/2007), Behrang Monajemi Nejad (since 01/2009), Vladislav Nenchev (since 05/2010), Johannes Schiffer (since 05/2011), Corinna Schultheiss (since 04/2010), Andreas Schulz (since 05/2009), Thomas Seel (since 04/2010), Raafat Shalaby (since 11/2006), Truong Duc Trung (since 10/2010), Alexej Tuchscherer (since 04/2011)

Technical and administrative support: Astrid Bergmann (since 02/2006), Ulrike Locherer (since 02/2006), Ralph Stephan (since 12/2009)

Funding

Of the 27 PhD students, postdocs and senior researchers that are currently members of the SCT Group and Control Systems Group, 10 are funded by TU Berlin or the MPI Magdeburg, and 17 are funded externally (EU, DFG, BMBF, etc.).

Former Group Members and Academic Visitors

The group is deeply indebted to the numerous former members and visitors for their collaboration and for the excellent input they provided during the period covered by this report. During this period, the following were group members: Ivan Angelov (MPI PhD student until 12/2008), Dmitry Gromov (TUB PhD student until 03/2009), Ahmed Attia (TUB Postdoc until 07/2010), Stephanie Geist (TUB PhD student until 12/2010), Carsten Conradi (MPI Postdoc until 12/2009), Vadim Azhmyakov (MPI Postdoc until 12/2008), Ishan Pendharkar (MPI Postdoc until 11/2008).

The following long-term (at least three months) visitors were or are active within the group: Mojtaba Barkhordari Yazdi (PhD student from the Iran University of Science and Technology), Diego Vieira, Eduardo Otte Hülse, Vinicius de Oliveira, Henrique Menarin, Germano Schafaschek (all final year students from the Universidade Federal de Santa Catarina (UFSC)), Emilia Ambrosini (PhD student from Politecnico di Milano), Prof. Sing Kiong Nguang (AvH fellow from the University of Auckland), Bérénice Kervazo (final year student from the University of Angers), Sneha Priya Murali, Amruta Patra (final year students from NIT Thuvakudi and Tirurchirappalli, respecively), Ciprian Pirna (PhD student fromTransilvania University of Brasov), Prof. Seong-Jin Park (Ajou University, Korea), Matteo Madaschi (PhD student from the University of Bergamo), Prof. Jianhua Zhang (East China University of Science and Technology (ECUST), Shanghai), Prof. Robert Shorten (Hamilton Institute, National University of Ireland (NUI) Maynooth), Shravan Sajja, Arieh Schlote (both PhD students from NUI Maynooth), Michele Cau (final year student from the University of

Cagliari), Yang Shaozeng (PhD student from ECUST, Shanghai), Helton Spahiu and Manush Mustafa (final year students from the University of Prishtina, Kosovo).

3 Survey of Research Projects

Some of our research projects aim at developing control synthesis methods (these are also referred to as “theoretical projects”), others at solving specific application problems. We try to keep a good balance between theoretical and application projects; we also attempt to motivate our theoretical work by immediately transferring its results into specific application projects. This is indicated in Fig. 1, where “theoretical projects” are shown close to the center of the orange disk and where projects have been arranged within “project areas”. The latter represent fairly general research fields which are meant to structure the overall research effort at the Max Planck Institute and to encourage cooperation between the Institute’s groups. In the following, we provide a list of our projects, including cooperating partners, funding sources and publications that have resulted from these projects in the period covered by this report. More detailed information on a small number of representative projects can be found in Section 4.

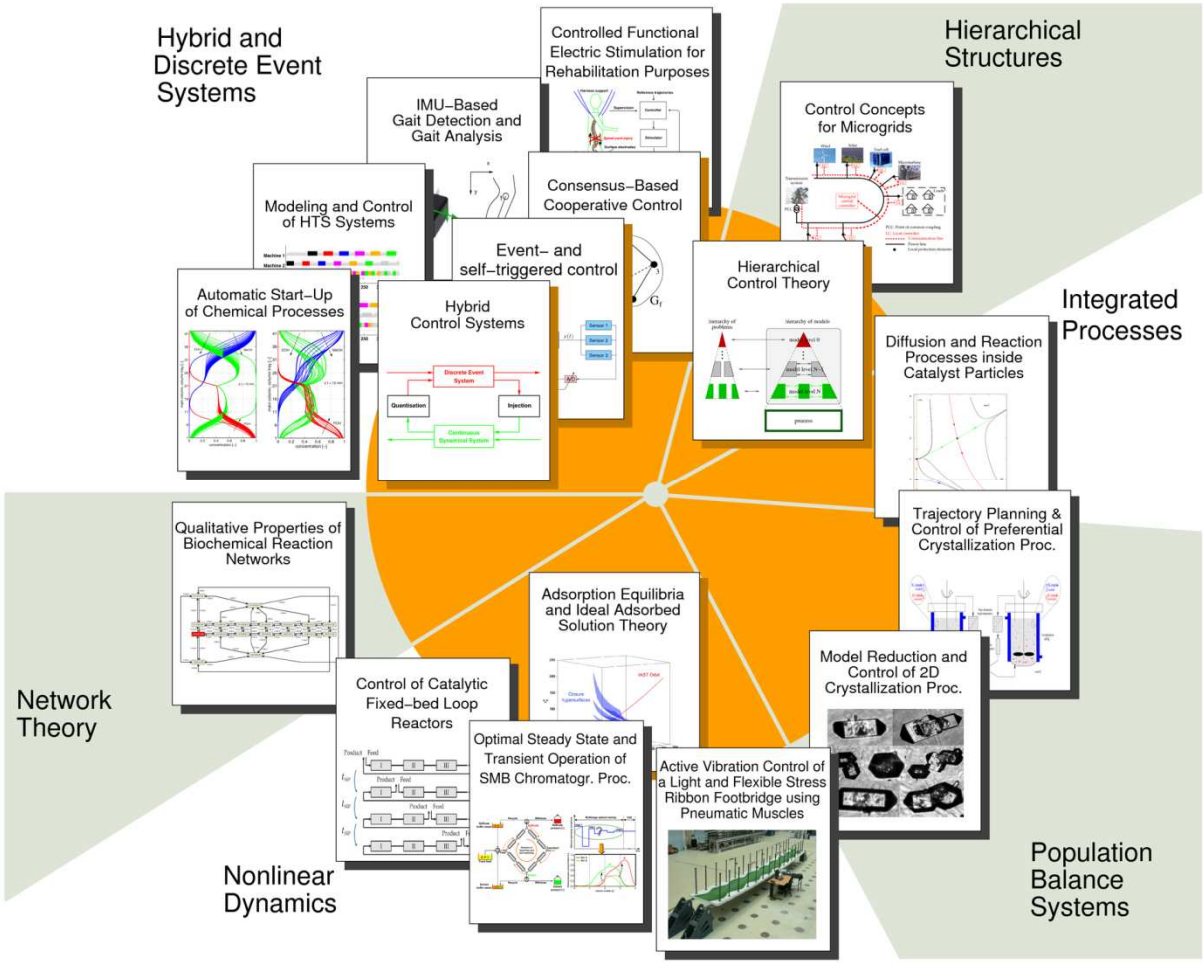

Fig. 1: Survey of research projects

Project: Hybrid Control Systems	
Hybrid control systems consist of continuous and discrete-event components. Such systems are both challenging from a theoretical point of view (this is a result of the heterogeneous nature of their state spaces) and ubiquitous in engineering applications, e.g., [R20]. We have investigated two different approaches. One is based on "safe" discrete approximations of continuous components, which translates the overall hybrid problem into a purely discrete one; in particular, in previous work, l-complete approximations were suggested as a suitable refinable abstraction technique. A short summary of the basic ideas and techniques of l-complete approximation is contained in the survey [53], while [68] shows how these approximations can be used to construct a decentralized set-valued state estimator. Recently, we have also investigated how some stability and optimality issues for specific classes of hybrid systems may be approached directly, i.e., without resorting to discrete approximations: stabilization of switched linear and nonlinear systems (e.g., [R9, R13, R25]) is treated in [65] and [78], respectively. In particular, in [46, 47, 45], the concept of common left eigenstructure assignment is exploited to achieve exponential stabilization of switched linear systems with single and multiple inputs. Finally, optimality issues for different classes of hybrid systems with autonomous switching have been investigated in [6, 5, 7]. A specific application combining elements of both approaches can be found in [33].	
Researchers	S. Geist, S. A. Attia, A.-K. Hess, Y. Kouhi, N. Bajcinca, J. Raisch
Funding	EU-HYCON, EU-HYCON2, MPI, TUB
Partners	Univ. Erlangen (T. Moor), CINVESTAV(V. Azhmyakov)

Project: Modeling and Control of High-Throughput Screening Systems	
High-Throughput Screening (HTS) plants are used for the analysis of chemical or biological substances where, for a large number of sample batches, several operations have to be executed in the same specific time scheme. This project addresses the scheduling problem for HTS processes, i.e., it aims at determining the optimal (in the sense of throughput maximization) sequence and timing for all operations during a screening run. We have focused on cyclic schedules, which considerably reduces the number of degrees of freedom. We have previously shown that within the developed framework globally optimal schedules can be computed efficiently for industrial size problems. Recent extensions concern the treatment of so-called pooling resources [56], the hierarchical nesting of cycles [55], and the design of feedback control using dioid methods [19, 21, 22, 23, 24, 20]. More information on the latter topic is presented in Section 4 of this report.	
Researchers	T. Brunsch, J. Raisch
Funding	EU-DISC, DAAD-Procope
Partners	CyBio AG, Univ. of Angers (Laurent Hardouin)

Project: Automatic Start-up of Chemical Processes	
During start-up of chemical processes, a wide operating range has to be covered, and a single linearized model is therefore not adequate for control synthesis. Start-up also often involves switching between distinct regimes and then exhibits both continuous and discrete features. In the past, we applied several methods developed in the context of our hybrid systems project to address start-up problems for specific plants. Recently, we have addressed a benchmark problem from the EU Network of Excellence HYCON, the optimal start-up of a novel open-plate reactor [42]. In cooperation with BASF AG, we have also developed a benchmark problem for the EU Network of Excellence HYCON2. This problem is concerned with the start-up of an integrated thermal separation unit.	
Researchers	D. Gromov, S. A. Attia, S. Geist, J. Raisch
Funding	BASF AG, EU-HYCON2, TUB
Partners	BASF AG

Project: Consensus-Based Cooperative Control	
Consensus algorithms, which have been used in the field of distributed computing for decades, have recently attracted renewed attention because they can be exploited for distributed cooperative control. Coordination between entities in a group requires that they share information over a network, which is usually modeled as a directed or undirected graph, and develop a consistent view regarding objectives and relevant information on the environment, i.e., reach a consensus. Within this context, we have investigated the following issues: (i) a specific class of consensus algorithms is the so-called max-consensus, which is particularly important in applications such as minimum time rendezvous and leader election, e.g., [R28]. In particular, we have proposed an approach that uses results from the field of max-plus algebra to analyze max-consensus algorithms in both time-invariant and time-variant communication topologies [62, 63]. (ii) We have also investigated convergence properties of consensus algorithms, characterized by the Laplacian matrix of the communication graph, for agents with double integrator dynamics. Position and velocity information is exchanged between the agents via different undirected communication networks. It turns out that consensus can be achieved even if neither of the two networks is connected [35, 34]. A similar scenario (identical directed communication graphs for position and velocity) is treated in [R32]. (iii) We have used cooperative communication and distributed optimization techniques to maximize the lifetime of wireless sensor networks in the context of slow-fading communication channels [16].	
Researchers	B. M. Nejad, D. Goldin, S. A. Attia, O. Bilenne, J. Raisch
Funding	Deutsche Telekom Stiftung, EU-HYCON2, HC3, TUB
Partners	Telecommunication Networks Group at TUB (A. Wolisz)

Project: Event- and Self-Triggered Control	
Event-triggered and self-triggered control have recently been proposed as implementation strategies that considerably reduce the resources required for control, e.g., [R1, R14]. The underlying idea behind these paradigms is to reduce the usage of the communication bandwidth by transmitting data only when needed to ensure the desired stability properties. Most of the existing techniques focus on the case of a single loop where all sensors are collocated. Such an assumption does not hold in many cases. Our work [67, 3] considers instead control systems where physically distributed sensors, controllers and actuators communicate via a shared wired channel. For this matter, we first develop a new prescriptive framework in [66] based on hybrid Lyapunov functions. This framework is then used to develop event-triggered and self-triggered strategies for distributed control loops (e.g., [R29]). Moreover, this approach allows us to recover and improve previous existing techniques for the case of collocated control loops. This work represents the first step towards a more fundamental question in distributed networked control: given a set of physically distributed sensors and actuators, how should communication between the different nodes be scheduled?	
Researchers	A. Anta
Funding	Alexander von Humboldt Foundation
Partners	R. Postoyan (CNRS Nancy, France), D. Nesic (Univ. of Melbourne, Australia), P. Tabuada (UCLA, USA)

Project: Controlled Functional Electrical Stimulation (FES) in the Rehabilitation of Spinal Cord Injured Persons and Stroke Patients
Electrical nerve-stimulation of paralyzed muscles can be used to generate muscle contractions. In combination with appropriate sensor technology and feedback control, this can be exploited to elicit functional movements, such as walking [60, 58, 61, 70, 71, 72], cycling [30, 1], reaching and grasping [43, 44], and even swallowing [59, 73]. Depending on the degree of disability, the goal may be temporary assistance, e.g., during re-learning of gait, or permanent replacement of lost motor functions (neuro-prostheses). In the context of control, the most challenging aspects are the complex interaction between FES, robotic support [54] and residual motor function of the patients, and the fact that for certain tasks as, e.g., walking or grasping, control has to cope with discrete changes of otherwise

continuous dynamics caused by interaction with the environment. In order to realize feedback control schemes, a number of sensor technologies are investigated such as inertial measurement units (IMUs) [61], bioimpedance [57] and electromyography [74, 75] for monitoring human movement.	
Subproject: Control of Endeffector-Based Rehabilitation Robotics in Combination with Electrical Stimulation for Gait Training after Stroke	
Researchers	T. Schauer, H. Nahrstaedt, R. Shalaby, J. Raisch
Funding	BMBF, TUB, Egyptian Government (scholarship)
Partners	Fraunhofer Institute for Production Systems and Design Technology (H. Schmidt, J. Krüger), Charité-Universitätsmedizin (S. Hesse), HASOMED GmbH, Politecnico di Milano (E. Ambrosini, S. Ferrante)
Subproject: Development of a Portable Endeffector-Based Hand/Arm Rehabilitation Robot combined with Functional Electrical Stimulation	
Researchers	D. Luo, T. Schauer
Funding	TUB, Chinese Academy of Sciences, MPI
Partners	Charité Universitätsmedizin Berlin (S. Hesse)
Subproject: Bioimpedance-Controlled Neuro-Prosthesis to Support Swallowing	
Researchers	H. Nahrstaedt, T. Schauer, J. Raisch
Funding	BMBF (Innovation Award 2009 for Medical Technology)
Partners	Unfallkrankenhaus Berlin (R. Seidl)
Subproject: Multimodal Neuro-Prosthesis for Daily Upper Limb Support	
Researchers	C. Klauer, T. Schauer
Funding	EU-MUNDUS (Strep FP7)
Partners	Politecnico di Milano (G. Ferrigno), ETH Zürich (S. Micera), TU Wien (M. Gföhler), TUB Machine Learning Group (K.-R. Müller), Hocoma AG
Subproject: Prospective Study on Breathing Synchronized Electrical Stimulation of the Abdominal Muscles in Patients with Acute and Chronic Tetraplegia	
Researchers	T. Schauer, R. Stephan
Funding	DGUV (Deutsche Gesetzliche Unfallversicherung), TUB
Partners	Unfallkrankenhaus Berlin (R. Seidl)
Subproject: Iterative Learning Control of FES-Assisted Gait Training/Drop Foot Stimulator	
Researchers	T. Seel, T Schauer, H. Nahrstaedt, J. Raisch
Funding	TUB
Partners	Charité-Universitätsmedizin Berlin (S. Hesse)

Project: IMU-based Gait Phase Detection and Gait Analysis in Amputees wearing Lower Extremity Prostheses	
This project is concerned with inertial measurement units (IMUs) that are attached to lower limb segments and provide accelerometer and gyroscope signals in three dimensions. In order to determine the position and orientation of the segments and the corresponding joint axes and angles from the raw data, one needs to develop appropriate online and offline estimation schemes that account for measurement biases. Unlike previous results [R22, R11], our approach will exploit the geometrical constraints induced by the joint mechanics instead of requiring complex calibration movements or exact sensor mounting. Furthermore, discrete events like heel strike and toe-off must be detected to determine the current gait phase, and a corresponding automaton model will be generated and updated online. The outlined measurement system will be designed to work on both the artificial and the healthy leg, and its accuracy and reliability will be compared to those of an optical 3D measurement system.	
Researchers	T. Seel, T. Schauer
Funding	BMBF (Innovation Award 2010 for Medical Technology)

Partners	TU Berlin Biomedical Engineering Group (M. Kraft), Orthopädische Klinik der Medizinischen Hochschule Hannover, Rehabtech Research Lab GmbH, Otto Bock HealthCare GmbH (S. Oehler)

Project: Qualitative Properties of Biochemical Reaction Networks

In this project, we have investigated whether a proposed biochemical reaction network with unknown or incompletely known parameters can generate an observed qualitative behavior. Clearly, if this is not the case, the suggested structure has been falsified and can be excluded from further consideration. The focus has been on mass action networks described by ODE models and their ability to admit the existence of multiple steady states (multistationarity) as a prerequisite for bi-stability. For mass action networks with certain structural properties, conditions for multistationarity are derived. These conditions take the form of linear inequality systems that are independent of parameter values [25, 27, 69, 26]. Some realistic reaction networks, however, do not possess the required structural properties. To address this problem, a unique decomposition has been proposed such that necessary and sufficient multistationarity conditions for the resulting subnetworks are guaranteed to take the form of linear inequalities. Given multistationarity in a subnetwork, an algorithm for the computation of rate constants in the overall network is proposed that guarantees steady states close to those of the subnetwork [31, 76]. These results are currently applied to networks describing the post translational modification of proteins (PTM networks). Such PTM networks are, for example, biochemical realizations of check points controlling the cell cycle (e.g., Sic1 in budding yeast). Another line of research investigates the Jacobian of mass-action network models and establishes conditions for points where the networks possess saddle-node type steady states. This has been successfully applied to a double-phosphorylation mechanism. Finally, together with the Biophysics Group at OvGU, D. Flockerzi has investigated bi-stability effects in gene regulation of *Rhodobacter Sphaeroides* [64], which explain the switch between aerobic and anaerobic mode.

Researchers	C. Conradi, D. Flockerzi, K. Holstein, J. Raisch
Funding	BMBF, MPI, EU-HYCON2
Partners	SBI Group, ARB Group, ETH Zürich (J. Stelling)

Project: Hierarchical Control Theory

Hierarchical control represents an attempt to handle complex problems by decomposing them into smaller sub-problems and reassembling their solutions into a “functioning” hierarchical structure, e.g., [R7]. In prior work, we have proposed a formal synthesis method that guarantees that the resulting overall control scheme does indeed satisfy the overall specifications if the sub-problem solutions meet suitably defined “local” specs. We are currently mostly interested in the implications of tightening/relaxing subsystem specifications, in characterizing achievable performance for specific control architectures, and in demonstrating the potential of the suggested approach by applying it to specific examples. [29] and [36] describe its application to a multi-product batch plant and a chromatographic batch separation process, where the plant topology can be switched online. [4] proposes a hybrid chemical engineering benchmark for hierarchical control.

Researchers	D. Gromov, S. Geist, A.-K. Hess, J. Raisch
Funding	DFG, TUB
Partners	Univ. Erlagen (T. Moor), PCF Group, FG Dynamik und Betrieb technischer Anlagen at TUB (G. Wozny)

Project: Control Concepts for Microgrids

Many renewable energy sources, such as wind or solar power, are uncertain by nature and thus not completely controllable. A large proportion of renewable sources comes from small-scale distributed generation and is connected to the low and medium voltage level. This is where also most loads can be found. Thus it seems natural to attempt balancing consumption and generation locally. The resulting local (micro) grids may be connected to the main distribution network, but can also be operated in

"island mode" during faults in the main grid [R17]. This scenario implies a number of challenging control problems, e.g., [R19], which we have recently started to investigate in cooperation with Siemens AG. These include choosing a suitable control architecture, handling the transition between connected and island modes and guaranteeing stability and performance in the presence of uncertainty which is inherent in renewable energy generation, e.g., [R12].	
Researchers	J. Schiffer, T. D. Trung, A. Anta, J. Raisch
Funding	Siemens AG, AvH-Foundation, Vietnamese Government (scholarship)
Partners	Siemens AG

Project: Trajectory Planning and Control of Preferential Crystallization Processes	
In this project, we investigate trajectory planning and feedback control of preferential crystallization processes for the separation of enantiomers. Our current research builds on prior work describing the use of orbital flatness properties for the control of certain classes of crystallization models. Detailed information on this project can be found in Section 4 of this report.	
Researchers	S. Hofmann, I. Angelov, J. Raisch
Funding	DFG
Partners	PCF Group (M.-P. Elsner, M. Eicke, A. Seidel-Morgenstern)

Project: Model Reduction and Control of 2D Crystallization Processes	
Crystallization models that take into account direction-dependent growth rates give rise to multi-dimensional population balance equations. We have investigated two problems for such systems: (i) D. Flockerzi has proposed a model reduction technique based on the quadrature method of moments [37, 77]. This method has been applied to a number of example problems, e.g., the direction-dependent growth of barium sulphate needle-shaped crystals, and has been shown to compare favorably to a number of alternative reduction methods. (ii) In practice, crystal shape is an important feature, and appropriate control schemes are therefore of paramount importance. Traditional techniques mostly use chemical additives for blocking or promoting the growth of certain crystal faces [R31]. In contrast, our work is based solely on the appropriate control of temperature. In particular, by "driving" the system through an appropriate sequence of growth and dissolution modes, it is possible to achieve morphologies which cannot be reached through a pure growth process [R27]. Switching is realized by determining suitable state manifolds. [9] investigates several optimal control problems for the single crystal case, and [13] proposes a convenient reformulation of the optimization problem as a convex program. These approaches have been carried over to crystal population systems in [12].	
Researchers	N. Bajcinca, D. Flockerzi
Funding	MPI
Partners	PSE Group (C. Borchert, K. Sundmacher), Fraunhofer Institute for Factory Operation & Automation

Project: Control of Catalytic Fixed-bed Loop Reactors	
An application for the use of catalytic fixed-bed reactors is the combustion of VOCs (volatile organic compounds) in industrial exhaust gases. This requires reactor temperatures above a certain ignition level. For the sake of energy efficiency, an auto-thermal mode of operation is desirable. In cooperation with the PCF group, we have recently started to investigate the control of a specific reactor configuration, the so called loop or simulated moving bed reactor (SMBR), where several feed locations can be realized using switching valves, e.g., [R3, R26]. We are mainly interested in robust switching schemes that ensure auto-thermal operation even in the presence of disturbances in the feed concentration and the gas flow velocity. An additional requirement is the prevention of local overheating which could damage the catalyst.	
Researchers	C. Schmuck
Funding	MPI
Partners	PCF Group (V. Zahn, A. Seidel-Morgenstern)

Project: Optimal Steady State and Transient Operation of SMB Chromatographic Processes

Simulated Moving Bed (SMB) chromatography integrating fractionation and feedback (FF-SMB) was proposed as a promising new concept by the PCF Group in 2007 [R16]. An overview on various SMB modifications can be found in [R23, R24]. Together with the PCF group, we have investigated model-based optimization of various FF-SMB configurations. In [49], it was demonstrated that optimal FF-SMB with fractionation of one outlet outperforms standard SMB both in terms of feed throughput and desorbent consumption. Fractionation of both outlets was investigated in [50], and it could be shown that achievable performance improves further. In [51], we successfully explored the possibility to enhance the potential of FF-SMB by additionally enriching the recycled fractions before feeding them back into the SMB unit. Another part of this project is concerned with the optimization of transient procedures for SMB processes. In particular, we have developed new multistage optimal startup and shutdown strategies [48, 52]. For this, we suggest a specially tailored decomposition algorithm to guarantee computational tractability. By examining a separation example with Langmuir isotherm, the feasibility of the solution algorithm is demonstrated. The results illustrate that the proposed start-up and shut-down procedures not only significantly shorten transient duration, but also drastically reduce desorbent usage. Furthermore, it can be guaranteed that the required product quality is also achieved during the transient phase.

Researchers	Suzhou Li
Funding	MPI
Partners	PCF Group, Y. Kawajiri (Georgia Tech)

Project: Adsorption Equilibria and Ideal Adsorbed Solution Theory

The competitive adsorption isotherms are the most essential information for the design and optimization of separation processes based on selective adsorption. In joint work with the PCF group [41], based on ideal adsorbed solution theory, a competitive adsorption isotherm model is derived for binary mixtures characterized by single component isotherms which are second order truncations of higher order equilibrium models. Here, analytical representations of the competitive isotherms are determined explicitly. Moreover, we have developed a new approach to solve the nonlinear equilibrium equations for mixtures with an arbitrary number of components characterized by rather general non-decreasing single component adsorption isotherm behavior. In addition, we have derived an analytical expression for the Jacobian of these equilibrium loadings revealing its hyperbolicity. This explicit form of the Jacobian improves significantly the numerics for multi-component adsorption dynamics. In related work with the PSD group on chromatographic processes, we provide spectral results for adsorption equilibria described by Modified Langmuir and Bi-Langmuir isotherms, and answer questions on strict or non-strict hyperbolicity and on the existence of watershed points. For ternary systems we show that hyperbolicity in the positive orthant may fail.

Researchers	D. Flockerzi
Funding	MPI
Partners	PCF Group, PSD Group

Project: Active Vibration Control of a Light and Flexible Stress Ribbon Footbridge using Pneumatic Muscles

In the lab of the Conceptual and Structural Design Group at TU Berlin, there is an experimental Carbon Fiber Reinforced Plastics (CFRP) stress ribbon bridge with 13 meters span. Its lightness and flexibility result in high vibration sensitivity. To reduce pedestrian-induced vibrations, very light pneumatic muscle actuators are placed at handrail level to provide control inputs. Based on a reduced discretized analytical model for the bridge [18], we have designed a multivariable velocity feedback control strategy to actively damp the first three vertical modes. To handle the nonlinearities of the muscle actuator, a subsidiary nonlinear force controller has been synthesized using exact linearization methods [17]. The resulting control scheme was validated in simulation and experiment. It is an attractive alternative to approaches where only passive damping (e.g., [R33]) is used.

Researchers	T. Schauer
Funding	TUB
Partners	Conceptual and Structural Design Group at TU Berlin (M. Schlaich, A. Bleicher)

Project: Diffusion and Reaction Processes inside Catalyst Particles	
In the analysis of the diffusive transport and chemical reaction of species inside a porous spherical catalyst particle, there arise mixed boundary value problems for coupled Lane-Emden equations. We have investigated the existence of solutions for such boundary value problems: By means of integral manifold theory we transform them into terminal value problems and comment on numerical implementations [32].	
Researchers	D. Flockerzi
Funding	MPI
Partners	PSE Group (K. Sundmacher)

4 Research Highlights

Our research has benefitted from numerous collaborations with colleagues from within and outside the MPI. It has also benefitted from participating in a number of (third party funded) interdisciplinary research initiatives. Amongst these are:

- The EU Network of Excellence **HYCON**: Hybrid Control – Taming Heterogeneity and Complexity of Networked Embedded Systems was active until the end of 2008 and involved 26 partners from 10 European countries. It aimed at establishing a durable community of researchers and practitioners, who develop and apply the hybrid systems approach to the design of networked embedded control systems, which are increasingly common in all major application areas.
- The European Embedded Control Institute (**EECI**) is an important outcome of HYCON. It is hosted by Supelec in Gif-sur-Yvette, but consists of individual and institutional members from different European countries. It aims at becoming a long-term world-wide renowned focal point by stimulating new collaborative (multi-national and multi-disciplinary) research on networked and embedded control.
- The International Curriculum Option (**ICO**) of Doctoral Studies in Hybrid Control for Complex, Distributed and Heterogeneous Embedded Systems is another long-term outcome of HYCON. It is a network of currently 17 European universities and, through institutionalized exchange programs, regular summer schools and meetings, provides a stimulating environment for Ph.D. students working on various aspects of hybrid control systems.
- **DISC** – Distributed Supervisory Control of Complex Plants is a European (Framework 7) Research Project involving 10 partners from 7 countries. It has started in September 2008 and aims at developing DES (discrete event systems) methods that exploit concurrency and modularity of large plants to reduce computational complexity.

- **The European Network of Excellence HYCON2** (Highly Complex and Networked Systems) started in September 2010 and will last four years. It aims at stimulating and establishing a long-term integration in the strategic field of control of complex, large-scale, and networked dynamical systems. It focuses in particular on the domains of ground and aerospace transportation, electrical power networks, process industries, and biological and medical systems. It involves 25 partners from 7 countries.
- **MUNDUS** (MUltimodal Neuroprosthesis for Daily Upper limb Support) is a small/ medium scale focused research project (STREP) funded by the European Commission within the 7th Framework Program. It is composed of 8 partners from both academia and industry. It started in 2010 and will run until 2013. MUNDUS aims to provide an assistive framework for recovering interaction capabilities of severely motor impaired people. The designed control systems will adapt to the level of severity or progression of the disease and will allow interaction via detecting the patients' movement intentions through various techniques.
- **RehaRobES** is a BMBF (Federal Ministry of Education and Research) funded project involving four academic and industrial partners, which started in 2007. It aims at developing control methods for novel rehabilitation systems combining end-effector based rehabilitation robotics and functional electrical muscle stimulation. It is expected that such systems will drastically improve the quality of gait training for stroke patients.
- **BigDysPro** is a joint project with the Trauma Hospital Berlin, which won the BMBF Innovation Award 2009 for Medical Technology (Innovationspreis Medizintechnik 2009). It is part of our research efforts in the area of FES (Functional Electrical Stimulation) for rehabilitation purposes and aims at supporting the process of swallowing for people who suffered strokes or craniocerebral injury.
- **meb-Go** is a joint project with the TUB Biomedical Engineering Group, the Hannover Medical School, Rehabtech Research Lab GmbH, and Otto Bock HealthCare GmbH. It aims at providing efficient and accurate estimation techniques to improve gait analysis for amputees with lower extremity prostheses. The project proposal won the BMBF Innovation Award 2010 for Medical Technology (Innovationspreis Medizintechnik 2010).
- Together with Andreas Seidel-Morgenstern's PCF-group we are involved in a DFG-funded research project ("Paketantrag") on Modeling and Control of Racemic Mixtures using Preferential Crystallization.

- We participate in the International Max Planck Research School (**IMPRS**) for Analysis, Design and Optimization in Chemical and Biochemical Process Engineering.
- **Network Mathematics** is a graduate program initiated by the Hamilton Institute at NUI (National University of Ireland) Maynooth and Trinity College Dublin with a number of international partners. It is built on the idea of a "virtual faculty": members of partner institutions have provided courses in the core scientific areas that form the building blocks of networking research: this includes stochastics; dynamics, optimization, and selected topics in linear and multi-linear algebra, together with a number of application courses. Our group participates in a twofold way: J. Raisch delivers courses on Discrete Event and Hybrid Systems, and Ph.D. students from the group attend courses given by other "virtual faculty" members.

In the following, we highlight a few of our group's research activities. The selection is meant to provide an idea of our research philosophy and therefore includes both projects of primarily theoretical focus and applied focus. On the more theoretical side, we briefly describe the use of dioid algebras for the control of high-throughput screening (HTS) systems. On the application side, we include two projects addressing problems in chemical engineering and medical engineering. The chemical engineering project has been investigated in close collaboration with other groups at the MPI.

4.1 Modeling and Control of HTS Systems

High-throughput screening (HTS) has become an important technology to rapidly test thousands of biochemical substances. In the pharmaceutical industries, for example, HTS is often used for a first screening in the process of drug discovery. In general, high-throughput screening plants are fully automated systems containing a fixed set of devices performing liquid handling, storage, reading, plate handling, and incubation steps (see Fig. 2). All operations which have to be conducted to analyze one set of substances are combined in a so-called batch. A set of substances consists of up to 1536 compounds which are aggregated on one microplate. Additional microplates may be included in a batch to convey reagents or waste material. To compare the screening results of different compound sets, the single batch time scheme, i.e., the sequence and the timing of activities for one batch, needs to be identical for all batches.

This project has been a long-running one involving several partners, most notably CyBio AG, a leading manufacturer of HTS plants. The project was first concerned with solving a specific scheduling task for HTS plants, namely to determine a sequence and a time scheme for all operations that will lead to maximal throughput or, equivalently, will need minimal time to finish a given screening task. The scheduling problem is characterized by a number of HTS specific requirements: (i) a single batch may pass the same machine more than once while progressing through several operations; (ii) more than one batch will be present in the system at the same time; (iii) there are no buffers between the machines; (iv) a single batch may occupy two or more resources simultaneously, e.g., when being transferred from one resource to another; (v) there will be lower and upper bounds (minimal and maximal

processing times) defined by the user. In many cases, due to the specific nature of substances to be screened, operating schemes in HTS have to be cyclic, i.e., the time distance between two corresponding activities in consecutive batches (“cycle time”) is required to be constant. Throughput maximization is then equivalent to minimization of cycle time. To formalize this scheduling problem, it can be written as a (generally very large) mixed integer nonlinear optimization problem (MINLP). However, even small MINLPs may be extremely hard to solve, hence an important step within this project was the discovery of a transformation that makes the problem a linear one. The resulting MILP (mixed integer linear problem) is an exact representation of the underlying scheduling problem and can be solved using, for example, branch and bound methods. The result is guaranteed to be a globally optimal solution. The developed algorithm to determine the globally optimal schedule for HTS systems has been implemented in CyBio’s current software. The described method has been successfully applied to sample scheduling problems for HTS systems, where screening runs involve up to 150 resource allocations per batch.

Fig. 2: High-throughput screening plant (CyBio AG, Jena).

The approach outlined above essentially constitutes an offline method, i.e., the generated schedule is a static one. In practice, however, unforeseen disturbances will frequently occur during run-time. To handle these, we have started investigating feedback approaches for HTS systems. This current part of the project is based on a cooperation with CyBio AG and the University of Angers, France, (Laurent Hardouin), and has been funded through the EU FP7 project DISC. Our feedback approach builds on the available offline schedule. The resulting feedback synthesis problem is (non-benevolently) nonlinear when considered in standard algebra. However, reformulating the problem in certain “tropical algebras” provides a linear representation. Formally, a tropical algebra is an idempotent semiring (also called dioid), i.e., a set D endowed with two binary operations $\oplus$ (addition) and $\otimes$ (multiplication), where addition is associative, commutative, and idempotent and multiplication is associative and distributive with respect to addition. The zero and unit element in dioids are usually denoted by ε and e, respectively. Due to the idempotency property of dioids a natural (partial) order can be defined, i.e., $a \oplus b = a \Leftrightarrow a \succeq b$. A widely known example for an idempotent semiring is the so-called $(\max,+)$-algebra, where $\oplus$ is defined to be the

standard maximum and $\otimes$ is the conventional addition in standard algebra. The zero (unit) element of $(\max,+)$-algebra is $\varepsilon = -\infty (e = 0)$, e.g., [R15].

For the modeling and control of HTS processes, it is convenient to use the dioid $\mathcal{M}_{in}^{ax}[\![\gamma,\delta]\!]$. Formally, this is the dioid of equivalence classes (quotient dioid) in $\mathbb{B}[\![\gamma,\delta]\!]$, where $\mathbb{B}[\![\gamma,\delta]\!]$ is the set of formal power series in two variables (γ,δ) with Boolean coefficients, i.e., $\mathbb{B} = \{\varepsilon, e\}$ and exponents in $\overline{\mathbb{Z}} = \mathbb{Z} \cup \{-\infty, \infty\}$ [R2]. One advantage of using this dioid is that it allows an efficient and compact way to formulate complex dependencies between starting and finishing times of activities in different batches.

A $\mathcal{M}_{in}^{ax}[\![\gamma,\delta]\!]$-model of an HTS process includes the user specifications for a single batch, i.e., the minimal and maximal processing times, and the sequencing of activities of different batches on each resource (provided by the optimal schedule determined offline). The model does, however, not encode the overall time scheme provided by the optimal schedule, as these degrees of freedom are necessary to implement feedback control. In general a multiplicative inverse may not exist in dioids. However, least upper bounds for the solution sets of $a \otimes x \preceq y$ and $x \otimes b \preceq y$ are uniquely defined. They are called residuals and can be used to determine appropriate control. In particular, it is possible to determine feedback controllers such that the closed-loop system is less or equal (in the sense of the partial order defined by the dioid $\mathcal{M}_{in}^{ax}[\![\gamma,\delta]\!]$ to a given reference model. For HTS systems the start events of all activities are usually chosen to be the control inputs u, i.e., the controller is able to delay the start of every activity. The control output y is the finish event of the batch, and the state variables x model all internal events that occur during the screening of a single batch. For a given reference system, residuation theory provides the largest feedback controller (in the above sense) such that the controlled system is less or equal to the reference model, i.e., the controller starts every activity as late as possible while maintaining the throughput of the reference model. Thus, the controller implements a just-in-time policy [R10]. If the reference model is chosen to achieve the maximal possible throughput, for example the throughput of the optimal schedule determined offline, the closed-loop system will operate with the highest possible throughput as well. Furthermore, the controller can react to unforeseen disturbances and is easily implemented in an industrial PLC.

So far we have mainly investigated the monolithic case, namely the case where all available information is centrally processed and fed back. However, as HTS systems (and the corresponding feedback control) tend to be complex, distributed control schemes are an attractive option. Within the EU-FP7 project DISC, we investigate to what extent available decentralized and distributed control concepts carry over to the dioid setting used in this project.

Current funding for this project is mainly through the EU-FP7 project DISC. Additional financial support has been provided by the bilateral French-German PROCOPE program. First results on the described results appeared in [19, 21, 22, 23, 24, 20].

4.2 Trajectory Planning and Control of Preferential Crystallization Processes

This research represents part of a DFG-funded co-operation project with the PCF group. It aims at using preferential crystallization for the separation of enantiomers. Enantiomers are chiral substances, which share many physical and chemical properties, but can differ, e.g., with respect to their metabolic effects. Control and optimization of preferential crystallization

has recently attracted increased attention, e.g., [R4]. In previous joint work with the PCF group (e.g. [2]), two different operating modes were suggested. In cyclic operating mode, batch crystallization steps for the two substances to be separated alternate. In each step, seed crystals for one of the two enantiomer species are added to an oversaturated solution. For conglomerate forming enantiomers, these crystals will grow and stay pure even for approximately racemic solutions. If operated in the so-called meta-stable area, secondary nucleation dominates primary nucleation. Hence, within each step, crystals of the seeded species will nucleate (and grow), but nucleation of the other species will be negligible. However, this will decrease the concentration of the seeded (preferred) enantiomer in the liquid phase, while the corresponding concentration of the other (counter) enantiomer will remain approximately constant. This, in turn, implies that eventually nucleation (and also growth) of the counter enantiomer will become significant, and, to maintain purity constraints, the process therefore has to be stopped. Hence, it is essential to reliably estimate purity from the available sensor data (temperature and concentration measurements). For this purpose, a nucleation observer was developed [39], which, for certain parametric model uncertainties and measurement uncertainty, provides a worst-case estimate of product purity.

In coupled mode, see Fig. 3, crystal-free liquid is continuously exchanged between two crystallizer vessels, and sufficiently pure fractions of both enantiomer species can be obtained simultaneously by adding the respective seed crystals to the two vessels. The main advantage of the coupled mode is the approximately symmetric decrease in concentrations of both enantiomer species in the liquid phase. This allows for a control scheme where, by suitably manipulating the vessel temperatures, supersaturation of the preferred enantiomer in the respective vessel can be kept constant without causing the corresponding supersaturation of the counter enantiomer to steadily increase (as would be the case in a batch step in the cyclic operating mode).

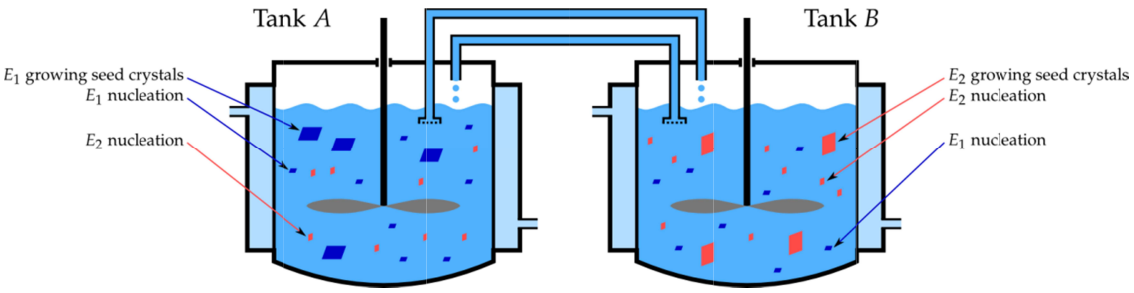

Fig. 3: Preferential crystallization in two coupled vessels

A starting point for much of our current research on the control of preferential crystallization processes has been our prior work on the use of orbital flatness concepts for trajectory planning and control of single-substance crystallization. An orbitally flat system can be transformed, via a suitable time-scaling, into a differentially flat system. This allows the analytic inversion of the system and therefore the convenient solution of the trajectory planning problem; it also facilitates the design of feedback controllers, and effectively transforms optimal control problems into static problems, which can be solved fast and efficiently. Not surprisingly, however, dynamic models for the crystallization of enantiomers turn out to be not orbitally flat, as they describe the simultaneous temporal evolution of two species. Hence transferring our previous results to the enantio-separation case is far from

straightforward. The following is a summary of our attempts to do so. Some of it has only been recently submitted for publication (*Hofmann, S. and J. Raisch:* Solutions to inversion problems in preferential crystallization of enantiomers - Part I and II, submitted to Chemical Engineering Science) and does therefore not appear in the list of references in this report. We have developed an inversion procedure which, for a single vessel batch process, can be briefly summarized as follows. (i) The model contains two population balance equations (PBEs), one for each enantiomer species. One species can be selected, and, as in the single-substance case, scaling time with the (size-independent) growth rate of its crystal population turns characteristic curves of the respective PBE into straight lines. Then, a specified final crystal size distribution (CSD) for that population can be easily mapped into a desired temporal evolution of the boundary condition, i.e., a desired temporal evolution of the (scaled) nucleation rate. (ii) Based on this information, a closed moment model for both species can be dynamically inverted in scaled time. In contrast to the single-substance case, this moment model exhibits nontrivial zero dynamics, even in transformed time. Therefore, differential equations have to be solved to finally obtain the desired temperature profile.

We now return to the coupled crystallizer configuration, which is a multi-input system. Our results enable the simultaneous realization of two prescribed final CSDs, i.e., in each tank, a final CSD for one of the two enantiomer species. For example, one could choose the desired final CSDs for species E_1 in vessel A and species E_2 in vessel B. In the example represented in Fig. 4, these are indicated in gray on the left. Note that we can only prescribe the parts of the overall CSDs that result from grown nucleated crystals. The parts representing grown seed crystals will not be affected in shape as the growth rates are assumed to be size-independent. To solve this inversion problem, we first compute the appropriate (scaled) nucleation rates for each tank, based on time-scaled population balance equations of the respective enantiomer species. Then, differential equations of a moment model for both tanks including the liquid exchange dynamics are solved. The latter can be done in original (non-scaled) time. Numerical studies show that this inversion technique works for a detailed model recently suggested by the PCF group. This model exhibits a fairly complex structure with strongly nonlinear nucleation and growth rates, and includes, e.g., heterogeneous primary nucleation, meaning that the nucleation rates for both enantiomers mutually depend on the CSD of the respective other enantiomer.

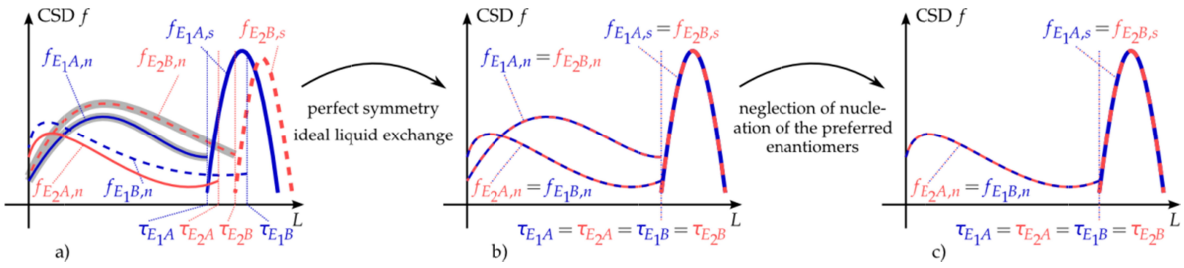

Fig. 4: Crystal size distributions (CSDs) involved in preferential crystallization in two coupled vessels; a) exact model; b), c) idealized models.

While these results allow the realization of prescribed CSDs on the basis of detailed process models, they are computationally much more demanding than the procedure suggested previously for single-substance crystallization. This motivated us to investigate a number of simplifying assumptions that turn the model equations into an (essentially) orbitally flat system. When liquid exchange in the coupled mode is infinitely fast and both crystallization

processes are perfectly symmetric (i.e., the expressions for growth and nucleation rates are symmetric, initial concentrations and seed CSDs are equal, and the same temperature signal is implemented in both tanks), the temporal evolution of the CSDs of the preferred enantiomers (E_1 in tank A and E_2 in tank B) will be identical. The same is true for the temporal evolution of the CSDs of the respective counter enantiomers (E_2 in tank A and E_1 in tank B); see the middle part of Fig. 4. Hence, in this case, the dynamics can be described by a model for a single vessel with identical growth rates for both enantiomers. A further simplification results from neglecting nucleation of the preferred enantiomer (see the right part of Fig. 4). This can make sense, if the mass from growing seed crystals is much higher than that stemming from secondary nucleation. In this case, the resulting model is "essentially" an orbitally flat one. By this we mean that in scaled time there exists an output which, together with a finite number of its derivatives, parametrizes all other system variables via a time-dependent law. This allows an efficient computation of a temperature signal that will achieve the desired CSDs or that will minimize a given cost function using methods from our work on the single-substance case. Note that optimization problems for this class of idealized systems can be solved even more efficiently using the recent results from [40]. For real-life applications, the described inversion-based synthesis of feed-forward control has to be augmented by suitable feedback control. The latter is needed to cope with structural and parametric model uncertainty and with disturbances acting on the plant. Some effort has therefore also gone in the design of feedback and, in co-operation with the PCF group, its experimental validation in a laboratory setup for the crystallization of L-/D-threonine. In this setup, only a small number of measurements are available. Temperatures and concentrations can be measured in both tanks, the latter via densiometers and polarimeters. Properties of the solid phase, on the other hand, are not directly measurable and, if required, need to be estimated (using, e.g., the worst case observer suggested in [39]). Also, crystallization temperatures can evidently not be manipulated directly, and low-level thermostat controllers are used to make temperatures track the provided reference signals. Specifically, as uncertainties and disturbances may cause significant deviations from the ideal symmetric case in the coupled mode, we devised a feedback controller to counteract these effects, which uses crystallization temperature in one of the vessels as the manipulated variable [38]. The effect of measurement noise proved to be particularly challenging. This was addressed by using a model-based filter. The resulting feedback controller was tested on our laboratory setup with satisfactory results. Although, because of the poor quality of sensor data, symmetry could only be achieved in a very approximate manner, this turned out to be not a fundamental problem: investigations by the PCF group seem to indicate that moderate asymmetries in the concentrations do not generally have a negative effect on purity [28].

There is still a number of challenging open control problems. These include robust control schemes which tolerate well-defined margins of uncertainty and the explicit treatment of size-dependent growth rates. Optimization and robust control of single-substance batch crystallization is a very active topic, e.g. [R8, R21]. We are optimistic that the ideas developed in [11] can be transferred to the case of preferential crystallization of enantiomers. The investigation of crystallization processes with size-dependent growth rate has profited from a cooperation with the PSE group. This issue has been addressed in [8, 15, 14]. The latter suggests a finite ODE model which can approximate the underlying infinite-dimensional system with a required accuracy. This scheme is suited for use in control problems, such as

dynamic inversion and optimal control. For instance, in [10] an efficient solution to optimal control of a single-substance batch crystallization process with size-dependent growth rate is found.

4.3 Controlled Functional Electrical Stimulation (FES) in the Rehabilitation of Stroke Patients and Patients with Spinal Cord Injuries

The overall theme of this project is to investigate the application of controlled functional electrical stimulation (FES) for the rehabilitation of stroke patients and persons with spinal cord injuries. It is well-known that electrical nerve stimulation can be used to generate contractions of paralyzed muscles. In combination with appropriate sensor technology and feedback control, this can be exploited to elicit functional movements, such as walking and cycling, and hence to restore certain motor functions. Depending on the degree of disability, the intention may be temporary assistance, e.g., during relearning of gait, or permanent replacement of lost motor functions (neuro-prosthesis). Beside these functional effects, FES has several secondary therapeutic benefits: it improves muscle size and strength, increases the range of joint motion and improves cardiopulmonary fitness by providing significant training effects. FES is therefore potentially more attractive for rehabilitation purposes than conventional methods such as passive bracing of the joints. Fig. 5 explains the principle of controlled FES for a specific problem, the control of the knee joint angle by quadriceps stimulation. The knee joint angle is measured and fed back to the controller, which generates a suitable stimulation pattern to achieve tracking of a reference trajectory.

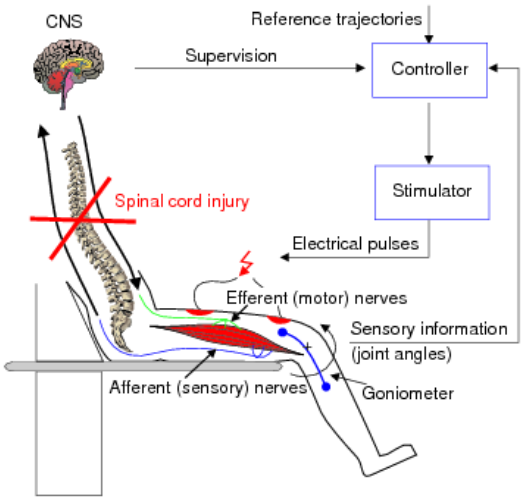

Fig. 5: Functional Electrical Stimulation (FES) for knee-joint angle control

Stimulation can either be applied directly to the peripheral motor nerves (as shown in Fig. 5) or, if the reflex arcs in the lower spinal cord are still intact, to the sensory nerves (neuro-modulation). The latter causes an indirect stimulation of motor nerves while ensuring the natural inhibition of antagonistic muscles. A general problem with FES is rapid muscle fatigue. External stimuli, which replace the missing commands from the central nervous system, tend to invert the recruitment order of muscle fibres: motorneurons with larger diameter are activated first as they have a lower threshold; they recruit the faster and more powerful (type 2 or white) fibres, which fatigue more quickly than the slower and less powerful (type 1 or red) muscle fibres. Electrical stimulation is realized by attaching surface

electrodes to the skin, because the alternative, implanting electrodes, is much less convenient and carries a serious risk of infection. The project is currently organized within six subprojects, addressing fundamental questions as well as aiming at transferring results into medical and therapeutical practice. Two of these subprojects are described in the sequel.

4.3.1 Iterative Learning Control of FES-Assisted Gait Training / Drop Foot Stimulator

Many people have walking deficits after suffering a stroke. Ineffective dorsiflexion during swing (drop-foot) is a particularly frequent phenomenon, which is conventionally treated by using passive ankle-foot orthoses. FES represents an attractive alternative. However, most commercially available stimulators are of the on/off type, where a simple heel switch inside the shoe triggers the stimulation. Stimulation intensity then remains constant during the swing phase. For such systems, the stimulation intensity either needs frequent manual adjustment, or must be set to an unnecessarily high value, which then causes rapid fatiguing of the stimulated muscle. We have therefore developed a control scheme inspired by Iterative Learning Control (ILC): we employ a time varying stimulation profile, which is only adjusted after the end of each step. Adjustment is based on the difference between the desired and the recorded angle profile during the previous step [60, 58]. In this way, the advantages of feed-forward and feedback are combined in an intuitive manner. The success of such a scheme of course depends critically on the available ankle-joint angle measurements. We have investigated two different sensor technologies: one approach uses an inertial sensor mounted on the shoe [61], the other one makes use of bioimpedance measurements via skin electrodes [60, 58]. Another challenge is the irregular gait of stroke patients and the resulting significant variation of the duration of the swing phase. More specifically, the swing phase of a step can be disrupted either by the patient putting the foot down intentionally, or by the toes touching ground early due to unsufficient stimulation intensity. Since all available results on ILC require constant cycle duration (e.g., [R5, R30]), we are developing an extension of the theoretic concepts, including stability and monotonicity criteria, for the case of variable cycle length. First results have appeared in [72]. We believe that these results will also be useful for other ILC applications where variable cycle length is a phenomenon that cannot be neglected.

4.3.2 Bioimpedance controlled neuro-prosthesis to support swallowing

Swallowing is a complex and vital process. Depending on the current phase of swallowing, it is either conscious or sub-conscious. Controlled by cortical processes which are coordinated in the brain stem (pattern generators), multiple muscles have to be activated in a timely manner for this purpose. Swallowing disorders (dysphagia) can lead to serious complications, including malnutrition and pneumonia, which may be fatal. The complete closure of the larynx and its timing take a central role in safe swallowing, especially since the larynx is a branching point between the trachea and the oesophagus. In case of closure failure, saliva, liquid or food may enter the airway (aspiration), with possible consequences as described above. The causes of swallowing disorders are mostly severe head injuries and strokes. Every second stroke patient suffers from dysphagia, and it is chronic in one quarter of the patients.

The primary objective of rehabilitation is the restoration of disturbed functions by, for example, sensory stimulation or teaching of special swallowing techniques. Necessary conditions for success are sufficient cortical potential after the injury and an existing connection from the cortex to the muscles. If this connection is lost or if the muscles cannot be sufficiently controlled, a rehabilitation of the swallowing process is not possible. Then, the patient is dependent on a diet via a feeding tube and a tracheal cannula. In these cases, electrical stimulation of the external laryngeal muscles as a therapeutic approach seems to enhance the swallowing process [73]. Another possibility is to stimulate the internal laryngeal muscles in such a way that the vocal cords close and aspiration can be prevented. In both cases, intramuscular stimulation seems to be superior to transcutaneous stimulation. Stimulation has to be applied in a timely manner. In previous studies, stimulation was triggered either by the patient himself via a hand-switch [R6] or by the electromyography (EMG) of submental muscles [R18]. However, neither method is able to adapt to the swallowing success or skills of the patient.

One approach to evaluate the swallowing success online is to measure bioimpedances (BI) at the neck. Impedance is defined as the relation of voltage to current over an electrical conductor. There are two possible methods to measure BI. In the two-point method, the voltage is measured directly over the current electrodes. The current, which is induced into the patient through the current electrodes, causes a voltage drop across the electrode-skin contact. As this resistance is time-variant, it will lead to a measurement error. This undesirable effect can be avoided by using the four-point measurement method, where voltage is recorded separately over additional electrodes by a high impedance instrumentation amplifier. Since no current can flow through the voltage electrodes, there is no disturbing voltage drop across the electrode-skin contact. We have developed a bioimpedance measurement instrument which supports both methods; however, the four-electrode method is preferred for measurements at the neck. In cooperation with the Unfallkrankenhaus Berlin (Trauma Hospital Berlin), we could demonstrate that a certain BI measurement (change in absolute value) correlates with the distance between the hyoid bone and the thyroid cartilage. This provides important information to assess the airway closure during swallowing. Another specific BI measurement at the neck can be used for the detection of aspiration events [59].

We believe that a system based on a combination of these BI measurements can serve as an adequate sensor for a neuro-prosthesis that supports swallowing by stimulating the appropriate muscles using intramuscular electrodes. The development of such a neuro-prosthesis is the goal of the research project BigDysPro, which received the Innovation Award 2009 for Medical Technology (Innovationspreis Medizintechnik 2009) from the Federal Ministry of Education and Research (BMBF). BigDysPro is a joint project with R. Seidl from the Trauma Hospital Berlin. The new system will continuously assess the success of stimulation by accessing BI measurements and adjust the stimulation intensity to the needs of the patient. To ensure synchronization between the start of the swallowing and stimulation processes, the BI-electrodes will also be used to record the remaining residual muscle activity by EMG and to trigger stimulation. Should the patient choke despite these measures, the device will be able to detect this from the BI measurements and will subsequently induce a protective or throat-clearing cough by another stimulation burst. In Fig. 6, the stimulation and measurement areas are illustrated. For the measurement of airway closure, changes in

the BI at the level of the epiglottic vallecula are acquired. Aspiration detection takes place via electrodes on the thyroid cartilage at the level of the vocal cords.

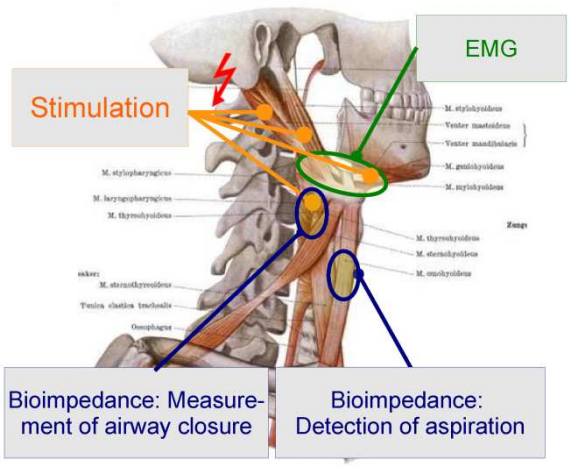

Fig. 6: Model of the measurement and stimulation system as basis for a swallowing neuro-prosthesis.

5 Research Related Activities

IPC Membership

J. Raisch was or is a member of the international program committees (IPC) of the following conferences or workshops.

- **WODES'08** (9th Int. Workshop on Discrete Event Systems, Gothenburg, 2008)
- **SPC2009** (6th Symposium on Process Control, Ploiesti, 2009)
- **ADHS09** (3rd IFAC Conf. Analysis and Design of Hybrid Systems, Zaragoza, 2009)
- **ADCHEM2009** (IFAC International Symposium on Advanced Control of Chemical Processes, Istanbul, 2009)
- **WODES 2010** (IFAC 10th Int. Workshop on Discrete Event Systems, Berlin, 2010)
- **DCDS'11** (3rd International Workshop on Dependable Control of Discrete Event Systems, Saarbrücken, 2011)
- **CDC/ECC2011** (50th IEEE Conference on Decision and Control and European Control Conference, Orlando, 2011)
- **ADHS12** (4th IFAC Conf. Analysis and Design of Hybrid Systems, Eindhoven, 2012)
- **WODES'12** (IFAC 11th Int. Workshop on Discrete Event Systems, Guadelajara, 2012)

T. Schauer was an IPC member of

- **MBEC2008** (4th European Congress of the International Federation for Medical and Biological Engineering, Antwerp, 2008)
- **AUTSYM08** (5th International Symposium on Automatic Control, Wismar, 2008)
- **CCA2008** (IEEE Int. Conference on Control Applications, San Antonio, 2008)

- **IFESS2010** (15th Annual International FES Society Conference and 10th Vienna Int. Workshop on FES, Vienna, Austria, 2010)
- **TAR2011** (Technically Assisted Rehabilitation - TAR 2011, 3rd European Conference, Berlin, 2011)

Organization of Workshops etc.

Our group organized **WODES 2010**, the 10th International Workshop on Discrete Event Systems, which was held at TU Berlin in September 2010 under the auspices of IFAC, with more than a hundred participants (J. Raisch was IPC and NOC chair).

Our group was also involved in the organization of the following workshops/symposia etc.

- **TAR2011 -** Technically Assisted Rehabilitation, was held at TU Berlin in March 2011 (T. Schauer was a member of the organizing committee).
- **AUTOMED'2009** - Workshop on Automatic Control in Medical Engineering, was held at TU Berlin in March 2009 (T. Schauer was a member of the organizing committee).
- **DCDS'11** - 3rd Int. Workshop on Dependable Control of Discrete Event Systems, was held in Saarbrücken in June 2011 (J. Raisch was a member of the NOC).
- **ACIDS** - The Symposium on Analysis & Control of Infinite-Dimensional Systems in the Engineering Sciences, was the second event in a series of bi-annual symposia which the MPI's Scientific Advisory Board suggested to organize. It took place in Magdeburg in November 2010 (J. Raisch was a member of the PC, J. Holzmann was responsible for the local organization).

Technical Committees & Administrative Duties

J. Raisch was vice-dean of the TUB Department of Electrical Engineering and Computer Science in 2010 and 2011. He represents TUB at the Fakultätentag für Elektrotechnik und Informationstechnik (FTEI), the German association of EE departments. He is a member of the Council of the European Union Control Association (EUCA). He is also a member of the IFAC (International Federation of Automatic Control) Technical Committee on Discrete Event and Hybrid Systems. T. Schauer is a member of the technical committees on Neuroprostheses, Rehabilitation Methods, and Automatic Control in Medical Engineering of the Deutsche Gesellschaft für biomedizinische Technik (DGBMT, German Association of Biomedical Engineering).

Editorial Duties and Journal Review Activities

J. Raisch was or is on the editorial board of the following journals:

- Electrical Engineering – Archiv für Elektrotechnik (Springer)
- European Journal of Control (Hermes), until 2010
- IEEE Transactions on Control Systems Technology

- Discrete Event Dynamic Systems (Springer)
- Int. Journal of Sensors, Wireless Communications & Control (Bentham Science)

Members of the group have acted as reviewers for the following journals: IEEE Transactions on Automatic Control, IEEE Transactions on Control Systems Technology, International Journal of Control, Journal of Process Control, Aiche Journal, at–Automatisierungstechnik, Automatica, Chemical Engineering Science, Discrete Event Dynamic Systems, Systems and Control Letters , Engineering Applications of Artificial Intelligence, Optimal Control – Applications & Methods, Electrical Engineering, Medical & Biological Engineering & Computing, International Journal of Robust and Nonlinear Control, Hybrid Systems and Applications, IEE Proc. Control Theory & Applications, Journal of Circuits, Systems and Computers, IEEE Transactions on Circuits and Systems, Zentralblatt für Mathematik und ihre Grenzgebiete, Simulation: Transactions of the Society for Modeling and Simulation International, Europ. J. Appl. Math., PLoS Computational Biology, Computer Methods and Programs in Biomedicine, Biomedical Engineering, IEEE Control Systems Magazine, Biomedical Signal Processing and Control, Journal of NeuroEngineering and Rehabilitation, Medical Engineering & Physics.

6 Teaching Activities, PhD Projects

Members of our team (J. Raisch, T. Schauer) teach most control related courses for EE and Computer Engineering (Technische Informatik) students at TUB. D. Flockerzi contributes significantly to the Systems Engineering and Cybernetics program at OvGU. Additional laboratory and seminar courses at TUB have been taught by team members.

Title of course	**Place**	**Lecturer**
Fundamentals of Control (BSc-level, 4 hours/week)	TUB	J. Raisch
Multivariable Control Systems (MSc-level, 4 hours/week)	TUB	J. Raisch
Discrete Event Systems (MSc-level, 4 hours/week)	TUB	J. Raisch
Hybrid Control Systems (MSc-level, 4 hours/week)	TUB	J. Raisch
Nonlinear Control Systems (MSc-level, 4 hours/week)	TUB	T. Schauer
Identification and Control in Medicine (MSc-level, 4 h/week)	TUB	T. Schauer
Distributed Parameter Systems (BSc-level, 4 hours/week)	OvGU	D. Flockerzi
Nonlinear Systems (MSc-level, 4 hours/week)	OvGU	D. Flockerzi
Stochastic Systems (MSc-level, 2 hours/week)	TUB/OvGU	N. Bajcinca

6.1 Teaching Related Activities

Funded by the European Union, we organize three ERASMUS/SOCRATES student exchange programs in the general area of systems and control: these exchange links are with the University of Glasgow (Dr. H. Gollee), UK, with the University of Cagliari (Prof. A. Giua), Italy, and the University of Angers (Prof. Laurent Hardouin), France. Moreover, J. Raisch is also responsible for the TUB Department of EE & CS dual degree program with Supelec, France, and has initiated an active student exchange program with the Universidade Federal de Santa Catarina (UFSC) (Prof. J. Cury), Brasil.

6.2 PhD Theses

The following PhD theses, supervised by J. Raisch, were successfully defended during the period covered by this report.

Title	PhD student	Date of defense
A new integrated control architecture for cyclic discrete event systems	Danjing Li	11/2008
Controlled FES-assisted Gait Training for Hemiplegic Stroke Patients Based on Inertial Sensors	Nils-Otto Negaard	11/2009
Analysis of Hierarchical Structures for Hybrid Control Systems	Dmitry Gromov	08/2010
Development of an Electromyography Detection System for the Control of Functional Electrical Stimulation in Neurological Rehabilitation	Raafat Shalaby	07/2011
Optimal Steady State and Transient Operation of Simulated Moving Bed Chromatographic Processes	Suzhou Li	Submitted 09/2011

J. Raisch acted as co-supervisor or external examiner for the following PhD theses:

Title	PhD student	Date of defense
Diagnosis and Identification of discrete event systems using Petri nets	Maria P. Cabasino (Univ. of Cagliari)	03/2009
Modeling and Simulation of Economic Systems Using Software Engineering Techniques	Sabrina Ecca (Univ. of Cagliari)	03/2009
Wavelet Spectrum Sensing and Transmission	Valeria Orani (Univ. of Cagliari)	03/2009
SOA based approach to the Next Generation Networks management	Paolo Anedda (Univ. of Cagliari)	03/2009
Logical Consensus and Distributed Intrusion Detection for Secure MultiAgent Systems	Adriano Fagiolini (Univ. of Pisa)	04/2009
Contract-based design for computation and verification of a closed loop hybrid system	Emanuele Mazzi (Univ. of Pisa)	04/2009
A particle approach to the analysis and estimation of nonlinear dynamical systems	E. Crisostomi (Univ. of Pisa)	04/2009
Beiträge zur Steuerung und Regelung von Mehrvariablen LTI-Systemen in polynomialer Matrizendarstellung	Sven-Olaf Lindert (TU Dresden)	10/2009
Hierarchical control of discrete event systems with inputs and outputs	Sebastian Perk (Univ. Erlangen)	02/2010
Compositional Analysis and Control of Dynamical Systems	Florian Kerber (Univ. Groningen)	03/2011

T. Schauer acted as co-supervisor for the following PhD thesis:

Title	PhD student	Date of defense
Aktive Schwingungskontrolle einer Spannbandbrücke mit pneumatischen Aktuatoren	Achim Bleicher (TUB)	03/2011

6.3 Diploma/Master Theses

During the period covered by this report, members of the team (both at the MPI and at TUB) have supervised 67 diploma or master theses, 3 by students from OvGU, 60 by TUB students, 4 by UFSC students. Moreover, numerous “Studienarbeiten” (pre-diplomas theses) and bachelor theses were supervised.

7 Awards

- B. M. Nejad, A. Attia and J. Raisch received a **best paper award at IEEE ICAT 2009** (22nd Int. Symposium on Information, Communication and Automation Technologies).
- Our joint research project BigDysPro (with R. Seidl from the Trauma Hospital Berlin) received the **Innovation Award 2009 for Medical Technology (Innovationspreis Medizintechnik 2009)** from the Federal Ministry of Education and Research (BMBF).
- Our joint research project meb-GO (with the TU Berlin Biomedical Engineering Group, the Orthopädische Klinik der Medizinischen Hochschule Hannover, Rehabtech Research Lab GmbH, and Otto Bock Health-Care GmbH) received the **Innovation Award 2010 for Medical Technology (Innovationspreis Medizintechnik 2010)** from the Federal Ministry of Education and Research (BMBF).
- Adolfo Anta is to receive the 2011 IEEE **George S. Axelby Outstanding Paper Award** for the paper “To sample or not to sample: Self-triggered control for nonlinear systems”, which he authored (with P. Tabuada) while being a Ph.D. student at UCLA.

8 Future Directions

We intend to bring together results from our projects on hybrid control systems, hierarchical control theory, consensus-based cooperative control and self-triggered control to provide a general time-varying distributed control architecture. The aim is to combine the efficiency of classical hierarchies with structural flexibility (including the ability to re-organize after failure of components) while minimizing the need for information exchange between components in the overall system.

We believe that such a unified framework will be important both for large scale control problems in engineering and for the analysis of biological systems. A specific engineering application we intend to emphasize is the efficient and reliable control of energy grids, which, due to the increasing importance of renewable sources, has become a challenging problem.

As can be seen from the report, the SCT Group has developed substantial and productive links with many other groups at the MPI. It is another aim for the next evaluation period to achieve a similar level of cooperation with the recently established groups, namely the CSC Group.

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(Please note that this is not a complete list of publications.)

Research Group:

Systems Biology (SBI)

Prof. Dr.-Ing. Ernst Dieter Gilles

This report covers the period from October 2008 to August 2011.

1 Introduction

Research of the multidisciplinary Systems Biology group (SBI) aimed at a qualitative and quantitative understanding of the complex regulatory and metabolic networks in living cells. By closely combining laboratory experiments with computational modeling and simulation, fundamental properties of living systems, such as robustness, multistationarity, stability and stochasticity were addressed. Furthermore, experimental design and model-based generation of hypotheses are major fields where experimental biology was guided by theoretical methods.

Research of the SBI group covers a large range of complexity, starting from bacteria (*Escherichia coli, Rhodospirillum rubrum*, *Ralstonia eutropha*) and unicellular eukaryotes (*Saccharomyces cerevisiae*) to higher eukaryotic cells (Hepatocytes). While some of the model systems were chosen because of unique experimental opportunities for studying specific aspects of cellular signaling and metabolism (e.g. redox control in *R. rubrum*), others such as *E. coli* or *S. cerevisiae* represent classical model organisms due to the experimental tools available for cultivation and genetic modification, and the huge amount of data known today for almost every aspect and molecular detail of these species. The diverse biological systems addressed by the group provide an attractive opportunity to identify general motifs of the biological circuits that bring about the complex non-linear network dynamics encountered in all living organisms. Central to all projects is the focus on signal transduction and regulation and its application to biotechnological and medical problems. The group achieves a strong interaction of experiment and theory. Especially the projects dealing with signaling and regulation in bacteria are based on a tight interaction of theory and carefully controlled experiments, conducted in a bioreactor facility of the MPI. We found this intimate collaboration to be indispensable for the success of Systems Biology, fueling an iterative process of data generation, setup of computational models, predictive simulation studies, and experimental model validation. Projects where the experimental aspects are not investigated at the institute are based on close collaborations with biological partners at the national and international level.

An important issue in Systems Biology is to conceive of generic theoretical methods and software tools that fit the particular requirements when modeling cellular systems. We hence apply methods from systems theory that allow decomposition and systematic analysis of signaling and metabolic networks. Systems Biology requires the development of appropriate software tools. For this purpose ProMoT/DIVA/Diana, a powerful general-purpose modeling and simulation framework for dynamical systems, is extended with special functionalities for modeling cellular systems, including routines for handling and visualizing large cellular networks.

The SBI group is actively involved in the research center “Dynamical Systems” a joint research project promoting interdisciplinary cooperation between systems engineering, biology, medicine and mathematics. This joined research project of the MPI and the OvGU is financed by the state of Saxony-Anhalt.

The SBI group was also very successful in applying for third party research funding offered by the BMBF (FORSYS, HepatoSys/Virtual Liver, SYSMO SUMO, ERASYSBIO). One particular success was the allocation of one of four BMBF-FORSYS-Centers MaCS to Magdeburg (MPI and OvGU). Prof. Gilles was speaker of this center until 2008. The total third party funding of the SBI group amounts to 8 million Euro from 2007 to 2011. The high

percentage of SBI funding by third party money implies that research topics are partially guided by the funding programs.

The group was led by Prof. Gilles until his retirement in May 2011. Internally, the group was structured into six research teams (Fig. 1) characterized by different research foci namely
1) Regulatory Circuits (E.D. Gilles),
2) Redox phenomena in photosynthetic bacteria (H. Grammel),
3) Systems biology of local and global regulations (K. Bettenbrock),
4) Modeling tools and databases for Systems Biology (S. Mirschel),
5) Design principles of Biological Networks (R. Straube) and
6) Qualitative dynamics of biochemical reaction networks (C. Conradi).

Prior to his appointment to the TU Munich Andreas Kremling led the team “Dynamics and control in cellular systems”. The strong collaboration both among the teams and with the ARB group led by Steffen Klamt has resulted in a significant number of joint research projects.

The retirement of Prof. Gilles in May 2011 brought about the need to restructure the SBI group (see General Overview and Outlook). In the following the research of the SBI group from 2008 until May 2011 is considered.

2 Members of the Research Group

Tab. 1: Members of the Systems Biology Group

	Status	**Membership**
Prof. E.D. Gilles	Head of Group	06/1996 – 05/2011
Dr. Detlev Bannasch	Senior Scientist	03/2005 – 12/2009
Dr. Katja Bettenbrock	Senior Scientist	since 09/1998
Jan Blumschein	Ph.D. Student	09/2002 – 01/2009
Anke Carius	Ph.D. Student	since 04/2007
Dr. Carsten Conradi	Senior Scientist	since 01/2010
Holger Conzelmann	Postdoc	07/2009 – 06/2010
Christian Ebeling	Ph.D. Student	11/2008 - 12/2009
Michael Ederer	Ph.D. Student	01/2007 – 02/2010
Stefan Gayer	Ph.D. Student	07/2007 – 05/2009
Dr. Hartmut Grammel	Senior Scientist	since 03/1998
Benjamin Herzer	Ph.D. Student	06/2008 – 12/2009
Jeremy Huard	Ph.D. Student	since 06/2004
Susann Jahn	Ph.D. Student	since 04/2007
Jim Joy	IMPRS Student	since 01/2008

Markus Koschorreck	Ph.D. Student	01/2005 – 09/2009
Katrin Kolczyk	Ph.D. Student	since 03/2007
Bernhard Kramer	Ph.D. Student	since 07/2010
Dr. Andreas Kremling	Senior Scientist	03/1998 – 12/2009
Alexander Lutz	Ph.D. Student	06/2008 -12/2010
Anja Marbach	Ph.D. Student	since 04/2007
Andrea Merbitz	Ph.D. Student	since 01/2011
Sebastian Mirschel	Ph.D. Student	since 06/2004
Markus Nees	Ph.D. Student	since 01/2009
Tobias Neuhaus	Ph.D. Student	02/2005 – 01/2010
Arturo Padilla	Scholarship holder	since 08/2007
Rakesh Pandey	IMPRS Student	since 10/2008
Michael Rempel	Ph.D. Student	04/2007 – 02/2011
Christiane Rudolf	Ph.D. Student	since 09/2007
Daniel Samaga	Ph.D. Student	since 02/2007
Rebekka Schlatter	Ph.D. Student	08/2008 – 06/2009
Hannah Sharp	Ph.D. Student	10/2006 – 12/2009
Stefan Stagge	Ph.D. Student	since 07/2007
Dr. Sonja Steinsiek	Senior Scientist	since 08/2007
Dr. Ronny Straube	Senior Scientist	since 12/2006
Lisa Zeiger	Ph.D. Student	since 07/2008
Technical Staff		
Andrea Focke	Laboratory	since 12/2003
Janine Holzmann	Secretary	02/2007 – 03/2011
Ruxandra Rehner	Laboratory	since 10/1999
Christine Richter	Laboratory	since 09/2007
Melanie Säger	Laboratory	since 09/2007
Steffi Strähler	Technical Support	since 02/2007
Helga Tietgens	Laboratory	since 07/2001
Renate Wagner	Secretary	since 06/1998

3 Survey of Research Projects

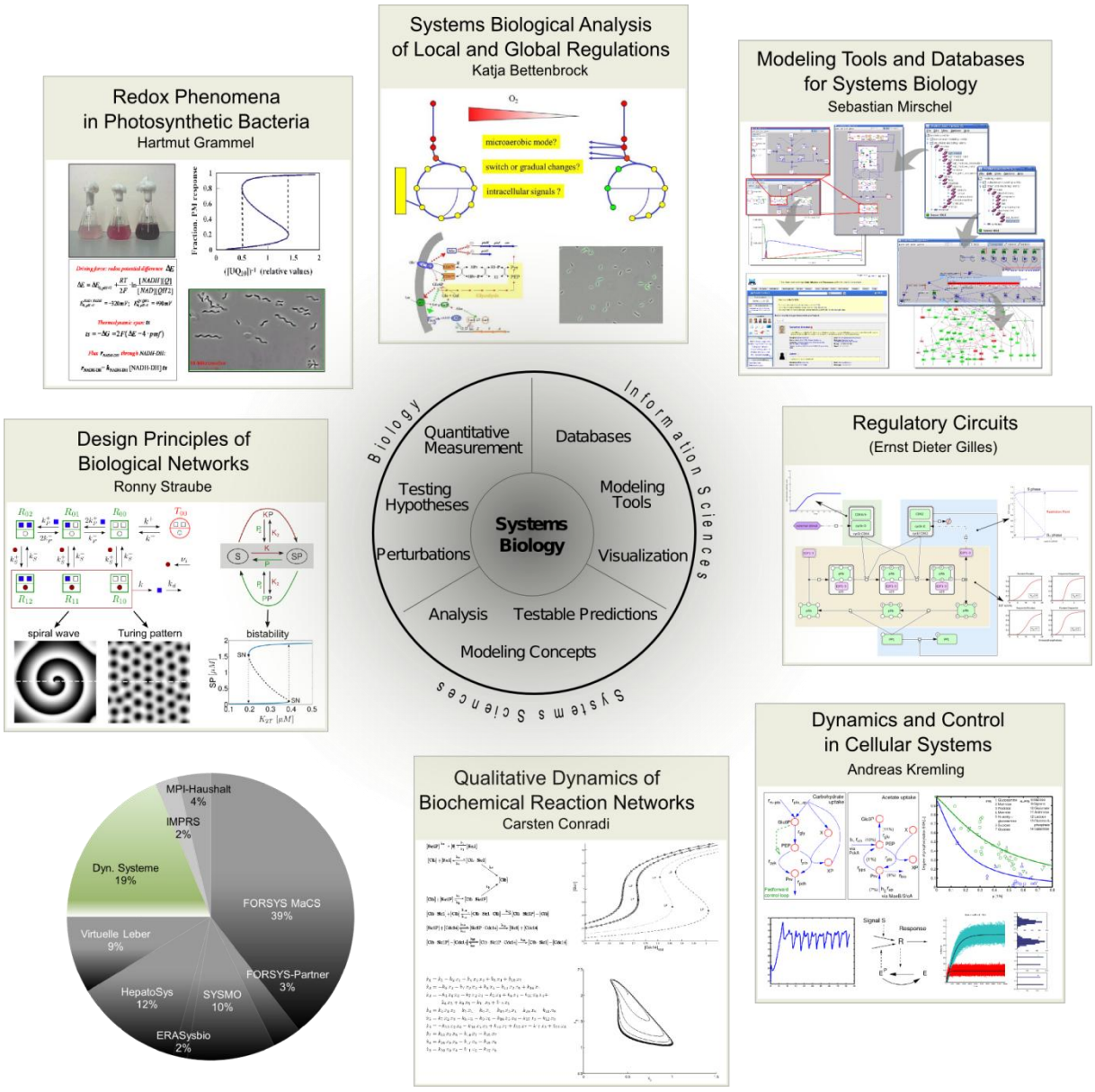

Fig. 1 Research teams and fundings of the SBI group

Tab. 2 Research Activities

Research team: Redox Phenomena in Photosynthetic Bacteria Dr. Hartmut Grammel	This team is a Junior Research Group of the BMBF FORSYS program from 2007 - 2011. The establishment of a facultative photosynthetic bacterium, *Rhodospirillum rubrum*, as a new model organism for Systems Biology and the exploitation of *R. rubrum* for biotechnological applications are the two ultimate project goals.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Experimental analysis of the thiol-redox-signaling network of *Rhodospirillum rubrum*	Carius	BMBF (FORSYS)	05/07 – 12/11	ARB (Klamt) Stuttgart Univ. (Ghosh) FRISYS, Freiburg (Becker)

Central metabolic pathway analysis and process optimization for application of *Rhodospirillum rubrum* in biotechnology	Rudolf	BMBF (FORSYS)	09/07 – 12/11	ARB (Klamt) PSD (Kienle) PoES (Krewer) FZ Jülich (Oldiges) Stuttgart Univ. (Ghosh, Sawodny) Ohio State Univ. (Tabita)
Systems-level analysis and model-based process control of microaerobic physiology	Zeiger	BMBF (FORSYS)	07/08 – 12/11	OvGU (Findeisen)

Research team: **Systems Biological Analysis of Local and Global Regulations** Dr. Katja Bettenbrock	This team focuses on the analysis of metabolic regulation in *E. coli*. Of special interest are the interactions between transcriptional regulators and metabolism on the level of local as well as of global control. Experiments deal with the analysis of populations and of single cells.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Analysis of cellular regulation with respect to the single cell level	Marbach	BMBF (FORSYS)	01/07 – 12/11	SBI (Straube)
Analysis of the interaction of carbon and nitrogen control	Jahn	BMBF (FORSYS)	01/07 – 12/11	Osnabrück Univ. (Jahreis)
Model-based modification of cellular regulation in *S. cerevisiae and E. coli*	Sharp Merbitz	BMBF (FORSYS)	01/07-12/09 01/11-12/11	Stuttgart Univ. (Hilt)
Impact of enzymatic reactions on the global control of the aerobic/anaerobic response	Steinsiek, Stagge	BMBF (SYSMO SUMO)	04/07-03/10	Stuttgart Univ. (Sawodny, Sauter) Amsterdam Univ. (Teixera de Mattos) Sheffield Univ. (Poole, Green, Holcombe)
Analysis of single cell behavior during changes in oxygen supply	Stagge, Marbach	BMBF (SYSMO SUMO2)	04/07 – 04/13	Stuttgart Univ. (Sawodny, Sauter) Amsterdam Univ. (Teixera de Mattos) Sheffield Univ. (Poole, Green, Holcombe)
Dynamics and regulation of the metabolic balance in *E. coli*	Nees	BMBF (FORSYS Partner)	01/09 – 12/11	Osnabrück Univ. (Jahreis) Jena Univ. (Schuster) HKI Jena (Guthke) HZI Brauschweig (Rinas) BioControl (Pfaff)
Systems understanding of microbial oxygen-dependent and independent catabolism ($SUMO_2$)	Steinsiek, Stagge	BMBF (SYSMO SUMO2)	04/11 – 04/13	Stuttgart Univ. (Sawodny, Ederer)

				Amsterdam Univ. (Teixera Mattos) Sheffield Univ. (Poole, Green, Holcombe) Edinburgh Univ. (Sanguinetti) SBI (Conradi)

Research team: **Dynamics and Control of Cellular Systems** Dr. Andreas Kremling	Mathematical modeling and model analysis for cellular systems; parameter identification and experimental design. The head of the team joins TU Munich since 2010.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Population based modeling of the K^+ uptake systems in *Escherichia coli*	Gayer	BMBF (SYSMO SUMO)	07/07 – 02/10	Munich Univ. (Jung) Vigo Univ. Spain (Banga)
Model set-up and analysis to describe metabolism, signal transduction and gene expression in *Pseudomonas putida*	Joy	IMPRS	01/08 – 12/11	HZI Braunschweig (Martins dos Santos) Hannover Univ. (Tümmler)
Dynamic modeling of regulatory and signal transduction networks (Catabolite repression in *E. coli*)	Kremling	BMBF (FORSYS)	01/07 – 12/09	SBI (Bettenbrock)
Analysis of bacterial regulation on a single cell level	D. Samaga	LSA	02/07	SBI (Bettenbrock, Straube)

Research team: **Modeling Tools and Databases for Systems Biology** Sebastian Mirschel	This team develops and provides scientific methods and related software tools for modeling and data management in systems biology. The modeling tool ProMoT supports efficient and comprehensible setup, editing and visualization of modular models using different modeling approaches. We are also dealing with different issues of model integration. The data management system MaCS-DB focuses on finding, sharing and exchanging the diversity of systems biology data.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Specialized visual editors for Systems Biology models	Kolczyk	BMBF (FORSYS)	03/07 – 12/09	EMBL Hinxton (Saez-Rodriguez)
A new approach for the setup of domain-oriented models of signal transduction	Kolczyk	BMBF (FORSYS)	01/10 – 12/11	EMBL Hinxton (Saez-Rodriguez) ARB (Klamt)
Concepts and tools for model integration	Rempel/ Kolczyk	BMBF (Virtual Liver)	04/07 – 12/09	Heidelberg Univ. (Kummer) MPI MG Berlin (Liebermeister)
Visualization of networks	Mirschel	BMBF (Virtual Liver)	06/04 – 12/09	IPK Gatersleben (Schreiber) ARB (Klamt)
Interfaces for component-based modeling and analysis tools	Mirschel	BMBF (Virtual Liver)	06/04 – 12/09	Heidelberg Univ. (Kummer)
Datamanagement for FORSYS MaCS	Mirschel	BMBF (FORSYS)	01/10 – 12/11	HITS gGmbH Heidelberg (Müller)

Research team: **Design Principles of Biological Networks** PD Dr. Ronny Straube	We use methods from applied mathematics, nonlinear dynamics and non-equilibrium statistical physics to investigate the design principles of biological systems. The long-term goal is to understand the relation between design and functionality of molecular reaction networks, especially in the presence of diffusive coupling and molecular noise.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Mathematical modeling of redox- and light-dependent gene regulation in photosynthetic bacteria	Pandey	IMPRS	10/08-09/11	SBI (Grammel)
Dynamical modeling of regulatory and signal transduction networks	Samaga, Straube	BMBF (FORSYS)	01/10-12/11	SBI (Bettenbrock)
Spatial aspects of intracellular signaling	Straube	LSA	12/06-12/09	Brit. Columbia Univ. (Ward)
Molecular mechanisms of pattern formation	Straube	LSA	12/06-12/09	OvGU (Mair)
Mathematical modeling of the central metabolism in *R. rubrum*	Straube	LSA	12/06-12/09	SBI (Grammel)

Research team: **Qualitative Dynamics of Biochemical Reaction Networks** Dr. Carsten Conradi	Our research aims at establishing (necessary and sufficient) parameter-independent conditions for selected *qualitative dynamical properties* of the mathematical models defined by reaction networks (currently multiple steady states and switching). To assess, ensure and improve the applicability, these conditions are applied to real-world biochemical reaction networks.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Multistationarity in mass action networks	Conradi	LSA	01/01 – 12/11	SCT (Flockerzi)
Chemical reaction systems with toric steady states	Conradi	BMBF FORSYS	10/08 – 12/11	Buenos Aires Univ.(Dickenstein Duke Univ. (Shiu)
Subnetwork analysis and integration of dynamic models	Conradi, Kolczyk	BMBF Virtual Liver	01/07 – 03/15	ETH Zurich (Stelling, Kaltenbach)
Qualitative dynamics of mass action networks	Conradi	LSA	01/09 – 12/11	SCT (Flockerzi)
Qualitative dynamics of PTM networks	Holstein	IMPRS	11/08 – 11/12	SCT (Flockerzi) Harvard Univ. (Gunawardena)
Qualitative dynamics of metabolic networks in *E.coli*	Kramer	BMBF FORSYS-Partner	05/10 – 12/11	SBI (Bettenbrock) Munich TU (Kremling)

Research team: **Senior Research team on Regulatory Circuits** Prof. Ernst Dieter Gilles	Our goal is to understand the regulatory circuits controlling intracellular signaling: (i) understand recurring molecular networks realizing important intracellular regulatory circuits, (ii) use mathematical models of these circuits to design extracellular controllers, e.g. for an optimization of biosynthesis.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Model-based synchronization of yeast cultures	Sharp	BMBF FORSYS	01/07 – 12/09	Stuttgart Univ. (Hilt, Sawodny)
Phototaxis in *Halobacteria*	Neuhaus	LSA	02/05 - 12/09	OvGU (Marwan)
Proliferation control in hepatocytes	Huard	BMBF Virtual Liver	01/04 - 12/11	DKFZ Heidelberg (Klingmüller)

4 Research Highlights

4.1 Research Team: Redox Phenomena in Photosynthetic Bacteria

Hartmut Grammel

This SBI team is an official Junior Research Group funded by the BMBF FORSYS program from 2007 - 2011.

4.1.1 Redox control of photosynthetic gene expression

The formation of intracytoplasmic photosynthetic membranes (PM) by facultative photosynthetic bacteria has become a prime example for exploring redox control of gene expression in response to oxygen and light [R22], [R2]. The redox state of the ubiquinone (UQ) pool has been suggested to play a key role as a molecular signal [R36]. It is particularly interesting that in *R. rubrum* the amount of PM is not only affected by the availability of oxygen and light but responds additionally to the supplied carbon substrate [14]. A growth medium containing two substrates, succinate and fructose, was found to elevate the amount of expressed PM under semi-aerobic dark conditions to maximal levels so far attainable only in photosynthetically-grown cells. This effect provides an experimental system for elucidating how growth conditions affect cellular redox signaling. As a valuable complementary tool, the computational model of the electron transport chain (ETC), developed by Klamt et al. [18], allows the simulation of how environmental factors oxygen and light as well as cytosolic metabolites such as NADH and succinate influence the redox state of UQ and other ETC components and thereby PM expression. The ETC model has been recently further validated by experimental determination of the effect of the light-intensity on the UQ redox state. As predicted by the model, we found that the UQ pool is getting more reduced under low-light and more oxidized at high-light conditions. Both simulation results as well as experimental data thus indicate that the well-known repression of PM formation by high light intensities could well be mediated by UQ redox signaling without any specific light sensor being involved. However, in contrast to the conditions generally applied in *in vitro* studies with purified redox sensor kinases, our *in vivo* data show only moderate fluctuation in the UQ redox state (from 30 % - 70 % reduced), suggesting that PM expression is regulated cooperatively by the redox state of the UQ pool.

Moreover, recently, we demonstrated that the situation is more complicated and includes the regulatory interaction of different cellular redox compartments. The low-molecular-weight thiol glutathione (GSH) is the most abundant cytosolic redox buffer in many prokaryotic and eukaryotic cells. GSH is known for its critical role in redox homeostasis, and in the defense of oxidative stress. Recently, Carius et al. [5] found that in *R. rubrum* the amount of PM can be drastically elevated by external supplementation of the growth medium with GSH but not with oxidized glutathione (GSSG). Experimental determination of the intracellular GSH/GSSG pool indicated that its redox potential varies between -182 mV and -217 mV and that the critical redox potential for inducing PM expression is about -210 mV on a GSH/GSSG redox scale. Furthermore, we found that *R. rubrum* cultures excrete substantial amounts of GSH to the environment. The computational ETC model was extended by GSH interacting with redox sensors of photosynthetic bacteria. For biochemical characterization, the aerobic repressor protein PpsR of *R. rubrum* was purified by overexpression in *E. coli* and subsequent affinity

tag chromatography. The redox-sensitivity of the protein towards GSH could be demonstrated *in vitro* by fluorescence measurements. We are currently exploring the molecular basis for the observed phenomenon in a number of further mutant strains.
This part of the *R. rubrum* project is a close collaboration with the theoretical teams of Steffen Klamt and Ronny Straube.

4.1.2 Central metabolic pathways and biotechnological application

The high potential of anoxygenic photosynthetic bacteria for applications in biotechnology, medicine and agriculture is well-documented by published research articles [R27], [R28], [R29] and patent database entries. Purple bacteria are natural producers of a range of physiological active chemicals such as vitamins (B12), coenzymes (Q10), porphyrines and others. The major hallmark of the present project is a cultivation system which allows the complete separation of the expression of PM from the availability of light in *R. rubrum* (see above). This system opens a novel perspective for the high level production of PM and associated products at large scale volumes. During the period under report, the elucidation of central metabolic pathways was a major goal. Comprehensive metabolite profiles have been determined from cells growing at aerobic and semi-aerobic conditions as well as under fermentative and phototrophic conditions. These analyses were performed in collaboration with the Forschungszentrum Jülich (Oldiges) and the results reflect the outstanding metabolic flexibility of purple bacteria. Experimental evidence obtained from cultures where acetate was employed as sole carbon source, indicate that aerobic and anaerobic fermentative metabolism employ different pathways for acetate and CO_2 assimilation [28]. While the novel ethylmalonyl-CoA pathway was the preferred route under aerobic conditions, the photosynthetic mechanisms are less clear. Also in cooperation with FZ Jülich, 13C-isotope-labelled metabolite profiles are currently obtained for directly determining metabolic fluxes under this condition. All theoretical aspects of central metabolic pathways, incl. 13C-metabolic flux analysis are addressed in close collaboration with the ARB group. A stoichiometric model of central metabolism, developed by the ARB group was applied for analyzing carbon and redox balancing and for understanding the metabolic basis of mutant phenotypes [15]. Flux balance analysis and elementary mode analysis will also be applied for optimizing the network for biotechnological applications.
During the period under report, we achieved another important milestone and increased the obtainable cell concentration in a bioreactor tremendously. Applying a kinetic process model for fed-batch cultivation resulted in high cell densities (HCD) of ca. 60 g/L cell dry weight, thus entering a range which is commonly employed in bioindustrial processes. Unfortunately, HCD cultures were strongly impaired in PM expression. It could be demonstrated that the inhibitory effect originates from soluble compounds present in the culture supernatant and the inhibition could be relieved by a perfusion cultivation process. An important finding was that HCD cultures excreted quorum sensing signaling molecules of the acyl homoserinelacton (AHL) type into the culture broth. Five different compounds could be isolated and identified by HPLC-MS so far. The biological activity of the AHLs was demonstrated in cooperation with the FORSYS center, Freiburg (FRISYS, Anke Becker) using engineered indicator strains. Ongoing tests shall clarify the effect of AHLs on photosynthetic gene expression and PM formation in HCD cultures.

The derived process models and HCD cultivation strategies were also applied to the BMBF FORSYS-partner project “Superexpression of industrially relevant carotenoids using a systems approach” in cooperation with University Stuttgart (Oliver Sawodny, Robin Ghosh). A further field of application is the production of biopolymers (polyhydroxyalkanoates) with *R. rubrum* and an industrially employed producer organism, *Ralstonia eutropha*. This work is a joint project with the PSD group (Achim Kienle) whose contribution is cybernetical modeling and expertise in theoretical analysis of population dynamics [13].
In the period under report, we additionally started a joint project with Ulrike Krewer (PoES-Group) based on the concept of "Energy Harvesting". The integration of small scale electrochemical fuel cells and *R. rubrum* bioreactor cultivations for utilizing biological hydrogen production is the overall topic. Mutant strains with increased hydrogen-productivity obtained recently from the lab of Robert Tabita, Ohio State University, Columbus will play a key role in this project.
Furthermore, in collaboration with the BPE group, the Grammel team contributed its expertise in bioreactor process development also to the large-scale cultivation of *Saccharomyces cerevisiae* and *Pichia pastoris* for producing recombinant proteins [1], [17].

4.2 Research Team: Systems Biological Analysis of Local and Global Regulations

Katja Bettenbrock

Bacteria have to adapt quickly and efficiently to changing conditions to secure survival and growth. Despite the fact that extracellular conditions have to be monitored most sensory systems perceive intracellular signals. Extracellular conditions obviously influence bacterial metabolism thereby generating signals that are sensed by the regulatory systems.

4.2.1 Systems biological analysis of the PEP dependent phosphotransferase System

The *E. coli* phosphoenolpyruvate-dependent phosphotransferase system (PTS) represents a paradigm for the coupling of metabolic and regulatory functions [R6]. The PTS is the main uptake system for glucose and a number of other carbohydrates in *E. coli*. A phosphoryl group stemming from PEP is transferred via the general PTS proteins (EI and HPr) to the substrate-specific EII that catalyze the uptake and concomitant phosphorylation of the substrate. In addition to their function in carbohydrate uptake, the PTS proteins, especially $EIIA^{Glc}$, perform important regulatory functions. $EIIA^{Glc}$ is responsible for controlling cAMP synthesis and thereby the activity of the global transcription factor cAMP.CRP that is predicted to control about 200 target promoters in *E. coli* [R6]. The PTS has been under investigation by this research team and the team of Andreas Kremling during the last years. A comprehensive mathematical model has been set up and validated with experiments [3]. Comparison to similar modeling approaches showed the strength of this particular model and the modeling approach [19]. Experiments carried out with different growth substrates showed that there was an obvious correlation between the growth rate that *E. coli* assumed on the different substrates and the phosphorylation state of $EIIA^{Glc}$. In addition, as expected a correlation of extracellular cAMP concentrations to $EIIA^{Glc}$ phosphorylation and specific

growth rate could be shown [4]. Careful analysis of the data with the help of a modified model allowed understanding for the first time how the nutritional state is sensed by *E. coli*. The cells sense the PEP to pyruvate ratio via the phosphorylation state of $EIIA^{Glc}$ and the other PTS proteins. Due the wiring of PTS and glycolysis this ratio reflects the flux through glycolysis and thereby the nutritional state [20].
In addition to the carbohydrate PTS, *E. coli* possesses a set of proteins showing homology to EI, HPr and EIIA, the so called nitrogen PTS (N-PTS). EIICB homologues involved with the N-PTS could not be identified so far. An involvement of the N-PTS in controlling K^+ uptake has been demonstrated [R24]. Experiments performed in our lab as part of MaCS showed that PtsN, the EIIA homologue, is influencing central metabolism, especially acetate overflow depending on its phosphorylation state. Currently studies are undertaken to identify the actual targets of this regulation that, according to our data, takes place at the level of protein activity.
Acetate overflow which is linked to the C-PTS and, as reported above, most probably also to the N-PTS is in the focus of the FORSYS Partner project “Dynamics of the metabolic balance in *E. coli*”. In this project the adaptation of *E. coli* to changing glucose concentrations and the role of the PEP:Prv node in this adaptation is investigated. The experimental investigations are closely connected to modeling studies performed in the team of Carsten Conradi.

4.2.2 Adaptation to changing oxygen concentrations

Another focus of the group was on the adaptation of *E. coli* to changing oxygen conditions as part of the SysMO SUMO and $SUMO_2$ consortia. By using a calibration method that allows a quantification of aerobiosis [R1], the adaptations of *E. coli* MG1655 and of isogenic mutants lacking Succinate Dehydrogenase (SDH) and Fumarate Reductase (FRD) to different aerobiosis levels was studied in continuous cultures. It could be shown that there are no obvious switching points but rather a gradual adaptation of metabolism from fermentation to respiration [30]. Gene expression adapted to the various conditions with different genes displaying distinct expression profiles. Gene expression analysis was performed via Real Time RT PCR, a method that was also applied in a collaboration project with the BPE group [36]. Although SDH and FRD are considered to be important enzymes for aerobic or anaerobic metabolism respectively, knock out of these genes had only slight effects, the most significant being that SDH knock out results in constitutive acetate overflow [30]. Besides the analysis of continuous cultivations different constant aerobiosis levels, the SUMO consortium analyzed shifts in aeration by microarray analysis and determined the activity of transcription factors, most importantly of ArcA and FNR [27]. An interesting outcome was that against expectation the activity of ArcA is not coupled to the redox state of ubiquinone [R11]. Also as part of the SUMO consortium a web service for the analysis of gene expression was developed [21].

4.2.3 Analysis of single cell behavior

In the SUMO project as well as in a MaCS project dealing with *lac* operon regulation a new focus was set on the analysis of single cell behavior. Methods were established and mutants were constructed that allowed for the analysis of gene expression at single cell level.

Interesting results could be obtained for the *lac* operon of *E. coli,* a paradigm system in bacterial genetics. It could be shown that the third gene of the *lac* operon, *lacA*, encodingtransacetylase which has been neglected in most studies, influences induction by the gratuitous inducer IPTG [22]. Bistability which was reported to occur at TMG (another artificial inducer) but not at IPTG induction [R23] could be demonstrated also after induction with IPTG. In collaboration with the Kremling and the Straube group the *lac* operon was also analyzed with the help of mathematical models. The models predict a bistability also for induction with lactose which is currently under experimental investigation. First results look promising. In addition to the *lac* operon, another system displaying bistability, namely different biomass yields during growth of *E. coli* in a mixture of glucose and glucose 6-phosphat, is observed. Theoretical studies by the Kremling team and of the PSD group indicated the existence of bistability at defined conditions. The theoretical studies could principally be confirmed but experimental analysis have not been completed yet.

4.2.4 Model-based modification of cellular regulation and metabolism

Another focus of this research team is going to be on the model-based modification and control of cellular functions. During the last years this method was applied to control cell cycle in *S. cerevisae*, in collaboration with W. Hilt of the University of Stuttgart. The project depended on the establishment of a light controlled gene expression system [R35] in *S. cerevisiae*. Despite extensive efforts this was not achieved. As the major experience of this team is in working with *E. coli*, model-based modification and online control of gene expression in *E. coli* will be a future focus of this group. Different light-controlled gene expression systems [R16], [R19] which are currently established in our lab, will be applied, in addition to traditional systems like the *tac* promoter. Motivated by metabolic engineering studies performed by the ARB group, we put the gluconeogenetic enzyme PEP Synthetase under the control of the *tac* promoter. It could already be demonstrated that the PEP:Prv ratio but also the production of organic acids can be systematically influenced.

4.2.5 Outlook

This research team is now part of the ESB group. Research on the aerob / anaerob response will continue as part of the SysMO SUMO2 consortium. In the next years, the focus of this team will be in the establishment and performance of methods that allow for an online control of intracellular fluxes. This will include the establishment and development of gene expressions systems that can be controlled online but also the development of strategies for the online measurement of important intracellular signaling molecules. This work will be performed in close collaboration with the ARB group (Steffen Klamt, Carsten Conradi). The second focus will be on the analysis of population vs. single cell behavior and on bistabilities in biological systems. This will again be done in collaboration with ARB group (Carsten Conradi, Ronny Straube) and the PSD group (Achim Kienle). In addition the team is currently identifying interesting collaboration projects with the PSE (Kai Sundmacher) and PCF (Andreas Seidel-Morgenstern) groups.

4.3 Research Team: Modeling Tools and Databases for Systems Biology

Sebastian Mirschel

In recent years, in systems biology research there has been a noticeable trend towards combining different modeling approaches and composing integrated models. Associated with that are issues such as higher model complexity and the need for standardization. Our research team participates in these essential research activities by developing and providing methods, software tools and scientific databases.
Especially the modular modeling concept and related applications for models of process engineering and systems biology has been subject to further investigations. In particular, these are editing functionality of modular models, decomposition techniques [R23] and efforts for model integration. All these outcomes are supported by adequate visualization methods. A central tool is the modeling framework ProMoT [24]. Dynamic and Boolean modeling is now well-established and integrated in different workflows e.g. modeling, simulation and analysis using ProMoT (see Fig. 2). For this purpose ProMoT was interfaced with tools such as Diana [R14] (with PSD group) and *CellNetAnalyzer* [R13] (with ARB group). In order to fasten the modeling process using different modeling approaches we are working on a concept for connecting qualitative and quantitative modeling.
A prequisite for successful integration and handling of different modeling approaches are data management and standardization. For this purpose we established a system for finding, sharing and exchanging data, models and workflows. This data management system is now provided and maintained for MaCS and some applications within the MPI.

4.3.1 Modular Modeling and ProMoT

Working with modular models has been improved in ProMoT. This includes mainly three aspects. First, editing of modular structures is more comprehensive. In particular, automatisms for composing or decomposing modules have been developed. In this context a technique for automatic modularization of SBML models was established [R25]. Second, an integration tool for modular models was implemented in ProMoT. In order to obtain a larger coherent model the assignment of elements from different models is an essential step in the integration process. In this step correct, partial or even conflicting assignments may occur. In the latter two cases, a successful manual assignment needs visual support. In the beginning model integration was facilitated using ProMoT. However, model integration is a complicated process and we are now cooperating with the Conradi team which develops a versatile integration workflow using additional software tools, e.g. [R15]. Third, visualization methods for the handling of modular models have been improved. For instance, in ProMoT it is now feasible to intuitively depict analysis results in the context of complex modular models e.g. visualization of an integrated, Boolean model including different signaling pathways (with ARB group).
All developed methods are part of the modeling tool ProMoT [24] which provides import and export of SBML models. The software can be downloaded free of charge from [16]. ProMoT and its interfaces to other tools provide a common software infrastructure that is used in several projects of the groups ARB (Steffen Klamt), PSD (Achim Kienle), PCF (Andreas

Seidel-Morgenstern) and PSE (Kai Sundmacher), and also on a national (University Stuttgart) and international level (EMBL Hinxton).

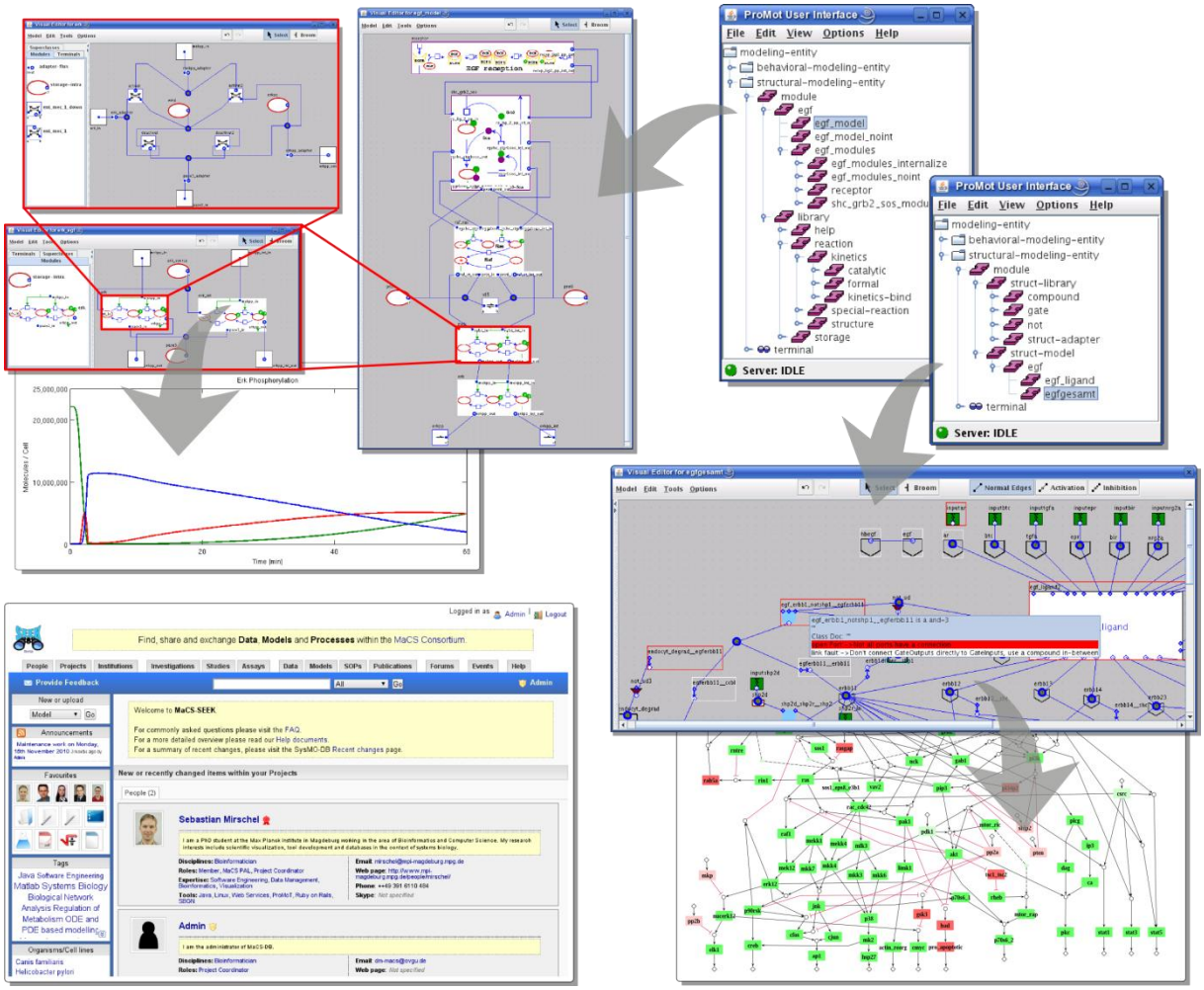

Fig. 2 Modular modeling with ProMoT using different modeling approaches (top, right); Data management using an intuitive web interface for accessing different types of data (bottom left).

4.3.2 A new approach for the setup of domain-oriented models of signal transduction

Various model types are used to model signaling pathways. Especially, qualitative and quantitative approaches are frequently applied. We focus on establishing a common model representation connecting rule-based modeling approaches [R8] and a specific Boolean modeling formalism [R13]. Therefore we developed a concept called Process-Interaction-Model (PIM). The PIM is a domain-oriented approach which is based on a detailed description of interactions between binding and modification processes that occur in complex signal transduction and regulatory networks. The representation incorporates the definition of molecules, domains, processes, interactions and parameters. The goal is to generate qualitative (Boolean) and quantitative (rule-based) models on the basis of the common representation. Thus one basis can be used to study a biological system at different levels of detail. The approach is supported in the modeling software ProMoT [24]. Libraries with building blocks and converters for different model specifications have been implemented.

This approach is developed in close cooperation with the ARB group (Steffen Klamt) and EMBL Hinxton (Julio Saez-Rodriguez).

4.3.3 Scientific Data Management

As a highly interdisciplinary research center, MaCS requires an appropriate system for managing, sharing and exchanging different types of data. Within the center different types of data are generated - ranging from experimental results, methodological data e.g. Standard Operating Procedures (SOPs) to models and software tools. For successful collaboration the data needs to be exchanged in a straightforward and easy-to-use way between and within the research groups. Thus, a scientific data management that focuses on handling and bridging the diversity of data and furthermore establishes a common understanding should be a key objective and an integral part of MaCS.
In 2010 we established a data management system (MaCS-DB) that provides a platform for sharing and exchanging data generated in MaCS and at the MPI. It is mainly based on the solution developed for the SysMO consortium [R39]. The software itself consists of a relational database storing all necessary information, a web interface giving access to the assets catalog, and mechanisms for different APIs interfacing external data repositories (see Fig. 2). For standardization purposes MaCS-DB follows the recommended formats and guidelines of the systems biology community, in particular Nature Protocols for SOPs; SBML, SBO and MIRIAM for models; DOI and PubMedID for publications and MIBBI for data sets [R4]. Through committed representatives of all participating research groups a constructive cooperation and further development is ensured. For knowledge transfer we cooperate with the HITS gGmbH Heidelberg (Wolfgang Müller) and the University of Manchester (Carole Goble). MaCS-DB is based on a flexible architecture and might be extended and used as a central service for systems biology research in Magdeburg in the future.

4.4 Research Team: Design Principles of Biological Networks

Ronny Straube

Despite recent advances in high-throughput methods for the quantitative analysis of large-scale cellular reaction networks we often still lack an intuitive understanding for the design principles and the respective functionality of the underlying network structure. Therefore, my team focuses on comparably small, yet biologically relevant, network structures (called network motifs) to reveal and analyze their advantages compared to alternative designs. We use methods from applied mathematics, nonlinear dynamics, and non-equilibrium statistical physics to understand the relation between design and functionality of molecular reaction networks, especially in the presence of diffusive coupling and molecular noise.

4.4.1 Redox- and Light-Dependent Gene Regulation in Purple Bacteria

Facultative photosynthetic bacteria switch their energy generation mechanism from respiration to photosynthesis depending on oxygen tension and light. Part of this transition is mediated by the aerobic transcriptional repressor PpsR. In *Rhodobacter sphaeroides*, the

repressive action of PpsR is antagonized by the redox- and blue-light-sensitive flavoprotein AppA [R3] which results in a unique phenotype: The repression of photosynthesis genes at intermediate oxygen levels and high light intensity [R34], which is believed to reduce the risk of photooxidative stress. To understand the mechanistic basis for the occurrence of this phenotype we developed a simple mathematical model [25] based on the structural knowledge of the AppA/PpsR interactions: The AppA-mediated reduction of PpsR and the light-dependent complex formation between the reduced forms of AppA and PpsR (Fig. 3). By a steady-state analysis we show that high-light repression can indeed occur at intermediate oxygen levels if PpsR is reduced on a faster timescale than AppA and if the electron transfer from AppA to PpsR is effectively irreversible. The model further predicts that if AppA is in excess over PpsR the transition from aerobic to anaerobic growth mode can occur via a bistable regime which has not been observed experimentally yet. We provide conditions for the emergence of bistability and discuss possible experimental verifications.

4.4.2 Molecular Mechanisms of Pattern Formation

Spiral-shaped concentration waves are common patterns in reaction-diffusion systems. For spiral waves the core acts as an organizing center which periodically emits wave fronts that are directed away from the spiral core [2]. However, oscillatory media also allow for inward propagating waves [R21] where the wave fronts propagate towards the spiral core. As yet, such antispirals have only been observed in purely chemical systems [R38, R33]. Recently, we reported on the first observation of inward rotating spiral waves in a biologically relevant enzyme system [34]. Experiments were done with yeast extracts where antispirals appeared as waves of glycolytic activity in an open spatial reactor. Simulations with the Gold-beter model [R12] have shown that the occurrence of antispirals crucially depends on the number of PFK subunits -- in agreement with the octameric structure of yeast PFK. In a subsequent study we found that the occurrence of antispirals also depends on the details of the mechanism for the allosteric activation of the PFK [32]. In particular, we showed that antispirals can arise if the PFK is activated in a sequential manner as in the Monod-Wyman-Changeux model (Fig. 3). In contrast, if activation occurs in a Hill-like fashion [R31], antispirals are suppressed by stationary Turing patterns. This analysis shows how the macroscopic patterns in a system depend on the underlying molecular reaction mechanism.

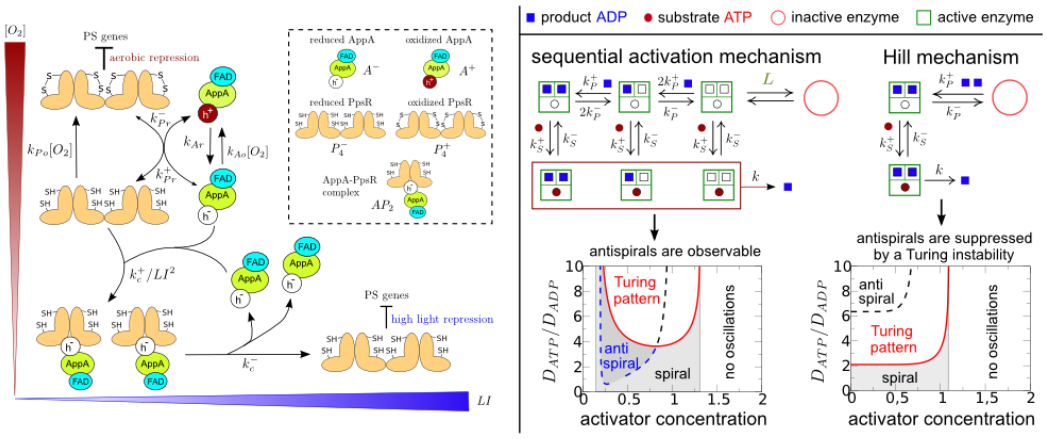

Fig. 3 Left panel: Model for the interaction between AppA and PpsR according to [25]. Right panel: Relation between the allosteric activation mechanism of the PFK and the occurrence of antispirals. Phase diagrams were obtained by mapping reaction-diffusion models to an associated complex Ginzburg-Landau equation [32].

4.4.3 Spatial Aspects of Intracellular Signaling

The time a diffusing molecule needs to reach a particular target inside the cell, the so-called mean first passage time (MFPT), is often the rate limiting step in the initiation of a signal transduction cascade and intracellular gradients of signaling molecules can provide positional information which restricts signaling to particular subcellular compartments. So far, explicit expressions for the MFPT or the spatial profile of signaling gradients were only available for simple geometries [R17], [R30], [R5]. Based on the theory of matched asymptotic expansions we calculated explicit expressions for the MFPT in the presence of multiple targets or exit sites for different 2d and 3d geometries [11], [6], [37]. These calculations indicate that the nucleus has many more pores (nuclear core complexes) than are required for an optimal exit time from the nucleus into the cytoplasm [6]. We also provide explicit expressions for the concentration profiles of activated signaling molecules for the case of signaling from multiple compartments inside a spherical cell. Solutions are given in terms of Green's or Neumann functions and their decay behavior can be used to classify intracellular signaling gradients according to their decay length [33]. In an invited contribution [31] we investigated the impact of molecular crowding on buffered Ca^{2+} diffusion.

4.4.4 Quantitative Modeling of the *lac* Operon in *E. coli*

Induction of the *lac* operon in *E. coli* represents a paradigm for bistability in biological systems. However, as yet, bistability has only been observed with artificial inducers such as thiomethyl-galactoside (TMG) [R23], and there is an ongoing debate about the conditions that are required to observe a bistable induction of the *lac* operon in the presence of natural inducers such as lactose [R26], [R20], [R7]. The major argument against bistability with lactose as an inducer is the growth-rate dependence of *lac* induction. We are currently testing this prediction experimentally in collaboration with team Bettenbrock (SBI group). We have used time series measurements of β-galactosidase activity in batch cultures to parametrize and validate an extension of the Narang model [R20]. Interestingly, it predicts a bistable induction even under physiological conditions and recent experiments are in qualitative agreement with that prediction. In the next step we will quantitatively compare the model predictions with experiments which could help to settle a longstanding question.

4.5 Research Team: Qualitative Dynamics of Biochemical Reaction Networks

Carsten Conradi

Mathematical modeling has long been recognised as an important tool in Biology, for example for (i) collecting and presenting the available biochemical knowledge in a formal way, for (ii) generating new biochemical insights (by comparing computational predictions with experimental observations), and for (iii) controlling biochemical systems in a desired way (by applying tools from control theory and biochemical engineering). Classical approaches for the latter two purposes, however, rely heavily on computational and numerical techniques. But realistic biological models are generally large in terms of states and (unknown) parameters and in most cases poorly parameterized (because of noisy measurement data of few components, a very small number of data points and only a limited

number of repetitions). This severely limits the generation of new biochemical insights by comparing computational predictions with experimental results as numerical techniques (e.g. simulations, bifurcation and sensitivity analysis) are not easily applicable. Instead, in order to generate new biochemical insights, the following question arises naturally: can a given reaction network reproduce an observed behavior at all, that is for any conceivable parameter vector?

Mathematically one is therefore interested in necessary and sufficient conditions for certain *qualitative dynamical properties* of the mathematical models defined by reaction networks (qualitative dynamical properties of interest in biochemical applications are, for example, the existence of multiple steady states, switching or oscillations). Our research consequently aims at establishing such necessary and sufficient conditions. To assess, ensure and improve their applicability, these conditions are applied to real-world biochemical reaction networks. So far the focus has been on the existence of multiple steady states (multistationarity), bistability and more general switching behaviour, as these are desired features of many mathematical models in Systems Biology; for example in modelling the cell cycle (where check points controlling cell cycle progression are often realized mathematically by bistable systems [R32]) or in modelling cellular differentiation (where different cell types are realized by different stable steady states [R37]). All results are currently limited to systems of ordinary differential equations (ODEs) derived from mass action networks, but extension to non-mass action kinetics will be an important part of our future research.

4.5.1 Multistationarity in mass action networks and chemical reaction systems with toric steady states

For mass action networks with certain structural properties conditions for multistationarity are derived. These conditions take the form of linear inequality systems that are independent of parameter values [7], [26] [8]. This has two advantages: (i) the linear inequality systems are not affected by the poor parameterization that is characteristic for models in Systems Biology and (ii) feasibility of linear inequality systems can be tested easily and reliably. Hence for networks where these conditions are applicable it is straightforward to decide about multistationarity. (For general mass action networks this is not the case, as, for example, multistationarity is equivalent to the existence of at least two positive solutions to a system of polynomial equations). Moreover, the conditions are constructive (in the sense that they allow the computation of pairs of steady states and parameter values [10], [7], [26]). As these conditions are only applicable to certain mass action networks, sufficient conditions have been derived that guarantee the necessity and sufficiency of the linear conditions. These have been formulated with the help of the two matrices encoding the structure of every mass action network, the *stoichiometric matrix* encoding the reactions and the reaction *rate-exponent matrix* whose columns define the reaction rates. The approach taken in *chemical reaction systems with toric steady states* is based on Algebraic Geometry and sufficient conditions to identify reaction networks where the linear conditions hold are stated in terms of the nullspace of the stoichiometric matrix [26]. The approach taken in *multistationarity in mass action networks* is similar to Feinberg's Chemical Reaction Network Theory (CRNT) [R9] and we view our results as complementary to those established in CRNT. Here sufficient conditions to identify reaction networks where the linear conditions hold are stated in terms of the stoichiometric matrix and the rate-exponent matrix [7].

4.5.2 Subnetwork analysis and model integration

Some realistic reaction networks are not directly amenable by the above mentioned theories, as they do not possess the required structural properties. To address this problem a unique decomposition of reaction networks into smaller subnetworks has been proposed and necessary and sufficient multistationarity conditions for these subnetworks are guaranteed to take the form of linear inequality systems. Moreover, given multistationarity in a subnetwork, an algorithm for the computation of rate constants of reactions in the overall network is proposed that guarantees steady states close to those of the subnetwork [12], [35]. Within the Virtual Liver consortium this algorithm will be adopted to model integration.

4.5.3 Qualitative Dynamics of mass action networks

Here conditions for switching behaviour are derived, for example by establishing points where the dynamical system undergoes a saddle-node bifurcation whereby the global stable manifold of the saddle is acting as a switching surface. This approach is based on the special structure of the Jacobian of a mass-action network [9]. It employs the fact that dynamical systems originating in Systems Biology often involve so-called *conservation relations* confining trajectories to affine linear subspaces of state space. Thus, the Jacobian of such a system evaluated at an arbitrary point in state space has at least as many zero eigenvalues as there are conservation relations. Consequently, for a saddle-node bifurcation to occur at a particular point in state space, the Jacobian has to have an *additional zero eigenvalue* at that point. In general mass-action systems undergo a saddle-node bifurcation at that point, yielding some form of bistability [8].
Our conditions take the form of linear inequality systems and are constructive (i.e. solutions to one of the inequality systems determine a state and parameter vector where the Jacobian has an additional zero eigenvalue). Infeasibility of all inequality systems does not exclude additional zero eigenvalues, hence feasibility of at least one inequality system is only sufficient for an additional eigenvalue (and thus usually for a saddle-node bifurcation). One significant advantage is that this linear inequality condition is sufficient for every mass action network as there are no constraints on the network structure.

4.5.4 Qualitative Dynamics of PTM networks

Here the theoretical results described above are applied to networks describing the post translational modification of proteins (PTM networks). Such PTM networks are, for example, biochemical realisations of check points controlling the cell cycle (e.g. Sic1 in budding yeast). As mathematical descriptions of these check point are generally associated with bistability [R32], conditions ensuring that a PTM network can exhibit multistationarity (a prerequisite of bistability) are of particular interest. Multistationarity has been established and analysed with respect to robustness for several such networks [29]. This project is funded by the IMPRS and co-supervised with Dietrich Flockerzi from the SCT group.

5 Selected Teaching Activities, PhD Projects and Habilitations

Tab. 3 Teaching activities

Title of lecture	Place	Lecturer
Grundlagen stochastischer Prozesse in biophysikalischen Systemen	Univ. Magdeburg	R. Straube
Systems Biology I	Univ. Magdeburg	A. Kremling
Systems Biology II	Univ. Magdeburg	A. Kremling
Microbiology	Univ. Magdeburg	K. Bettenbrock H. Grammel
Environmental Biotechnology/Umweltbiotechnologie	Univ. Magdeburg	H. Grammel
Theoretical methods in Systems Biology	Univ. Magdeburg	C. Conradi

Tab. 4 PhD Projects

Title	Group Member	finished
Experimental analysis of the thiol redox signaling network in photosynthetic bacteria	Anke Carius	
Mathematical modeling of biochemical signal transduction pathways in mammalian cells – a domain-oriented approach to reduce combinatorial complexity	Holger Conzelmann	12/2008
Thermokinetic modeling and model reduction of reaction networks	Michael Ederer	11/2009
Dynamische Modellierung und Analyse der Signaltransduktion und Regulation der K^+-Homöostase bei *E. coli*	Stefan Gayer	
Modeling the mitogen-dependent control of hepatocyte proliferation	Jeremy Huard	
Molecular biological and biochemical investigations characterizing the regulatory function of the nitrogen PTS in *Escherichia coli* LJ110	Susann Jahn	
An extended framework for dynamic flux balance analysis	Jim Joy	
Reduced order modeling and analysis of cellular signal transduction	Markus Koschorreck	03/2009
Graph based methods for analysis and composition of ODE models in systems biology	Katrin Kolczyk	
Qualitative dynamics and control of metabolic networks in *E. coli*	Bernhard Kramer	
Analysis of *lac* operon induction at population and at single cell level	Anja Marbach	
Regulation der Hefezelle durch lichtvermittelte Kontrolle des mitotischen Zellzyklusprogramms	Andrea Merbitz	
An interactive multiscale visual interface for exploring complex structures of modular models in Systems Biology	Sebastian Mirschel	
Reaktion von Glukose-limitierten *E. coli* Zellen auf Shifts und Pulse	Markus Nees	
Mathematical modeling of gene regulatory networks in photosynthetic bacteria	Rakesh Pandey	
Analysis of central metabolic pathways and process optimization for application of *Rhodospirillum rubrum* in biotechnology	Christiane Rudolf	
Mathematical modeling of the *lac* operon in *E. coli*	Daniel Samaga	
Aerobiosis dependent adaptation of central metabolism of *E. coli* MG1655 and analysis of bimodal phenomena of acetate metabolism	Stefan Stagge	
Systems-level analysis and model-based control of microaerobic physiology	Lisa Zeiger	

Tab. 5 Habilitations

Title	Group Member	finished
Einsatz ingenieurwissenschaftlicher Methoden in der Systembiologie	Andreas Kremling	2009
Räumliche Aspekte intrazellulärer Signalübertragung und Musterbildung in der Glykolyse	Ronny Straube	2011

6 Selected Memberships, Appointments, Awards

Conradi, C. Research fellowship at the Statistical and Applied Mathematical Sciences Institute (SAMSI) in Durham, USA (2008/2009)

Kremling, A. Appointment TU Munich (2010)

Zeiger, L. DECHEMA Polytechnic Award of the Max Buchner Research Foundation for diploma thesis (2009)

7 Future Directions

With the retirement of Prof. Gilles in May 2011, the SBI group has lost its status as an individual MPI research group. Because of the success of the group over the last years and its important role for the research profile of the institute as well as according to the SAB recommendation of 2009, it is however committed by the directorial board of the MPI to maintain Systems Biology as a core discipline at the institute. However, previous ideas to continue with a successor of Prof. Gilles as a research group or even at the department level have been considered not to provide a quick and adequate solution for the group (an additional department although not primarily intended at the moment, could nevertheless again become more attractive in the mid-term or long-term perspective of the institute).
Instead, the general strategy of the MPI for the SBI group is not to pursue with an individual research group, but to transform Systems Biology into a more integral part of the institute.
Currently, a research initiative of the MPI and the OvGU aims in establishing “Biosystems Engineering" as a new multidisciplinary and highly innovative research field in Magdeburg. It is expected that the theoretical and experimental expertise of the former SBI group will significantly contribute to this development. The theoretical competence (research teams of Carsten Conradi, Sebastian Mirschel and Ronny Straube) is now largely focused in the ARB group of Steffen Klamt. The experimental expertise in genetic engineering, molecular biology, biochemical analysis of microbial cells and bioreactor cultivations has been re-organized into two complementary teams headed by Katja Bettenbrock (Genetic Engineering, Molecular Biology, Gene Expression Profiling) and Hartmut Grammel (Bioreactor Cultivation, Biochemical Analysis, Metabolomics). The two teams together will build a new unit denoted as “Central Research Unit Experimental Systems Biology” which consists of Katja Bettenbrock, Hartmut Grammel and three additional technical assistants. The group will be included in the established allocation of the institute’s budget, accordingly. This construction is intended to make the highly-equipped lab facilities and analytical

instruments as well as the knowledge in performing appropriate experiments available also to those MPI groups which now enter the field of Biosystems Engineering without very much prior expertise in these techniques.
In the last years, the SBI projects were almost exclusively funded by grants successfully acquired by the senior scientists of the group. It is supported by the institute that beside the integration in joint collaborative projects with other MPI groups, the PIs (group leaders Klamt, Bettenbrock, Grammel) are free to apply for future third party funding for continuing their own independent research and to initiate new projects.
Currently, Katja Bettenbrock and Hartmut Grammel are applying for grants and are preparing joint projects with the individual MPI research groups. Here again, the close relation to the ARB group ensures that the essential interaction of theory and experiment - well-established during the common SBI group membership – will be realized in all these attempts. Future projects will emphasize the key aspects of the current Biosystems Engineering initiative.

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(Please note that this is not a complete list of publications.)

Research Group:

Analysis and Redesign of Biological Networks (ARB)

Dr.-Ing. Steffen Klamt

This report covers the period from October 2008 to August 2011.

1 Introduction

The Junior Research Group *Analysis and Redesign of Biological Networks* (ARB) was founded in February 2009 and originated from the former SBI Research Team of Steffen Klamt. The research activities of the ARB group lie in the field of Systems Biology and are centered around the development and application of theoretical methods for computer-aided *analysis, inference* and *targeted modification* of biological networks. Complementary to activities in the SBI group, the focus of the ARB group is mainly on medium- and large-scale cellular networks, where - despite increasing amounts of experimental data - biological knowledge is usually incomplete and of qualitative nature, hampering the construction of quantitative and predictive dynamic models. Accordingly, the ARB group develops and applies modeling techniques that are abstract enough to cope with qualitative and semi-quantitative biological information (e.g. on network structure or “ups and downs” of concentrations), yet allowing one to give meaningful predictions and to enhance our understanding of biological processes and systems. As a key ingredient for Systems Biology, we employ these theoretical methods in close collaboration with experimental groups to gain insights into the functioning of realistic signaling and metabolic networks. An ultimate goal is to use mathematical models to rationally redesign these networks, e.g. for bio-based production of value-added chemicals or for designing drug therapies to treat human diseases.

The ARB group collaborates with biological and theoretical partners from the MPI as well as from other national and international research institutes. Several collaborations were established on the basis of externally funded projects (FORSYS; Virtual Liver; CDS). Some projects are conducted in close collaboration with the former SBI group, e.g. in combined theoretical and experimental studies on metabolism and biotechnological applications of *E. coli* (Bettenbrock) and *R. rubrum* (Grammel). Projects performed with other groups of the MPI include (i) the study of mammalian cell metabolism for improved production of viruses and recombinant proteins (BPE group), (ii) novel algorithms for biological network inference (PSE group) and (iii) new methods to deduce qualitative properties of the dynamic behavior of biological reaction networks from network structure (SCT group). Founded in 2007 as a joint project of the OvGU and the MPI, the Magdeburg Centre for Systems Biology (MaCS) has become a crystallization point for Systems Biology research in Magdeburg. It is funded by the BMBF as one of the four FORSYS centres and was positively evaluated in 2009. The ARB group is an active member (and S. Klamt is vice-speaker) of MaCS and uses this platform to conduct and foster interdisciplinary projects with partners from the MPI and the OvGU. Furthermore, the ARB group collaborates with external biological partners in several projects on model-based analysis of mammalian signaling networks, e.g. with the German Cancer Research Institute (within the “Virtual Liver” consortium) and with groups from the Harvard Medical School (US), the University of Surrey (UK) and the Technical University of Athens (Greece). Finally, projects on mathematical and computational aspects of biological network analysis are jointly conducted with groups from the University in Jena, the Helmholtz Center Munich, the EBI in Hinxton (UK) and the ETH in Zurich (see Table below).

After the retirement of Prof. Gilles in June 2011 (at the end of the reporting period), the theoretically oriented research teams of the SBI group (Conradi, Straube, Mirschel) joined the ARB group. Perspectives of the extended ARB group will be discussed in section 7; the present report focuses on the activities before this re-structuring.

2 Members of the Research Group

	Status	**Joined MPI**
Dr. Steffen Klamt	Head of the Group	05/1998
Dr. Axel von Kamp	Postdoc	10/2007
Regina Samaga	Ph.D. Student	09/2006
Oliver Hädicke	Ph.D. Student	03/2007
Anke Ryll	Ph.D. Student	12/2010

3 Survey of Research Projects

The research activities of the ARB group divide into four major topics: (1) Modeling and rational redesign of metabolic networks; (2) Qualitative modeling of cellular signaling networks; (3) Biological network inference; and (4) Software *CellNetAnalyzer*.

Modeling and Rational Redesign of Metabolic Networks	This project deals with the development of novel methods for analysis and (re)design of metabolic networks. Developed algorithms are employed to analyze and/or engineer metabolic networks of bacteria and mammalian cells.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Mathematical approaches for rational (re)design of metabolic networks	Hädicke, von Kamp, Klamt	BMBF (FORSYS) LSA	since 03/2007	ETH Zurich (Dr. Haus); Univ. of Jena (Prof. Kaleta)
Applications of metabolic engineering	Hädicke, von Kamp, Klamt	BMBF (FORSYS)	since 03/2010	SBI (Dr. Grammel, Dr. Bettenbrock); BPE (Prof. Reichl); Humboldt University Berlin (Dr. Steuer);
Metabolic modeling and network analysis of photosynthetic bacteria	Hädicke, Klamt	BMBF (FORSYS)	since 01/2007	SBI (Dr. Grammel)
Qualitative Modeling of Cellular Signaling Networks	Quantitative modeling of large cellular signaling networks is often infeasible due to insufficient knowledge of mechanistic details and kinetic parameters. We develop and deploy modeling techniques capable of making testable qualitative predictions based on the known network structure. In collaboration with biological partners, we apply these methods to study large-scale signaling networks, in particular from hepatocytes within the “Virtual Liver” consortium.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Methods for modeling large-scale signaling networks	Samaga, von Kamp, Klamt	BMBF (Virtual Liver, FORSYS)	since 01/2006	EBI Hinxton (Dr. Saez-Rodriguez); Helmholtz Centre Munich (Prof. Theis)
Computing intervention strategies in signaling networks	Samaga, von Kamp, Klamt	BMBF (Virtual Liver, FORSYS)	01/2008-01/2010	
Qualitative perturbation analysis of ODEs based on interaction graphs	Samaga, Klamt	BMBF (FORSYS)	since 01/2009	SCT (Prof. Flockerzi)

Logical modeling of signaling networks in hepatocytes	Samaga, Ryll, Klamt	BMBF (Virtual Liver)	since 01/2007	German Cancer Research Institute (Dr. Klingmüller); Harvard Medical School (Prof. Sorger); NTU Athens (Dr. Alexopoulos); OvGU (Prof. Schaper)
Modeling of interacting mycobacteria and macrophages (TBHOSTNET)	von Kamp, Klamt	ERA-NET	since 03/2010	University of Surrey, UK (Prof. Kierzek)
Biological Network Inference	The wiring diagrams of many gene regulatory and some signaling networks are largely unknown. We elaborate and apply novel algorithms to infer the network structure from experimental data.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Network inference based on transitive reduction	Klamt	MPI	since 05/2009	PSE (Prof. Sundmacher)
Network inference based on logical modeling	Samaga, Klamt	BMBF (Virtual Liver)	since 01/2009	EBI Hinxton (Dr. Saez-Rodriguez); NTU Athens (Dr. Alexopoulos)
Software *CellNetAnalyzer*	The development of the MATLAB toolbox *CellNetAnalyzer* is a long-term project of the group. Novel algorithms for biological network analysis are continuously being integrated.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
(Further) development of *CellNetAnalyzer*	Samaga, von Kamp, Klamt Hädicke	BMBF (FORSYS, Virtual Liver)	since 2000	Mirschel, Kolczyk (SBI)

4 Research Highlights

4.1 Modeling and Rational Redesign of Metabolic Networks

4.1.1 Mathematical Approaches for Strain Optimization and Their Applications

Theoretical methods for modeling and targeted modification of metabolic networks based on stoichiometric models represent a long-term focus of our research. Stoichiometric or constraint-based modeling of metabolic networks relies mainly on network structure (possibly in combination with measured fluxes) and is thus independent of usually unknown kinetic mechanisms and parameters. Metabolic network models for diverse organisms have been reconstructed over the last years from genomic and biochemical information stored in databases [R3,R6]. Despite their static nature, stoichiometric models – in combination with tailored modeling techniques such as flux balance analysis [R11] or elementary-modes analysis [R12] – allow one to analyze a number of functional properties of metabolic networks and to make predictions, e.g. on gene essentialities and growth phenotypes [R3,R6]. They were also used successfully to study biotechnological capabilities of the respective organisms and to identify suitable intervention and design strategies for optimizing production processes [R2,R3,R6,R7,R16,R17]. A particular class of techniques relies on *Elementary Modes* (EMs) representing minimal functional units (pathways or cycles) of a reaction network [R13,R15]. The set of EMs characterizes the full spectrum of possible metabolic behaviors in steady state and facilitates the search for intervention strategies, as shown for example, by Srienc and co-workers in several case studies with *E. coli* (e.g. [R15,R16,R17]).

In the reporting period we devised two novel methods for strain optimization relying on EMs. The first, *constrained Minimal Cuts Sets* [4], represents a generalization of the Minimal Cut Sets (MCSs) approach introduced earlier by us. It aims at identifying minimal combinations of reaction/gene knockouts which guarantee blocking of undesired network functions or behaviors (e.g. synthesis of undesired by-products) while retaining desired functionalities (e.g. coupled product and biomass synthesis). Undesired functions are characterized by a set of *target EMs* (to be eliminated) and desired functions by a set of *desired EMs* (see Fig. 1a). The latter represent the side constraints and at least some desired EMs must not be disrupted by the MCSs. Using appropriate algorithms (see below) all equivalent knockout solutions can then be computed of which the best solution in terms of practical realization can be selected. The constrained MCSs approach offers an enormous flexibility in defining and solving knockout problems. Several other techniques (including e.g. OptKnock [R2] and the method of Srienc et al. [R16,R17]) are special cases of and can therefore be reformulated as constrained MCSs problems. Our method also allows the computation of robust knockout strategies for coupled product and biomass synthesis (Fig. 1b) which subsequently allow the use of adaptive evolution to further optimize producer strains [R8].

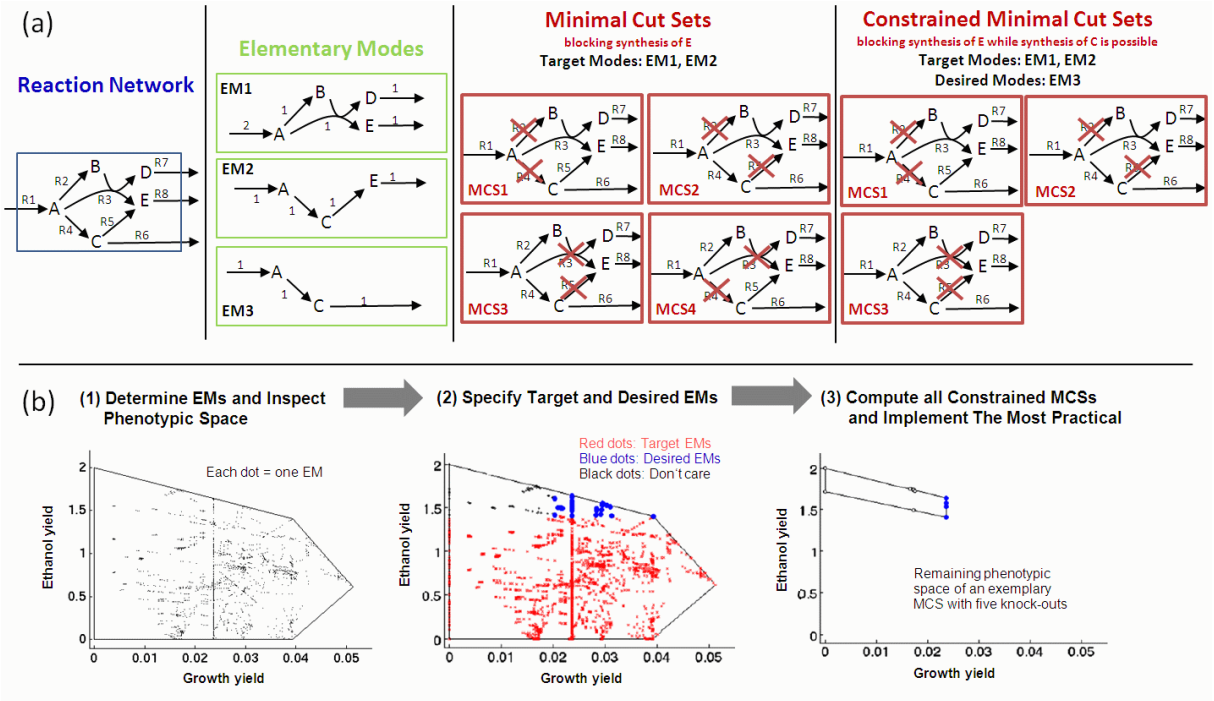

Fig.1: Principle and application of constrained MCSs. (a) Example network with EMs, MCSs and constrained MCSs (only internal reactions (R2-R5) are considered as removable). (b) Realistic example of metabolic network redesign [4]: the goal is to find intervention strategies for *E. coli* (anaerobic growth on glucose) which couple high-yield production of ethanol with low-yield growth. EMs with an ethanol-yield below 1.4 are selected as target modes (must be eliminated by the MCSs). From the remaining EMs those with relatively high biomass-yield (at least 0.02) become desired modes from which at least one must not be hit by the MCSs. In total, 1988 constrained MCSs solve the intervention problem.

The computation (enumeration) of EMs and MCSs is a difficult combinatorial problem and currently restricts their use to medium-scale networks. In collaboration with mathematicians from the OvGU Magdeburg / ETH Zurich we developed and tested several new algorithmic approaches [1,19]. For example, the MCS problem turned out to be strongly related to the *transversal hypergraph* problem and we identified the Berge algorithm as the best performing algorithm in the context of metabolic networks [19]. The general relevance of hypergraphs as

network models in Systems Biology was also discussed by us in a perspective paper [9]. Another very interesting finding was that EMs and MCSs are dual descriptions of metabolic network functions. In fact, recent results demonstrate that MCSs can be computed as EMs in a dual stoichiometric network [1]. This inherent relationship provides a promising new paradigm for analyzing function and dysfunction in biological networks. Finally, to make EM-based methods amenable to genome-scale networks, we are currently collaborating with Prof. Kaleta (University of Jena) to develop techniques for sampling of EMs.

Most stoichiometric optimization techniques identify genetic targets to increase product yield. Our second optimization framework CASOP (Computational Approach for Strain Optimization aiming at high Productivity) uses a heuristic method to identify interventions increasing the *specific productivity* of the strains [3]. To this end, CASOP estimates the relative contribution of a reaction to product yield and network capacity (and thus to productivity) by analyzing the spectrum of available conversion routes (EMs). As a result, CASOP delivers a reaction ranking suggesting gene knockout and – in contrast to many other stoichiometric optimization techniques – also over-expression candidates. The methodology is also well-suited to evaluate co-factor requirements in conjunction with product synthesis [3]. For example, we found that if *E. coli* produces succinate (a highly relevant platform chemical) with nearly maximum yield under anaerobic conditions, NADH and CO_2 can become stoichiometrically limiting whereas ATP might be present in excess – a counter-intuitive finding as the situation under normal anaerobic growth condition is exactly the opposite.

CASOP and constrained MCSs were implemented in *CellNetAnalyzer* (section 4.4) and a comparison of their predictions with published (tested) knockout strategies demonstrated a proof of principle. In several joint projects with experimental partners, many from the MPI, we are currently employing these methods in biotechnologically relevant applications:

- Optimization of the production of selected (value-added) fermentation products of *E. coli* (with Bettenbrock, SBI group). As a key approach we try to perturb certain co-factor pools (predicted by CASOP) to increase the performance of *E. coli* strains.
- Biotechnological applications of *R. rubrum* (with Grammel; see also below).
- Improving the production of viruses and recombinant proteins by mammalian cells by metabolic modeling and medium optimization (with BPE group).
- Metabolic engineering for cyanobacterial biofuel production (with Dr. Steuer, Berlin).

4.1.2 Metabolic Modeling of *Rhodospirillum rubrum*

Apart from targeted design of metabolic networks, we employ metabolic modeling to characterise physiological properties of the metabolism of selected organisms. A long-term project in this direction is the collaboration with Dr. Grammel (SBI) where we combine modeling and experimental studies to understand the versatile metabolism of *R. rubrum*, a representative of purple nonsulfur bacteria (PNSB; see SBI report). A particular focus of these joint studies is to clarify aspects of redox balancing and redox-mediated regulation allowing these bacteria to switch between different (e.g. photosynthetic and respiratory) lifestyles. A first milestone was a kinetic model of the electron transport chain of PNSB, which made important predictions [20]. For example, simulations showed a stronger reduction of ubiquinone when switching from high-light to low-light conditions, supporting the hypothesis that the redox state of ubiquinone is a suitable signal for controlling photosynthetic gene expression. The model also predicted the optimal light intensity at which PNSB can produce the highest amount of ATP - a result with important implications, e.g. for biotechnological applications.

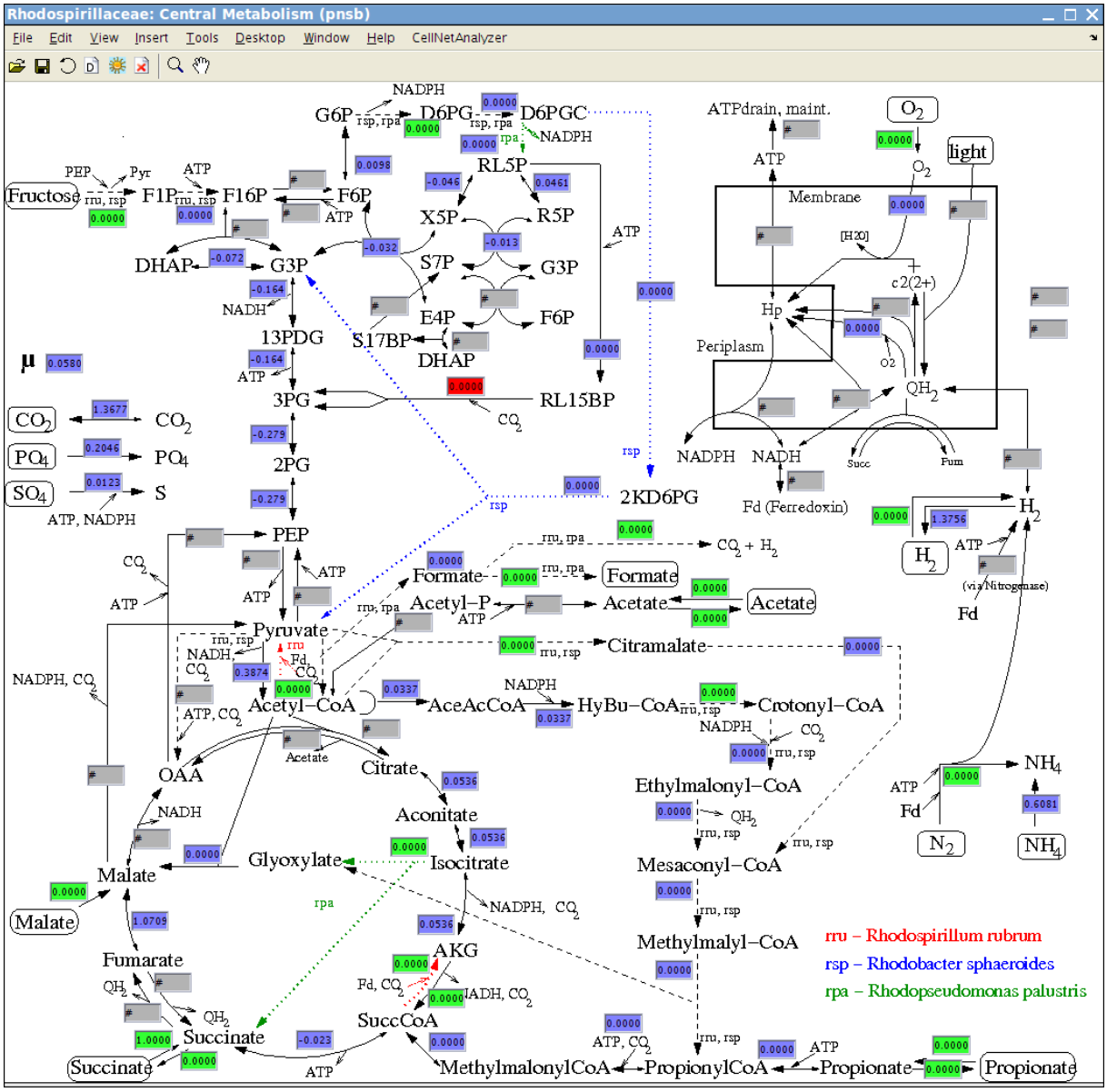

Fig. 2: Network model of the central metabolism of PNSB in *CellNetAnalyzer*. The depicted scenario simulates photoheterotrophic growth of PNSB on succinate predicting that hydrogen release occurs if CO_2 fixation via the Calvin cycle is blocked (red box: knock-out of the gene encoding for RubisCO (the key enzyme of the Calvin cycle); green boxes: prescribed fluxes; blue boxes: uniquely calculable reaction rates; gray boxes: non-calculable fluxes).

For examining the central metabolism of PNSB where kinetic modeling becomes prohibitive, we constructed an extended stoichiometric model comprising 142 reactions and 119 metabolites [5] which was implemented and analyzed in *CellNetAnalyzer* (Fig. 2). Based on flux variability analysis the model (i) revealed non-intuitive metabolic constraints related to redox homeostasis under photoheterotrophic growth of PNSB (e.g. requirement of CO_2 fixing pathways even if CO_2 is released in the net); (ii) reproduced various quantitative experimental data, and (iii) led to several new hypotheses. The model also enabled us to discriminate between different acetate assimilation pathways proposed recently. Furthermore, we used the model to study the capabilities of PNSB for biohydrogen production ([5] and Fig. 2). We currently employ the model for 13C flux analysis and plan to use it as a tool for rationally engineering *R. rubrum* towards biotechnological applications (see also SBI report).

4.2 Qualitative Modeling of Cellular Signaling Networks

4.2.1 Theoretical and Algorithmic Developments

Dynamic models of single biological signaling pathways have been shown to exhibit considerable explanatory and predictive power (e.g. [R13]). However, similar as in metabolic networks, a major obstacle for predictive quantitative modeling of *large-scale* cellular signal transduction systems is the typical lack of precise quantitative descriptions of the involved mechanisms. Qualitative modeling approaches for signaling networks that are capable of giving meaningful and testable predictions on the basis of the known network structure and semi-quantitative information have therefore become an important field of research in Systems Biology [R1,R5,R14]. Although successful for metabolic networks, stoichiometric models are not suitable to study information flows in signaling networks. In 2006 we proposed a novel methodology for qualitative modeling of signaling and regulatory networks (Fig. 3) based on the two related formalisms of *interaction (influence) graphs* (signed directed graphs) and *logical or Boolean models* (Klamt et al.; BMC Bioinformatics, 7:56 (2006) – this paper was recently highlighted as a core paper for Biological Network Modeling by ScienceWatch® [17]). The novelty of this approach is (i) the integrated analysis of interaction graphs and logical models by representing the latter as *logical interaction hypergraphs* (from which the interaction graph can easily be derived), and (ii) the introduction of several new techniques to analyze those models and to confront them with experimental data.

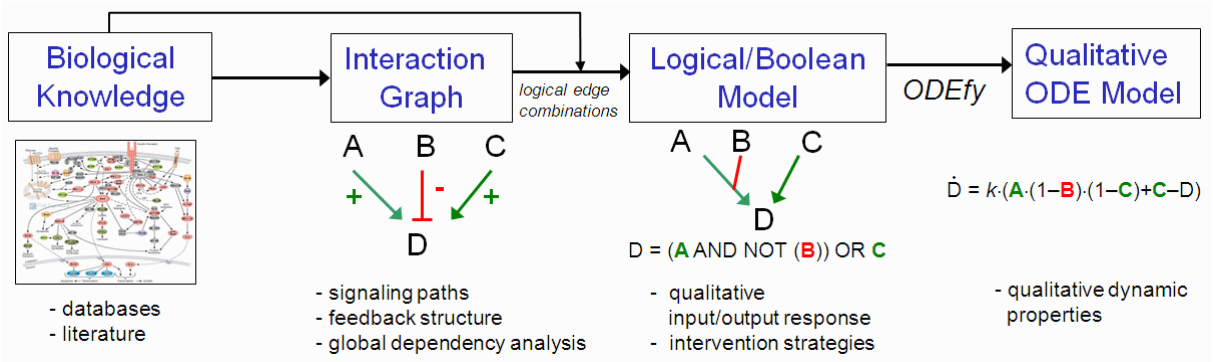

Fig. 3: Qualitative modeling formalisms for cellular signaling networks establishing a modeling pipeline. The transformation of interaction graphs to logical models and of the latter to qualitative ODE models is conservative with respect to properties of the more abstract model.

During the reporting period we extended this theoretical framework by qualitative ODE models (see 4.2.3) and by several new algorithms. One key algorithmic problem for analyzing interaction graphs is the determination of shortest positive and shortest negative paths between pairs of nodes. Somewhat surprising, this problem is much more complicated (NP-complete) than the well-known shortest-path problem in unsigned graphs. Although of fundamental importance for studying causality, only a few algorithms dealing with this problem have been published so far. We devised new algorithmic variants for computing exact or approximate results performing well in biological networks with hundreds of nodes [7].

Aberrant behavior of signaling networks is the cause for many diseases such as cancer. An important application of modeling is therefore the identification of potential (drug) targets [18]. To this end, we introduced the concept of minimal intervention sets (MISs) for logical networks. MISs are minimal combinations of knockouts (or inhibitions) and constitutive

activations of proteins that will lead to a desired response or behavior (e.g. (in-)activation of certain genes) [13]. The idea of MISs is similar to MCSs in metabolic networks (see 4.1.1) and leads again to a highly combinatorial problem. However, it requires a completely different algorithmic procedure to calculate MISs. In [13] we presented such an algorithm which, as another example for using methods from the engineering sciences in Systems Biology, employs techniques from electrical engineering (e.g. fault equivalence classes) for search space reduction. We demonstrated the performance of this procedure in large-scale networks and also highlighted further applications of MISs, e.g. as a diagnosis tool.

4.2.2 Applications

We used our modeling framework to study signal transduction networks of growth factors (e.g. EGF, HGF) and cytokines (IL-1, IL-6) in mammalian cells. The procedure usually involves three steps (Fig. 4): (i) Construction of a logical model by an extensive literature and database search; (ii) analysis of the logical model and its underlying interaction graph to characterize functional properties (such as interdependencies, feedback structure, qualitative input-output response); and (iii) comparison of selected model predictions with experimental data, preferably from stimulus-response experiments. As a fourth step, model-based data analysis may lead to a refinement of the model structure with respect to the investigated cell type (signaling pathways may have distinct characteristics in different cell types).

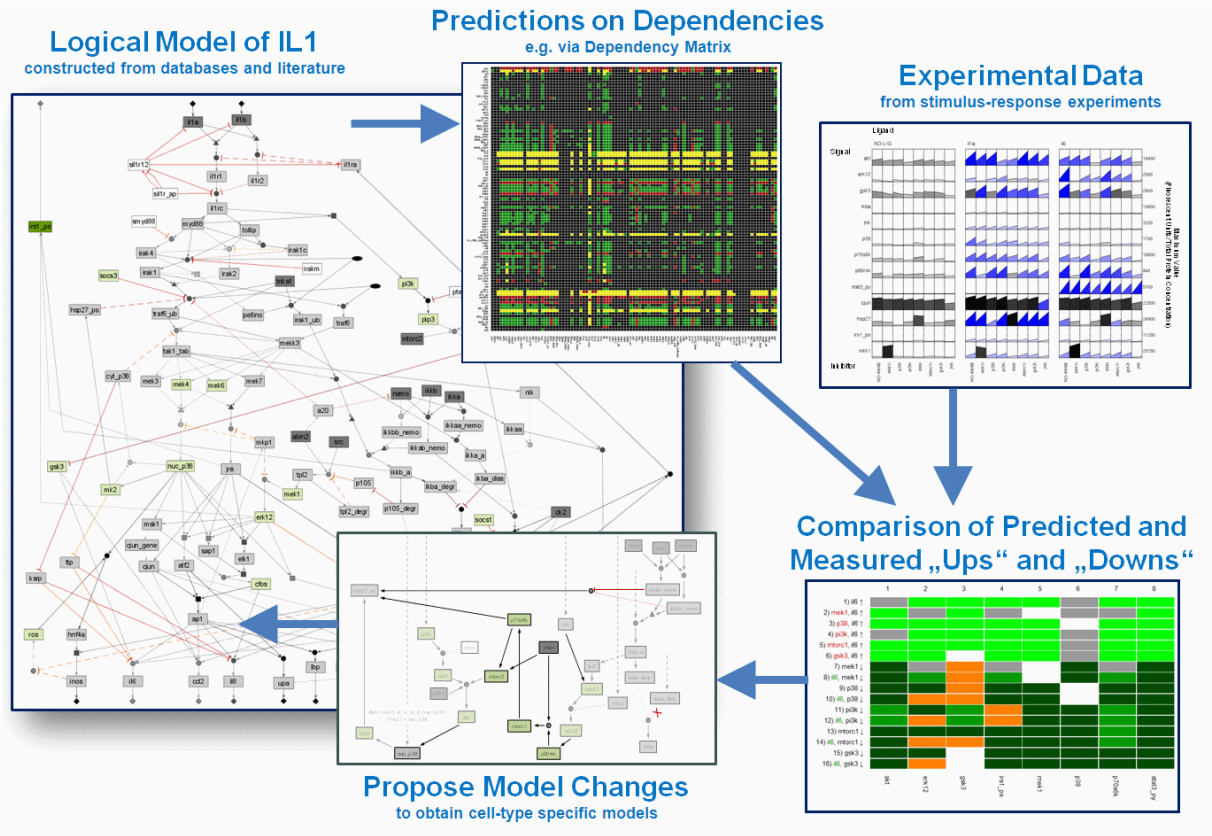

Fig. 4: Workflow for analyzing cellular signaling networks based on logical models and phosphoproteomic experimental data (example: IL1 signaling [10]).

As part of the “Virtual Liver” project, many of the models we reconstructed were investigated in the context of hepatocytes, the major cell type of the liver. Experimental data were provided by our collaborators Prof. Sorger (Harvard Medical School), Dr. Saez-Rodriguez (EBI

Hinxton, UK) and Dr. Alexopoulos (NTU Athens). They established a high-throughput experimental pipeline to measure the activation (phosphorylation) level of key proteins in hepatocytes in response to combinatorial stimulations with different growth factors and cytokines (triggering the signaling cascades) and inhibitors (deactivating certain proteins). The EGF/ErbB receptor signaling network model was the first where we used such a dataset to detect inconsistencies between model predictions and experimental results (e.g. regarding "ups" and "downs" of protein phosphorylation levels). One tool to detect those inconsistencies is the *dependency matrix* computed from the interaction graph (Fig. 4). By analyzing the paths and cycles in the network, this matrix displays the expected qualitative effects when perturbing certain nodes. For example, an up (down) regulation of node X is expected if only positive (negative) paths from the perturbed node Y to node X exist. In the EGF network, detected inconsistencies gave hints to missing or inactive connections in the network and led to new hypotheses on the network structure [14]. A similar study was recently conducted with logical models of interleukins 1 (IL-1) and 6 (IL-6), two important cytokines involved in inflammation processes. We again validated the models with respect to hepatocytes using experimental data produced by our partner Dr. Alexopoulos (Athens) and could again draw conclusions on topological particularities of these signaling pathways in hepatocytes [10,11].
As mentioned above, if enough data are available, one may automatically optimize (rewire) the network structure to obtain topologies that are consistent with the observed behavior. With Dr. Saez-Rodriguez et al. [12] we presented such an approach which optimizes logical models towards cell-type specific networks. A similar approach is currently employed in collaboration with Dr. Klingmüller (DKFZ Heidelberg) to elucidate the feedback and feedforward structure of the HGF (hepatocyte growth factor) signaling pathway in hepatocytes.

4.2.3 From Qualitative Models to the Dynamic Behavior

The studies mentioned above demonstrate that our qualitative modeling framework helps to uncover important functional properties of signaling networks and to test the compatibility of a network topology with data from stimulus-response experiments. However, it is clear that not only structural but also dynamic and quantitative aspect must be taken into account, e.g. to understand the misbalance of signaling pathways in disease phenotypes. An important step is therefore to close the gap between qualitative/static and dynamic modeling approaches. A first development in this direction was ODEfy, a new method to transform Boolean models into (qualitative) ODE models by multivariate interpolation [15] (with Prof. Theis, Munich). Taking T-cell activation [15] and *E. coli*'s *lac* operon [2] as biological examples, we could demonstrate how these ODE models, once their parameters have been estimated from experimental data, allow studies on aspects of the dynamic behavior of the investigated network. ODEfy completes our modeling pipeline (Fig. 3) consisting now of three different levels of model descriptions which can be converted into each other in a conservative way, i.e. properties calculated in a more abstract model (e.g. feedback loops in the interaction graph or minimal intervention sets in the logical model) are preserved in the more detailed model.
Another systems-theoretical approach is currently being developed with Prof. Flockerzi (SCT group) which is based on the *sign structure* of the Jacobian matrix of an ODE system. This sign structure is often constant in biological systems (i.e. independent of parameter values and state variables) and gives rise to an interaction graph. For certain classes of systems, key properties of their dynamics can be derived from their interaction graphs (e.g. non-existence of multiple steady states [R10]). We are working on techniques by which the

direction of the *initial* and *steady-state* response upon system perturbation can be inferred purely from the topology underlying the ODEs. This is possible for systems fulfilling certain criteria in their feedback and feedforward loops and we are currently trying to expand this class of systems where such parameter-free predictions on network behavior can be made.

4.3 Novel Methods for Biological Network Inference

The methods presented in previous sections start with a given structure of a biological network. However, the topology of many gene regulatory and some signaling networks is still largely or at least partially unknown. Network inference (reverse engineering) is therefore an important research field of Systems Biology [R4,R9]. The ARB group became recently interested in network inference methods, initially motivated by the problem to optimize a given structure of a signaling network based on stimulus response experiments (see 4.2.2 and [12]). We then turned our attention to inference methods by which interaction networks can be reconstructed without prior knowledge. Driven by our preliminary work on interaction graphs, in collaboration with the PSE group we elaborated a novel algorithm that reconstructs wiring diagrams of gene regulatory or signaling networks from high-throughput experimental data [8]. The method was called TRANSWESD and is based on a novel variant of Transitive Reduction in Weighted Signed Digraphs. It involves three steps (Fig. 5): (i) systematic perturbation (e.g. knockout) experiments; (ii) construction of a signed *perturbation graph* capturing the observed influences from (i); and (iii) use of transitive reduction to detect and remove edges that likely represent indirect effects. Compared to existing approaches, advantages of TRANSWESD are that it (a) accounts for edge signs, (b) uses edge weights to quantify the strengths of relationships avoiding the removal of true positive edges, and (c) can deal with cyclic networks where other methods often fail [8].

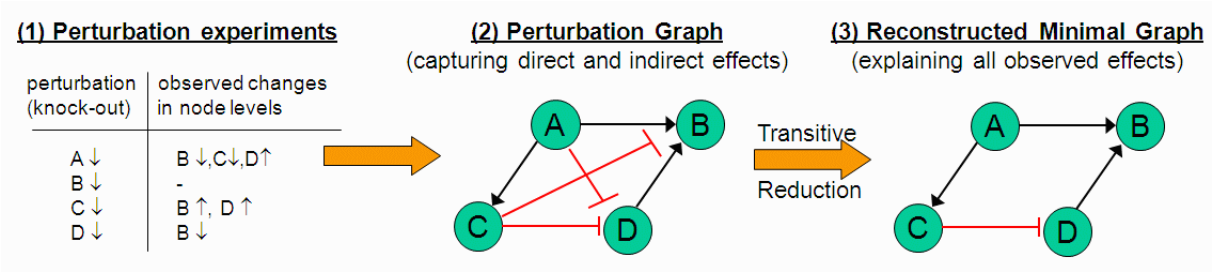

Fig. 5: Basic idea of Transitive Reduction. Systematic perturbation experiments indicate direct and indirect influences captured by signed edges in the perturbation graph. An edge is afterwards removed (because assumed to reflect indirect effects) if an alternative path exists that has the same sign and connects the same two nodes. TRANSWESD is based on this scheme but uses several more complicated rules, e.g. to deal with cyclic networks and to avoid pruning of true feedforward loops.

To benchmark TRANSWESD, we took part in the 4-th DREAM challenge 2009. The DREAM (Dialogue of Reverse Engineering Assessments and Methods) initiative offers a platform for objective assessment of rivaling reverse engineering methods based on annual challenges [R9]. We participated in the *in-silico network reconstruction* challenge where artificial gene networks with 100 nodes had to be identified on the basis of virtual measurements taken from stochastic simulations of these networks. With the submitted results, TRANSWESD was ranked 3rd (out of 19 submissions) giving a proof of principle. Meanwhile we have further improved this method and are currently planning to use it in a joint project with the HZI Braunschweig for infering gene networks in the pathogen *Pseudomonas aeruginosa*.

4.4 CellNetAnalyzer

For more than 10 years, we have been developing *CellNetAnalyzer* (CNA), an interactive MATLAB package for biological network analysis (Fig. 2). CNA provides a comprehensive set of algorithms for studying structure and function of metabolic as well as signal transduction networks. The toolbox is being extended continuously with novel algorithms, including those developed by ourselves (all methods described in 4.1-4.3 were implemented in CNA) but also other methods popular and frequently used in this field. Together with the ProMoT team (SBI group), we constantly optimized the interplay and exchange of data and models between ProMoT (model setup/visualization) and CNA (model analysis).
A notable recent extension was the development of an Application Programming Interface (API) for CNA [6]. CNA provides *interactive network maps* as a convenient means of input and result visualization (see Fig. 2). However, for some applications it is desirable to have CNA's functionality also accessible in batch mode, e.g. for automatic data processing or for calling algorithms of CNA from other applications. The developed API allows users (i) to access the content of network models in CNA, (ii) to use CNA's network analysis capabilities independently of the GUI, and (iii) to interact with the GUI to facilitate the development of graphical plugins. The API will further broaden the scope of potential applications of CNA.
CNA is freely available for academic use [16] and is, probably due to its continuous maintenance and further development, actively used by the community (more than 1500 downloads from external institutions during the last three years). Seven commercial licenses of CNA were meanwhile purchased by industrial companies (distributed by Max Planck Innovations).

5 Selected Teaching Activities, PhD Projects and Habilitations

Teaching activities:

- S. Klamt teaches the bachelor course „Structural and functional analysis of cellular networks" on a regular (yearly) basis at the OvGU.
- Three Master theses were supervised by the ARB group.

Current Ph.D. projects:

- R. Samaga: Qualitative modeling of cellular signaling networks.
- O. Hädicke: Novel computational methods for rational strain design.
- A. Ryll: Modeling of inflammatory signaling pathways and gene regulatory networks in hepatocytes.

6 Selected Memberships, Appointments, Awards

Offers:

- 2008: Steffen Klamt received an offer as Juniorprofessor (with tenure track) for Bioinformatics at the Ludwig Maximilians University Munich (declined).
- 2008: Steffen Klamt received an offer as Juniorprofessor (with tenure track) for Systems Biology at the Heinrich Heine University Düsseldorf (declined).

Memberships:

- September 2009: Steffen Klamt became member of the DECHEMA working group "Systems and Synthetic Biology".
- January 2010: Steffen Klamt was appointed as vice-speaker of the Magdeburg Centre for Systems Biology (MaCS).
- October 2009: Steffen Klamt became Associate Editor of *BioSystems.*
- April 2010: Steffen Klamt became Associate Editor of *BMC Systems Biology.*

7 Future Directions

After several discussions concerning the restructuring of the Systems Biology research activities (SBI and ARB group) at the MPI after the retirement of Prof. Gilles, it was decided to integrate the theoretically oriented research teams of the former SBI group into the ARB group in June 2011 (see General Overview section of the MPI report). Dr. Klamt, who is currently holding a W2 tenure track position, will continue to head the extended ARB group. With this restructuring and a positive evaluation of the research of Dr. Klamt, a long-term continuation of a significant level of research activities at the MPI in the field of Theoretical and Computational Systems Biology would become possible. The three research teams joining the ARB group are (for a detailed description of their research activities see SBI report):

- "Qualitative dynamics of biochemical reaction networks" (Dr. Conradi)
- "Design principles of biological networks" (Dr. Straube)
- "Modeling tools and databases for Systems Biology" (Mirschel)

It is planned to keep a semi-autonomous status of the three teams within the ARB group, similar as in the former SBI group. Due to already existing collaborations, joint activities (e.g. PhD seminar on Theoretical Systems Biology) and several overlapping research topics (e.g. qualitative dynamics of biological reaction networks (Conradi, [21]); redox regulation in *R. rubrum* (Straube, [20]); Systems Biology software tools (Mirschel)) the integration of the former SBI teams took place smoothly.

Although the spectrum of research topics of the ARB group has grown with the three integrated teams, e.g. regarding dynamic and stochastic modeling of smaller network motifs (Straube), its mission, namely the development and application of methods and tools for the analysis, reconstruction and targeted modification of biological networks remained the same. With *Biosystems Engineering* as a recently established research focus of all groups at the MPI, the use of systems-theoretical and computational methods to describe and rationally redesign biological systems will play an increasingly important role in the research of the ARB group. In this regard, joint research projects with other MPI groups, e.g. on combining different (stoichiometric, cybernetic, kinetic) modeling approaches to optimally reengineer metabolic networks, are planned (with PSE, PSD, BPE). Apart from engineering aspects, methods that help to gain novel insights in the functioning of biological systems and that deliver testable predictions driving the iterative cycle between modeling and experiments are another central topic of our research. The established interdisciplinary collaborations between the ARB group and the former experimental SBI teams (Dr. Grammel, Dr. Bettenbrock; now Experimental Systems Biology group) will be continued in future projects. Finally, computationally intensive studies conducted in the ARB group will benefit from the new computer cluster *otto* managed by the CSC group.

Since all members of the ARB group (except the group leader) are currently financed by third-party funding, the continuation of the successful fund raising activities will be vital and an essential challenge for the ARB group. To this end, several new joint grant proposals with partners from the MPI and other institutes have been submitted recently or are in preparation.

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Research Group:

Bioprocess Engineering (BPE)

Prof. Dr.-Ing. Udo Reichl

This report covers the period from October 2008 to August 2011

1 Group Introduction

Research of the BPE group focuses on cell culture bioprocesses for the production of viral vaccines and recombinant proteins. This includes upstream processing, molecular biology of virus-host cell interactions, downstream processing, bioprocess analytics at the proteome and the glycome level, and establishment of mathematical modeling. In the period of October 2008 to August 2011 the analysis and the design of upstream as well as downstream processing has been supported thoroughly by newly developed assays and the consequent use of analytical methods established previously. Based on the comprehensive experimental data sets, understanding of the prerequisites and the conditions for optimization of cell growth and product formation has been improved significantly. This was only possible due to strong interactions between the members of the BPE Group, close collaboration with other MPI groups and the research activities at the OvGU (only covered in part in this report). Furthermore, the number of scientists of the BPE Group has grown significantly with the successful progress in research activities covered by the MPI's budget, and the increased number of third party projects (several BMBF projects and collaborations with industry). This is also reflected in the high number of publications (58, including conference papers and book contributions), and theses finished (1 habilitation treatise, 6 Ph.D. theses) in the time period covered.

Work on upstream processing in animal cell culture has focused on the extension in the number of cell lines handled. This includes the use of adherent Vero cells, the generation of Madin Darby canine kidney (MDCK) suspension cell lines (in collaboration with Prof. K. Scharfenberg, University of Applied Sciences Emden/Leer, Germany), and investigations involving human (AGE1.HN, CAP) as well as duck suspension cell lines (AGE1.CR) provided by industrial partners (ProBioGen AG, Berlin, Germany; Cevec Pharmaceuticals GmbH, Köln, Germany). As a result, options for process comparison, design and optimization have increased significantly [1,2,3]. Furthermore, options for high-density cultivations avoiding so-called density effects have been successfully evaluated [4]. Other parts of our activities are covered in an expert review of Genzel and Reichl, which focuses on the use of continuous cell lines as production system for influenza vaccines [5]. Furthermore, the range of specific and highly sensitive assays established to characterize cell growth and product formation over the previous years, was applied to address a variety of challenging questions. For instance, which impact viral infections have on cultured animal cells at the extracellular and intracellular level of metabolites [6,7], and whether this results in changes in enzyme activities in glycolysis, citric acid cycle, pentose phosphate pathway or amino acid metabolism [8]. In addition, these assay platforms were used within our research activities in the FORSYS partner's project "Systems biology of cell culture for biologics" (SysLogics). Here, assay platforms are used to generate experimental data for growth of human AGE1.HN (non-producer) and AGE1.HN.AAT (alpha-1-antitrypsin producer) cells in batch and continuous culture. Furthermore, gene expression and proteomic studies as well as flow cytometry and metabolic pathway analysis are being performed in collaboration with five academic partners.

In addition, our understanding of virus host cell interaction concerning the impact of signal transduction on virus spreading and yields in influenza virus production could be improved greatly. This includes results concerning the influence of interferon-related host cell

responses by Frensing *et al.* [9] and related studies [10,11] and new insights concerning the role of trypsin during virus replication in cell culture processes [12].
Establishment of flow cytometric assays for monitoring progress of infection and apoptosis in populations of cells by Schulze-Horsel *et al.* [13] has enabled us to address a number of highly interesting questions related to the dynamics of infections and virus-induced apoptosis for various influenza strains in bioreactors. Quality of experimental data, i.e. availability of times series describing changes in the distributions of cellular subpopulations has stimulated a number of research activities towards implementation of powerful mathematical models using ODE-based approaches [14], population balances [15] and Monte Carlo simulations [16,17]. Due to the enormous complexity of the theoretical analysis a close collaboration with members of the PSE and PSDS Groups was essential.
The main reason for the establishment of mammalian cell cultures is the need for therapeutic proteins with post-translational modifications, i.e. monoclonal antibodies in CHO cells or viral antigens. Receptor binding, fusion activity and antigenic properties of viral antigens largely depend on correct glycosylation. While the quality of antibodies and other recombinant proteins concerning their glycosylation is routinely monitored in production processes, the impact of cultivation systems, cultivation parameters, cell lines or media on the glycosylation of viral antigens is largely unknown. This is mainly due to the complexity of assays required for corresponding analyses. With the progress made by the team supervised by Dr. E. Rapp, a highly sensitive high-throughput assay is now available, which enables routine monitoring, and (partly) identification of glycan structures of viral antigens, recombinant proteins and other carbohydrates (e.g. milk sugars) (Schwarzer *et al.* [18,19] and Rödig *et al.* [20]). Compared to established methods in glycoanalytics based on liquid chromatography this assay is an order of magnitude more sensitive and up to three orders of magnitude faster. The excellent performance of this assay platform resulted in several collaborations with industry (Merck Serono S.p.A. Rome, Italy; Milupa GmbH, Danone Centre for Specialised Nutrition, Breast Milk Research Friedrichsdorf, Germany) and academic partners (e.g. Prof. M. Wuhrer, Leiden Univ. Medical Center, the Netherlands).
As in the previous years, downstream processing of virus particles, viral vectors and recombinant proteins was an important part of research activities. The use of new technologies such as sulfated membrane adsorbers for economic pseudo-affinity capture of influenza virus particles [21], and the purification of cell culture-derived MVA virus by pseudo-affinity membrane adsorbers and hydrophobic interaction chromatography [22,23] resulted in significant improvements in process economy. Both methods resulted in patent applications of Dr. M. Wolffs team (see last report) and with an industrial partner (Bavarian Nordic A/S, Kvistgard, Denmark) [24]. Part of these activities were also described in an expert review by Wolff and Reichl on “downstream processing of cell culture-derived virus particles" [25]. Finally, in cooperation with academic partners (PCF and PSE Group; Prof. S. Lauffer, Tübingen, Germany) and industrial partners (IDT Biologika GmbH, Dessau-Roßlau, Germany; Merckle Biotec GmbH, Ulm, Germany; EMC microcollections GmbH, Tübingen, Germany), the BMBF-funded project “Use of synthetic ligands for purification of sialic acid-containing, recombinant proteins and viral antigen” is being pursued.

2 Members of the BPE Research Group

As of July 2011, the BPE research group consisted of 4 senior scientists, 15 Ph.D. students, and various diploma, bachelor and master students as well as technical assistants.

Tab. 1: Members of the Bioprocess Engineering Group

	Research Topics	**Group Member**
Head of Group		
Prof. Dr.-Ing. U. Reichl	Director & Head of Research Group	since 07/2000
Senior Scientists		
PD Y. Genzel	Upstream processing	since 01/2001
Dr. T. Frensing	Molecular biology	since 08/2007
Dr. E. Rapp	Bioprocess analytics	since 03/2008
Dr. M. Wolff	Downstream processing (OvGU)	since 01/2005
Ph.D. Students		
Dipl.-Ing. S. Freund	Dynamic models / Metabolic flux analysis	since 04/2008
Dipl.-Ing. S. Heldt	Mathematical modeling of virus dynamics	since 12/2009
Dipl.-Ing. R. Heyer	Metaproteome analysis of biogas plants	since 06/2011
Dipl.-Ing. M. Hoffmann	Gylcopeptide analysis by mass spectrometry / proteomics	since 04/2011
Dipl.-Biochem. B. Isken	Cell physiology by flow cytometry	since 10/2008
Dipl.-Ing. R. Janke	Enzyme activities	since 03/2007
Technical Biologist (Dipl. t.o.) T. Jarosch	Affinity chromatography	since 04/2009
Dipl.-Ing. R. Kottler	Glycosylation in human milk	since 11/2010
Dipl.-Bioing. T. Kröber	Adjuvants / Simulated moving bed chromatography	since 09/2007
Dipl.-Biotech. V. Lohr	AGE1.CR cells for influenza and MVA virus replication	since 06/2008
Dipl.-Ing. T. Muth	Software tools for glycomics	since 06/2011
Dipl.-Ing. (FH) A. Rath	AGE1.HN cells: metabolism and process optimization	since 07/2008
Dipl.-Ing. M. Rehberg	Dynamic modeling of central energy and carbon metabolism	since 12/2009
Dipl.-Ing. J. Rödig	Glycosylation of viral proteins	since 09/2008
Dipl.-Ing. (FH) C. Seitz	Interferon response and host cell signaling	since 04/2007
Dipl.-Ing. A. Bock	High-cell density cultivation, mathematical modeling	03/2003-02/2009
Dipl.-Biol. S. Kluge	Proteomics	09/2009-12/2010
Dipl.-Ing. L. Opitz	Lectin-affinity chromatography	07/2005-12/2009
Dipl.-Ing. M. N. Popov	Segregation instability of experimental plasmids	01/2006-12/2008

Dipl.-Ing. C. Riedele	Microbial communities and antibodies	04/2009-06/2011
Dipl.-Ing. J. Ritter	Intracellular metabolomics	12/2003-04/2009
Dipl.-Ing. T. Rudolph	Bayes approaches	04/2008-03/2011
Dipl.-Biotech. J. Schulze-Horsel	Cell physiology by flow cytometry	09/2003-12/2008
Visiting Scientists		
Prof. R. Wickramasinghe	Colorado State University: Biomedical Engineering, virus purification	several visits of 1-2 weeks
M. Sc. P. R. Amable	Federal University of Rio de Janeiro: Purification of *Factor XIII.*	08/2008-08/2009
M. Sc. S. Rourou	Institut Pasteur de Tunis: Proteomics for rabies virus infection	01/2009-04/2009 11/2009-12/2009
M. Sc. D. A. de Mattos	Federal University of Rio de Janeiro: Production & Purification of *Factor X.*	03/2009-09/2010
Technical Staff		
Dipl.-Ing. (FH) I. Behrendt	Technician, upstream processing	since 07/2001
F. Hasewinkel	Laboratory coworker	since 08/2002
Dipl.-Ing. (FH) S. Janke	Technician, downstream processing	since 11/2002
Dipl.-Ing. (FH) B. Köhler	Technician, glycomics and proteomics	since 08/2009
S. König	Technician, upstream processing	since 08/2001
C. Siewert	Technician, upstream processing	since 10/2009
N. Wynserski	Technician, molecular biology	since 08/2007
B. Sc. C. Ziemann	Technician, downstream processing	since 02/2009
A. Frauendienst	Secretary of BPE group	since 08/2010
S. Behling	Secretary of BPE group	03/2003-09/2010
L. Geisler	Technician, microbiology	07/2003-09/2009
Dipl.-Ing (FH) A. Müller	Technician, downstream processing	03/2010-03/2011
Dipl.-Ing. (FH) A. Zimmermann	Technician, downstream processing	12/2003-03/2009
Group at OvGU: Bioprocess Engineering		
Ph.D. Students: Dipl.-Ing. B. Heynisch, Dipl.-Ing. L. Fischer, Dipl.-Biol. S. Kluge, Dipl.-Ing. (FH) A. Lagoda, Dipl.-Ing. M. Meininger, Dipl.-Ing. C. Riedele, Dipl.-Ing. M. Rüger, Dipl.-Biochem. A. Serve (8) Senior Scientists: Dr. D. Benndorf, Dr. M. Wolff; Technician: C. Best Secretary OvGU: T. Mund		

3 Survey of Research Projects of BPE Group

The current research projects of the BPE group are summarized below.

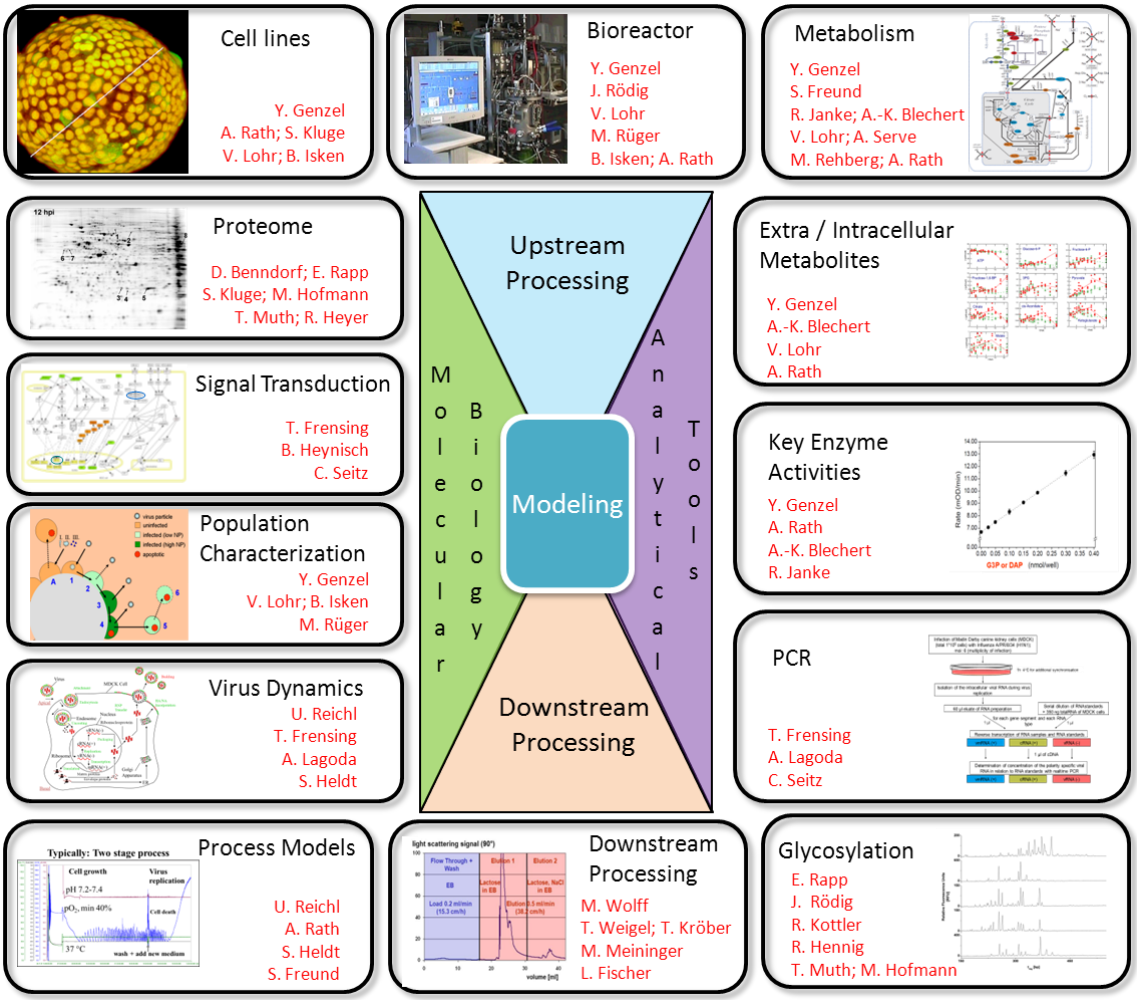

Fig. 1: Survey of research areas and projects of the BPE group

Upstream Processing

Monitoring, design and optimization of bioprocesses Coordinator: PD Y. Genzel	- Integrated concepts for design and optimization of vaccine production processes - Animal cell culture - Flow cytometry (physiological status of cells, virus replication dynamics)			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Influenza vaccine production in microcarrier systems and suspension cells	Y. Genzel		since 07/2000	FH Emden (Prof. K. Scharfenberg); IBET (Dr. A.S. Coroadinha; CEVEC (Dr. G. Schiedner), OvGU (Prof. Thévenin), CNRC BRI (Dr. A. Kamen)
Flow cytometric analysis of virus-induced apotosis and virus replication	B. Isken J. Schulze-Horsel		since 10/2008	PSD Group (Prof. A. Kienle); PSE Group (Dr. A. Voigt)

Characterization of growth, metabolism and product formation of avian designer cells	V. Lohr		since 06/2008	ARB Group (Dr. S. Klamt), ProBioGen (Dr. I. Jordan, Dr. V. Sandig) LMU Munich (Prof. G. Sutter) Polymun Scientific GmbH (Prof. H. Katinger, Dr. D. Katinger)
Monitoring and control of high density cell culture systems	A. Bock		03/2006-06/2010	

Quantitative analysis of metabolic and regulatory networks of cellular systems Coordinator: PD Y. Genzel	- Quantitative analysis of virus replication dynamics - Analysis of extra- and intracellular metabolites concentrations, enzyme activity assays			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Quantitative analysis of energy metabolism of animal cells	A. Rath M. Rehberg J.B. Ritter	BMBF-SysLogics	since 12/2009	SysLogics; ESB Group (Dr. K. Bettenbrock)
Biomolecular analysis of dynamic interactions between influenza viruses and host cells	A. Lagoda D. Vester		since 05/2005	ESB Group (Dr. K. Bettenbrock)
Enzymatic characterization of mammalian cells	R. Janke	BMBF-FORSYS	since 03/2007	MPI Golm (Prof. M. Stitt); TU Delft (A. Wahl)

Molecular Biology

Virus-host cell interactions Coordinator: Dr. T. Frensing	- Cellular pathogen defense in influenza vaccine production - Deep sequencing of influenza virus strains - Cellular signal transduction in virus-infected cells			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
The role of IFN and other host cell defense mechanisms in influenza vaccine production	T. Frensing C. Seitz		since 05/2007	University of Freiburg (Prof. G. Kochs), HZI, Braunschweig (Dr. HJ. Hauser, Dr. D. Wirth)
Impact of trypsin on cellular defense in MDCK cells	C. Seitz		since 01/2010	
Sequence analysis of influenza virus strains	T. Frensing J. Rödig		since 06/2009	Friedrich Loeffler Institute, (Dr. D. Hoeper)
Analysis of virus-induced signaling pathways in mammalian host cell systems	B. Heynisch	BMBF-FORSYS / OvGU	since 05/2007	OvGU (Prof. M. Naumann)

Downstream Processing

Downstream Processing and chromatographic methods Coordinator: Dr. M. Wolff	- Generic process for purification of virus particles or viral proteins - Lectins, synthetic ligands and matrices for affinity chromatography - Methods for quantification of virus particles and viral proteins			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Downstream processing of influenza virus	T. Jarosch		since 04/2009	
Continuous purification of influenza virus	T. Kröber	BMBF	since 06/2010	PCF (Prof. A. Seidel-Morgenstern) IDT Biologika (Dr. B. Hundt)
Molecular modeling of affinity ligands	M. Wolff A. Serve	BMBF	since 10/2008	MSD (Dr. M. Stein)
Modeling of membrane separations processes	M. Wolff	BMBF/MPI	since 10/2008	PSE (Prof. K. Sundmacher)
Purification of viral particles via monoliths	M. Wolff		since 03/2011	BIA Separations d.o.o.
Purification of recombinant proteins	M. Wolff P.R. Amable D.A. de Mattos	DAAD/MPI	09/2008 - 09/2010	Federal University of Rio de Janeiro (Prof. Leda dos Reis Castilho)
Purification of virus particles via sulfated cellulose membrane adsorbers	M. Wolff L. Fischer		since 04/2011	Sartorius Stedim Biotech GmbH
Downstream processing of influenza virus via bi-functional porous beads	T. Jarosch L. Fischer M. Wolff		since 07/2011	GE Healthcare Life Science (Peder Bergvall)
Clarification of influenza virus harvests from MDCK cultures	T. Jarosch M. Meininger M. Wolff		since 07/2011	Pall International Sarl (Ph.D. A. Onraedt)

Proteomics and Glycomis

Qualitative and quantitative analysis of bio(techno)logical systems on glycome level Coordinator: Dr. E. Rapp	- High-throughput glycoanalysis - Glycoprofiling of natural and recombinant glycoproteins - Glycoprofiling of body fluid glycomes - Glycoanalysis of milk			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Development of a high-throughput glycoanalysis tool, utilizing a multiplexing capillary-DNA-sequenzer	R. Hennig R. Kottler M. Borowiak J. Schwarzer		since 01/2005	
Glycoprofiling of the influenza virus hemagglutinin: Method development and comparison of different viruses and host cell lines	Y. Genzel J. Schwarzer		since 01/2005	ProBioGen (Dr. I. Jordan; V. Sandig)
Glycoprofiling of the influenza virus hemagglutinin: Changes during adaption processes and influence	Y. Genzel J. Rödig		since 10/2008	ProBioGen (Dr. I. Jordan; V. Sandig) Friedrich Loeffler

of cultivation conditions				Institute (Dr. D. Hoeper)
High-throughput glycoprofiling of the human blood serum glycome	R. Hennig M. Borowiak		since 03/2009	Leiden Univ. Medical Center (Prof. Dr. M. Wuhrer)
High-throughput glycoprofiling of oligosaccharides in human/animal milk	R. Kottler		since 10/2009	Milupa GmbH, Danone Centre for Specialised Nutrition (Dr. B. Stahl)

Qualitative and quantitative analysis of bio(techno)logical systems on proteome level Coordinator: Dr. E. Rapp	- Qualitative and quantitative proteomics - Analysis of virus / host-cell interaction at the proteome level - Proteome analysis of bacteria			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Differential protein expression analysis of dynamic interactions between influenza virus and mammalian host cells	D. Vester S. Kluge Y. Genzel		since 01/2005	
Adherent versus suspension cell line: A proteomic evaluation	Y. Genzel S. Kluge D. Vester		since 10/2009	FH Emden (Prof. K. Scharfenberg)
Proteomic tracking to monitor population dynamics and species interaction in bacterial mixed cultures	S. Kluge M. Hoffmann		since 10/2008	OvGU Magdeburg (Dr. D. Benndorf)

Mathematical modeling approaches

Mathematical modeling of cellular systems Coordinator: Prof. U. Reichl	- Detailed mathematical models for virus replication and protein production in mammalian cells			
	Scientists	**Funded by**	**Period**	**Partners**
SysLogics – Dynamic Modeling of Central Metabolism	A. Rath S. Freund	BMBF-SysLogics	07/2008-06/2011	7 partners from academia and industry
Modeling the dynamics of influenza virus replication in mammalian cells	S. Heldt T. Frensing	MaCS	Since 12/2009	OvGU Magdeburg (BPE: Dipl. Ing. (FH) A. Lagoda)
Dynamics of glycolysis and citric acid cycle in mammalian cells	Y. Genzel M. Rehberg		since 12/2009	

Mathematical modeling, simulation and control of bioprocesses Coordinator: Prof. U. Reichl	- Unstructured, segregated mathematical models for MDCK cell growth and influenza virus replication in microcarrier culture			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Model-based investigation of influenza virus replication in mammalian cell culture	S. Heldt		Since 12/2009	OvGU Magdeburg (BPE: Dipl. Ing. (FH) A. Lagoda)

Projects: Chair of Bioprocess Engineering (OvGU)

Dynamics of microbial communities	Experimental characterization and mathematical modeling of microbial growth dynamics in batch and continuous culture. Application of T-RFLP analysis for quantification in microbial communities of bacterial species related to cystic fibrosis disease; Funding: Saxony-Anhalt	Period: 05/2002-07/2011	Scientist: C. Riedele
Flow cytometric analysis of a medically relevant three-species bacterial community	Flow cytometric analysis of proliferation activity of bacteria in pure and mixed culture under different cultivation conditions (batch, chemostat) using DAPI staining techniques Partners: Müller, Helmholtz Center of Environmental Research, Leipzig, Germany	Start: 09/2007	Scientist: M. Rüger
Meta-proteome analysis of microbial mixed cultures	Experimental characterization of meta-proteome dynamics of bacterial communities, e.g. - Bacterial species related to cystic fibrosis disease - Bacteria of sewage sludge from membrane bioreactors used in municipal wastewater treatment - Bacteria in biogas reactors	Start: 01/2008	Scientist: Dr. D. Benndorf
Virus-host cell interaction at proteome and RNA level	Biomolecular analysis of dynamic interactions between influenza viruses and their host cells on the proteomic and mRNA level	Start: 05/2005	Scientist: D. Vester A. Lagoda
Purification of vaccinia virus	Affinity chromatography of vaccinia virus Partners: Bavarian NordicA/S, Kvisgard, Denmark and Sartorius Stedim Biotech GmbH (Germany)	Start: 03/2007	Scientist: Dr. M. Wolff
Influenza virus-induced signaling	Analysis of influenza virus-induced signaling in mammalian host cell systems Funding: FORSYS, BMBF	Start: 05/2007	Scientist: B. Heynisch
Biosystems Engineering	Coordination: Diploma degree program Biosystems Engineering Funding: FORSYS, BMBF	Start: 08/2007	Scientist: Dr. D. Benndorf
BMBF Project: Downstream processing of recombinant proteins	OvGU, MPI, Merckle Biotec GmbH EMC microcollections GmbH Institute of Pharmacy, University of Tübingen	Start: 10/2008	Scientist: Dr. M. Wolff M. Meininger
BMBF Project: Downstream Processing of influenza virus	OvGU, Chair of Bioprocess Engineering IDT Biologika GmbH EMC microcollections GmbH	Start: 10/2008	Scientist: Dr. M. Wolff A. Serve

Projects: Cooperation with other Institutions and Industry

Analysis of the antiviral activity of canine Mx proteins	University Freiburg, Germany	Period: 2008-2011	Scientist:Dr T. Frensing
Application of the high-throughput glycoanalysis tool for glycoprofiling of recombinant glycoproteins	Merck Serono S.p.A. Rome, Italy (an affiliate of Merck KGaA)	Start: 09/2009	Scientist: Dr. E. Rapp
BMBF Project: Downstream processing of influenza virus	OvGU, Chair of Bioprocess Engineering IDT Biologika GmbH, Germany EMC microcollections GmbH, Germany	Start: 10/2008	Scientist: Dr. M. Wolff

Cold-adapted influenza virus in AGE1.CR cells	ProBioGen AG, Berlin, Germany Polymun Scientific GmbH, Vienna, Austria	Start: 2010	Scientists: PD Y. Genzel V. Lohr
Computational Fluid Dynamics and wave bioreactor cultivation	OvGU, Lehrstuhl für Strömungsmechanik und Strömungstechnik; Wave Biotech, Wädenswil, Switzerland	Start: 2008	Scientists: Prof. U. Reichl PD Y. Genzel
Downstream processing of recombinant proteins	OvGU, Chair of Bioprocess Engineering Merckle Biotec GmbH EMC microcollections GmbH Institute of Pharmacy University of Tübingen	Start: 10/2008	Scientist: Dr. M. Wolff
Downstream processing of blood coagulation factor VIII and X	Federal University of Rio de Janeiro (UFRJ), Brazil	Start: 08/2008	Scientist: Dr. M. Wolff PD Y. Genzel
Enzyme assays for animal cell Culture	MPI Golm TU Delft, The Netherlands	Start: 2007	Scientist: PD Y. Genzel
Experimental characterization and mathematical modeling of microbial communities	Partners: Müller, Helmholtz Center of Environmental Research, Leipzig, Germany	Start: 04/2008	Scientist: Dr. D. Benndorf
Glycoanalysis of influenza virus Hemagglutinin	Novartis Vaccines AG, Marburg, Germany	Start: 11/2007	Scientist: Dr. E. Rapp
Glycoanalysis of α1-antitrypsin	ProBioGen AG, Berlin, Germany	Start: 03/2007	Scientist: Dr. E. Rapp
Glycoanalysis of recombinant glycoproteins	Bayer Pharma AG, Wuppertal, Germany	Start: 05/2011	Scientist: Dr. E. Rapp
Glycoanalysis of recombinant glycoproteins	Roche Diagnostics GmbH, Penzberg, Germany	Start: 07/2011	Scientist: Dr. E. Rapp
Heat exchanger for sample preparation	bbi-biotech, Magdeburg, Germany	Start: 2010	Scientists: Prof. U. Reichl A. Rath
Implementation of high-throughput glycoanalysis into process monitoring of recombinant glycoprotein production	Merck Serono S.p.A. Vevey, Switzerland (an affiliate of Merck KGaA)	Start: 09/2009	Scientist: Dr. E. Rapp
Influenza production in CAP cells	CEVEC Pharmaceuticals GmbH, Cologne, Germany	Start: 2009	Scientist: PD Y. Genzel
Influenza production in Rousettus cells	ProBioGen AG, Berlin, Germany	Start: 2010	Scientist: PD Y. Genzel
MDCK cells in suspension	University of Applied Sciences Emden/Leer	Start: 2007	Scientist: PD Y. Genzel
Metaproteomics of sewage sludge from membrane bioreactors	OvGU Magdeburg, Germany IRSA CNR Bari, Itlay	Start: 10/2008	Scientist: Dr. E. Rapp

Metaproteomics of biogas producing microbial communities	OvGU Magdeburg, Germany Leibniz Institute for Agricultural Engineering Potsdam-Bornim, Germany	Start: 09/2009	Scientist: Dr. E. Rapp
Purification and characterization of hydroquinone dioxygenase from *Sphingomonas sp.* strain TTNP 3	OvGU Magdeburg, Germany University of Applied Science, Switzerland	Start: 09/2009	Scientist: Dr. E. Rapp
Online metabolite sensors for stirred tank bioreactors	C-CIT AG, Wädenswil, Switzerland	Period: 2009-2010	Scientist: PD Y. Genzel
Perfusion for influenza production with HEK293 cells	CNRC BRI, Montreal, Canada	Period: 3 months 2010	Scientists: PD Y. Genzel V. Lohr
Purification of influenza virus particles via monoliths	BIA Separations d.o.o.	Start: 03/2001	Scientist: Dr. M. Wolff
Proteomics of rabies virus production in Vero cells	Institute Pasteur, Tunis, Tunisia	Start: 2008	Scientists: PD Y. Genzel Dr. E. Rapp
Response of *Pseudomonas putida* KT2440 to phenol at the level of membrane proteome	OvGU Magdeburg, Germany IBB, Technical University of Lisboa, Portugal	Start: 01/2009	Scientist: Dr. E. Rapp
Sequence analysis of influenza viruses	Friedrich Loeffler Instiute, Riems Island, Germany	Start: 06/2009	Scientist: Dr. T. Frensing
Sulfated cellulose membrane adsorbers	Sartorius Stedim Biotech GmbH, Germany	Start: 04/2011	Scientist: Dr. M. Wolff
Suspension MDCK for canine Adenovirus production	University of Applied Sciences Emden/Leer IBET, Portugal	Start: 2009	Scientist: PD Y. Genzel
VA-egfp production in AGE1.CR cells	ProBioGen AG, Berlin, Germany LMU Munich, Germany	Start: 2009	Scientists: PD Y. Genzel V. Lohr
Virus titers of bad producing influenza virus vaccine strains	Novartis Vaccines AG, Marburg, Germany	Period: 2009	Scientist: PD Y. Genzel
Vaccinia virus purification	Bavarian Nordic, Denmark Sartorius Stedim Biotech GmbH, Germany	Start: 10/2007	Scientist: Dr. M. Wolff

4 Research Highlights

4.1 Upstream Processing: Viral Vaccine Production and its Analytics

The well-established process of influenza virus vaccine production in adherent MDCK cells [4] allowed next steps towards process variations regarding use of host cell lines and virus strains, but also towards establishment of process strategies aiming at high cell density. The analytical platform developed could now be applied for characterization of various other

processes using new cell lines for recombinant protein production (alpha-1-antitrypsin, factor X) and other viruses (MVA). Analytical tools were continuously improved to address questions contributing to the design and optimization of cell culture processes, to support collaborations with academia, to offer solutions to industrial partners, and to enable establishment and validation of mathematical models.

Bioprocess Engineering on Viral Vaccine Production towards Suspension Cells and High Cell Density

Early developments in cell culture derived influenza vaccine manufacturing considered either MDCK (canine) or Vero (African green monkey) cells as possible production cells [R1, R2] [5]. As both cell lines grow adherently, microcarrier-based processes were considered first. Today, new cell lines have been designed specifically for use in vaccine production (PER.C6 (human), AGE1.CR (duck), CAP technology (human), etc.) [R3-R5]. These cell lines were directly conceived for easier processes with suspension cells growing in serum free or chemically defined medium to high cell densities allowing higher passage numbers. With the given analytical platform (extracellular metabolites, intracellular metabolites) evaluation of these new cell lines for influenza virus production was of interest for two industrial partners (cooperation with ProBioGen AG and CEVEC Pharmaceuticals GmbH). Novartis Vaccines (Marburg, Germany) is using a suspension MDCK cell line for their influenza vaccine production [R6]. Unfortunately, this cell line is not available for research. However, in cooperation with Prof. K. Scharfenberg (University of Applied Sciences Emden/Leer, Germany) a new suspension MDCK cell line (MDCK.SUS2) could be created from the adherent MDCK cell line used in our group [2]. This cell line seems also to be a good candidate for canine adenovirus vector production (cooperation with Dr. A.S. Coroadinha, IBET/ITQB-UNL, Lisbon, Portugal). In parallel, van Wielink *et al.* developed a suspension MDCK cell line and showed their possible use for H5N1 influenza viruses [R7]. Later, Le Ru *et al.* demonstrated that HEK293 (human) suspension cells also show potential for influenza virus production [R8]. As a visiting scientist at CNRC BRI, Montreal, Canada (Dr. A. Kamen) V. Lohr could show increased productivities for HEK293 cultivations in perfusion mode [26].

Based on these developments, the influenza vaccine process established in our group was adapted to compare performance of the newly available cell lines using equine, swine and several human influenza vaccine strains. Each new cell line showed its specificities and process variations required for successful virus production [1-3, 26] (see Table 2). Currently, the duck cell line AGE1.CR is further used in cooperation with Polymune (Vienna, Austria) to evaluate replication of cold-adapted influenza viruses in a single-use high-cell density process.

The production of MVA virus is of interest as it might be a candidate to produce viral vectors for gene therapy or Malaria and HIV treatment [R9-R13]. In cooperation with Prof. G. Sutter (LM University Munich, Germany) MVA-egfp virus production in AGE1.CR.pIX cells is used for detailed flow-cytometric investigations of virus replication of this very promising virus production process [3].

Lessons learned from these process variations:

- All influenza viruses need an adaptation to new host cell lines.
- Optimized trypsin concentration is needed for each cell line, each medium and each cultivation system used.
- There is no “best producer” cell line, each has its advantages and disadvantages, but with respect to pandemic threats, several host cell candidates and process options are now available.

Tab. 2: Portfolio of cell lines used in upstream processing

Cell Line	Supplier	Source	att[1]	med[2]	Cell n°[3]	Product	Specifics
MDCK	ECACC	canine	adh	SFM	11 x 10^6	influenza	reference process
Vero	ECACC	Afr. green monkey	adh	SFM	2 x 10^6	influenza	reference process
MDCK.SUS2	KS[4]	canine	sus	CD	3 x 10^6	influenza, Adenovirus	adh vs sus
HEK293	AK[5]	human	sus	SFM	10 x 10^6	influenza	perfusion
AGE1.CR	ProBioGen	duck	sus	CD	9 x 10^6	influenza, MVA	high density, cold adapted infl.
AGE1.CR.pIX	ProBioGen	duck	sus	CD	9 x 10^6	influenza, MVA	MVA-egfp
Rousettus[6]	ProBioGen	fruit bat	adh	SCM	-	(influenza), MVA	-
CAP	CEVEC	human	sus	SFM	4 x 10^6	influenza	human
AGE1.hn	ProBioGen	human	sus	CD	5 x 10^6	-	-
AGE1.hn.aat	ProBioGen	human	sus	CD	5 x 10^6	AAT	AAT
CHO	LC[7]	hamster	adh	SFM	-	Factor X	Factor X

[1] att: attachment of cells? – adh: adherent; sus: suspension

[2] med: possible cell growth medium: SFM: serum free medium; CD: chemically defined; SCM: serum containing medium

[3] cell n°: maximum cell numbers reached

[4] KS: cooperation with K. Scharfenberg (University of Applied Sciences Emden/Leer)

[5] AK: cooperation with A. Kamen (Biotechnology Research Institute, NRC-BRI, Canada)

[6] *Rousettus aegytiacus* [R14]

[7] LC: cooperation with L. Castilho (Federal University of Rio de Janeiro, Brazil)

Detailed Process Data for New Insights on Metabolism and Virus Dynamics

For design and improvement of cell culture processes a clear understanding of possible bottlenecks is required. In virus or recombinant protein production limitations can originate from low levels of substrates, accumulation of inhibitors, missing enzyme activities, cell cycle blocking, early apoptosis or problems in post-translational modifications. The established assay platform for monitoring of extracellular and intracellular metabolites for adherent cells [27] was therefore adapted to monitor growth and product formation of suspension cells. For

example, within the SysLogics consortium (FORSYS partners, BMBF), continuous cultivation experiments with new human designer cell lines (AGE1.HN, AGE1.HN.AAT) were set up and analyzed in detail concerning the metabolism during recombinant protein production.
Additionally, a method to determine maximal enzyme activities of central carbon metabolism developed for plant cells (MPI Golm, M. Stitt) was adapted and expanded to the animal cell culture applications [8, 28, 29] (see Fig. 2) (ForSys MACS project). With more than 20 extracellular metabolite concentrations, 30 intracellular metabolite concentrations and 28 enzyme activity levels new insights in cell metabolism are possible [6,9]. Surprisingly, based on enzyme activity measurements, some assumptions of the metabolic flux model established by Wahl *et al.* [30] had to be revised regarding pathways involved in MDCK cell growth in glutamine-free medium containing pyruvate [31]. Furthermore, for all cell lines currently used, pyruvate seems to be a key metabolite (cooperation with ARB Group).
Comparing enzyme activity data of influenza virus-infected with mock-infected MDCK cells showed an important role of lipid metabolism for virus synthesis. (Fig. 2) [33]. A difference between both experimental conditions, however, was not identified in experiments that monitored levels of intracellular metabolites in glycolysis and citric acid cycle [27]. Interestingly, a possible impact of lipid metabolism on virus replication was also identified by Rodrigues *et al.* who investigated the role of lipids in media considered for retroviral vector production [R15]. Work is in progress to further investigate the impact of lipid metabolism on virus replication on the extracellular and intracellular level.
Data on cell populations from flow cytometry could be used to develop a mathematical model on virus dynamics showing that only adherent cells produce virus [14]. Together with efforts in host signaling (Dr. T. Frensing team), proteomic and PCR data now give a more complete picture on virus-host-cell interaction [33-35].

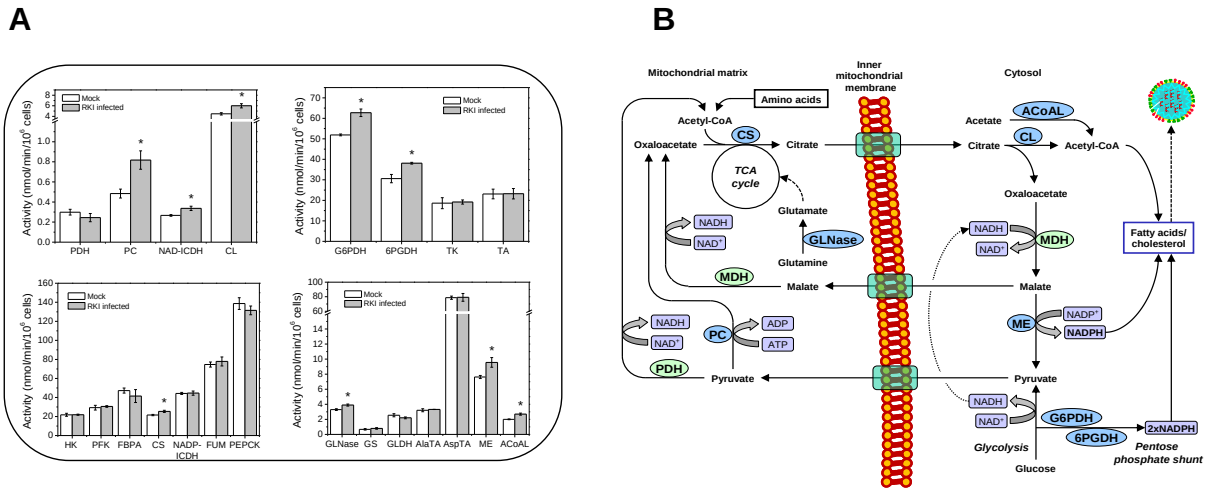

Fig. 2: (A) Specific enzyme activities of central carbon metabolism in influenza A infected and mock infected MDCK cells 9 h post infection. (significant difference: *) **(B)** Reaction network scheme on central carbon metabolism with up-regulated enzymes during influenza infection of MDCK cell highlighted in blue [16]. Abbreviations: 6PGDH, 6-phosphogluconate dehydrogenase; ACoAL, acetate-CoA ligase; CL, citrate lyase; CS, citrate synthase; G6PDH, glucose-6-phosphate dehydrogenase; GLNase, glutaminase; MDH, malate dehydrogenase; ME, malic enzyme; PDH, pyruvate dehydrogenase; PC, pyruvate carboxylase.

4.2 Cellular Pathogen Defense in Influenza Vaccine Production

Mammalian cells possess sophisticated mechanism for pathogen defense. Cells are able to sense virus infections, and as a response they secrete interferon (IFN), which activates defense mechanisms in an autocrine and paracrine fashion [R16]. So far, very little is known how these mechanisms affect virus replication in cell culture-based vaccine production processes. Therefore, the induction of IFN and activation of the so-called antiviral state in the frequently used cell line MDCK infected with influenza virus was analyzed. On the one hand, phospho-specific antibodies were used to monitor the activity of relevant signal transduction pathways. This work was initially supported by Prof. M. Naumann (Medical Faculty, OvGU Magdeburg, Germany) who is studying signal transduction in *Helicobacter pylori* infected epithelial cells (BMBF: FORSYS project). On the other hand, expression of IFN and IFN-stimulated genes were measured by real-time PCR (supported by Dr. HJ. Hauser, HZI Braunschweig, Germany). Both approaches showed that influenza virus strains, i.e. two variants of influenza A/Puerto Rico/8/34 (H1N1), differ in the activation of cellular defense mechanisms [10,11]. This raised the question if IFN induction and subsequent activation of the antiviral state limit the influenza virus yield in vaccine manufacturing. To address this question, it was analyzed whether the inhibition of IFN signaling can increase the virus replication in MDCK cells. In addition, cells were stimulated with IFN to demonstrate how cellular defense mechanisms can reduce virus replication.

Surprisingly, neither activation nor inhibition of the cellular defense had a significant impact on final influenza A virus yields in adherent MDCK cells. Stimulation with IFN slowed down the virus replication at early time points but finally the same titer was reached as in controls without IFN stimulation. In contrast, efficient suppression of IFN signaling by over-expression of the viral antagonist phosphoprotein P (from rabies virus) had virtually no impact on virus replication [11].

Influenza B viruses differ from influenza A viruses with respect to their ability to counteract cellular defense mechanisms. In particular, it was shown that influenza B viruses are sensitive against the antiviral effect of the IFN-stimulated gene 15 (ISG15). Therefore, influenza B viruses (but not influenza A viruses) developed mechanisms to sequester ISG15. However, this antagonistic mechanism works only in human cells and not in the canine cell line MDCK [R17]. Hence, we also studied the influence of cellular defense mechanisms of MDCK cells on influenza B virus propagation. Again, no increase of virus titers was achieved by suppression of cellular defense and no decrease was observed after activation of the antiviral state [9]. Therefore, cellular defense mechanisms of MDCK cells were found to be insufficient to reduce influenza A and B virus replication in bioprocesses.

Several reasons for this exceptional low influence of the antiviral defense in MDCK cells have been identified. First, in collaboration with Prof. G. Kochs (Virology, University Freiburg, Germany) it was shown that the myxovirus resistance (Mx) proteins of MDCK cells lack the antiviral activity, which represents a key defense mechanism against influenza viruses in many species including humans [R18]. Canine Mx proteins failed to inhibit influenza A as well as influenza B virus replication [9,11]. Moreover, analysis of antiviral host response demonstrated that the addition of trypsin during influenza virus infections keeps cellular defense at a low level (Fig. 3). Trypsin is used for the proteolytic activation of new virions and enables multi-cycle virus replication. However, trypsin not only cleaves the viral surface

protein hemagglutinin (HA) but also extracellular cytokines such as IFN. Therefore, the addition of trypsin results in rapid virus spreading and concurrent reduction of antiviral host cell signaling [12]. Furthermore, our data suggest that the speed of both intracellular virus replication and virus spreading in the host cell population determines if virus replication can outrun host cell defense mechanisms. The influenza virus replication in MDCK cells is comparatively fast and process condition in bioreactors enable rapid virus spreading which allows viruses to replicate before antiviral mechanisms become fully activated.
In summary, IFN signaling has only a minor effect on influenza virus replication in MDCK cells, which makes these cells an ideal system for high yield vaccine production.

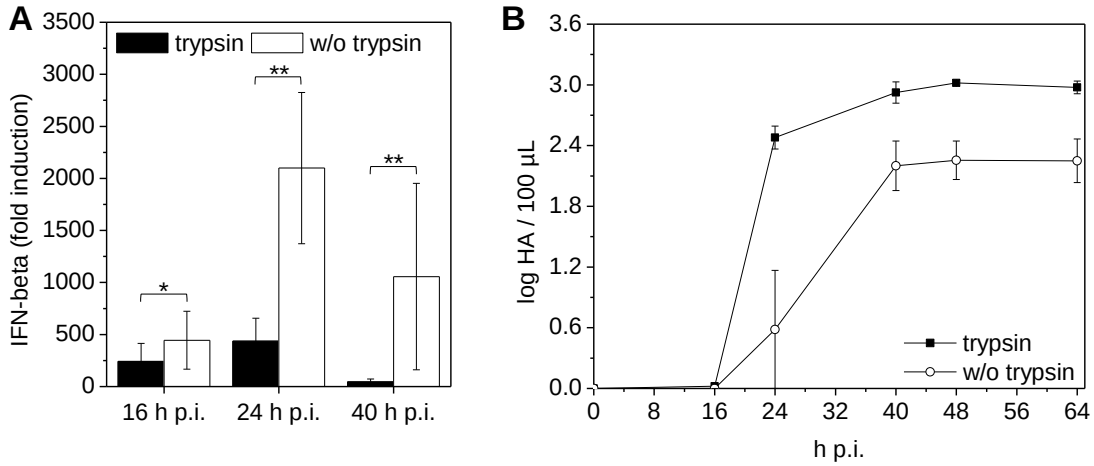

Fig. 3: Impact of trypsin supplementation on IFN signaling and virus replication. MDCK cells were infected with influenza A/PuertoRico/8/34 (m.o.i. 0.025) with or without trypsin addition. **(A)** IFN-β expression was determined by qRT-PCR relative to a MOCK-infected sample. The data shown represents the median ± median absolute deviation of 9 independent experiments. (*) $p < 0.05$, (**) $p < 0.01$ Friedman test. **(B)** Influenza virus titers were determined by hemagglutination assay.

4.3 Development of Downstream Processes for the Production of Viral Vaccines and Recombinant Proteins

Current activities in the area of downstream processing of viral vaccines focus on purification of cell culture-derived human influenza virus and smallpox virus (Vaccinia virus) are briefly described below. The present status of downstream processing of cell culture-derived virus particles was summarized for the journal Expert Review of Vaccines. The overview includes methods such as precipitation, flocculation, extraction, centrifugation, microfiltration, ultrafiltration, bead-based and membrane-based chromatography, and the use of monoliths. In addition, it addresses issues concerning the application of continuous chromatography methods, i.e. simulated moving bed chromatography, and the utilization of kits for small and medium scale purifications and concentrations of virus particles and vectors for gene therapy. Finally, examples for complete purification trains are presented for DSP of virus particles for therapeutic applications and vaccine manufacturing [25].

Design and Optimization in Purification of Cell Culture-Derived Virus Particles

MVA-BN® is a smallpox vaccine based on the Modified Vaccinia Ankara (MVA) virus, which demonstrated superior safety compared to traditional smallpox vaccines based on native Vaccinia virus strains. Furthermore, re-engineered MVA-BN® is a robust vector that allows establishment of an interesting platform technology for vaccine delivery systems. Even though pre-existing immunity against vaccinia viruses in smallpox vaccinated people may affect MVA-gene therapy efficacy, MVA has some attractive properties for their application as a gene therapy vector: (1) Poxviruses are highly stable, (2) large amount of foreign DNA can be integrated into the viral genome without loss of infectivity, (3) the safety record of MVA, and (4) ability to induce humoral and cellular immunogenicity [R19]. Currently several preclinical studies and clinical trials are carried out with MVA vectors to potentially treat rabies, measles, Dengue fever, influenza, malaria, tuberculosis, HIV and different types of cancer [R19-R22].

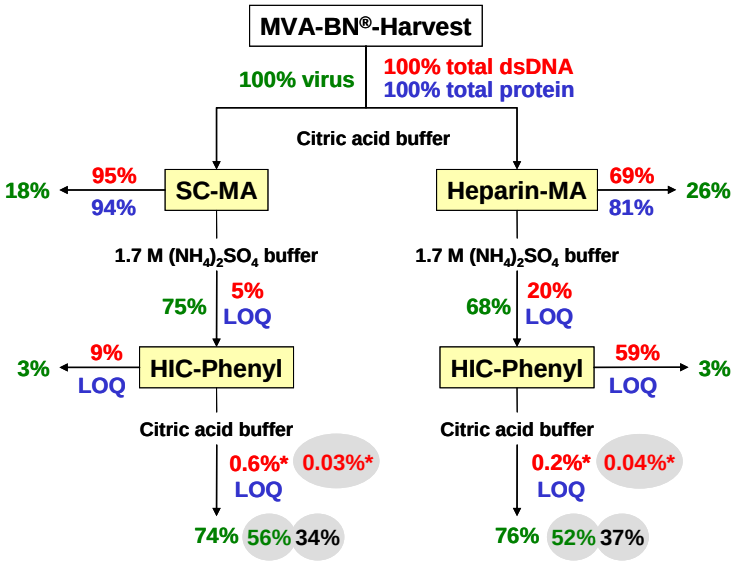

Fig. 4: Purification of cell culture-derived MVA-BN® by a combination of SC-MA or heparin-MA with HIC-Phenyl column chromatography.

Since 2007 a new downstream process (DSP) for purification of cell culture-derived MVA virus has been developed in collaboration with Bavarian Nordic A/S, Kvistgard (Denmark), Sartorius Stedim Biotech GmbH, Göttingen (Germany) and the OvGU. Up to the year 2009 studies focused on the initial capture step based on different types of membrane adsorbers (MA), i.e. ion exchange MA and pseudo-affinity (heparin and sulfated cellulose) MA [22,23]. Heparin MA were a research product from Sartorius Stedim Biotech GmbH. Sulfated cellulose membranes (SC-MA) were prepared by a technology patented by Dr. Wolff's team (US 2010/0093059 A1), and comprise a chemical modification of reinforced cellulose membranes with a pore size of 3 to 5 µm (Sartorius Stedim Biotech GmbH). Pseudo-affinity membranes were the most promising for large scale operation in terms of viral recovery as well as total DNA and protein depletion. However, to achieve a DNA contamination level acceptable for human vaccines improvements were required. For this purpose hydrophobic

interaction chromatography was used in addition to the pseudo affinity MA as a subsequent unit operation. After screening for an optimal HIC ligand (phenyl) the final DNA content could be reduced to 0.1% to 2.5% of the starting material with overall recoveries of active virus particles ranging from 34 to 37% (Fig. 4; [22]; US 2010/0119552 A1). The wide range in the concentration of contaminating DNA in the product fraction results from batch-to-batch variations of the bioreactor harvests.
Therefore, further investigations concerning consistency of upstream processing and the impact of differences in DNA contaminations in virus harvests are required to assure a robust production process. Protein levels after SC-MA and HIC-phenyl chromatography purification, however, were always below 25 µg per dose (Fig. 4) and comply with requirements for newly licensed cell culture-derived human vaccine products.

Cell Culture-derived Influenza Virus

Motivated by the recent pandemic threats of influenza a number of laboratories worked on the development of cell culture-derived influenza vaccine production. For the downstream side the center of attention was on the development of improved assays for process characterizations, specific chromatography media e.g. to substitute the frequently applied Cellufine® Sulfate for the capturing of influenza virus particles [R22] and on the use of chromatographic matrices with improved volumetric throughputs. These matrices include monoliths [R23, R24] and membrane adsorbers, which are currently also tested for the purification of viral gene therapy vectors [R25-R30] and other viral vaccines [R31].
A focus in our laboratory has been on affinity-based capturing methods for inactivated and clarified (depth filtration, 0.45 µm) cell culture-derived influenza virus particles. As for the MVA-BN® project, sulfated reinforced cellulose membranes were tested for the capturing of influenza virus particles. In industrial processes Cellufine® sulfate, a bead based sulfated cellulose, is commonly used for this purpose. The major drawback of Cellufine® sulfate bead chromatography of influenza virus purification is the low productivity, which can be overcome by the application of sulfated reinforced cellulose membranes (US 2010 0093059-A1; [21]). Industrial production of sulfated cellulose membrane adsorbers for the purification of different virus particles is currently investigated in collaboration with Sartorius Stedim Biotech GmbH.

4.4 Proteomics and Glycomis

To explore qualitative and quantitative data of cell cultures on the proteome level, several experimental platforms have been established. Qualitative and quantitative proteomics was initially used to answer specific questions concerning the glycosylation of HA-antigens of cell culture-derived influenza A virus strains. Furthermore, this technique is also exploited to address questions regarding bacterial growth behavior. Therefore, qualitative and quantitative analysis on proteome level is performed using a set of gel-electrophoresis techniques for protein separation (and quantification), in combination with (two-dimensional) high performance liquid chromatography coupled online and offline to tandem mass spectrometry for protein identification. Finally, questions concerning the analysis of glycosylation of other proteins (i.e. monoclonal antibodies, human milk oligosaccharides, and the human plasma N-glycome) are increasingly addressed. Therefore, an automated high-

throughput (HTP) and high-resolution analysis tool, utilizing a multiplexed capillary DNA-sequencer - including automated data evaluation - was developed.

Proteomics - Analysis of Virus-Host Cell Interaction at the Proteome Level

The analytical methods established are complementing other genomic and metabolic approaches of the BPE Group, all focusing on the characterization of the dynamic interaction of the influenza virus with mammalian host cells. In one example, two adherent cell lines were compared – a canine cell line (MDCK) widely used for vaccine production [R32,R33] and a human lung carcinoma cell line (A549) as a reference model [R34,R35] to obtain insights into virus-host cell interactions on the proteome level [34]. The findings of this quantitative proteome-wide profiling of virus infection provided many interesting insights concerning virus-induced changes in cellular processes, in particular, those related to apoptosis and stress response. They also gave hints on proteins and cellular pathways involved in intracellular virus replication. In another example, the dynamic cellular host cell response induced by influenza virus infection with a human A/PR/8/34 (H1N1) strain obtained from two different suppliers (RKI, Germany and NIBSC, UK) in two different vaccine production cell lines (MDCK and Vero) was investigated on the proteome-level [34]. In addition, progress of infection with both strains was characterized by flow cytometry and analysis of relevant signal transduction pathways. Currently, differences on the proteome level between an adherent and a suspension MDCK cell line are being investigated [2]. As expected, significant changes on the protein level during adaptation of the adherent MDCK cell line to growth in suspension are already identified.

Proteome Analysis of Bacteria

In cooperation with research activities at the Chair of Bioprocess Engineering at the OvGU, the methods addressed above for qualitative and quantitative proteomics are also used to investigate bacteria and bacterial growth, respectively. This includes, for example, investigations to obtain insights into the adaptive response mechanisms of *Pseudomonas putida* KT2440 to phenol, involving the membrane proteome [36], studies concerning the approval and identification of (new) enzymes found in strain TTNP3 of *Sphingomonas sp.* [38], and projects regarding the metaproteome analysis of sewage sludge from membrane bioreactors used in municipal wastewater treatment [38]. Furthermore, a method for proteomic tracking was developed and applied to monitor the population dynamics and species interaction of a mucoviscidosis relevant bacterial mixed culture [39].

Glycomics

Glycomics is a rapidly emerging field that can be viewed as a complement to other „omics“-approaches including proteomics and genomics. Of particular interest is the analysis of recombinant proteins and viral antigens produced in mammalian cell culture, which play an important role in the manufacturing of vaccines and other biopharmaceuticals. Appropriated glycoanalytical tools are needed to assist the necessary analytics along up-to-date development strategies (e.g.: “design of experiment (DoE)” or “quality by design (QbD)”), to analyze the impact of process modifications in upstream processing (e.g. media changes or cultivation parameters), and to monitor crucial unit operations in downstream processing.

In order to enhance and improve the comparatively limited options for glycoanalysis, automated HTP and high-resolution analysis methods including automated data evaluation have been established. This includes several mass spectrometry and liquid chromatography based analysis techniques, and electromigrative separation techniques for the analysis of oligosaccharides. Focus was on the use of multiplexed capillary gel electrophoresis with laser induced fluorescence detection (CGE-LIF) utilizing a DNA-sequencer [R36, 40-47], a method that was applied in numerous internal and external collaborations.

Method and Software Development for High-Throughput Glycosylation Pattern Analysis of Glycoproteins Utilizing a Multiplexing Capillary-DNA-Sequencer

The aim of this project was to further investigate and to improve the innovative CGE-LIF approach for various fields of application with respect to sample preparation, separation and data analysis. First, sample preparation method and workflow were optimized with respect to performance and feasibility regarding HTP (see Fig. 5) [42,45,46]. Second, the separation parameters were evaluated to find the optimum for an automated separation for each of a set of different types of samples [45]. Third, data analysis was automated, developing a novel modular software tool for data processing and data analysis, interfacing a corresponding oligosaccharide database [40,41,43]. Using this software tool, the generated "normalized" electropherograms of glycomoieties ("fingerprints") can be evaluated on two stages: "simple" qualitative and quantitative fingerprint comparison and structural elucidation of each single glycocomponent. This novel modular glycoanalysis system now allows automated, highly sensitive instrument, laboratory and operator independent high-throughput HTP glycoanalysis, even when operated by non-experts. The application of this technique to glycoanalysis using instruments with up to 96 capillaries in parallel, results in massive reduction of the effective separation time per sample combined with an impressive sensitivity achieved due to LIF detection and therefore, shows high potential for HTP glycoprofiling of glycoconjugates. This is in contrast to the currently prevailing methods, where multiplexing with respect to high-throughput is highly cost and lab-space intensive and consumes a great deal of manpower from general as well as expert staff.

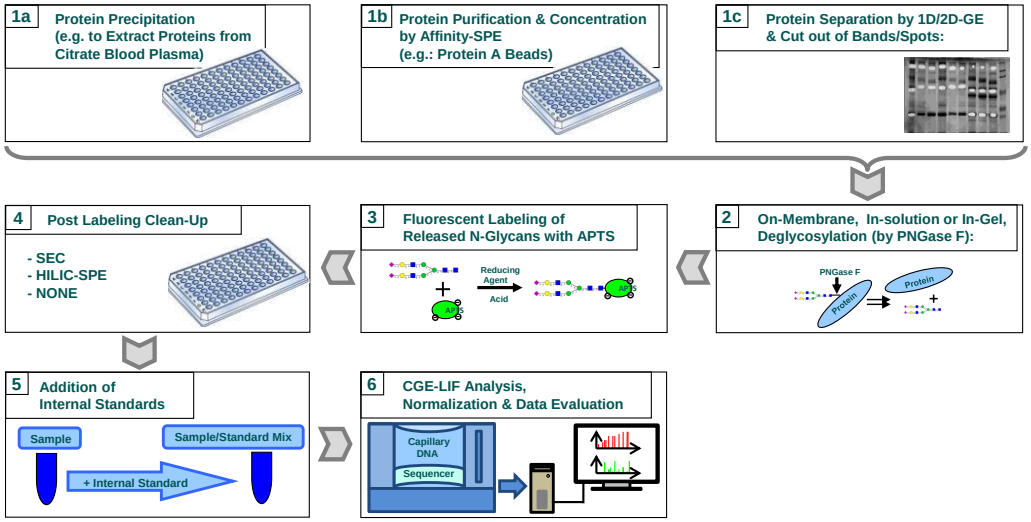

Fig. 5: Workflow of high-throughput glycosylation pattern analysis of glycoproteins utilizing a multiplexing capillary-DNA-sequencer.

Application of the High-Throughput Glycosylation Pattern Analysis Tool/System

Using the developed HTP glycoanalysis system, the glycosylation patterns of viral surface proteins from unit operations in up- and downstream processing could be easily characterized. This mainly concerns the glycosylation of hemagglutinin (HA), the most abundant and immunogenic of the influenza virus surface glycoproteins. In addition, it involves the characterization of the influence of cell lines and virus strains [18,19], of adaptation to new host cell lines [20,48], and cultivation conditions [1,4]. Furthermore, the method is implemented in HTP glycosylation analysis of human plasma N-glycome of clinical samples [13, 17]. Another project utilizing this glycoanalysis approach is the HTP characterization of human milk oligosaccharides (HMOS) [R37]. The role and significance of HMOS is still not fully understood. Therefore, the identification and characterization of oligosaccharide structures is required [R6]. In combination with an in-house HMOS database, the generated HMOS "fingerprints" can be used for in-depth analysis, i.e.: structural elucidation of each single compound and its relative quantification. The method developed was tested on various HMOS samples (time series of different donors) [47].

4.5 Mathematical Modeling Approaches

Activities concerning the development of mathematical models have focused on four main topics: (i) steady state and dynamic models describing the metabolism of mammalian cells, (ii) the validation and further development of single cell infection models, (iii) the establishment of population balance models to describe virus spreading and apoptosis at various degrees of resolution, and (iv) computational fluid dynamics to analyze mixing and growth of adherent cell lines in wave®bioreactors. Only the latter two topics will be considered in the following.

Infection Dynamics and Virus-Induced Apoptosis: Flow Cytometry and Mathematical Modeling

In cell culture-derived vaccine production differences in infection dynamics, virus-induced apoptosis, cell lysis and virus yields are observed depending on host cell line and virus strain. Comparatively little is known concerning details of virus-host cell interaction on a cellular level and virus spreading in a population of cells in the bioreactors. Therefore, the infection of MDCK cells with different influenza A virus strains in lab-scale microcarrier culture was investigated by flow cytometry. Together with the infection status of cells, virus-induced apoptosis was monitored. An ODE-based model has been formulated to describe changes in the concentration of uninfected and infected adherent cells, dynamics of virus particle release (infectious virions, hemagglutinin content), and the time course of the percentage composition of the cell population (Fig. 6) [14].

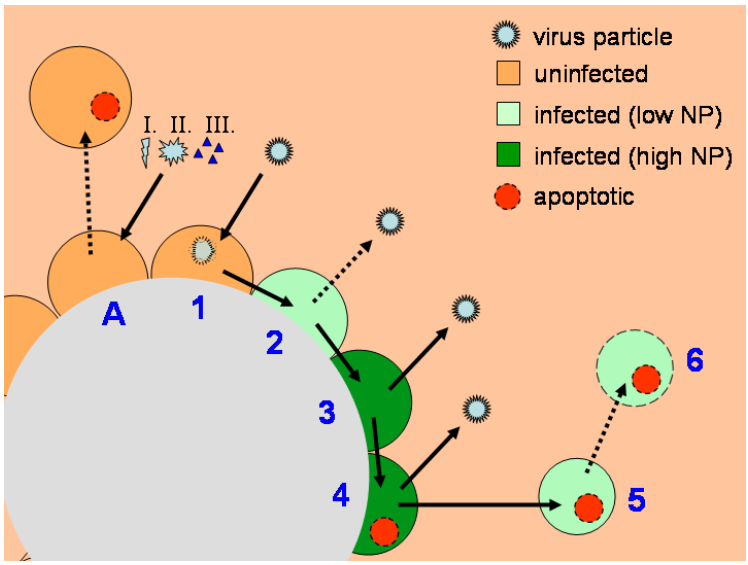

Fig. 6: Infection model for adherent MDCK cells on microcarrier infected with influenza A virus [14]

The mathematical model mentioned above, however, only used part of the information available from flow cytometry. In particular, the changes in distributions of measured cell subpopulations (unimodal and bimodal distributions have been identified) during the time course of infection were neglected. Therefore, to use completely all information available Monte Carlo approaches [16,17] and population balance approaches [15,50] have been developed to describe virus dynamics in bioreactors with the PSE and PSPD Group, respectively. Work is in progress to establish powerful experimental and theoretical tools to further explore the highly interesting questions concerning the biological mechanisms involved (i.e. the impact of strains, multiplicity of infection, signal transduction, etc.) and their consequences for design of vaccine production processes.

Experimental Characterization of Flow Conditions in Bioreactors with Wave-Induced Motion

Disposable bioreactors such as wave®bioreactors were introduced for production of biologicals in the late 90s [R38,R39]. Often, their use resulted in markedly different characteristics in cell growth or differences in product yields, which were difficult to explain. While most interpretations of the results obtained assumed this to be related to superior shear stress characteristics in these shaken systems, comparatively few quantitative information was available on the flow properties through a complex, non-linear coupling between the continuous flow phase and the dispersed microcarrier and cell populations. To overcome these limitations a Computational Fluid Dynamics (CFD) approach was employed for the detailed analysis of the cultivation process together with the unsteady flow conditions in close collaboration with Prof. D. Thevenin's group (Laboratory of Fluid Dynamics and Technical Flows) at the OvGU. Therefore, three-dimensional simulations taking into account the exact geometry of the cell bags [49] obtained during standard operation by a laser measurement technique were performed using the industrial CFD code ANSYS-FLUENT® 6.3. In order to describe correctly the free liquid surface in an unsteady manner, the three-dimensional calculations were extended with the Volume of Fluid (VOF) method leading to

even higher computational costs. All flow conditions found by CFD have been validated quantitatively concerning liquid surface height, flow velocity and shear stress by comparison with experimental data. Finally, based on the realistic flow conditions described by the three-dimensional simulations, a kinetic model and PBM equations were implemented in the CFD code via user-defined scalars and functions [51]. As a result, not only realistic simulations concerning the distributions of microcarriers in cell bags were obtained (Fig. 7) but also growth of populations of suspension and adherent cells could be analyzed quantitatively in detail under a variety of cultivations conditions (Fig. 8).

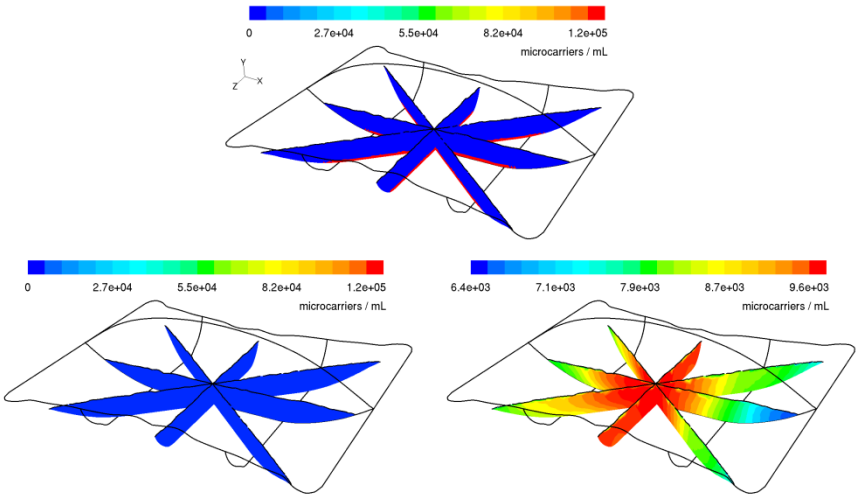

Fig. 7: Homogenization of microcarrier (MC) distribution induced by the unsteady flow movement in a 2 L cellbag. The MCs are initially (t = 0) all located at the bottom of the bag (top image). The distribution of the MC after 15 rocking cycles (t ~ 60 s) of mixing process is shown with a fixed color-map (bottom left) and with a min/max adapted color-map (bottom right), as obtained by standard method of moments [52].

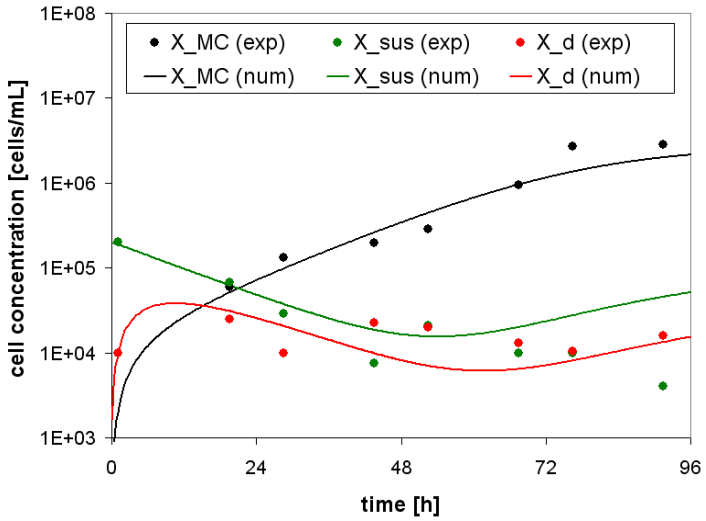

Fig. 8: Evolution of cells on microcarriers (black) and in suspension (green for viable, red for dead) according to zero-dimensional simulation using the retained optimal set of parameters (lines) compared with experimental data (symbols) [52].

5 Selected Teaching Activities, Diploma Projects, Ph.D. Projects and Habilitations

Prof. Reichl and Dr. Benndorf (OvGU) are coordinating the interdisciplinary study program Biosystems Engineering, which is offered as a Bachelor of Science since the winter semester of 2006/2007. In spring 2011 a consecutive Master of Science program started. Currently, there are 90 diploma and 173 B. Sc. / M. Sc. students enrolled (summer semester 2011), with more than 300 applications (60 students accepted) for winter semester 2011/2012. Both, the B. Sc. and the M. Sc. Program have been granted an accreditation in July 2011. The International Max Planck Research School for Analysis, Design and Optimization in Chemical and Biochemical Process Engineering, which was established in close collaboration with the OvGU Magdeburg in 2007, has currently more than 42 Ph.D. students enrolled.

5.1 Lectures at the OvGU (Prof. U. Reichl):

- Biochemical engineering (3 SWS; German)
- Laboratory course - Biochemical engineering I (1 SWS; German)
- Biochemical engineering (2 SWS; IMPRS, English; with Genzel (MPI))
- Mathematical modeling of bioprocesses (2 SWS, German)
- Exercise - Mathematical modeling of bioprocesses (1 SWS, German)
- Cell culture engineering (2 SWS; German, English; with Genzel (MPI))
- Laboratory course – Cell culture engineering (2 SWS, English; with Genzel / Frensing (MPI))
- Microbiology (2 SWS, with Grammel (MPI) / Benndorf (OvGU))
- Laboratory course – Microbiology (1 SWS; German with Benndorf (OvGU))

5.2 Supervision of Habilitation treatise and Ph.D. theses

Tab. 3: Finalized Habilitation treatise and Ph.D. theses

Group member	Habilitation	Finished
PD. Y. Genzel	Upstream processing issues in influenza vaccine production using animal cell technology	12/2009
	Ph.D.	
Schmidt, J. K.	Quantitative Experimental Characterization and Mathematical Modeling of Mixed Culture Dynamics	10/2008
Kalbfuß, B.	Downstream Processing of Influenza Whole-Virions for Vaccine Production	08/2009
Ritter, J.	Charakterisierung tierischer Zellkulturen anhand einer Quantifizierung intrazellulärer Metaboliten aus dem Zentralstoffwechsel	04/2010
Opitz, L.	Development and Characterization of Affinity- and Pseudo-affinity-based Methods for Cell Culture-derived Influenza Virus Capturing	07/2010
Schulze-Horsel, J.	Zellphysiologische Charakterisierung von Zellkulturen in der Influenza-Impfstoffproduktion	02/2011
Vester, D.	Molecular Biological Analysis of Dynamic Interactions between Influenza Viruses and Host Cells – Host Cell Proteomes and Viral Replication Dynamics	04/2011

At present there are 15 Ph.D. students in the BPE Group and 8 Ph.D. students at the OvGU, supervised by U. Reichl, Y. Genzel, T. Frensing, E. Rapp, D. Benndorf and M. Wolff (see survey of Research Projects).

6 Selected Memberships, Appointments and Awards (U. Reichl)

- Member of the Perspective Commission of the CPT (Chemistry, Physics & Technology) Section, MPG (2003 - 2010)
- Member of the Foundation Committee of the MPG-CAS Institute “Computational Biology”, Shanghai, China) (since 2004)
- Spokesperson of the IMPRS Magdeburg (since 2007)
- Coordinator of the CNRS and MPG collaboration in the field of “Systems Biology” (Post-doctoral program in Systems Biology and GDRE European Research Network in Systems Biology)(since 2007)
- Member of the Board of Trustees, EU Liaison Office of the German Research Organisations, KOWI, Brussels (since 2007)
- Member of the Board of Directors of the DECHEMA e. V. – Society for Chemical Engineering and Biotechnology, Frankfurt/Main (since 2009)
- Member of the Advisory Board: Engineering Life Science
- Member of the Scientific Board, Zenit GmbH, Magdeburg (since 2010)
- Managing Director of the Institute for Process Engineering, OvGU Magdeburg (2009-2010)
- Managing Director of the MPI (since 2011)

7 Future Directions

Research activities of the group will continue with challenging topics related to cell growth and product formation in mammalian cell cultures. First of all, question concerning cell growth and metabolism will be addressed. This includes the integration of data obtained from measurement of extra- and intracellular substrate, inhibitor and metabolite concentrations and information regarding the level of enzyme activities. Based on recent findings that lipid metabolism might play a key role in virus particle generation [32], assays to monitor precursor and metabolite levels of lipid synthesis pathways should be established. Due to the complexity of this task, i.e. the need to set up new assays, options for collaborations with external partners are sought for. Increased complexity is also to be considered when aiming at processes in higher cell densities using fed-batch or perfusion systems. In particular the supply of substrates, the prevention of inhibitor accumulation, aeration, and the monitoring of the physiological status of cells under these process conditions will be a further challenge.
To improve understanding of the impact of medium changes on cellular energy and carbon metabolism dynamic mathematical models for glycolysis and citric acid cycle will be established in parallel. In particular, the switch towards maintenance metabolism at the end of the cell growth phase and impact of washing steps and the replacement of media for the

initiation of the virus infection phase will be investigated in more detail. First results towards this goal have been achieved already based on the excellent data base generated in the Ph.D. thesis of Ritter [53]. However, to determine kinetics of individual reaction steps and to estimate model parameters, a close link to small scale experiments will also be required in the future. This activity will be supported by steady state analyses of mammalian cell metabolism and further elaboration of properties of the metabolic network in close collaboration with the ARB Group. Within this collaboration the properties of so-called designer cells provided by an industrial partner (ProBioGen), i.e. AGE1.CR (duck cells) and AGE1.HN (human cells) will be considered. Eventually, this will allow for the comparison of metabolic profiles of a variety of cell lines with a different background (duck, dog, human), and to draw general conclusions concerning metabolic capacities of mammalian cells in bioprocess engineering. Finally, this will also contribute to a significant extension of the expertise of the BPE Group regarding production cell lines.

Use of flow cytometry for process monitoring has already opened up a rich field of applications and collaborations, both with the PSE and the PSPD Group. So far, experiments have been performed mainly in small to medium scale stirred tank bioreactors (0.5 L to 5 L working volume). This involved very time consuming experiments and availability of comparatively large sample volumes, but allowed inference for individual experiments only. Therefore, current activities are directed towards establishment of experiments in small scale cultures using T-flasks. Here, reproducibility of experiments can be assessed, batch-to-batch variations of kinetic parameters analyzed, one-to-one comparisons of a group of virus strains performed or the impact of variations in cultivation conditions in the same virus-host cell system monitored. In addition, work is in progress towards single cell analysis using multi-well plates. As a result basic mechanisms of virus spreading, virus-induced apoptosis and cell-specific details of virus replication can be resolved in unprecedented resolution. Furthermore, a rich source of information for Monte Carlo simulations, and the further improvement and validation of population balance models will be obtained and existing collaborations with the PSE and the PSPD Group will be clearly stimulated. In addition, single cell analyses complemented with information from PCR-based techniques [35] and antigen yield measurements will provide an extremely valuable database for further development of mathematical models describing single-cell infection dynamics [54]. Eventually, this will allow a linkage of strain-related single cell events to macroscopic properties observed during virus replication phase in bioprocesses.

So far, the optimization of virus production (vaccines, viral vectors) relies mainly on process measures. There are only limited options to improve either the virus strains themselves (i.e. generation of reassortants) or specific properties of viral vectors (i.e. plasmid modifications). Therefore, improvement of cell lines itself is a highly attractive but - due to the enormous complexity of virus-host cell interactions - extremely ambitious goal. Any delay in virus-induced apoptosis, for example, would directly improve virus titers in vaccine production [56]. However, in genome-wide RNAi screen in A549 cells other cellular targets have been identified as well [R40]. Therefore, attempts will be made towards the specific optimization of cell lines. Ideally, this will be done in a well-defined human cell line to allow defined testing of factors involved in the up-regulation of intracellular virus replication, specific modulation of key functions of mammalian cells, and fast generation of stable producer cell lines (BMBF

research proposal: MPI, CEVEC Pharmaceuticals, Helmholtz Centre for Infection Research, MPP for Infection Biology).

With the progress made towards robust and high-sensitive glycomis, the next steps will be directed towards (i) extension of the number of structures available in the existing data base for automated glycan identification, and (ii) the automated analysis of MS/MS data for identification of glycan structures. Furthermore, and in collaboration with external partners (MPI of Colloids and Interfaces), the impact of changes in glycosylation patterns (host cell, cultivation conditions, process deviations) on immunogenicity and potency of vaccines should be addressed. The methods established so far focus on the monitoring and characterization of glycan fingerprints. They also allow the evaluation of the impact of process modifications or process failures on antigen quality, and the screening of samples for biomarker discovery. In a next step, specific questions concerning the role of individual glycans on critical parameters of antigen quality should be addressed. For instance, consequences of changes in glycan fingerprints or differences in glycan abundance on immunogenicity of vaccines or the efficacy of viral vectors in gene therapy should be assessed. Due to the highly interdisciplinary character of such investigations and the requirement of animal testing, third party funding will be required. Finally, it is planned to outsource some of the extremely powerful tools for glycomics developed over the years in limited liability cooperation (GmbH) to offer high-quality services to customers from academia and industry. The scope of applications ranges from clinical studies where thousands of samples have to be analyzed for identification of biomarkers, process development and quality control in biopharmaceutical industry to applications in the food industry.

Finally, as in the previous years, activities in downstream processing of biologicals will be continued in close collaboration with the Chair of Bioprocess Engineering at the OvGU. Based on the results obtained, i.e. the design of efficient processes for purification of virus particles and viral vectors, attempts towards the establishment of more efficient processes will be made. This includes a continuation of research directed towards membrane chromatography. In collaboration with the PSE Group, efforts towards a quantitative understanding of purification of model substances (virus particles, viral antigens) using membrane adsorbers including the assessment of the impact of process contaminations (proteins, DNA) on yield and purity will be made. For validation of model assumptions, a Biacore 3000 system can be used (in collaboration with the Chair of Bioprocess Engineering, OvGU). Furthermore, the design of continuous purification methods for efficient processing of large volumes of virus harvests from bioreactors will be in the focus of activities. The latter relies on advances in the sterile design of simulated moving bed chromatography equipment (which allows validation of the corresponding equipment according to cGMP guidelines) and will be pursued in close collaboration with the PCF Group. Ideally, a combination of unit operations can be applied. An attractive option would be, for example, an integration of size exclusion chromatography for enrichment of large, intact virus particles and ion exchange chromatography for DNA removal. In addition, in collaboration with MSD Group, options to use theoretical methods of “Molecular Modeling” to support the solution of the separation problems, i.e. affinity-based separations will be pursued.

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