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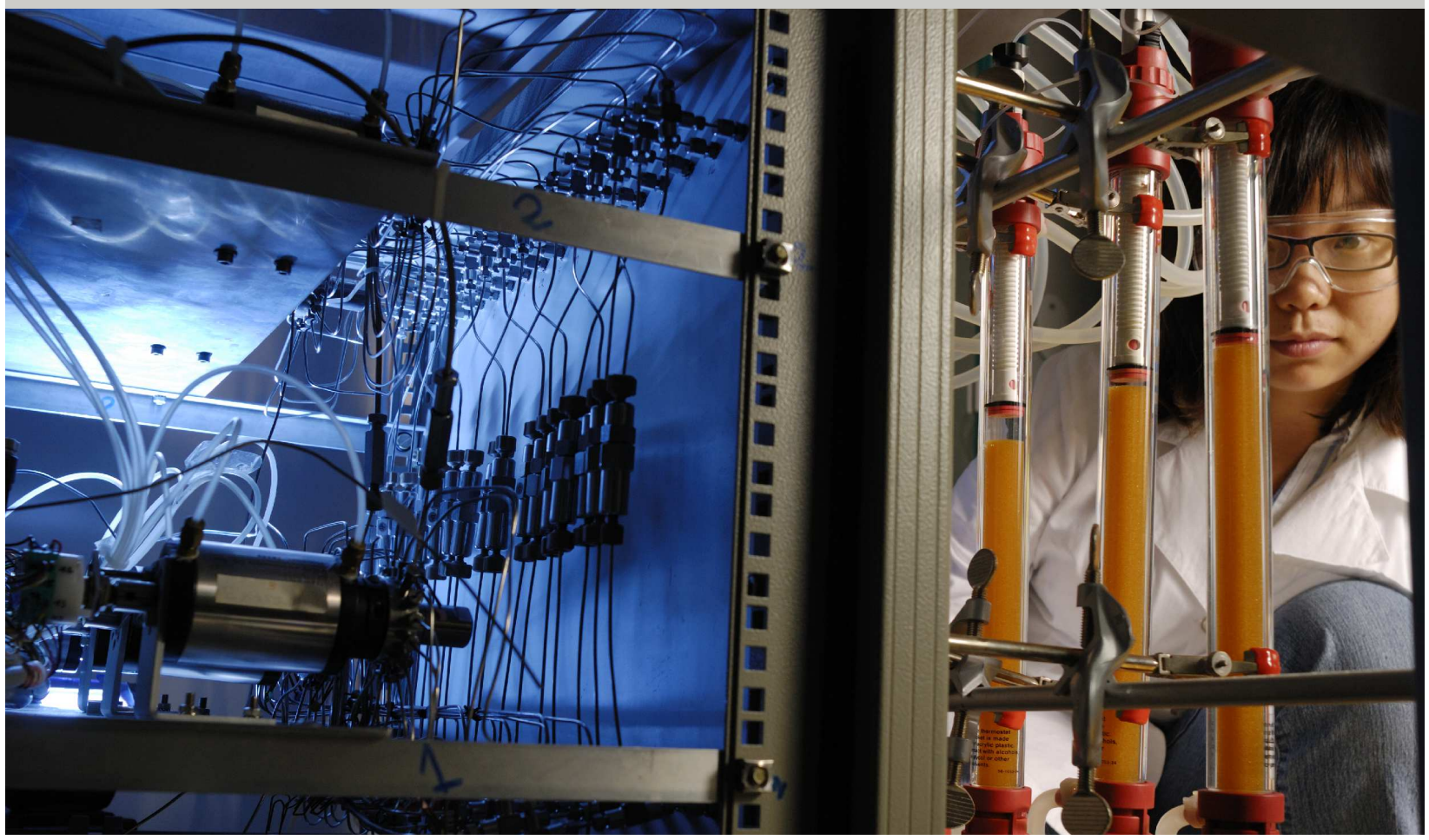
Max Planck Institute for
Dynamics of Complex
Technical Systems

MAX–PLANCK–INSTITUT
DYNAMIK KOMPLEXER
TECHNISCHER SYSTEME
MAGDEBURG



Max Planck Institute for
Dynamics of Complex Technical Systems

Sandtorstrasse 1
D-39106 Magdeburg/ Germany

Phone: +49 (0) 391 6110 0
Fax: +49 (0) 391 6110 500
Email: secretary@mpi-magdeburg.mpg.de

www.mpi-magdeburg.mpg.de

Table of Contents

Members of the Scientific Advisory Board vii

Frequently used Abbreviations viii

Overview 1

1 Present Status 2

2 Important Developments in the Period of this Report 3

3 Concept and Organization of Research 5

4 Project Areas at MPI 7
4.1 Research Area: Network Theory 7
4.2 Research Area: Hierarchical Structures 8
4.3 Research Area: Population Balance Systems 9
4.4 Research Area: Integrated Processes 10
4.5 Research Area: Coupled Processes 10
4.6 Research Area: Hybrid and Discrete Event Systems 11

5 Dynamics of Population Balance Systems: An Example of an Interdisciplinary Collaborative Research Cluster at the MPI 12

6 Publications 13

7 Scientific and Technical Staff 16

8 Cooperation with OvGU Magdeburg and Teaching Activities 21

9 IMPRS Magdeburg 22

10 Important Joint Research Projects 23

11 International Collaborations 25

12 Workshops and Symposia 27

13 Summary and Outlook 28

Research Group Physical and Chemical Foundations of Process Engineering (PCF) 31

1 Group Introduction 32

2 Members of the Research Group 33

3 Survey of Research Projects 35

4 Research Highlights 39

4.1 Project “Solution of population balance equations” ... 39
4.2 Project “Solid-liquid equilibria in ternary chiral systems” ... 39
4.3 Project: “Determination and analysis of adsorption isotherms” ... 41
4.4 Project “Molecular simulation of liquid-solid-interfaces” ... 41
4.5 Project “Electroosmotic transport in multiparticle systems” ... 43
4.6 Projects “Chromatographic resolution of biomolecules” and “SMB chromatography with fractionation and feedback” ... 43
4.7 Project “Thermal effects in reactive chromatography” ... 45
4.8 Project “Mass and heat transfer through porous media” ... 45
4.9 Project “Dosing concepts using tubular membrane reactors” ... 46
4.10 Project “Estimation of free model parameters” ... 47
4.11 Project “Coupling crystallizers” ... 47
4.12 Project “Chromatography or membrane separation prior to subsequent crystallization” ... 49
4.13 Project “Combining enantioseparation and enzymatic racemization” ... 50
4.14 Project “European project INTENANT” ... 51

5 Teaching Activities, Habilitations, Ph.D. and Master Projects ... 52

6 Selected Memberships, Appointments and Awards ... 54

7 Future Directions ... 54

8 References ... 55

Research Group Physical and Chemical Process Engineering (PCP) ... 63

1 Group Introduction ... 64

2 Members of the Research Groups ... 67

3 Research Activities ... 69

4 Research Highlights ... 73
4.1 Population Balance Systems (incl. Junior Research Group "Population Dynamics") ... 73
4.2 Integrated Processes ... 80
4.3 Coupled Processes (incl. Otto Hahn Group "Portable Energy Systems") ... 86

5 Selected Teaching Activities and Ph.D. projects ... 91
5.1 Teaching Activities at OvGU ... 91
5.2 Additional Teaching Activities ... 92
5.3 Supervision of Ph.D. Theses ... 92

6 Selected Memberships, Appointments, Awards ... 93

7 Future Directions ... 94

8 References ... 96

Research Group Process Synthesis and Dynamics (PSD) 103

1 Group Introduction 104

2 Members of the Research Group 105

3 Survey of Research Projects 106

4 Research Highlights 112
4.1 Design of Advanced and Integrated Chromatographic Processes 112
4.2 Model Based Analysis and Control of PEM Fuel Cells 116
4.3 State Estimation of Particle Size Distributions 119
4.4 Population Balance Modeling of Influenza Virus Replication during Vaccine Production 121
4.5 A New Method for Optimal Experimental Design 123

5 Teaching Activities, Diploma, Ph.D. and Habilitation Projects 125

6 Offers, Appointments and Awards 127

7 Future Directions 128

8 References 129

Research Group Systems and Control Theory (SCT) 133

1 Group Introduction 134

2 Group Members and Funding 135

3 Survey of Research Projects 136

4 Research Highlights 142
4.1 Optimal Hybrid Control Systems 144
4.2 Trajectory Planning and Control of Preferential Crystallization Processes 146
4.3 Analysis of Biological Reaction Networks 150
4.4 Controlled Functional Electrical Stimulation (FES) in the Rehabilitation of Stroke Patients and Patients with Spinal Cord Injuries 152

5 Research Related Activities 156

6 Teaching Activities 158
6.1 Teaching at OvGU 158
6.2 Teaching at TUB 159
6.3 Teaching Related Activities 159
6.4 Ph.D Theses 159
6.5 Diploma/Master Theses 160

7 Awards, Fellowships, Appointments 160

8 Future Directions 161

9 References 162

Research Group Molecular Network Analysis (MNA).....167

1 Group Introduction 168

2 Members of the Research Group 170

3 Survey of Research Projects 171

4 Research Highlights 173
4.1 Phototaxis in Halobacterium salinarum..... 173
4.2 Control of Sporulation in Physarum polycephalum..... 177
4.3 Automatic Network Reconstruction..... 185

5 Teaching Activities 185

6 Recent Appointments and Awards 185

7 Future Directions 185

8 References..... 186

Research Group Systems Biology (SBI).....189

1 Group Introduction 190

2 Members of the Research Group 193

3 Research Activities..... 194

4 Research Highlights 197
4.1 Junior Research Group: Redox Phenomena in Photosynthetic Bacteria (Hartmut Grammel) 197
4.2 Junior Research Group: Systems Biological Analysis of Local and Global Regulations (Katja Bettenbrock) 201
4.3 Junior Research Group: Dynamics and Control in Cellular Systems (Andreas Kremling)..... 203
4.4 Junior Research Group : Structural and Functional Analysis of Cellular Networks (Steffen Klamt) 206
4.5 Junior Research Group : Tools and Concepts for Modeling and Simulation (Sebastian Mirschel) 210
4.6 Junior Research Group: Advanced Concepts for Kinetic Modelling (Michael Ederer) 212
4.7 Senior Research Group: Regulatory Circuits (Ernst Dieter Gilles)..... 214

5 Selected Teaching Activities, Diploma Projects, Ph.D. Projects 217

6 Selected Memberships, Appointments and Awards 218

7 Future Directions 218

8 References..... 219

Research Group Bioprocess Engineering (BPE) 223

1 Group Introduction 224

2 Members of the BPE Research Group 225

3 Survey of research projects of BPE Group 227

4 Research Highlights 232
4.1 Metabolic Flux and Intracellular Metabolite Concentrations during Adherent Cell Growth and Infection 232
4.2 Development of Downstream Processes for the Production of Viral Vaccines and Recombinant Proteins 237
4.3 Proteomics and Glycomics 241
4.4 Signal Transduction and Apoptosis in Virus-infected Cells 246
4.5 Organization of Symposia and Workshops 248

5 Selected Teaching Activities, Diploma Projects, PhD Projects and Habilitations 249
5.1 Lectures at the OvGU (Prof. U. Reichl): 249
5.2 Diploma projects (September 2005 to July 2008) 249
5.3 Supervision of Ph.D. Theses (September 2005 to July 2008) 250
5.4 External evaluations (September 2005 to July 2008) 251

6 Selected Memberships, Appointments and Awards (Udo Reichl) 251

7 Future Directions 251

8 References 253

Members of the Scientific Advisory Board

Frequently used Abbreviations

Research Groups

BPE	Bioprocess Engineering
MNA	Molecular Network Analysis
PCF	Physical and Chemical Foundations of Process Engineering
PCP	Physical and Chemical Process Engineering
PSD	Process Synthesis and Process Dynamics
SBI	Systems Biology
SCT	Systems and Control Theory

Junior Research Groups

PDY	Population Dynamics
OH	Otto Hahn Group “Portable Energy Systems”

Funding Organizations

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 “Dynamical Systems in Biomedicine and Process Engineering”
CPTS	Chemistry, Physics and Technology Section of MPG
DAAD	German Academic Exchange Service
DFG	German Science Foundation
EU	European Union
EU-HYCON	European Union Network of Excellence: Hybrid Control - Taming Heterogeneity and Complexity in Networked Embedded Systems
FES	Functional Electrical Stimulation
IMPRS	International Max Planck Research School
IPC	International Program Committee
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”
TUB	Technical University Berlin
VW	Volkswagen Foundation

Max Planck Institute
for Dynamics of Complex Technical Systems
Magdeburg

Overview

by
the Managing Director Andreas Seidel-Morgenstern

W. Marwan, A. Seidel-Morgenstern, E.D. Gilles, A. Kienle, U. Krewer,
H. Briesen, K. Sundmacher, U. Reichl, J. Raisch

1 Present Status

The scientific work at the Max Planck Institute for Dynamics of Complex Technical Systems (MPI) began in March 1998. In August 2001 the entire institute moved into a newly constructed building located near the Otto von Guericke University of Magdeburg (OvGU), which is an important cooperation partner for the various research groups of the MPI.

Evaluations of the MPI by the Scientific Advisory Board (SAB) took place in June 2003 and in December 2005.

The present board of directors consists of three active scientific members of the Max Planck Society (MPG), Professors Udo Reichl (Department for Bioprocess Engineering, BPE), Andreas Seidel-Morgenstern (Department for Physical and Chemical Foundations of Process Engineering, PCF) and Kai Sundmacher (Department for Physical and Chemical Process Engineering, PCP). All three are also full professors at the OvGU (Faculty of Process and Systems Engineering). Before becoming emeritus in May 2008, 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 three active department heads, there are currently the following four research groups at the MPI: Process Synthesis and Process Dynamics (PSD) group headed by Prof. Achim Kienle; Systems and Control Theory (SCT) group headed by Prof. Jörg Raisch; Molecular Network Analysis (MNA) group headed by Prof. Wolfgang Marwan and the Systems Biology (SBI) group, which will be headed by Prof. Gilles until 2011.

Prof. Kienle is also a full professor at the OvGU Faculty of Electrical Engineering and Information Technology. In 2006 Prof. Raisch left the OvGU where he was full professor for Systems Theory in Engineering and now holds the Chair of Control Systems at the Technical University in Berlin. The MPG appointed both Prof. Kienle and Prof. Raisch as External Scientific Members of the MPI. Supported by an initiative of the OvGU and the MPG in April 2005, Prof. Marwan was appointed as full professor for Regulatory Biology at the OvGU Faculty of Natural Sciences. This group was initially fully-funded by the MPG. However, starting in January 2009, the MNA group will be completely funded by the OvGU, according to an agreement between MPG and OvGU which was fixed when founding the MNA group.

In addition to the seven groups already mentioned, two Junior Research Groups started their work in 2007 and 2008, namely the Population Dynamics (PDY) group headed by Dr. Heiko Briesen and the Otto Hahn group Portable Energy Systems (OH) headed by Dr. Ulrike Krewer. Their reports are incorporated in the report of the PCP group. Dr. Briesen's group is closely linked to the PCP research group headed by Prof. Sundmacher. Dr. Krewer's OH group is an independent Junior Research Group funded by central funds of the MPG. Further Junior Research Groups also exist within the SBI group.

The number of Ph.D. students, postdoctoral scientists, visiting scientists, and members of the technical staff has steadily increased during the period covered by this report (see Fig. 1). As of July 2008, the total number of staff employed at the MPI was 216.

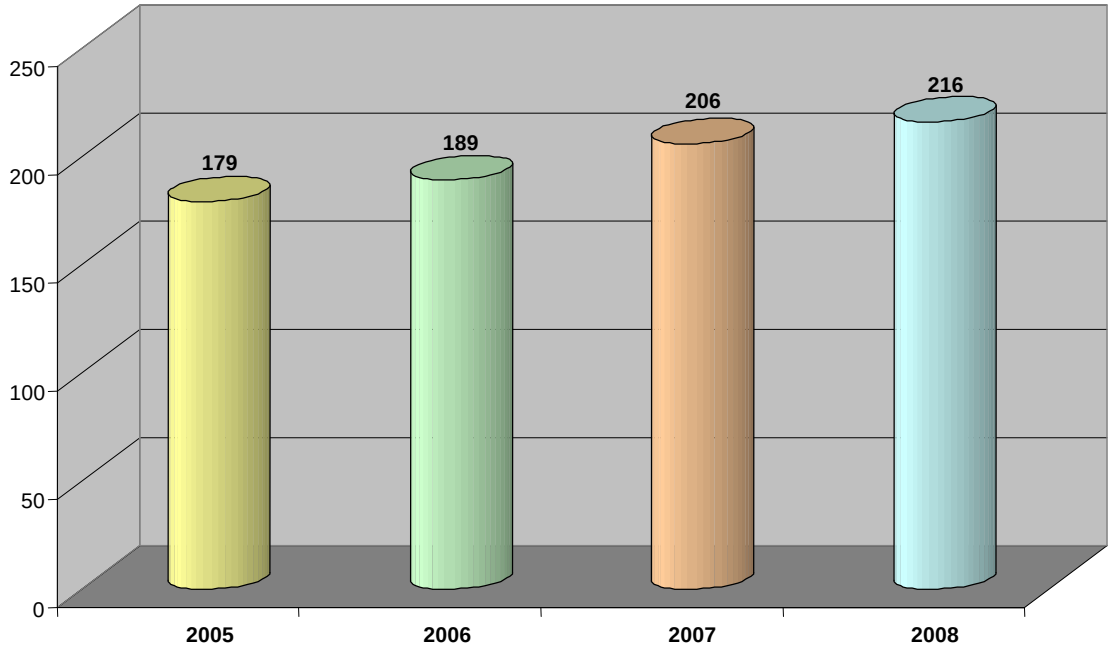


Fig. 1: Development of the total number of MPI staff between 2005 and 2008 (as of July 31).

2 Important Developments in the Period of this Report

In 2008 the President of the MPG thanked Professor Caines (Montreal) and Professor Reuß (Stuttgart) for their substantial and valuable support given over the last six years to the MPI as SAB members. The appointments of Professor Antsaklis, Professor Morbidelli, Professor Santamaria, Professor Scott, and Professor Strohrmann were extended. Invitations to become new SAB members were accepted by Professor Blossey (Lille), Professor Carrondo (Lisbon), Professor Doherty (Santa

Barbara) and Professor Noll (Bielefeld).

As identified by the SAB during its last visit, the two most important tasks facing the institute in the period covering this report were related to finding a successor for Prof. Gilles as director for the research area of Systems Theory and securing the future of the emerging field of Systems Biology.

The institute performed an extensive search to find a suitable candidate for the Systems Theory position. In particular, together with members of an MPG appointment commission, a colloquium entitled “Trends in Systems and Control Theory” was organized at the MPI (March 1-2, 2006). All efforts and activities undertaken demonstrated the difficulty of recruiting a scientist who is able to represent the whole field of Systems Theory, including synthesis, analysis and control, and who is simultaneously available to take this position. For this reason the search activities were focused on appointing a director, who would be able to cover this essential research field in the institute. Due to the competence in the PSD and SCT groups regarding high level synthesis and control problems, the search concentrated on identifying a scientist possessing superior expertise in Systems Analysis. In October 2007, after considering several options, the institute proposed a candidate to the Chemistry, Physics and Technology Section (CPTS) of the MPG and an appointment commission was formed. The review process and the evaluation of the candidate did not lead to a coherent opinion in the commission and the institute withdrew the proposal in June 2008.

In 2007 the Presidium of the MPG decided neither to initiate the foundation of an entire MPI dedicated to Systems Biology nor dedicate a department in one of the existing MPIs. Thus, unfortunately, a detailed concept developed and suggested by our institute, which was intended to secure and continue the corresponding activities in Magdeburg after the retirement of Prof. Gilles, could not be realized.

In its last report, the SAB recommended strengthening the activities of other emerging fields, namely (1) Molecular Modeling, (2) Population Balance Systems and (3) Stochastic Modeling and Analysis. In all these areas research was intensified as documented in the individual reports of the research groups. Regarding subject (2) the Junior Research Group “Population Dynamics” was founded. Attempts undertaken to recruit other suitable researchers as leaders of Junior Research Groups have not yet been successful.

An ongoing and still unsolved problem for the MPI is the fact that the OvGU and the

Federal State of Saxony-Anhalt did not keep the promise to finalize a new building for the Faculty of Process and Systems Engineering by 2007. This building is needed for research activities of the OvGU Professors Marwan, Reichl, Seidel-Morgenstern and Sundmacher, which are currently accommodated in the MPI building. In particular, the blockage of laboratory capacity presents a serious obstacle for further growth of the MPI.

The SAB also recommended organizing an International Graduate School. Based on a successful proposal of the MPI and the OvGU, the International Max Planck Research School (IMPRS) for Analysis, Design, and Optimization in Chemical and Biochemical Process Engineering started in October 2007 with the first graduate students.

Within the period covered by this report, a Board of Trustees was appointed to accompany and support the work of the MPI. Current members of the board are Dr. Lutz Trümper (Mayor of Magdeburg), Dr. Kurt Wagemann (Manager of the Department for Research Funding of the Dechema Society for Chemical Engineering and Biotechnology), Elke Lüdecke (Director of MDR Landesfunkhaus Sachsen-Anhalt), Dr. Heinz Hofmann (Manager of IDT Biologika GmbH), Dr. Uwe Küster (parliamentary director of SPD fraction in the Bundestag), Dr. Eduardo Mendoza (Faculty for Physics at University of Munich), Dr. Helmut Mothes (Head of Process Technology at Bayer Technology Services), Dr. Eva E. Wille (Publishing Manager of Wiley-VCH) and Prof. Klaus Erich Pollmann (Rector of the OvGU). This board met in 2006 and 2007 and has already helped to effectively increase the public visibility of the MPI. The meeting in 2007 was important because it put additional pressure on the Federal State of Saxony-Anhalt regarding the promised building project.

An enjoyable day for recapitulating the first 10 years of the MPI was given during a colloquium organized on May 30, 2008. On this day our institute also took the opportunity to thank Prof. Gilles for his extraordinary work as the MPI founding director. The institute was very pleased that the President of the MPG supported a continuation of Prof. Gilles' activity as a supervisor of the numerous promising third party projects running in the area of Systems Biology.

3 Concept and Organization of Research

The institute is focused on analyzing, designing and controlling of processes relevant in chemical engineering, biotechnology and systems biology. This objective not only

requires a sound knowledge of the specific processes as well as the underlying physical, chemical or biological phenomena, but also requires engineering and mathematical tools for the analysis and synthesis of dynamic systems. Therefore, at the MPI engineers work in close cooperation with chemists, biologists and mathematicians. An overview of main research fields of the institute is depicted in Fig. 2.

Applications cover the synthesis, analysis and control of chemical reactors and separation processes; the collection of thermodynamic and kinetic data; the design and optimization of bioprocesses; biomedical applications and the analysis of molecular networks in biological systems. All these research topics share a common theme: they all incorporate methods and tools provided by systems science, so that systems science is an important integrating factor in the institute.

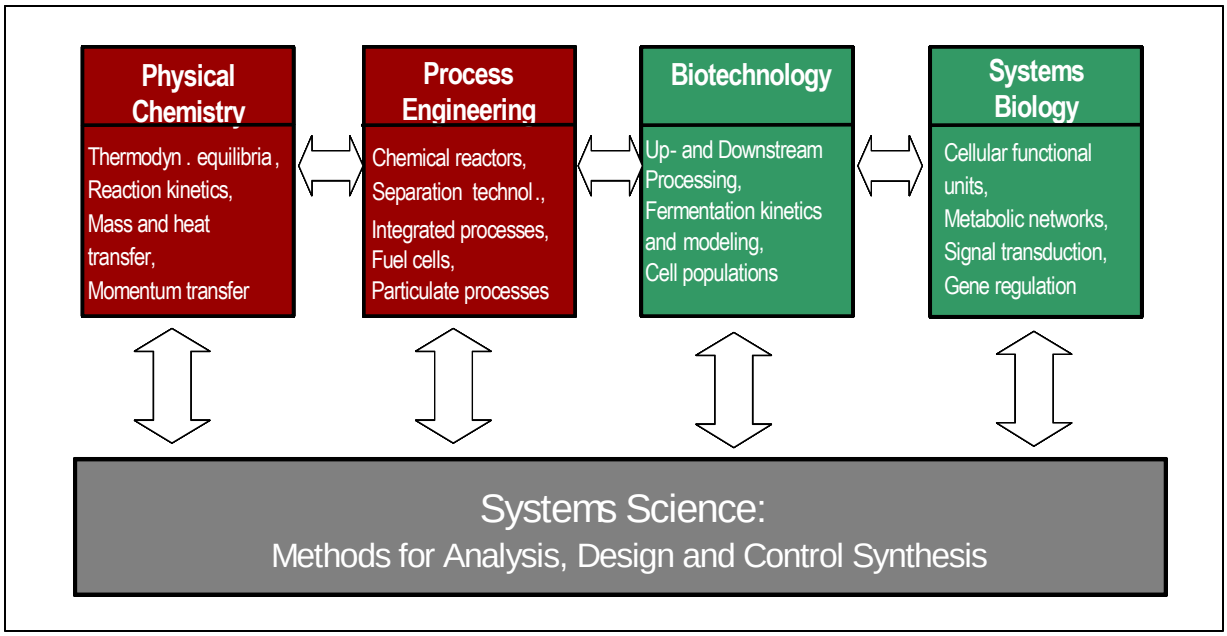


Fig. 2: Main research fields at the MPI.

The interdisciplinary character of the MPI implies a structure that does not allow for strictly separated departments. Instead, in order to stimulate and intensify collaboration within the institute, research groups have been established. Another important advantage of the group structure is that it facilitates the adoption of new research directions with greater ease than a more rigid departmental structure.

To strengthen interdisciplinary cooperation, researchers from different groups work together in various project areas. Each research project as well as each of its subprojects at the institute is related to one of these projects areas. Hence, scientists

from several disciplines share their particular perceptions and methods in the examination of a certain research topic. The interdisciplinary approach of the MPI is manifested in two respects. First, several methods and approaches from chemistry, mathematics and engineering are used to examine one objective from different perspectives. Second, often the same method is employed to investigate problems from several different application areas.

An overview of the present status of interdisciplinary collaboration is given in the matrix of research activities given in Tab. 1.

Tab. 1: Project areas and research groups as of September 2008.

Project Areas / Res. Groups	Network Theory	Hierarchical Structures	Population Balance Systems	Integrated Processes	Coupled Processes	Hybrid and Discrete Event Systems
Physical and Chemical Foundations of Process Eng. (PCF)			●	●	●	●
Physical and Chemical Process Eng. (PCP)			●	●	●	
Process Synthesis and Process Dynamics (PSPD)		●	●	●		●
Systems and Control Theory (SCT)	●	●	●	●	●	●
Molecular Network Analysis (MNA)		●				●
Systems Biology (SBI)	●	●				
Bioprocess Eng. (BPE)	●	●	●		●	
Otto Hahn Group (OH)					●	

The six project areas indicated in Tab. 1 were described in detail in our last report to the SAB. These areas have been proven to be very suitable to characterize, focus and present the research interests and activities of the whole institute. A short description of these research areas is given below.

4 Project Areas at MPI

4.1 Research Area: Network Theory

The purpose of this project area is to simplify model development by systemizing

modeling approaches for chemical and biochemical processes. The goal of the systematic modeling approach is the subdivision of process models into elementary modeling units. These modeling units are elements of a modeling library and can be combined to new models of arbitrary complexity. The modular approach offers the following advantages: a) frequently used sub models need not be re-implemented again and again but are available from a model database; b) alternative approaches, e.g. for the description of diffusion processes, can be exchanged easily; c) during model formulation, the modeler can concentrate on the underlying physical assumptions without being concerned with the mathematical representation, d) the transparency and re-usability of existing models is increased.

These network theoretical concepts provide a sound basis for the development of suitable methods and tools for modeling of complex processes relevant in chemical or biochemical engineering and systems biology.

One research focus is the modeling of complex systems in a modular fashion. Here, the modular modeling approach is an integral part of a tool (ProMoT, Diana) which facilitates the convenient setup, editing and simulation of different systems such as membrane reactors, fuel cell systems, metabolic pathways or signaling cascades.

The research also focuses on the comprehensive structural and functional analysis of large-scale cellular networks. The new developed methods are continuously implemented in a software (CellNetAnalyzer).

The methods and tools are developed in the groups SBI and PSD. They are a common infrastructure that is used in many projects of the groups MNA, PSPD, BPE and SBI and the international scientific community.

4.2 Research Area: 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. Traditional methods for the synthesis of process control strategies are based on an isolated treatment of small and, typically, rather simple components; obviously, such an approach does not live up to the requirements of an increasingly complex and integrated reality. It will inevitably lead to unsatisfactory, and, therefore far from optimal, solutions. On the other hand, treating a complex overall system as some type of unstructured conglomerate is unacceptable as the difficulties related to computational implementation usually grow exponentially in relation to the size of the

problem.

Hierarchical approaches are a possible solution to this dilemma. These approaches 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 such an approach is extremely intuitive, as of yet, 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.

Nature makes efficient use of some sort of hierarchical structure. If one succeeds in understanding the principles of such biological regulatory processes, a systems theoretic approach can help to transfer these principles to complex control problems, e.g. within the field of chemical engineering, where the task is to control material or energy flow.

4.3 Research Area: Population Balance Systems

Populations of similar objects are frequently characterized by a distribution of certain properties. Typical examples are solid particles, emulsion droplets, molecules or cells. Some important parameters 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 also depend on the local positions of the objects (e.g. in a stirred reactor). 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 and for virus spreading in populations of cells.

Although there are significant differences between the processes mentioned above, population balance models allow the dynamics of the distribution of the different specific properties to be described in a unified manner. Preliminary examples of the successful application of a rigorous mathematical modeling for predicting particle size

distributions in crystallization processes and chain length distributions in polymerization processes have been developed in the last several years. However, there are challenging unexplored areas and applications that require further intensive research in order to be able to design and optimize processes with distributed parameters.

4.4 Research Area: Integrated Processes

In the chemical industry and in biotechnology, the conversion of substances and purification of the desired products is usually carried out in sequentially structured reaction-separation trains. In many cases, the performance of this classical chemical process structure can be significantly improved by integrative coupling of different process units. 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.

The foremost objectives of the research within this project area are the development of new concepts of integrated processes, the investigation of their efficiency, and the enhancement of availability for technical application. For these reasons, experimental tools and theoretical methods are intimately combined.

The preparation of the applicability of new processes in an industrial scale relies on mini-plant technologies used in the institute's experimental investigations.

Ongoing subjects of our research are reactive distillation processes, chromatographic reactors, low-temperature and high-temperature fuel cells, reactive membrane separation and membrane reactors.

4.5 Research Area: Coupled Processes

Complex processes routinely consist of several individual sub-processes interacting in tandem. Numerous examples are found in biology and technology, e.g. the

coupling of metabolic and regulatory networks in cellular systems, or the combination of processes or individual process units in biochemical engineering. Targeted manipulations of the genome of production cell lines would enhance specific productivity and, in conjunction with suitable process control strategies, assist the increase of biotechnological process yields. As far as chemical engineering systems are concerned not only overall yields and product purity but also material and energy recycles between individual process units account for an optimal overall utilization of raw materials and energy.

Analysis, design and optimization of coupled 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 common interest is directed towards optimal design and control of the respective coupled processes. Currently application examples from chemical process engineering, energy systems engineering and biosystems engineering are considered in this research area.

4.6 Research Area: 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. Finally, 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.

5 Dynamics of Population Balance Systems: An Example of an Interdisciplinary Collaborative Research Cluster at the MPI

The project area Population Balance Systems remains a good example for interdisciplinary system-oriented collaboration carried out between the different research groups. In the period of the report, significant progress was achieved in different areas and new projects were successfully initiated. The collaboration between the PCF, PCP, BPE, PSD, and SCT groups has intensified in order to develop model-based methods and tools for the analysis, design and control of population balance systems. The ongoing vision is to develop a methodology which enables the reliable prediction of the operating behavior of the required production process systems and the simultaneous design of suitable control strategies in order to produce a particle population with a specific desired property distribution.

Within this framework, the process-oriented groups (PCP, PCF, BPE) analyze challenging chemical and biotechnological applications in which complex populations such as competing populations, nested populations and multidimensional populations are encountered. The chosen process examples are the crystallization of enantiomers (PCF group), nano-particle precipitation in emulsions (PCP group), and virus-host cell systems in bioreactors (BPE group). These processes are investigated using advanced experimental techniques for the collection of thermodynamic and kinetic data, particularly emphasizing the analysis of the micro-kinetics of particle nucleation, growth, aggregation and breakage at single particles as well as at particle populations under well-defined conditions. The two system-oriented groups (PSD and SCT) focus e.g. on the analysis of the nonlinear process behavior, state-estimation methods, mathematical model reduction, optimal trajectory design for batch systems and control of continuously operated particulate processes. The models applied are typically based on population balance equations describing the dispersed phase.

Within the period of this report the activities of the institute in the area of Population Balance Systems were further extended which is reflected by several joint publications, partly prepared with colleagues from OvGU and MPG, and several new collaborative projects which have been acquired:

a) BMBF-funded joint research project of the PCP and PSD groups on “Efficient mathematical methods and algorithms for the simulation of particle populations in

3D flow fields (SimPaTurS)" with partners from OvGU (Prof. Tobiska), the University of Saarland (Prof. John) and the MPI for Mathematics in the Sciences in Leipzig (Prof. Hackbusch),

b) DAAD-supported collaborative project of the PCP group with Purdue University (Prof. Ramkrishna) on "Evolution of crystal shape distributions",

c) DFG-funded joint project of the PCF group with the TUB group of Prof. Raisch on "Coupling and control of crystallisers for enantioseparation",

d) DFG-funded joint project of the PCF group with RWTH Aachen and University of Karlsruhe on "Coupling membrane separation and crystallisation to separate enantiomers",

e) LSA-funded joint projects on "Heteroaggregation processes in biomedical systems (PCP group with Prof. Naumann from the medical school of OvGU) and on "Stochastic modeling of virus replication in mammalian cells" (BPE, PSD and PCP groups), both being embedded in the Magdeburg research center "Dynamical Systems" (CDS).

f) The topic "crystallization" is also one of the major work packages of the European project "INTENANT" coordinated by the PCF group (Work package 4, chaired by Prof. Coquerel in Rouen). This project starts to support and influence substantially the MPI work carried out in this area.

g) Furthermore, active collaborations exist with Prof. Thévenin (OvGU Department of Fluid Mechanics) on fluid dynamic simulations of systems containing particle populations, and with Prof. Warnecke (OvGU Department of Mathematics) on the numerical solution of population balance equations.

In addition, the project area "Population Balance Systems" was significantly strengthened by the arrival of Dr. Briesen at the MPI. The Junior Research Group "Population Dynamics" (PDY) concentrates on predictive modeling concepts for population systems. Projects comprise detailed physical modeling of the governing rate processes, deterministic and stochastic solution techniques for multidimensional population balance problems as well as multiscale integration of continuous and discrete modeling approaches.

6 Publications

A complete list of publications and papers submitted by the research groups will be finalized in December 2008 as a supplement to this report. A summary is provided

below of the general development of MPI publications from 1998 until July 2008. Fig. 3 shows the distribution of journal articles, conference contributions, Ph.D. theses and book contributions over the past ten years.

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 is 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 (June 27, 2008), a total of 411 journal articles have been published with at least one author assigned to the MPI address.

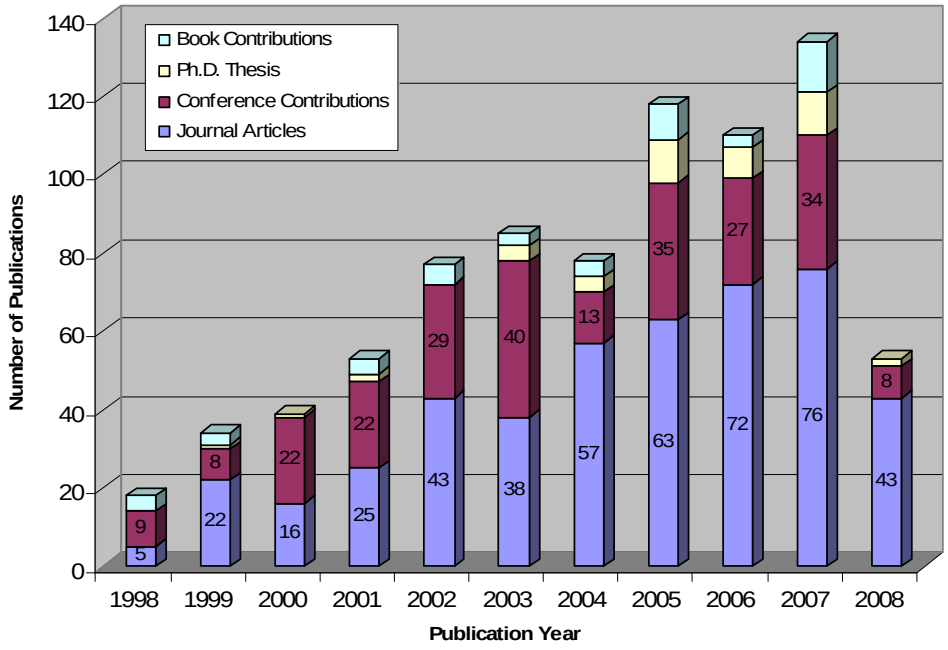


Fig. 3: Development of the number of articles published in journals, conference contributions, PhD. theses and book contributions during the period 1998 - July 2008.

Fig. 4 shows the number of citations per year (not cumulative) of the 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 “sales curve” is a significant indicator of the research impact of a corresponding research institute. The graph reveals that the number of citing papers per year of MPI papers has increased continuously.

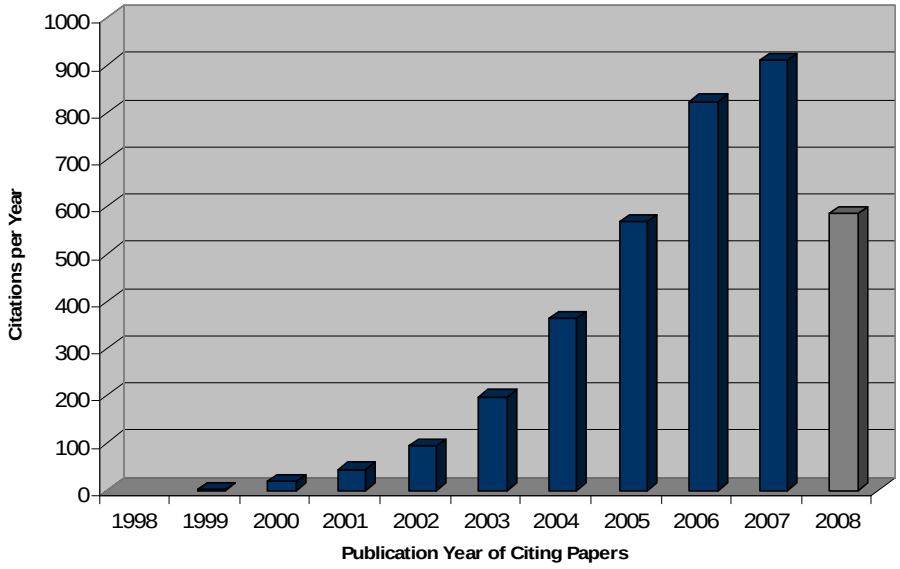


Fig. 4: Time-dependent impact of MPI papers, expressed as number of citations per year.

The running average of the impact of papers within the first years after their publication may be consulted for checking 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.

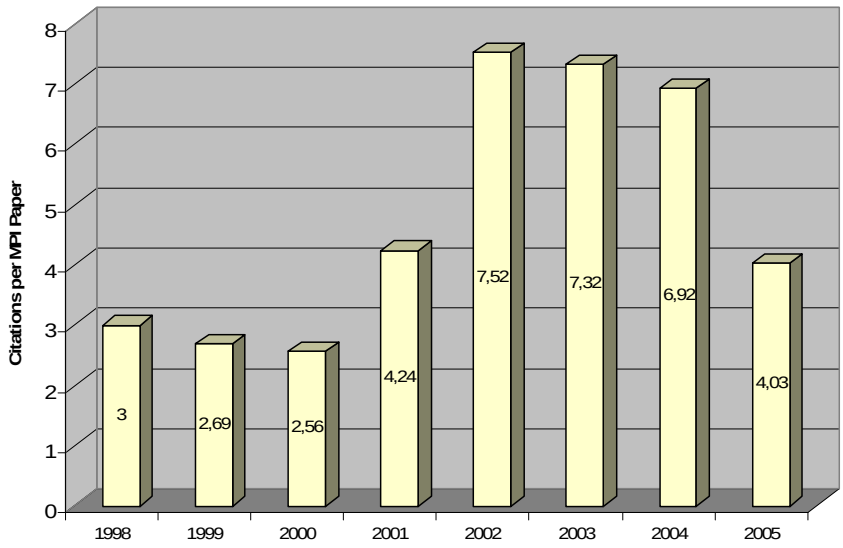


Fig. 5: Running average of impact of MPI papers within the first 2 - 3 years after publication.

Since 2002, each MPI paper receives roughly six citations within the first 2 – 3 years of publication. This is above the average number of around four citations per paper in the same time frame as quoted in the ISI Essential Science Indicators (ESI-2007) 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 holds $C > 1$ means above average and $C < 1$ below average. The C-index of the MPI is currently 1.20 (time period 2002 – 2006; source: National Citation Report for Germany). This indicates that the articles of the MPI in this field enjoyed a greater visibility than all the articles published in the same journals, taken as a whole. The evaluated 236 articles revealed 1306 citations, i. e. on average they were cited 5.53 times.

7 Scientific and Technical Staff

In this section, 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 31, 2008, a total of 216 employees were working at 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 (31%). Another 21% 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 MPI while studying at the OvGU. The research work at MPI is an important additional experience for their education and gives us the chance to identify the students most capable of pursuing Ph.D. studies after graduation.

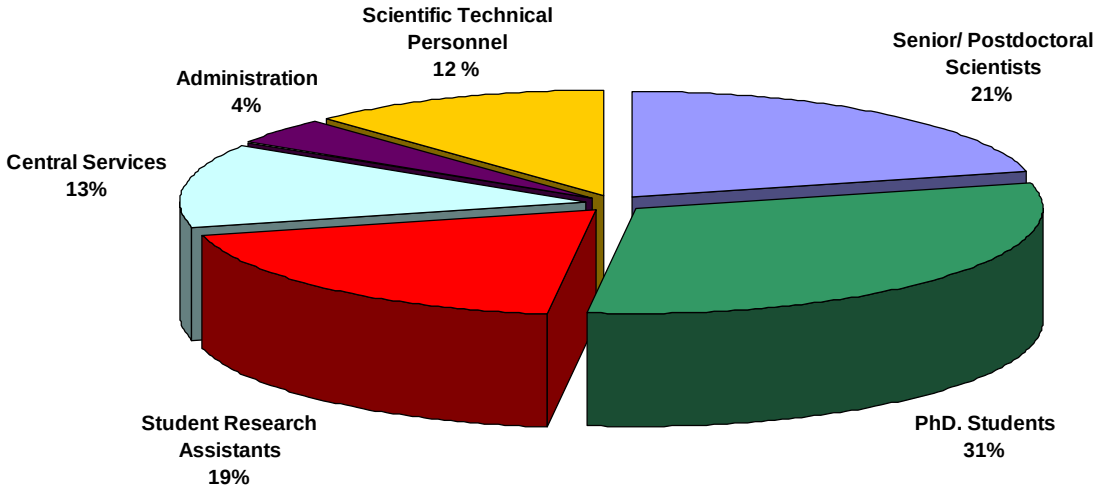


Fig. 6: Composition of MPI personnel as of July 31, 2008.

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 (12%). Moreover, 13% of the MPI staff represents central services such as the library, secretarial services, 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 2005 the total number of employees has increased by about 21%. With the accommodation of the MNA group and the ongoing activities of the Chairs of the OvGU in laboratories of the MPI, the corresponding capacities are fully used.

The age distribution of the employees is displayed in Fig. 7. At present about 51% of the institute's staff are less than 30 years old. Only about 5% 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, 2008, there were 112 scientists employed at the MPI, 46 of them senior and postdoctoral scientists and 66 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.

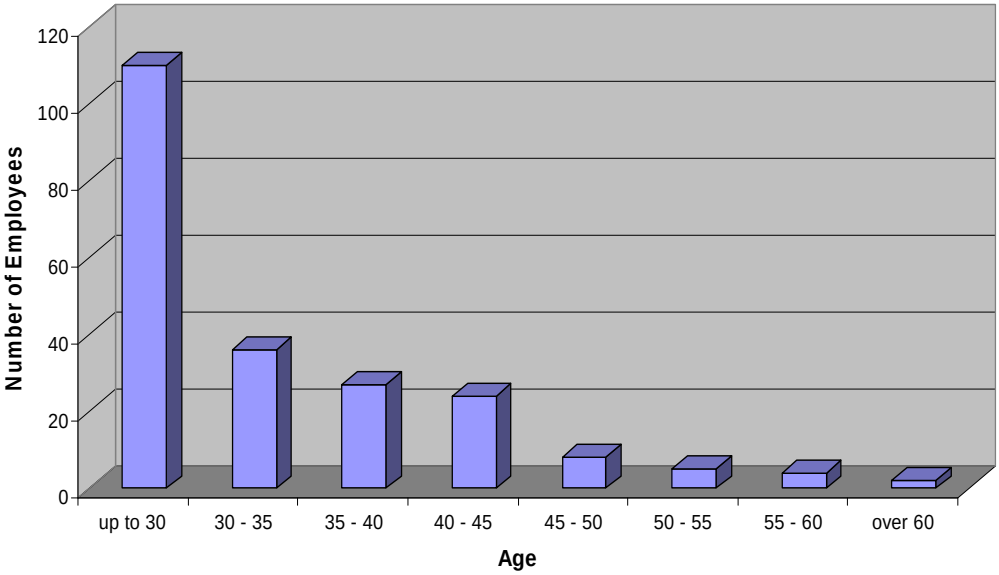


Fig. 7: Age distribution of all MPI employees as of July 31, 2008.

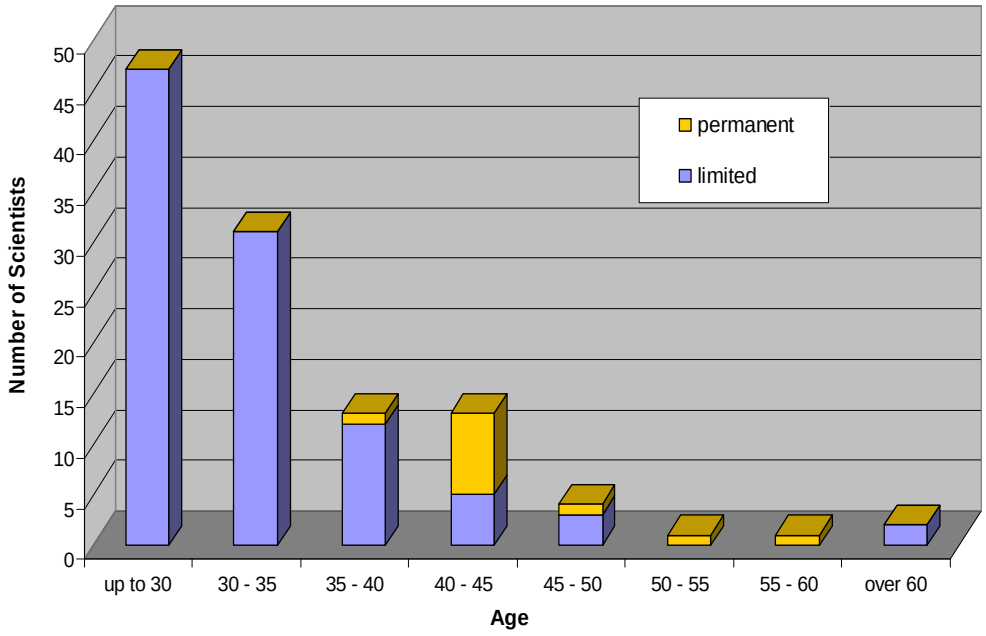


Fig. 8: Age distribution of MPI scientists divided into permanent and temporary employments as of July 31, 2008.

Fig. 9 shows the distribution of our scientific coworkers according to gender. The percentage of female scientists is about 19%. This is a higher proportion of women than normally encountered in engineering sciences in Germany.

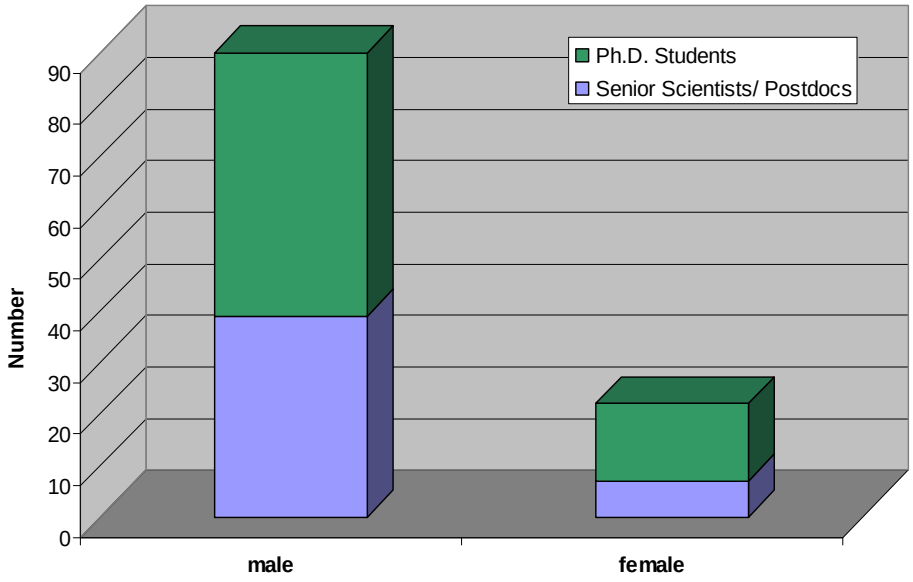


Fig. 9: Gender distribution of scientists as of July 31, 2008.

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 faculties for Chemical and Process Engineering, Electrical Engineering and Information Technology or Natural Sciences. 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 (Fig. 10).

Over the last 3 years the fraction of students coming from abroad was in the range between 30 and 43 percent, which clearly shows that our institute is very attractive to students from international schools.

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.

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 2006 to August 2008, a total of 53 German scientists and 120 guest scientists from abroad visited our institute. Among the international guests, 70 came from European countries, 12 from America, the rest from Asia and Australia.

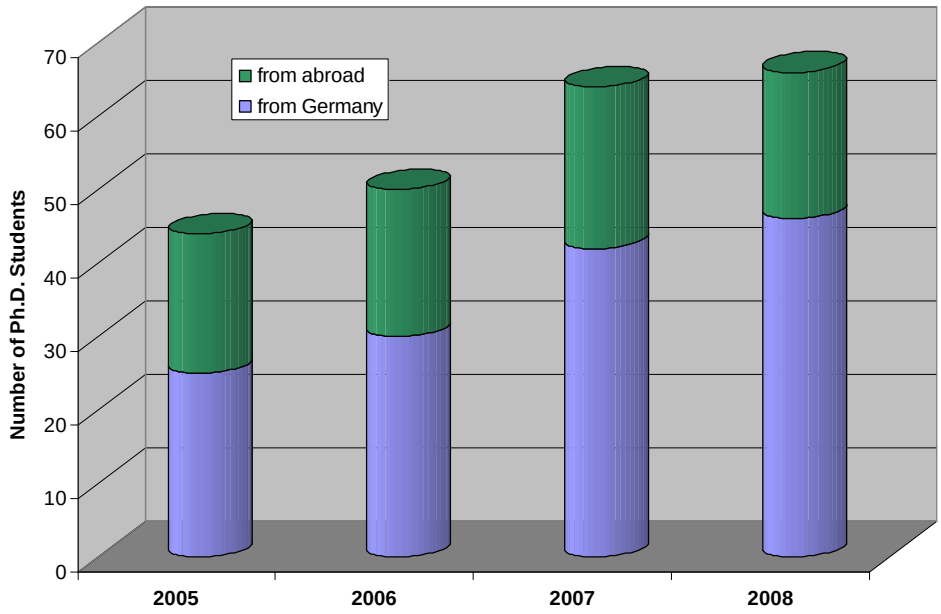


Fig. 10: Number of Ph.D. students over the last 3 years from abroad and from Germany.

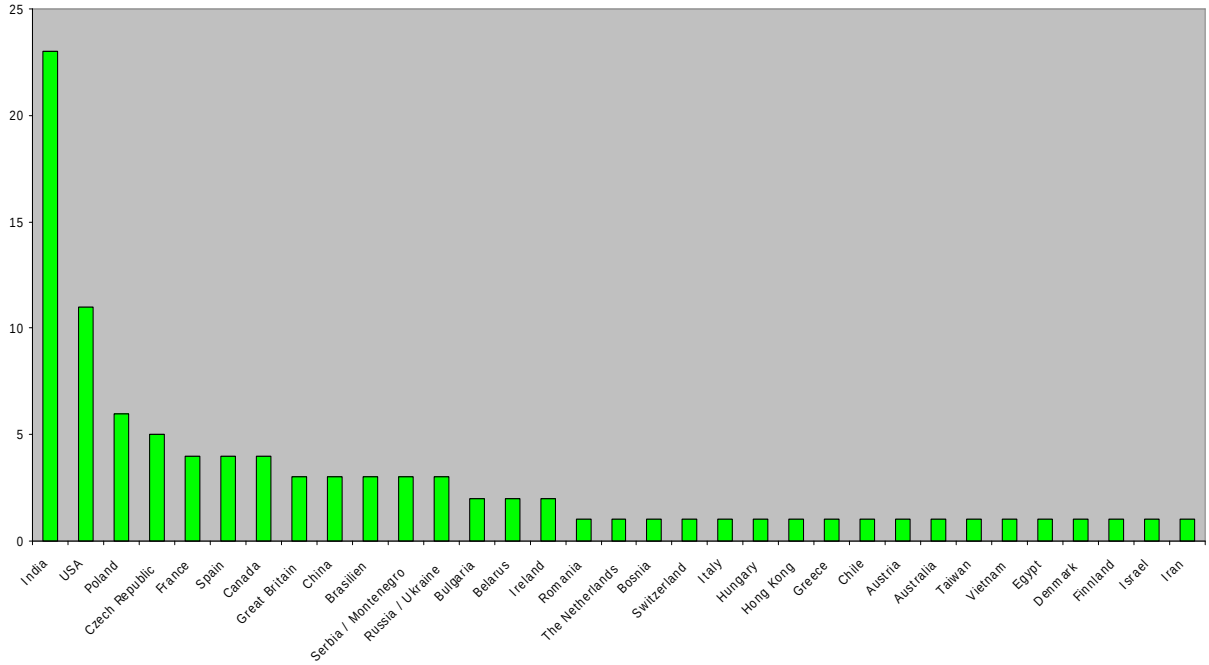


Fig. 11: Number of visits by international scientists from 2005 - June 2008 (with a stay of at least two days).

8 Cooperation with OvGU Magdeburg and Teaching Activities

As outlined in section 1, three directors of the MPI (U. Reichl, A. Seidel-Morgenstern, K. Sundmacher) are appointed professors at the Faculty of Process and Systems Engineering, and two heads of MPI research groups (A. Kienle, W. Marwan) are appointed professors at the Faculty of Electrical Engineering and Information Technology and at the Faculty of Natural Sciences, respectively.

There are also extensive teaching activities carried out by the research group heads and various other scientists of the MPI research groups at the OvGU. These comprise specialized lectures, mandatory lectures and laboratory courses as well as supervision of diploma 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.

The above-mentioned colleagues have been also closely involved in the recently finalized process of transforming the former diploma curricula at the OvGU into new consecutive bachelor and master curricula (Bologna Process).

At present there are concrete activities of the MPI in the following diploma (phasing out), bachelor and master courses:

- Systems Engineering and Cybernetics
- Environmental and Energy Process Engineering
- Molecular and Structural Product Design
- Chemical and Process Engineering
- Biosystems Engineering

In addition to our teaching activities and to our contributions in the strategic development of the profile of the engineering programs at OvGU, the MPI invests a considerable amount of energy to directly approach students from high schools of the Federal State of Saxony-Anhalt and 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 organized and taught 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. After the successful termination of a “NaT-working project” (NaT: Natural and Technical sciences), funded by the Robert-Bosch-Foundation until 2005, the MPI continues to maintain successful direct partnerships with five regional high schools.

9 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 50 IMPRS offer 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.

As recommended by the SAB in its last report, 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. At the same time, 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. Twelve research groups were involved in the IMPRS proposal, six 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.

After approval of the proposal, research projects investigated at the IMPRS Magdeburg focus on modeling technical and biological processes and are located at the interface of mathematics and engineering. The funding of the IMPRS (approx. 5 million EUR for 6 years) allows supporting up to 30 doctoral students at a time. Emphasis is on mathematical and systems (both theoretical or applied) and experimental aspects:

- 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.

In October 2007, the first ten students from four continents started their doctoral projects at the IMPRS Magdeburg. Since the beginning of the summer term 2008, 20 doctoral students have been enrolled. With a third call for applications for the winter term 2008, it is hoped that the school can be further extended. 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 probably apply similar modeling tools or theoretical concepts.

Fig. 12: Group of IMPRS students and supervisors, June 2008, during the first IMPRS workshop in Wittenberg

10 Important Joint Research Projects

Many research projects are being pursued jointly between MPI research groups and external partners from academic 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 is focused on “Integrated process systems for converting biomass to electricity in fuel cells (Pro Bio)”. The project is funded for three years by MPG and FhG with the MPI being the Pro Bio-coordinator.
- In June 2008, a project funded for three years started within the 7th Framework Program of the European Union. Partners from six countries are studying various pathways to produce pure enantiomers. The MPI is coordinating this so-called “INTENANT project” (INTegrated synthesis and purification of single ENANTiomers).

Funded by the German Science Foundation (DFG) and in cooperation with the OvGU, MPI scientist are currently involved in two larger research units (*“DFG-Forschergruppen”*):

- DFG research unit 447: “Membrane Supported Reaction Engineering”: This is being done in collaboration with the Department of Process and Systems Engineering and the Department for Mathematics (until 2008);

- DFG research unit 468: “Methods of Discrete Mathematics for Synthesis and Control of Chemical Processes”: This is in collaboration with the OvGU Department of Mathematics and the Department of Electrical Engineering (until 2009).

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

- “Restructuring of colloidal aggregates in a shear field”, a cooperation with RWTH Aachen (Prof. M. Behr) within the DFG Priority Program 1272 “Colloidal Engineering”;
- “Coupled crystallizers for enantioseparation”, a cooperation with Technical University Berlin (J. Raisch);
- “Coupling membrane separation and crystallization for enantioseparation”, a cooperation with RWTH Aachen (K. Leonhardt) and Technical University of Karlsruhe (W. Schaber).

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):

- 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-Center “MaCS”**:** “Systems analysis of signalling and regulatory networks: from basic principles to complex cellular interactions” (one of four national centers, Partner: OvGU);
- FORSYS-Partner: “Dynamics and regulation of the metabolic balance in *E. coli”* (Partners: University of Osnabrück, University of Jena, HZI);
- FORSYS-Partner “Syslogics” (Partners: Technical University of Hamburg-Harburg, University of Bielefeld, University of Saarland, University of Hanover, Helmholtz Centre for Infection Research Brunswick, Probiogen AG Berlin)
- “A Systems Biology Approach towards Predictive Cancer Therapy” (Partner: CSB University of Stuttgart);
- “Development of a photosynthetic bacterium, Rhodospirillum rubrum for superexpression of industrially relevant carotenoids using a systems approach” (Partner: University of Stuttgart);
- HepatoSys (Systems Biology Competence Network): “Technology platform for bio informatics/modeling” (Partners: MPI, Humboldt University Berlin, EML

Research GmbH Heidelberg);

- SysMo (Systems Biology of Microorganisms): “Systems analysis of process-induced stresses: towards a quantum increase in performance of pseudomonas putida as the cell factory of choice white biotechnology” (Partners: University of Stuttgart, University of Sheffield, University of Amsterdam);
- QuantPro: “Quantitative Analyse zur Beschreibung dynamischer Prozesse in lebenden Systemen” (Partner: Helmholtz Zentrum München).

The Research Center “Dynamical Systems in Biomedicine and Process Engineering” (CDS) as one of five Centers of Excellence in the Federal State of Saxony-Anhalt will continue to be supported by LSA (Partners: OvGU, MPI).

The Federal State of Saxony-Anhalt is also funding the new junior research group NEWE (“Electrochemical Converters in Energy Networks (NEWE)”, 2008 – 2010) which is a joint activity of the MPI together with the OvGU and the Fraunhofer Institute (IFF) in Magdeburg.

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).

11 International Collaborations

Collaboration of the MPI with foreign partners has further increased in the last three years. The following table summarizes the most important academic partner institutions and fields of cooperation:

Tab. 2: Current international collaborations of the MPI

Partner institution	**Name of project**
Europe	
University of Surrey, Guildford, UK, Prof. McFadden	Metabolic network analysis and metabolic flux analysis
University of Sheffield, UK, Prof. Pool	A systems biological approach to understanding bacterial responses to oxygen
Institute of Medical Sciences, University of Aberdeen, UK, Prof. Booth	Modeling ion homeostasis in bacteria
University of Manchester, UK, Prof. Davey	Crystallization, EU project “INTENANT”
Centro Nacional de Biotecnología CSIC, Madrid, Spain, Prof. de Lorenzo	Modeling catabolite repression in P. putida

University of Rouen, France, Prof. Coquerel	Crystallization, EU project “INTENANT”
CNRS Toulouse, France, Prof. Plaquevent	Síntesis, EU project “INTENANT”
Department of Biochemistry, University of Groningen, The Netherlands, Prof. Poolman	Modeling ion homeostasis in bacteria
ETH Zürich, Switzerland, Prof. Stelling, Prof. Mazzotti, Prof. Panke	Chromatography and Racemization (EU project “INTENANT”); Analysis of Biological Reaction Networks
Politecnico di Milano, Italy, Prof. Fuganti, Prof. Ferrante	Synthesis of enantiomers, EU project “INTENANT”, Controlled functional electrical stimulation
Uni of Cagliari, Italy, Prof. Giua, Prof. Seatzu	Hybrid systems
Stockholm University, Sweden, Prof. Bäckval	Racemization of enantiomers, EU project “INTENANT
Helsinki University of Technology, Finland	Catalytic reactors
Lappeenranta University of Technology, Finland, Prof. Paateero, Dr. Sainio	Chromatographic reactors
Institute of Biotechnology, Lithuania, Prof. Antoniukas	Design, scale up and process optimization for recombinant hantavirus NP expression
TU Donezk, Ukraine, Prof. Svjatnyj	Simulation software DIANA
Technical Univ. of Rzeszów, Poland, Prof. Antos	Preparative chromatography
ICT Prague, Czech Republic	Electro-membrane reactors
UCTM Sofia, Bulgaria	Kinetic analysis of electrochemical reactions
Bulgarian Academy of Sciences Sofia, Bulgaria, Prof. Ivanov, Prof. Nacheva	Segregation instability of expression plasmids carrying the human interferon gamma gene in *E. coli*
University of Belgrade, Serbia, Prof. Petkovska	Determination of adsorption isotherms, Dynamic analysis of electrochemical systems
University of Ploiesti, Romania, Prof. Radulescu, Prof. Paraschiv	Dynamics and control of reactive distillation columns
Asia	
IIT Madras, India, Prof. Pushpavanam	Nonlinear dynamics of continuous cell cultures; Hydrodynamics in expanded beds
IIT Bombay, India, Prof. Mahajani	Reactive distillation and hydrogenation processes; Synthesis of combined reaction distillation processes
NCL Punai, India, Prof. Kulkarni	Microreaction systems
ECUST Shanghai, China, Prof. Qi	Process intensification methods
Tongji University Shanghai, China, Prof. Zhou	Fuel cell systems

Australia	
Melbourne University, Prof. Davoren	Hierarchical control theory; Hybrid Control Systems
Americas	
Purdue University, USA, Prof. Ramkrishna	Nonlinear dynamics of continuous cell cultures; Population balances; Crystal shape evolution
MIT, Harvard Medical School, Boston, USA, Prof. Sorger	Modeling large-scale signal transduction networks in eukaryotes
Thomas Jefferson University, USA, Prof. Kholodenko	Modeling concepts for signaling networks
University of Delaware, Newark, USA	Modeling VIP activated gene expression in SCN cells through the VPAC2 receptor mediated cAMP/PKA signal transduction pathway ?
University of Tennessee, USA, Prof. Guiochon	Preparative chromatography
Colorado State University, USA, Prof. Wickramasinghe	Membrane filtration and adsorption, IREE undergraduate research exchange program
Clemson University, USA, Prof. Husson	Functionalized membranes, IREE undergraduate research exchange program
Federal University of Rio de Janeiro, Brazil, Prof. Castilho	Development and optimization of a biotechnological process to produce factor VII
CINVESTAV, Mexico, Prof. Azhmyakov	Hybrid control systems
Africa	
Institute Pasteur, Tunis, Tunesia, Prof. Kallel	Differential protein expression of rabies virus infected cells

12 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:

- Symposium “Trends in Systems and Control Theory”, Magdeburg, March 1-2, 2006, Organization: BPE group
- Workshop “Systems Biology”, Leipzig, January 12-13, 2007, Organization: BPE group
- Regional Dechema-Colloquium “Neue Einsatzfelder für Emulsionen in der Chemischen Prozesstechnik”, Magdeburg, April 19, 2007, Organization: PCP group

- MPG-CNRS Joint Workshop on Systems Biology, Berlin, September 24-26, 2007, Organization: BPE group
- Dechema Regional Colloquium “Integrierte Verfahren zur Synthese und Trennung von Enantiomeren”, Magdeburg, November 20, 2007, Organization: PCF group
- Indo-German Workshop on “Advances in Reaction and Separation Processes”, IIT Madras, Madras, India, February 18-20, 2008, Organization: IIT Madras and PCF group
- Symposium on “Information and Control Hierarchies: Foundations, Computation and Applications”, Magdeburg, May 22-23, 2008, Organization: SCT group
- BIWIC 2008: “15th International Workshop on Industrial Crystallization”, Magdeburg, September 10-12, 2008, Organization: PCF group
- Foundations of Systems Biology in Engineering (FOSBE), Stuttgart, September 09-12, 2007, Organization: SBI group

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

13 Summary and Outlook

The present board of MPI directors consists of three scientific members of the MPG active in the areas of chemical engineering (Prof. Seidel-Morgenstern), process systems engineering (Prof. Sundmacher) and bioprocess engineering (Prof. Reichl). Prof. E. D. Gilles retired in May 2008 as the head of the Department for “System Theoretical Fundamentals of Process and Bioprocess Engineering”. In the important – and for the institute integrating – research field of Systems Science there are currently activities of the SCT group (Prof. J. Raisch, Control) and the PSD group (Prof. Kienle, Synthesis). Research in the field of Systems Biology is carried out by the SBI group (Prof. Gilles), the BPE group (Prof. Reichl) and the MNA group (Prof. Marwan). The newly established Junior Research Group “Portable Energy Systems” (Dr. Krewer) strengthens the MPI’s research activities in the field of energy systems engineering. Dr. Briesen (Head of the Junior Research Group “Population Dynamics”) will soon leave the institute to build up a chair for Process Systems Engineering at the Technical University in Munich. To fill his junior research position, the MPI is currently trying to identify a successor.

Within the period covered by this report the staff of the MPI grew continuously. Further possible and intended growth is currently limited by space. This is essentially due to the fact that the OvGU and the Federal State of Saxony-Anhalt did not keep their promise to finalize a new building in 2007 and return laboratory and office space rented in the MPI by the university chairs of Profs. Marwan, Reichl, Seidel-Morgenstern and Sundmacher.

Compared to the last report period, the output of publications of the MPI has further increased. The institute's visibility in this respect is clearly above the average of research institutions active in the corresponding field.

A sign of the increased reputation of the MPI is seen by the amount of international collaborations, the growing number of invitations for our scientists to present results at international conferences and also the increasing number of workshops and conferences organized directly by MPI co-workers.

In the period covered by this report there was a considerabe increase in the acquisition of third party funding. This is significantly due to the broad and successful activities of Prof. Gilles and the SBI group. However, also all the other groups secured valuable third party funding from German and European sources and from the industry.

The most difficult task for the MPI within the period of this report was the identification of a successor for Prof. Gilles. Despite significant attempts, the intensive search performed by the institute in order to fill the director's position for the field of Systems Theory has not been successful. It remains the clear and most important goal of the institute to appoint a fourth director as soon as possible. This should ideally be a scientist who has a strong background in theory.

Significant activities of our and other Max Planck Institutes, also from the Biology and Medicine Section, which were devoted to initiate within the MPG the foundation of a new MPI dedicated to Systems Biology or a department in one of the existing MPIs (e.g. in our institute as suggested by the SAB during its last visit), were not successful. Fortunately, within the period of this report there was a smooth incorporation of the MNA group into the institute, hence further enhancing the expertise in biological sciences. Prof. Marwan will continue to cooperate with the MPI even after his transition to the OvGU in January 2009.

Until 2011 the activities of our institute in the dynamically developing field of Systems Biology will be secured due to the successful acquisition of external sources and the

ongoing availability of Prof. Gilles as the head of the SBI group. To keep a significant level of systems biology related research in Magdeburg and to avoid risks related to drain of excellent senior scientists to other universities and research institutes, our MPI intends to install two W2 positions.

Another important future research field is the design and analysis of sustainable energy systems in which several MPI research groups (PCP, PSD, OH) are active. Based on several successful joint projects which were started during the period of this report (e.g. the PROBIO project), further intensification of research activities on energy systems is currently planned. In the first step, the new junior research group “Electrochemical Converters in Energy Networks” has been established in early 2008 as a joint initiative of the MPI, the OvGU, and the Fraunhofer Institute in Magdeburg, with funding from the Federal State of Saxony-Anhalt.

To strengthen research in the field of molecular modeling, which is of relevance for several projects of the MPI, it is planned to build up a corresponding Junior Research Group.

The MPI intends to continue ongoing collaborations with the OvGU and to further extend activities within the research center “Dynamic Systems in Biomedicine and Process Engineering” currently funded by the Federal State of Saxony-Anhalt.

Teaching activities will remain a focus of collaboration with the different departments of the OvGU. The recently established bachelor and master programs have attracted an increasing number of students. In the future, the stabilization of the number of students at least at the current level, and a further increase in the quality of teaching, will be the main goals as is the further successful development of the “International Max Planck Research School”.

Research Group:

Physical and Chemical Foundations

of Process Engineering (PCF)

Prof. Dr.-Ing. Andreas Seidel-Morgenstern

This report covers the period from January 2006 to September 2008.

1 Introduction

A main focus of the research of the Physical and Chemical Foundations of Process Engineering (PCF) group is the development of processes for the separation of mixtures exploiting selective crystallization, chromatography and membranes. In order to study these processes, systematic experimental and theoretical investigations are undertaken with different model systems. During the last several years, the work of the PCF group has been concentrated in particular on studying reaction and separation processes leading to pure enantiomers. A successful EU-proposal devoted entirely to this objective was initiated. Since June 2008, a strong European consortium (11 partners from 6 countries) works under the coordination of the PCF group on the INTENANT project (INTegrated synthesis and purification of single ENANTiomers).

A second important direction of the PCF group's research is the study of the potential for combining various separation processes to improve the resolution of mixtures or to integrate reaction and separation processes in order to improve conversion and selectivity with respect to certain target components. Of particular interest remain investigations of the combination of reactions with chromatographic and membrane separations (chromatographic and membrane reactors).

In order to reach a quantitative understanding and to predict the processes of interest, the most relevant thermodynamic and kinetic parameters must be known. Thus, the activities of the group focus on developing and validating suitable experimental methods as well as reliable mathematical models which can be used for process optimization and control. In the period of this report, more emphasis was set on applying modern statistical methods in order to evaluate critically the confidences of parameters determined. As recommended by the SAB, efforts were also undertaken to gain better understanding using molecular simulation methods.

Several projects were performed jointly with other groups at the MPI. Examples are the analysis of new types of simulated moving bed processes and chromatographic reactors in cooperation with the PSD group (A. Kienle), the investigation of chromatographic techniques in the downstream processing of biomolecules in cooperation with the BPE group (U. Reichl), the analysis of different kinds of membrane reactors with the PCP group (K. Sundmacher), the investigation of the dynamics of enantioselective crystallization processes together with the SCT group

(J. Raisch), and the statistical analysis of experimental data with the SBI group (E. D. Gilles).

Intensive and successful cooperation devoted to quantify electrokinetic phenomena and the dynamics of capillary electrochromatography was conducted in collaboration with Prof. Tallarek (formerly OvGU, now University of Marburg).

Besides the INTENANT project, several other new research proposals were confirmed. Two major projects were granted by the German Science Foundation to support our work in the area of crystallization. Three new bilateral project proposals supporting cooperation with Poland, Finland and Spain were approved (funded by the DAAD and the corresponding partner organizations).

In February 2008, the PCF group organized in Madras, together with Prof. Pushpavanam, an Indian-German Workshop on “New Trends in Reaction and Separation Processes” and in September 2008 in Magdeburg the “15th International Workshop on Industrial Crystallization (BIWIC)”. The PCF group was further involved in the organization of several other international conferences (e.g. “International Symposium on Chemical Reaction Engineering (ISCRE-19)” in Potsdam and “Symposium on Preparative and Industrial Chromatography (SPICA)”, in 2006 and 2008).

Within the period of this report the PCF group has published more than 60 research papers in international scientific journals, filed 3 patents and finalized successfully 12 Ph.D. projects.

2 Members of the Research Group

The staff of the PCF group is summarized in the following table.

Tab. 1: Members of Research Group “Physical and Chemical Foundations of Process Engineering”

Dr. habil. H. Lorenz	Staff scientist, permanent, Particulate systems, since 01.10.1998
Dr. E. Rapp	Staff scientist (jointly with the BPE group), permanent, Chromatography and mass spectrometry, since 01.02.2003
Dr. M. P. Elsner	Postdoc, Crystallization by entrainment, since 01.01.2003
Dr. J. von Langermann	Postdoc, Production of enantiomers, since 01.07.2008
Dr. S. Melnikov	Postdoc, Molecular modeling, since 01.04.2008
Dr. D. Hlushkou	Postdoc, Simulation of electrokinetic mass transfer, between 01.09.2005 and 30.06.2008
Dr. Y. Kawajiri	Postdoc, AvH scholar, Process optimization, between 01.10.2007 and 22.08.2008

Dr. L. Zhang	Postdoc, Chiral separation, between 10.01.2006 and 31.12.2007
Dipl.-Ing. F. Czapla	Ph.D. student, Crystallization, since 01.04.2005
M. Sc. A. Damtew	Ph.D. student, Gradient chromatography, since 01.01.2007
Dipl.-Ing. M. Eicke	Ph.D. student, Coupled crystallizers, since 15.06.2008
Dipl.-Ing. C. Hamel	Ph.D. student, Membrane reactors, between 01.11.2002 and 30.04.2007, thesis defended (February 2008)
Dipl.-Ing. M. Ilić	Ph.D. student, Thermodynamics of adsorption, since 01.02.2004, thesis defended (July 2008)
Dipl.-Biotech. C. Keßler	Ph.D. student, Preparative chromatography, between 01.01.2005 and 31.08.2008
Dipl.-Ing. L. Klukas	Ph.D. student, Coupling membrane separation and crystallization, since 01.08.2008
Dipl.-Ing. A. Marković	Ph.D. student, Transport in porous glass, since 01.01.2007
Dipl.-Ing. T. Le Minh	Ph.D. student, Quantifying solubility, since 01.04.2008
Dipl.-Ing. J. Nowak	Ph.D. student, Chromatographic separation of ternary mixtures, since 01.03.2007
M. Sc. S. Palani	Ph.D. student (DAAD scholar, joint supervision with IIT Madras), since 01.10.2007
Dipl.-Ing. K. Petruševska-Seebach	Ph.D. student, Enantioseparation and racemization, since 01.07.2006
Dipl.-Ing. D. Polenske	Ph.D. student, Preferential crystallization, since 01.03.2004
Dipl.-Chem. A. Seebach	Ph.D. student, Chiral membranes, between 15.07.2002 and 31.01.2008
Dipl.-Ing. B. Sreedhar	Ph.D. student, Solid phase gradients in chromatography, since 01.10.2007
Dipl.-Ing. V. S. Sistla	Ph.D. student, Crystallization of diastereomers, since 01.05.2008
Dipl.-Chem. D. Stoltenberg	Ph.D. student, Functionalized surfaces, since 01.06.2008
M. Sc. S. Tulashie	Ph.D. student, Chiral solvents, between 01.04.2005 and 31.07.2008
Dipl.-Ing. V. Zahn	Ph.D. student, Loop-reactors, since 01.01.2007
Dipl.-Ing. G. Ziomek	Ph.D. student, Optimization of crystallizers, between 01.01.2004 and 29.02.2008
Dr. T. Wolff	Technician, permanent, since 01.11.2001
J. Protzmann	Technician, permanent, since 01.01.2002
J. Kaufmann	Technician, permanent, since 01.02.1999
L. Borchert	Technician, permanent, since 01.02.2005
J. Wilke	Technician, between 01.01.2008 and 30.06.2009
A. Raasch	Secretary, permanent, since 16.07.2002
M. Bratz	Secretary, between 01.02.2007 and 31.01.2009
S. Leuchtenberg	Trainee, between 01.09.2005 and 28.02.2009

There is a close cooperation of the members of the PCF group with the following scientific co-workers of the related university Chair for Chemical Process Engineering (headed also by Prof. Seidel-Morgenstern): Dr.-Ing. C. Hamel, Dipl.-Ing. T. H. Duc, Dipl.-Ing. L. Gueorguieva, Dipl.-Ing. H. Haida, Dipl.-Ing. H. Kaemmerer, Dipl.-Ing. T. Lehmann and M. Sc. S. Tulashie. In the following report they are marked with an asterisk (*).

The research work of the PCF group was stimulated and enriched during the last two years by several guest scientists, e.g. Prof. Schlünder (Karlsruhe), Profs. Pushpavanam and Jayaraman (IIT Madras), Prof. Coquerel (University of Rouen), Prof. Petkovska (University of Belgrade), Prof. Antos (University of Rzeszów), Prof. Eic (University of New Brunswick), Dr. Uchytil (Czech Academy of Sciences).

3 Survey of Research Projects

The current research projects of the PCF group are summarized below. They are ordered according to the project areas summarized in the introduction of this report.

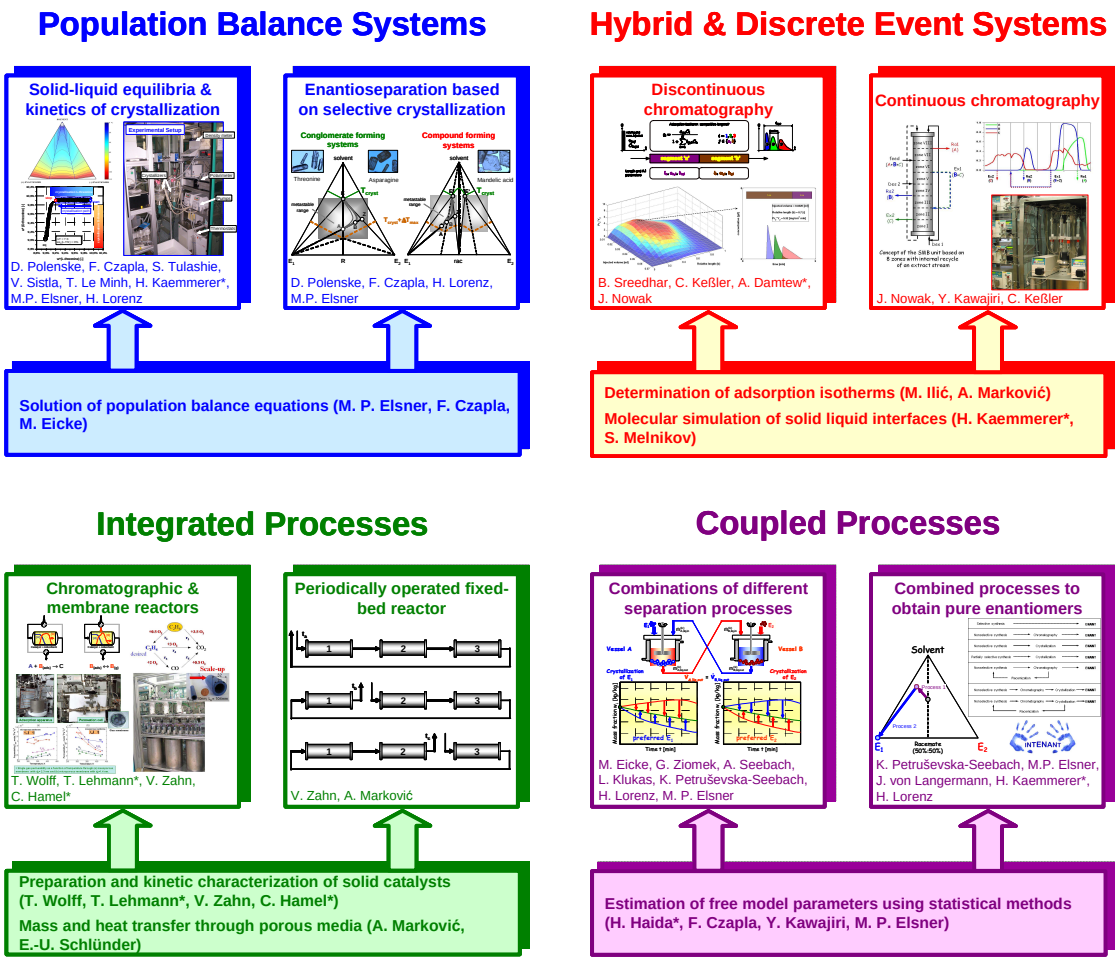


Fig. 1: Survey of research areas and projects of the PCF group.

Project Area: Population Balance Systems

Tab. 2: Projects within the project area “Population Balance Systems”

Project: Selective crystallization	Based on a sound knowledge of the underlying thermo-dynamic and kinetic basics it is the main focus of this project to better understand, design and optimize crystallization processes aiming to isolate pure components from mixtures (e.g. pure enantiomers from racemic mixtures).			
Subprojects	**Scientists**	**Funding**	**Start**	**Partners**
Solution of population balance equations	M. P. Elsner M. Eicke F. Czapla	MPI DFG	2005	MPI [PCP] OvGU Profs. Warnecke and Thévenin
Solid-liquid equilibria in ternary chiral systems	D. Polenske H. Kaemmerer* S. Tulashie T. Le Minh V. Sistla H. Lorenz	MPI	2001	Univ. Dortmund Prof. Sadowski Sci.Comp.Mod. Dr. van Lenthe RWTH Aachen Dr. Klankermeyer
Crystallization kinetics	F. Czapla, H. Haida* M. P. Elsner H. Lorenz	MPI	2005	MPI [PCP]
Enantioseparation based on selective crystallization	D. Polenske F. Czapla L. Klukas M. P. Elsner H. Lorenz	MPI DFG	2005	MPI [SCT, PSD] Univ. Rouen Prof. Coquerel OvGU Prof. Thévenin
Crystallization-based industrial separations	H. Kaemmerer* H. Lorenz	Industry	2006	AstraZeneca Solvay DOMO Amino GmbH

Project Area: Hybrid and Discrete Event Systems

Tab. 3: Projects within the project area “Hybrid and Discrete Event Systems”

Project: Discontinuous and continuous chromatography	The focus of this project is to better understand, design and optimize challenging chromatographic separation processes to be performed with single columns or innovative multi-column arrangements. An important part of the project is the quantification of the underlying equilibria.			
Subprojects	**Scientists**	**Funding**	**Start**	**Partners**
Determination and analysis of adsorption isotherms	M. Ilić A. Marković	MPI Chinese Acad. Sci.	2005 – 2008	Univ. Belgrade Prof. Petkovska Univ. Dalian Prof. W. Zhang
Molecular simulation of liquid-solid-interfaces	S. Melnikov H. Kaemmerer*	MPI	2006	Univ. Marburg Prof. Tallarek Univ. Tennessee Prof. Guiochon
Electroosmotic transport in multiparticle systems	D. Hlushkou I. Nischang*	MPI	2005	Univ. Marburg Prof. Tallarek MPI [BPE]
Preparative gradient chromatography	B. Sreedhar C. Keßler A. Damtew	MPI DAAD-1 DAAD-2	2004	IIT Madras Prof. Pushpavanam Univ. Rzeszów Prof. Antos

Chromatographic resolution of biomolecules	C. Keßler L. Gueorguieva* S. Palani, E. Rapp	MPI DAAD-1	2005	MPI [BPE] IIT Madras Prof. Jayaraman
Chromatographic separation of ternary or "quasi-ternary" mixtures	C. Keßler B. Sreedhar J. Nowak Y. Kawajiri	MPI DFG [OvGU] AvH	2005	MPI [BPE, PSD] Univ. Rzeszów Prof. Antos Univ. Brunswick Prof. Hempel OvGU Profs. Tobiska and Weismantel
Improved SMB chroma-tography with fractionation and feedback	C. Keßler	MPI	2007	MPI [SCT]

Project Area: Integrated Processes

Tab. 4: Projects within the project area "Integrated Processes"

Project: Reactor cascades	The objective is to better understand, design and optimize forced transient operation of catalytic reactors, in particular of connections of several fixed-bed reactors.			
Subproject	**Scientists**	**Funding**	**Start**	**Partners**
Preparation and kinetic characterization of solid catalysts	T. Wolff C. Hamel* T. Lehmann* V. Zahn	MPI DFG[OvGU]	2003	MPI [PCP, PSD] FHI of MPG Prof. Schlögl OvGU Prof. Weiß
Periodically operated fixed-bed reactors	V. Zahn, C. Hamel* T. Lehmann* A. Marković	MPI Solvay-Foundat.	2007	MPI [PSD] Univ. Belgrade Dr. Petkovska
Project: Chromato-graphic reactors	The main focus of this project is to better understand, design and optimize novel processes combining chemical reaction with in situ chromatographic separation.			
Subprojects	**Scientists**	**Funding**	**Start**	**Partners**
Analysis of single column operation	T. Vu*	MPI Vietn. Gov.	2004 - 2007	MPI [PSD]
Thermal effects in reactive chromatography	L. Zhang	DAAD-3	2006	MPI [PSD] U. Lappeenranta Dr. Sainio
Project: Membrane reactors	The focus is to better develop, design and optimize processes combining chemical reaction with membrane separation processes.			
Subproject	**Scientists**	**Funding**	**Start**	**Partners**
Mass and heat transfer through porous media	A. Marković E.-U. Schlünder	MPI DFG[OvGU]	2005	Univ. Halle Dr. Enke Czech Ac. Sci. Dr. Uchytil OVGU Prof. Tsotsas
Dosing concepts using tubular membrane reactors	C. Hamel* Á. Tóta* V. Zahn	DFG[OvGU] DAAD-1 DAAD-4 MPI	2002	MPI [PCP, PSD] IIT Madras Prof. Pushpavanam Univ. Oviedo Prof. Diez TU Darmstadt Prof. Claus Inocerm GmbH OvGU several groups

Characterizing and application of dense perovskite membranes for catalytic processes	C. Hamel*	BMBF[OvGU]	2003 - 2007	Univ. Hanover, RWTH Aachen, Uhde, Borsig, OvGU Prof. Tsotsas

Project Area: Coupled Processes

Tab. 5: Projects within the project area “Coupled Processes”

Project: Combinations of different types of separation processes	There is a potential seen of efficiently coupling different types of separation processes in order to improve access to pure products. The objective of this project is to understand, design and optimize different process combinations.			
Subprojects	**Scientists**	**Funding**	**Start**	**Partners**
Estimation of free model parameters using advanced statistical methods	H. Haida*, F. Czapla M. Joshi*, M. P. Elsner, Y. Kawajiri	MPI Fed. State (Saxony-Anhalt)	2005	MPI [SBI]
Coupling crystallizers	M. Eicke, G. Ziomek M. P. Elsner	DFG	2007	TU Berlin Prof. Raisch
Chromatography and subsequent crystallization	M. P. Elsner K. Petruševska-Seebach H. Lorenz	MPI DAAD-2	2007	MPI [PSD] Univ. Rzeszów Prof. Antos
Membrane separation and coupled subsequent crystallization	Axel Seebach L. Klukas H. Lorenz	DFG	2005	Univ. Lund Dr. Yilmaz Univ. Karlsruhe Prof. Schaber RWTH Aachen Dr. Leonhard
Enantioseparation of racemic compound forming chiral substances using a preferential crystallization step	H. Lorenz D. Polenske	MPI	2006	Univ. Rouen Prof. Coquerel
Project: Combined processes to obtain pure enantiomers	The focus of this key project for the PCF group is to better understand, design and optimize coupled reaction and processes aiming to provide pure enantiomers. Hereby chromatography and crystallization play an important role as separation processes. In order to increase yields, a particular racemization step of the “unwanted” counter-enantiomer is of interest.			
Subprojects	**Scientists**	**Funding**	**Start**	**Partners**
Combining enantiosepa-ration and enzymatic racemization	K. Petruševska-Seebach M. P. Elsner	MPI Helmholtz Society	2007	FZ Jülich Dr. Lütz Prof. Wandrey
INTegrated synthesis and purification of single ENANTiomers (INTENANT project)	H. Kaemmerer* J. v. Langermann H. Lorenz	EU-Frame work program 7 (FP7)	2008	MPI [PSD] ETH Zürich Univ. Rouen Univ. Toulouse Univ. Manchester Polytechn.Milano Univ. Stockholm AstraZeneca Bayer Techn. Serv. Molisa GmbH Dechema

4 Research Highlights

In the following section, selected results obtained within the period of this report are given for some of the projects summarized above.

4.1 Project “Solution of population balance equations”

Quantitative description and optimization of crystallization processes requires efficient numerical solutions of population balance equations as outlined extensively in a special issue of Chemical Engineering and Processing edited recently by three of the MPI research group leaders (Kienle et al., 2006).

In close cooperation with the Institute for Analysis and Numerics at the OvGU, high resolution finite volume schemes and the method of characteristics capable to solve models of various complexity were developed and applied in the PCF group. Considered were simple growth dominated crystallization processes, preferential crystallization processes, fines dissolution and multidimensional population balances (Qamar et al., 2006; Qamar et al., 2007; Qamar et al., 2008a; Qamar et al., 2008b). Further, a Laplace transformation-based technique was developed for the reconstruction of crystal size distributions based on (Qamar et al., 2008c). Numerical and analytical aspects of moment methods were applied successfully in cooperation with the PCP group and Prof. Thévenin (OvGU) (Öncül et al., 2006). Considering also the potential of the commercial tool “Parsival”, from the numerical point of view many problems related to the quantification of crystallization processes can now be solved satisfactorily. Significant challenges still lie in the area of solving multidimensional problems, e.g. quantifying simultaneously crystal size and shape development and in the area of polymorphism.

4.2 Project “Solid-liquid equilibria in ternary chiral systems”

Thermodynamic properties, in particular the solubility of organic molecules in aqueous and in typical HPLC solvents, are of great interest for the design of separation processes. Significant activities are currently concentrated in the PCF group on measuring solubility data. The knowledge of the underlying solid/liquid phase diagrams is of particular importance when designing and optimizing crystallization-based enantioseparation processes (Lorenz et al., 2006). Within the period covered by this report, various ternary solubility phase diagrams have been determined for complex chiral systems that are of interest for pharmaceutical and fine

chemical industries. Challenging examples of determined phase diagrams are those of malic acid in acetone (Kaemmerer et al., 2007; Kaemmerer et al., 2008a), methionine, serine and propranolol hydrochloride in water (Kaemmerer et al., 2008b; Polenske et al., 2007) and those of different chiral model substances in chiral solvents (including ionic liquids) (Tulashie et al., 2008).

As an example the solubility phase diagram of propranolol hydrochloride in water is shown in Fig. 2. The enantiomers form an intermediate racemic compound at their 50:50 ratio. The eutectic composition in this particular chiral system is found very close to the racemic composition making propranolol hydrochloride a potential candidate for integrated separation processes as studied in the PCF group. Just a slight enantiomeric enrichment is required to enable e.g. a preferential crystallization. The general feasibility of such a process has already been demonstrated (Polenske et al., 2007) and was recently patented (Seidel-Morgenstern et al., 2007).

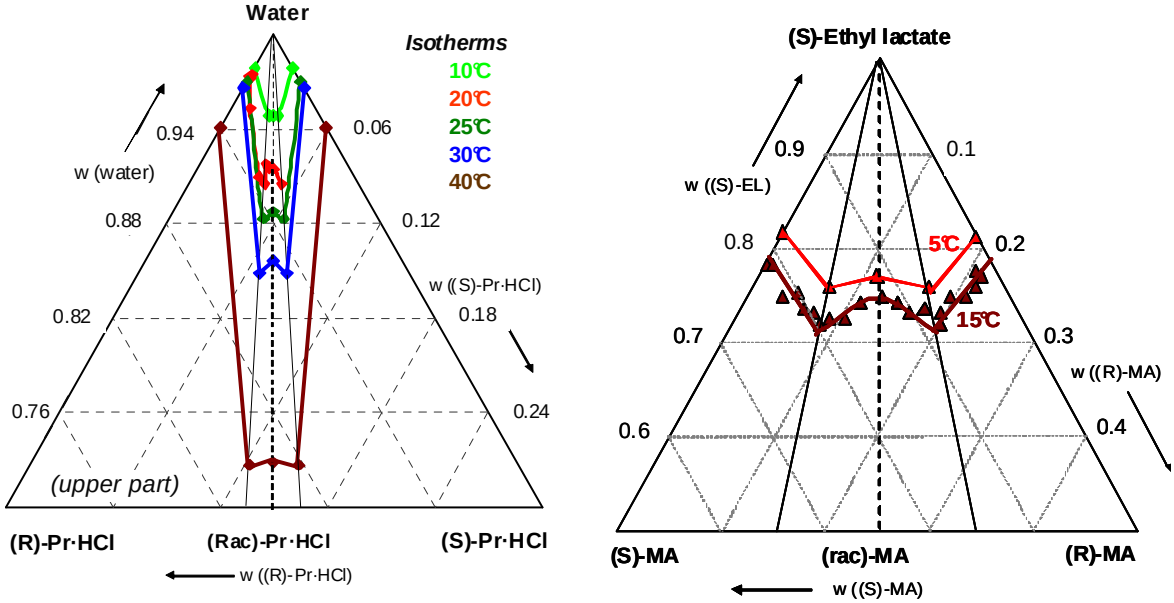


Fig. 2: Solubility phase diagrams of the propranolol hydrochloride enantiomers (Pr·HCl) in water and the mandelic acid enantiomers (MA) in (S)-ethyl lactate.

In Fig. 2, the ternary solubility phase diagram of the mandelic acid enantiomers in (S)-ethyl lactate as a chiral solvent (Tulashie et al., 2008) is also presented. It is interesting that no asymmetry is induced in the phase diagram and the symmetry around the racemic axis still holds. As far as we observed it up to now, there seems to be no significant chiral recognition in solution phase. It should be added here that the measurement of concentration and enantiomeric excess in presence of chiral solvents, in particular of ionic liquids, is not a trivial task (Tulashie et al., 2008).

4.3 Project: “Determination and analysis of adsorption isotherms”

Adsorption isotherms are the main prerequisite to quantify chromatographic separation processes. In the period of the report a new method for estimation of adsorption isotherms of dissolved components has been developed theoretically, which is based on the analysis of the nonlinear frequency response (FR) of a chromatographic column subjected to sinusoidal inlet concentration changes (Petkovska and Seidel-Morgenstern, 2005; Ilić et al., 2007a). In (Ilić et al., 2007b) it was shown experimentally that using this method allows for the determination of the first three local isotherm derivatives at certain steady-state concentrations from the low frequency asymptotes of the corresponding first and higher order FR functions. The method can be applied for measuring of single solute (Ilić et al., 2008) and also binary adsorption isotherms (Ilić, 2008). The latter case is of particular interest when the adsorption of two enantiomers on a chiral stationary phase must be quantified.

Single and competitive adsorption isotherms of inert and adsorbable gases on porous glass were determined using a volumetric technique together with Dr. Uchytil from the Czech Academy of Sciences (Řezníčková Čermáková et al., 2008). The data obtained were required in order to understand the complex transport through such type of materials.

4.4 Project “Molecular simulation of liquid-solid-interfaces”

Parallel to the experimental determination of solid-liquid equilibria, theoretical methods are increasingly applied. The *Co*nductor-like *S*creening *Mo*del (COSMO) together with the statistical *S*egment *A*ctivity *C*oefficient (SAC) approach was used to estimate intermolecular interactions based on the molecular structure of the molecules in the mixture. With the help of computational quantum mechanics and via solvation thermodynamics, the activity coefficients of the components in the mixture can be derived. By combination of this technique and a correlative approach (like Non Random Two Liquid (NRTL)) more challenging phase diagrams of non-ideal compound forming systems can be predicted almost a priori. Thus, the time needed for screening of the most promising solvent or solvent mixtures for a separation by crystallization can be shortened (Kaemmerer et al., 2008b). It was shown for a number of compound forming systems of enantiomers that the NRTL model, once correlated with selected binary experimental data, simplifies the determination of the ternary solution phase diagram in various solvents (Kaemmerer et al., 2008c).

First attempts of more detailed molecular modeling of chromatographic processes were made together with the University of Tennessee by studying the separation of the enantiomers of Tröger's base on a chiral polysaccharide stationary phase (Mihlbachler et al., 2006).

More detailed molecular dynamics (MD) studies were devoted to better understanding the separation mechanisms exploited extensively in reversed phase liquid chromatography (RPLC). Experimental properties of RPLC systems are essentially determined by processes taking place in the extremely thin layer on the chemically modified silica surfaces. In cooperation with U. Tallarek (formerly OvGU), who left the group in 2007 to take up a position at the University of Marburg, molecular dynamics simulations treating atom interactions explicitly were carried out for a silica surface modified by octyl-dimethylsilyl and trimethylsilyl groups and water/acetonitrile mixtures. A broad range of volumetric water/acetonitrile mixture compositions has been simulated for two cases of silanol activity: the undissociated silanol groups and the fully dehydrated silanol in combination with provided Na^+ ions. The density profiles of the system's components (Fig. 3), the structure of the bonded phase, the solvent orientational arrangement, the water/acetonitrile mixture heterogeneity and preferential solvation of Na^+ ions in the mixture have been examined. (Melnikov et al., 2008).

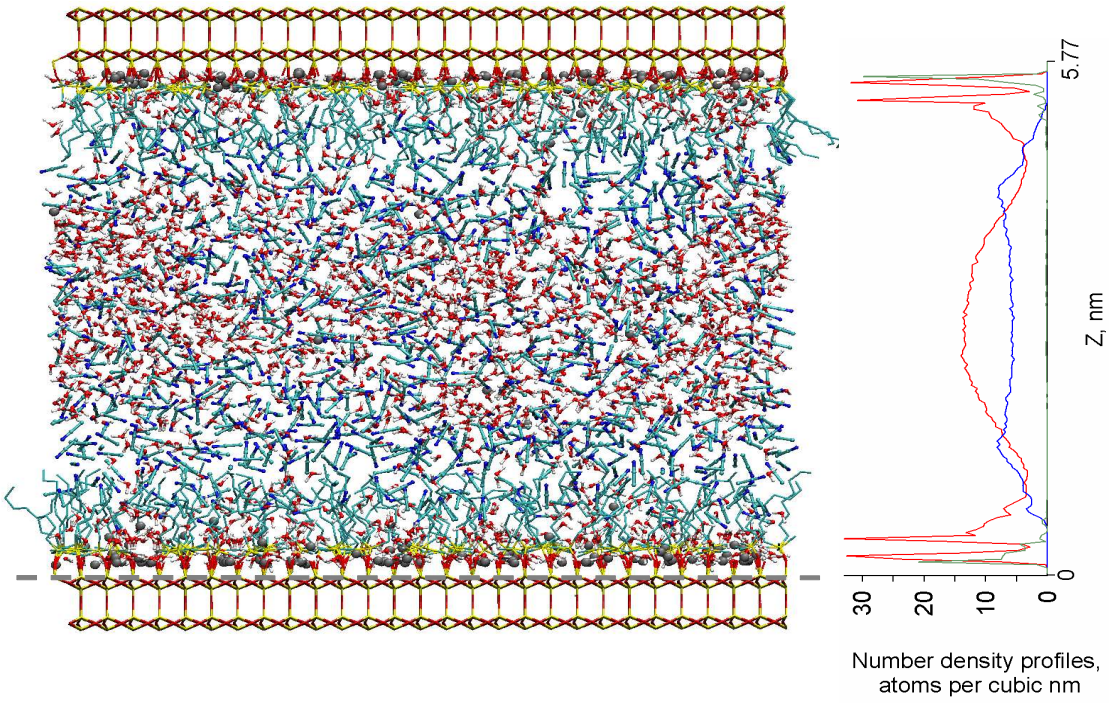


Fig. 3: Simulated final conformation of a reversed phase system and corresponding atom density profile, i.e. ionic silanol groups for a 40/60=water/acetonitrile mobile phase. Atoms are color coded: oxygen, red; hydrogen (of water and silanol), white; carbon and hydrocarbon group, cyan; nitrogen, blue; sodium, tan.

4.5 Project “Electroosmotic transport in multiparticle systems”

Also in cooperation with U. Tallarek (University of Marburg), the application of electric fields to perform efficient separation capillaries or narrow channels has been studied. Within the period of this report, in particular, effects of dispersion in random sphere packings have been simulated using extensive numerical simulations exploiting the Lattice-Boltzmann method. In this way, complicated and undesired dispersion effects could be quantified (Hlushkou et al., 2007). Experimental investigations were devoted to study together with the BPE group effects of concentration polarization in multiparticle systems (Nischang et al., 2007) and to demonstrate convincingly the occurrence of nonequilibrium electroosmotic slips in monolithic structures (Nischang et al., 2008).

4.6 Projects “Chromatographic resolution of biomolecules” and “SMB chromatography with fractionation and feedback”

In cooperation with Prof. Tobiska (OvGU) an efficient numerical method was developed to calculate cyclic steady states of periodically operated multicolumn chromatography (Lübke et al., 2007). Together with the PSD group a theoretical contribution could be made in order to design and optimize chromatographic separation processes under reduced purity requirements (Kaspereit et al., 2007).

Together with the BPE and SCT groups, the potential of size exclusion chromatography to purify the human influenza virus was studied theoretically and experimentally (Kalbfuß-Zimmermann et al., 2008). A characterization of the hydrodynamics of expanded bed chromatography as an important step to optimize this separation and purification process was also performed with the BPE group and with the IIT in Madras (Prof. Pushpavanam) (Bandaru Krishna et al., 2007).

Together with the Faculty of Medicine of OvGU, the soybean protein P34 was successfully purified in a preparative scale (Sewekow et al., 2008).

Classical 4-zone-Simulated Moving Bed (SMB) chromatography was applied successfully in an experimental study devoted to the separation of the two enantiomers of the amino acid methionine using a new macrocyclic chiral stationary phase (Zhang et al., 2007). In order to improve SMB chromatography, the classical isocratic 4-zone-implementation form was modified in several ways. Combining gradient operation with a reduced zone number and an open liquid loop allowed for the separation of an antibody from a binary model mixture as well as the isolation of

a bone growth factor from a partially undefined multi-component solution (Gueorguieva et al., 2006; Keßler et al., 2007). If a ternary or “pseudo-ternary” mixture has to be separated completely, different schemes are needed. Therefore, several possibilities using connected 4-zone sub-units as building-blocks were investigated (Keßler and Seidel-Morgenstern, 2006) and evaluated regarding their potential to isolate a “middle” component from ternary and quaternary solutions. It could be shown theoretically that incorporating either a purge stream or an internal concentration step renders an 8-zone unit with internal recycle feasible. Within the period of this report another focal point was the development of a new Fractionation and Feed-back SMB (FF-SMB) strategy (Keßler and Seidel-Morgenstern, 2007; Keßler and Seidel-Morgenstern, 2008). This concept is based on a combination of periodic, non-constant product collection at one or both outlet ports with an internal recycle and re-feeding of the “non-product” fraction (Fig. 4). Using an appropriate feeding scheme accounting for the underlying isotherms as well as implementation-specific aspects, it could be shown on the basis of extensive simulation studies that process performance can be improved significantly (Fig. 4).

A review summarizing new variants of the classical SMB process was given recently (Seidel-Morgenstern et al., 2008).

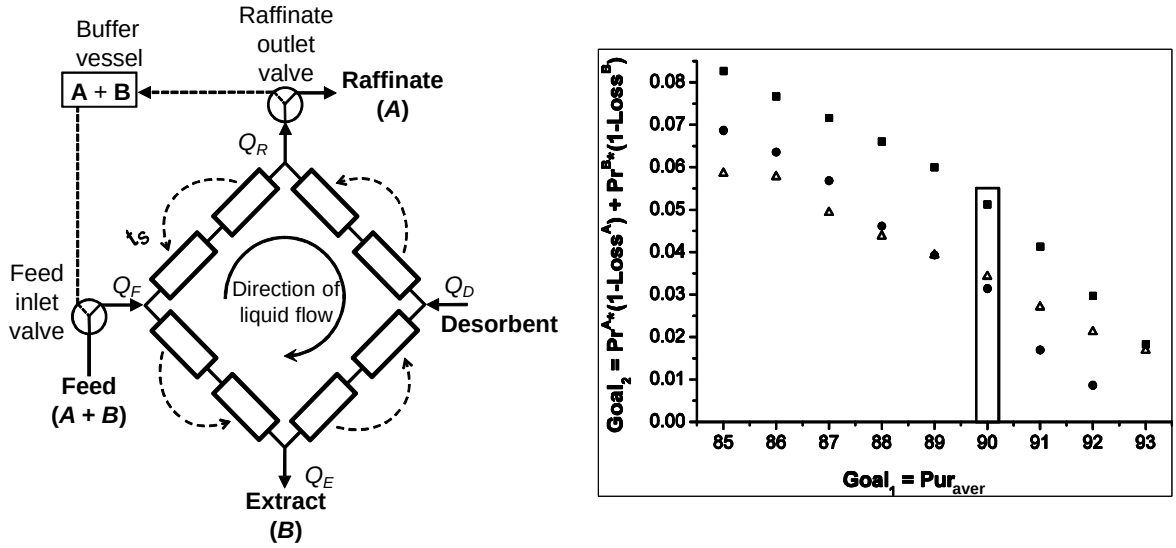


Fig. 4: Schematic representation of FF-SMB using the raffinate port for fractionation (left) and Pareto-optimal conditions obtained by extensive simulation studies for FF-SMB (squares), Fractionation without recycle (triangles) and conventional SMB (circles) (Keßler and Seidel-Morgenstern, 2008)

4.7 Project “Thermal effects in reactive chromatography”

Concerning the application of a combined reaction and chromatographic separation process, activities were concentrated on evaluating the extent and the potential of nonlinear effects in liquid/solid systems. An experimental study using an acidic ion exchange resin as catalyst and adsorbent and simple ester hydrolysis and esterification reactions revealed in a periodically operated lab-scale multi-column unit surprisingly large deviations from isothermal behavior (Fig. 5).

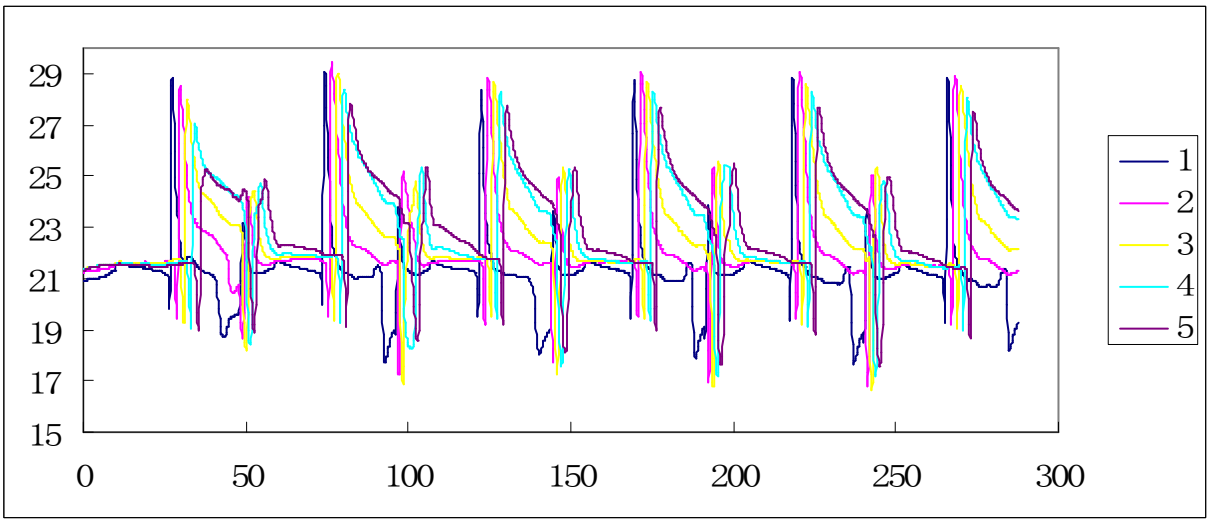


Fig. 5: Experimentally determined cyclic behavior of temperature at five discrete positions of a cascade of 8 periodically operated chromatographic reactors (esterification of acetic acid with methanol).

A quantitative analysis of a single fixed-bed performed together with the PSD group and the Lappeenranta University in Finland was based initially on the simplifying equilibrium theory (Sainio et al., 2007). Due to the joint thermal effects caused by reaction, adsorption and mixing, a quantitative analysis is complex and is the subject of current work.

4.8 Project “Mass and heat transfer through porous media”

The quantitative description of reaction and separation processes very often requires the understanding of mass and heat transfer processes in porous media.

In cooperation with Prof. Tsotsas (OvGU), a major research project supported by the DFG and devoted to understand and quantify heat transfer in porous ceramic composite membranes was finalized successfully (Hussain et al., 2006).

Mass transport of gases in porous glass membranes of different pore size range (1.4 nm and 4.2 nm) supplied by Dr. Enke (University Halle) was examined in detail in a cooperation with Prof. Schlünder (Karlsruhe) and Dr. Uchytil (Czech Academy of

Sciences, Prague). It was observed and quantified how gas separation can be dramatically influenced due to changes in the gas transport mechanism. Higher selectivity is achieved primarily as a result of surface diffusion and molecular sieving effects (Schlünder et al., 2006; Uchytil et al., 2007; Marković et al., 2008a; Marković et al., 2008b).

Oxygen transfer based on ion transport occurring in perovskite structures could be predicted in a wide parameter range in cooperation with Prof. Caro from the University of Hanover (Hamel et al., 2006; Hamel, 2008).

Specific aspects related to the effect of capillary condensation on transport in porous glass (Uchytil et al., 2007) and pervaporation through zeolite membranes (Weyd et al., 2006; Weyd et al., 2008) were studied in further cooperation projects.

4.9 Project “Dosing concepts using tubular membrane reactors”

Activities devoted to the systematic investigation of reaction processes supported by membrane separation were continued and completed successfully. This work was supported by the German Research Foundation (DFG) within the major research project “Membrane supported reaction engineering” which was carried out in collaboration with several groups at the MPI and OvGU (Spokesperson: Prof. Seidel-Morgenstern). A summary of the results is being worked on and will be available soon as a book (Seidel-Morgenstern, 2009).

Intensive research in the PCF group and the related university group was directed at investigating the possibility of dosing oxygen via porous membranes into a reactor in which heterogeneously catalyzed selective oxidation reactions (ethane to ethylene and propane to propylene) were carried out. The kinetics of the reaction network were quantified in detail in extensive studies (Joshi et al., 2006a; Klose et al., 2007; Joshi, 2007).

Within the period of this report an extensive pilot scale study was accomplished which revealed that, aside from adjusting local oxygen concentrations, it is also necessary to carefully analyze the residence time behavior of the different reactants (Hamel et al., 2008).

A review on theoretical aspects of modeling membrane reactors was published (Tóta et al., 2007). In cooperation with several partners of the ConNeCat project funded by the BMBF, a common review was given on the state of the art regarding the

application of catalytic membrane reactors for partial oxidations (Caro et al., 2007a; Caro et al., 2007b).

Recently an interesting theoretical result was obtained which is related to transient behavior of reactors and which possesses relevance for forced periodic operation of chemical reactors in general. In cooperation with Prof. Petkovska (University of Belgrade) it could be shown that an evaluation of the second order frequency response function provides a fast way of quickly evaluating the potential of such forced transient reactor regimes (Marković et al, 2008c).

4.10 Project “Estimation of free model parameters”

In cooperation with the SBI group (Dr. Kremling), specific aspects of uncertainty in parameter estimation were analyzed. In particular the potential of the bootstrap method for quantifying uncertainties was demonstrated successfully for various examples originating in adsorption and reaction engineering (Joshi et al., 2006b; Joshi et al., 2006c). This method is based on generating, in addition to real experimental data, a larger set of hypothetical data located randomly in certain predefined regions of the observations. A systematic model reduction and evaluation of the number of identifiable parameters was performed by consequent determination and evaluation of collinearity indices. Recently the potential of the method was used to estimate successfully parameters in nucleation and growth rate models from results of seeded and auto-seeded polythermal preferential crystallization experiments (Vollbrecht, 2007; Czapla et al., 2008; Kawajiri et al., 2008; Haida et al., 2008).

4.11 Project “Coupling crystallizers”

An attractive process for gaining pure enantiomers from racemic mixtures is the so-called enantioselective preferential crystallization (Lorenz et al., 2006; Angelov et al., 2006). In a batch crystallizer, conglomerate systems tend to reach an equilibrium state in solution in which the liquid phase will have racemic composition and the solid phase will consist of a mixture of crystals of both enantiomers. However, before approaching this state, it is possible to preferentially produce kinetically controlled just one of the enantiomers after seeding the solution with homochiral crystals. This process has been used up to now predominantly in the batch mode using a single crystallizer. An optimization of the corresponding process could be presented, in

cooperation with the SCT group, for the production of the amino acid threonine (Angelov et al., 2008).

During preferential crystallization in a conventional single batch process, the concentration of the desired enantiomer is permanently decreasing in the solution, whereas the concentration of the unwanted counter-enantiomer remains constant. This observation led to the idea to study an arrangement which might provide a better performance. The coupling of crystallizers via the liquid phase was studied in detail, i.e., a crystal free mother liquor exchange between two vessels operating in parallel. Because of this exchange, the liquid phase shows a higher overall concentration of the preferred enantiomer in that vessel in which the preferred enantiomer was seeded. Thus, the supersaturation level corresponding to the crystallization driving force is higher during the whole process in comparison to the case without an exchange (simple batch mode). Additionally, the concentration of the counter-enantiomer in the liquid phase for each of the vessels decreases. For the borderline case of an infinitely fast exchange racemic (50:50), composition is reached in the fluid phases of both vessels.

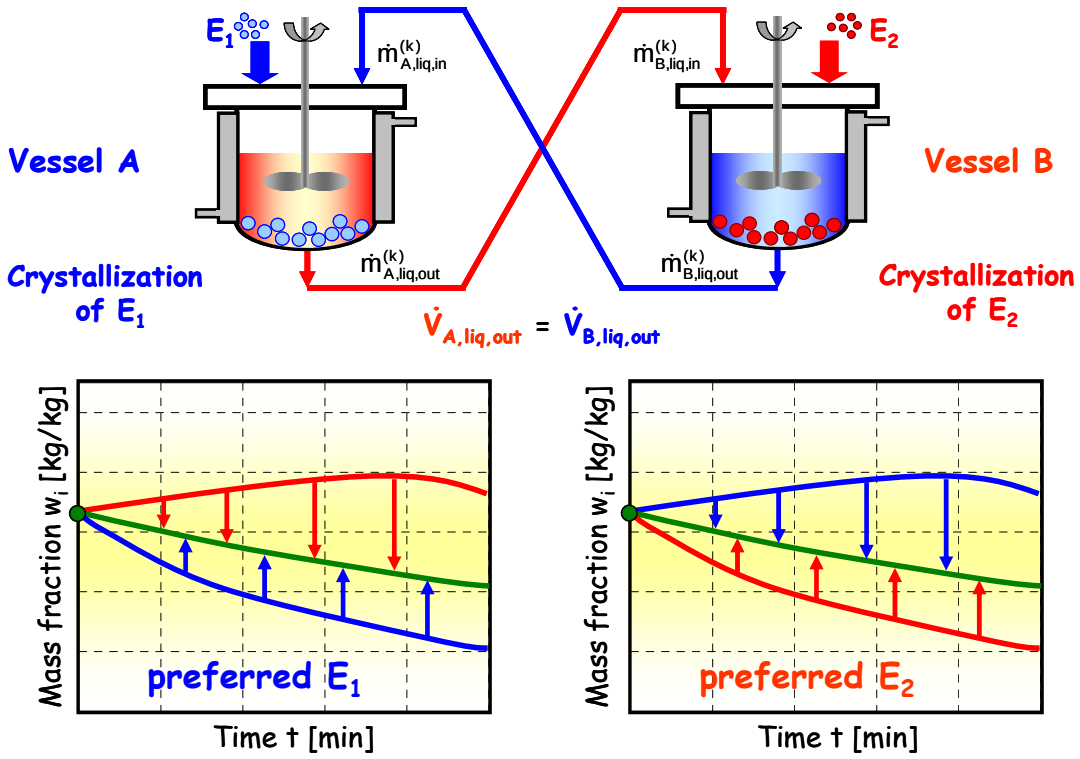


Fig. 6: Simultaneous preferential crystallization process: Concept of arranging two crystallizers (where initially both enantiomers E_1 and E_2 have been seeded) coupled via the liquid phase.

The process described in Fig. 6 mimics a racemization reaction occurring in the liquid phase. The described effect of decreasing the counter-enantiomer concentration in that crystallizer in which the preferred enantiomer shall be gained makes the probability for primary nucleation lower. This provides the potential to enhance the productivity. Based on a simplified approach, the more attractive and effective operation mode using two batch crystallizers coupled via their liquid phases has been investigated theoretically (Elsner et al., 2007) and, again for the threonine system, experimentally (Elsner et al., 2008). Promising results have been achieved, thus encouraging us to further study this process variant.

The effect of racemization by exchanging the fluid phase allows the specific manipulation of concentration profiles and seems to be a suitable lever for process intensification on the apparatus level.

4.12 Project “Chromatography or membrane separation prior to subsequent crystallization”

Possible enantioseparation techniques were studied in a joint project with the OvGU and Schering AG (Berlin, now Bayer-Schering). Continuous SMB chromatography was designed for the delivery of partially enriched products. The desired final purity was then achieved through selective crystallization. For an industrially relevant component it was demonstrated that this arrangement has the potential to improve the overall performance in comparison to the exclusive application of the expensive chromatographic step (Gedicke et al., 2007). A methodology was developed which allows evaluation of the potential of such coupled processes for other separation problems requiring minimal thermodynamic information, such as adsorption isotherms and eutectic compositions (Kaspereit et al., 2006).

A promising and relatively new method for separating chiral compounds is based on applying special functional polymers, which are called Molecularly Imprinted Polymers (MIPs). These materials might be applicable batch wise in chromatographic columns or continuously in form of enantioselective membranes. As a first step in evaluating the application of MIPs in a continuous enantioseparation process various membrane materials were prepared and evaluated. The ability to separate racemic aqueous solutions of Z-phenylalanine with MIPs based on 4-vinylpyridine as the functional monomer could be demonstrated successfully (Seebach and Seidel-Morgenstern, 2007).

Recently, together with the Universities of Karlsruhe and Aachen, a larger DFG supported project started in which membranes containing an enantioselective carrier will be studied in combination with a subsequent crystallization step.

4.13 Project “Combining enantioseparation and enzymatic racemization”

In a newly established cooperation with Research Center Jülich a new direction of research started in the PCF group. The importance and potential of integrated racemization (or enantiomerization) of the “unwanted” counter-enantiomer was identified as a major tool to enhance yields in the course of producing pure enantiomers. By coupling crystallization for preferential conglomerates and racemization, the theoretical yields of a pure enantiomer can reach 100% (Lütz et al., 2006). Our goal in this project is to develop a comprehensive study for each of the two single steps and to investigate them systematically together. The first promising results have been achieved for the amino acid DL-asparagine dissolved in water. The enzyme applied for racemization (from pseudomonas putida bacteria) was isolated in the Research Center Jülich (Institute for Biotechnology-2) and characterized in a joint work (Würges et al., 2008).

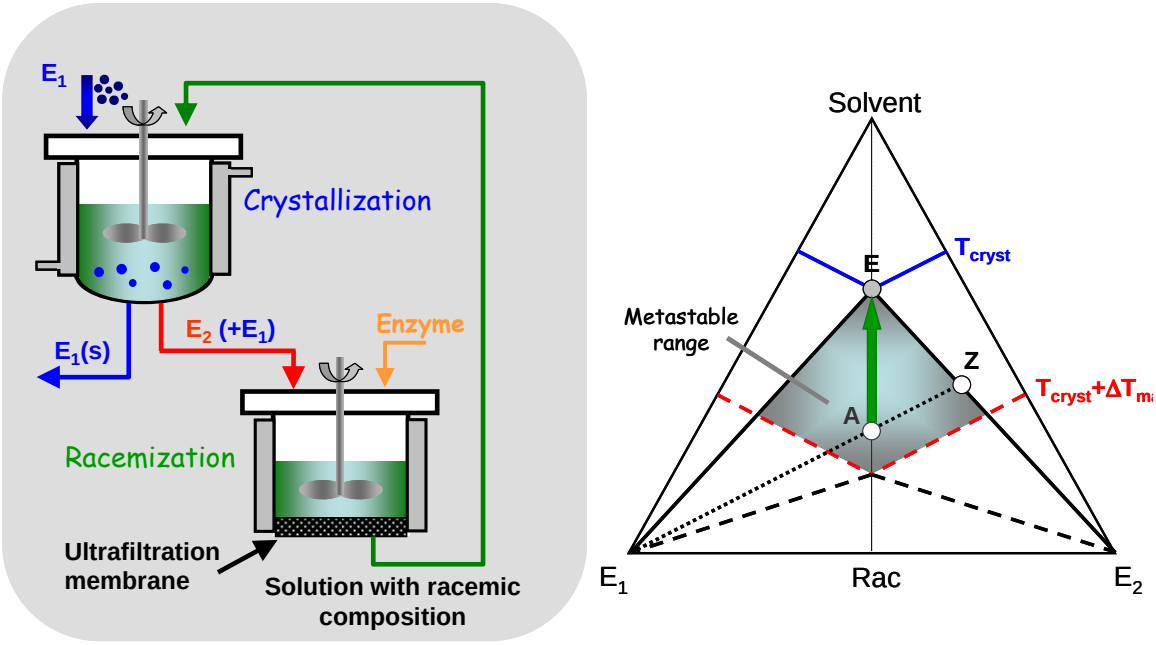


Fig. 7: Coupling preferential crystallization with racemization to enhance overall yields of producing pure enantiomers. Possible trajectories of the liquid phase composition in a crystallizer are illustrated in the phase diagram for a conglomerate forming system.

4.14 Project “European project INTENANT”

Usually in industry racemic mixtures of chiral substances are produced, although in most cases only one of the enantiomers shows the required properties with regard to therapeutic activities or metabolism. Consequently, the need of pure enantiomers in the pharmaceutical industry, food industry, cosmetics and agrochemical industry is tremendously increasing.

Separation of racemic mixtures by chromatography, crystallization or membrane processes to get access to pure enantiomers is studied in several projects of the PCF group (e.g. in projects 4.2, 4.6, 4.11 – 4.13 described above). Almost no expertise is available in the group regarding synthesis concepts to tackle the same problem by producing partially enriched mixtures or even the pure enantiomers by typically catalyzed selective reactions.

To submit a major research proposal to the European Union within the new Framework Program FP7, a strong consortium was formed under the leadership of the PCF group in order to form an alliance of chemical (synthesis) and physical (separation) methods to improve the access to pure enantiomers. On June 1, 2008, the project “INTegrated synthesis and purification of single ENANTiomers” started (INTENANT, 2008). Several of the process options indicated in Fig. 8 will be studied by 11 partners from 6 countries using model systems as well as industrially relevant compounds as target molecules.

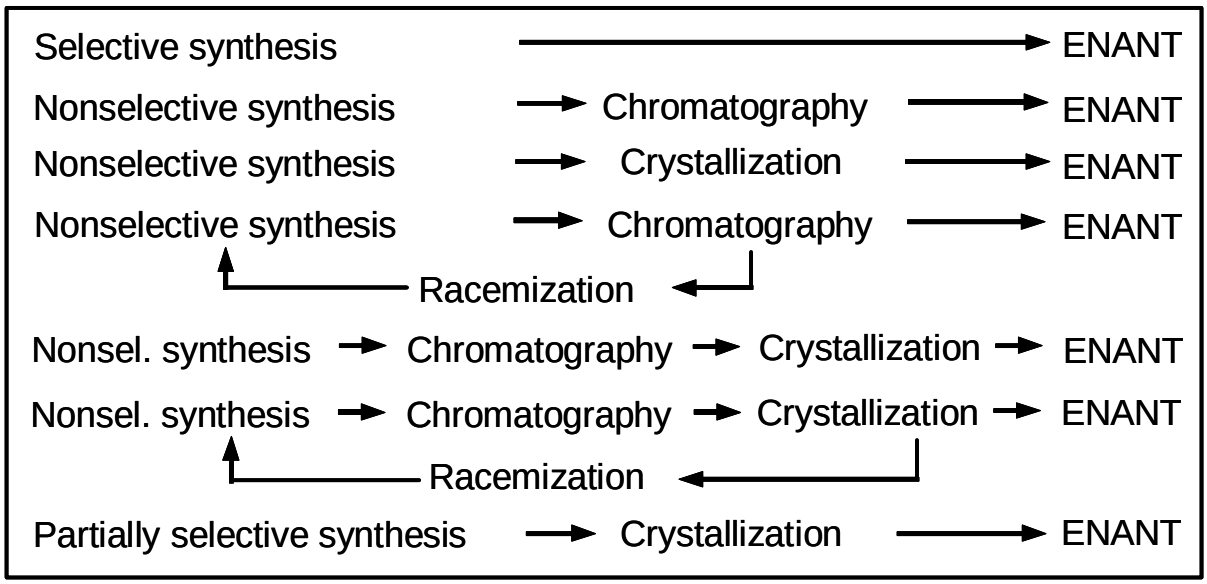


Fig. 8: Options to obtain pure enantiomers (ENANT) investigated within the INTENANT-project

5 Teaching Activities, Habilitations, Ph.D. and Master Projects

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

Chemical Reaction Engineering (summer terms, German and English)

Adsorption and Heterogeneous Catalysis (winter terms, German)

Numerical Methods in Chemical Process Engineering (summer terms, German)

Safety in Chemical Reactions (winter terms, English)

Chemical Process Technology (winter terms, German, with H. Lorenz)

Lectures of Dr. H. Lorenz (at OvGU)

Technical Chemistry (winter terms, English)

Modern Analytical Methods in Industrial Chemistry (summer terms, English)

Chemical Process Technology (winter terms, German, with A. Seidel-Morgenstern)

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

Crystallization processes (winter terms, German)

Habilitation project defended at OvGU in the period of the report

Tab. 6: Habilitation project defended at OvGU (cooperation with PSD group)

F. Klose	Structure-Activity Relations of Supported Vanadia Catalysts and the Potential of Membrane Reactors for the Oxidative Dehydrogenation of Ethane	2007

Ph.D. projects defended at OvGU in the period of the report

Tab. 7: Ph.D. theses supervised by A. Seidel-Morgenstern (* Ph.D. students of the OvGU group, °external Ph.D. students)

T.-P. Mai*	Experimental investigation of heterogeneously catalyzed hydrolysis of esters	2006
A. Perlberg	Untersuchungen zum Einfluss des Gegenenantiomers bei der enantioselektiven Kristallisation aus Lösungen	2006
J. Battke°	Interaktion von Sorption und Reaktion bei der Dehalogenierung von halogenorganischen Verbindungen in Wasser	2006
M. Kaspereit	Separation of enantiomers by a process combination of chromatography and crystallisation	2006
M. Joshi*	Statistical analysis of models and parameters in chemical and biochemical reaction networks	2007
D. Sapoundjiev	Löslichkeitsgleichgewichte von Stereoisomeren – Bedeutung, experimentelle Ermittlung und Anwendung	2007
A. Schlinkert*	Entwicklung einer Impulsmethode zur Ermittlung thermodynamischer und reaktionskinetischer Parameter in der heterogenen Katalyse	2007
B. Vollbrecht*	Zur Kinetik der Methanolsynthese an einem technischen Cu/ZnOAl_2O_3-Katalysator	2007

T. Vu-Dinh*	Analysis of heterogeneously catalyzed ester hydrolysis reaction in a fixed-bed chromatographic reactor	2007
M. Weyd°	Charakterisierung hydrophober ZSM-5 Zeolithmembranen und deren Anwendung zur Trennung von Wasser-Ethanol-Gemischen durch Pervaporation	2007
C. Hamel	Experimentelle und modellbasierte Studien zur Herstellung kurzkettiger Alkene sowie von Synthesegas unter Verwendung poröser und dichter Membranen	2008
M. Ilić	Development and application of a nonlinear frequency response method for estimation of single solute and competitive adsorption isotherms	2008

There are currently 18 Ph.D. projects in progress in the PCF group and 5 in the university group.

Selected Diploma and Master Projects (OvGU)

Tab. 8: Selected Diploma and Master projects supervised by A. Seidel-Morgenstern

A. Guadalupe O. Camarena	Statistical analysis of adsorption equilibrium data
Y. Sonavane	Screening of stationary phases for the separation of immuno-globulins
I. Monono	Feasibility study of resolution of pharmaceutically relevant chiral substances by Preferential Crystallisation
D. Thakur	Structure-activity relations in the catalytic oxidation of hydrocarbons
B. Bhut	Diffusion through molecularly imprinted polymers
J. Garcia Palacios	Optimization and analysis of possible column arrangements in preparative chromatography for multicomponent mixtures
A. Ashfaq	Numerical solutions of population balances for crystallization processes
H. Haida	Messung und Auswertung reaktionskinetischer Daten zur Selektivhydrierung von Ethin im Integralreaktor
T. Meixus Fernandez	Combination of recycling chromatography and racemisation reaction for the production of pure enantiomers
D. Hai Do	Experimental investigation of the oxidative dehydrogenation of ethane on $VO_x/\gamma Al_2O_3$ catalysts in packed bed membrane reactors
L. Fernandez Lopez	Theoretical and experimental study on polythermal operation or enantioselective preferential crystallization
B. Sreedhar	Model based analysis of mass transfer resistances in packed bed membrane reactors
C. Parzyk	Theoretische und experimentelle Untersuchung von Übertragungsreaktionen bei der radikalischen Polymerisation von Acrylsäure
V. Zahn	Experimentelle Untersuchungen zum Einfluss unterschiedlicher Vermischungsstrategien auf die Fällung eines pharmazeutischen Wirkstoffs

In total there have been 16 diploma and master projects supervised and finalized during the period covered by this report.

6 Selected Memberships, Appointments and Awards

Andreas Seidel-Morgenstern

Since 2002	Scientific member of MPG and Director of the MPI 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	Chairman of Board of Trustees of Ernest Solvay Foundation, Hanover
2007 – 2008	Managing Director of the Max Planck Institute of Dynamics of Complex Technical Systems in Magdeburg
2008	Honorary Doctorate of Lappeenranta University of Technology (Finland)
2008	Elected member of the Commission of the Senate of the German Science Foundation (DFG) for Collaborative Research Units (SFB)

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

Malte Kaspereit (now PSD group)

2006	Research Award of Saxony-Anhalt Chamber of Industry and Commerce (IHK) for Research

Christof Hamel (now university group)

2008	Award for best Ph.D. thesis submitted in this year at the Faculty for Process and Systems Engineering of OvGU

7 Future Directions

Concentrating efforts on the recently started EU project “INTENANT” and the two larger DFG projects, the PCF group plans to continue studying enantioseparation in a broad sense. Resolution by crystallization, chromatography, and membrane separation will be investigated individually and in various combinations. By extending the application of molecular modeling methods, it will be attempted to better understand the underlying separation mechanisms in order to design efficient separation and purification processes. It is an ongoing goal to strengthen these activities by forming a corresponding Junior Research Group.

The investigation of population balance systems will be an ongoing area of intensive cooperation between several groups at MPI (PCP, PSD, SCT, BPE) and OvGU in the next few years.

Another important activity of our group will be the continuation of systematic work to study and develop various types of innovative reactor concepts as chromatographic and membrane reactors. After studying up to now mainly membrane reactors for exploiting a controlled dosing of oxygen, future work will be also devoted to improving selectivity in isomerization and metathesis reactions. To reach this goal, new multi-fixed-bed reactor arrangements will be studied.

A further goal of the PCF group is to extend the experience gained during the last years in the area of chromatographic separation processes. Here a further intensification of the cooperation with the BPE group is planned. The mathematical modeling of the isolation and purification of larger biomolecules and viruses will be the focus of joint efforts.

The PCF group will continue to contribute to teaching activities at the OvGU. New lectures are under preparation.

In general, it will remain the mission of our group to develop, analyze and design reaction and separation processes based on a sound and reliable data basis.

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This list does not represent a complete list of the publications of the PCF group.

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Research Group:

Physical and Chemical Process Engineering (PCP)

Prof. Dr.-Ing. Kai Sundmacher

This report covers the period from January 2006 to September 2008.
It also contains the reports of the Junior Research Groups Population Dynamics and Portable Energy Systems (Otto Hahn Group)

1 Group Introduction

The research activities of the group **Physical and Chemical Process Engineering (PCP)** are focused on the analysis and design of efficient process systems for the production of valuable products (chemicals or energy) from raw materials. Both process analysis and process design can only be accomplished adequately if the considered process systems are investigated carefully with regard to their multi-level structure, as illustrated in Figure 1. The *plant level* of each production process can be decomposed into several *process units*, each consisting of a number of interacting phases. Each phase can be represented as a distributed *particle population*, i.e. an ensemble of interacting *single particles* such as molecules, crystals, bubbles, etc.

With regard to this multi-level structure, process analysis is a top-down procedure, dealing with the modular decomposition of larger entities into smaller units, while process design is a bottom-up task, aiming at the aggregation of functional modules from lower to upper levels in order to generate a complete production system. For both tasks, analysis and design, one needs quantitative information for all relevant mechanisms involved at the different process levels. For this purpose, in all their research projects, the group tries to identify adequate mathematical process models from suitable experimental data which are collected from well-defined set-ups in the group's own labs or from external partners (academic and industrial).

All projects of the PCP group are fully embedded into the MPI's project area structure which is outlined in the overview of this status report. As summarized in Figure 1, the group contributes to three project areas, namely population balance systems (i.e. the particle population level or single particle level), integrated processes (i.e. the process unit level), and coupled processes (i.e. plant level). With regard to **Population Balance Systems**, the group has further extended its research activities by establishing the new **Junior Research Group "Population Dynamics" (PDY group)** in 2007, with Dr. Heiko Briesen as scientific head. The focus of this group is on deterministic and stochastic approaches for modelling and simulation of particle populations which are characterized by more than one internal and/or external coordinate, i.e. multidimensional particle populations.

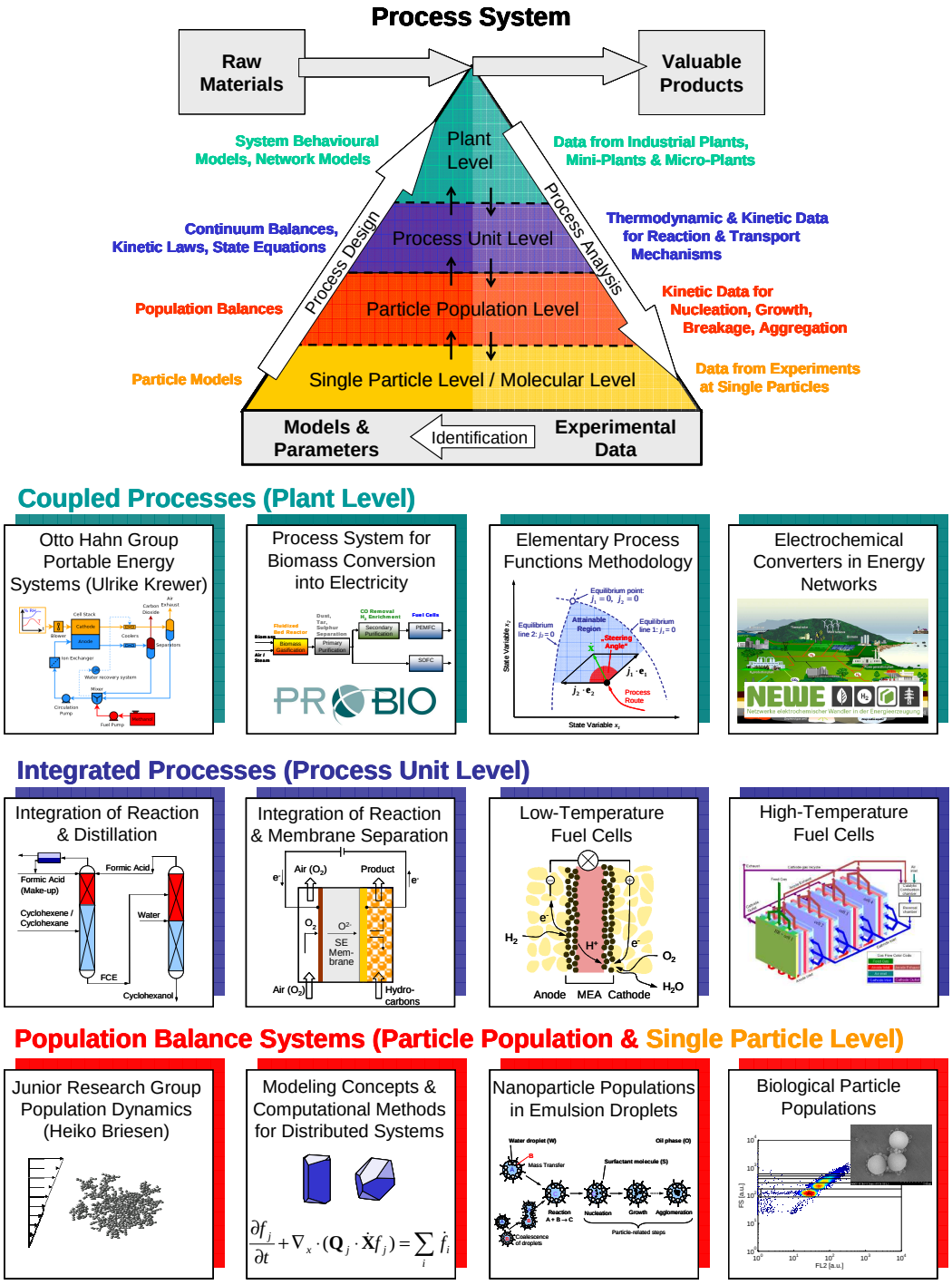

Fig.1: Survey of research activities of PCP group, including the junior research group Population Dynamics and the junior research group Portable Energy Systems (Otto-Hahn group).

Also within the area of particle population systems, numerical algorithms for the efficient solution of related population balance equations are developed in close collaboration with three mathematical groups (Prof. John/University of Saarland; Prof. Hackbusch/MPI for Mathematics in the Sciences, Leipzig; Prof. Tobiska/OvGU). System-oriented investigations are performed together with several external and internal partners (Prof. Ramkrishna/Purdue University; Prof. Flockerzi/SCT group;

Prof. Kienle/PSD group). This methodological work is closely combined with challenging process examples, namely nucleation and growth of nanoparticles in emulsions droplets, and aggregation phenomena in biological particle populations. In the latter case, new collaborations were created with the group of Prof. Naumann (Medical faculty at OvGU) and the BPE group (Prof. Reichl), partly funded by the Research Center “Dynamical Systems” (CDS) in Magdeburg. Regarding the experimental activities in this area, a broad variety of inline, online and offline methods for particle characterization were established in partnership with the Institute for Experimental Physics at OvGU, and the PCF group (Prof. Seidel-Morgenstern).

In the area of **Integrated Processes**, our group continued its research activities to integrate chemical reactions into distillation processes or membrane separation processes. As an important result of this strategy, novel reactive separation systems were proposed for cyclohexanol production from cyclohexene and for octane production from isobutene. This project was funded by the Volkswagen Foundation and performed together with IIT Bombay, Prof. Mahajani. Furthermore, low and high-temperature fuel cells are investigated as multifunctional process units where electro-chemical reactions and trans-membrane transport of ionic species are closely combined. As an interesting example, in a long-term partnership with the company CFC Solutions, Ottobrunn/Germany, the group pursues the model-based hierarchical analysis of Molten Carbonate Fuel Cells (MCFC) from the single electrode level up to the stack level. In a similar manner, the dynamic behavior of Proton Exchange Membrane Fuel Cells (PEMFC), Direct Methanol Fuel Cells (DMFC) and Enzymatic Fuel Cells (EFC) is currently analyzed. As an innovative method for model discrimination and failure diagnosis, nonlinear frequency response analysis (NFRA) was introduced in collaboration with Prof. Petkovska (Belgrade University).

The third cluster of PCP research projects is located in the area of **Coupled Processes**. As significant extension of the existing research activities in this field, the new **Otto Hahn group “Portable Energy Systems” (OH group)** was started in January 2008 with Dr. Ulrike Krewer, previously at Samsung/Korea, being appointed as the head of this independent junior research group. The OH group’s research is focused on the design and analysis of portable systems, combing micro- and mini-fuel cells (DMFC, PEMFC) with miniaturized devices for mass transport and separation.

As second important activity in the area of Coupled Processes, the joint research project PROBIO was started in 2007 in collaboration with two Fraunhofer Institutes (IKTS in Dresden, IFF in Magdeburg) in order to develop a novel biomass-fed fuel cell system. To attain this long-term goal, computer-aided process design methods and process analysis tools are combined with experimental investigations.

In a further long-term project, the PCP group started to develop a flux-oriented methodology for the systematic analysis and design of coupled chemical processes from the molecular level up to the plant level. According to this concept, “Elementary Process Functions” are aggregated to functional modules which are linked to complete process routes leading from given educts to desired products. The final goal is to identify time-optimal and/or energy-optimal process routes within the thermodynamic state space.

As a fourth activity in the same research area, the PCP group very recently started the new project “Electrochemical Converters in Energy Networks (NEWE)”, which is funded by the Federal State of Saxony Anhalt from 2008 to 2010. The scientific goal here is to investigate coupling effects between different renewable energy sources, such as wind turbines, photovoltaic devices and fuel cells. The research will be performed in close collaboration with the Department for Electrical Engineering at OvGU and the Fraunhofer Institute IFF.

2 Members of the Research Groups

Since 2001, Kai Sundmacher, being Director for Process Engineering at the MPI, has guided the research activities of the PCP group and his university group, the Process Systems Engineering group (PSE) at Otto-von-Guericke-University Magdeburg (OvGU), simultaneously. In coordinating the scientific projects, he is supported by experienced senior scientists (four in PCP group and two in PSE group; Table 1).

Tab. 1: Composition of PCP Group, Junior Research Groups and PSE Group as of October 1, 2008.

	Status	**Joined MPI**
PCP Group		
Prof. Dr. Kai Sundmacher	Director & Head of the Group	since 10/1998
Dr. Hannsjörg Freund	Scientific Project Coordinator	since 09/2005
Dr. Richard Hanke-Rauschenbach	Scientific Project Coordinator	since 11/2001
Dr. Peter Heidebrecht	Scientific Project Coordinator	since 09/2005
Dr. Liisa Rihko-Struckmann	Scientific Project Coordinator	since 01/2001

Dr. Vladimir Galvita	Postdoc	09/2002-07/2007
Dr. Amit Katariya	Postdoc	since 12/2006
Dr. Mantravadi Vasudeva Kumar	Postdoc	since 10/2008
Dr. Rakesh Kumar	Postdoc	since 10/2006
Dr. Hui Lu	Postdoc	09/2006-08/2008
Dr. Pavankumar Malladi	Postdoc	since 09/2008
Dr. Suman Thotla	Postdoc	since 07/2008
Rayees Ahamed	Ph.D. Student	since 11/2006
Christian Borchert	Ph.D. Student	since 07/2007
Michael Fricke	Ph.D. Student	since 11/2005
Benny Hartono	Ph.D. Student	since 10/2008
Christoph Hertel	Ph.D. Student	since 04/2007
Ivan Ivanov	Ph.D. Student	since 01/2007
Christian Oettel	Ph.D. Student	since 07/2007
Andreas Peschel	Ph.D. Student	since 11/2007
Silvia Piewek	Ph.D. Student	since 08/2008
Sascha Rollié	Ph.D. Student	since 05/2006
Yaoli Song	Ph.D. Student	since 06/2001
Kongmeng Ye	Ph.D. Student	since 09/2008
Junior Research Group Population Dynamics (PDY group):		
Dr. Heiko Briesen	Head of the Group	since 07/2007
Dr. Soumik Banerjee	Postdoc	since 07/2008
Dr. Volker Becker	Postdoc	since 09/2007
Dr. Juan Diaz	Postdoc	since 10/2008
Junior Research Group Portable Energy Systems (OH group):		
Dr. Ulrike Krewer	Head of the Group	since 01/2008
Dr. Federico Zenith	Postdoc	since 04/2008
Maik Kraus	Ph.D. Student	since 12/2008
Technical Staff:		
Dr. Liisa Rihko-Struckmann	Coordinator of Technical Staff	since 01/2001
Jessica Bunge	Laboratory Assistant	since 02/2008
Markus Ikert	Laboratory Assistant	since 05/2006
Bianka Stein	Laboratory Assistant	since 10/2001
Linda Oettel	Laboratory Engineer	07/2007-07/2008
Torsten Schröder	Laboratory Engineer	since 01/2002
Patrick Siegmund	Laboratory Engineer	since 02/2003

Visiting Scientists:		
Prof. Mihai Christov	UCTM Sofia, Bulgaria	10/2005-01/2006
Prof. Pavel Hasal	ICT Prague, Czech Republic	several visits of 1-2 weeks
Prof. Sanjay Mahajani	IIT Bombay, India	several visits of 1-2 weeks
Prof. Doraiswami Ramkrishna	Purdue University, USA	several visits of 1-2 weeks
Prof. Ernst-Ulrich Schlünder	TH Karlsruhe, Germany	since 04/2000
Process Systems Engineering (PSE) Group at OvGU:		
Prof. Dr. Kai Sundmacher	Head of the Group	since 10/1999
Dr. Tanja Vidaković	Scientific Project Coordinator	since 10/2005
Dr. Andreas Voigt	Scientific Project Coordinator	since 11/2003
Dr. Chafika Ait Aissa	Postdoc	since 10/2007
Boris Bensmann	Ph.D. Student	since 08/2008
Thomas Kadyk	Ph.D. Student	since 03/2006
Roberto Lemoine	Ph.D. Student	since 09/2007
Matthias Pfafferodt	Ph.D. Student	since 04/2004
Christiane Steyer	Ph.D. Student	since 11/1999
Evelin Felsch	Laboratory Assistant	since 01/2000
Martin Dietrich	Laboratory Assistent	since 01/2008

3 Research Activities

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

Project Area: Population Balance Systems

Project: **Junior Research Group Population Dynamics** Head of Group: Dr. Briesen	This group strengthens existing activities in the area of population dynamics and sets a particular focus in selected fields. The long term objective is to provide multi-scale, predictive models for the kinetics (aggregation processes, crystal growth) of selected population-based processes (crystallization, precipitation).			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Restructuring of colloidal aggregates in shear flows	Becker	DFG (Priority Program 1273)	Since 10/2007	RWTH Aachen (Prof. Behr)
Molecular dynamics simulation of crystal growth	Banerjee	MPI	Since 07/2008	University of Cambridge (Prof. Frenkel)
Simulation of aggregation for complex shaped particles	Briesen	MPI	Since 07/2007	

Project: **Modelling Concepts and Computational Methods for Distributed Systems** Coordinator: Dr. Voigt*	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 the crystal shape evolution is a long-term goal.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
SimPaTurS: Simulation of crystal populations in turbulent flow fields	Borchert, Voigt*	BMBF, MPI, OvGU	Since 07/2007	Univ. Saarbrücken (Prof. John), MPI-Leipzig (Prof. Hackbusch), OvGU (Prof. Tobiska)
Model-based analysis of crystal shape evolution	Borchert	MPI	Since 07/2007	Purdue University (Prof. Ramkrishna), PCF group (Dr. Lorenz)
Semi-batch experiments on anisotropic crystal growth	C. Steyer*, Voigt*	OvGU, MPI	Since 05/2004	PSD group (Dr. Mangold)
Stability analysis of reactive crystallization processes	Heineken, Voigt*	MPI, OvGU	Since 04/2006	SCT group (Prof. Flockerzi)

Project: **Nanoparticle Populations in Emulsion Droplets** Coordinator: Dr. Voigt*	Emulsion droplets can be used as micro-reactors for the synthesis of nanoparticles. In this project, different emulsion-assisted precipitation processes are characterized experimentally and population balance models are formulated in order to identify suitable process variables for tailoring the particle size distributions.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Coalescence-based emulsion-assisted nanoparticle precipitation	Aditya-warman*, Niemann, Rauscher, Voigt*	MPI, OvGU	04/2001-02/2008	OvGU (Dr. Veit, Prof. Thévenin)
Diffusion-based emulsion-assisted nanoparticle precipitation	Fricke, Voigt*	MPI	Since 09/2006	Univ. of Karlsruhe (Prof. Schuchmann)
Novel emulsion systems as precipitation media	Gao, Voigt*	MPI, OvGU	09/2005-11/2007	OvGU (Dr. Hilfert)

Project: **Biological Particle Populations** Coordinator: Dr. Voigt*	In this project, populations of biological particles are investigated in the framework of population balance modeling concepts. Virus replication, aggregation of cells and nanoparticles, and the separation of proteins from biological mixtures are considered as challenging process examples.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Monte Carlo simulation of virus replication in cell populations	Voigt*, Diaz*, Briesen	OvGU, CDS, MPI	Since 09/2006	BPE group (Prof. Reichl), PSD group (Prof. Kienle)
Homo- and heteroaggregation in mixed particle-cell populations	Rollié, Briesen	CDS, MPI	Since 09/2006	OvGU (Prof. Naumann), MPI-Mainz (Prof. Butt), BPE group (Prof. Reichl)
Separation of biological mixtures in membrane adsorbers	Malladi	BMBF, MPI	Since 09/2008	BPE group (Prof. Reichl, Dr. Wolff), PCF group (Prof. Seidel-M.)

Project Area: Integrated Processes

Project: **Integration of Reaction and Distillation** Coordinator: Dr. Freund	Focus is on design and analysis of reactive distillation processes where liquid phase splitting and networks of chemical reactions give rise to complex system behavior. Conceptual design methods, rigorous simulations and miniplant experiments are closely combined.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Conceptual design of a novel reactive distillation process	F. Steyer, Freund	MPI	06/2000-02/2008	SCT Group (Prof. Flockerzi)
Computer-aided analysis of reactive distillation processes with liquid phase splitting	Katariya, Ahamed, Freund	MPI	Since 12/2006	University Ploiesti (Dr. Radulescu), PSD Group (Prof. Kienle)
Experimental validation in a miniplant for cyclohexanol synthesis	R. Kumar, Thotla, Freund	MPI	Since 10/2006	
Coupling of chemical reactions in reactive-distillation processes	Chalakova*, Katariya, Freund	VW, OvGU, MPI	Since 01/2002	IIT Bombay (Prof. Mahajani, Prof. Aghalayam)

Project: **Integration of Reaction and Membrane Separation** Coordinator: Dr. Rihko-Struckmann	In this project, the integration of chemical reaction and membrane separation in a single process unit is investigated. Ion conducting membranes are used for electrically controlled dosing of oxygen into partial oxidation processes. Furthermore, porous membranes are applied to design micro-separators.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Experimental analysis and modeling of electrochemical membrane reactors	Chalakov*, Ye, Munder, Rihko-S.	DFG, MPI	01/2001-02/2008	DFG research group 447 (Prof. Weiß), PCF Group (Dr. Klose)
Reactive and non-reactive micro-separators	Ait-Aissa*	OvGU	Since 10/2007	

Project: **Low-Temperature Fuel Cells** Coordinator: Dr. Vidaković*	In this project, the dynamic behavior of PEM Fuel Cells (PEMFC), Direct Methanol Fuel Cells (DMFC) and Enzymatic Fuel Cells is analyzed. Methods for system diagnosis, model discrimination, distributed modeling and experimental validation are closely combined.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Nonlinear dynamics of PEMFC	Hanke-R.	MPI	Since 01/2002	PSD Group (Dr. Mangold)
Nonlinear frequency response analysis (NFRA) for fuel cell diagnosis and model discrimination	Kadyk*, Vidaković*, Hanke-R.	MPI, LSA, OvGU	Since 03/2006	Univ. Belgrade (Prof. Petkovska), OvGU (Prof. Lindemann, Prof. Styczynski)
Analysis of DMFC electrode kinetics	Vidaković*, Krewer	MPI, OvGU	07/2002-06/2007	MPI-Mülheim (Prof. Bönnemann), UCTM Sofia (Prof. Christov)
3D modeling of fuel cells	Song	MPI	Since 06/2001	
Enzymatic fuel cells	Ivanov, Vidaković*	MPI, OvGU	Since 01/2007	SBI group, Jacobs University Bremen (Prof. Schwaneberg)

Project: **High-Temperature Fuel Cells** Coordinator: Dr. Heidebrecht	Molten Carbonate Fuel Cells (MCFC) are complex, highly integrated process units. The long-term project goal is to develop predictive distributed models for systematic design, analysis and optimization of stacks.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
MCFC electrode models	Piewek, Heidebrecht	DFG, MPI	Since 08/2008	CFC Sol./Ottobrunn
MCFC flow field models	Pfafferodt*, Heidebrecht	CFC, MPI	04/2006-12/2008	CFC Sol./Ottobrunn
MCFC stack models and their experimental validation	Gunder-mann*, Pfafferodt*, Piewek, Heidebrecht	BMBF, CFC, DFG, MPI	Since 01/2001	PSD group (Dr. Mangold), University Bayreuth (Prof. Pesch), IPF/Magdeburg, CFC Sol./Ottobrunn

Project Area: Coupled Processes

Project: **Otto Hahn Group** **Portable Energy Systems** Head of Group: Dr. Krewer	This junior research group is developing portable fuel cell systems (PEM-based fuel cell technologies), thereby linking model-based and experimental tools in order to optimize heat and mass fluxes in single components and in systems.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
System analysis of direct methanol fuel cell systems	Zenith, Krewer	MPS	Since 01/2008	SCT group (Dr. Bajcinca)
Components for direct methanol fuel cell systems	Krewer, Kraus	MPS	Since 08/2008	Institut für Mikrotechnik Mainz Ltd. (Dr. Kolb)

Project: **Process System for Biomass Conversion into Electricity (PROBIO)** Coordinators: Dr. Heidebrecht (Theory), Dr. Rihko-Struckmann (Exp.)	In this joint research project, a process is developed for the production of electrical energy from biomass using fuel cells. Novel reactor concepts (CWGSR, EPrOx) are developed for efficient hydrogen purification. Conceptual system design and experiments are performed in close collaboration with two Fraunhofer Institutes (IFF, IKTS).			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Conceptual design of biomass-fed fuel cell systems	Hartono, Hertel, Heidebrecht	MPG/FhG, MPI	Since 03/2007	Fraunhofer Institutes (IFF/Magdeburg, IKTS/Dresden)
CWGSR: Cyclic water gas shift reactor for H_2 purification	Datta, Heidebrecht, M.V. Kumar, Rihko-S.	MPG/FhG, LSA, MPI	Since 11/2003	Carnegie Mellon Univ. (Prof. Biegler), PCF group (Dr. Lorenz)
EPrOx: Electrochemical reactor for preferential oxidation of CO	Lu, Hanke-Rauschen-bach, Rihko-Struckmann	MPG/FhG, MPI	Since 09/2006	
High-temperature PEM fuel cells	C. Oettel, Rihko-Struckmann	MPG/FhG, MPI	Since 07/2007	Fumatech Ltd./ St. Ingbert

Project: **Elementary Process Functions Methodology for Analysis and Design of Chemical Processes** Coordinator: Dr. Freund	Within this project, a flux-oriented methodology for the systematic analysis and design of chemical processes is developed. Using this theoretical framework, we try to find time-optimal and/or energy-optimal process routes and identify resistances in individual process steps that limit the overall process performance. A chemical production process and an energy storage process are considered as interesting examples.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Theoretical framework of Elementary Process Functions	Freund, Sundmacher	MPI	Since 12/2006	
Optimal design of reaction-separation processes	Peschel, Freund	IMPRS, MPI	Since 11/2007	SCT group (Dr. Bajcinca), TU Berlin (Prof. Schomäker)
Chemical storage of renewable energy by CO_2 reduction	Rihko-Struckmann, Hanke-R.	BMBF, MPI	Since 07/2008	MPI-Mülheim (Prof. Schüth)

Project: **Electrochemical Converters in Energy Networks (NEWE)** Coordinator: Dr. Hanke-Rauschenbach	This project focuses on electrochemical converters, such as fuel cells being embedded in energy networks. Of special interest is the analysis of the interrelationships within single fuel cell systems. In a second step, the coordinated operation of groups of fuel cell systems connected to the electric grid will be investigated.			
Subprojects	**Scientists**	**Funded by**	**Period**	**Partners**
Model-based control of stationary PEMFC systems	Lemoine*, Hanke-R.	IMPRS, LSA, MPI	Since 09/2007	OvGU (Prof. Styczynski, Prof. Lindemann), IFF (Dr. Thomas)
Load management of fuel cells as auxiliary power units	Bensmann*, Hanke-R.	LSA, MPI	Since 08/2008	OvGU (Prof. Styczynski Prof. Lindemann), IFF (Dr. Thomas)

4 Research Highlights

4.1 Population Balance Systems

4.1.1 Junior Research Group Population Dynamics

The current focus of the JRG Population Dynamics (PDY) is on predictive modelling of rate processes for particulate population systems. These rate processes include crystal growth, aggregation/agglomeration, restructuring and breakage/attrition. Understanding of these rate processes is the prerequisite for meaningful models with extrapolative capabilities. It is proposed that predictive modelling will only be possible with a particle characterization which extends beyond the size of the particles. A suitable shape characterization is of particular interest. The investigation of particle shape necessitates the use of multidimensional deterministic population balance models or even stochastic models.

Restructuring of colloidal aggregates in shear environments

Existing theories for colloidal interaction largely neglect restructuring of colloidal aggregates. Under typical process conditions, however, hydrodynamic forces lead to structural changes which in turn affect downstream processing or product quality. Within the DFG Priority Program 1273 “Colloidal Processing”, it is theoretically investigated how colloidal aggregates act in a shear environment. The project is conducted in collaboration with Prof. M. Behr from RWTH Aachen. The RWTH group provides detailed analysis of the flow field around colloidal aggregates and the resulting hydrodynamic forces. The PDY group uses these detailed data to formulate models of reduced complexity. These reduced models are feasible to be integrated in discrete element simulations to resolve actual restructuring.

Currently, colloidal interaction forces do not consider tangential forces between primary particles. However, our findings indicate that the experimental restructuring behavior as reported in literature can not be explained without tangential forces. A new interaction model has been set up which successfully describes the observed behavior (Becker et al., 2008). As these models are validated in future work, they can be used to provide predictive restructuring rates to be incorporated in multidimensional population balance formulations.

Monte-Carlo simulation of complex aggregation phenomena

Particle aggregation can lead to complex shaped structures. Traditional deterministic population balance modelling does not allow for an adequate representation of these complex shapes. By the use of stochastic (Monte-Carlo) simulation techniques, the investigation of aggregate structure formation becomes feasible. However, special measures have to be taken to render computational effort acceptable. A hierarchical aggregate characterization has been introduced (see Fig. 2, left) which allows particle representations at different levels of detail (Briesen, 2006). With this hierarchical characterization, aggregate structures can be represented in a realistic manner. The available particle detail opens new opportunities towards advanced modelling of aggregation or breakage phenomena and product characterisation. As shown in Figure 2 (centre and right) it is e.g. capable of qualitatively reflecting the influence of different growth rates at the particle neck promoting stability of larger aggregates.

Current efforts focus on experimental validation using Paracetamol aggregates. Paracetamol has been chosen as a test system as it shows a strong variability in structure depending on solvent composition and process conditions.

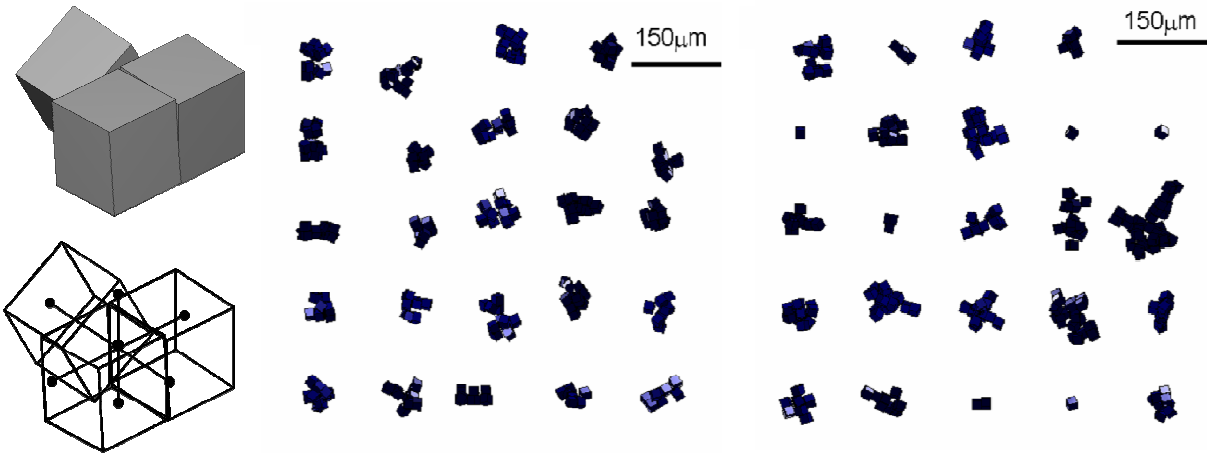

Fig. 2: Left: Detailed (top) and reduced (bottom) characterization (in terms of a system of seven point masses) of a simple aggregate. Simulated representative aggregate structures for different process conditions (center: low growth rate; right: high growth rate).

4.1.2 Modelling Concepts and Computational Methods for Distributed Systems

Dynamic analysis and computational methods

A collaborative subproject with the SCT group (Prof. Flockerzi) has been established to investigate the impact of the nonlinearity of nucleation and growth kinetics on the dynamics of precipitation reactors (Heineken et al., 2007; Voigt et al., 2008). It was found that open flow systems can exhibit oscillating behavior of the particle size distribution at certain operating parameters (see Fig. 3). Moreover, breakage and aggregation phenomena can strongly affect the process behavior. Then, the underlying partial differential equations involve integral operators which act on the full property space, thus are computationally expensive. Together with the group of Prof. Hackbusch (MPI for Mathematics in the Sciences, Leipzig) new numerical methods were developed which can handle those operators very efficiently (Koch et al., 2006, 2007, 2008).

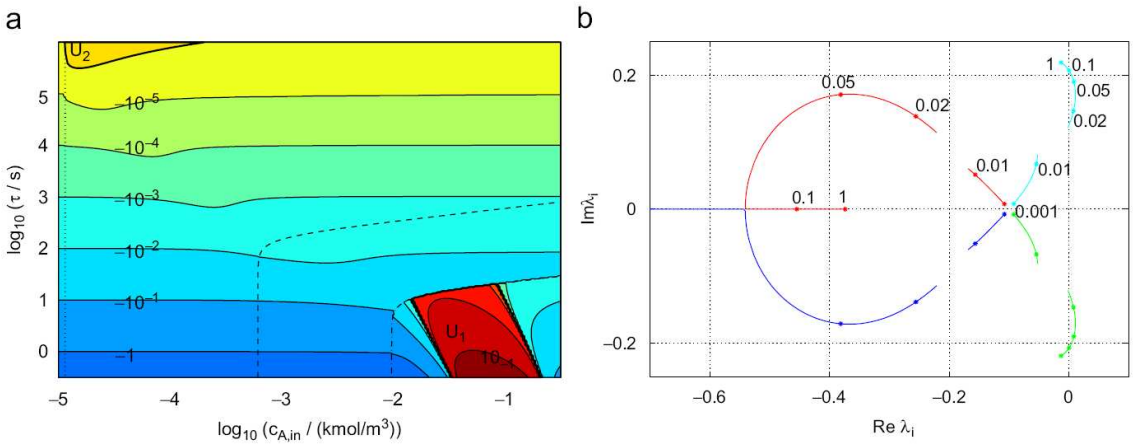

Fig. 3: Left: maximum of real part of eigenvalues as function of feed concentration $c_{A,in}$ and residence time τ. Right: eigenvalues for τ = 10 s and $c_{A,in}$ = 0.001…1 kmol/m^3.

Shape distribution modelling

During the last few years, the control not only of the crystal size, but also of the crystal shape, has attracted great attention in the scientific community. The crystal shape can be described by a geometrical property state vector, that is, the property distribution function of the crystal population is multidimensional. It is a well known fact that faceted crystals can exhibit growth anisotropy, i.e. crystals grow at different rates in different directions. Thus, in order to understand and control the dynamic evolution of the crystal shape distribution, we started to develop a theoretical concept which allows the incorporation of detailed single crystal information (e.g. growth rates) into a population balance model of the considered system (see Fig. 4). Based on this framework one can show, e.g. how the crystal shape distribution changes for adjustable operating parameters (Borchert et al., 2008). This theoretical work is conducted in close collaboration with Prof. Ramkrishna from Purdue University.

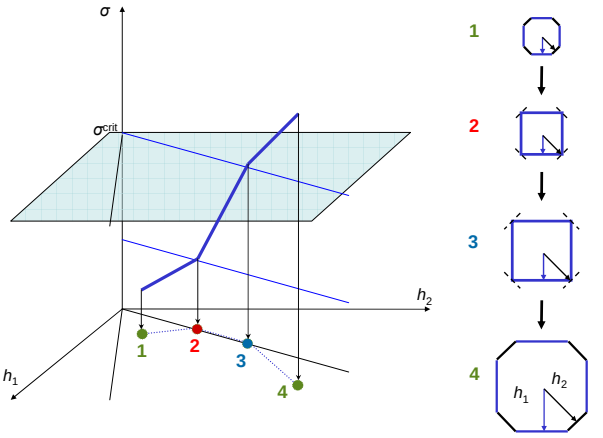

Fig. 4: Trajectory in state space for evolution of a simple crystal geometry. Face-specific growth rates change their ratio depending on the supersaturation level. The disappearance of one crystal face (states 2 and 3) results in lower dimensional dynamics. This has to be thoroughly accounted for in population balance modeling.

At the same time, the PCP group investigates crystal shape evolution experimentally, using urea crystallization and barium sulphate precipitation (Steyer, C. et al., 2008 a,b) as model systems. Face-specific crystal growth rates are determined in collaboration with the PCF group. In a further collaboration, model-based measurement techniques were developed and validated together with the PSD group (Mangold et al., 2008).

Coupling population balances and complex flow fields

The multidimensionality of the crystal state has to be further extended when considering not only the internal particle property but also its spatial position within a process. Then, the number density is defined in an at least 4-dimensional space (3 external coordinates + 1 internal property coordinate). Efficiently solving a coupled set of population balances along with the Navier-Stokes equations is a challenge

which the PCP group is currently tackling in the BMBF-funded joint research project SimPaTurS, together with three mathematical groups (Prof. Hackbusch / Leipzig, Prof. John / Saarbrücken, Prof. Tobiska / Magdeburg) and the PSD group. While in our former cooperation, together with the group of Prof. Thévenin from OvGU, the population balance was reduced to sets of moment equations (Öncül et al., 2006), in the SimPaTurS project the particle size distribution will be resolved in full detail using FEM discretization schemes (John et al., 2008).

4.1.3 Nanoparticle Populations in Emulsion Droplets

The vision of this project is to control the size and shape of nanoparticles (d_p < 100 nm) by means of an emulsion-assisted precipitation process, i.e. a process where water-in-oil droplets act as micro-reactors for particle synthesis (see Fig. 5). In order to initiate particle formation, dissolved reactants are contacted either via droplet coalescence or via diffusion from the continuous phase into droplets.

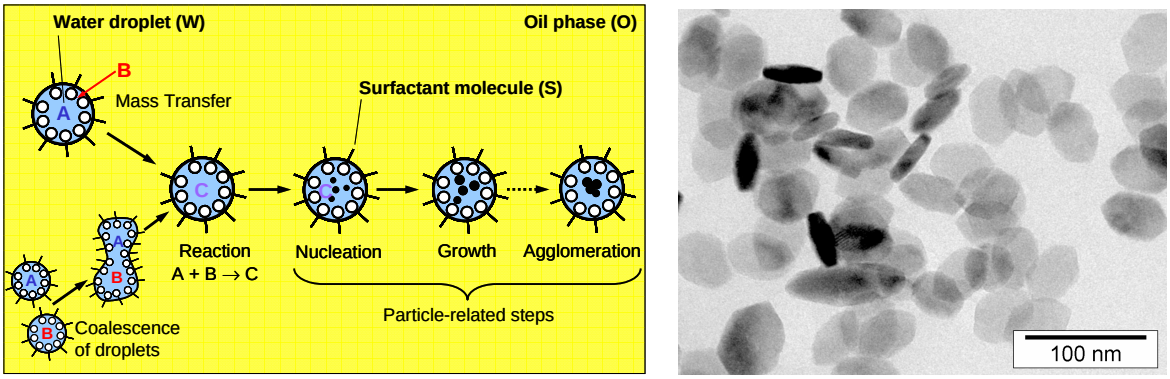

Fig. 5: Left: Scheme of emulsion-assisted particle precipitation process; right: hexagonal disc-shaped $BaSO_4$ nanoparticles synthesized in water-in-oil microemulsion (Niemann et al., 2008).

The coalescence-based method was investigated experimentally as well as theoretically for precipitation of barium sulfate and of calcium carbonate nanoparticles by using water-in-oil-microemulsion droplets having a diameter of 5 to 10 nm (Niemann et al., 2006). In systematic parameter studies, the feed ratio of dissolved reactants was identified as suitable control variable for the particle size (Adityawarman et al., 2008). Further experimental studies by Niemann (2008a) elucidated the nucleation and growth mechanisms in microemulsion droplet populations, in particular with regard to the influence of the droplet size on the size and shape of the resulting solid particles. The structure of the prepared nanoparticles was analyzed with High Resolution TEM in collaboration with the Center of Microstructure Physics at OvGU (Dr. P. Veit) and also with XRD in collaboration with the PCF group (Dr. Lorenz).

The dynamics of nucleation and growth of solid particles within an ensemble of droplets was successfully described by means of a multidimensional population balance model, being formulated in terms of discrete numbers of the reacting species which were stored within the water core of each droplet (Niemann et al., 2008b). A reduced variant of this model was coupled to a detailed fluid dynamic model of a semi-batch stirred tank reactor in collaboration with Prof. Thévenin at OvGU (Öncül et al., 2008). Based on this work it turned out that an emulsion-assisted precipitation process leads to a much more homogeneous macro-mixture of the reactor content.
Thus, nanoparticles with a very narrow size distribution can be produced via emulsion-assisted precipitation. But a key aspect for this technology is the ability to adjust the size of the emulsion droplets in order to tune the size of the solid particles to be produced. In this respect we found in a series of experimental studies that the properties of reverse microemulsions change significantly by substitution of water with ionic liquids (Gao et al., 2008 a,b,c,d). For instance, the addition of small amounts of water to the ionic liquid microemulsion bmimBF_4/TritonX-100/cyclo-hexane offers the possibility to adjust the droplet size from 10 to 30 nm.
Currently, the group's focus in this research project is on diffusion-based precipitation of metal oxide nanoparticles in kinetically stabilized water-in-oil-miniemulsions. This process is of high industrial relevance due to the fact that only 2 wt.% of surfactant are sufficient to generate 1 μm-sized droplets. Population balance modeling and first experiments performed by our group have shown that, at appropriate operating conditions, one is able to synthesize particles of about 20 nm size in miniemulsion droplets (Fricke et al., 2008). In order to be able to control the formation of particles in these droplets, it will be of fundamental importance to investigate the transport of reactant molecules across the droplet's oil-water interface at which surfactant molecules are dynamically adsorbing during particle formation. For this purpose, we will perform single-droplet experiments in a surface-tension measuring device and use the collected data for the validation of the formulated population balance model.

4.1.4 Biological Particle Systems

In biological particle populations, the individuals (e.g. cells) are often characterized by a high number of internal states. Moreover, the process kinetics on the single particle level (e.g. aggregation) is often not really understood. Both aspects make biological populations a very interesting and challenging topic from the point of view

of population balance modelling and analysis. This was the motivation for the PCP group to start research activities in this area.

Virus replication in mammalian cells is a process example from the BPE group, in which a high number of internal states has to be accounted for in order to describe the dynamics of cell infection. A possible technique to deal with such a high dimensional cell population is the Monte Carlo approach, as demonstrated successfully in a joint research activity together with the BPE group and the PSD group (Sidorenko et al., 2008 a,b).

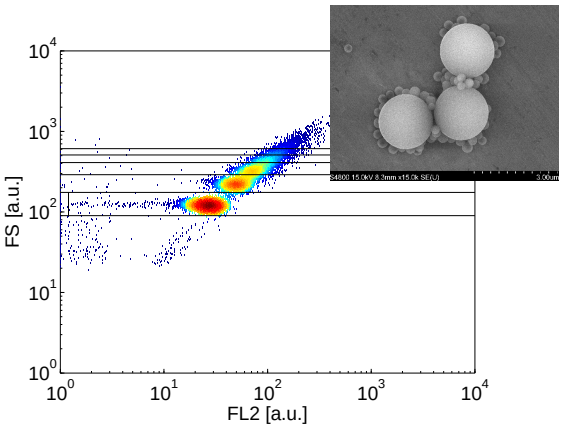

Fig. 6: 2-dimensional aggregate distribution presented as dot plot by flow cytometry. Inset: SEM image of heteroaggregate.

While the mathematical description of cell infection leads to growth-dominated population balances, the interaction of nanoparticles with cell populations – as they occur in targeted drug delivery – is dominated by homo- and heteroaggregation phenomena. For their quantitative analysis, our group has recently established flow cytometry as a key tool for the characterization of heteroaggregates (Rollié et al., 2008a). Via fluorescence labelling of one particle species, the state of aggregation can be determined as a multidimensional particle number distribution (see Fig. 6).

The flow cytometry data are used for the validation of a discrete population balance model which is currently under development in cooperation with the PDY group (Rollié et al., 2008b). In this model, the microscopic aggregation rates between particle clusters of different composition are based on the DLVO theory (van der Waals forces and electrostatic forces). But for a realistic description of heteroaggregation, the DLVO approach has to be extended to include solvation effects. In order to formulate realistic potential functions, we are currently planning measurements of interaction potentials at single aggregates by means of atomic force microscopy (AFM) in cooperation with Prof. Butt at the MPI for Polymer Research.

By now, experiments have been carried out with binary mixtures of polymer particles. In the next step, our goal is to transfer and apply the developed experimental techniques and modelling tools to a real biological problem, namely preferential cell targeting. With respect to drug targeting by nanoparticles, the above described

fundamental investigations may support the optimization procedures in carrier design and dosing strategies. The forthcoming biological experiments will be performed in cooperation with Prof. Naumann and his group at the medical school of OvGU.

4.2 Integrated Processes

4.2.1 Integration of Reaction and Distillation

In the time period covered by this report, the PCP group continued its research on the integration of chemical reaction and distillation processes into multifunctional units (Sundmacher et al., 2006). The focus of the work is on the development of methods and tools for the design and analysis of reactive distillation processes where liquid phase instabilities and networks of parallel and/or consecutive reactions give rise to complex system behavior. For the detailed analysis of the nonlinear process behavior and for optimal process design, rigorous simulation models have been developed and applied. Besides several principal case studies (Qi et al., 2006a, 2006b), also together with the PSD group (Gangadwala et al., 2007; Radulescu et al., 2008), this was in detail exemplarily done with regard to the development of two novel reactive distillation processes.

The first one deals with the synthesis of cyclohexanol by indirect hydration of cyclohexene. This reaction was chosen as an example that features limited mutual solubilities of the reactants, which leads to a strong influence of liquid phase instabilities on the process behavior. We could demonstrate the feasibility of our proposed novel process scheme consisting of two coupled reactive distillation columns (see Fig. 7) by means of residue curve map analysis (Steyer, F. et al., 2008), using our own experimentally determined kinetics for the reaction network (Steyer, F. et al., 2007). The subsequent rigorous column simulation studies revealed the unique advantages of the new process, namely the possibility to achieve full conversion of cyclohexene in the first column as well as high selectivities towards the desired product cyclohexanol in the second column (Katariya et al., 2008). The observed multiplicities that occur in the second column and the resulting small operating window (see Fig. 7) prove the necessity of detailed simulations based on reliable thermodynamic and kinetic data. In addition to the simulations, the experimental validation of the proposed concept is essential. Extensive measurements were carried out at our miniplant-scale reactive distillation setup for the first column of this process; experiments regarding the second column will be performed in the near

future. The collected experimental data – together with the simulations – allows for the extrapolation towards a full-scale plant and thus for bridging the gap between scientific work and industrial application.

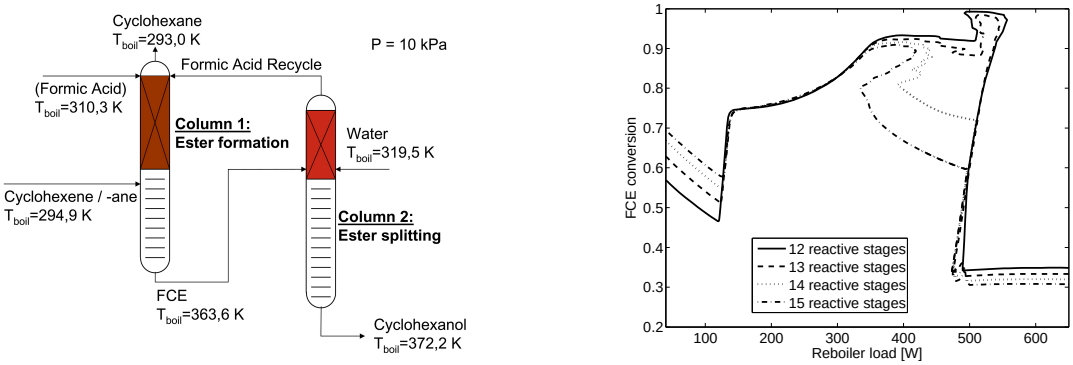

Fig. 7: Novel cyclohexanol production process based on coupled reactive distillation columns (left) and bifurcation diagram for the ester splitting column (right).

The second process of interest exemplifies the advantages – but also the complexity – of a reactive distillation process when a network of parallel and consecutive reactions is involved. As a technically relevant model reaction system, the production of isooctane from isobutene by dimerization and hydrogenation is investigated. Simulation and experimental studies (Talwalkar et al., 2006, 2007) have been carried out in close collaboration with the IIT Bombay in a joint research project that was funded by the Volkswagen Foundation. For feasibility studies (Kamath et al., 2006a), our potential singular point surface concept was extended to systems with non-condensable reactants (Ivanova et al., 2006). For the identification of an optimal process design, different process alternatives with different levels of integration have been evaluated systematically (Kamath et al., 2006b; Chalakova et al., 2008). Recently, the studies were extended to account for the processes at the catalyst level, i.e. the consideration of the intraparticle transport processes and their influence on the overall process behavior.

4.2.2 Integration of Reaction and Membrane Separation

This research project is embedded in the DFG research group 447 „Membrane Supported Reaction Engineering", which was established at OvGU in 2001 and continued until March 2008. The contribution of the PCP group was the theoretical analysis and experimental development of a novel integrated process, namely an electrochemical membrane reactor (EMR) for partial oxidation of light hydrocarbons. As the key element of this process, an oxygen ion conducting solid oxide membrane enables the precise dosing of oxygen via Faradaic coupling of the external electric

current and the internal oxygen mass transfer through the membrane (Chalakov et al., 2007a). Our theoretical reactor analysis revealed that a significant selectivity enhancement of the desired intermediate can be obtained by forced periodic operation (see Fig. 8), which can be easily established in an EMR via dynamic variation of the electric current (Munder et al., 2007).

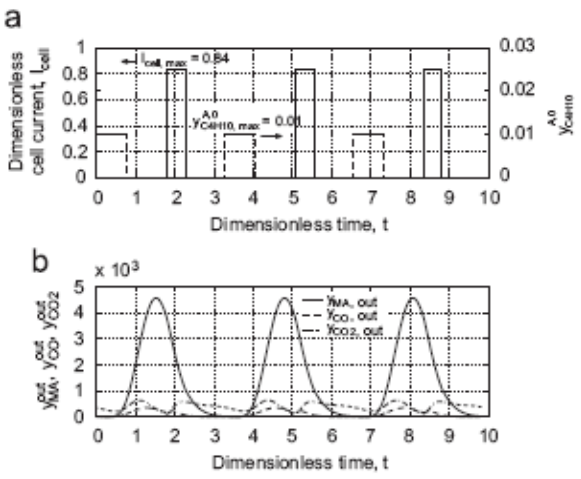

Fig. 8: Forced periodic operation of electrochemical membrane reactor: (a) square-wave input of cell current and 1% butane in N_2 (N_2 flush between pulses); (b) oxidation products at the reactor outlet (MA = maleic acid; CO; CO_2).

For the construction of the EMR, both the catalytic and electrical properties of the reactor materials are of crucial importance for optimal operation (Rihko-Struckmann et al., 2006). In collaboration with the group of Prof. Weiß at OvGU, the non-uniform spatial distribution of the VPO catalyst oxidation state, determined by XPS, was found to be related to the local oxygen-to-butane distribution in the reactor (Suchorski et al., 2007). The electrochemically pumped oxygen was found to be more reactive, but less selective to the desired intermediate product both in butane partial oxidation to maleic anhydride (Ye et al., 2006) and in ethane oxidative dehydrogenation to ethylene (Chalakov et al., 2007b). Detailed models which describe the oxygen ion transfer, the anodic and cathodic electrode reactions, and also the kinetics of gas phase reactions were developed and experimentally validated for the two mentioned model reaction systems (Munder et al., 2007; Chalakov et al., 2008).

4.2.3 Low-Temperature Fuel Cells

The first objective of our research in this project is to understand the nonlinear dynamic behavior of low-temperature fuel cells by means of mathematical process models, and to validate these models experimentally, particularly under dynamic operating conditions. The second objective is to develop new techniques for the dynamic analysis of the investigated fuel cells, namely polymer electrolyte membrane fuel cells (PEMFC), direct methanol fuel cells (DMFC) and enzymatic fuel cells (EFC).

Proton Exchange Membrane Fuel Cells (PEMFC)

PEMFC possess a multitude of sources that can result in a nonlinear operating behavior. There are strongly nonlinear rate laws for the electrochemical reactions taking place. Along with this, mass transport within the various fuel cell layers follows nonlinear kinetics, due to coupled driving forces acting on multicomponent mixtures. Moreover two-phase flow can occur due to the condensation of product water. As one of the most important results in this project, we discovered bistable current-voltage characteristics of PEMFC being operated with low humidified feed gases (Hanke-Rauschenbach et al., 2008a). In a theoretical and experimental analysis the PEMFC was found to exhibit current-voltage curves with pronounced local extrema in a parameter range that is of practical interest when operated at constant feed flow rates (see Fig. 9). This causes steady-state multiplicities in the potentiostatic and rheostatic operation mode. The reason for this behavior is an autocatalytic water production mechanism. At small relative humidity of the feed gas, the current-voltage curve possesses an isolated high-current branch, the existence of which we recently confirmed experimentally.

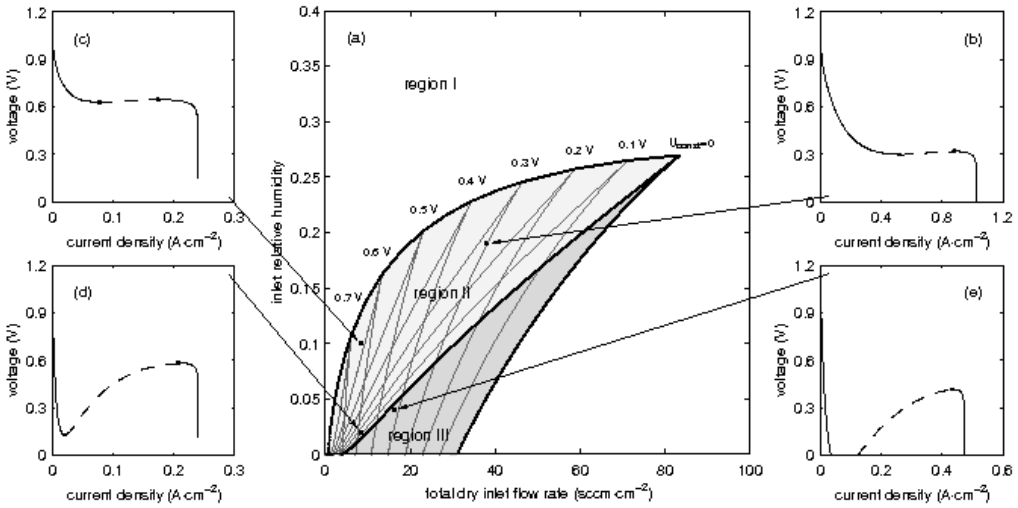

Fig. 9: Two-parameter bifurcation map for potentiostatic operation and corresponding current-voltage curves in different regimes. Dashed lines indicate unstable branches of i-U curves at potentiostatic operation.

Direct Methanol Fuel Cell (DMFC)

The DMFC has been extensively studied by the PCP group at different levels of complexity. Investigations at the system level (Schultz et al., 2007a) were complemented by detailed analysis of transport phenomena, such as methanol crossover (Schultz et al., 2006) and convective transport in anode flow fields (Krewer et al., 2007a; Song et al., 2008). A suitable anode reaction mechanism was identified from

steady state polarization experiments and AC impedance spectroscopy, based on a state space model formulation and its transformation into the frequency domain (Krewer et al., 2006a). The kinetic investigations were performed in collaboration with Prof. Christov from UCTM, Sofia, Bulgaria. The identified rate expressions were integrated into a DMFC model for predicting the fuel cell response behavior to perturbations of methanol feed concentration (Schultz et al., 2007b) and changes of the electric current (Krewer et al., 2006b, 2007b). Additionally, the kinetic model was used for the characterization of anode catalysts which were prepared by different synthesis methods in collaboration with Prof. Bönnemann from the MPI for Coal Research in Mülheim (Vidaković et al., 2007a). Furthermore, CO stripping was established as a fast dynamic method for the determination of the electrochemically active catalyst surface area (Vidaković et al., 2007b, 2008). In the future, all DMFC research activities will be exclusively continued by the OH group (Dr. Krewer) with focus on the integration of the DMFC into portable energy systems (see section 4.3.1 of this report).

Enzymatic Fuel Cells (EFC)

Enzymes are highly selective and active catalysts which may become an alternative to noble metal catalysts in electrochemical applications. As a first example of this kind, our group investigated a multi-functional unit which integrates a fuel cell stack and an enzymatic electro-membrane reactor, in a cooperative project with Prof. Hasal from ICT Prague, Czech Republic (Kukula et al., 2006).

Moreover, the PCP group started research activities on enzymatic fuel cells (EFC) which might be used as a power source for implantable medical devices, using glucose as fuel. The application of enzymes as catalysts enables a membrane-less fuel cell construction. One of the major challenges in this field is the efficient coupling of enzymes to electrode surfaces (Yu et al., 2007; Ivanov et al., 2008a). Therefore, different methods for enzyme-electrode coupling have been screened in the first phase of this sub-project. Certain charge transfer complexes have been identified as suitable coupling element (Ivanov et al., 2008b). In the next phase, the focus of this sub-project will be on the design and construction of an EFC prototype, followed by model-supported investigations of the dynamic response behavior to changes of glucose concentration. Cooperation partners in this project are Dr. Grammel (SBI group) and Prof. Schwaneberg from the Jacobs University Bremen (isolation of new enzymes for glucose oxidation).

Methods for fuel cell diagnosis and model discrimination

Nonlinear frequency response analysis (NFRA) is a quasi-stationary method for the identification of nonlinear systems, which is based on the excitation by harmonic input signals with larger amplitudes. NFRA can be regarded as a generalization of electrochemical impedance spectroscopy (EIS), which is a well established method in electrochemistry. To the best of our knowledge, we are the first group that is going to develop and apply NFRA for the investigation of electrochemical systems. This project is being done in cooperation with Prof. Petkovska (University of Belgrade, Serbia). The main advantage of NFRA is the fact that a set of frequency response functions (FRF) is obtained, which contain different information on the properties of the investigated system. Thus, the second and higher order FRF can be used for model discrimination and also for precise parameter estimation.

Currently, we have used NFRA for the discrimination of kinetic models in electrochemical methanol oxidation. For this purpose, higher order FRF have been derived and analyzed (Bensmann et al., 2008). It clearly turned out that the second order FRF of rivaling models show qualitative differences which enable discrimination between them (Fig. 10). As a second example, the PCP group has investigated NFRA as method for PEM fuel cell diagnosis (Kadyk et al., 2008). The goal of this study was to distinguish between different PEMFC failures, namely membrane dehydration, pore flooding and CO poisoning. The analysis revealed that the second order FRF provides sufficient information to clearly separate CO poisoning from other effects whereas dehydration and flooding can be clearly distinguished by the first order FRF.

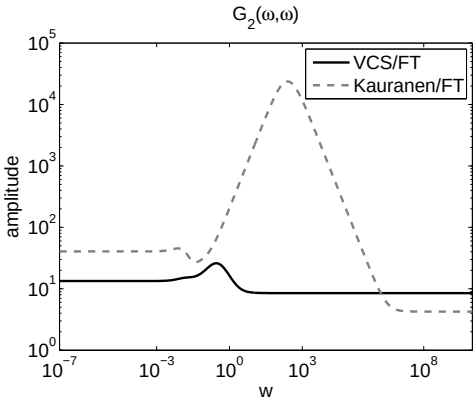

Fig. 10: Second order FRF for electrochemical methanol oxidation at a PtRu catalyst, predicted by two competing models.

4.2.4 High-Temperature Fuel Cells

This project focuses on the model-based design and analysis of the Molten Carbonate Fuel Cell (MCFC) as a challenging example for a highly integrated process unit (Heidebrecht et al., 2006). During the first part of the report period, an existing single cell model has been extended to include an indirect internal reforming unit (IIR) and has been validated with experimental data, collected from an industrial scale MCFC

plant (Gundermann et al. 2006, 2008a,b). Based on this model, a state estimator was developed together with the PSD group and tested at the same industrial fuel cell facility (Grötsch et al., 2006). These results were obtained in a joint research project funded by the BMBF and published as a monograph (Sundmacher et al., 2006), which we published together with our project partners (PSD group, Prof. Pesch's group at Bayreuth University, company IPF Ltd. in Magdeburg, company CFC Solutions Ltd. in Ottobrunn).

Based on the results obtained thus far in the BMBF project, the development of a predictive MCFC model has been continued in a bilateral collaboration of the PCP group with the company CFC Solutions, with financial support from the BMWi. Model development is based on a multi-scale approach in order to transfer information about the microscopic transport processes at the reforming catalyst level onto the mesoscopic level, i.e. a complete internal reforming (IIR) unit of the MCFC (see Fig. 11). This reformer model has been combined with several fuel cells to a symmetry unit which contains all relevant information to study the behavior of the whole MCFC stack (Pfafferodt et al., 2008). On each scale, experimental data from the industrial partner are used for parameter estimation. The application of this multi-scale model yields valuable insight, e.g. into the temperature distribution being established by interaction of the endothermic reforming reactions and the exothermic electrochemical reactions. For further intensification of these modelling activities, since August 2008 the DFG is funding a three-year project which deals with the development of advanced models for the porous electrodes and their interaction with the liquid electrolyte.

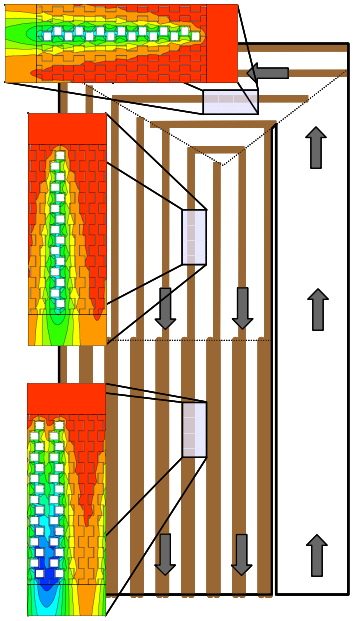

Fig. 11: Coupling of microscopic and mesoscopic scales in the MCFC's reformer model.

4.3 Coupled Processes

4.3.1 Junior Research Group Portable Energy Systems (Otto Hahn Group)

The group was founded in January 2008 and aims to contribute solutions to current issues of portable fuel cell systems, such as autonomous operation and miniaturization, by combined theoretical system analysis and experimental system develop-

ment. In system analysis, the complex transport and reaction processes within fuel cell systems will be investigated, and the outcome is used to develop and evaluate new components and concepts for fuel cell systems. The approach is also aiming at the evaluation of system analysis tools with regard to their practical applicability.

System Analysis of Direct Methanol Fuel Cell Systems

Direct methanol fuel cells (DMFC) are seen as the favorite choice for portable systems (Fig. 12). Optimal water and temperature management is essential for small, autonomously operating fuel cell systems, since they do not have access to external resources such as a water supply facility. This subproject focuses on conducting system analysis and optimization of portable DMFC systems. A model library of system components is set-up to build a reference DMFC system. Mass and heat fluxes inside this system quantify its behaviour at standard and at extreme conditions. The identification of critical system parameters is followed by the development of strategies to improve robustness of the heat and water balance in DMFC systems. Model-based evaluation of new system concepts is closely combined with experimental validation.

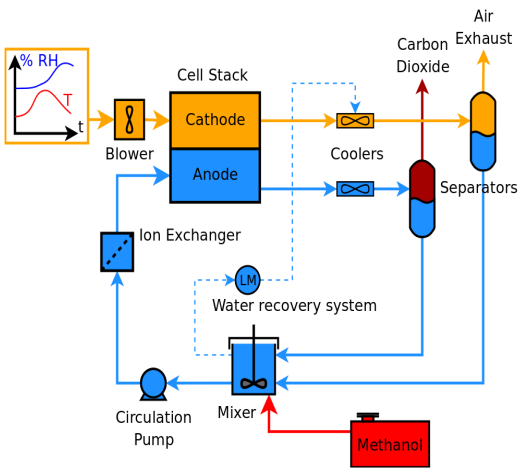

Fig. 12: Direct Methanol Fuel Cell system.

Components for Direct Methanol Fuel Cell Systems

Changes in environmental or operating conditions are major challenges to portable fuel cells, since they cause disturbances in the water and thermal balance. In order to guarantee autonomous operation also under extreme conditions, water and thermal management issues need to be addressed during the design stage of portable fuel cell systems. This subproject investigates components that serve to improve water and thermal management in DMFC systems. Examples are orientation independent gas-liquid separation units to remove carbon dioxide or to recycle product water from the cathode exhaust, and micro heat exchangers. Experimental and model-based studies evaluate gas-liquid separation techniques based on membrane technology and capillary forces with regard to selectivity, dependence on surrounding conditions and robustness. Identified material and separator designs are subsequently built into micro separator units and their effect on complete DMFC systems is evaluated.

4.3.2 PROBIO: Process Systems for Biomass Conversion into Electricity

This joint research project is performed together with two institutions from the Fraunhofer society, namely the IFF in Magdeburg and the IKTS in Dresden. It was started in 2007 with financial support from the innovation fund of the president of the Max Planck Society. The scientific aim of PROBIO is to develop an integrated process which combines biomass gasification for hydrogen generation in a fluidized bed with electricity production by hydrogen oxidation in fuel cells (PEMFC or SOFC). The product gas from biomass gasification contains many impurities which have to be removed in a number of primary (dust, tar, etc.) and secondary cleaning steps (carbon monoxide), as illustrated in Figure 13. The main contributions of the PCP group to this project are model-based system design, experimental and theoretical investigation of process alternatives for secondary gas cleaning, and analysis of the CO-tolerance of high-temperature PEMFCs.

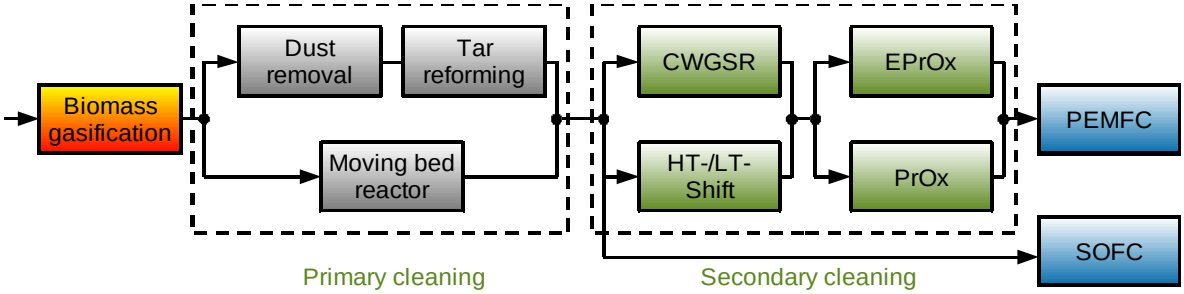

Fig. 13: Generalized flow sheet of the PROBIO process illustrating alternative steps for gas cleaning.

With regard to secondary gas cleaning, the PCP group is currently analyzing two innovative process units which are able to reduce the CO content of the gas mixture very efficiently, namely a cyclic water gas shift reactor (CWGSR) and an electrochemical reactor for preferential CO-oxidation (EPrOx). Our research activities on these two reactors are briefly highlighted in the following.

CWGSR: Cyclic Water Gas Shift Reactor

The CWGSR is based upon the periodic reduction of a fixed bed of iron oxide by use of the pre-cleaned product gas coming from biomass gasification which contains CO and H_2, and the subsequent re-oxidation with steam by which very pure hydrogen can be produced for the PEMFC (Fig. 14). As fixed bed material, the mixed oxide Fe_2O_3-$Ce_{0.5}Zr_{0.5}O_2$ has been developed which combines high activity with high oxygen storage capacity and low degradation rates. This material was characterized in detail using TGA, XRD, TPR, TPD, REM, $C^{18}O$ isotope exchange and FT-IR

techniques (Galvita et al., 2007a,b; 2008a). The hydrogen generated during the re-oxidation phase contains a very low concentration of CO, and is directly applicable to the PEMFC (Galvita et al., 2008b). At very deep reduction of iron oxide in the CWGSR, some carbon can be deposited due to the Boudouard reaction. Thus, CO traces in the hydrogen gas can be observed during the re-oxidation phase (Galvita et al., 2008c). Our current research activities focus on the quantitative description of the reduction/re-oxidation mechanisms, on the formulation of a suitable reaction kinetic model (Heidebrecht et al., 2008a) and on model-based reactor design (Heidebrecht et al., 2008b,c).

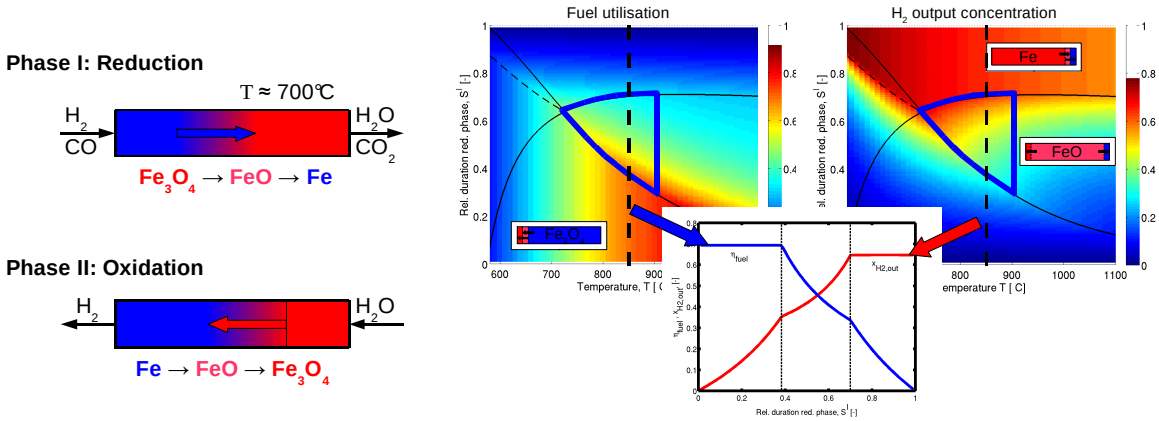

Fig. 14: Principle of cyclic water gas shift reactor (left); predicted fuel utilization and H_2 concentration (right).

EPrOx: Electrochemical Preferential Oxidation of CO

Classical preferential oxidation of CO (PrOx) in a hydrogen-rich gas down to a level of 10 - 20 ppm is carried out in a process unit which typically constitutes up to 15% of the overall volume of a fuel cell system. Furthermore, the undesired oxidation of hydrogen reduces the overall process efficiency. Recently, Zhang and Datta (JES 152, 2005, A1180) suggested a novel electrochemical preferential oxidation process (EPrOx) which might have the potential to replace PrOx. The working principle of the EPrOx reactor is similar to the PEM fuel cell. But unlike that type of cell, a bimetallic catalyst (PtRu/C) is used at the anode which accelerates the selective electro-oxidation of CO. The EPrOx reactor can exhibit autonomous potential oscillations in the galvanostatic operating mode (Zhang and Datta, JES 149, 2002, A1423). As an extension of the work of these authors, our group investigates coupled EPrOx reactors. Cascading of two or more of these reactors becomes meaningful when the amount of CO to be oxidized is increasing (i.e. at increasing flow rate of the fuel gas or increasing CO concentration at the inlet of the EPrOx device). With the help of a mathematical model, we predicted (Hanke-Rauschenbach et al., 2008b) and experi-

mentally proved (Lu et al., 2008a,b) the crucial importance of the configuration of the electrical connection of the cells.

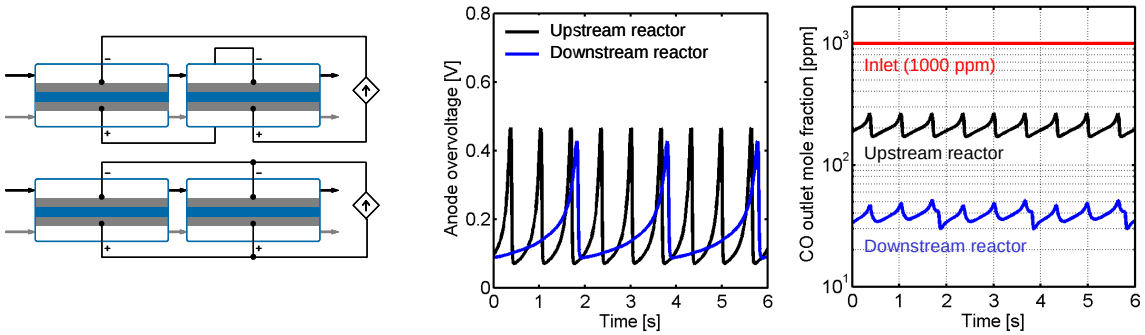

Fig. 15: Coupled EPrOx reactors in series and parallel connection (left); oscillations of voltage (middle) and CO concentration (right) for series connection.

While two EPrOx reactors in electrical parallel connection exhibit almost the same CO conversion as a single one, a series connection yields an increase of up to 20%. Thus, for EPrOx scale-up, electrical stacking of the reactors will be more promising than increasing the active area of a single cell. The reason for this behavior is due to the fact that the oscillation period of CO oxidation adjusts to the CO level in the feed gas. A parallel electrical connection of two reactors forces them to oscillate at identical frequency which is always a compromise between the optimal frequencies of the two reactors. It turns out that the downstream reactor enslaves the upstream reactor. But in an electrical series connection, each of the reactors can adjust its frequency independently.

4.3.3 Elementary Process Functions Methodology

This project was started in 2007 as a theoretical study of a methodology for the systematic analysis and design of coupled chemical processes from the molecular level up to the plant level. A successful intensification of a chemical process requires a holistic view of the process and a systematic debottlenecking, which is obtained by identifying and eliminating the main transport resistances that limit the overall process performance and thus can be considered as rate-determining steps of the process. Within this project we want to overcome the classical concept of “unit operations”. Instead, we propose a more rigorous function-based approach that focuses on the underlying fundamental physico-chemical driving forces and fluxes (Freund et al., 2008a; Sundmacher et al., 2008). For this purpose, we decompose the chemical process into functional modules that fulfill specific tasks in the course of the process. When a volume element passes such a functional module, its state is

changed as a result of the fluxes that occur. The functional modules itself can be further decomposed and represented by specific generalized flux vectors and elementary process functions (Fig. 16). These are the basis vectors in the thermodynamic state space which span the attainable region for the process route. Using this approach we can design the whole process route from the starting point (educts) to the final point (products) by selectively adjusting the fluxes at each point. The developed theoretical framework can be applied for the investigation of process routes at different levels. The most detailed level is the single particle level, at which we consider phenomena on the scale of individual molecules. At the next level we consider molecule populations that build up a thermodynamical phase (particle population level). In a process, the thermodynamical phase(s) are embedded into individual process units (process unit level). Usually, a whole process consists of several coupled process units. The interconnection between the individual process units and thus the overall process flowsheet can finally be analyzed at the superordinated plant level. This multi-level approach is especially helpful in the systematic analysis and classification of suitable measures for process intensification (Freund et al., 2008b).

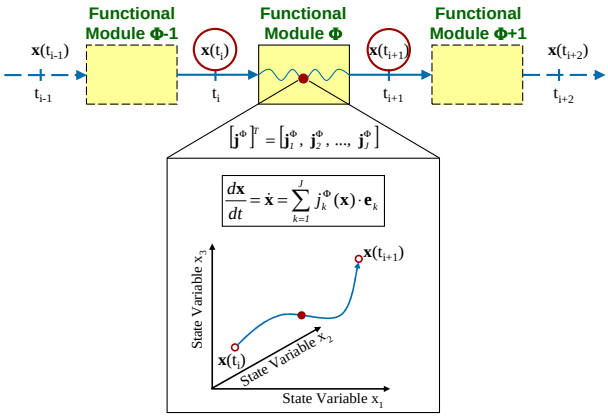

Fig. 16: Process route "inside" a functional module, determined by the generalized flux vector $\mathbf{j}^{\Phi}$ and the elementary process functions $\mathbf{e}_k$ (basis vectors in state space).

5 Selected Teaching Activities and Ph.D. projects

5.1 Teaching Activities at OvGU

- Course on Process Dynamics (Voigt)
- Course on Process Systems Engineering (Freund, Sundmacher)
- Course on Process Simulation (Freund)
- Course on Process Optimization (Heidebrecht)
- Course on Experimental Design and Parameter Estimation (Sundmacher)
- Course on Population Balance Systems (Voigt)
- Course on Molecular Modeling (Voigt)
- Course on Fuel Cell Technology (Hanke-Rauschenbach, Heidebrecht)
- Course on Electrochemical Process Engineering (Vidaković)

5.2 Additional Teaching Activities

The PCP group continued to coordinate the established NaT-working project (NaT stands for “Natural and Engineering Sciences”) together with the systems theory group at OvGU (Prof. Findeisen). This project is an initiative to attract students from regional high schools into engineering programs at OvGU. Furthermore, each spring and fall, the PCP group organizes a one-week laboratory course to introduce 30 to 40 high school students to chemical and systems engineering.

5.3 Supervision of Ph.D. Theses

(* Ph.D. students of the OvGU group)

Adityawarman, D.*	$BaSO_4$ nanoparticle precipitation in microemulsions	Finished in 2007
Ahamed, R.	Nonlinear dynamics of gas-liquid-liquid reactors	Since 2006 (in preparation)
Bensmann, B.*	Load management of fuel cell auxiliary power units	Since 2008 (in preparation)
Borchert, C.	Crystal morphology evolution	Since 2007 (in preparation)
Chalakov, L.*	Ethane partial oxidation in SEMR	Since 2003 (submitted)
Chalakova, M.*	Coupled chemical reactions in a reactive distillation process for the production of isooctane	Since 2002 (submitted)
Fricke, M.	Emulsion-assisted nanoparticle precipitation	Since 2006 (in preparation)
Gundermann, M.*	Validation of a fuel cell model using an industrial MCFC	Finished in 2007
Hanke-Rauschenbach, R.	Hierarchical modeling and nonlinear analysis of PEMFC	Finished in 2007
Hertel, C.	Conceptual design of biomass-fed fuel cell systems	Since 2007 (in preparation)
Huang, Y.S.	Mass transfer effects on reactive separation processes	Finished in 2005
Ivanov, I.	Enzymatic fuel cells: Experiments and modelling	Since 2007 (in preparation)
Kadyk, T.*	Nonlinear frequency response analysis of PEMFC	Since 2006 (in preparation)
Krewer, U.	System-oriented analysis of the DMFC	Finished in 2005
Lemoine, R.	Model-based control of stationary PEMFC systems	Since 2007 (in preparation)
Munder, B.	Controlled partial oxidation of hydrocarbons in SEMR	Since 2001 (submitted)
Niemann, B.	Population balance modelling of precipitation in microemulsions	Finished in 2008
Oettel, C.	Analysis of high-temperature PEM fuel cells (HT-PEM)	Since 2007 (in preparation)
Peschel, A.	Optimal design of reaction-separation processes	Since 2007 (in preparation)

Pfafferodt, M.*	Multiscale modelling of fuel cells	Since 2004 (in preparation)
Piewek, S.	Physically motivated MCFC electrode models	Since 2008 (in preparation)
Rauscher, F.	Experimental analysis of nanoparticle synthesis in microemulsions	Finished in 2006
Rollié, S.	Flow cytometry analysis and population balance modeling of aggregation processes in cell-particle systems	Since 2006 (in preparation)
Song, Y.	3D analysis and model reduction of low temperature fuel cells	Since 2001 (in preparation)
Steyer, C.*	Morphology evolution of particles in bulk precipitation	Since 1999 (in preparation)
Steyer, F.	Production of cyclohexanol from cyclohexene via a coupled reactive distillation process	Since 2000 (submitted)
Ye, K.	Model-based analysis of reaction-separation processes	Since 2008 (in preparation)

In addition, K. Sundmacher served as supervisor for several diploma projects and as a member of several habilitation and doctoral committees.

6 Selected Memberships, Appointments, Awards

B. Bensmann

2007 Solvay Scholarship for Research Project at Belgrade University/Serbia

C. Borchert

2006/2007 DAAD Scholarship for Masters Project at Purdue University/USA

H. Briesen

2007-2008 W2 Head of Junior Research Group Population Dynamics

2008 Habilitation at RWTH Aachen for Model-based Particle Technology

11/2008 W3 Professorship Process Systems Engineering at TU Munich

H. Freund

2007 Chem. Eng. Sci. (Elsevier) Most Cited Paper 2003-2006 Award

since 2008 Chair Elect of AIChE Proc. Dev. Division Area Process Intensification

since 2008 Int. Adv. Comm. Member WCCE-8 Symposium Process Intensification

P. Heidebrecht

2007 Chem. Eng. Sci. (Elsevier) Most Cited Paper 2003-2006 Award

02-04/2008 DAAD Fellowship for Research Project at Carnegie Mellon Univ./USA

C. Hertel

2008 DECHEMA Chemical Engineering Student Award 2008

U. Krewer

2006 Karin Witte Award for best PhD thesis at OvGU in 2006

2006 Gold medal in the Samsung SDI Paper Award 2006/Korea

2007 Otto Hahn Medal 2007 of Max Planck Society

since 2008 W2 Head of Otto-Hahn Group Portable Energy Systems

K. Sundmacher

since 1999 Full Professor for Process Systems Engineering at OvGU

since 2001 Scientific Member and Director for Process Engineering at MPI

since 2003 Executive Editor of the journal Chemical Engineering Science

2003-2004 Managing Director of MPI

since 2006 Member of Selection Committee of the German Scholarship Foundation

since 2006 Ed. Advisory Board of Ullmann's Encyclopedia of Industrial Chemistry

since 2007 Chair of GAFOE (German-American Frontiers of Eng. Symposia)

since 2008 Advisory Board Member of Tongji University and ECUST, P.R. China

7 Future Directions

Population balance systems

The application of population balance models accounting for crystal shape is a hot topic in the chemical engineering community. Thus, the PCP group will further intensify its modelling efforts in this direction. Design of experimental setups with which one can observe the evolution of shape distributions will be extended. Optimal control and trajectory planning with regard to shape distribution optimization is another theme we have currently started working on.

With regard to the research activities of the PDY group, Dr. Briesen just recently accepted the offer for a W3 Professorship on Process Systems Engineering at the Technical University of Munich. Nevertheless, the collaboration between Dr. Briesen and the PCP group will continue with focus on stochastic modelling of virus replication, experimental characterization of aggregate shapes, and multi-dimensional population balance modelling of aggregation phenomena.

Regarding biological systems, we will further extend our collaboration with the medical school of OvGU (Prof. Naumann) concerning model-based methods for the optimal design of stimulus-response experiments on mammalian cells, both on the single-cell level as well as on the cell population level.

In addition, a new BMBF joint project on biological particle systems will be started in early 2009 together with the BPE and PCF groups. In this project, the PCP group will

model and simulate membrane affinity adsorption by means of population balance models, whereby using component-lumping strategies for model reduction.

Integrated Processes

Our research activities in this area will be directed towards integrated micro-process units. In particular in the area of micro-separators, there are still many open questions for fundamental research. The PCP group has just started to design a novel micro-membrane distillation unit and is currently planning to establish a micro-process laboratory in order to extend experimental investigations in this field.

With respect to fuel cells, the research on the DMFC will be continued by the OH group (Dr. Krewer) with emphasis of system-level aspects, while the PCP group itself will focus on EFC, PEMFC and MCFC. In the last field, BMWi-funding of a “light-house project” is expected within the National Innovation Program (NIP) on Hydrogen Technology and Fuel Cells (due to start at the end of 2008).

Coupled Processes

In its second year, 2009, the OH group (Dr. Krewer) will focus on the extension of the experimental basis for all forthcoming investigations. Studies on diagnosis and control of flooding in semi-passive and passive fuel cell systems are scheduled to start in March 2009.

Regarding the PROBIO project, our research activities on the CWGSR and the EPrOx reactor will be continued with emphasis on model-assisted studies to support optimal process design. A pilot-scale CWGSR is set up to investigate the long-term dynamics and stability of this reactor. In the beginning of 2010, the second phase of PROBIO is planned to start, where a complete biomass-fed fuel cell power plant will be erected and operated in the MPI’s Technikum.

Also in the area of renewable energy technologies, from 2008 until 2010 the new research project NEWE (Electrochemical Energy Converters in Energy Networks) will be performed in collaboration with the Electrical Engineering Department at OvGU, funded by the research ministry of the Federal State of Saxony-Anhalt.

Furthermore, we recently attracted a BMBF-funded pilot study on the thermodynamic analysis of storage concepts for renewable energies by means of the conversion of CO2 to liquid components. This study is planned to form the basis for a joint research project which is to be established together with several external partners from academia and industry.

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Please note that this list does not represent a complete list of publications.

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Research Group:

Process Synthesis and Dynamics (PSD)

Prof. Dr.-Ing. Achim Kienle

This report covers the period from January 2006 to September 2008.

1 Introduction

The research of the Process Synthesis and Dynamics group is concerned with the synthesis, analysis and control of complex systems. It provides and develops methods and tools for computer-aided modeling and simulation, nonlinear system analysis, process design and process control including state estimation and optimal experimental design. Traditionally, the main field of application are chemical processes and fuel cell systems. Besides, there is a growing interest in biological systems, where we also see a large potential for our methods and tools.

The PSD group closely cooperates with the chair for Automation/Modeling at the Otto-von-Guericke University. Both groups are headed by Achim Kienle, who holds a professorial position at the university and has also been appointed by the Max Planck Society as an external scientific member of the MPI.

The PSD group has strong interactions with most of the other research groups at the MPI. Together with the SBI group it develops the modeling and simulation software ProMoT/Diva/Diana. Together with the PCF group we are working on the design of advanced chromatographic processes. In this context, we are also involved in the new INTENANT project, which is concerned with the integration of reaction and separation steps to improve the production of pure enantiomers and which is funded by the European Commission. Together with the PCP group we are working on nonlinear analysis and control of fuel cell systems and synthesis of integrated reaction distillation processes, among others. Together with Dietrich Flockerzi from the SCT group, theoretical problems are studied arising from nonlinear dynamics and model reduction of chemical processes. Together with the BPE group we are working on the population balance modeling of virus replication in mammalian cell cultures.

The majority of the PSD group is funded by third parties. Besides the EU it attracts funds from various sources like the national science foundation DFG, the federal ministry of education and research, as well as the local ministry of education and research in Saxony-Anhalt. A detailed list is given in the next section.

During this period of report, the PSD group has published more than 40 research papers in international scientific journals and finalized successfully 7 Ph.D. projects.

2 Members of the Research Group

Head of the group:

Prof. Dr.-Ing. Achim Kienle, professor at the Otto von Guericke University Magdeburg, and external scientific member of the Max Planck Institute

Secretary:

Carolyn Mangold (working part time for PSD group)

Senior Researchers:

Michael Mangold (MPI, since March 1998)

Malte Kaspereit (MPI, since January 2005)

Ph.D students:

Andre Franz (MPI, since January 2008)

Jignesh Gangadwala (DFG, August 2002 – February 2008)

Markus Grötsch (BMBF, since March 2005)

Mykhalylo Krasnyk (BMBF, since January 2004)

Javier Garcia Palacios (IMPRS, since October 2006)

Ganesh Paramasivan (IMPRS, since April 2008)

Rene Schenkendorf (DynSys, since March 2007)

Subramaniam Swernath (IMPRS, since August 2008)

Fan Zhang (DFG, April 2003 – October 2008)

N.N. (EU)

Funding:

MPI – Max Planck Institute

DFG – German Science Foundation (Deutsche Forschungsgemeinschaft)

BMBF – Federal Ministry of Education and Research

IMPRS – International Max Planck Research School

DynSys – Excellence Cluster ‘Dynamic Systems in Process Engineering and Biomedicine’, Ministry of Education and Research of the state Saxony Anhalt

EU – European project INTENANT

Group members at the university:

Ilknur Disli, Marco Fütterer, Thomas Müller, Stefan Palis, Steffen Sommer

In addition to this, the PSD group received input from several guest scientists including Prof. Ramkrishna (Purdue University), Prof. Pushpavanam (IIT Madras), Prof. Mahajani (IIT Bombay), Profs. Radulescu and Paraschiv (University of Ploesti), Prof.

Svjatnyj (TU Donezk), Dr. Kulkarni (NCL Punai) and hosted a number of Master and Ph.D. students from the U.S., India, Romania and Ukraine within joint research projects with funding provided by MPI, DAAD, the Humboldt foundation and the Pro3 competence network for chemical engineering.

3 Survey of Research Projects

Fig. 1 gives a survey of the research projects of the PSD group. As stated above, we provide and develop methods and tools for computer-aided modeling and simulation, nonlinear system analysis, process design and process control including state estimation and optimal experimental design. These methods are applied to various fields of application from the different projects areas of the Max-Planck-Institute as indicated in Fig. 1. A short description of the projects is given subsequently.

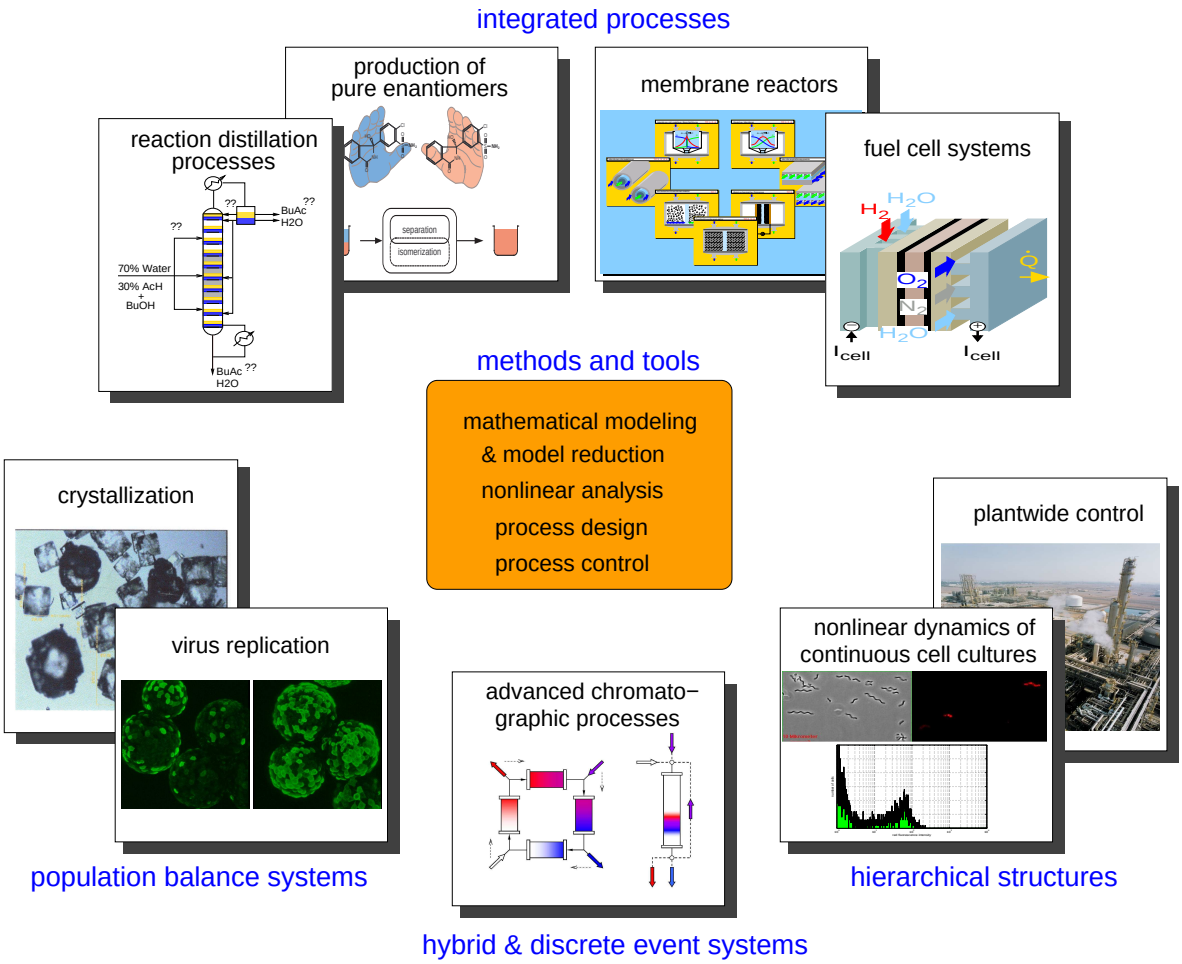

Fig. 1: Overview of the research projects of the PSD group

Tab. 2: Project Areas

Project Area: Integrated Processes

Project:	**Synthesis of Combined Reaction Distillation Processes**
Abstract:	Chemical reaction and separation by distillation can be integrated on the flowsheet level in various ways. Typical examples are reactive distillation columns and/or nonreactive distillation columns with side reactors and/or pre reactors. MINLP optimization can be used to determine optimal process configurations and optimal operating conditions. However, due to nonconvexity, this class of problems is usually difficult to solve for the global optimum. Together with the Weismantel group (Institute of Mathematical Optimization, OvGU) new global optimization strategies are being explored (Gangadwala et al., 2006; Haus et al., 2006; Gangadwala et al., 2008; Jach et al.,2008) and innovative applications are proposed (Gangadwala et al., 2006; Gangadwala and Kienle, 2007; Gangadwala et al., 2007a, 2007b, 2008). Recently, focus has been on new reactive distillation processes for removing acetic acid from waste waters. Together with Dietrich Flockerzi from the SCT group, theoretical problems are being studied arising from model reduction of reactive distillation processes (Flockerzi et al., 2007).
Researchers:	J. Gangadwala
Partners:	SCT group, PCP group, R. Weismantel/ OvGU, S.Mahajani/ IIT Bombay (India), G. Radulescu/ University of Ploesti (Romania)
Funding:	DFG research group FOR 468
Start:	2003-2009

Project:	**Synthesis of Integrated Processes for the Production of Pure Enantiomers**
Abstract:	Enantiomers are isomers of extreme relevance in the production of pharmaceuticals and fine chemicals. The objective of this project is to improve the production of pure enantiomers by clever combinations of reaction and separation steps. First promising results were obtained for the combination of racemization reactions and chromatographic separation techniques including SMB, SSR, and elution chromatography (Kaspereit et al., 2008; Garcia Palacios et al., 2008a, 2008b). Further details are given in the research highlights section.
Researchers:	M. Kaspereit, J. Garcia Palacios, S. Swernath, N.N.
Partners:	M. Kaspereit, J. Garcia Palacios, S. Swernath, N.N.
Funding:	MPI, IMPRS, EU within the INTENANT project
Start:	2006

Project:	**Model Based Design of Fuel Cell Systems - Analysis of Multiplicities and Dynamic Instabilities**
Abstract:	Potential sources of instabilities and nonlinear behavior in high temperature and low temperature fuel cells are being studied. For high temperature fuel cells, the focus is on temperature-induced pattern formation (Mangold et al., 2006; Krasnyk et al., 2007b). In low temperature fuel cells, the control of the liquid water content is a special challenge for process operation (Hanke-Rauschenbach et al. 2008). In low temperature fuel cells, the control of the liquid water content is a

	special challenge for process operation (Grötsch et al., 2008; Grötsch and Mangold, 2008). The formation of liquid water has been identified as a potential source of steady state multiplicities and instabilities. The project is part of the project network PEMDesign that focuses on the scale transition from the investigation of microscopic phenomena to the simulation of fuel cell systems. Further details are given in the research highlights section.
Researchers:	M. Grötsch, M. Krasnyk, M. Mangold
Partners:	Albert-Ludwigs-Universität Freiburg, Fraunhofer Institut ISE Freiburg, Fraunhofer Institut ITWM Kaiserslautern, Ruprecht-Karls-Universität Heidelberg, Universität Karlsruhe (TH)
Funding:	BMBF
Start:	2005-2007

Project:	**Control of Fuel Cell Systems**
Abstract:	This project studies advanced control methods for fuel cell systems. In the past, focus was on high temperature fuel cells (Mangold and Sheng, 2006; Grötsch, Mangold, Sheng and Kienle, 2006; Grötsch, Gundermann, Mangold, Kienle and Sundmacher, 2006; Sheng, Mangold, and Kienle 2006). Recently, the focus has shifted to PEM fuel cells as well as their interaction with power conditioning units (DC/DC or DC/AC converters). As a novel approach for control of fuel cells, passivity based controllers are considered. Principles of irreversible thermodynamics are applied to derive suitable Lyapunov functions, which is the main challenge in this approach (Mangold, Borngräber and Grötsch, 2008a). Further details are given in the research highlights section.
Researchers:	M. Grötsch, M. Mangold
Funding:	MPI
Start:	2007

Project:	**Dynamics of Membrane Reactors**
Abstract:	Within this joint research project different types of membrane reactors are investigated theoretically and experimentally. As an example, partial oxidation of hydrocarbons is considered. The objective is to improve selectivity of these reactions at high conversions. The contributions of the PSD group focus on mathematical modeling including parameter estimation and optimal experimental design of different reactor concepts (Mangold et al., 2008; Zhang, 2008) and an investigation of nonlinear dynamics and pattern formation in membrane reactors (Zhang et al., 2006; Mangold et al., 2008).
Researchers:	F. Zhang, M. Mangold
Funding:	PCF group, members of DFG research group 447
Start:	2002-2008

Project Area: Hierarchical Structures

Project:	**Synthesis of Plantwide Control Strategies**
Abstract:	The project is concerned with the synthesis of plantwide control strategies for multi-unit chemical plants using methods from discrete and mixed-integer optimization. Depending on the metric unit used to measure the performance of the control strategy, this will lead to complex optimization problems with linear or nonlinear, static or dynamic constraints. To handle such complexity, hierarchical decomposition strategies can be applied.
Researchers:	G. Paramasivan
Partners:	R. Weismantel, Institute for Mathematical Optimization, OvGU
Funding:	IMPRS
Start:	2008

Project:	**Nonlinear Dynamics of Continuous Cell Cultures**
Abstract:	In this project the effect of metabolic regulation on nonlinear behavior of continuous cell cultures is studied experimentally and theoretically. For the theoretical description cybernetic models as introduced by Ramkrishna and Co-workers were used in a first step (Vasudeva, Zeyer, Kienle, and Pushpavanam, 2008). It has been shown that these models are able to predict the effect of regulation on the overall behavior at least qualitatively. Focus in this project is on two application examples. The first is concerned with multiple steady states in PHB (bioplastic) production in alcaligenes eutrophus and rhodospirillum rubrum. The second is concerned with self sustained oscillations in escherichia coli through activation of the methylglyoxal pathway. Results are also compared with more detailed models developed in the SBI group.
Researchers:	A. Franz, I. Disli
Partners:	SBI group, Prof. Ramkrishna/ Purdue University, Prof. Pushpavanam/ IIT Madras
Funding:	MPI, MaCS (Magdeburg Center for Systems Biology)
Start:	2007 (MaCS)

Project Area: Hybrid and Discrete Event Systems

Project:	**Design of Simulated Moving Bed Chromatography**
Abstract:	Existing design methods for SMB processes are limited to cases where pure products are desired. For limited product purities, expensive model-based optimization was used. Within the project, existing design methods based on equilibrium theory are extended in various directions including also limited product purities (Kaspereit et al., 2007; Kaspereit, 2008; Forssen et al., 2008). The approach is first developed for systems with Langmuir adsorption isotherms and will be extended to more complex isotherm models and operating modes. Further details are given in the research highlights section
Researchers:	M. Kaspereit

Partners:	A. Seidel-Morgenstern (MPI), D. Flockerzi (MPI), T. Fornstedt (Uppsala University, Sweden)
Funding:	MPI
Start:	2006

Project:	**Design and Optimization of Steady State Recycling Chromatography**
Abstract:	Steady State Recycling (SSR) Chromatography is a periodic, pseudocontinuous operating mode for binary chromatographic separations involving a recycle. It is particularly attractive for enantioseparations, since it can overcome yield limitations. However, its full potential is yet unexploited, mainly due to a lack of proper design tools. Within the project, equilibrium theory is applied to devise a simplified method for optimal design of SSR processes under arbitrary purity requirements. Results are verified in experimental studies (Sainio and Kaspereit, 2008). Further details are given in the research highlights section.
Researchers:	M. Kaspereit
Partners:	A. Seidel-Morgenstern (MPI), T. Sainio (TU Lappeenranta, Finland)
Funding:	German Academic Exchange Service until 12/2008, MPI
Start:	2006

Project Area: Population Balance Systems

Project:	**Simulation of Particle Populations in Turbulent Flows**
Abstract:	The interaction of crystal formation and fluid dynamics is considered. An industrial crystallizer for urea production is used as an application example. The project's objectives are the development of reduced models for process control purposes.
Researchers:	M. Krasnyk, M. Mangold
Partners:	Otto-von-Guericke University, PCP group, MPI for Mathematics in the Sciences, Leipzig, Saarbrücken University, BASF AG
Funding:	BMBF
Start:	2007

Project:	**State Estimation of Particulate Processes**
Abstract:	The online measurement of property distributions is a challenging task, especially if the particles are very small. Often, only measurements of integral properties like total particle concentration or average particle size are available online. Even if there are distributed measurements, e.g. of chord length distributions, the reconstruction of size distributions is still hard due to the ill-posedness of the inverse problem. This project aims at overcoming these difficulties by model based measurement techniques. Nonlinear Kalman filters and moving horizon estimator schemes are used to combine the information content of online measurements with model predictions of population balance models (Mangold et al., 2006, 2007, 2008b). Further details are given in the research highlights section.

Partners:	PCP group
Funding:	MPI
Start:	2006

Project:	**Virus Replication during Vaccine Production**
Abstract:	Together with the BPT group, influenza virus infection in host-cell cultures of vaccine production processes are studied theoretically and experimentally. The theoretical work aims at mathematical modeling using population balances (Müller et al., 2008) or kinetic Monte-Carlo approaches (Sidorenko et al., 2008a, 2008b). The objective is to gain a better understanding of the biological processes that can be used for process optimization in the longer term. Further details are given in the research highlights section.
Researchers:	T. Müller
Partners:	BPT group, PCP group (A. Voigt)
Funding:	DynSys
Start:	2006

Method Projects

Project:	**Advanced Computer Tools for Process Modeling and Nonlinear Analysis**
Abstract:	Within this project, the modeling and simulation software ProMoT/Diva/Diana is being developed. Recently, emphasis has been on advanced computational methods and tools for nonlinear analysis of large scale systems involving the direct computation of bifurcation points and higher order singularities, recursive projection methods and some parallel computing (Krasnyk et al., 2007a, 2006; Dosta et al., 2008).
Researchers:	M. Krasnyk, M. Dosta, M. Mangold
Partners:	SBI group
Funding:	MPI, Pro3
Start:	1998

Project:	**Optimal Experimental Design for Structure and Parameter Identification**
Abstract:	New methods for optimal experimental design are developed in this project. Emphasis is on biological applications (Schenkendorf et al., 2008a, 2008b). Further details are given in the research highlights section.
Researchers:	R. Schenkendorf, M. Mangold
Partners:	SBI group
Funding:	DynSys
Start:	2007

4 Research Highlights

4.1 Design of Advanced and Integrated Chromatographic Processes

Preparative chromatography is well-established in manufacturing of pharmaceuticals, fine chemicals, or biotechnological products. However, the optimal design of chromatographic processes is not trivial, in particular for modern, rather complex operating modes. This is due to the discrete events involved in such processes and the underlying, typically nonlinear, thermodynamic equilibria. Below a summary is given on developed methods that largely simplify the design of such processes. Another area of work is the integration of chemical reaction and chromatographic processes, which is of high interest in, for example, the production of pure enantiomers. Investigations are devoted to the synthesis and the optimal design of corresponding new process schemes.

Design of SMB Chromatography for Arbitrary Purity Requirements

Simulated moving bed (SMB) chromatography is employed a series connection of several chromatographic columns, which are switched periodically against the fluid flow. This “simulates” a counter-current of liquid and solid phases and - if designed properly - allows for a continuous separation at often superior performance when compared to classical single-column chromatography.

Established design approaches assume a real counter-current between solid and liquid phases (i.e., a true moving bed, TMB). The most accepted method derived on this basis is the “triangle theory”[1]. The method is based on equilibrium theory (i.e., it neglects dispersion and assumes local equilibrium) and predicts optimal values for the design parameters (i.e., the four internal flow rates of the process).

The existing design methods hold for the case of complete separation only (i.e., both product streams are pure). This is a limitation, since pure products are not always required and separation costs generally decrease significantly with decreasing purity requirements. Conventionally, SMB separations with lower purity requirements are designed using numerically expensive optimizations of a process model. Furthermore, typically only two of the four design parameters are optimized (i.e., the flow rates in the four zones of such unit).

[1] G. Storti, M. Mazzotti, M. Morbidelli. AIChE J. 39 (1993), p. 471-492.

On the basis of equilibrium theory, it was possible to derive a simple design procedure for SMB processes under nonlinear conditions for arbitrary purity requirements of the two product streams (Kaspereit et al., 2007). Conventional optimizations using an equilibrium-dispersive TMB model were carried out. The results are summarized in Fig. 2 and demonstrate the mentioned enhancement of the performance at lower purities. It could also be demonstrated that for such incomplete separations the optimization of all four flow rates (instead of only two) creates an additional benefit (symbols in Fig. 2). The developed equilibrium design method accurately reproduces these obtained optima (Fig. 2, solid lines).

The new equilibrium design method is much simpler to apply than the “optimization approach”, since it requires the solution of a simple system of nonlinear equations. The approach, thus, also allows for extensive parametric studies and, for example, the design of processes combining, for example, SMB chromatography and crystallization (Kaspereit et al., 2005).

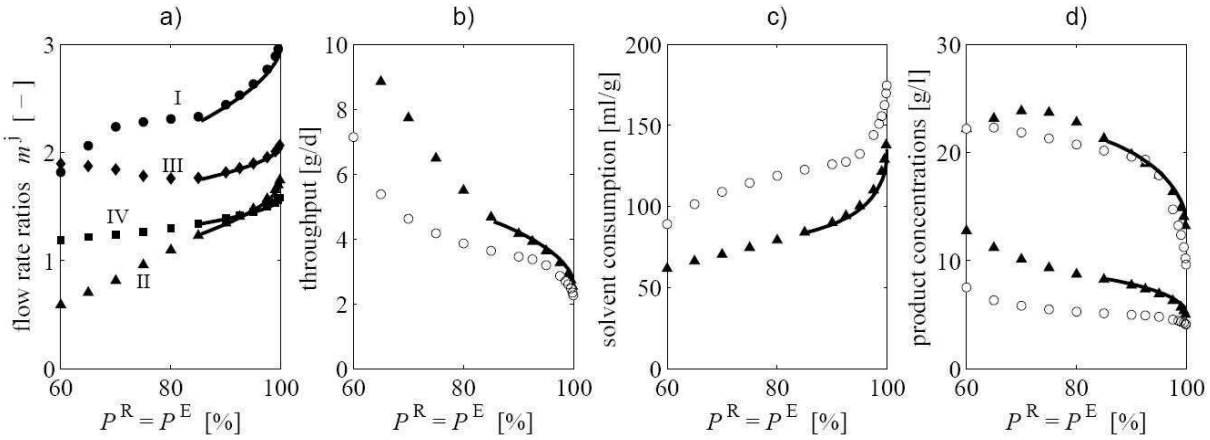

Fig. 2: Comparison between optimization results (symbols) and the equilibrium design method (lines) for TMB processes with different purity requirements. a) Design parameters (dimensionless flow rates) as function of the desired outlet purity; b) through d) corresponding process performance. Open symbols - optimization of flow rates in zones II and III; filled symbols - optimization of all four flow rates; lines – developed design method.

Analysis and Design of SSR Chromatography

While SMB chromatography is becoming state-of-the-art, many separations rely on single column processes. Typically, these are characterized by a strong tradeoff between key performance parameters like productivity and recovery yield. Recycle-based schemes are a viable option to overcome this limitation. One of them is the socalled steady state recycling (SSR). In this process, larger injections can be performed. These entail unresolved fractions at the column outlet, which are mixed with

fresh feed and then re-injected. After a number of repetitions the SSR mode reaches a periodic steady state, similar to the SMB process.

Although SSR chromatography is commercialized, the established design method is of empirical nature[2]. It applies only for complete separation; however, it neither guarantees the desired pure products, nor does it predict the steady state. The challenge in designing an SSR system lies in its difficult process dynamics and the need to determine four different cut times. A rather involved equilibrium-based procedure exists[3], but holds, again, only for complete separation.

Using equilibrium theory, it was possible to develop a comparably straightforward method for analysis and design of SSR chromatography under arbitrary purity or yield requirements (Sainio and Kaspereit, 2008). The approach applies to SSR processes in so-called mixed-recycle operation and exploits the fact that (for systems with Langmuirtype adsorption isotherms) basically only the front of the concentration profiles depends on the injection conditions. The method directly predicts optimal design parameters and the steady state without the need to perform dynamic simulations. It therefore largely simplifies optimal design of SSR processes and simultaneously enables evaluation of process performance.

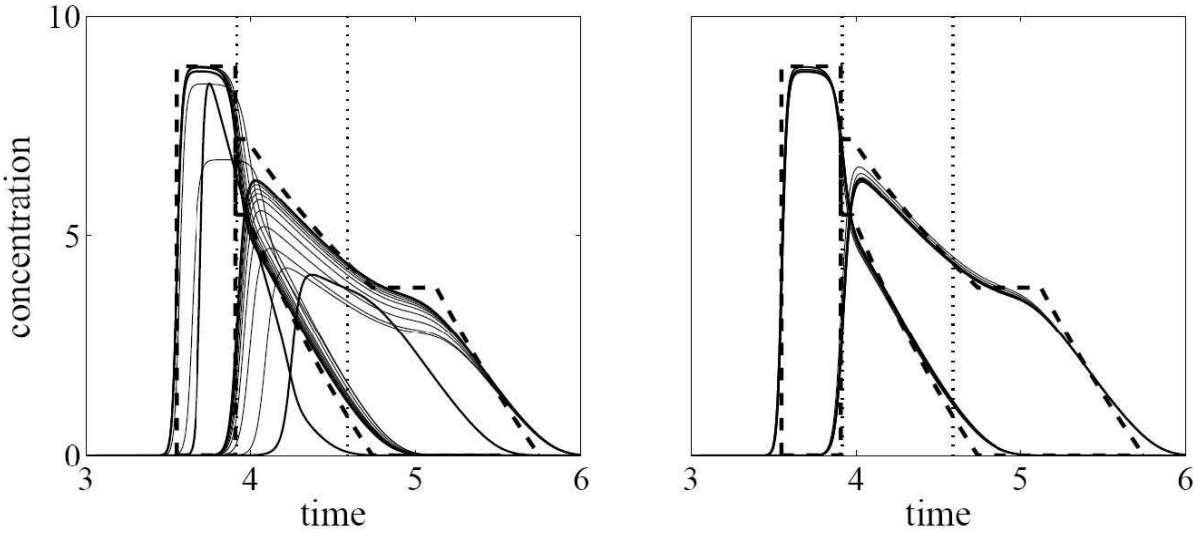

Fig. 3: Model-based comparison of two different startup strategies for SSR chromatography. Left - conventional "bottom-up" strategy. There, the process is initiated by a small injection. The concentration profiles (solid lines) build up gradually until steady state is attained after about 25 cycles. Right – rapid startup by "full" injections using the predicted steady state composition (dashed lines). Steady state is attained after 4 cycles.

[2] C. M. Grill. J. Chromatogr. A 796 (1998), p. 101-113.

[3] M. Bailly and D. Tondeur. Chem. Engng. Sci. 37 (1982), p. 1199-1212.

A significant benefit of the method is the prediction of the steady state. As demonstrated in Fig. 3, this can be utilized to shorten the pronounced startup period of SSR processes by performing the first injection using the predicted steady state concentration.

Integration of Chromatography and Enantiomerization Reactions

Enantiomers are stereoisomers structured like mirror-images. Since usually only one enantiomer has the desired physiological effect (the other might be ineffective or harmful), pure single enantiomers are of high importance in the pharmaceutical and fine chemical industries. A main problem related to obtaining a pure enantiomer is that its direct selective synthesis is often not feasible or too expensive. Conventional synthetic procedures are less expensive, but they deliver the 1:1 mixture of the two enantiomers, which necessitates a subsequent separation. Obviously, the overall yield reachable by this approach is limited only to 50 %. Therefore, it is desirable to combine enantioseparations with an interconversion (i.e., isomerization or enantiomerization) of the undesired form. This could be performed using either i) a classical reactor-separatorrecycle system or ii) via an integrated process that combines reaction and separation within a single unit. Ultimately, such process schemes would allow for a yield of 100 %. These studies will be further intensified within the joint European research project INTENANT, starting in June 2008. There, focus is on the synthesis of optimal process schemes and development of shortcut methods for performance evaluation for systems that incorporate different unit operations (like, for example, chemical synthesis, chromatography, crystallization, enantiomerization).

Since chromatography is one of the major technologies for enantioseparations, initial investigations were devoted to its combination with enantiomerizations. Relevant physico-chemical parameters (i.e., competitive adsorption isotherms and reaction kinetics) were determined experimentally for the model substance chlorthalidone (Kaspereit et al., 2008). As shown in Fig. 4, the parameters enable a quantitative dynamic modeling of both chromatography and the (homogeneously catalyzed) enantiomerization. First results were obtained for a flowsheet-integration of SSR chromatography and enantiomerization in the recycle stream (Kaspereit et al., 2008).

Based on the experimental results, a systematic theoretical study was performed of integrated processes that combine SMB chromatography and enantiomerization. Process schemes of different degrees of integration were developed and investigated

by optimization of corresponding process models. Concepts studied range from reactor-separator-recycle systems to fully integrated schemes with distributed reactivity. The most important result is that the latter can be significantly superior to the former (as well as to conventional side reactor systems). However, this requires spatially distributing the reactivity within the apparatus (Kaspereit et al., 2008; Garcia Palacios et al., 2008a). The framework and methods that were recently developed from equilibrium theory for reactive systems (Grüner and Kienle, 2004; Grüner et al., 2006; Sainio et al., 2007) allow for a full explanation of the obtained results. Currently, different options are under investigation that allow for such spatial distribution (Garcia Palacios et al., 2008b).

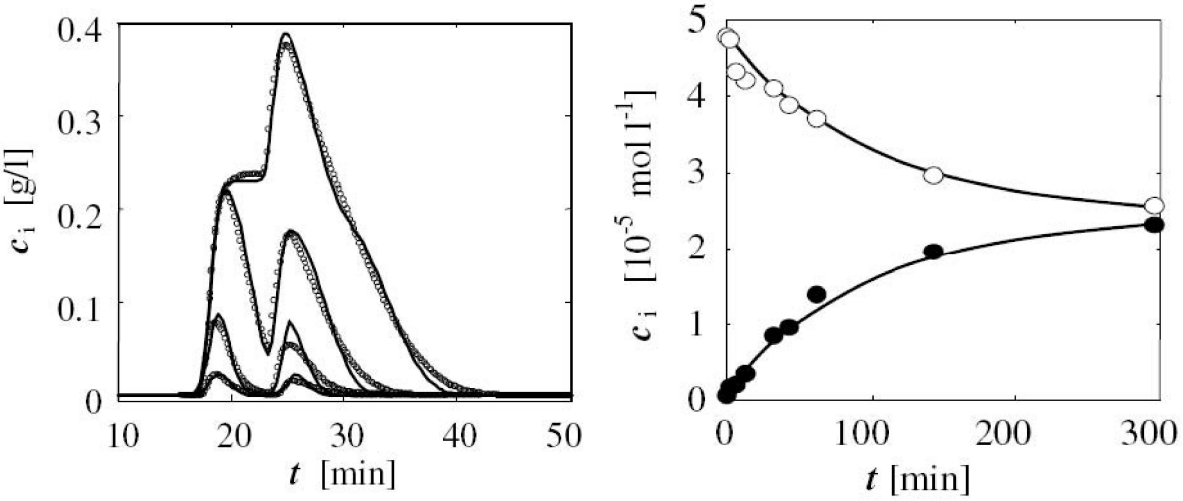

Fig. 4: Comparison between experiments (symbols) and simulations (lines) for the model system. Left - chromatograms for different injection volumes. Right – example for enantiomerization reaction at 40°C.

4.2 Model Based Analysis and Control of PEM Fuel Cells

Development and Analysis of Two-Phase PEM Fuel Cell Models for Process Control

Proton exchange membrane fuel cells (PEMFCs) are an attractive technology for the efficient generation of electrical energy. The behavior of low temperature fuel cells is strongly affected by the water content of the cell: on the one hand, insufficient humidity of the membrane reduces its conductivity; on the other hand, condensed liquid water may block the gas channels in the diffusion layers and the active electrode areas. Therefore, water management is a crucial part of the process control of PEMFCs. In order to do model based process control, there is a clear need for reliable two-phase PEMFC models of reasonable complexity, but there is a lack of such models in available literature. A low-order two-phase PEMFC model has been devel-

oped during this project. In a first step, a spatially distributed model with discretization in through-plane direction (Fig. 5) was investigated by bifurcation analysis (Grötsch et al., 2008). It could be shown that the formation of liquid water causes multiple

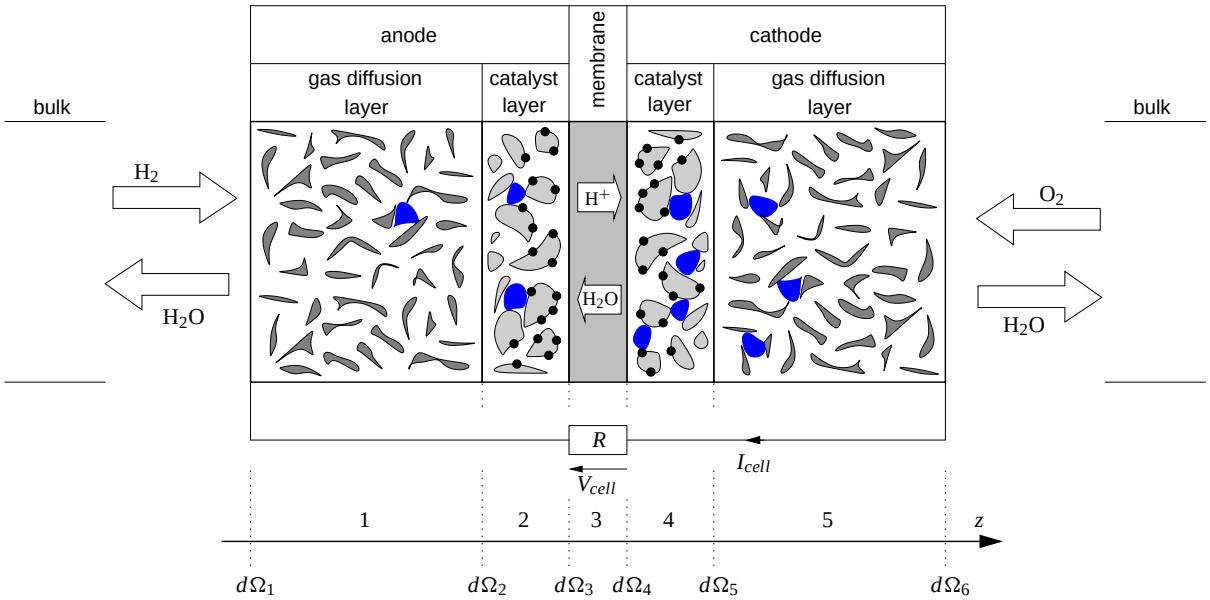

Fig. 5: Structure of the analyzed two-phase PEMFC models: gas diffusion layers, catalysts layers and membrane are considered; z is the space coordinate of the distributed model.

steady states especially under operation conditions with high current densities. In a second step, a low order lumped model was derived from the distributed model (Grötsch and Mangold, 2008). As can be seen from Fig. 6, the qualitative and the quantitative behavior of the reduced model and the detailed model agree well, and the reduced model appears suitable for model based process control purposes.

Passivity Based Control of PEM Fuel Cells

PEMFCs are highly integrated nonlinear processes with complex interactions between external electrical load and electrochemical reactions as well as heat, mass and charge transport inside the cell. Furthermore, the number of manipulated and controlled variables in PEMFCs is rather large. Controlled variables typically are the cell voltage, the cell power, the cell temperature and the water content; manipulated variables may be the gas flows and gas compositions on anode side and on cathode side, or the amount of heat removed by the cooling system. These properties pose challenges for the controller design of PEMFCs. The choice of a suitable control structure and the pairing of inputs and outputs is nontrivial. The majority of publications on PEMFC control takes a rather empirical approach to solve this problem.

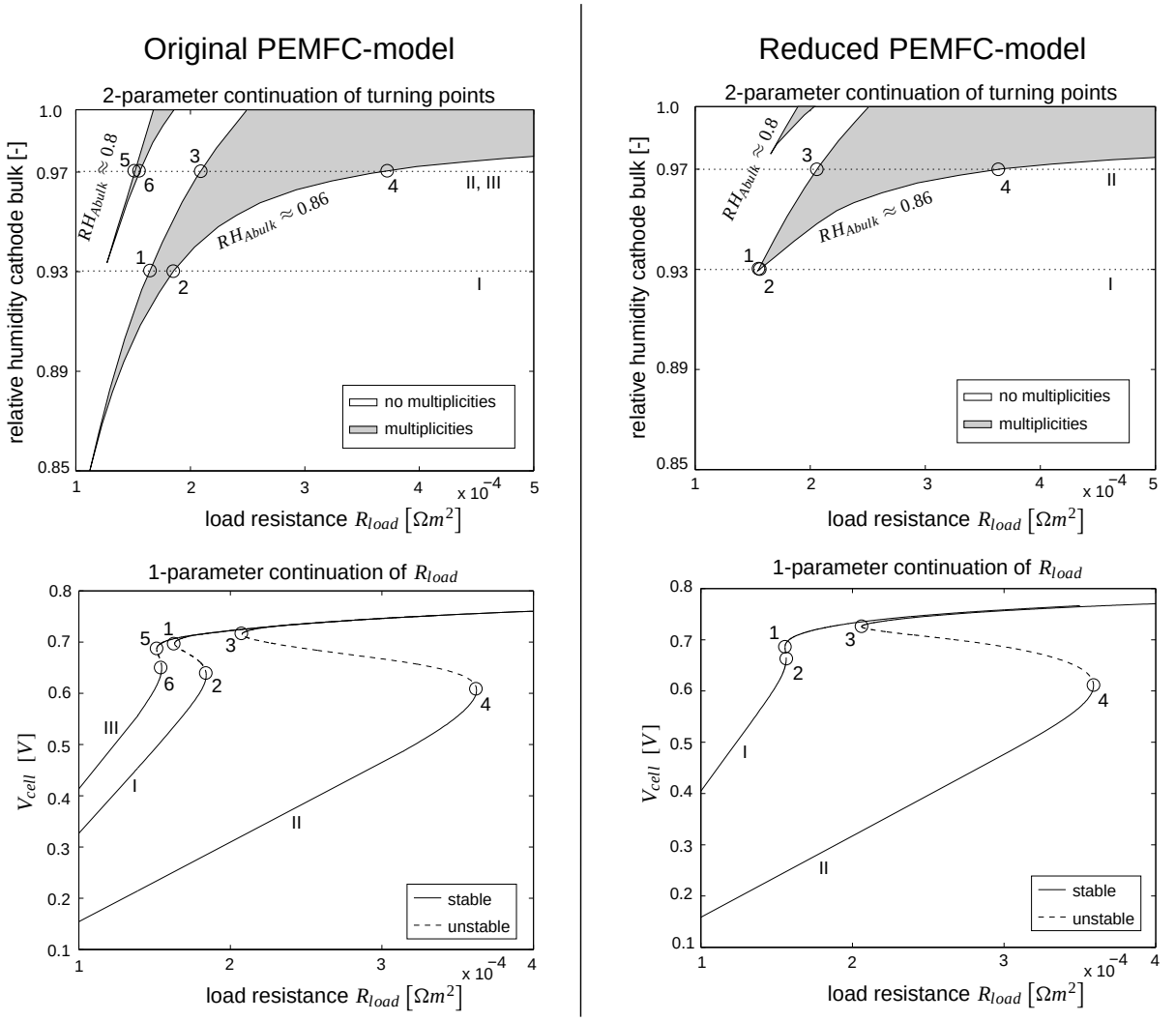

Figure 6: Comparison of spatially distributed two-phase model (left column) and lumped two-phase model (right column).

Usually, linear controllers are designed and the loop pairing is done heuristically. In this project, a controller approach for PEMFCs is considered that is based on passivity. Passive systems have a number of advantageous properties that make them attractive for control purposes. For example, various connections of passive systems can be shown to result in a coupled system that is again passive. Controller design methods for passive systems, which guarantee global stability of the closed loop system, are readily available. However, the application of this theory to a complex electrochemical process like a fuel cell is difficult because it is not straight-forward to find a suitable Lyapunov function. To overcome this problem, Ydstie and co-workers suggested an approach based on the principles of irreversible thermodynamics. This approach is extended here to electrochemical processes and applied to PEMFCs. A first tentative result is shown in Fig. 7: The figure shows a load change in a PEMFC with dead end configuration on anode side. The gas flows on anode and on cathode

side as well as the cell current and the amount of cooling are controlled. Fig. 7 compares the behavior of the nonlinear passivity based controller with a simple PID control. One can see that the nonlinear control achieves a much smoother transient in the cell humidity and keeps the relative humidity below 100 %, whereas the linear control temporarily increases the humidity up to 100 % and causes condensation of liquid water.

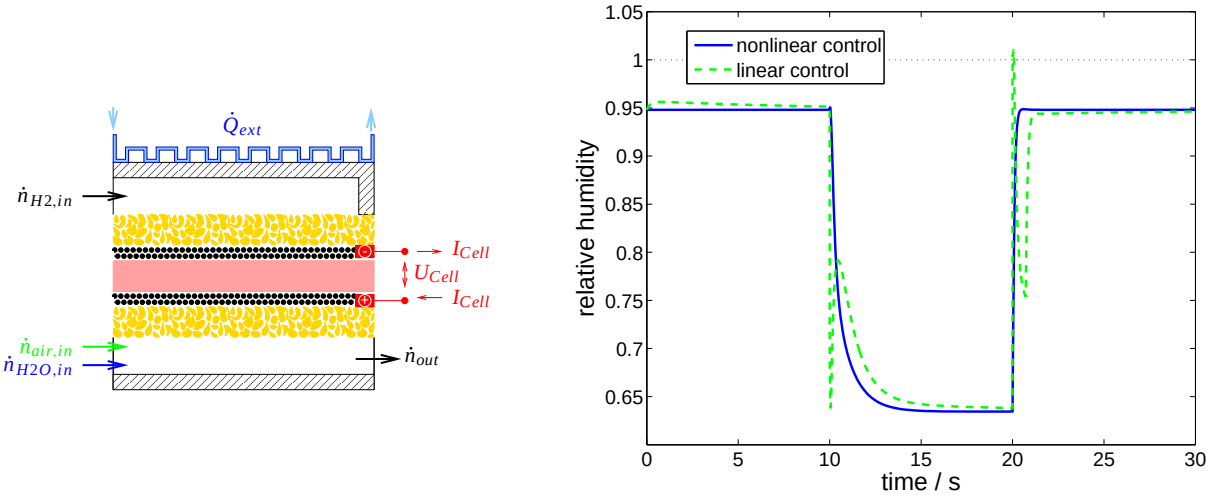

Figure 7: Passivity based control of a PEMFC: simulation of relative humidity on the cathode side during a load change; comparison between conventional PID control and passivity based control.

4.3 State Estimation of Particle Size Distributions

Property distributions of disperse products often determine the quality of a chemical product. Therefore, it is desirable to monitor distributions of particle properties, e.g. characteristic particle lengths, online. However, a direct online measurement of property distributions may be a very challenging task. Even if distributed measurements are available, they will not always inform about the property one is actually interested in, and a transformation of measured properties (e.g. chord length distribution) to desired properties (e.g. size distribution) is often non-trivial and ill-posed. The problem becomes even more difficult if only integral properties like the average particle or the total particle concentrations can be measured online, as is typical for very small particles.

The use of model based measurement techniques is a promising approach to overcome the problem of measuring property distributions online. The idea of a state estimator or observer is to combine model information and measurement information: Online simulations of a process model give estimates of non-measurable system states; the measurement information is used to compensate inevitable errors and inaccuracies in the model formulation, the model parameters and the initial conditions.

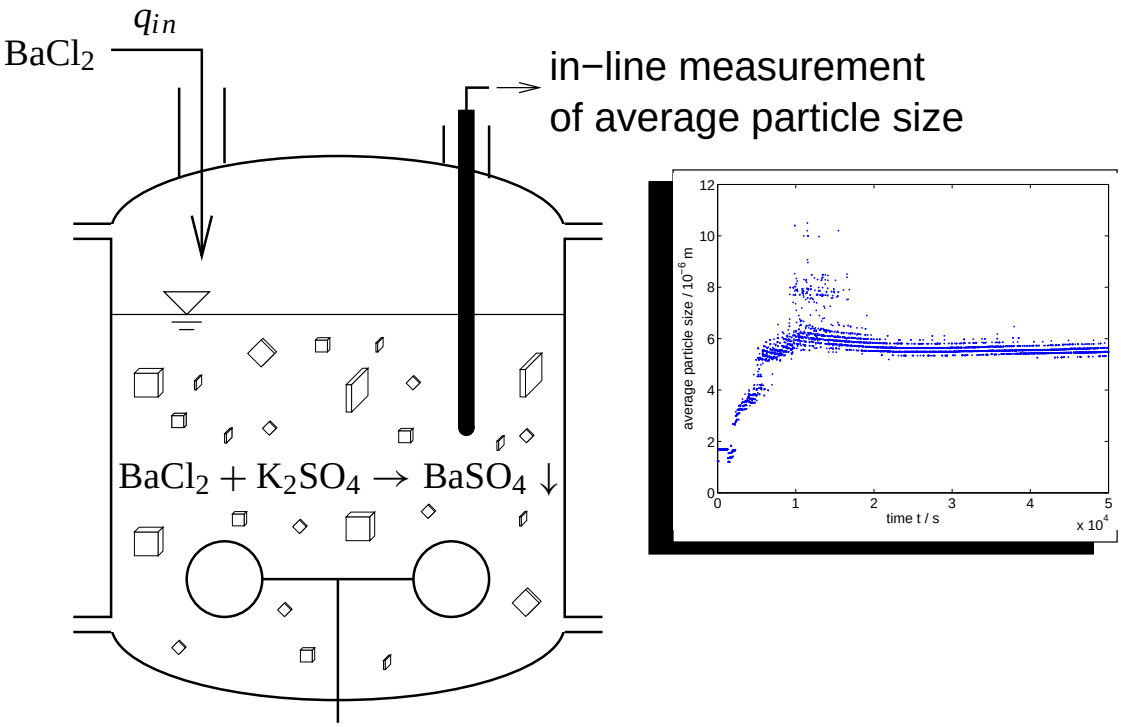

Fig. 8: Process scheme of a semi-batch reactor for the precipitation of barium sulphate; diagram: average particle size measured by an Aello probe

In this work (Mangold et al., 2008b), state estimators have been developed for the precipitation of barium sulphate from potassium sulphate and barium chloride in a semi-batch reactor (see Fig. 8). The particles' average size is measured by an online probe (Aello 1400 In-Line Sensor). The process is described by perfectly mixed mass balance equations for the liquid phase and by a one-dimensional population balance equation for the disperse phase that accounts for nucleation and for growth of the particles. Based on this process model, an Unscented Kalman Filter and a Moving Horizon Estimator have been designed and tested in simulations. Both approaches are able to estimate the particle size distribution with reasonable accuracy and prove to be robust against measurement noise and large errors in the initial conditions (see Fig. 9). Future work in this field will focus on a more detailed description of the fluid dynamics in the state estimator model. As a state estimator design on the basis of a CFD model is hardly feasible, this will require efficient model reduction techniques. POD methods seem to be a promising approach for this problem.

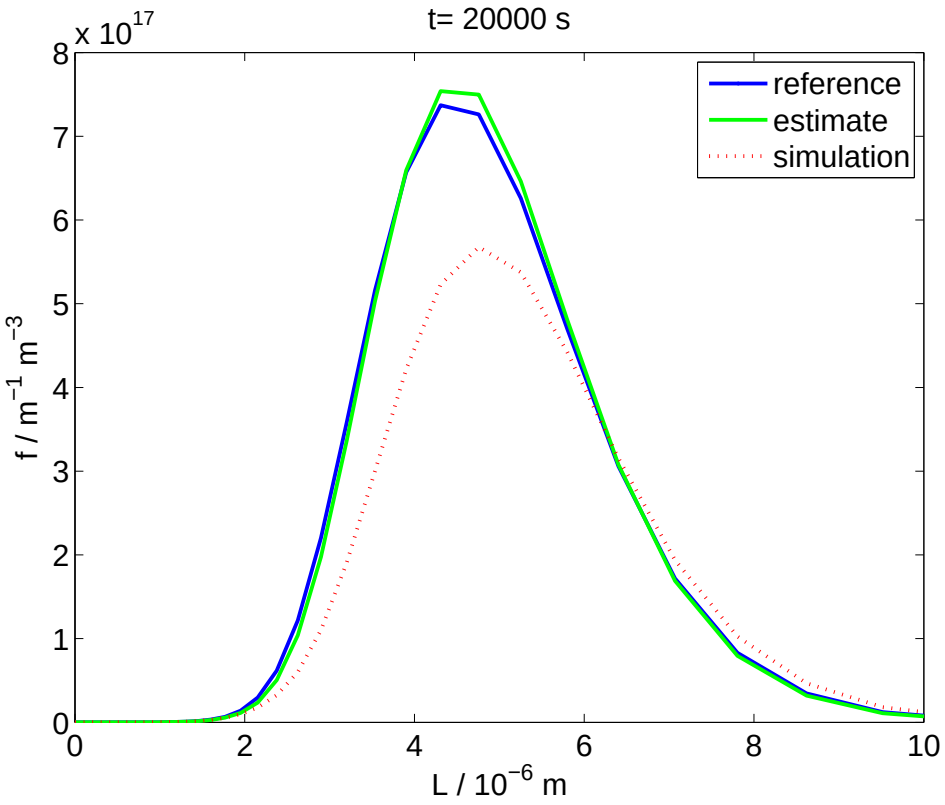

Figure 9: Simulation result of an Unscented Kalman Filter for the precipitation reactor; reconstructed size distribution at a fixed time point for an initial error of 50 % in the liquid phase concentrations and of 20 % in the size distribution; red dotted line indicates results of a simulation with identical initial conditions as the filter, but without filter correction; this demonstrates the effectiveness of the filter update.

4.4 Population Balance Modeling of Influenza Virus Replication during Vaccine Production

Together with the BPE group, population balance modeling of virus replication in mammalian cell cultures is being studied. Starting point was a lumped model introduced by Möhler et al. (Möhler et al., 2005) taking into account free virons, infected and uninfected cells. Infected cells were not further discriminated. The time difference between the initial infection of the cell culture and the release of newly produced viruses was modeled with a simple delay. When fitted to experimental data, the model provides a reasonable description of integral data but is not able to predict differentiation of infected cells and the delay between infection and release.

Experimentally, differentiation of infected cells is measured with flow cytometry. Through specific staining the amount of viral protein in each cell of a specific sample can be measured. This reveals a big variety in the state of the infected cells. To account for this variety, a distributed model was developed using a deterministic approach with population balance equations (Müller et al.,2008) and a stochastic kinetic

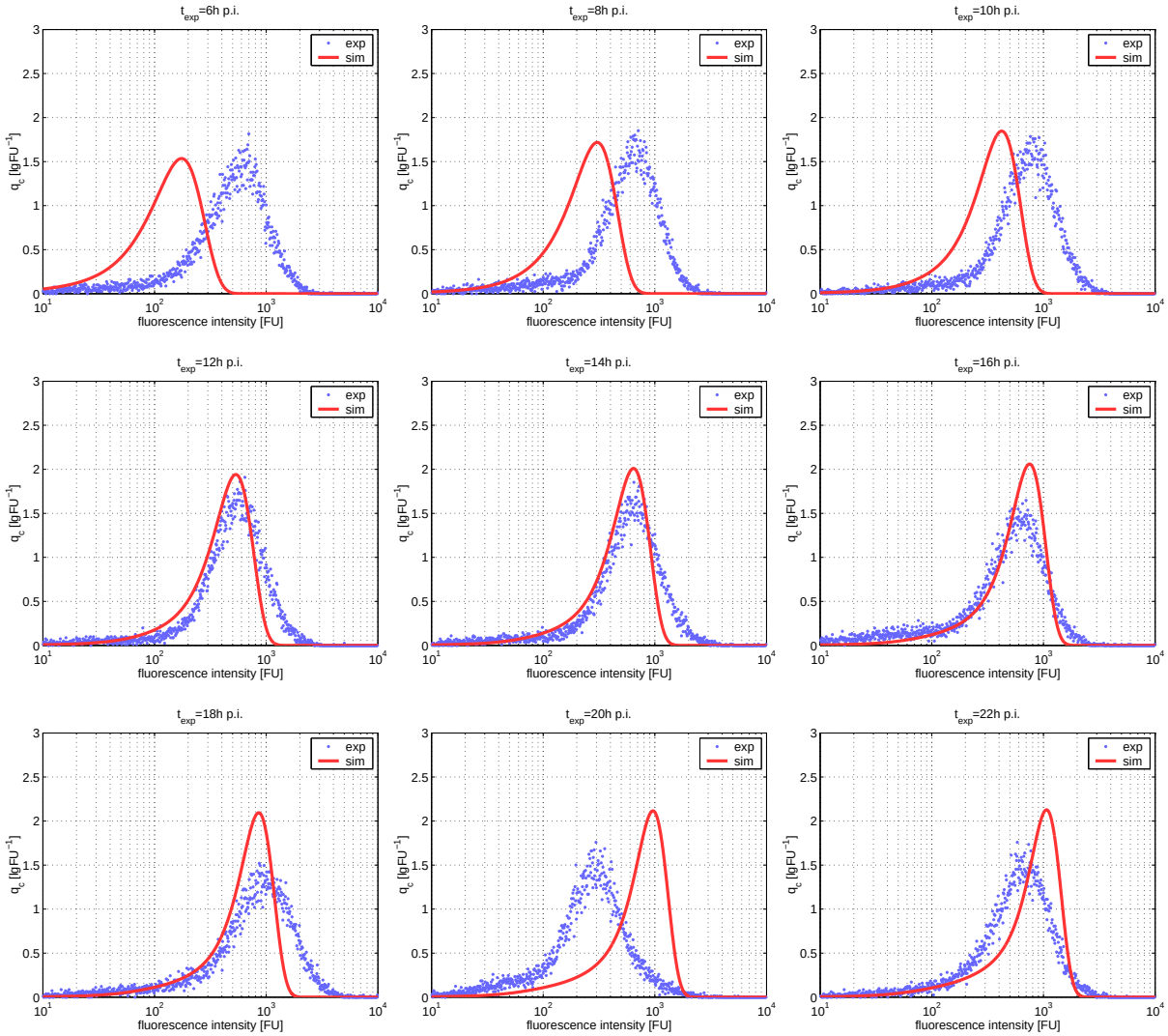

Figure 10: Influenza virus replication in MDCK cells. Comparison between simulation and experimental fluorescence data from flow cytometry.

Monte-Carlo approach (Sidorenko et al., 2008a). The “degree of infection” was used as an internal coordinate. It represents the number of virus equivalents in one cell and is proportional to the sensor signal obtained by flow cytometry. Virus dynamics and host cell physiology was described by unstructured global kinetics equivalent to the lumped model. In both cases the integral dynamics agrees well with the lumped model. The reason for this is that the lumped model essentially represents the zeroth order moment of the distributed model. In addition, the evolution of the distribution as measured by flow cytometry could be predicted reasonably well over a first time period where the average degree of infection increases monotonically (Fig. 10). A backshift of the fluorescence distribution as observed in the second period of the experiments (not shown in Fig. 10) could not be reproduced.

Therefore, in a next step, a more detailed model of the replication mechanism was formulated, comprising a total number of 14 individual reactions for transcription, pro-

tein, RNA and RNP synthesis and degradation (Sidorenko et al., 2008b). Cell physiology was again described by simple global kinetics. Resource limitations were not taken into account. Due to the high number of internal coordinates (ca. 10) only a Monte-Carlo approach was feasible. With the model the delay between infection and release could be predicted withing first approximation, whereas the backshift of the fluorescence distribution at later times could not.

More recent investigations indicate that the backshift can be explained through a variation of replication and release rates with the cell's state of infection. Corresponding models are under development. Another challenging question for future research is to explain and predict differences in productivity for different virus types.

4.5 A New Method for Optimal Experimental Design

Identifying unknown model parameters from experimental data is a key step in the development of physical or biological models. Because biological experiments are especially expensive and time consuming, it is important to design the experiments in such a way that maximum information content can be drawn out of the measured data. This is the objective of optimal experimental design (OED). Typically OED aims at choosing experimental conditions such that an objective function is minimized that depends on the confidence intervals of the identified parameters. Obtaining these confidence intervals for nonlinear systems is by no means a trivial task. A widely used approach is to approximate the covariances of the identified model parameters by the inverse of the Fisher information matrix (FIM). However, this standard approach suffers from a number of serious deficits: First, it gives only a lower bound for the covariances, whereas the actual covariances may be much bigger in systems that depend nonlinearly on the parameters. Second, the FIM approach postulates unbiased parameter estimation, whereas in nonlinear systems a bias in the estimated parameter values is nearly inevitable. In this work, a new approach is proposed that overcomes the flaws of the FIM method (Schenkendorf et al., 2008b).

The idea is to get the expectations and the covariances of the estimated parameters from so-called sigma points, i.e. by disturbing the measurement data by a certain amount, by identifying the parameters from each disturbed data set, and by finally averaging over the identification results. Because the disturbances are not chosen randomly as in Monte Carlo or bootstrap methods but deliberately, a comparatively small number of disturbed data sets - or sigma points - is sufficient to get an accurate

estimate of expectations and covariances. The sigma point method has proven to be successful in the field of nonlinear Kalman filtering, but to our knowledge has not yet been used for experimental design. The usefulness of the new method is illustrated in Fig. 11.

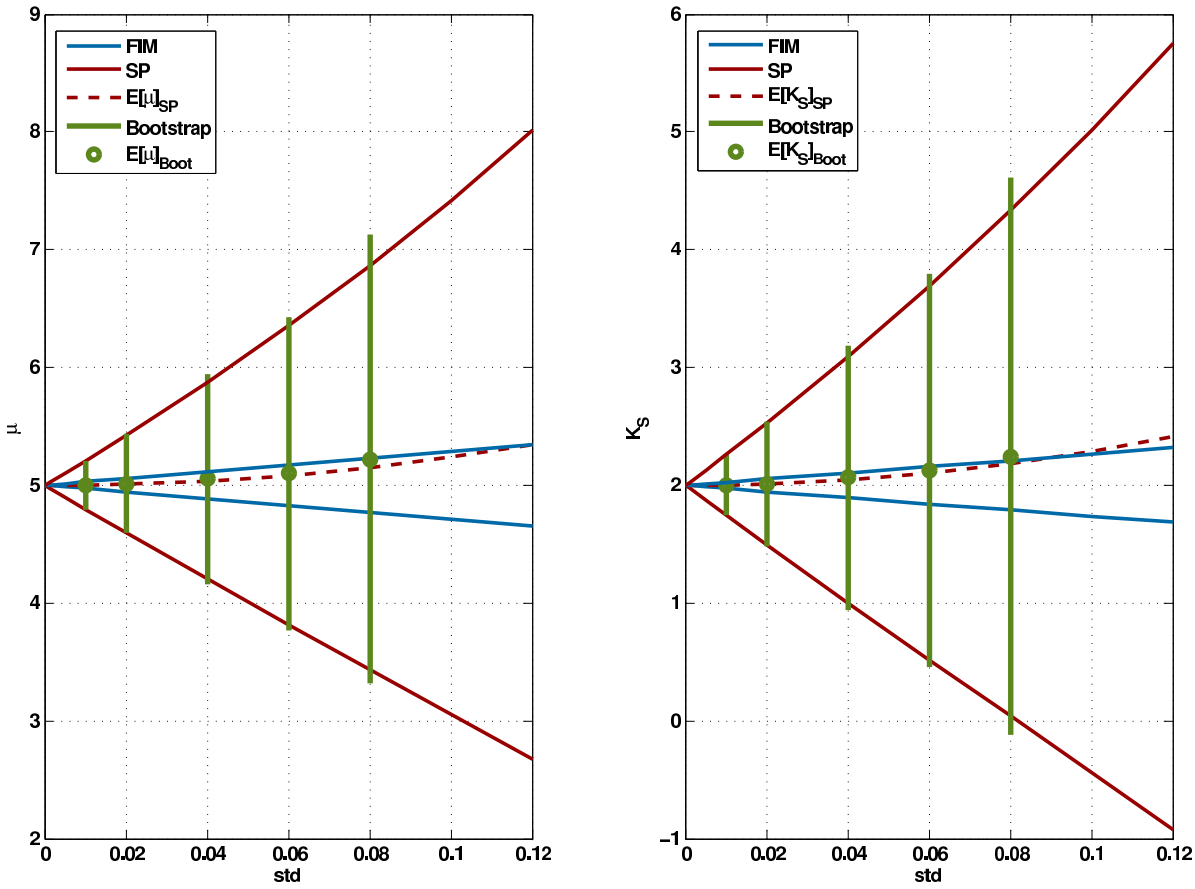

Figure 11: Comparison of Fisher Information Matrix method (FIM) and sigma point method (SP). Expectation and variances of two kinetic parameters are computed for different standard deviations (std) of the measurement noise. FIM underestimates the variances and gives no information on the bias of the estimates. SP agrees well with bootstrap results used as a reference.

The test problem is to identify the parameters K_S (substrate affinity constant) and μ (maximum growth rate) of Michealis Menten kinetics in a simple biological system. Covariances and mean values of the identified parameters are computed by the FIM method and by the sigma point method for different standard deviations of the measurement noise. The results of a bootstrap analysis are used as a reference solution. One can see that the traditional FIM method clearly underestimates the covariances of K_S and μ. Furthermore it becomes obvious that the assumption of an unbiased parameter identification, which underlies the FIM method, is not justified in this case. In contrast, the sigma point method computes parameter mean values and covariances that agree very well with the results of the boot strap. The computational effort of the sigma point method is higher than that of the FIM method but much lower than the

computational effort of the bootstrap. In conclusion, the use of the new sigma point method for optimal experimental design is a good compromise between computation time and accuracy and superior to the Fisher information matrix approach.

5 Teaching Activities, Diploma, Ph.D. and Habilitation Projects

After Jörg Raisch left the Otto-von-Guericke-University in Magdeburg in the beginning of 2006, Achim Kienle took over responsibility for studies in Systems Engineering and Technical Cybernetics. With the help of the PSD and also the SCT group, the program could be maintained. Meanwhile quite a number of cybernetics students are doing student, diploma and PhD projects at the Max Planck Institute. The number of excellent students among them is clearly above average.

In addition to our own teaching activities, responsibility was also taken for education in systems theory and control engineering for biosystems students and almost all other engineering students including chemical, mechanical and electrical engineers.

In fall 2007 Rolf Findeisen was appointed successor of Jörg Raisch at the OvGU. He brought additional expertise in nonlinear and model predictive control as well as systems biology to Magdeburg.

During the period covered by this report A. Kienle taught the following courses:

- Nonlinear Process Dynamics
- Process Systems Modeling
- Systems Identification
- Signals and Systems
- Control Engineering
- Chemical Process Control
- Modeling of Physiological Systems
- Seminar on 1st order quasilinear Partial Differential Equations

M. Mangold taught

- Process Systems Engineering
- Systems Theory
- State Estimation

M. Kaspereit taught

- Adsorption and Heterogeneous Catalysis

Selected Diploma and Master projects 2006-2008:

- T. Faulwasser (2006). A model based analysis of the dynamics of PEM fuel cells during load changes.
- T. Müller (2007). Influenza virus replication in MDCK cell cultures during vaccine production.
- P. Borngräber (2007). State estimation and inventory control of PEM fuel cell systems.
- R. Schenkendorf (2007). State estimation methods for precipitation processes.
- A. Bohmann (2007). On the existence and computation of reaction invariants.
- T. Meixus Fernandez (2007). Combination of recycling chromatography and racemization reaction for the production of pure enantiomers.
- A. Franz (2007). Mathematical modeling of polyhydoxybutyrate production in bacterial cell cultures using cybernetic models.
- C. Kunde (2008). An evaluation of membrane and tubular reactors using optimization methods.
- K. Subramanian (2008). Theoretical and experimental investigation of steady state recycling chromatography.
- J. Böhm (2008). Development of an energy management system.
- S. Piewek (2008). Modeling and analysis of a fuel cell system operated under conditions.
- A. Bück (2008). Passivity based control of spatially distributed models of fuel cell.

Ph.D projects finished during the period covered by this report:

- K. Pathath (2006). Nonlinear oscillations in crystallization process.
- M. Häfele (2006). Nonlinear dynamics and optimal operation of a plant for the production of low density polyethylene.
- J. Gangadwala (2007). Optimal design of combined reaction distillation processes.
- S. Grüner (2007). Nonlinear wave propagation in reaction separation processes - Theory and applications.
- M. Sheng (2007). Nonlinear model reduction and control of molten carbonate fuel cell systems with internal reforming.

- M. Krasnyk (2008). DIANA an object-oriented tool for nonlinear analysis of chemical processes.
- F. Zhang (2008). Model identification and model based analysis of membrane reactors.

Current Ph.D. projects:

- T. Müller. Population balance modeling of virus infection and replication processes.
- A. Franz. Nonlinear dynamics of polyhydroxybutyrate production in bacterial cell cultures.
- M. Grötsch. Analysis and control of PEM fuel cell systems.
- S. Swernath. Optimization of integrated processes for the production of pure enantiomers.
- J. Garcia Palacios. Integrating continuous chromatography and racemisation reactions for the production of pure enantiomers.
- G. Paramsivan. Control structure selection for multi-unit chemical plants using methods from integer and mixed integer optimization.
- R. Schenkendorf. Optimal experimental design.

Habilitation projects finished during the period covered by this report:

- M. Mangold (2006). Computer aided modeling, analysis and design of membran reactors and fuel cells.

Current Habilitation projects:

- K.-P. Zeyer. Nonlinear behavior of chemical reactors and separators.
- M. Kaspereit. Design of advanced and integrated chromatographic processes.

6 Offers, Appointments and Awards

- 2006-2008 Achim Kienle was elected Dean of the Electrical Engineering and Information Technology Department at OvGU.
- 2007 Stefan Grüner received the award for the best PhD Thesis of the Department for Electrical Engineering and Information Technology in 2007.
- 2007 Achim Kienle became an official “External Scientific Member” of the Max Planck Institute in Magdeburg through appointment by the Max Planck Society.

- 2008 Achim Kienle was appointed as one of three chairmen of the excellence cluster “Dynamic Systems in Process and Engineering and Biomedicine” following Ernst Dieter Gilles.
- 2008 Klaus Peter-Zeyer whose scientific work is closely related to the PSD group received an offer as Professor for Physical Chemistry at the University of Applied Sciences in Munich.

7 Future Directions

Some perspectives for future work are as follows:

Chemical systems

In chemical engineering the European INTENANT project coordinated by A. Seidel-Morgenstern offers various opportunities for productive research. The objective is to improve the production of pure enantiomers by a clever combination of reaction and separation steps. The first promising results were obtained for the combination of racemization reactions and chromatographic separations. Introducing separation steps into the chemical synthesis has hardly been considered so far. The objective of the PSD group is to develop methods and tools for systematically identifying promising process combinations.

Energy systems

Here, advanced control of fuel cell systems also under multiphase conditions is an interesting topic for future research. In addition, coordination control of decentralized energy production and consumption in so-called 'smart grids' is becoming more and more important. A common project in cooperation with the PCP group is in preparation.

Bio systems

So far, modeling of biosystems in the PSD group was mostly driven by mechanistic interpretation, e.g. in the population balance modeling of virus replication and the cybernetic modeling of PHB production. The objective is to include more and more biological knowledge to improve the predictive capabilities of the models. For this, close cooperation with the BPE and the SBI group and other partners of the Magdeburg Center for Systems Biology (MaCS) is required and the methods for parameter identification and optimal experimental design have to be further developed.

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Sidorenko, Y., Voigt, A., Schulze-Horsel, J., Reichl, U., and Kienle, A. (2008b). Stochastic population balance modeling of influenza virus replication in vaccine production processes. ii. detailed description of the replication mechanism. *Chem. Engng. Sci.*, *63*, 2299-2304.

Vasudeva, M. K., Zeyer, K.-P., Kienle, A., and Pushpavanam, S. (2008). The effect of maintenance on stability and multiplicity of steady states in continuous cell cultures.. Accepted for publication in *Mathematics and Computers in Simulation*.

Zhang, F. (2008). Model identification and model based analysis of membrane reactors.. Ph.D. Thesis, Otto-von-Guericke-Universität.

Zhang, F., Mangold, M., and Kienle, A. (2006). Stationary spatially periodic and aperiodic solutions in membrane reactors. *Chem. Engng. Sci.*, *61*, 7161-7170.

A complete list of publications is provided separately.

Research Group:

Systems and Control Theory (SCT)

Prof. Dr.-Ing. Jörg Raisch

This report covers the period from January 2006 to September 2008.

1 Group Introduction

The Systems and Control Theory Group cooperates closely with the Control Systems Group (“Fachgebiet Regelungssysteme”) at TUB. Both groups are headed by Jörg Raisch, who holds a full time (W3) professorial position at TUB, and has also been appointed by the MPG as an external scientific member (*Auswärtiges Wissenschaftliches Mitglied*) of the MPI.

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, it 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 large 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 unique mathematical framework, SCT provides a common language that allows scientists and engineers with extremely diverse technical backgrounds to communicate and hence generates 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 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 TUB.

Jörg Raisch has held his current position at TUB since March 2006. Before that, he was a (C4) professor at the OvGU. This report therefore includes aspects (teaching, Ph.D degrees) from both universities.

2 Group Members and Funding

As of September 30th, 2008, the SCT group at MPI Magdeburg consists of the following members:

Ph.D students and Postdocs:

Ivan Angelov (since July 2003)

Naim Bajcinca (since March 2008)

Carsten Conradi (since May 2006)

Dmitry Gromov (since December 2007)

Suzhou Li (since October 2006)

Dongfeng Luo (since December 2007)

Senior Researcher:

Dietrich Flockerzi (joined SCT group October 2003)

Secretary:

Janine Holzmann (since February 2004, working part time (25%) for SCT group)

Group leader:

Jörg Raisch (head of the SCT group since March 1998, Professor at TUB since March 2006, Professor at the OvGU from September 2000 to February 2006, and External Scientific Member of the MPI since 2002)

Funding

Current funding sources (as of September 30th, 2008) for Ph.D students, postdocs and senior researchers of MPI and University research groups are shown in the following table. It indicates that currently about 25% of our overall funding is from the MPI, with the rest evenly split between University and third party sources.

Tab. 1:

TU Berlin	Max Planck Institute	Third party funding
T. Schauer (BAT Ib)	I. Angelov (E 13)	T. Brunsch (BAT IIa)
S. Geist (BAT IIa)	D. Flockerzi (E15)	C. Conradi (E 13)
S. A. Attia (BAT IIa)	N. Bajcinca (E 13)	D. Luo (Ph.D scholarship)
N.N. (BAT IIa)	D. Gromov (E 13)	S. Guma (Ph.D scholarship)
J. Raisch (W3)	S. Li (Ph.D scholarship)	S. Hofmann (BAT IIa)
		H. Nahrstaedt (BAT IIa)
		R. Shalaby (Ph.D scholarship)
		N.N. (BAT IIa)

Former Group Members and Academic Visitors

The group is deeply indebted to numerous former members and visitors for their collaboration and for the excellent input they provided. During the period covered by this report, the following were group members: Danjing Li (MPI Ph.D student until 04/2007), Nils-Otto Negård, (MPI Ph.D student until 10/2006), Robert Salbert (MPI researcher until 06/2006), Tina Paschedag (MPI researcher from 07/2007 until 10/2007), Steffen Sommer (MPI postdoc until 03/2006), Ishan Pendharkar (MPI postdoc from 11/2006 until 09/2007), Johan Reger (MPI postdoc from 11/2007 until 06/2008), Christoph Horst (TUB researcher from 10/2006 until 12/2006), Florian Knorn (TUB researcher from 11/2006 until 01/2007), Vadim Azhmyakov (TUB postdoc from 03/2006 until 07/2007), Gunther Reißig (TUB postdoc from 03/2006 until 01/2008), Kai Wulff (TUB postdoc from 03/2006 until 02/2008).
Long-term (at least one month) visitors were: Shweta Shah, Onkar Dalal (both IIT students), Carlos Gonzaga, Tiago Albrecht de Freitas, Humberto Riella, Diego Vieira (all final year students from the Universidade Federal de Santa Catarina), Dr. Melha Bitam (INSA Lyon), Emilia Ambrosini (Politecnico di Milano), Prof. Christopher King (Northeastern University, Boston, USA), Prof. Robert Shorten (National University of Ireland Maynooth), Prof. Muhammed Abdelati (Islamic University of Gaza), Prof. Peter Caines (McGill University), Prof. Muhammed T. Hussein (Islamic University of Gaza), Mojtaba Barkhordari Yazdi (Iran University of Science and Technology, Tehran), Dr. Seshagiri Rao (National Institute of Technology, India).

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 match projects in the sense that results obtained from theoretical work are immediately transferred into specific application projects. This is indicated in Fig. 1, where “theoretical projects” are shown close to the centre 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 MPI and to encourage cooperation between the Institute’s groups. In the following, we provide a list of our projects, including information on cooperating partners and, if applicable, external funding sources. More detailed infor-

mation on a small number of representative projects can be found in Section 4. It should be noted that we have established joint projects with all chemical engineering groups at the MPI (PCP, PSD, PCF) and the bio(engineering) groups SBI and BPE.

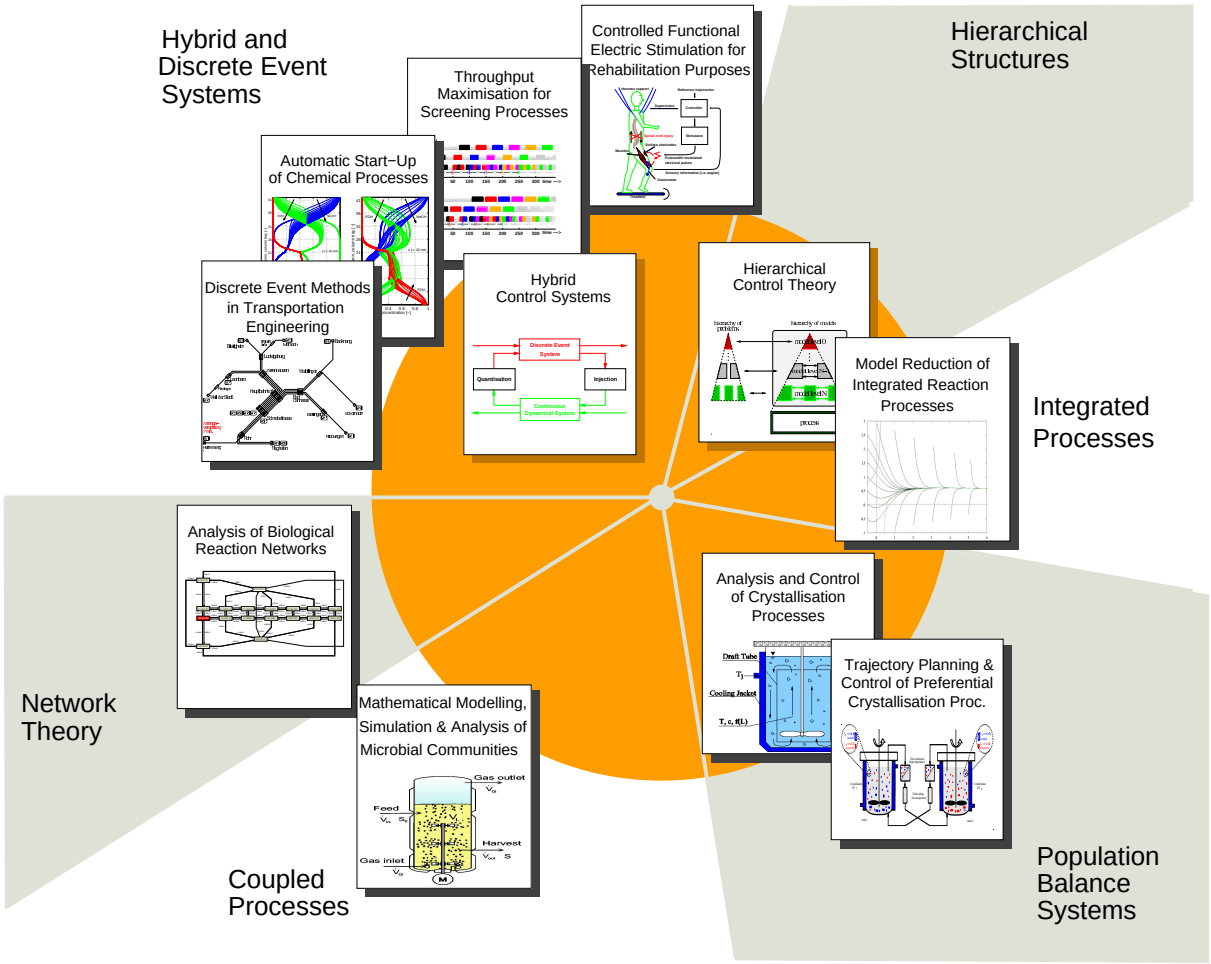

Fig. 1: Survey of research projects

Tab. 2: Project Areas

Project Area: Hybrid and Discrete-Event Systems

Project:	**Hybrid Control Systems**
Abstract:	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. We have been investigating two different approaches: one is based on “safe” discrete approximations of continuous components, which translates the overall hybrid problem into a purely discrete one; recent research has focused on ways to handle intrinsic complexity problems by employing specification dependent abstraction refinement (Moor et al., 2006) or by imposing specific control structure. Alternatively, some stability and optimality issues for specific classes of hybrid systems may be approached directly: stability of switched linear systems has been treated in (Pendharkar et al., 2007 a, 2007 b, 2008); optimality issues for different classes of hybrid systems with autonomous switching are treated in

	(Azhmyakov and Raisch, 2006; Azhmyakov et al., 2007; Attia et al., 2007; Azhmyakov et al., 2008). Finally, a combination of both approaches has been outlined in (Seatzu et al., 2006; Geist et al., 2008).
Researchers:	D. Gromov, N. Bajcinca, S. Geist (TUB), S.A. Attia (TUB, MPI until Oct. 2007), J. Raisch
Partners:	University of Erlangen (T. Moor), Melbourne University (J. Davoren), University of Cagliari (A. Giua, C. Seatzu), CINVESTAV (V. Azhmyakov)
Funding:	DFG, DAAD (Vigoni program), EU-HYCON, MPI, TUB

Project:	**Throughput Maximization for Screening Processes**
Abstract:	High Throughput Screening (HTS) plants are used for 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 reduce 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 (Mayer et al., 2008a) and the hierarchical nesting of cycles (Mayer et al., 2008 b).
Researchers:	T. Brunsch (TUB), K. Wulff (OvGU and TUB until Febr. 2008), C. Horst (TUB until Dec. 2006), J. Raisch
Partners:	CyBio AG, BASF AG, Mathematics Dept. OvGU
Funding:	EU-DISC, LSA-DS, BASF AG, TUB

Project:	**Application of Discrete-Event Methods in Transportation Engineering**
Abstract:	Max-Plus-Algebra is an established method in DES (discrete event systems) theory, which is particularly useful for investigating cyclic processes, e.g. identifying bottlenecks and predicting propagation of delays. After successfully applying it to analyze a suburban train network, we are currently investigating its use for online rescheduling and, in combination with suitable continuous control, in a hierarchical feedback scheme for the overall control of transportation networks (Li et al., 2007).
Researchers:	D. Li (MPI until April 2007), T. Brunsch (TUB), J. Raisch
Funding:	MPI, EU-DISC

Project:	**Automatic Start-up of Chemical Processes**
Abstract:	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 two benchmark problems from

	the EU Network of Excellence HYCON, namely the optimal start-up of a novel open-plate reactor (Kaya et al., 2008) and of a system of evaporators (Gromov and Raisch, 2008). In cooperation with the PCP group, we have investigated the start-up of a reactive distillation column (Sommer et al., 2006).
Researchers:	D. Gromov, S.A. Attia (TUB, MPI until Oct. 2007), S. Sommer (MPI until March 2006)
Partners	PCP Group
Funding	MPI, TUB, EU-HYCON

Project:	**Controlled Functional Electrical Stimulation (FES) in the Rehabilitation of Spinal Cord Injured Persons and Stroke Patients**
Abstract:	Electrical nerve-stimulation of paralysed 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 (Nahrstaedt et al., 2008 a & b) and cycling (Schauer et al., 2006; Ambrosini et al., 2008; Ferrante et al., 2008). Depending on the degree of disability, the goal may be temporary assistance, e.g. during relearning of gait, or permanent replacement of lost motor functions (neuroprostheses). In the context of control, the most challenging aspects are the interaction between FES 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 (Negård et al., 2006).
Subproject:	**Control of Endeffector-Based Rehabilitation Robotics in Combination with Electrical Stimulation for Gait Training after Stroke**
Researchers:	T. Schauer (TUB, MPI until May 2006), H. Nahrstaedt (TUB)
Partners:	Fraunhofer Institute for Production Systems and Design Technology (H. Schmidt, J. Krüger), Charité – Universitätsmedizin Berlin, HASOMED GmbH, Politecnico di Milano (S. Ferrante)
Funding:	BMBF, TUB
Subproject:	**Electromyography-based control of FES in the Rehabilitation of Hemiparetic Patients**
Researchers:	T. Schauer (TUB, MPI until May 2006), R. Salbert (MPI until June 2006), R. Shalaby (TUB)
Partners:	Charité – Universitätsmedizin Berlin (S. Hesse), Haynl-Elektronik GmbH Schönebeck
Funding:	BMBF, MPI, TUB, Egyptian Government (scholarship)
Subproject:	**Control of FES-assisted Gait Training (Drop Foot Stimulator)**
Researchers:	T. Schauer (TUB, MPI until May 2006), N.-O. Negård (MPI until Oct. 2006), H. Nahrstaedt
Partners:	Charité – Universitätsmedizin Berlin (S. Hesse), St. Mauritius Therapieklinik Meerbusch (V. Hömberg), HASOMED GmbH Magdeburg
Funding:	MPI, TUB, Hasomed GmbH
Subproject:	**Development of a Portable Endeffector-Based Hand/Arm Rehabilitation Robot combined with Functional Electrical Stimulation**
Researchers:	T. Schauer (TUB, MPI until May 2006), D. Luo (MPI)
Partners:	Charité – Universitätsmedizin Berlin (S. Hesse)
Funding:	Chinese Academy of Sciences, TUB

Project Area: Network Theory

Project:	**Analysis of Biological Reaction Networks**
Abstract:	Cellular functions are realized by complex networks of chemical reactions. In most cases, however, several reaction schemes can be considered as plausible a-priori hypotheses. This project aims at providing a set of methods that can be used to safely discard hypotheses on the basis of qualitative properties or measurement information. The task becomes even more challenging when taking into account that reaction parameters are usually not precisely known. Investigated methods include the construction of “safe” approximating automata and, more recently, the extension and application of Feinberg’s Chemical Reaction Network Theory. The latter connects qualitative properties of ODEs describing a given reaction network (as, e.g., the existence of multiple steady states) to the network structure. In particular, its assertions are independent of parameter values and only assume that all kinetics are of mass-action form. Results have been reported in (Conradi et al., 2007 a, 2007 b, 2008; Saez-Rodriguez et al., 2008).
Researchers:	C. Conradi, D. Flockerzi, J. Raisch
Partners:	SBI group (E.-D. Gilles, S. Klamt), ETH Zürich (J. Stelling)
Funding:	LSA-DS, MPI

Project Area: Hierarchical Structures

Project:	**Hierarchical Control Theory**
Abstract:	Hierarchical control can be interpreted as an attempt to handle complex problems by decomposing them into smaller subproblems and reassembling their solutions into a “functioning” hierarchical structure. So far, heuristic approaches have been prevalent. However, they cannot guarantee that the overall solution does indeed meet the specifications. In contrast, our project aims at a formal synthesis method that can provide such a guarantee. Our approach is based on a hierarchy of models describing a given plant at various levels of abstraction and has been successfully applied to a discontinuous multi-product batch plant (Raisch and Moor, 2008). Currently, we are interested in characterising achievable performance for specific control architectures. We also investigate the trade-off between performance loss and design simplification if low-level control is used to enforce specific properties as, e.g., monotonicity (Gromov and Raisch, 2006). Our current application example is a chromatographic batch seperation process, where the plant topology can be switched online.
Researchers:	D. Gromov, S. Li, S. Geist (TUB), J. Raisch
Partners:	University of Erlangen (T. Moor), Melbourne University (J. Davoren), PCF group (A. Seidel-Morgenstern)
Funding:	DFG, MPI, TUB

Project Area: Population Balance Systems

Project:	**Analysis and Control of Crystallization Processes**
Abstract:	In the chemical and pharmaceutical industries, crystallization is used for the production of solids from liquids. Product quality usually depends heavily on crystal size distribution (CSD), whose dynamics can be described by population balance models. In the past, we investi-

	gated robust stabilization and disturbance rejection for continuously operated crystallizers using infinite-dimensional feedback synthesis techniques. Subsequently, our focus has been on trajectory planning and feedback control for batch crystallizers. Using flatness based methods, we have shown how to analytically derive a cooling policy that will achieve a desired CSD at the end of a batch run and how to design feedback control to track the chosen trajectory in the presence of model errors and disturbances (Vollmer and Raisch, 2006). In the analysis of continuous nonlinear precipitation processes we have investigated stability issues in barium sulphate precipitation as well as QMOM-reduction schemes for bivariate population balances (Heineken et al., 2006 & 2007).
Researchers:	I. Angelov, J. Raisch, D. Flockerzi
Partners:	PCF Group (M. P. Elsner, A. Seidel-Morgenstern), PCP Group (W. Heineken, A. Voigt, K. Sundmacher)
Funding:	MPI

Project:	**Trajectory Planning and Control of Preferential Crystallization Processes**
Abstract:	Based on the results from our project on flatness-based control of batch crystallization processes, we are currently investigating the use of preferential crystallization for the separation of enantiomers. This involves simulation (Qamar et al., 2006 & 2008 a; John et al., 2007), optimisation (Angelov et al., 2006), and control (Angelov et al., 2008) aspects. Details can be found in Section 4.
Researchers:	I. Angelov, S. Hofmann (TUB), J. Raisch
Partners:	PCF Group (M. P. Elsner, A. Seidel-Morgenstern), OvGU Math. Dept. (V. John, G. Warnecke), OvGU Chem. Eng. Dept. (D. Thévenin)
Funding:	MPI, DFG

Project Area: Integrated Processes

Project:	**Model Reduction of Integrated Reaction Processes**
Abstract:	Reaction invariants are of fundamental importance for the design of integrated reaction separation processes with fast chemical reactions. Even for reactions in ideal homogeneous liquid phase there is a need for an effective algorithm for the computation of reaction invariants and for a rigorous mathematical proof that the reduced system is not only a projected system of differential-algebraic type, but a faithful lower-dimensional system of ordinary differential equations. Based on many examples during the last 15 years, it has been a belief that every set of linearly independent chemical reaction processes possesses at least one feasible set of reaction invariants. We have given a formal proof. In addition, we provide a systematic procedure for computing such a feasible set (Flockerzi et al., 2007).
Researchers:	D. Flockerzi
Partners:	PSD group (A. Kienle)
Funding:	MPI

Project Area: Coupled Processes

Project:	**Mathematical Modelling, Simulation and Analysis of Microbial Communities**
Abstract:	The competition of microbial communities with three species (Burkholderia cepacia, Staphylococcus aureus, Pseudomonas aeruginosa) is modelled by chemostat-like equations incorporating additional features as, e.g. a second metabolite, the possibility of direct interspecific competition and the appearance of an inhibiting toxin or antibiotic. Coexistence results for the reduced Burkholderia–Staphylococcus model have been obtained (Heßeler et al., 2006). Moreover, we have addressed the purification of human influenza virus and have provided an interpretation of size-exclusive chromotography as a linear transfer system (Kalbfuss et al., 2008).
Researchers:	D. Flockerzi
Partners:	BPE group (U. Reichl, B. Kalbfuß), OvGU (J. Schmidt), PCF group (A. Seidel-Morgenstern)
Funding:	MPI

4 Research Highlights

Our research has benefited from numerous collaborations with colleagues from within and outside the MPI. It has also benefited from participation 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* has been active from 2004 till 2008 and has involved 26 partners from 10 European countries. It aims 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.
- *FG468* is a DFG-funded research unit (*Forschergruppe*) devoted to the study of "Methods from Discrete Mathematics for the Synthesis and Control of Chemical Processes". It has been active since 2003 and will continue into 2009.
- Recently, a so-called "Paketantrag" on *Modelling and Control of Racemic Mixtures using Preferential Crystallization* was approved by DFG. This is a bilateral project involving our group and Andreas Seidel-Morgenstern's PCF-group.
- *RehaRobES* is a BMBF funded project involving 4 academic and industrial partners, which started in 2008. 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.
- We participate in the *International Max Planck Research School (IMPRS) for Analysis, Design and Optimization in Chemical and Biochemical Process Engineering*.

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 recent contributions within our project on hybrid control systems. On the application side, we include three projects addressing problems in chemical engineering, systems biology, and medical engineering, respectively. Two of the three application projects have been investigated in close collaboration with other groups at the MPI.

4.1 Optimal Hybrid Control Systems

Hybrid systems consist of continuous and discrete event components. Control synthesis for such systems is a challenge because of the heterogeneous nature of their state spaces. Our group previously focused on so-called abstraction based approaches to hybrid systems. There, the underlying idea is to approximate continuous dynamics by suitable discrete event systems (DES). If specifications can be formulated in terms of discrete variables, this translates the given hybrid problem into a purely discrete one, which can subsequently be addressed using established methods from the area of DES theory. If the discrete approximations satisfy certain properties regarding their external behavior, it can be shown that any solution to the approximated (discrete) problem is a valid solution to the underlying (hybrid) problem. We have suggested *l*-complete approximation as a particularly suitable abstraction technique, which lends itself easily to global refinement. Unfortunately, increasing approximation accuracy is accompanied by an (exponential) increase in complexity, which of course affects the subsequent control synthesis step. As possible remedies for the complexity problem, we investigated modular and hierarchical control ideas and suggested a framework for specification dependent refinement (Moor et al., 2006).

With V. Azhmyakov and S.A. Attia joining our group, we then became interested in the theory of optimal hybrid control. Hybrid optimal control problems are highly nontrivial, as one has to deal not only with the infinite dimensional optimization problems related to the continuous dynamics, but also with a potential combinatorial explosion related to the discrete part. Because of the large number of potential applications, there has been considerable interest in optimal hybrid control problems, with important contributions from CLARKE, ANTSAKLIS, CAINES, EGERSTADT, PICCOLI and their coworkers. One of the most convenient ways to deal with the problem is to formulate it as a sequential problem i.e., for a particular execution the time axis is partitioned into subintervals. In each interval, the discrete state remains constant, and the continuous dynamics is characterized by a set of ODEs. Transitions between intervals / discrete states are either triggered internally (typically by the continuous state “hitting” some manifold) or externally (by a discrete control signal). The former is often referred to as autonomous switching, the latter as controlled switching.

We have focused on some specific, but practically important, classes of hybrid systems and derived necessary conditions of optimality and efficient conceptual algo-

rithms to solve the related problems: first, we have investigated hybrid systems with autonomous switching and continuous control inputs. In contrast to the work by CAINES and co-workers, we derived necessary optimality conditions without recourse to the technique of needle variations. Instead we apply a generalized Lagrange multiplier rule (Azhmyakov et al., 2007). This allows us to obtain necessary conditions for a *weak minimum* as opposed to the Maximum Principle, which gives necessary conditions for a *strong minimum*. The difference between the two types of minima is the norm used to compare two feasible trajectories. The weak necessary conditions of optimality are said to hold if the continuous trajectories associated with the same discrete state are compared in the sense of the infinity norm in contrast to a strong minimum, where the 1-norm is usually employed. The problem is first formulated as an abstract optimization problem in an appropriate Sobolev space. The differential equations are considered as operators acting on Sobolev spaces, and the switching surfaces are embedded into the operator as equality constraints. A generalized Lagrange multiplier is then applied to extract the necessary conditions of optimality.

As a second class, we have investigated hybrid systems with autonomous switching where discrete transitions are accompanied by instantaneous changes (jumps) in the continuous states and where these state jumps (i.e., the differences between “new” and “old” values of the continuous states) can be considered as the sole control variables. Hybrid systems with jumps in the continuous states are often referred to as *impulsive hybrid systems*. In a first step, necessary conditions of optimality are established based on a variational approach. For this, a smooth variation preserving the switching sequence for the discrete state is introduced around the optimal trajectory. Applying the Lagrange principle gives a sequence of boundary-value problems that need to be solved and an equality condition on the gradient of the cost functional with respect to the jump parameters. Closed form expressions of the gradient are then obtained using a parameter variation where the effects of parametric variation are propagated on the whole trajectory. An algorithm based on gradient descent techniques is then proposed together with some convergence results. The algorithm uses forward / backward integration of the system dynamics and the adjoint equations together with a pointwise update of the jump parameters (Attia et al., 2007).

As a third class, we have considered hybrid systems with autonomous switching, continuous control inputs and controlled state jumps. Using a simple transformation, the problem under study can be formulated as a hybrid systems with autonomous

switching where jump parameters are considered as a part of the control. Based on the results in (Azhmyakov et al., 2007), we develop a new set of necessary conditions of optimality (Azhmyakov et al., 2008). A combination of the algorithm developed for the class of impulsive autonomous hybrid systems (Attia et al., 2007) together with a gradient based approach (Azhmyakov and Raisch, 2006) for updating the control can be used to extract both the continuous control signals and the controlled jump parameters.

4.2 Trajectory Planning and Control of Preferential Crystallization Processes

This research represents part of a DFG-funded joint project with the PCF group. Some aspects also involve the Mathematics and the Chemical Engineering Departments at OvGU. Our contribution is based on extensive previous research on control of crystallization processes, most of it by former Ph. D student U. VOLLMER. This will be briefly summarized first. Crystallization dynamics is usually dominated by nucleation, i.e. the production of new crystals, and crystal growth. Supersaturation, which is generated either by cooling or by evaporation of solvent, represents the driving force for both processes. Furthermore, phenomena such as attrition, breakage and agglomeration of crystals may occur. Product quality often depends heavily on *crystal size distribution* (CSD), i.e. the distribution of crystals with respect to crystal size. The evolution of the CSD over time is usually modelled by a *population balance equation* (PBE). This is a partial differential equation, sometimes with an additional integral part representing breakage, attrition, and agglomeration phenomena. It is coupled to one or more ordinary differential equations (ODEs) resulting from a solute mole balance of the liquid phase and, if necessary, an energy balance of the system. In the past, we investigated robust stabilisation and disturbance rejection for continuously operated crystallizers using infinite-dimensional H_∞-feedback synthesis techniques. We then shifted attention to the problems of trajectory planning and feedback control for batch crystallizers. In batch mode, the crystallizer is initially filled with undersaturated solution, and supersaturation may be generated by gradual cooling. The CSD obtained at the end of the batch is determined by the temperature-time profile applied to the process. This essentially defines an open-loop control, or trajectory planning, problem, namely, how to find a temperature signal producing a predefined CSD. A solution to this problem was developed based on a standard population balance model from the literature. This model allows the derivation of a closed set of ordinary

differential equations for a finite number of leading moments of the CSD. Through an appropriate scaling of time, the resulting finite-dimensional model can be made *differentially flat*. Flat systems possess an intrinsic invertibility property which is extremely useful for trajectory planning purposes. Based on this property and the fact that the same scaling of time makes the PBE a simple transport equation with constant coefficients, we developed a procedure which enables the analytic computation of the corresponding temperature profile for any desired (and physically meaningful) final CSD. Finally, we used the fact that flat systems are feedback linearizable to design a closed loop control scheme that tracks the previously designed trajectory in the presence of modelling errors and disturbances. A summary of our results can be found in (Vollmer and Raisch, 2006).

In close cooperation with the PCF group, we have started to investigate control problems for preferential batch crystallization processes. Preferential crystallization is used for the separation of enantiomers – substances with very similar physical and chemical properties but rather different metabolic effects. The basic idea in preferential crystallization is quite simple. Both enantiomers are initially dissolved, and the solution is kept in a temperature range where primary nucleation is of much less importance than secondary nucleation. Hence, after seeding one of the two enantiomers, say E1, it will be almost exclusively the seeded enantiomer that will crystallize – existing crystals will grow and secondary nucleation will generate further E1 crystals. This will of course consume E1 in the liquid phase, reduce supersaturation and therefore “slow down” the desired crystallization process. To ensure required product purity, the process has to be stopped before – via primary nucleation – too many crystals of the counterenantiomer E2 are being generated. This basic single-batch procedure can be extended to a cyclic batch scheme for the production of both enantiomers. A possible configuration, consisting of two batch crystallizers, is shown in Fig. 2. In the beginning, racemic mixture is filled into one of the two vessels (represented by an A in the ternary phase diagram in Fig. 2).

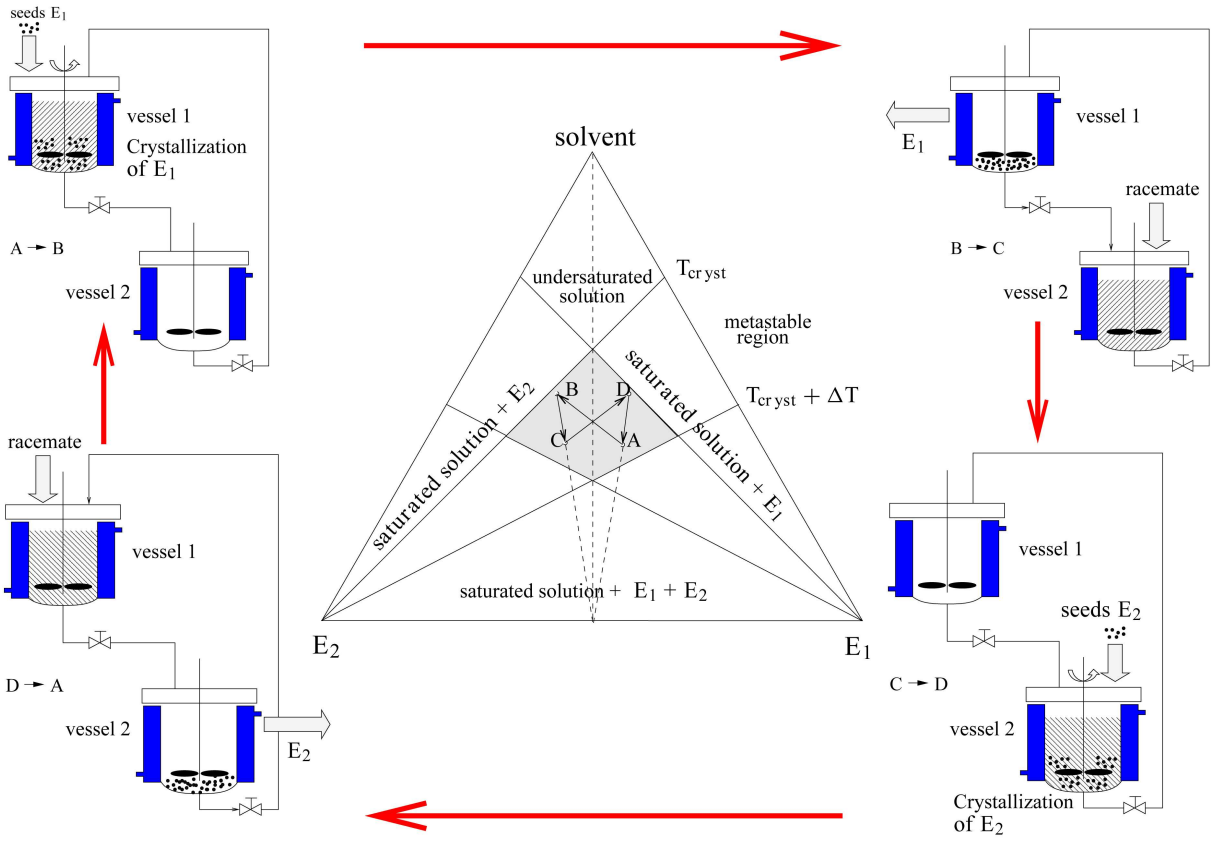

Fig. 2: Cyclic batch process for enantiomer separation

Seeding E1 crystals initiates the single batch process described above $(A \rightarrow B)$. After stopping the process, crystalline E1 is harvested by transfering the liquid into a second crystallizer vessel. Racemic mixture is added $(B \rightarrow C)$, and E2 crystals are seeded. This initiates a second batch process where crystalline E2 is produced $(C \rightarrow D)$. Stopping the process, transferring the liquid contents into the first vessel and again adding racemic mixture will finish the first cycle of the process $(D \rightarrow A)$. Apart from a minimum required purity, control specifications include quality requirements related to the shapes of the product CSDs for E1 and E2. The resulting control problem is intrinsically hybrid: single batch process dynamics is continuous, but discrete events are obviously of paramount importance for the overall cyclic batch scheme. Control inputs include the crystallizer (or heat jacket) temperature signal, the seed CSD and the amount of added racemic mixture for each single batch process, and the inter-batch switching pattern. As a first step, we investigated the optimization of single batches with respect to the seed CSD, both for the isothermal (Angelov et al., 2006) and the non-isothermal case (Angelov et al., 2008).

We started off with a fairly simple model consisting of two PDEs (with growth rates assumed to be independent of particle size, secondary nucleation for the seeded enantiomer and primary nucleation for the unseeded enantiomer) coupled with two ODEs representing mass balances. This model has been subsequently refined by the PCF group. In its latest version, both primary and secondary nucleation are explicitly modelled for each of the enantiomers, and primary nucleation is further subdivided into a homogeneous and a heterogeneous case. Further improvements in the model are size-dependent growth rates and the addition of an energy balance to model the interaction with a cooling unit. Accurate simulation of such models is far from non-trivial; therefore, in cooperation with the Numerical Mathematics Group at OvGU and the PCF group, reliable and accurate numerical methods and simulation tools have been investigated. This includes finite volume schemes, the method of characteristics, and a combination of the two approaches (Qamar et al., 2006, 2008 a, 2008 b). Crystal growth is driven by supersaturation, which, in turn, can be influenced via the crystalliser temperature. However, in the cyclic batch scheme, this dependence cannot be exploited properly: each attempt to keep supersaturation for the currently desired enantiomer at an appropriate level for a long period of time would lead to an unacceptable increase of supersaturation for the (undesired) counterenantiomer. This is the motivation for investigating the alternative configuration shown in Fig. 3. There, E1 and E2 are crystallized simultaneously in two separate vessels, and crystal free solution is continuously exchanged between the two crystallizers. This implies that concentrations of E1 and E2 are simultaneously reduced in the liquid phase, and it will therefore be possible to keep supersaturation for both enantiomers at higher levels. The resulting increase in productivity does not come for free, however, as additional hardware is needed to guarantee that the exchanged liquid does not contain any crystals. Degrees of freedom for this control problem include temperature signals and seed CSDs in both crystallizers and the flow rate between the vessels.

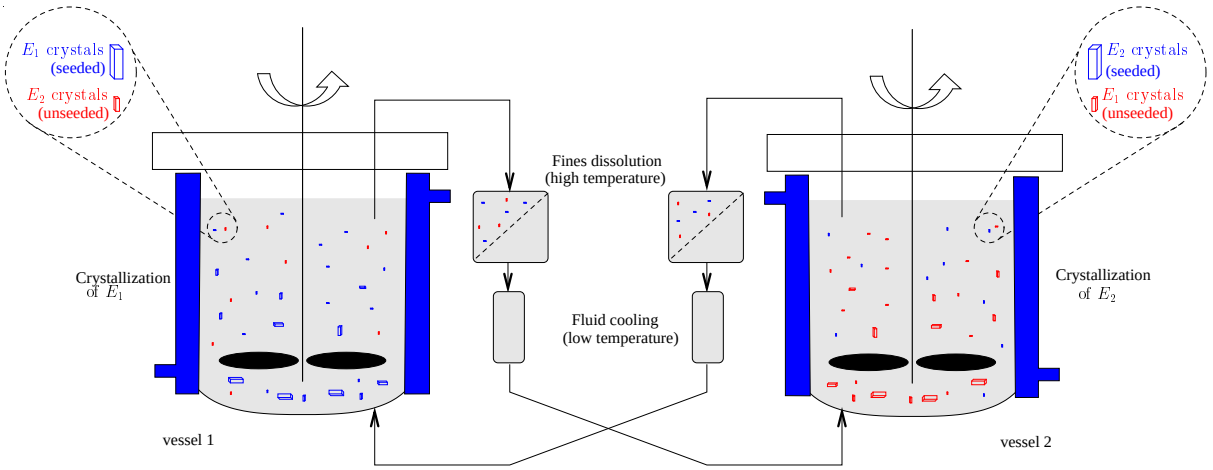

Fig. 3: Simultaneous batch-crystallisation

4.3 Analysis of Biological Reaction Networks

(Bio)chemical reaction networks are characterized by nonlinearity, by high complexity (due to the number of components and interactions), and often by poor practical observability. This imposes considerable challenges for modelling, systems identification and analysis. One particularly interesting (and relevant) question is the following: suppose in a given network both structure and (reaction) parameters are uncertain; are there network topologies that, for no possible set of parameter values, match certain experimentally observed qualitative behavior patterns? If the answer is affirmative, these topologies and the corresponding model hypotheses can clearly be discarded. The answer requires a detailed knowledge of the relation between (bio)chemical reaction network structure on the one hand and qualitative properties of the associated system of ordinary differential equations (ODEs) on the other hand. One particular qualitative behavior is “multistationarity”, i.e., the existence of more than one positive steady state solution to the ODEs derived from the biochemical reaction network.

The standard model of biochemical reaction networks with mass action kinetics is a first order ODE for the concentration vector x of the n involved species. The right hand side of this vector ODE is given by the product of the so-called stoichiometric matrix N and a vector $R(k,x)$ of reaction rates depending on a positive parameter vector k. If the matrix N does not have full row rank, the state is algebraically confined by a system of affine equations. Multistationarity is then equivalent to the existence of a vector k of (positive) rate constants such that the ODE possesses two different positive steady state solutions satisfying the same algebraic constraints. In

chemical engineering, the problem of multistationarity was extensively investigated in the 1980s and 1990s. A partial answer was given by FEINBERGs Chemical Reaction Network Theory (CRNT), which is based on a certain network property called "network deficiency". For networks of deficiency 0 or 1, the existence of multistationarity depends on the feasibility of a system of linear inequalities and can therefore be correctly predicted by CNRT. In these cases, if multistationarity is possible, CNRT will provide a feasible parameter vector k and corresponding steady states x_1 and x_2. If the deficiency is greater than one, the theory might not be decisive, as nonlinear inequalities have to be considered. Current implementations are limited to relatively small networks; thus, a straightforward application to realistic networks is usually impossible. However, for certain large networks, results may be derived from subnetwork analysis. This has been described in (Conradi et al., 2007 a), which also contains an application to network structures arising in the cell cycle control of *Saccharomyces cerevisiae*.

We have also pursued a different approach: in a first step, the algebraic constraints are disregarded and the solution set (x_1, x_2, k) is parametrized via solutions of a new system of equations obtained by transforming the defining equations. This step is based on the idea of generators for pointed polyhedral cones, in particular generators for the intersection of the kernel of the stoichiometric matrix N and the nonnegative orthant of the n-dimensional Euclidean space. Solvability conditions in the new parameters take the form of polynomial equations. For many reaction networks of biological relevance, the transformed equations can be reduced to a system of linear equations. In a second step, these results are extended to the differential-algebraic system of interest. Necessary and sufficient conditions for the existence of a (positive) parameter vector and a pair of different positive steady state solutions of the differential-algebraic system are derived. Details can be found in C. CONRADI's Ph.D thesis.

This two-step procedure has been successfully applied to a double-phosphorylation mechanism (Conradi et al., 2008) and a variety of network structures that can be considered as building blocks of many signal transduction networks (Saez-Rodriguez et al., 2008). Moreover, we have shown that, at least for some specific network structures, it is possible to analytically determine parameter vectors and critical states, where certain bifurcation phenomena occur (see (Conradi et al., 2007 b) for saddle-node bifurcations).

4.4 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. 4 explains the principle of controlled FES for a specific problem, the control of 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.

Stimulation can either be applied directly to the peripheral motor nerves (as shown in Fig. 4) 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, but 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 four subprojects, addressing fundamental questions as well as aiming at transferring results into medical and therapeutical practice.

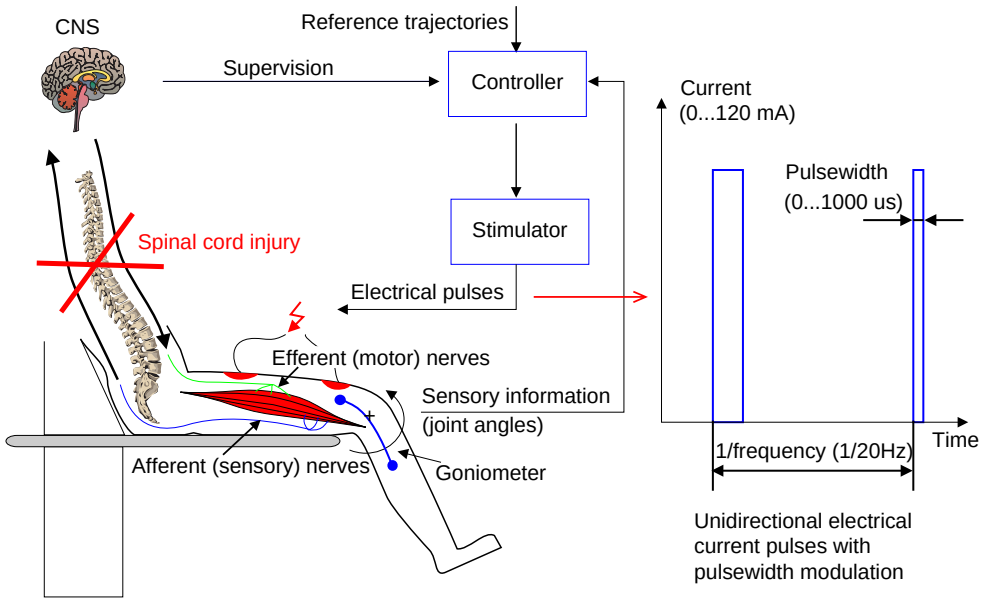

Fig. 4: Functional Electrical Stimulation (FES) for knee-joint angle control

Control of Endeffector-Based Rehabilitation Robotics in Combination with Electrical Stimulation for Gait Training after Stroke

The use of robotic devices has become popular for the rehabilitation of stroke patients as they allow frequent repetitions of movements with a high degree of precision. However, in the standard configuration, the patient has a mere passive role, i.e. s/he can neither actively contribute to the movement nor influence its pattern. The aim of this subproject is twofold: through the use of haptic control and biofeedback, the patient may, depending on her/his abilities, exert influence on the movement pattern; by including functional electrical stimulation of paralysed muscles, exercise is intensified to provide the benefits described above. This research is a joint initiative involving our group, the Fraunhofer Institute for Production Systems and Design Technology, the university hospital Charité in Berlin, and an SME in Magdeburg (Hasomed GmbH). To prepare patients for gait training, the realization of less complex movement patterns as, e.g., cycling has proven useful (Schauer et al., 2006). As a consequence, both gait training machines and cycling ergometers have been equipped to measure the interaction between patient and device and to register the volitional muscle activity of the patient using electromyography (EMG). The overall control scheme has of course to generate physiologically desirable muscle activation patterns and movements. For example, symmetry of torque generation in both the impaired and the healthy leg is a prime objective during FES cycling exercises. To achieve this, a suitable controller has been developed in collaboration with a group

from Politecnico di Milano (Ambrosini et al., 2008). In the context of this cooperation, we have also investigated the optimisation of stimulation patterns for FES cycling (Ferrante et al., 2008).

Electromyography-Based Control of FES in the Rehabilitation of Hemiparetic Patients

Because of the interference caused by voluntary muscle activity, controlled FES for hemiparetic patients is a potentially more demanding problem than for paraplegic persons. In this BMBF funded subproject, we have investigated how to detect such voluntary muscle activity through electromyography (EMG) and how to exploit this information when controlling lower- and upper-limb movements by FES (Fig. 5). Simultaneously applying electrical stimulation and performing EMG measurements on the same muscle group requires special hardware and signal processing routines in order to minimize stimulation artefacts within the EMG measurements. Suitable hardware was developed in cooperation with the SME Haynl GmbH, located near Magdeburg. Because both voluntary activities and activities initiated by FES compete for the same resource (i.e., a muscle), naive strategies, such as choosing the stimulation intensity proportional to the measured EMG signal, do not show desired results. This phenomenon has been investigated in (Schauer et al., 2007), a suitable (gain-scheduled) control scheme was presented in (Shalaby et al., 2008). Based on the available results, we aim at developing a functional electro-therapy for the impaired upper limb of stroke patients. The EMG-controlled system shall enable the patient to carry out complex functional tasks, such as grasping and reaching. Textile electrodes integrated in a garment will be used to handle multiple stimulation and EMG channels.

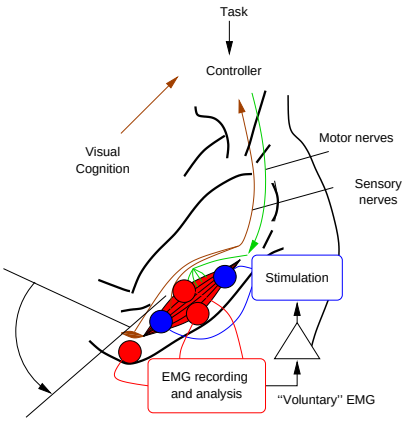

Fig. 5: Principle of EMG-Controlled Electrical Stimulation

Control of FES-Assisted Gait Training / Drop Foot Stimulator

Many people have walking deficits after stroke. Ineffective dorsiflexion during swing (drop-foot) is a particularly frequent phenomenon. A conventional treatment is a passive ankle-foot orthosis. 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 has to be set to a unnecessarily high value, which then causes rapid fatiguing of the stimulated muscle. Conventional feedback, where the ankle-joint angle is sampled at high frequency and the stimulation intensity is then instantly adjusted, is not a realistic alternative unless particularly simple adjustment rules are used. We have therefore investigated a control scheme inspired by Iterative Learning Control: 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 (Nahrstaedt et al., 2008 b). In this way, the advantages of feedforward and feedback are combined in an intuitive manner. The success of such a scheme of course depends critically on the available ankle-joint measurements. We have investigated two different sensor technologies: one approach uses an inertial sensor mounted on the shoe to estimate the angle of the foot with respect to the ground. A successful implementation has been described in (Negård et al., 2006). Based on the available sensor information, we also realised a gait phase detection system such that a heel switch becomes redundant. A promising alternative is the use of bioimpedance to measure the ankle-joint angle directly. The feasibility of employing such an angle measurement was demonstrated in (Nahrstaedt et al., 2008 a). A gait phase detection based on bioimpendance measurements is currently investigated.

Development of a Portable Endeffector-Based Hand/Arm Rehabilitation Robot combined with Functional Electrical Stimulation

We recently started to develop a small and portable robotic device which assists stroke patients when practicing arm and hand movements at home. The device can be thought of as some kind of motor driven computer mouse. The affected hand is attached to the device while the arm is (partially) supported by an additional passive device. The control concept is based on ideas previously developed in other subprojects: interaction forces between the hand and the robot are sensed and used to infer

the required support by the robot. In addition, FES may be employed to make the paretic muscles contribute actively to the desired movement. To control stimulation intensity, EMG signals are used to measure the patients' volitional muscle activities.

5 Research Related Activities

IPC Membership

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

MCBMS06	6th IFAC Symp. on Modelling and Control in Biomedical Systems, Reims, 2006
SPC2006	5th Symposium on Process Control, Ploiesti, 2006
ADHS06	2nd IFAC Conference on Analysis and Design of Hybrid Systems, Alghero, 2006
WODES'06	Workshop on Discrete Event Systems, Ann Arbor, 2006
WODES'08	Workshop on Discrete Event Systems, Gothenburg, 2008
ADHS09	3rd IFAC Conference on Analysis and Design of Hybrid Systems, Zaragoza, 2009
ADCHEM2009	IFAC International Symposium on Advanced Control of Chemical Processes, Istanbul, 2009

V. Azhmyakov was an IPC member of

IXth International Workshop on Stability and Oscillations of Nonlinear Control Systems, Moscow, 2006

T. Schauer is an IPC member of

CCA2008 IEEE International Conference on Control Applications, San Antonio, 2008

MBEC2008 4th European Congress of the International Federation for Medical and Biological Engineering, Antwerp, 2008

AUTSYM08 5th International Symposium on Automatic Control, Wismar, 2008.

Organization of Workshops etc.

Symposium on Information and Control Hierarchies: Foundations, Computation and Applications This was the first event in a new series of bi-annual symposia which the MPI's Scientific Advisory Board suggested the SCT group to organize. The series aims at highlighting the interplay between systems & control theory, chemical and bioprocess engineering, and systems biology. The first event, dedicated to the topic of Hierarchical Systems, was held in May 2008. There were fifteen invited

speakers from eight European and American countries, all experts in Hierarchical Systems, but from different scientific communities. The Symposium provided an interdisciplinary platform, where new ideas were enthusiastically discussed and exchanged. Presentations addressed questions related to systems theoretic frameworks for hierarchical control architectures; they covered analysis aspects for hierarchically structured biological networks and hierarchical implementations of plantwide process control systems. Special thanks for the successful local organisation are due to J. Holzmann and the MPI public relations coordinator, S. Frankmölle.

Technical Committees

J. Raisch is a member of the IFAC (International Federation of Automatic Control) Technical Committee on Discrete Event and Hybrid Systems.

Editorial Duties and Journal Review Activities

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

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

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, Part I + II, 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.*

6 Teaching Activities

6.1 Teaching at OvGU

Most of J. Raisch's teaching at OvGU was related to the degree program, Systemtechnik und Technische Kybernetik (Systems Engineering and Cybernetics), which he was instrumental in building up. His teaching activities within this program continued into the summer semester 2006, when he had already taken up his new position at TUB. During the period covered by this report, he taught the following courses:

- Cybernetics (winter 2005/06, 1st semester, 3 hours/week)
- Introduction to Systems Theory (summer 2006, 2nd semester, 4 hours/week, with C. Conradi)
- Systems Theory (winter 2005/06, 5th semester, 3 hours/week)
- Discrete Event Systems II (winter 2005/06, 7th semester, 3 hours/week)
- Control Engineering (winter 2005/06, 5th semester, 3 hours/week)

G. Reißig taught

- Nonlinear Dynamic Systems (winter 2005/06, 7th semester, 3 hours/week)

T. Schauer taught

- Nonlinear Control (winter 2005/06, 7th semester, 3 hours/week)

C. Conradi taught

- Cybernetics (winter 2006/07 and 2007/08, 1st semester, 3 hours/week)
- Introduction to Systems Theory (summer 2006 (with J. Raisch) and summer 2007, 2nd semester, 4 hours/week)

D. Flockerzi contributes significantly to the Systems Engineering and Cybernetics program. He teaches the following courses:

- Distributed Parameter Systems (4th semester, 4 hours/week)
- Nonlinear Systems (7th semester, 3 hours/week)
- Partial Differential Equations in Science and Engineering (elective, 7th semester, WS 2005/06, 3 hours/week)
- Reaction Networks (elective, 8th semester, summer 2007, 4 hours/week)

6.2 Teaching at TUB

J. Raisch teaches the following courses on a regular (i.e., yearly) basis

- Fundamentals of Control (BSc-level, 4 hours/week)
- Multivariable Control Systems (MSc-level, 4 hours/week)
- Discrete Event Systems (MSC-level, 4 hours/week)

T. Schauer teaches the courses

- Nonlinear Control Systems (MSc-level, 4 hours/week)
- Identification and Control in Medicine (MSc-level, 4 hours/week)

Additional laboratory and seminar courses have been taught by members of the TUB part of the group.

6.3 Teaching Related Activities

Funded by the European Union, we organize two ERASMUS/SOCRATES student exchange programs in the general area of systems and control: one of these exchange links is with the **University of Glasgow (Dr. H. Gollee)**, UK, the other with the **University of Cagliari (Prof. A. Giua)**, Italy.

Moreover, we have initiated an active student exchange program with the **Universidade Federal de Santa Catarina (UFSC) (Prof. J. Cury)**, Brazil.

6.4 Ph.D Theses

J. Raisch has supervised/supervises the following Ph.D projects:

A. **Itigin**	Hierarchical hybrid control systems	December 2005
B.V. **Mishra**	Control of multiproduct batch plants	June 2006
E. **Mayer**	Scheduling and control of cyclic discrete-event systems	June 2007
C. **Conradi**	Analysis of biochemical reaction networks	February 2008
D. **Li**	A new integrated control architecture for cyclic discrete event systems	Submitted
N.O. **Negård**	Controlled FES-Assisted Gait Training for Hemiplegic Stroke Patients based on Inertial Sensors	Submitted
D. **Gromov**	Analysis of hierarchical structures for hybrid control systems	To be submitted in 2008
I. **Angelov**	Optimization and control of preferential crystallization processes	To be submitted in 2008
S. **Geist**	Low-level feedback synthesis in hierarchical hybrid control structures	In preparation
H. **Nahrstaedt**	Iterative Learning Control of Neuroprosthetic Devices using Bioimpedance and Electromyography Measurements	In preparation

S. **Li**	Optimization and control of SMB processes with recycle	In preparation
D. **Luo**	A Mobile Endeffector-Based Hand/Arm Rehabilitation Robot combined with FES	In preparation
S. **Guma**	Optimal control over wireless networks	In preparation
R. **Shalaby**	EMG-Controlled Functional Electro-Therapy for the Upper Limbs after Stroke	In preparation
S. **Hofmann**	Trajectory planning and control of batch processes for the separation of enantiomers via preferential crystallization	In preparation

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

J. **Winkler** TU Dresden	Beiträge zur Regelung des Czochralski-Kristallzüchtungsprozesses zur Herstellung von Verbindungshalbleitern	June 2007
C. **Fleischer** TU Berlin	Controlling Exoskeletons with EMG signals and a Biomechanical Body Model	July 2007
S. **Solmaz** National University of Ireland, Maynooth	Topics in Automative Rollover Prevention: Robust and Adaptive Switching Strategies for Estimation and Control	November 2007
M. **Neumann** TU Berlin	Taktile Bedienung redundanter mobiler Manipulatoren mit einem sechsdimensionalen Kraft-Momenten-Sensor	July 2008

6.5 Diploma/Master Theses

During the period covered by this report, members of the group (both at the MPI and at TUB) have supervised 22 Diploma or Master theses, 9 by students from OvGU, 9 by TUB students, 3 by UFSC students, and one by a student from TU Darmstadt. Group members have co-supervised four theses that were done abroad (at the University of Newcastle, Australia, the National University of Ireland, Maynooth, Princeton University, and the University of Toronto). Moreover, numerous *Studienarbeiten* (pre-Diploma theses) and Bachelor theses were supervised.

7 Awards, Fellowships, Appointments

During the period covered by this report:

J. Reger was offered a W3 professorial position for Control Engineering at Technische Universität Ilmenau and a W2 position at the University of Ulm. He has accepted the offer from TU Ilmenau and has started his new position in July 2008;

V. Azhmyakov was offered a research position at Centro de Investigación y de Estudios Avanzados del Instituto Politécnico Nacional (CINVESTAV), Mexico City, and a W2 professorship at the University of Applied Sciences Cologne. He has accepted the offer from CINVESTAV.

C. Conradi has been awarded a fellowship at the Statistical and Applied Mathematical Sciences Institute (SAMSI), in Raleigh, NC.

8 Future Directions

One of the strategic aims for the next evaluation period is to further strengthen the cooperation with other MPI groups. The following research endeavors provide specific examples: Naim Bajcinca, a new postdoc in the SCT group, will work on the interface between SCT and PCP group. He aims at applying ideas from hybrid systems and robustness theory to a crystallization process with face-specific growth rates, which allows for simultaneous manipulation of crystal size and shape. S. Li, who has a good background in chromatographic separation processes, will work with members of the PCF group on optimization and control problems for Simulated Moving Bed (SMB) Processes with Recycle. On the more theoretical side, we intend to build on our extensive work on hybrid and hierarchical systems to investigate problems for networked and cooperative control. This line of research will be embedded in a number of new interdisciplinary research initiatives:

- *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 will provide 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 will participate in a twofold way: J. Raisch will deliver courses on Discrete Event and Hybrid Systems, and Ph.D students from the group will be able to receive financial assistance to attend courses given by other “virtual faculty” members.
- *DISC – Distributed Supervisory Control of Complex Plants* is a European (Framework 7) Research Project involving 10 partners from 7 countries. It 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.
- *Human-Centric Communication Cluster (H-C3)* is an initiative by TUB and several other research institutions, which will be funded by the Government of Berlin. Currently, as a first step, a graduate school has been implemented. In

the context of H-C3, both the control of networks and the control over networks pose interesting research problems.

- We participate in a major new research initiative by several aerospace, computer science and electrical engineering groups which aims at investigating problems related to swarms of satellites. Our contribution will focus on cooperative ways for trajectory planning and control.
- We participate in a proposal to establish an Advanced Control Training Site (ACTS) under the EU Marie Curie Program. If accepted, the site will focus on problems of networked embedded control systems.

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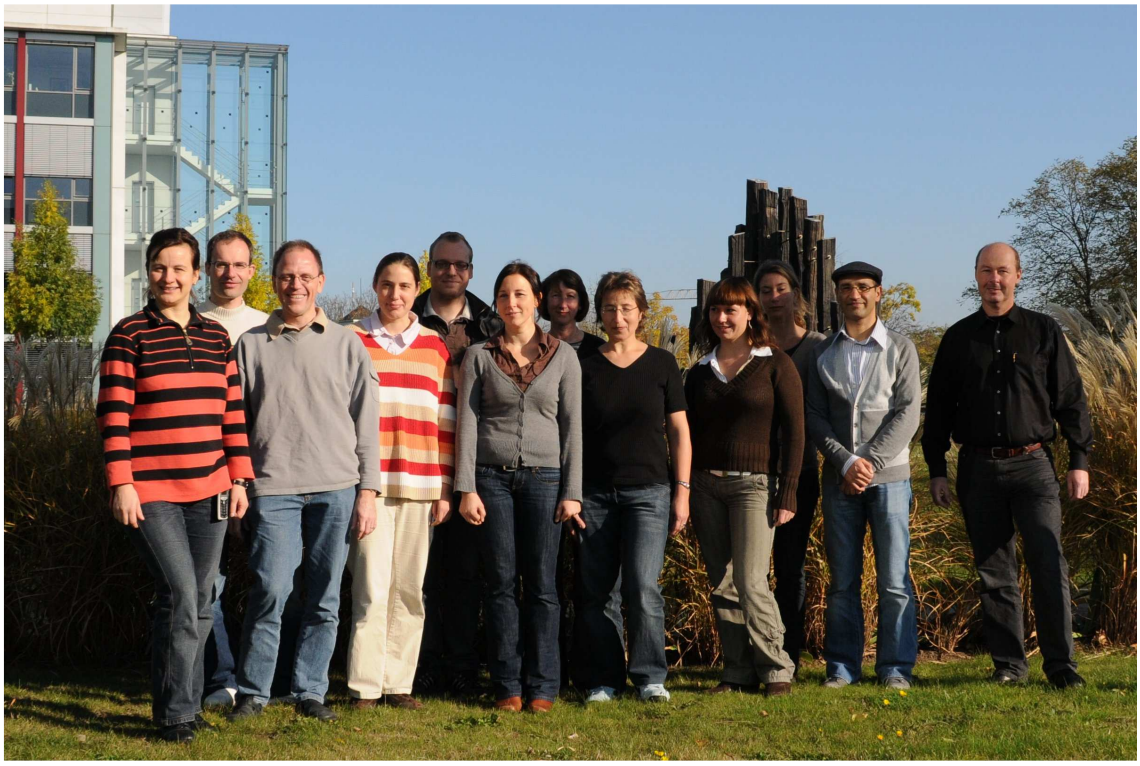
This does not represent a complete list of publications 2006-2008. A complete list is provided separately.

Research Group:

Molecular Network Analysis (MNA)

Prof. Dr. rer. nat. Wolfgang Marwan



This report covers the period from January 2006 to September 2008

1 Group Introduction

The Molecular Network Analysis Group was founded in April 2005 as part of a cooperation contract between the Max Planck Society and the Otto-von-Guericke-University of Magdeburg. According to the contract, the group is funded until end of 2008 jointly by the Max Planck Society, the MPI for Biochemistry and the MPI for Dynamics of Complex Technical Systems where it is accomodated during that initial period, though it is run as a pure University group from the administrational point of view. After 2008, when the cooperation contract with the Max Planck Society expires, the group will be funded at a reduced volume by the University and will finally move into the new building "Verfahrenstechnik" at the University which is currently under construction. Due to administrational and technical reasons, the laboratories of the Marwan group have only been ready to use since August 2006; therefore **this final report covers the experimental work performed within a period of two years only**.

The MNA Group develops new experimental and theoretical concepts to analyse the structure and dynamics of regulatory networks. The challenge is to systematically study network function at the molecular level while working with the intact system as far as possible. This requires special experimental techniques allowing for a systematic perturbation of the system to generate quantitative and time-resolved data, and it requires theoretical methods tailored to evaluate them. The expectation is that a systematic study of the in vivo activity of molecules as elements of functional network modules will provide complementing information to that obtained by conventional experimental techniques which focus either on the biological role of selected proteins or genes or on large data sets obtained through omics approaches.

The experimental work of the group focuses on two model systems, a small network of interacting proteins, mediating the behavioral response of Halobacterium salinarum in response to visible light (phototaxis) and a large genetic network which controls commitment to cell differentiation in the eukaryote Physarum polycephalum. According to our experience, performing research on networks of different molecular complexity stimulates and facilitates the development of both experimental and theoretical approaches to reconstruct (reverse engineer) molecular networks from experimental data and to analyse their dynamic behavior.

By studying phototaxis in Halobacterium, we learned to determine the kinetic behavior of the sensory rhodopsin-transducer heterotetramer in vivo without depending on a priori knowledge of the highly non-linear functional interactions of this photoreceptor with other network building blocks, just by evaluating the output at the flagellar motor (Marwan and Oesterhelt, 1990; Marwan et al., 1995). The results could be verified by in vivo spectroscopic measurements because the sensory rhodopsin molecule reversibly changes its color upon activation. These studies suggested that it is possible to analyse the activity of the elements (or nodes) of a regulatory network in vivo quantitatively and time-resolved once a node-specific perturbation tool is available. This was the rationale of taking a systems biology approach to cell differentiation in the model Physarum polycephalum. Ad hoc, we developed a method, time-resolved somatic complementation analysis. By fusion of mutant cells and cytoplasmic mixing, it is now possible to systematically probe the structure and dynamics of the regulatory network in a time-resolved manner.

With this model system in hand, the long-term goal is now to identify as many molecular components as possible which are involved in the differentiation control and to reconstruct their causal network of interactions. Since this systematic approach is not hypothesis-driven in terms of function of molecules known from literature, we hope and expect that matching the resulting network with the canonical pathways of cellular signal transduction will yield considerable new information on hitherto uncharacterized molecules and their functional interaction in terms of cellular regulation.

Experimentally, network components are identified by combining genetic, genomic, biochemical and functional studies (mutant isolation, map-based cloning, transcriptome analysis, single cell proteomics). The functional interaction of the components is then studied by applying a transient perturbation to the system and by following the response of the network in a time-resolved manner, again by employing different analytical techniques. The resulting time series data are then used to infer (reconstruct) the network topology, determine the rate constants and analyse the dynamic properties of the network. This is done in iterative cycles of experimentation and computation.

We use stochastic Petri nets as computational framework for modeling and simulation. A stochastic version of a well-established Petri net tool developed in cooperation with Monika Heiner (Cottbus) allows the generation of coherent,

composable, and executable models that represent different types of molecular and functional data at arbitrary levels of abstraction. Deterministic, stochastic, discrete or continuous simulations (or combinations thereof) can be performed and the models may be exported in SBML format. As mathematical graphs, Petri nets can be generated and analysed through graph theoretical approaches. In cooperation with mathematicians Annegret Wagler and Robert Weismantel, we have developed an algorithm for the automatic reconstruction of causal interaction networks from experimental time-series data sets. The important feature of this algorithm is that it delivers a complete list of alternative network structures that are compatible with the experimental results. This completeness is guaranteed by mathematical proof (Marwan et al., 2008).

Both frameworks, automatic network reconstruction and stochastic Petri nets which were developed for modeling Halobacterium phototaxis and Physarum sporulation, seem widely applicable to regulatory phenomena in molecular cell biology. This potential is now being explored in cooperative projects of medical relevance involving clinical partners.

2 Members of the Research Group

Tab. 1: Members of the Research Group

Group Member	**Status**	**Background**	**Funding**	**Joined MNA in**
Israel W. Barrantes	PhD student	Molecular Biology	IMPRS	17.09.2007
Dr. Markus Haas	Staff Scientist	Molecular Biology	MPG	15.07.2005
Dr. Xenia Hoffmann	Postdoc	Molecular Biology	FORSYS	01.09.2006
Dr. Anke Jungebloud	Staff Scientist	Molecular Biology	MPG	14.04.2008
Bärbel Lorenz	Technician	Microbiology	MPG	01.09.2005
Dr. Sonja Meyer	Postdoc	Bioinformatics	FORSYS	01.01.2007
Dr. Justin Pachebat	Postdoc	Molecular Biology	DynSys	01.05.2007
Regina Pflug	Technician	Microbiology	FORSYS	01.04.2007
Christian Rohr	PhD student	Computer Science	IMPRS	01.01.2008
Bianca Steidler	Technician	Molecular Biology	MPG	01.09.2005
Janine Stierwald	Secretary	Secretary	OvGU/ FORSYS	01.09.2007
Stefan Streif	PhD student	Control Engineering	MPG	21.11.2005
Dr. Jens Tesmer	Postoc	Microbiology	MPIDKTS	01.03.2007

3 Survey of Research Projects

Tab. 2: Phototaxis Network in Halobacterium

Project:	**Phototaxis Network in *Halobacterium***
Abstract:	We reconstruct and analyze the dynamic properties of the signal transduction network mediating phototaxis in *Halobacterium salinarum*. The network integrates and processes light, chemical, bioenergetic and metabolic stimuli to finally control the swimming behaviour of the cell. The mechanisms of sensory integration, adaptation, differential regulation of gain and motor control are investigated at the molecular systems level by combining experimental and theoretical approaches. Phototaxis in *Halobacterium* is the only example where signal transduction in archaea, the third branch of life, is investigated in depth.
Subproject:	**The archaeal flagellar motor**
Researchers:	S. Streif, W. Marwan
Partners:	W. Staudinger, D. Oesterhelt, MPI Martinsried
Funding:	MPG
Start:	01.05.2005
Subproject:	**Sensory adaptation and gain control in phototaxis**
Researchers:	S. Streif, W. Marwan
Partners:	E. D. Gilles D. Oesterhelt, MPI Martinsried
Funding:	MPG
Start:	21.11.2005
Subproject:	**Discrete event modeling of the phototaxis signal transduction network**
Researchers:	W. Marwan, S. Streif
Partners:	C. Maus, A. Uhrmacher, University of Rostock
Funding:	DynSys
Start:	15. 9. 2008

Tab. 3: Analysis of the sporulation control network in *Physarum polycephalum*

Project:	**Analysis of the sporulation control network in *Physarum polycephalum*: A pipeline for gene discovery, gene function analysis, and regulatory network reconstruction**
Abstract:	The project aims to reconstruct the regulatory network which controls the decision of a eukaryotic cell to terminal differentiation. Network topology and dynamic behavior are analyzed by combining genetic, genomic, biochemical and functional studies (mutant isolation, cDNA sequencing, single cell proteomics, etc.), systematic network perturbation (time-resolved somatic complementation analysis), and different reverse engineering approaches.
Subproject:	**Genetic mapping and molecular cloning of sporulation mutants**
Researchers:	M. Haas, W. Marwan, B. Lorenz, R. Pflug, B. Steidler
Funding:	MPG
Start:	01.08.2006

Subproject:	**Analysis of the *Physarum polycephalum* transcriptome**
Researchers:	W. I. Barrantes, S. Meyer, W. Marwan
Partners:	G. Glöckner, IMB Jena
Funding:	MPG, IMPRS
Start:	17.09.2007
Subproject:	**Control of differential gene expression during commitment of cells to differtiation and reconstruction of the underlying regulatory network**
Researchers:	X. Hoffmann, A. Jungebloud, J. Tesmer, W. Marwan
Funding:	FORSYS
Start:	02.01.2007
Subproject:	**HAPPY mapping of the *Physarum polycephalum* genome**
Researchers:	J. Pachebat, W. Marwan
Partners:	P.H. Dear, Laboratory of Molecular Biology, MRC, Cambridge, UK
Funding:	DynSys, MPG
Start:	01.05.2007
Subproject:	**A reverse genetics pipeline based on a *Physarum polycephalum* mutant library**
Researchers:	A. Jungebloud, M. Haas, W. Marwan, B. Lorenz, R. Pflug, B. Steidler
Funding:	FORSYS, DynSys, MPG
Start:	15. 9. 2008

Tab. 4: Network reconstruction and Petri net modeling

Project:	**Network reconstruction and Petri net modeling**
Abstract:	The reconstruction (inference) of the topology and the dynamic behavior of regulatory networks from experimental data is a central topic in systems biology. We have invented and are now in the process of further developing a discrete mathematical algorithm for the proof-based automatic reconstruction of such networks from experimental time series data sets. The output of this algorithm is represented as a Petri net. At the same time we are developing a framework for stochastic Petri net modeling, model checking and simulation of molecular regulatory networks. This framework allows the generation of coherent, composable and executable models that integrate different types of molecular and functional data at arbitrary levels of abstraction. The framework is applied to different problems in basic research as well as medical research with clinical partners.
Subproject:	**Automatic network reconstruction**
Researchers:	W. Marwan
Partners:	M. Durzinsky, A. Wagler & R. Weismantel, Institute for Mathematical Optimization, University of Magdeburg
Funding:	FORSYS
Start:	1. 11. 2006

Subproject:	**Petri net tool development**	
Researchers:	C. Rohr, W. Marwan	
Partners:	M. Heiner, Brandenburg Technical University Cottbus	
Funding:	IMPRS	
Start:	02.01.2008	
Subproject:	**Network motifs: reconstruction of topology and dynamic behaviour from time series data sets**	
Researchers:	W. Marwan	
Partners:	D. Gilbert, University of Glasgow / London M. Heiner, Brandenburg Technical University Cottbus A. Wagler, R. Weismantel, University of Magdeburg	
Funding:	DynSys	
Start:	25. 6. 2008	
Subproject:	**A Systems Biology Approach towards Predictive Cancer Therapy**	
Researchers:	W. Marwan	
Partners:	K. Pfizenmaier and Consortium	
Funding:	FORSYS Partner program	
Start:	01.08.2008	
Subproject:	**Modelling Pain Switches**	
Researchers:	W. Marwan, N.N.	
Clinical Partners:	Ch. Stein, Free University of Berlin R. Baron, University of Kiel	
Partners:	P. Reeh, University of Erlangen M. Heiner, University of Cottbus T. Hucho, MPI-MG, Berlin	F. Herberg, University of Kassel H. Seitz, MPI-MG, Berlin Microdiscovery GmbH, Berlin
Funding:	MedSys (BMBF)	
Start:	2. 1. 2009	

4 Research Highlights

4.1 Phototaxis in Halobacterium salinarum

4.1.1 Phototaxis in Halobacterium salinarum: an Example of Archaeal Signal Transduction

The tree of life is divided into three main branches: bacteria, archaea, and eukaryotes. Although many aspects of signaling and regulation have been investigated in eukarya and bacteria, the only signal transduction system that is understood in considerable detail in the archaeal branch of life is the biochemical network mediating phototaxis in Halobacterium salinarum.

Since most of the molecules involved in signaling and regulation are different in eukarya and bacteria, identifying the molecules involved in archaeal signaling and understanding the dynamics of their interaction is not only interesting but also gives valuable insight into how signaling systems evolve.

The signaling network that mediates phototaxis in Halobacterium (Fig. 1) is composed of protein modules, orthologs of which are also found in bacterial signaling systems, although there is considerable variation and diversification in the archaeal systems (http://www.halolex.mpg.de).

Instead of four methyl-accepting chemotaxis proteins (MCPs) which function as chemoreceptors for specific compounds in E. coli, there are sixteen orthologs in Halobacterium which greatly increases the spectrum of stimuli to be sensed. In Halobacterium, visible light is sensed by sensory rhodopsins, seven-helix transmembrane proteins that form stable complexes with their specific MCP-type signal transducer, the activity of which feeds into a two-component system regulating the probability of switching the rotational sense of the flagellar motor. The halobacterial system is composed of more protein elements than the chemotaxis system of E. coli, and some of the additional molecules are also found in Bacillus subtilis.

Because activation of different, antagonistically acting photoreceptors can be precisely triggered with visible light, the dynamics of sensory signal processing and behavioral control can be more easily investigated than in bacteria. In cooperation with Ernst Dieter Gilles, we were successful in establishing the first coherent model that links receptor activation to cellular motility behaviour in a prokaryote (Fig. 1).

Although the sensory systems mediating archaeal phototaxis and bacterial chemotaxis rely on orthologous protein elements, they regulate a completely different target, since the flagellar motor of archaea with its protein building blocks is not at all related to the bacterial counterpart. This becomes a fascinating example of how functional modules of biochemical networks can be recombined during evolution. In addition, it provides a convincing, evolutionary argument in favour of the view that functional modules within cellular regulatory networks truly exist and that they evolve as modules.

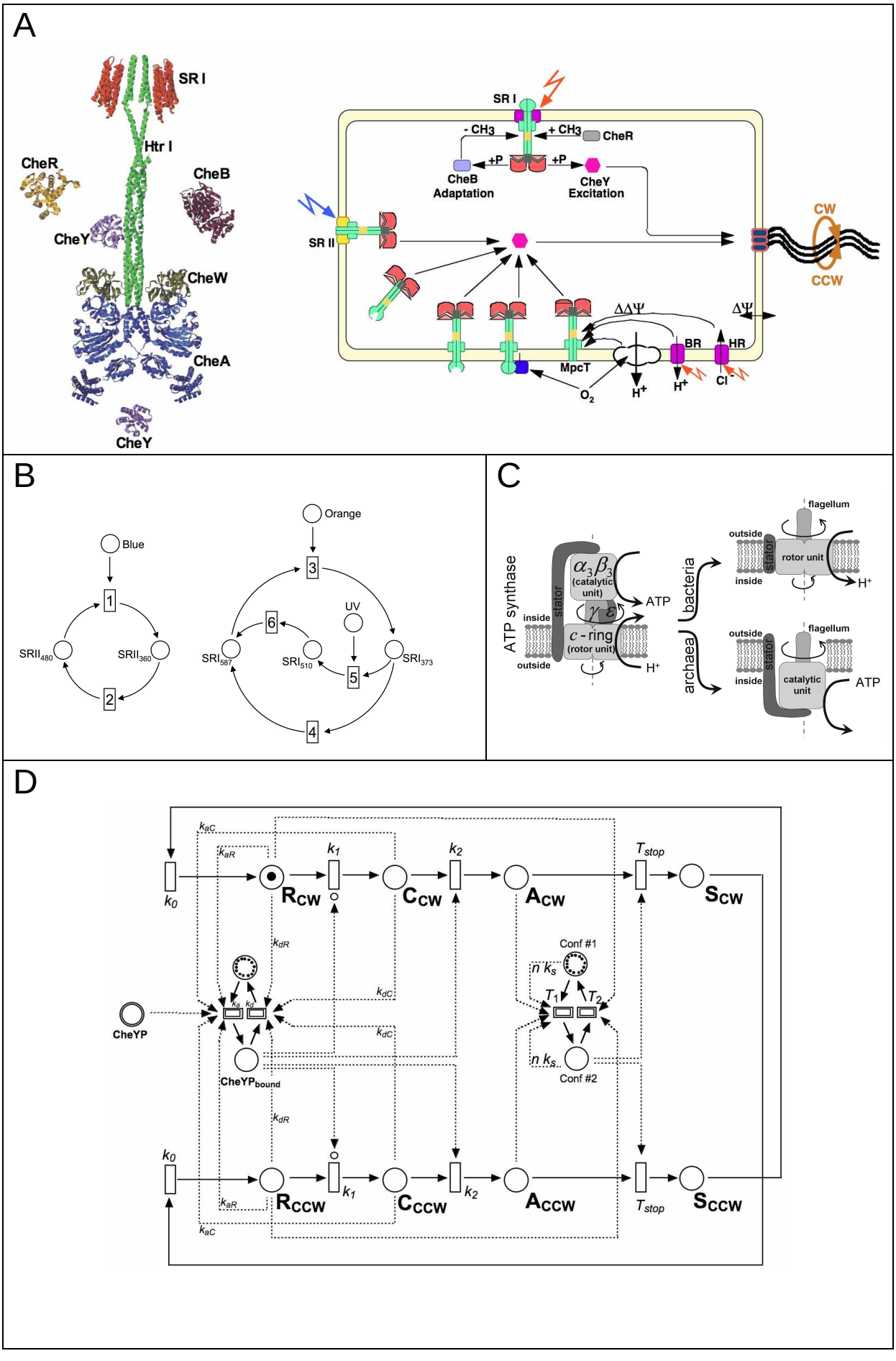
4.1.2 The Archaeal Flagellar Motor: a New Force-generating Molecular Maschine

In cooperation with Dieter Oesterhelt's group at the Max-Planck-Institute for Biochemistry we have shown that the halobacterial flagellar motor is driven by ATP and not by ion motive force as is the case in bacterial prokaryotes (Fig. 1C). Although both the archaeal and the bacterial flagellar motor are rotary devices that convert chemical into mechanical energy, both organelles are composed of non-related

protein subunits. This difference in composition and the use of ATP as fuel characterizes the halobacterial flagellar motor as a new type of force-generating molecular maschine. Known molecular motors in eukaryotes are Actin-Myosin, Tublulin-Dynein, Tubulin-Kinesin (all driven by ATP) and in bacteria the flagellar motor (driven by proton or ion gradients) and the type IV secretion system (driven by ATP). The ATP synthase present in all organisms reversibly converts proton motive force in ATP and its catalytic mechanism involves the rotation of its subunits.

4.1.3 A new Setup for Computer-controlled Stimulation of Halobacterium Cells and Measurement of its Behavioral Responses

We have designed and assembled a new setup for computer-controlled stimulation of halobacterial cells. It consists of two sources for visible stimulus light coupled through light guides into a phase contrast microscope used for observation of halobacterial cells under infrared observation light (which is not seen by the cells). The optical elements were especially designed to maximize the available intensity of stimulation light. The light sources are equipped with a filter wheel for the production of monochromatic light of different wavelengths, an attenuator wheel used to control the light intensity and a shutter. All optical elements are controlled by a computer through two serial ports which allows the precise application of any desired stimulus light pattern. For the sake of maximal flexibility in experimental design, the software was written in-house. The light emitted from the computer-controlled light sources can be either used to specifically stimulate the sensory rhodopsin photoreceptors, the light-driven proton pump bacteriorhodopsin (to study signaling mediated through changes in proton motive force) or to release caged chemostimuli. The behavioural responses of individual cells are recorded and quantitatively evaluated by a computer-assisted motion analysis system which is linked to the computers that control stimulus delivery. The set up is now extensively used to generate the experimental data required for reverse engineering of the phototaxis network.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CheYP
CheYPbound
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Conf #2
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Fig. 1: Systems biology of phototaxis in *Halobacterium*.

A) Right: Schematic representation of the protein network mediating the swimming response of *H. salinarum* to light (phototaxis) or chemical stimuli (chemotaxis). Environmental and internal signals of different kind are detected by stimulus-specific receptor and/or transducer molecules that feed into a common signal processing system controling the switch between clockwise and counterclockwise rotation of the flagellar motor. Sensory adaptation is mediated by negative feed-back via CheB methylesterase. Left: The sensory rhodopsin I-transducer heterotetramer with bound or interacting signaling molecules as obtained by molecular modeling. Light excitation causes a steric trigger upon photon absorption by the sensory rhodopsins (red) which results in tilting the coiled coil helices of the transducer homodimer (green) relative to each other (Klare *et al.*, 2004). Biochemical evidence indicates that this conformational change alters the activity of the associated signaling molecules.

B) Photocycles of the photoreceptors sensory rhodopsin I and -II. The Petri nets were reconstructed from boolean time series data sets with the help of an automatic network reconstruction algorithm (Durzinsky *et al.*, 2008). The algorithm revealed the two photoreceptors as distinct molecules and provided a mathematical proof that no other network connectivity is compatible with the data set. The output of the algorithm is in agreement with the photocycle models obtained heuristically from a large set of biochemical, spectroscopic, and genetic data.

C) Functional comparison of the ATP-driven archaeal flagellar motor (lower right) with the proton-driven bacterial flagellar motor (upper right) and the proton-translocating ATP synthase, where the three functional principles (proton translocation, ATP synthesis/hydrolysis, and rotary motion) cooperate (Streif *et al.*, 2008).

D) Petri net representation of the switch complex of the halobacterial (archaeal) flagellar motor. Switching of the rotational sense of the motor is controled by the phosphorylated form of the small regulatory protein CheY (CheYP). It is obvious from the scheme that the switch complex performs considerable processing and filtering of the input signal CheYP. The model has been reimplemented from an ODE model developed for the flagellar motor switch based on a large set of experimental data (Nutsch *et al.*, 2003; Nutsch *et al.*, 2005).

4.1.4 A Kinetic Model for Sensory Adaptation Through Reversible Methylation of the Transducer Proteins

Using genetic, biochemical and behavioural data we are reconstructing the feed-back regulatory network that mediates sensory adaptation through reversible methylation of the transducer proteins. Most of the transducer proteins contain two methylation sites. The model predicts that one methylation site is activating and the second is deactivating the signaling domain to control the activity of the kinase CheA.

4.2 Control of Sporulation in Physarum polycephalum

4.2.1 Physarum polycephalum is the Unicellular Genetic Model Organism Most Closely Related to Animals

In cooperation with Gernot Glöckner (Jena) we have generated and sequenced a normalized full-length cDNA library from sporulation-competent plasmodial cells. Sequences of more than 90% of the 6000 genes expressed in the sporulation-competent stage were obtained, and for each sequence the corresponding full-length clone is now available (Glöckner et al., 2008). We have communicated the results

obtained by cDNA sequencing to the National Human Genome Research Initiative (NHGRI), where the complete Physarum polycephalum genome is sequenced. Currently, genomic sequence information with 14-fold coverage is available. In addition, we have performed a transcription profiling by 454 sequencing of cDNAs prepared from early committed cells as compared to competent but not induced cells. By counting the number of sequences obtained for each contig, the relative abundance for almost each expressed gene was obtained, as well as for the genes differentially expressed in early committed as compared to competent cells. This data set is a valuable resource for various future experimental approaches.

With the help of the cDNA sequences, we have prepared a survey of the domains of proteins known to be involved in signal transduction and transcriptional regulation and searched for orthologous domains in different organisms ranging from green algae to humans (Barrantes et al., 2008). Surprisingly, we found that Physarum contains orthologs of many signal transduction proteins known from animals, including tyrosine kinases, several oncogenes, and tumour suppressor genes. A phylogenetic analysis of orthologs of mammalian signal transduction protein, including domains of cytoplasmic tyrosine kinases, receptor tyrosine kinases and transcription factors revealed that Physarum together with Dictyostelium is the genetic model system which is most closely related to animals (Fig. 2).

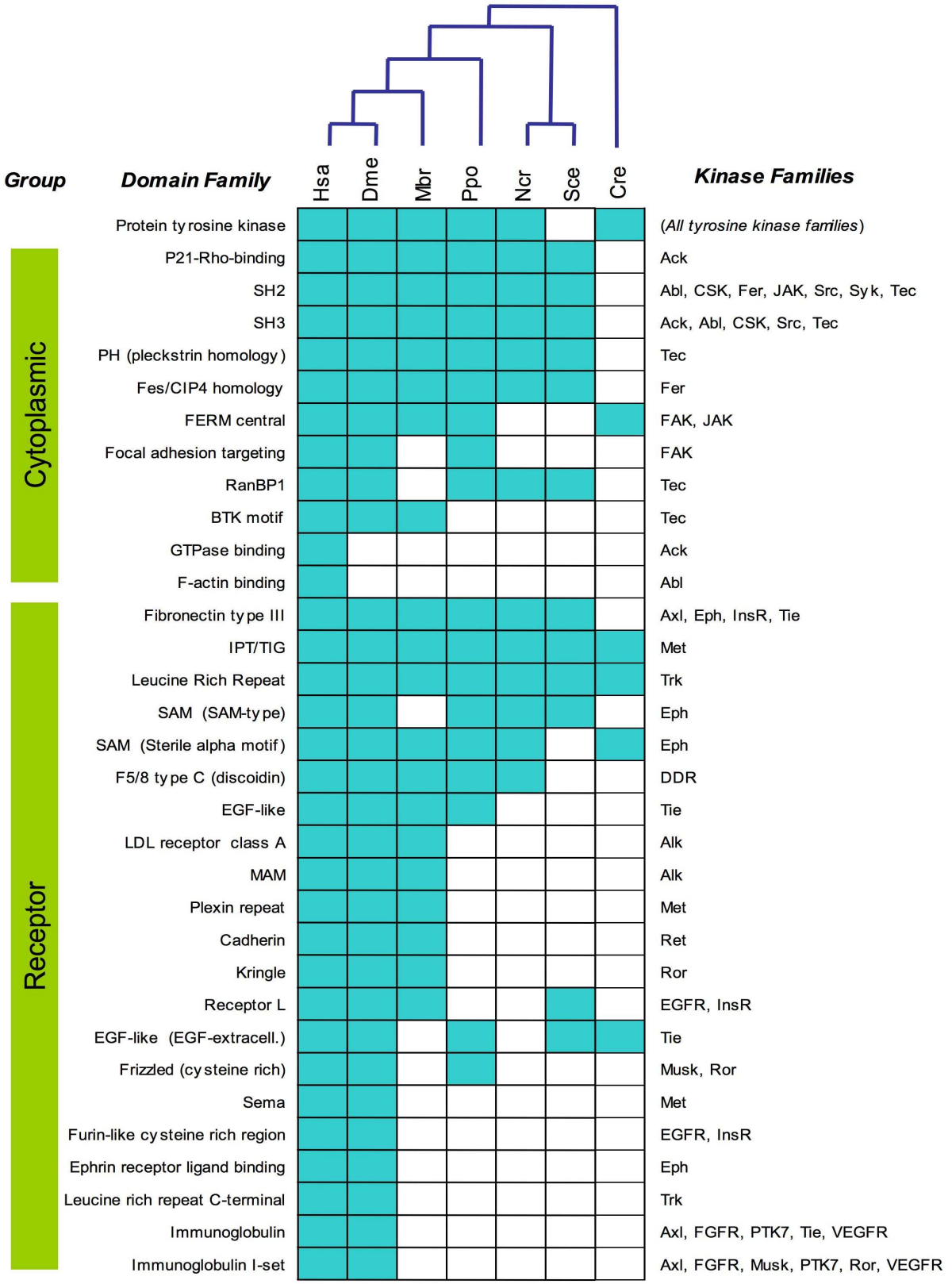

Fig. 2: Distribution of domains associated with tyrosine kinases in Physarum as compared to other species. A filled box means that at least one protein model containing a given domain that constitutes a member of a tyrosine kinase family has been identified by Pfam search. Associated tyrosine kinase groups (cytoplasmic or receptor) and their families, are also listed for each domain. Considered taxa are: C. reinhardtii (Cre), P. polycephalum (Ppo), M. brevicollis (Mbr), S. cerevisiae (Sce), N. crassa (Ncr), D. melanogaster (Dme), and H. sapiens (Hsa). The derived phylogenetic tree on top of the figure places Physarum next to Choanoflagellates (Mbr), the closest relatives of animals (Barrantes et al., 2008).

4.2.2 Sporulation in Physarum polycephalum: A model of Eukaryotic Cell Differentiation

During its developmental cycle, the lower eukaryote Physarum polycephalum differentiates into eight specialized cell types, each characterized by a special morphology, function and gene expression pattern. One of these cell types is a multinucleate giant cell, a so-called plasmodium, which exhibits two hallmarks characteristic for stem cells in animals: unlimited replicative potential and the ability to terminally differentiate into different, specialized cell types. The decision between alternative developmental pathways, spherulation or sporulation, can be monitored experimentally. A short pulse of visible light makes a competent plasmodium proceed through at least two subsequent commitment points and finally results in a seemingly irreversible program of differential gene expression mediating the formation of differentiated fruiting bodies, completed at about 18 hours after the inductive pulse (Marwan, 2003).

The combination of two special properties makes the plasmodium a suitable model for our investigations. Firstly, all nuclei of this giant single cell display strict synchrony with respect to cell cycle and differentiation (Burland et al., 1993). This may be caused by the vigorous acto-myosin powered cytoplasmic streaming, abolishing concentration gradients of any regulatory protein or second messenger. Secondly, plamodia spontaneously fuse upon contact with each other and their cytoplasms readily and completely mix. This property has been exploited in the early 1970s for fundamental investigations on the eukaryotic cell cycle and the role of cytoplasmic factors in its control (Sachsenmaier et al., 1972).

We have shown that any mutant gene product can be titrated against its corresponding wild-type counterpart by fusing two plasmodia of appropriate relative size (Fig. 3). We have also shown that this perturbation can be performed in a time-resolved manner, if the two plasmodia are in different physiological state while their cytoplasms mix (Starostzik and Marwan, 1998). Based on these findings we have started to analyze the structure and dynamics of the entire network that mediates control of sporulation and aim to identify as many of its molecular components as possible.

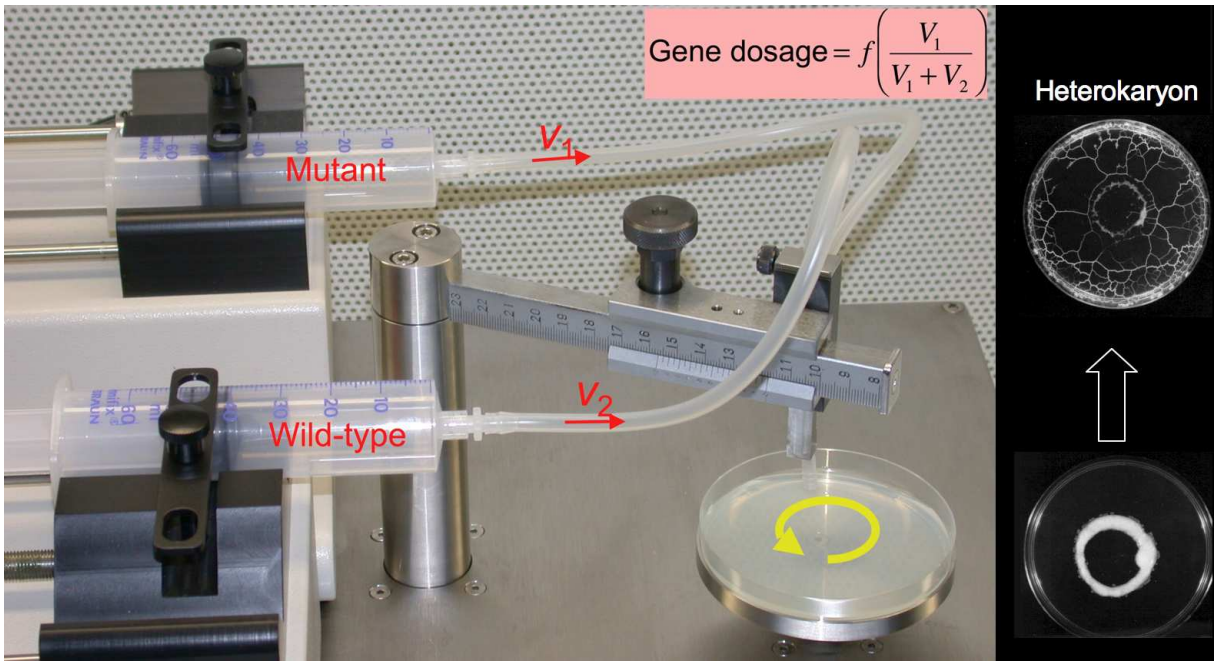

Fig. 3: Gene dosage titration in Physarum polycephalum. We have constructed a device where two syringe pumps are controled by computer to apply a ring of microplasmodial pellet on an agar plate. Each syringe contains the cell mass (paste) of a wild-type or mutant strain. The relative amount of the two strains applied to the plate is adjusted through the relative speed of the two pumps. Right: After one day of incubation, the plasmodial cells within the ring fuse to give a big single cell, a so-called heterokaryon, containing a mixture of two genetically different nuclear populations. With this approach the dosage of each gene tagged by mutation can be adjusted at arbitrarily fine resolution.

4.2.3 Isolation and Genetic Analysis of Mutants Altered in Sporulation Control: Tagging the Nodes of the Network by Forward and Reverse Genetics

Physarum polycephalum is a genetic organism and its life cycle allows for the application of sophisticated genetic techniques. Using a temperature-sensitive mating type mutation, the life cycle can be switched from haploid to diploid and vice versa at will. This allows for the generation of mutants of mono-nucleate, haploid amoebae and also to screen for phenotypes in haploid plasmodia derived from them, while at the same time keeping all options for genetic analysis through crossing and segregation analyses. We have established a genetic screening procedure for mutants altered in the control of sporulation after chemical mutagenesis with Ethylnitrosourea, which allows for large scale generation of mutants (Sujatha et al., 2005) that randomly tag the nodes of the sporulation control network. Through generating point mutations, it seems at least in principle possible to tag all genes involved in sporulation control.

In order to identify the sporulation control genes at the molecular level, we have established a genetic mapping procedure based on single nucleotide polymorphisms (SNP's). Mutants are first crossed with a wild-type strain, then the progeny is screened for phenotype expression and finally the mutated gene is mapped by

following the co-segregation of SNP markers with the phenotype (Fig. 4). To allow for efficient mapping, we are identifying several hundred SNPs and are now using robotics.

At the same time we are preparing a HAPPY map, which is a physical map of the genome in cooperation with P.H. Dear (Cambridge, UK). The map will contain 6000 markers, each mapping in an gene expressed in sporulation-competent plasmodia. Cloning chemically induced point mutations by way of mapping is straight forward and certainly not less efficient than targeted or random transgenic gene disruption techniques, since performing a segregation analysis saves time-consuming rounds of verification that would otherwise be necessary.

In order to obtain loss-of-function mutants and allelic series of pre-defined genes, we are currently developing a library which contains knockout strains for all genes. The library is made of mononucleate diploid amoebae. Since less than 3% of all genes are expected to be haploinsufficient, point mutations even in those genes which cause a lethal phenotype in homozygotes can be obtained. To find a mutant in the gene of interest, the library is screened employing a PCR-based technique (Mashimo et al., 2008).

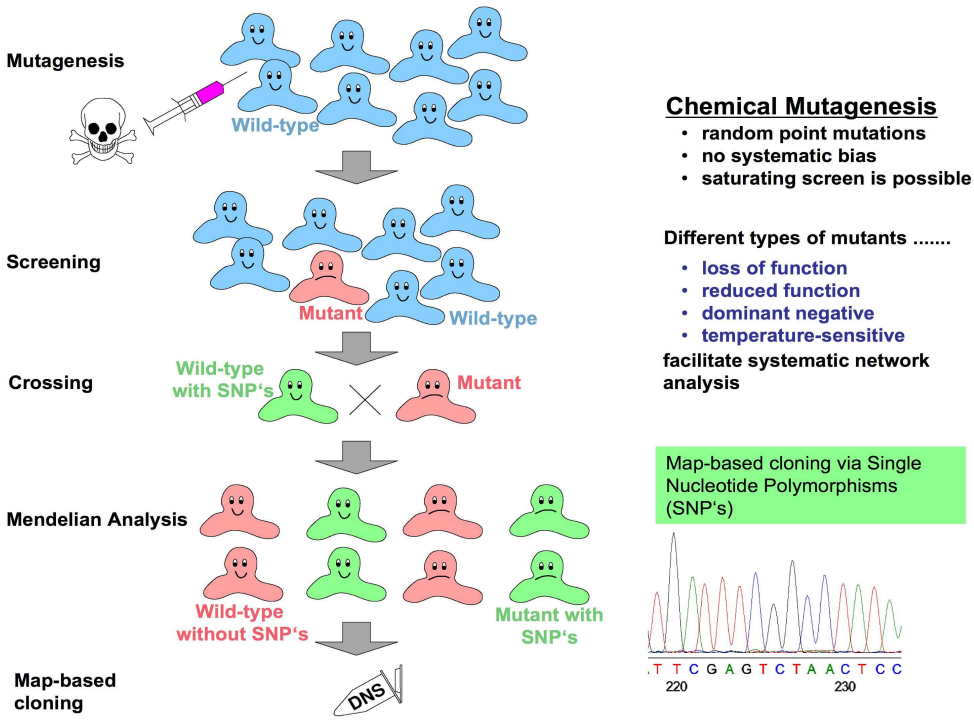

Fig. 4: Forward genetic approach to identify the nodes of the sporulation control network on a systematic basis. Physarum amoebae are mutagenized by ethylnitrosourea and mutants screened for alterations in the ability to form fruiting bodies (a cell differentiation process). In order to identify the mutation which causes the phenotype, a mutant is crossed with a wild-type strain which carries many single nucleotide polymorphisms (SNP's) due to natural variation. Following genetic recombination, the offspring is analysed for the cosegregation of phenotype with various SNP's that serve as genetic markers. Finally, the mutated gene can be identified by map-based cloning.

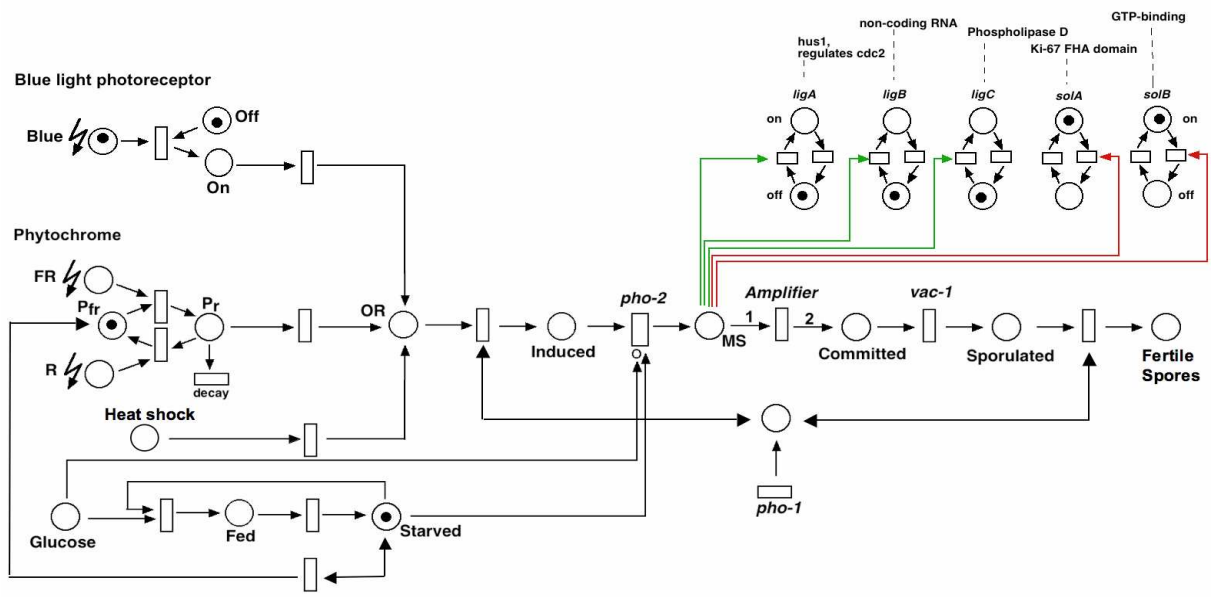

Fig. 5: Petri net model of sporulation control in Physarum polycephalum as reconstructed from experimental data. The model quantitatively predicts the probabilistic response (fruiting body and spore formation) of wild-type and mutants to environmental factors (light, heat shock, and glucose supply). The Petri nets can consistently represent causally connected processes at arbitraty level of abstraction, e.g. quantitatively linking single molecule events to the macroscopic behavior of a cell.

4.2.4 A Reverse Engineering Framework for the Sporulation Control Network

We have developed a theoretical framework to reconstruct (reverse engineer) the sporulation control network (Fig. 5) from time-resolved somatic complementation results and other experimental data based on hierarchical Petri net modeling and simulation (Marwan et al., 2005).

In time-resolved somatic complementation experiments, a cell with a block in the sporulation control network is induced by a light pulse and subsequently fused with a non-induced cell which is blocked at a different node of the network. By systematic variation of the delay time between receptor activation (induction) and the time of cell fusion, the signal flow through the network can be detected in a time-resolved manner (Marwan and Starostzik, 2002; Marwan, 2003). The network is then reconstructed computationally with the experimental results obtained on different mutant pairs.

The molecular network of sporulation control is reconstructed in the form of a stochastic Petri net. A Petri net is a bipartite directed graph, a mathematical structure which can be used as a formal modeling language (Pinney et al., 2003). Petri nets are able to consistently display all kind of functional and molecular data within one single, coherent model, while being able to describe processes occurring at different levels of abstraction in a consistent and formally correct way (Wagler et al., 2008).

Individual elements of the net, places or transitions can be resolved into subnetworks that, at the end, stoichiometrically and mechanistically describe individual (bio-) chemical reactions.

In its graphical representation a Petri net can be easily read and intuitively understood by biologists having no mathematical skills. Being executable, the graphical representation of a Petri net can be run to perform numerical simulations in order to reproduce quantitative experimental results and to validate eventually unproven assumptions. In addition to running simulations, a Petri net can be subjected to rigorous mathematical treatment in order to prove structural and functional properties (Marwan et al., 2008).

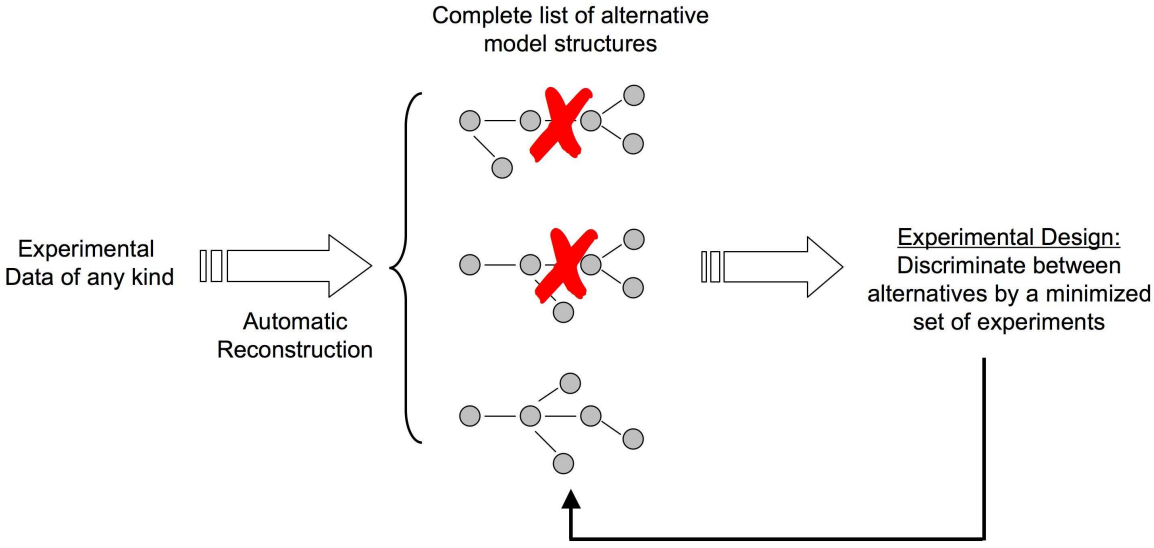

Fig. 6: Use of Automatic Network Reconstruction to prove a network structure by disproving its alternatives. Experimental data of any kind are used to generate a complete list of model structures that are able to reproduce the experimental data. The data set is made large enough that only few alternative structures remain. The completeness of the list of alternatives is guaranteed by a mathematical proof. The alternatives are subsequently used to identify a minimal set of experiments the results of which allow to discriminate between the alternatives. The structure of the finally remaining network is proven if all alternatives of the list could be excluded by experimental evidence (Durzinsky et al., 2008).

4.3 Automatic Network Reconstruction

In cooperation with Annegret Wagler and Robert Weismantel from the Otto-von-Guericke University, we have developed an algorithm for the automatic reconstruction of causal interaction networks from experimental time-series data sets (Durzinsky et al., 2008; Marwan et al., 2008).

Starting from a discrete time-series data set, the algorithm performs vector operations that in the end yield the incidence matrix of a Petri net (Fig. 1B). As proven mathematically, the algorithm provides a complete set of network structures that are able to reproduce the experimental data set including the corresponding partial order of reactions (Fig. 6). The tremendous advantage of this algorithm as compared to conventional network inference methods is that the automatic network reconstruction finds all possible explanations of a set of experiments independent of personal skill or bias in interpretation of experimental results. It also defines a minimal set of experiments necessary to determine alternative models. Experimental design based on automatic network reconstruction hence can help to avoid experiments the results of which do not allow firm conclusions to be drawn. Since the algorithm is computationally expensive in its current implementation, the work now focuses on the design of a computationally efficient algorithm that allows the reconstruction of large networks with hundreds of components.

5 Teaching Activities

Members of the MNA group are in charge of the biochemistry education of Biosystemtechnik undergraduates and of the education in "Regulationsbiologie" (Molecular Cybernetics) of Biosystemtechnik graduates.

6 Recent Appointments and Awards

In 2008, W. Marwan was appointed as spokesman of the Magdeburg Centre for Systems Biology (MaCS).

7 Future Directions

Since the financial support of the MNA group by the Max Planck Society expires end of 2008, the group will continue at the University as an integral part of the recently founded „Magdeburg Centre for Systems Biology“ (one of the four German Systems

Biology Centers established by the Research Ministry BMBF) in performing the research program described below.

Through the intersectional cooperation with E. D. Gilles and D. Oesterhelt, phototaxis in *Halobacterium* became a paradigm for the development of new theoretical approaches to the systems biology of molecular networks, and we could show that these concepts can be successfully applied to more complex eukaryotic cells. Because the development of theoretical and computational approaches is much more easy with this small network of interacting proteins, halobacterial phototaxis will remain a fundamental component of our future systems biology research.

At the level of the eukaryotic cell, the Marwan group will focus on contributing to one of the major open questions in molecular cell biology, namely on identifying the circuitry that switches the stem cell-like state of a eukaryotic cell to commitment and differentiation. As *Physarum* is very accessible to systems level-oriented experimental approaches by providing unique experimental options, this will be addressed by systematically isolating mutants that are affected in the ability to differentiate, identifying the affected genes by map-based cloning and reconstructing the network of their regulatory interactions by computational approaches. The necessary experimental data will be obtained through physiological studies and time-resolved mutant complementation experiments which are evaluated at the phenotypic level, at the level of differential gene expression, and on the level of the proteome. We hope and expect that our system-oriented approach within the next five years will deliver a comprehensive dynamic model of commitment and cell differentiation which considerably extends the canonic pathways known today.

8 References

(This is not a full list of publications of the MNA Group)

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Marwan, W.: Theory of time-resolved somatic complementation and its use for the analysis of the sporulation control network of *Physarum polycephalum*. *Genetics* **164**, 105-15 (2003)

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Research Group:

Systems Biology (SBI)

Prof. Dr.-Ing. Ernst Dieter Gilles

This report covers the period from January 2006 to September 2008.

1 Group Introduction

Computational modeling and simulation of living systems in multidisciplinary research groups has now become a generally accepted meaning of the term *Systems Biology*. While this attribute also applies for the activities in this field at MPI, the SBI group is characterized by a number of features which create a distinctive identity of the group when compared to similar institutions such as (i) The high impact of engineering science for analyzing biological systems at the structural and functional level. Here, we address fundamental properties of living systems, such as robustness, multistationarity, stability or hierarchy. Furthermore, experimental design and model-based generation of hypotheses are major fields where experimental biology is guided by methods of control engineering. (ii) The different levels of biological complexity and different scales of time and space, represented by appropriate model organisms that are addressed experimentally and theoretically. Current projects of the group cover a large range of complexity, starting from bacteria (*E. coli*, *Rhodospirillum rubrum*, Halobacteria) via unicellular eukaryotes (*Saccharomyces cerevisiae*) to higher eukaryotic cells, functioning in the context of multicellular organs and tissues (hepatocytes, immune cells, epithelial cells). While some of the model systems were chosen because of unique experimental opportunities for studying specific aspects of cellular signalling (redox control in *R. rubrum*, see 4.1), others such as *E. coli* or *S. cerevisiae* represent classical model organisms due to the experimental tools for cultivation and genetic modification, and the huge amount of data available today for almost every aspect and molecular detail in 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. (iii) The focus on signal transduction and regulation that is central to all projects, and its application to biotechnological and medical problems. (iv) Close integration of theory and experiment. Especially the projects dealing with signaling and regulation in bacteria (4.1 & 4.2), are based on a tight interaction of theory and carefully controlled experiments, conducted in a bioreactor facility of the institute. We found this intimate collaboration to be indispensible 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 aspect is not realized 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 generic theoretical methods and software tools that fit the particular requirements when modeling cellular systems. We also apply methods from systems theory that allow decomposition and a modular analysis of signaling networks. Systems Biology requires the development of appropriate software tools. Our effort is twofold: ProMoT/DIVA/Diana is a powerful general-purpose modeling and simulation framework for dynamical systems and is based on a modular modeling concept reflecting the modular structure of biological systems. It is being extended with special functionalities for modeling cellular systems, including routines for handling and visualizing large cellular networks. CellNetAnalyzer, the second software tool developed in our group, is a graphical user interface facilitating comprehensive topological studies in large-scale biochemical networks.

Cellular systems and some classes of complex technical processes (e.g. chemical, traffic, information) share a number of essential design principles. A typical property is ‘robustness’, which is a desired goal of technical processes and an inherent property of biological systems. Thus engineers may learn from cellular systems how to construct a robust functionality by applying appropriate control techniques in which successful design principles of technical systems may help the systems biologists to identify and to understand cellular regulatory circuits. Other examples of common design principles are modularization and hierarchical structuring.

Based on this kind of reasoning the SBI group took the initiative to establish a new joint research project promoting interdisciplinary cooperation between systems engineering, biology, medicine and mathematics. The state of Saxony-Anhalt financed this research project from 2004 to 2006 and further developed it into the research center ‘Dynamical Systems’ at the MPI and the OvGU. After a successful evaluation the research center was provided funding in the annual amount of 2.3 mil. € (2007 to 2011). The SBI group is substantially involved in this center. Prof. Gilles was the speaker until 2008, when his directorship at the MPI expired.

The SBI group was very successful in applying for third party research funding offered by the BMBF (FORSYS, HepatoSys, SysMO). One particular success was the allocation of one of four BMBF-FORSYS-Centers to Magdeburg (MPI and OvGU). Prof. Gilles was speaker of this center until 2008. The total third party funding

of the SBI group amounts at 8 mil. € from 2007 to 2011. To work on all the research projects funded by these grants, the size of the SBI group had to be increased during the last year.

The exclusive funding of the SBI personnel by third party money brings about some obvious problems. In order to ensure a long-term existence of the group at the MPI, the SBI group urgently requires an appropriate incorporation into the structure of the MPI. This could be achieved by a fifth department. Another solution to this problem would be the assignment of two W2 professorships in Systems Biology (theoretical and experimental) into the structure of the MPI. This solution could take into account the interdisciplinary character of Systems Biology.

To relieve Prof. Gilles from a part of his burden and responsibilities as leader of the SBI group a restructuring was carried out. The group consists now of 6 junior research groups and one senior research group. The restructuring allows highly motivated and excellent young scientists to develop their scientific profiles in their function as group leaders.

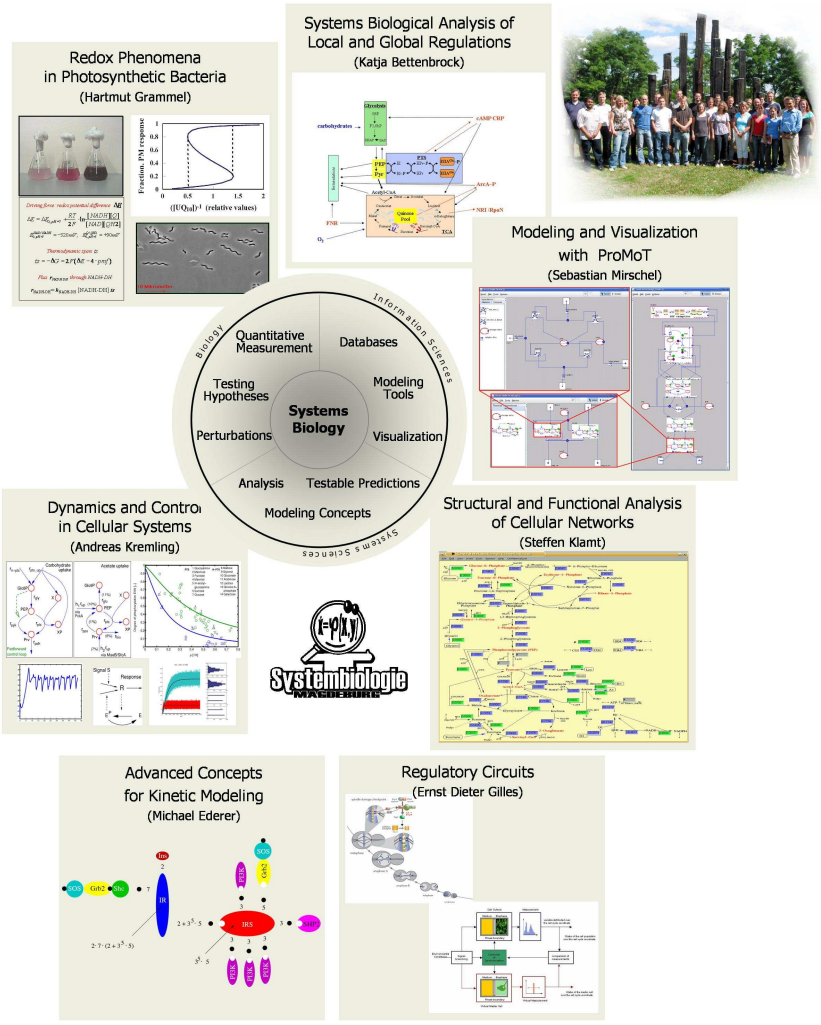

Fig. 1: Research activities of the SBI group

2 Members of the Research Group

Tab. 1: Members of the group

Group Member	Status	Joined MPI
Prof. Ernst Dieter **Gilles**	Head of the Group	
Tobias **Backfisch**	Ph.D. Student	07/2001 -12/2006
Dr. Detlev **Bannasch**	Postdoc	03/2005
Dr. Katja **Bettenbrock**	Postdoc	09/1998
Ralph **Bittner**	Ph.D. Student	09/1999 – 12/2007
Jan **Blumschein**	Ph.D. Student	09/2002
Anke **Carius**	Ph.D. Student	04/2007
Holger **Conzelmann**	Ph.D. Student	01/2007 - 07/2008
Michael **Ederer**	Ph.D. Student	01/2007
Stefan **Gayer**	Ph.D. Student	07/2007
Martin **Ginkel**	Ph.D. Student	11/1998 – 03/2008
Dr. Hartmut **Grammel**	Postdoc	03/1998
Oliver **Hädicke**	Ph.D. Student	03/2007
Benjamin **Herzer**	Ph.D. Student	06/2008
Jeremy **Huard**	Ph.D. Student	06/2004
Susann **Jahn**	Ph.D. Student	04/2007
Jim **Joy**	IMPRS Student	01/2008
Axel von **Kamp**	Postdoc	10/2007
Dr. Steffen **Klamt**	Postdoc	05/1998
Markus **Koschorreck**	Ph.D. Student	01/2005
Dr. Andreas **Kremling**	Postdoc	03/1998
Axel **Lachmeier**	Ph.D. Student	11/2007
Alexander **Lutz**	Ph.D. Student	06/2008
Anja **Medger**	Ph.D. Student	04/2007
Sebastian **Mirschel**	Ph.D. Student	06/2004
Tobias **Neuhaus**	Ph.D. Student	02/2005
Arturo **Padilla**	Scholarship holder	08/2007
Michael **Rempel**	Ph.D. Student	04/2007
Christiane **Rudolf**	Ph.D. Student	09/2007
Julio **Saez Rodriguez**	Ph.D. Student	03/2002 – 01/2007
Daniel **Samaga**	Ph.D. Student	02/2007
Regina **Samaga**	Ph.D. Student	09/2006
Rebekka **Schlatter**	Ph.D. Student	08/2008
Hannah **Sharp**	Ph.D. Student	10/2006
Andrea **Spitzner**	Ph.D. Student	09/2006 – 01/2008
Stefan **Stagge**	Ph.D. Student	07/2007
Katrin **Steinmetz**	Ph.D. Student	03/2007
Sonja **Steinsiek**	Postdoc	08/2007
Ronny **Straube**	Postdoc	12/2006
Lisa **Zeiger**	Ph.D. Student	07/2008

Technical staff:		
Andrea **Focke**	Laboratory	12/2003
Janine **Holzmann**	Secretary	02/2007
Ruxandra **Rehner**	Laboratory	10/1999
Christine **Richter**	Laboratory	09/2007
Melanie **Säger**	Laboratory	09/2007
Steffi **Strähler**	Technical Support	02/2007
Helga **Tietgens**	Laboratory	07/2001
Renate **Wagner**	Secretary	06/1998

Tab. 2: Visiting Scientists

Prof. Joseph Lengeler	University Osnabrück, Germany
Prof. Doraiswami Ramkrishna	University of West Lafayette, USA

3 Research Activities

Project Area: Hierarchical Structures

Junior Research Group (leader: Hartmut Grammel): Redox Phenomena in Photosynthetic Bacteria – Applications in Systems Biology and Biotechnology				
Title / Subproject	**Scientists**	**Funded by**	**Start**	**Partners**
Redox analysis of thiol-networks in R. rubrum.	Carius	BMBF	05/07	Straube, Hädicke
^{13}C metabolic flux analysis of biotechnological applications	Rudolf	BMBF	09/07	Klamt, Haedicke, Wahl (BPE); Stuttgart Univ. (Ghosh/ Sawodny)
Modeling of central metabolic pathways	Straube	BMBF	12/06	Hädicke
Model-based process control	Zeiger	BMBF	07/08	

Junior Research Group (leader: Katja Bettenbrock) : Systems Biological Analysis of Local and Global Regulations				
Title / Subproject	**Scientists**	**Funded by**	**Start**	**Partners**
Analysis of cellular regulation with respect to the single cell level	Medger	BMBF	01/07	
Analysis of the interaction of carbon and nitrogen control	Jahn	BMBF	01/07	Osnabrück Univ. (Jahreis)
Model-based modification of cellular regulation in *S. cerevisiael*	Sharp	BMBF	01/07	Stuttgart Univ. (Hilt)

Impact of enzymatic reactions on the global control of the aerob/anaerob response	Steinsiek, Stagge	BMBF	04/07	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, Medger	BMBF	04/07	Stuttgart Univ. (Sawodny, Sauter) Amsterdam Univ. (Teixera de Mattos) Sheffield Univ. (Poole, Green, Holcombe)
Model-based modification of cellular regulation in *E. coli*	Strähler	LSA	01/07	Stuttgart Univ. (Hilt)

Project Area: Network Theory

Junior Research Group (leader: Steffen Klamt) Structural and Functional Analysis of Cellular Networks				
Title / Subproject	**Scientists**	**Funded by**	**Start**	**Partners**
Reconstruction and analysis of logical models of mammalian signaling pathways	R. Samaga	BMBF	01/07	Harvard Medical School (Sorger)
Methods and tools for qualitative modeling of signaling and regulatory networks	R. Samaga	BMBF	01/05	OvGU (Haus, Weismantel)
Knock-out strategies in metabolic networks	Hädicke	LSA	01/07	OvGU (Haus); Fraser Univ. (Stephen)
Algorithms/Software for network analysis	von Kamp	LSA	01/07	Helmholtz-Center Munich (Theis)
Modeling T-Cell receptor activation	Saez-Rodriguez	LSA	01/05	OvGU (Schraven)
Modeling of HGF and *H.pylori* induced c-Met signaling	Saez-Rodriguez	LSA MPI	03/98	OvGU (Prof. Naumann)

Junior Research Group (leader: Andreas Kremling) Dynamics and Control of Cellular Systems				
Title / Project	**Scientists**	**Funded by**	**Start**	**Partners**
Population based modeling of the K^+ uptake systems in Escherichia coli	Gayer	BMBF	07/07	LMU Munich (Jung) Vigo Univ., Spain (Banga)
Model set-up and analysis to describe metabolism, signal transduction and gene expression in Pseudomonas putida	Joy	MPG BMBF	01/08	HZI Braunschweig (Martins dos Santos) Hannover Univ. (Tümmler)

Dynamic modeling of regulatory and signal transduction networks (Catabolite repression in E. coli)	Kremling	BMBF	01/07	

Model validation, parameter analysis and experimental design	Kremling	BMBF	01/07	
Analysis of bacterial regulation on a single cell level	D. Samaga	LSA	02/07	

Junior Research Group (leader: Sebastian Mirschel): Tools and Concepts for Modeling and Simulation				
Title / Subproject	**Scientists**	**Funded by**	**Start**	**Partners**
Modeling and Simulation tool ProMot/DIVA/Diana for biological systems	Ginkel	MPI	01/99	Donezk Univ. (Svjatnyi) MPI (PDS group)
Specialized Visual Editors for Systems Biology Models	Steinmetz	BMBF	03/07	MPI (BPE group)
Concepts and tools for model integration	Rempel	BMBF	04/07	Heidelberg Univ. (Kummer); MPI MG Berlin (Liebermeister)
Visualization of networks	Mirschel	BMBF	06/04	IPK Gatersleben (Schreiber)
Interfaces for component-based modeling and analysis tools	Mirschel	BMBF	06/04	Heidelberg Univ. (Kummer)

Junior Research Group (leader: Michael Ederer): Advanced Concepts for Kinetic Modeling				
Title / Subproject	**Scientists**	**Funded by**	**Start**	**Partners**
Exact model reduction for signal transduction networks	Conzelmann	BMBF	10/06	HepatoSys
Reduced-order modeling of signal transduction networks	Koschorreck	BMBF	04/05	Freiburg Univ. (Timmer, Rodriguez);
Modeling of the Rhodopsin network	Schlatter	BMBF	08/08	Helmholtz Zentrum München (Ueffing)
Thermodynamic constraints in kinetic modelling	Ederer	BMBF	10/04	Stuttgart Univ. (Sawodny); Sheffield Univ. (Poole)

Senior Research Group (leader: Ernst Dieter Gilles): Regulatory Circuits				
Title / Subproject	**Scientists**	**Funded by**	**Start**	**Partners**
Model-based synchronization of yeast cultures	Sharp	BMBF	01/07	Stuttgart Univ. (Hilt, Sawodny)
Phototaxis in Halobacteria	Neuhaus	LSA	02/05	MNA
Proliferation control in hepatocytes	Huard	BMBF	01/04	DKFZ Heidelberg (Klingmüller)

4 Research Highlights

4.1 Junior Research Group: Redox Phenomena in Photosynthetic Bacteria (Hartmut Grammel)

The group develops and applies both experimental tools and computational models for achieving two ultimate goals: (i) the establishment of a facultative photosynthetic bacterium, *Rhodospirillum rubrum*, as a new model organism for Systems Biology, and (ii) the development of *R. rubrum* as a producer organism for biotechnology. Both issues are tightly connected by the obtained experimental data and the application of the different modeling approaches.

Systems Biology of Redox Control in Photosynthetic Bacteria

The choice for *R. rubrum* as a model organism for Systems Biology is governed by the existence of an endogenous redox indicator – the highly pigmented intracytoplasmic photosynthetic membrane (ICM) – in this organism, which is synthesized depending on the redox conditions of the environment (Fig. 2).

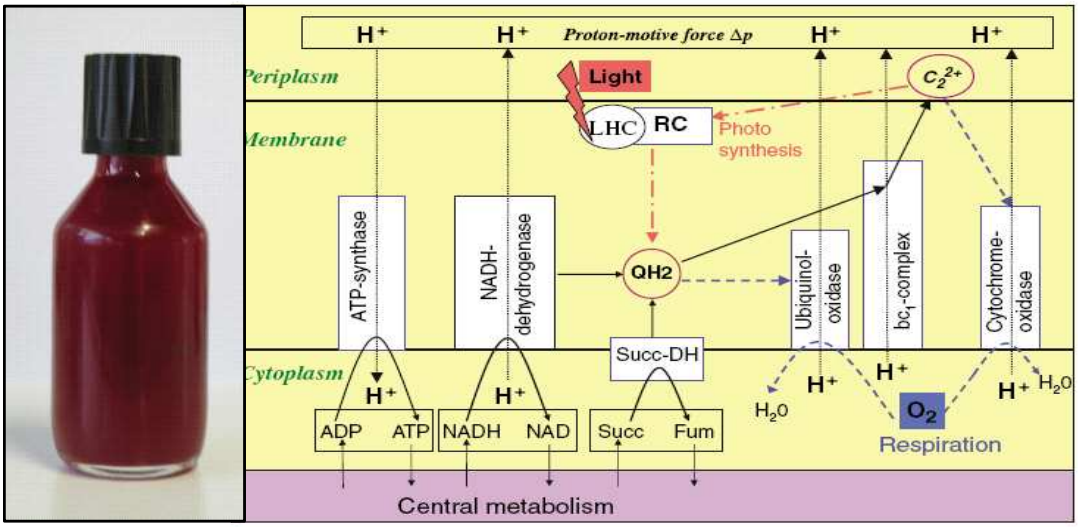

Fig. 2: Photosynthetic membranes and electron transfer processes in R. rubrum. Left: appearance of a light-grown culture. Right: reactions and components included in the computational ETC model.

Current hypotheses assign a central role for redox levels of electron transport chain (ETC) components in regulation of ICM biosynthesis, with the redox state of the membrane-localized ubiquinone (UQ) pool being a key factor. In a previous study, we have presented a speculative model of how high levels of ICM, which so far could only be obtained in light-grown cultures, can be produced by using a two-substrate growth medium which mimics light-signaling in the dark (Grammel et al., 2003).

During the period dealt with in this report, we have analyzed the ETC present in the membranes of *R. rubrum* in bioreactor experiments as well as by computational modeling under photosynthetic and respiratory conditions.

Using a stoichiometric model where all the individual electron transfer reactions of photosynthesis and respiration were included (Fig. 2), the structural capabilities of the system were analyzed by metabolic network analysis (Klamt et al., 2008). As a result, nine elementary modes were revealed as minimal subnetworks, able to operate under steady state conditions.

However, this kind of analysis only yields structural information. To see the system working with the background of a living cellular environment requires the inclusion of metabolite and enzyme concentrations and thermodynamic driving forces. We therefore constructed a kinetic model based on the differences in the midpoint potentials of the participating redox couples (Klamt et al., 2008). In simulation studies, the level of ICM corresponded to the reduction grade of UQ and corresponded inversely to the cbb3 oxidase electron flow which is fully consistent with experimental observations. The results illustrate the value and applicability of the present model in deriving qualitative predictions of the behaviour of bacterial ETC which can be validated experimentally.

As an important step towards modeling redox metabolism in *R. rubrum* at the systems level, we have recently started with kinetic modeling of central metabolic pathways. This development represents the ongoing cooperation with the JRG Klamt. It is intended to derive a module “central metabolic pathways” (CMP), which produces the parameters that are currently required by the ETC model as input variables, as output information. The connection of the CMP module to the ETC module will allow the performance of *in silico* experiments, similar to wetlab experiments, with only the growth conditions (substrate concentrations) being required as starting values.

In addition to the modeling approach, the UQ pool from bioreactor cultures was also determined experimentally by rapid sampling, organic extraction and HPLC/DAD-MS analysis (Grammel and Ghosh, 2008). Qualitatively, we found a strong correlation between the redox state of UQ_{10} and the level of expressed ICM. However, changes in the redox levels appeared to be rather modest. In contrast to the “highly reduced” or “highly oxidized” pools, implicated in current models of UQ-signaling, the redox state of UQ was found to hover at about 30 mV around its midpoint potential at +90

mV. This value is far from the midpoint potential of its supposed corresponding sensor kinase (RegB) where two redox active Cys-residues in the cytoplasmic domain with $E^{0,}$ = -294 mV mV are critical for redox regulation. Furthermore, a novel analysis of the ICM induction in response to the quinone redox state suggests that the induction process is highly cooperative and bistable, thus rendering the system unresponsive to rapid fluctuations of the UQ redox state. Our results are probably generally applicable to quinone redox regulation in bacteria.

In a collaboration with the PCP group (Ivan Ivanov) we also use their expertise in immobilizing redox mediators at electrode surfaces, for developing an affinity chromatography matrix for screening UQ redox sensors in membrane fractions of *R. rubrum*.

Development of *Rhodospirillum rubrum* for Applications in Biotechnology

The development of a growth medium in combination with a process control strategy for reliably adjusting semi-aerobic conditions allows for expression of high levels of photosynthetic membranes in the dark, using common bioreactor technology. The procedure therefore provides a novel light-independent access to the well-known potential of photosynthetic bacteria for producing valuable products, which can be derived from the photosynthetic metabolism. Fields of application that are currently adressed by the group include the production of porphyrines, biopolymers, carotenoids and hydrogen. In future developments, the enormous capacity of *R. rubrum* for producing ICM shall also be employed for the production of recombinant membrane proteins.

The maximal obtainable cell number in a bioreactor is a key factor for estimating the volumetric yields that can be expected in industrial applications. For this purpose, process control strategies were optimized by applying an unstructured model, which is based on mixed-substrate kinetics (Zeiger, 2008). The maximum cell density obtained with an exponential feeding strategy was ~ 50 g dry weight per liter. To our knowledge this cell concentration has never been reached before with this organism or closely related species. A biochemical analysis of high cell density cultures showed interesting differences to batch cultures, such as a large accumulation of protoporphyrin IX. This finding indicates a reorganization of metabolic fluxes through the haem and bacteriochlorophyll biosynthetic pathways. The analysis of the observed regulatory effects will be a main focus of further studies.

For deriving realistic models of central metabolic pathways in producer strains, the metabolic fluxes will be determined experimentally using ^{13}C isotope-based metabolic profiling. The analytical determination of metabolites, the interpretation of the ^{13}C isotope data and the setup of metabolic flux models is supported by a collaboration with Aljosha Wahl, BPE group. Currently, the analytical methodology and equipment are being put into operation. In first experiments, intermediates of the glycolytic pathway, the pentose phosphate cycle and the TCA cycle could be determined in cell extracts by LC-MS/MS.

In a cooperation project with Achim Kienle, PSD group, we applied cybernetic modeling to polyhydroxyalkanoate (PHA) metabolism in two different microorganisms: *Alcaligenes eutrophus* and *Rhodospirillum rubrum*. PHA's are becoming increasingly attractive as sustainable biopolymers (bioplastics) due to their biodegradability and their production from renewable resources. Structured cybernetic models were developed for both organisms for describing synthesis and biodegradation of PHA's under different growth conditions (Franz, 2007). The results of these simulation studies can now be validated experimentally.

In 2007, the group successfully applied for a further research grant in the framework of the FORSYS-partner initiative of the BMBF. In the project entitled "Development of a Photosynthetic Bacterium, Rhodospirillum rubrum for Superexpression of Industrially Relevant Carotenoids Using a Systems Approach" it is intended to use a combination of systems-level mathematical modelling and metabolic engineering to optimize carotenoid production in *R. rubrum* to a level which is industrially attractive. The project is part of the extensive joint collaboration between the partners at the University of Stuttgart (Ghosh/Sawodny) and the MPI (Grammel). Key mutants produced by the Ghosh group and exhibiting flux changes probably important for carotenoid biosynthesis will be transferred to Magdeburg for detailed metabolome analysis by experimental (LC/MS + ^{13}C-flux analysis) and modeling techniques.

In a collaboration with the BPE group (Prof. Udo Reichl), the group contributed its expertise to a project "Hantavirus Nucleocapsid Protein Expression in Saccharomyces cerevisiae for Vaccines and Diagnostics". The results obtained during the period under report (Antoniukas et al., 2006 & 2008) provide a basis for the increasingly desired industrial production of a recombinant hantavirus vaccine.

4.2 Junior Research Group: Systems Biological Analysis of Local and Global Regulations (Katja Bettenbrock)

The life style of bacteria requires quick and efficient adaptation mechanisms to secure survival and growth under changing environments. In addition to the strong and obvious effects on the expression of genes for e.g. uptake systems or stress response proteins, a slight modulation of the central metabolic pathways takes place. Interestingly, the genes for the corresponding enzymes are often regulated by more than one global regulator. In spite of the knowledge concerning the physiology and details about signaling pathways in *E. coli*, a comprehensive understanding of the interplay of these regulators and of the intracellular signals they respond to is still lacking. This is due to the fact that the different pathways, signaling as well as metabolic pathways, are highly interconnected and hence difficult to analyze.

This junior research group (JRG) focuses on the holistic analysis of the interplay of metabolic and signaling pathways. We perform an in depth analysis of the physiology and the regulations by using defined mutant strains that are grown under different, well-controlled culture conditions. The analyses performed include measurements on the level of metabolites, RNA and protein. The experimental studies are closely connected to theoretical studies mostly by joined projects with other JRG and external partners.

One set of experiments concentrated on the analysis of carbohydrate metabolism. Here “Catabolite Repression” and the bacterial PEP-dependent phosphotransferase system (PTS) have been in the focus. We performed extensive studies that comprised the analyses of a defined wildtype strain as well as of isogenic mutant strains and different growth conditions ranging from batch growth with one or two substrates to steady state growth in continuous bioreactor experiments. The data obtained were used for the set up and validation of a comprehensive mathematical model considering the different levels of a cell, namely metabolites and proteins as well as gene expression (Kremling et al., 2001; Kremling et al., 2004; Bettenbrock et al., 2006). This model probably represents the most extensive and best validated model of the PTS published so far. The studies showed that it is possible to model such a complex system in detail and they also gave important clues about how to validate a model.

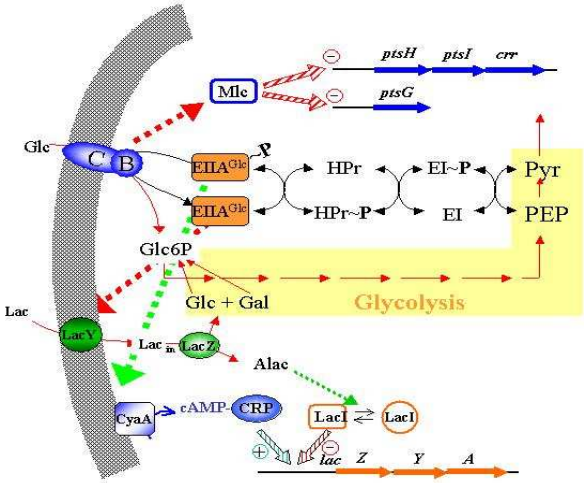

Fig. 3: The PTS of *E. coli* and some of its regulatory interactions

We showed that for the signaling properties of the PTS the type of the carbon source (PTS-substrate vs. non-PTS-substrate) is less important than the quality of the carbon source. Substrates enabling fast growth led to low phosphorylation states of the PTS protein $EIIA^{Crr}$ (Bettenbrock et al., 2007) and hence to low cAMP levels. The difference between PTS substrates and non-PTS-substrates was much less obvious than commonly thought. Obviously, the PEP to Prv ratio is an excellent indicator of the nutritional state of the cell. The experimental studies were again supplemented by extensive theoretical analyses that helped in understanding how this PEP to Prv ratio is adjusted in the cell and why the phosphorylation state of the PTS proteins is optimally suited as a sensor for this ratio (Kremling et al., 2007a; Kremling et al., 2008).

To further analyze the importance of the PEP to pyruvate ratio a project has been started that aims to vary this ratio by applying an external, model based control of the expression of PEP and Prv metabolizing enzymes. For this purpose a light controlled promotor is used that can be regulated by applying different light intensities. This approach is analogous to the model-based control of the yeast cell cycle (project of group Gilles) and is performed in close cooperation to this project.

During the last years the studies concerning the interaction of central metabolism and global regulation have been extended. As part of the transnational SysMO SUMO initiative (funded by the BMBF) that is focused on the aerob / anaerob response in *E. coli*, we are investigating the regulation of gene coding for TCA enzymes using the global regulators CRP, FNR and ArcAB. In addition, we are interested in the impact

of specific enzymes on the activity of the global regulators. In collaboration with Michael Ederer a reduced modeling approach indicated that metabolite ratios might represent intracellular signals for some global regulators, similar to the PEP and pyruvate ratio for the PTS. This hypothesis is currently being tested by performing bioreactor studies with defined aerobiosis states and by measuring metabolite concentrations as well as gene expression and the activity of the global regulators. In addition, knock-out strains lacking enzymes of the TCA and mutants with changed regulation of TCA enzymes have been constructed and are currently being characterized.

In another newly started project, which is part of the FORSYS program MACS, research is being carried out regarding the interaction of the carbon regulation by the PTS with nitrogen regulation. Carbon and nitrogen control meet at the level of the TCA indicating that again metabolic signals have to be coordinated. In addition *E. coli* owns the so-called nitrogen PTS, a set of proteins with homology similar to the carbon PTS that might link carbon and nitrogen control. We have constructed mutants in these proteins and are analyzing growth of both the wildtype strain and of the mutants with various combinations of carbon and nitrogen sources. First results indicate that the $EIIA^{Ntr}$ indeed influences growth on selected carbon and nitrogen sources. This will be further analyzed by performing gene expression and proteome studies.

Another interesting task is the analysis of single cell versus population behavior. We started to analyze different carbohydrate uptake systems with respect to their ability to show multistationarity, and we will analyze whether multistationarity can show up under microaerobic conditions. To achieve this, we created GFP fusions to the promotors of interest and we are analyzing the fluorescence distribution via microscopy and flow cytometry. First results promise interesting insights into gene regulation in *E. coli*.

4.3 Junior Research Group: Dynamics and Control in Cellular Systems (Andreas Kremling)

Cellular systems are characterized by a high number of interacting components which build complex biochemical networks. Many of the individual processes inside a cell are very well understood from the biological point of view; however, the interplay between the different cellular levels can hardly be predicted. Here, mathematical models come into play that allow a formalization of the biological knowledge and a

comparison with quantitative experimental data. The intention of my research group is (i) to set up mathematical models that could be validated with quantitative experimental data and (ii) to analyze the models with respect to their dynamical behavior, robustness, control structures, accuracy of the kinetic parameters, and predictive power.

In the projects, different modeling approaches (deterministic, stochastic) are applied, depending on the biological knowledge, the experimental data and the application of the model. Besides modeling activities, method development in the field of parameter identification is a major part of the work. Here, the focus is on the determination of parameter confidence regions of systems that are nonlinear in the parameters.

Carbohydrate uptake in *E. coli*

In cooperation with the group of Katja Bettenbrock's group at MPI Magdeburg a number of experiments were performed to describe the dynamics of different carbohydrate systems as detailed as possible. The deterministic model set up so far comprises 50 state variables and approx. 150 kinetic parameters. To validate the model, a data base with 18 experiments (different mixtures of main substrates, different pre-culture conditions, wild type and 6 mutant strains) was used. Nearly 30% of the kinetic parameters could be determined (Bettenbrock et al., 2006).

Model analysis reveals that the PEP/pyruvate ratio is a key parameter to describe gene expression in the system. To adjust different PEP/pyruvate ratios and to measure the degree of phosphorylation of EIIA, additional experiments were performed with 14 different carbohydrates (Bettenbrock et al., 2007). The measurements were used to verify a reduced model that describes the fluxes through glycolysis representing the growth rate of the cells and relates the PEP/pyruvate ratio to the degree of phosphorylation of protein EIIA. The model comprises only four state variables and is calibrated with six parameters (Kremling et al., 2007). The reduced model was analyzed with respect to variations in the measured data and with respect to variations of the kinetic parameters. It turns out, that a feedforward loop – the activation of pyruvate kinase by Fru-1,6-Bisphosphate – is an important structural element. It guarantees a robust behavior with respect to alterations in the kinetic parameters and the measured data in contrast to model variants that don't include the activation (Kremling et al., 2008). With the model at hand, uptake of a broad spectrum of substrates, including also acetate, could now be described and could be understood from the point of signal transduction and processing.

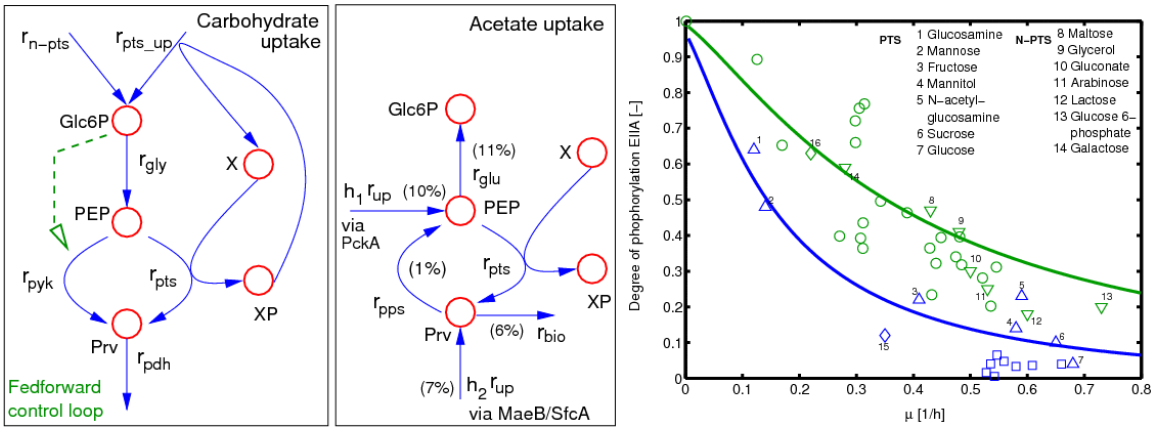

Fig. 4: Scheme of carbohydrate uptake with feed-forward activation (left). Scheme of acetate metabolism (middle). Comparison of experimental results with steady-state simulation studies for different carbohydrates (right).

Current work focuses on the comparison of different control structures present in carbohydrate uptake systems. These structures are characterized by the number of operons involved, the location of the inducer in the network and the influence of global regulators like Crp. In a first step, data base knowledge for more than 50 carbohydrates is being collected and represented for further exploitation.

Stochastic modeling

Models set up to describe carbohydrate uptake so far are deterministic and are based on o.d.e`s. However, if the number of molecules is low, the deterministic approach is not valid anymore and the stochastic modeling framework has to be applied. In a new project started in 2007, as a first step for modeling single cell dynamics, we transformed an o.d.e model of the *lac* operon into a set of nine elementary reactions. Verification of the “Chemical Master Equation” model was obtained by analysis of quantitative and qualitative behavior of the system regarding temporal dynamics and multiple steady-states. Preliminary results show significant differences between stochastic and deterministic simulations of the CME model regarding dynamics and bistability.

Determination of parameter confidence intervals with the Bootstrap Method

Due to nonlinearities in the model equations, the calculation of parameter uncertainties is a crucial step in parameter identification. Classical approaches like the determination of the Fisher-Information-Matrix (FIM) lead to an underestimation of

the confidence regions of the parameters. Therefore, new methods have been developed and applied by the group in recent years.

The bootstrap method is a statistical procedure that surmounts the theoretical limitations by assessing the uncertainties in statistics with data from finite samples. Like a Monte-Carlo method, the bootstrap method uses stochastic elements and repeated simulations to analyze the properties of the system under consideration. As a result, parametric histograms are obtained that can be further analyzed. The method was originally developed for medical systems (B. Efron and R. J. Tibshirani: An Introduction to the Bootstrap, Chapman & Hall, 1998) and was extended in such a way that it can be used to assess parameter uncertainties in dynamical systems. We successfully applied the method to a cellular network (Joshi et al., 2006a) and to a chemical reaction network (Joshi et al., 2006b). It could be shown that the parameter confidence regions are underestimated by a factor of 4 by the FIM in comparison with the bootstrap approach.

The disadvantage of the bootstrap method is the long duration of the calculations on the computer. Based on ideas from control theory, we successfully adopted a method from filter theory, the Sigma-point method, to overcome this problem and to reduce the computational time quite significantly (R. Schenkendorf et al., 2008).

4.4 Junior Research Group : Structural and Functional Analysis of Cellular Networks (Steffen Klamt)

One ultimate goal of systems biology is the construction of quantitative models of cellular networks. Whereas molecular networks of moderate size have been modeled successfully in this way, the knowledge of mechanistic details and kinetic parameters is often too limited to allow for the set-up of *predictive* quantitative models of large-scale networks. The mission of this junior research group is therefore the development and application of qualitative and topology-based modeling techniques for systems biology. We are particularly interested in methods which deliver *testable* predictions and hypotheses (driving the iterative cycle between experiment and modeling) and support the functional (re)design of biological networks. Cellular networks can be of type *mass-flow* (metabolic) or *signal-flow* (signaling, gene regulatory) implying different but often strongly related methodologies for their analysis.

Signaling networks

During the last three years, the focus of the group was on developing new formalisms and algorithms towards structural and qualitative analysis of signal-flow networks (Klamt et al., 2006a; Klamt et al. 2007). We use two different — but closely related — formalisms for representing and analyzing signaling networks. *Interaction graphs* (signed directed graphs) allow us to identify e.g. signaling paths, feedback loops or network-wide dependencies between compounds. For the latter we introduced the concept of the *dependency matrix* displaying for each component how (e.g. positively or negatively) it may affect the other nodes in the network. For example, we say that a node A is an activator (inhibitor) for node B if there are only positive (negative) paths connecting A with B. Using such relationships we can give strong qualitative predictions on how a perturbation in a certain node will change the level (up/down) of the other nodes giving us a valuable tool to detect inconsistencies between knowledge and measured data (see below). *Logical or Boolean networks* provide another modeling framework for signal-flow networks. They have been used for a long time to model gene regulatory networks of moderate size (10-20 nodes). Using a hypergraphical representation of Boolean networks (Klamt et al., 2006a) and introducing some particular techniques we made this qualitative modeling approach also amenable to large-scale signaling networks. The logical framework facilitates the simulation of the qualitative input-output response (possibly in combination with network interventions) and allows one to search for proper intervention strategies (*minimal intervention sets*; e.g. combinations of knock-outs) enforcing or repressing a particular behavior.

In close collaboration with biological/medical groups we have been applying these techniques for examining realistic signaling networks from different scopes:

(i) Together with the Institute of Immunology (OvGU) we investigated a logical model (94 nodes, 123 interactions) of the signaling network involved in T-cell activation (Saez-Rodriguez et al., 2007). The model revealed important structural features and it recapitulates the observed global network behavior for an array of published data on T-cell activation in wild-type and knock-out conditions. The model inspired immunologists to ask new questions and in this way it predicted unexpected signaling events that could be subsequently experimentally validated. The model also revealed potential failure modes in network functioning and provided candidates for missing links.

ii) In cooperation with the Institute of Experimental Internal Medicine (OvGU) we studied an example of host-pathogen systems biology (Franke et al., 2008): the signaling network of the mammalian c-Met receptor is normally stimulated by its ligand HGF promoting mitogenesis, motogenesis, and morphogenesis in a wide range of tissues. In epithelial cells, the human microbial pathogen *Helicobacter pylori* (an inducer of e.g. chronic gastritis) may modulate the c-Met receptor and promotes thereby cellular processes leading to cell scattering, which can contribute to the invasiveness of tumor cells. We implemented a model of the c-Met signal transduction network in our logical modeling framework and studied how it is interfered by *H. pylori* infection. As an important result, using our formalism of minimal intervention sets (MISs) we identified phospholipase Cγ1 as knock-out target repressing cell scattering induced by *H. pylori* whereas HGF treated cells would still show normal behavior. This result was confirmed experimentally in MDCK cells using a specific pharmacological inhibitor. This example showed the potential of MISs for target identification.

iii) In a current project we have been establishing a large-scale logical model for the epidermal growth factor (EGF) and ErbB receptor signaling pathway (Figure 5), arguably the best-studied receptor system in mammalian cells (Samaga et al., 2008). Apart from studying important functional features, this is the first logical model that we confronted with high-throughput data (from primary hepatocytes and the HepG2 cell line). The data were produced by a unique experimental set-up in the lab of Peter Sorger (Harvard Medical School) measuring the activation (phosphorylation) state of several proteins resulting from combinatorial experiments (different ligands for stimulating the network; different inhibitors permanently deactivating specific proteins in the network). Assessing this unique set of data with our network-based approach, we were able to uncover inconsistencies between experimental results and our current qualitative knowledge and thereby generate new hypotheses.

Metabolic networks

Metabolic network analysis is another important research area of this JRG. During the last evaluation period we refined the concept of minimal cut sets (or minimal failure modes) in metabolic networks (Klamt, 2006) and improved the algorithm for their calculation (Haus et al., 2008) as well as the calculation of their dual counterparts, the elementary modes (Klamt et al., 2005). We are actively involved in

applying these methods to realistic (metabolic) networks: in cooperation with the JRG of Grammel, we developed a model for the electron transport chain of the facultative phototrophic purple nonsulfur bacteria (Klamt et al., 2008). In another project we were involved in constructing and analyzing a genome-scale metabolic model of *Mycobacterium tuberculosis* (the intracellular parasite that causes Tuberculosis). The model successfully simulated many of the growth properties of these bacteria and provided a means to predict the phenotype of mutants (Beste et al., 2007). Together with the SCT group we also employed tools of stoichiometric network analysis for studying the ability of biological networks to display multi-stable behavior (Saez-Rodriguez et al., 2008).

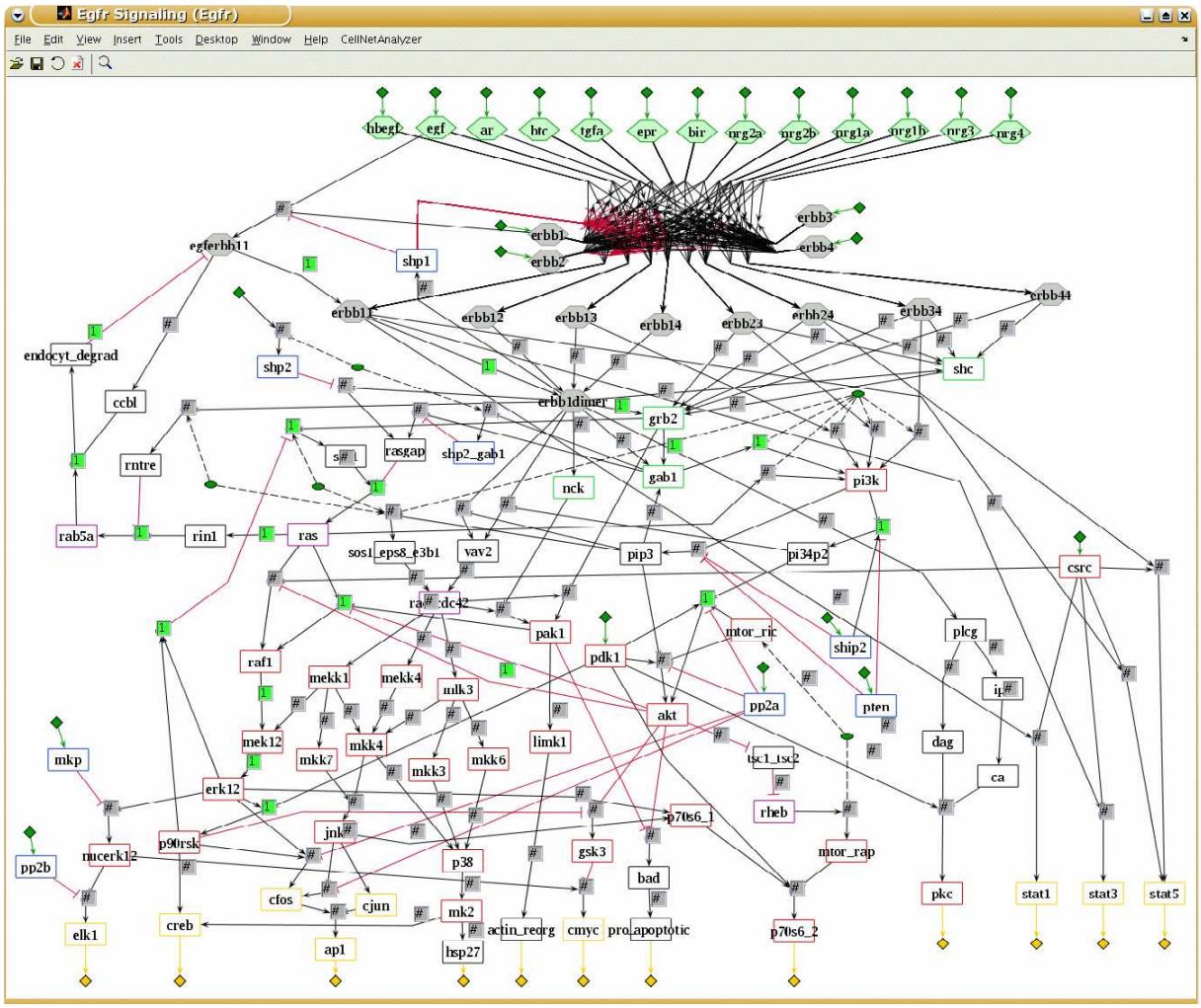

Fig. 5: Logical model of the EGFR/ErbB signaling network in *CellNetAnalyzer* (screenshot; map and model were created with ProMoT). Text boxes with green background indicate a negative feedback loop in the network.

CellNetAnalyzer

For more than eight years, we have been developing CellNetAnalyzer**,** a MATLAB toolbox facilitating, in an interactive and visual manner, a comprehensive structural and functional analysis of metabolic and signaling networks. Novel algorithms are continuously integrated rendering *CellNetAnalyzer* one of the most popular tools in this field: since 2006 it has been downloaded by more than 1000 groups worldwide and commercial licenses have been purchased by six industrial companies (distributed via Max Planck Innovations). Model exchange between ProMoT (model construction and visualization) and *CellNetAnalyzer* (model analysis) has been strongly improved, in particular for logical networks. Figure 5 shows an example of an interactive network map displaying the EGFR/ErbB signaling network discussed above. *CellNetAnalyzer* is also actively used by the BPE group for modelling signalling and metabolic networks in mammalian cells.

4.5 Junior Research Group : Tools and Concepts for Modeling and Simulation (Sebastian Mirschel)

Research in the field of systems biology requires powerful computing tools for modeling, visualization, simulation, system analysis and synthesis as well as a powerful modeling concept, to systematically describe the biological systems under investigation. In a long-term project the SBI group has developed a modular modeling concept for the description of intracellular reaction and regulation networks, which is based on network theory. This concept is implemented in software tools and applied in several modeling projects.

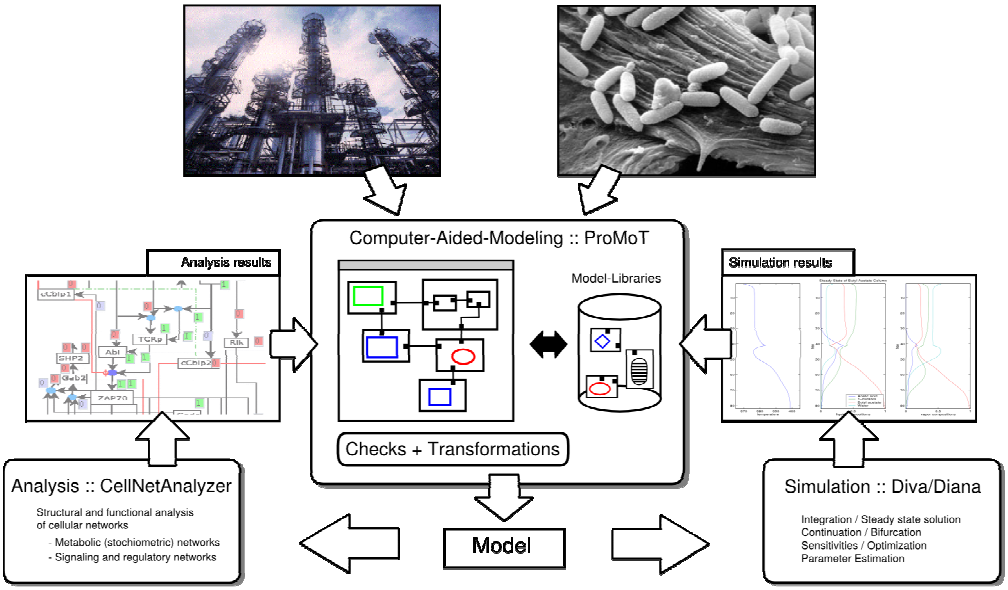

Fig. 6: Modeling and Simulation using software tools ProMot, DIVA, Diana and CellNetAnalyzer

The overall aim of this junior research group is to provide software tools which support efficient and comprehensible editing, visualization, validation, analysis, exchange and integration of models. A special focus is the object-oriented modeling tool ProMoT (Mangold et al., 2005; Saez-Rodriguez et al., 2006; Waschler et al., 2006; Krasnyk et al., 2006) which provides libraries with sub-models for different application areas based on the modular modeling concept.

Additionally to the common quantitative (kinetic) modeling approach, ProMoT supports also a logical (Boolean) modeling formalism (Klamt et al., 2006a) which results in a qualitative description of the model (Fig. 6). A cooperation with the Harvard Medical School was established which concentrates on the further improvement of the logical approach.

ProMoT provides a visual editor for user-friendly, graphical set-up and modification of a model. For that, editing shortcuts are available to combine frequently used editing steps, which are based on analysis of interaction pattern of modelers. These shortcuts allow for the exelaration of the editing process for beginners as well as for advanced modelers.

The editing step is assisted by advanced visualization techniques. These offer a flexible visual presentation allowing the user to tailor visualizations specifically to the current task in the modeling process. More precisely, techniques are implemented that reduce visual complexity by presenting only a subset of the model containing essential information. This results in a less cluttered and more descriptive visualization. Another approach is motivated by the growing interest in qualitative/structural analysis over the last years. Here, visualization techniques provide an adequate representation of the logical model formalism (Fig. 5) and an intuitive visual presentation for the interpretation of analysis results. They are of great value in order to interpret and discuss specific results in interdisciplinary teams.

Model validation in ProMoT can be handled by different options. One method is the online check for structural modeling errors that shortens the time for setting up a correct model. Another option is the use of structural analysis algorithms which provide helpful information for the modeler to resolve consistency errors and for exact simplifications of the model for efficient numerical solution.

ProMoT is able to generate models for different simulation and analysis tools and allows the exchange of dynamical and logical models using SBML or CellNetAnalyzer format, respectively. Logical models can be analyzed using

CellNetAnalyzer (Klamt et al., 2007), which in turn provides data for the visualization of results directly mapped to the model in ProMoT.

The simulation environments DIVA and Diana offer simulation, parameter analysis, parameter estimation and bifurcation analysis. Diana (Krasnyk et al., 2006) implements several recent improvements in the fields of nonlinear analysis, optimization and state estimation (Krasnyk et al., 2007). The Diana project is done in close cooperation with the Donezk Technical University.

The tools described above are a common infrastructure that is used in many projects of the groups PSD, BPE, PCP and SBI.

4.6 Junior Research Group: Advanced Concepts for Kinetic Modelling (Michael Ederer)

We are further developing the kinetic modelling formalism in order to make it more applicable to biochemical reaction networks. We identified two major but related problem fields: (1) the explicit acknowledgement of thermodynamic constraints in kinetic modelling and (2) the model reduction or the reduced-order modelling of large systems.

Most parts of this research are done in close cooperation with the *Institute for System Dynamics (ISYS)* of the *University of Stuttgart* (O. Sawodny and T. Sauter). Several members of the SBI are hosted by the ISYS. They also participate in projects of the *Center for Systems Biology* of the University of Stuttgart.

Basic constraints in mathematical models

Thermodynamic constraints in kinetic models: We developed the Thermodynamic-Kinetic Modelling (TKM) approach (Ederer et al., 2007a). TKM is a modelling formalism that structurally guarantees the thermodynamic validity of models without an explicit formulation and solution of the Wegscheider conditions. Based on an analogy to electrical models, we developed a graphical representation of thermodynamic-kinetic models (see Fig. 7; Ederer et al., 2007b).

Under certain conditions thermodynamic-kinetic models can be reduced by a method based on the theory of singular perturbations. Currently, we use the TKM formalism to build a reduced-order model of the global oxygen response of *E. coli* (SysMO initiative, SUMO consortium).

Constraints on Evolutionary Dynamics: Microbial populations in chemostats undergo an evolutionary adaptation to the respective growth conditions. The

adaptation is based on a concurrence situation between spontaneously emerging mutants. By simple mathematical models and a Lyapunov argument similar to those appearing in thermodynamics we derived basic constraints on the evolutionary dynamics. We discussed possibilities to exploit these dynamics for the development of production strains (Feuer et al, 2007 & 2008).

Signal transduction and combinatorial complexity

Modelling of signal transduction systems is an important tool for understanding their design principles and their possible malfunctioning which then leads to diseases. We modelled insulin signalling and clearance that explains observed variations in the insulin clearance rates (Koschorrek et al., 2008a).

Combinatorial complexity is a challenging problem for the modelling of cellular signal transduction since the association of a few proteins can give rise to an enormous amount of feasible protein complexes (Fig. 7). This leads to enormous problems in the detailed, un-reduced modelling of systems with inherent combinatorial complexity.

Exact model reduction: The exact model reduction approach (Conzelmann, H. et al., 2006, 2008a & 2008b) allows for the reduction of state variables that are uncontrollable and/or unobservable and therefore do not affect the input/output behavior of the system.

The developed method is based on a formal separation of the system states into observable and unobservable controllable and uncontrollable using an adequate state space transformation (Conzelmann et al., 2006). We extended this approach to facilitate the direct generation of the exactly reduced model equations (Conzelmann et al., 2008). This approach is based on a separation of independent signal flows within a signalling cascade and modelling them separately.

Layer-based modelling: Layer-based modelling is a reduced order modeling technique with a high approximation quality. It is based on an interaction graph that defines the modularity of the model and results in a reduced model with a pronounced modular structure (Koschorreck et al., 2007). The resulting modules can be modelled separately from each other. As an example, modelling of the insulin signalling system is possible with only 214 ODEs, instead of the 1.5*10^8 needed when using conventional modelling. The combination of layer-based modelling and exact model reduction results in a further reduction of the model size (e.g. only 56 ODEs are necessary for a model of insulin signalling).

We developed ALC (Automated Layer Construction), a computer program that highly simplifies the building of layer-based models (Koschorreck et al., 2008).

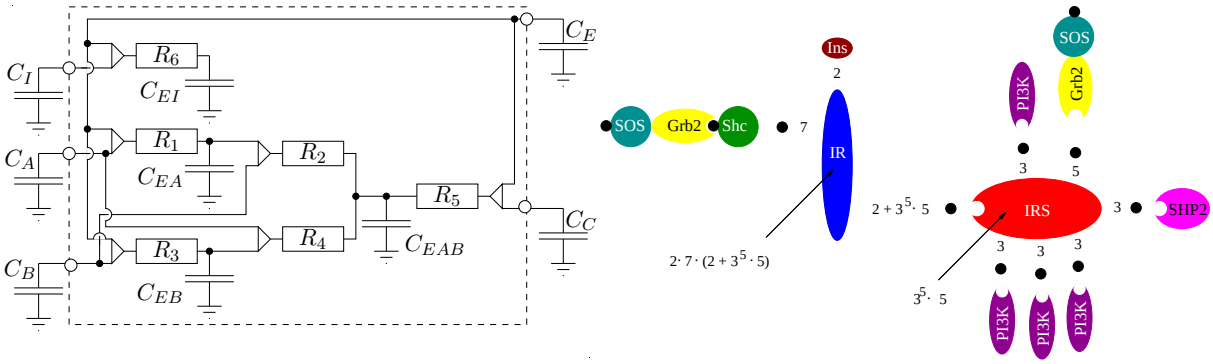

Fig. 7: Left: TKM model of an enzyme catalyzed reaction. Right: Combinatorial complexity at the insulin receptor

4.7 Senior Research Group: Regulatory Circuits (Ernst Dieter Gilles)

Signaling networks represent appropriate systems for investigating regulatory circuits. In this group we focus on two different levels of regulation in very distinct organisms. One level aims to reveal biological control patterns in molecular networks that regulate a particular cellular function (*Proliferation control in Hepatocytes, Phototaxis in Halobacteria*). The other level concentrates on an engineering approach reflecting the future use of such models. The comparison of an experimental system controlled by an external regulation with its *in silico* description allows for an optimization of its biosynthesis in view of concrete applications (Synchronization of yeast cultures). The concept of this group serves then an essential goal of systems biology, that is the development of cellular models and their use in larger scale projects.

Phototaxis in *Halobacteria* (Tobias Neuhaus)

Halobacterium salinarum is able to swim back and forth by rotating a polarly inserted flagellar bundle clockwise or counterclockwise. To find those sites of their environment that provide optimal light conditions, cells respond to changes in the light intensity rather than to its absolute value, i.e. they differentiate the time-dependence of the sensory input signal. In the last years we developed a very detailled model for the flagellar motor, which describes the eight kinetic phases of the symmetric switch cycle of this motor. This kinetic model in combination with a simple adaptational mechanism, based on Barkai & Leibler, correctly reproduces most

experimental results on halobacterial motor switching and its sensory control (Nutsch et al., 2003 & 2005).

But in particular in the domain of signal transduction and adaptation there are several open questions. (i) The phenomenon of different methylation patterns in *H. salinarum* and *E. coli.* Due to demethylation of transducers in *E. coli* repellant and attractant stimuli result in an increase and decrease, respectively, in the methanol evolution rate. In contrast, in *H. salinarum* both repellant and attractant stimuli result in an increase in methanol evolution rate. (ii) Another fundamental question related to the adaptation mechanism is whether a global or local adaptation takes place in the transducers. In the local variant only the stimulated receptor-transducer-complexes will be adapted by methylation or demethylation, whereas in the global variant all transducers are involved in the adaptation process. (iii) Depending on this global or local way of adaptation we should observe an influence between different stimulated receptor species or not. But also cluster building could have an effect on this phenomenon. Currently our research is focused on these problems to get a deeper insight in the signal transduction and adaptation mechanism.

Proliferation Control in Hepatocytes (Jérémy Huard)

In this project, a model of the G1/S transition has been developed in order to exhibit the links between mitogenic stimulations forwarded by signal transduction pathways and the early phase of the mammalian cell cycle. We have been analyzing the effects of multisite phosphorylation and the effects of processivity/distributivity and the use of diverse kinetics on the stability of the system combined with feedback loops. Bistability is a possible explanation for the Restriction Point phenomena and it can be reached combining a module exhibiting ultrasensitivity to a positive feedback loop. This pattern occurs several times in the molecular network of the mammalian cell cycle, which could explain its ‘robustness’ and allows for a fair modularization. Indeed part of this work aims to find a good modularization of the interaction network so as to identify subnetworks responsible for a specific dynamic behavior (like multistability). The model has been implemented in the modeling tool ProMoT, which uses the concept of “modularity”. The present project is part of the the Hepatosys network, a nation-wide systems biology initiative funded by the BMBF focusing on hepatocytes. Experimental data are currently being produced by our collaborator Stephanie Müller, PhD student in the group of Prof. Klingmüller (DKFZ, Heidelberg).

Synchronization of yeast cultures by model-based modification of cellular regulation (Hannah Sharp)

This project reflects the engineering approach of controlling an experimental system based on its *in silico* description for special applications like optimizing its biosynthesis by means of external regulation. In one important application, we choose the problem of synchronizing cell cultures. In cell cultures the individual cells are generally distributed over the different phases of cell cycle. Hence, measured concentrations or production rates represent mean values of the culture. We established a new and non-invasive method for the synchronization of yeast cells by influencing their progression through cell cycle by external control signals. This method enables us to trigger cell cycle transition by a light-induced switch of gene transcription. As a target of this switch Cdc20 was chosen, which functions as an essential inductor of mitosis. Yeast cells were modified in such a way that allows an external light-dependent control of the promotor of *CDC20*. We are now able to induce its expression externally by application of a red light pulse and repress it under the exposure of far-red light. To develop model-based measurements and optimal control strategies for permanently maintaining synchronous yeast cultures, we developed parallel to the light-dependent cell culture an *in silico* cell population mimicing the features of the biological population. As starting point we used a very comprehensive single cell model of the budding yeast cell cycle of Chen et al. (Mol. Biol. Cell 15, pp. 3841-3862 (2004)). The model has been modified to include the features of the light-inducible system and has been implemented in the modeling tool ProMoT. Additionally, a simulation framework for modeling and simulation of growing populations of hybrid models has been developed in DIANA. Thus, a stable and sustaining synchronization of an *in silico* yeast population under external *CDC20* control could be shown. Since the modelling part of this project takes place in Magdeburg, the experimental part is performed in collaboration with Prof. Hilt from the Institute of Biochemistry at Stuttgart University.

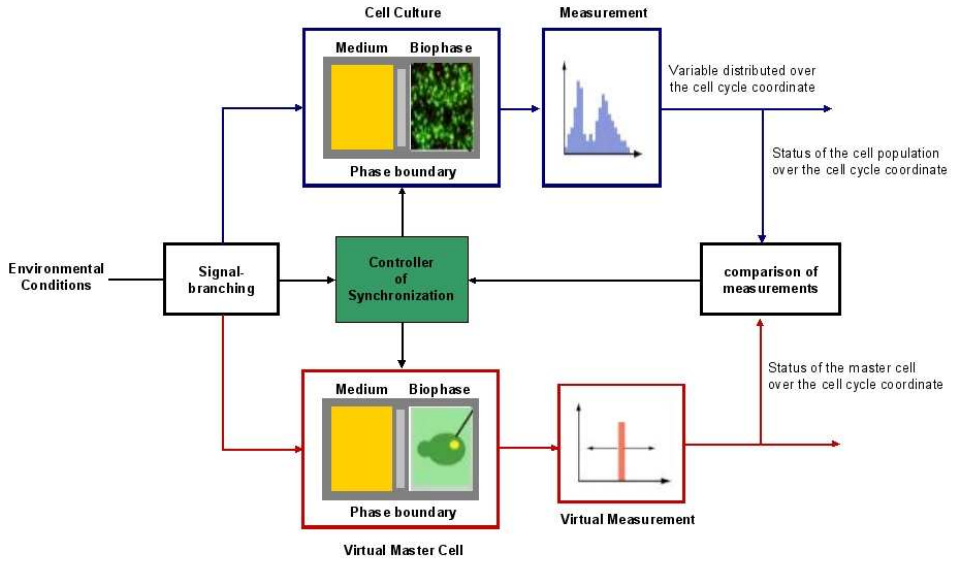

Fig. 8: Regulation of a cell population using external stimulation

5 Selected Teaching Activities, Diploma Projects, Ph.D. Projects

Tab. 3: Teaching activities

Title of lecture	**Place**	**Lecturer**
Control Theory for Biosystems Engineering	Univ. Stuttgart	M. Koschorrek
Systems Theory for Chemical Engineering	Univ. Stuttgart	H. Conzelmann M. Ederer
Seminar Technical Cybernetics	Univ. Stuttgart	H. Conzelmann M. Koschorrek M. Ederer
Introduction to Systems Biology	Univ. Stuttgart	M. Ederer
Structural and Functional Analysis of Cellular Networks	Univ. Magdeburg	S. Klamt
Systems Biology I	Univ. Magdeburg	A. Kremling
Systems Biology II	Univ. Magdeburg	A. Kremling S. Klamt M. Ginkel
Microbiology	Univ. Magdeburg	K. Bettenbrock H. Grammel
Environmental Biotechnology	Univ.Magdeburg	H. Grammel

Tab. 4: Supervision of Diploma and Master Projects

Student	**Title**	**Training place/ Advisor**
Schiffter, R.	Structural Kinetic Modeling of the Central Metabolism of *E.coli*	Univ. Magdeburg/ A. Kremling
Aschenbrenner, E.	Layout of hierarchical Structured Graphs Using Data from Systems Biology	Univ. Magdeburg/ S. Mirschel

Thiele, M.	Quantitative Real-Time-PCR Analysis of Influenza-Virus	TU Braunschweig/ K. Bettenbrock
Seitz, C.	Quantitative Real-Time-PCR Analysis of Influenza-Virus	FH Südfestfahlen/ K. Bettenbrock
Zeiger, L.	Process Control for High Cell Density cultivation of *Rhodospirillum rubrum*	FH Esslingen/ H. Grammel
Franz, A.	Cybernetic Modeling of Polyhydroxybutyrate Formation in Microorganisms	Univ. Magdeburg/ H. Grammel

Tab. 5: Ph.D. projects (finished)

Group member	**Title**	**Finished in**
Saez-Rodriguez, Julio	Modular analysis of Signal Transduction Networks	2007

6 Selected Memberships, Appointments and Awards

Gilles, E.D.

2006 Arnold-Eucken-Medal for achievements in the field of Technology

2006 Member of the Scientific Advisory Board of the Scientific Center of Saxony Anhalt Lutherstadt Wittenberg e. V.

Saez-Rodriguez, J.

2008 Ph.D Thesis (Modular Analysis of Signal Transduction Networks) awarded with MTZ Award for Systems Biology

7 Future Directions

The majority of the projects of the SBI group are funded by the BMBF (HepatoSys, FORSYS, SYSMO) and the Saxony-Anhalt Ministry of Education (Research Center 'Dynamical Systems'). The expected continuation of these running research initiatives and the participation in new funding initiatives of the BMBF (e.g. MedSys) will sustain the financial support for these projects at least until 2011. Beyond 2011, in addition to third-party funding, we expect that a permanent establishment of systems biology activities at the MPI will have been attained.

Apart from continuation and intensification of the running projects we see several major topics for our future work which are also of general importance for systems biology research:

- Expanding: concepts for model merging and for tool integration.
- Closing the gap between qualitative and dynamic modeling: methods for analyzing qualitative (parameter-independent) properties of the dynamics of cellular networks.

- Modeling and experimental analysis of single bacterial cells.
- Monitoring in-vivo dynamics of cellular components and signals.
- Identification (and testing) of intervention strategies with applications in biosystems engineering and medical research.
- Theoretical Methods for Synthetic Biology
- Extending our network of cooperations with biologists and theoretically working groups.

In conclusion, with a solid background in the engineering sciences and by pursuing a strongly interdisciplinary approach the SBI group will continue elucidating systems-theoretical properties and principles of prokaryotic as well as eukaryotic systems.

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Research Group:

Bioprocess Engineering (BPE)

Prof. Dr.-Ing. Udo Reichl

This report covers the period from January 2006 to September 2008

1 Group Introduction

Over the last three years, the theoretical and, in particular, experimental research of the BPE Group has been further expanded with focus on upstream processing in mammalian cell culture and downstream processing of virus particles and viral antigens. Research on growth, metabolism and virus replication in adherent, MDCK cells remained the center of activities. Additional projects concentrating on the dynamics of protein expression of infected cells, changes in intracellular vmRNA levels and the influence of signal transduction processes during influenza virus infections have been extended. It concerns for example the impact of interferon (α, β) release and influenza virus induced apoptosis on virus dynamics and virus yields. Furthermore, new cell lines were introduced to broaden the scope of research and to address aspects of cell growth and virus replication, which cannot be investigated using MDCK cells. An example of this is the impact on cellular interferon response on virus yield. The latter involves work with adherent Vero cells used as an alternative host cell system in commercial influenza vaccine production. Furthermore, newly generated human and avian designer cell lines (supplied by ProBioGen AG, Berlin, Germany) have been cultivated in various cell culture systems. These cells grow in suspension culture and are considered potential candidates for vaccine and recombinant protein production. In addition, the number of influenza virus strains handled has been increased. This concerns particularly the use of seasonal human influenza A and B viruses, which allowed extending the significance of studies with regard to design and optimization in downstream processing of viral vaccines.

Studies related to mink enteritis virus propagation in embryonic feline lung cells (Hundt et al. 2007) and process optimization for up and downstream processing of *Parapoxvirus ovis* in bovine kidney cells (Pohlscheidt et al. 2007) were successfully completed. The main results of research related to vaccine production, mathematical modeling of virus replication and downstream processing of viral vaccines were summarized in contributions to various textbooks (i) Genzel and Reichl (2007): *Vaccine production – state of the art and future needs in upstream processing*, (ii) Reichl and Sidorenko (2006): Virus-host cell interaction, and (iii) Kalbfuß and Reichl (2008): *Viral Vaccine Purification*.

Besides mammalian cell culture, bioprocesses related to protein expression in the yeast *Saccharomyces cerevisiae* (Antoniukas et al, 2006, 2007; Sidorenko et al., 2008) and investigations characterizing the impact of plasmid construction on segregation instability and human interferon-γ yields in *Escherichia coli* have been pursued provided that scientific support by external partners was available. Research activities concerning the dynamics of microbial communities related to cystic fibrosis (Schmidt et al. 2007) have been centered at the BPE Group at the OvGU and broadened to include single and mixed species' responses to antibiotics pulses in continuous cultivations, characterization of dynamics of species' meta-proteome composition as well as cell cycle and viability analyses by flow cytometry.

2 Members of the BPE Research Group

As of July 2008, the research group BPE consisted of 4 scientists with PhDs, 13 PhD students, diploma students, and technical assistants. As in previous years, laboratory capacities have been restricted due to constant delays in the start of the construction of the chemical engineering building at the OvGU.

Tab. 1: Composition of BPE Group as of July 2008

Group Member	Status	Background	joined BPE in
Prof. Dr. U. Reichl	Head of Group		01.07.2000
Dr. T. Frensing	Scientific Employee	Biology	15.08.2007
Dr. Y. Genzel	Scientific Employee	Biotechnology	01.01.2001
Dr. E. Rapp	Scientific Employee	(Bio-) Analytical Chemistry	01.03.2008
Dr. Y. Sidorenko	Scientific Employee	Mathematics	01.08.2001 (until 30.11.2007)
Dr. A. Wahl	Scientific Employee	Bioprocess Engineering	15.04.2006 (until 14.08.2008)
Dr. M. Wolff	Scientific Employee	Biotechnology	01.01.2005 (until 28.02.2008)
Dipl.-Ing. S. Freund	PhD student	Bioengineering	01.04.2008
Dipl.-Ing. A. Bock	PhD student	Process Engineering	01.03.2003
Dipl.-Ing. R. Janke	PhD student	Bioprocess Engineering	15.03.2007
Dipl.-Ing. (FH) B. Kalbfuß	PhD student	Biotechnology	01.11.2003 (until 30.09.2008)
Dipl.-Ing. T. Kröber	PhD student	Bioengineering	01.09.2007
Dipl.-Biotechnol. V. Lohr	PhD student	Biotechnology	01.06.2008
Dipl.-Ing. L. Opitz	PhD student	Bioprocess Engineering	01.07.2005
Dipl.-Ing. M. N. Popov	PhD student	Chemical Eng. / Biotechnology	01.01.2006
Dipl.-Ing. (FH) A. Rath	PhD student	Biotechnology	01.07.2008

Dipl.-Ing. J. Ritter	PhD student	Biotechnology	01.12.2003
Dipl.-Ing. T. Rudolph	PhD student	Food Technology	01.04.2008
Dipl.-Biotech. J. Schulze-Horsel	PhD student	Molecular Biotechnology	15.09.2003
Dipl.-Ing. (FH) J. Schwarzer	PhD student	Analytical Chemistry	15.01.2003 (until 30.06.2008)
Dipl.-Ing. C. Seitz	PhD student	Biotechnology	15.04.2007
Technical Staff			
Dipl.-Ing. (FH) I. Behrendt	Technician	Biotechnology	01.07.2001
L. Geisler	Technician	Chemistry	15.07.2003
S. König	Technician	Analytical Chemistry	01.08.2001
Dipl.-Ing. (FH) S. Lehmann	Technician	Biotechnology	01.11.2002
N. Wynserski	Technician	Biology	01.08.2007
Dipl.-Ing. (FH) Anke Zimmermann	Technician	Biotechnology	01.12.2003
F. Hasewinkel		Chemistry	01.08.2002

At the Chair of Bioprocess Engineering at the OvGU the research group consists of Prof. U. Reichl, 2 senior scientist (D. Benndorf, M. Wolff), 4 PhD students (B. Heynisch, C. Riedele, M. Rüger, D. Vester), 2 technical assistants (C. Best, C. Siewert), and several diploma students.

3 Survey of research projects of BPE Group

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

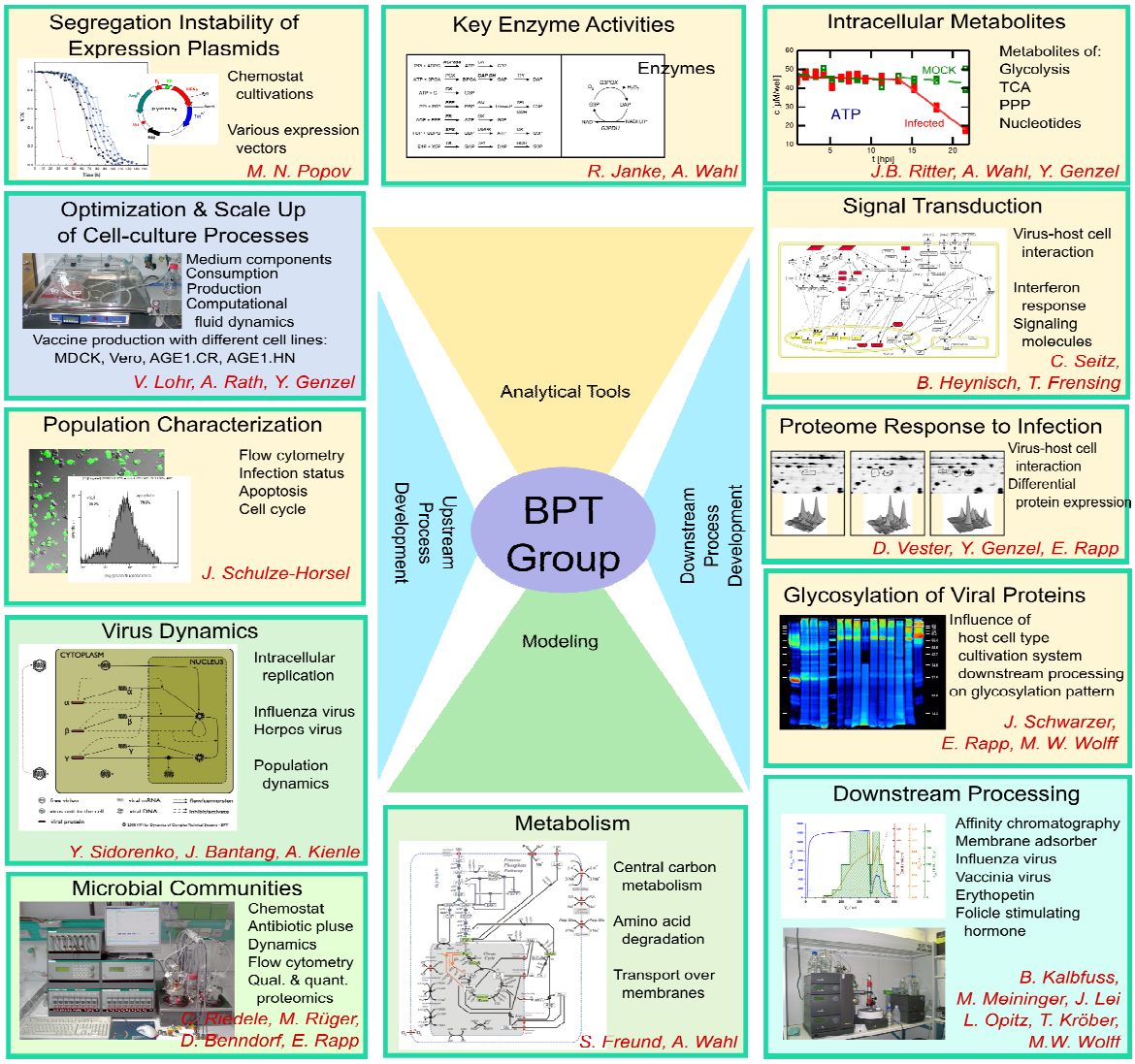

Fig 1: Survey of research areas and projects of the BPE group.

Project Area: Hierarchical Structures

Tab. 2: Projects

Project: Mathematical modeling of cellular systems	- Detailed mathematical models for virus replication in mammalian cells - Segregation of plasmids and protein yields in *E. coli* fermentations			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject Segregation instability of expression plasmids carrying the human interferon gamma gene in *E. coli*	U. Reichl M.N. Popov	MPI/ DFG	01/2006	Nacheva, Institute of Molecular Biology (Bulgarian Academy of Science)
Subproject Dynamical model of herpesvirus replication	U. Reichl J. Bantang	MPI	11/2007	Rädler/Mendoza, Faculty of Physics, LMU, Munich
Project: Mathematical modeling, simulation and control of bioprocesses	- Unstructured, segregated mathematical models for MDCK cell growth and influenza virus replication in microcarrier culture			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject Development of bioprocess concepts in viral vaccine production	U. Reichl A. Bock	MPI	01/2000	BPE, OvGU
Project: Signal transduction and apoptosis in virus-infected cells	Characterization of virus-host cell interaction in mammalian cell culture			
Subproject The role of IFN and other host cell defense mechanisms in influenza vaccine production	T. Frensing C. Seitz	MPI/BMBF	05/2007	Hauser, Wirth Helmholtz Center for Infection Research, Braunschweig
Subproject Analysis of virus-induced signaling pathways in mammalian host cell systems	T. Frensing B. Heynisch	MPI/ BMBF/ Chair of Bioprocess Engineering, OvGU	05/2007	Naumann, Institute of Experimental Internal Medicine Medical Faculty, OvGU

Project Area: Population Balance Systems

Tab. 3: Projects

Project: Dynamics of virus-host cell populations in bioreactors	- Population balance systems to characterize virus spreading and infection processes - Quantitative analysis of flow cytometry data sets			
Subproject Physiological status of mammalian cells during cell growth and viral infection	U. Reichl J. Schulze-Horsel	MPI	09/2003	Kienle, PSD Group

Project Area: Coupled Processes

Tab. 4: Projects

Project: Monitoring, design and optimization of bioprocesses	- Integrated concepts for design and optimization of vaccine production processes - Mammalian cell culture - Yeast expression systems			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject Influenza vaccine production in microcarrier systems	Y. Genzel	MPI	07/2000	BPE, OvGU
Subproject Design, scale up and process optimization for recombinant hantavirus NP expression in *S. cerevisiae* for vaccines and diagnostics	U. Reichl L. Antoniukas	MPI	01/2003 05/2008	Grammel, SBI Group, MPI Institute of Biotechnology, Vilnius, Lithuania Friedrich-Löffler-Institute, Wusterhausen, Germany
Subproject Monitoring and control of high density cell culture systems	U. Reichl A. Bock T. Rudolph	MPI /IMPRS	03/2003	BPE, OvGU
Subproject Cell growth and metabolism in human suspension cells	Y. Genzel A. Rath	MPI / BMBF	07/2008	SysLogics
Subproject MVA and influenza virus production in avain designer cell lines	Y. Genzel V. Lohr	MPI	07/2008	ProBioGen AG, Berlin, Germany
Project: Downstream processsing of viral and recombinant proteins	- Generic processes 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			

Title	Scientists	Funded by	Start	Partners
Subproject Downstream processing of influenza virus	U. Reichl B. Kalbfuß	MPI	01/2002	BPE, OvGU
Subproject Affinity Chromatography of Influenza Virus	M. Wolff L. Opitz	MPI	01/2005	BPE, OvGU
Subproject Particulate formulation of influenza virus antigen	U. Reichl T. Kröber	MPI	09/2007	Sundmacher PCP Group

Project: Quantitative analysis of metabolic and regulatory networks of cellular systems	- Flow cytometric and microscopical analysis of cell status and virus replication dynamics - Quantitative analysis of virus replication dynamics - Proteomics, differential protein expression analysis by 2D-DIGE and mass spectrometry - Glycomics, quantitative and qualitative analysis of glycosylation patterns by CGE and MS - Analysis of extra- and intracellular metabolites concentrations, enzyme activity assays - ^{13}C isotopomer analysis			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject Cell growth and virus replication in perfusion systems	U. Reichl Y. Genzel A. Bock	MPI	07/2000	BPE, OvGU
Subproject Microscopical analysis	U. Reichl, J. Schulze-Horsel	MPI	01/2000	BPE, OvGU
Subproject Quantitative analysis of energy metabolism of animal cells	Y. Genzel J. Ritter	MPI	01/2002	Gilles SBI Group
Subproject Analysis of glycosylation of the influenza A virus HA	E. Rapp J. Schwarzer	MPI	01/2005	
Subproject Physiological status of mammalian cells during growth and viral infection	U. Reichl J. Schulze-Horsel	MPI	09/2003	Kienle, PSD Group
Subproject Biomolecular analysis of dynamic interactions between influenza viruses and host cells	Y. Genzel D. Vester E. Rapp	MPI	05/2005	Benndorf, OvGU Bettenbrock, SBI Group
Subproject Enzymatic characterization of mammalian cells	A. Wahl R. Janke	MPI	04/2007	MPI Molecular Plant Physiology, Golm

Project Area: Network Theory

Tab. 5: Projects

Project: A systems biology approach to mammalian cell metabolism	A. Wahl R. Janke S. Freund	MPI/BMBF	01/2005	SysLogics, Klamt, SBI Group SFACN Group, MPI Molecular Plant Physiology, Golm

Projects: Chair of Bioprocess Engineering (OvGU)

Tab. 6: Projects

Project: Dynamics of microbial communities C. Riedele (Start: May 2002)	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
Project: Flow cytometric analysis of a medically relevant three-species bacterial community M. Rüger (Start: September 2007)	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
Project: Meta-proteome analysis of a heterogeneous microbial culture D. Benndorf (Start: January 2008)	Experimental characterization of meta-proteome dynamics of microbial communities, e.g. bacterial species related to cystic fibrosis disease
Project D. Vester (Start May 2005)	Biomolecular analysis of dynamic interactions between influenza viruses and their host cells on the proteomic and mRNA level
Project M. Wolff (Start March 2007)	Affinity chromatography of vaccinia virus Partners: Bavarian Nordic, Kvisgard, Denmark
Project B. Heynisch (Start April 2007)	Analysis of influenza virus-induced signaling in mammalian host cell systems Funding: FORSYS, BMBF
Project D. Benndorf (Start August 2007)	Coordination: Diploma course Biosystems Engineering Funding: FORSYS, BMBF
Project M. Pohlscheidt (Finished 2005)	Development and optimization of a procedure for the production of *parapoxvirus ovis* in microcarrier culture Funding: Bayer HealthCare AG, Wuppertal, Germany

Projects: Cooperation with other Institutions and Industry

Tab. 7: Projects

Project: Analysis of milk sugars (Start April 2007)	Milupa GmbH, Germany
Project: Analysis of Influenza Virus Hemagglutinin (Start November 2007)	Chiron/Novartis AG, Marburg, Germany
Project: Analysis of a1-Antitrypsin Glycosylation (Start March 2007)	ProBioGen AG, Berlin, Germany
Project: Experimental characterization and mathematical modeling of microbial communities (Start April 2008)	Helmholtz Center of Environmental Research Flow Cytometry Gruppe Leipzig, Germany
Project: Vaccinia virus purification (Start March 2007)	Bavarian Nordic, Denmark Sartorius Stedim Biotech GmbH, Germany
BMBF Project: Downstream process-sing of recombinant proteins (Start October 2008)	OvGU, Chair of Bioprocess Engineering Merckle Biotec GmbH EMC microcollections GmbH Prof. S. Laufer, Institute of Pharmacy University of Tübingen
BMBF Project: Downstream process-sing of influenza virus (Start October 2008)	OvGU, Chair of Bioprocess Engineering IDT Biologika GmbH EMC microcollections GmbH
Project: Microsensor Influenza (2007-2008)	Institute for Microtechnology, TU Braunschweig

4 Research Highlights

4.1 Metabolic Flux and Intracellular Metabolite Concentrations during Adherent Cell Growth and Infection

The flux through the metabolic reaction network of a cell (Fig. 2) depends on various cellular properties, in particular enzyme concentrations, enzyme activities and metabolite concentrations. In order to observe the cellular metabolic state, several analytical tools have been established or are currently being developed. Focus of the analysis is (i) the influence of different cultivation conditions (especially media) on the central carbon metabolism, (ii) the distribution of fluxes during different cell growth phases of a cultivation (exponential, confluency), and (iii) the response of central carbon metabolism to viral infection.

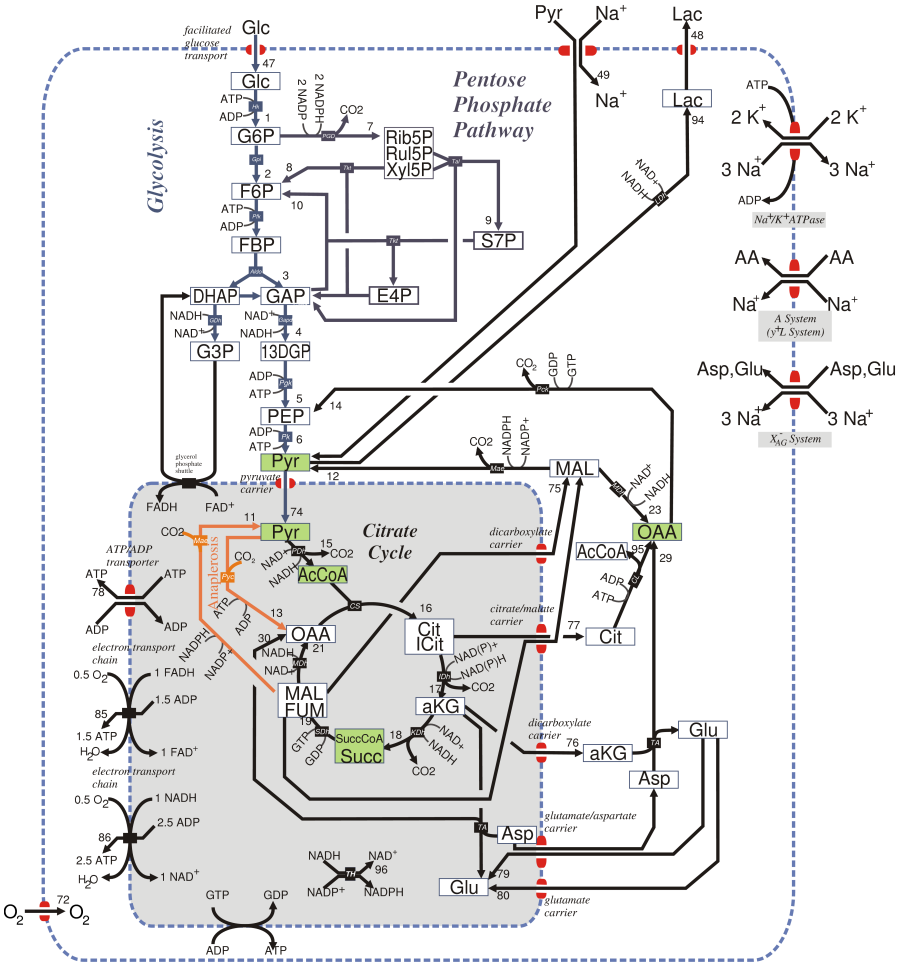

Fig 2: Graphical representation of the metabolic reaction network (in total 112 reactions, 72 metabolites) of an adherent MDCK cell (Wahl et al, 2008). The model includes two compartments, cytosol and mitochondria that are interconnected by transporters. Uptake of amino acids and carboxylic acids is coupled with ATP consumption (not shown). Metabolites displayed on green are “entry points” of amino acid degradation (not shown).

4.1.1 Intracellular Fluxes

For the estimation of intracellular fluxes, metabolic flux analysis is applied. Within this project a close cooperation with S. Klamt (SBI Group) supports the evaluation of data using the software-tool CellNetAnalyzer. Based on extracellular uptake and release rate measurements and a reaction network established for adherently growing MDCK cells (Fig. 2; Wahl et al., 2008) intracellular flux rates are calculated. Additionally, if growth phases are observed, the biomass composition has to be known to estimate the demand of carbon and energy for cell growth.

Metabolic flux analysis requires a steady-state for balancing. Because no real steady-state can be achieved with adherent cells (chemostat cultivation is not possible) phases of quasi stationarity have been determined (Fig. 3).

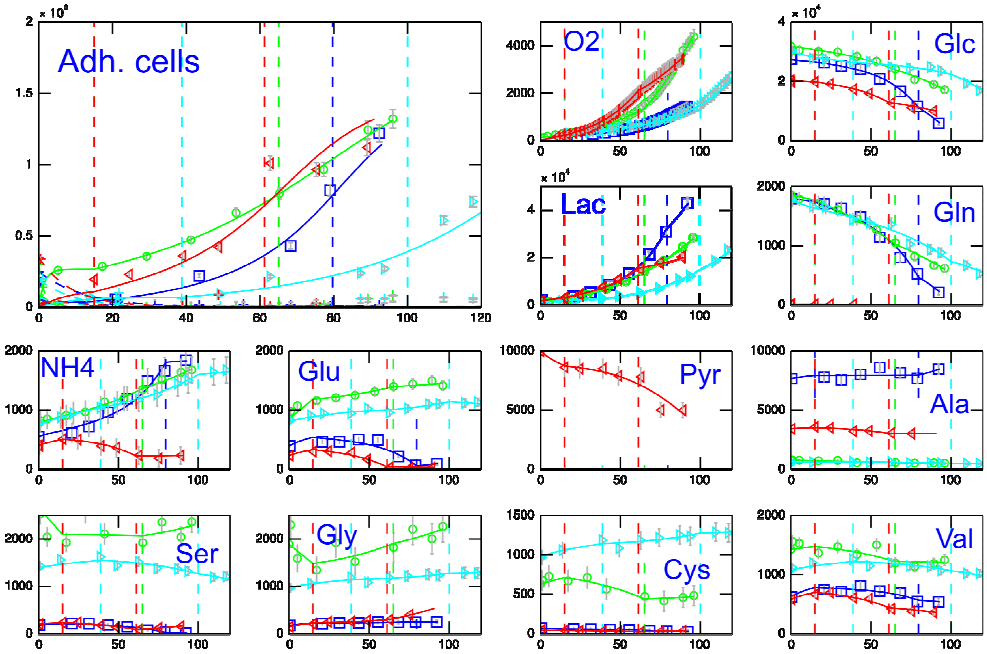

Fig. 3: Adherent cell numbers and concentration measurements under different conditions (GMEM with glutamine, GMEM with pyruvate). The lines represent the fitting of experimental data using a model that assumes constant specific rates during a phase. The rate and the phase change time points are determined by parameter fitting.

Cultivation on microcarriers can be divided into a phase of cell attachment, cell growth, reduced growth, confluency and infection. Some of these phases seem to exhibit a quasi stationary behaviour. The extracellular concentrations of glucose, lactate, ammonia and 18 amino acids as well as cell numbers on microcarriers and in suspension of different cultivations have been measured. Additionally, the oxygen consumption has been calculated from the pO_2 signal. Especially during exponential growth, the growth rate, as well as the consumption of main substrates and product release seems to be constant (Fig. 3). After this phase, growth is slowly reduced, which is presumably due to space limitations. Even though the specific growth rate is not constant, uptake and release rates seem to be constant. Confluency was not reached in a standard cultivation after four days; hence this phase was not analyzed. Also, the phase after infection has not been studied in bioreactor cultivation because infection with low multiplicity of infection (MOI) used in a realistic production process leads to a highly complex behavior. In the beginning only a small amount of cells are infected producing virus particles that will infect further cells. Thus, there is no homogeneous population and no stationary state can be reached.

A phase model based on constant specific rates and growth dependent on the available space has been set up. Parameter optimization was used to determine the

points in time of phase changes and the specific rates in each phase. The optimization was divided in two steps (i) determination of the phase time points based on cell counts and oxygen transfer rate, and (ii) determination of the single specific uptake and production rates.

The phase model has been applied to various cultivation conditions (Fig. 4, GMEM with glutamine, GMEM with pyruvate addition and no glutamine, and serum-free Episerf Medium). The reproduction of the extracellular measurements under these conditions was satisfactory and therefore the assumption of quasi steady-states seems applicable (Fig. 4). In the end, the specific rates and also the accuracies of the estimation were obtained. These rates are now used in metabolic flux analysis to determine flux distributions under different cultivation conditions. To support the interpretation of the flux distributions, a theoretic flux distribution representing an "optimal" cell that consumes a minimum amount of carbon for growth was calculated.

Fig. 4 shows a comparison of optimal and experimentally determined uptake rates under conditions containing glutamine and pyruvate (Sidorenko et al, 2008). As expected, the minimum uptake of glucose is far below the observed rate (13 times lower compared to glutamine condition) and respiration has to be much higher to achieve an efficient use of nutrients. In comparison to the glutamine condition, growth in medium containing pyruvate is closer to an optimal cell. The overall turnover of ATP is comparable (Fig. 4), though the balance between glycolysis and respiration is different, thus leading to overall higher carbon consumption.

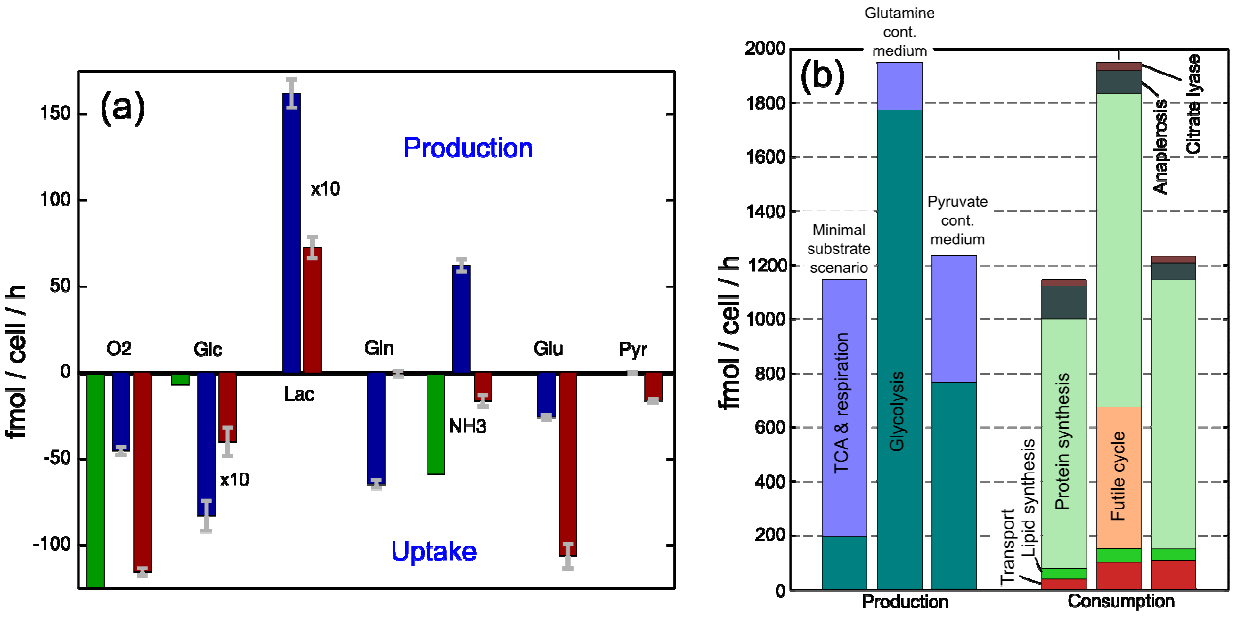

Fig. 4: (a) Specific uptake rates under different conditions (green: calculated from minimum consumption, blue: glutamine containing medium, red: pyruvate containing medium). (b) ATP turnover under different conditions.

4.1.2 Intracellular Metabolites

The intracellular concentrations especially of nucleotides and compounds of the central carbon metabolism can give clues to possible bottlenecks in metabolism, e.g. the accumulation of intermediates or the depletion of energy transporters like ATP. This information is important in order to optimize growth conditions (e.g. supplementation with additional substrates) and to identify bottlenecks in the supply of precursors and energy for virus synthesis. For the determination of intracellular metabolite concentrations, sensitive measurement techniques and an appropriate extraction method have to be established. For adherent MDCK and Vero cells an extraction protocol has been worked out using experimental design strategies (Ritter et al. 2008). Ion-chromatography coupled with mass spectroscopy (IC-MS) is used for the measurement of intracellular concentrations (Ritter et al, 2007).

In order to study the influence of viral infection and replication a synchronous infection is needed. Therefore, infection was performed at high MOI (20) in static culture systems (6-wellplates). As control a MOCK infection (V-Medium without virus) was performed. Fig. 5 (left) shows the time course of a virus production (HA) with H1N1/PR8 (RKI). Fig. 5 (right) displays the time course of chosen metabolites. Especially ATP is at a constant level until about 13 hours post infection (hpi). Shortly after the first release of virus particles the amount of ATP strongly decreases. In order to determine the reasons for this behavior, additional experiments and measurements, e.g. flow cytometry, have to be performed. One hypothesis could be a disruption of the mitochondrial membrane as a consequence of apoptosis. In this case no ATP can be regenerated by the action of TCA and respiratory chain. A hint on a possible decrease in TCA activity is given by the drop in concentration of citrate, cis-aconitate and ketoglutarate after 13 hpi. At this point in time also an increase in lactate excretion and glucose uptake rate (data not shown) was also observed.

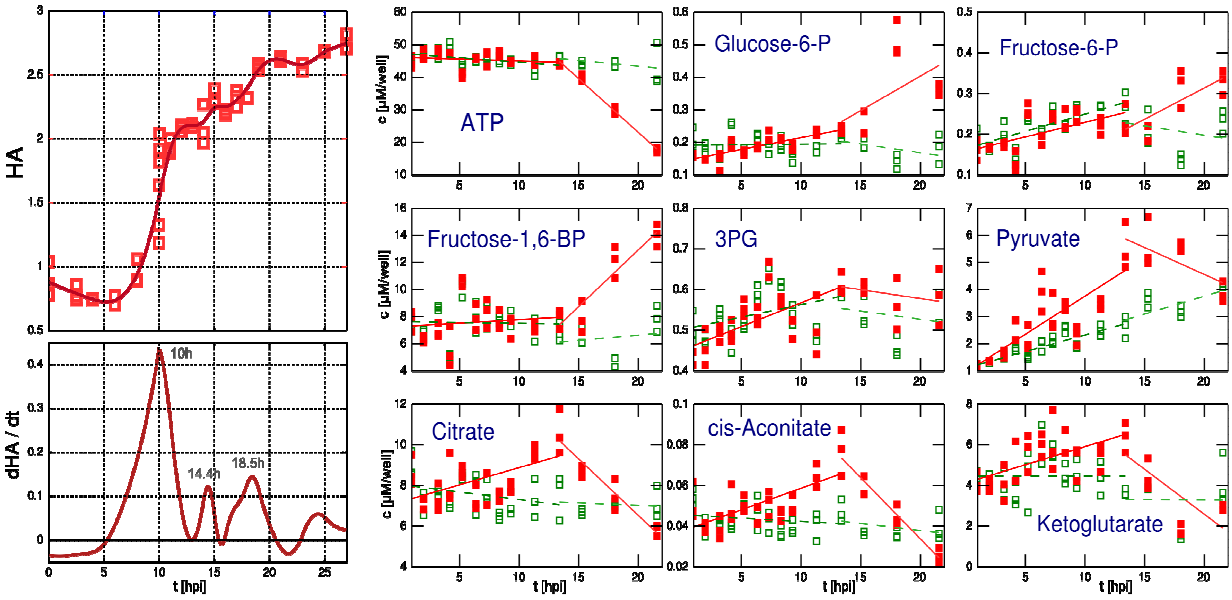

Fig. 5: Time course of HA and intracellular metabolites after infection with MOI 20.

4.2 Development of Downstream Processes for the Production of Viral Vaccines and Recombinant Proteins

4.2.1 Downstream Processes of Viral Vaccines

Current activities in the area of downstream processes of viral vaccine focus on purification of cell culture-derived human influenza vaccines and smallpox vaccines (Vaccinia virus).

4.2.1.1 Design and Optimization in DSP of Cell Culture-derived Vaccinia Virus (MVA-BN®)

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® represents as a robust vector an interesting platform technology not only for vaccine delivery systems like e.g. HIV, Dengue fever, Japanese encephalitis but also as a vector for gene therapy, e.g. cancer treatment.

In collaboration with Bavarian Nordic GmbH, Sartorius Biotec GmbH and the OvGU downstream processes are being developed for new production process of mammalian cell culture-derived Vaccinia virus (MVA-BN®). New upstream processes are focusing on designer cell lines versus the currently used primary cells. Hence, an enhanced downstream process is required in order to meet the stringent production requirements for regulatory approval. Focus of the new downstream process is on increased recovery of the viral particles and an improvement in reduction of contaminating host cell proteins and host cell DNA. Studies are currently focusing on

the initial capture step based on different types of membrane adsorbers (MA) such as ion exchange (Q, D, S and C) and pseudo-affinity (heparin and sulfated cellulose) membranes. The heparin MA are a research product of Sartorius Biotec GmbH. Sulfated cellulose membranes (SCM) are prepared using in-house technology (Wolff et al., 2008b) based on a chemical modification of reinforced cellulose membranes with a pore size of 3 to 5 µm (Sartorius Biotec GmbH). Comparisons of different MA with column based Cellufine® sulfate chromatography (CC) indicated that the heparin pseudo-affinity MA allowed under the applied running conditions the highest overall viral recovery, followed by SCM, Cellufine® Sulfate column chromatography and anionic MA (Fig. 6).

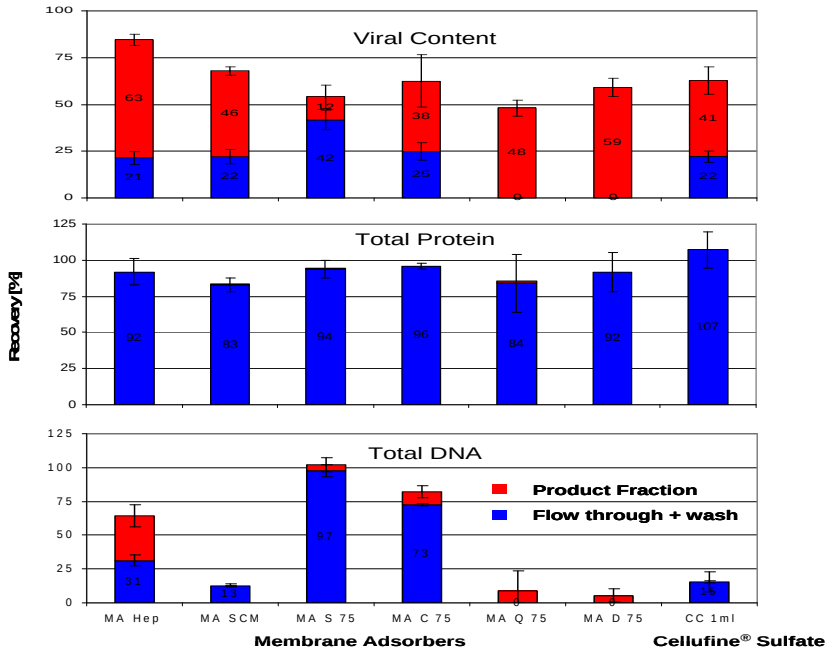

Fig. 6: Comparison of membrane adsorbers (MA) and column based Cellufine® sulfate chromatography (CC) as capture step for cell culture derived Vaccinia virus (MVA-BN®). Bars represent SD of the mean of three experiments measured in triplicates.

All tested chromatography media were suitable to remove the majority of contaminating host cell proteins (Fig. 6). However, the product fractions of heparin MA chromatography contained more than 30% of the initial DNA. Comparing these MA to other tested chromatography methods, the heparin MA revealed the lowest depletion of host cell DNA under the applied running conditions. Under identical running conditions the amount of total DNA in the product fraction of the SCM and Cellufine® sulfate chromatography was below the quantification limit. However, during alkaline loading conditions Cellufine® sulfate showed significantly higher viral capacities than the SCM MA. The optimal operating condition for the process has yet to be identified.

4.2.1.2 Cell Culture-derived Influenza Virus

During the last years several different purification schemes and individual unit operations for the DSP of inactivated whole influenza virus particles have been developed. Initially equine influenza virus (A/Newmarket 1/93; (H3N8)) had been chosen as model virus, later the human influenza virus A/Puerto Rico/8/34; H1N1 had been used as model. More recently, the current A and B strains of the seasonal human vaccines were applied for the design and optimization of DSP of influenza vaccines.

One focus of the DSP has been on affinity based capturing methods for inactivated, clarified cell culture-derived influenza virus particles. As pseudo affinity media various immobilized lectins, metal ions, and sulfated cellulose were applied. In an extended lectin screen a galactosyl (α 1-3) galactose specific lectin (*Euonymus europaeus* lectin) was identified being suitable to capture MDCK cell derived influenza virus particles (A/PuertoRico/8/34; H1N1) (Opitz et al., 2007a). Further studies evaluated favorable adsorption matrices for the affinity capture step: (i) reinforced cellulose membranes and (ii) a polymer bead from Galab Technologies GmbH (Opitz et al., 2007b). These chromatography media resulted in a viral recovery greater than 95% of the starting material based on the hemagglutination assay. In the case of the MA, total protein and host cell DNA reduction based on the starting material concentrations amounted to 69% and 99%, respectively. Evaluations of the general applicability of the EEL-affinity chromatography indicated comparable results for different human and equine strains of Influenza A virus and for human influenza B. However, glycosylation patterns of viral membrane proteins strongly depend on the host cell. This is reflected in an inefficient capturing of Vero cell-derived influenza virus particles by EEL-chromatography (Opitz et al., 2008a) and indicated in glycan analysis studies (Schwarzer et al., 2008). In the case of varying host cells, corresponding lectins would have to be identified.

A general concern associated with affinity chromatography is the leaching of bioactive compounds (Wolff and Reichl, 2008c). This accounts in particular for lectins having the potential to be toxic. As an alternative, pseudo affinity chromatography via heparin or sulfated cellulose can be applied. Cellufine® sulfate is currently used in a commercial vaccine manufacturing process for capturing influenza virus particles (Novarits AG). The major drawback of Cellufine® sulfate bead chromatography for influenza virus purification is its comparatively low productivity, which can be

overcome by the application of sulfated reinforced cellulose membranes (Wolff et al., 2008a; Wolff et al., 2008b; Opitz et al., 2008b). A direct comparison revealed an improvement in the overall viral recovery by a significant reduction of the host cell DNA contamination of the product fraction (Fig. 7).

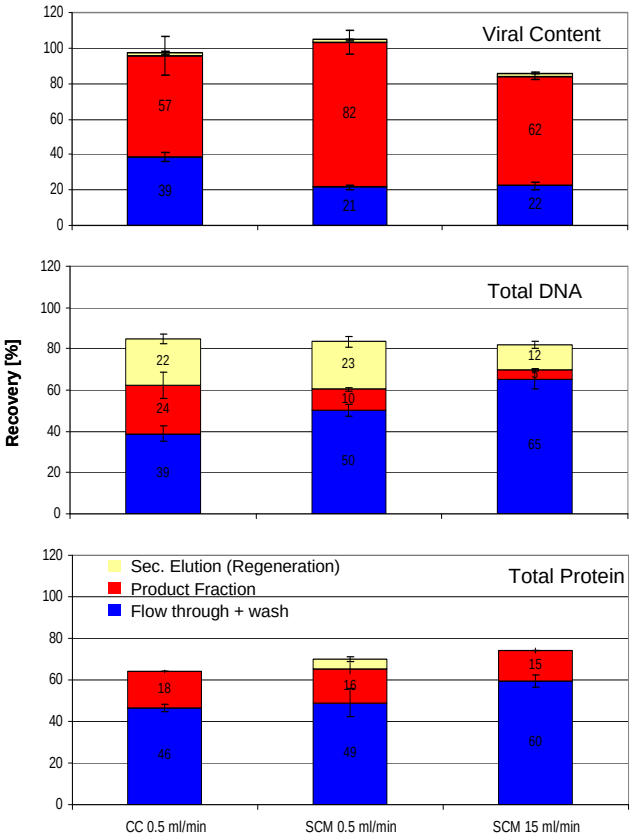

Fig. 7: Comparison of sulfated reinforced cellulose membrane adsorbers (SCM) with Cellufine® Sulfate column chromatography (CC) for a capturing of cell culture-derived influenza virus (A/Puerto Rico/8/34; H1N1). Bars represent SD of the mean of three experiments measured in triplicates.

As a further option, affinity chromatography based on immobilized metal ions is currently being evaluated. Initial results indicate promising total viral recoveries and similar contaminant depletions as compared to the SCM unit operation.

A generic scheme for the downstream process of MDCK cell-derived human influenza virus based on (i) clarification by depth filtration (0.45 µm), (ii) β-propiolacton inactivation, (iii) concentration via cross-flow ultrafiltration, (4) size exclusion chromatography, and (iv) anion exchange chromatography resulted in an overall virus yield of 53%. Total protein and host cell DNA removal based on the starting material was 96.5% and 99.8%, respectively (Kalbfuß et al., 2007a, b, c).

Although the reduction of contaminating host cell proteins and DNA is comparatively high, it is still not sufficient for human vaccine production. Attempts to further reduce

the level of contaminating host cell DNA were done by selective precipitations of host cell DNA from inactivated and clarified cell culture supernatant by a following diafiltration to remove the precipitation agent (Kröber et al., 2008). The drawback of this method is the identification of highly specific non-toxic precipitation agents. The currently applied model compounds are toxic and require an improved specificity. An overview on downstream processes established in the BPT group is shown in Fig. 8).

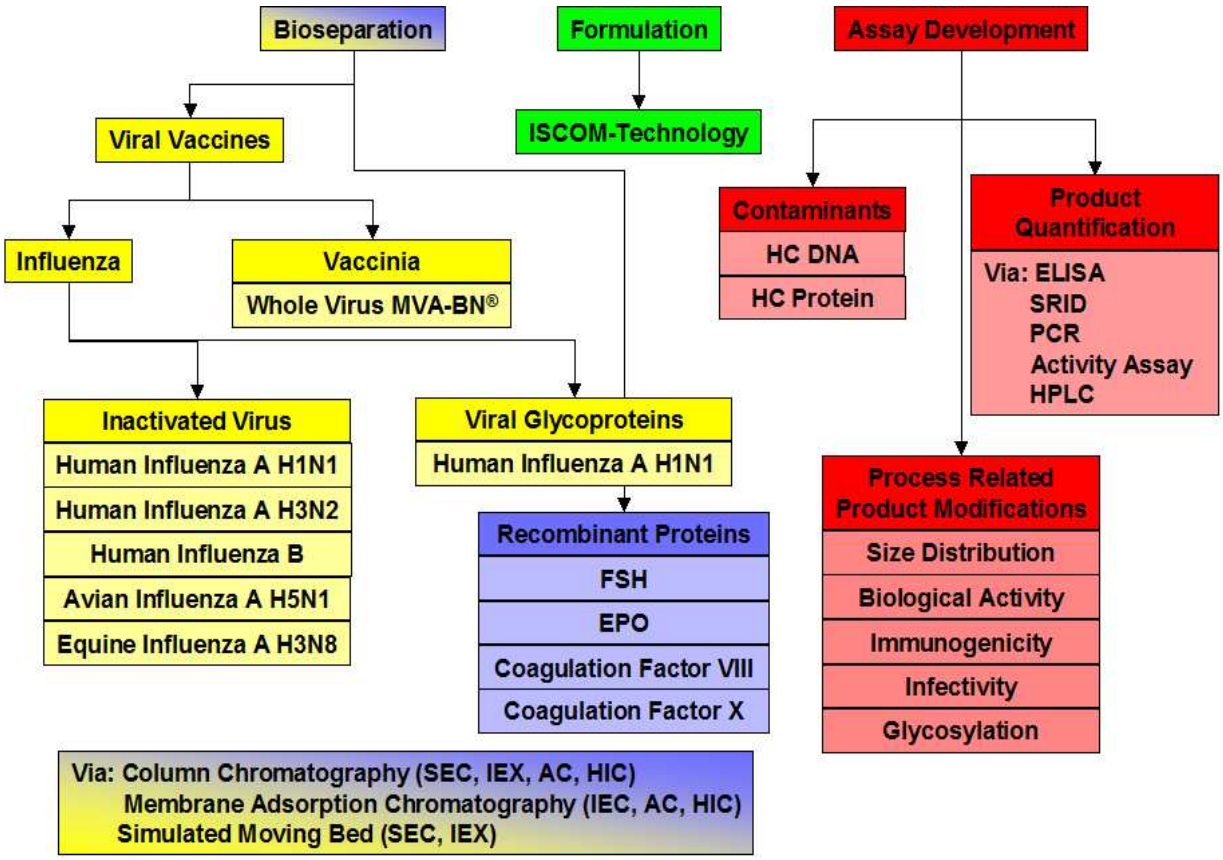

Fig. 8: Overview of current downstream processes

4.3 Proteomics and Glycomics

To explore qualitative and quantitative data of cell cultures on various levels, several experimental platforms have been established: physiological level (microscopy, flow cytometry), genome level (real-time PCR), proteome level (qualitative and quantitative proteomics), metabolome level (qualitative and quantitative metabolic (flux) analysis). These allow very specific questions concerning mammalian cell growth and virus-related bioprocesses to be addressed.

Qualitative and quantitative analysis on proteome level is performed using a set of gel-electrophoresis techniques (2D-DIGE) for protein separation (and quantification), in combination with two-dimensional high performance liquid chromatography coupled online to tandem mass spectrometry (2D-nanoHPLC-MS/MS) for protein

identification. The methods are also used to investigate bacterial growth (regulation and control in *E. coli*, K. Bettenbrock, SBI Group), and the meta-proteome of microbial communities (D. Benndorf, BPE, OvGU).

4.3.1 Virus-Host Cell Interaction at the Proteome Level

This project focuses on the dynamic interaction of the influenza virus with its mammalian host cell. The first aim was to characterize host cell protein expression changes in various mammalian cells after infection with different influenza virus strains. In addition, proteome changes related to cultivation conditions are investigated.

Differentially expressed host cell proteins over the time course of an infection phase were detected (quantitatively) by 2D-DIGE. Differences in relative protein expression were quantified to trace time dependent changes of the cellular proteome composition. Up and downregulated proteins were digested enzymatically and identified via nanoHPLC-MS/MS utilizing the MASCOT protein identification system (Fig. 9a). The dynamic host cell proteomes of different cell lines (e.g.: canine MDCK and human A549) after infection with different influenza strains was elucidated and compared (Fig. 9b). Interestingly, the same virus strain induces significantly different host defence mechanisms in canine (MDCK) and human (A549) cells (Vester et al., 2007). Proteins identified are reported to be involved in a wide spectrum of cellular functions and host defense mechanisms including: apoptosis, cytoskeletal rearrangement, protein synthesis, and protein degradation. Distinct proteome patterns with differentially regulated proteins over time showed dynamic host cell response mechanisms in both the early and late phase of infection. Surprisingly, significant differences in host cell response were observed when comparing results from virtually the same virus strain (H1N1) obtained from different suppliers (RKI, Germany and NIBSC, UK), which clearly indicates a strong influence of only a few mutations of the viral genome on virus-host cell interaction.

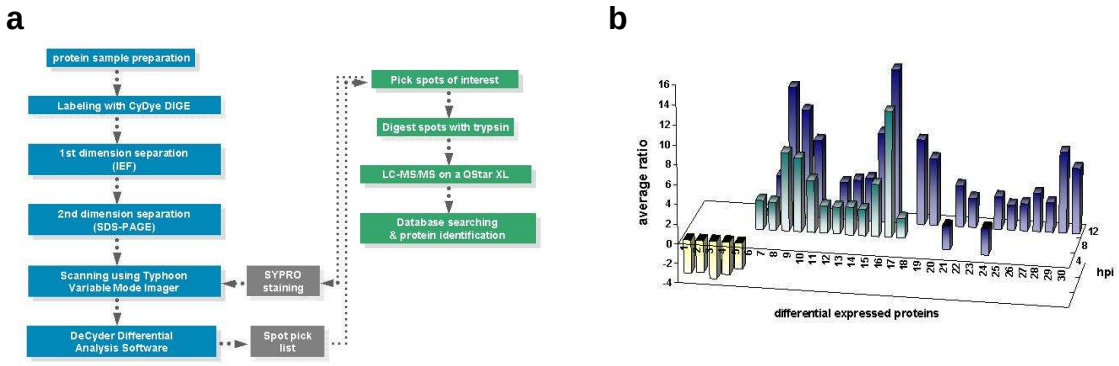

Fig. 9: a) Process scheme for differential protein abundance analysis and protein identification, using the 2D-DIGE system and nanoHPLC-MS/MS. b) Effect of influenza A infection on the proteome of mammalian cells. The bar chart represents the average ratio of the spot volume of all differential expressed protein spots at three time points post infection (4 h, 8 h, 12 h).

4.3.2 Glycomics

Monoclonal antibodies, recombinant and viral glycoproteins produced in mammalian cell culture play an important role in manufacturing biopharmaceuticals. To ensure consistent quality of the corresponding products, glycosylation profiles have to be closely controlled, as glycosylation potentially affects important properties, including bioactivity and antigenicity. Glycosylation patterns of viral surface proteins from unit operations in up and downstream processing are characterized by high performance liquid chromatography (HPLC), multi-capillary gel electrophoresis (CGE), each with either laser induced fluorescence (LIF) or mass spectrometric (MS) detection (collaboration with PCF Group and external partners: ProBioGen, Berlin, Chiron/Novartis AG, Marburg, Germany).

The main questions addressed regarding the glycosylation of the major viral membrane proteins hemagglutinin (HA) and neuraminidase (NA), are e.g.: the influence of host cell lines and cultivation conditions, impact of inactivation procedures and changes in glycosylation profiles in downstream processing.

4.3.2.1 Method Development and Automated High Throughput Identification of Carbohydrates and Carbohydrate Mixture Composition Patterns

The workflow (Fig. 10) involves virus purification directly from cell culture supernatants, protein separation by SDS-PAGE, endo- and exoglycosidase-cleavage of *N*-glycans, desalting and CGE-LIF (Schwarzer et al., 2008). The *N*-glycans are analyzed in two stages (i) simple glycosylation pattern profiling that allows the

comparison of “glycan-pool fingerprints” and (ii) structural identification of detected glycans via database matching, and additionally, sequencing of glycans if required.

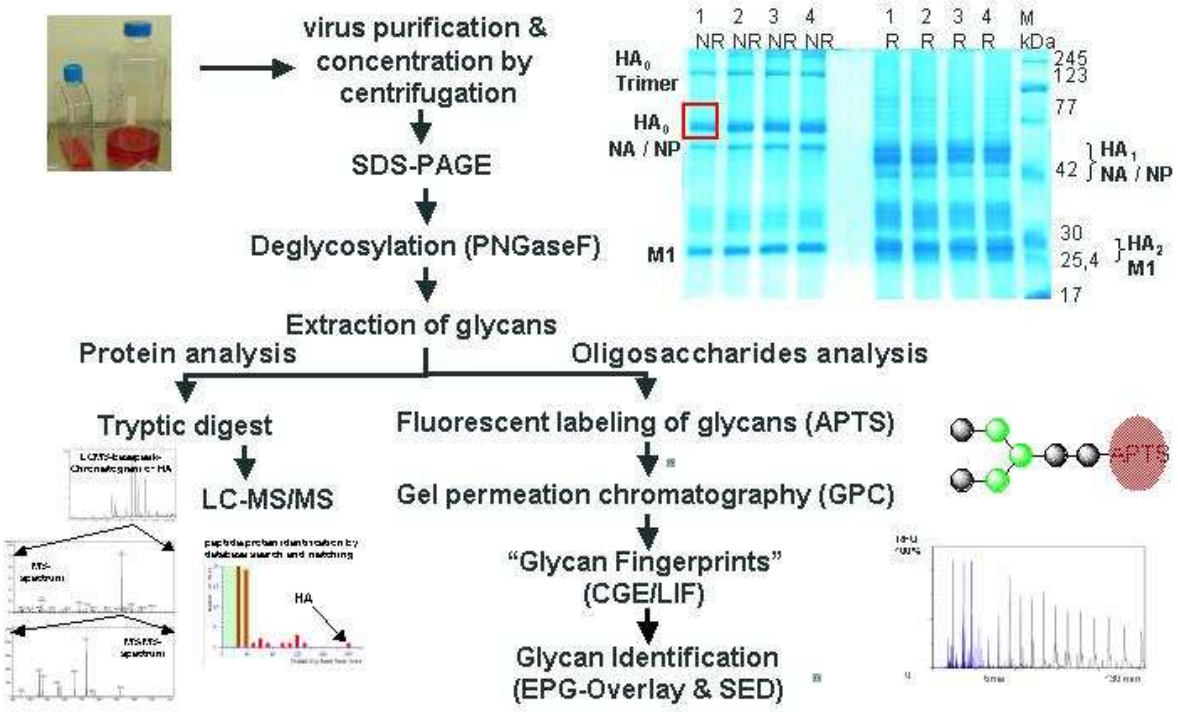

Fig. 10: Workflow for protein identification and *N*-glycan analysis of mammalian cell culture-derived influenza virus HA.

Excellent long-term reproducibility concerning migration time and peak heights were obtained (Schwarzer et al., 2008) making this method a valuable tool for identification of carbohydrate compositions out of highly complex carbohydrate mixtures, as well as for determination of carbohydrate mixture composition patterns. Based on the determination of migration time indices (Fig. 11) by multi-capillary gel electrophoresis, laser induced fluorescence (CGE-LIF), carbohydrate components are identified by matching of standard migration time indices from a database (Rapp et al., 2008). For this purpose a software package for data processing and visualization, based on an integrated database containing normalized migration times of known carbohydrates as standards, is currently being established.

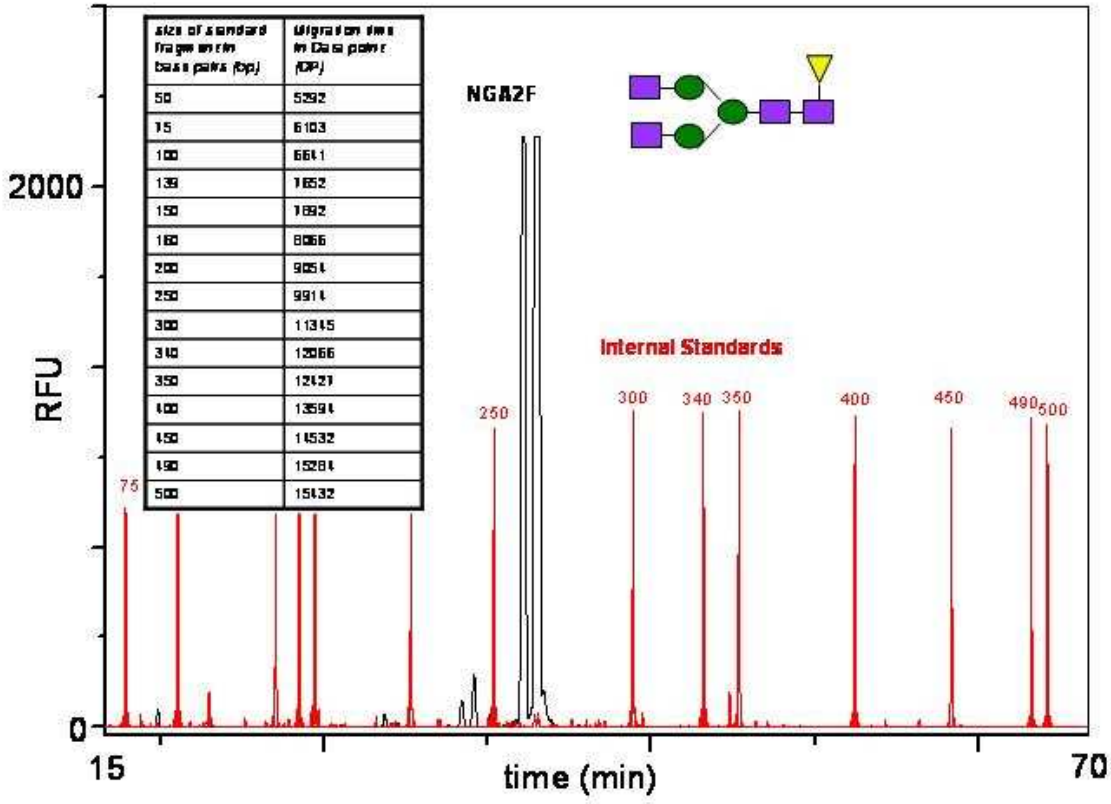

Fig. 11: Electropherogram of the *N*-glycan NGA2F obtained by CGE-LIF (overlay, internal standard ladder trace).

4.3.2.2 Profiling Influenza A Virus Hemagglutinin N-Glycosylation During Vaccine Production

The approach (Fig. 10), allowed the characterization of *N*-glycosylation patterns of viral membrane glycoproteins. HA is the most abundant and immunogenic influenza virus surface glycoprotein. The functional role of the glycans is still not completely understood. However, it is known that structural modifications of these *N*-glycans can influence viral replication dynamics and immune response after vaccination. The glycosylation pattern can be affected by the virus strain, the glycosylation machinery of the host cell (Fig. 12), cultivation conditions in upstream processing and via incipient degradation of glycoproteins during virus inactivation and downstream processing. Hence, monitoring of the glycosylation pattern during vaccine manufacturing could be used for process control and as a method to characterize properties of antigens, which might be highly relevant for antigenicity and immunogenicity of vaccines.

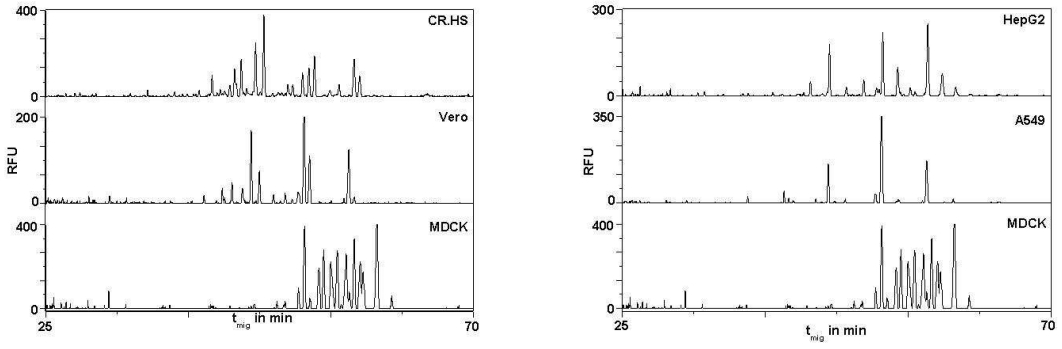

Fig. 12: Shifted overlay of HA *N*-glycan fingerprints of influenza A/PR/8/34 (H1N1) produced in MDCK, Vero, CR.HS, A549 and HepG2 cells.

4.4 Signal Transduction and Apoptosis in Virus-infected Cells

As part of the innate immune response a virus-infected mammalian cell activates a diverse and complex signal transduction network to establish the host cell defense (Fig. 13). The virus is sensed by pattern recognition receptors (PRRs), which activate intracellular signaling pathways leading to the induction of interferon (IFN). IFN is a key player in the pathogen defense and activates a variety of antiviral genes by paracrine and autocrine signaling. Among these antiviral genes the Mx (myxovirus resistance) proteins are known to exert an antiviral effect on the influenza virus replication. Furthermore, the infected cells can induce apoptosis to reduce the degree of virus propagation. The virus itself tries to evade these defense mechanisms by producing the non-structural protein NS1, which interferes with the host defense at multiple levels.

So far it is not known to which extent the antiviral host cell defense limits influenza virus vaccine production in mammalian cell cultures. As a starting point we are focusing on interferon and apoptosis related effects.

A 2D-DIGE (see 4.3.1) approach, which compared protein expression of uninfected and infected MDCK cells, identified Mx proteins among other proteins to be up-regulated (D. Vester et al., 2008). Since these Mx proteins are stringently induced by IFN signaling, a quantitative real-time PCR was set up (supported by Prof. H. Hauser, HZI Braunschweig, Germany) to monitor the expression of IFN, Mx and viral NS1 during the infection. Results clearly indicate the relationship between IFN induction, counteracted by newly synthesized viral NS1 protein and the subsequent induction of antiviral genes like Mx1 (Fig. 14).

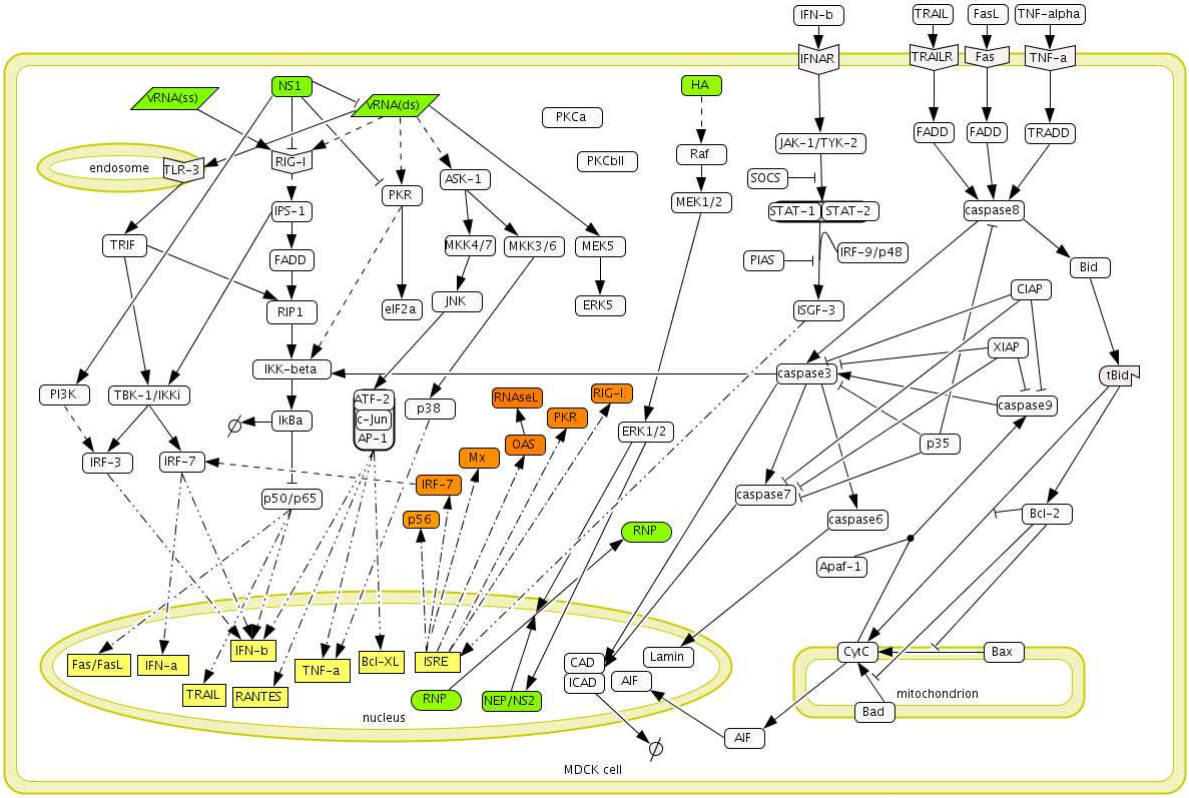

Fig. 13: Scheme of the signal transduction network in a mammalian cell infected with influenza virus. Viral components are depicted in green, genes are colored in yellow and antiviral IFN-stimulated genes are shown in orange.

Within the Forsys project WPB 9 (Dynamics of Influenza A Virus Replication in Epithelial Cells) different molecular biological methods are being adapted to elucidate the signal transduction in the canine MDCK cell line. Phospho-specific antibodies against human or mouse proteins are being tested on canine probes to identify the signaling cascades leading to the induction of the host cell defense. This work is supported by Prof. M. Naumann (Medical Faculty, OvGU), who is studying signal transduction in Helicobacter pylori infected MDCK cells.

Luciferase reporter assays are being used to complement the analysis of the signaling network at the gene regulation level. Based on a structural qualitative model of the antiviral signaling network that is currently being developed with the support of S. Klamt and S. Mirschel (SBI group) we expect to get a better understanding of the relevance of signaling events in cell culture-based vaccine production, and to further elucidate virus-host cell interactions under highly controlled process conditions. Furthermore, we are interested in the antiviral capacity of canine Mx1 and Mx2 proteins in comparison to their well-characterized human and mouse counterparts. Therefore the canine Mx proteins were cloned into epitop-tagged expression vectors and will be characterized in collaboration with Georg Kochs

(Department of Virology, Universitätsklinikum Freiburg). Overall, it is anticipated that the elucidation of influenza-induced antiviral signaling pathways may lead to new targets for the optimization of cell culture-based vaccine production process.

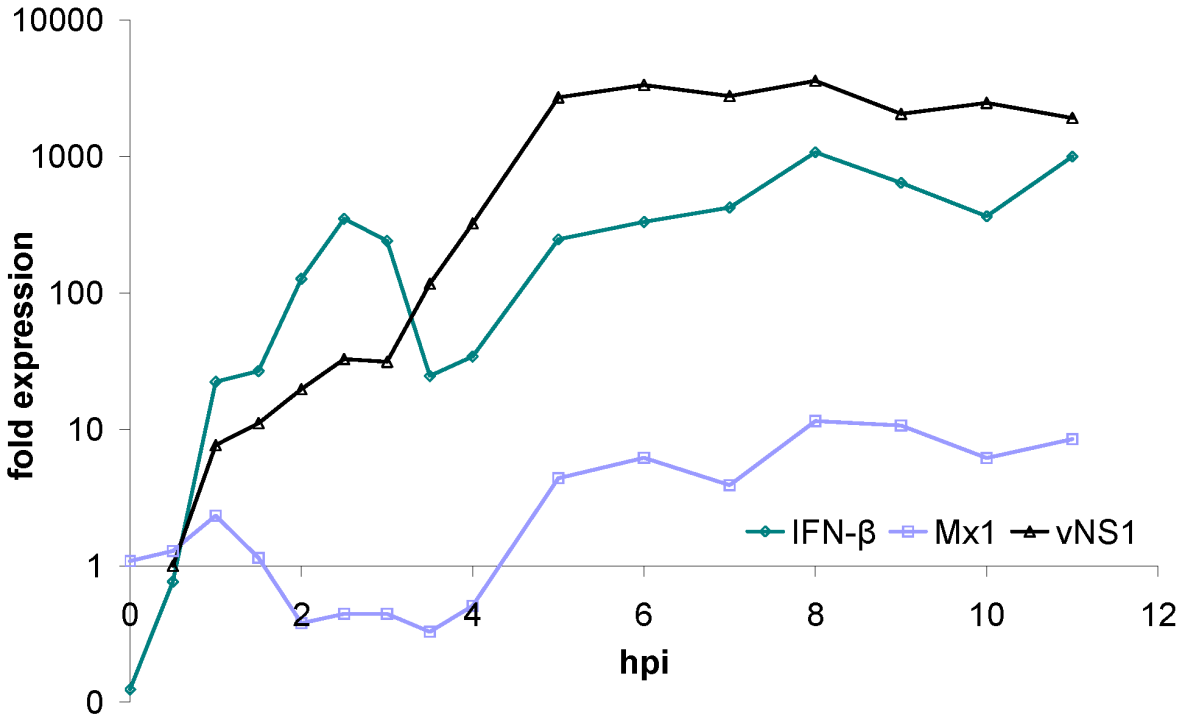

Fig. 14: Real-time PCR quantification of Interferon-beta (IFN-B), myxovirus resistance protein 1 (Mx1) and influenza non-structural protein 1 (NS1). MDCK cells were infected with influenza A/PR/8/34 (NIBSC) with MOI 5 and samples were taken at high frequency at the indicated time post infection. Results are shown as fold expression relative to untreated samples.

4.5 Organization of Symposia and Workshops

- Symposium „Trends in Systems and Control Theory“, 1 - 2 March, 2006 Magdeburg, Germany
- Workshop Viral Dynamics, CCEX 2006, April 23 – 28, Chateau Fairmont Whistler, Canada
- Workshop Systems Biology, January 12-13, 2007, MPI, Leipzig, Germany
- MPG-CNRS Joint Workshop on Systems Biology, September 24 – 26, 2007, Harnackhaus, Berlin; Germany
- Symposium: Information and Control Hierarchies: Foundations, Computation and Applications, May 22 - 23, 2008, MPI Magdeburg, Germany

5 Selected Teaching Activities, Diploma Projects, PhD Projects and Habilitations

In 2004 the interdisciplinary diploma study course Biosystems Engineering was successfully established together with the Faculty of Electrical Engineering and Information Technology, the Faculty for Natural Science and the Medical Faculty. Since the winter semester of 2006/2007 it is offered as a Bachelor of Science program. In 2011 a consecutive Master of Science program will be offered. Currently, there are 161 diploma and 52 Bachelor of science students enrolled, with more than 300 applications (50 students accepted) for winter semester 2008/2009.

In 2007 the International Max Planck Research School for Analysis, Design and Optimization in Chemical and Biochemical Process Engineering was established at the OvGU Magdeburg. Currently, there are more than 25 PhD students enrolled.

5.1 Lectures at the OvGU (Prof. U. Reichl):

- Biochemical engineering (3 SWS; German, English)
- Laboratory course - Biochemical engineering I (1 SWS; German, English)
- Mathematical modeling of bioprocesses (2 SWS, German)
- Exercise - Mathematical modeling of bioprocesses (1 SWS, German)
- Cell culture engineering (2 SWS; German, English)
- Laboratory course – Cell culture engineering (2 SWS, English)
- Microbiology (2 SWS, with Grammel / Bettenbrock SBI Group)
- Laboratory course – Microbiology (1 SWS; German)

5.2 Diploma projects (September 2005 to July 2008)

Tab. 8: Diploma Projects supervised by U. Reichl

Riedele, Christian	Entwicklung eines Microcarrier-basierten Herstellungs-verfahrens für einen Impfstoff gegen Schweine-Influenza
Straube, Sabine	Kultivierung von felinen Lungenfibroblasten und Vermehrung von Nerz Enteritus Virus in Microcarriersystemen bei Batch- und Perfusions-Betrieb
Klawisch, Alexander	Validierung der Sterilfiltration
Wolff, Sabrina	Optimierung der Virusvermehrung von rekombinanten MVA und FP Vektoren in HEF Suspensionskultur
Heßeler, Julia	Theoretical Analysis and Mathematical Modeling of Microbial Species in a Chemostat - How to Achieve Coexistence of Competing Species

Deshpande, Kedar	Quantification of Influenza Virus Hemagglutinin (HA) by Reversed Phase – High pressure Liquid Chromatography (RP-HPLC) method
Salaklang, Jatuporn	Development of a Lectin-Affinity Chromatography for the Downstream Processing of Influenza A Virus Vaccines
Regestein, Lars	Mathematische Modellierung einer drei Spezies Mischkultur im Chemostat: Einfluss von Medienzusammensetzung und Stoffwechselcharakteristika auf Koexistenz
Eisold, Katrin	Reinigung von humanem Influenzavirus aus Säugerzellkultur
Thiele, Morries	Optimierung von Real-Time PCR zum Nachweis von RNA-Spezies aus Influenza A/PR/8/34
Kröber, Tina	Ernte und Reinigung von humanem Influenzavirus aus Säugerzellkultur
Schulze, Mareike	Influenza – Virusproduktion in tierischen Zellkulturen: Untersuchungen zur Zellphysiologie
Seitz, Claudius	Molekularbiologische Untersuchungen an Influenza-Viren mittels quantitativer Realtime-PCR
Dietzsch, Christian	Influenza Impfstoffherstellung mit adhärenten Vero Zellen
Knöchlein, Anne	Ernte von Influenza Virus aus tierischer Zellkultur
Christel, Jessica	Herstellung und Charakterisierung von PEGylierten Standardproteinen für die Testung von Chromatografischen Trägermaterialien
Lohr, Verena	Die aviären Designerzellen CR.HS und CR.MCX – Wachstum und Produktion von modifizierten Vacciniavirus Ankara (MVA)
Rath, Alexander	Influenza-Impfstoffproduktion in zwei permanenten aviären Designerzelllinien

5.3 Supervision of Ph.D. Theses (September 2005 to July 2008)

Tab. 9: Ph.D. theses supervised by U. Reichl

Holtmann, D	Electro-Chemical Monitoring of Microbial Activity - Fundamentals and Application in Waste Water Treatment
Pohlscheidt, M.	Entwicklung und Optimierung eines Verfahrens zur Viruspropagation von Parapoxvirus Ovis NZ-2
Sidorenko, I,	Mathematische Modellierung von Influenza Virus Replikation in Säugerzellen
Möhler, L.	Segregierte mathematische Modelle zum Wachstum adhärenter tierischer Zellen (MDCK) und zur Influenza Virus Replikation
Hundt, B.	Entwicklung und Optimierung eines Herstellungsprozesses für einen Parvovirus-Impfstoff im Rührreaktor und Wave®Bioreaktor

At present there are 7 PhD students in the BPE Group and 6 PhD students at the OvGU, supervised by U. Reichl, T. Frensing, Y. Genzel, E. Rapp, A. Wahl, and M. Wolff (see survey of Research Projects)

5.4 External evaluations (September 2005 to July 2008)

- Appointment Committee of the MPG, Mühlheim (2005)
- Appointment Committee of the MPG, Jena (2005)
- Appointment Committee of the OvGU, Magdeburg (2007 – 2008)
- Appointment Committee of the MPG, Leipzig (2007 – 2008)

6 Selected Memberships, Appointments and Awards (Udo Reichl)

- Member of the Perspective Commission of the CPT (Chemistry, Physics & Technology) Section, MPG (since 2003)
- Member of the Foundation Committee of the MPG-CAS Institute "Computational Biology", (Shanghai, China) (since 2004)
- Managing Director of the MPI (2005 – 2006)
- Spokesperson of the IMPRS Magdeburg (since 2007)
- Member of the Intersectional Expert Committee of Systems Biology, MPG (since 2006)
- Member of the Board of Trustees, EU Liaison Office of the German Research Organisations, KOWI, Brussels (since 2007)

7 Future Directions

The main focus of research activities over the next several years will remain on mammalian cell culture of adherent and suspension cell lines, virus-host cell interaction, and virus propagation in stirred tank and wave®bioreactors. In addition, projects related to recombinant protein expression in mammalian cells will be extended. Supported by external funding of projects related to systems biology (Forsys, SysLogics; BMBF funding), basic research on mammalian cell metabolism will remain one of the main activities of the BPE Group. Besides determination of extracellular metabolite uptake and release rates, measurements of intracellular metabolite concentrations and high-throughput analysis of key enzyme activity levels (glycolysis, TCA; MPI for Molecular Plant Physiology, Prof. Stitt, Golm) will be performed for improving metabolic flux analysis and development of dynamic models of cell growth. Significant efforts will be directed towards the confirmation and theoretical analysis of the structure of metabolic networks (Wahl et al., 2008). This includes ^{13}C isotopomer analysis with internal and external partners (SBI group; SysLogics, BMBF) and the attempt to include information concerning the spatial

distribution of intracellular metabolites, in particular concentration differences between cytosol and mitochondria (SysLogics, BMBF). The latter will be experimentally extremely challenging due to the lack of established methods and problems to evaluate results by (internal) standards. To complement research pursued with adherently growing MDCK cells, growth and product formation (viral antigens, recombinant proteins) of new human designer cell lines will be thoroughly characterized. These suspension cells are provided by ProBioGen (ProBioGen AG, Berlin, Germany) within the SysLogics project (BMBF). Cultivation will be performed under serum free conditions in batch and continuous culture in small scale stirred tank bioreactors. Therefore, quasi steady-state assumptions - necessary for MDCK microcarrier cultivations - are not required for facilitating experimental investigations. Also, accuracy of cell concentration and cell volume measurements of suspension cultures is higher allowing a more reliable determination of specific rates.

Progress in understanding virus-host cell interaction and optimization of virus yields in vaccine manufacturing relies not only on improvement of cell culture conditions. Often, any attempt to improve virus yields by increasing cell concentration fails due to reduction in cell specific virus yields (so-called “cell density effect”). In addition, multiplicity of infection (MOI) has a profound effect on virus yields for various influenza A strains (e.g. A/Wisconsin/67/2005 HGR, H3N2). Therefore, efforts to better characterize virus replication on a cellular level will continue. This includes the use of RT-PCR and proteomics to analyze intracellular virus replication and host cell response mechanisms. Also, studies with regard to signal transduction pathways (as relevant in vaccine manufacturing) will be extended to improve understanding of antiviral factors decreasing cell specific virus yields. Work will be complemented by flow cytometric studies and - in collaboration PSD Group (A. Kienle) - theoretical analysis of population dynamics (Sidorenko et al., 2007; Müller et al., 2008).

Downstream processing of cultivation broths consisting of highly complex mixtures of hundreds of compounds will also remain a focus of research activities. As in previous years, work will be conducted in close cooperation with the Chair of Bioprocess Engineering (OvGU, Magdeburg). Based on the successful establishment of a generic process for influenza virus purification (Kalbfuß et al.,2007a) and work on affinity chromatography based methods (Opitz et al., 2006; Opitz et al. 2007) a proposal was successfully evaluated by the BMBF, which will allow the extention our activities towards affinity based capturing of recombinant proteins (e.g.

erythropoietin, follicle-stimulating hormone) and viral antigens (influenza A virus; human, swine, avian H5N1). Collaborating partners are Merckle Biotec (Ulm, Germany), EMC microcollections GmbH (Tübingen; Germany), IDT Biologika GmbH (Dessau-Roßlau, Germany), Prof. Laufer (Chair of Pharmaceutical Chemistry, TU Tübingen, Germany), A. Seidel-Morgenstern (PCF Group) and K. Sundmacher (PCP Group). In addition to experimental work regarding capturing of sialated glycoproteins by small peptide ligands, questions concerning continuous purification of viral antigens by simulated moving bed chromatography (PCF Group) and modeling of ligand-target protein interaction (PCP Group) will be in the focus of this project.

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