MAX-PLANCK-GESELLSCHAFT

Scientific Report 2003 – 2005

Max Planck Institute for
Dynamics of Complex
Technical Systems

MAX–PLANCK–INSTITUT
DYNAMIK KOMPLEXER
TECHNISCHER SYSTEME
MAGDEBURG

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Members of the Scientific Advisory Board

Frequently Used Abbreviations

Research Groups of the Max Planck Institute

BPE	Bioprocess Engineering
INS	Integrated Navigation Systems
MF	Mathematical Foundations of Dynamical Systems
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

Funding Organizations

AiF	Working Party of Industrial Research Associations
BMBF	Federal Ministry of Education and Research
BMWi	Federal Ministry of Economics and Technology
DAAD	German Academic Exchange Service
DFG	German Science Foundation
EU	European Union
KM-LAS	Ministry of Education and Cultural Affairs of Saxony-Anhalt
LSA	German Federal State of Saxony-Anhalt
MPG	Max Planck Society
MPI	Max Planck Institute for Dynamics of Complex Technical Systems
OvGU	Otto von Guericke University Magdeburg
Pro3	Competence Network on Process Engineering
VW	Volkswagen Foundation
WTZ	Programme “Scientific-technical Cooperation” funded by BMBF

Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg

Overview

by the Managing Director Udo Reichl

Heads of MPI research groups:
U. Reichl, J. Raisch, E.D. Gilles, K. Sundmacher, A. Seidel-Morgenstern, A. Kienle (not shown: W. Marwan)

1 Present Status

The scientific work at the Max Planck Institute for Dynamics of Complex Technical Systems (MPI) began in March 1998 in a temporary space rented in the ZENIT-building on the campus of the Medical Department at the Otto-von-Guericke-University of Magdeburg (OvGU). In August 2001 the entire institute moved into a newly constructed building located near the OvGU where the scientific work was continued in September 2001. Since then research activity has been significantly expanded and a close collaboration between the different research groups and the departments at the OvGU have formed an excellent platform for successful developments as a whole.

The present board of directors consists of three active scientific members of the Max Planck Society (MPG). Prof. Dr.-Ing. E. D. Gilles, who was the foundation director of the institute and the director of the Department for “System Theoretical Fundamentals of Process and Bioprocess Engineering” retired at the end of May 2004. Due to a consolidation program by the MPG and the corresponding cutbacks in the institute’s budget, the MPG decided to delay the search for a successor. To assure an effective representation of the associated research topics, Prof. E. D. Gilles, the MPG and the board of directors agreed that he would act as a provisional department head until May 2008. As a consequence of that decision, he continues his position as head of the Systems Biology group (SBI). The Integrated Navigation Systems group (INS) is being phased out since the research has matured. In addition, support of the Systems and Control Theory group (SCT) headed by Prof. Dr.-Ing. J. Raisch continues to ensure that the Systems Science approach will remain an integrating factor for basic research in biochemical and chemical engineering and biology. As recommended in the last report of the Scientific Advisory Board (SAB), research activities of the Mathematical Foundations of Dynamical Systems group (MF), headed by Prof. Dr. D. Flockerzi, were incorporated into the SCT group. Therefore, Prof. Flockerzi will continue to provide substantial mathematical support for all MPI research groups.

At the end of 2004 the new research group Molecular Network Analysis (MNA) was established. This group is headed by Prof. W. Marwan, formerly a Research Professor at the University of Hertfordshire (UK), who holds a full professorship for Regulative Biology in the Department of Natural Sciences at the OvGU since 2005.

The foundation for his group at the MPI is based on an initiative instigated by Prof. Gilles and the group of Prof. Oesterhelt at the MPI for Biochemistry in Martinsried (Germany). It is expected that the MNA group, which focuses on the experimental analysis of molecular networks in prokaryotes and lower eukaryotes, will closely collaborate with the SBI and the Bioprocess Engineering group (BPE) of Prof. U. Reichl. In addition to the substantial expansion of experimental expertise in biological systems, new possibilities in the theoretical description of molecular networks are underway.

In the course of reorganizations and establishment of one new research 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 (Fig.1). As of August 2005, the total number of staff employed at the MPI was 174.

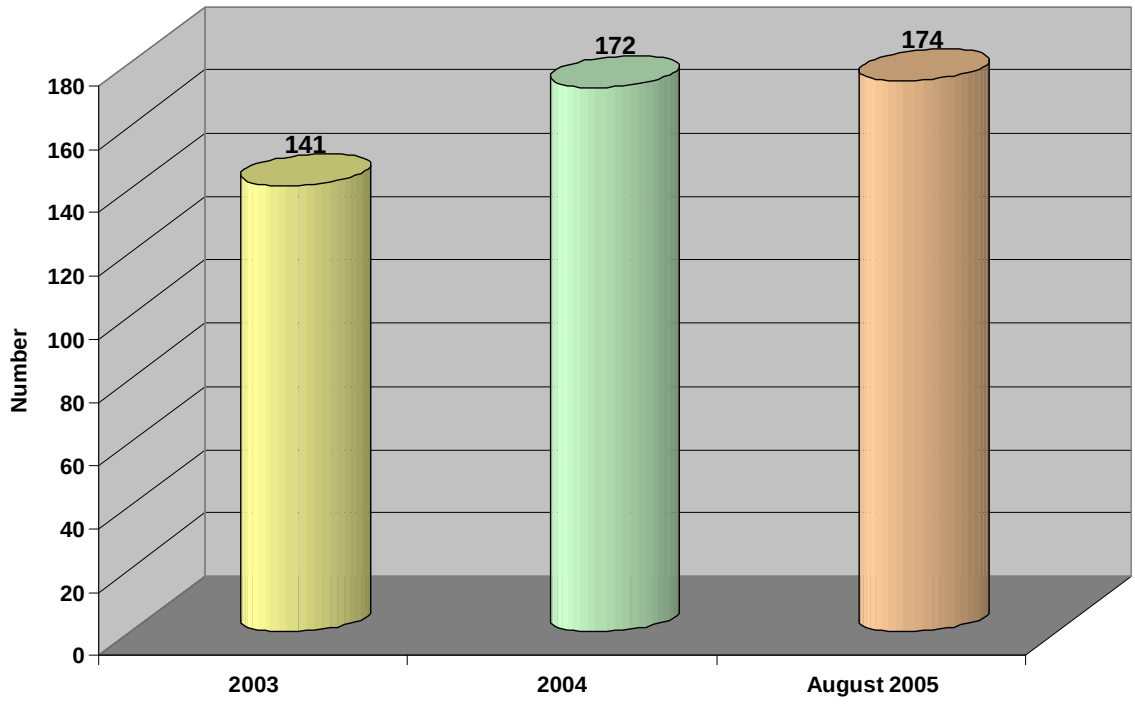

Fig.1 Development of the total number of MPI staff from 2003 to August 2005.

2 Concept and Organization of Research

The institute is principally an institute of basic engineering science, which has taken on the challenge to design, structure and control technological processes, concentrating on chemical engineering, biotechnology and systems biology. Facing this challenge not only requires a sound knowledge of technical and biological 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, engineers are in close cooperation with chemists, biologists and mathematicians.

An overview of the principle concentrations 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 basic 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's research philosophy.

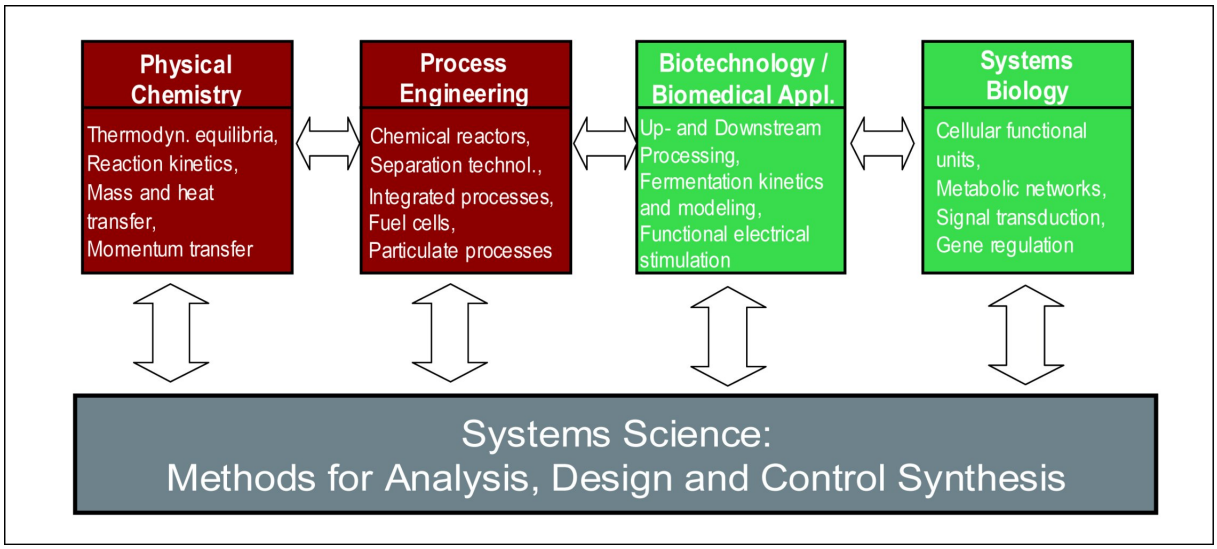

Fig.2 Systems science as integrating factor for the various research activities at the MPI.

The interdisciplinary character of the MPI implies a structure that does not allow for strictly separated departments. Instead, in order to achieve a maximum degree of collaboration within the institute, research groups have been established.

An 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. Currently, seven active research groups are on the premises. Group names and leaders are detailed in Fig.3.

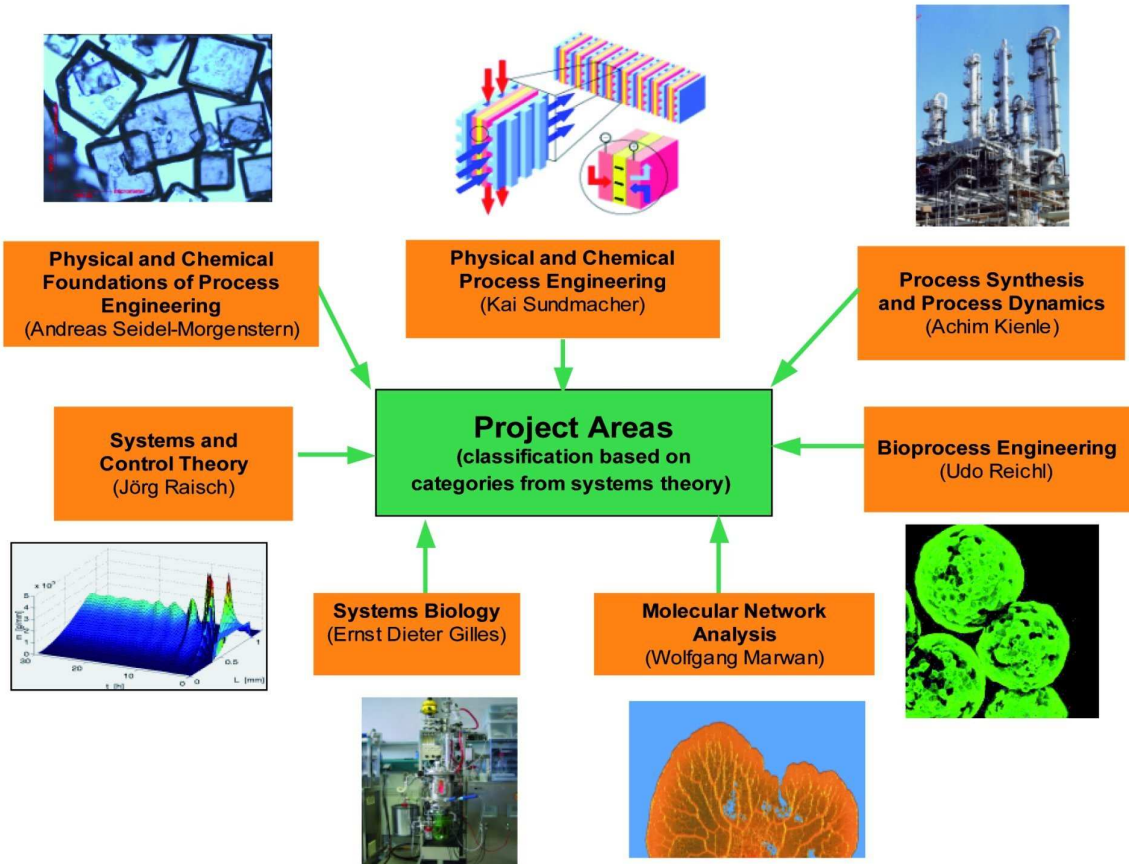

Fig.3 Overview on research groups cooperating within the various project areas.

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 project areas. Hence, scientists from several disciplines share their particular perceptions and methodologies 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 on the present status of interdisciplinary collaboration is given in the matrix of research activities in Table 1. Two main changes have been implemented since the last report (2003). The Molecular Network Analysis group (MNA) was introduced while, according to the recommendations of the SAB, the MF and the INS groups were discontinued (see section 1). In addition, the project area Reduced Models was closed due to the phasing-out of several research projects. Currently, it is being discussed whether new project areas should be started. Promising options could be in the area of structure and parameter identification or molecular modeling.

Table 1: Project areas and research groups as of August 2005.

Research Groups	Physical and Chemical Foundations of Process Eng.	Physical and Chemical Process Eng.	Process Synthesis and Process Dynamics	Systems and Control Theory	Molecular Network Analysis	Systems Biology	Bio-process Eng.
Project Areas	**PCF**	**PCP**	**PSD**	**SCT**	**MNA**	**SBI**	**BPE**
Network Theory		●	●			●	●
Hierarchical Structures			●	●	●	●	●
Population Balance Systems	●	●	●	●			●
Integrated Processes	●	●	●	●			
Coupled Processes	●		●	●		●	●
Hybrid and Discrete Event Systems	●	●		●	●		

3 Project Areas at MPI

The following sections outline the primary objectives of the current MPI project areas:

3.1 Research Area: Network Theory

Mathematical models are widely accepted as useful tools for the solution of many technical problems.

Mathematical modeling aids in the design of experiments while increasing specificity, the evaluation of experimental results in greater detail, or the acceleration the development of novel technical solutions. However, the successful application of model-based methods is dependent upon the availability of reliable models.

A reliable model must be comprised of all the available, known scientific knowledge applying to the problem at hand. Therefore, a complete model is highly complex. Further, the development of complete models is expensive and requires a clear understanding of the system and theoretical capability. The purpose of this project area is to simplify model development by systemizing modeling approaches for chemical and biochemical processes; thereby integrating computer aided tools into the modeling process. 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:

- Frequently used sub models need not to be re-implemented again and again but are available from a model database,
- Alternative approaches, such as for the description of diffusion processes, can be exchanged easily,
- During model formulation, the modeler can concentrate on the underlying physical assumptions without being concerned with the mathematical representation,
- The transparency and re-usability of existing models is increased.

The provision of a common software environment to set-up and analyze the models allows very intensive cooperation between members of different groups. Under development is the software ProMoT, which generates simulation models for the simulation environment DIVA. Since one numerical analysis tool cannot fulfill the needs of all simulation users, current work on ProMoT focuses on providing input files for other simulation tools.

Network theory plays a fundamental role in the development of methods and tools that are particularly suited for the structural and qualitative analysis of cellular networks. An example is the special application software FluxAnalyzer designed for the structural and steady state analysis of metabolic and regulatory networks. Such analyses are conceived and employed by the Systems Biology, Molecular Network Analysis and Bioprocess Engineering groups.

In a similar manner, network theoretical concepts and modular tools (ProMoT) are also developed and applied to model complex chemical engineering processes such as membrane reactors and fuel cell systems.

3.2 Research Area: Hierarchical Structures

In many areas of application, process complexity has increased tremendously over the last few years, often defying the use of traditional synthesis and control methods. With sound theoretical concepts only beginning to emerge, heuristic approaches prevail at the moment. They are intrinsically problem specific and typically involve an extensive trial-and-error stage. Clearly, a mathematically consistent and interdisciplinary way of treating complex synthesis and control problems is therefore highly desirable.

The growing complexity in technical processes is primarily due to the increasing interaction between different components in large-scale systems. In chemical engineering, for example, there is a trend towards production plants, relying to a greater extent, on energy integration and material recycling in order to improve processes both in an economical and ecological sense. This development constitutes an enormous challenge to systems and control theory: 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.

Hence, an essential objective within the described project area is the further development of this strategy in order to increase practical applicability.

Important new impetus for the solution of this problem can be expected from a close cooperation between the areas of systems theory and biology: the abstracting approach of systems theory facilitates the discovery and use of analogies between problems from nature and technology.

Nature, for example, is capable of very efficiently solving extremely complex regulatory tasks in a huge variety of completely different organisms. Apparently nature also makes 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 then to complex control problems within the fields of chemical engineering, where the task is to control material or energy flow, to name two. A more fundamental understanding of the basic principles utilized within nature to structure and solve complex biological regulatory tasks can, therefore also, be beneficial when addressing problems with designing complex control systems for diverse technical applications.

3.3 Research Area: Population Balance Systems

Populations of similar objects are frequently characterized by a distribution of certain properties. Typical examples are particles of a solid, molecules or cells. Some important parameters required for the characterization of these objects are, for example, their size and shape, their chain length or moisture content. 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. Examples would be in either comminution or precipitation processes to produce 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.

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.

A few 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 over the last years. However, there are many areas and applications that require further intensive research in order to be able to design and optimize processes with distributed parameters. One field of interest is the development of process monitoring techniques which are required to follow changes within the relevant distribution functions. There is a need for efficient numerical methods to solve the underlying balance equations. Furthermore, reliable scale up concepts need to be developed, and improved control strategies for population balance systems are required.

3.4 Research Area: Integrated Processes

In chemical industry, 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 processes very often gives rise to synergetic effects which can be technically exploited. Through suitable process design, an efficient and environmentally benign process operation can be achieved. Possible advantages of process integration are:

- higher productivity
- higher selectivity
- reduced energy consumption
- improved operational safety
- 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 domain 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 on an industrial scale relies on mini-plant technologies used in the institute's experimental investigations.
Reactive distillation processes, reactive membrane separation, chromatographic reactors, low-temperature and high-temperature fuel cells, and membrane reactors are subjects of our current research activities.

3.5 Research Area: Coupled Processes

Complex processes routinely consist of several individual sub-processes interacting in tandem. Numerous examples are found in biology and technology, namely the coupling of metabolic and regulatory networks in cellular systems, or the combination of processes or individual process units in biochemical engineering.
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 behavior of the coupled overall process can not be correctly predicted through dependence upon previous knowledge of the individual units, particularly when a qualitatively new behavior emerges from the coupling. As an illustrative example, consider two stable subsystems, which, after coupling, result in one unstable overall system. It is to be emphasized that the abstract methods of systems theory, which are essentially and originally independent of any particular application, are of crucial importance when coupled processes are under consideration.
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 utilization of raw materials and energy alike. Typical examples are reactor-separator-systems where unconverted reactants are separated from the products and subsequently recycled to the reactor or integrated concepts for the downstream processing of pharmaceuticals. The common interest in all these cases is directed towards optimal design and control of the respective coupled processes.

In addition, in biotechnological applications, prokaryotic and eukaryotic cells are of considerable interest. Bacteria, fungi, yeast, and mammalian cells are extensively used for the production of a wide scale of products ranging from simple organic compounds to highly specific pharmaceuticals.

A detailed analysis of factors influencing cell growth and product formation contributes to optimization of bioprocesses. In addition, targeted manipulations of the genome of production cell lines would enhance specific productivity and, in conjuncture with suitable process control strategies assist the increase of biotechnological process yields. In addition, progress in understanding biological systems on a cellular level is prerequisite for further advances in medicine. The detailed analysis of the complex metabolic, regulatory and signal transduction pathways of mammalian cells, for instance, not only elucidates the properties of cellular networks, but also assists in the identification of possible targets for drug development, contributing to an enhanced understanding of the underlying cause of many diseases.

3.6 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 in a real production plant, 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 (logic) control functions influence, and are influenced by, continuous plant and controller dynamics.

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

At the MPI, interdisciplinary system-oriented collaboration between the different research groups is considered as one of the key factors for the institute's overall scientific success. As an excellent example for an interdisciplinary project structure, the project area Population Balance Systems is briefly outlined in the following.

As depicted in Fig.4, an intense collaboration is established between the PCF, PCP, BPE, PSD, and SCT groups. The general aim of this collaboration is to develop model-based methods and tools for the analysis, design and control of population balance systems. The 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 a suitable control strategy, 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 emphasising on 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 on the analysis of the nonlinear process behavior, state-estimation methods and mathematical model reduction, optimal trajectory design for batch systems and control of continuously operated particulate processes. The collaborative research is based on population balance equations describing the dispersed phase. These are coupled with mass, energy and momentum conservation equations of the continuous phase.

The outlined project area is also an excellent example of intense scientific cooperation between the MPI and collaborating groups located at the OvGU.

Due to the fact that population balance models comprise partial integro-differential equations, efficient methods for their numerical solution and simulation are required.

Such methods are developed at the Department of Mathematics (Prof. Tobiska, Prof. Warnecke) and at the Department of Fluid Mechanics (Prof. Thevenin). Furthermore, the group of Prof. Hackbusch at the MPI for Mathematics in the Sciences, Leipzig, collaborates in the field of numerical solution of integral source and sink terms, which are typical for population balance systems.

At the OvGU additional interesting processes are investigated, such as fluidized bed agglomeration and granulation (Prof. Tsotsas, Prof. Mörl), which are also included in the research network. Furthermore, it is important to mention that several young independent researchers of the MPI and the OvGU are integrated in this cluster of research activities (Dr. Elsner, Jun.-Prof. Heinrich, Dr. Lorenz, Dr. Mangold, Dr. Voigt).

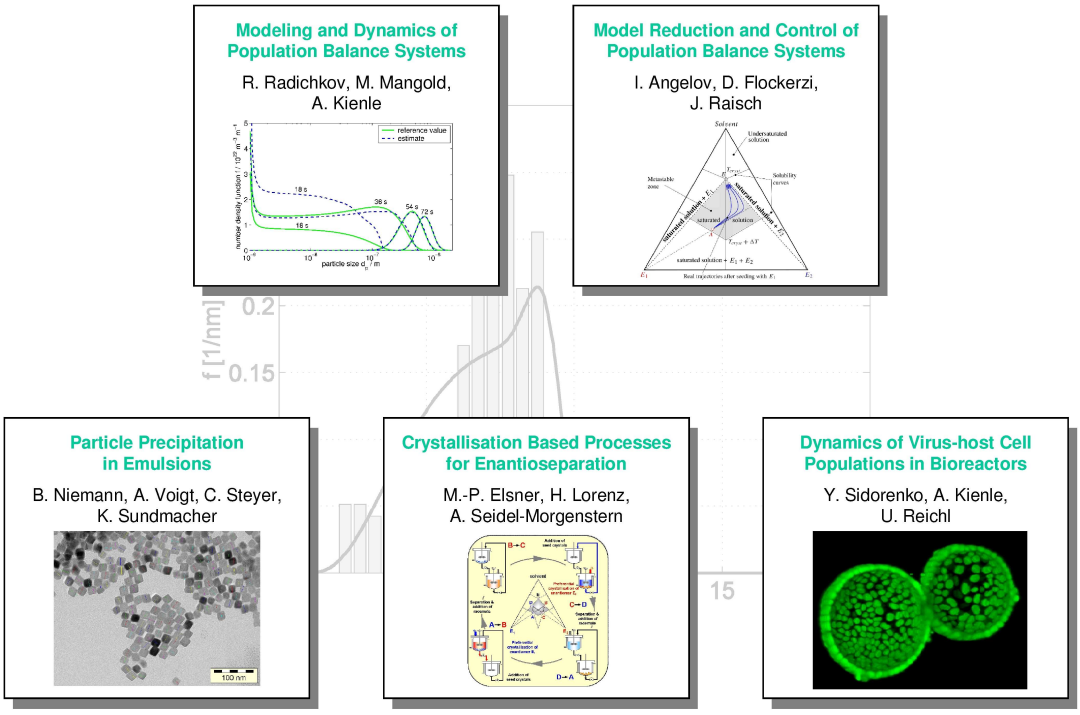

Fig.4 Research activities in the project cluster “Dynamics of Population Balance Systems”.

5 Publications

A complete list of publications and papers submitted (status November 2005) by the research groups is provided in a supplemental volume for this report. In the following, a survey of the general development of MPI publications since its start-up (1998 to 2004) is given.

As can be seen from Fig. 5, there was a continuous increase in the total number of published journal articles and conference contributions.

The total number of the institute's publications from 1998 to 2004 was 349 (journal articles: 143, conference contributions: 206).

Since the last status report, 2001/2002, the total number of contributions has increased by 24%, 2003/2004 versus 2001/2002. During the same period of time the percentage of journal articles to conference contributions has also increased from 57% to 64%, respectively. From January to August 2005 a total of 58 contributions has been published. However, it should be considered that depending on the publication culture of certain engineering disciplines established at the MPI, either journal publications or conference contributions can be considered to have greater prestige.

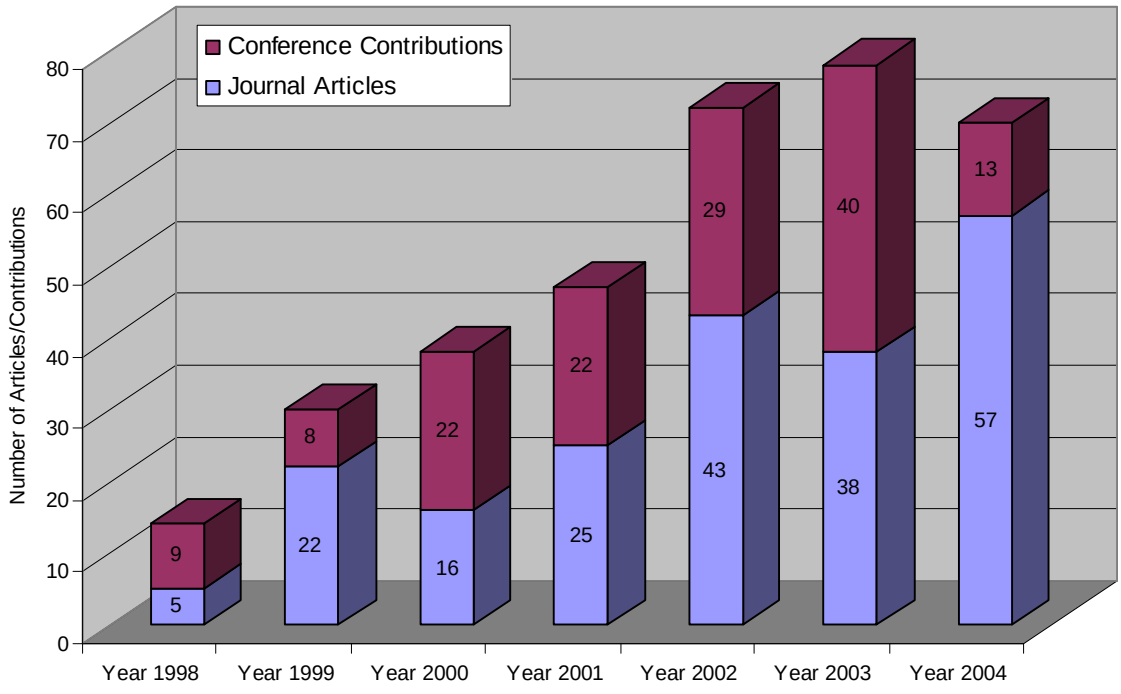

Fig.5 Development of the number of articles published in journals and the number of conference contributions during the period 1998-2004.

Fig.6 illustrates the running average on the impact of MPI publications within the first 2 to 3 years after publication. The impact of our publications has increased steadily from about 3 (1998) to 6.5 (2002), which is clearly better than the average impact factor of 3 for engineering sciences and 3.7 for multidisciplinary reported from ISI (National Science Indicators, 1994-2004) for the various scientific disciplines. Obviously, the MPI publications were well accepted in the related scientific engineering communities.

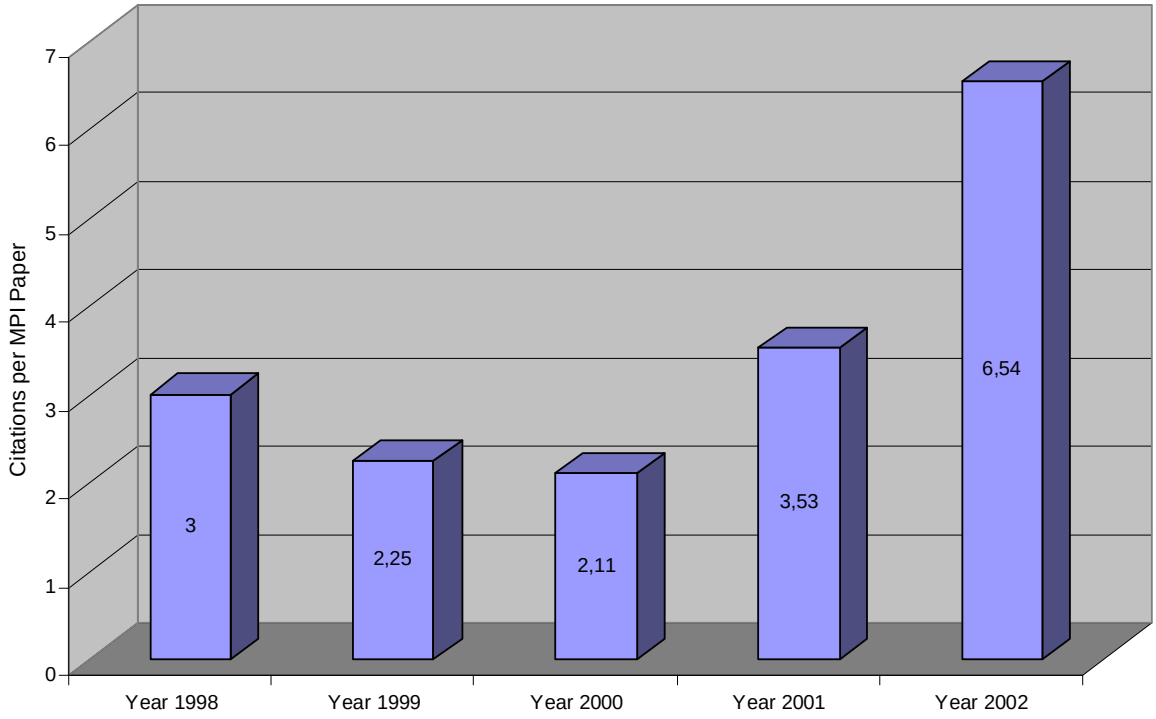

Fig.6 Running average of the impact of MPI publications within the first 2 to 3 years after publication.

6 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 August 2005, a total of 174 employees were employed by the MPI. As illustrated in Fig. 7, the largest fraction of staff is held by our students working towards a Ph.D. degree. They are about one third of the overall workforce (27%). Another 20% of our workforce is senior and postdoctoral scientists.

The scientific staff is supported by student research assistants (22% of workforce). These are undergraduates who do their work at MPI in parallel to their studies 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. In addition, many research assistants simultaneously prepare their student theses (“Studienarbeit”) or diploma/master theses.

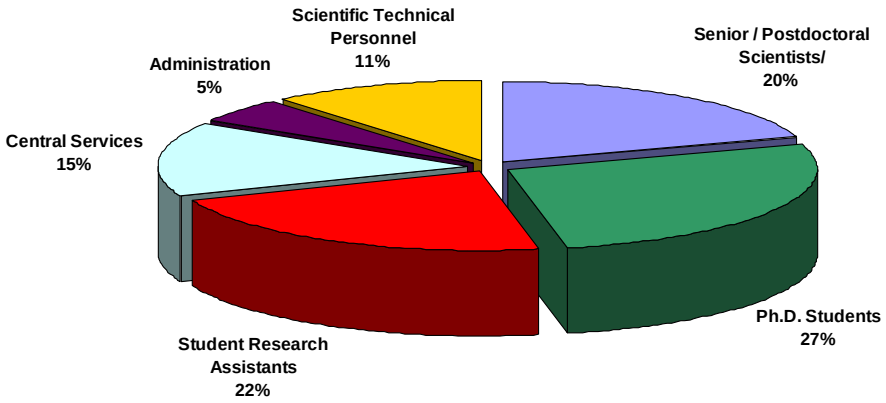

Fig. 7 Composition of MPI personnel as of 31 August 2005.

In order to prepare and perform the experimental work in the institute’s chemical and biological laboratories the scientists are also supported by laboratory technicians and engineers (11%). Moreover, 15% of the MPI staff represent central services such as the library, the secretarial service, the computer service, 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 who supports the scientists in project budgeting, collecting offers for and purchasing of technical devices, etc. This staff is only 5% of the total number of employees.

Sine 2003 the total number of employees has increased slightly by about 23%. With the start-up of the MNA group and the ongoing activities of the Chairs of the OvGU (until March 2007) the laboratory capacities are fully used.

However, in offices there are about 31 working places left for extension of existing groups and theoretical research projects financed by external funding.

6.1 Age and Gender Distribution

The average age of all 174 coworkers is only about 33 years old. The age distribution is displayed in Fig.8. At present about 45% of the institute's staff are less than 30 years old. Only about 5% of the workforce are age 50 and older.

As additional information, the age distribution of all scientists is shown in Fig.9, which specifies also the fraction of permanent and temporary employments in the 5-year age groups. As of 31 August 2005, there were 82 scientists employed at the MPI, 35 of them senior and postdoctoral scientists, 47 of them Ph.D. students. Of these scientists, 60% are 35 years old or less which reflects a very young scientific workforce at our MPI. At present only 13 scientists hold permanent positions, which is in full agreement with the employment policy of the MPG.

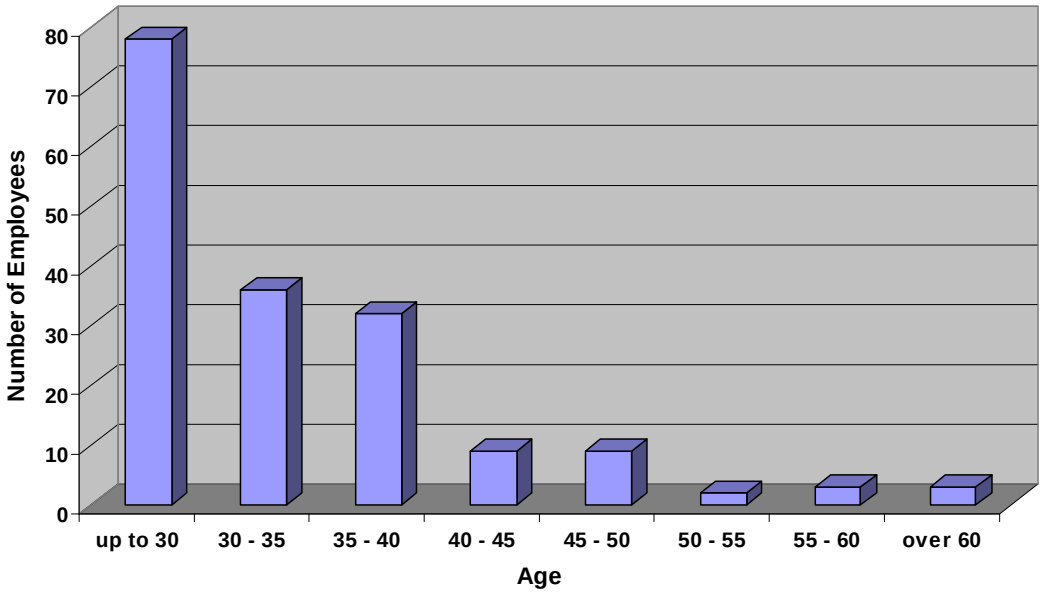

Fig. 8 Age distribution of all MPI employees as of 31 August 2005.

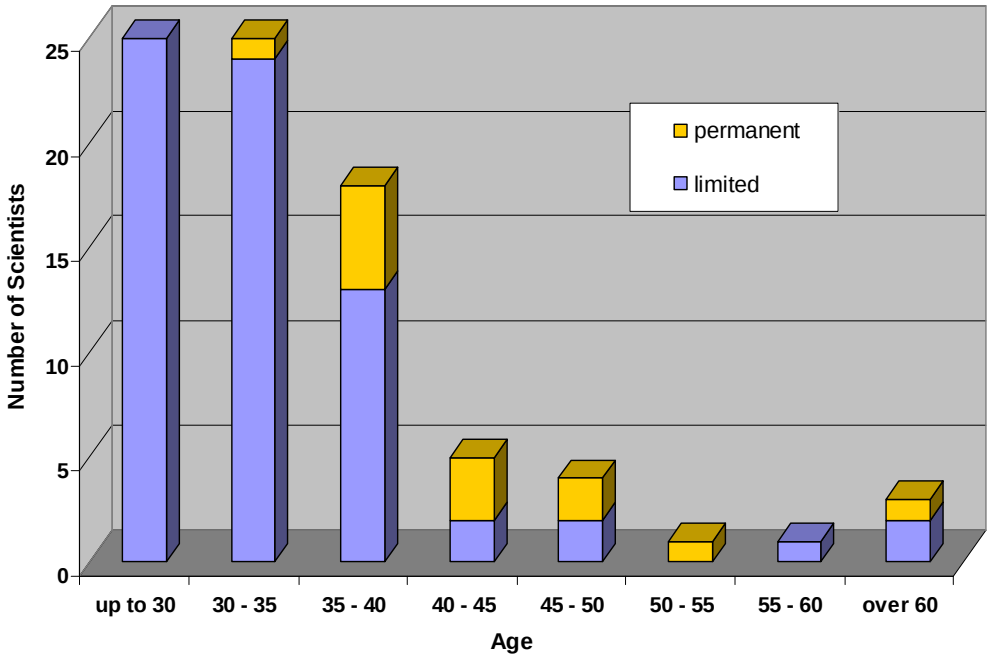

Fig. 9 Age distribution of MPI scientists divided into permanent and temporary employments as of August 2005.

Fig.10 shows the distribution of our scientific coworkers according to gender. The percentage of female scientists is about 16%. This is a considerably higher proportion of females than normally encountered in engineering sciences in Germany.

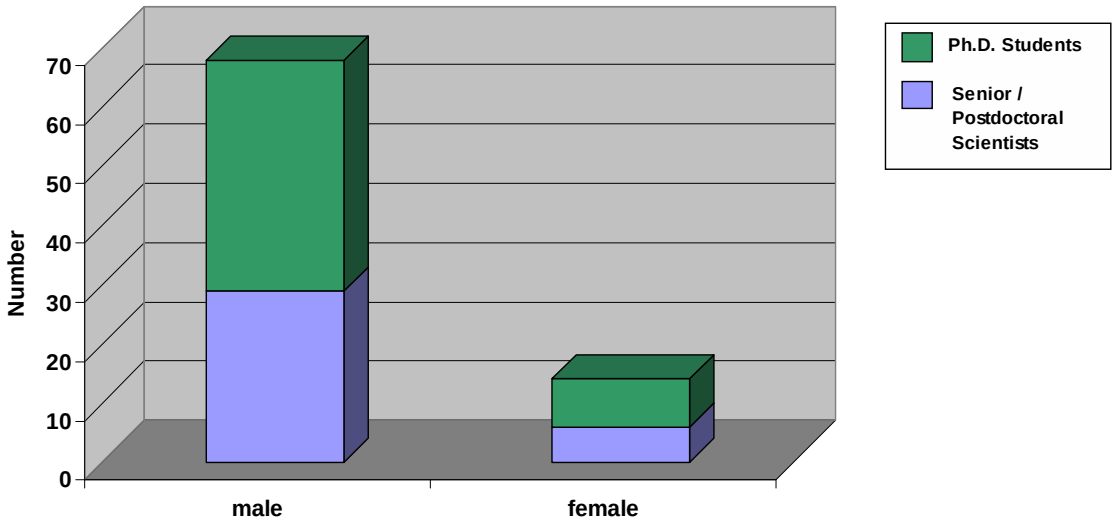

Fig.10 Gender distribution of scientists as of 31 August 2005.

6.2 Graduate Students

As pointed out above, the graduate students represent about one-third of the total MPI staff and two-thirds of scientific coworkers. All of them are registered at the OvGU and are seeking a Ph.D. degree in Chemical and Process Engineering or in Engineering Cybernetics. Compared to the period covered by the previous status report the number of Ph.D. students has stabilized at an average number of about 47 scientists (Fig. 11).

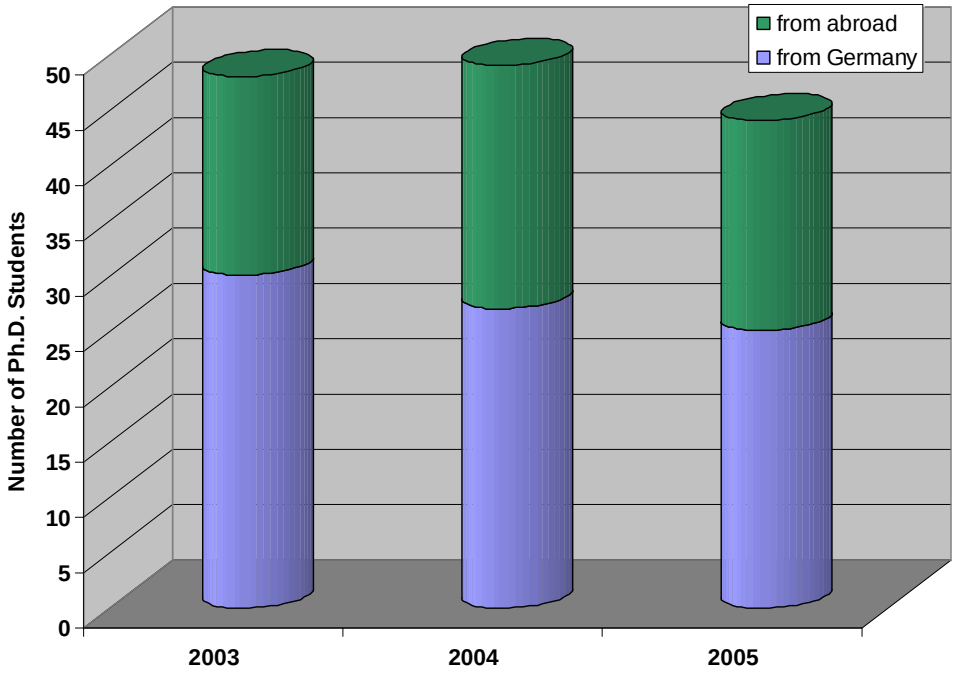

Fig. 11 Number of Ph.D. students over the last 3 years from abroad and from Germany.

Over the last 3 years the portion of students coming from abroad was in the range 38 to 45 percent, which clearly shows that our institute is highly attractive to engineering students from international schools.

Due to the steady increase in the number of students in “Chemical Engineering” (88 in German study courses; year 2004) and “Systems Engineering and Cybernetics” (39, year 2004) at the OvGU we expect a rise in the total number of Ph.D. students over the next years. In particular, the high number of students enrolled in the new diploma study course “Biosystems and Technology” (Biosystemtechnik) is expected to support our extended activities in biochemical engineering, biomedical applications and systems biology. In addition, about 100 students started in the English study courses “Chemical and Process Engineering” and “Quality, Safety and Environment” in 2004.

Most of the students of these master courses come from Asia, especially China and India. Another large group originates from east European countries, mainly Bulgaria, Czech Republic, Romania, Ukraine and Russia, which is mainly due to traditionally excellent collaborations between east German universities and their academic partner institutions in eastern Europe. Recently, the international teaching activities of the Department of Process and Systems Engineering have been further extended by the successful application for a grant by the DAAD and the German Science Foundation (DFG) to establish an international doctoral study program in “Chemical and Biochemical Engineering”.

6.3 Guest Scientists

The MPI has intense interactions with a large number of short-term visiting scientists as reflected by Fig.12 which illustrates the distribution of these visitors with respect to their home countries.

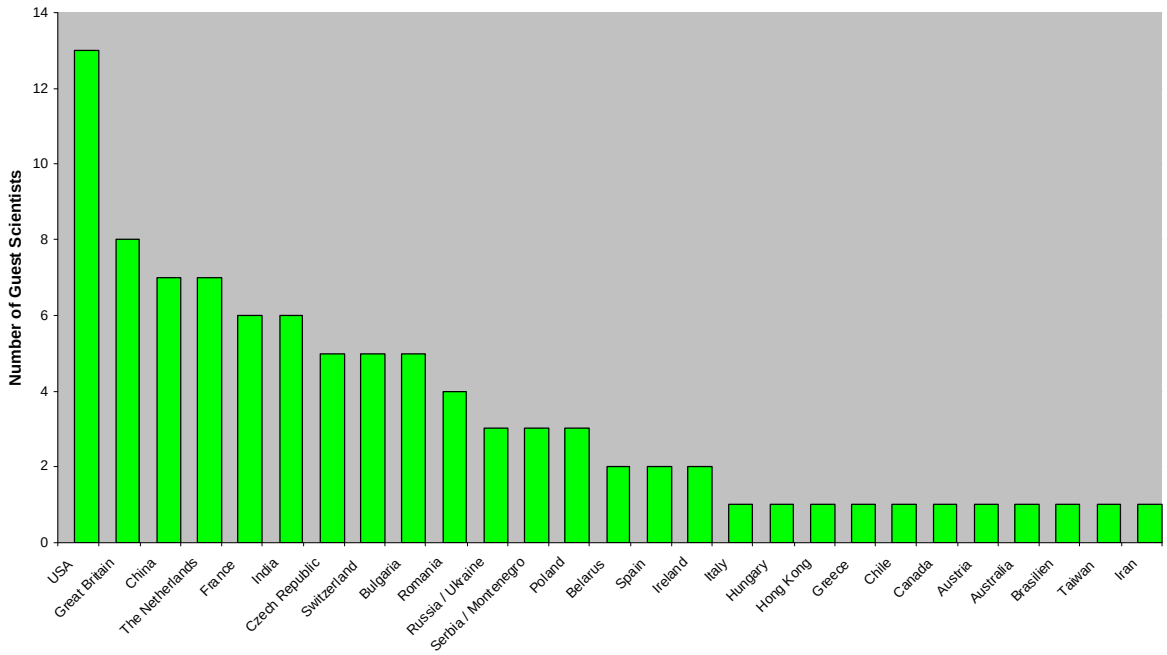

Fig. 12 Number of visits by international scientists from 2003 to 2005 (with a stay of at least two days)

Among the visitors are guest professors who stay for several months to work directly within one of the research groups, scientific visitors who give courses and talks during a stay of several days, and experts from industry who come to exchange ideas on common research projects.

From 2003 to August 2005, a total of 84 German scientists and 95 guest scientists from abroad visited our institute. Among the international guests, 60.4% came from the European countries, 13.5% from America, the rest from Asia and Australia.

7 Teaching Activities and Recruiting of Students

As previously reported teaching activities of the heads and various scientists of the MPI research groups are focused 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. At present there are the following diploma and master courses:

- Systems Engineering and Cybernetics (5 years, diploma program)
- Environmental and Energy Process Engineering (5 years, diploma program)
- Molecular and Structural Product Design (5 years, diploma program)
- Chemical and Process Engineering (1.5 years, master program)
- Biosystems and Technology (5 years, diploma program)

As a result of the initiative of Prof. E.D. Gilles and Prof. U. Reichl the interdisciplinary diploma study course “Biosystems and Technology” (Biosystemtechnik) was introduced in 2004 together with the Department of Electrical Engineering and Information Technology, the Department for Natural Science and the Medical Department. The course is supervised and organized by the Chair of Bioprocess Engineering at the OvGU (U. Reichl) and has attracted more than 180 students in the first year (2004/2005). Focus of this diploma course is a combination of lectures introducing in the principles of bio-medical sciences together, courses in mathematics, physics, systems theory and classical engineering sciences. In the future we expect the graduates of this diploma program to support our extending research activities in the rapidly evolving area of systems biology, for example for basic research in biochemical engineering, biomedicine and theoretical biology.

In addition to our teaching activities and to our contributions in the strategic development of the profile of the engineering programs at OvGU, we directly approach pupils from high schools of the German Federal State Saxony-Anhalt to

study engineering sciences or natural sciences. At present there are several activities:

- A “NaT-working project” (NaT: Natural and Technical sciences) was established which is a very successful direct partnership of the MPI with five regional high schools. This project is being funded by the Robert-Bosch-Foundation and will end in 2005. For the coming years we are looking for options to either continue this activity with other financial resources or to switch to a local “Jugend forscht” project.
- On a regular basis, the MPI offers one-week laboratory courses, each spring and each fall, for interested pupils 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.

8 Cooperation with Otto-von-Guericke-University Magdeburg

As outlined in section 2, three directors of the MPI (U. Reichl, A. Seidel-Morgenstern, K. Sundmacher) are appointed professors at the Department for Process and Systems Engineering and two heads of MPI research groups (A. Kienle, J. Raisch) are appointed professors at the Department for Electrical Engineering. Furthermore, E.D. Gilles is an honorary professor at the Department for Process and Systems Engineering. In the year 2004 W. Marwan, who heads the new research group “Molecular Network Analysis”, was appointed professor at the Department for Natural Sciences.

A further option for the intensification of the collaboration between the MPI and the Department for Process and Systems Engineering is expected after start-up of the new chair for “Food Processing Technology” in 2006. The appointment procedure has been started in 2004.

9 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. Here only the most

important, larger projects are given. At present there are three joint DFG research units (“Forschergruppen”):

- DFG research unit 447: “Membrane Supported Reaction Engineering”, 8 sub-projects in collaboration with the Department for Process and Systems Engineering and the Department for Mathematics (extended until 2007)
- DFG research unit 468: “Methods of Discrete Mathematics for Synthesis and Control of Chemical Processes”, 5 sub-projects in collaboration with the Department for Mathematics and the Department for Electrical Engineering (proposal for an extension positively evaluated).
- DFG research unit 521: “Regulation of Immunological Processes by Membrane Proximal Signaling Modules**”**, 1 sub-project in collaboration with the Department of Medicine (extended until September 2006)

During the period of this report, several members of the MPI research groups have been involved in the following Collaborative Research Centers (SFB = Sonderforschungsbereiche):

- SFB 412: “Computer Aided Modeling and Simulation for the Analysis, Synthesis and Control of Chemical Processes” (cooperation with partners at the University of Stuttgart, successfully terminated in 2004)
- SFB 495: “Topology and Dynamics of Signaling Processes”
- SFB 578: “From Gene to Product” (cooperation with partners at the University of Braunschweig)

Further collaborations between MPI research groups and university groups are established in the framework of several joint projects supported by the Federal Ministry of Education and Research (BMBF). In these projects, industrial partners are also involved:

- BMBF joint project: “Optimal Control of Molten Carbonate Fuel Cells (MCFC) using Methods of Nonlinear Dynamics” (Partners: MPI, OvGU, University of Bayreuth, Companies: IPF Ltd./Magdeburg, MTU Ltd./Munich)
- BMBF joint project: “Coupling of Chromatography and Crystallization” (Partners: MPI, OvGU, Companies: Schering AG/Berlin, Axiva Ltd./Frankfurt; successfully terminated)
- BMBF joint project: “CELLular Eukaryotic proteome-Code deciphering Technology” (CELLECT) (Partners: MPI, OvGU, University of Stuttgart, Company: Meltec Ltd./Magdeburg, successfully terminated)

- BMBF systems biology competence network “HepatoSys”: Technology platform for bio informatics/modeling (Partners: MPI, Humboldt University Berlin, EML Research GmbH Heidelberg)
- BMBF joint research project: “Model based design of fuel cells and fuel cell systems” (Partners: MPI, Institute for Solar Energy Systems (ISE), Freiburg; Fraunhofer Institute for Industrial Mathematics (ITWM), Kaiserslautern; University of Freiburg, Department of Applied Mathematics; University of Heidelberg, Center for Scientific Computing (IWR); University of Karlsruhe, Department of Material Sciences in Electrical Engineering)

In the area of Systems and Control Engineering, the joint research project on “Controlled Functional Electrical Stimulation (FES) in the Rehabilitation of Spinal Cord Injured Persons and Stroke Patients” is funded by the Federal State of Saxony-Anhalt and the BMBF (Project “Innomed”). The MPI’s partners are the OvGU, the company Hasomed Ltd. and the MEDIAN-Klinik NRZ in Magdeburg.

In addition, a new joint research project “Dynamic Systems” with a similar structure as the MPI has been founded in Magdeburg (speaker Prof. E.D. Gilles) in 2004. Scientists from the MPI and the OvGU (Department of Electrical Engineering and Information Technology, Department for Mathematics, Medical Department, Department of Process and Systems Engineering) closely collaborate in various projects to further intensify the cooperation between the engineering, systems and biomedical sciences in Magdeburg. The project is funded by the Federal State of Saxony-Anhalt.

10 Competence Network on Process Engineering

The MPI is a founding member of the German Competence Network on Process Engineering („Kompetenznetz Verfahrenstechnik Pro3”), which was initiated in February 2000 jointly with the University of Stuttgart, the University of Karlsruhe, the University of Kaiserslautern, and several industrial companies. These are BASF AG, Cognis Deutschland Ltd., Degussa AG, IPF KG, Lurgi AG, Merck KG, Rauschert Verfahrenstechnik Ltd., and Siemens AG. Prof. Gilles is one of the founding members and he is the executive chairman of the Pro3 network.

The competence network’s goal is to find new technical solutions in process and bioprocess engineering, to “speed up the transfer of knowledge from fundamental

research to industrial applications", to promote excellent educational activities in process engineering, and to attract highly qualified national and international students, postdoctoral and guest scientists. The main focus of the research activities within the competence network is on "process design, process control, and product design" (Pro3).

The network is structured into working committees that meet regularly to initiate research projects, to organize workshops on new topics in process engineering and to exchange experiences. Three heads of the MPI research groups are chairmen of the working committees for integrated processes (A. Seidel-Morgenstern), fuel cell systems (K. Sundmacher), and modeling of population dynamics of disperse and polymeric systems (A. Kienle).

The MPI received financial support from the competence network in the form of scholarships, start-up funding for a project on reactive separation, and support for carrying out international workshops (see section 13).

11 International Collaborations

The following list summarizes the most important collaborations which have been established with academic partner institutions from abroad:

Europe

- TU Donezk, Ukraine: Plant-wide control of chemical processes
- UCTM Sofia, Bulgaria: Kinetic analysis of electrochemical methanol oxidation
- Politechnico di Milano, Italy: Controlled functional electrical stimulation
- University of Glasgow, UK: Controlled functional electrical stimulation
- University of Rouen, France: Crystallization by entrainment
- University of Belgrade, Serbia: Determination of adsorption isotherms
- ICTP, Czech Republic: Electro-membrane reactors
- Institute of Biotechnology, Lithuania: Large-scale production and characterization of recombinant viral proteins in *S. cerevisiae*
- Russian Academy of Science: Influenza virus replication in MDCK cells
- University of Belgrade, Serbia: Electrochemistry
- Helsinki University of Technology, Finland: Catalytic reactors
- TU Donezk, Ukraine: Nonlinear Dynamics of Reactor Separator Networks

- Faculté Polytechnique de Mons, Belgium: Simulated Moving Bed Processes (Subproject: Control of Moving Bed Chromatographic Processes)
- School of Biomedical and Molecular Sciences, Guildford, University of Surrey, UK: Applying metabolic network analysis and metabolic flux analysis to biotechnologically relevant micro-organisms
- Technical University of Rzeszow, Poland: Preparative chromatography

Asia/Australia

- IIT Madras, India: Nonlinear dynamics of reactor separator networks
- IIT Madras, India: Hydrodynamics in expanded beds
- IIT Bombay, India: Reactive Distillation Processes (Subprojects: Nonlinear Dynamics of Reactive Distillation Processes and Synthesis of Combined Reaction Distillation Processes)
- Australian National University: Hybrid control systems
- Melbourne University, Australia: Hybrid control systems

America

- Purdue University, USA: Nonlinear dynamics of bioreactors described by cybernetic models
- Purdue University, USA: Population balance modeling
- IIT Chicago, USA: Thermal analysis in crystallization
- University of California, Santa Barbara, USA: Methods for model discrimination and reverse engineering/ Robustness analysis in circadian clocks
- CALTECH, USA: Systems Biology Markup Language (SBML)
- MIT, USA: Signal-transduction and regulation in eukaryotes
- Thomas Jefferson University, USA: Analysis of signaling pathways in hepatocytes
- Jefferson Medical College, USA: Computational modeling of the angiotensin II/AT1 Receptor mediated Ca2+ dynamics in neurons
- Dept. of Chemical Engineering and Delaware Biotechnology Institute, University of Delaware, Newark/USA: Modeling VIP activated gene expression

in SCN cells through the VPAC2 receptor mediated cAMP/PKA signal transduction pathway in silico

- University of Tennessee, USA: Preparative chromatography
- Colorado State University, USA: Membrane Filtration

Workshops and Symposia

During the last two and a half years, our research groups have organized several symposia, workshops and seminars with participants from European and American countries:

- Dechema-Regionalkolloquium "Reaktions- und Trenntechnik bei der Gewinnung von Enantiomeren", Magdeburg, November 2003
- International Max Planck Symposium "Integrated Chemical Processes", Magdeburg, March 2004
- Intersectional Symposium of the MPG, “Trends in Interdisciplinary Basic Sciences”, Berlin, November 2004
- 2nd International Symposium on “Particulate Processes”, Magdeburg, November 2004
- Dechema-Regionalkolloquium "Einsatz elektrischer Felder in verfahrenstechnischen Prozessen", Magdeburg, November 2004
- Workshop on Petri Nets in Biology , Magdeburg, May 2005
- Dechema-Regionalkolloquium "Potentiale des Molecular Modelling für die Verfahrenstechnik", Magdeburg, November 2005

Currently, preparations are being started for the start of a biannual conference series in “Complex Dynamic Systems”. In 2006 a first symposium on “Hierarchical Systems” is planned, which will be organized by P. J. Antsaklis, P. E. Caines, A. Kienle, J. Raisch and U. Reichl (scientific committee).

Research Group:

Physical and Chemical Foundations of Process Engineering (PCF)

Prof. Dr.-Ing. Andreas Seidel-Morgenstern

This report covers the period from May 2003 to September 2005

1 Group Introduction

One focus of the research of the physical and chemical foundations of process engineering group (PCF) 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. A main topic is the separation of enantiomers. In order to acquire a quantitative understanding and to predict the processes, the most relevant thermodynamic and kinetic parameters are identified and determined. The activities also focus on developing and validating suitable mathematical models which can be used for process optimization and control.

A second important direction of the PCF group's research is the study of the potential for combining reaction and separation processes in order to improve conversion and selectivity with respect to a certain target component. Of particular interest is the combination of reactions with chromatographic and membrane separations (chromatographic and membrane reactors). There are also intensive investigations regarding the coupling of different separation processes in order to resolve complex mixtures.

The research work of the group was stimulated and enriched in the last two years by several guest scientists, e.g. Prof. Weibing Zhang (Dalian), Prof. Pushpavanam (Madras), Dr. Uchytil (Prague), Prof. Coquerel (Rouen) and Prof. Schlünder (Karlsruhe).

Within the period of this report the group has published more than 40 research papers. Four habilitations and seven Ph.D. projects were finished successfully.

Third party projects studying the potential of membrane reactors (German Science Foundation) and coupling chromatography and crystallization (German Research Ministry, Schering company) were successfully continued. New projects supporting cooperation with Poland and India were granted (DAAD). Further project proposals are currently under review.

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 (Prof. Kienle), the evaluation of the potential of confocal laser microscopy and mass spectroscopy for investigating

chromatographic separation processes in cooperation with the BPE group (Prof. Reichl), the analysis of different kind of membrane reactors with the PCP group (Prof. Sundmacher), the investigation of the dynamics of enantioselective crystallization processes together with the SCT group (Prof. Raisch), and the statistical analysis of experimental data with the SBI group (Prof. Gilles).

Intensive and successful cooperation devoted to quantification of electrokinetic phenomena and the dynamics of capillary electrochromatography is conducted in collaboration with Prof. Tallarek (OvGU).

2 Members of the Research Group

As of September 30, 2005, the group of Prof. Seidel-Morgenstern consists of eight scientists with a Ph.D. (including five postdocs) and nine graduate students working on their Ph.D. (two of them in joint projects with a foreign university). The scientific and technical staff is summarized below:

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, permanent, Capillary Electro-chromatography and mass spectrometry, since 01.02.2003
Dr. M. P. Elsner	Postdoc, Crystallization by entrainment, since 01.01.2003
Dr. A. Grandeury	Postdoc, Crystallization, since 01.01.2005
Dr. D. Hlushkou	Postdoc, Electrokinetic mass transfer, since 01.09.2005
Dr. Y. Shan	Postdoc, Gradients in liquid chromatography, since 01.10.2002 until 30.09.2005
Dr. J. Yang	Postdoc, Mass transfer through porous media, since 01.01.2003 until 30.09.2005
Dipl.-Ing. F. Czapla	Ph.D. student, Crystallization, since 01.04.2005
Dipl.-Ing. C. Hamel	Ph.D. student, Membrane reactors, since 01.11.2002
Dipl.-Ing. M. Ilić	Ph.D. student, Thermodynamics of adsorption, since 01.02.2004
Dipl.-Ing. M. Kaspereit	Ph.D. student, Competitive Adsorption and preparative chromatography, since 17.01.2000 until 31.12.2004
Dipl.-Biotechnol. C. Keßler	Ph.D. student, Preparative chromatography, since 01.01.2005
Dipl.-Ing. D. Polenske	Ph.D. student, Preferential crystallization, since 01.03.2004

Dipl.-Ing. D. Sapoundjiev	Ph.D. student, Solubilities of enantiomers, since 01.06.2005 until 30.09.2005
Dipl.-Chem. A. Seebach	Ph.D. student, Chiral membranes, since 15.07.2002
Dipl.-Ing. G. Ziomek	Ph.D. student, Optimization, since 01.01.2004
Dr. T. Wolff	Technician, since 01.11.2001
J. Protzmann	Technician, since 01.01.2002
M.Sc. S. Tulashie	Technician, since 01.08.2005
J. Kaufmann	Technician, since 01.02.1999
L. Borchert	Technician, since 01.02.2005
A. Raasch	Secretary, since 16.07.2002
S. Leuchtenberg	Trainee, since 01.09.2005

There is an intensive cooperation with the following scientific co-workers of the related University group (Chair for Chemical Process Engineering):

Prof. U. Tallarek, Dr. A. Höltzel, M.Sc. A. Damtew, Dipl.-Ing. K. Gedicke, Dipl.-Ing. L. Gueorguieva, M.Sc. M. Joshi, Dipl.-Ing. A. Marković, Dipl.-Ing. I. Nischang, M.Sc. M. Phong, Dipl.-Ing. Á. Tóta, M.Sc. T. Vu Dinh

3 Survey of Research Projects

The current research projects are summarized below. Since most of these projects are performed in close cooperation with other groups at the MPI, the projects are ordered according to the project areas investigated at the institute. For several projects, the cooperation with groups from the Chair for Chemical Process Engineering at the OvGU is also indicated.

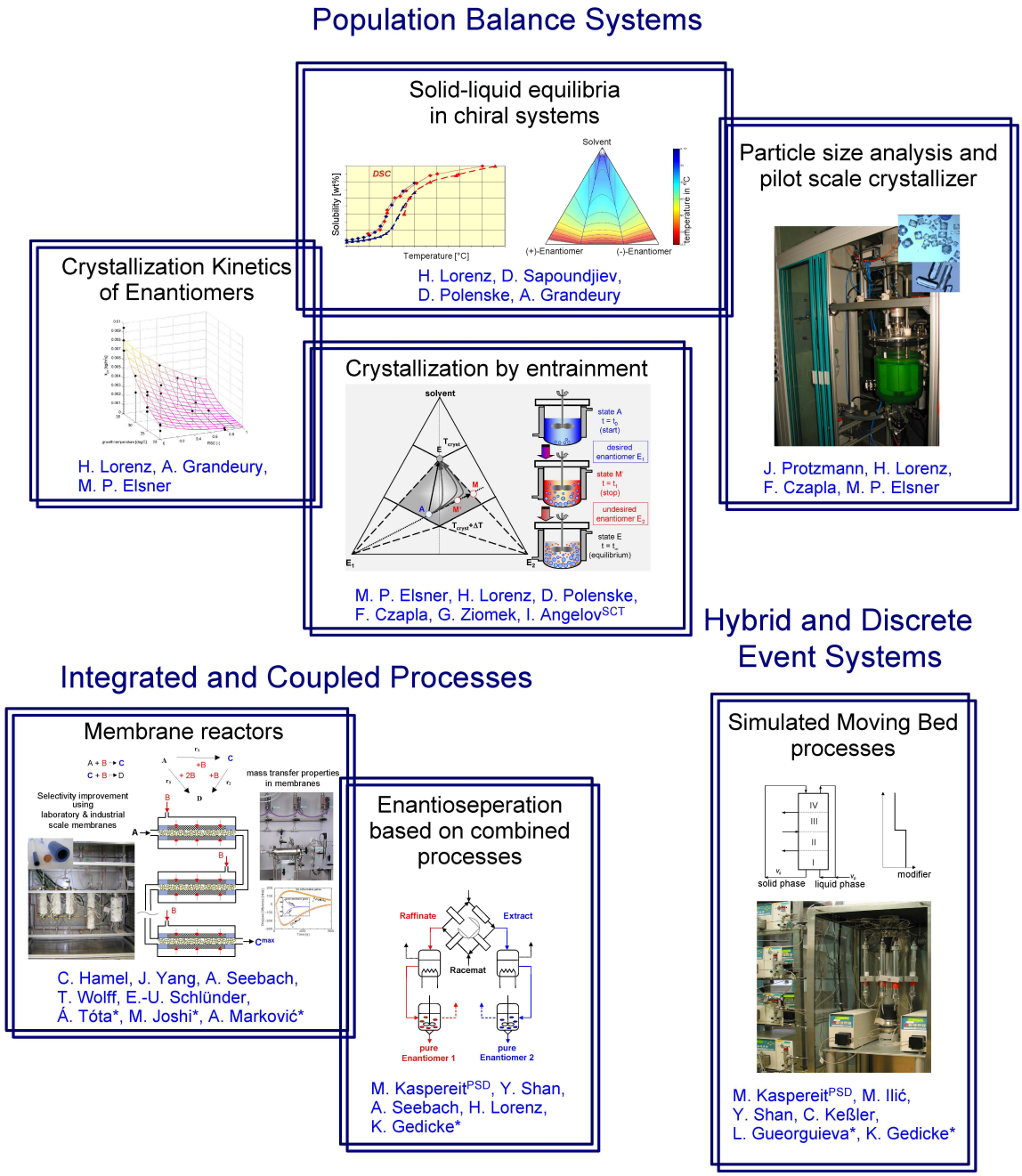

Fig. 1: Survey of research areas and projects of the PCF group.

3.1 Projects of the Research Group "Physical and Chemical Foundations of Process Engineering"

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

Project Area: Population Balance Systems

Title	Scientists	Funded by	Start	Partners
Project: Crystallization				
Subproject: Solid-liquid equilibria in ternary chiral systems	A. Grandeury H. Lorenz D. Polenske D. Sapoundjiev	MPI	1999	OvGU
Subproject: Crystallization kinetics of enantiomers	A. Grandeury H. Lorenz M. P. Elsner	MPI	2000	OvGU
Subproject: Crystallization based processes for enantioseparation	F. Czapla M. P. Elsner H. Lorenz D. Polenske G. Ziomek	MPI Dechema	2000	OvGU MPI SCT, PSD Schering AG Univ. Rouen Prof. Coquerel Pro3

Project Area: Integrated Processes

Title	Scientists	Funded by	Start	Partners
Project: Membrane reactors				
Subproject: Characterization of catalysts and determination of reaction rates	C. Hamel T. Wolff M. Joshi* Á. Tóta*	DFG MPI	2000	OvGU MPI PCP, PSD, SBI FHI (MPG) Prof. Schlögl TU Darmstadt Prof. Claus
Subproject: Mass and heat transfer through porous media	J. Yang D. Hlushkou A. Seebach E.-U. Schlünder A. Marković*	DFG MPI	1998	OvGU Czech Ac. Sci. Dr. Uchytil Uni Belgrade Prof. Petkovska

	U. Tallarek*			
Subproject: Dosing concepts using tubular membrane reactors	C. Hamel T. Wolff Á. Tóta*	DFG MPI	2001	OvGU Prof. Tsotsas Inocerm GmbH MPI PSD
Subproject: Ceramic (dense perowskites) membranes for catalysis	C. Hamel	BMBF	2003	OvGU Prof. Tsotsas Uni Hanover RWTH Aachen IGB-FhG Uhde Borsig
Project: Chromatographic reactors				
Subproject: Analysis of reactive chromatography	Y. Shan T. Vu*	MPI OvGU	2002	MPI PSD

Project Area: Coupled Processes

Title	Scientists	Funded by	Start	Partners
Project: Separations based on combined processes				
Subproject: Chromatography and subsequent crystallization	H. Lorenz K. Gedicke*	DAAD BMBF	2000	OvGU Schering AG Uni Rzeszów Prof. Antos
Subproject: Chiral membranes	A. Seebach	MPI	2002	Technical Uni Berlin Uni Lund
Subproject: Chromatographic resolution	C. Keßler E. Rapp Y. Shan G. Ziomek K. Gedicke*	DAAD	2000	OvGU MPI BPE IIT Madras Prof. Pushpavanam Uni Dalian

				Prof. Zhang
Subproject: Membrane separation and subsequent crystallization	H. Lorenz A. Seebach	MPI	2002	Uni Karlsruhe Uni Aachen

Project Area: Hybrid and Discrete Event Systems

Title	Scientists	Funded by	Start	Partners
Project: Simulated moving bed (SMB) processes				
Subproject: Determination of adsorption isotherms	M. Ilić	MPI	2001	OvGU Uni Belgrad Prof. Petkovska
Subproject: Continuous gradient chromatography	L. Gueorguieva* C. Keßler G. Ziomek	MPI	2000	Uni Rzeszów Prof. Antos
Subproject: Separation of ternary mixtures	C. Keßler Y. Shan	MPI	2003	OvGU Prof. Tobiska, Prof. Weismantel MPI PSD, BPE

4 Research Highlights

4.1 Physical and Chemical Data required for the Analysis and Design of Separation and Reaction Processes

The development and production of new products with improved or previously unknown properties increasingly requires the application of new and more complex technologies. In order to understand and optimize the underlying processes, a large number of physical and chemical data and parameters must be known. Often these data must be measured. One goal of the PCF group is to determine physical and chemical data which are relevant to the chemical engineering and bioengineering processes investigated at the MPI. Due to their importance for the understanding and design of separation and reaction processes, the focus is on determining the following parameters or functions:

- Solid-liquid phase equilibria (melting diagrams, solubilities)
- Growth rates of crystals

- Adsorption equilibria
- Transport rates in porous media (diffusion coefficients, permeabilities)
- Heat capacities and phase transition enthalpies
- Reaction rates

Depending on the specific type of data, different experimental techniques and equipment are utilized. Besides the application and improvement of established techniques, the primary goal is the development of new concepts allowing the determination of reliable data in less time using lower quantities of reagents. Below selected results that have been achieved in the period of this report will be summarized.

In the scope of a joint project for combining crystallization and chromatography for efficient enantioseparation (in cooperation with the company Schering, Berlin) extensive research was carried out for the determination of solid-liquid equilibria of a diastereomeric organic intermediate of an API (Active Pharmaceutical Ingredient). This thermodynamic data is required when designing a crystallization process. In **Fig. 2 (left)** the binary melting point phase diagram of the isomeric system is presented. The two epimers form a eutectic system. In addition, partial miscibility in the solid state is detected for contents below approx. 3 and above approx. 96 wt.-% of the α-epimer at the eutectic temperature.

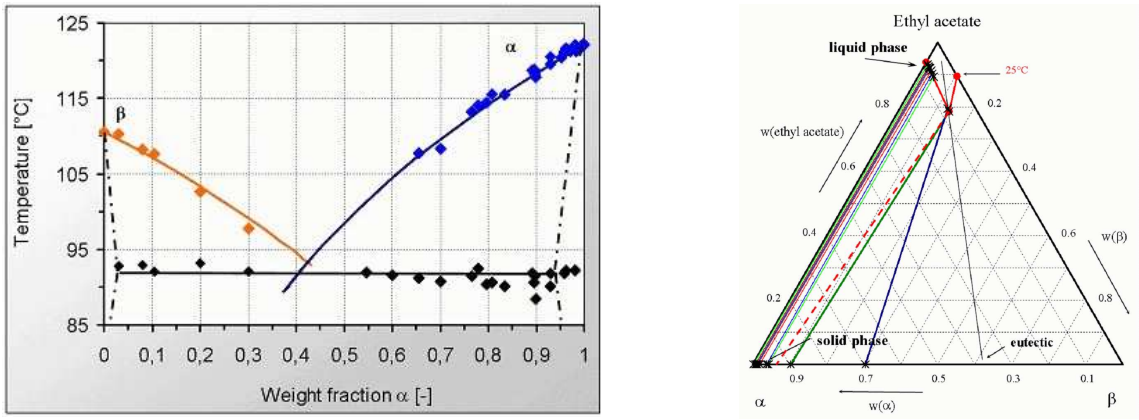

Fig. 2: **(left)** Melting point phase diagram of an isomeric system; **(right)** Solubility phase diagram of the α- and β-isomers of the diastereomeric intermediate in ethyl acetate (Gedicke et al., 2005).

Confirming the binary data, the ternary solubility phase diagram demonstrates the typical shape of a eutectic (conglomerate forming) system **(Fig. 2 (right)).**

Particular efforts were devoted to study the crystal growth of enantiomers. Kinetics of crystal growth is of great significance for the design and optimization of crystallization

based enantioseparation because of its influence on crystal and process related characteristics such as crystal size, shape, purity and productivity. Based on previous developments of measurement techniques for monitoring crystal growth in batch crystallization, systematic experimental and theoretical investigations were performed to study different aspects of crystal growth of enantiomers in chiral systems (Perlberg et al., 2005). In particular, the significant influence of the counter enantiomer on the growth rate of the target enantiomer was examined **(Fig. 3 (left))**. A change of the crystal habit of (S)-mandelic acid crystals was observed as a function of the concentration of the counter enantiomer **(Fig. 3 (right))** (Perlberg et al., 2005).

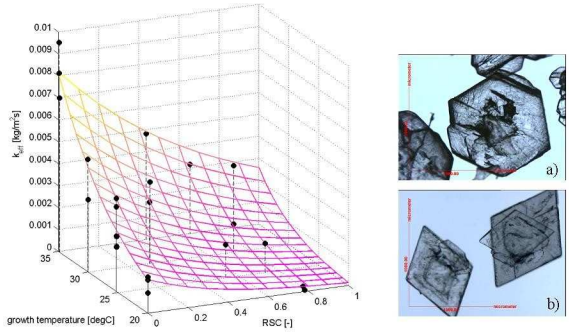

Fig. 3: **(left)** Effective growth rate constant k_{eff} versus growth temperature and the relative solvent composition RSC for growth of (S)-mandelic acid from aqueous solution; **(right)** Microscopic images of (S)-mandelic acid crystals obtained a) in absence and b) in presence of the counter enantiomer in solution.

Despite the fact that stereoselectivity of a crystal lattice involves weak interaction differences, enantiospecificities determined in a parallel theoretical study agree well with the experimental observations and explain the morphologic changes observed (Grandeury et al., 2005a).

Several projects were devoted to measure and model adsorption isotherms needed for the analysis of chromatographic separation processes. A review paper summarized the most important results achieved (Seidel-Morgenstern, 2004).

A theoretical analysis of a chromatographic column based on the Volterra series and generalized Fourier transform, combined with an equilibrium-dispersive model, has shown that the frequency response information can be used for the estimation of adsorption isotherms (Petkovska and Seidel-Morgenstern, 2005). Recently the applicability of the method was proven experimentally (Fig. 4, Ilić et al., 2005).

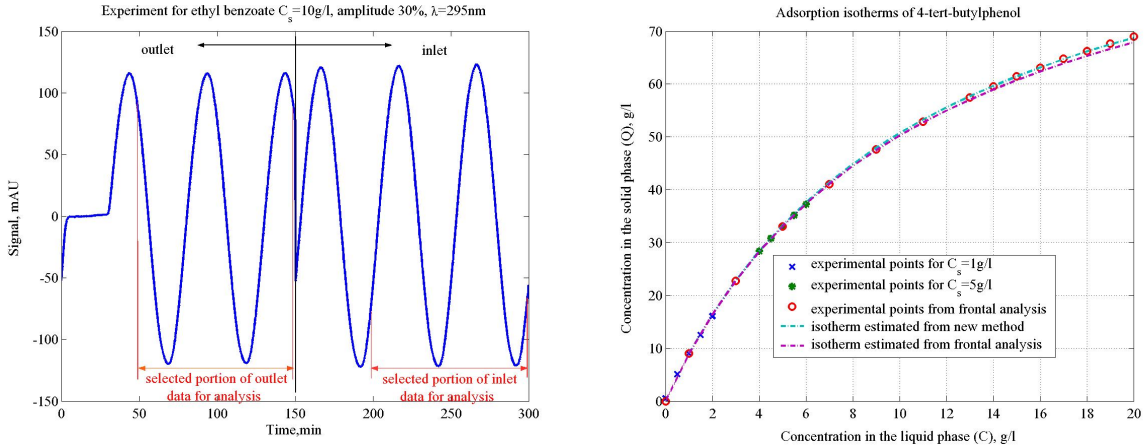

Fig. 4: **(left)** Example of periodic input and output data; **(right)** Determined adsorption isotherm of 4-tert-butylphenol (Ilić et al., 2005).

Reliable knowledge about the underlying reaction kinetics is required in order to mathematically describe and design chemical reactors. As an important basis for the DFG-group 447 “Membranunterstützte Reaktionsführung” (cooperation with PCP (Prof. Sundmacher) and PSD (Prof. Kienle)) the kinetics of the oxidative dehydrogenation of ethane to ethylene were studied. Conversion and selectivity data for three supported transition metal catalysts and the applied Al_2O_3-support were analyzed in a wide parameter range (Fig. 5**).**

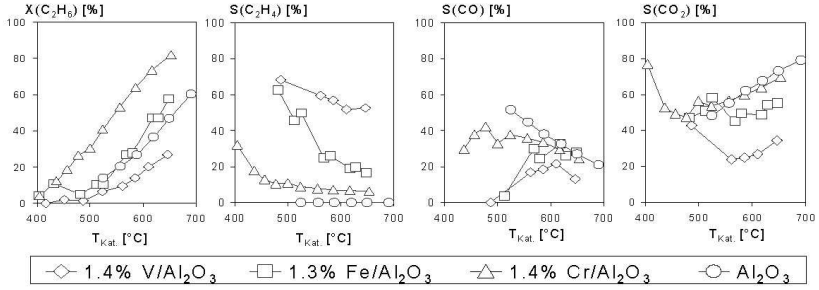

Fig. 5: Conversion (X) and selectivity (S) for different transition metal components as a function of temperature. Conditions: 0.7 % ethane in air, GHSV = 38000 h^{-1} (Klose et al., 2004a, 2004b).

In another cooperation with Prof. Claus (TU Darmstadt) the selective hydrogenation of acrolein to allyl alcohol on a silver catalyst supported on SiO_2 was investigated. The principle reactions of the identified network are illustrated in Fig. 6**a).** Measurements were performed in order to determine kinetic parameters by varying the temperature and the partial pressure. Fig. 6**b)** illustrates the conversion of acrolein and the corresponding yield with respect to allyl alcohol and/or propionaldehyde (Hamel et al., 2005).

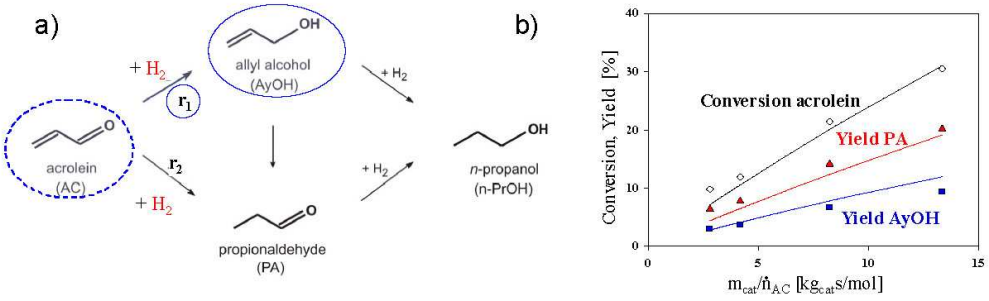

Fig. 6: **a)** Reaction network of the hydrogenation of acrolein to allyl alcohol; **b)** Conversion and yield as a function of space velocity (Ag/SiO_2 catalyst) (Hamel et al., 2005).

4.2 Analysis and Design of Separation Processes

In the PCF group several separation problems were investigated in detail. A main topic was the development and design of processes capable to isolate and purify fine chemicals. A particularly difficult task in this area is the separation of enantiomers. Isolation of the desired species can be achieved by special crystallization processes, membrane separation and preparative chromatography.

Significant progress has been achieved in analyzing and developing the principle of preferential crystallization, which is applicable to conglomerates and illustrated in **Fig. 7** using a ternary phase diagram**.** An initially undersaturated solution at temperature $T_{cryst}+\Delta T$ can be supersaturated, but will remain clear, if it is rapidly cooled down to a temperature, T_{cryst}, within the metastable zone. Retarded, its composition will change in order to reach the thermodynamic equilibrium. In the equilibrium state the liquid phase will have racemic composition (point E) and the solid phase will consist of a mixture of crystals of both enantiomers. However, after seeding with homochiral crystals the system does not reach the point E directly but moves along curved trajectories. Thus, under special conditions and in a restricted time interval it is possible to preferentially produce crystals of only the desired enantiomer (Elsner et al., 2005a; Lorenz et al., 2005).

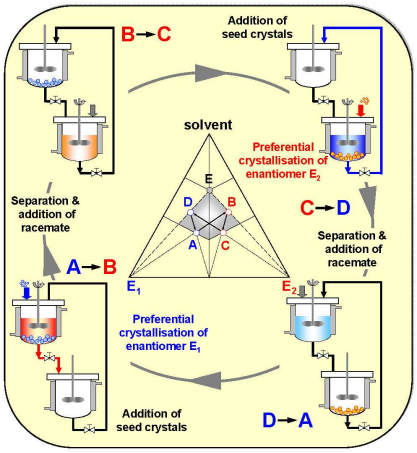

Fig. 7: Principle of the preferential crystallization and a possible cyclic operation mode.

A typical experimental run, which was carried out to preferentially crystallize L-threonine (E1), is illustrated in **Fig. 8.** The observed concentration profile is satisfactorily predicted by a model describing the time period, in which the desired enantiomer E1 is exclusively crystallized. In order to enhance productivity, a cyclic operation mode enables an attractive quasi-continuous enantioseparation. The principle is illustrated schematically in **Fig. 7.**

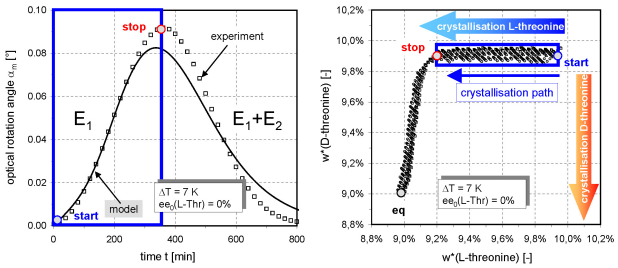

Fig. 8: Typical optical rotation angle curve **(left)** and trajectories **(right)** for reproducible batch experiments. Comparison (left) of the experimental α-curve obtained by seeding with L-threonine (E_1) crystals with simulations (Elsner et al., 2005a).

Simultaneous crystallization of both enantiomers in two separate vessels with an exchange of crystal-free mother liquid enables the deceleration of decreasing growth rates. An evaluation of the potential of this new crystallizer configuration, as well as its robustness and control is the main subject of joint research with the SCT group (Prof. Raisch) (Elsner et al., 2005b; Angelov et al., 2005). First optimization results allow for the comparison and assessment of different rivaling configurations (Ziomek et al., 2005a). In cooperation with the group of Prof. Thévenin (OvGU) preliminary studies devoted to the evaluation of the impact of hydrodynamics on the crystallization processes were conducted (Önçül et al., 2005a; Önçül et al., 2005b).

Recently it was demonstrated for the first time that the principle of preferential crystallization can also be applied to compound forming systems (Polenske et al., 2005; Seidel-Morgenstern et al., 2005).

A new challenging field of research in separation science is the use of the supramolecular recognition phenomenon to achieve a desired stereodifferentiation. Supramolecular chiral host molecules can be used to form diastereomeric complexes with a racemic guest that shows distinct physical properties (Fig. 9) (Grandeury et al., 2005b).

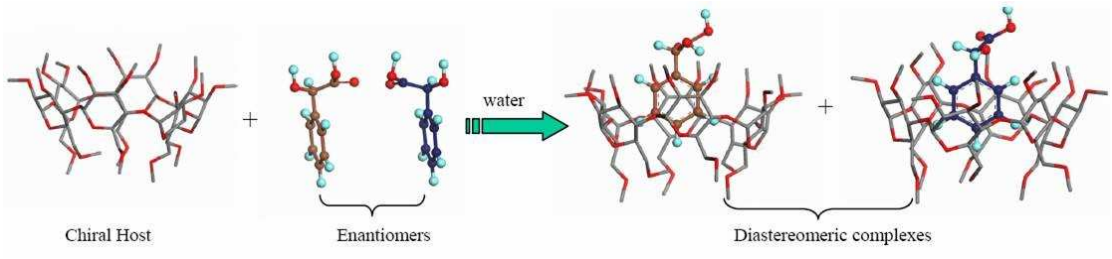

Fig. 9: Derivatization of a racemic mixture of mandelic acid ((*R*)-MA in blue, (*S*)-MA in brown) through the formation of supramolecular complexes with permethylated alpha-cyclodextrin. Hydrogen atoms of the macrocyle have been omitted for the sake of clarity. (Grandeury et al., 2005b)

A promising new method for separating chiral compounds is based on applying functional polymers, which are called Molecularly Imprinted Polymers (MIPs). Typically, enantioseparation by crystallization does not work with a racemic feed but can yield enantiopure crystals when enriched solutions are used. These solutions may be provided by enantioselective membrane separation. To establish the application of MIPs as a separation material in a continuous enantioseparation process various membrane materials were prepared and evaluated. The ability to separate racemic aqueous solutions of mandelic acid with MIPs was demonstrated successfully (Seebach et al., 2005).

Previous studies developing a new mode for continuously operated chromatographic separation processes were successfully continued in cooperation with the PSD group (Schramm et al., 2003a,b; Schramm et al., 2004). In addition, new complementary activities were initiated for the quantification and optimization of batch processes, which are more suitable to separate mixtures with more than two components. In particular, isocratic and gradient elution concepts were compared quantitatively (Shan and Seidel-Morgenstern, 2004, 2005a; Seidel-Morgenstern, 2005a). **Fig. 10** presents determined optimized shapes of solvent composition gradients and the corresponding elution profiles for separations of ternary mixtures.

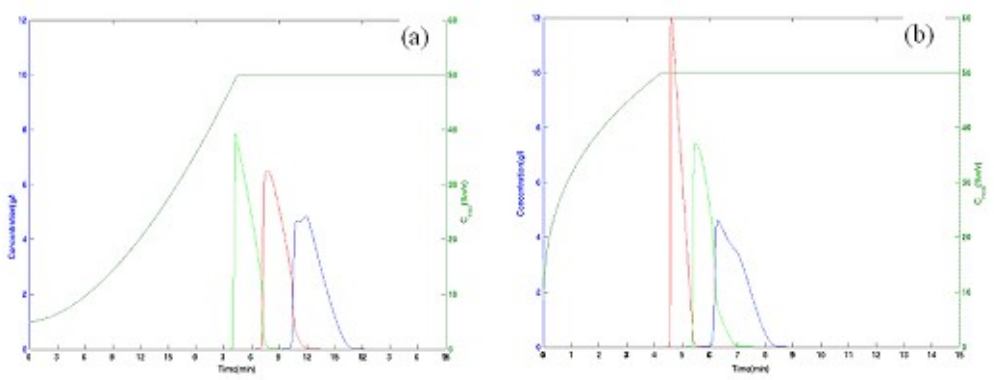

Fig. 10: Optimized gradient shapes and corresponding elution profiles of ternary mixture for two different chromatographic systems (Shan and Seidel-Morgenstern, 2005a).

There have also been studies carried out for the evaluation of the potential for using batch chromatography as an enrichment step before treating selected fractions in a continuously operated process (Shan and Seidel-Morgenstern, 2005b) and of radial chromatography (Zhang et al., 2005). Instructive results have been achieved comparing different possibilities for connecting a given number of chromatographic columns in parallel or in series (Ziomek et al., 2005b).

In cooperation with U. Tallarek (OvGU) in recent years, several aspects of chromatographic separation have been investigated: the application of smaller column dimensions to reduce sample amounts and time for analysis, monolithic stationary phases to reduce pressure drops, and electric fields to increase separation efficiencies. In these areas, innovative experimental and theoretical results have been obtained (Pačes et al., 2003; Hlushkou et al., 2004, 2005; Leinweber et al., 2005). In cooperation with the BPE group (Prof. Reichl) the effects of diffusion, electroosmosis and electrophoresis have been studied using Confocal Laser Microscopy (Tallarek et al., 2003). To facilitate direct online coupling of separation capillaries to mass spectrometry, a new simple and versatile sheathless low-flow ESI interface was developed and patented (Rapp et al., 2005).

Description and quantification of mass transfer rates is essential and indispensable for the successful application of membrane separation processes. In cooperation with Dr. Uchytil (Prague) and Prof. Schlünder (Karlsruhe), the mass transfer properties of different porous membranes were studied and quantified (Yang et al., 2005; Uchytil et al., 2005; Schlünder et al., 2005). A setup developed and a typical result are shown in **Fig. 11**.

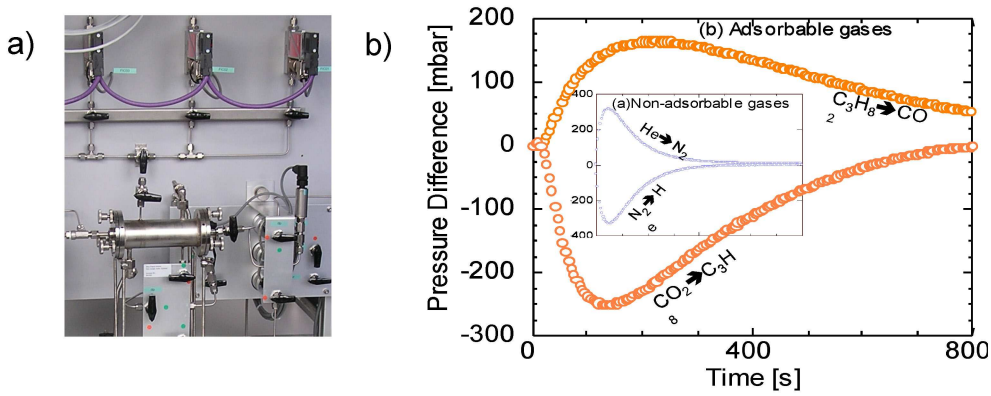

Fig. 11: **a)** Experimental setup (modified Wicke Kallenbach cell); **b)** Obtained pressure response curves for two transient exchange experiments using a porous glass membrane.

4.3 Integration and Combination of Several Processes

At the MPI, several forms of process integration are under investigation. Essential results of numerous collaborations have been recently summarized with the PCP and PSD groups (Sundmacher et al., 2005; Kienle et al., 2005).

Using equilibrium theory, in cooperation with the PSD group, new insight regarding the feasibility of simultaneuos total reactant conversion and total product separation in chromatographic reactors was acquired (Vu et al., 2005).

Possible enantioseparation techniques were studied in a joint project with the OvGU and Schering AG. Continuous SMB chromatography was designed for the delivery of partially enriched products. The desired final purity was then achieved through selective crystallization, as indicated in Fig. 12. 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 (Kaspereit et al., 2005). 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 composition from phase diagrams (Gedicke et al., 2005). Typical results are shown in Fig. 12 for the separation of the mandelic acid enantiomers.

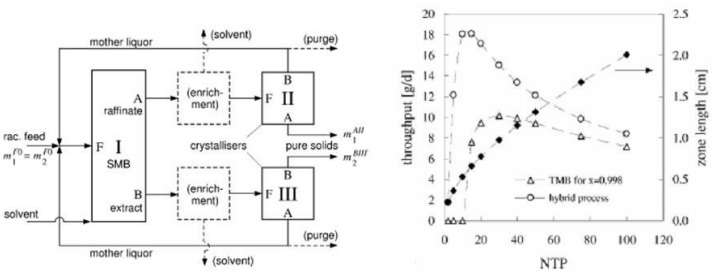

Fig. 12: **(left)** Example for two coupled separation processes. A racemic feed is partially resolved by SMB-chromatography and then split into the pure enantiomers by subsequent enantioselective crystallization. **(right)** Numerical simulation for mandelic acid enantiomers reveals the possibility of increased throughput of the coupled process (open circles) compared to the stand alone chromatographic separation (triangles). (Kaspereit et al., 2005).

Activities devoted to the systematic investigation of reaction processes supported by membrane separation were continued successfully. This work was supported by the German Research Foundation (DFG) and carried out in collaboration with several groups at the MPI and OvGU.

Intensive research in our group was directed at investigating the possibility of dosing one or more reactants into a reactor via membranes (Tóta et al., 2004; Klose et al., 2004b; Seidel-Morgenstern, 2005b). It was demonstrated, theoretically, that aside from adjusting local concentrations, it is also necessary to carefully analyze the residence time behavior of the different reactants (Hamel et al., 2003; Thomas et al., 2004; Kleinert et al., 2005). It was also demonstrated that a distributed dosing of excess hydrogen possesses the potential to improve significantly the selectivity of hydrogenation reactions (Hamel et al., 2005; **Fig. 13**). Significant efforts were devoted together with Prof. Tsotsas (OvGU) to study the important aspect of heat transfer through the membranes (Hussain et al., 2005).

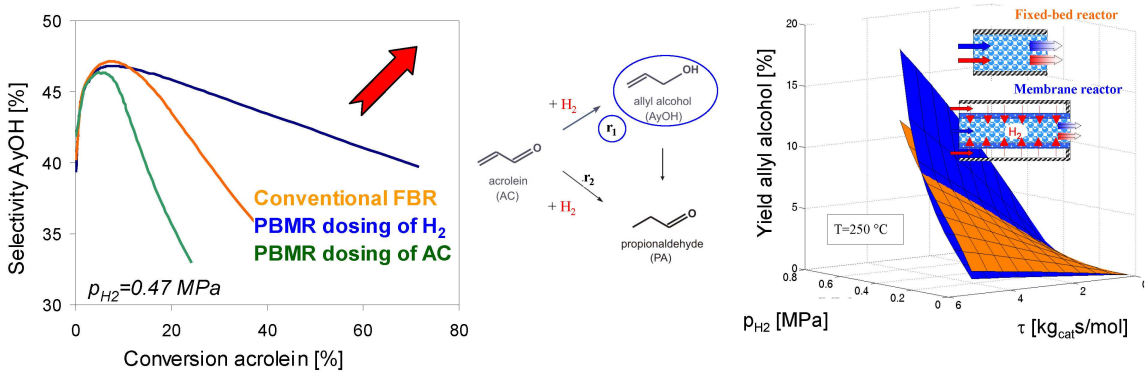

Fig. 13: Selected results analyzing the hydrogenation of acrolein to allyl alcohol.

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

Lectures of Prof. A. Seidel-Morgenstern:

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

Lectures of Dr. H. Lorenz:

- Technical Chemistry in Chemical and Process Engineering (OvGU, winter terms, in English)
- Modern Analytical Methods in Chemical Industry (OvGU, winter terms, with Prof. H. Weiß and Dr. F. Klose)
- Solid-Liquid Equilibria (University of Rouen, France, summer terms 2002, 2004, in English)

Habilitations

- D. Antos, “Gradient techniques in preparative chromatography modeling and experimental realization”, 2003
- E. Müller, “Polymerized chromatographic partition supports for bioseparation. Production and application“, 2003 (joint supervision with BPE group)
- H. Lorenz, ”Heterogeneous processes considering the oxidation of solid material and the crystallization from solutions“, 2004
- U. Tallarek, “Electrokinetic flow and transport in porous media: Experimental methods, numerical analysis, and applications”, 2004

Ph.D. Projects (^{1} = in preparation, ^{2} = university group)

- S. Thomas^{2}, “Controlled reactant feeding in membrane reactors for optimising the yield of desired intermediate products in parallel and subsequent reactions”, 2003
- D. Hlushkou, “Numerical Simulation of fluid flow and mass transport in (electro) chromatographic systems”, 2004
- T. Falk^{2}, “Analysis of a chromatographic reactor”, submitted

- F. Leinweber[2], “Investigations on the dynamic of diffusive and electrokinetic mass transport in consolidated porous materials”, 2004
- D. Beltcheva[2], “Theoretical and experimental study of gradient countercurrent chromatography under linear conditions”, 2004
- G. Chen[2], “Experimental investigation of capillary electrochromatography”, 2004
- N. Emberger[2], “Selective oxidation of butane”, 2005
- F. Czapla[1], “Efficient crystallization techniques for enantioseparation“
- C. Hamel[1], “Analysis of a multistage membrane reactor”
- M. Ilić[1], “Thermodynamic aspects of adsorption”
- M. Kaspereit[1], “Analysis of competitive adsorption equilibria”
- C. Keßler[1], “Simulated moving-bed chromatography of multicomponent protein mixtures“
- A. Perlberg[1], “Growth rates in enantioselective crystallization”
- D. Polenske[1], “Preferential Crystallisation as an innovative method for the resolution of racemates of chiral systems forming conglomerates and compounds“
- D. Sapoundjiev[1], “Determination and analysis of solid-liquid equilibria”
- A. Seebach[1], “Chiral membranes”
- G. Ziomek[1], “Investigation on stochastic optimization methods for selected process engineering problems“
- A. Damtew[1,2], “Analysis of the Potential of Solvent Gradients in Preparative Chromatography“
- K. Gedicke[1,2], “Coupling crystallization and chromatography for enantioseparation”
- L. Gueorguieva[1,2], “Gradient Elution chromatography”
- M. Joshi[1,2], “Reaction rates in catalytic-partial oxidation”
- I. Nischang[1,2], “Investigations on the dynamics of electrokinetic mass transport in hierarchically structured monolithic and particulate materials“
- M. Phong[1,2], “Reaction calorimetry to determine reaction rates”
- Á. Tóta[1,2], “Membrane reactors for partial oxidations”
- B. Vollbrecht[1,2], “Kinetics of the methanol synthesis under transient conditions”
- T. Vu Dinh[1,2], “Hydrolysis reactions in a chromatographic reactor”

Selected Diploma Projects in 2003 - 2005 (OvGU):

- N. M. Adityawarman, “Experimental and theoretical investigation of the chromatographic separation of a ternary mixture using chromatography“
- E. Agopovic, “Quantification of the distribution balances of water-dissolved oligosaccharides on a zeolite”
- E. Alonso Muslera, “Experimental determination for the separation of racemic mixtures using Preferential Crystallization in quasi- continuous operation”
- U. Börner, “Contributions to the development of monolithic stationary phases from molecular stamped polymers”
- A. Braumann, “Flowsheet-simulation of a large-scale process for the crystallization and recovery of an inorganic salt“
- I. Nischang, “Characterization of silica-based monoliths for capillary electrochromatography”
- D. Polenske, “Preferential crystallization as a method for the separation of chiral systems”
- A. Rodriguez, “Start-up of operation of the bench-scale plant Coupled Fixed-Bed Reactors”“
- Y. Shi, “Analysis of the elution order and the consequences of column overloading for the homologous series of the alkanes in normal phase chromatography“

6 Selected Memberships, Appointments and Awards

Andreas Seidel-Morgenstern

08 / 1998	External Scientific Member of Max Planck Society
since 1998	Member of Board of “Technical Reactions” of Dechema (Society for Chemical Technology and Biotechnology)
since 1998	Member of Board of “Reaction Engineering” of Society of Process Engineering and Chemical Engineering (GVC) of the Association of German Engineers (VDI), Düsseldorf
1998, 1999, 2000, 2004	Award of Faculty of Process and Systems Engineering (OvGU) for supervising the best doctoral thesis of the year
since 1999	Member of Otto von Guericke Society, Magdeburg
2000	Max Buchner Award of Dechema
since 2000	Member of Board of GVC/VDI

since 2000 Member of Scientific Board of Nordzucker AG, Braunschweig

since 2001 Elected Referee of the German Research Foundation for Chemical and Thermal Process Engineering

since 2001 Member of Board of Trustees of Ernest Solvay Foundation, Hanover

since 2001 Member of the International Editorial Board of the “Journal of Chromatography A” (Elsevier, Amsterdam)

2002 Otto von Guericke Research Award of OvGU

since 07/2002 Scientific Member of Max Planck Society and a director of the Max Planck Institute for Dynamics of Complex Technical Systems

since 04/2005 Dean of the Faculty of Process and Systems Engineering of OvGU

since 2005 Member of the Board of the Journal “Chemie-Ingenieur-Technik” (Wiley-VCH, Weinheim)

Heike Lorenz

1998 Grant of state of Sachsen Anhalt to support Habilitation

1999 Award for Young Researcher in Technical Chemistry (DECHEMA)

2002, 2004 Guest Professorship at the University of Rouen/France, Faculty of Science and Engineering, Department of Chemistry

since 2004 Member of Board of “Crystallization” of Society of Process Engineering and Chemical Engineering (GVC) of the Association of German Engineers (VDI), Düsseldorf

Christof Hamel

2003 Award for best Diploma thesis 2002 (Association of German Engineers, VDI, in Sachsen-Anhalt)

2003 Faculty Award of the Faculty of Process and Systems Engineering of the OvGU for his Diploma thesis

7 Future Directions

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. The goal is to attain a basic understanding of the underlying separation mechanisms as well as to design efficient processes from an engineering point of view.

The investigation of population balance systems will be an area of intense cooperation between several groups at the MPI (PCP, PSD. SCT) and the OvGU in the next few years. Our work on selective crystallization of enantiomers is characterized by coupled and competing growth of two types of crystal populations and will be an essential part of these joint activities.

Another important activity of our group will be the continuation and extension of the systematic research work regarding various types of membrane reactor concepts. After studying up to now mainly membrane reactors for exploiting a controlled dosing of oxygen, in future work also the potential to improve selective hydrogenations is a target.

A further goal of the PCF group is to extend the experience collected in 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.

The optimized application of electrical fields in chemical engineering applications will also remain a topic of investigation for our group.

Based on the potential of the concept, the expertise acquired up to now and the broad range of ongoing activity at the MPI, research work to further improve understanding of multifunctional reactors and integrated processes will be carried out.

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

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Research Group:

Physical and Chemical Process Engineering (PCP)

Prof. Dr.-Ing. Kai Sundmacher

This report covers the period from May 2003 to September 2005.

1 Group Introduction

The research of the Physical and Chemical Process Engineering (PCP) group covers the design, operation and analysis of complex chemical processes. The primary focus is on the system-orientated analysis of all physical and chemical phenomena involved and their interactions in hierarchical time and length scales. In particular, PCP focuses on the quantitative characterization and description of the physical and chemical transport phenomena. Additional attention is paid to the analysis of the nonlinear dynamic behavior of the processes and systems under investigation. Therefore, methods of mathematical modeling and simulation are closely combined with experimental concepts for model validation.

The current research activities of the PCP group are located in four MPI project areas (see figure 1 in section 3). Within the project area **Integrated Processes**, the group's research is focused on studying reactive separations, fuel cells and membrane reactors. For the model-based analysis of fuel cells, hierarchical modeling strategies were developed and a virtual fuel cell laboratory was set up within the project area **Network Theory**. A novel reactor concept for the production of pure hydrogen for fuel cells in a periodically operated multi-bed steam reformer is analyzed in the project area **Hybrid and Discrete Event Systems**. Last, but not least, in full accordance to the SAB recommendations of the evaluation in 2003, the PCP group has intensified its research activities within the project area **Population Balance Systems**. Using nanoparticle precipitation processes in bulk solutions and emulsions as examples, multidimensional population balances were solved and Monte-Carlo methods were established to analyze the dynamics of the considered particulate systems. In all four research areas, collaborative projects with other MPI groups (PSD, SCT, PCF, BPE) were established, thereby using the institute's system science concept as common umbrella.

Since 2001, Kai Sundmacher, being the Director for Process Engineering at the MPI, has guided the research activities of the PCP group and the university chair for Process Systems Engineering (PSE) at the Otto-von-Guericke University Magdeburg (OvGU), simultaneously. Both groups collaborate intensively, which is reflected in a number of common research projects.

2 Members of the Research Group

As of September 30th 2005, the group consisted of eight scientists with Ph.D. degrees and 11 graduate students working towards a Ph.D. During 2003-2005 two group members received their Ph.D. degree and six additional Ph.D. students have submitted their dissertations to the Otto-von-Guericke University Magdeburg. The defenses will take place in the next few months (see also Table 3). Since 2003, the group has published about 50 articles to international scientific journals.

Nearly all scientists of the PCP group work in non-permanent positions. The only permanent position is held by Dr. Rihko-Struckmann who – in addition to her research activities – is responsible for the co-ordination of the group's technical staff. This staff consists of two process engineers and two laboratory coworkers who support the PCP scientists, regardless which special research topic is addressed. Furthermore, the research is supported by several undergraduate students from the OvGU who are currently working on their master/diploma theses.

At the university, currently six Ph.D. students are preparing their dissertation theses. All of them are engaged in topics which have direct links to MPI research projects. Furthermore, one postdoctoral researcher (Dr. Voigt) completes the scientific work group under the direction of the university. All scientists are supported by E. Felsch who is responsible for the chair's preparative and analytical chemistry.

Tab. 1: Composition of PCP group

	Research Topics	**Membership**
Head of Group		
Prof. Dr. K. Sundmacher	Reactive separations, fuel cells, electrochemical membrane processes, population balance systems: modeling, analysis, design, experimental validation	since 10/1998
Postdocs		
Dr. H. Freund	Integrated processes: modeling, analysis	since 09/2005
Dr. V. Galvita	Fuel cells, reforming: process/catalyst development	since 09/2002
Dr. P. Heidebrecht	Fuel cells, reforming: modeling, optimization	since 09/2005
Dr. Z. Qi	Reactive separation: modeling, nonlinear dynamics	since 09/1999
Dr. L.K. Rihko-Struckmann	Electrochemical membrane reactors: experimental analysis; Co-ordination of the group's technical staff	since 01/2001

Dr. T. Schultz	Fuel cells, membranes: modeling, exp. analysis	since 05/1999
Dr. A. Voigt	Particulate precipitation: Monte-Carlo simulation	11/2003 - 08/2005
Dr. E. Yu	Enzymatic fuel cells: experimental analysis	since 01/2005
Ph.D. Students		
R. Hanke-Rauschenbach	PEM fuel cells: modeling, nonlinear dynamics	since 11/2001
Y.S. Huang	Reactive membrane separation: modeling	since 11/2001
J. Koch	Population balances: numerical algorithms	since 06/2004
U. Krewer	Direct Methanol Fuel Cell: modeling, analysis	10/2001 - 10/2005
B. Munder	Electrochemical membrane reactors: modeling	since 04/2001
B. Niemann	Nanoparticle precipitation: population balances	since 10/2002
F. Rauscher	Nanoparticle precipitation: experimental analysis	04/2001 - 08/2005
Y. Song	Direct Methanol Fuel Cell: fluid dynamics	since 06/2001
F. Steyer	Reactive distillation: modeling, exp. analysis	06/2000 - 09/2005
T. Vidakovic	Fuel cells electrode kinetics: experimental analysis	07/2002 - 09/2004
Y. Ye	Electrochemical membrane reactors: exp. analysis	11/2001 - 08/2005
Visiting Scientists		
Prof. Dr. M. Christov	Guest professor from UCTM Sofia: Electrochemistry of fuel cells, modeling, experimental analysis	09/2003-02/2004 10/2004-01/2004
Prof. Dr. P. Hasal	Visiting professor from ICT Prague: Electro-membrane processes (within BMBF/WTZ project)	several visits of 1-2 weeks
Prof. Dr. S. Mahajani	Visiting professor from IIT Bombay: Reactive separation (within VW-Foundation project)	several visits of 1-2 weeks
Prof. Dr. D. Ramkrishna	Visiting professor from Purdue University: Population balance modeling (Humboldt award fellow)	several visits of 1-2 weeks
Prof. Dr. E.U. Schlünder	Honorary scientist from Uni Karlsruhe: Reactive membrane processes, modeling, exp. analysis	since 04/2000
Technical Staff		
C. Fuchs	Laboratory assistant: fuel cells, electrode and catalyst preparation, chemical analytics	since 04/2004
T. Schröder	Laboratory engineer:plant design and operation, safety issues, maintenance	since 01/2002
P. Siegmund	Laboratory engineer: plant design and operation, safety issues, maintenance	since 02/2003
B. Stein	Laboratory assistant: separation processes, particulate processes, chemical analytics	since 10/2001
Group at OvGU: Process Systems Engineering		
Ph.D. Students: D. Adityawarman, L. Chalakov, M. Gundermann, M. Ivanova, M. Pfafferodt, C. Steyer, Postdoc: Dr. A. Voigt, Laboratory Coworker: E. Felsch		

3 Research Highlights

The current research projects of the PCP group are illustrated in Fig.1. More detailed information is collected in Table 2 where the projects are classified according to the project area structure established by the MPI. Most of the PCP projects are performed in close collaboration with other MPI groups and/or external partners at universities and research institutions. Since the PCP group interacts strongly with the Process Systems Engineering (PSE) group at Otto-von-Guericke University Magdeburg, a significant number of the listed subprojects are carried out in collaboration with PSE scientists.

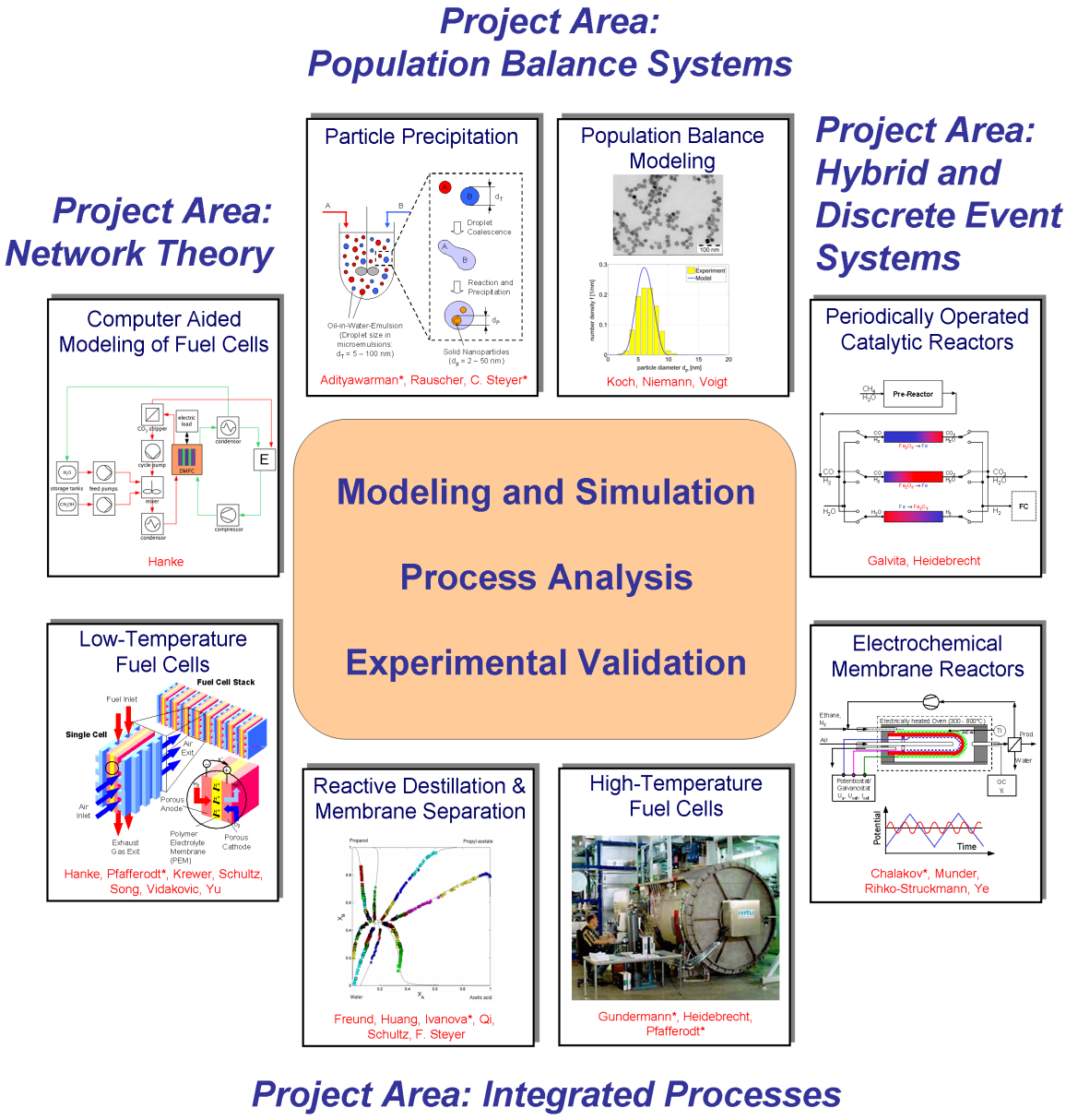

Fig.1: Survey of PCP research areas and projects (* = scientific coworkers of the group Process Systems Engineering at Otto-von-Guericke University Magdeburg, OvGU)

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

Project Area: Integrated Processes

Project: **Reactive Distillation and Membrane Separation**	A reactive distillation process combines reaction and distillation in one single unit. The benefits of this approach can be lower energy consumption and a reduction in the number of process units. However, the combination also results in a more complex process behavior. A detailed analysis of this behavior is the subject of this project. The PCP group activities are focused on the analysis of • the nonlinear process behavior, • reaction mixtures exhibiting liquid phase instabilities, • coupled reactions in combination with separation, • the influence of membranes on the feasible product spectrum of a reactive separation process, • micro-units being used for reactive separation.			
Subprojects	**Scientists**	**Funded by**	**Start**	**Partners**
Feasibility analysis of reactive distillation processes	Qi	MPI	09/1999	SCT Group (Flockerzi)
Reactive distillation with liquid phase splitting	F. Steyer, Qi	MPI	09/1999	PSD Group (Radulescu), SCT Group (Flockerzi), Companies: Oxeno, Degussa
Coupling of chemical reactions in a reactive distillation process	Ivanova*, Qi	VW, OvGU, MPI	01/2001	IIT Bombay (Prof. Mahajani, Prof. Aghalayam)
Reactive membrane separation	Huang, Schlünder	MPI	11/2001	PSD Group (Mangold)
Reactive micro-separators	Schultz	MPI	01/2005	PSD Group (Zeyer)

Project: **Low-Temperature Fuel Cells**	This project is focused on the analysis of the complex interaction of reaction and transport phenomena involved in low-temperature fuel cells processes. The investigated types of cells are PEM Fuel Cells (PEMFC), Direct Methanol Fuel Cells (DMFC) and Enzymatic Fuel Cells. The objectives are • to analyze the input-output behavior to these fuel cell systems with respect to dynamic load changes, • to develop reliable, i.e. validated process models for all sub-units of a fuel cell (electrodes, membrane, manifolds, single cells, cell stacks) and • to derive reduced process models for control purposes.			
Subprojects	**Scientists**	**Funded by**	**Start**	**Partners**
Experimental and model-based analysis of DMFC dynamics	Schultz, Krewer	MPI	05/1999	Uni Karlsruhe (Prof. Kind), OvGU (Prof. Hauptmann)

Analysis of DMFC electrode kinetics	Vidakovic, Krewer, Christov, Schultz	MPI	07/2002	MPI for Coal Research (Prof. Bönnemann)
Computational fluid dynamics of fuel cells	Pfafferodt*, Song, Krewer	OvGU MPI	06/2001	OvGU (Prof.Thévenin, Prof. Tobiska)
Nonlinear dynamics of PEM fuel cells	Hanke-Rauschen-bach	MPI	01/2002	PSD Group (Mangold)
Integration of fuel cells with electro-membrane reactors	Schultz	BMBF	01/2003	ICT Prague (Prof. Hasal)
Enzymatic fuel cells	Yu	MPI	01/2005	BPE Group (Genzel)

Project: **High-Temperature Fuel Cells**	The Molten Carbonate Fuel Cell (MCFC) is a high temperature fuel cell which permits internal steam reforming of methane. Appropriate process models are being developed and validated experimentally. Based on this, model-based observers can be designed and tested. The PCP group is involved in the development of fuel cell models and the experimental validation studies at a 300 kW MCFC power plant. Furthermore, the nonlinear process behaviour of these high-temperature fuel cells is analyzed theoretically.			
Subprojects	**Scientists**	**Funded by**	**Start**	**Partners**
Model-based analysis of DIR-MCFC processes	Heidebrecht, Pfafferodt*	OvGU	01/2001	PSD Group (Mangold), Uni Bayreuth (Prof. Pesch)
Experimental model validation of a large scale DIR-MCFC	Gundermann Heidebrecht	BMBF	05/2002	PSD Group (Mangold, Sheng), Companies: IPF, MTU
Nonlinear analysis of high-temperature fuel cells	Sundmacher	MPI	01/2004	PSD Group (Mangold, Krasnyk)

Project: **Membrane Reactors**	In this project, key problems related to the application of membrane reactors for controlled reactant dosing are studied. A main goal is to derive general criteria that will allow the potential of the principle to be quantitatively evaluated, and to be compared to conventional fixed-bed reactors. The objectives of the PCP research activities are • investigation of electrochemical reactors based on oxygen-ion conducting membranes and their use for the partial oxidation of light alkanes (ethane, butane), • modeling these membrane reactors as a prerequisite for the analysis of transport resistances and for optimal process operation and control.			
Subprojects	**Scientists**	**Funded by**	**Start**	**Partners**
Experimental analysis of electrochemical membrane reactors	Chalakov*, Ye, Rihko-Struckmann	DFG, OvGU, MPI	01/2001	DFG research group 447 (Prof. Weiß), PCF Group (Klose)
Modeling of electrochemical membrane reactors	Munder	MPI	04/2001	DFG research group 447, IKTS/Dresden

Project Area: Network Theory

Project: **Computer Aided Modeling of Chemical Processes**	In various research projects dealing with complex system dynamics, mathematical models are of great importance. These models have to be developed in a systematic manner and should be implemented in a comprehensible and reusable form. Within this project, the PCP group's research activities are focused on the establishment of a Virtual Fuel Cell Lab as a framework for model-based studies of the dynamics operating behaviour of single fuel cells, stack and fuel cell based power plants.			
Subprojects	**Scientists**	**Funded by**	**Start**	**Partners**
Computer aided modeling of fuel cell systems	Hanke-Rauschen-bach	MPI	11/2001	PSD Group (Mangold)

Project Area: Hybrid and Discrete-Event Systems

Project: **Stationary Power Supply Systems based on PEM Fuel Cells**	Within this project the PCP group investigates a steam reforming reactor for the production of very pure hydrogen as feed gas for Polymer Electrolyte Membrane (PEM) fuel cells. The reactor is designed as a periodically operated multi-tube fixed bed system. The project is focused on the analysis, optimal design and operation of this novel reactor.			
Subprojects	**Scientists**	**Funded by**	**Start**	**Partners**
Steam reforming in a periodically operated catalytic reactor	Galvita, Heidebrecht	LSA, MPI	11/2003	OvGU (Prof. Styczynski)

Project Area: Population Balance Systems

Project: **Particle Precipitation**	The production of fine particles with well-defined properties in the nano- or micrometer range is of major importance for various technological applications such as ceramic materials, semiconductors and catalyst precursors. The objectives of this project are • to achieve a fundamental understanding of the population dynamics of bulk and emulsion precipitation processes, • to describe precipitation processes in terms of several internal coordinates using population balances and Monte-Carlo-simulations, • to validate process models experimentally and • to use the validated process models for state estimation purposes.			
Subprojects	**Scientists**	**Funded by**	**Start**	**Partners**
Microemulsion-assisted precipitation of nanoparticles	Rauscher, Aditya-warman*	MPI, OvGU	04/2001	OvGU (Veit), PCF group (Lorenz)
Population balance modelling of bulk precipitation	C. Steyer*, Voigt	OvGU, MPI	05/2004	PSD Group (Mangold), SCT Group (Flockerzi), OvGU (Prof. Tobiska, Prof. Thévenin)
Population balance modeling of emulsion-assisted precipitation	Niemann	MPI	10/2002	Purdue University (Prof. Ramkrishna), Sheffield University (Prof. Mahoney)
Monte-Carlo simulation of emulsion-assisted precipitation processes	Voigt	MPI, OvGU	11/2003	PSD Group (Mangold)
Numerical algorithms for population balances	Koch	MPI	06/2004	MPI for Math. in the Sciences (Prof. Hackbusch)
State estimation of precipitation processes	Voigt, Niemann	MPI, OvGU	01/2005	PSD Group (Mangold)

3.1 Integrated Processes

In the project area **Integrated Processes**, the PCP group has a number of activities in the fields of reactive separations, fuel cells and membrane reactors. Within this area, the group collaborates intensively with the PSD and PCF groups. This collaboration is also reflected by a common book publication edited by the three heads of these groups (Sundmacher, K., et al., 2005a), (Kienle, A., et al., 2005).

3.1.1 Reactive Distillation and Membrane Separation

Over the past few years, the primary focus of the group's research was the development of generally applicable methods to predict feasible products of complex reactive separation processes. For the evaluation of the predicted products, detailed process simulations were carried out. The considered applications of this methodology are reactive distillation processes with and without liquid phase splitting, processes with multiple chemical reactions, reactive stripping processes, and processes with integrated membranes.

Feasibility analysis of reactive distillation processes

In order to analyse possible products from reactive distillation and reactive membrane separation processes, the concept of the potential singular point surface (PSPS) was introduced, and further developed in collaboration with the SCT group. This concept is applicable to systems being controlled either by chemical thermodynamics or by chemical kinetics (Qi, Z., et al., 2004a; Qi, Z., et al., 2005). It can be also applied to mass transfer controlled processes, such as reactive stripping and reactive membrane separations (Qi, Z., et al., 2004b).

Reactive distillation with liquid phase splitting

The PSPS method was extended to include systems which show instabilities of the reactive liquid phase. Such systems very often appear under real industrial conditions. As an example, the synthesis of cyclohexanol from cyclohexene and water was studied. In order to carry out reliable process simulations, extensive LLE and VLLE measurements were carried out (Steyer, F., et al., 2004). To simulate such processes, VLLE calculations have to be carried out in each simulation step, which is known to increase the computational time significantly. Therefore, the PCP group has developed a new rate-based approach, which is much faster than previously published classical algorithms (Steyer, F., et al., 2005). The mathematical properties

of different numerical schemes were explored in collaboration with the SCT group. This rate-based method is now also used by the PSD group for the simulation of the butylacetate process.

Coupling of chemical reactions in a reactive distillation process

Attractive synergetic effects can be achieved when several chemical reactions are combined with a distillation process. This is the subject of a collaborative research project with the Indian Institute of Technology (IIT) Bombay (Talwalkar, S., et al., 2005), funded by the Volkswagen Foundation (Germany). As a technically relevant model reaction, the dimerization of isobutene and its simultaneous hydrogenation to iso-octane is investigated by means of process models and experimental studies. To design the conceptual framework for this process, the previously described PSPS method, which was developed for reactive distillation processes, was extended to processes including mixtures with non-condensable reactants (Ivanova, M., et al., 2005). In the second step, the feasibility of isobutene dimerization under reactive distillation conditions was demonstrated (Kamath, R., et al., 2005).

Reactive membrane separation

The attainable products of a reactive separation process can be shifted to absolutely new parts of the composition space, if suitable membranes are integrated into the process. As an example, Figure 2 shows the PSPS for the dehydration of butanediol. By integration of a Knudsen membrane, the vertical hyperbolic product curves (Figure 2, left) can be turned into horizontal ones (Figure 2, right), so that a THF-rich mixture instead of a water-rich mixture can be obtained (Huang, Y.S., et al., 2004).

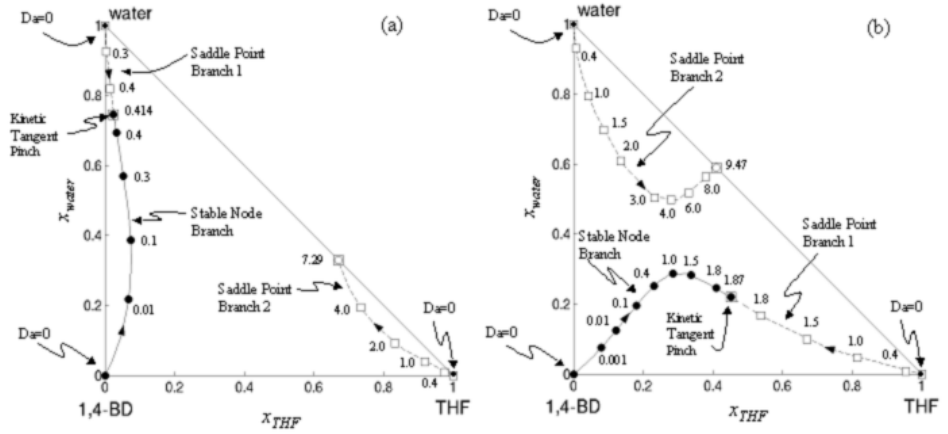

Fig.2: Potential singular point curves (PSPS) and bifurcation behaviour for system: 1,4-BD → THF + Water (p = 5 atm). (a) Reactive distillation (b) Reactive membrane separation with Knudsen diffusivities.
Legend: o Unstable Node, □ Saddle Point, • Stable Node

Membranes can also be used to shift the location of reactive azeotropes, which is of fundamental importance for the design of reactive separation processes. Figure 3 (left) demonstrates the existence of a reactive azeotrope in the reactive mixture propanol/acetic acid/propyl acetate/water, as predicted theoretically, and could also be confirmed experimentally (Huang, Y.S., et al., 2005a). The right hand side of Figure 3 illustrates predicted residue curves for the same system, but under the influence of a porous polycarbonate membrane. A significant shift of the azeotropic point can be expected. Since the new singular point is not only influenced by thermodynamic properties, but also by the mass transfer properties of the membrane, the PCP group suggested to call such a point a reactive a-rheo-trope ("the composition of the liquid phase does not change with mass fluxes") (Huang, Y.S., et al., 2005b).

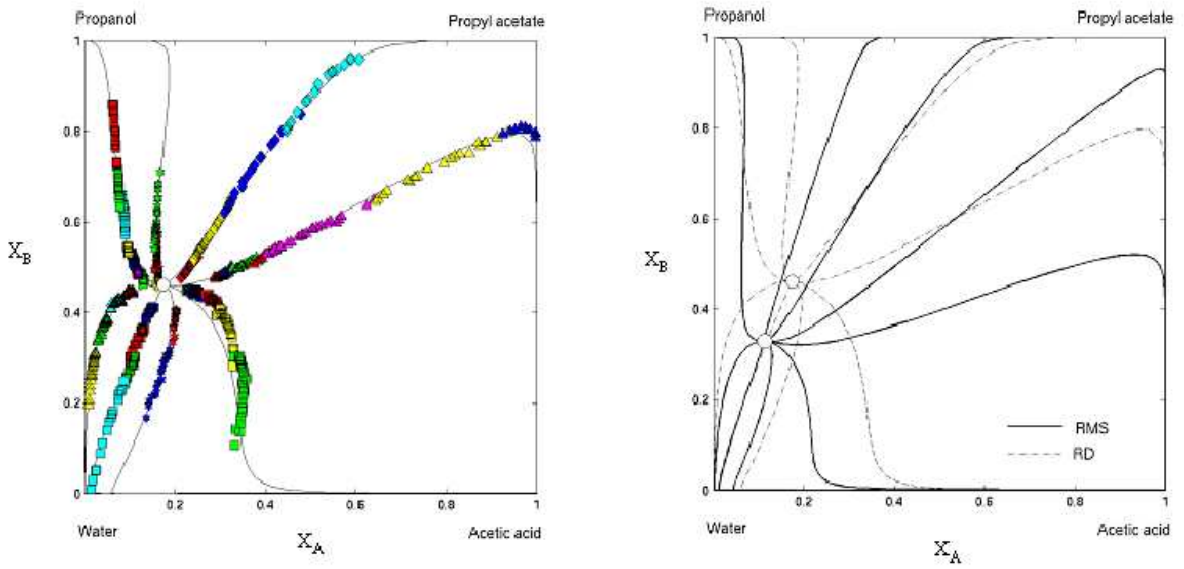

Fig.3: Residue curve maps for the synthesis reaction of propyl acetate ($Da \rightarrow \infty$) (a) Experimental validation of reactive distillation RCM (b) Prediction of the reactive arheotrope under the influence of porous polycarbonate membrane of pore size 50 nm.

3.1.2 Low-temperature Fuel Cells

The PCP group has been working on low-temperature fuel cells since May 1999. Since then, several subprojects were established, which focus on the Direct Methanol Fuel Cell (DMFC) and the Proton Exchange Membrane Fuel Cell (PEMFC).

Experimental and model-based analysis of DMFC dynamics

Since 2002, extensive studies have been carried out with the DMFC miniplant to analyze the steady-state and dynamic DMFC behavior (current-voltage

characteristics, responses to step-changes in electrical cell current and methanol feed concentration). In addition, crossover fluxes of methanol and water from anode to cathode were determined experimentally (Schultz, T., 2004; Schultz, T., et al., 2005a).

To analyze the experimental data, dynamic process models were developed with varying levels of complexity. A very detailed one-dimensional model that focuses on a realistic description of transport processes inside the porous structures in the membrane electrode assembly (MEA), while assuming simple one-step reaction mechanisms for both electrode reactions was formulated. The model accounts for the complex membrane swelling and the sorption equilibria on both sides of the membrane by calculating the activities of the mobile species inside the PEM using a Flory-Huggins activity model. Multi-component mass transport in all MEA layers is described by a generalized Maxwell-Stefan approach. The model has proven to be capable of correctly predicting methanol and water crossover fluxes through the PEM for a broad range of operating conditions with a single set of model parameters (Schultz, T., 2004; Schultz, T., et al., 2005a; Schultz, T., et al., 2005b).

Analysis of DMFC electrode kinetics

Besides the transport phenomena in the membrane, the complex multi-step electrode reactions significantly influence the dynamic behavior of the DMFC. Therefore, the anode kinetics was analyzed experimentally by means of electrochemical impedance spectroscopy (EIS) and cyclovoltammetry (CV). Evidently, carbon oxide species (e.g. CO) adsorbed to the anode platinum catalyst play a major role, as well as the formation of ruthenium hydroxide, Ru-OH, from ruthenium and water (Vidakovic, T., 2005; Vidakovic, T., et al., 2005). From these results, a suitable anode reaction mechanism was identified based on a state space model being formulated and transformed into the frequency domain (Figure 4) (Krewer, U., et al., 2005a,b).

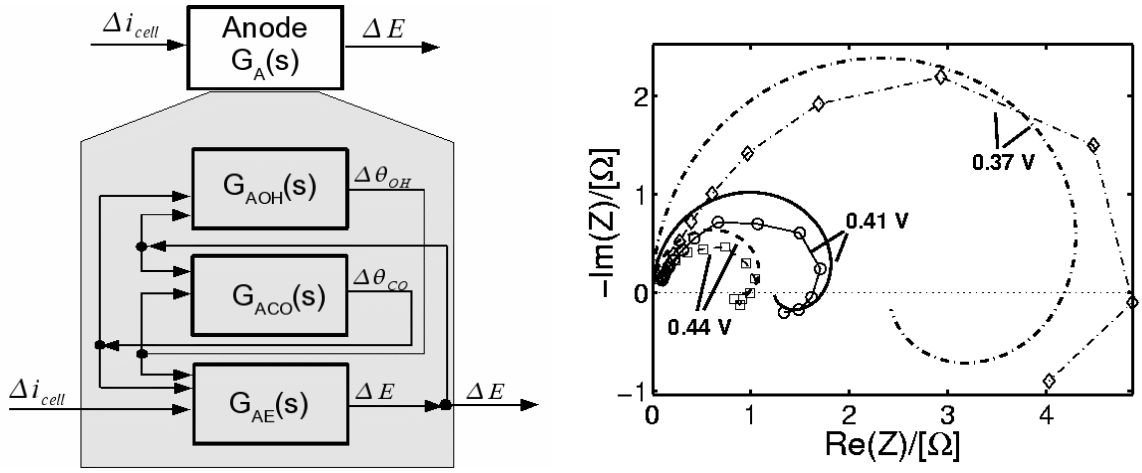

Fig.4: Block diagram of DMFC anode model (left), and simulated and experimental EIS data (right)

This anode kinetics, and the determined parameters, have been combined with the complex membrane transport model (mentioned in the previous section). With the help of the resulting complex DMFC model, predictions of the dynamic response of the DMFC are also possible (Figure 5, Model III) (Schultz, T., et al., 2005c).

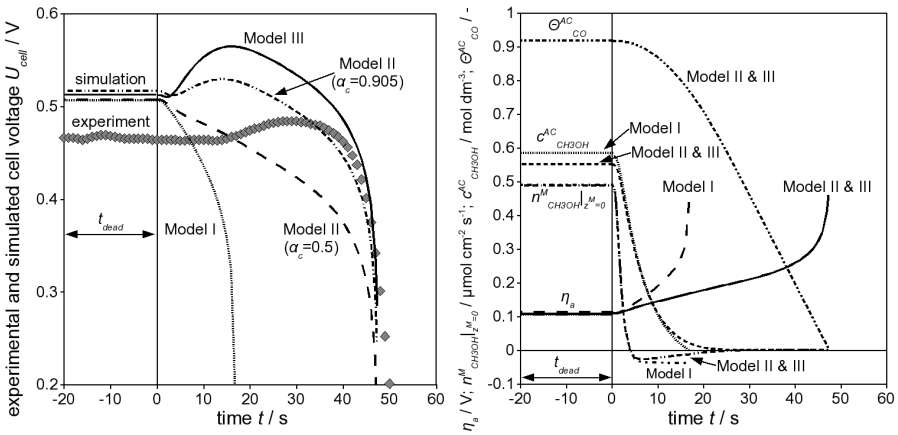

Fig.5: Dynamic simulation of DMFC showing impact of different electrode kinetics (Model I, II, III), especially the importance of accounting for adsorbed reaction intermediates on the anode (CO surface coverage $\theta^{AC}{}_{CO}$)

Nonlinear dynamics of PEM fuel cells

Not only the DMFC shows complex dynamic behaviour, but also the hydrogen-fed PEMFC. Here, the water content dependent conductivity of the membrane in combination with the water content dependent electric current can lead to nonlinear phenomena, such as multiple steady-states, oscillations or “wet spots”. Some recent results from bifurcation analysis are exhibited in Figure 6. They were obtained using hierarchical modeling strategies for a single-cell PEMFC (see section 3.2 on Network Theory). This research was done in close collaboration with the PSD group.

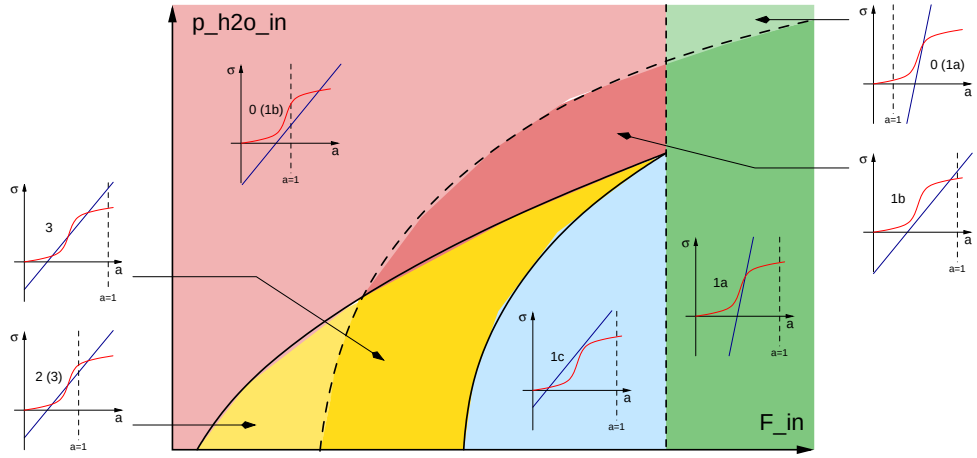

Fig.6: Qualitative two-parameter bifurcation diagram for a simplified PEM fuel cell model in resistostatic operation mode, showing regions of three to zero solutions.

3.1.3 High-temperature Fuel Cells

In this project, the complex behavior of Molten Carbonate Fuel Cells (MCFC) and Solid Oxide Fuel Cells (SOFC) is being investigated in close collaboration with the PSD group. The focus here is on the analysis of the direct mass and heat integration of the fuel reforming process and the electrochemical conversion of the produced hydrogen. This so-called DIR-MCFC concept is illustrated in Figure 7 (left).

Designing and operating such a highly integrated fuel cell system is a great challenge. Classical, intuition-based methods are not appropriate. Therefore, the PCP group developed a rigorous model-based approach for conceptual design, optimization of catalyst distribution and to observe the internal 3-dimensional temperature distribution within the fuel cell stack.

Model-based analysis of DIR-MCFC processes

A dynamic, spatially distributed mathematical model for a single representative cell, including several other compartments (Figure 7, right), was derived in terms of dimensionless parameters (Heidebrecht, P., 2005; Heidebrecht, P., et al, 2005a).

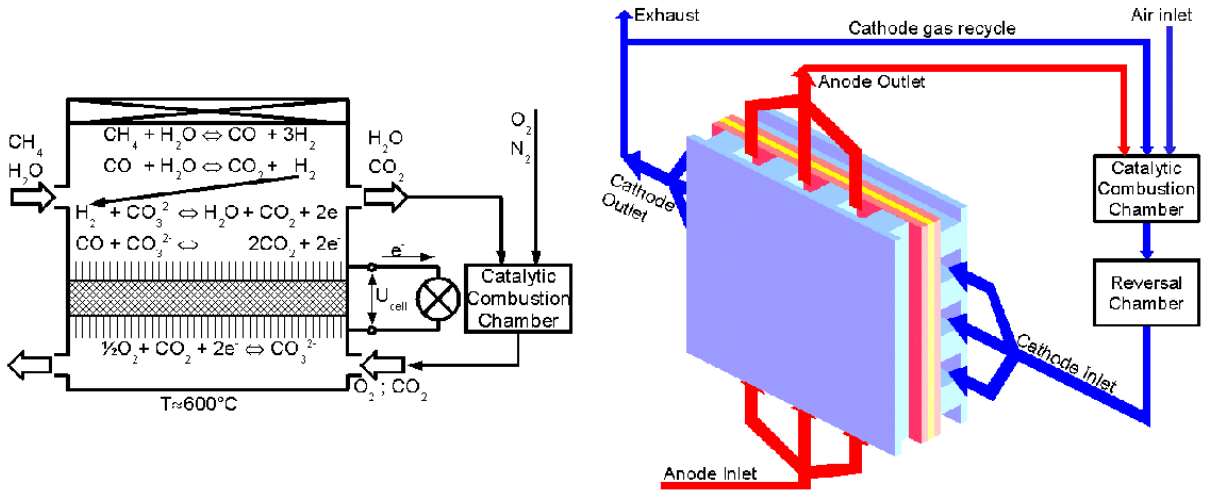

Fig.7: Schematic of MCFC with DIR (left), compartments and mass flows of the 2D MCFC model (right)

The model consists of coupled hyperbolic and parabolic partial differential equations in space and time, several ordinary differential equations, and a number of algebraic equations. This set contains strong non-linear terms and requires special numerical solution methods, which were partly developed in collaboration with the University of Bayreuth (Prof. Pesch). The complex MCFC model was also used to derive simplified model descriptions, which were applied towards optimization of the reforming catalyst distribution (Figure 8), conceptual process design (Heidebrecht, P., et al., 2005b,c), and process control (Mangold, M., et al., 2004a).

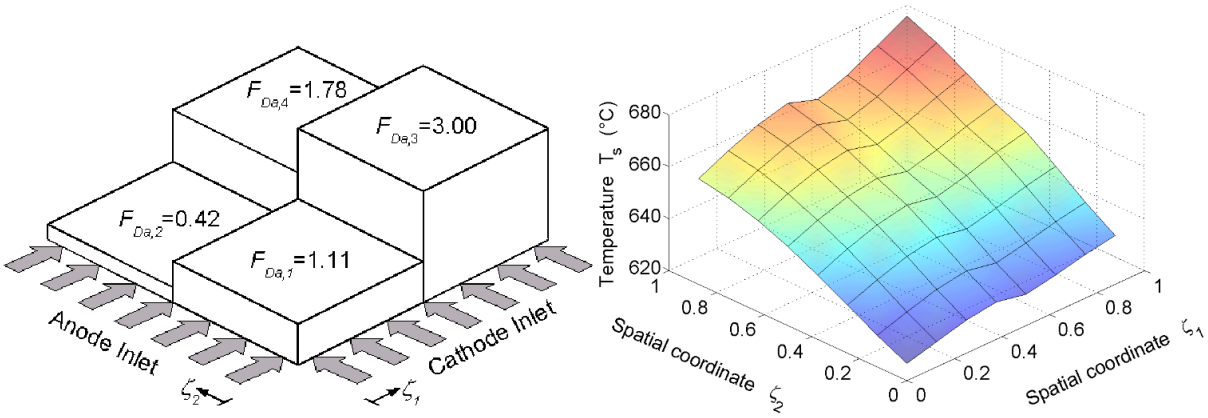

Fig.8: Optimal distribution of reforming catalyst in terms of relative catalyst density (left), resulting spatial temperature distribution (right).

Experimental model validation of a large scale DIR-MCFC

On a BMBF research project in conjunction with several partners from academia and industry, the PCP group uses the presented model-based methods to predict the temperature field inside a large scale DIR-MCFC power plant (HotModule^{TM} by MTU

CFC Solutions GmbH, Germany). This information is used by the PSD group to develop a model-based monitoring and control system.

The whole strategy requires reliable process models of suitable complexity and corresponding parameters. Currently, the PCP group is collecting data from the previously mentioned industrial MCFC unit in operation at the university hospital in Magdeburg. This is a very challenging task, as the complexity of this 300-cell stack with its various auxiliary units greatly exceeds that of typical lab-scale MCFCs.

Nonlinear dynamics of high-temperature fuel cells

In high temperature fuel cells, the spatial temperature distribution is of great importance. The nonlinear interaction of temperature-dependent ion conduction, heat conduction in the electrolyte and Joule heating can lead to thermal instabilities and hot spots (Mangold, M., et al., 2004b; Mangold, M., et al., 2005). Multiple steady states were predicted to occur at cell currents which are only slightly higher than typical currents in today's fuel cells (Figure 9). Some operating states are associated with sharp temperature peaks, which can significantly reduce the life time of the fuel cell. Interestingly, there are some unstable steady states being associated with a more homogeneous temperature profile. Stabilizing these states by means of process control might be a promising approach to operate future fuel cell systems at higher current densities. This work is conducted in collaboration with the PSD group.

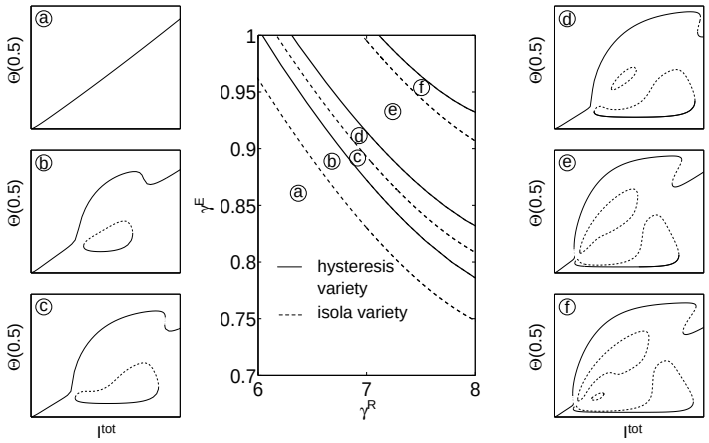

Fig.9: Bifurcation analysis of high-temp. fuel cell model; Center: Co-dimension 1 singularities in the parameter plane spanned by Arrhenius numbers of electrochemical reaction and the electrolyte's electrical conductivity, respectively. Surrounding diagrams: Continuation of steady-state solutions using total cell current as bifurcation parameter.

3.1.4 Membrane Reactors

As part of the DFG research group "Membrane Supported Reaction Engineering", established at OvGU, novel electrochemical membrane reactors (EMR) for partial

oxidation of hydrocarbons are designed and novel operating strategies are developed. The EMR has several advantages compared to the conventional co-feed packed bed reactors, e.g. more evenly distributed reagent supply and better temperature control, leading to increased selectivity towards valuable intermediates (Sundmacher, K., et al., 2005). The core of the reactor is an oxygen ion conducting solid oxide membrane, across which oxygen is supplied electrochemically to the reaction zone (Figure 10). The research is carried out in close collaboration with the PCF group and with the group of Prof. Weiss at OvGU (Suchorski, Y., et al., 2005).

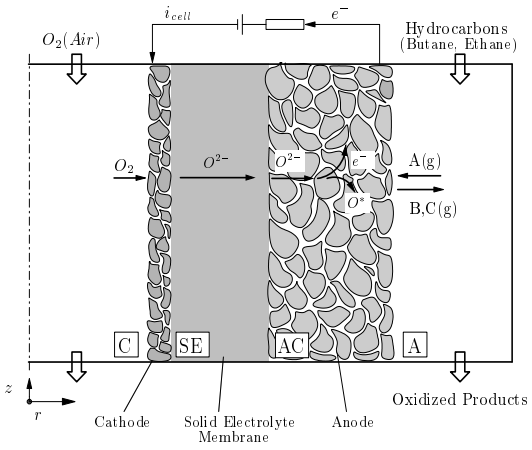

Fig.10: Schematic of electrochemical membrane reactor (EMR)

Experimental analysis of electrochemical membrane reactors

Based on conductivity investigations by electrochemical impedance spectroscopy (EIS), a feasible anode structure based on a VPO catalyst was developed. The partial oxidation of butane to maleic anhydride was used as a reaction example of technical relevance. Experiments have confirmed the feasibility of the novel reactor concept. It was determined that the selectivity towards maleic anhydride has a maximum at a certain current density (Ye, Y., et al., 2004).

Recently, periodic operation of the EMR was also investigated. It was determined, that the VPO catalyst can be regenerated by electrochemical oxygen pumping (EOP, Figure 11) (Ye, Y., et al., 2005).

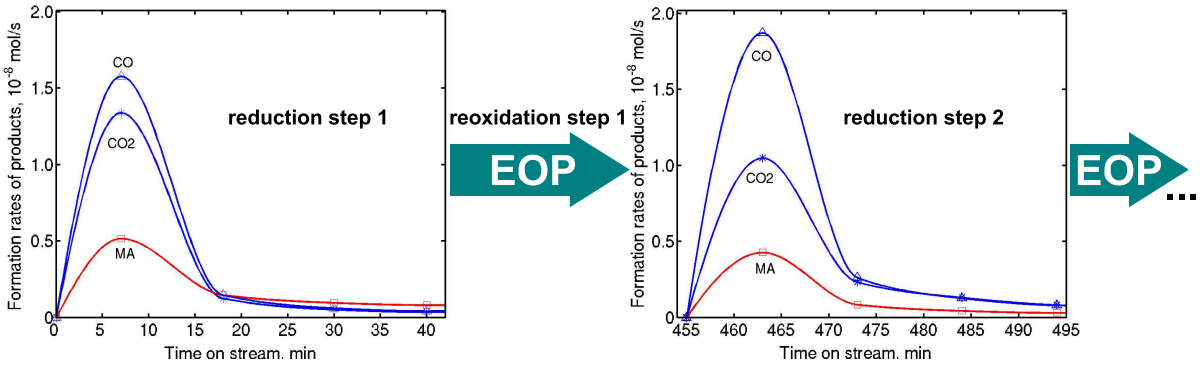

Fig.11: Experimental results from EMR redox cycle operation (production of maleic anhydride, MA, and intermediary catalyst reoxidation by electrochemical oxygen pumping, EOP)

Modeling of electrochemical membrane reactors

In an accompanying subproject, the capability of conducting partial oxidation reactions in electrochemical membrane reactors has been analyzed theoretically. A one-plus-one dimensional model was formulated to describe the mass and charge transport processes taking place within the anode structure and the adjacent gas flow channels (Munder, B., et al., 2005). Experimental results of steady state operation were used to validate the process model and to identify key parameters. This knowledge will be used to optimize the operation of the EMR.

3.2 Network Theory

In this project area, the PCP group contributes one subproject dealing with a hierarchical concept for fuel cell system modeling. This work is conducted together with partners from the PSD group.

3.2.1 Computer-Aided Modeling of Fuel Cell Systems

The design and analysis of fuel cell systems requires flexible modeling and simulation tools. In this subproject, a modular concept is realized which is based on the network theory for chemical engineering processes. The concept is used to introduce a structured library for the generation of fuel cell and fuel cell system models (Virtual Fuel Cell Laboratory: Hanke, R., et al, 2005). According to this concept, the models are structured in a vertical direction (i.e. different hierarchical levels) as well as in an horizontal direction (i.e. into so-called components and coupling elements), as illustrated in Figure 12. The hierarchical structure enables the user to focus on any detail, and to modify this detail by replacing one elementary block by another.

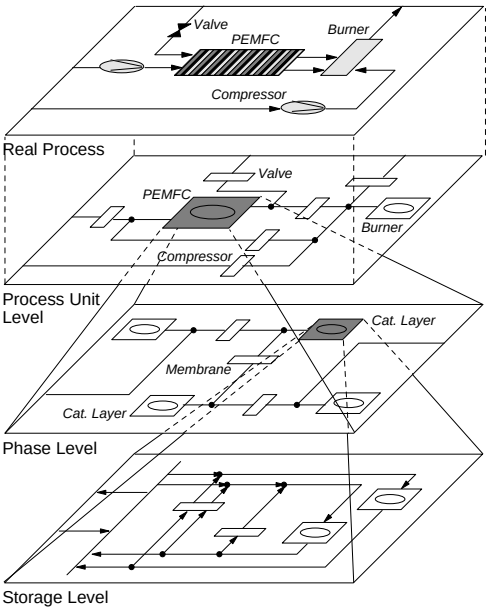

Fig.12: Levels of process structuring for a fuel cell system.

3.3 Hybrid and Discrete Event Systems

Within this project area, the PCP group develops and analyses a novel reactor concept for the generation of pure hydrogen for PEM fuel cells. This concept is based on the periodic operation of a multi-tube fixed bed catalytic reactor. This research is part of a joint research project with the OvGU (Prof. Styczynski), funded by the ministry of research of Saxony-Anhalt.

3.3.1 Periodic Catalytic Reactors: Steam Reforming

A two-stage reactor system was proposed and investigated. The first stage is a continuously operated, classical methane steam reformer, producing carbon monoxide and hydrogen (Figure 13, left: synthesis gas reactor). This mixture is fed to the second stage, which is a multi-tube reactor with a fixed bed of a special iron oxide (Figure 13, right). The reactor tubes in this second stage are cyclically operated in two alternate steps: In the first step, the carbon monoxide/hydrogen mixture from the first stage is oxidized to carbon dioxide and water consuming oxygen supplied from the catalyst (reduction step). Before the catalyst bed is completely reduced, the reactor is switched to the second step, in which water vapor is fed. The water re-oxidizes the catalyst while hydrogen is produced (oxidation step). A mixture of this pure hydrogen and unreacted water vapor, suitable for feeding a low-temperature fuel cell, leaves the reactor. By the cyclic switching of the multiple tube reactors of

the second stage, continuous hydrogen production can be realized. The feasibility of the second stage was proven recently (Galvita, V., et al., 2005).

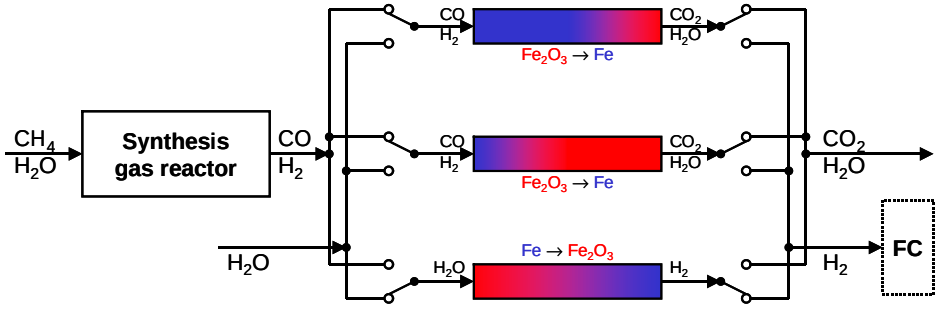

Fig.13: Conceptual design of periodically operated methane steam reformer system

3.4 Population Balance Systems

The group's research in this area concentrates on the experimental and theoretical investigation of nanoparticle precipitation in bulk solution and in emulsion droplets. Nanoparticles are of technical interest for a variety of applications ranging from composites, surfaces, coatings, catalysts, magnetic storages, pharmaceuticals etc.

3.4.1 Particle Precipitation

Microemulsion-assisted precipitation of nanoparticles

In order to apply water-in-oil microemulsions for particle precipitation, the phase behavior (droplet size, stability, viscosity) was determined experimentally in dependence on the emulsion composition and temperature. The mixture water/cyclohexane/surfactant Marlipal O13/40 was used as technically relevant model system. The precipitation of barium sulfate (Adityawarman, D., et al., 2005) and calcium carbonate (Rauscher, F., et al., 2005) were chosen as model reactions. The influence of the solutes on the phase diagram was investigated to obtain suitable process conditions. The influence of the most important process operating parameters (initial reactant concentration, feed amount, feed rate, holding time, stirring rate, microemulsion composition, reaction temperature) was studied systematically in a semi-batch reactor. The produced nanoparticles were analyzed with high-resolution transmission electron microscopy (Figure 14) in collaboration with the Centre of Microstructure Physics at the OvGU (Dr. P. Veit) and the PCF group (XRD measurements).

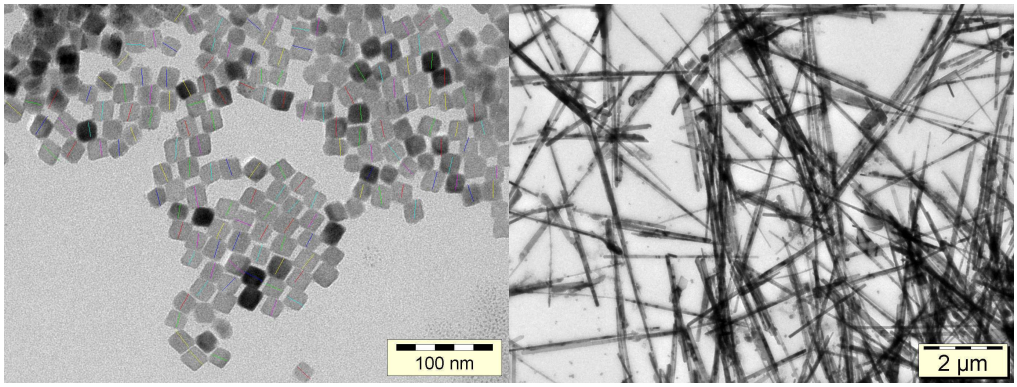

Fig.14: TEM pictures of crystalline barium sulfate (left) and calcium carbonate needle-like nanoparticles (right).

In the case of barium sulfate nanoparticles, the initial concentration ratio of the two reactants could be singled out as a significant control parameter for the particle size (Adityawarman, D., et al., 2005). A surprising result was obtained when the holding time was varied for calcium carbonate. Here, long needle-like nanoparticles were observed (Rauscher, F., et al., 2005).

Population balance modeling of bulk precipitation

In the microemulsion experiments it was discovered that the macroscopic mixing of the microemulsion did not have a significant impact on the results. As this is known to be different for bulk precipitation, in an additional subproject, the influence of turbulent mixing was studied in bulk phase experiments using the barium sulfate precipitation as example. For the theoretical interpretation of the obtained results, a population balance model is formulated and combined with a CFD (computational fluid dynamics) simulation. Two solution strategies are currently pursued: A moment approach was combined with the CFD solver Fluent in collaboration with the OvGU group of Prof. Thevenin (Öncül, A., et al., 2005a,b) and a full FEM discretisation was applied to all external and internal coordinates in collaboration with the group of Prof. Tobiska (OvGU).

Population balance modeling of emulsion-assisted precipitation

For the theoretical description of particle precipitation in emulsion droplets, various population balance models are currently developed by the PCP group. The challenge of the modeling results from the fact, that the droplet population is characterized by several internal coordinates which have to be treated simultaneously. These coordinates are the droplet size, the concentrations of the reactants inside the

droplets, and the size of the precipitated particles. Moreover, in emulsion precipitation several population dynamic mechanisms interact with each other, such as droplet coalescence and breakage, particle nucleation and growth, and, possibly, also particle agglomeration. Because of this complexity, simplified (i.e. reduced) model descriptions have to be developed. As an initial approach, an instantaneous chemical reaction was assumed (Niemann, B., et al., 2005). Recently, the case of instantaneous droplet exchange was also considered. First results based on this assumption show a reasonable agreement to the experimental data (Figure 15, left). The numerical treatment of the droplet coalescence and breakage kernels represents a further challenge for this project. This subject is further addressed in collaboration with Prof. Hackbusch (MPI for Mathematic in the Sciences, Leipzig).

Monte-Carlo simulation of emulsion-assisted precipitation processes

Due to the high dimensionality of the previously described population system, a population balance approach must be simplified. The resulting simplifications can be relaxed, if the particle precipitation process is represented by a discrete, stochastic model using the principles of Monte-Carlo simulation (Voigt, A., et al., 2005; Adityawarman, D., et al., 2005). Based on Monte-Carlo simulation, a sensitivity analysis of the particle precipitation process in microemulsions was carried out. As demonstrated in Figure 15 (right), experimental and simulation results were in agreement. This agreement was achieved by adjusting the key parameters associated with particle nucleation.

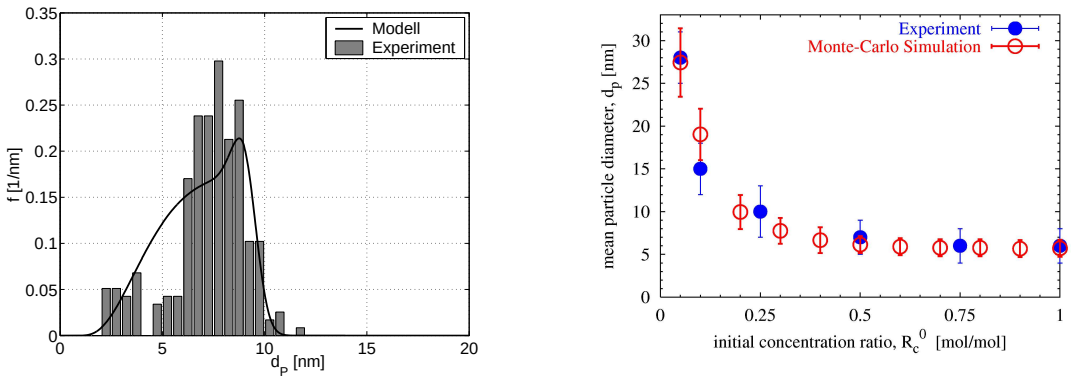

Fig.15: Comparison between experimental and simulation data for barium sulfate precipitation in microemulsion. Left: Population balance model; Right: Monte-Carlo simulation for variation of initial concentration ratio.

State estimation of precipitation processes

The focus of this subproject is the development of methods for model-based estimation of particle size distribution in precipitation processes. A new state estimation technique has been developed in collaboration with the PSD group (Mangold, M., et al., 2006). The method is based on process models contributed by the previously described subprojects. The particle size distribution is estimated from easily accessible experimental variables such as the mean particle size. This estimation requires systematic model validation which is a future subject of the group's research activities.

4 Future Directions

Integrated Processes

In the past few years, the PCP group has generated significant knowledge about modeling dynamic behavior and design of reactive distillation processes. In the future, this knowledge will be used to focus on model-based control and operation, thereby strengthening the collaboration with the SCT and the PSD groups. A first project was already started with the SCT group on startup of reactive distillation columns by means of feedback control strategies (Sommer, S., et al., 2006).

The PCP group will, in collaboration with the PCF group, continue its activities in the field of reactive membrane separation processes, extending the experimental investigations to include continuous setups. Furthermore, the use of micro membrane separators offers very promising perspectives. Micro systems might not only be an efficient experimental tool for validation purposes, but can also offer additional separation effects, such as surface tension driven flow.

Concerning fuel cells, the PCP group has collected significant knowledge on how to model electrode kinetics and mass transport phenomena in different layers, as well as on how to carry out systematic experimental validation. Based on that, single cell models of different complexity were developed for the different fuel cell types. In the next few years, the focus of the groups research will be directed towards system control. For this purpose, model reduction plays a major role. Moreover, with respect to large-scale stacks, distributed models in terms of two, or even three, space coordinates must be developed, and auxiliary units have to be integrated. To realize this, CFD approaches and multi-scale modeling techniques - in combination with the existing models - have to be explored.

Bio fuel cells offer new possibilities for generation of electrical energy, especially for biomedical applications. The design of such systems is a demanding task and requires the combination of expertise from process engineering as well as from biocatalysis. The PCP group has started first activities here (Yu, E.H., et al., 2005) in collaboration with the BPE group (Genzel).

Hybrid and Discrete Event Systems

The preliminary studies on the periodic reforming process described above have proven the feasibility of this new process concept. The detailed analysis of the dynamic behavior of this hybrid system is an interesting challenge in itself. But the long-term vision here is to combine this dynamic process with a PEM fuel cell in order to analyze and control an entire energy generation system. This task can only be successfully addressed by means of the system science approach of the MPI, primarily in collaboration with the SCT and the PSD group.

Population Balance Systems

Based on the existing process models for particle precipitation in bulk phase and in microemulsions, reduced models and control strategies for semi-batch reactors will be developed in close collaboration with the SCT group (Heinecken, Flockerzi) and with the PSD group (Mangold, Kienle), respectively. Moreover, particle precipitation in macroemulsions will be considered, a process technology of considerable interest with respect to industrial application. As a long-term perspective, model-based control strategies shall be developed for macroemulsion precipitation. This requires a thorough understanding and analysis of the underlying population dynamic mechanisms. Amongst them, the nucleation of solid particles in emulsion droplets must be investigated experimentally (e.g. using XRD in collaboration with the PCF group) and described on the molecular level applying modern modeling tools. Furthermore, droplet coalescence and breakage phenomena will be subject to further experimental and modeling activities. With regard to the particle properties, emulsion precipitation can not only be used to control the size distribution, but also the shape and morphology. This leads to highly dimensional population balance models in terms of internal coordinates. In addition, the external coordinates of the process (space coordinates) must be considered in order to be able to describe large-scale reactors. The whole field of particle precipitations offers excellent opportunities to

apply system science concepts and, due to the complexity of the considered emulsion systems, it is of long-term interest for the PCP group.

5 Selected Teaching Activities and Ph.D. Projects

5.1 Teaching Activities at OvGU (Lecturers of the PCP Group)

- Course on Process Systems Engineering (Sundmacher)
- Course on Process Dynamics (Sundmacher)
- Course on Population Balance Systems (Sundmacher, Voigt)
- Course on Process Optimization (Heidebrecht)
- Course on Molecular Modeling (Voigt)
- Course on Fuel Cells (Heidebrecht, Schultz, Hanke-Rauschenbach)

5.2 Supervision of Ph.D. Theses

Tab. 3: Ph.D. theses supervised by K. Sundmacher (* Ph.D. students of the OvGU group)

Adityawarman, D.*	$BaSO_4$ nanoparticle precipitation in non-ionic micro-emulsions: Experiments and model-based analysis	2001-2005 (submitted)
Chalakov, L.*	Ethane partial oxidation in a solid electrolyte membrane reactor	since 2003 (in preparation)
Gundermann, M.*	Validation of a fuel cell model using an industrial MCFC power plant	since 2002 (in preparation)
Hanke-Rauschenbach, R.	Hierarchical modeling and nonlinear analysis of PEM fuel cells	since 2001 (in preparation)
Heidebrecht, P.*	Modelling, analysis and optimization of a Molten Carbonate Fuel Cell with Direct Internal Reforming, (DIR-MCFC)	2001-2004 (finished)
Huang, Y.S.	Influence of mass transfer effects on reactive separation processes – discovery of reactive arheotropes	2001-2005 (submitted)
Ivanova, M.*	Coupled chemical reactions in a reactive distillation process for the production of isooctane	since 2002 (in preparation)
Koch, J.	Efficient treatment of integral operators in population dynamic models	2002-2005 (submitted)
Krewer, U.	Dynamics of Direct Methanol Fuel Cells: System analysis and modelling	since 2001 (submitted)
Munder, B.	Reactor design and process operation strategies for the controlled partial oxidation of hydrocarbons in electrochemical membrane reactors	since 2001 (in preparation)
Niemann, B.	Population balance modelling of precipitation in emulsions	since 2002 (in preparation)
Pfafferodt, M.*	Multiscale modelling of fuel cells	since 2004 (in preparation)

Rauscher, F.	Process analysis of nanoparticle synthesis in microemulsions	since 2001 (in preparation)
Schultz, T.	Experimental and model-based analysis of the steady-state and dynamic operating behaviour of the Direct Methanol Fuel Cell	1999-2004 (finished)
Song, Y.	Computational fluid dynamics for DMFC flow field analysis	since 2001 (in preparation)
Steyer, C.*	Population dynamics of particle precipitation in bulk phase	since 1999 (in preparation)
Steyer, F.	Modelling and analysis of a reactive distillation process with liquid phase splitting	2000-2005 (submitted)
Vidakovic, T.	Kinetics of methanol electrooxidation on PtRu catalysts in a membrane electrode assembly	2002-2005 (finished)
Ye, Y.	Experimental study on n-butane partial oxidation to maleic anhydride in a solid electrolyte membrane reactor	2001-2005 (submitted)

K. Sundmacher also acted as examiner for the Habilitation thesis of Dr. M. Mangold (2005), and the Ph.D. thesis of M. Boder (2004 at University of Erlangen-Nürnberg), of O. Angeles-Palacios (2005 at OvGU) and of S. Schmidt (2005 at University of Kaiserslautern).

5.3 Diploma Projects

Tab. 4: Diploma projects supervised by K. Sundmacher (OvGU; * students from other universities)

Kamath, R.S.	Dimerization of isobutene by reactive distillation: Process analysis and comparison with conventional reactor concepts	2005
Menendez, D.F.	Fluid dynamic characterization of anode flow beds of direct methanol fuel cells	2003
Naydenov, D.	Analysis of the dynamic behaviour of direct methanol fuel cells	2003
Özbay, T. *	Analysis of the dynamic response of direct methanol fuel cells to changes in the feed concentrations	2005
Pfafferodt, M.	Extension of a simulation module in FEMLAB for the modelling of a solid oxide fuel cell (SOFC) in vehicular applications	2004
Radichkov, R.	Modelling and dynamic simulation of reactive distillation columns with equilibrium stage model and mass transport model	2003
Rio Fernandez, L.	Precipitation of $CaCO_3$ particles in non-ionic w/o microemulsions	2003
Seliger, B.	Modelling and dynamic simulation of an air separation unit as part of an IGCC power plant	2004

Tulashie, S.	Investigation into residue curve maps and heterogeneous kinetics of prophylacetate syntesis reaction	2005

5.4 Additional Teaching Activities

The PCP group continued to coordinate the established NaT-working project (NaT is short for “Natural Sciences and Technology”) together with the SCT group (Prof. J. Raisch). This project is funded by the Robert-Bosch-Foundation. It is an initiative to attract students from regional high schools into engineering programs at OvGU.
Furthermore, each spring and fall, the PCP group is organizing a one-week laboratory course to introduce high school students into chemical engineering.

6 Selected Memberships, Appointments, Awards

K. Sundmacher

since 1999 Full Professor for Process Systems Engineering at OvGU

since 2001 Scientific Member and Director for Process Engineering at MPI

since 2001 Editorial Board Member of Chemical Engineering and Processing

since 2001 Appointed Member of Reaction Engineering Working Party of GVC

since 2002 Appointed Member of Research Advisory Board of Karl Winnacker Institute, Frankfurt/M.

since 2003 Appointed Member of Electrochemical Processes Working Party of DECHEMA

since 2003 Appointed Member of GVC Scientific Advisory Board

since 2003 Executive Editoral Board Member of Chemical Engineering Science

2003-2004 Managing Director of MPI

since 2005 Managing Director of the Institute for Process Engineering at OvGU

L.K. Rihko-Struckmann

since 2004 Appointed Independent Expert as Evaluator in the 6th Framework Programme of the European Community

T. Schultz

2004 Best Poster Award for the Contribution “Multi-functional Unit Combining a Fuel Cell and an Enzyme Electro-Membrane Reactor: Concepts, Design, Experiments”, ICCMR-6, 6-9 July 2004, Lahnstein, Germany.

7 Selected Publications (May 2003 – September 2005)

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

Adityawarman, D., A. Voigt, P. Veit and K. Sundmacher: Precipitation of $BaSO_4$ Nanoparticles in Non-Ionic Microemulsions: Identification of Suitable Control Variables. Chemical Engineering Science **60**, 3373-3381 (2005)

Galvita, V. and K. Sundmacher: Hydrogen Production from Methane by Steam Reforming in a Periodically Operated Two-Layer Catalytic Reactor. Applied Catalysis A: General **289**, 121-127 (2005)

Hanke, R., M. Mangold and K. Sundmacher: Application of Hierarchical Process Modelling Strategies to Fuel Cell Systems – towards a Virtual Fuel Cell Laboratory. Fuel Cells **5**, 133-147 (2005)

Heidebrecht, P.: Modelling, Analysis and Optimisation of a Molten Carbonate Fuel Cell with Direct Internal Reforming (DIR-MCFC). Fortschritt-Berichte, VDI-Verlag, Düsseldorf (2005).

Heidebrecht, P. and K. Sundmacher: Dynamic 2D Model of a Crossflow Molten Carbonate Fuel Cell with Direct Internal Reforming (DIR-MCFC). Journal of the Electrochemical Society (2005a), in press.

Heidebrecht, P. and K. Sundmacher: Optimisation of Reforming Catalyst Distribution in a Crossflow Molten Carbonate Fuel Cell with Direct Internal Reforming. Industrial and Engineering Chemistry Research **44**, 3522-3528 (2005b)

Heidebrecht, P. and K. Sundmacher: Conceptual Design of Integration of Reforming and Oxidation Reaction in High Temperature Fuel Cells. Journal Power Sources **145**, 40-49 (2005c)

Huang, Y.S., K. Sundmacher, Z. Qi and E.U. Schlünder: Residue Curve Maps of Reactive Membrane Separation. Chemical Engineering Science **59**, 2863-2879 (2004)

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Research Group:

Process Synthesis and Process Dynamics (PSD)

Prof. Dr.-Ing. Achim Kienle

This report covers the period from May 2003 to September 2005.

1 Group Introduction

The research of the Process Synthesis and Dynamics group focuses on computer-aided analysis, synthesis and control of complex chemical processes. For that purpose, suitable mathematical modeling techniques as well as suitable methods and tools for model-based analysis and synthesis are developed. Special emphasis is on nonlinear dynamics, which can be the source for unexpected and surprising behavior. A thorough understanding of nonlinear dynamics is not only of scientific interest but also a necessary prerequisite for optimal design and operation of chemical processes.

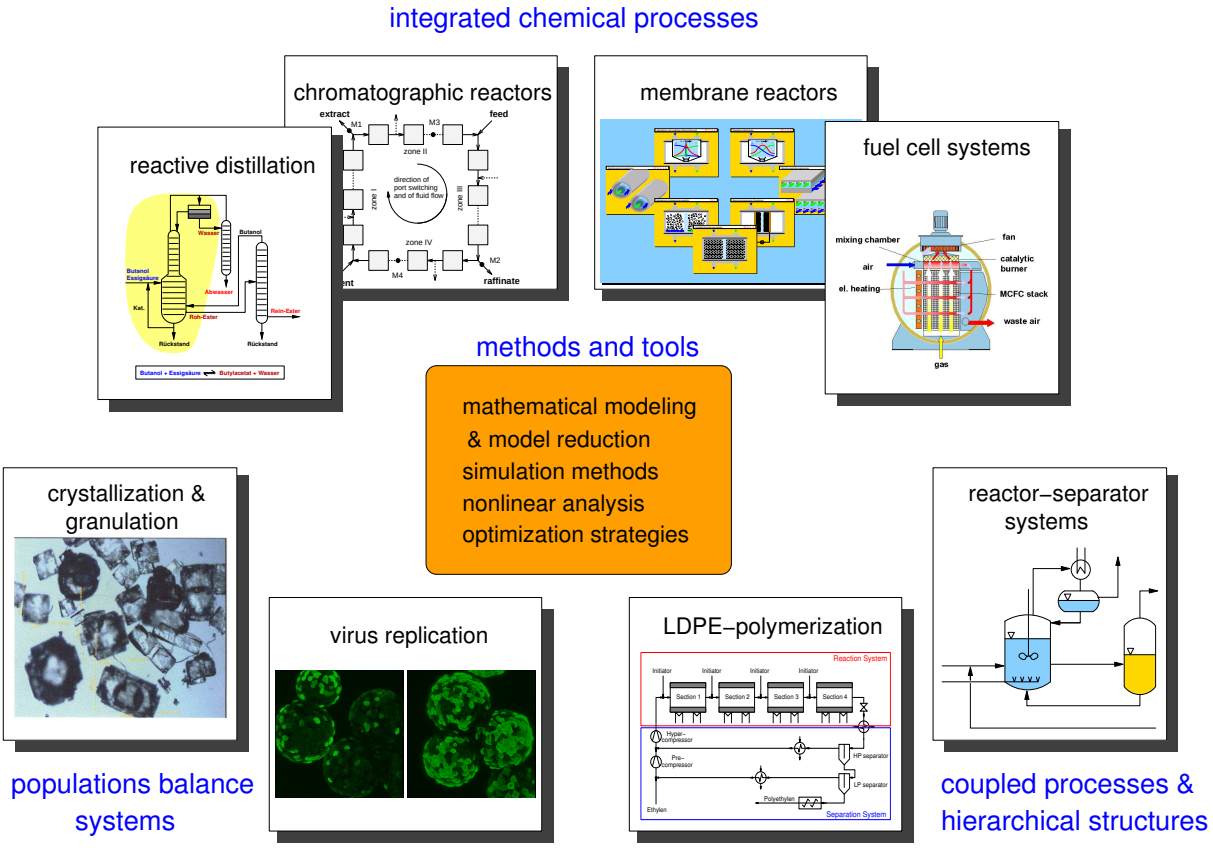


Fig. 1: Overview of the research activities of the process synthesis and dynamics group.

The above mentioned methods and tools are applied to various challenging example processes. An updated condensed overview is given in **Fig. 1**. For a detailed list of current projects the reader is referred to section 3 of this group report. Current applications include: **integrated processes** like reactive distillation processes, chromatographic reactors, membrane reactors, and fuel cell systems; **population balance systems** like crystallization processes, granulation processes, and very

recently also population balance modeling of virus replication in cell cultures; **multi unit chemical plants** consisting of reactors and separators with mass and energy recycles. The latter activity is located in the project areas **coupled processes** and **hierarchical structures**.

The research of the PSD group is well connected to most of the other groups at the MPI. With its expertise in dynamics and process control it helps to bridge the gap between physico-chemical fundamentals and process engineering on the one hand and systems and control theory on the other hand. Together with the SBI group it develops the modeling and simulation software ProMoT/Diva and supports its application within the other research groups.
During the period of this report the first generation of Ph.D. students of the PSD group have finished their work at the MPI and a new generation has started. Consequently, some research activities were stopped. Others were continued with new objectives. Further, some new research activities were established. Since 2003, the group has published about 40 articles in international scientific journals.

2 People

Head of the group

- Prof. Dr.-Ing. Achim Kienle, professor at the Otto-von-Guericke-University Magdeburg

Secretary (part-time working)

- Carolyn Apelt

Ph.D. students

- Min Sheng (since 06/2001)
- Jignesh Gangadwala (since 08/2002)
- Fan Zhang (since 04/2003)
- Stefan Schwarzkopf (since 01/2005)
- Markus Grötsch (since 03/2005)
- Michael Krasnyk (since 01/2004)
- Rusi Radichkov (since 01/2005)

Postdocs

- Michael Mangold (since 03/1998)
- Malte Kaspereit (since 01/2005)
- Gabriel Radulescu (since 02/2004)

One Postdoc (Kaspereit) and three of the Ph.D. students (Gangadwala, Krasnyk, Sheng) are funded from third parties (2x German Science Foundation (DFG), 2x Federal Ministry of Science and Research (BMBF).

Ph.D. students, who have finished their work during the period covered by this report

- Häfele (03/1998 - 12/2003)
- Waschler (09/1998 - 08/2004)
- Grüner (06/1999 - 05/2004)
- Pathath (06/1999 - 05/2004)
- Angeles (10/1999 - 03/2005)
- Schramm (08/2000 - 09/2004)
- Chebotarov (03/2001 - 02/2004)

Group members at the university

- Ilknur Disli-Uslu
- Marco Fütterer
- Günter Müller
- Frank Klose

Guests

- Prof. D. Ramkrishna, Purdue University (several visits within a joint research project funded by Humboldt Foundation)
- Amol Kulkarni (04/2004 - 03/2005, Humboldt fellow)
- Prof. S. Pushpavanam (several visits within a joint research project funded by Volkswagen Foundation and MPI)

- Prof. V. Svjatnyj (several visits within a joint research project funded by the German Ministry of Education and Research and MPI)
- Alexey Milokhov (10/2004 - 09/2005, Pro3 research fellowship)
- Kateryna Bondareva (10/2004 - 09/2005, Pro3 research fellowship)
- Andriy Chut (09/2002 - 08/2003, Pro3 research fellowship)
- Konstantin Teplynskyj (09/2002 - 08/2003, Pro3 research fellowship)
- Michael Krasnyk (09/2002 - 08/2003, Pro3 research fellowship)

3 Projects

Project Area: **Integrated Processes**

Project: **Equilibrium Theory for Integrated Reaction Separation Processes**	A unifying theory is developed for understanding and predicting the dynamic behavior of integrated reaction separation processes including reactive distillation columns, membrane reactors and chromatographic reactors, for example. It reveals inherent limitations of these processes and can be used for conceptual process design and the design of new control strategies. Practical application to chromatographic reactors is studied in joint research with the PCF group within the project *Analysis of reactive batch chromatography*. Mathematical aspects are studied in joint research with Dietrich Flockerzi from then SCT group within the project *Model reduction of integrated reaction separation processes*. More details are given in the research highlights section.			
	Scientists	**Funded by**	**Start**	**Partners**
	Grüner (finished) Kaspereit	DFG within the joint research project SFB 412 until 12/2004, MPI	2002	PCF group, SCT group

Project: Reactive Distillation	Reactive distillation integrates chemical reaction and distillation into a single processing unit. Optimal design and operation of such an integrated process can be difficult due to increased complexity. Current activities are concerned with the dynamics of processes with a potential phase split of the liquid phase and the development of new optimization strategies for the optimal design of combined reaction distillation processes also including alternative configurations like advanced side reactor concepts, for example. More details about the latter are given in the research highlights section. The first activity is a collaboration with the PCP group.			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject: Nonlinear Dynamics of Reactive Distillation Processes	Radulescu	MPI	2004	PCP group, Prof. Mahajani, IIT Bombay
Subproject: Synthesis of Combined Reaction Distillation Processes	Gangad-wala	DFG (DFG research group 468)	2002	Prof. Weismantel, Mathematics Dept., OvGU; Prof. Mahajani, IIT Bombay

Project: Membrane Reactors	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, dynamics and control of different reactor concepts.			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject: Nonlinear dynamics and control of membrane reactors	Zhang, Mangold	DFG (DFG research group 447)	2001	Members of DFG research group 447 at the OvGU

Project: High-Temperature Fuel Cells	The project's topic is an industrial 300 kW fuel cell stack located in the Magdeburg University hospital. Dynamic models of the stack as well as control strategies are developed and validated experimentally. The main activities of the PSD group within this project are the nonlinear analysis of the cell behavior as well as the development of a state estimator for the fuel cell stack. More details are given in the research highlights section.			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject: Dynamics and State Estimation of the Molten Carbonate Fuel Cell	Sheng, Krasnyk, Mangold	BMBF	2001	PCP group; Prof. Pesch, University of Bayreuth; MTU CFC Solutions; IPF-Magdeburg

Project: Low-Temperature Fuel Cells	Within this project, the PSD group focuses on the model based analysis of PEM fuel cells. The activities are part of the BMBF funded network "Model Based Design of Fuel Cells and Fuel Cell Systems: PEMDesign". The network intends to develop and to apply mathematical methods for a computer based design of PEM fuel cells, fuel cells stacks, and complete PEM fuel cell systems. The partners develop fuel cell models on different scales, starting from detailed models for electrodes and gas diffusion layers, and going from CFD models for cell stacks up to models of the total system. The activities of the MPI Magdeburg in this framework concentrate on models on the system scale that are suitable for addressing process control problems. This involves the derivation of simplified models from the partners' detailed reference models by model reduction techniques and the analysis of the nonlinear behaviour of PEM fuel cell systems.			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject: Nonlinear Model Reduction of Fuel Cell Systems	Grötsch, Mangold	BMBF	2005	ISE Freiburg; ITWM Kaisers-lautern; University of Freiburg; IWR Heidelberg; University of Karlsruhe

Project Area: Population Balance Systems

Project: Crystallization	Crystallization from solution or melt serves for the production of solids and/or for purification. In the first period, focus in this subproject was on theoretical and experimental investigation of population balance modeling and self-sustained oscillations in continuous crystallization processes. Future work will focus on nonlinear dynamics of preferential crystallization processes for enantioseparation.			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject: Nonlinear Dynamics of Crystallization Processes	Pathath (finished), NN	MPI	1999	PCF group; SCT group; ISR, University of Stuttgart

Project: Particle Formation in Fluidized Beds	Particle formation in fluidized beds includes agglomeration and granulation processes which play an important role in many special chemistry and food industry applications. Like in continuous crystallization processes instabilities may arise. Main activities in this subproject comprise theoretical and experimental investigations on population balance modeling and nonlinear dynamics in fluidized bed spray granulation processes. Experiments are done at the Otto-von-Guericke-University.			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject: Nonlinear Dynamics of Fluidized Bed Spray Granulation Processes	Radichkov	MPI	2004	Prof. Mörl, Prof. Tsotsas, Jun. Prof. S. Heinrich, Chemical Engineering Dept., OvGU; SCT group

Project: Virus Replication and Spreading in Host-Cell Populations	Together with the BPE group 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 or kinetic Monte-Carlo approaches.			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
	NN, Kienle	MPI	2004	BPE group

Project Area: Coupled Processes

Project: Nonlinear Dynamics of Reactor Separator Networks	Highly integrated chemical product plants typically involve many mass and energy recycles, which determine the dynamic behavior of these plants to a large extent. In this project the influence of these recycles is studied systematically starting from simple model systems up to industrial example processes. Impressing industrial examples include large scale acetic acid and polyethylene production plants.			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
	Häfele (finished), Waschler (finished), Zeyer	VW-Foundation until 07/2005, MPI	2001	Prof. Pushpavanam, IIT Madras; BASELL, Wesseling; Prof. Svjatnyj, TU-Donezk, Ukrania; AZOT, Sewerodonezk, Ukrainia

Project: Nonlinear Dynamics of Bio Reactors Described by Cybernetic Models	Cybernetic models of biological systems were developed by the group of Prof. Ramkrishna. They represent a macroscopic approach to model metabolic regulation. They are able to predict multiple steady states in hybridoma reactors, which were also observed in experiments. In joint research with the group of Prof. Ramkrishna the nonlinear behavior predicted by these models is investigated.			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
	Kienle	Humboldt-Foundation, MPI	2001	Prof. Ramkrishna, Purdue University, U.S.A.

Project Area: Hierarchical Structures

Project: Plantwide control of chemical processes	This project aims at the application of hierarchical concepts for designing plantwide control strategies for chemical processes. Challenging applications include the large scale acetic acid plant already mentioned above and a system of coupled distillation columns.			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
	Waschler	BMBF, MPI	2001	SCT group, Prof. Svjatnyj, TU Donezk, Ukraine, and AZOT, Sewerodo-nezk, Ukraine

Project Area: Hybrid and Discrete-Event Systems

Project: Simulated Moving Bed Processes	Simulated moving bed separation (SMB) processes gain increasing importance for the separation of pharmaceutical compounds, in fine chemistry and biotechnology. Unfortunately, optimal operation of SMB processes is highly sensitive to disturbances. Therefore, suitable control strategies are developed and tested within our subproject and new modes of operating SMB processes are explored.			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject: Control of Moving Bed Chromatographic Processes	Schramm (finished), Schwarzkopf, Kaspereit	MPI	2000	PCF group; Prof. Vande Wouwer, Faculté Polytechnique de Mons, Belgium

Project: Control of Discontinuously Operated Multi Product Plants	Multi product batch plants are used for the production of fine and specialty chemicals. In such plants different products share the same piece of equipment. The standard approach for operating multi product plants is based on recipes. This approach provides solutions, which are (i) often far from optimal and (ii) essentially open-loop and therefore sensitive wrt. unforeseen disturbances. Together with the SCT group alternative control strategies are explored.			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
	Kienle	DFG (DFG research group 468)	2002	SCT group; Members of DFG research group 468 at the OvGU

Project Area: **Network Theory**

Project: Computer Aided Modeling of Chemical Processes	This project is concerned with the development of concepts for computer aided modeling and simulation of chemical processes, their implementation within the modeling/simulation tool ProMot/DIVA, and their practical application to challenging processes investigated at the MPI. In addition, a new simulation tool DIANA is developed using modern software technologies. The development of methods and tools is done in close cooperation with the SBI group.			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject: Modular Description of Membrane Reactors	Mangold	DFG (DFG research group 447)	2001	PCP group; Members of DFG research group 447 at the OvGU
Subproject: Modeling and Simulation Tool ProMot/DIVA (DIANA)	Krasnyk, Mangold	PRO3, MPI	1998	SBI group

4 Research Highlights

4.1 Equilibrium Theory for Integrated Reaction Separation Processes

Integration of chemical reaction and separation can be very attractive compared to conventional processes where reaction and separation are carried out in different devices. Main advantage for equilibrium limited reversible reactions lies in a possible

shift of the chemical equilibrium to the product side by simultaneous separation of the reaction products, which can lead to almost one hundred percent conversion with simultaneous separation of the products. Depending on the separation principle different types of integrated reaction separation processes can be distinguished like reactive distillation columns, or chromatographic reactors, for example. A recent overview was given in (Sundmacher et al., 2005). Today, reactive distillation seems fairly well understood and has several impressing industrial applications (Sundmacher and Kienle, 2003). Compared to that, reactive chromatography is still in an early state of development. Powerful theoretical concepts for understanding and designing such processes are considered as a major key to success.

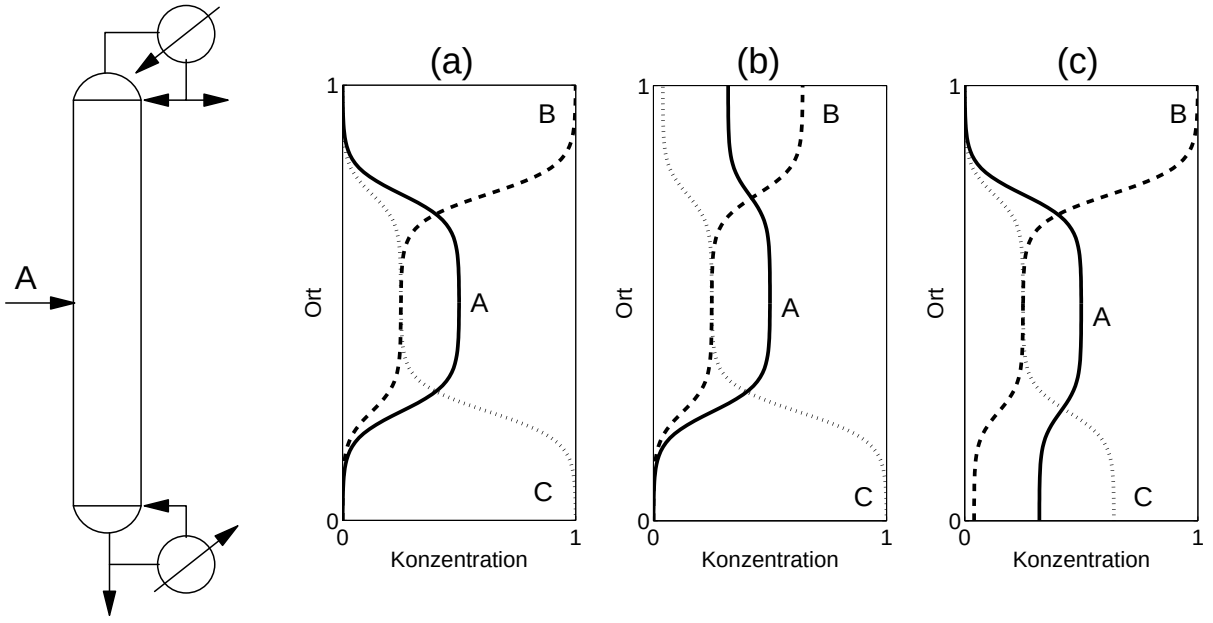


Fig. 2: Characteristic steady state concentration profiles in a reactive distillation column with a chemical reaction of type 2*A*«*B*+*C* in the liquid phase. (a) Reactant A has intermediate volatility. (b) Reactant A has highest volatility. (c) Reactant A has lowest volatility.

For that purpose, a unifying theoretical approach for analyzing and understanding the dynamics of integrated reaction separation processes was proposed (Grüner and Kienle, 2004; Grüner et al., 2005). The approach is based on the assumption of simultaneous phase and reaction equilibrium and can be viewed as an extension of the well-known equilibrium theory (Rhee et al. 1986; Rhee et al. 1989). It makes use of transformed concentration variables which were first introduced by Doherty and co-workers for the steady state design of reactive distillation processes (Ung and Doherty, 1995). The concept provides profound insight into the dynamic behavior of integrated reaction separation processes and reveals inherent bounds of feasible

operation caused by reactive azeotropy. This is illustrated in **Fig. 2** and **3** for reactions of type $2A \leftrightarrow B+C$. **Fig. 2** shows some characteristic steady state profiles in a reactive distillation column for three different cases. Only if reactant A has intermediate volatility, total conversion and total separation is possible and pure products can be obtained at the bottom and the top of the column provided the column is long enough. If reactant A has highest or lowest volatility, the profiles at the top or the bottom approach a constant state with finite concentration of all three components. This limiting state represents a reactive azeotrope, which can not be crossed due to mutual compensation of reaction and separation.

Analogous patterns of behavior are found in a fixed bed chromatographic reactor as illustrated in **Fig. 3** for a pulse injection of reactant A. Again, only if reactant A has intermediate adsorptivity, total conversion and total separation is possible and two separate pulses of pure products can be obtained provided the chromatographic column is long enough. If reactant A has highest or lowest adsorptivity the pulse in the rear or in the front will always contain a mixture of all three components, which is the perfect analogy to reactive azeotropy in reactive distillation and is readily predicted with the new theory (Grüner and Kienle, 2004).

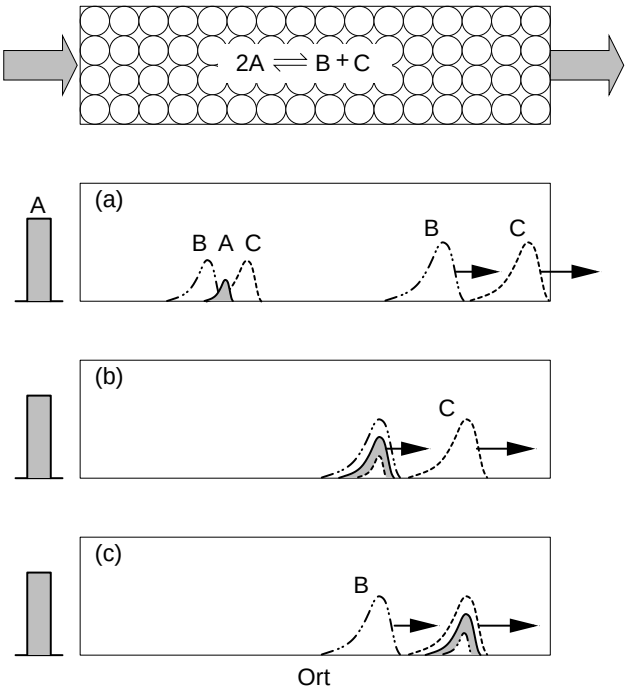


Fig. 3: Characteristic pulse patterns in a fixed bed chromatographic reactor with a chemical reaction of type $2A \leftrightarrow B+C$ in the liquid phase. (a) Reactant *A* has intermediate adsorptivity. (b) Reactant *A* has highest adsorptivity. (c) Reactant *A* has lowest adsorptivity.

Surprisingly a different type of behavior of fixed bed chromatographic reactors is observed for reactions of type $A \leftrightarrow B+C$. Here, total conversion and total separation is possible in all three cases, independent of the order of adsorptivities. This is hard to predict from intuition only and therefore clearly illustrates the usefulness of the developed theory (Vu et al., 2005).

First results of the new theory were already presented during the last evaluation and were published meanwhile (Grüner and Kienle, 2004). Recent progress was made as follows

- Extension of the concepts to multireaction systems and application to some rather complex practical application problems (Grüner et al., 2005), including the reactive separation of binaphthol enantiomers by achiral chromatography taken from (Baciocchi et al., 2002) and a two-step industrial reactive distillation process.
- Application to membrane reactors with variable flow rates due to unidirectional mass transfer accross the membrane (Grüner et al., 2005).
- Application to ester hydrolysis reactions in a fixed-bed chromatographic reactor in cooperation with the PCF group (Vu et al., 2005). The hydrolysis reactions were carried out with water in excess. Under these conditions, the behavior is equivalent to reactions of type $A \leftrightarrow B+C$ discussed above. In the concentration range under consideration the reactant (ester) has the highest adsorptivity. Nevertheless, total conversion and total separation is possible as predicted by the theory. This is in agreement with experimental results of the PCF group illustrated in **Fig. 4.**

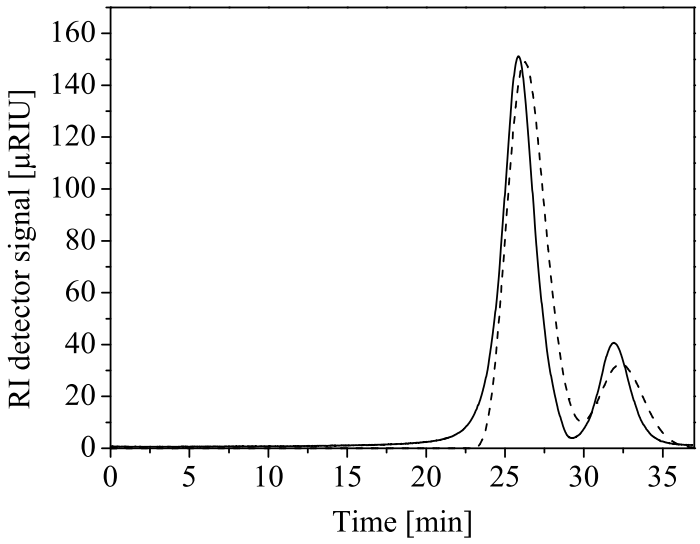


Fig. 4: Experimental (solid line) and simulated elution profile (dashed line) for MF hydrolysis taken from (Vu et al., 2005).

Furthermore, the influence of finite reaction kinetics and axial dispersion was studied using a rate model. From these investigations a two step design procedure for chromatographic fixed-bed reactors was proposed. In a first step equilibrium theory is used to check whether total conversion and total separation is possible for any column length. Afterwards, the rate model is used to determine the column length required to achieve the desired purities.

- Mathematical aspects have been treated by D. Flockerzi from the SCT group. These comprise the selection of a suitable set of transformed variables from different choices and a mathematical proof that the transformation is bijective.

Current work is concerned with an extension of the theory to account for

- heat effects
- variable flow rates due to nonequimolar reactions and
- finite reaction and mass transfer kinetics

which have been neglected in a first step. Interesting new applications are seen in the field of sorption enhanced gas phase reactions. Experimental work in cooperation with the PCF group will also be extended.

4.2 Synthesis of Combined Reaction Distillation Processes

Within the DFG research group FOR 468 new optimization strategies for combined reaction distillation processes were developed in joint research with the Discrete Optimization Group of Prof. Weismantel from the Otto-von-Guericke-University

Magdeburg. Typical examples for combined reaction distillation processes include reactor separator recycle systems, reactive distillation columns or advanced side reactor concepts, which have triggered great interest in the community due to their flexibility. Which of these options the best is, strongly depends on the physical and chemical properties of the reaction systems and the constraints (costs, desired production rates etc.). Minimization of a total annualized cost of some suitable superstructures including the relevant process candidates can provide a suitable platform to determine the optimal design. However, this class of optimization problems is difficult to solve. They are usually highly nonlinear and comprise continuous as well as discrete decision variables leading to a mixed-integer nonlinear program (MINLP).

For the solution of the resulting optimization problems local MINLP optimization methods are available and have been applied with some success to reactive distillation processes (Stein, 2003). Main advantage of this approach is its ability to efficiently handle large problems. However, due to the nonlinearity of the problem only local optima can be found. To overcome this problem in engineering applications often stochastic optimization methods like genetic algorithms are applied. These are usually computationally much more expensive. Further, due to the probabilistic approach they also cannot provide any guarantee for global optimality.

To overcome the problems associated with both approaches, a new combined strategy was proposed (Gangadwala et al., 2005a; Gangadwala et al., 2005b). In a first step, standard local MINLP optimization methods are applied to obtain a quick preliminary ranking of suitable process candidates. Afterwards, the result is checked by a new global approach. It is based on linear relaxations of the feasible region as illustrated in **Fig. 5**

Since, the solution set of the linear relaxation indicated by the shaded region in **Fig. 5** contains all feasible solutions of the original nonlinear problem indicated by the solid line in **Fig. 5**, the minimum cost of the linear relaxation provides a lower bound to the minimum costs of the original problem. The bound can be refined successively as indicated in **Fig. 5**.

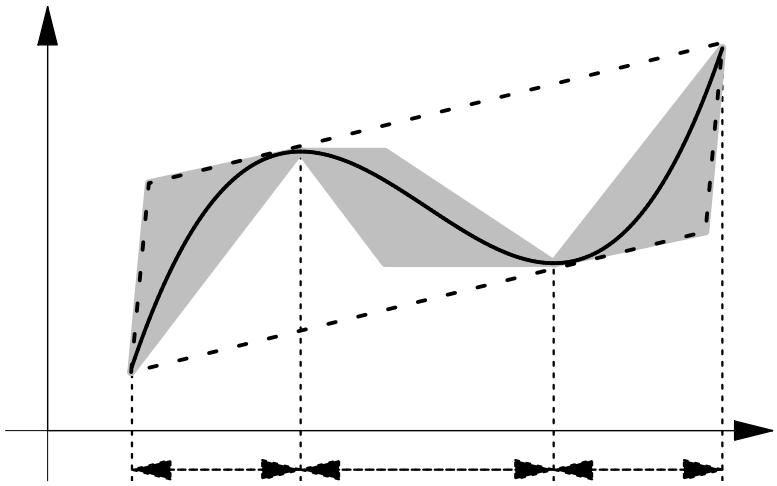
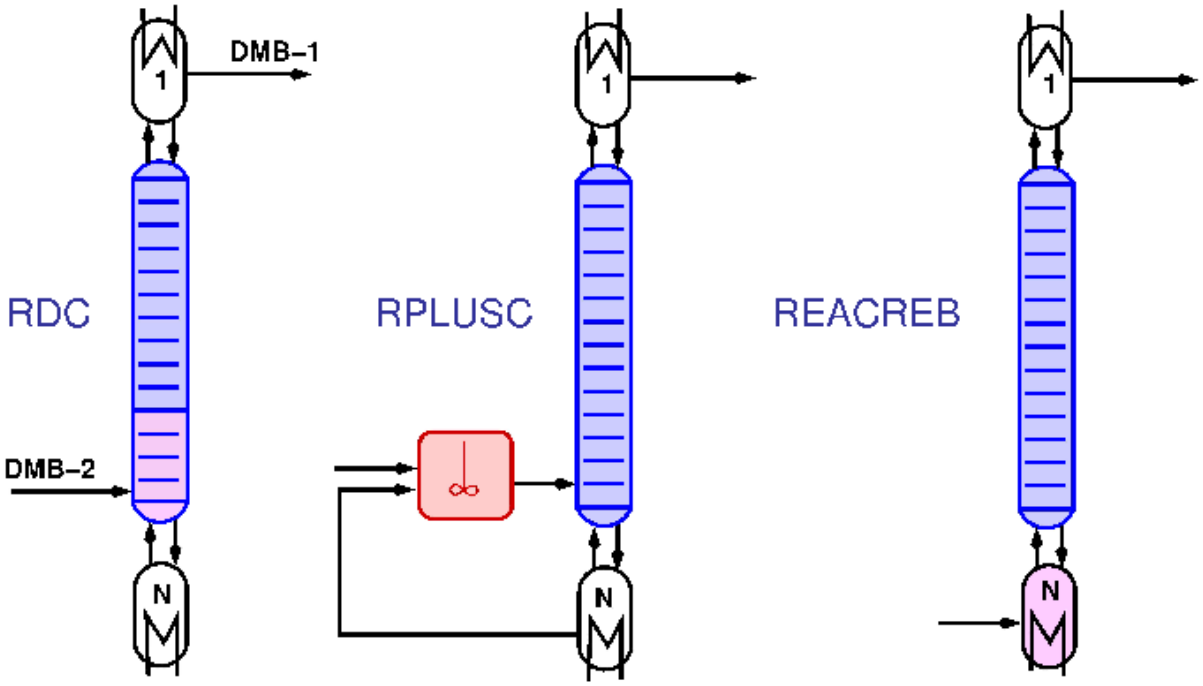


Fig. 5: Linear relaxations.

As an innovative benchmark problem isomerization of 2,3-Dimethylbutene-2 (DMB-2) to 2,3-Dimethylbutene-1 (DMB-1) was considered (Gangadwala et al., 2005a; Gangadwala et al., 2005b). DMB-1 is used as a key component for the production of musk fragrances and insecticides. The difference in boiling point temperatures of the two isomers is significant. Further, the rate of reaction is sufficiently high for the operating conditions usually employed in a distillation column, so that reactive distillation seems to be a suitable process candidate. Other options as illustrated in **Fig. 6** are a reactor separator system with recycle or a reactor with a nonreactive distillation column on top, which was already described in the patent literature (Kent et al., 1989). Kinetics was measured for an Amberlyst 15 catalyst and a suitable mathematical model was formulated.

Results of the local MINLP optimization are shown in the table of **Fig. 6**. They indicate that reactive distillation is the best and the solution described in the patent literature by far the worst option under the given constraints. The latter was therefore not considered any further. With the new approach it was now shown that the lower bound for the second best is always greater than the local minimum of the best solution and thereby proven that reactive distillation is superior to the reactor separator configuration.

The approach is currently limited to relatively simple systems. Future work will focus on an extension to more complex systems. A typical example, which was already treated in some detail in cooperation with the group of Prof. Mahajani from IIT Bombay is the production of butyl acetate (Gangadwala et al., 2003; Gangadwala et al., 2004; Gangadwala and Kienle, 2005).



	Total Cost	RR	N	N_R	feed tray
RDC	183000	13.99	24	20-23	23rd
RPLUSC	187000	14.57	22	-	20th
REACREB	302000	32.51	21	21st	21st

Fig. 6: Production of DMB-1 by isomerisation from DMB-2 by combined reaction distillation processes. Process candidates and results from a local MINLP optimization.

4.3 Nonlinear Analysis and State Estimation of High Temperature Fuel Cells

Since 2002, the PSD group has studied the dynamic behaviour of a molten carbonate fuel cell (MCFC) system within a joint research project with the PCP group and two other partners from academia and industry. The project is funded by the German Ministry for Education and Research. Focus is on a prototype of an industrial MCFC system which is illustrated in **Fig. 7** and which is used as a power supply system at the Magdeburg university hospital. This prototype is called HotModule due to the high temperatures in MCFC systems.

High temperature fuel cells are a promising new technology for the decentralized generation of electricity and heat, because in comparison to conventional processes they have an unsurpassed electrical efficiency. For the process operation of high

temperature fuel cells, the temperature management inside the cell stack is crucial. Too low temperatures as well as too high temperatures and strong spatial temperature gradients have to be avoided in order to keep the system in a safe and efficient state. Therefore, the activities of the PSD group in this project focus on understanding the nonlinear thermal behavior of the system on the one hand, and on state estimation of stack temperatures on the other hand.

Fig. 7: The 200 kW MCFC stack HotModule at the Magdeburg university hospital operated by IPF Magdeburg and investigated within a joint research project funded by the BMBF.

It was found that the temperature dependence of the electrolyte's electrical conductivity may cause thermal instabilities and high temperature peaks (Mangold et al., 2004a; Mangold et al. 2005). These results are presented in more detail in the PCP group report.

The development of a state estimator for the HotModule is motivated by the fact that the system offers only very limited online measurement information. Only the outlet temperatures of the gases and the cell voltage can be measured continuously; in addition, a gas chromatograph measures the composition of the gases at anode and cathode outlet in intervals of about one hour. The state estimator is to provide the operating personal with additional information on the state of the system, e.g. on the temperatures, the gas composition, and the electrical potential fields inside the cell stack. As a starting point, a spatially 2D model of the system is used, which was developed by P. Heidebrecht from the PCP group. This model was validated in experiments and was found to describe the HotModule with reasonable accuracy. However, it is too complex to serve as a basis for a state estimator. Therefore, in a

first step, a reduced model was developed using Galerkin's method in combination with the Karhunen-Loève decomposition technique (Mangold and Sheng, 2004). The resulting differential algebraic system reduces the system order as well as the required CPU time for the numerical solution by a factor of about 100 compared to the spatially discretized reference model. The simulation results obtained with the reduced and with the reference model agree well, as can be seen from **Fig. 8**.

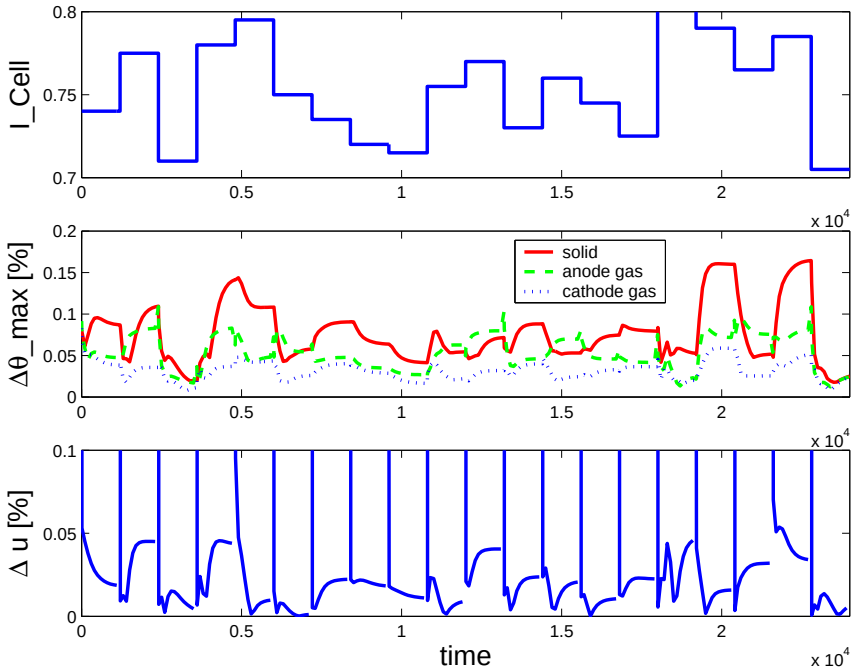


Fig. 8: Model reduction of a 2D MCFC model (Grötsch et al., 2005). Comparison between the reduced model's response to a randomly varying cell current and the reference model's response; top diagram: dimensionless cell current used as input signal for the models; middle diagram: maximal relative error of the temperatures in the stack; bottom diagram: maximum voltage error.

Based on the reduced model, the observability of the system was investigated. The system was found to be locally observable, if the cell voltage and the outlet temperatures of the gases are measured. This means that the state estimator can replace the slow and expensive measurement of the gas composition by the gas chromatograph. Finally, a Luenberger observer (Mangold et al., 2004b) and an extended Kalman filter (Grötsch et al., 2005) were designed using the reduced model and tested in simulations. Especially the extended Kalman filter can be tuned easily and proves to have a good convergence behavior for different operation points as shown in **Fig. 9**. Currently, the extended Kalman filter is tested with real measurement data from the HotModule.

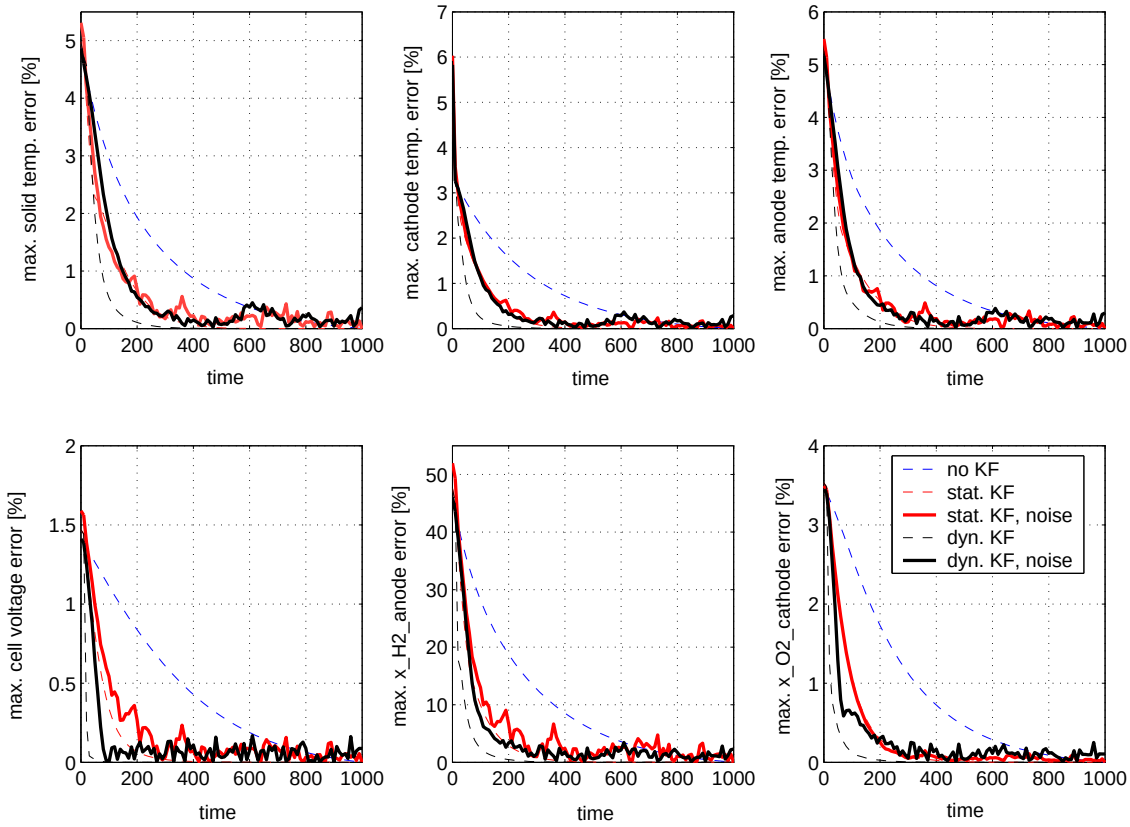


Fig. 9: Convergence behaviour of a static and a dynamic Kalman filter for the HotModule (Grötsch et al., 2005); simulation results with artificial noise are used as virtual measurement data.

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

5.1 Teaching Activities

- Regular teaching activities of A. Kienle at the Otto-von-Guericke-University Magdeburg involve
  - a course on nonlinear process dynamics
  - a course on process modeling
  - a course on process identification
  - a basic course on control
  - a course on chemical process control
  - a course on modeling and control in medicine
  - practical training
- M. Mangold is giving a course on process and systems engineering at the Otto-von-Guericke-University

- F. Klose is involved in an introductory course on chemistry for chemical process engineers at the Otto-von-Guericke-University

5.2 Diploma Projects, finished during the period covered by this report

- P. Alvarez Blanco, Analysis of Autonomous Periodic States in Coupled Fixed-Bed Reactors, 2003.
- A. Linhart, Model reduction of Chemical Processes using Slow Manifolds, 2003.
- V. Krishna, Stability of Reactor Separator Systems, 2004
- V. K. Surasani, Isothermal and Nonisothermal Analysis of Diffusion Processes in Inorganic Membranes, 2005.
- I. Farooq, Investigations of Coupled Heat and Mass Transfer in Tubular Inorganic Membranes, 2005.
- M. Grötsch, Development and Test of an Extended Kalman Filter for a Molten Carbonate Fuel Cell, 2005.
- F. Buhrandt, Modeling and Simulation of Thermally Coupled Fixed-Bed Reactors, 2005.

5.3 Ph.D. Projects, finished during the period covered by this report

1. R. Waschler, Nonlinear Dynamics of Chemical Processes with Recycles, 2005.
2. H. Schramm, New Modes of Operation and Control of Chromatographic Simulated Moving Bed Processes, 2005.
3. O. Angeles-Palacios, Development and Application of a Library of Elementary Model Entities for Vapour-liquid Chemical Processes, 2005.
4. M. Häfele, Nonlinear dynamics and optimal operation of a plant for the production of low density polyethylene, 2005.
5. P. Pathath, Nonlinear Oscillations in Continuous Crystallization Processes, 2005.
6. S. Grüner, Nonlinear Wave Propagation in Reaction Separation Processes - Theory and Applications, 2005.

5.4 Current Ph.D. Projects

1. M. Sheng, Low-Order Dynamic Models for Fuel Cells.
2. J. Gangadwala, Synthesis of Combined Reaction Distillation Processes.

3. F. Zhang, Nonlinear Dynamics and Dynamic Operation of Membrane Reactors.
4. S. Schwarzkopf, Low-Order Dynamic Models for the Control of Separation Processes.
5. M. Grötsch, Model-Based Control of PEM Fuel Cell Systems
6. M. Krasnyk, Methods and Tools for Nonlinear Analysis of Complex Chemical Systems.
7. R. Radichkov, Nonlinear Dynamics of Particulate Processes.

5.5 Current Habilitation Projects

- M. Mangold, Modular Modelling, Dynamics and Control of Membrane Reactors and Fuell Cells.
- F. Klose, Reactor Concepts for Catalytic Oxidation of Hydrocarbons.

6 Future Directions

Some of the future directions were already indicated in the research highlights section. In addition, further potential for the future development of the PSD group in the next two years is seen in the following fields:

- **Modeling and dynamics of population balance systems.** Theoretical and experimental results on population balance modeling and self-sustained oscillations for continuous crystallization processes were obtained. We plan to extend this work in cooperation with the PCF group to preferential crystallization of enantioseparation processes. Focus there is on uniqueness and stability of cyclic steady states.

  Another interesting application which is studied in cooperation with Jun. Prof. Heinrich from the Otto-von-Guericke-University is concerned with uniqueness and stability of steady states in continuous fluidized bed spray granulation. This process shows amazing parallels to continuous crystallization.

  For the numerical analysis of population balance systems advanced numerical methods and tools have to be developed.
- **Modeling and dynamics of biological systems.** Research on population balance modeling of virus replication in cell cultures of vaccine production processes was initiated in cooperation with the BPE group and will be further intensified. Another interesting field of research is concerned with the

nonlinear dynamics of biological systems. First steps in this direction were already made together with Prof. Ramkrishna from Purdue University.

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

Research Group:

Systems and Control Theory (SCT)

Prof. Dr.-Ing. Jörg Raisch

This report covers the period from 1 May 2003 to 31 July 2005.

1 Group Introduction

The Systems and Control Theory Group cooperates closely with the research group on Systems Theory in Engineering ("Lehrstuhl für Systemtheorie technischer Prozesse") at the neighbouring Otto-von-Guericke University. Both groups are headed by Jörg Raisch, who holds a full time (C4) professorial position at the Otto-von-Guericke University, and has also been appointed external scientific member (Auswärtiges Wissenschaftliches Mitglied) by the Max Planck Society. Both groups' research interests are – not surprisingly – in the area of Systems and Control Theory (SCT). Roughly speaking, the subject of SCT 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 allowing scientists and engineers with extremely diverse technical backgrounds to communicate and hence to generate considerable synergy effects. This general perspective of SCT is reflected in our group's 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 Max-Planck-Institute for Dynamics of Complex Technical Systems and to strengthen interdisciplinary research at the Otto-von-Guericke University.

2 Group Members and Funding

2.1 SCT group members

As of 1 August 2005, the group consists of the following members:

Ph.D. students and Postdocs:

Ivan Angelov (since July 1, 2003)

Nils-Otto Negård (since April 1, 2002)

Robert Salbert (since December 1, 2004)

Brahmdatta Mishra (since July 1, 2000)

Thomas Schauer (since December 1, 2001)

Steffen Sommer (since April 1, 2004)

Danjing Li (since July 15, 2001)

Senior Researcher:

Dietrich Flockerzi (joined SCT group October 1, 2003)

Secretaries:

Christiane Püschel (since August 1, 2000, currently on maternal leave)

Janine Holzmann (since February 1, 2004)

Group leader:

Jörg Raisch (since March 1998), Professor at OvG University Magdeburg since Sep. 2000 and External Scientific Member of the Max Planck Institute for Dynamics of Complex Technical Systems since Feb. 2002

2.2 Funding

Funding sources for Ph.D students, postdocs and senior researchers of MPI and University research groups are shown in the following table. It indicates that currently less than 25 % of our overall funding is from the MPI, with the rest evenly split between University and third party sources.

Tab. 1: Funding Sources

Max Planck Institute	OvG University	Third Party Funding
I. Angelov (Ph.D. scholarship)	C. Conradi (BAT II a)	V. Azhmyakov (BAT II a)
D. Flockerzi (BAT I a)	S. Geist (BAT II a)	B.V. Mishra (Ph.D. scholarship)
D. Li (BAT II a, 50 %)	D. Gromov (BAT II a)	N.-O. Negård (BAT II a)
T. Schauer (BAT I b)	J. Raisch (C4)	R. Salbert (BAT II a)
S. Sommer (postdoc scholarship)	G. Reißig (C1)	J. Stanczyk (BAT II a)
		K. Wulff (BAT II a)

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 intended to structure the overall research effort at the Max Planck Institute and to encourage cooperation between the Institute's groups. In the following, we provide a list of our projects, including information on cooperating partners and, if applicable, external funding sources. More detailed information on a small number of representative projects can be found in Section 4.

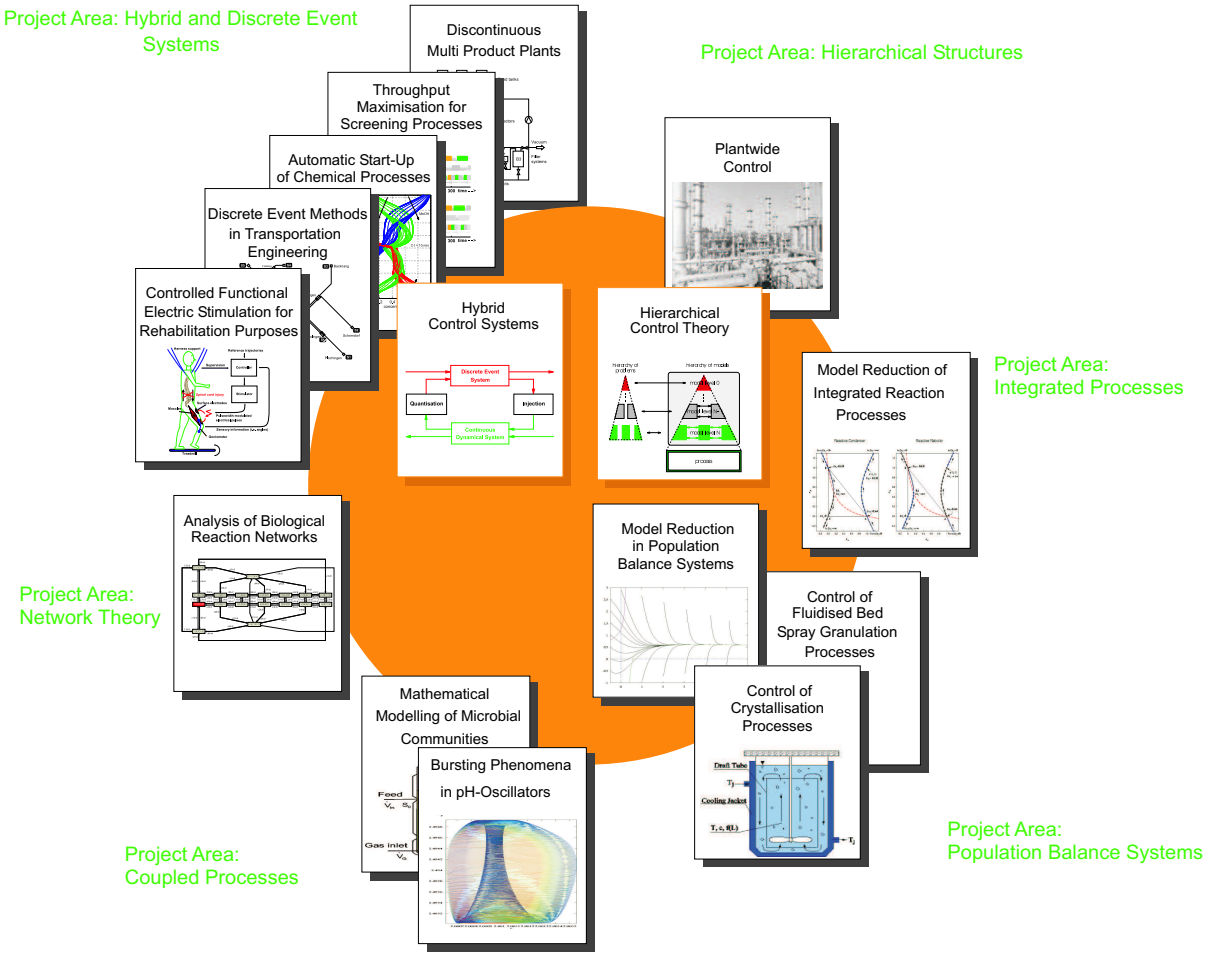

Fig. 1: Survey of research projects

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. Compared to the last status report, the number of such projects has increased significantly.

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. Although such systems are ubiquitous in engineering (and elsewhere), a generally feasible solution method does not yet exist. We follow an approach that is based on “safe” discrete approximations of continuous components [1]. This approach translates the overall hybrid problem into a purely discrete one, which can subsequently be solved using established methods from discrete-event systems theory. Our current research focuses on ways to handle intrinsic complexity problems by, e.g., imposing a hierarchical control structure [2] or by employing specification dependent abstraction refinement [3]. Another focus is the combination of abstraction-based supervisory control and optimal switching based on continuous measurement information [4, 5, 6].
Researchers:	J. Raisch, D. Gromov (OvGU), S. Geist (OvGU), V. Azhmyakov (OvGU)
Partners:	Universität Erlangen (T. Moor), Melbourne University (J. Davoren), University of Cagliari (A. Giua, C. Seatzu)
Funding:	DFG, DAAD (Vigoni program), EU-HYCON, OvGU

Project:	**Throughput Maximisation 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 maximisation) sequence and timing for all operations during a screening run [7, 8, 9, 10]. Similar problems of throughput

	maximisation arise in other laboratory automation contexts, and one such problem is currently being investigated with a partner from industry.
Researchers:	K. Wulff (OvGU), J. Raisch
Partners:	CyBio AG, BASF AG, Mathematics Dept. OvGU (R. Weismantel)
Funding:	KM-LSA, BASF AG
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. We applied it successfully to analyse the suburban train network of Stuttgart [11]. It can also be used for online rescheduling and, in combination with suitable continuous control, in a hierarchical feedback scheme for the overall control of transportation networks [12, 13].
Researchers:	D. Li, J. Stanczyk (OvGU)
Funding:	MPI

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 linearised model is therefore not adequate for control synthesis. We have investigated two approaches that are based on our group's work on hybrid systems: (i) if specifications are "coarse" enough to be formalised as discrete dynamic models, the problem can be addressed using abstraction-based methods. This has been demonstrated for a two-column distillation system [14]. (ii) If specifications are continuous, we apply a hierarchical scheme, where a discrete high-level controller switches between suitable continuous low-level controllers. In cooperation with the PCP group, this is currently being applied to the start-up of a reactive distillation column.
Researchers:	S. Sommer, A. Itigin (Stuttgart University), J. Raisch
Partners:	Stuttgart University (A. Itigin), PCP Group (Z. Qi, K. Sundmacher)
Funding:	MPI

Project:	**Control of Discontinuously Operated Multi Product Plants**
Abstract:	Control of discontinuously operated multiproduct plants is a highly nontrivial hybrid control problem. In practice, recipe-based approaches prevail. They provide solutions, which are (i) often even nominally far from optimal and (ii) open-loop and therefore extremely sensitive to unforeseen disturbances [15]. We investigate an alternative control strategy, where complexity of the overall hybrid control synthesis problem is mitigated by imposing a hierarchical control architecture [16, 17].
Researchers:	B. V. Mishra (OvGU), J. Stanczyk (OvGU), S. Geist (OvGU), J. Raisch
Partners:	PSD Group (A. Kienle), Universität Erlangen (T. Moor),
Funding:	DFG (DFG-Forschergruppe 468), Pro3, EU-HYCON, OvGU

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 and cycling [18, 19]. Depending on the degree of disability, the goal may be temporary assistance, e.g. during re-learning of gait, or permanent replacement of lost motor functions (neuro-prostheses). In the context of control, the most challenging aspects are the interaction between FES and voluntary muscle activity [20] and the complexity of neuro-musculoskeletal systems. Another challenge is 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.
Subproject:	**Nonlinear Modelling, Identification and Robust Control of Electrically Stimulated Muscles**
Researchers:	T. Schauer, N.-O. Negård
Partners:	University of Bergamo (F. Previdi), University of Glasgow (K. Hunt)
Funding:	MPI

Subproject:	**Electromyography-based control of FES in the Rehabilitation of Hemiparetic Patients**
Researchers:	T. Schauer, R. Salbert, N.-O. Negård
Partners:	Median Klinik NRZ Magdeburg (P. Schoenle), Median Klinik Berlin (S. Hesse), Otto-von-Guericke University – Dept. Of Medicine (F. Awiszus), Haynl-Elektronik GmbH Schönebeck
Funding:	BMBF, MPI
Subproject:	**Control of FES-assisted Gait Training**
Researchers:	T. Schauer, N.-O. Negård, R. Salbert
Partners:	Median Klinik NRZ Magdeburg (P. Schoenle), Median Klinik Berlin (S. Hesse), Hedon-Klinik Lingen (T. Mokrusch), HASOMED GmbH Magdeburg, Krauth & Timmermann GmbH Hamburg
Funding:	MPI
Subproject:	**Development of Mobile and Stationary FES-cycling Systems with Motor Assist**
Researchers:	T. Schauer, N.-O. Negård
Partners:	Hasomed GmbH, Median Klinik NRZ Magdeburg, University of Glasgow, Politecnico di Milano (G. Ferrigno)
Funding:	BMBF

Project Area: Network Theory

Project:	**Analysis of Biological Reaction Networks**
Abstract:	Cellular functions are realised 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. Methods include the construction of “safe'' approximating automata and, more recently, the 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. First results are reported in [21].
Researchers:	C. Conradi (OvGU), J. Raisch

Partners:	SBI Group (J. Saez-Rodriguez, E.-D. Gilles), ETH Zürich (J. Stelling), Rutgers University (E. Sontag)
Funding:	OvGU

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 focuses on 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 [2, 17]. Currently, we are interested in characterising achievable performance for specific control architectures.
Researchers:	D. Gromov (OvGU), J. Raisch
Partners:	Univ. Erlangen (T. Moor), Melbourne University (J. Davoren)
Funding:	OvGU, application for DFG funding submitted

Project:	**Plantwide Control in Chemical Engineering**
Abstract:	This project aims at applying hierarchical concepts to design a plantwide control strategy for an acetic acid production plant in Sewerodonetsk, Ukraine. A complex dynamic plant model has been developed by the PSD Group and is being validated through experimental data. Several aspects make the problem extremely demanding from a control point of view: the model is high-order and nonlinear, it reflects material recycles between different parts of the plant, and its structure changes instantaneously after the occurrence of certain internal events (e.g. phase splits).
Researchers:	A. Kienle (PSD Group), N.N.
Partners:	PSD Group, AZOT Sewerodonetsk
Funding:	OvGU

Project Area: Population Balance Systems

Project:	**Model Reduction of Population Balance Dynamics**
Abstract:	Population balance models are complex infinite-dimensional systems. The interaction of hyperbolic partial differential equations with ordinary differential equations involving integral terms often exhibits a low-dimensional dominant behaviour. In this new project, we will investigate whether this can be related to the existence of inertial manifolds or intrinsic low-dimensional manifolds.
Researchers:	D. Flockerzi
Partners:	PCP group
Funding:	MPI

Project:	**Control of Crystallisation Processes**
Abstract:	In the chemical and pharmaceutical industries, crystallisation 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 investigated robust stabilisation and disturbance rejection for continuously operated crystallisers using infinite-dimensional H_∞ feedback synthesis techniques [22]. Our current focus is on trajectory planning and feedback control for batch crystallisers. 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 [23, 24, 25], and how to design feedback control to track the chosen trajectory in the presence of model errors and disturbances [26]. At present, we investigate how to extend this approach to preferential crystallisation problems, which are used for the separation of enantiomers [27, 28].
Researchers:	I. Angelov, J. Raisch
Partners:	PCF Group (M. P. Elsner, A. Seidel-Morgenstern)
Funding:	MPI, application for DFG funding submitted

Project:	**Control of Continuous Fluidised Bed Spray Granulation**
Abstract:	In this new project, we address both set-point control and start-up problems for a continuous fluidised bed spray granulation process. For set-point control, we use infinite-dimensional H_∞ methods, which we

	have successfully applied before to continuous crystallisation control problems [22]. For start-up, we adapt hierarchical abstraction-based methods [2, 14] that have been developed in two of our other research projects.
Researchers:	N.N., J. Raisch
Partners:	OvGU (S. Heinrich)
Funding:	application for DFG funding submitted

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. Extensions into several directions, e.g. to homogeneous reactions with nonideal liquid phase, to heterogeneously catalysed reactions and eventually to PDE-models of separation columns, will be studied within this project.
Researchers:	D. Flockerzi
Partners:	PSD group
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 [29].The full three-species-dynamics will be investigated theoretically and experimentally.
Researchers:	D. Flockerzi
Partners:	BPE group (U. Reichl), OvGU (J. Schmidt), Univ. Tübingen (K. P. Hadeler)
Funding:	MPI

Project:	**Bursting Phenomena in pH-Oscillators**
Abstract:	Our method of quasi-integrals for the reduction of chemical reaction networks has been successfully applied to pH-oscillators [30, 31]. The transition from simple periodic to bursting behaviour and the periodic-chaotic progression of mixed-mode states could be resolved at least numerically. In parts, the numerical resolution still needs to be supported by rigorous proofs. On the other hand, since the quasi-integral reduction method is not restricted to mass-action kinetics, the underlying bifurcation routes from simple to complex behaviour will be elucidated for a broad spectrum of reaction mechanisms.
Researchers:	D. Flockerzi
Partners:	OvGU (S. C. Müller)
Funding:	MPI

4 Research Highlights

In the following, we will 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 a project on hierarchical control. On the application side, we include two projects addressing problems in chemical engineering and systems biology. Both application projects have been investigated in close collaboration with other groups at the MPI.

4.1 Hierarchical Control

Complexity represents a major concern in many control problems, and it is common engineering knowledge that suitable decomposition techniques form a necessary ingredient for any systematic treatment of complex control problems. Hierarchical approaches, where several control layers interact, are a particularly attractive way of

problem decomposition as they provide an extremely intuitive control architecture. Complexity problems are especially pronounced for hybrid control synthesis problems, and this has motivated the particular line of research described below.

In cooperation with T. Moor from Erlangen University and J. Davoren from Melbourne University, we have developed a hierarchical control synthesis framework which is general enough to encompass both continuous and discrete levels. Unlike heuristic approaches, our synthesis framework guarantees that the control layers interact "properly" and do indeed enforce the overall specifications for the considered plant model. Its elegance stems from the fact that the specifications for lower control levels can be considered suitable abstractions which may be used as a basis for the synthesis of high-level controllers. Formulating specifications for the lower control levels may rely on engineering intuition. In fact, our approach allows to encapsulate engineering intuition within a formal framework, hence exploiting positive aspects of intuition while preventing misguided aspects from causing havoc within the synthesis step. To keep exposition reasonably straightforward, we focus on the two-level control architecture shown in Fig. 2. Low-level control is implemented by a layer

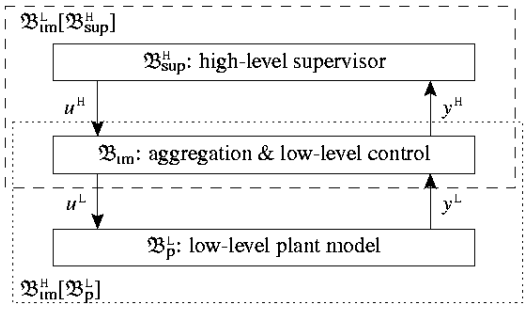

Fig. 2: Two-level control architecture

communicating with the plant via low-level (physical) signals u^L and y^L and with the high-level supervisor via high-level (abstract) signals u^H and y^H. Apart from implementing low-level control mechanisms corresponding to high-level commands u^H, the intermediate layer aggregates low-level measurement information y^L to provide high-level information y^H to the high-level supervisor. Aggregation may be both in signal space and in time, i.e. the time axis for high-level signals may be "coarser" than for low-level signals. We denote the behaviours of low-level plant model, intermediate layer and high-level control by B^L_P, B_{im}, and B^H_{sup}, respectively. Note that in this scenario, B^L_P and B^H_{sup} are behaviours on W_L and W_H, while B_{im} is a

behaviour on $W_H \times W_L$, where $W_H := U_H \times Y_H$ and $W_L := U_L \times Y_L$ represent the high and low-level signal sets.

The control synthesis task then is to come up with a two-level controller $(B_{im}, B^H_{\sup})$ such that (i) the overall controller $B^L_{im}\left[B^H_{\sup}\right]$ restricts the plant behaviour to a given specification behaviour B^L_{spec}, (ii) the overall controller is admissible to the plant model, (iii) the high-level controller is admissible to $B^H_{im}\left[B^L_P\right]$ i.e., the plant under low-level control. In this context, admissibility of a controller means the following: the controller respects the plant's input/output structure, and any trajectory that plant and controller have "agreed on" in the past can be extended into the future.

In [2,17], we have discussed which properties of plant model and control layers will guarantee that admissibility conditions (ii) and (iii) hold. In particular, we have shown that very weak requirements on plant model and high-level supervisor will suffice for any combination of the intermediate layers shown in Fig. 3. In fact, these types of

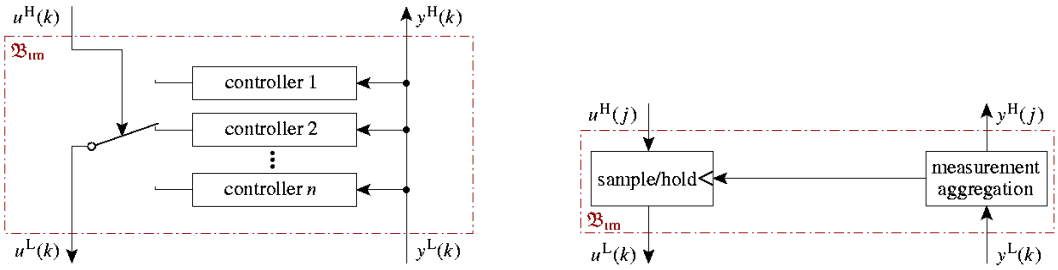

Fig. 3: Intermediate layers implementing switching between low-level controllers (left) and measurement aggregation in time and signal space (right).

intermediate layers are precisely the ones that are needed in most application problems. In [2,17], we have also proposed a bottom-up design procedure for B_{im} and $B^H_{\sup}$: in a first step, the intended relation between high-level and low-level signals is formalised by a specification B^{HL}_{spec}. Clearly, it is in this step where engineering intuition is "embedded" into our formal framework. In a second step, using standard control synthesis methods, we need to design the intermediate layer such that the specification B^{HL}_{spec} holds. In a third step, synthesis of high-level control is addressed. It can be based on a suitable abstraction of $B^H_{im}\left[B^L_P\right]$, the plant model under low-level control, and a suitable translation of B^L_{spec} into high-level specifications. In particular, we propose to use the high-level projection of B^{HL}_{spec} as an abstraction of the plant

model under low-level control. If both synthesis steps succeed, we can guarantee that the resulting overall controller indeed enforces the original specifications B^L_{spec} for the underlying plant model B^L_{spec}.

In [17], we have also discussed how the remaining degrees of freedom can be used to address performance optimisation issues. The potential of our approach has been demonstrated by applying it to a multiproduct batch control problem, where the specification is to produce the desired product volumes with minimal cost subject to quality and safety constraints [16, 17].

4.2 Control of Batch Crystallisation Processes

In the chemical and pharmaceutical industries, crystallization is used for the production of solids from liquids. Supersaturation, which is generated either by cooling or by evaporation of solvent, represents the driving force for the two processes dominating crystallisation dynamics: nucleation, i.e. the production of new crystals, and crystal growth. Furthermore, phenomena such as attrition, breakage and agglomeration of crystals may occur.

Since nucleation, growth, etc. take place simultaneously, crystals of different sizes are present in a crystalliser. Product quality 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. Hence, commonly accepted models for crystallisation processes are relatively complex, nonlinear, infinite-dimensional systems. This makes model-based controller synthesis a challenging task. In the past, we investigated robust stabilisation and disturbance rejection for continuously operated crystallisers using infinite-dimensional H_∞-feedback synthesis techniques, e.g. [22].

Our current focus is on trajectory planning and feedback control for batch crystallisers. In batch mode, the crystalliser is initially filled with undersaturated solution. Supersaturation is generated by gradual cooling (Fig. 4). 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.

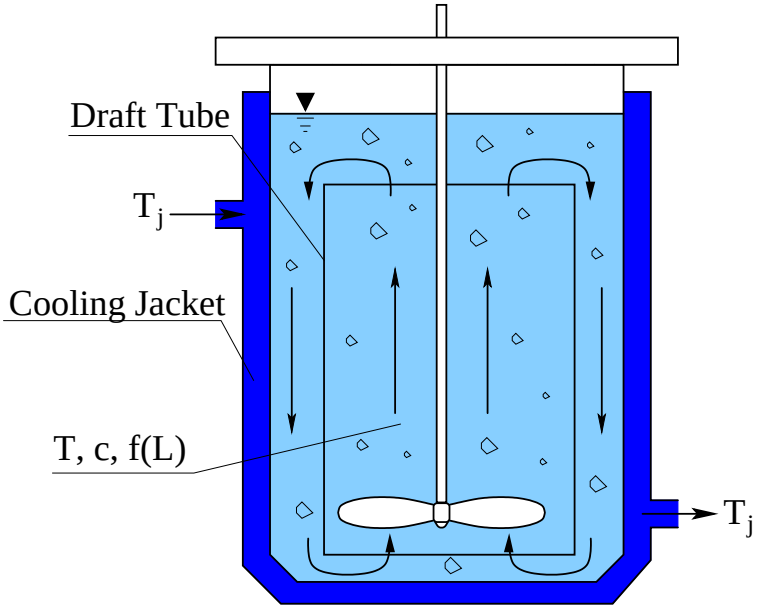

Fig. 4: Batch crystallizer

A solution to this problem has been 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. The solution makes use of the flatness concept from nonlinear control theory: a dynamic system is called differentially flat if there exists a “flat output”, which completely parameterises the system state and its input. This can be interpreted as an invertibility property and is extremely useful for the solution of open loop control problems. Although the system of moment equations derived from the PBE form is not flat, it can be made so by applying state dependent scaling of time. Such systems are called orbitally flat. Applying the same scaling of time to the PBE yields a simple transport equation. Exploiting these two properties – orbital flatness of the moment equations and the simple structure of the time scaled PBE – the open loop control problem can be solved in a very elegant way. A procedure has been developed which enables the analytic computation of the corresponding temperature profile for any desired (and physically meaningful) final CSD [25]. Based on these results, it is also possible to determine a control policy that optimises the final CSD by solving a static optimization problem [24]. Finally, in [26], we use the fact that flat systems are

feedback linearisable to design a closed loop control scheme that tracks the previously designed trajectory in the presence of modelling errors and disturbances.

Recently, in close cooperation with the PCF group, we have started to investigate control problems for batchwise preferential crystallisation processes. Preferential crystallisation is used for the separation of enantiomers – substances with identical physical and chemical properties but different metabolic effects. The basic idea in preferential crystallisation 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 ("metastable region"). Hence, after seeding one of the two enantiomers, say E1, it will be almost exclusively the seeded enantiomer that will crystallise – 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 crystallisation 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 formed. 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 crystallisers, is shown in Fig. 5.

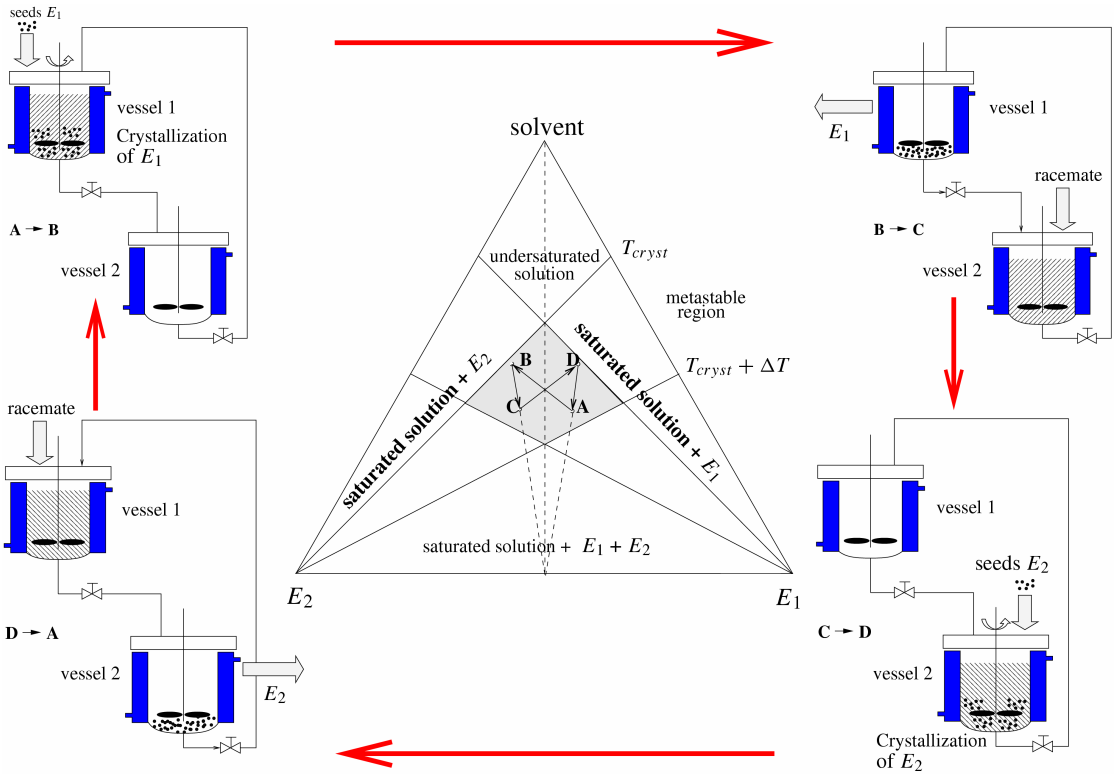

Fig. 5: Cyclic batch process for enantiomer separation.

In the beginning, mixture is filled into one of the two vessels (represented by an A in the ternary phase diagram in Fig. 5). Seeding E1 crystals initiates the single batch process described above ($A \rightarrow B$). After stopping the process, crystalline E1 is harvested by transferring the liquid into a second crystallizer vessel. Racemic mixture (containing equal amount of dissolved E1 and E2) 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 again adding racemic mixture will finish the first cycle of the process ($D \rightarrow A$) [27]. 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 crystalliser (or heat jacket) temperature signal, the seed CSD [28] and the amount of added racemic mixture for each single batch process, and the inter-batch switching pattern.

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. 6.

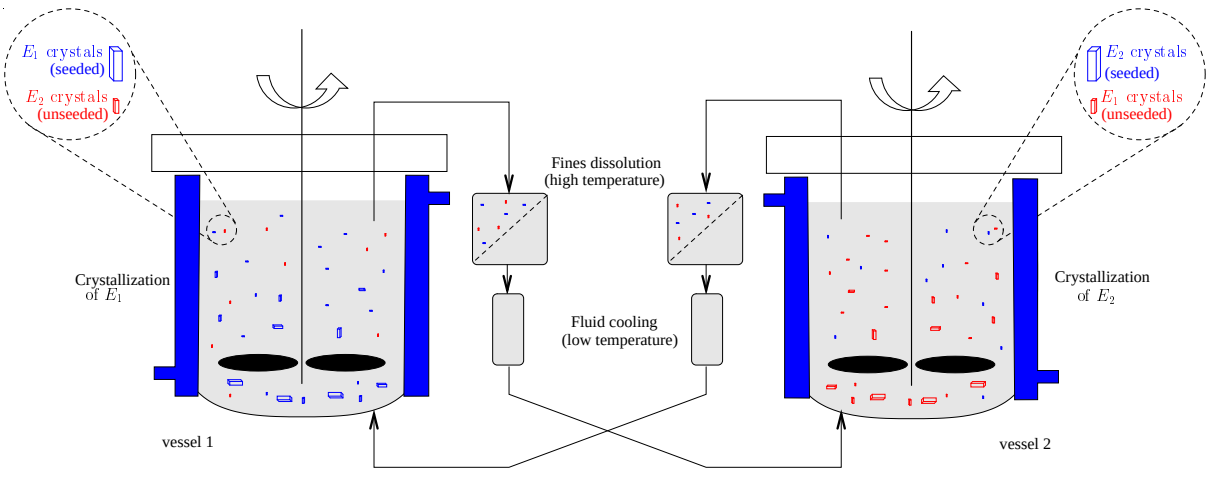

Fig. 6: Simultaneous batch-crystallisation.

There, E1 and E2 are crystallised simultaneously in two separate vessels, and crystal free solution is continuously exchanged between the two crystallisers. 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 crystallisers and the flow rate between the vessels.

4.3 Analysis of Biological Reaction Networks

In chemical engineering and in biology, reaction networks are of paramount importance. Most “real world” networks are of enormous complexity. In cell biology, e.g., complexity often stems from the large number of strongly interacting components. The dynamics of such systems can rarely be understood by chemical or biological intuition alone. Mathematical modelling is therefore an especially attractive route to understand their functioning. In the process of “building” a mathematical model, however, one often faces uncertainty with respect to both network topology and reaction mechanisms. This usually implies the existence of several plausible hypotheses regarding the investigated reaction scheme; hence, according to BAILEY, mathematical modelling basically means the development of families of differently structured models followed by a model discrimination step.

The standard modelling procedure is as follows: each candidate network (hypothesis) is translated into a set of ordinary differential equations with yet unknown parameters. Then an identification scheme is used that fits the unknown parameters in each set of differential equations to experimental data. Clearly, this is an extremely time-consuming procedure. If, for the currently investigated hypothesis, a satisfactory set of parameter values can be established, it is concluded that the hypothesis is a valid explanation of reality, and the corresponding candidate network, together with the resulting set of parameter values, is accepted as a possible dynamical model. However, if the identification procedure does not come up with a satisfactory set of parameters, it is only safe to discard the candidate network under consideration, if the error function is globally convex. As the latter is rarely the case, this procedure is only semi-conclusive and therefore not a sound basis for falsifying network

hypotheses. These drawbacks are the motivation for our research on using qualitative network properties to conclusively rule out certain candidate networks. It is pursued in close cooperation with the SBI group at the MPI.

To date we have been investigating two approaches. One method is to construct safe discrete approximations of the continuous dynamic models associated with each reaction network. For this purpose, every network structure is translated into a finite state machine. Under some mild assumptions regarding the properties of the reaction kinetics involved, it can be shown that on a suitable discrete signal space this automaton is a conservative approximation of all possible sets of ordinary differential equations that can be derived for the network. If this automaton fails to explain available experimental data, the corresponding network structure can therefore be safely discarded. This research builds on methods that have been developed within our project on hybrid control systems, and also benefits from a recently established cooperation with the Discrete Optimisation Group at the Otto-von-Guericke University.

The second method currently under investigation is the incorporation of knowledge on the number of steady states into the process of model discrimination: suppose, e.g., that the existence of multiple steady states has been observed in experiments. It is then natural to ask which of the postulated network structures can, for some conceivable parameter vector, exhibit such a qualitative property. To this end FEINBERG'S Chemical Reaction Network Theory (CNRT) is applied. CNRT connects qualitative properties of ODEs corresponding to a reaction network to the network structure. In particular, its assertions are independent of specific parameter values and its only assumption is that all kinetics are of mass-action form. More specifically, we use Chemical Reaction Network Theory to identify those candidate networks that can exhibit multistationarity. Observation of multistationarity in experiments consequently falsifies all other networks.

This procedure has been successfully applied to different reaction networks representing a single layer of the well studied Mitogen-activated protein kinase (MAPK) cascade. For example, recent results by Markevich et al. show that multilayered protein kinase cascades can exhibit multistationarity even on a single cascade level. Using CRNT, it is possible to show that the assumption of a distributive mechanism for double phosphorylation and dephosphorylation is crucial

for multistationarity on the single cascade level; reaction networks incorporating different hypotheses for this step can therefore be safely discarded [21].

4.4 Research Related Activities

IPC Member (J. Raisch)

ADHS03	1st IFAC Conference on Analysis and Design of Hybrid Systems, St. Malo, 2003
CESA2003	IMACS/IEEE Conference on Computational Engineering in Systems Applications, Lille, 2003
SPC2003	4th International Symposium on Process Control, Ploiesti, 2003
WODES04	7th IFAC Workshop on Discrete Event Systems, Reims, 2004
IEHSC05	International Embedded and Hybrid Systems Conference, Singapore, 2005
ADHS06	2nd IFAC Conference on Analysis and Design of Hybrid Systems, Alghero, 2006
MCBMS06	6th IFAC Symposium on Modelling and Control in Biomedical Systems, Reims, 2006
WODES06	Workshop on Discrete Event Systems, Ann Arbor, 2006

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)

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.

5 Teaching Activities

5.1 Systems Engineering and Cybernetics

Most of our teaching activity is related to the new degree program, “Systemtechnik und Technische Kybernetik (Systems Engineering and Cybernetics)”, at the Otto-von-Guericke-University Magdeburg. It provides extensive coverage of various aspects of modelling, analysis and control of dynamical systems. A new (and we think successful) feature is to provide students with an intuition for dynamics and control at a very early stage, even before they have acquired an adequate mathematical background and to provide more formal details as they progress. Within the program, the following courses are taught by Jörg Raisch on a regular basis (either during the summer or the winter semester).

Cybernetics (1st semester, 3 hours/week)

Introduction to Systems Theory (2nd semester, 4 hours/week)

Distributed Parameter Systems (4th semester, 4 hours/week)

Systems Theory (5th semester, 3 hours/week)

Discrete Event Systems I (6th semester, 3 hours/week)

Discrete Event Systems II (7th semester, 3 hours/week)

Robust Multivariable Control (8th semester, 3 hours/week)

Within the Systems Engineering and Cybernetics program, Dietrich Flockerzi teaches the course:

Nonlinear Systems (7th semester, 3 hours/week)

5.2 Regular Courses for Other Programs

For a larger group of students (enrolled in Electrical Engineering, Information Technologies, and Mechatronics programs), J. Raisch teaches the following courses:

Signals and Systems (with G. Reißig, 4th semester, 3 hours/week)

Control Engineering (5th semester, 3 hours/week)

5.3 Non-compulsory Courses

The following courses, taught by D. Flockerzi and T. Schauer, are non-compulsory but are taken as elective courses by the majority of systems engineering and cybernetics students:

Nonlinear Control (T. Schauer, 7th semester, 3 hours/week)

Modelling and Control in Medicine (T. Schauer, 8th semester, 2 hours/week)

Model Reduction in Engineering and Biology (D. Flockerzi, 7th semester, 4 hours/week)

Partial Differential Equations in Science and Engineering (D. Flockerzi, 5th / 7th semester, 3 hours/week)

5.4 Teaching Related Activities

Together with the PCP group, we coordinate a **NaT-Working** project to attract students from Magdeburg high schools into engineering programs. NaT-Working (NaT is short for “Natural and Technical/engineering sciences”) has been initiated and is being funded by ROBERT BOSCH FOUNDATION; it aims at promoting local partnerships between schools, science and engineering departments at universities, and research institutions.

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 Ploiesti (Prof. N. Paraschiv),** Romania, 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),** Brasil.

5.5 Ph.D Theses

Jörg Raisch has supervised the following Ph.D projects:

U. Vollmer: Control of crystallisation processes, May 2005

A. Itigin: Hierarchical hybrid control systems, submitted in July 2005

E. Mayer: Scheduling and control of cyclic discrete-event systems, to be submitted in 2005

B.V. Mishra: Control of multiproduct batch plants, to be submitted in 2005

C. Conradi: Analysis of biochemical reaction networks, in preparation

D. Gromov: Low-dimensional manifolds in hierarchical control systems, in preparation

D. Li: A new integrated control architecture for cyclic rail systems, in preparation

N.O. Negård: Nonlinear control of neuroprostheses by means of Functional Electrical Stimulation, in preparation

I. Angelov: Control of particulate processes, in preparation

S. Geist: Optimal Hybrid Control Systems, in preparation

R. Salbert: Aspects of FES in Rehabilitation Engineering, in preparation

Jörg Raisch acted as external examiner for the following Ph.D theses:

Y. Pang (University of Strathclyde): Control synthesis and optimization for hybrid systems, September 2004

M. Smith (Australian National University): Reachability Operators and Hybrid Systems, February 2005

5.6 Diploma/Master Theses

The following Diploma/Master theses have been supervised by members of the SCT group:

F. Baldissera: Application of a Hybrid Systems Approach to the Swing-Up Problem of an Inverted Pendulum; final year thesis, UFSC, February 2004

G. Figueira Althoff: Supervisory Control of Hybrid Systems: Theoretical and Application Issues Concerning the l-Complete Approximation Approach; final year thesis, UFSC, September 2004

S. Geist: Reachable Sets of Autonomes Systems, Diploma thesis, September 2004

E. Ferchland: Continuous state control of blood glucose using discrete-time measurements, Diploma thesis, October 2004

R. Salbert: Controlled FES lower limb cycle ergometry in stroke, Diploma thesis, October 2004

J. Heßeler: Theoretical Analysis and Mathematical Modelling of Microbial Species in a Chemostat – How to Achieve Coexistence of Competing Species, Diploma thesis Univ. Tübingen, February 2005

S. Haumann: Nonlinear Output Feedback Control – of a Pneumatic Muscle Actuator System, Diploma thesis, (with Prof. Previdi, University of Bergamo), May 2005

Qianru Qi: Model Reduction by Slow Invariant and by Intrinsic Low-Dimensional Manifolds, Master thesis Univ. Kaiserslautern, September 2005

6 Awards, Fellowships, Appointments

During the period covered by this report, J. Raisch was offered the following professorships (chairs) at Universities

- Chair for Complex Dynamic Systems, Department of Electrical Engineering, Technical University of Vienna, Austria
- W3-Professur (Chair) for Control Systems at the Dept. of Electrical Engineering and Computer Science, Technical University of Berlin

During the period covered by this report, J. Raisch has been managing director of the Institute of Automatic Control (Institut für Automatisierungstechnik) at Otto-von-Guericke University.

7 Future Directions

The future direction of the SCT group at the Max Planck Institute depends very much on whether the University part of our group will relocate to another city. Any such move would of course affect the internal project balance between the group's two parts. If a relocation of the University part were to take place, it would, e.g., make sense to move our (fairly large) project on functional electric stimulation from the MPI to the new university environment, as the latter will offer favourable conditions for medical engineering. On the other hand, it would also make sense to focus projects

on chemical engineering control applications at the MPI. Irrespective of the decision, additional third party grants need to be acquired to compensate for the anticipated decline in MPI funding. The most attractive way of doing this is of course to participate in major national or international research networks or initiatives, as this will also strengthen intra- and interdisciplinary cooperation.

At the moment, we participate in the following research networks and initiatives:

- HYCON ("Hybrid Control: Taming Heterogeneity and Complexity in Networked Embedded Systems") is a Network of Excellence within the 6th Framework Programme for European Research & Technological Development (FP6) and connects 23 European research groups in the area of hybrid systems. The network has been in existence for a year and is expected to continue for another three years.
- FG468 is a DFG-funded research unit (Forschergruppe) devoted to the study of "Methods form Discrete Mathematics for the Synthesis and Control of Chemical Processes". It has been running for three years and, if evaluated positively, is expected to be continued for another three years.
- The Ministry of Education and Cultural Affairs of Saxony-Anhalt has established a research centre for dynamic systems, which aims at exploring systems theoretic issues in both biological and technical systems. The initial funding period is 30 months and will last until the end of 2006.
- SCODES (Supervisory COntrol of Distributed and Embedded Systems) is a research proposal coordinated by A. Giua from the University of Cagliari. It is to be submitted as a STREP (Strategic Targeted REsearch Project) within FP6 in autumn 2005.
- We also participate in a major research initiative on particulate processes, which is coordinated by K. Sundmacher. It aims to bring together chemical engineers, mathematicians and systems and control persons to investigate modelling, analysis and control issues for this important class of chemical processes.

8 References

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Appendix: List of Abbreviations

OvGU	Otto-von-Guericke University Magdeburg
MPI	Max Planck Institute for Dynamics of Complex Technical Systems
BMBF	Federal Ministry of Education and Research
BMWi	Federal Ministry of Economics and Technology
DFG	German Research Council (Deutsche Forschungsgemeinschaft)
DAAD	German Academic Exchange Service
AiF	German Federation of Industrial Cooperative Research Associations (Arbeitsgemeinschaft industrieller Forschungs-vereinigungen)
KM-LSA	Ministry of Education and Cultural Affairs (Saxony-Anhalt), Kultusministerium des Landes Sachsen-Anhalt
Pro3	Kompetenznetz Verfahrenstechnik Pro3

EU-HYCON	European Union Network of Excellence HYCON (Hybrid Control: Taming Heterogeneity and Complexity in Networked Embedded Systems)
SCT Group	Systems and Control Theory Group at MPI
PSD Group	Process Synthesis and Process Dynamics Group at MPI
PCP Group	Physical and Chemical Process Engineering Group at MPI
PCF Group	Physical and Chemical Foundations of Process Engineering Group at MPI
SBI Group	Systems Biology Group at MPI
BPE Group	Bioprocess Engineering Group at MPI
IPC	International Program Committee
FES	Functional Electrical Stimulation

Research Group:

Molecular Network Analysis (MNA)

Prof. Dr. rer. nat. Wolfgang Marwan

This is an outlook of the Molecular Network Analysis Group.

1 Group Introduction

The Molecular Network Analysis Group (MNA) was founded in April 2005 based on a cooperation contract of the Max-Planck-Society and the Otto-von-Guericke-University of Magdeburg. The group is funded for the first four years jointly by the Max-Planck-Society, the MPI for Biochemistry, and the MPI for Dynamics of Complex Technical Systems; MNA's current address for the initial funding cycle. After the initial funding cycle, the group will be transferred to the University at reduced volume and with an enhanced teaching load. At this time MNA will move into a new University building, Verfahrenstechnik, currently under construction.

The fundamental concept driving MNA is the idea that by examining molecular pathways and their regulation in vivo, MNA can then develop functional network modules that will describe these pathways in greater detail than previous experimental methods. These functional network modules can then be used to complement the information obtained by conventional experimental techniques, which focus on the biological role of a particular protein or gene, or on large data sets obtained through various omics approaches. MNA's purpose is therefore, the study of molecular network function while maintaining an almost intact in vivo system. Meeting this challenge will require the development of special experimental techniques, which will allow the systematic perturbation of the system to generate quantitative and time-resolved data. Further, MNA will develop theoretical tools to evaluate the data generated.

Experimentally, MNA focuses on two molecular networks: a small network, mediating the phototaxic response of the prokaryote, *Halobacterium salinarum,* to visible light, and a larger network regulating cell differentiation in the eukaryote, *Physarum polycephalum*. By analysing networks of different molecular complexity we hope to develop efficient and theory-based experimental approaches to reconstruct (reverse engineer) molecular networks from functional studies. The study of phototaxis in *Halobacterium* led to the determination of the kinetic behaviour of the sensory rhodopsin-transducer heterotetramer *in vivo* without requiring *a priori* knowledge of the other network components (Marwan, Wolfgang, et al., 1990 a; 1995). The results could be verified by *in vivo* spectroscopic measurements since the sensory rhodopsin molecule reversibly changes its colour upon activation. Further, evaluation of the output at the flagellar motor led to an understanding of non-linear functional

interactions of the photoreceptor with other network building blocks. These studies suggest that it is possible to analyse the activity of any element (or node) of a regulatory network *in vivo,* quantitatively and in a time-resolved manner, if a tool to study that specific node is available. This concept led to the development of time-resolved somatic complementation analysis used to understand the structure and dynamics of the sporulation control network in the eukaryote *Physarum polycephalum.*

2 Members of the Research Group

Head of Group

- Prof. Dr. rer. nat. Wolfgang Marwan

Secretary

- Janine Holzmann (part time)

Postdocs

- Ayesha Carter, PhD
- Dr. Doerte Gade
- Dr. Markus Haas

PhD students

- NN
- NN

Technicians

- Baerbel Lorenz (starting in September 2005)
- Bianca Steidler (starting in September 2005)

3 Survey of Research Projects

Tab 1: Project Area: Hierarchical Structures

Project:	**Photo- and Chemotaxis in *Halobacterium***
Abstract:	The goals of this project are the analysis and subsequent reverse engineering of the signal transduction network that senses and processes light, chemical, bioenergetic and metabolic signals to finally control the flagellar motor. 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.
Subproject:	**A coherent model for phototaxis sensing and response of halobacteria**
Researchers:	T. Nutsch, W. Marwan
Partners:	E.-D. Gilles, D. Oesterhelt
Funding:	MPI
Start:	2001
Subproject:	**Modelling the switch complex of the archaeal flagellar motor**
Researchers:	T. Nutsch, W. Marwan
Partners:	E.-D. Gilles, D. Oesterhelt
Funding:	MPI
Start:	2003
Subproject:	**The molecular mechanisms of sensory adaptation and gain control in halobacterial photo- and chemotaxis.**
Researchers:	T. Neuhaus, W. Staudinger, W. Marwan
Partners:	E.-D. Gilles, D. Oesterhelt
Funding:	MPI
Start:	2005

Tab 2: Project Area: Hybrid and Discrete Event Systems

Project:	**Analysis of the sporulation control network in *Physarum polycephalum***
Abstract:	The aims of this project are directed at understanding how the eukaryotic cell decides to terminally differentiate and what processes make this decision irreversible. The molecular network that controls subsequent commitment points will be 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:	**Reverse engineering of the sporulation control network by hierarchical Petri net modeling and simulation**
Researchers:	W. Marwan
Start:	2004
Subproject:	**Identification and analysis of the sporulation control network**
Researchers:	N.N., W. Marwan
Partners:	S. Klamt, E.-D. Gilles
Funding:	MPI
Start:	2005
Subproject:	**Can the structure of a subnetwork be mathematically proofed through discrete optimization?**
Researchers:	N.N., W. Marwan
Partners:	A. Wagler, R. Weismantel, Institut fuer Mathematische Optimierung, Otto-von-Guericke Universitaet Magdeburg
Funding:	GRK/DFG
Start:	2005
Subproject:	**Sequencing of an arrayed normalized full-length cDNA library from sporulation-competent plasmodia**
Researchers:	W. Marwan
Partners:	G. Gloeckner, IMB Jena; G. Werner-Felmayer, University of Innsbruck
Funding:	University of Innsbruck, IMB Jena, MPI
Start:	2004
Subproject:	**Set up of a gene discovery pipeline**
Researchers:	M. Haas, W. Marwan
Partners:	G. Gloeckner, IMB Jena; P.H. Dear, MRC Cambridge
Funding:	MPI; significant additional funding required
Start:	2005
Subproject:	**Single cell proteomics: dynamics of the cytoplasmic and the nuclear proteome on the way to commitment to terminal differentiation**
Researchers:	D. Gade
Partners:	E. Rapp, Bioprocess Engineering

Funding:	MPI
Start:	2005
Subproject:	**The role of cell cycle regulation and apoptosis in the developmental decision to sporulate**
Researchers:	A. Carter
Partners:	----
Funding:	MPI
Start:	2005

4 Research Highlights

4.1 Phototaxis in *Halobacterium salinarum*

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

The evolutionary tree is divided into three major catagories: bacterial, archaeal and eukaryotic. The molecular pathways regulating signal transduction in eukarya and bacteria are not closely evolutionarily conserved, however, those pathways studied in archaea have been demonstrated to be similar to bacterial pathways. Therefore, identifying the molecules involved in archaeal signal transduction and understanding the dynamics of their interaction is not only of basic scientific interest but may give insight into how signal transduction pathways evolved. While signal transduction has been closely examined 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.*

The signal transduction network mediating phototaxis in *Halobacterium* (Fig. 1) is composed of protein modules also found in bacterial signal transduction systems, although there is considerable variation and diversification in the archaeal systems. Instead of four methyl-accepting chemotaxis proteins (MCPs), which function as chemoreceptors for specific compounds in *E. coli*, there are thirteen orthologues in *Halobacterium* (http://www.halolex.mpg.de), which greatly increase the spectrum of stimuli to be sensed. 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 these sensory rhodopsins feeds into a two-component system regulating the probability of switching the rotational sense of the flagellar motor. The signal transduction pathway of *Halobacterium* is composed of a

larger number of protein elements than the chemotaxis signalling pathways of *E. coli*, and some of these additional molecules can also be found in *Bacillus subtilis*. Although the signalling pathways mediating archaeal phototaxis and bacterial chemotaxis rely on orthologous protein elements, they control completely different targets. The flagellar motor of archaea differs from its bacterial counterpart; an interesting example of how functional modules of biochemical networks recombine during evolution. None of these signal transduction networks are fully understood at the molecular level. In particular, the function of the additional proteins found in *Bacillus* and *Halobacterium* has yet to be elucidated. Currently there is no comprehensive model capable of quantitatively representing the events from receptor activation to motor response in any bacterium.

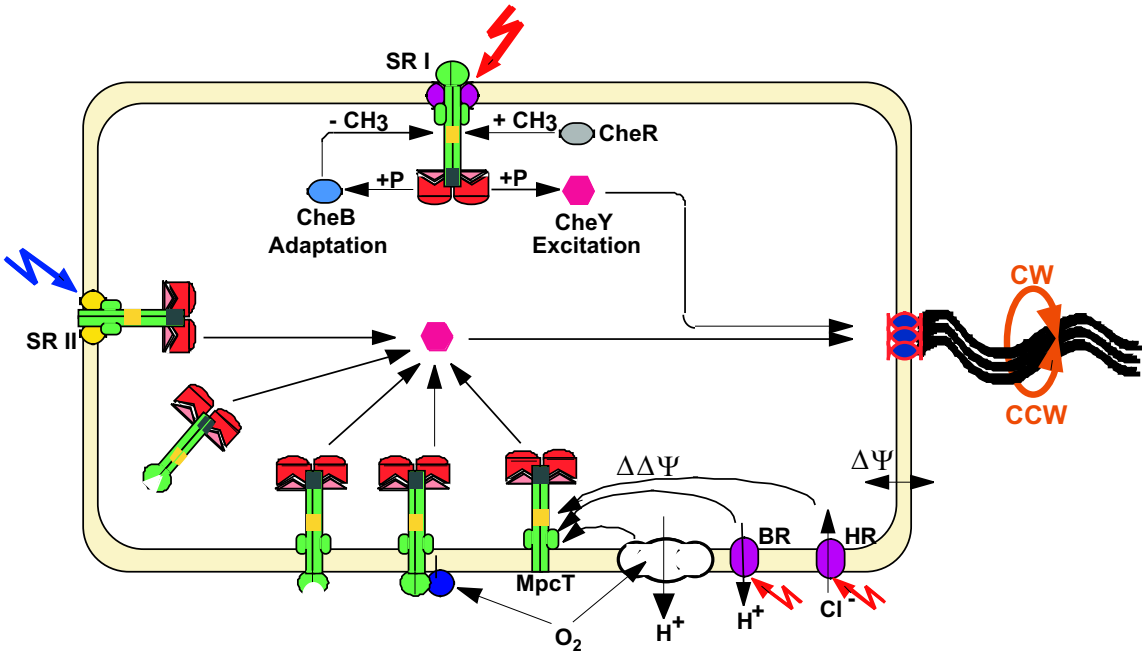

Fig. 1: Photo- and chemotaxis in *Halobacterium salinarum*. Part of the molecular interactions controlling the behavioural response of the cell to different input stimuli are schematically shown.

4.1.2 A New Set-Up for Computer-controlled Stimulation of *Halobacterium* Cells and Measurement of its Behavioural Responses

Previous work has resulted in the design and assembly of a new set-up for computer-controlled stimulation of halobacterial cells (Fig. 2). The set-up is comprised of two sources for stimulation by visible light coupled through light guides into a phase contrast microscope used for observation of halobacterial cells under infrared light (which cannot be detected by the cells). It was of particular importance that the

optical elements maximize the available intensity of stimulating light. To that end, the light sources were equipped with a filter wheel for the production of monochromatic light of differing wavelengths, an attenuator wheel used to control the light intensity, and a shutter. All optical elements are monitored by a computer with two serial ports, which allows the precise application of any desired stimulus light pattern. In order to maximize experimental design flexibility, the software was written in house. The light emitted from the computer-controlled light sources can be used either to specifically stimulate the sensory rhodopsin photoreceptors, or the light-driven proton pump bacteriorhodopsin (to study signaling mediated through changes in proton motive force). In addition, it can also be used to release caged chemostimuli or caged fumarate, a motor switching signal (Marwan, Wolfgang, et al., 1990 b; Montrone, Marco, et al., 1993). The behavioural responses of individual cells are recorded and quantitatively evaluated by a computer-assisted motion analysis system, which is coupled to the computers controlling stimulus delivery. The set up will be widely used to generate the experimental data required for reverse engineering of the phototaxis network.

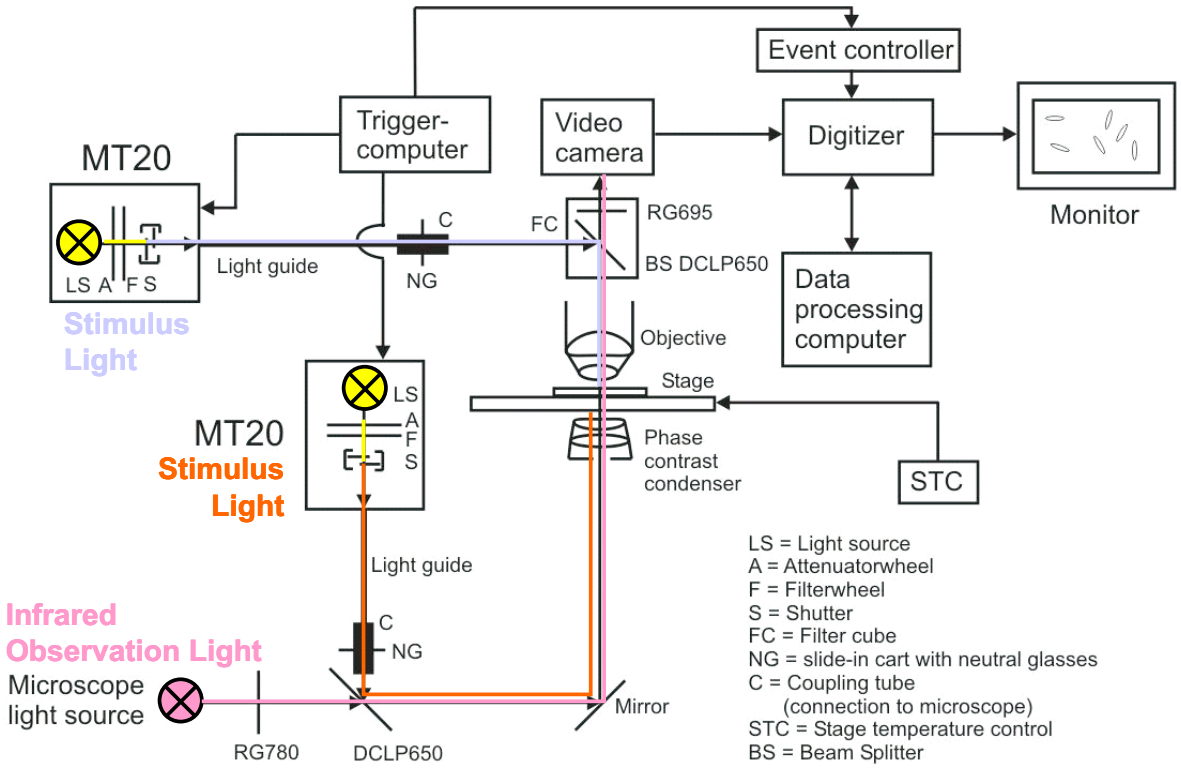

Fig. 2: Set-up for computer-controlled stimulation of *Halobacterium* cells and automatic tracking of their swimming behaviour by processing of digitized video data.

4.1.3 A Coherent Mathematical Model for Sensing and Response

A coherent mathematical model describing the signalling network in halobacterial phototaxis has been developed. The model describes photoreception through the sensory rhodopsin-transducer complex, signal relay and amplification by the CheA/CheY two-component system and negative feed-back through CheA-dependent, CheB-mediated reversible demethylation of the transducer complex. The model quantitatively describes the response of the cells to single and double pulse stimulation, which is used to probe the kinetics of signal formation (Nutsch, Torsten, et al., 2003).

As a logical second step, the switch complex of the archaeal flagellar motor was reverse engineered (Nutsch, Torsten, et al., 2005). These experiments demonstrated that the switch complex is composed of 44 functionally coupled subunits that bind CheYP with different affinity depending on their conformational state (Fig. 3). Surprisingly, a considerable part of the intelligence of the halobacterial phototaxis system in response to various stimulus types (visible light, chemicals and metabolic signals) is due to signal processing performed by the multimeric switch complex of the flagellar motor. This finding suggests that during evolution, the archaeal flagellar motor might originally have mediated movement by directly responding to input by metabolic signals (Marwan, Wolfgang, et al., 1990 b) and was only later coupled to the highly tuned two-component phosphorylation cascade mediated by specific receptors.

At present, the mathematical model qualitatively and quantitatively reproduces the huge body of experimental results obtained over more than 30 years of research on halobacterial phototaxis. The intention is to use this model as a basis to explore the molecular mechanisms of adaptation through reversible methylation of transducer complexes, the regulation of gain, the role of additional network components (e.g. CheD, CheJ1-3), and the various relays of the two-component phosphorylation cascade to metabolic signals.

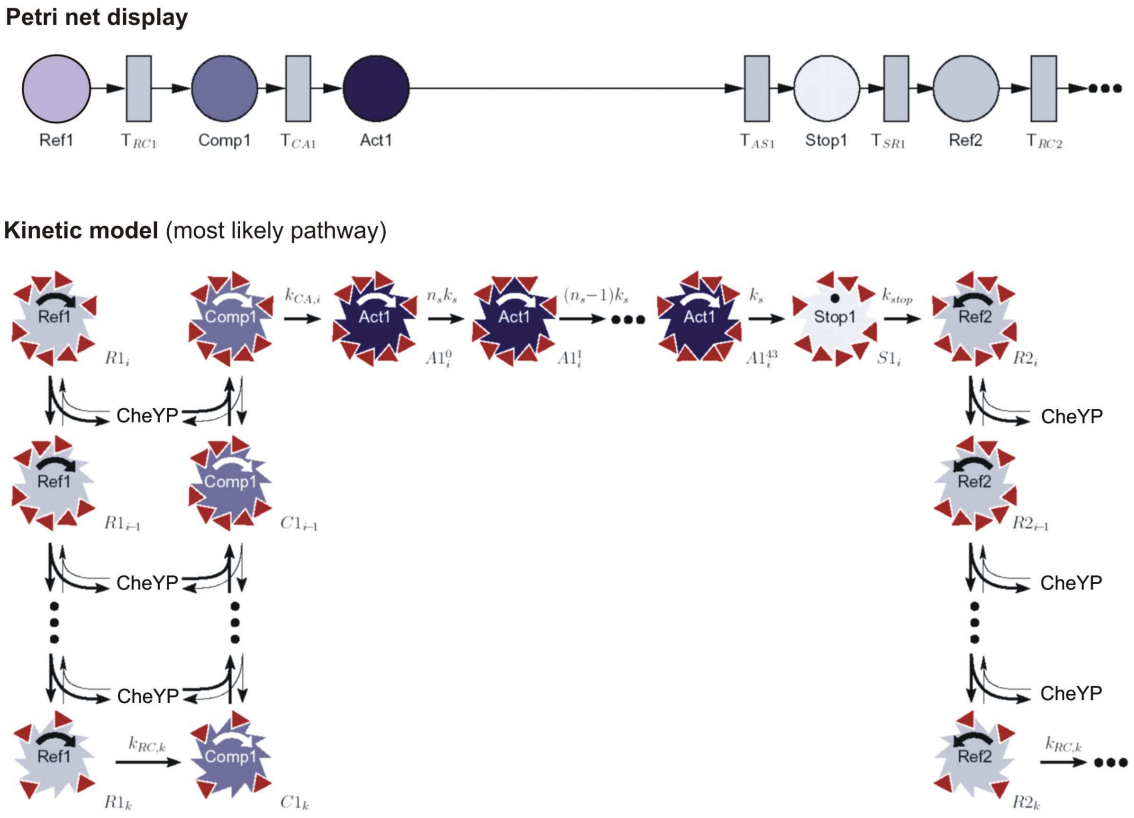

Fig. 3: Mechanistic presentation of the kinetic model of the flagellar motor switch complex and its sensory control through CheYP. The most probable pathway of the complex from clockwise to counterclockwise motor rotation is shown.

4.2 Control of Sporulation in *Physarum polycephalum*

4.2.1 Sporulation in *Physarum polycephalum*: A model of Eukaryotic Cell Differentiation

Lately, human embryonic stem cell research has been of much political interest. The medical and scientific promise of such research must be balanced against the ethical concerns of using a potential human life for research. One alternative to the problem is to utilize lower eukaryotic organisms to study developmental differentiation and then apply those findings to the human development. *Physarum polycephalum* is a promising alternative organism for several reasons. The organisms known genes are surprisingly well conserved when compared to the human genome and during its developmental cycle, *Physarum polycephalum* differentiates into 10 easily manipulated cell types. One of these cell types is a multinucleate giant cell, referred to as a plasmodium, which exhibits some of the hallmarks that characterize a stem cell: unlimited replicative potential and the ability to terminally differentiate into variable, specialized cell types. The decision to differentiate into other cell types can be controlled experimentally, allowing the study of the molecular pathways that

generally regulate the decision to differentiate. For example, when a mature plasmodium is transferred from glucose rich media to a starvation media, it differentiates into its sporulation competent cell type, going from a large cell mass to a branching, sporulation ready network of veins. After a prescribed period of time, a short pulse of visible light will force the competent plasmodium to proceed through at least two known subsequent commitment points; finally resulting in an irreversible program of differential gene expression. This change in gene expression mediates the formation of differentiated fruiting bodies (Fig. 4), at approximately 18 hours after the initial pulse of light (Marwan, Wolfgang, 2003 a).

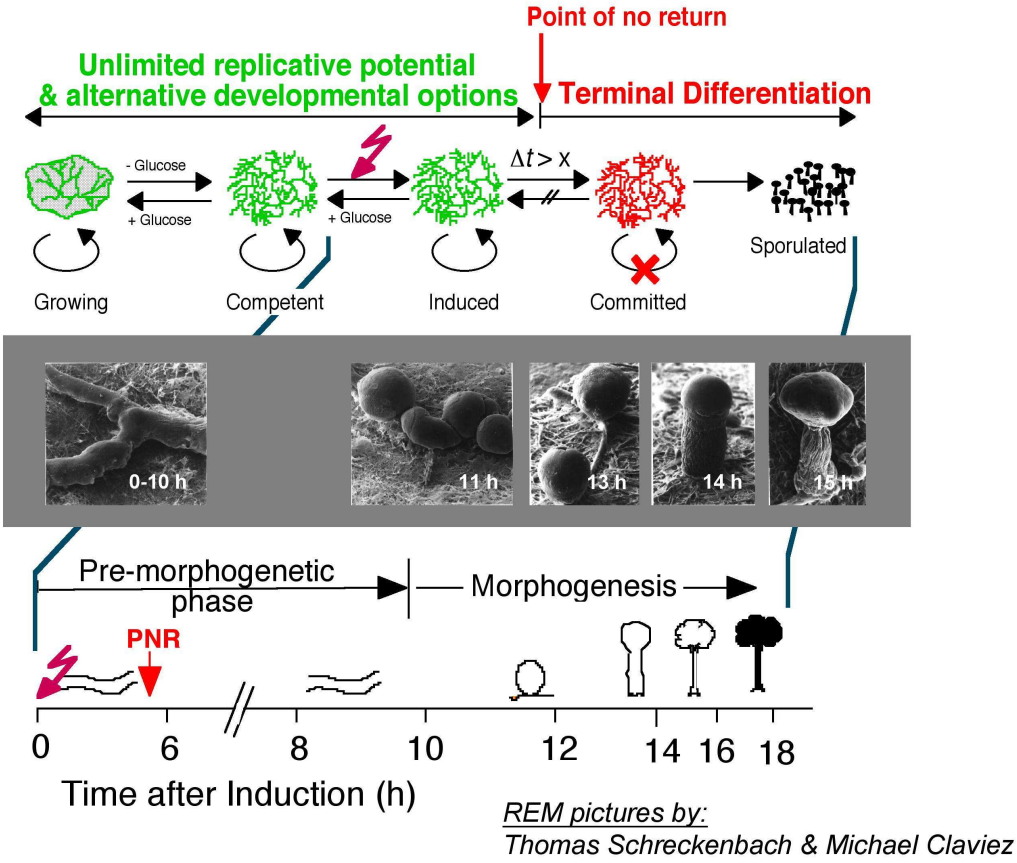

Fig. 4: Plasmodial development and sensory control of commitment and sporulation in *Physarum polycephlum*. Upon passing the point of no return (PNR) at 5 hours after being induced by light (flash symbol), the plasmodial cell irreversibly loses its unlimited replicative potential and is committed to terminal diferentia tion.

In addition to this undifferentiated single cell state, *Physarum* exhibits two unique characteristics that enhance its significance as an experimental organism. First, all nuclei within this giant single cell undergo cell cycle and differentiation remodelling simultaneously during the organism's life span (Burland, Timothy G., et al., 1993).

Second, plamodia of proper mating genotypes will fuse cell membranes upon contact with each other combining cytoplasmic material. A mutant gene product can be titrated against its corresponding wild-type counterpart by fusing two plasmodia of appropriate relative size and this perturbation can be performed in a time-resolved manner, if the two plasmodia are in different physiological states during cytoplasmic fusion (Starostzik, Christine, et al., 1998). Previous experiments in the 1970's utilized these characteristics to study the eukaryotic cell cycle and the role of cytoplasmic factors in cell cycle regulation. Similar cell fusion experiments performed with mammalian cells yielded corresponding results (Johnson, Robert T., et al., 1970; Rao, Potu N., et al., 1970; Sachsenmaier, Wilhelm, et al., 1972). Further studies will analyze the structure and dynamics of the molecular network mediating *Physarum* sporulation.

The life cycle and genetic make up of *Physarum polycephalum* make it an ideal organism for very sophisticated genetic manipulations. Using a temperature-sensitive mating type mutation, the life cycle can be switched from haploid to diploid and *vice versa* at will (Fig. 5). The capability to switch back and forth between DNA contents allows the generation of mutants of mono-nucleate, haploid amoebae and the subsequent screening for haploid plasmodial phenotypes. A genetic screen for mutants with compromised sporulation after chemical mutagenesis with Ethylnitrosourea has been established, allowing for large-scale generation of mutants (Sujatha, Arumugam, et al., 2005) within the sporulation control network. The experimental procedures developed can also be used to screen an antisense expression library for genes involved in the control of commitment and sporulation.

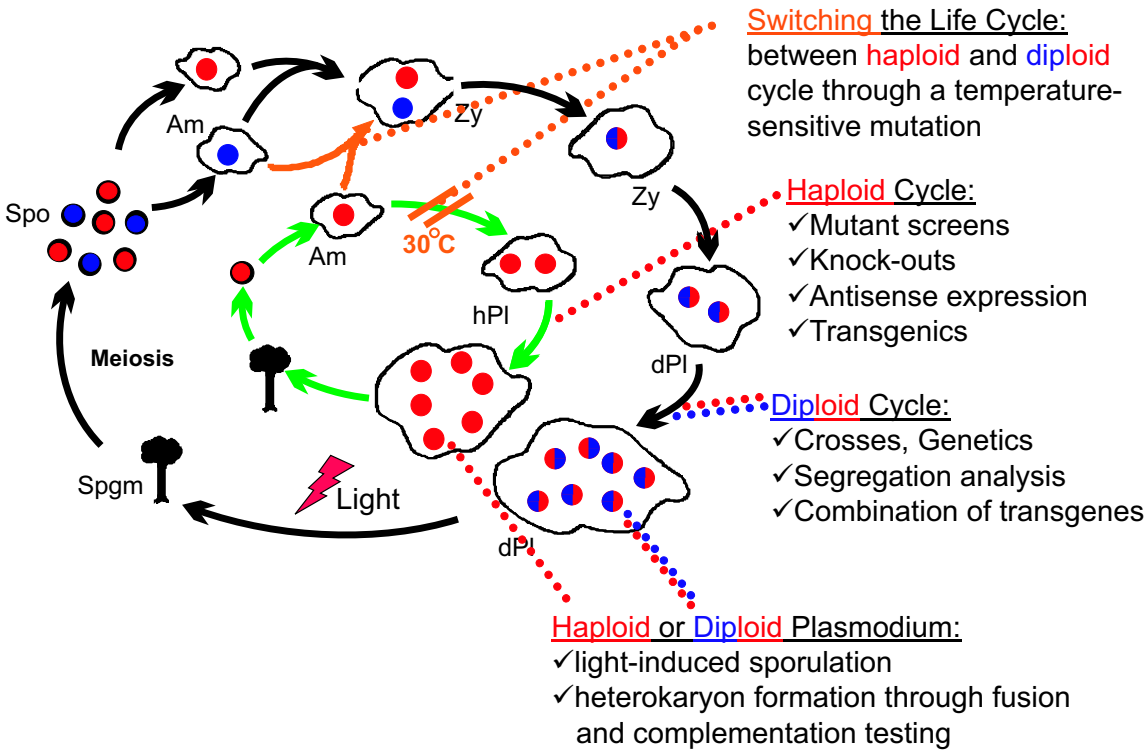

Fig. 5: Life cycle of *Physarum polycephalum* and its use for genetics.

4.2.2 Time-resolved Somatic Complementation Analysis of Mutants Altered in Sporulation Control: Probing the Signal Flux Through the Network

Complementation is the production of a wild-type phenotype when two recessive mutant alleles are united in the same cell (Griffiths, Anthony J. F., et al., 1999). Genetic complementation tests can be performed either by crossing two homozygous mutant strains of an experimental organism or by fusion of two mutant cells through heterokaryon formation. In such heterokaryons, two nuclear populations mix and although the individual nuclei originating from the two parent strains do not fuse, their gene products are exchanged through the cytoplasm and provide the biochemical basis for the complementation effect. Complementation testing through plasmodial fusion and cytoplasmic complementation, when compared to genetic complementation by mutant crossing, has proven to be a highly developmentally descriptive complementation assay. One can vary the developmental time point of mutant fusion and therefore gain a better understanding of the importance of particular genetic interactions at particular times during development (Fig. 6). By performing the experiment with two mutants that carry blocks at two different nodes

of the network, the signal flow through these nodes can be detected in a time-resolved manner (Marwan, Wolfgang, et al., 2002; 2003).

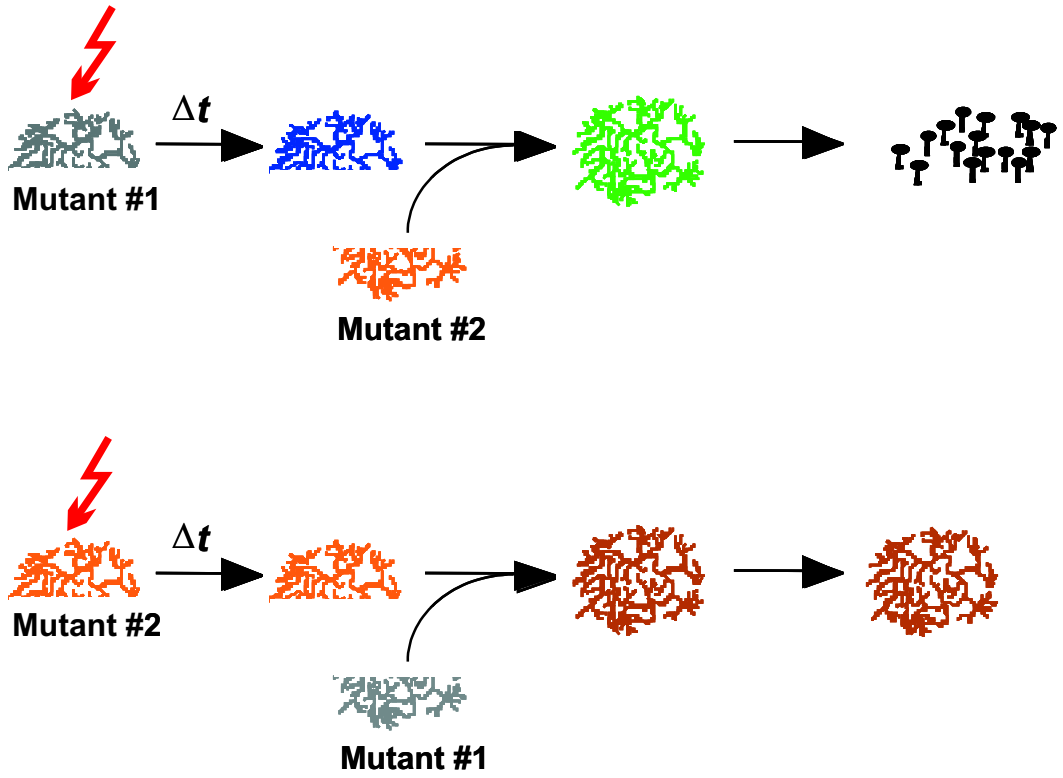

Fig. 6: Scheme of a time-resolved somatic complementation experiment performed by fusion of two mutant plasmodia. Only one plasmodial cell of two mutants is induced by visible light (flash symbol). Complementation depends on (1) which of the two cells has been induced and it depends on (2) the correct delay time between light induction and fusion, which can be evaluated to monitor the ongoing signaling processes.

4.2.3 A Reverse Engineering Framework for the Sporulation Control Network

A theoretical framework to reconstruct (reverse engineer) the sporulation control network from time-resolved somatic complementation results and other experimental data based on hierarchical Petri net modeling and simulation has been developed (Marwan, Wolfgang, et al., 2005). A Petri net is a bipartite directed graph, a mathematical structure built on the basis of precisely defined rules (Baumgarten, Bernd, 1996; Pinney, John W., et al., 2003). Petri nets are able to consistently display functional and molecular data within one single, coherent model, while at the same time describe processes occurring at different levels of complexity. 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 without a mathematical background, and yet can also be numerically simulated to reproduce quantitative and time-resolved experimental results. In addition, it can be converted into other graph types for further mathematical analyses. Based on the theory of time-resolved somatic complementation (Marwan, Wolfgang, 2003 b), the theoretical framework should consistently reverse engineer the molecular network (Marwan, Wolfgang, et al., 2005), whose resolution depends upon the number of elements identified by mutation or other analytical methods.

4.2.4 Sequencing of an Arrayed Normalized Full-length cDNA Library and Preparation of an Antisense Expression Screen

In cooperation with Gernot Gloeckner at the Institute of Molecular Biotechnology in Jena, a normalized full-length cDNA library from sporulation-competent plasmodia has been sequenced. Sequencing of 10,000 clones yielded an approximately two-fold coverage of the 5,000 expressed genes. For each sequence obtained, the corresponding full-length clone is now available (Fig. 7).

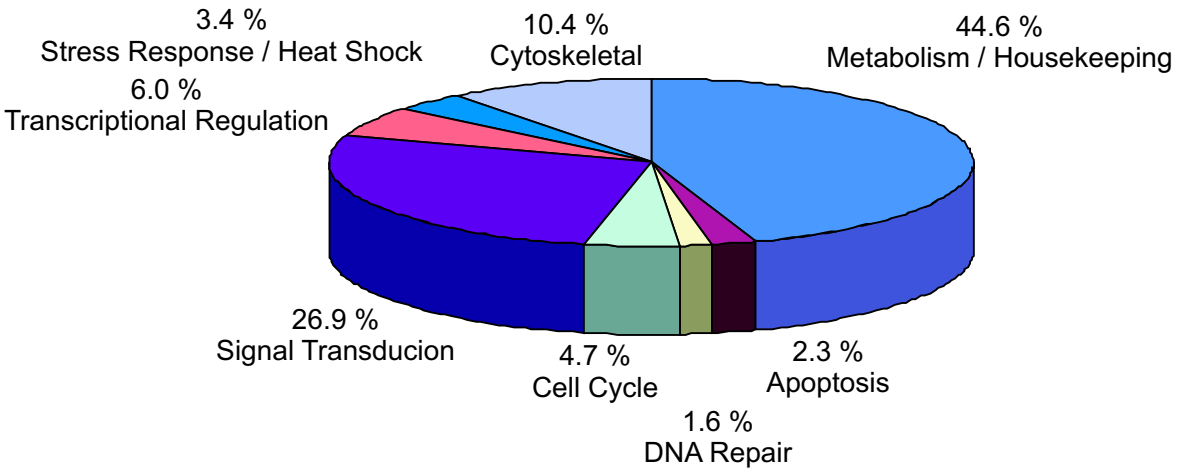

Fig. 7: Assignment of Physarum cDNAs from our sequencing project to genes with known function from other organisms and grouping into functional categories.

It has recently been demonstrated that expression of antisense RNA can knock down genes in *Physarum polycephalum* (Materna, Stefan C. et al., 2005). The vectors

developed for this purpose can now be used to screen knockouts of selected genes or all members of a class of genes with the corresponding arrayed clones of the sequenced cDNA libaray. The results obtained by cDNA sequencing were communicated to the National Human Genome Research Initiative (NHGRI), which is currently sequencing the complete *Physarum polycephalum* genome.

4.2.5 Setting up of a Gene Discovery Pipeline

After establishing the experimental and theoretical foundations for the generation of mutants, their time-resolved somatic complementation and the reverse engineering of the network from complementation data, the next steps will be the systematic screening and characterization of mutants and the molecular identification of the genes, defining the biochemical elements of the network.

To be thorough, we must choose mutagenesis and screening conditions that do not systematically miss certain classes of genes due to their regulatory properties (i.e. nodes that are redundant or lethal upon deletion). Therefore screens based on chemically induced point mutations must be included, since antisense expression screens or knockouts by gene replacement will not yield all types of genes.

To allow for map-based cloning, which greatly pays off when genes tagged by point mutation are to be cloned on a systematic basis, we plan to generate a HAPPY map in cooparation with Gernot Gloeckner at the Institute for Molecular Biotechnology at Jena and Paul H. Dear at Medical Research Council (MRC), Cambridge, UK.

4.2.6 Single Cell Proteomics: Dynamics of the Cytoplasmic and the Nuclear Proteome on the Way to Commitment to Terminal Differentiation

In order to monitor the regulatory processes and the effects of mutations at the level of the proteome, a proteomics pipeline consisting of the 2D-DIGE technology (fluorescence two-dimensional Difference Gel Electrophoresis) and a spot picker has been set up. In cooperation with Erdmann Rapp, we have established the identification of picked *Physarum* protein spots by mass spectrometry. The sequenced normalized cDNA library now allows the identification of almost all proteins picked from a 2D gel with multiple samples taken from the same single cell at different stages before and after commitment.

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 Appointments and Awards

In 2003, W. Marwan was appointed as research professor at the Science and Technology Research Centre at the University of Hertfordshire, UK.
In 2004 W. Marwan was offered a tenured full professor position at Virginia Tech, Blacksburg, VA (USA) and subsequently a full professor position at the Otto-von-Guericke University, which he finally accepted.

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Research Group:

Systems Biology (SBI)

Prof. Dr.-Ing. Ernst Dieter Gilles

This report covers the period from May 2003 to September 2005.

1 Group Introduction

As an emerging field of interdisciplinary research, Systems Biology studies the interplay of relevant components of a specific cellular system with the help of a system-theoretical framework. Only such a holistic approach will be able to link qualitative biological knowledge with the overwhelming amount of quantitative and qualitative data that is currently produced by cell biologists. The Systems Biology approach is expected to lead to a better understanding of the phenomena of cellular life and to allow better and faster solutions to medical and biotechnological problems.

According to the interdisciplinary character of Systems Biology, the SBI group consists of researchers from biology, systems science and computer science working jointly on a number of projects. Model organisms investigated by our group experimentally as well as by mathematical modeling are the eubacteria *E. coli* and *R. rubrum*. Accordingly, projects dealing with these organisms are one highlight of our research. Additionally, as an important strategy of our group, several collaborations with external biologists have been established during the last years. This includes a close collaboration with Prof. Marwan (formerly University of Hertfordshire; since 2005 MPI/University Magdeburg) on phototaxis of Halobacteria. Modeling only prokaryotic systems would disregard the higher complexity that appears in eukaryotic organisms. We therefore initiated several research projects dealing with eukaryotic signal transduction pathways, in particular those involved in apoptosis, proliferation and cell cycle. Recently we established a new cooperation with Prof. Schraven (Institute for Immunology, University Magdeburg) on the immunological important signaling pathways controlling T-cell activation. As an important aspect, the broad spectrum of cellular systems we are modeling will enable us to compare prokaryotic with eukaryotic signal transduction systems and to see whether they require different modeling concepts or not. Besides, a broad basis of case studies is required, when general design principles and system-theoretic properties of living systems (like robustness and modularity) are examined.

An important issue in Systems Biology is to conceive generic theoretical methods and software tools that fit the particular requirements when modeling cellular systems. Our activities in this area include the elaboration of a method to reduce the combinatorial explosion arising in modeling the occupancy of binding sites of

proteins. We also apply methods from systems theory that allow decomposition and a modular analysis of signaling networks. Structural analysis of cellular networks and understanding the design principles behind the robust behavior of cellular systems are another two important fields of our theoretical research.

Systems biology requires the development of appropriate software tools. Our effort is twofold: ProMot/DIVA is a powerful general-purpose simulator of 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 visualizing large cellular networks. FluxAnalyzer, the second software tool developed in our group, is a graphical user interface facilitating comprehensive topological studies in large-scale biochemical networks.

Several of these methodological projects are funded by the “Systems of Life – Systems Biology” research initiative (German Federal Ministry of Education and Research (BMBF)). Within this initiative, our group is a member of the modeling platform (speaker Prof. Gilles) supporting systems biology projects on hepatocytes and we are also involved in modeling important signal transduction pathways of the liver.

At the MPI Magdeburg, our Systems Biology group is in close neighborhood of (chemical) engineers and systems scientists. Systems theory is an essential part of systems biology and (bio)chemical engineering. Accordingly, in several projects we work jointly in cooperation with other research groups of the MPI, including projects on model discrimination (with SCT), parameter estimation methods (PCF), modeling and simulation platforms (ProMot/DIVA; with PSD, PCF) and metabolic network analysis (with BPE).

Furthermore, cellular and complex technical (chemical plants, traffic, internet) systems share a number of design principles. A typical example is “robustness”, which is a desired goal in technical processes and a realized (inherent) property of biological systems. Thus, engineers may learn from cellular systems how to construct and to control a robust functionality, whereas successful design principles of technical systems may help the (systems) biologist to identify and to understand cellular regulatory circuits. Other examples of common design principles are modularization and hierarchical structuring.

As a consequent step, funded by the government of Sachsen-Anhalt, a new joint research project “Dynamical Systems” has been founded in Magdeburg in 2004. Scientists from the MPI and University Magdeburg (involved faculties: chemical engineering, electrical engineering, medicine, mathematics) extend the collaboration between the engineering, systems and biomedical sciences in Magdeburg. The systems biology group of the MPI is substantially involved in this new initiative; Prof. Gilles is speaker of it.

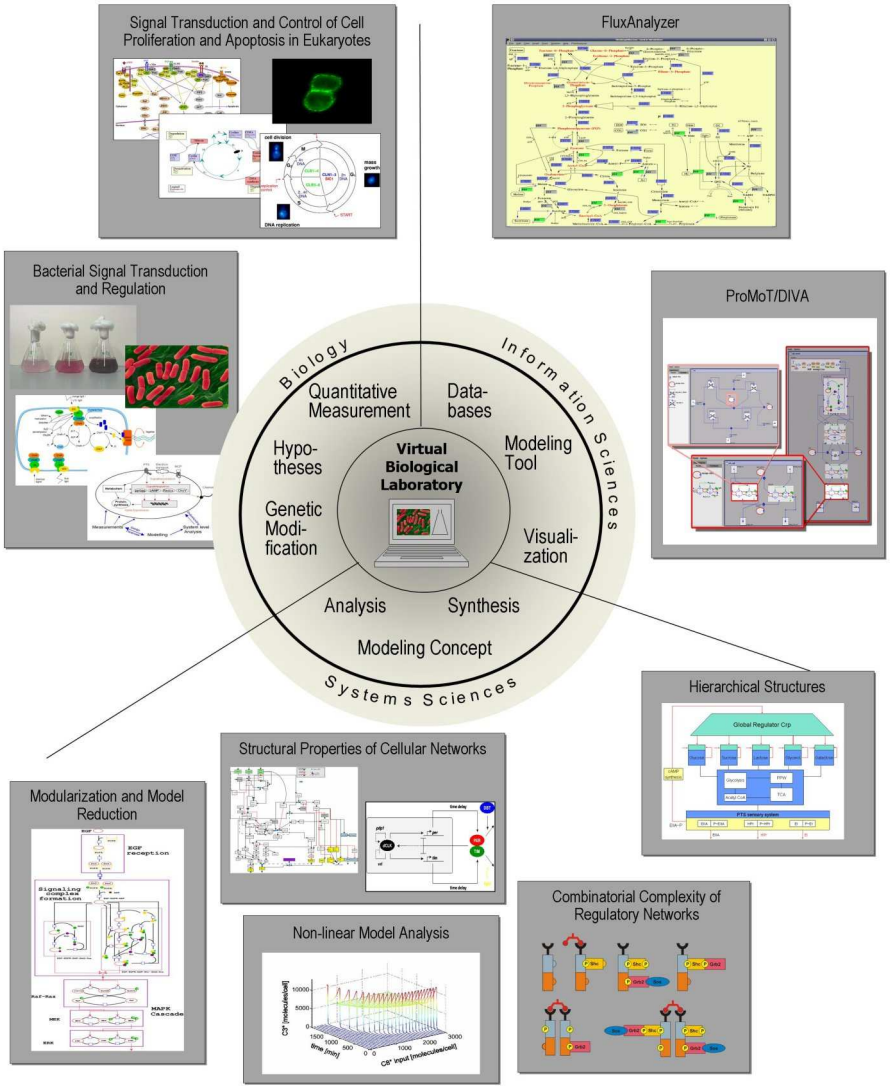

Fig. 1: Research activities of the SBI group

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	
Dr. Detlev **Bannasch**	Postdoc	03/2005
Dr. Katja **Bettenbrock**	Scientific Employee	09/1998
Ralph **Bittner**	Ph.D. Student	09/1999
Jan **Blumschein**	Ph.D. Student	09/2002
Dr. Hartmut **Grammel**	Scientific Employee	03/1998
Dr. Steffen **Klamt**	Postdoc	05/1998
Dr. Andreas **Kremling**	Scientific Employee	03/1998
Tobias **Backfisch**	Ph.D. Student	03/2000
Sophia **Fischer**	Ph.D. Student	03/2001 - 02/2005
Martin **Ginkel**	Ph.D. Student	11/1998
Rebecca **Hemmenway**	internship	06/2005
Jeremy **Huard**	Ph.D. Student	06/2004
Sebastian **Mirschel**	Ph.D. Student	06/2004
Tobias **Neuhaus**	Ph.D. Student	02/2005
Torsten **Nutsch**	Ph.D. Student	01/2000 - 12/2004
Julio **Saez Rodriguez**	Ph.D. Student	03/2002
Dr. Jörg **Stelling**	Ph.D. Student	08/1998 - 01/2005
Xiaoqian **Wang**	Ph.D. Student	06/2004
Technical staff:		
Andrea **Focke**	Laboratory Co-worker	12/2003
Britta **Laube**	Laboratory Co-worker	04/1999 - 09/2003
Helga **Tietgens**	Laboratory Co-worker	07/2001
Ruxandra **Rehner**	Laboratory Co-worker	10/1999
Group at Stuttgart University:		
Holger **Conzelmann**	Ph.D. Student	10/2003
Dr. Sybille **Ebert**	Postdoc	05/2003 - 08/2005
Michael **Ederer**	Ph.D. Student	02/2003
Markus **Koschorreck**	Ph.D. Student	04/2005
Dr. Thomas **Sauter**	Postdoc	01/1998

Tab. 2: Visiting Scientists

Prof. Joseph Lengeler	University Osnabrück, Germany
Octavian Bucur	University Bucharest, Romania
Prof. Doraiswami Ramkrishna	University West Lafayette, USA
Neda Bagheri	University Santa Barbara, USA

3 Research Activities

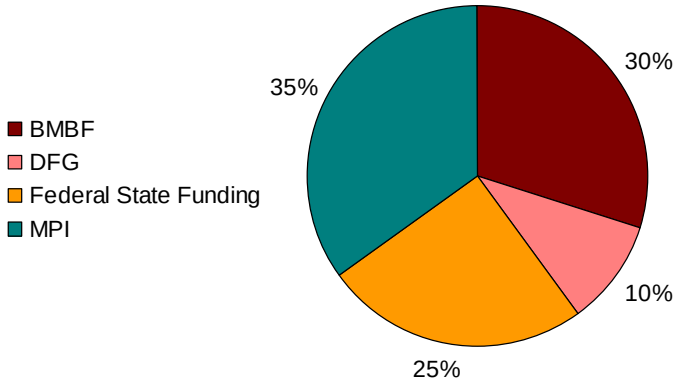

Fig. 2: Funding of the projects of the SBI-group

Tab 3: Project Area: Hierarchical Structures

Project: **Signal transduction and regulation in bacterial cells and eukaryotes**	The analysis of regulatory processes is the key to a better understanding of the behavior of cellular systems. We investigate a number of prokaryotic and eukaryotic regulatory and signal transduction systems. The activities are focused on: • Set up of detailed mathematical models • Experimental investigations to stimulate the biological system in different ways (nutrient limitation, mutations) • Modular/hierarchical structuring of signal transduction networks • Model analysis with system-theoretical methods			
Title / Subproject	**Scientists**	**Funded by**	**Start**	**Partners**
Mathematical modeling of cell cycle regulation in eukaryotes	Huard, Stelling	BMBF, SFB 495	03/98	Leipzig Univ. (Prof. Bader), Stuttgart Univ. (Prof. Seufert)
Analysis of the T-cell receptor induced MAP kinase cascade	Saez-Rodriguez, Wang	DFG	07/03	Magdeburg Univ. (Prof. Schraven)
HGF/c-Met signaling pathway and *H. pylori*	Ebert	Federal state funding	07/04	Magdeburg Univ. (Prof. Naumann)
Redox control in photosynthetic bacteria	Grammel, Klamt, Sommer	Federal state funding, MPI	03/98	Stuttgart Univ. (Prof. Ghosh), Magdeburg Univ. (Prof. Reichl)
Catabolite repression in *E. coli*	Bettenbrock, Ederer, Fischer, Kremling	Federal state funding, MPI	03/98	Osnabrück Univ. (Prof. Lengeler, Dr. Jahreis)
Regulation of the stress sigma factor σ^S in *E. coli*	Backfisch	MPI	01/01	FU Berlin (Prof. Hengge)
EGF-induced MAP kinase cascade	Schöberl, Saez- Rodriguez	Federal state funding, SFB 495, MPI	04/00 -	Stuttgart Univ. (Prof. Pfizenmaier), MIT Boston (Prof. Lauffenburger)

Tab 4: Project Area: Coupled Processes

Project: **Coupled processes in cellular systems**	Cellular systems are characterized by coupling of metabolic and regulatory processes. Furthermore, the regulatory machinery is set up by highly coupled signaling pathways and regulatory systems. This coupling gives rise to a non intuitively understandable complex behavior. Activities are focused on: • Analysis of coupled signaling pathways • Coupling of gene expression to signal transduction • Coupling of signaling processes to flagella motor			
Title / Subproject	**Scientists**	**Funded by**	**Start**	**Partners**
Analysis of pro- and ant apoptotic signaling pathways	Sauter, Saez-Rodriguez, Koschorreck	BMBF	04/04	Philadelphia Univ. (Prof.Kholodenko), Leipzig Univ. (Prof. Bader)
Two-component signal transduction in *E. coli*	Kremling	DFG, MPI	07/02	Univ. Munich (Prof. Jung)
Interaction of global regulators in *E. coli*	Bettenbrock, Kremling, Ederer	Federal state funding, MPI	01/03	Stuttgart Univ. (ISR), Freiburg Univ. (Prof. Rak)
Phototaxis in *Halobacterium salinarium*	Neuhaus, Nutsch	MPI	01/01	MPI Biochemie (Prof. Oesterhelt), MPI (MNA group)

Tab. 5: Project Area: Network Theory

Project: **Computer Aided Modeling and analyses of cellular systems**	In various projects dealing with complex system dynamics, mathematical models are of great importance. These models have to be developed in a systematic manner and should be implemented in a comprehensible and reusable form. These projects investigate the field of computer-aided modeling and work on developing computer tools for the set up and numerical analysis of these models. Activities are focused on: • Software tools to support model setup and simulation • Development of methods for model analysis (structural properties, experimental design) • Visualization of genetic networks • Development of model libraries for all subprojects			
Title / Subproject	**Scientists**	**Funded by**	**Start**	**Partners**
Visualization of complex networks	Mirschel, Ginkel	BMBF	06/04	
Structural and qualitative analysis of regulatory networks	Klamt Saez-Rodriguez	BMBF	04/04	MDC Berlin (Dr. Schuster)
Modeling concept for regulatory networks	Conzelmann Saez-Rodriguez	BMBF	04/04	Philadelphia Univ. (Prof. Kholodenko)
Model based measurements in cell culture reactors	Kremling, Koschorreck	BMBF	04/04	Leipzig Univ. (Prof. Bader)
Methods for model discrimination and reverse engineering	Kremling, Fischer, Sauter	MPI	07/02	California Univ. (Prof. F. Doyle)
Modular modeling concept and modular	Kremling, Saez-Rodriguez	MPI	01/01	Osnabrück Univ. (Prof. Lengeler),

	analysis of signaling network				MPI (PSD, SCT group)
	Stoichiometric network and metabolic pathway analysis	Klamt, Stelling	MPI	01/01	MDC Berlin (Dr. Schuster), MPI (SCT, BPE group)
	Modeling and simulation tool ProMoT/DIVA for biological systems	Ginkel, Mirschel	MPI	01/99	Donezk Univ. (Prof. Svjatnyi), MPI (PSD group)
	Robustness analysis in circadian clocks	Stelling	MPI	07/02 -	California Univ. (Prof. F. Doyle)

4 Research Highlights

4.1 Research Highlight: Bacterial Signal Transduction and Regulation

Introduction and objectives

Bacteria are able to respond very efficiently to alterations of the environmental conditions. To cope with these changes they posses a number of sensory and regulatory systems those allow a fast and precise response. Because of the complex interactions of bacterial signal transduction systems with each other and with central metabolic pathways, these systems are impossible to interpret intuitively. Understanding these systems and cellular behavior requires the combination of biological methods that analyze molecular mechanisms of signal perception and transduction with powerful mathematical and system theoretical methods that allow the analysis of complex systems even in a quantitative manner.

In the SBI group different bacterial signal transduction systems are under investigation starting from relatively simple specific regulations to complex global regulatory systems. While the focus of projects dealing with the simple systems is to understand and investigate the basics of signal transduction and regulation (from a theoretical point of view) the focus of the projects dealing with complex regulations is to understand the interactions of different regulatory and metabolic systems as well as to find methods or approaches for modularization, model reduction, model discrimination and linkage of models.

4.1.1 Catabolite Repression in *E. coli*

Catabolite Repression is a global regulatory phenomenon in *E. coli* that influences the expression of a number of genes that code for metabolism of carbohydrates and amino acids or that are involved in stress response, DNA replication etc. The regulations are exerted by the PEP-dependent phosphotransferase system (PTS)

especially by $EIIA^{Glc}$. In this project biological experiments and mathematical modeling have been combined in order to gain in the understanding of catabolite repression.

A set of isogenic mutant strains was constructed and analyzed in various batch experiments of continuous cultures and pulse experiments. The experiments were designed in order to gain information about the dynamics of $EIIA^{Glc}$ phosphorylation state, cAMP concentrations and gene expression during changes of the environment and were used for the validation of a dynamic mathematical model (Kremling et al, 2003, Kremling et al., 2004a, Sauter and Gilles, 2004). During the validation process the structure of the model had to be refined. In most cases regulatory processes had to be incorporated or they had to be described in more detail, e.g. the regulation of the pts operon by $cAMP{\cdot}CRP$ and by the global regulator Mlc had to be considered. Another important result of the model validation was that the kinetics used for the description of enzymatic reactions might have important influence on the simulation results. The $EIIA^{Glc}$ phosphorylation state determined experimentally could not be reproduced for a set of experiments. Sensitivity analyses hinted to an inadequate description of pyruvate kinase. After changing the kinetics of pyruvate kinase from Michaelis-Menten to Hill type, the $EIIA^{Glc}$ phosphorylation state could be described correctly. As a result of the validation procedure a model exists that describes about 38 enzymatic reactions, including gene expression for some of these, and the dynamics of more then 50 metabolites. Based on the experiments with the help of the ProMot/Diva environment (Ginkel et al. 2003), a great part of parameters could be estimated. The results show that it is possible to validate a detailed mathematical model with a limited set of measured variables if mutant strains and varying experimental conditions are used. It also shows that models can be valuable tools in order to analyze complex biological systems because inadequate assumptions about the regulation will become obvious during appropriate model validation (Bettenbrock et al., submitted, Kremling et al. 2005).

According to the modular modeling concept, cells are composed of a limited set of modules. For each module key compounds exist that are indicators of the current state of the module. If confirmed, this concept will provide an important approach to model reduction. $EIIA^{Glc}$ phosphorylation state and cAMP concentrations could be such key components of the module “Carbohydrate Metabolism”. They were analyzed under various experimental conditions. It became obvious that $EIIA^{Glc}$

phosphorylation state varies with growth rate and is coupled to cAMP production. The results indicated that the most important inputs on $EIIA^{Glc}$ phosphorylation state are the pyruvate and PEP concentrations in the cell. Unlike previously assumed it is less important whether a PTS substrate is transported or not. This reveals that the PTS can be regarded as a sensor for the global status of the module “Carbohydrate Metabolism”. The results confirm the hypothesis that there are only few key components in the cell that have to be monitored in order to analyze the general state of the cell.

In the project closely linked to “Catabolite Repression”, we are investigating the bgl-operon of *E. coli*, coding for the ß-glucoside-PTS. It is regulated by an indetermination mechanism that controls the bgl-operon expression in dependence of the phosphorylation state of the PTS components. A simple model showed that due to a positive feedback given by the mechanism of indetermination bistable behavior is possible. This is currently investigated by single cell measurements.

In another interesting subproject dealing with a typical two-component system KdpD/KdpE a model was set up to describe the phosphorylation reactions as well as binding of the KdpE regulator to its DNA binding site. The model was validated by in vitro assays and by measurements with wild type and mutant strains (performed in collaboration with Prof. Jung, University of Munich) (Kremling et al., 2004d). Based on the experiments and model analysis a yet unknown control loop could be identified. The time course of the concentrations of the target proteins, KdpFABC, could only be explained if either the rate of protein synthesis or the rate of protein degradation is controlled. Mathematical modeling will now be used to design a new experiment that will allow distinguishing between both hypotheses.

Similar results were obtained in a subproject dealing with the regulation of the stress sigma factor σ^S in *E. coli*. The core regulation of rpoS with transcription, translation, proteolysis and competition of the sigma factors for polymerase was investigated with a mathematical model. Analyses revealed the importance of homeostatic feedback regulation of σ^S and the response regulator RssB for the dynamics and reliability of the stress responses invoked by σ^S. Testing of hypotheses on a novel translational regulation that has recently been found during experiments performed in the group of Prof. Hengge (FU Berlin) showed that a direct mechanism of feedback regulation by σ^S itself cannot explain the experimental observations. Therefore investigations can

be constrained to the search for an indirect mechanism that involves additional (unknown) intermediates (Backfisch et al., 2005).

4.1.2 Redox Control in Photosynthetic Bacteria

In facultative photosynthetic bacteria, the biosynthesis of photosynthetic membranes (PM) is controlled in a complex way in response to environmental signals such as molecular oxygen and light intensity. Current hypotheses assign a central role to the redox levels of electron transport chain (ETC) components in signal transduction and control of photosynthetic gene expression. We studied the level of cellular redox metabolites and PM formation under different growth conditions in *Rhodospirillum rubrum* by a combination of mathematical modeling and bioreactor experiments. For *R. rubrum* a high-level expression medium has been developed, that yields PM levels under semi-aerobic conditions in the dark, comparable to those observed under phototrophic growth. This finding presents a promising starting point for the elucidation of the molecular signals, which govern PM induction, and raises the question of how the different stimuli (oxygen, light, growth substrates) affect the redox state of ETC's.

Redox control in *R. rubrum* was studied in wild type and mutant strains, defective in ubiquinone-10 (coenzyme Q10, UQ) biosynthesis. Absorbance of the light-harvesting complexes and reaction centers was measured spectroscopically and employed as marker for photosynthetic gene expression.

A mathematical model was developed for the simulation of redox ratios of ETC components under different growth conditions (Klamt, 2005b). These redox states are coupled to the genetic control of PM expression by two signal transduction systems at the level of the Cbb3 oxidase (via RegA/RegB two component system) and the UQ pool (via PpsR repressor). Simulations, using experimentally determined NAD(P)H/NAD(P), ATP, ADP und AMP concentrations as input, predict that UQ is reduced most under low light conditions and gets more oxidized under high light, semi-aerobic dark and aerobic dark growth conditions. Model predictions were verified by the quantitative determination of cellular UQH_2/UQ and of PM levels in bioreactor experiments. Furthermore, quinone profiling by HPLC-MS showed the presence of the alternative quinone rhodoquinone, regardless of the growth condition. While the physiological function of rhodoquinone in *R. rubrum* is still enigmatic, our analysis of bioreactor cultures led to a new hypothesis of how the

interplay of different quinone species affects redox signaling in *R. rubrum* in a complex way by coupling central carbon metabolic pathways to membrane electron transfer processes (Grammel et al., 2003).

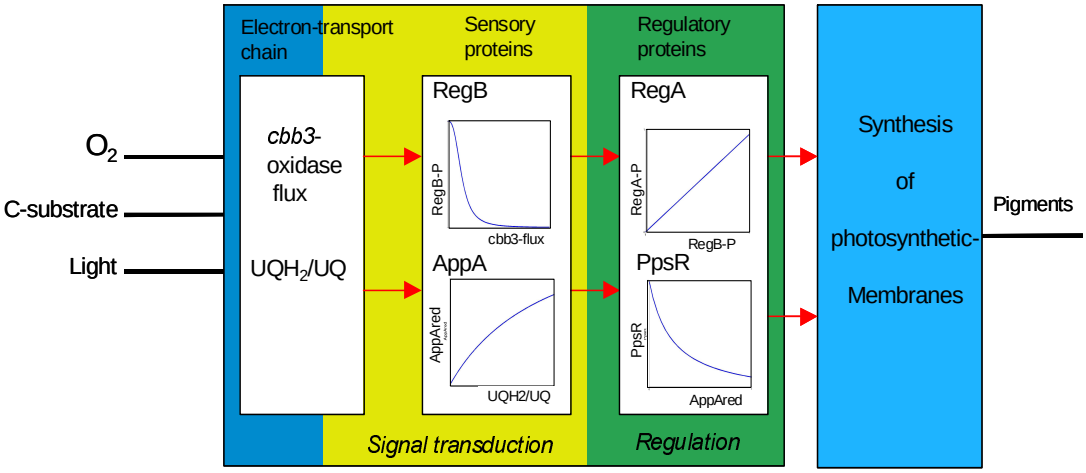

Fig. 3: Redox control of photosynthetic gene expression: Schematic model structure.

Recently we isolated a mutant strain, *R. rubrum* SN20 with reduced UQ levels, due to a defective ubiD gene. Biochemical and spectroscopic analysis showed the presence of functional reaction centers, but lower levels of light-harvesting complex under photosynthetic as well as semi-aerobic conditions. Our results provide the first direct evidence for the quantitative role of UQ in photosynthetic gene regulation.

4.1.3 Phototaxis in Halobacteria

Halobacterium salinarum is able to swim back and forth by rotating a polarly inserted flagellar bundle clockwise or counterclockwise. Unstimulated cells spontaneously switch the rotational sense from time to time performing a random walk. *H. salinarum* can use orange light as a source of energy via the action of the light-driven ion pump Bacteriorhodopsin. A simple kind of color vision (specific for orange, blue and ultraviolet light) allows the cells to swim to those sites of their environment that provide optimal light conditions. Sensing orange light makes a cell to continue swimming until the maximal available intensity is reached. In contrast, blue or ultraviolet light makes a cell reverse its swimming direction and to flee those 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.

For three years we have been modeling the phototactic behavior of *H. salinarum* (Nutsch et al., 2003). The experimental part of our work is achieved by our cooperation partners Prof. Dr. D. Oesterhelt (Max-Planck-Institute for Biochemistry,

Martinsried, Germany) and by Prof. Dr. W. Marwan (formerly University Hertfordshire; since 2005 MPI/University Magdeburg.

By reverse engineering we have detected eight kinetic phases of the symmetric switch cycle of the flagellar motor. Upon switching the rotational sense, the flagellar motor proceeds through four subsequent functional states, named the Refractory-, the Competent-, the Active-, and the Stop-Phase, from which the rotational sense is switched again (Nutsch et al., 2005).

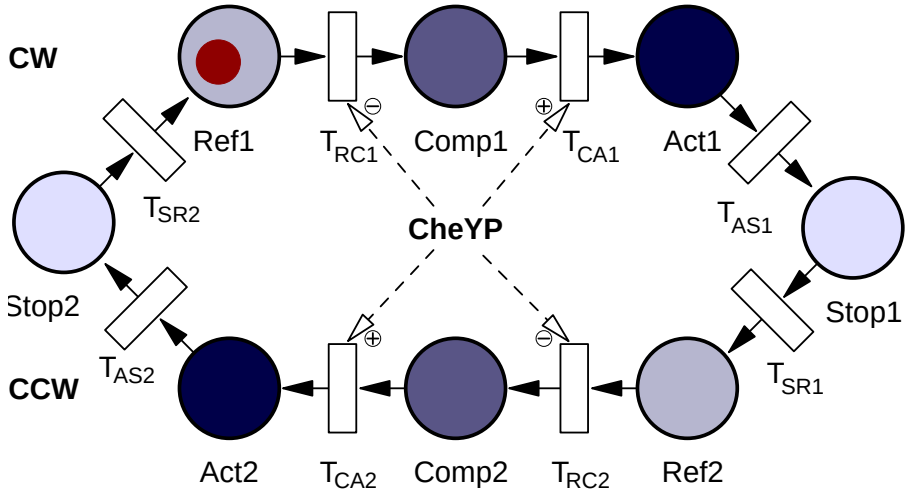

Fig. 4: Petri-Net-Model of all eight functional states of the switch complex. The probability that transition T_{CA1} and T_{CA2} switch is positively regulated by the concentration of CheYP, while it is negatively regulated for T_{CR1} and T_{CR2}. This influence is symbolized by the arrows and a plus or minus sign, respectively.

In the following we estimated the number of rate-limiting steps for each underlying process, necessary to describe its kinetic behavior. Thereby the probability distribution of the duration of the Stop-Phase could be best described by a single first-order reaction. The best representation for the Competent-Phase and the Active-Phase could be achieved through 10 and 44 independent parallel reactions respectively. This led to the conclusion that the switch complex could consist of 44 subunits which all proceed synchronously through the functional states and that each subunit can bind CheYP and that their occupancy level might control the transition probability to the subsequent functional states.

This detailed 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. It explains the motor switching behavior after single and double blue light pulses as well as the spontaneous switching behavior. Even such seemingly paradox results like the repellant effect of an orange light pulse applied after a repellant stimulus are explained by our model.

In our future work we want to extend the model for the receptor-transducer-complex, which plays an important role in the adaptation mechanism, since some effects of this mechanism are still unresolved.

Outlook and perspectives

The results derived from the analysis of bacterial regulatory systems demonstrate that mathematical modeling is an appropriate means for understanding such systems. The most important tasks for the future will be to bring together the various results and to analyze whether there are properties of bacterial regulatory systems that are common to all systems observed so far. The property to establish bistable behavior might be one such common characteristic that will be investigated in detail with model analysis as well as with experiments.

Another important task will be to find appropriate methods for modularization of bacterial systems. This will provide means for model reduction but also means for the setup of models covering broader parts of cells. This future work might e.g. enable one to merge the models of catabolite repression, the *bgl*-operon, σ^S and the two-component system.

Bottom-up approaches, like those used in most subprojects, will always be dependent on detailed biological knowledge. Modeling of global regulatory systems or even their interactions is, additionaly complicated by the size of the involved metabolic and regulatory networks. To cope with this high complexity, strategies for reduced-order modeling of interacting regulatory systems are going to be developed. In a first approach reduced order modeling was tested for the description of central metabolism of *E. coli* in dependence of different oxygen concentrations. By systematically applying the quasistationarity assumption for compounds with high turnover (metabolites) and the rapid equilibrium assumption for fast reactions one can reduce the number of variables and parameters significantly.

In the future this approach will be extended for the analysis of interaction of global regulatory systems in *E. coli*. Here, methods of designing new experiments become more and more important (Kremling et. al. 2004c). The theoretical approach will be accompanied by experimental approaches and will further demand the establishment of global analysis techniques like e.g. analysis of metabolome, transcriptome and proteome. These techniques will be established in close cooperation with the BPE and MNA groups.

4.2 Research Highlight : Signal Transduction and Control of Cell Proliferation and Apoptosis in Eukaryotes

Introduction and objectives

Although important general regulation properties can be deduced from the study of bacterial cells, the analysis of regulatory networks in eukaryotes remains a real challenge due to their higher complexity. An important issue that we are addressing is the control of signal transduction and more particularly of pro- and anti-apoptotic signals. Their balance is the determining factor for either cell proliferation (= completion of the cell cycle) or apoptosis (= programmed cell death) which, in the case of disorder can lead to diseases like cancer. Modeling those mechanisms could allow a better understanding of the organization of the molecular network as well as the design of new biological experiments eventually leading to the identification of potential drug targets. Our group works within the Platform Modeling of the BMBF initiative “Systems Biology – Systems of life” which focuses on hepatocytes. In addition, the study of signal transduction is also applied to the immune system, in particular to T-cell receptor induced signaling.

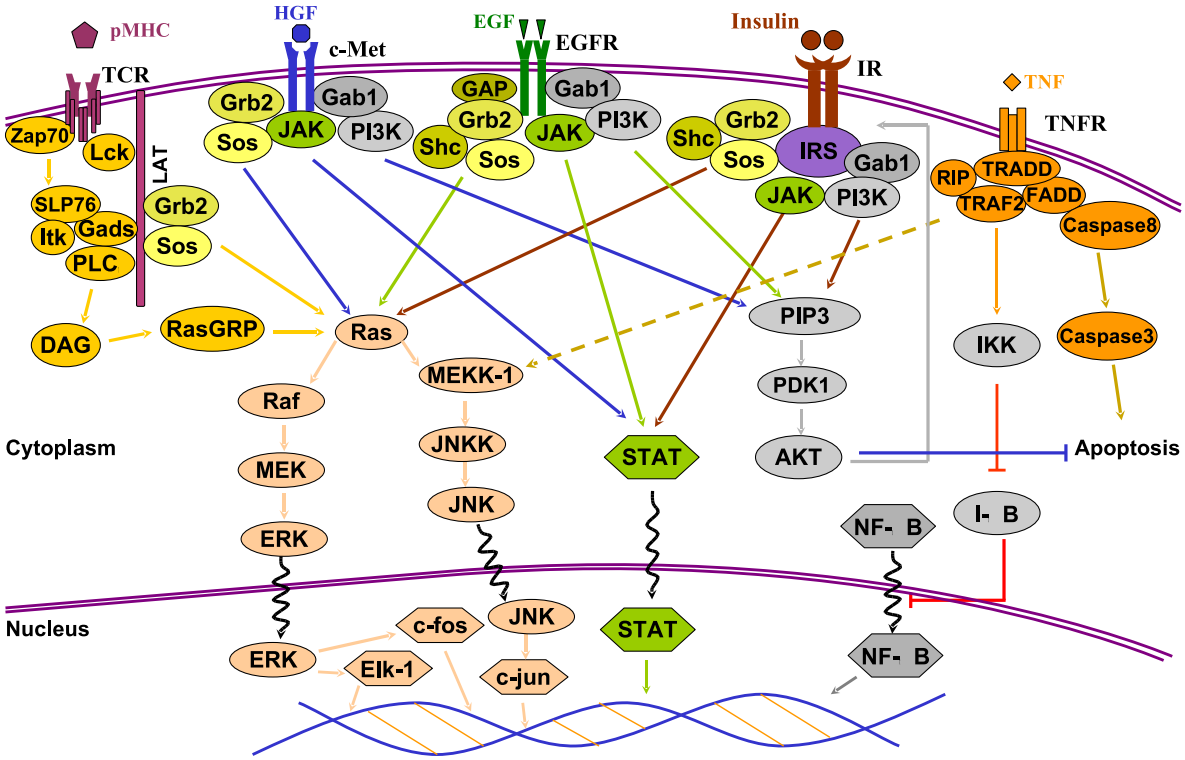

Fig. 5: Overview of the signaling pathways analyzed in our group

As shown in the above picture, one protein can be activated via several pathways. The function and extent of these crosstalks are rarely defined but play a major role in

the overall behavior of the signal transduction network of a cell. Models describing several pathways and their interactions will help to get a better understanding of signaling.

In order to deal with their inherent complexity, the systems are decomposed into modules according to the modular modeling concept facilitated by the use of ProMoT. We also take into account the combinatorial complexity due to the formation of protein complexes and apply it to the systems under study. Finally, in order to analyze such complicated, interlaced networks and their ability to keep their functionalities in case of genetic or environmental perturbations, methods for sensitivity analysis have to be developed. This has been done via the example of the circadian clock in Drosophila.

4.2.1 Analysis of Pro- and Ant apoptotic Signaling Pathways

From the range of signaling systems in mammalian cells we have focused on two families: receptor tyrosine kinases (RTKs), in particular EGF-, HGF- and Insulin-receptors, and the death receptors TNF-R1 and -R2.

Our first efforts concentrated on the development of a detailed model of the anti-apoptotic signals, in particular the EGF receptor activated MAP kinase cascade (Schoeberl et al., 2002) which was subsequently decomposed in a modular manner (Saez-Rodriguez et al., 2004, Saez-Rodriguez et al., 2005) and analyzed. It could be shown that the low sensitivity to ligand concentration can be traced back to the saturation of the ERK module. Furthermore, based on simulation studies the models of the individual modules could be simplified significantly (Conzelmann et al. 2004). Currently, we are extending the analysis to other RTKs (insulin receptor and c-Met). Our group is a founding member of the International Receptor Tyrosine Kinase (RTK) Networks Consortium (www.rtkconsort.org).

Apoptosis is an important physiological process crucially involved in development and homeostasis of multicellular organisms. Although the major signaling pathways have been unraveled, a detailed mechanistic understanding of the complex underlying network remains elusive. We have translated the current knowledge of the molecular mechanisms of the death-receptor-activated caspase cascade into a mathematical model. A reduction down to the apoptotic core machinery enables the application of bifurcation methods to evaluate the system behavior within a wide range of parameters. Using parameter values from the literature, the model reveals

an unstable status of survival/life steady state indicating the need for further control. Based on recent publications we tested one additional regulatory mechanism at the level of initiator caspase activation and demonstrated that the resulting system displays desired characteristics such as bistability. In addition, the results from our model studies allowed us to reconcile the fast kinetics of caspase 3 activation observed at the single cell level with the much slower kinetics found at the level of a cell population (Eißing et al., 2004).

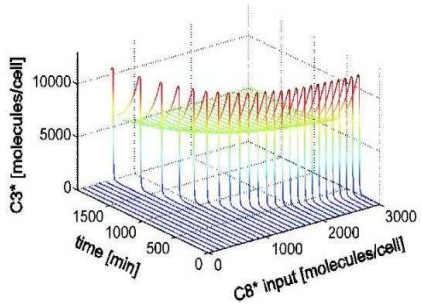

Fig. 6: Simulation experiments (with varying initial C8* concentrations) showing the bistable behavior of the model

4.2.2 Analysis of the T-Cell Receptor induced MAP Kinase Cascade

T-lymphocytes play a predominant role in the immune system. Their key ability is to distinguish foreign, potentially dangerous agents among the myriads of components of our own body and react appropriately. T-cells recognize antigens by means of the T-cell receptor (TCR). The binding of the antigen to the TCR triggers several signaling cascades, among them the ERK MAP kinase cascade.

The aim of this project is, in collaboration with the Institute for Immunology at the University of Magdeburg (Prof. Schraven), to analyze the dynamics of the MAP kinase cascade upon TCR activation in transgenic mice.

Current work pursues a model discrimination: it could be shown that solely the well known elements of the signaling network cannot reproduce the experimental data, and we are now testing potential regulatory mechanisms (feedback inhibition, degradation, etc.) to see which one could be responsible for the observed dynamics. Furthermore, we are analyzing a larger T-cell signaling network using structural approaches (see Research Highlight 4.3.2).

4.2.3 Mathematical Modeling of Cell Cycle Regulation in Eukaryotes

As an example of complex regulatory networks, a detailed model of the yeast cell cycle (S. cerevisiae) was developed, with special focus on the mitotic control,

presenting four distinct checkpoints and thus a relatively high complexity (Stelling and Gilles, 2004; StellingPhD, 2004). Although alternative approaches like graph theory or structural analysis exhibit important properties of the network such as pathway redundancy or even robustness, only a mechanistic model allows for precise simulations of dynamic systems and corresponding predictions (Stelling, 2004). In a context of scarce experimental data and/or biological knowledge, the parameter identifiability becomes an important issue. In accordance with the concept of High Optimized Tolerance (Stelling et al., 2004), robustness and sensitivity were proved to coexist.

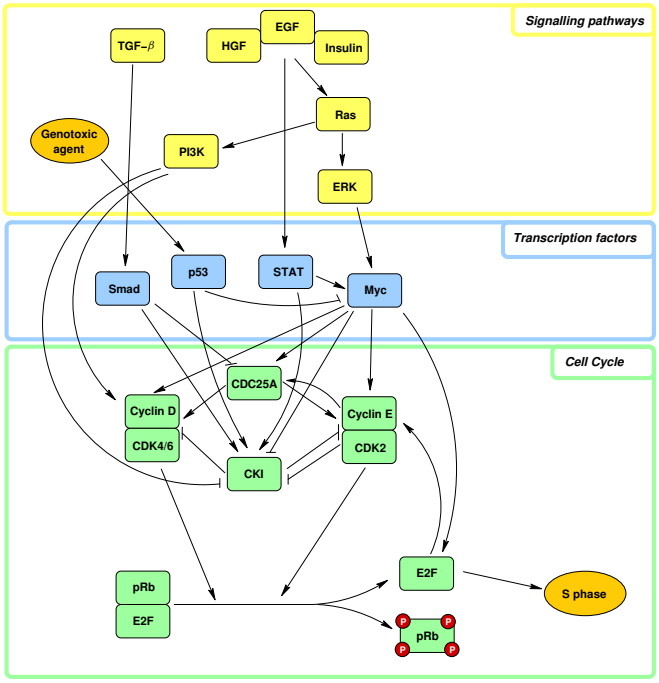

Fig. 7: Connecting signaling transduction pathways to cell cycle

As the cell cycle machinery is a conserved system in evolution, the yeast cell cycle presents many similarities with higher eukaryotes. A current project focuses on the proliferation control in hepatocytes. Analyzing cell proliferation and specifically proliferation control, implies the consideration of the cell cycle mechanism itself in addition to its interaction with signal transduction pathways such as EGF, HGF or TGF-β. They activate a sequence of events mainly controlled by cyclins complexed with cyclin dependent kinases (CDK), which leads to the progressive activation of the transcription factor E2F, controlling the S-phase entry. The switch occurring at this point is irreversible and followed under normal conditions by the cell cycle completion. Thus the restriction point (i.e. G1-to-S transition) measures the intensity

of the mitogenic signals before switching from preparation to proliferation. This is the most important event of the proliferation decision. We are addressing the issue of irreversibility as well as other questions by system-theoretical methods, e.g. bifurcation analysis.

4.2.4 Modeling Concept for Interactions of Macromolecules

Receptor-mediated signal transduction is the subject of intense research since it plays a crucial role in the regulation of a variety of cellular functions. The ligand binding to a receptor triggers conformational changes that allow for receptor dimerization and phosphorylation of numerous residues. The subsequent formation of multiprotein signaling complexes on these receptors and their scaffolding adaptor proteins initiates a variety of signaling pathways. The number of feasible different multiprotein species grows exponentially with the number of binding domains, and can easily reach thousands or even millions. Models accounting for this combinatorial variety become extremely huge and impractical for many applications.

However, we are able to show that under realistic assumptions on domain interactions, the resulting models are able to be lumped together and therefore the dynamics of the considered signaling pathways can be described exactly by reduced models (Conzelmann et al., 2005, Saez-Rodriguez 2005b). In most relevant cases the models can be reduced from thousands or even millions of ODEs down to a few hundred or even less. Additionally, the reduced models feature a modular and hierarchical structure, which extremely simplifies e.g. model analysis or parameter identification. Thus, the method we developed provides a rigorous way to handle a large class of signaling and regulation networks. In addition, the states of the reduced models describe biologically highly relevant quantities like levels of occupancy of the binding domains. This implies that molecular domains and not molecules are the fundamental elements of signal transduction.

In contrast to many other model reduction methods our approach is independent of exact numerical values. Often, only qualitative biological knowledge about domain interactions is needed to derive reduced model equations. For instance, data reported for receptor tyrosine kinases provide qualitative knowledge about domain interactions. The ligand binding to these receptors controls their dimerization and the rate of phosphorylation of docking sites, which bind multiple partners.

4.2.5 Robustness Analysis in Circadian Clocks

Robustness, a relative insensitivity to perturbations, is a key characteristic of living cells. As such, robust performance was a plausible objective during evolution, shaping the design of genetic circuits and driving the complexity of cellular control. In turn, one can hope to obtain clues on cellular design principles by formal robustness analysis of present-day control in cellular systems, especially when it includes mathematically controlled comparisons. This requires elucidating specific structural characteristics that are responsible for robust performance. Even for genetic circuits of moderate complexity, however, these features are presently unclear.

Formal sensitivity analysis allows one to investigate the robustness and fragility of mathematical models for regulatory networks, but it yields only local properties with respect to a particular choice of parameter values. We proposed that by systematically investigating the parameter space, one can derive more global properties specific for the design of a genetic circuit. Our analysis focuses on the genetic oscillator responsible for generating circadian rhythms in Drosophila as a prototypic dynamic regulatory system. By comparing closely related mathematical models representing alternative feedback architectures, we showed that the regulatory structure largely determines the trade-off between robustness and fragility (Stelling et al., 2004; StellingPhD, 2004).

At a detailed level, rank-ordered parameter sensitivities can be employed, for instance, to correctly identify protein phosphorylation as an influential process determining the oscillator's period. More generally, sensitivity analysis reveals `hidden´ mechanisms of hierarchical control through general cellular components. This concurs with the theoretical insight that hierarchies might be important for achieving robustness. The complex feedback structures encountered in vivo, however, do not seem to enhance robustness per se, but to reflect a careful management of robustness that is adjusted to both the physiological function of the clock and its operating conditions. They confer robust precision and adjustability of the clock in the face of frequently occurring perturbations, while simultaneously reducing the risk of catastrophic failure in more rare scenarios.

The example of circadian oscillators, hence, aligns well with studies on bacterial chemotaxis in demonstrating that analysis of how robust the system is helps one to understand the design of gene circuits derived from their physiological role (Zak et al., 2005). In particular, it delivers hypotheses that reach beyond those from

homologies in components or network structures alone. The methods showed promise for generalization to more complex biological systems.

Outlook and perspectives

The use of an object-oriented software such as ProMoT eases the coupling of the models of complementary signaling pathways. This can be applied to study the crosstalk phenomena emerging from the proteins shared by different receptors, like for example the transcription factor NF-κB which can be activated by two different anti-apoptotic pathways downstream of TNF-R1 as well as by an insulin-receptor induced pathway or pro-apoptotic pathways.

In the same order of ideas, we plan to connect signal transduction to cell cycle in order to be able to predict the decision of a mammalian cell (i.e. proliferation or death) given a mitogenic stimulation. This aims to the identification of extremely important proteins that can become potential drug targets.

In another project related to signaling pathways, we investigate the interaction between the bacterium Helicobacter pylori and the epithelial cells of the stomach, with a special emphasis on how H. pylori influences c-Met signaling for its own benefit.

4.3 Research Highlight : Qualitative and Structural Analysis of Cellular Networks

Introduction and objectives

Systems biology aims to provide a holistic understanding of biological networks. One of the ultimate goals is the construction of dynamic models, whose parameters are measured or estimated with the help of systematic experiments. However, in large networks with hundreds of players and interactions, the available set of quantitative data is often not sufficient for building predictive dynamic models. Here, qualitative approaches relying solely on the often well-known network structure may, nevertheless, provide helpful insights.

4.3.1 Stoichiometric Network and Metabolic Pathway Analysis

The goal of stoichiometric (structural) analysis is to clarify the relationships between structure, function and regulation in metabolic networks. Stoichiometric studies are based on topological information and do not require kinetic data. For about four years, our group has been developing methods and tools for stoichiometric network

analysis, mainly relying on the concept of elementary modes. Our contributions include a large-scale assessment of elementary modes emerging in the central metabolism of *E. coli* (Stelling et al., 2002), the development of a comprehensive software platform for stoichiometric network analyses (FluxAnalyzer; Klamt et al. 2003b), studies on the combinatorial complexity of pathway analysis (Klamt et al., (2002b), a theoretical comparison of the two most prominent concepts for network-based pathways (Klamt et al., 2003a) and a work highlighting the rule of elementary modes for calculability issues in metabolic flux analysis (Klamt et al., 2002a).

In the last evaluation period we consequently continued and extended our research on metabolic network analysis. We introduced the concept of minimal cut sets as a dual theory to elementary modes (Klamt et al., 2004a, 2005a). Whereas elementary modes represent operational modes, i.e. smallest sets of reactions able to perform a function, minimal cut sets (MCSs) are in contrast non-decomposable failure modes, i.e. smallest sets of reactions whose removal will repress certain network functions. We gave a mathematical definition of MCSs and devised an algorithm for computing all MCSs with respect to a user-defined deletion task (Klamt, 2005a). A number of potential applications have been pointed out, in particular for target identification and structural fragility (robustness) analysis. We determined and examined all the MCSs that inhibit growth of *E. coli* (Klamt et al., 2004a). This study highlighted that the overall network fragility as well as the places of local fragilities in the network do strongly depend on environmental conditions (e.g. available substrates) and are thus properties that cannot be assigned to a network structure without a clear specification of the environment.

The computation of elementary modes in large networks is a hard computational task and requires therefore sophisticated algorithms. In cooperation with Julien Gagneur (Cellzome AG) the algorithmic approaches for computing elementary modes were reviewed and unified (Gagneur et al., 2004). We showed that computing the set of elementary modes is equivalent to computing the set of extreme rays of a convex cone. This equivalence offers opportunities for employing tools from polyhedral computation for metabolic pathway analysis. From this general theoretical framework we introduced a new method, the binary approach, which computes the elementary modes as binary patterns of participating reactions from which the respective stoichiometric coefficients can be computed in a post-processing step. The new binary approach decreases the memory demand up to 96% without loss of speed

giving the most efficient method available for computing elementary modes to date. Examples showed that the binary approach facilitates the computation of elementary modes in considerably larger networks (Gagneur et al., 2004).

Our software package FluxAnalyzer is still being developed and continuously extended by new functionalities and algorithms for metabolic pathway analysis (Klamt et al., 2003b, Kremling et al., 2004). The newly elaborated binary algorithm for elementary-modes computation has been incorporated (Gagneur et al., 2004) and the computation and assessment of minimal cut sets is now also supported by FluxAnalyzer (Klamt et al., 2004a]. FluxAnalyzer is also used by BPE for network analysis of mammalian cells. In addition, more than 250 copies of the FluxAnalyzer have been requested by international research groups and 3 industrial corporations.

4.3.2 Structural and Qualitative Analysis of Signaling and Regulatory Networks

Whereas the theory for stoichiometric analysis of metabolic networks is now established and extensively used by the scientific community, only few approaches are available facilitating a structural analysis of signaling and regulatory/genetic networks in a similar way. Such methods will become essential for studying large-scale signaling networks which are currently under reconstruction. In a recently started project we therefore investigate which methods can be employed for a functional analysis of cellular interaction networks. The applicability of developed algorithms will be tested in realistic signaling networks. Here is a brief overview on the results we obtained in the first months of this project (Klamt et al., 2005c).

At first we examined whether stoichiometric models of signaling networks are an appropriate description facilitating a functional network analysis. Using realistic networks we came to the conclusion that this is not the case because flows of signals and information (typical for that kind of networks) cannot be represented properly in a mass-flow oriented model.

We therefore pursue two different formalisms for representing signaling and regulatory networks: interaction graphs and the more refined approach of (logical) interaction hypergraphs. Important structural objects that can be identified in interaction graphs are feedback loops and signaling paths. We developed algorithms that compute all feedback circuits and all signaling paths between arbitrary pairs of species. Interaction hypergprahs are a particular way to represent Boolean concatenations of signals in interaction networks. This representation facilitates a

logical steady-state analysis in interaction networks and allows studying the logical response of the network for different input stimuli or after network interventions.
FluxAnalyzer is now being extended to facilitate the analysis of interaction graphs and hypergraphs. Furthermore, logical models can now also be constructed in ProMot and exported for detailed analysis to FluxAnalyzer.
In parallel we are building up an extensive, detailed and 'hand-made' logical model of the T-cell signaling network in collaboration with the institute of immunology at the University of Magdeburg (see project 4.2.2). This model will help us to test the novel methods. Model predictions will be verified experimentally at the institute of immunology. We also plan to investigate other signaling and regulatory networks, partially complementary to dynamic models studied by our group.

4.4 Research Highlight : Tools and Concepts for Modeling and Simulation

Introduction and objectives

Research in the field of systems biology requires powerful computing tools for modeling, simulation, system analysis and synthesis as well as a powerful modeling concept to systematically describe the biological systems under investigation. In a long-term effort 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 applied in different modeling projects and is now extended with a specialized method to model the interactions of intracellular macromolecules like proteins and DNA (see section 4.2.4).

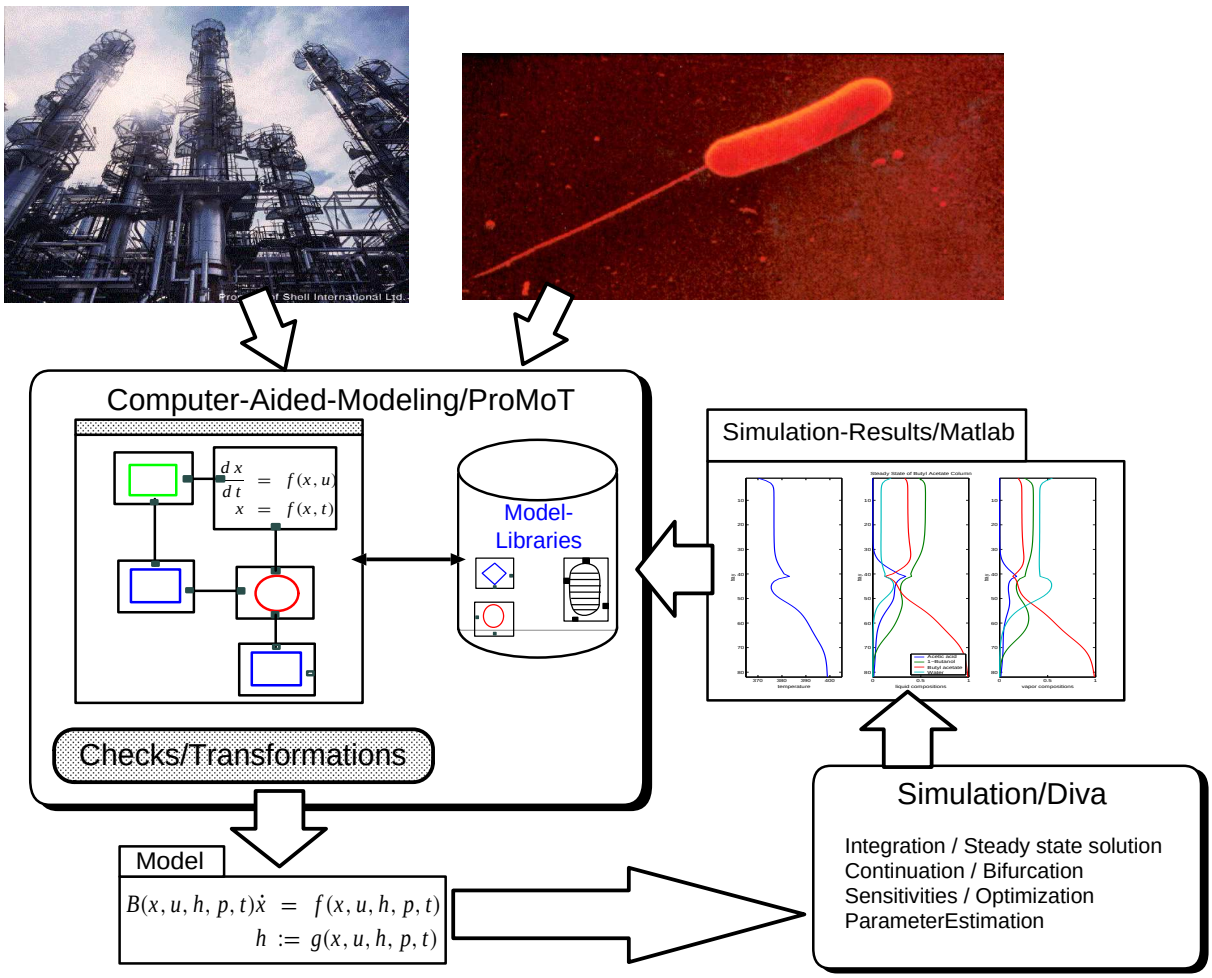

Fig. 8: Structure of ProMoT/DIVA

The overall aim is to provide software tools (especially in the fields of process engineering and systems biology) for supporting model set-up, model exchange and model analysis. The modeling tool ProMoT provides a large library with sub-models based on the modular modeling concept mentioned above. ProMoT can generate models for different simulation and analysis tools and allows the exchange of models via the common description language SBIML. Since the recent models become more and more complex, visualization methods have been developed and implemented into the modeling tool, which use adaptive techniques to provide the user only with essential information regarding a specific task in the modeling process.

The simulation environment DIVA allows simulation as well as parameter analysis, parameter estimation and bifurcation analysis, but this tool is strongly dependent on commercial numerical libraries. To overcome the limitation and to modernize the simulation software, a new simulation tool Diana is under development. The tools described above are a common infrastructure that is used for many projects of the groups PSD, BPE, PCP and SBI.

4.4.1 Modeling and Simulation Environment Promot/Diana/Diva

Independently of the application field modular models are implemented in the equation-based and object-oriented modeling tool ProMoT (Ginkel et al., 2003; Mangold et. al., 2005; Kremling et. al., 2004b). This modeling tool supports the development of modules as classes in an object-oriented inheritance hierarchy which is especially suited to build extensible libraries of reusable modules.

There exists a variety of systematically developed, specialized modeling libraries for i) biochemical reaction networks, ii) intracellular signal transduction systems with protein-protein interactions, iii) industrial reaction and separation processes with interacting vapor and liquid phases, iv) fixed bed gas-phase reactors, v) membrane-based separation and reaction apparatuses and vi) fuel cells. These libraries are developed and applied in different groups of the MPI.

Models in ProMoT can be developed graphically as a flow-chart of connected modules within a GUI or using a modeling language. The tool supports the exchange of models with other software tools in system biology by import and export of the Systems Biology Markup Language (SBML). For modelers in Systems Biology it becomes more and more important to be able to apply different tools with different strengths to the same model without the need of reimplementation and to supply a standardized functional model as supplement for publications via SBIML.

The mathematical model representation in ProMoT is symbolic and declarative. This allows applying several algorithms to the underlying differential-algebraic equation set of the models before simulation. Structural analysis algorithms are used to provide helpful information for the modeler to resolve consistency errors in the model as well as to simplify the model for efficient numerical solution. ProMoT allows using the implemented models in the numerical simulation environments DIVA, Diana and Matlab. The new project Diana (Krasnyk et al.) has been started to reimplement numerical methods of DIVA in an extensible and object-oriented way. The overall goal is to provide an extensible simulation tool, which uses only freely available software components. This new simulation tool is based on CAPE-Open interfaces, which allow for interoperability with other simulation environments in the field of process engineering. The tool provides the user with efficient numerical methods, implemented in C++ as well as with a scripting language which allows to implement own algorithms and extensions easily. The work in this project is done in close cooperation with the PSD group and the Donezk Technical University.

4.4.2 Visualization of Complex Biochemical Networks

The increasing complexity of mathematical models in Systems Biology (e.g. signal transduction pathways) results in a representation by large-scale graphical networks. Dealing with a specific task, these networks hold too many entities and relations to be comprehensible to the user.

Consequently, adaptive visualization methods are required which reduce visual complexity by presenting only a visually modified subset of the available network regarding the current user task. This results in a less cluttered and more descriptive visualization, which supports the user in modeling and analysis.

Adaptive visualization techniques can be established by using adaptive space filling techniques like Fisheye Views and/or by adaptive filtering techniques like Semantic Zooming that reduce the amount of display information. The level of abstraction is based on data derived from model structure, model semantics and the current task.

In a first step the EGF induced MAPK cascade model (see section 4.2.1) is used and visualized before any adaptive technique is used (see Fig. 9a). Applying the Fisheye View technique, focused elements and their global relationships are emphasized (see Fig. 9b). Using filtering techniques, elements which are not currently focused are de-emphasized or hidden (see Fig. 9c). Accordingly, the visual complexity can be reduced within a dense visualization regarding a specific task (cp. Fig. 9a - 9c).

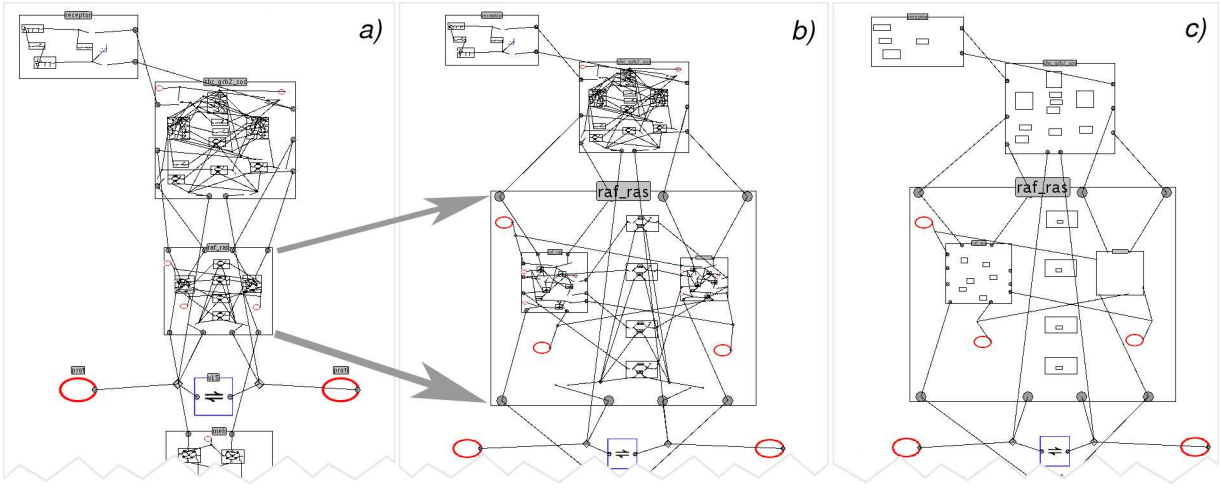

Fig. 9: EGF induced MAPK cascade model: a) before any adaptive method is applied b) using the Fisheye View technique to increase focused elements in size and show more detail c) applying filtering techniques to display only those elements that are essential regarding the current user task.

Outlook and perspectives

Visualization techniques can provide an adaptive and interactive view of dynamic models regarding the current user task. For the next step, the developed methods will also be extended to meet visualization requirements of structural models (see section 4.3.2). Another important task will be the visualization of multiprotein signaling complexes (see section 4.2.4).

The new simulation environment Diana is planned to be released in the beginning of 2006. It will be extended with further algorithms of DIVA and it will be the basis of development for new numerical tools especially in the field of optimization for process design and model identification.

5 Future Directions

The SBI group deals with a number of systems all related to signal transduction and regulation in biological systems. Several of these projects are going to be continued in the future and interesting results are expected, both with respect to the single projects as well as with respect to the discovery of common structures and modules. Future directions for several projects have been described in the “Highlights” chapter.

Important upcoming research activities of the SBI group will focus on the system theoretical analysis of running projects. These analyses are especially important because their results are supposed to strengthen the application and exploitation of mathematical modeling for the understanding of biological systems. The main topics will be:

- Structural analysis of large signaling networks
- Identification and analysis of modules and motifs
- Analysis and identification of hierarchies
- Analysis of non-linear properties
- Development of tools for modeling, simulation and visualization
- Analysis of interaction of signal transduction and control of cell proliferation, apoptosis and differentiation

The subprojects under investigation will serve as model systems for the application of these topics. The theoretical activities will be accompanied by experimental analysis. Here similar to the models the activities will shift from the analysis of specific systems to a global analysis of cellular behavior. Methods for global analysis of cell

metabolism and regulation are going to be exploited. Activities to establish such methods have already been started in cooperation with the BPE and MNA groups.

The future activities of the SBI group are going to be embedded in upcoming and running third party projects. The modeling of the “T-cell receptor induced MAP Kinase Cascade” will be continued in a second period of funding of a DFG research group.

The BMBF initiative “Systems Biology - Systems of Life” is presently running and the application for a second period of funding is in preparation. In addition the joint research project “Dynamische Systeme” funded by the Land Sachsen-Anhalt is to be extended to a research centre. Systems biology will be one of its main focuses. Within the scope of the research centre but also with respect to collaboration of groups within the MPI, the SBI group is going to extend its research to mathematical modeling of the networks, which are under investigation in the MNA group. The analysis of cell differentiation of *Physarum polycephalum* fits well to the upcoming activities of modeling global regulatory phenomena.

Concluding, the systems biology group will continue the successful interdisciplinary approach. By emphasizing systems theoretical analyses inherent principles of biological systems (prokaryotic as well as eukaryotic) are going to be investigated.

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

Title of lecture	**Place**	**Lecturer**
Dynamik verfahrenstechnischer Systeme	Univ. Stuttgart	E.D. Gilles
Mathematical methods in ecological technologies	FH Magdeburg	A. Kremling
Umweltbiotechnologie/Biologische Grundlagen	Univ. Magdeburg	H. Grammel
Systems Biology	Univ. Magdeburg	A. Kremling

Tab. 6: Supervision of Diploma and Master Projects

Student	**Title**	**Training place/ Advisor**
Conzelmann, H.	Modeling and Analysis of the EGF signaling pathway and caspase activation	Univ. Stuttgart/ J. Saez-Rodriguez
Ferrari, C.	Modeling and Analysis of the Angiotensin II-mediated effects on the activity of NTS neurons	Univ. Stuttgart/ T. Sauter
Fey, D.	Model reduction of signaling networks using a domain-oriented approach	Univ. Stuttgart/ H. Conzelmann
Fuchs, G.	A dynamic model of the tricarboxylic acid cycle (TCA)	Univ. Stuttgart/ M. Ederer
Hammerle, A.	Analysis of multistability of signal transduction modules	Univ. Magdeburg/ J. Saez-Rodriguez

Regner, J.	Effects of RGS on Angiotensin II signaling in Neurons	Univ. Stuttgart/ T. Sauter
Schenkendorf, R.	Einsatz modellgestützter Mess-verfahren bei zellulären Systemen	Univ. Magdeburg/ A. Kremling
Stieghahn, M.	Interaktive Exploration hierarchischer Netzwerke	Univ. Magdeburg/ M. Ginkel
Weiss, M.	Analyse der Regulation des Phosphotransferasesystems (PTS)	Univ. Stuttgart/ T. Sauter
Gerbeth, R.	Modellierung der Ammoniumassimilation in *E. coli*	Univ. Stuttgart/ M. Ederer
Hensel, S.	Beziehung zwischen Sensitivitäten und kinetischen Parametern in Reaktionsnetzwerken	Univ. Stuttgart/ M. Ederer

Tab. 7: Ph.D. projects (finished)

Group member	**Title**	**Finished in**
Kammerer, Christine	Modellierung des Wachstums- und Produkt-bildungsverhaltens von Actinomyceten	2005
Klamt, Steffen	Strukturelle Analyse von Stoffwechselnetzen illustriert am bakteriellen Redox- und Zentralstoffwechsel	2005
Sauter, Thomas	Die Bakterielle Signalverarbeitung am Beispiel des Sucrose Phosphotransferasesystems in *E. coli* – Modellierung und experimentelle Überprüfung	2003
Stelling, Jörg	Systems analysis of robustness in cellular networks	2004

7 Selected Memberships, Appointments and Awards

Gilles, E.D.

2004 7th Nordic Process Control Award of Nordic Working Group

2005 Karl-Küpfmüller-Ring

2005 Honorary Doctorate of Magdeburg University, Germany

Conzelmann, Holger

2003 Diploma Thesis (Modeling and analysis of the EGF signaling pathway and caspase activation) awarded with Lewa Preis

8 References

Backfisch, T., M. Pruteanu, R. Hengge and E.D. Gilles: Mathematical Model of *rpoS* Regulation in *E. coli*. In: FOSBE Conference Proceedings (2005)

Bettenbrock K., S. Fischer, A. Kremling, T. Sauter, K. Jahreis and E.D. Gilles: A quantitative approach to catabolite repression in *Escherichia col*i. In: JBC (submitted)

Conzelmann, H., J. Saez-Rodriguez, T. Sauter, E. Bullinger, F. Allgöwer and E.D. Gilles: Reduction of Mathematical Models of Signal Transduction Networks: Simulation-Based Approach Applied to EGF Receptor Signaling. In: Systems Biology (1):159-169 (2004)

Conzelmann, H., J. Saez-Rodriguez, T. Sauter, B.N. Kholodenko, E.D. Gilles: A domain-oriented approach to the reduction of combinatorial complexity in signal transduction networks. In: BMC Bioinformatics (submitted)

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

Research Group:

Bioprocess Engineering (BPE)

Prof. Dr.-Ing. Udo Reichl

This report covers the period from May 2003 to September 2005.

1 Group Introduction

In the last two years, the theoretical and experimental research of the BPE Group has been extended significantly. A certain steady state of continuous activity and, a coherent research program has been implemented.

Laboratories now provide an excellent infrastructure for mammalian cell culture using a broad scope of cultivation technologies. These technologies range from static systems, wave bioreactors and parallel small scale cultivations systems to large scale bioreactors with working volume capacities of up to 20 liters. Highly reproducible experimental conditions are achieved by digital control systems and newly developed on-line sampling devices. In addition, the scope of validated off-line assays has been extended significantly. These extensions allow for the characterization of cellular metabolism and physiological status of the cells, and viral mRNA, protein and virus particle synthesis as well as virus yields. In part the laboratories remain connected to the SBI Group and the Chair of Bioprocess Engineering at the OvGU (cultivation of prokaryotes and yeast cells, analytical methods). Most research focuses on viral based cell culture processes, for example production of influenza A virus vaccine, as described in the previous evaluation report. Based on detailed experimental studies dealing with the optimization of cell growth, virus particle yield and cultivation conditions, structured mathematical models describing cellular metabolism and virus dynamics in bioreactors as well as virus replication in individual cells are developed. Assay development, experimental design, data analysis and mathematical modeling are considered as an integrated approach to understand the biological structure of relevant aspects of microorganisms used in bioprocesses and to design and optimize upstream and downstream processing. In addition, mathematical models serve as a basis for making dependable predictions about modifications on production cell lines, virus strains and process conditions.

Other virus-host cell systems are being investigated in collaboration with the Chair of Bioprocess Engineering at the OvGU and industrial partners. These comprise swine influenza A virus, mink enteritis virus, parapoxvirus and viral vectors coding for HIV surface proteins in various cell lines. Furthermore, the yeast S. cerevisiae is being studied as an expression system for hanta virus nucleocapsid for vaccines and diagnostics.

Since the middle of 2004 a proteomics platform has been set up successfully, in collaboration with the MNA and the SBI Group, to investigate biological hypotheses and to support mathematical modeling activities relating to the various research projects on *E. coli*, P. polycephalum and influenza virus-mammalian cell interaction. In the same year, additional laboratory capacity was established by refurbishing rooms in the ground floor originally intended exclusively for work with radioactive material to support extended research activities in downstream processing of biologicals.

2 Members of the BPE Research Group

As of June 20, 2005, the BPE research group consisted of 4 scientists with PhDs, 8 PhD students, diploma students, and technical assistants.

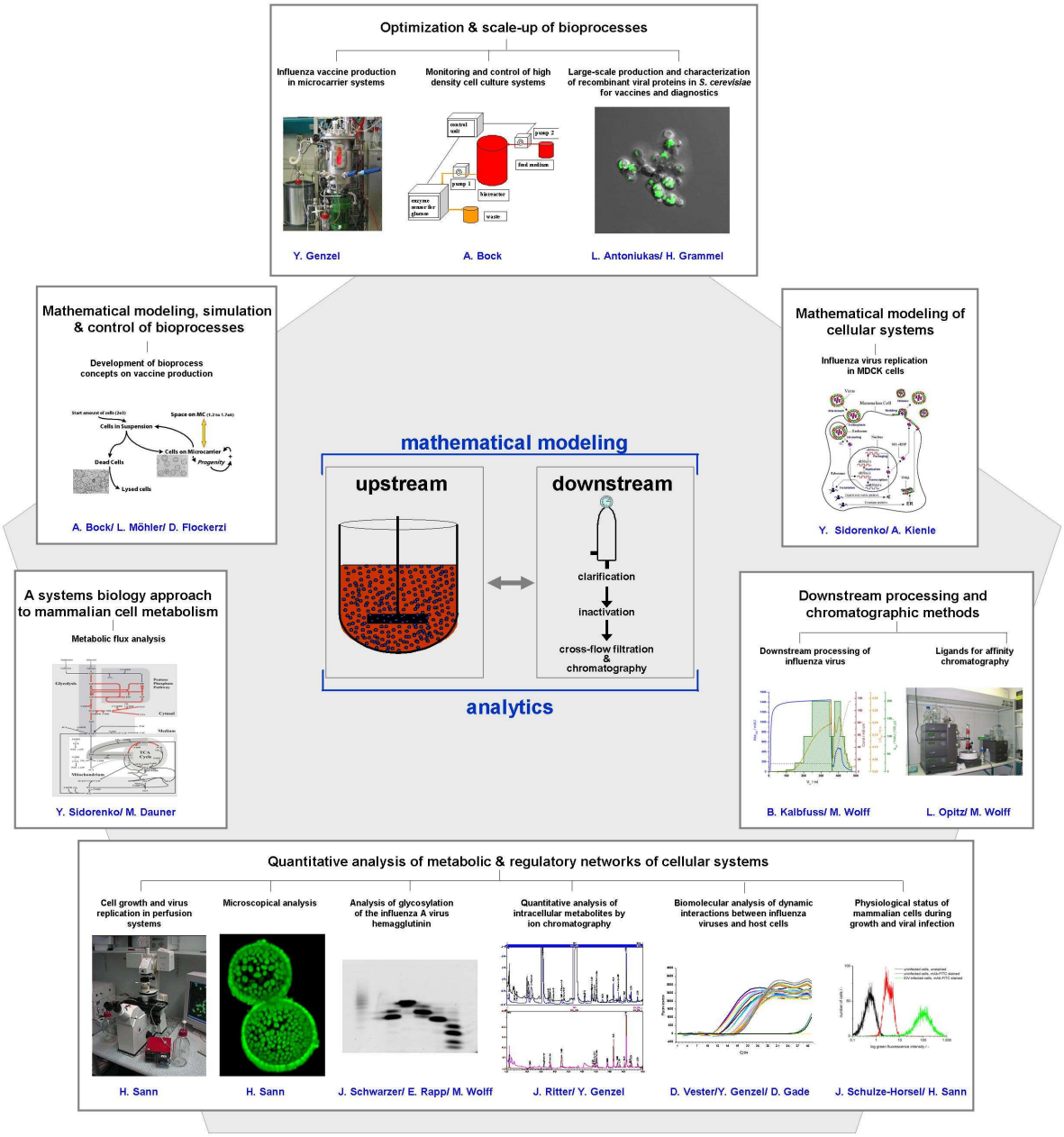
Composition of BPE Group as of 20 June 2005

Group Member	**Status**	**Background**	**Joined BPE in**
Prof. Dr. U. Reichl	Head of Group		01.07.2000
Dr.rer.nat. Y. Genzel	Scientific Employee	Biotechnology	01.01.2001
Dr.rer.nat. H. Sann	Scientific Employee	Biology	01.07.2000
Dr. M. Wolff	Scientific Employee	Biotechnology	01.01.2005
Dr. sc. nat. M. Dauner	Scientific Employee	Biotechnology	01.11.2004
Dipl.-Ing. J. Ritter	PhD student	Biotechnology	01.12.2003
L. Antoniukas, MA	PhD student (Scholarship)	Biology	01.01.2003
Dipl.-Ing. A. Bock	PhD student	Process Engineering	01.03.2003
Dipl.-Ing. (FH) J. Schwarzer	PhD student	Analytical Chemistry	15.01.2003
Dipl.-Ing. (FH) B. Kalbfuß	PhD student	Biotechnology	01.11.2003
Dipl.-Ing. L. Opitz	PhD student	Bioprocess Engineering	01.07.2005

Dipl.-Biotech. J. Schulze-Horsel	PhD student	Molecular Biotechnology	15.09.2003
Dipl.-Biol. D. Vester	PhD student	Biology	01.05.2005
Technical Staff			
Dipl.-Ing. (FH) I. Behrendt	Technician	Biotechnology	01.07.2001
S. König	Technician	Analytical Chemistry	01.08.2001
Dipl.-Ing. (FH) S. Lehmann	Technician	Biotechnology	01.11.2002
L. Geisler	Technician	Chemistry	15.07.2003
Dipl.-Ing. (FH) A. Zimmermann	Technician	Biotechnology	01.12.2003
F. Hasewinkel	Worker	Chemistry	01.08.2002

As the Chair of Bioprocess Engineering at the OvGU the head of the research group, Prof. U. Reichl, supervises 7 PhD students (H. Sommer, J. Schmidt, L. Möhler, M. Pohlscheidt, Y. Sidorenko, D. Holtmann, M. Popow) and several diploma students.

3 Survey of research projects of BPE Group



Project Area: Hierarchical Structures

Project Mathematical modeling of cellular systems	• Detailed mathematical models for influenza virus replication in MDCK cells			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject Influenza virus replication in MDCK cells	Y. Sidorenko	MPI/ Chair of Bioprocess Engineering, OvGU	08/2001	Institute of Numerical Mathematics (Russian Academy of Science)

Project Area: Coupled Processes

Project Optimization and scale-up of bioprocesses	• Development and optimization of integrated concepts to design and control vaccine production processes, quantitative analysis of cell metabolism and virus replication • Analysis and optimization of expression levels and yield, plasmid stability, purification regimen for large-scale production of recombinant proteins, characterization of recombinant proteins, immunogenicity and efficacy • High density and perfusion systems for process optimization, mathematical modeling of vaccine production processes, sampling and on-line monitoring, process control			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject Influenza vaccine production in microcarrier systems	Y. Genzel	MPI	01/2001	Chair of Bioprocess Engineering, OvGU
Subproject Design, scale up and process optimization for recombinant hantavirus NP expression in *S. cerevisiae* for vaccines and diagnostics	L. Antoniukas	MPI	01/2003	Friedrich-Löffler Institut, Wusterhausen Germany
Subproject Monitoring and control of high density cell culture systems	A. Bock	MPI	03/2003	Chair of Biopro-cess Engineering, OvGU
Project Downstream processing and chromatographic methods	• Crossflow-filtration, gel and expanded bed chromatography for purification of virus particles or viral proteins, polyclonals as ligands, new 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	B. Kalbfuss	MPI	02/2002	Chair of Bioprocess Engineering, OvGU

Subproject Affinity Chromatography of Influenza Virus	M. Wolff	MPI	02/2002	Chair of Bioprocess Engineering, OvGU
Project Quantitative analysis of metabolic and regulatory networks of cellular systems	• Microscopic analysis (fluorescence, laser scanning microscopy, image processing), analysis of cell growth and virus replication in perfusion systems (single cells, aggregates), quantitative analysis of virus replication dynamics • Mass spectrometry (QTOF) for characterization of proteins, 2-D gel and capillary electrophoresis for protein separation, proteomics • HPLC (integrated amperometry) for phosphorylated carbohydrates of glycolysis, HPLC (conductivity, UV/Vis) for metabolites of citric acid cycle			

Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject Cell growth and virus replication in perfusion systems	H. Sann/ A. Bock	MPI	07/2000	
Subproject Microscopic analysis	H. Sann	MPI	07/2000	Chair of Bioprocess Engineering, OvGU
Subproject Quantitative analysis of energy metabolism of animal cells	J. Ritter	MPI	01/2002	E.D. Gilles SBI Group
Subproject Analysis of glycosylation of the influenza virus hemagglutinin	J. Schwarzer	MPI	01/2003	E. Rapp, PCF Group
Subproject Physiological status of mammalian cells during growth and viral infection	J. Schulze – Horsel	MPI	01/2003	A. Kienle, PSD Group
Subproject Biomolecular analysis of dynamic interactions between influenza viruses and host cells	D. Vester	MPI	01/2005	M. Marwan, MNA Group

Project Area: Network Theory

Project A systems biology approach to mammalian cell metabolism	M. Dauner	MPI	11/2004	INSILICO biotechnology GmbH Stuttgart, Germany

Project Area: Population Balance Systems

Project Dynamics of virus-host cell populations in bioreactors	Y. Sidorenko / NN	MPI	01/2005	A. Kienle PSD Group

Projects: Chair of Bioprocess Engineering (OvGU)

Project Process analysis and optimization of a vaccine production of mink enteritis virus, B. Hundt (Start: February 2002)	Optimization of cell growth and virus replication in static cultures and microcarrier systems, cultivation of primary and transformed cell lines in protein free and serum free media, process monitoring, scale-up of adherent cell lines

Project Mathematical model of cell growth and replication of influenza viruses in MDCK cells L. Möhler (Start: October 1999)	Unstructured and structured models of metabolism of animal cells, cell growth of adherent cell lines, virus growth dynamics, time delay systems, influence of parameter variation on yields Partners: D. Flockerzi, SCT Group
Project Dynamics of microbial communities J. Schmidt (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 Partners: D. Flockerzi, SCT Group K.P Hadeler, University Tübingen
Project Genetics of the central carbon metabolism in *Rhodospirillum rubrum*, H. Sommer Start: December 2000	Mutagenesis of genes of main carbon metabolic pathways, influence of mutations on carbon fluxes during growth on various substrates under different cultivation conditions, construction of a transhydrogenase deletion mutant to disturb the flow of electrons from catabolic to anabolic pathways Partners: H. Grammel, SBI Group

Projects: Cooperation with other Institutions and Industry

Project Development of cultivation methods for large scale production of mink enteritis vaccines, September 2002 – October 2003	OvGU, Chair of Bioprocess Engineering Impfstoffwerk Dessau-Tornau GmbH, Germany
Project Entwicklung und Erprobung Prozessführungskonzepten zur Herstellung von inaktivierten Virusimpfstoffen, June 2001 – May 2004	HWP (Hochschulwissenschaftsprogramm), Sachsen-Anhalt
Project Entwicklung eines Verfahrens für die großtechnische Herstellung von rekombinanten MVA als AIDS Vakzine in permanenten Hühnerembryofibroblasten – Voruntersuchung, March 2003 – December 2003	OvGU, Chair of Bioprocess Engineering Impfstoffwerk Dessau-Tornau GmbH, Germany
Project Development of cultivation strategies for UMNSAH/DF 1 March 2003 – December 2003	OvGU, Chair of Bioprocess Engineering Impfstoffwerk Dessau-Tornau GmbH, Germany
Project Cultivation methods for manufacturing of recombinant HIV vaccines, March 2003 – December 2003	OvGU, Chair of Bioprocess Engineering Impfstoffwerk Dessau-Tornau GmbH, Germany
Project Bioreaktor mit Sensortechnik, November 2004 – December 2004	AZA, Sachsen-Anhalt

Project Optimization Study: Characterization and Optimization of Recombinant Modified Vaccinia Ankara Propagation in Primary Chicken Embryo Fibroblasts for Vaccine Production, July 2004 – May 2005	OvGU, Chair of Bioprocess Engineering Impfstoffwerk Dessau-Tornau GmbH, Germany/ International AIDS Vaccine Initiative (IAVI), USA
Project Downstream Processing of Viral Vaccines, Junie2004 – December 2004	TOSOH BIOSCIENCE GmbH, Germany
Project Evaluation of membrane techniques in downstream processing of influenza virus, August 2004 – November 2004	SARTORIUS AG, Germany
Project Entwicklung eines Microcarrier-basierten Herstellungsverfahrens für einen Impfstoff gegen Schweine-Influenza, October 2004 – May 2005	OvGU, Chair of Bioprocess Engineering Impfstoffwerk Dessau-Tornau GmbH, Germany
Project Charakterisierung eines automatischen, sterilen, totvolumenfreien Probenahme-Moduls für Bioreaktoren May 2005 – January 2006	SARTORIUS AG, B. Braun Biotech, Germany
Project Virusaufreinigung mittels Membranrekuperator, August 2005 – November 2005	SARTORIUS AG, Germany

4 Research Highlights

4.1 Optimization and Scale-up of Bioprocesses: Different Media, Cultivation Vessels and Higher Cell Densities

Large scale production of influenza virus for a vaccine can be achieved through the cultivation of adherent mammalian cells (MDCK cells) on microcarriers in serum-containing medium. When cells have grown to confluency, they are transferred to serum-free medium and are infected with influenza virus. Virus replication results in apoptosis, cell breakage and virus release (Genzel et al. 2004a). After release, the viruses must be inactivated and purified to obtain a killed virus vaccine.

There are several levels at which this process can be optimized. The following sections detail three projects that examine different ways to optimize viral production.

4.1.1 Omission of Medium-Exchange Steps for Infection by Using Serum-Free Medium

Mammalian cell culture media contain about 50 different components. These components include salts, vitamins, amino acids, glucose and growth factors. Additionally, serum and peptones are added in concentrations up to 10 %. Serum containing media have a high protein load (up to 10 g/L) rendering product purification more difficult. Serum is undefined, resulting in considerable lot-to-lot variations, is expensive and contains a risk of contamination with viruses, mycoplasms and prions. Therefore, serum-free media (SFM) have been developed. However, SFM are not completely defined media. SFM typically contain low molecular weight digests such as yeast extracts, plant or animal tissue hydrolysates instead of serum. Hydrolysates contain mainly free amino acids and peptides, but also vitamins, minerals and other undefined components. Necessary proteins such as growth factors are then added in low amounts to these media (up to 1 g/L). Usually, cells have to be adapted to growth in serum-free media. Often cells grow slower and for every cell line the best medium has to be identified.

A low protein content would allow omission of the medium exchange step during influenza virus production. For a better binding and entry of influenza to the host cells trypsin is added at time of infection. Serum inhibits trypsin activity, peptides do not.

Neither limitations nor inhibiting concentrations are observed when using the serum-free medium Ex-Cell MDCK (JRH Bioscience) without medium exchange (Fig. 1). Similar virus titers as those observed for serum containing media were obtained. Significant changes in metabolism were noted for glutamine uptake and ammonia release after virus infection and for changes in glutamate concentration during cell growth. In addition glucose uptake and amino acid profiles were different for this medium (Genzel et al. 2005c, 2005d, 2005e). Human influenza in this medium was produced in collaboration with GE Healthcare on questions concerning downstream processing (see 4.3).

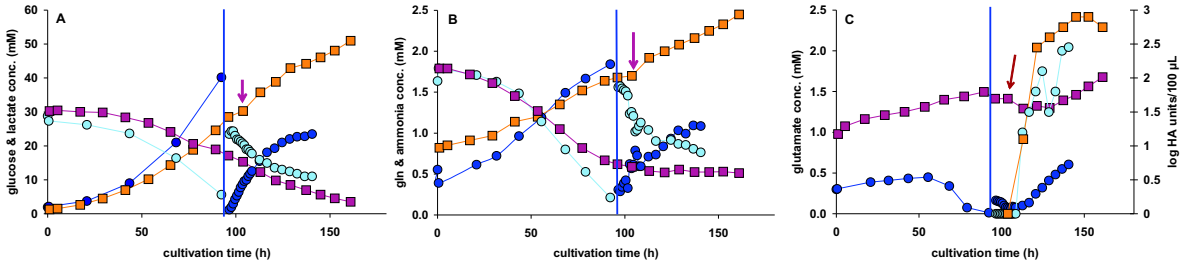


Fig. 1: Release & uptake of metabolites and virus titer in serum containing and serum-free medium during growth of MDCK cells in a 5L stirred tank bioreactor (0-93 h; 0-104 h respectively) and during influenza virus production (93-141 h, equine influenza, vertical line; 104-161 h, human influenza, arrow respectively). (A) serum containing: ● glucose, ● lactate; serum-free: ■ glucose, ■ lactate; (B) serum containing: ● glutamine, ● ammonia; serum-free: ■ glutamine, ■ ammonia; (C) serum containing: ● HA-value, ● glutamate; serum-free: ■ glutamate, ■ HA-value.

4.1.2 Different Cultivation Technologies: Disposable Cell Bags in a Wave Bioreactor

The typical vessels used to cultivate adherent mammalian cells on a large scale are roller bottles, cell factories or bioreactors. In industry vaccine production is performed in microcarrier cultures and cells are cultivated in stirred tank bioreactors at the 5000 L scale. The recently developed Wave bioreactor with disposable cell bags of 500 L wv might be an alternative for medium scale processes. Production of influenza virus with MDCK cells in serum containing medium with 2 and 4 g/L microcarriers has been successfully completed (Fig. 2). This method achived higher cell densities than those from a stirred tank bioreactor. However, virus titers could not be improved (Genzel et al. submitted b & c). Further experiments, especially on cell physiology, might help to improve viral yields (Schulze-Horsel et al. submitted).

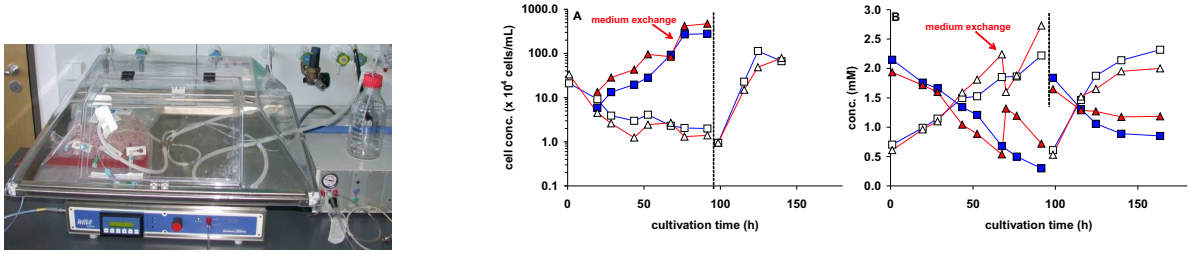


Fig. 2: Left: Wave bioreactor with a 1L wv cell bag; middle & right: cell numbers, release & uptake of metabolites in serum containing medium during growth of MDCK cells in a wave reactor (0-99 h) and during equine influenza virus production (99-164 h, dashed vertical line). ■ 2 g/L Cytodex 1; ▲ 4 g/L Cytodex 1 (arrow indicates medium exchange of 500 mL medium). For (A): cells on microcarriers: ■; ▲, cells in supernatant: □; △. For (B): glutamine: ■; ▲; ammonia: □; △ .

4.1.3 Different Cultivation Strategies: Perfusion Mode for Higher Cell Densities

Mathematical models of viral replication dynamics indicate that increasing the number of virus producing cells should increase the viral yield (Möhler et al., 2005). For adherent cell lines this means that the microcarrier concentration has to be increased to provide sufficient surface area for cell growth. Typically, limitations or inhibitions occur at higher cell densities and medium has to be exchanged or some components have to be readministered to the medium. A simple strategy is to exchange half the working volume at a given time (Fig. 2a & b). As a result higher cell number with twice the microcarrier concentration was obtained. A more sophisticated strategy is perfusion, the addition of new medium or only buffer with limiting compoments and simultaneous removal of spent medium with cell retention. We have tested different perfusion modes and could see a clear increase in cell number for a closed-loop glucose control (Fig. 3) (Bock and Reichl, submitted, Sann et al. 2004).

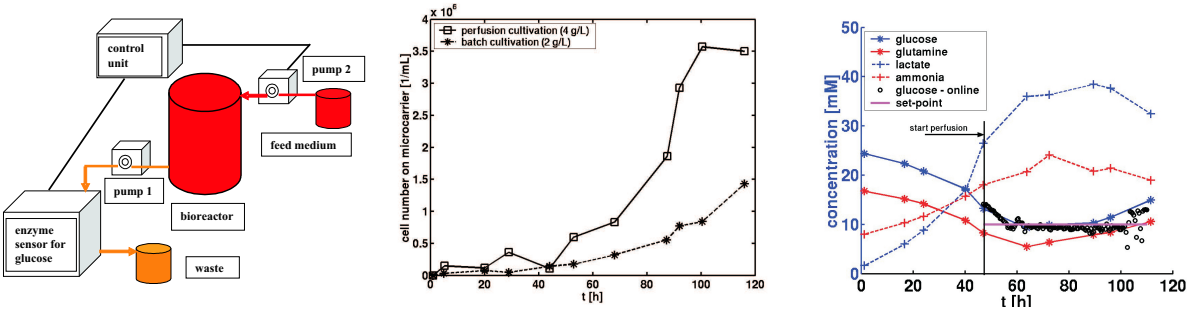


Fig. 3: Left: Scheme for closed-loop glucose control; middle: cell numbers on microcarriers during growth of MDCK cells in a 5L-stirred tank bioreactor (0-118 h). ✱ 2 g/L Cytodex 1 batch; □ 4 g/L Cytodex 1 with perfusion as shown left; right: Glucose on- and off-line data as well as lactate data for the perfusion cultivation as shown left.

4.2 Quantitative Analysis of Metabolic and Regulatory Networks of Cellular Systems: Details in Metabolism for Influenza Vaccine Production

Determining limitations or inhibitions for cell metabolism of adherent cells like MDCK cells demands detailed analytics of intra- and extracellular metabolites. Flow cytometry can complete the picture on cell physiology, for example to determine the percentage of apoptotic cells. Moreover, analysis of the viral genome and protein expression in infected cells can elucidate replication dynamics. The strong impact of small changes in medium composition and virus infection on metabolism has been shown experimentally (Genzel et al. 2005a and 2004a). Metabolic flux analysis and mathematical modeling of these observations can give us further insight.

4.2.1 Influence of Medium Components on Metabolism

Often in cell culture media glutamine is used as the primary metabolite because it is a precursor for several anabolic pathways (Fig. 4).

One consequence of using these metabolic pathways is the accumulation of ammonia during cell growth. High ammonia concentrations result in reduced cell and product yields depending on cell line and process conditions. Several methods have been devised for the reduction of ammonia concentration in cultivation broths.

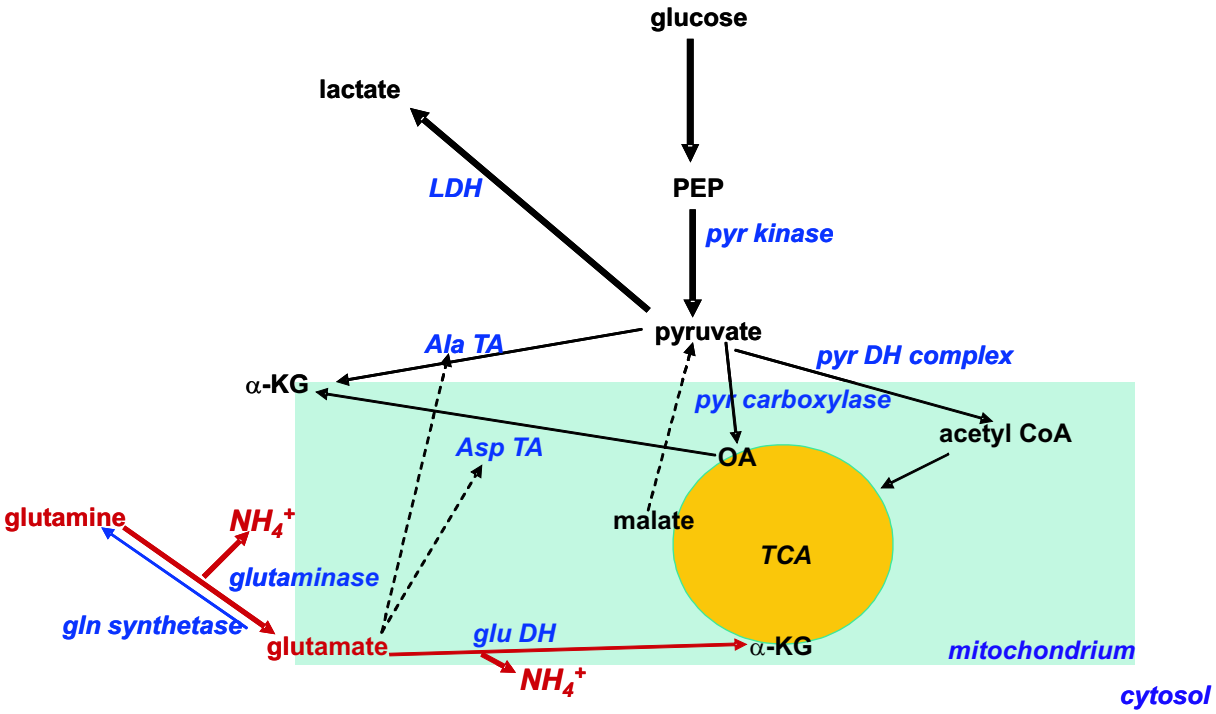


Fig. 4: Simplified scheme on glutamine metabolism in mammalian cells (LDH: lactate dehydrogenase, DH: dehydrogenase, TA: transaminase, KG: ketoglutarate, OA: oxaloacetate, TCA: tricarboxylic acid cycle)

We found that the replacement of glutamine (2 mM) by pyruvate (10 mM) supported cell growth without adaptation for at least 19 passages without reducing growth rates of different adherent commercial cell lines (MDCK, BHK21, CHO-K1) in serum containing and serum-free media (Genzel et al. 2005a and 2005b).

With the use of pyruvate as the predominant metabolic substrate, there is no requirement for adaptation and the switch from glutamine containing to pyruvate containing medium completely avoids the accumulation of ammonia for MDCK cells (Fig. 5). Furthermore, glucose consumption and therefore the build-up of growth inhibiting lactate concentrations was reduced. Analysis of amino acid metabolism during cell growth and virus propagation indicates a switch in several metabolic pathways channeling precursors into the TCA cycle (data not shown), but the exact mechanisms require more detailed analysis (see 4.2).

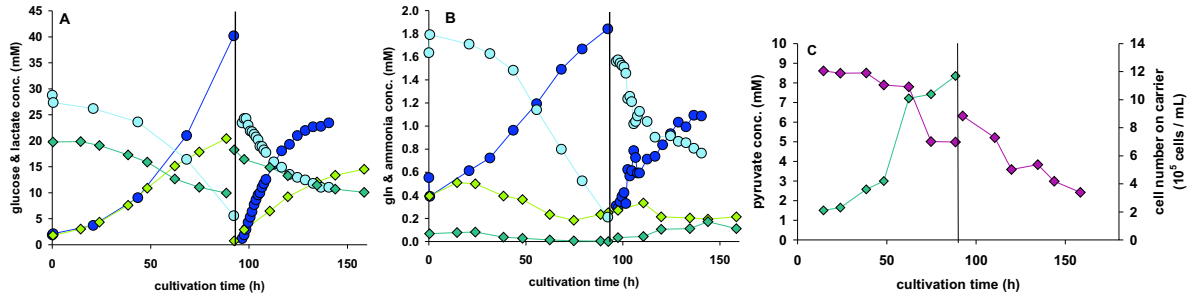


Fig. 5: Release & uptake of metabolites, cell numbers in gln-medium and pyr-medium during growth of MDCK cells in a 5L stirred tank bioreactor (0-93 h) and during influenza virus production (93-158 h, vertical line). (A) gln-medium: ● glucose, ● lactate; pyr-medium: ◆ glucose, ◆ lactate; (B) gln-medium: ● glutamine, ● ammonia; pyr-medium: ◆ glutamine, ◆ ammonia; (C) pyr-medium: ◆ pyruvate, ◆ cell number on carrier.

4.2.2 Influence of Virus Infection on Metabolism

What happens to the cell metabolism when the cells are infected with a virus? Cells start to produce virus particles and eventually undergo apoptosis. Extracellularly a significantly higher glucose uptake and lactate release for infected cells, is observed while glutamine metabolism does not seem to be affected (Fig. 6) (Genzel et al. 2005 c, Schulze-Horsel et al. 2005).

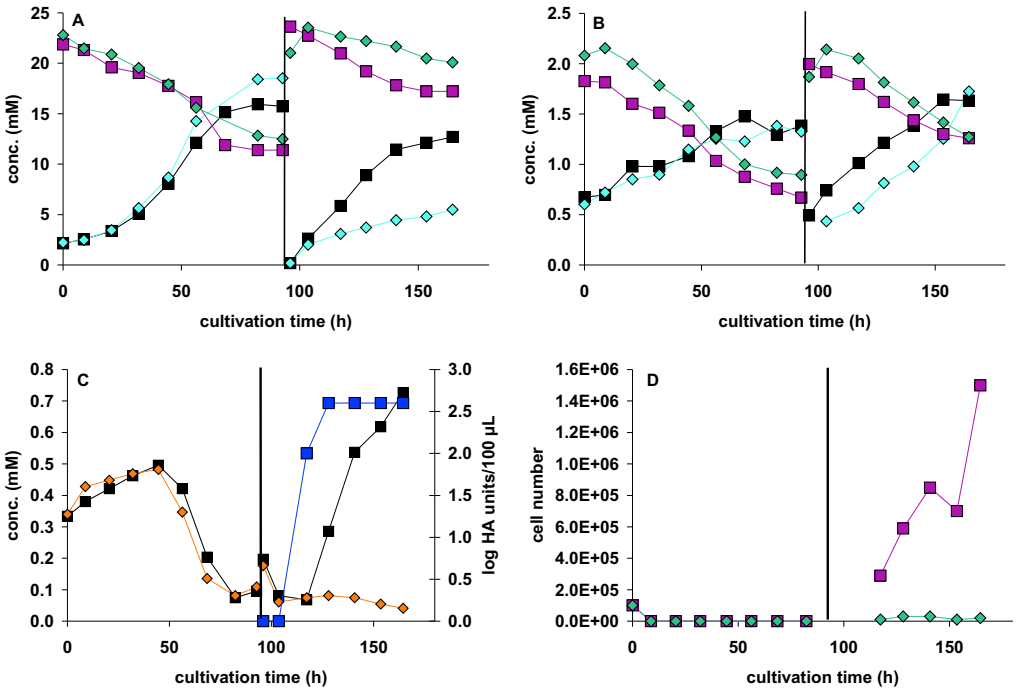


Fig. 6: Release & uptake of metabolites, cell numbers and virus titer in infected and mock-infected roller bottle during growth of MDCK cells (0-96 h) and during influenza virus production (96-165 h, vertical line). (A) infected: ■ glucose, ■ lactate; mock-infected: ◆ glucose, ◆ lactate; (B) infected: ■ glutamine, ■ ammonia; mock-infected: ◆ glutamine, ◆ ammonia; (C) infected: ■ HA-value, ■ glutamate; mock-infected: ◆ glutamate; (D) cell number in supernatant: ■ infected, ◆ mock-infected.

After a period of 21 h a strong glutamate release is detected in infected cells, corresponding to an increase in cell number in the supernatant. For mock-infected cells no increase was observed in glutamate concentration or cell number in the supernatant. Changes in metabolism and leakage or release of broken cells has yet to be determined.

4.2.3 Analytical Methods for Data on Metabolism

Currently, metabolites like glucose, glutamine, glutamate, lactate and ammonia can be measured easily and quickly with biosensors. For other metabolites HPLC methods are often required. For the quantification of amino acids in cell culture medium we use anion exchange chromatography with integrated pulsed amperometric detection (Genzel et al. 2004b). Pyruvate concentration in cell culture medium was determined by anion exchange chromatography but with conductivity detection, as the enzymatic assay using LDH activity was negatively influenced by glutamine (Genzel et al. 2005a). To quantify the intra- and extracellular metabolites of glycolysis, TCA cycle as well as nucleotides again anion exchange chromatography is used (Fig. 7). Here, parallel conductivity and UV detection allows to quantify some components that are not completely separated by chromatography (Ritter et al. submitted a & b). These analytical methods are also used by SBI and MNA Group.

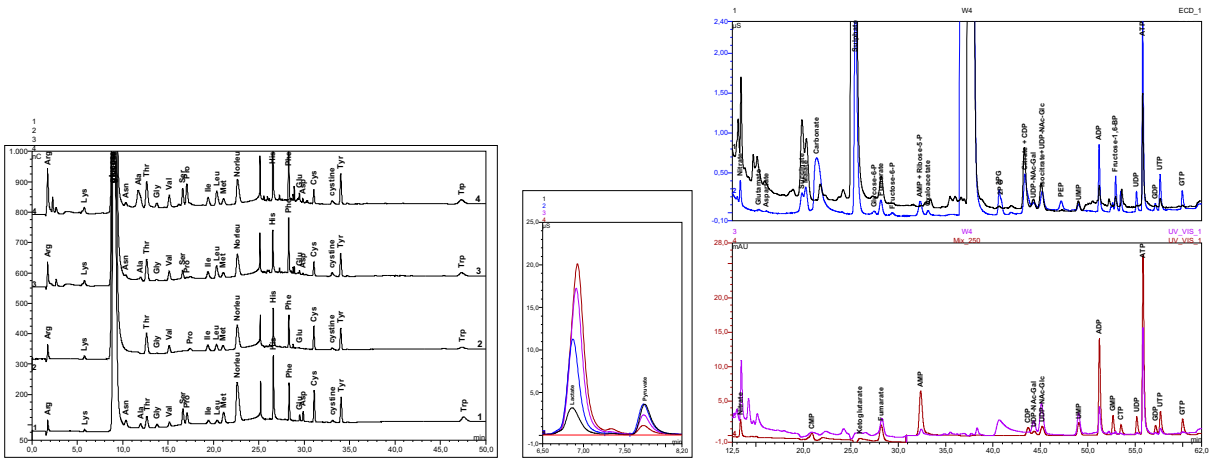


Fig. 7: Chromatograms from anion chromatography used for metabolite analysis: left: amino acid analysis (Genzel et al. 2004b); middle: pyruvate analysis (Genzel et al. 2005a); right: nucleotides, organic acids, phosphorylated sugars and other intracellular metabolites (Ritter et al. submitted a & b) all showing cultivation samples & standards

4.3 Mathematical Modeling, Simulation and Control of Bioprocesses

Mathematical models describe several key aspects from the cellular to the process level. As an example of a highly structured model for virus-host cell interaction on the cellular level we are investigating influenza A virus replication in single MDCK cells (Sidorenko and Reichl, 2004). This project is discussed in more detail in the next chapter (see 4.3.1). In collaboration with PhD students of the Chair of Bioprocess Engineering and D. Flockerzi (SCT Group) models describing cell growth and virus replication in microcarrier systems (Möhler et al., 2005) are being developed. To better understand cellular metabolism under different cell growth phases and culture conditions (see 4.2) highly structured metabolic network models for MDCK cells are currently being set-up and examined by metabolic flux analysis (MFA, see 4.3.2) and the software tool FluxAnalyzer developed by the SBI Group.

4.3.1 Structured Model of Influenza Virus Replication in MDCK Cells

Due to the detailed characterization of structure and life cycle of influenza A virus, the availability of well-characterized cell systems for studying virus propagation in animal and human cell lines under controlled conditions and its relevance as a human pathogen influenza A virus is – next to bacteriophages and HIV - an excellent “model virus” for systems biology. The following mathematical model can be considered a first step towards a structured mathematical model, which describes the complete influenza A life cycle in animal cells (Sidorenko and Reichl, 2004). The purpose of this model is two fold: a) to analyze the key processes of virus replication on a cellular level, and b) to better understand rate determining steps and factors limiting intracellular virus growth in mammalian cells for the design and optimization of virus-related production processes.

A small sample of simulation results for the influenza model are shown in figures 8-10. Immediately after infection the number of extracellular virions decreases and within 134 min more than 90% are taken up by the cell (Fig. 8). Consequently, both the number of virions attached to the surface and, with a short delay, the number of virions incorporated into endosomes increases. From the endosomes, individual viral ribonucleoprotein complexes (vRNPs) are released into the cytoplasm and begin to accumulate in the nucleus.

The maximum number of parental vRNPs in the cytoplasm and in the nucleus is found 38 min and 99 min post infection, respectively.

After 30 min p.i. first viral messenger RNAs (vmRNAs(+)) are synthesized in the nucleus and between 1 and 2 h p.i. the number of vmRNAs(+) in the nucleus increases significantly before it achieves a steady state due to continuous export into the cytoplasm and degradation. About 40 to 44 min p.i. the first vmRNAs(+) are found in the cytoplasm, where they accumulate. The switch from vmRNA(+) production to viral genome replication (cRNA(+) and vRNAs(-) synthesis) starts about 55 min p.i. when a significant amount of newly produced nucleoproteins have accumulated in the nucleus (Fig. 9). About 4 hours p.i. cRNA(+) is synthesized at almost maximum rate. As a consequence, the viral genome is replicated and the assembly of new vRNP complexes is initiated in the nucleus. Approximately 2.5 hours p.i., the first virions are released into the extracellular medium (Fig. 10). Initially, the number of released virions increases exponentially as vRNP formation and budding are not limited in precursor supply. As soon as viral proteins or vRNAs(-) become limiting, viral growth increases proportionally to the square of time.

In total the cell produces about 8000 virions within 12 h before it dies due to viral interference with basic cellular processes or viral induced apoptosis.

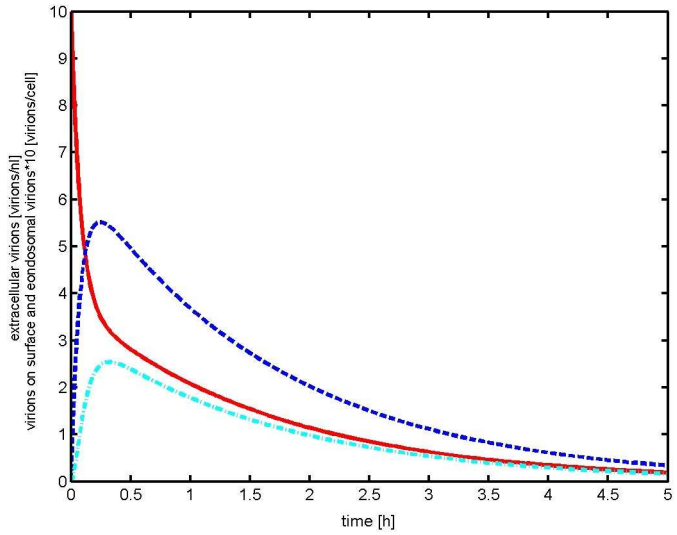


Fig. 8: Virus attachment and endocytosis: Free extracellular virions (—, red); virions attached to the cellular surface membrane (---, blue) and virions (-·-·-, cyan) incorporated by endocytosis.

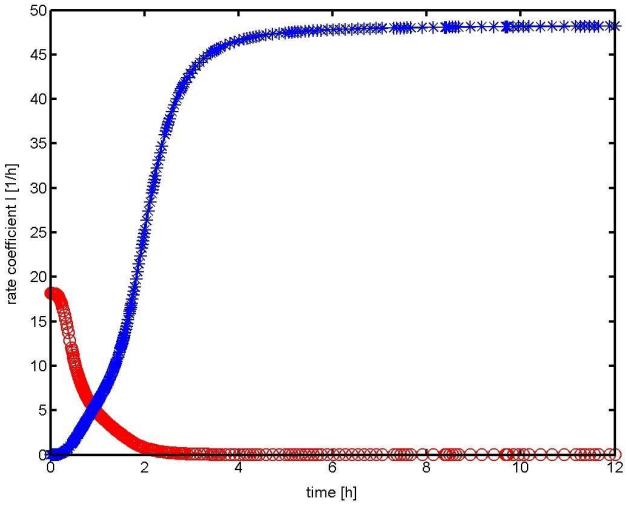


Fig. 9: Switch from viral transcription to viral genome replication: Rate coefficients of vmRNA(+) synthesis (-o-o-, red) and cRNA(+) production (-x-x-, blue).

The model is represented by a system of 43 nonlinear ordinary differential equations (ODE) and 81 parameters. About half of these parameters (42) are confirmed by experimentation in this laboratory or others. The non-confirmed parameters (39), such as degradation rate coefficients and parameters describing the switch from vmRNA(+) synthesis to viral genome replication, were estimated according to the average duration of individual replication steps and overall viral dynamics. Extensive experimental studies (microscopy, PCR, proteomics) are in progress to determine kinetics and parameters focusing on viral mRNA synthesis, onset of viral genome replication and intracellular viral protein accumulation.

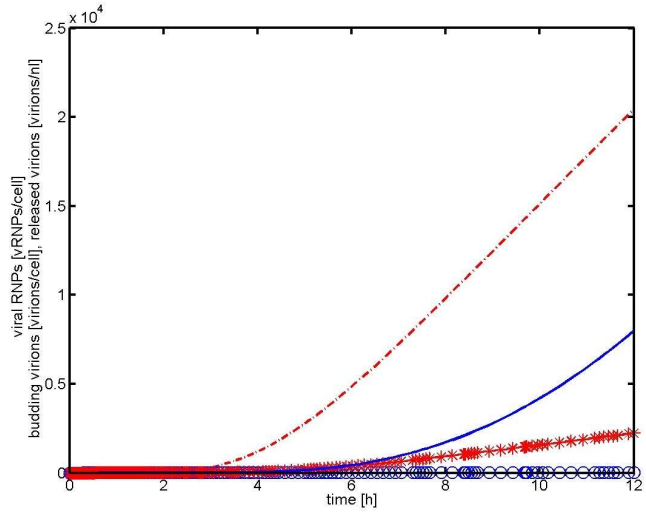


Fig. 10: Viral components at the budding step: In the nucleus vRNPs (-·-·-, red) accumulate while virion formation is limited by the number of vRNPs in the cytoplasm (-o-o-, blue) during budding. Progeny virions are formed at the surface membrane of the host cell (-x-x-, red), and released into the extracellular medium (—, blue). The maximum number of released virions is about 8000 per cell.

4.3.2 Metabolic Flux Analysis

Metabolic Flux Analysis (MFA) is a means of organizing complex data sets on metabolic rates and proving their consistency. Moreover, MFA allows the resolution of intracellular fluxes, thereby providing a way to elucidate common regulatory principles in central carbon metabolism.

With respect to MDCK cells, this project focuses on 3 particular goals:

1) Influences on central carbon metabolism by different media, cultivation systems and process regimes.
2) The correlation of the energy metabolism with cell growth characteristics and apoptosis.
3) The response of the central carbon metabolism to viral infection and the burden of vaccine production.

MFA is a four step procedure: extracellular uptake and secretion rates need to be determine, a representative biochemical reaction network has to be established, that relates the fluxes into and out of the system; if growth of biomass takes place, precursor demands for the biosynthesis of the cells need to be analyzed, and balances need to be drawn on every system component (Dauner and Sauer, 2001).

Metabolic rates of 18 amino acids, glucose, galactose, pyruvate, lactate, ammonia and oxygen as well as virus and cell numbers were determined in a standardized production process (see 4.2). Carbon and nitrogen balances were analyzed and closure was confirmed. This way additional metabolic pathways for alternative substrates, like peptides or oligosaccharides, were eliminated. Analysis of the physiological data revealed, that MDCK cell growth and virus replication in microcarrier culture can be divided into five characteristic phases; comprising seeding phase: 0-20 h, exponential phase 20-55 h, linear phase: 55-95 h, infection phase: 95-107.5 h, and virus release phase 107.5-150 h (Dauner et al., 2005, in preparation). For these phases, regression analysis for the measured rates was carried out in order to obtain specific uptake and release rates of the above mentioned compounds uptake and release. (Fig. 11).

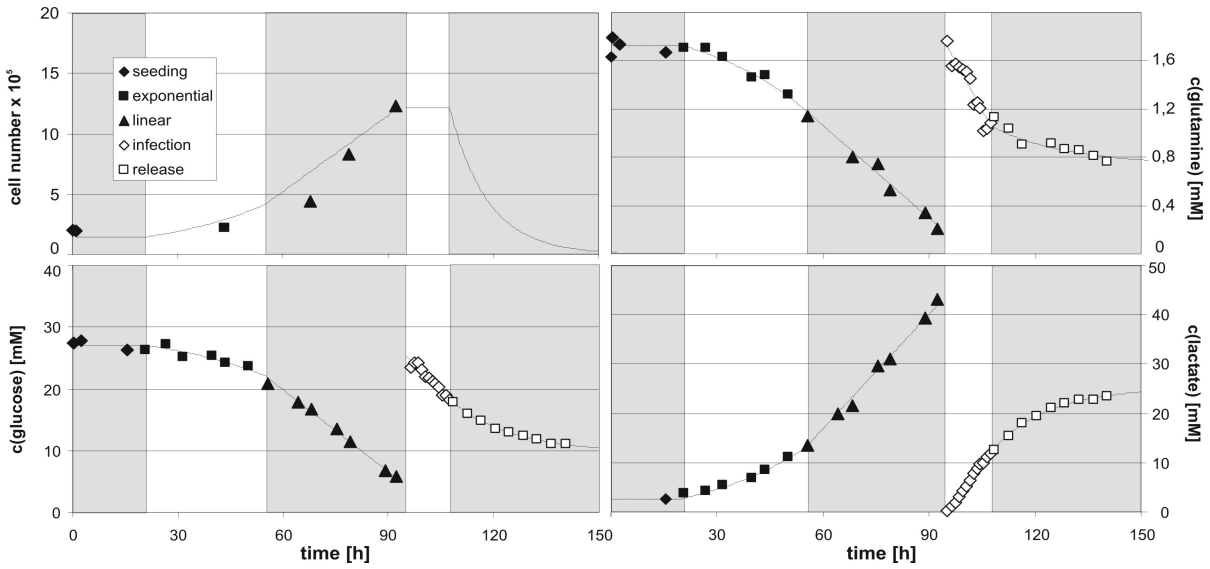


Fig. 11: Cell numbers (upper left) and concentration profiles of glutamine (upper right), glucose (lower left) and lactate (lower right) during the standardized vaccine production process. For MFA the process was divided into 5 characteristic stages, the seeding (0-20h), exponential (20-55h), linear (55-95h), infection (95-107.5) and virus release (107.5-150h) phase, denoted by gray and white shadings. The lines represent the results of the multiparameter regression analysis.

A detailed metabolic flux map was constructed, representing the main metabolic pathways of MDCK cells. The primary focus of the analysis was on cellular compartmentalization and transport in between the cellular compartments. As MDCK cells are adherent cells that form polarized layers, localization and activity of the different transporter systems was carefully ascertained based on recent literature findings. MDCK cells have been isolated from renal epithelial cells. Therefore, it is possible that they exhibit a functional urea cycle. To that end, an assay for the determination of urea in cell culture media was established. Significant levels of urea were not detected. Another potential product of renal cell metabolism is D-lactate, that can be formed either through the detoxification of methylglyoxal or through the racemase reaction from L-lactate. Again significant levels of D-lactate were not detected.

Precursor requirements for the biomass and virus formation were deduced from reported composition of MDCK cells and influenza virus and assuming standard biosynthetic pathways. Carbon flux into biomass formation even in the exponential and linear phase was below 12% of the overall carbon uptake. Carbon flux into virus production during the phase of virus release was below 1%. Consequently, exact determination of biomass composition seems to be of only minor relevance in the calculation of intracellular flux distributions.

Based upon these findings, a model of central carbon metabolism in MDCK cells was developed (Fig. 12).

This model comprises 68 reactions connecting 41 intracellular metabolite pools to the flux measurements from 26 observed extracellular state variables. One degree of freedom remained that was fixed by setting either the flux through pyruvate carboxylase or the malic enzyme to zero, eliminating a futile cycle constituted by malic enzyme, pyruvate carboxylase and malate dehydrogenase reaction. Flux solutions were calculated using the software FluxAnalyzer from S. Klamt (SBI Group).

In comparing the exponential to the linear phase it was determined that specific glucose uptake rate, flux from glutamate to oxoglutarate and, flux through malic enzyme decreases. In contrast, TCA flux from oxoglutarate to fumarate increases. In glutamine-free medium, comparable trends were observed, but overall specific rates were lower than in the glutamine containing media, with the exception of the TCA flux from oxoglutarate to fumarate (Dauner et al., 2005, in preparation, Sidorenko et al., 2005, in preparation).

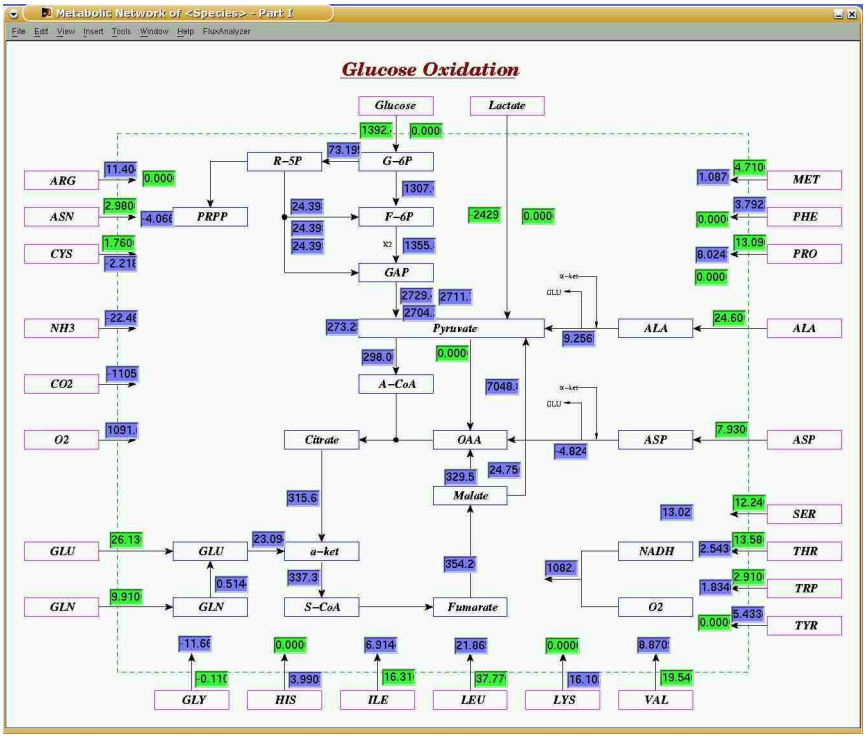


Fig. 12: Model of MDCK cell metabolism in Flux Analyzer. Values given represent flux solution in the linear phase of the standardized vaccine production process.

In the future, the model will be further refined to put emphasis upon the validation of the metabolic pathways through integration of proteome, transcriptome and metabolome data (see 4.2 and present research activities of SBI and MNA Group).

In collaboration with INSILICO biotechnology GmbH, Stuttgart, labeling experiments have been carried out and will be analyzed in order to validate assumptions on cofactor requirements and futile cycles.

4.4 Development of Downstream Processes for the Production of Viral Vaccines – Exemplified for Influenza A Virus Vaccine

The commercial production of inactivated human influenza vaccines relies on the cultivation of the virus in embryonated hen's eggs. However, to overcome production limitations and to reduce possible negative side effects such as allergic or autoimmune reactions, many vaccine production facilities are currently establishing animal cell culture based upstream processes. Hence, new downstream processing schemes including appropriate assays for their characterization, have to be developed to account for the upstream modifications. We are developing methods for the downstream processing of MDCK cell-derived influenza A virus and various assays (e.g. hemagglutinin-quantification ELISA, neuraminidase activity) for their evaluation.

A method for the processing of equine influenza A New Market 1/93 (H3N8) (Nayak et al., accepted; Nayak and Reichl, 2004) is based on a sequence of downstream processing steps comprising depth filtration (Polyfil II, 5µm and 1µm), inactivation with binary ethyleneimine (BEI), ultrafiltration (UF, 20-50 fold, Sartocon PES, 100 kDa MW cut off), and size exclusion chromatography (SEC, Sepharose CL2B). The downstream process of a single batch was characterized via the hemagglutinin (HA) activity, total protein and DNA content as shown in table 1. In summary, the overall viral recovery was 35.8% and the level of host cell DNA and total protein was reduced by 98.7% and 95.7%, respectively.

Tab. 1: Recovery and mass balance during downstream processing of equine influenza virus.

Steps	Concentration factor		% recovery (HA)	% protein reduction	% DNA reduction
	HA	Volume			
Inactivation	1.00	1.0	100	0.0	0.0
UF (retentate)	22.4	16.7	94.8	87.6	92.7
UF (retentate + wash)	8.92	8.92	100	85.6	92.4
SEC (virus peak)	0.13	0.33	37.8	65.8	82.2
SEC (pooled fraction)	0.02	0.03	70.0	< LOD*	50.0
Overall	2.82	5.6	35.8	95.7	98.7

*** limit of detection**

While a combination of UF and SEC steps seems to be robust and reproducible enough for routine large scale applications, viral-recovery as well as overall process economy, need improvement. In addition, investigations were extended to include human influenza A virus (A/PR/8/34 (H1N1) produced in serum free media due to the increasing relevance of influenza vaccines for humans. Viral recoveries were primarily enhanced by screening for optimal filter units, optimizing individual unit operations such as cross flow filtration conditions and methods, and selecting the most suitable SEC-medium.

The newly developed process (Fig. 13) is based on a sequence of unit operations comprised of depth filtration (Flotrex AP (CFAP 96), 0.65 µm), inactivation (β-propiolacton), filtration (Memtrex MP (CPPM 94), 0.45 µm), UF (Xampler, 750 kDa), and SEC (Sepharose 4FF). Characterization of individual unit operations resulted in a superior overall viral recovery of approximately 82.6% (overall recovery estimated from individual experiments) as illustrated in table 2.

Tab. 2: Recovery and contaminant reduction during downstream processing of human influenza virus.

Steps	Concentration factor (Volume)	% recovery (HA)	% protein reduction	% DNA reduction
Pre-Inactivation Filtration	1.0; n: 13	86.1; n: 11	n.d.	n.d.
Post-Inactivation Filtration	1.0; n: 15	94.6; n: 14	3.4; n: 7	9.4; n: 8
UF	28; n: 2	100.0; n: 2	84; n: 2	71; n: 2
SEC	n.d.	89.6; n: 2	65.7; n: 2	62.1; n: 2

n.d.: not determined; n: number of experiments

However, the remaining DNA concentration after SEC needs to be further reduced for vaccine applications. Influenza A virus has at a neutral pH (PBS, pH 7.3) a net negative charge. Therefore, Ion-exchange chromatography (IEX) can be considered as an additional option for virus purification.. First results applying the virus containing SEC-fractions onto a strong anion exchange (Q Sepharose XL) chromatography have indicated that the contaminating DNA can be separated from the viral proteins resulting a viral yield of 84% by a DNA elimination of 98%. Similar promising results were obtained with an ion-exchange membrane (Sartobind Q) by an increased viral purification capacity compared to the sepharose chromatography. Hence, the addition of an anion exchange chromatography (AEX) step could successfully finalize the downstream process for influenza A vaccine production. A reversed order of the SEC and AEX will be tested in the future to allow for the combined removal of the eluting AEX-salt and product impurities. In addition, a collaboration with the PCF Group has been initiated to model SEC and AEX processes assisting experimental design and optimization studies for the influenza A vaccine purification.

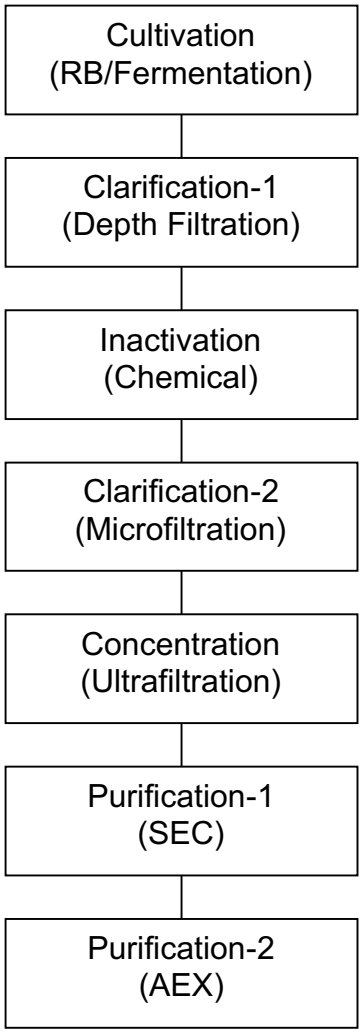


Fig.13: Influenza A virus downstream processing scheme

An alternative approach for the described process is the introduction of affinity chromatography (AC) as a capture step. Affinity based methods allow the combination of concentration and separation steps more efficiently than any other unit operation. In the case of influenza A virus AC can be based on antibodies or lectins towards HA, the most abundant (Wagner Ralf et al., 2002) and the most immunogenic viral surface glycoprotein (Lamb, Robert A. and Krug, Robert, M., 2001). First studies with an antibody-AC based on goat polyclonal antibodies against the equine influenza virus New Market 1/93 (H3N8) have shown that after a wash step an elution with 3 M $MgCl_2$ resulted in 100% yield of the viral protein based on HA activity by a potentially complete removal of contaminating DNA.

Lectin-AC may be more universally applicable as a ligand for the various influenza virus subtypes. The majority of the characterized HA N-linked glycan structures are of the complex type of glycans (Mir-Shekari et al., 1997) terminating in galactose and sialic acid. Hence, lectins specific for these terminal residues can be used to capture influenza A viruses and virally encoded HA. Lectin-blot studies with peanut agglutinin (PNA) and sambucus nigra agglutinin (SNA) suggested the possibility for a selective capture of viral proteins in comparison with host cell proteins (MDCK).

The nature and extent of HA-glycosylation has been implicated to effect its receptor binding properties and the virulence of the influenza virus (Mir-Shekari et al., 1997). Therefore, a lectin based capture step would additionally have the advantage to separate viruses or HA-glycoproteins with inferior glycan structures from the product. To account for the importance of the HA-glycosylation we are currently establishing analytical methods such as fluorophore-assisted carbohydrate capillary electrophoresis and matrix-assisted laser desorption mass spectrometry to characterize process related glycosylation deviations.

4.5 Organization of Symposia and Workshops

- Intersectional Symposium of the MPG, “Trends in Interdisciplinary Basic Sciences”, November 2004, Harnackhaus Berlin

5 Selected Teaching Activities, Diploma Projects, PhD Projects and Habilitations

- Starting in 2004 an interdisciplinary diploma study course “Biosystemtechnik” (Biosystems and Technology) was successfully established together with the Faculty of Electrical Engineering and Information Technology, Faculty for Natural Science and the Medical Faculty. The course is supervised and organized by the Chair of Bioprocess Engineering at the OvGU (U. Reichl) and has attracted more than 180 students in the first semester (2004/ 2005)

Lectures at OvGU (Prof. U. Reichl):

- Biochemical engineering I (German, English)
- Laboratory course - Biochemical engineering I (German, English)
- Mathematical Modeling - Modeling of bioprocesses (German)
- Biochemical engineering II – Animal Cell Culture Technology (English)
- Laboratory course – Biochemical engineering II (English)
- Modeling of cellular systems - Systems Biology II (German, with SBI Group)
- Microbiology (German, with Medical Faculty; SBI Group)

Diploma projects

2003

Dinkova, Anna: Untersuchungen zur Partikelanalyse am Beispiel von Latexstandards und Influenza Virus mittels Asymmetrischer Fluss Feld Fluss Fraktionierung

2004

Schäfer, Bastian: Comparison of Pure and Mixed Bacterial Cultures in a 2-L-Stirred Tank Reactor in Batch and Chemostat Mode

Fischer, Marlies: Optimierung des Zellwachstums von MDCK Zellen & Influenzavirusproduktio in serumfreien Medien (ExCell) – Hochzelldichtekultivierung von Daten für Stoffflussanalyse

Olmer, Ruth: Kultivierung von MDCK-Zellen und Influenza-A-Virusproduktion im Wave Bioreaktor

2005

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

PhD Projects

At present there are 7 PhD students at the BPE Group and 6 PhD students at the OvGU, supervised by U. Reichl, Y. Genzel. and M. Wolff (see survey of Research Projects)

2005

Holtmann, Dirk: Electro-Chemical Monitoring of Microbial Activity - Fundamentals and Application in Waste Water Treatment, DECHEMA

Pohlscheidt, Michael: Entwicklung und Optimierung eines Verfahrens zur Viruspropagation von Parapoxvirus Ovis NZ-2, Bayer AG

Sidorenko Ioury: Mathematische Modellierung von Influenza Virus Replikation in Säugerzellen, OvGU, Chair of Bioprocess Engineering

Habilitationen

2003

Müller, Dr. Egbert: Polymere Oberflächenbeschichtungen – eine Methode zur Herstellung von Trägermaterialien für die Biochromatographie, Fakultät Verfahrens- und Systemtechnik, OvGU Magdeburg

External Evaluations

2003

- Appointment Committee of the MPG (MPI for Polymer Research Dortmund, Technical University Darmstadt)

2004

- Appointment Committee of the OvGU, Magdeburg
- Appointment Committee of the MPG, Jena
- Appointment Committee of the MPG, Stuttgart

6 Selected Memberships, Appointments and Awards

Prof. Udo Reichl Scientific Member of the MPG and Head of the Chair of Bioprocess Engineering, OvGU, Magdeburg

start 2002 - Consultant, biochemical industry, Bayer AG

start 2003 - Managing Director; Institute for Process Engineering, OvGU (2003-2004)

- Scientific Member of the Advisory Board – Journal "Engineering in Life Sciences"

- Perspective Commission of Chemistry, Physics & Technology Section, MPG

start 2004 **-** Foundation Committee of the MPG-CAS Institute "Computational Biology", (Shanghai, China)

start 2005 Managing Director of the MPI
Intersectional Expert Committee of Systems Biology

7 Future Directions

The primary focus of future research activities over the next years will remain on cell culture technology, metabolism of eukaryotic cells, product formation, and downstream processing of biotechnologically derived products. In particular, basic research on mammalian cell growth, cell physiology and virus-host cell interactions in addition to research projects on virus-related bioprocesses will continue because of their enormous impact on human and animal health and the general importance of eukaryotic cells in pharmaceutical industry.

Continued in understanding growth and product formation of mammalian cells used in the bioprocesses relies on accurate and sensitive assays for the determination of extracellular and intracellular metabolites required for fueling reactions, i.e. supply of ATP, redox equivalents and formation of precursors for biosynthesis. In addition, accumulation and depletion of compounds inhibiting or promoting cell growth have to be monitored. Therefore, development of new assays to obtain relevant information on media and status of host cells in bioreactors will be continued. So far, more than 10 parameters (e.g. metabolites, cell numbers, HA, on-line signals from bioreactors, etc.) are routinely determined during cell growth and virus replication, together with more than 20 additional parameters (amino acids, pyruvate, lactate dehydrogenase, enzyme activities, etc.) for addressing specific questions. In the near future, the determination of another 20 to 30 metabolites of glycolysis and TCA cycle will be available.

While this amount of data clearly improves general understanding of bioprocesses inferences based on this huge amount of experimental data are only feasible by developing and validating appropriate mathematical models. Therefore, mathematical modeling for cell growth (Möhler et al., 2005, in preparation) and virus replication (Möhler et al., 2005; Sidorenko et al., 2004) will continue over the next years. One focal point will be on cellular metabolism, i.e. models covering the range from metabolic flux analysis confirmed by isotopomere labeling experiments to highly structured models describing cell growth phase in bioreactors. The purpose of these models is 1) to improve our understanding of mammalian cell metabolism in different bioreactor systems (static cultures, roller bottles, suspension cultures), 2) to design and optimize media and feeding strategies (repeated-batch, fed batch, perfusion) to maximize cell numbers, and 3) to characterize optimal conditions for infection in the

subsequent process steps. The other focal point is related to virus replication itself. While it is relatively simple to set-up detailed models for the infection of single cells, validation of such models is an extremely challenging and time consuming task. As already mentioned above, an experimental platform (PCR, proteomics, flow cytometry) has been constructed, which will allow us to address very specific questions on virus-host cell interaction.

These comprise time course of cell cycle, viral genome replication (PCR, flow cytometry; BPE Group) and the monitoring of viral protein synthesis during infection (proteomics, together with MNA and SBI Group) as well as aspects of influenza virus induced apoptosis (collaboration with external partners, Prof. Ludwig, Institut für Molekulare Virologie, ZMBE Münster and Prof. Naumann, OvGU, Magdeburg). In addition, based on a reduced model of virus replication in single cells (Sidorenko et al., 2004), the time course of infection in population of cells will be investigated together with A. Kienle (PSD Group).

Downstream processing of fermentation broths consisting of highly complex mixtures of hundreds of compounds will be a challenging task over the next years. Previously, the focus of our work has been on characterizing and optimizing individual unit operations required for the purification of viruses for inactivated vaccines. Much on this work was done in close collaboration with the Chair of Bioprocess Engineering (OvGU, Magdeburg) and partners from industry, namely Amersham (GE Healthcare), Sartorius and TOSOH. This work will continue to a certain degree, i.e. to optimally combine unit operations for improving yields and purity of viral proteins and to investigate influences of process modifications (upstream, inactivation) on performance of subsequent purification and polishing steps. In collaboration with the PCF Group basic mathematical models describing virus purification in gel chromatography and ion exchange chromatography will be developed. Furthermore, the use of affinity chromatography as a single unit operation for the highly specific purification of virions and viral membrane proteins (hemagglutinine) will be investigated in detail. Another focus will be the characterization of glycosylation patterns of viral surface proteins in up- and downstream processing by mass spectrometry and multi-capillary electrophoresis (collaboration with PCF Group and external partners, Linhardt, RPI, Troy, NY, USA). Main questions to be addressed will be 1) influence of host cells and cultivation conditions, 2) impact of inactivation procedures and 3) changes in glycosylation patterns during concentration and chromatography steps.

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

Research Group:

Integrated Navigation Systems (INS)

Prof. Dr.-Ing. Ernst Dieter Gilles

This is the final report for the research group.

Regarding to the recommendations of the scientific advisory board in June 2003 the research group Integrated Navigation Systems has been closed in October 2003. Following is a short overview regarding to the completed research projects.

1 Completed projects

1.1 Virtual navigation environment

Project status: Finished

Results: Recent enhancements included the simulation of various sensor types and sensor failures, and the integration of electronic charts in ECDIS standard format.

1.2 Automatic chart generation

Project status: Finished

Results: The quality of condensed radar images has been improved by variable echo shortening and an additional offset compensation. A reviewed algorithm provides substantial reductions in computing time.

1.3 High performance radar interface

Project status: Finished

Results: The development of high-performance PCI radar interface board, Linux kernel drivers and application software has been completed. Full functionality has

been proven in test runs under real application conditions involving different types of radar devices on commercial ships.

Remaining research activities are being continued under supervision of Prof. Gilles financed by third-party funds.

2 Continued project

Elbe project "Development and Testing of an Integrated Navigation System for the Special Requirements of the Elbe Waterway", third-party funded by the State of Sachsen-Anhalt

Results: Achievements in minimizing the impact of sensor failures have been made both at sensor and control side. The drift dynamics model as a part of the steering dynamics has been extended by taking the effect of water current into account.

Current activities are focused on experimental validation of the steering model and its application to control, both based on estimation of the water current velocity.
Another aspect is the optimal design of guiding lines.