MAX-PLANCK-GESELLSCHAFT

Scientific Report 1998 - 2003

Max Planck Institute for Dynamics of Complex Tecnical Systems

Max Planck Institute for
Dynamics of Complex Technical Systems

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Table of Contents

List of Frequently Used Abbreviations

MPI Research Groups

PSD	Process Synthesis and Process Dynamics
PCP	Physical and Chemical Process Engineering
SCT	Systems and Control Theory
PCF	Physical and Chemical Foundations of Process Engineering
BPE	Bioprocess Engineering
SBI	Systems Biology
MF	Mathematical Foundations of Dynamical Systems
INS	Integrated Navigation Systems

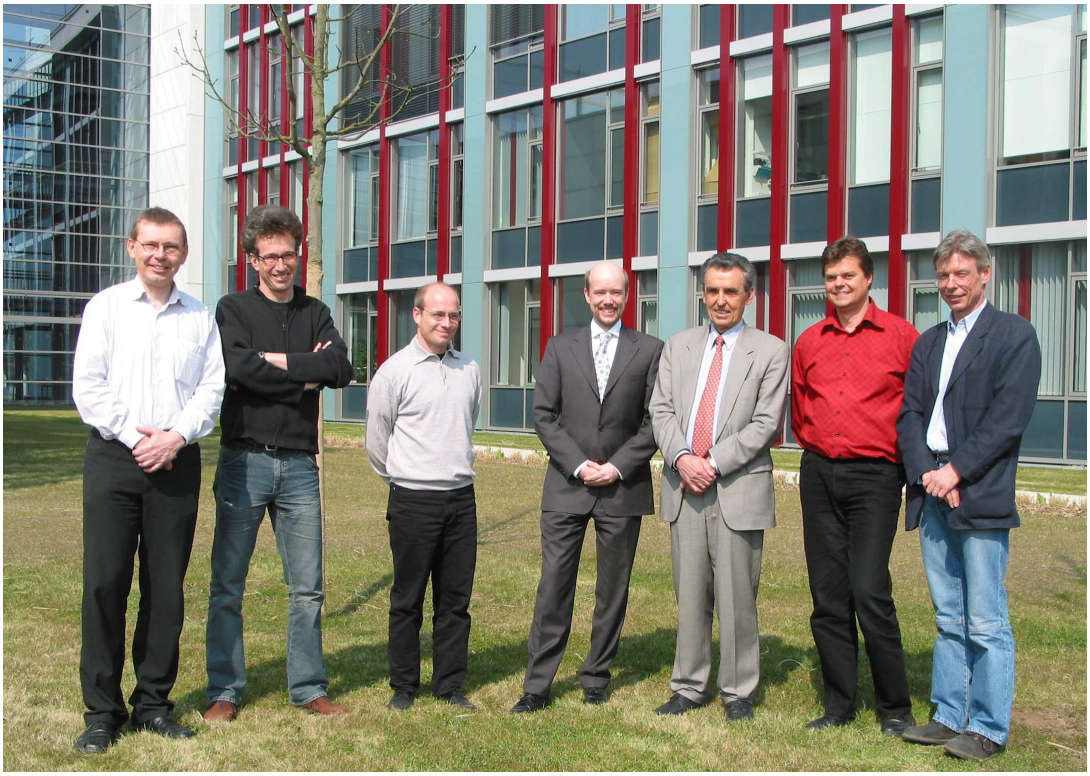
Funding Organisations

AiF	Working Party of Industrial Research Associations
BMBF	Federal Ministry of Education and Research
DFG	German Science Foundation
EU	European Union
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 Kai Sundmacher



Period from 1998 to 2003
Heads of MPI research groups: A. Seidel-Morgenstern, J. Raisch, A. Kienle, K. Sundmacher, E.D. Gilles, U.Reichl, D. Flockerzi

1. The First Institute within the Max Planck Society Representing the Engineering Sciences

At the beginning of the 21st century the global society faces a problem. Given limited resources and a rapidly growing population, how it is possible to render modern production processes more economic while at the same time keeping up and improving upon ecological standards?

There can be no doubt this problem requires solutions that are both fast and feasible. On the other hand it is obvious that the desired solutions should by no means have an ad hoc character. Instead, the concept of sustainability should serve as a guideline for all new developments. In order to avoid adverse effects it is crucial to have at one's disposal detailed knowledge of the fundamentals that govern the technological processes one is dealing with. However, such fundamental knowledge has traditionally only been attributed to the basic sciences like physics, chemistry and biology. In contrast, the engineering sciences have traditionally been restricted to the mere application of scientific knowledge. To some extent this situation had decoupled them from the fundamental sciences.

For quite a while, industry and much of society have urged scientists to overcome this apparent gap. The engineering sciences should approach the fundamental sciences without missing out on concrete practical requirements. In other words: The modern engineering sciences are increasingly obliged to bridge the gap between basic research and industrial application.

However, new prerequisites are required to make this essential bridging feasible. Thanks to the immense increase in computing power and capacity it is now possible to deal with systems of equations as they originate from the underlying processes, and that are both very large and difficult to solve. Yet, tackling today's problems is not done by simply relying on computer power. In fact, the engineering sciences themselves have to focus to a greater extent on the development of new theoretical concepts. Therefore, it is their task to further promote the **paradigm shift in the engineering sciences** towards a research that is increasingly focused on the development of new system-oriented methods and tools that are suitable for the analysis, synthesis and control of complex technical and biological systems.

The Max Planck Society, which is by charter devoted to fundamental research, has paid tribute to this trend by founding the Max Planck Institute for Dynamics of Complex Technical Systems. It is here that, within a highly interdisciplinary research concept, chemical and control engineers, bio-engineers and system scientists are doing research together with mathematicians as well as natural and computer scientists. Their main aim is to develop new methods to render dynamic processes more efficient with a clear emphasis on chemical and

bio-chemical processes. In this respect, there are two critical goals that must be met. First, the understanding of processes concerned with the synthesis and separation of substances both in chemical and biological systems must be augmented. Second, the ultimate objective is to subsequently use this knowledge to manipulate the respective processes to achieve the desired result.

2. Foundation and Growth

In 1996 the senate of the Max Planck Society (MPG) decided to establish the Max Planck Institute for Dynamics of Complex Technical Systems following the recommendations of a mixed commission of experts from the MPG and from various engineering research societies in Germany to found the first institute that is dedicated to the engineering sciences. Prof. Dr.-Ing. Dr. h.c. mult. **Ernst Dieter Gilles** (Univer-sity of Stuttgart) was appointed as the founding director of the institute. Because the **Otto-von-Guericke-University Magdeburg (OvGU)** has a long standing tradition of excellence in the engineering sciences, Magdeburg was identified as a suitable place for the establishment of this new MPI.

The scientific work at MPI started in March 1998 in a temporary space (1300 m^2 area) rented in the ZENIT-building on the campus of the medical faculty at OvGU. Simultaneously, the realization of the MPI's new building (5700 m^2 area) located near the Elbe river was planned and prepared. The construction was started in fall 1999 and finished in summer 2001. In August 2001 the entire institute moved into the new building where the scientific work was continued in September 2001. A very important prerequisite for our experimentally oriented research activities was the establishment of a bench scale laboratory hall (200 m^2 area in main hall) including satellite rooms for conducting experiments that are potentially explosive.

As an important condition for the successful scientific establishment of the MPI and for its interaction with OvGU, the new faculty for Process and Systems Engineering was founded, which became one of the most important scientific collaboration partners of the institute.

Within OvGU, new chairs were founded which play a key role in the interface to the MPI. These are the chairs for Bioprocess Engineering, Process Systems Engineering and Systems Theory of Technical Processes.

From 2000 to 2002 the board of MPI directors was completed by three appointments. These positions were filled in conjunction with three university chairs at the faculty for Process and Systems Engineering. Prof. Dr.-Ing. **Udo Reichl**, formerly with the company Essex Ltd., joined the institute in July 2000 as the director for the research field of Bioprocess Engineering. He is also full professor for the same area at OvGU. In July 2001,

Prof. Dr.-Ing. **Kai Sundmacher**, formerly with Clausthal University, was appointed director for the research field of Process Engineering in conjunction with a full professorship for Process Systems Engineering at OvGU which he has held since 1999. A year later, Prof. Dr.-Ing. **Andreas Seidel-Morgenstern**, who has been a full professor for Chemical Process Engineering at OvGU since 1995 and who had been an external MPI scientific member since 1998 became the institute's fourth director. He guides the MPI's research activities on Physical and Chemical Foundations of Process Engineering. After these appointments, since fall 2002, the MPI's founding director, Prof. Ernst Dieter Gilles who is also a honorary professor at OvGU, has focused his activities on the System Theoretical Fundamentals of Process and Bioprocess Engineering.

In November 2001, the institute was proud to be able to involve Prof. Dr.-Ing. **Jörg Raisch** closely into its research activities as an appointed external scientific member of the MPI. Prof. Raisch founded the MPI research group on System and Control Theory in June 1998, and has guided it since. Simultaneously, he is a full professor of Systems Theory of Technical Processes at the electrical engineering department of the OvGU.

The collaborations of the MPI with the electrical engineering department in Magdeburg were further intensified when Prof. Dr.-Ing. **Achim Kienle,** who has guided an MPI research group on Process Synthesis and Dynamics since March 1998 and prepared his habilitation thesis at the MPI, became full professor for Automation/Modeling in 2002.

In July 2000, Prof. Dr. **Dietrich Flockerzi** joined the MPI. He established a research group dealing with the mathematical foundations of dynamical systems in May 2001. He is also a lecturer in engineering cybernetics at OvGU.

In the course of the directors' appointments and the establishment of a total of eight research groups (for more details see section 4), the number of Ph.D. students, postdoctoral scientists, visiting scientists, and members of the technical staff was steadily growing during the period covered by this report (see Fig. 1). By the end of April 2003, the total number of staff employed at the MPI was 152.

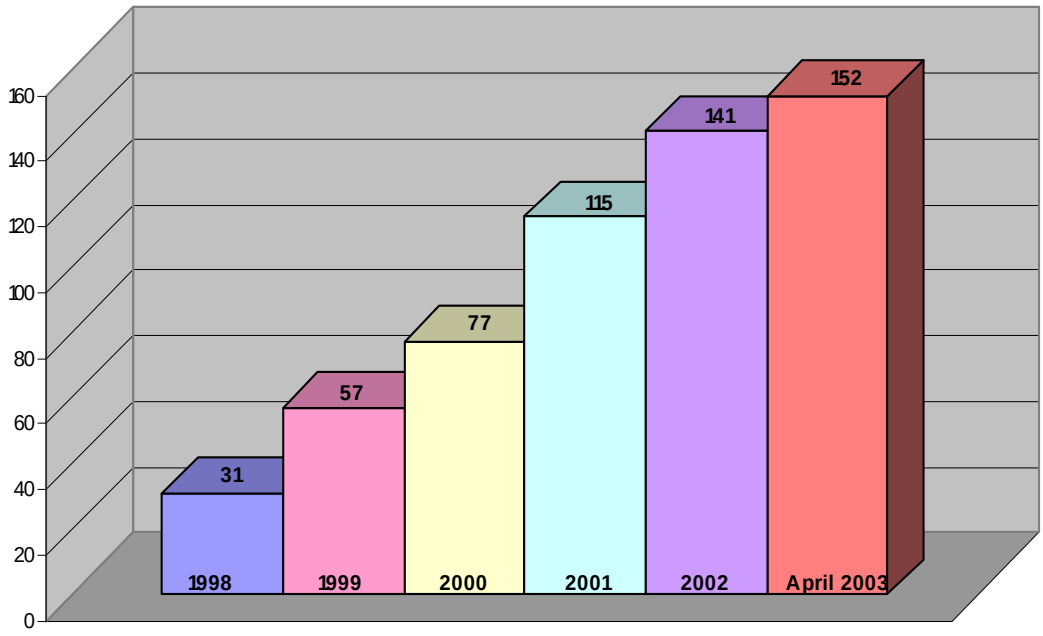


Fig. 1: Development of total number of MPI staff from March 1998 to April 2003.

3. Research Concept

Technological processes must meet increasingly high and diverse specifications. It does not suffice that, for example, in a chemical plant a specific product is synthesized but it must also be produced meeting high quality standards at minimal environmental pollution, most economical usage of resources and maximum yield. Our institute is facing the challenge of **designing, structuring and controlling technological processes, with particular focus on chemical engineering and biotechnology**.

This not only requires a sound knowledge of technical plants and the underlying physical, chemical or biological phenomena, but methods from engineering and mathematics for the analysis and synthesis of dynamic systems are also indispensable. Therefore, engineers are closely cooperating with chemists, biologists and mathematicians.

Research topics treated at the institute are rather diverse. As illustrated in Fig. 2, they cover the synthesis, analysis and control of chemical reactors and separation processes; the collection of thermodynamic and kinetic basic data; the study of biochemical processes; the analysis of networks of functional units in biological cells; and the design of integrated navigation systems. However, all these research activities share a common basis: they are all related to methods and tools which are provided by **system sciences**, i.e. system sciences is an important **integrating factor** in the institute's research concept.

In particular, all research projects are related to dynamic process models, i.e. suitable mathematical descriptions of the time-dependent behavior of the considered processes. Due to the diversity of chemical unit operations and apparatuses concerning the development of chemical process models, one focus is on systematization of model building. The object is to support and partly automate the modeling procedure using methods from computer science. For this purpose, a software package is being developed at the MPI that is already being used for the systematic modeling of chemical as well as biological systems. When modeling cellular systems in biology, it is necessary to identify metabolic pathways and signal transduction units and to describe them in submodels. The dynamic model of the whole biological cell is then composed of many of such submodels.

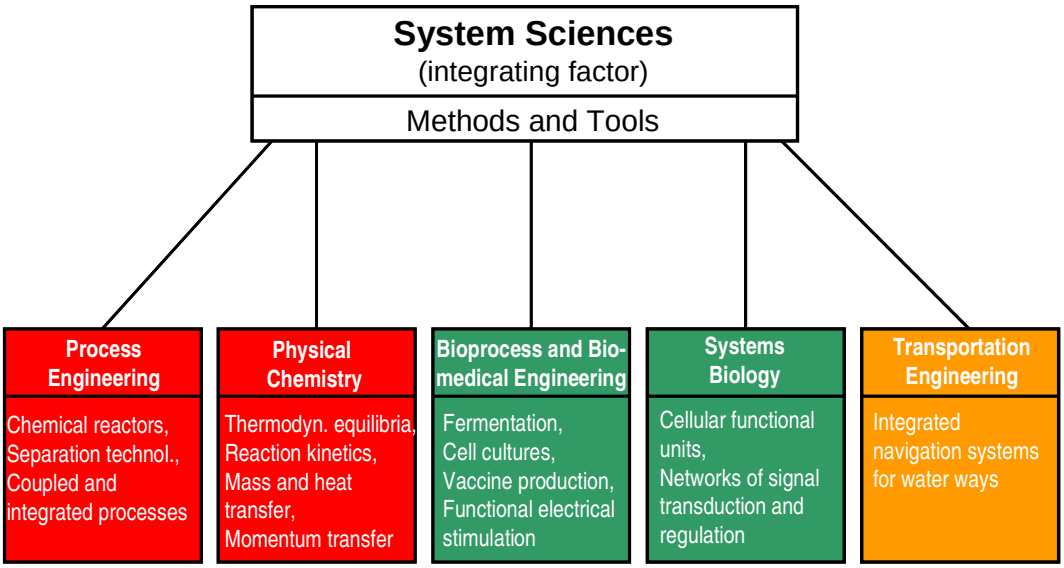


Fig. 2: System sciences as integrating factor for the diverse research activities at MPI.

This systematic modeling procedure generally yields the structure of a process model. Specific values for unknown parameters have to be determined by experimentation. Furthermore, such models deduced from theoretical considerations require experimental validation. To conduct these experiments, the MPI is equipped with **chemical and biological laboratories** as well as a **multi-floor open-bay lab** where **bench-scale pilot plants** can be set up.

Based on process models, the dynamics of technical and biological processes can be studied. Using mathematical methods, it is, for example, possible to analyze which **qualitative dynamic behavior** a plant can exhibit depending on its operating conditions. Via computer simulations, critical states can be investigated without risk, or tedious experiments can be replaced with computations that take merely seconds.

Most importantly, however, it is possible to use process models to solve the core problem of engineering: process synthesis, layout, and control, i.e. **the design of technical plants and processes.** A single apparatus can be properly dimensioned and designed, whole groups of apparatuses can be assembled to build complete production plants, or several basic functions can be integrated in a single unit. Such extensively interconnected or integrated plants show a level of complexity that makes it impossible to understand or control them without the use of model based methods. To find the most advantageous design for a plant, **mathematical optimization methods** can be used, and in computer simulations the behavior of different variants can be compared.

For safe and economic operation of such plants, **control engineering** plays a crucial role. However, with increasing complexity of a plant, the design of control structures becomes more and more demanding. To find the optimal control control strategies, advanced methods of model based controller synthesis and model reduction techniques are essential.

Engineering problems always focus on the solution of real world problems. Therefore, solutions that were developed using mathematical models will eventually have to demonstrate their effectiveness in experimental tests which are carried out in the institute's labs and in collaboration with industrial partners.

4. Organisation of Research

The MPI's research is focused on challenging, complex technical and biological systems, which require a maximum degree of **interdisciplinary interactions** between different scientific disciplines in order to create new and successful solutions. In order to achieve a maximum degree of interdisciplinary collaboration within the institute, the classical departmental structure was made more flexible by the establishment of **research groups**. As an important advantage of this group structure, it allows the MPI to adopt new research directions more quickly than a rigid departmental structure. At the moment, eight research groups are active whose names and leaders are given in Fig. 3.

The board of directors makes decisions regarding the establishment of new research groups and approves the research budgets applied for by the groups. To strengthen the interdisciplinary cooperation, researchers from different groups work together in project areas. Each research project and each of its subprojects at the institute is related to one of these projects areas. Hence, scientists from several disciplines share their specific perceptions and methodologies in the examination of a certain research topic.

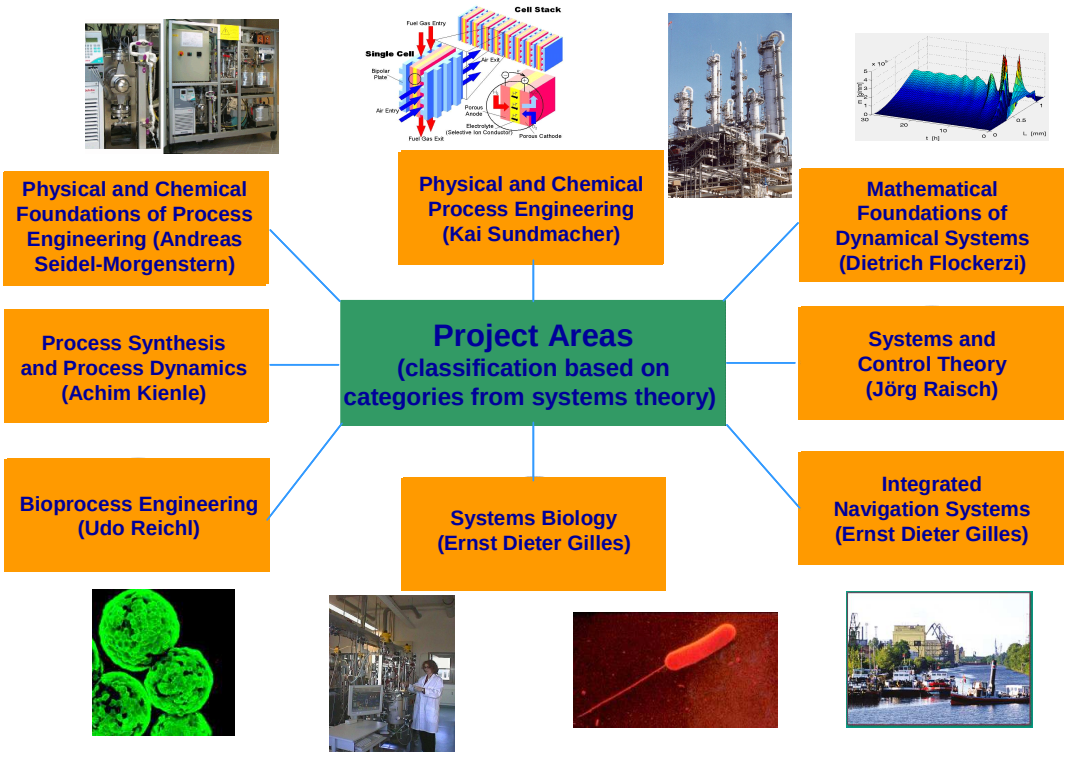


Fig. 3: Research groups cooperate within project areas.

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 object from different perspectives. Second, often the same method is employed to investigate problems from several different application areas. Thus, interdisciplinary cooperation is of great importance to the research being done at our Max Planck institute as can be seen from the matrix of research activities in Table 1.

Table 1: Activities of research groups in MPI project areas as of April 2003.

Research Groups	Process Synthesis and Process Dynamics	Physical and Chemical Process Eng.	Systems and Control Theory	Physical and Chemical Found. Pro. Eng.	Biopro-cess Engi-neering	Systems Biology	Math. Found. of Dynam. Systems	Integrated Naviga-tion Systems
Project Areas	**PSD**	**PCP**	**SCT**	**PCF**	**BPE**	**SBI**	**MF**	**INS**
Network Theory	●	●				●		●
Hierarchical Structures	●		●		●	●		●
Population Balance Systems	●	●	●	●				
Reduced Models	●		●				●	
Integrated Processes	●	●		●			●	
Coupled Processes	●	●			●		●	
Hybrid and Discrete Event Systems	●		●	●				

From time to time, the position of each research project in its related project area and the participation of the MPI research groups are revised. Depending on the development of the scientific focus of a certain project, it might be moved into another project area. Simultaneously, depending on the scientific expertise needed in the considered project, further MPI research groups will be included in the research activities. In this respect, the matrix organization of MPI is a very useful and flexible platform to carry out research projects and to push them forward into new, promising directions.

5. Project Areas at MPI

In the following, the main objectives and the contents of the established MPI project areas will be outlined.

5.1. Research Area: Network Theory

Mathematical models have been widely accepted as useful tools for the solution of many technical problems. **Mathematical modeling** can help to plan more specific experiments, to evaluate experimental results in greater detail, or to accelerate the development of novel technical solutions, for example. However, sufficiently reliable models are a prerequisite for the successful application of model-based methods. The models must comprise the complete scientific knowledge necessary to solve a specific problem. Therefore, they have to be very complex in many cases. The development of new models is time-consuming and requires extensive knowledge and experience. The purpose of this project area is to simplify the model development by **systematizing the modeling approaches** for chemical and biochemical processes, and by integrating computer aided tools into the modeling process. The basic idea of the systematic modeling approach pursued here is to **subdivide process models** into **elementary modeling units**. The modeling units are elements of a modeling library and can be combined into new models of arbitrary complexity. This **modular approach** offers the following advantages:

- Frequently used submodels need not be re-created again and again but are available from a model database.
- Alternative approaches, e.g. for the description of diffusion or reaction processes, can be exchanged easily.
- During model formulation, the modeler can concentrate on the underlying physical assumptions without being bothered by the mathematical representation.
- The transparency and reusability of existing models is increased.

In the framework of several current projects, model databases for different chemical and biochemical processes are being developed. Implementation and utilization of the modeling units require a suitable computer tool. The computer aided modeling system **ProMoT** (Process Modeling Tool) is such a tool.

5.2. Research Area: Hierarchical Structures

In many areas of application, process complexity has increased tremendously during the last few years, often defying the use of traditional synthesis and control methods. In the absence of sound theoretical concepts, heuristic approaches are prevalent at the moment. They are intrinsically problem specific and typically involve an extensive trial-and-error stage. Clearly, a mathematically consistent way of treating complex synthesis and control problems would be 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 recycles 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; such an approach obviously does not meet the requirements of an increasingly complex and integrated reality. It will inevitably lead to unsatisfactory (i.e. far from optimal) solutions. On the other hand, treating a complex overall system as some type of unstructured conglomerate is clearly out of the question as the difficulties related to computational implementation usually grow exponentially with problem size.

Hierarchical approaches may offer a cure for this dilemma. They rely on **decomposing the overall problem into sub-problems** and reassembling their solutions in a hierarchical structure. Sub-problems are solved using process models of different abstraction levels: **higher-level, long-term decisions** are made 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, so far a systematic and mathematically sound strategy only exists in a rudimentary form. Hence, an essential objective within this project area is to improve the practical applicability of this strategy.

Important new advances 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 them to complex control problems from the fields of chemical engineering (where the task is to control material and energy flows) and transportation systems (where traffic flows are to be controlled), to name two. A more fundamental understanding of the basic principles used by nature to structure and solve complex biological regulatory tasks can therefore also be beneficial when addressing problems of how to design complex control systems for diverse technical applications.

5.3. 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 needed to characterize these objects are, for example, their size and shape or 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, e.g., for **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 first examples of successfully applying a rigorous mathematical modeling for predicting particle size distributions in crystallization processes and chain length distributions in polymerization processes have been given in 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 of 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.

5.4. Research Area: Reduced Models

The synthesis and control of processes in chemical engineering and of biological systems have a decisive influence on the quality of the products and on the production costs. Safety regulations, environmental aspects and energy specifications must also be taken into account when designing process strategies.

Synthesis and control methods are based on **mathematical models describing the relevant features of the underlying real process**. On the one hand, rigorous detailed mathematical modeling of technical processes or cellular systems offers a precise approximation of the real process, on the other hand it will inevitably lead to models of high dimension and of high structural complexity. As a consequence, such detailed models may be too complicated for a rigorous analysis of their dynamical behavior and for a practical design of efficient control strategies. Moreover their size and complexity may pose numerical problems and result in computational costs one might not be willing to accept. Furthermore, it is (in general) quite a delicate decision whether a “successful” numerical routine really has produced the correct answers.

In **biological systems** the complex functionality of metabolic and regulatory networks and of cell cycles needs to be mapped out. Based on systems theory and on the cooperation with biologists and computer scientists, mathematical models of amenable size and structure are established. The decomposition (modularisation) of a network and the analysis of the resulting subnets (modules) and their interconnections is an approach that promises to be successful in tackling the manifold aspects of biological networks, aiming at a better understanding based on reduced models.

Always keeping in mind the specific problem formulation, for example,

- to detect multiple steady states, oscillations or bursting phenomena,
- to analyze the pathways in signal transduction and in metabolic or regulatory networks,
- to optimize biological processes,
- to improve the process design,
- to design a robust control scheme in the presence of uncertainties,
- to detect and compensate disturbances,

one is thus interested in **reduced models of the underlying process**. These simplified models should still be capable of reflecting the essentials of the dynamical behavior and should allow the construction of effective and computable control strategies. In the project

area Reduced Models, mathematical methods and tools such as invariant manifolds and waveform solutions are developed that lead to reduced models possessing the necessary precision for the specific task. The concepts derived from the reduced model are sufficient to arrive at efficient strategies for the synthesis and control of the real process under consideration.

5.5. Research Area: Integrated Processes

In the chemical industries, the conversion of substances and the purification of the desired products usually are carried out in sequentially structured reaction-separation trains. In many cases, the performance of this classical chemical process structure can be significantly improved by an 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. By 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 operational behavior of an integrated process unit can be much more complex than the behavior of a single unit. Therefore, **suitable methods for process design and control** have to be developed and applied, ensuring optimal and safe operation of the considered integrated process.

The major objectives of the research in this project domain are to **develop new concepts for process integration**, to investigate their efficiency and to make them available for technical application. For this purpose, experimental tools and theoretical methods are closely combined. To prepare the applicability of new processes on an industrial scale, miniplant technologies are used intensively in the institute's experimental investigations. Reactive distillation processes, chromatographic reactors, direct fuel cells, membrane reactors and fixed bed reactors with thermally coupled reaction zones are subjects of our current research activities in this project area.

5.6. Research Area: Coupled Processes

Complex processes commonly consist of several individual sub-processes interacting with each other. Typical examples are:

- metabolic and regulatory networks in biological systems,
- production processes in chemical engineering,
- combined transport and traffic systems.

In general it is not possible to correctly predict the behavior of the coupled overall process just by relying on knowledge about the individual units. This is because a **qualitatively new behavior** may emerge 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 problems of analysis, optimal design and control of coupled processes are approached.

In the area of **biological systems**, it is especially animal cells and microorganisms that are of interest as these produce desired vaccines, recombinant proteins, antibiotics and hormones. A detailed analysis of the complex metabolic, regulatory and signal transduction pathways will contribute to a better understanding of cell growth, gene expression and formation of various products. Thus, with the help of well-specified manipulations of the genome or suitable process control strategies, it will be possible to increase the productivity of industrially relevant strains and to optimize bio-technological processes. Moreover, it is expected that general principles can be deduced from the highly integrated, natural cellular processes, which can then be applied to and used, in technical systems.

As far as **chemical engineering systems** are concerned, 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. Highly integrated gas production and purification processes coupled with fuel cells that serve as decentralized energy supply systems as well as integrated concepts for the production of biological agents in bio-reactors with downstream post-processing are further examples.

The common interest in all these cases is directed towards optimal design and control of the respective coupled processes.

Yet another area where coupled and highly complex processes are encountered is the realm of modern **traffic engineering**. For example, the interplay between transport systems

on both roads and railways has to be coordinated. High precision navigation on inland waterways constitutes a further illustrative example.

5.7. 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 plant, for example the crossing of well-defined threshold values by temperature or pressure variables. If only the temporal order of events matters, 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 discrete event systems** have to be used. Examples are timed automata, timed Petri nets, and 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.

Technical examples which fall into the category of hybrid and discrete event systems are Simulated Moving Bed (SMB) chromatographic processes, discontinuously operated multiproduct batch plants, automatic start-up of chemical processes, and biological processes in cells. In cells metabolic processes are continuous, while the decisions often take place on higher regulatory levels in a discrete manner.

6. The Project “Crystallization”: An Example of Interdisciplinary Cooperation of MPI Research Groups

The project “Crystallization” is part of the project area Population Balance Systems. It is carried out in interdisciplinary collaboration between the research groups Process Dynamics and Synthesis (PSD), Physical and Chemical Foundations of Process Engineering (PCF) and Systems and Control Theory (SCT). Crystallization from solution or melt is a very important unit operation which serves for the production of solids and for purification/separation purposes. Product quality usually depends strongly on the crystal size distribution that can be described by population balance models. The three MPI research groups listed above study the complex dynamics and control of crystallization processes by means of experimental and theoretical tools in linked subprojects as illustrated in Fig. 4.

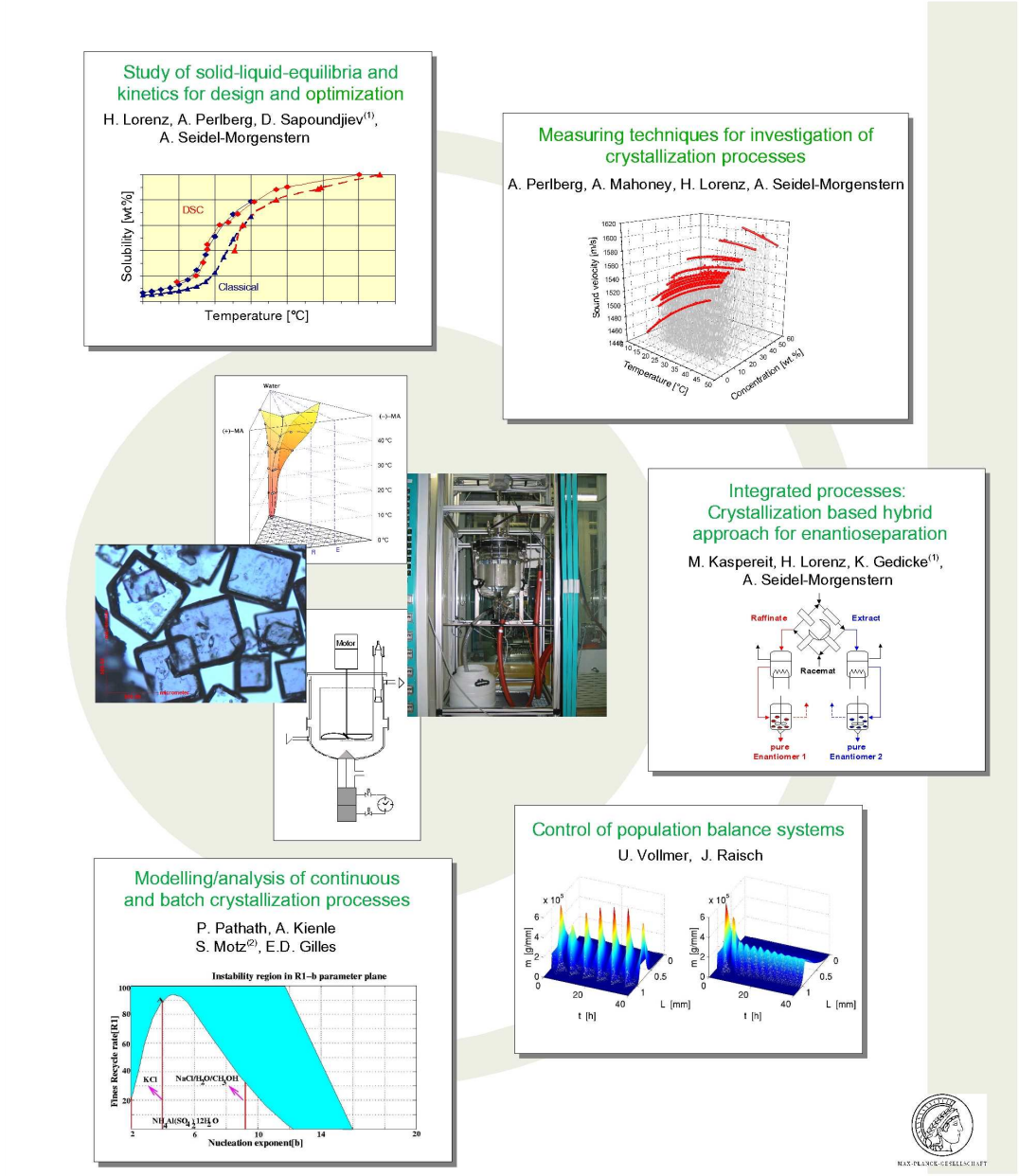


Fig. 4: Linked research activities in the project “Crystallization”. (1) OvGU, (2) University of Stuttgart.

The PSD groups focus is on the investigation of autonomous oscillations, which may frequently arise in continuous crystallizers with fines dissolution and product classification. The objective is to gain a better understanding of the behavior and to develop suitable methods for designing and operating crystallization processes with potential instabilities. The PCF group is active in using crystallization techniques for separation and purification of chemicals, particularly enantiomers. They provide data on solid-liquid equilibria and crystallization kinetics, and develop the experimental basis for determination of essential

process parameters to be fed into the population balance models developed by the PSD group. Based on these population balance models, the SCT group designs H_∞-feedback controllers which are able to remove the aforementioned sustained oscillations in continuous crystallizers. Furthermore, control strategies for the production of predefined crystal size distributions in batch crystallizers are developed using methods from nonlinear control theory.

Similarly, there are several other research projects at MPI where scientists from different research groups work closely together to bring in different expertises and views which are indispensable in attaining innovative solutions to challenging scientific problems. Examples for such fruitful interdisciplinary collaborations are the projects on **Reactive Distillation, Molten Carbonate Fuel Cells, Simulated Moving Beds, Biological Reaction Networks**, etc.

7. Publications

The complete publication lists of the research groups are provided in a supplemental volume to this status report. Here, we focus on an overall survey of the general development of MPI publications during the period of this report.

As can be seen from Fig. 5, there was a continuous increase of the total number of published **journal articles** and **conference contributions**. The total number of the institute's publications from 1998 to the end of 2002 was 201 (journal articles: 111, conference contribution: 90). At this point, it should be mentioned that depending on the publication culture of certain engineering disciplines established at the MPI, either journal publications or conference contributions can have more prestige.

Following the MPG standards, Fig. 6 illustrates the development of the proportion of MPI journals articles which were registered in the **Science Citation Index** (SCI, in total: 72), and in the **Databank Cluster** which includes CAPLUS, INSPEC, COMPENDEX and SCI (DB-Cluster: in total 94). Over the years, there is a clear increase of the number of registered publications.

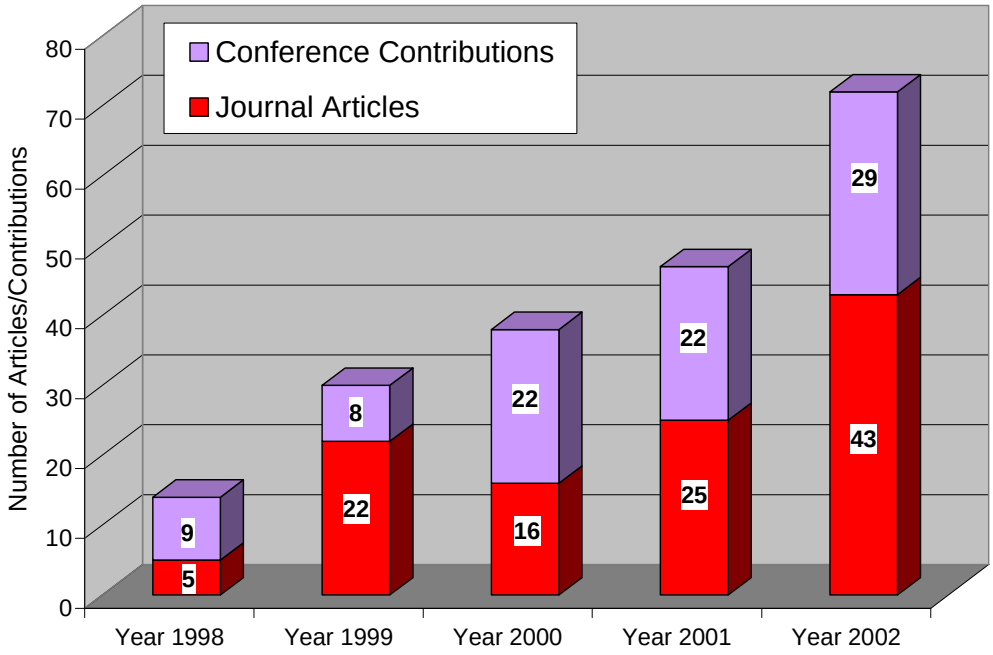


Fig. 5: Development of the number of articles published in journals and the number of conference contributions during the period 1998-2002.

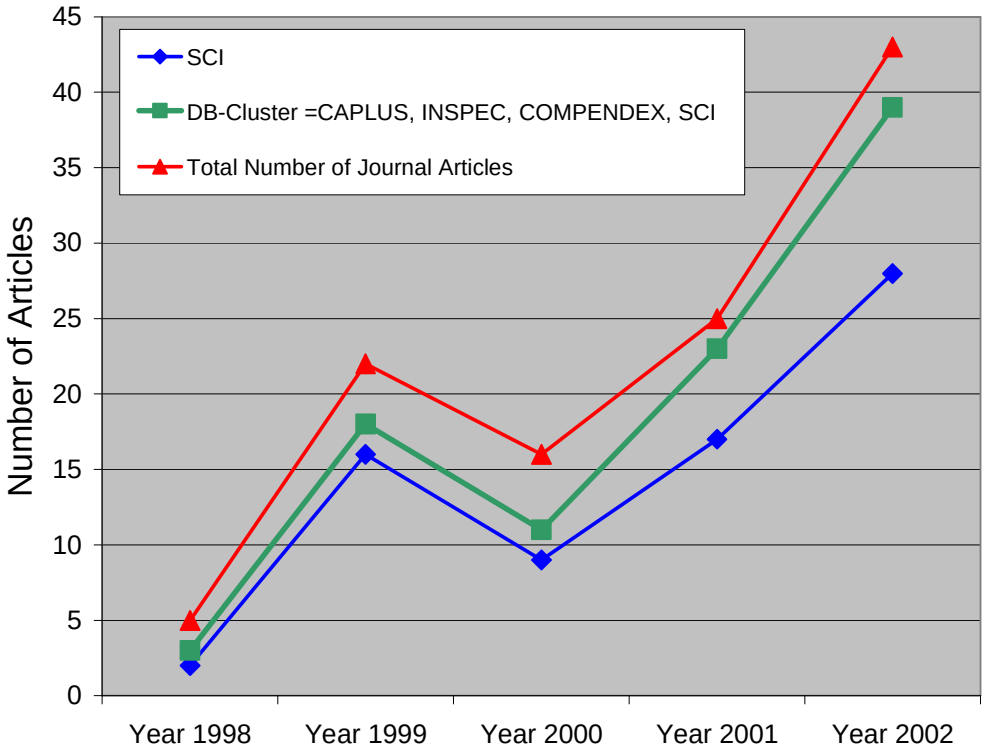


Fig. 6: Development of the number of published articles during the period 1998-2002.

The minimum of articles around the year 2000 is due to special conditions in the early phase of the institute's operation:

- restricted laboratory space which limited the growth and possibilities of our experimentally-oriented research groups during their stay in the temporary rooms at the ZENIT-building,
- considerable planning activities for the new MPI building in which the scientific and technical staff were strongly involved, and increased activities for selecting, purchasing and starting new experimental devices which bound considerable time in the early phase,
- establishment of several new joint research projects together with OvGU and other partners (DFG research groups, BMBF joint proposals),
- establishment of several new university chairs and their groups in conjunction with the MPI research groups.

We also carried out a citation analysis on the MPI publications registered both in the SCI and in the DB-Cluster. The essential results are documented in Fig. 7. It shows the **short-term-impact** of cited publications for papers published during the first three years of the Institute. The average number of citations per paper is given for the time period 1998-2003. For **SCI-papers** it is **3.72** and for the **papers in the DB-Custer** it is **3.29**.

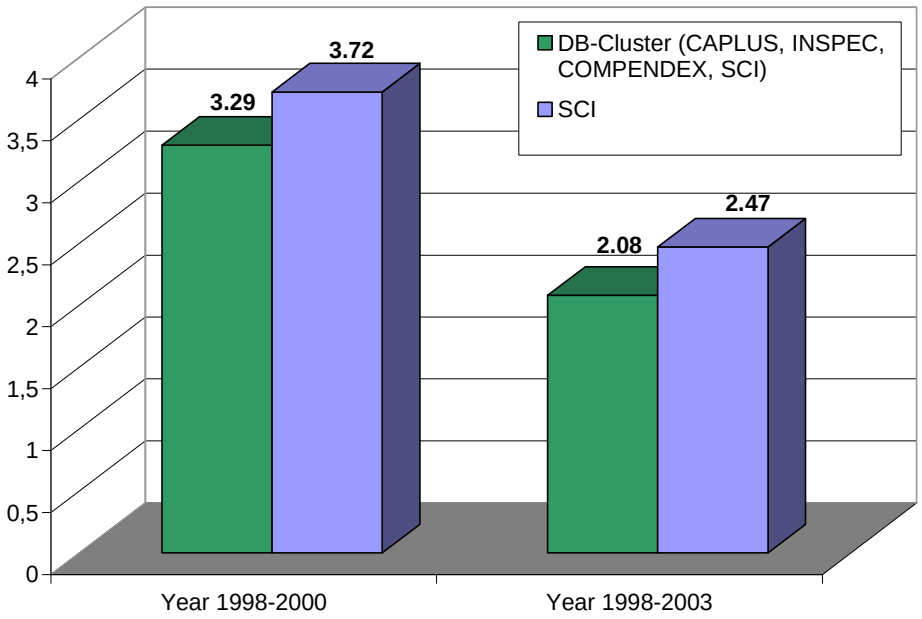


Fig. 7: Average number of citations of an MPI publication. According to Science Citation Index (SCI) and Databank Cluster (DB-Cluster).

This is significantly higher than the average value in the engineering sciences which is 2.9 according to the analysis of the Institute for Scientific Information (ISI National Science Indicators, 1981-1995). Obviously, the MPI publications were well accepted in the related scientific engineering communities. Of course, if papers which appeared from 2001 to April 2003 were also included into the analysis, the average citation rates are lower because these papers did not have enough time to be cited.

8. 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 31 December 2002, a total of 141 employees were working at the MPI. As illustrated by Fig. 8, 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. About one fifth of our workforce was **senior scientists and postdocs**, i.e. experienced scientists with a Ph.D. degree.

In carrying out the research projects, the scientific staff was supported by 24 student **research assistants** (17% of workforce). These are undergraduates who do their work at MPI in parallel to their studies at OvGU. The research work at MPI is an important additional experience for their education and gives us the chance to identify the students being most capable of pursuing Ph.D. studies after they graduated. Very often our research assistants simultaneously prepare their student theses (“Studienarbeit”) or diploma/master theses.

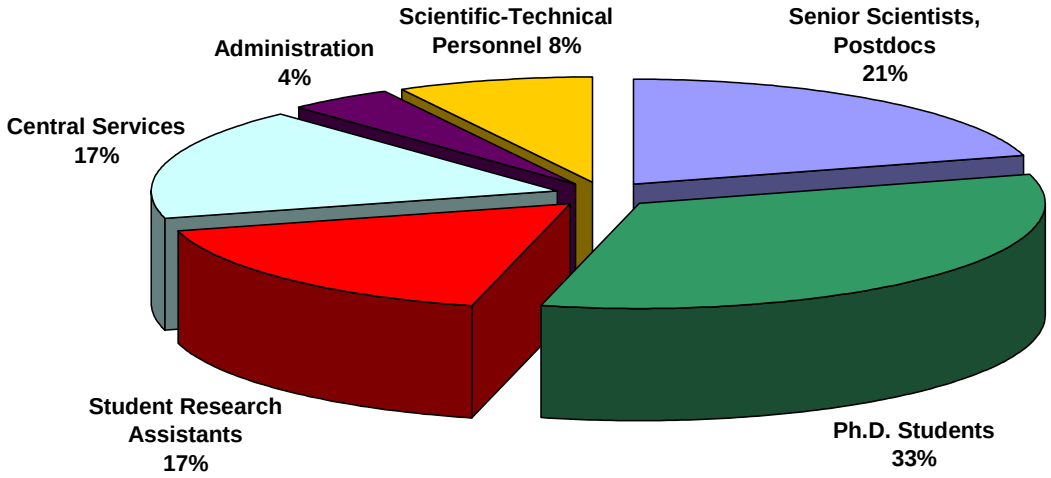


Fig. 8: Composition of MPI personnel as of 31 December 2002.

For preparing and performing the experimental work in the institute's chemical and biological laboratories the scientists are also supported by a total of 11 laboratory technicians and engineers. This indispensable **scientific-technical personnel** makes up 8% of the MPI workforce. Moreover, 17% of the MPI staff represent the **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 4% of the total number of employees.

It is worth mentioning that the number of available working places in the MPI's new building is 205. Thus, there are about 60 spaces left which will be filled in the next few years primarily by personnel payed from external funds. Many activities are currently under way to attract additional external funds from third parties.

8.1. Age and Gender Distribution

The **average age** of all 141 coworkers is only about **33 years** old. The age distribution is displayed in Fig. 9. It is remarkable that nearly half of the institute's staff are less than 30 years old. Only about 6% of the workforce are age 50 and older.

As additional information, the **age distribution of all scientists** is depicted in Fig. 10 which specifies also the fraction of permanent and temporary employments in the 5-year age groups. As of 31 December 2002, there were 76 scientists employed at the MPI, 29 of them senior scientists and postdocs, 47 of them Ph.D. students. Of these scientists, 75% are 35 years old or less which reflects a very young scientific workforce at our MPI. Overall only 10 scientific coworkers of 76 hold permanent positions. This is in full agreement with the overall policy of the Max Planck Society to operate its institutes with a relatively small number of permanent scientific staff.

Fig. 11 shows the distribution of our scientific coworkers according to gender. The percentage of **female scientists** is about 21%. This is a considerably higher proportion of females than normally encountered in engineering sciences in Germany.

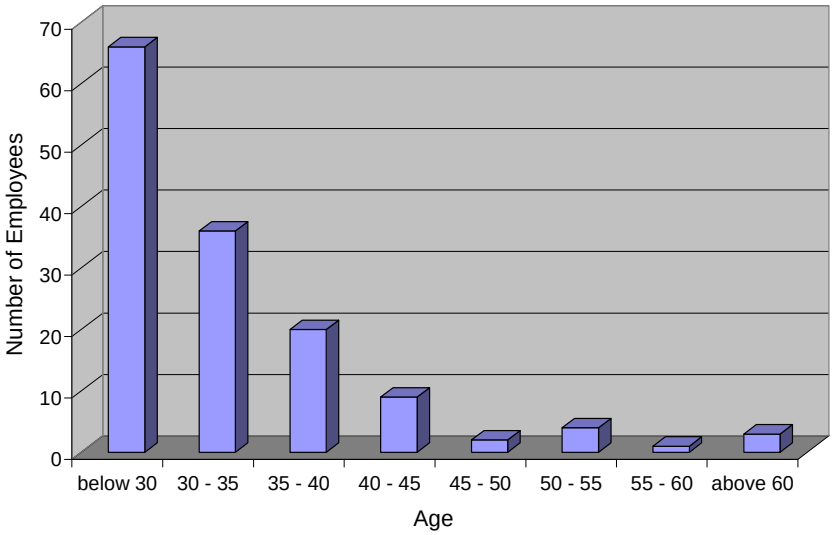


Fig. 9: Age distribution of all MPI employees as of 31 December 2002.

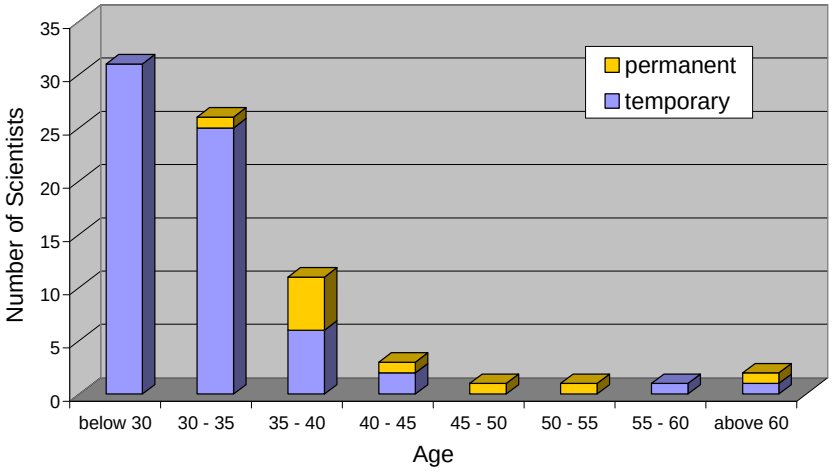


Fig. 10: Age distribution of MPI scientists divided into permanent and temporary employments as of 31 December 2002.

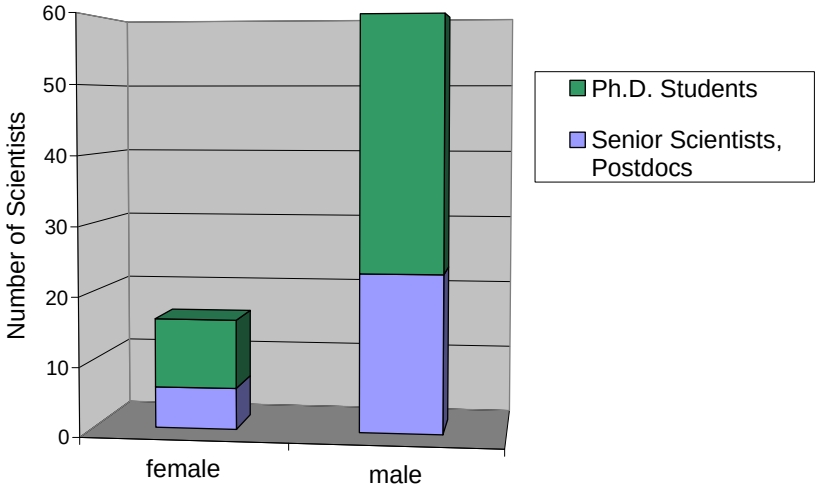


Fig. 11: Gender distribution of scientists as of 31st December 2002.

8.2. Graduate Students

As pointed out above, the graduate students represent 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. Fig. 12 gives a survey of the development of the number of Ph.D. students from the foundation of the institute to the end of 2002. The total number of graduate students has steadily increased during the last few years.

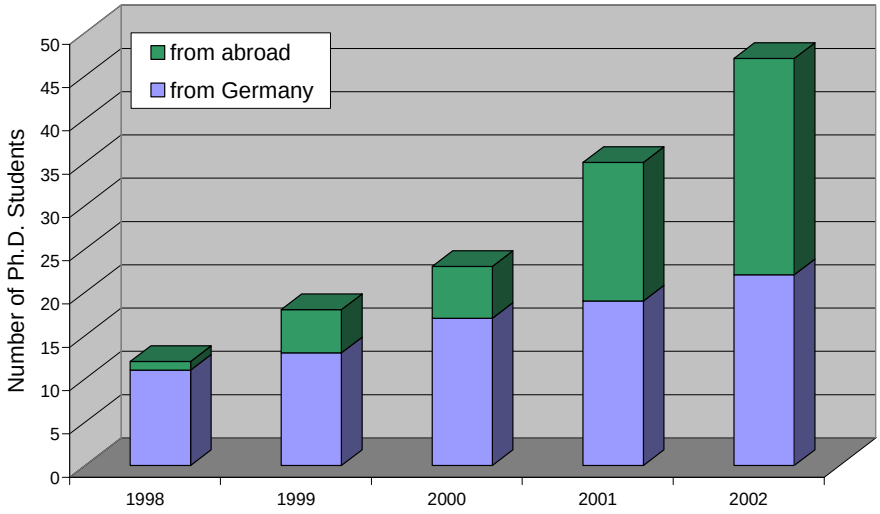


Fig. 12: Development of the number of Ph.D. students from abroad and from Germany.

The same is true for the portion of students coming from abroad, whose percentage is now more than 50%. This clearly shows that our institute is highly attractive to engineering students from national as well as from international schools. It is important to mention that this trend was achieved despite the fact that the number of students in chemical engineering and related disciplines in Germany has been continuously decreasing for the last decade. This is the reason for our current efforts to initiate new masters and diploma programs together with our colleagues at OvGU. In the future, we expect a further increase in the number of international students, which is also due to the increasing number of short-term guest scientists who very often act as a bridge to attract new students.

The largest fraction of foreign Ph.D. students comes from Asia, especially China and India. The second largest group originates from east European countries, mainly Bulgaria, Czech Republic, Romania, Ukraine and Russia. This is mainly due to traditionally excellent collaborations between east German universities and their academic partner institutions in eastern Europe. In the future we would like to further extend the collaborations with east European universities and academies, also in the framework of common research projects.

8.3. Guest Scientists

The MPI has intense interactions with a large number of short-term visiting scientists as reflected by Fig. 13 which illustrates the distribution of these visitors with respect to their home countries.

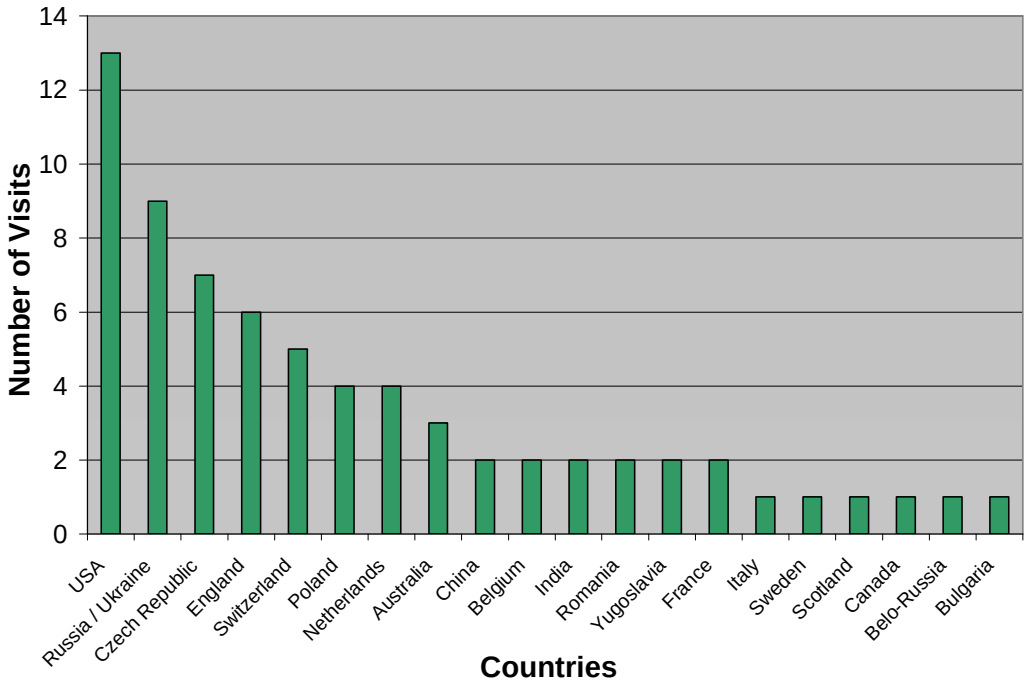


Fig. 13: Number of visits by international scientists to the MPI from 1998 to 2002 (with a stay of at least two days).

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 1998 to 2002, a total of 95 German scientists and 69 guest scientists from abroad visited our institute. Among the international guests, 86% came from the European countries, 9% from America, the rest from Asia and Australia.

9. Teaching Activities and Recruiting of Students

The teaching activities of the heads of the MPI research groups are focused at OvGU. They also give specialized lectures, mandatory lectures, and laboratory courses and act as supervisors for diploma and master theses. For details, the reader is referred to the research group reports. Additionally, some group heads have given courses at the University of Stuttgart. Ph.D. students from the MPI participate as assistants for the student practical exercises accompanying the lectures at OvGU. The topics of our teaching activities are closely related to the new diploma and master programs which were started at OvGU in recent years with significant encouragement from the MPI side:

- Systems Engineering and Cybernetics (5 years, diploma program)
- Computer Aided Process Design (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)

These programs were introduced because the traditional process engineering program is currently not able to attract enough German students. This is a phenomenon which can be observed at universities throughout Germany. On the other hand, industrial companies have a very strong need in excellently educated chemical and process engineers. However, in contrast to the classical chemical engineering education, more system-oriented engineers are needed who are better prepared to synthesize, analyze and control complex chemical and biotechnological processes from the molecular level up to the plant level. This is the background for our intense efforts to contribute to the development of attractive new curricula in the field of process and systems engineering.

In addition to our teaching activities and to our contributions in the strategic development of the profile of the engineering programs at OvGU, we also try to directly attract students from high schools of the German federal state Saxony-Anhalt to study engineering sciences or natural sciences. In this respect, two important activities were started:

- A **NaT-working project** (NaT: Natural and Technical sciences) was initiated in a direct partnership of the MPI with five regional high schools. This project is being funded by the Robert-Bosch-Foundation for three years.
- On a regular basis, the MPI offers **one-week laboratory courses**, each spring and each fall, for interested students from high schools in Saxony-Anhalt. These courses are organized and taught by our Ph.D. students.

10. Cooperations with Otto-von-Guericke-University Magdeburg

Many research projects of our institute are performed in close collaboration with universities in Germany and in abroad. At the institute's location, the intense partnership with OvGU is of particular importance. Although the OvGU, which was founded in 1993, is amongst the youngest in Germany, it has a long and successful tradition: it evolved from the former University of Technology, a Teachers' Training College, and the well-known Medical Academy at Magdeburg. About 9500 young people, many of them from abroad, are studying in one of the nine departments. The MPI building is located at the edge of the OvGU campus with a short distance to most departments.

As a prerequisite for the establishment of the MPI in Magdeburg, in 1997 the Department of Process and Systems Engineering was newly founded by merging the already existing institute for chemistry, the institute for process engineering, the institute for plant design and environmental engineering, and the institute for fluid dynamics and thermodynamics. Currently, 11 full professors, 2 associate professors and 2 assistant professors are active in the department.

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.

11. 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. In particular, two joint research groups ("Forschergruppen") were successfully applied for together with members of OvGU departments, and were funded by the German Science Foundation (DFG):

- DFG research group 447: **Membrane Supported Reaction Engineering**: 8 sub-projects in collaboration with the Department for Process and Systems Engineering and the Department for Mathematics,
- DFG research group 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.

- Moreover, during the period of this report, there have been a number of DFG projects in cooperation with partners at the University of Stuttgart in the framework of special research areas (SFB = Sonderforschungsbereiche):
- SFB 412: **Computer Aided Modeling and Simulation for the Analysis, Synthesis and Control of Chemical Processes**
- SFB 495: **Topology and Dynamics of Signal Transduction Processes**

In SFB 412 several MPI research groups have been involved in projects on structured modeling of chemical and biological systems, the development of tools for computer aided modeling of chemical and biological systems, the development of low order dynamic models using nonlinear waves, the development of hierarchical concepts for process control, and population balance modeling of crystallization processes. The **modeling tool ProMoT** and the **simulation environment DIVA** are an outcome of the SFB 412. These tools are further developed at the MPI and used for various applications including membrane reactors, fuel cells, reactive distillation, systems biology, etc.

Further collaborations between MPI research groups and university groups were established in the framework of several joint projects supported by the Federal Ministry of Education and Research (BMBF). In these project, 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)
- BMBF joint project: **CELLular Eucariotic proteome-Code deciphering Technology** (“CELLECT”) (Partners: MPI, OvGU, University of Stuttgart, Company: Meltec Ltd./Magdeburg)

In the area of Systems and Control Engineering, a 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.

12. 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, Merk KG, Rauschert Verfahrenstechnik Ltd., and Siemens AG.

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, postdocs 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 14).

13. International Collaborations

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

Europe

- TU Donezk, Ukraine: Plantwide 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: Crystallisation by entrainment
- University of Belgrade, Serbia: Determination of adsorption isotherms
- ICTP, Czech Republic: Electromembrane 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

Asia/Australia

- IIT Madras, India: Nonlinear dynamics of reactor separator networks
- IIT Bombay, India: Reactive distillation with non-condensable reactants
- Shanghai Jiaotong University, China: Modeling and control of Molten Carbonate Fuel Cells (MCFC)
- Australian National University: Hybrid control systems
- Melbourne University, Australia: Hybrid control systems

America

- Purdue University, USA: Nonlinear dynamics of bioreactors described by cybernetic models
- IIT Chicago, USA: Thermal analysis in crystallization
- Univ. 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

14. Workshops and Symposia

During the last five years, our research groups have organized several international workshops with participants from European and American countries:

- Workshop on **Particulate Processes** (2000): The contributions were published in a special issue of *Chemical Engineering Science*.
- Workshop on **Reactive Distillation** (2001): The contributions were published in a book by Wiley-VCH which appeared in January 2003.
- Workshop on **Hierarchical Concepts for Complex Technical and Biological Systems** (2001). During this workshop the idea was created to initiate a related joint project proposal was for the 6th Framework Programme of the European Commission.
- Workshop on **Flatness-based Control of Distributed Parameter Systems** (2003).
- Meeting of the **International *E. coli* Alliance** (2003).

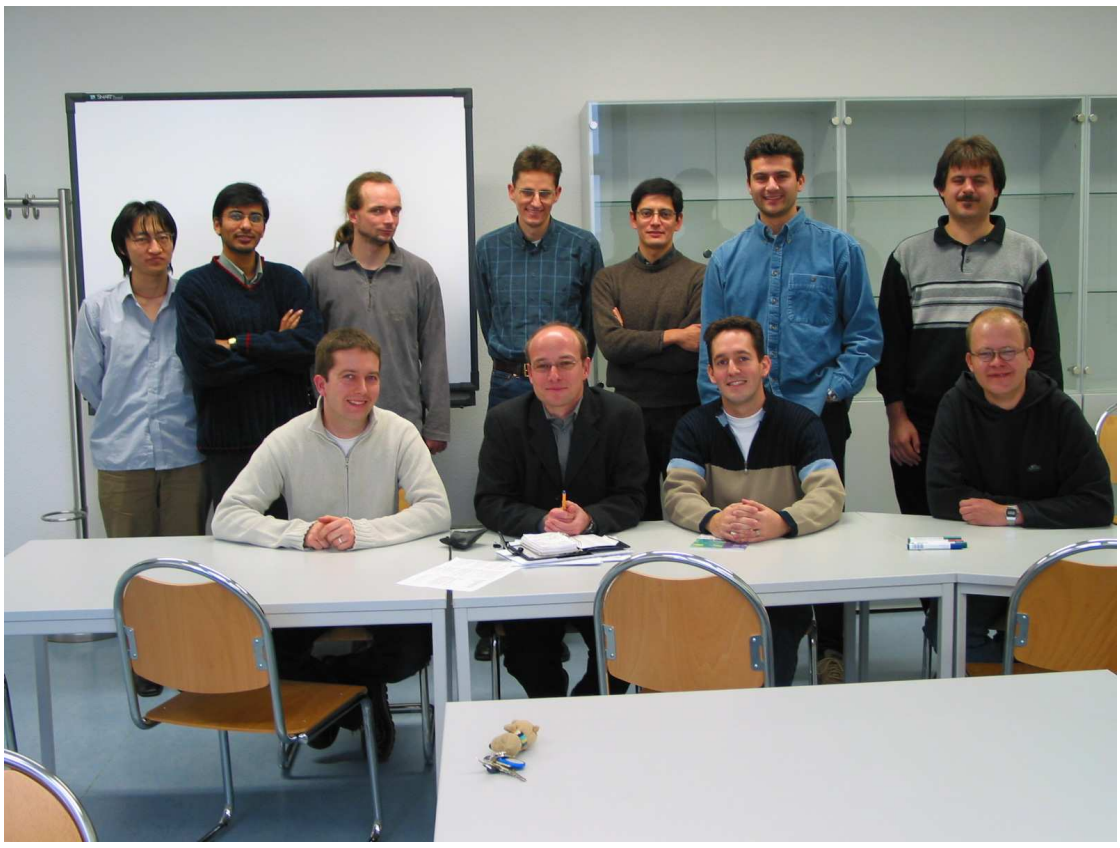
For the first and second of these workshops, the MPI received supporting funds from the German Competence Network “Verfahrenstechnik Pro3”. In close cooperation with the DECHEMA, the VDI (German Association of Engineers) and the Otto-von-Guericke-University Magdeburg, a series of one-day **DECHEMA Regional Colloquia** was initiated with participants from academic institutions and industrial companies. The discussed topics were **Fuel Cells Systems** (2000), **Fluidized Beds** (2002) and **Perspectives for Membrane Processes in Catalytic Processes** (2003).

Moreover, in 2002 the MPI organized a workshop on **Modern Methods of Particle Analysis – Applications, Problems, Limits and Comparability** with significant assistance from colleagues at the OvGU.

Research Group:

Process Synthesis and Dynamics (PSD)

Prof. Dr.-Ing. Achim Kienle



This report covers the period from 1 March 1998 to 30 April 2003.

1. PSD 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 of chemical processes, which can be a source of 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.

The above mentioned methods and tools are applied to various challenging example processes. An overview is given in Fig. 14. Current applications include: **integrated processes** like reactive distillation processes, coupled fixed bed reactors with recuperative heat exchange, membrane reactors, and a high temperature fuel cell with internal reforming; **particulate systems** like crystallization processes and a polymerization process for the production of low density polyethylene; **hybrid systems** like simulated moving bed chromatographic processes and multi product batch plants; continuously operated multi unit chemical plants consisting of reactors and separators with mass and energy recycles. This last activity is allocated to the project areas **coupled processes** and **hierarchical concepts**.

The PSD group has been supporting the establishment of the Max Planck Institute from the very beginning. The research activities of the PSD group are located at the interface between chemical engineering, systems dynamics and process control. Together with the SBI group it develops the modeling and simulation software ProMoT/Diva and supports its application within the other research groups.

The head of the research group, Achim Kienle, has recently accepted a position as a full professor at the OvGU. In the future, all research of the PSD group will be done in close cooperation with his university group.

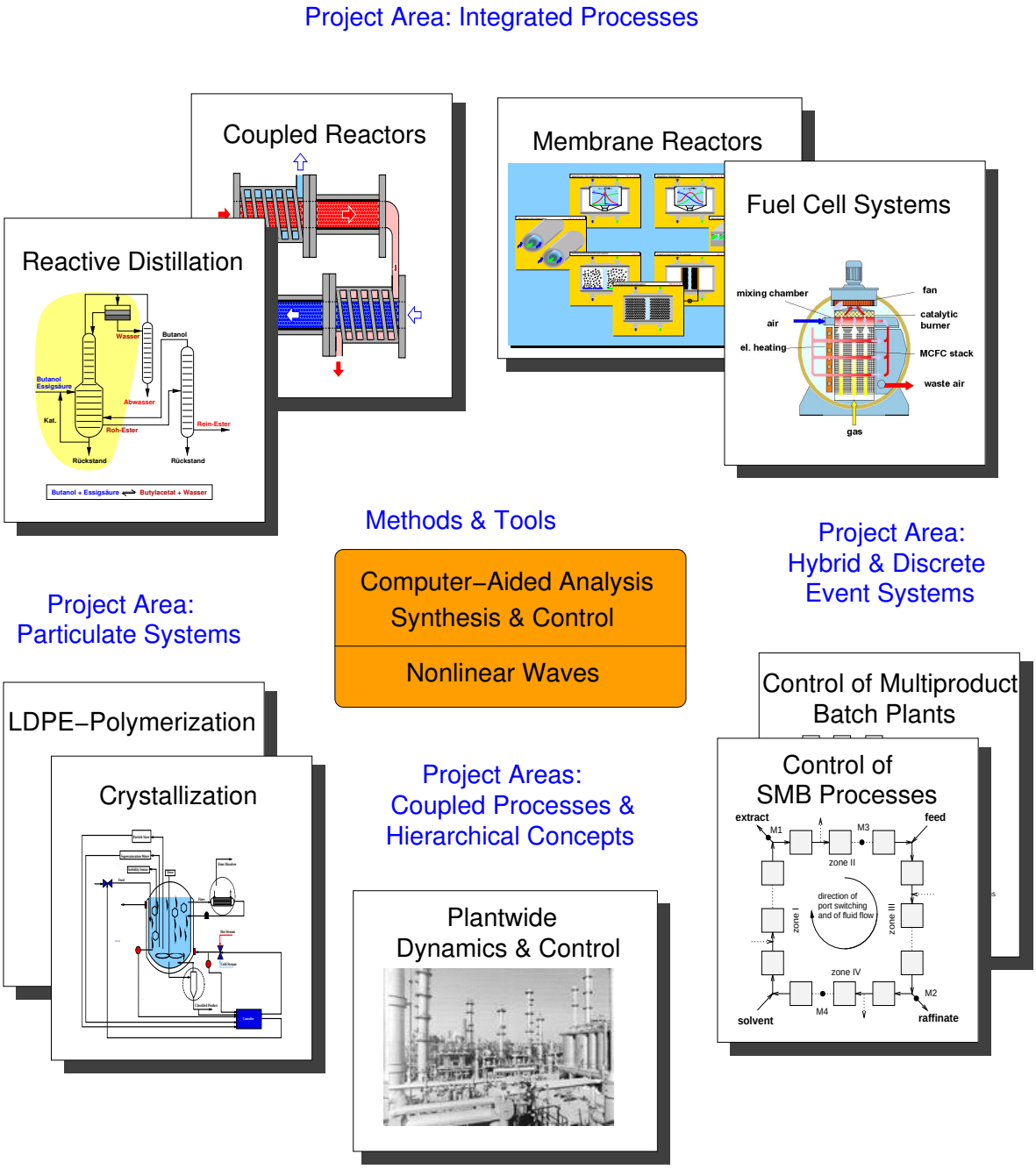


Fig. 14: Overview of the research activities of the process synthesis and dynamics group.

2. Members of the PSD Research Group

Head of Group

- Prof. Dr.-Ing. Achim Kienle, professor at the OvGU**.**

Secretary

- From July 2003, the group activities will be supported by a part-time working secretary.

Postdocs

- Mangold (since 03/1998)
- Klose (since 03/1999)

Ph.D. Students

- Häfele (since 03/1998)
- Waschler (since 09/1998)
- Pathath (since 06/1999)
- Angeles (since 10/1999)
- Schramm (since 08/2000)
- Tschebotarjov (since 03/2001)
- Sheng (since 06/2001)
- Gangadwala (since 08/2002)
- Fan (since 04/2003)
- Three of the Ph.D. students are funded by third parties (2xDFG, 1xBMBF).

Former Members of the Group

- E. Stein
- S. Svjatnyj

3. Survey of Research Projects

Project area: Network Theory

Project:	**Computer Aided Modeling of Chemical Processes**
Abstract:	A modeling concept for the systematic formulation of physical and chemical models is being developed. The modeling concept provides the theoretical framework for the development of the computer aided modeling tool ProMoT. The concept is applied to various classes of processes that are currently being investigated at the MPI, including fixed bed and membrane reactors, fuel cell systems, and reactive gas-liquid systems. More details are given in the research highlights section.
Subproject:	**Structured modeling of chemical processes**
Researchers:	M. Mangold
Partners:	SBI group; Members of joint research project SFB 412 at the University of Stuttgart
Funding:	MPI
Start:	1998
Subproject:	**Modular description of membrane reactors and fuel cells**
Researchers:	M. Mangold
Partners:	PCP group; Members of DFG research group 447 at the OvGU
Funding:	DFG (DFG research group 447)
Start:	2001
Subproject:	**Development of an object-oriented model library for chemical plants**
Researchers:	O. Angeles-Palacios, R. Waschler, A. Kienle
Partners:	SBI group
Funding:	MPI
Start:	1999

Project area: Reduced Models

Project:	**Reduced Order Modeling of Chemical Processes using Nonlinear Wave Propagation Phenomena**
Abstract:	The dynamic behavior of many chemical processes is governed by propagating temperature and concentration fronts, called nonlinear waves. In this project nonlinear wave propagation in chemical processes is analyzed mathematically. The results are used for nonlinear model reduction. Subsequently, the low order dynamic models are applied for model-based measurement and control of chemical processes. More details are given in the research highlights section.
Researchers:	A. Kienle, S. Grüner (ISR/ University of Stuttgart)
Partners:	Members of joint research project SFB 412 at the University of Stuttgart
Funding:	DFG (SFB 412)
Start:	1998

Project area: Integrated Processes

Project:	**Reactive Distillation**
Abstract:	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. The main achievements of the PSD group in the field of reactive distillation have been concerned with nonlinear dynamics (uniqueness and stability of steady states, periodic behavior etc.), control and optimal design of reactive distillation processes using optimization methods. In addition, new fields of applications of the reactive distillation technology are being explored. More details are given in the research highlights section.
Subproject:	**Nonlinear Dynamics and Control of Reactive Distillation Processes**
Researchers:	A. Kienle; K.D. Mohl & S. Grüner, ISR, University of Stuttgart

Partners:	PCP group; Prof. Marquardt, RWTH Aachen; Bayer AG
Funding:	MPI
Start:	1998
Subproject:	**Synthesis of Reactive Distillation Processes**
Researchers:	E. Stein, J. Gangadwala, A. Kienle
Partners:	PCP group; Prof. Weissmantel, Mathematics Dept., OvGU; Prof. Mahajani, IIT Bombay
Funding:	MPI, since 2002 DFG (DFG research group)
Start:	1998
Subproject:	**Reactive separation processes in coupled column systems**
Researchers:	E. Stein, A. Kienle
Partners:	PCP group
Funding:	MPI
Start:	2000

Project:	**Coupled Fixed Bed Reactors**
Abstract:	A novel reactor concept is being investigated that makes use of circulating reaction fronts. Autonomous periodic operation is achieved through internal thermal feedback. Potential benefits of periodic operation are explored for different classes of chemical reactions such as weakly exothermic, equilibrium limited, or consecutive reaction mechanisms with catalyst regeneration.
Researchers	F. Klose, M. Mangold
Partners:	Prof. Adler, University of Halle
Funding:	MPI
Start	2002

Project:	**Membrane Reactors**
Abstract:	Within this joint research project different types of membrane reactors are investigated theoretically and experimentally. As an example partial oxidation of hydrocarbons is being considered. The objective is to improve selectivity of these reactions at high conversions. The contributions of the PSD group are focused on catalyst preparation, the investigation of reaction mechanisms and kinetics, mathematical modeling, dynamics and control of different reactor concepts.
Subproject:	**Preparation and characterization of catalysts and membranes**
Researcher:	F. Klose
Partners:	PCF group, Members of DFG research group 447 at the University of Magdeburg
Funding:	DFG (DFG research group 447), MPI
Start:	2000
Subproject:	**Kinetics of selective catalytic oxidations**
Researcher:	F. Klose
Partners:	PCF group; Members of DFG research group 447 at the University of Magdeburg
Funding:	DFG (DFG research group 447), MPI
Start:	2000
Subproject:	**Nonlinear dynamics and control of membrane reactors**
Researchers:	Z. Fan, M. Mangold
Partners:	PCP group; Members of DFG research group 447 at the University of Magdeburg
Funding:	DFG (DFG research group 447), MPI
Start:	2001

Project:	**Optimal Control of Molten Carbonate Fuel Cells (MCFC) using Methods from Nonlinear Dynamics**

Abstract:	The project's focus 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.
Subproject:	**Dynamics and control of the molten carbonate fuel cell**
Researcher:	M. Mangold, S. Min
Partners:	PCP group; Prof. Pesch, University of Bayreuth; MTU-Friedrichshafen; IPF-Magdeburg
Funding:	BMBF
Start:	2001

Project area: Coupled Processes

Project:	**Nonlinear Dynamics of Reactor Separator Networks**
Abstract:	Highly integrated chemical production 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. More details are given in the research highlights section.
Researchers:	K.P. Zeyer, A. Kienle, R. Waschler
Partners:	MF group; Prof. Pushpavanam & Prof. Krishnaiah, IIT Madras, India; AZOT, Sewerodonezk, Ukraine
Funding:	VW-Foundation, MPI
Start:	2001

Project:	**Nonlinear Dynamics of Bioreactors described by Cybernetic Models**
Abstract:	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. The nonlinear behavior predicted by these models is being investigated In

	joint research with the group of Prof. Ramkrishna.
Researchers:	A. Kienle
Partners:	A. Namjoshi, Prof. Ramkrishna, Purdue University, U.S.A.
Funding:	Humboldt-Foundation, MPI
Start:	2001

Project area: Hierarchical Structures

Project:	**Plantwide Control of Chemical Processes**
Abstract:	Together with the SCT group hierarchical concepts are being applied for plantwide control of highly integrated chemical plants. Currently, a plant for the production of acetic acid in Sewerodonezk, Ukraine, is considered as an example. As a first step, a detailed dynamic model was developed and validated using experimental data from the plant.
Researchers:	R. Waschler, A. Kienle
Partners:	SCT group, Prof. Sviatnyi, TU Donezk, Ukraine, and AZOT, Sewerodonezk, Ukraine
Funding:	BMBF, MPI
Start:	2001

Project area: Hybrid and Discrete-Event Systems

Project:	**Simulated Moving Bed (SMB) Processes**
Abstract:	Simulated moving bed separation (SMB) processes are increasingly important for the purification 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. More details are given in the research highlights section.
Subproject:	**Control of moving bed chromatographic processes**
Researcher:	H. Schramm, A. Kienle

Partners:	PCF group; Prof. Vande Wouwer, Faculte Polytechnique Mons, Belgium
Funding:	MPI
Start:	2000

Project:	**Control of Discontinuously Operated Multi Product Plants**
Abstract:	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 with regard to unforeseen disturbances. Alternative control strategies are being explored together with the SCT group.
Researchers:	A. Kienle
Partners:	SCT group; Members of DFG research group 468 at the OvGU
Funding:	DFG (DFG research group 468)
Start:	2002

Project area: Population Balance Systems

Project:	**Crystallization**
Abstract:	Crystallization from solution or melt serves for the production of solids and/or for purification. The focus of this subproject is the experimental and theoretical investigation of autonomous oscillations, which may frequently arise in continuous crystallizers with fines dissolution and product classification. The objective is to gain a better understanding of this behavior and to develop suitable methods for designing and operating crystallization processes with potential instabilities.
Subproject:	**Nonlinear Dynamics of Crystallization Processes**
Researcher:	P-K. Pathath
Partners:	PCF group; SCT group**;** ISR, University of Stuttgart

Funding:	MPI
Start:	1999

Project:	**Optimal Control of Polymerization Reactors**
Abstract:	The project aims at developing suitable control strategies for the advanced operation of polymerization processes, including load and grade changes. Currently, an industrial production plant for low density polyethylene is being considered as an example.
Researchers:	M. Häfele
Partners:	BASF and BASELL, Ludwigshafen
Funding:	MPI, European Union (in preparation)
Start:	1999

4. Research Highlights

4.1. Computer Aided Modeling of Chemical Processes

Modern industrial chemical processes are highly integrated systems with a complex dynamic behavior. A thorough understanding of such processes requires detailed mathematical models based on physical and chemical knowledge. The development and implementation of such models of chemical processes is a demanding and time consuming task. The aim of computer aided modeling systems is to facilitate and accelerate the model implementation. A computer aided modeling system should enable its users to incorporate their process knowledge into a simulation model without being bothered by algebraic manipulations or mechanical coding work. The development of a computer aided modeling system can be subdivided into two major parts. The first step is the structuring of the physical and chemical modeling knowledge into elements of a model library. The second step is the development of a software tool that is able to retrieve the modeling information from the library and to generate simulation programs from that information. The work of this research group addresses both steps.

As a guideline for the structuring of chemical process models, Gilles [1] proposed the Network Theory for Chemical and Biochemical Processes. In joint research these concepts were extended to spatially distributed systems and population balance systems [9].

According to this concept, models can be structured in a horizontal direction, i.e. on one level of detailedness of the model description, and in a vertical direction, by decomposing a coarse model description into subunits on a more detailed level. The horizontal structure provides a high flexibility for the model library. The vertical structure improves the transparency and readability of the structured model. As a very similar methodology can be used for the structuring of microbiological models, it is possible to use the same computer tool for the development of chemical and biological models. That tool - the Process Modeling Tool ProMoT - is being developed in joint research with the SBI group.

ProMoT is an object-oriented tool for the equation based modeling of chemical and biological processes. It is based on a structured and equation-based modeling approach. Process models in ProMoT consist of modules which can be aggregated to hierarchies of arbitrary depth. All modeling entities in ProMoT are organized in a specialization hierarchy with multiple inheritance. Models in ProMoT can be implemented using either a text-based modeling language or a graphical user interface.

The modeling tool ProMoT is used in the framework of the DFG research group “Membrane Supported Reaction Engineering" located at the OvGU. The DFG research group investigates different types of membrane reactors, identifies new application fields for membrane reactors, and assesses the potential of membrane reactors for selective oxidations. The PSD group of the Max Planck Institute Magdeburg contributes to the joint project by identifying reaction kinetics and by developing a library of re-usable fixed bed reactor and membrane reactor models [8]. The model library has proved to be rather flexible and applicable not only to membrane reactors, but also to other membrane processes. Currently, the library is being used by the group of A. Seidel-Morgenstern to model a liquid phase membrane separation process. As a fuel cell can be regarded as an electrochemical membrane reactor, there are also connections to the activities of K. Sundmacher’s group. The PSD and the PCP groups collaborate closely on the development of structured models of fuel cell systems and their implementation in ProMoT. Further applications of systematic modeling are multiphase reactors and reaction separation processes. A model library for such processes is currently being developed. It will support the institute's activities in the area of reactive distillation processes and plantwide control problems.

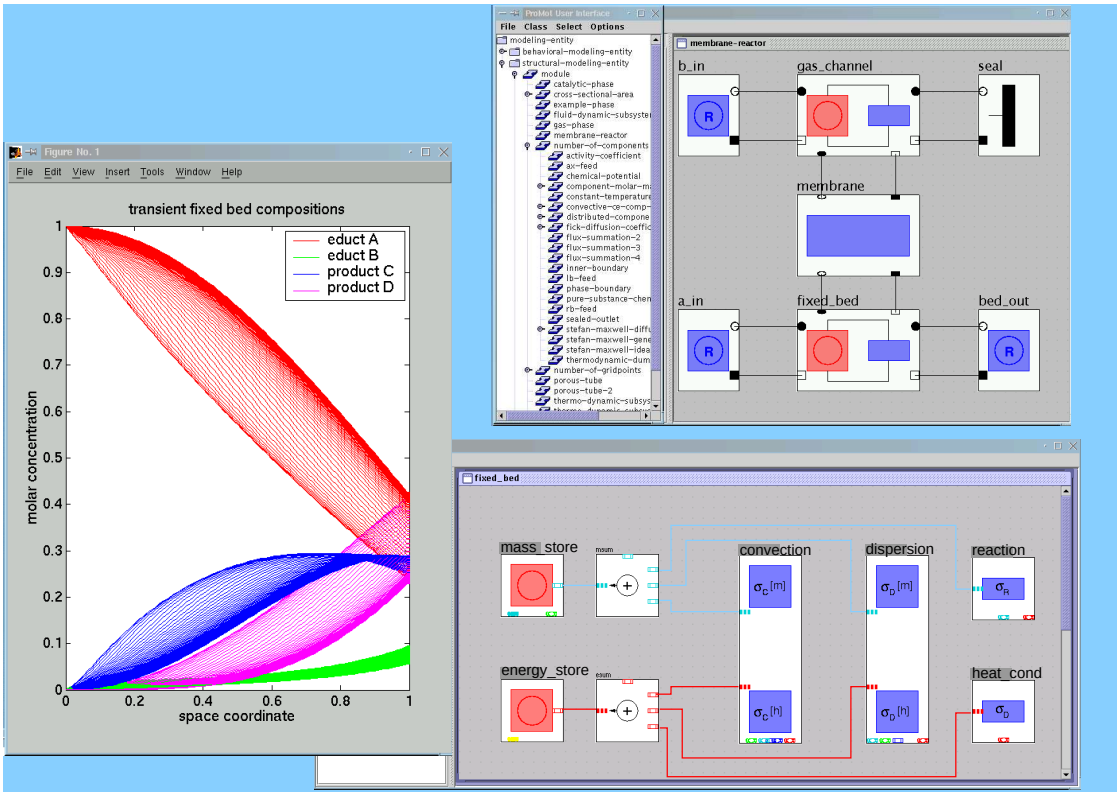


Fig. 15: Screenshot of a membrane reactor model implemented in ProMoT.

4.2. Nonlinear Wave Propagation in Chemical Processes

The dynamic behavior of many chemical processes is governed by spatio temporal pattern formation also termed as nonlinear wave propagation. Typical examples for this type of behavior are traveling reaction zones in catalytic fixed bed reactors and traveling mass transfer fronts in separation processes. The investigation of nonlinear wave propagation in chemical processes often provides easy understanding of the dynamics without tedious calculations and thereby leads the way to new ideas for model reduction, and improved process operation and control.

Our research on nonlinear wave propagation in chemical processes is integrated within the joint research project SFB 412 on “Computer aided modeling and simulation for the analysis, synthesis and control of chemical processes”, which is located at the University of Stuttgart and funded by the DFG.

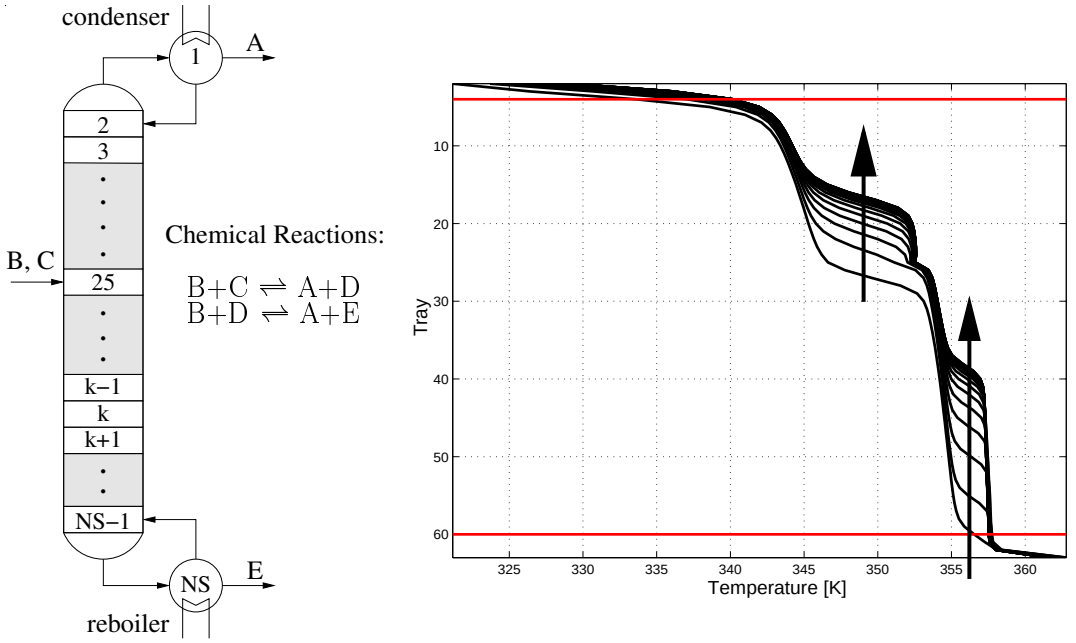


Fig. 16: Traveling temperature fronts in an industrial reactive distillation column after a step change of the heat duty.

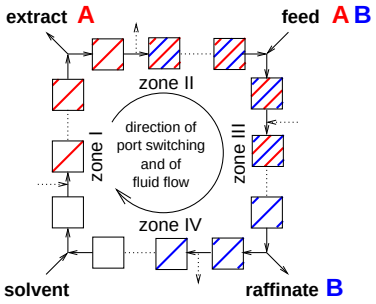
Initial contributions were concerned with nonlinear wave propagation and nonlinear model reduction for nonreactive multicomponent distillation processes [4]. It was shown that the concentration and temperature profiles in such a system can be easily constructed from a linear superposition of elementary nonlinear waves. These results were used for nonlinear model reduction. Subsequently, these low-order dynamic models were used for the generation of a supervisory control system for the startup of distillation plants in joint research with the SCT group [7], for open-loop dynamic optimization of load and specification changes [18], and for nonlinear model predictive control of distillation columns [3]. Other successful applications of nonlinear waves are concerned with the control of simulated moving bed chromatographic processes, which will be discussed in more detail in the next section.

Recent contributions are concerned with nonlinear wave propagation in combined reaction separation processes [5,6,2]. Typical examples for combined reaction separation processes are reactive distillation processes, chromatographic reactors, and membrane reactors. These types of processes have received a lot of attention in the chemical engineering community during the last decade due to potential economic benefits. However, only little was known about their dynamic behavior when we started with our research.

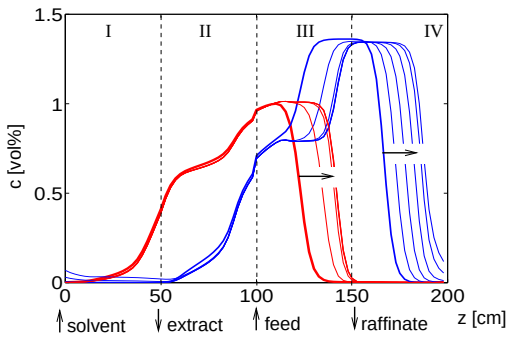
A general framework for analyzing and understanding the dynamics of these processes was developed. In a first step, simultaneous phase and reaction equilibrium was assumed. The theory makes use of transformed concentration variables, which were first introduced by Doherty and co-workers for the steady state design of reactive distillation processes. It is shown that these transformed variables can be directly generalized to the dynamic problem considered here. Furthermore, they can also be applied to other reactive separation processes, for example fixed bed or countercurrent chromatographic reactors. They provide profound insight into the dynamic behavior of these processes and reveal bounds of feasible operation caused by reactive azeotropy. It was shown that reactive azeotropy, which is a well-known phenomenon in reactive distillation, may also arise under very similar conditions in other reactive separation processes, e.g. chromatographic reactors.

4.3. New Modes of Operation and Control of Simulated Moving Bed Chromatographic Processes

Chromatographic separation processes are increasingly applied to the purification of pharmaceutical compounds in fine chemistry or biotechnology.



1. *Scheme of the SMB process*



2. *Dynamic behavior*

3. *Test plant*

Fig. 17: Simulated moving bed chromatography.

Due to a higher productivity, lower solvent consumption and a better exploitation of the adsorbent phase in comparison to the classical batch separations, the concept of the simulated moving bed (SMB) is currently the preferred method of solving a large number of separation problems.

The SMB process consists of a number of chromatographic columns, connected in series. Two input nodes, feed and solvent, and two outputs, extract and raffinate, define four different separation zones. The components A and B are separated by using a simulated countercurrent flow between the liquid and the solid phase. The movement of the solid phase is approximated by cyclic switching of the inlet and outlet ports in the direction of the fluid flow. If the flow rates of the liquid and the adsorbent phase are chosen properly, the more strongly adsorbed component A can be withdrawn with the extract and component B appears in the raffinate.

Unfortunately, the operation of an SMB unit close to its economic optimum causes a high sensitivity to disturbances. Even small fluctuations of the operating parameters may lead to a contamination of the products. Optimal operation of SMB processes in practice will therefore require some suitable feedback control. Due to the mixed continuous and discrete dynamics of the SMB process and the rather low availability of measurement information, control of SMB processes to ensure a safe and economical operation while guaranteeing the product specifications is a challenging task. For industrial production processes, simple control algorithms that can be easily implemented and handled by the operators are preferred.

Therefore, two different relatively simple but efficient control strategies were developed [13]. The first method represents an inferential control scheme, which was motivated by established techniques for distillation column control. The position of concentration fronts in the SMB unit is inferred via UV measurements in each separation section of the apparatus. No mathematical model is required. The controller rejects disturbances by stabilizing the position of these characteristic concentration fronts. This control technique works well for constant feed concentration. Hence, this strategy is suitable if the feed is supplied in larger batches from previous reaction processes. This is the case in a large number of practical applications. However, because of the indirect control of the product purities with UV signals, an offset in the product purity may occur for processes with unforeseen disturbances of the feed concentration. Nevertheless, this offset is significantly smaller than in the open loop system.

The second algorithm is a model based controller and enables more direct control of the desired product purities. It makes use of the nonlinear wave characteristics of the process. The desired product purities are adjusted by directly manipulating the location of the different concentration fronts in the process. Again this is achieved with simple PI-control. For the

practical implementation of this control strategy the concentration profiles are reconstructed from UV measurements by means of a state observer. Hence, detailed knowledge of the adsorption isotherms is required. The control algorithm automatically adjusts maximum productivity and minimum solvent consumption without longwinded optimization calculations. This control algorithm can therefore also be used for fast optimization of SMB processes.

This control strategy is very useful for a comfortable realization of some new ideas for operating SMB processes with periodic forcing of some suitable operating parameters within every single switching interval. In particular, a new mode of operation with periodic forcing of the feed concentration was developed in joint research with the PCF group of A. Seidel-Morgenstern [14,15] and filed as a patent [16]. The new mode of operation is called 'ModiCon', which is an abbreviation for modified concentrations. The method can be easily applied to SMB plants using standard equipment (e.g. gradient pumps). It was shown that the productivity of SMB processes can be increased significantly through ModiCon with simultaneous reduction of the solvent consumption. In addition, the desired product purity can be directly adjusted by feedback control.

4.4. Synthesis, Dynamics and Control of Reactive Distillation Processes

Reactive distillation integrates chemical reaction and distillation into a single processing unit. Such an integrated process can be very economical compared to conventional processes where reaction and separation are carried out in different processing units. However, design and operation of such an integrated process can be difficult due to the increased complexity.

Besides the theoretical investigations on nonlinear wave propagation in reactive distillation processes mentioned above, main achievements of the PSD group in the field of reactive distillation are concerned with stability and uniqueness of steady states, and control as well as computer aided synthesis of reactive distillation processes. Many results have been obtained in joint research with the PCP group of A. Sundmacher.

It was shown that multiple steady states, bistability and nonlinear oscillations may arise quite frequently in reactive distillation and may complicate column operation. Different sources for these patterns of behavior were systematically identified [6]. Emphasis was on kinetic instabilities, which are caused by self-inhibition of the heterogenous catalyst and which may arise quite frequently in heterogeneously catalyzed reactive distillation processes. The production of fuel additives by reactive distillation was considered as a practical example [10,11]. These investigations provided the first rigorous experimental verification of multiple steady states in reactive distillation. Further, fundamental insight into the dynamic behavior of

reactive distillation processes was obtained and conclusions for safe and reliable column operation were drawn.

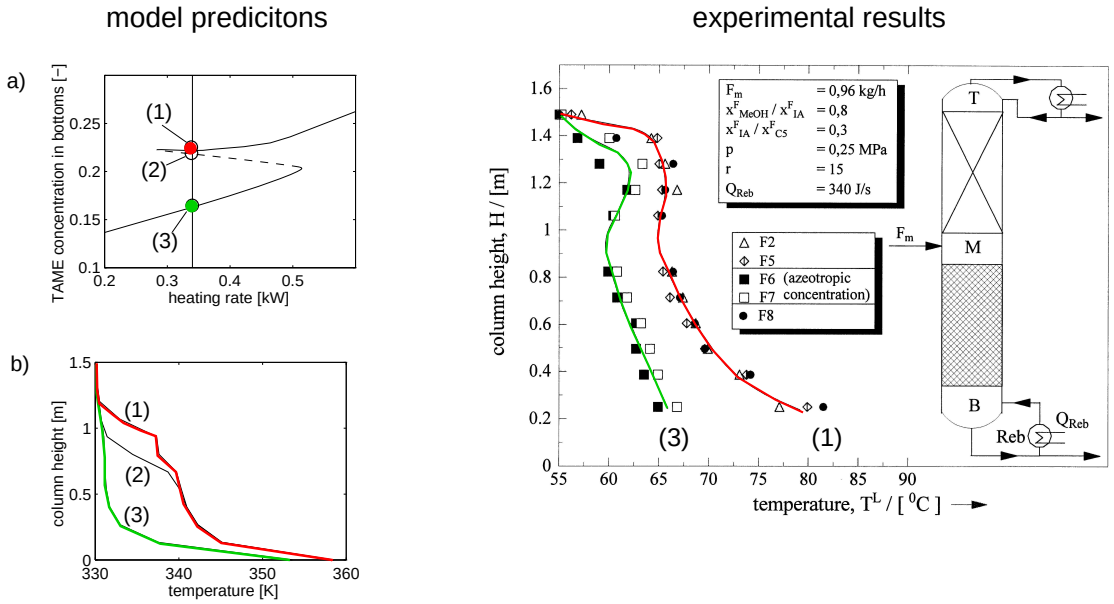


Fig. 18: Multiple steady states for the production of fuel ether TAME by reactive distillation.

First encouraging results were obtained for computer aided synthesis of reactive distillation processes using mixed-integer nonlinear programming techniques combined with physical insight [17]. However, at the moment this approach is limited to simple model systems. For more complex systems computational difficulties may arise. Depending on the starting conditions, either many different local optima are found or no solution at all. Further developments on the optimization strategy, including suitable modeling approaches, the generation of suitable superstructures and starting values, and improved optimization algorithms are being investigated in a joint research project with Prof. Weissmantel from the Mathematics Department of the OvGU. The project is funded by the German Science Foundation (DFG).

Reactive separation processes for closely boiling mixtures were proposed as a new field of application for the reactive distillation technology, [19,17]. Typical examples are mixtures of hydrocarbon isomers, which play an important role in the chemical process industry and are usually hard to separate. A typical separation problem is the separation of isobutene from the C4 fraction of a cracking plant. The proposed reactive separation processes are illustrated schematically in Fig. 19.

To achieve the separation a reactive entrainer is added, which selectively reacts in a first reactive distillation column with the component to be separated. Simultaneously the reaction product can be separated from the inert components in the first column. In a second column, the reaction product is split back into the reactants. Simultaneously, the reactive entrainer and the desired component can be isolated in the product streams of the second column and the entrainer can be recycled to the first column.

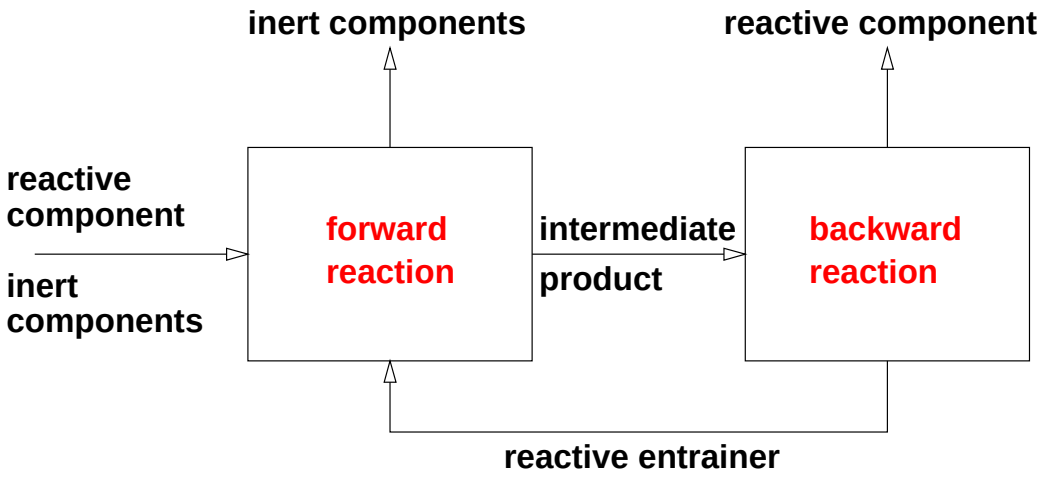


Fig. 19: Simplified flowsheet of the proposed reactive separation process.

The separation of iso-olefines from hydrocarbon mixtures by etherification or hydration reactions were studied as possible applications of these reactive separation processes [19,17]. The ideas were filed as a patent [20].

4.5. Nonlinear Dynamics of Reactor Separator Networks

Conventional chemical process plants typically consist of reactors and separators. In the reactors, reactants are partially converted to desired products and in the subsequent separators unreacted reactants are separated from the products and recycled into the reactor. A typical industrial example process, which is being studied in the Process Synthesis and Dynamics Group within a joint BMBF research project with TU-Donezk and the AZOT company from Ukraine, is illustrated in Fig. 20.

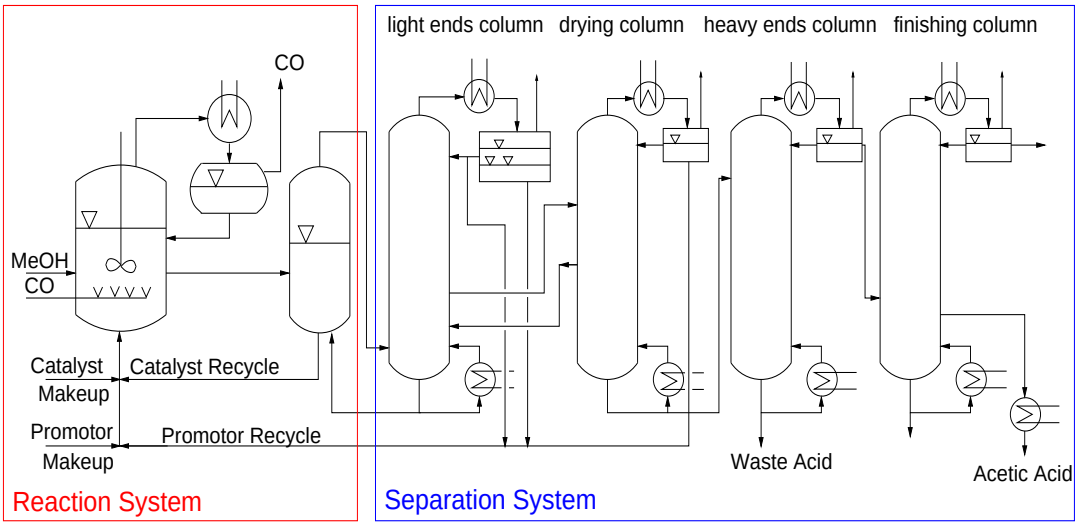


Fig. 20: Simplified flowsheet of an industrial plant for the production of acetic acid.

Another industrial application studied in joint research with the BASF and BASELL companies is a plant for the production of low density polyethylene as illustrated in Fig. 21.

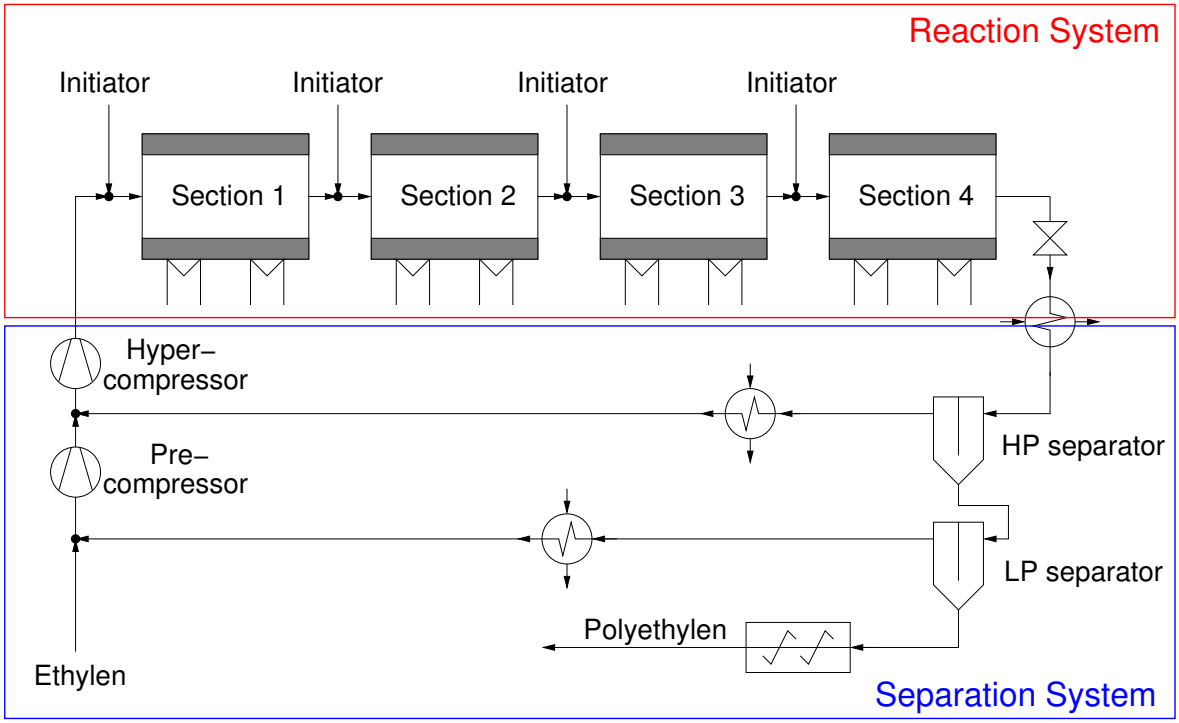


Fig. 21: Simplified flowsheet of an industrial plant for the production of low density polyethylene.

It was found that both processes can show intricate nonlinear behavior including multiple steady states, nonlinear oscillations and high sensitivity to disturbances. Further it was found that this behavior is directly related to the recycles in the respective plant.

To fully understand the different patterns of behavior which can arise in such recycle systems, a simple model system was analyzed in a first step. This model system consists of a continuous stirred tank reactor and a flash with reactant recycle. Relevant issues are feasibility, uniqueness and stability of steady states, as well as sensitivity to disturbances. Due to the simplicity, an analytical approach was possible using methods from stability, bifurcation and singularity theory. The analytical results were validated by some numerical investigations using advanced continuation techniques.

It was shown that the behavior crucially depends on the structure of the underlying base-control involving level and flow controllers [12]. Even for a simple isothermal reactor with a first order reaction, complex patterns of behavior can be introduced by the recycle. Depending on the underlying base-control, either no steady state at all, a multiplicity of steady states or nonlinear oscillations may occur. Suitable control structures were determined which allow smooth and stable operation under all conditions [21]. Recently, the investigations were extended to systems with finite delay in the recycle. Nonlinear dynamics of the underlying system of delay differential equations is a new and challenging field of research, which will be further investigated together with the MF group.

The results mentioned above have been obtained in joint research with Prof. Pushpavanam from the Indian Institute of Technology in Madras. The project is financially supported by the VW-Foundation within the program “Joint Research Projects in the Natural, Engineering and Economic Sciences with Institutes in Africa, Asia and Latin America”.

5. Selected Teaching Activities, Ph.D. Projects

5.1. Teaching Activities

- M. Mangold gave a course on modeling and analysis of chemical processes at the University of Hannover
- M. Mangold is giving a course on process and systems engineering at the OvGU
- F. Klose is involved in an introductory course on chemistry for chemical process engineers at the OvGU
- During his habilitation A. Kienle gave a course on “Nonlinear wave propagation in chemical processes” at the University of Stuttgart

Regular teaching activities of A. Kienle at the OvGU Magdeburg involve

- a course on nonlinear process dynamics
- a course on process modeling
- a course on process identification
- a course on chemical process control is in preparation
- practical training

5.2. Ph.D. Projects

- M. Mangold, Nonlinear Analysis and Technical Application of Circulating Reaction Zones, 2000
- E. Stein, Synthesis of Reactive Distillation Processes, 2003
- H. Schramm, New Modes of Operation and Control of Chromatographic Simulated Moving Bed Processes, in preparation
- M. Häfele, Optimal Control of Fixed Bed Reactor for the Production of Low Density Polyethylene, in preparation
- R. Waschler, Plantwide Dynamics and Control of Chemical Processes, in preparation
- P. Pathath, Nonlinear Dynamics of Crystallization Processes, in preparation

- O. Angeles-Palacios, Development of an Object-Oriented Model Library for Chemical Plants, in preparation
- J. Gangadwala, Advanced Synthesis of Reactive Distillation Processes, in preparation
- S. Min, Low-order Dynamic Models for Fuel Cells, in preparation

5.3. Habilitations

- Kienle, Nonlinear Dynamics of Chemical Processes, University of Stuttgart, 2002
- M. Mangold, Modular Modelling, Dynamics and Control of Membrane Reactors and Fuell Cells, in preparation
- F. Klose, Reactor Concepts for Catalytic Oxidation of Hydrocarbons, in preparation

6. Appointments and Awards

6.1. Appointments

In 2002, A. Kienle received offers of the chairs for Process Engineering at the TU-Hamburg-Harburg and for Automation/Modeling at the OvGU Magdeburg, which he finally accepted.

6.2. Awards

- In 1999, F. Klose received an award for his Ph.D. Thesis endowed with
- 3500 Euro from Johannes Fehr Company, Kassel-Lohfelden
- In 2000, M. Mangold received an award for his Ph. D. Thesis endowed with
- 1500 Euro from LEWA company, Leonberg

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A complete list of publications of the PSD group is given in the supplements.

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Research Group:

Physical and Chemical Process Engineering (PCP)

Prof. Dr.-Ing. Kai Sundmacher

This report covers the period from 1 October 1998 to 30 April 2003.

1. PCP Group Introduction

The MPI Research Group “Physical and Chemical Process Engineering (PCP)” was founded in October 1998 with Kai Sundmacher as the head. In 1999, he was appointed to a full professorship as the new chair for Process Systems Engineering (PSE) at the Otto-von-Guericke-University Magdeburg (OvGU). Since then, K. Sundmacher has guided the research activities of the PCP group and the university chair simultaneously. Both groups have very intense scientific collaborations, which are reflected in a number of common research projects. In July 2001, K. Sundmacher was appointed as Director at MPI where he is responsible for the field of process engineering.

The research of the group “Physical and Chemical Process Engineering (PCP)” covers the design, operation and analysis of complex chemical processes. It is focused on the system-orientated analysis of all physical and chemical phenomena involved and their interaction on hierarchical time and length scales. Special attention is paid to the quantitative characterization and description of the physical and chemical transport phenomena as well as 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. Among the latter, miniplant technology is a unique and important tool in the group’s experimental investigations. Experiments in the miniplant environment allow the extrapolation of the collected data towards industrial macroscales. This is very important to the ability to transfer fundamentally new reaction and separation technologies developed at MPI into industrial application.

The current research activities of the PCP group are clustered in four fields:

- multifunctional reactors and reactive separations (since 10/1998),
- fuel cell processes (since 10/1998),
- electrochemical membrane processes (since 01/2001),
- dynamics of particulate systems (since 04/2001).

The list of these four research fields corresponds to the chronological order in which the research activities were started at MPI and the scientific staff was hired.

2. Members of the PCP Research Group

As of 30 April 2003, the group of Prof. Sundmacher consisted of six scientists with Ph.D. degrees, including one guest scientist from UCTM Sofia (Prof. M. Christov) and one honorary scientist from Karlsruhe University (Prof. E.U. Schlünder), and 11 graduate students working towards a Ph.D. In accordance with the MPI research structure, the PCP group is organized in four project teams clustered according to the major research activities as given in section 1 of this group report (see following Table, next page).

All scientists work in non-permanent positions. Out of the 16 scientists working in the PCP group, 50% come from abroad. As technical staff, one process engineer and one laboratory coworker support the PCP scientists regardless which special research topic is addressed. Furthermore, the research is supported by nine undergraduate students from the Otto-von-Guericke-University Magdeburg. Five of them are currently working on their Diploma thesis supervised by PCP scientists.

It should be mentioned that all group members still belong to the first generation of Ph.D. students and scientists because the typical duration to prepare a Ph.D. thesis in process engineering is about four years. This is compounded by the fact that as part of their work, most Ph.D. students had to support the design of new experimental devices such as special miniplants which were available after the new MPI building was ready for use in September 2001. Therefore, as a result of the MPI foundation history and the scientific culture in process engineering, the first PCP group members will receive their Ph.D. degrees in 2004.

In accordance with the collaboration contract between MPI and Otto-von-Guericke-University, Prof. Sundmacher also guides the research activities of the university chair for Process Systems Engineering. At the University, currently six Ph.D. students (D. Adityawarman, L. Chalakov, P. Heidebrecht, M. Ivanova, C. Steyer, M. Gundermann) are working on the preparation of their theses. All of them are engaged in topics which have direct links to MPI research projects. Furthermore, one researcher with a Ph.D. degree (Dr. R. Frömmichen) completes the scientific work group under the direction of the university chair. All scientists are supported by E. Felsch who is responsible for the chair's preparative and analytical chemistry.

Composition of PCP group as of 30 April 2003

Group Member	Status	Background	joined PCP in
Prof. K. Sundmacher	Head of the Group	Chemical and Process Engineering	01.10.1998
Project Team: Multifunctional Reactors and Reactive Separations			
Dr. Z. Qi	Postdoc	Chemical Engineering	01.09.1999
F. Steyer	Ph.D. Student	Process and Energy Engineering	01.06.2000
Y.S. Huang	Ph.D. Student	Chemical Engineering	01.11.2001
Prof. E.U. Schlünder	Honorary Scientist	Process Engineering	01.04.2000
Project Team: Fuel Cell Processes			
T. Schultz	Ph.D. Student	Chemical Engineering	01.05.1999
U. Krewer	Ph.D. Student	Chemical Engineering	01.10.2001
T. Vidakovic	Ph.D. Student	Electrochemistry	01.07.2002
Y. Song	Ph.D. Student	Fluid Dynamics	01.06.2001
R. Hanke	Ph.D. Student	Energy Engineering	01.11.2001
Dr. V. Galvita	Postdoc	Surface Chemistry and Catalysis	01.09.2002
Prof. M. Christov	Visiting Scientist	Physical Chemistry and Electrochemistry	Two visits since 10.09.2002
Project Team: Electrochemical Membrane Reactors			
Dr. L. Rihko-Struckmann	Postdoc	Chemical Engineering	01.01.2001
B. Munder	Ph.D. Student	Process Engineering	01.04.2001
Y. Ye	Ph.D. Student	Chemical Engineering	01.11.2001
Project Team: Dynamics of Particulate Systems			
F. Rauscher	Ph.D. Student	Chemical Engineering	01.04.2001
B. Niemann	Ph.D. Student	Chemical Engineering	01.10.2002
Dr. A. Voigt	Postdoc	Theoretical Physics	01.11.2003
Technical Staff			
B. Stein	Laboratory Coworker	Analytical Chemistry	15.10.2001
T. Schröder	Laboratory Engineer	Process Engineering	01.01.2002

Group at OvGU: Process Systems Engineering
D. Adityawarman, L. Chalakov, M. Gundermann, P. Heidebrecht, M. Ivanova, C. Steyer Ph.D. Students; Dr. R. Frömmichen: Postdoc; E. Felsch: Laboratory Coworker

3. Survey of Research Projects

The current research projects of the PCP group are illustrated in Fig. 22. More detailed information is collected on page 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. Several projects are carried out also in collaboration with industrial partners aiming to transfer fundamental MPI research results into industrial applications.

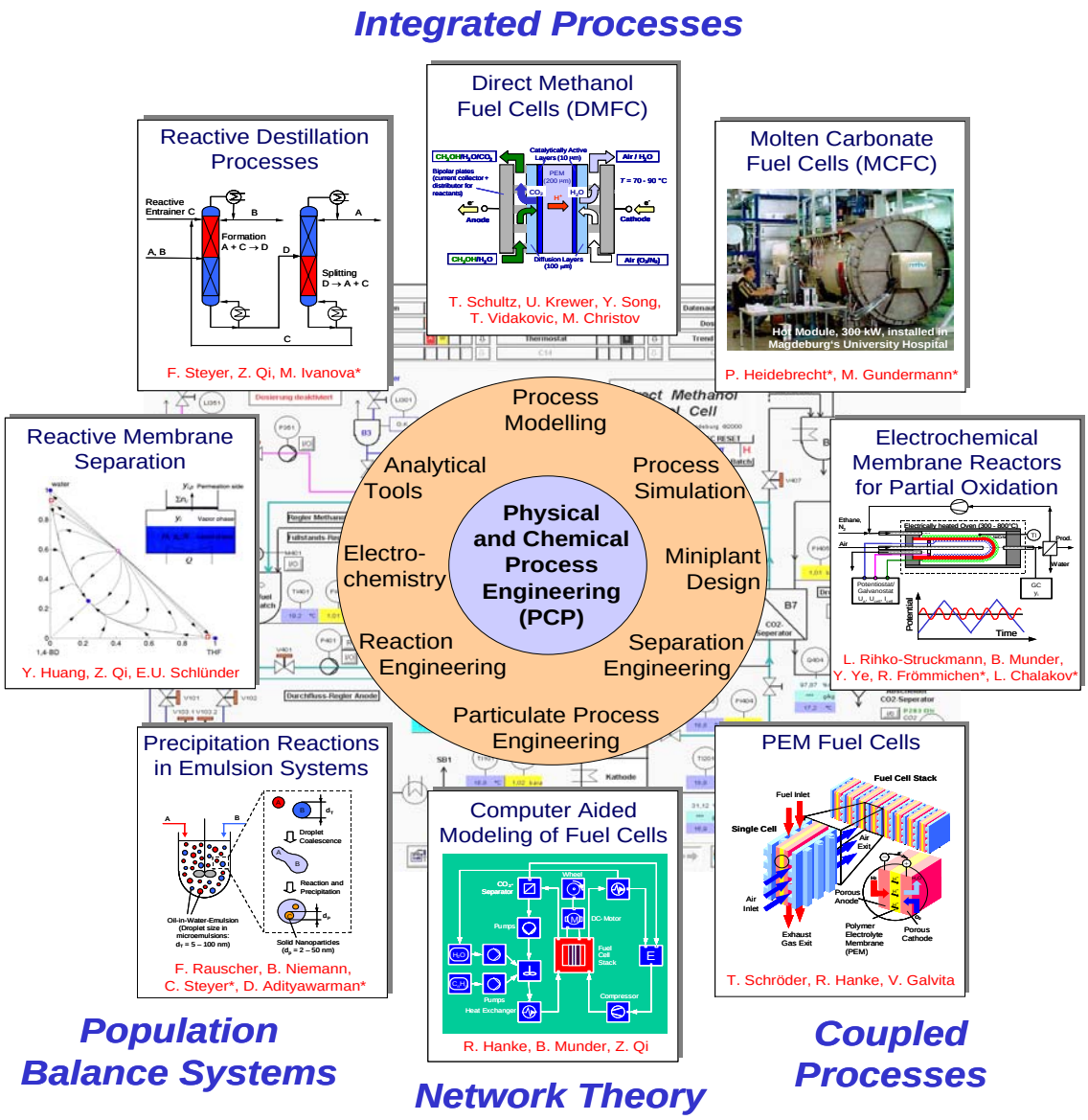

Fig. 22: Survey of PCP research areas and projects (* = scientific coworkers of the group Process Systems Engineering at Otto-von-Guericke University Magdeburg).

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.

Survey of research projects of PCP group

Project Area: Integrated Processes

Project: **Reactive Distillation**	Reactive distillation combines reaction and distillation in one single unit. The benefits of this approach are lower energy consumption and a reduction in the number of process units. However, this 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: • experimental investigation of reactive distillation using miniplant technology, • reaction systems undergoing liquid phase splitting, • coupled reactive distillation columns for the sepa-ration of closely boiling mixtures, • use of reactive distillation for oxidation and hydro-genation processes.			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject: Experimental methods for the analysis of reactive distillation processes	F. Steyer	MPI	06/2000	PSD Group
Subproject: Reactive distillation with liquid phase splitting	F. Steyer Z. Qi	MPI	09/1999	Uni Erlangen (Prof. Schwieger)
Subproject: Coupled reactive distillation columns	Z. Qi	MPI	09/1999	PSD Group
Subproject: Reactive distillation with non-condensable reactants	M. Ivanova Z. Qi	OvGU	01/2001	IIT Bombay (Prof. Mahajani, Prof. Aghalayam)

Project: **Reactive membrane separation**	Membranes are used to enhance the selectivity of sepa-ration in reactive permeation processes. The feasible product spectrum of the reactive separation process is efficiently influenced, e.g. by means of zeolithic gradient membranes. The PCP research in this project deals with • experimental analysis of membrane permeation in combination with liquid phase reactions, • determination of feasible products from reactive membrane separation by means of singularity analysis.

Subproject: Singularity analysis of reactive separations	Z. Qi Y.S. Huang	MPI	09/1999	MF Group
Subproject: Experimental analysis of reactive membrane separation	E. Schlünder Y.S. Huang	MPI/Pro3	11/2001	Uni Erlangen (Prof. Schwieger), GFT, Homburg

Project: **Direct Methanol Fuel Cells (DMFC)**	The Direct Methanol Fuel Cell (DMFC) integrates abstraction of hydrogen from methanol and its electro-chemical conversion in one single unit. The project is focused on the experimental and model-based analysis of the complex interaction of all reaction and transport phenomena involved in the fuel cell process. The current PCP group research activities are related to: • experimental investigations on the miniplant scale, • understanding the mechanism of methanol oxidation by Electrochemical Impedance Spectroscopy (EIS), • analysis of the influence of the anodic flow field, • coupling of a DMFC and an electrochemical membrane reactor.			
Subproject: Experimental and Model based Analysis of the DMFC	T. Schultz	MPI	05/1999	ZSW Ulm (Dr. Jörissen)
Subproject: Analysis of Reaction Mechanism of Electrochemical Methanol Oxidation	T. Vidakovic U. Krewer M. Christov	MPI	07/2002	MPI for Coal Research (Prof. Bönnemann)
Subproject: Analysis of Fluid Dynamics in the DMFC	U. Krewer Y. Song	MPI	06/2001	OvGU (Prof. Tobiska, Prof. Thevenin)
Subproject: Integration of Fuel Cells with Electro-Membrane Reactors	T. Schultz T. Schröder	BMBF/ WTZ	01/2003	ICT Prague (Prof. Hasal)

Project: **Optimal Control of Molten Carbonate Fuel Cells (MCFC) using Methods from Nonlinear Dynamics**	The Molten Carbonate Fuel Cell (MCFC) is a high temperature fuel cell which permits internal steam reforming of methane within the anode compartment. Appropriate process models are being developed and validated experimentally. Based on these models control strategies will be designed and tested. The PCP group is involved in two subprojects: • development of a family of fuel cell models of different complexity to describe MCFC operation under dynamic and steady state conditions, • experimental studies at a 300 kW MCFC of type “Hot Module” in order to validate selected MCFC models and to test developed control strategies.

Subproject: Modeling of the MCFC process	P. Heide-brecht	OvGU	01/2001	PSD Group, Uni Bayreuth (Prof. Pesch), SJTU (Prof. Weng)
Subproject: Experimental analysis of large scale MCFCs	M. Gunder-mann	BMBF	05/2002	IPF GmbH, MTU CFC Solutions GmbH

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: • the development of a new electrochemical mem-brane reactor based on oxygen-ion conducting membranes and its implementation for partial oxidation of light alkanes such as ethane and butane, • modeling the membrane reactor as a prerequisite for the analysis of transport resistances and for optimial process control using electrochemical variables.			
Subproject: Electrochemical Membrane Reactors for Partial Oxidation	L. Rihko-Struckmann B. Munder Y. Ye R. Frömmi-chen L. Chalakov	MPI/ DFG/ OvGU	01/2001	OvGU (Prof. Rau), PCF Group (Prof. Seidel-M.), MPI for Solid State Research (Prof. Aldinger)
Subproject: Modeling of Electrochemical Membrane Reactors	B. Munder L. Rihko-Struckmann	MPI	04/2001	PSD Group

Project Area: Coupled Processes

Project: **Stationary Power Supply Systems based on Proton Exchange Membrane (PEM) Fuel Cells**	In the low to medium power range (1-100 kW), systems based on Proton Exchange Membrane (PEM) fuel cells combined with hydrogen processors are promising devices for future dispersed power units. The objective of this project is • to analyze the operational behavior of PEM fuel cells fed with reformate gases, • to test a hydrogen generator for liquid fuels in

	combination with a PEM fuel cell.			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject: Experimental Analysis of PEM Fuel Cell Dynamics	T. Schröder R. Hanke	MPI	01/2002	FuelCon AG
Subproject: Hydrogen Generation from Renewable Resources	V. Galvita	MPI	09/2002	Fritz-Haber-Inst. of MPG, Berlin (Dr. Jentoft)

Project Area: Population Balance Systems

Project: **Precipitation Reactions in Emulsion Systems**	The production of particles in the nano- or micrometer range is of major importance for various technological applications such as ceramic materials, semiconductors and catalysts. Particles with a narrow size distribution can be produced via precipitation in emulsion systems. The objective of the project is to understand the dynamics of this complex process with the help of experimental and theoretical methods: • the thermodynamic and kinetic analysis of water-in-oil emulsion systems suitable for precipitations, • the analysis of kinetics of precipitation reactions, • the development of a process technology for particle precipitation in microemulsions, • modeling and simulation of process dynamics by means of population balance equations and Monte-Carlo techniques.			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject: Experimental Methods for the Analysis of Precipitation and Emulsion Dynamics	F. Rauscher D. Aditya-warman	MPI/ OvGU	04/2001	Microstructure Center of OvGU (Dr. Veit)
Subproject: Modeling of Precipitation and Emulsion Systems	B. Niemann C. Steyer A. Voigt	MPI/ OvGU	10/2002	MPI for Math. in the Sciences (Prof. Hack-busch), Purdue Univ. (Prof. Ramkrishna)

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. The PCP research activities are focused on: • the establishment of a Virtual Fuel Cell Lab as a framework for the simulation of various operational scenarios of fuel cell stacks and complex fuel cell based power plants.			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject: Computer aided modeling of fuel cell systems	R. Hanke	MPI	11/2001	PSD Group

4. Research Highlights

4.1 Reactive Separations

4.1.1 Kinetic Instabilities in Reactive Distillation

One of the key issues for the conceptual design and for the understanding of the operational behavior of reactive distillation processes using heterogeneous catalysts as distillation packing is the detailed analysis of the reaction micro- and macrokinetics [1]. In particular, Prof. Sundmacher, in close cooperation with Prof. Kienle and colleagues at Stuttgart University, contributed to the understanding of kinetic instabilities observed in catalytic distillation columns, exemplified by the synthesis of the fuel ethers MTBE and TAME from methanol and isobutene or methanol and isoamylenes, respectively [2,3].

4.1.2 Reaction Distillation with Liquid Phase Splitting

In the open literature, so far there is very limited information on reactive distillation in systems undergoing liquid phase splitting although there may be a number of potential applications in the production of important chemicals. Therefore, the PCP group decided to investigate the fundamentals of this type of process in more detail, both by model-based process analysis and with miniplant experiments. As a suitable model reaction, the hydration of cyclohexene using solid acid catalysts was selected. The liquid-liquid equilibria as well as the vapor-liquid equilibria of this reaction system were investigated [4]. Macroreticular ion exchange resins and zeolites were found to be suitable catalysts. New structured packings coated with zeolite catalysts are being developed in collaboration with Prof. Schwieger, University of Erlangen-Nürnberg.

In order to understand the behavior of reactive distillation in the presence of liquid phase splitting, residue curve maps (RCM) were investigated. Special attention was given to the possibly different reaction rates in the two coexisting liquid phases. As illustrated in Fig. 23,

from the bifurcation analysis of the RCMs, feasible distillate and bottom products of a countercurrent reactive distillation column were identified [5,6]. It was found out that a hybrid column, combining reactive and nonreactive zones, is required to obtain high purity cyclohexanol (Fig. 24). Based on these results, a reactive distillation miniplant was planned and realized in the institute's laboratory. The miniplant is currently being prepared for first reactive distillation experiments.

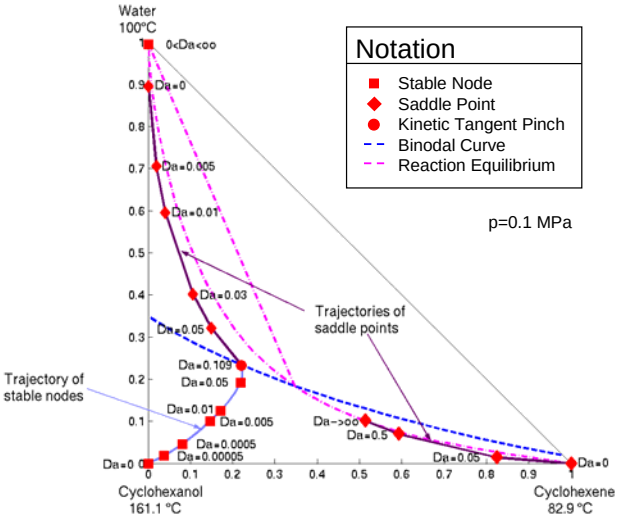

Fig. 23: Bifurcation diagram of singular point in dependence on the Darmköhler number [5].

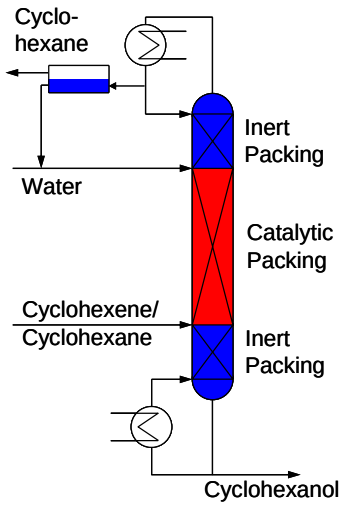

Fig. 24: Flow scheme of proposed reactive distillation process for cyclohexanol synthesis [4].

4.1.3 Coupled Reactive Distillation Columns

For the separation of closely boiling mixtures (isobutene from C4 crack fractions) coupled reactive distillation columns offer the possibility of significantly reducing the number of operating units and their energy demands. This useful process was worked out and patented in close collaboration with the PSD group of Prof. Kienle [7-10]. As illustrated in Fig. 25, in the first hybrid column the reactive component isobutene reacts with methanol reversibly to methyl-tert.-butylether (MTBE). Since the other C4 components are nonreactive with respect to methanol, they leave the column with the distillate. Due to its high boiling point, MTBE is obtained as bottom product which is fed to the second column. There, it is split back into isobutene, which is the desired top product, and methanol which is recycled to the first column. The catalyst percentage per distillation tray was found to be a key parameter for the qualities of the top and bottom products. It should be mentioned that this coupled column

scheme is applicable to all closely boiling mixtures whose components have different reactivity.

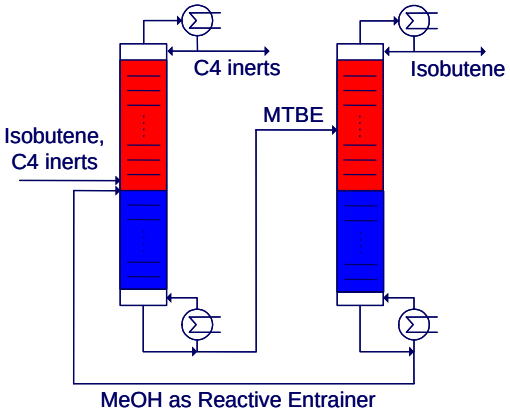

Fig. 25: Coupled reactive distillation columns for the separation of C4 fractions [7].

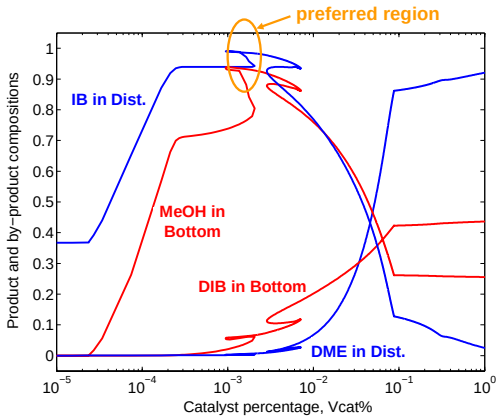

Fig. 26: Product composition of MTBE splitting column versus catalyst percentage [10].

4.1.4 Feasible Products of Reactive Separations

For the conceptual design of continuous countercurrent reactive distillation processes there is a need to predict the composition of the feasible top and bottom products. These products can be identified as stable singular points of a reactive condenser and a reactive reboiler, respectively. The singular point equations and their bifurcational behavior were investigated in collaboration with Prof. Flockerzi (MF group) [11]. For a given reactive mixture, all potential top and bottom products are located on a unique singular point curve. The location of this curve is strongly influenced by interfacial vapor-liquid mass transfer resistances. In Fig. 27, the shadowed areas indicate the product regions that can be attained if membranes are applied in order to control the mass transfer of components between the vapor phase and the reactive liquid phase [12]. Recently, we proposed a new set of generalized transformed composition variables which are useful for the identification of reactive azeotropes in both phase equilibrium controlled and mass transfer controlled systems [13].

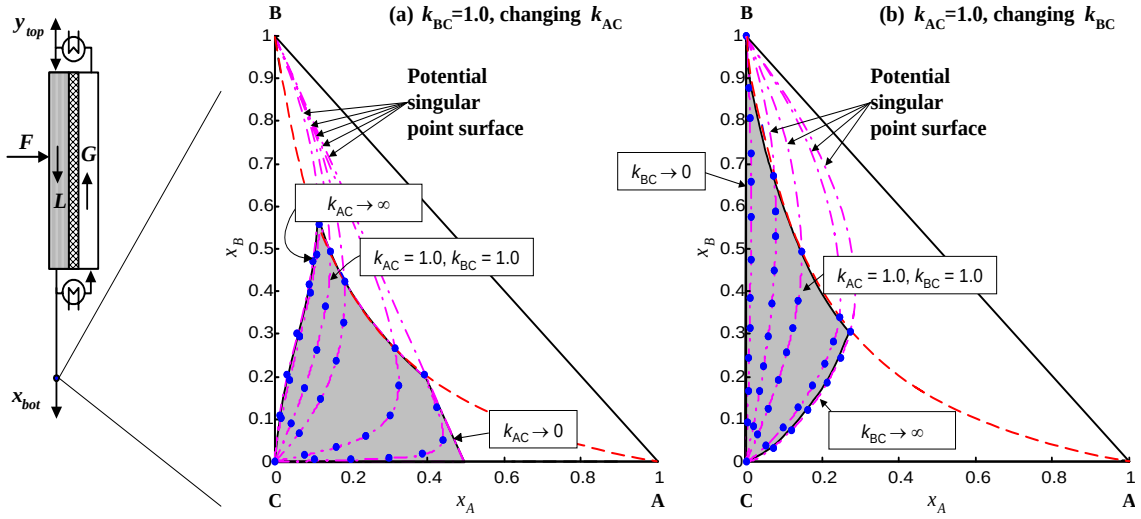

Fig. 27 Feasible bottom product regions (shadowed) of a membrane reactor at different mass transfer coefficients in the membrane for the reaction A + B ⇔ C (dashed: chem. Equilibrium line) [12].

4.2 Fuel Cell Processes

4.2.1 Direct Methanol Fuel Cells (DMFC)

The PCP research activities on DMFCs were dedicated to the detailed understanding of the operational behavior of liquid fed DMFCs equipped with polymeric proton exchange membranes (PEM). This type of cell is an excellent candidate for future generations of mobile power supply systems since it combines an easy storage of the fuel, the direct integration of hydrogen abstraction from methanol into the anodic oxidation process, and operation at low temperatures allowing for highly dynamic load variations. On the other hand, due to the high degree of process integration realized in the DMFC concept, there are a number of fundamental drawbacks to overcome to enable its later use in technical systems.

Fig. 28: DMFC miniplant installed in technical hall.

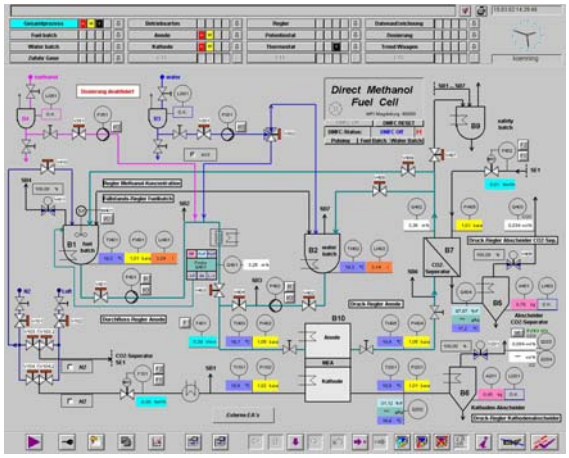

Fig. 29: Screenshot of miniplant flow sheet.

The research subprojects in the DMFC area during the period covered by this report were guided by three main objectives:

(i) development and realization a fully automatized miniplant system (see Fig. 28 and Fig. 29) that allows accurate mass balancing of the DMFC compartments and its peripherals, and is suitable for steady state and dynamic experiments in order to collect data for establishing dynamic process models [14-20],

(ii) experimental and model-based analysis of the mechanism of electrochemical methanol oxidation by means of dynamic electroanalytical methods such as EIS, CV, etc. [21-23],

(iii) detailed analysis of the fluid flow and transport phenomena within the DMFC anode manifold by means of experimental techniques and CFD tools [24].

The first model-based dynamic analysis of the DMFC operational behavior was developed and published in collaboration with the group of Prof. Scott at the University of Newcastle [18]. Fig. 30 shows some illustrative results of dynamic experiments that were carried out under a periodically pulsed methanol feed concentration. This led to the important finding of a significant increase in the average cell voltage at reduced fuel consumption. The comparison between the experimental dynamic data (Fig. 30, top) and simulated results (Fig. 30, bottom) shows a good qualitative agreement. The model data revealed that the methanol crossover transport through the membrane is the key issue for an adequate description of the dynamic fuel cell behavior. By dynamic feeding, the methanol crossover can be significantly decreased and this results in a considerable increase in the cathode potential.

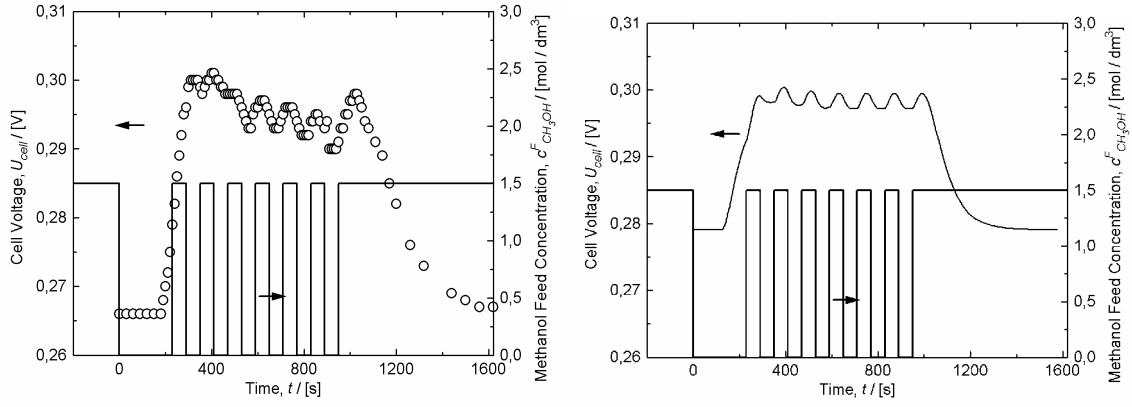

Fig. 30: Cell voltage response to periodically pulsed methanol feed concentration: experimental data (top) and simulation (bottom) at T=70°C, cFCH3OH=1.5 mol/l, VF=1.36 ml/min, pa=0.1 MPa, pc=0.3 MPa [18].

In order to get a more detailed insight into the dynamics of the complex coupled transport processes, a special DMFC miniplant was designed suitable for monitoring the fuel cell behavior under various load scenarios. As an example of the dynamic results obtained with the miniplant, the observed cell voltage nonlinear response behavior to a sharp block pulse of the current density starting from open circuit level is depicted in Fig. 31.

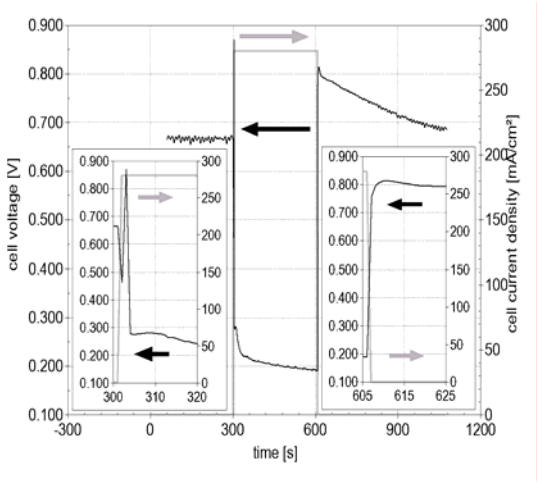

Fig. 31: Cell voltage response to a pulse change of the current density obtained from a miniplant experiment [20].

For the interpretation of the miniplant data, a rigorous fuel cell model was derived which describes the multicomponent mass, charge, and energy transport within the electrode diffusion layers, the catalyst layers and the PEM. This spatially distributed model is based on the generalized Maxwell-Stefan equations [20].

Validated rate equations are still missing in the open literature for the quantitative description of the reaction processes taking place in the catalyst layers. This is why the PCP group started to investigate the electrochemical oxidation of methanol at small scale half cells (area: 2 cm^2) by means of a novel cyclone flow cell which yields rate data at well defined flow conditions [21]. Work was also done with one of the most important electroanalytical tool, alternating current Electrochemical Impedance Spectros-copy (AC-EIS) in close collaboration with Prof. Christov from UCTM Sofia [22]. For the interpretation of the obtained impedance spectra (Fig. 32), rigorous nonlinear models are being derived which must also account for time drift effects of certain parameters. This approach leads to a much higher consistency of the identified parameters than the classical interpretation via electric equivalent circuits.

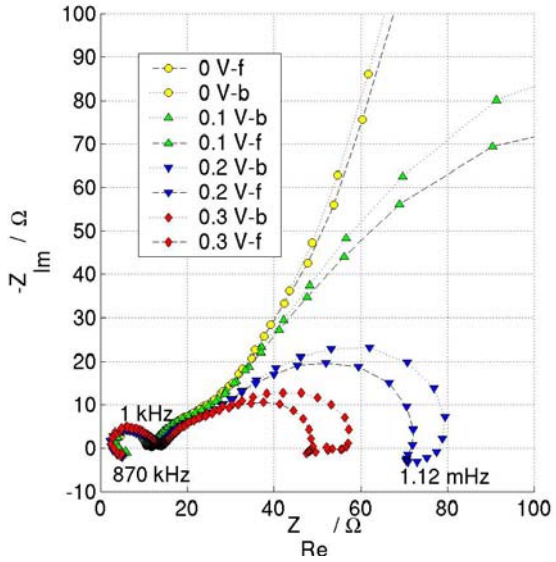

Fig. 32 Impedance spectra for electrochemical methanol oxidation at carbon supported Pt/Ru electrodes [21]. (f = increasing, b = decreasing frequencies)

In order to be able to transfer these mesoscopic rate data to the macroscale of a real fuel cell, the concentration and temperatures fields in the anodic and cathodic flow compartments have to be determined. For this important scale-up task, the PCP group follows the approach to develop reduced flow field models starting from rigorous flow field simulations (CFD = computational fluid dynamics). As a first step, the dynamics of the concentration distribution in the laminar flow field of a selected channel geometry was investigated both experimentally by means of flow visualization techniques and by 3D flow field simulations (see Fig. 33). The latter were carried out in close collaboration with the group of Prof. Tobiska from Mathematics Department at OvGU [24].

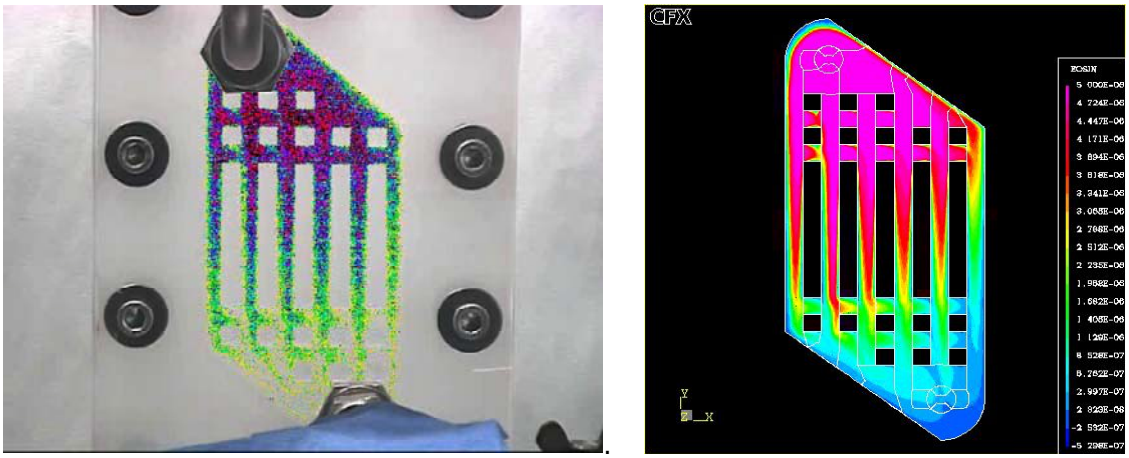

Fig. 33: Snapshot of the dynamic tracer mixing process in the liquid filled anode manifold of a DMFC, left: experimental tracer visualisation, right: 3D CFD simulation carried out with CFX [24].

4.2.2 Molten Carbonate Fuel Cells (MCFC)

Since May 2002, the PCP group has analyzed the process dynamics for Molten Carbonate Fuel Cells (MCFC) within a joint research project with four partners, which is funded by the German Ministry for Research (BMBF) and coordinated by Prof. Sundmacher.

As an Important basis for the experimental part of this reearch project, a 300 kW MCFC stack (Hot Module by com-pany MTU-Friedrichshafen) was installed in the power supply system of the University Hospital in Magdeburg by the collaborating company IPF. The installed MCFC stack consists of 300 single cells and is operated at 600°C using natural gas as feed. As a special feature of this process, the fuel component methane is internally converted by steam reforming into hydrogen which is then directly oxidized at the MCFC anode (see Fig. 34).

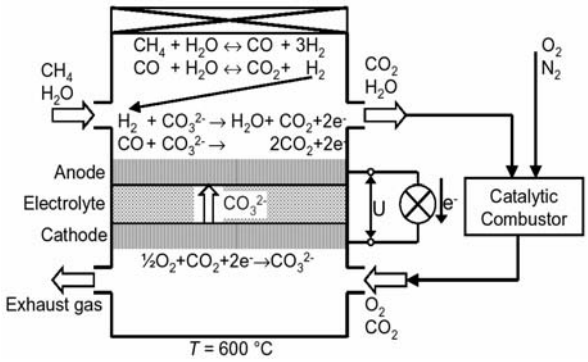

Fig. 34: Working principle of Molten Carbonate Fuel Cell with direct internal reforming.
As an important basis for the experimental part of this research project, a 300 kW MCFC

This leads to a direct heat and mass integration. The exothermic hydrogen oxidation supplies its heat of reaction to the endothermic reforming reaction, while the latter reaction supplies hydrogen to the electrochemical oxidation. By this integration concept, very high degrees of fuel conversion and current yield are achievable. As a further feature of the MCFC integration concept, the carbon dioxide produced at the anode is fed to the cathode side where it is consumed by electrochemical reduction with oxygen to carbonate ions which are transported through the electrolyte melt. The objectives of MPI research in the field of the MCFC are the following:

(i) formulation of a hierarchical family of MCFC process models of different complexity in order to understand the nonlinear dynamic properties of the MCFC stack at various operating conditions,

(ii) experimental validation of the model-based predictions and the derived control strategies using the 300 kW MCFC stack installed at the University hospital,

(iii) development of optimized process operating strategies based on reduced process models in close collaboration with the PSD group (Prof. Kienle).

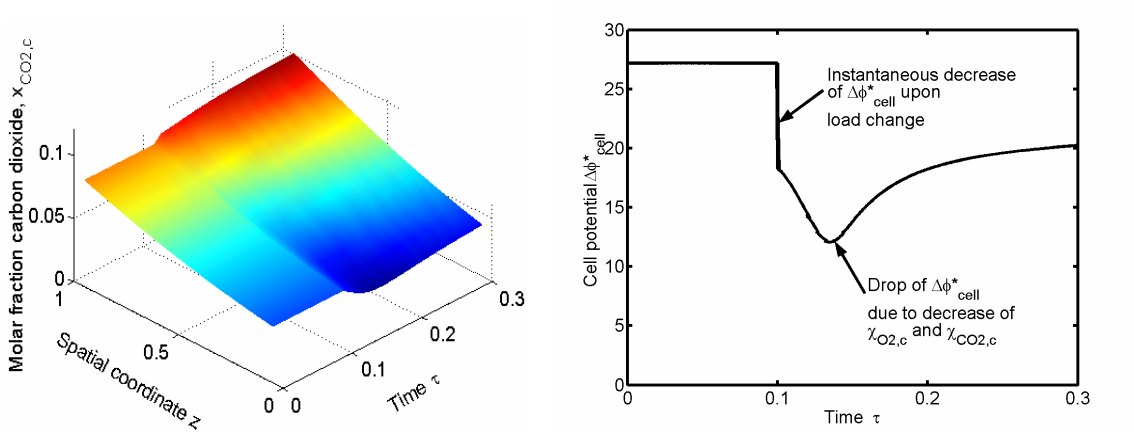

Fig. 35: Step responses of MCFC state variables to current load change (dimensionless quantities). Left: CO_2 concentration along the cathode channel; right: overall cell potential [25].

In the In the MCFC stack, the anodic and cathodic reactants are transported in crosscurrent directions to each other. Therefore, a 2D simulation is required to describe this real process adequately. As the first step towards such a complex 2D cell model, the PCP group and the Chair for Process Systems Engineering formulated a 1D countercurrent MCFC model [25, 26]. The spatial discretization of the coupled mass, energy and charge balances results in a large scale differential-algebraic system (DAE). Depending on the model formulation, DAEs of index one or two are obtained. Their numerical solution was partly

realized in cooperation with the PSD group of Prof. Kienle and the group of Prof. Pesch at the University of Bayreuth. Fig. 35 illustrates the predicted MCFC response behavior to a step input of the electric cell current in terms of the cathodic carbon dioxide concentration and in terms of the cell voltage.

4.3 Electrochemical Membrane Reactors

Since 1999, the PCP group has been using fuel cell principles to design electrochemical membrane reactors which can be used not only for the production of electricity, but also for gas purification [27-28]. Recently, a new type of high-temperature electrochemical membrane reactor was proposed for the controlled partial oxidation of light alkanes based on oxygen ion conducting membranes. The research is carried out in close cooperation with the Chair for Technical Chemistry at OvGU (Prof. Rau) and the PCF group (Prof. Seidel-Morgenstern) within a research network entitled “Membrane Supported Reaction Engineering” which is funded by the German Science Foundation (DFG).

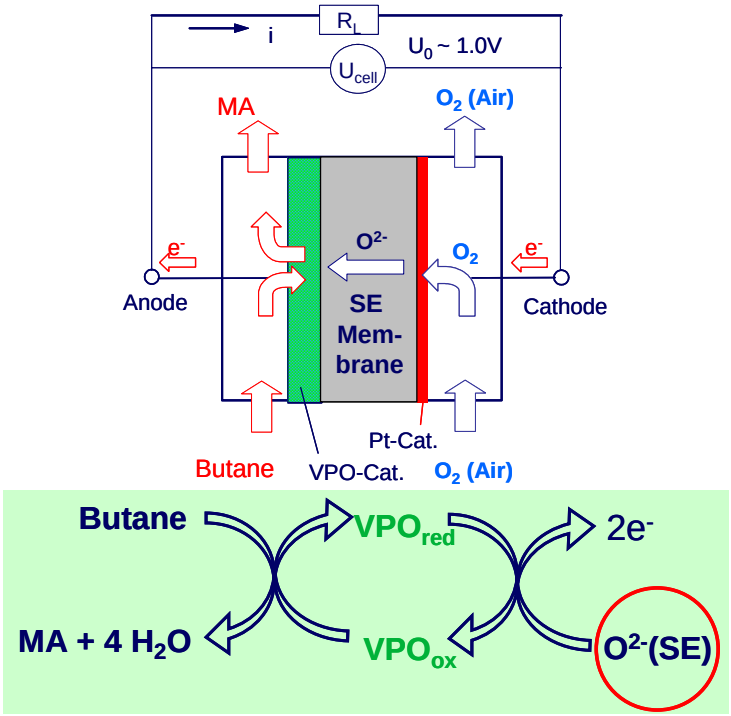

Fig. 36: Working principle of electrochemical membrane reactor for partial oxidation of butane to malenic acid (MA) [28.

Fig. 36 illustrates the proposed reactor concept which is subject of a patent application [29]. The cathode compartment is fed with air whose oxygen is reduced to oxygen ions at a

platinum catalyst layer. These ions are transported through the solid electrolyte (SE) membrane (e.g. yttria doped zirconia or scandia doped zirconia, YSZ / ScSZ) to the anode catalyst layer. In the case of butane partial oxidation, a VPO catalyst is used. The catalyst activity and selectivity for partial oxidation of butane to malenic anhydride depends on its oxidation state. The basic idea of the electrochemical reactor concept is to control the catalyst oxidation state (VPO_{red}/VPO_{ox}) via the flux of oxygen ions from the cathode to the anode, which in turn can be controlled by adjusting the external electric current. The controllability of the catalyst selectivity makes this process very attractive not only for butane oxidation, but also for other partial oxidations of light alkanes.

As an important requirement to the feasibility of this electrochemical membrane reactor, the operating temperature of the ion conducting membrane has to match the operating window of the oxidation catalyst. Therefore, membrane materials must have a reasonable conductivity at temperatures around 400°C.

This is also to avoid the deposition of carbon at the anode. In cooperation with the Max Planck Institute for Solid State Research, Stuttgart (group of Prof. Aldinger), new perovskite materials (LSGM = $La_{0.9}Sr_{0.1}Ga_{0.85}Mg_{0.15}O_{3-\delta}$) were tested as membranes because they have reasonable ionic conductivity at temperatures from 400 to 600°C, i.e. within the operating window of the VPO catalyst which itself is a mixed conductor.

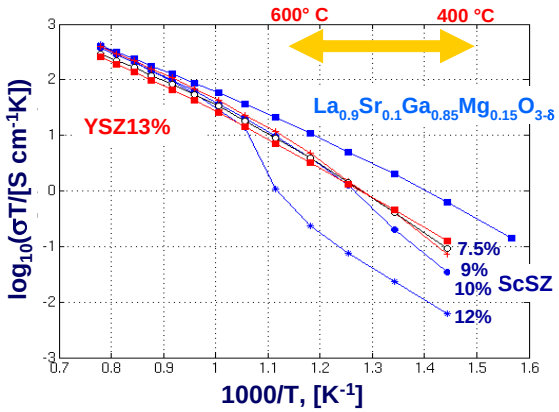

Fig. 37: Ionic conductivities of different membrane materials in dependence on temperature [30].

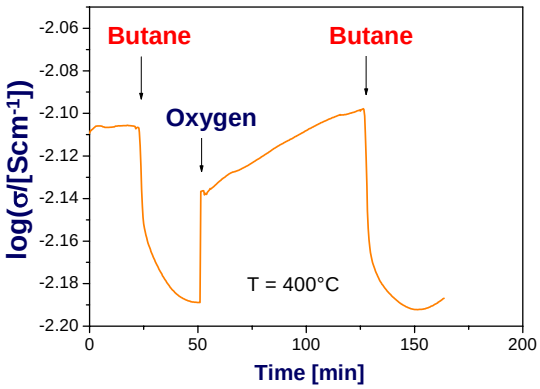

Fig. 38: Change of total conductivity of VPO catalyst by alternating butane and oxygene feed [30].

In this long-term research project, our research activities are currently focused on identifying and quantifying all relevant transport and reaction phenomena in the membrane-catalyst-assembly, by systematic experiments as well as by the formulation of adequate process models [30]. Electrochemical impedance spectroscopy (EIS) is used to determine

the ionic conductivity of membrane materials and to investigate the ionic/n-type/p-type conductivity domains of the VPO catalyst (see in Fig. 37 and Fig. 38).

4.4 Dynamics of Particulate Processes

Particle precipitations are often very fast ionic reactions taking place in an aqueous phase. The size of the particles formed depends on the local supersaturation and the local growth conditions within the solution. Due to high reaction rates, precipitation processes are controlled mainly by the mixing phenomena of the ionic reactants in the bulk solution. This is why precipitation processes and the resulting particle size distribution are very sensitive with respect to the flow field within the reactor. In order to decouple the particle generation processes from the fluid dynamic conditions, we use water-in-oil-microemulsions as reaction media. These microemulsions are thermodynamically stable emulsions (droplet diameter 5 - 100 nm) can exhibit a complex phase behavior whose characterisation is the subject of our current laboratory activities. Fig. 39 illustrates the basic idea of the proposed emulsion precipitation process. The precipitation reaction A + B ⇔ C(solid) is started from two microemulsions which are fed into a stirred tank reactor. The reactants A and B which are stored in the emulsion droplets, meet due to droplet exchange phenomena and subsequently undergo a chemical conversion. This creates a supersaturation in the droplets which is needed to generate nuclei which, in turn, permit particle growth.

Precipitation in microemulsions, due to the limited amount of reactants dissolved in a single droplet, can produce nanosized solid particles with a very narrow size distribution.

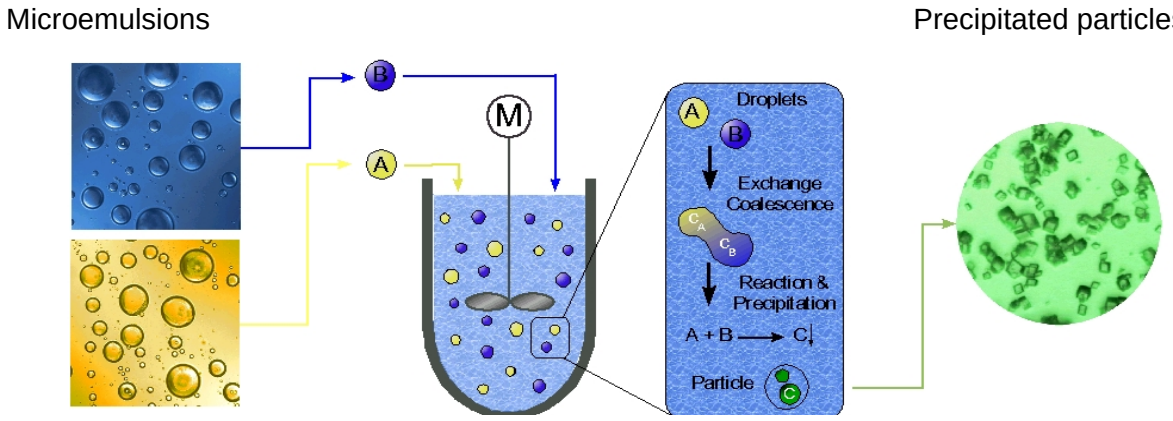

Fig. 39: Formation of solid particles by precipitation in microemulsions: principle of the process.

As a model reaction, we are currently investigating the precipitation of calcium carbonate particles in cyclohexane/water/Marlipal microemulsions [31]. Dynamic light scattering (DLS) and SEM are used as analytical tools for offline particle size analysis. Together with the chair for process systems engineering at OvGU a special miniplant was developed with online particle size analysis based on ultrasound extinction. For the analysis of the composition and morphology of the solid particles formed, an X-ray diffraction (XRD) device was purchased together with the PSF group (Prof. Seidel-Morgenstern).

Parallel to the experimental investigations, the PCP group has started to model the emulsion precipitation process by means of population balance equations. Their solution is the subject of a collaboration with the group of Prof. Hackbusch at the Max Planck Institute for Mathematics in the Sciences, Leipzig. Furthermore, we started to apply Monte-Carlo techniques to simulate the dynamics of multidimensional property distributions. A close collaboration with Prof. Ramkrishna at the University of Purdue, USA, is in preparation.

5. Selected Teaching Activities, Ph.D. Projects

5.1 Teaching Activities at OvGU (K. Sundmacher)

- Course on Process Systems Engineering
- Course on Process Dynamics
- Course on Process Optimization
- Course on Fuel Cells

5.2 Supervision of Ph.D. Theses (in preparation, * Ph.D. students of Univ. group):

Adityawarman, D.	Experimental analysis of population dynamics of an emulsion precipitation process	since 2001
Gundermann, M.	Experimental analysis of Molten Carbonate Fuel Cells	since 2002
Hanke, R.	Process dynamics of PEM fuel cells fed with reformate gases	Since 2001
Heidebrecht, P.	Model based analysis of Molten Carbonate Fuel Cells with direct internal reforming	Since 2001
Huang, Y.S.	Process analysis of reactive membrane separations	Since 2001
Ivanova, M.	Selective partial oxidations by reactive distillation	Since 2002
Krewer, U.	On the impact of electrode kinetics and fluid dynamics on	Since 2001

	the performance of DMFCs	
Munder, B.	Analysis of electrochemical membrane reactors for partial oxidations of light alkanes	since 2001
Niemann, B.	Multidimensional population dynamics of precipitation processes	since 2002
Rauscher, F.	Analysis of precipitation processes in microemulsion systems	since 2001
Schultz, T.	Dynamics of the Direct Methanol Fuel Cell	since 1999
Song, Y.	Computational fluid dynamics for DMFC flow field analysis	since 2001
Steyer, C.	Population balance approach for precipitation processes	since 1999
Steyer, F.	Cyclohexene hydration by reactive distillation	since 2000
Vidakovic, T.	Kinetic analysis of electrochemical methanol oxidation	since 2002
Ye, Y.	Characterization of partial oxidation processes at oxygen-ion conducting membranes	since 2001

K. Sundmacher acted as external examiner for the Ph.D. theses of M. Mangold (2000) and K.D. Mohl (2002), both at University of Stuttgart, C. Möser (2000), Y. Wu (2001), E. Stein (2003) and M. Purmann (2003), all at OvGU, and P. Pääkkönen (2003, at Helsinki University of Technology).

Moreover, the PCP group coordinates a NaT-working project (NaT is short for “Natural and Engineering Sciences”) 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 students from Magdeburg high schools into chemical engineering processes.

6. Selected Memberships, Appointments and Awards

K. Sundmacher

1998	Zerbe Award, German Scientific Society for Petrochemistry (DGMK)
1999	Arnold Eucken Award, German Society of Chemical Engineers (GVC)
since 1999	Full Professor for Process Systems Engineering at Otto-von-Guericke-University Magdeburg
since 2001	Editorial Board Member of *Chemical Engineering and Processing*
since 2001	Appointed Member of Reaction Engineering Working Party of GVC
since 2001	Appointed Member of Reaction Engineering Working Party of DECHEMA
since 2001	Scientific Member and Director for Process Engineering at MPI
since 2002	Appointed Member of DECHEMA Research Advisory Board
since 2003	Chairman of Fuel Cell Working Party in Competence Network Pro3
since 2003	Managing Director of MPI
since 2003	Executive Editoral Board Member of *Chemical Engineering Science*

B. Munder

2001	Prize for best diploma thesis, Clausthal University of Technology

R. Hanke

2002	Prize for best diploma thesis, Institute for Energetics e.V., Leipzig

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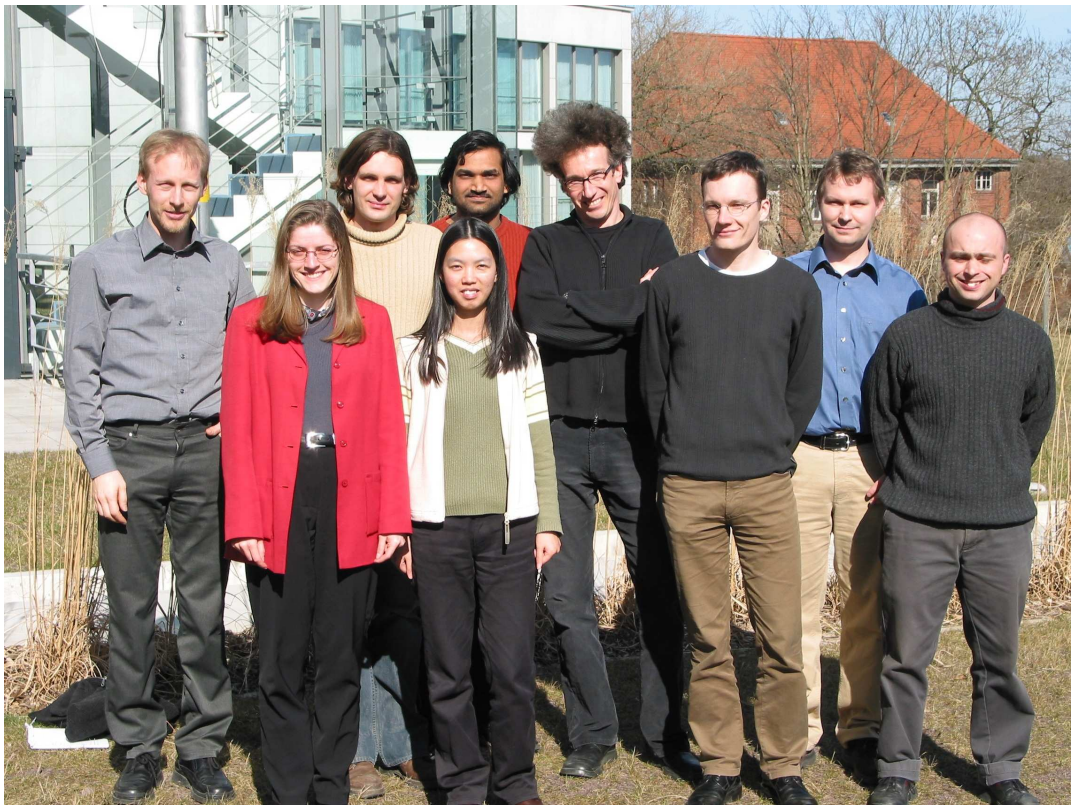
Research Group:

Systems and Control Theory (SCT)

Prof. Dr.-Ing. Jörg Raisch



This report covers the period from 1 June 1998 to 30 April 2003

1. SCT Group Introduction

The Systems and Control Theory Group was founded in 1998. It cooperates closely with the research group on Systems Theory in Engineering ("Lehrstuhl für Systemtheorie technischer Prozesse") at the Otto-von-Guericke University. The university group was established in September 2000 and is also headed by Jörg Raisch. The group's research interests are – not surprisingly – in the area of Systems and Control Theory (SCT). SCT has been recognised as a research area in its own right for several decades. Roughly speaking, its subject is the analysis and synthesis of dynamical systems, in particular the design of control systems. As a result, SCT provides an array of analysis and synthesis methods and tools which have been successfully applied to solve a great number of application problems. Additionally, it has served as a bridge between a variety of application areas, e. g. chemical engineering, mechanical and manufacturing engineering, economics, biology, etc. By translating specific application problems into a unique mathematical framework, SCT provides a common language that allows scientists and engineers with extremely diverse technical backgrounds to communicate and hence generates considerable synergy effects.

This general perspective of SCT is reflected in our 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.

2. Members of the SCT Group

As of March 1, 2003, the group consists of six Ph.D. students, a postdoc and a secretary.

Ph.D. students:

- E. Mayer (since Nov. 1, 1998)
- N.-O. Negård (since April 1, 2002)
- U. Vollmer (since Feb. 1, 1998)
- D. Gromov (since Nov. 1, 2001)
- D. Li (since July 15, 2001)
- B.V. Mishra (since July 1, 2000)

Postdoc:

T. Schauer (since Dec. 1, 2001)

Secretary:

C. Zalewski (since Aug. 1, 2000), jointly funded by OvG University

Group leader:

J. 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)

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. 40. It is followed by a list of 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.

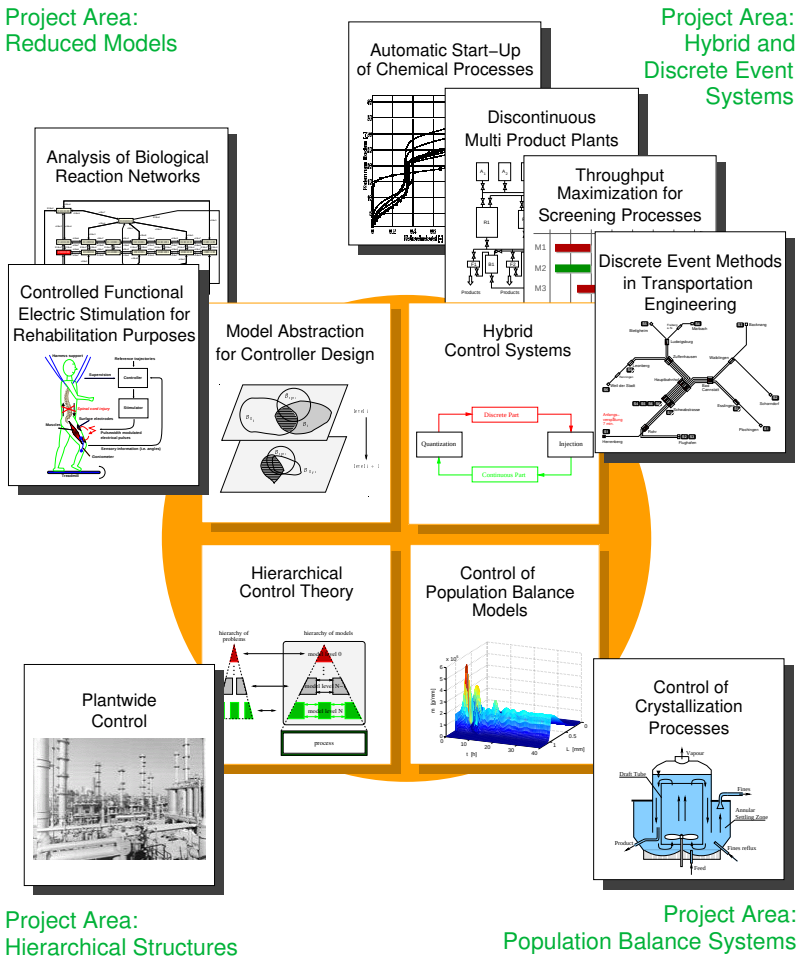


Fig. 40: Survey of research projects.

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, a generally feasible solution method does not yet exist. We follow an approach that is based on “safe” discrete approximations of continuous components. 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.
Researchers:	D. Gromov, J. Raisch
Partners:	Australian National University (T. Moor), Melbourne University (J. Davoren), University of Cagliari (A. Giua)
Funding:	DFG (Schwerpunktprogramm KONDISK), DAAD (Vigoni program), MPI, OvGU
Start:	06/1998

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.
Researchers:	E. Mayer, J. Raisch
Partners:	CyBio AG, Mathematics Dept. OvGU (R. Weismantel)
Funding:	BMWi (AiF)
Start:	04/2001

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. It has been applied to analyse the suburban train network of Stuttgart and to investigate inland waterways where synchronisation is required for locks and narrow stretches. 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.
Researchers:	D. Li, E. Mayer
Partners:	INS Group
Funding:	MPI
Start:	11/1998

Project:	**Automatic Start-up of Chemical Processes**
Abstract:	The start-up problem for chemical processes is essentially characterised by two aspects: (i) as a wide operating range has to be covered, linearised models are not adequate; (ii) specifications are "coarse" and can therefore often be formalised by discrete dynamic models. This makes start-up a hybrid control task, which can be addressed using methods developed in our group's project on hybrid control systems. These methods have been successfully applied to a distillation column system.
Researchers:	A. Itigin (Stuttgart University), J. Raisch
Partners:	Stuttgart University (A. Itigin), PSD Group
Funding:	DFG (Sonderforschungsbereich 412), OvGU, Stuttgart University
Start:	06/1998

Project:	**Control of Discontinuously Operated Multiproduct Plants**
Abstract:	Control of discontinuously operated multiproduct plants is a highly nontrivial hybrid control problem. In practice, recipe-based approaches are prevalent. They provide solutions which are (i) often even nominally far from optimal and (ii) open-loop and therefore extremely sensitive to unforeseen disturbances. We investigate an alternative control strategy which combines an optimisation based approach with an abstraction-based method from hybrid systems theory.
Researchers:	B.V. Mishra, J. Stanczyk (OvGU), A. Kienle (PSD Group), J. Raisch
Partners:	PSD Group, Mathematics Dept. OvGU (A. Pott)
Funding:	DFG (DFG-Forschergruppe 468), MPI
Start:	08/2002

Project area: Reduced Models

Project:	**Model Abstraction for Control Purposes**
Abstract:	There exists a natural tradeoff between model accuracy and model simplicity. In control applications, there is a particularly large scope for model simplification (approximation, abstraction), as feedback constitutes an efficient way of “combatting” model uncertainty. A central requirement within this context is “safety”: each controller enforcing the specifications for a safe abstraction must be guaranteed to “work properly” for the underlying system.
Researchers:	J. Raisch
Partners:	Australian National University (T. Moor), Memorial University (S. O’Young)
Funding:	DFG (Schwerpunktprogramm KONDISK), MPI, OvGU
Start:	06/1998

Project:	**Controlled Functional Electrical Stimulation (FES) in the Rehabilitation of Stroke Patients and Patients with Spinal Cord Injuries**
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. 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 and the complexity of neuro-musculoskeletal systems, the latter requiring the use of reduced models.
Subproject:	**Nonlinear Modelling, Identification and Robust Control of Electrically Stimulated Muscles**
Researchers:	T. Schauer, N.-O. Negård
Partners:	Politecnico di Milano (F. Previdi), University of Glasgow (K. Hunt), Imperial College London (A. Astolfi)
Funding:	MPI
Start:	12/2001
Subproject:	**Electromyography-based Control of FES in the Rehabilitation of Hemiparetic Patients**
Researchers:	T. Schauer, N.-O. Negård
Partners:	Median Klinik NRZ Magdeburg (P. Schönle)
Funding:	LSA, MPI
Start:	11/2002
Subproject:	**Control of FES-assisted Gait Training**
Researchers:	T. Schauer, N.-O. Negård
Partners:	Median Klinik NRZ Magdeburg, Hedon-Klinik Lingen, Krauth & Timmermann GmbH Hamburg
Funding:	MPI
Start:	03/2003
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
Funding:	BMBF (applied), MPI
Start:	12/2001

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.
Researchers:	C. Conradi (OvGU), J. Raisch
Partners:	SBI Group
Funding:	OvGU, MPI
Start:	01/2000

Project area: Hierarchical Structures

Project:	**Hierarchical Control Theory**
Abstract:	Hierarchical control can be interpreted as an attempt to handle complex problems by decomposing them into smaller subproblems and reassembling their solutions into a “functioning” hierarchical structure. So far, heuristic approaches have been prevalent. However, they cannot guarantee that the overall solution does indeed meet the specifications. In contrast, our project aims at a formal synthesis method that can provide such a guarantee. Our approach is based on a hierarchy of models describing a given plant at various levels of abstraction.
Researchers:	D. Gromov, A. Itigin (Stuttgart University), J. Raisch
Partners:	Stuttgart University (A. Itigin), Australian National University (T. Moor)
Funding:	DFG (Sonderforschungsbereich 412), MPI
Start:	01/1999

Project:	**Plantwide Control of Chemical Processes**
Abstract:	This projects 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	R. Waschler and A. Kienle (PSD Group), J. Raisch
Partners:	PSD Group, AZOT (Sewerodonetsk)
Funding:	MPI
Start:	09/2001

Project area: Population Balance Systems

Project:	**H_∞-Control of Population Balance Systems**
Abstract:	Many processes, such as crystallisation and polymerisation, are characterised by a large number of individual particles which differ with respect to one or more properties. The temporal evolution of the distribution density is typically described by a partial integro-differential equation (population balance model), where the integral part represents “nonlocal effects”. For a simple class of population balance models (linear, with concentrated control input and measurement signals), infinite-dimensional H_∞-control theory can be adapted to optimise performance, subject to the usual stability constraints.
Researchers:	U. Vollmer, J. Raisch
Funding:	MPI
Start:	06/1998

Project:	**Crystallisation**
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. Our group investigates two control problems for crystallisation processes. First, continuously operated crystallisers often exhibit sustained oscillations around the desired operating point, which need to be removed to provide constant product quality. This is achieved by applying H_∞ feedback techniques. Second, in batch crystallisation, the CSD at the end of a batch-run needs to be shaped according to product specification, e.g., by selecting a suitable cooling policy. The cooling policy, in turn, is generated using flatness-based control theory.
Subproject:	**Control of Crystallisation Processes**
Researchers:	U. Vollmer, J. Raisch
Partners:	PCF Group, PSD Group, Stuttgart University (S. Motz)
Funding:	MPI
Start:	06/1998

4. Research Highlights

In the following, we highlight a few of our group's research activities. The selection is meant to provide an idea of our research philosophy and therefore includes both projects of primarily theoretical focus and applied focus.

4.1. Control of Crystallisation Processes

In the chemical and pharmaceutical industries, crystallisation 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, both for continuously operated and batch crystallisers.

4.1.1. Continuous Crystallisation

Dissolution of small crystals (fines dissolution) is frequently used in industrial continuous crystallisation plants (Fig. 41) to improve the product CSD. This effectively shifts the CSD towards larger crystal sizes and often makes the distribution narrower. However, these benefits are being paid for by a deterioration of the dynamic process behaviour: fines dissolution often leads to sustained oscillations of CSD and solute

concentration around the designated operating point. Clearly, this interferes with the aim of providing constant product quality and therefore motivates the design of suitable feedback controllers to stabilise the crystalliser at high fines dissolution rates.

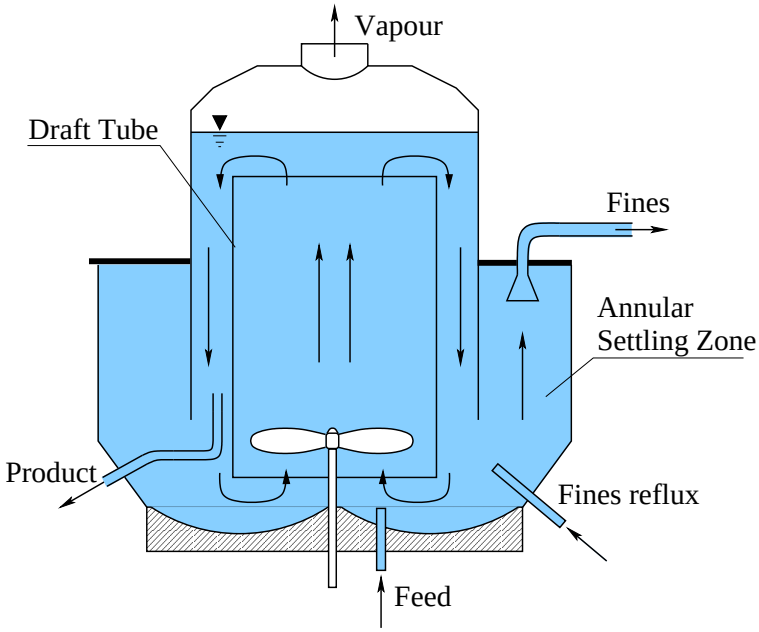


Fig. 41: Continuous crystalliser.

A detailed population balance model for an evaporative crystalliser has been developed by our cooperation partners at the University of Stuttgart [3]. In a first step, based on physical considerations, this model is simplified to allow analytical determination of the steady state. This step does *not* include lumping of the model and hence preserves the infinite-dimensional nature of the system. We can now linearise around the steady state to obtain a transfer function relating the control input (the fines dissolution rate) to the third moment of the CSD, which is assumed to be the measured output. Reflecting the infinite-dimensional character, the transfer function is irrational with infinitely many poles and zeros. Clearly, as we use a linearised version of an already simplified model, we need to emphasise *robustness* during the control design, i.e. we seek a controller that will tolerate a large degree of model uncertainty. H_∞-theory provides a framework for the synthesis of robust controllers, which has recently been extended to a class of infinite-dimensional systems. In a related project (see Section 3), we have shown that this approach also covers the type of population balance models we obtain in a crystallisation context. Applying this method to the problem at hand yields an irrational controller transfer function [2], which, for implementation purposes, needs to be approximated by a rational, i.e. finite-dimensional, transfer function corresponding to a finite set of ordinary differential equations. Simulations of the resulting controller in closed loop with the detailed population balance model from [3] are shown in Fig. 42. They demonstrate the effectiveness of our approach.

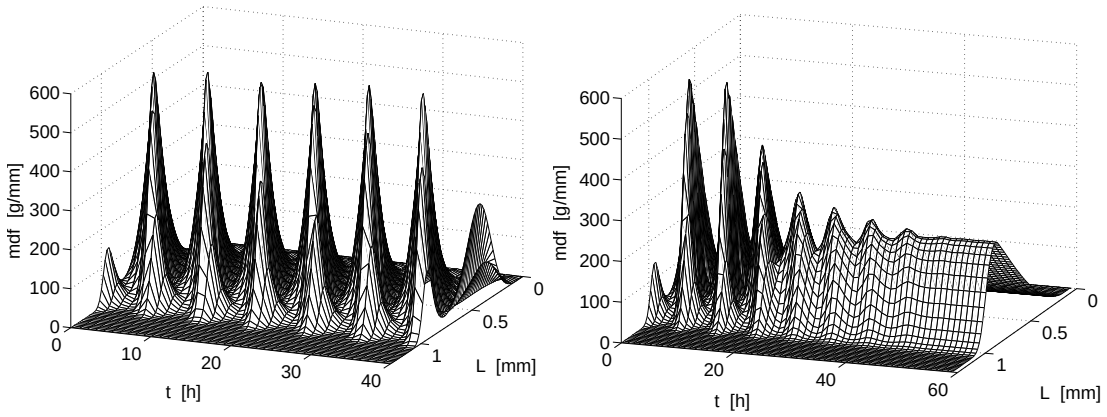


Fig. 42: Oscillating CSD without control (left); control switched on at $t_0 = 10h$ (right).

Nevertheless, one might ask what we gain by pursuing a *late lumping* philosophy, i.e. by lumping the controller instead of the process model. The gain is twofold. First, late lumping preserves the infinite-dimensional nature and, as a consequence, physical intuition during the entire design process. This is especially important in H_∞-synthesis, where a proper choice of weighting factors in the cost function is extremely difficult without that sort of intuition. Second, with late lumping, it is possible to quantify the degree of suboptimality implied by the lumping-related approximation.

4.1.2. Batch Crystallisation

The control problem posed by the batch-wise operation of crystallisation plants is quite different. In batch crystallisation, the vessel is initially filled with undersaturated solution. Supersaturation is generated by gradual cooling (Fig. 43). 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 problem, namely how to find a temperature trajectory producing a predefined CSD.

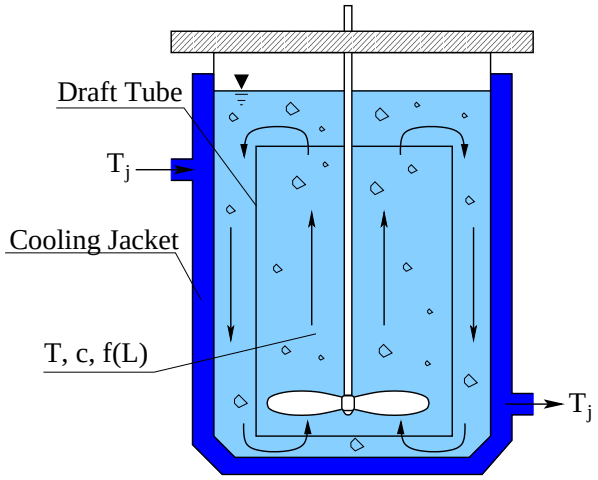


Fig. 43: Batch crystalliser

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 is a function of the system state and input, such that, conversely, the state and input of the system can be expressed as functions of the flat output and finitely many of its time derivatives. This represents an invertibility property which 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) CSD [4, 5]. Based on these results, it is also possible to determine a control policy that optimises the final CSD by solving a *static* optimisation problem. Simulation results for a typical optimization problem – maximising the ratio of final seed crystal mass and nucleated crystal mass – are shown in the right half of Fig. 44. The left half of the figure shows the temporal evolution of the CSD obtained from a conventional linear cooling policy. To obtain experimental validation for both the continuous and the batch control results, we cooperate with the PCF group.

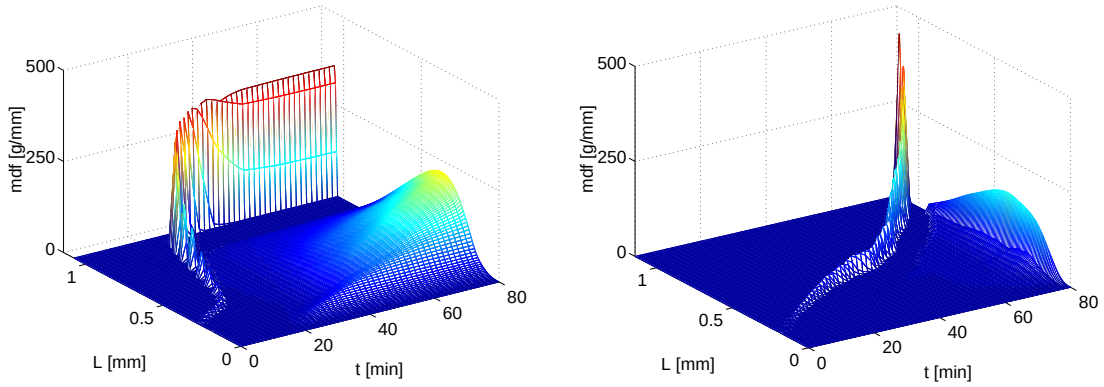


Fig. 44: Temporal evolution of CSD in a batch crystalliser: linear cooling policy (left), optimal cooling policy (right).

4.2. Hybrid Control Systems

The control of physical or chemical processes by digital computer programs often leads to heterogeneous systems which include both continuous and discrete-event dynamics. Such *hybrid control systems* generally exhibit highly complex behaviour. From an engineering point of view, the systematic design of hybrid control systems is of particular importance. This represents a mathematically challenging task, primarily because of the nature of hybrid state sets: purely continuous systems usually exhibit a nice (vector space) structure. This implies that a rich set of analysis tools can be applied to investigate continuous system dynamics. Purely discrete systems can be described by discrete, and in most cases finite, state sets. Hence, the dynamical behaviour of finite discrete systems can, at least in principle, be completely investigated by finite enumeration type methods. The state set of a hybrid system is the product of the state sets of its constituent components. In general, it is therefore neither finite nor does it exhibit vector space structure.

A natural approach to avoiding this problem is to resort to approximation-based control synthesis methods: roughly speaking, the external behaviour of the continuous component is approximated by a discrete-event system (DES); if the specifications are also discrete, this turns the hybrid control problem into a purely discrete one, which, in a subsequent step, can be addressed using established methods from the field of DES theory. Approximation-based synthesis of hybrid control systems has been an active area of research for a number of years, with important contributions from, among others, P. ANTSAKLIS', B. KROGH'S AND J. LUNZE'S groups. All of these approaches require the approximation to be *safe*, meaning that any controller enforcing the specifications for the discrete approximation must be guaranteed to do the same for the underlying continuous model. Failure of successful

controller synthesis on the approximation level, however, does not imply that the hybrid control problem cannot be solved, as increasing approximation accuracy may still allow determination of an adequate controller. We have therefore suggested a method that provides a set of discrete approximations (all of them realisable by finite automata), which are strictly ordered with respect to approximation accuracy, e.g. [6, 7]. These "l-complete approximations" exactly represent the external behaviour of the continuous system under consideration over an interval of $l+1$ sampling instants [8, 13], where sampling may either be equidistant, i.e. clock-driven [9], or event-triggered [10]. Clearly, increasing l will increase approximation accuracy, but will also (exponentially) increase complexity. In cooperation with T. MOOR from the Australian National University and J. DAVOREN from the University of Melbourne, we have explored a number of promising approaches to alleviate this problem.

Increasing the integer parameter l increases approximation accuracy *uniformly* – even though the given specifications may only require a refinement of certain aspects of the discrete approximation. Hence, in [14], we developed a procedure that, in case of failure during the controller synthesis step, locates the potential reason for failure in the currently used approximation. The refinement procedure then focuses its efforts on those aspects of the approximation that have caused the failure instead of doing an unspecific global refinement.

Another approach to counter the increase of complexity is the use of modular controllers. In [11], we identified conditions under which two discrete controllers, each enforcing a particular specification for a continuous plant model, will have an admissible parallel composition that enforces both specifications simultaneously.

Hierarchical control can be interpreted as an attempt to handle complex problems by decomposing them into smaller subproblems and reassembling their solutions in a hierarchical structure. In the context of hybrid systems, formal methods have been explored, e.g., by P. CAINES' and S. SASTRY'S groups. In our project on hierarchical control systems, we have investigated an approach that is based on a hierarchy of models describing a given plant at various levels of abstraction. It captures intuitive concepts like information aggregation between different levels of control and, in [15], has been applied to a hybrid control setting. In [16], we considered a more specific hierarchical hybrid control architecture in some detail. It is characterised by a high-level discrete-event controller that switches between a finite number of low-level continuous controllers attached to a given continuous plant. From an application point of view, this architecture is attractive because it may be computationally much more efficient to generate safe approximations for the closed-loop composition of a low-level controller and the plant model than for the latter alone.

Obvious examples are low-level controllers which asymptotically force the continuous state onto a lower-dimensional manifold.

To compute l-complete or other safe approximations, one basically needs to propagate bounded subsets of the plant state space under the flow corresponding to the plant dynamics, and to intersect the results with other bounded sets. This clearly represents a major problem for nonlinear flows. In practice, one often resorts to exhaustive simulation type methods, where instead of a set, a large number of single points is propagated over time. This not only interferes with the aim of finding a *safe* approximation, but also drastically increases computational requirements, especially for high-dimensional systems. In cooperation with D. FLOCKERZI, we have investigated a class of nonlinear systems where safe approximations can be computed very efficiently: monotone dynamical systems, which are fairly common in chemical engineering applications, are characterised by the fact that there exists a partial order in the state space which is preserved under the progress of time.

In cooperation with the PSD group, we successfully used our results to synthesise a discrete-event controller for the automatic start-up of a distillation column. Controller synthesis was based on a nonlinear 42nd order plant model; the specification was to drive the plant state into a well-defined vicinity of the desired operating point within 20 minutes. Fig. 45 shows a comparison between the open-loop case, where the control inputs corresponding to the desired operating point were applied to the plant model, and the closed-loop case consisting of continuous plant model and discrete controller [12]. In the former case, it takes many hours to converge to the desired target region (indicated by horizontal lines), in the latter case, this is achieved, as required, within 20 minutes.

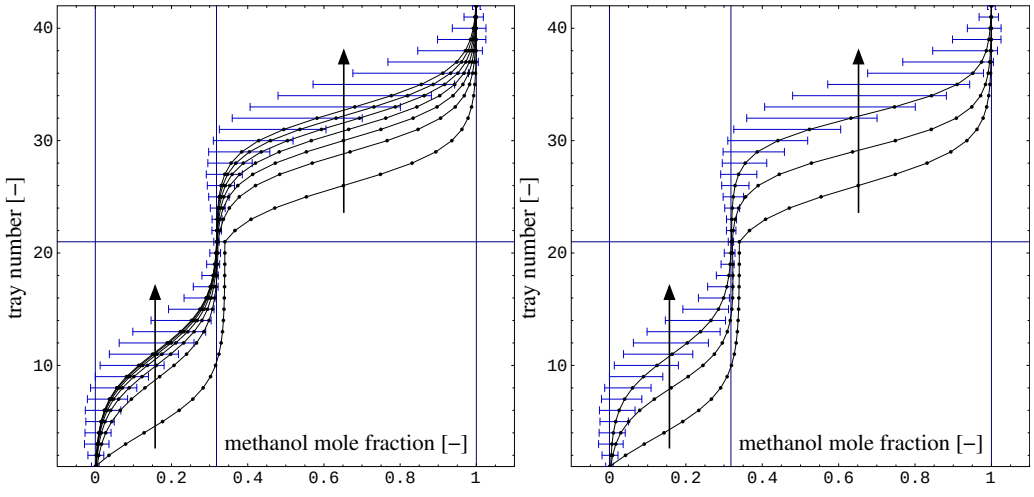


Fig. 45: Start-up of a distillation column: open-loop (left, $\Delta = 5h$), closed-loop (right, $\Delta = 10\,\mathrm{min}$).

4.3. Throughput Maximisation for Screening Systems

High Throughput Screening (HTS) plants are used for analysis of chemical or biological substances. Although hundreds of substances are aggregated on a single microplate (“batch”), a large number of batches have to pass through the plant resources, e.g. incubators, liquid handling devices, transport devices, etc., in the same specific time scheme. This motivates the specific scheduling task for HTS plants, namely to determine a sequence and time scheme for all operations that will lead to maximal throughput or, equivalently, will need minimal time to achieve a desired throughput. The task is set apart from scheduling problems in other applications areas by a number of requirements: while progressing through several operations, each single batch may pass the same machine more than once; more than one batch will be present in the system at the same time, and there are no buffers between the machines; a batch may occupy two or more machines simultaneously when being transferred from one machine to another; additionally, there will be upper time bounds (“due dates”) defined by the user.

A number of scheduling approaches have been suggested for specialized HTS plants. However, as development goes towards large flexible HTS plants (Fig. 46), a general scheduling approach is needed which can be used independently of the specific combination of machines and transport devices.

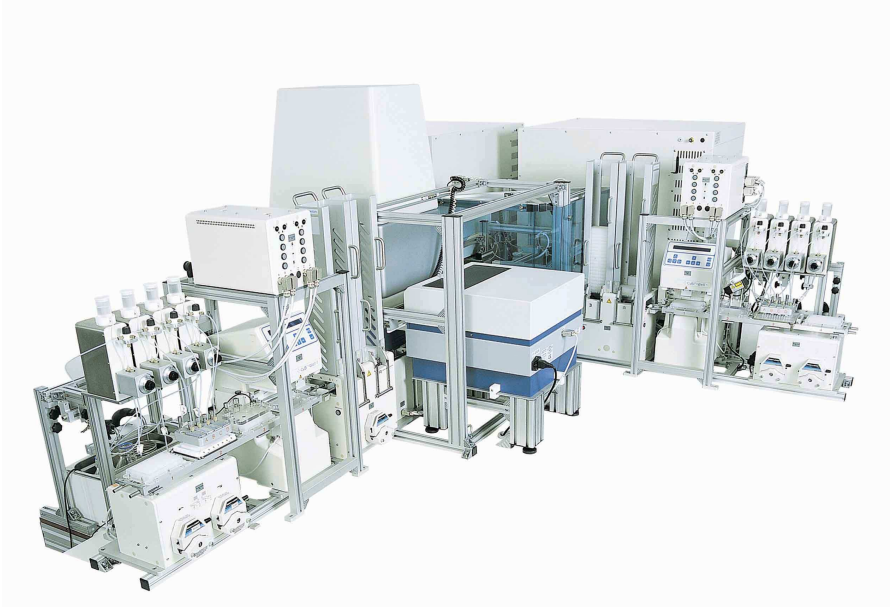


Fig. 46: Flexible scheduling plant (CyBio AG, Jena).

This project represents a cooperation with CYBIO AG, a leading manufacturer of HTS plants. In many cases, due to the specific nature of the substances to be screened,

operating schemes in their plants have to be strictly cyclic, i.e. the time distance between two consecutive batches (“cycle time”) is required to be constant (see Fig. 47). Throughput maximisation is then equivalent to minimisation of cycle time. To formalise this scheduling problem, we need a mathematical model for cyclic processes and for all constraints to be satisfied. A key ingredient is a compact and effective formulation for the so called disjunctive constraints, which state that no resource of the plant can be used by more than one batch simultaneously. Based on this, the scheduling problem can be reformulated as a (generally very large) mixed integer nonlinear optimisation problem (MINLP). Next, the size of the problem formulation can be reduced considerably by using a suitable parametrisation for the degrees of freedom of the scheduling task. However, even small MINLPs may be extremely hard to solve, hence an important step within this project was the discovery of a transformation that makes the problem a linear one. The resulting MILP (mixed integer linear problem) is an exact representation of the underlying scheduling problem and can be solved using, for example, branch and bound methods. The result is guaranteed to be a globally optimal solution. An illustrative example is given in Fig. 47: the top part shows a cyclic operating scheme for a problem requiring six allocations on three resources per batch. The lower part shows the corresponding minimal cycle-time scheme. Interestingly, completion of a single batch takes longer in the optimal scheme.

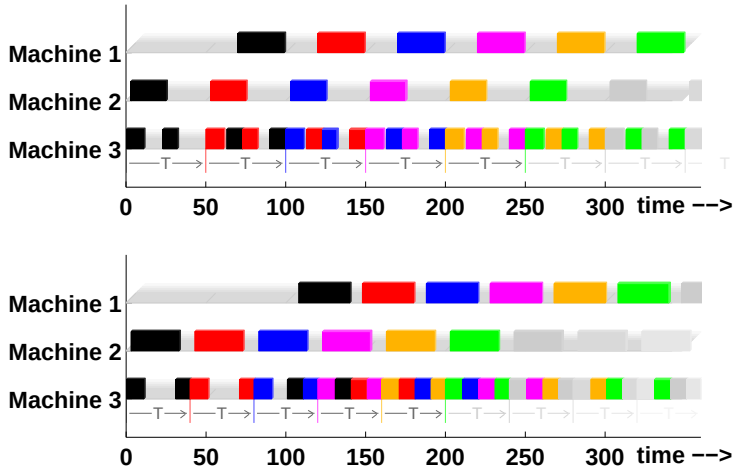


Fig. 47: Examples for cyclic operating scheme (Gantt charts). Individual batches are shown in different colors.

The proposed method has been successfully applied to a sample scheduling problem for a modern, fully automated flexible HTS system, where screening runs involve up to 150 resource allocations per batch. So far, we have only investigated the optimal open-loop case. In a next step, closed-loop aspects such as re-scheduling after failures will be taken

into account. The funding for this project has been provided by the German Ministry of Economics and Technology (BMWi) under their AiF-scheme. First results appeared in [17].

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

The overall theme of this project is to investigate the application of controlled functional electrical stimulation (FES) for the rehabilitation stroke patients and patients with spinal cord injuries. It is well known that electrical nerve-stimulation can be used to generate contractions of paralysed muscles. In combination with appropriate sensor technology and feedback control, this can be exploited to elicit functional movements, such as walking and cycling, and hence to restore certain motor functions. Depending on the degree of disability, the intention may be temporary assistance, e.g., during re-learning of gait, or permanent replacement of lost motor functions (neuro-prosthesis). Beside these functional effects, FES has several secondary therapeutic benefits: it improves muscle size and strength, increases the range of joint motion and improves cardiopulmonary fitness by providing significant training effects. FES is therefore potentially more attractive for rehabilitation purposes than conventional methods such as passive bracing of the joints. Fig. 48 explains the principle of controlled FES for a specific problem, the control of knee-joint angle by quadricep stimulation.

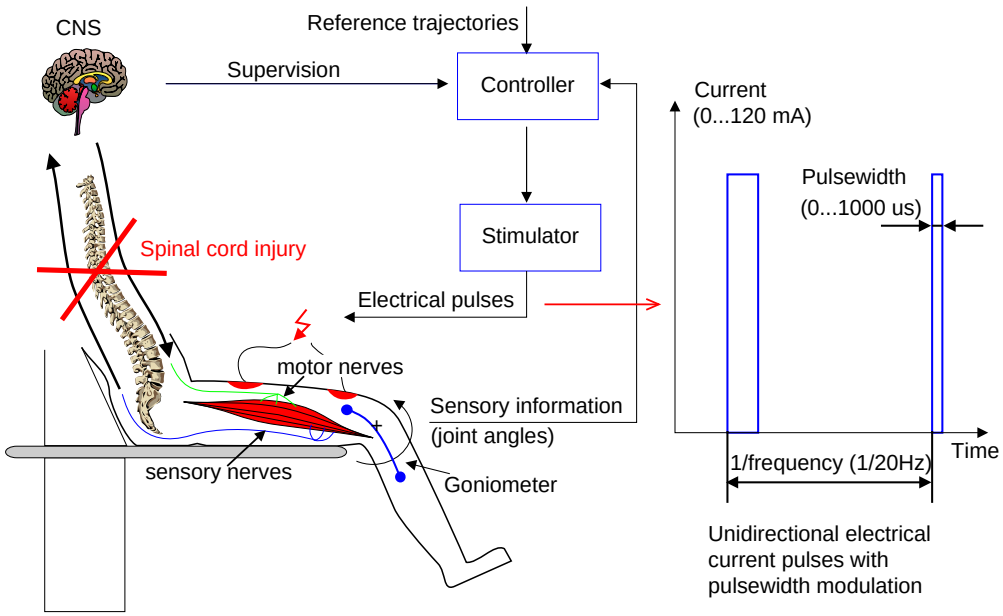


Fig. 48: Functional Electrical Stimulation (FES) for knee-joint angle control.

The knee-joint angle is measured and fed back to the controller, which generates a suitable stimulation pattern to achieve tracking of a reference trajectory. Stimulation can either be applied directly to the peripheral motor nerves (as shown in Fig. 48) or, if the reflex arcs in the lower spinal cord are still intact, to the sensory nerves. The latter causes an indirect stimulation of motor nerves while ensuring the natural inhibition of antagonistic muscles. A general problem with FES is rapid muscle fatigue. External stimuli, which replace the missing commands from the central nervous system, tend to invert the recruitment order of muscle fibres: motorneurons with larger diameter are activated first as they have a lower threshold; they recruit the faster and more powerful (type 2 or white) fibres, which fatigue more quickly than the slower, but less powerful, type 1 or red muscle fibres. Electrical stimulation is realised by attaching surface electrodes to the skin, because the alternative, implanting electrodes, is much less convenient and carries a serious risk of infection.

Our FES project builds on extensive previous studies at a number of institutions, e.g. the Centre for Rehabilitation Engineering (CRE) at the University of Glasgow. Both investigators in our FES project, T. Schauer and N.-O. Negård, were with the CRE before joining our group in late 2001 and early 2002, respectively. The project is organised within four subprojects, the first two addressing fundamental questions in the FES context, the other two aiming at transferring results into medical and therapeutical practice.

4.4.1. Nonlinear Modelling, Identification and Robust Control of Electrically Stimulated Muscles

Neuro-musculoskeletal systems are complex, nonlinear and, due to muscle fatigue, rapidly time-varying. An adaptive scheme based on on-line identification of simplified model structures is therefore an attractive possibility for controller design. In this context, restrictions imposed by the intended use in a clinical environment are of prime importance. For example, goniometer measurements of joint angles are to be preferred to powerful optical analysis systems, simply because the latter may be affected by physiotherapists working with the patient. The identification scheme proposed in [21] takes such restrictions into account. An implicit self-tuning scheme, which does not need explicit identification of a plant model, has also been investigated and is described in [18]. Another approach is to work with less detailed model information, to emphasise robustness during controller design and to accept a certain degree of performance degradation. We have applied backstepping control synthesis techniques to a lower-limb model reflecting the well-known equations of motion and passive joint properties, but containing only an extremely rudimentary description of muscle dynamics plus the corresponding uncertainty bounds [20]. Within this

subproject, we cooperate with the University of Glasgow (K. Hunt), the Politecnico di Milano (F. Previdi), and Imperial College London (A. Astolfi).

4.4.2. Electromyography-based Control of FES in the Rehabilitation of Hemiparetic Patients

Because of the interference caused by voluntary muscle activity, controlled FES in hemiparetic patients is a potentially more demanding problem. In this subproject, we investigate how to detect such voluntary muscle activity through electromyography (EMG) and how to exploit this information when controlling lower-limb movements by FES. Simultaneously applying electrical stimulation and performing EMG measurements on the same muscle group requires special hardware and signal processing routines in order to minimise stimulation artefacts within the EMG measurements. This is currently being investigated in the gait analysis laboratory at the MPI, which has recently been established with funds from the Ministry of Education and Cultural Affairs of Saxony-Anhalt. Medical assistance is provided by our cooperation partner, the neurological rehabilitation centre MEDIAN KLINIK NRZ (P. Schönle).

4.4.3. Control of FES-assisted Gait Training

Treadmill training with partial body weight support represents a promising new rehabilitation technique for improving the mobility of hemiparetic patients. Peripheral stimulus due to repeated strides on a motorised treadmill assisted by physiotherapists may lead to a reorganisation and an activation of spinal circuits and reflexes which allow an independent motor control of gait at spinal level. We intend to improve this technique by means of multichannel FES of the initially paralysed muscles (Fig. 49).

Goniometers, inertial sensors and force sensitive resistors are employed to determine joint angles, gait phases, foot clearance and stride length for feedback control. An improvement in gait quality in the early stage of rehabilitation and an increased amount of training are expected. Similar to treadmill trainers, electromechanical gait trainers can be enhanced by FES. Using gait trainers, the control of FES is simplified, as the position of the legs is constrained to a predefined path; this reduces the mechanical degrees of freedom. For this subproject, there are two medical and one industrial cooperation partners, MEDIAN KLINIK NRZ, HEDON-KLINIK, and KRAUTH & TIMMERMANN GMBH.

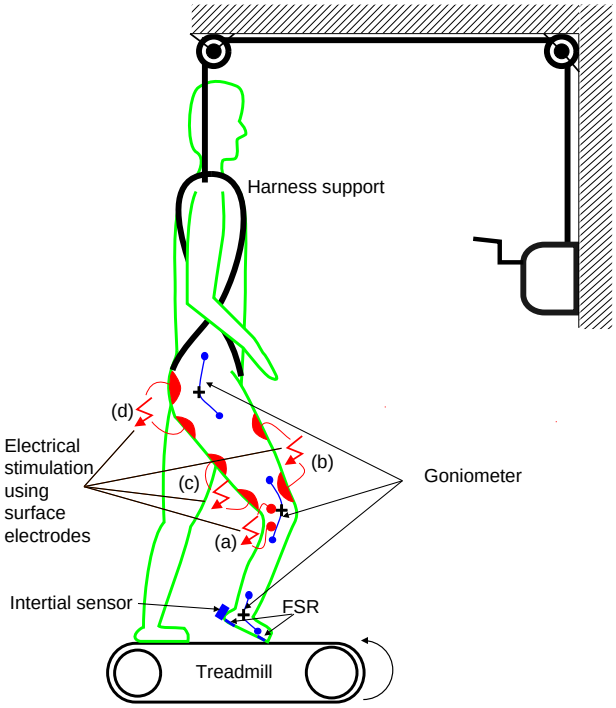


Fig. 49: Treadmill training using multichannel FES: (a) peroneal nerve stimulation, (b) quadricep muscle group, (c) hamstring muscle group, (d) gluteus maximus.

4.4.4. Development of Mobile and Stationary FES-cycling Systems with Motor Assist

FES-cycling represents another promising rehabilitation tool. Crank angle and cadence are measured and fed back to generate a suitable stimulation pattern for the major leg muscles [19]. Additional force sensors are used to tune the stimulation pattern. This is particularly important for hemiparetic patients, where voluntary muscle activity must be taken into account to achieve good results. In cooperation with the Centre for Rehabilitation Engineering at the University of Glasgow and HASOMED GMBH, a biomedical engineering company, our group is developing motor assisted FES-cycling systems. They are based on commercially available ergometers and recumbent tricycles.

4.5. Research Related Activities

Organisation of International Workshops (J. Raisch)

- **HCCS01** International Workshop on Hierachical Concepts in Complex Technical and Biological Systems, Magdeburg, November 2001 (with U. Reichl)
- **FBC03** Tutorial on Flatness Based Control of Distributed Parameter Systems, Magdeburg, February 24th – 28th, 2003 (with J. Rudolph)

IPC Member (J. Raisch)

- **ADPM2000** 4ème Conférence Internationale sur l'Automatisation des Processus Mixtes: les Systèmes Dynamiques Hybrides, Dortmund, 2000
- **HSCC2000** 3rd International Workshop on Hybrid Systems: Computation and Control, Pittsburgh, 2000
- **WODES2000** 5th Workshop on Discrete Event Systems, Ghent, 2000
- **SPC2000** 3rd Symposium on Process Control, Ploiesti, 2000
- **ADHS03** IFAC Conference on Analysis and Design of Hybrid Systems, St. Malo, 2003
- **CESA2003** IMACS/IEEE Conference on Computational Engineering in Systems Applications, Lille, 2003

(Co-) Organisation of Invited Sessions (J. Raisch)

- **ECC99** European Control Conference, Karlsruhe, 1999, special session on "Discrete-Event Models and Supervisory Control for Continuous and Hybrid Systems" (with J. Lunze)
- **ADHS03** IFAC Conference on Analysis and Design of Hybrid Systems, St. Malo, 2003, special session on "Hierarchical approaches to Hybrid Control Systems Design" (with T. Moor)
- **MMAR2003** 9th IEEE International Conference on Methods and Models in Automation and Robotics, Miedzyzdroje, Poland, 2003, special session on "Analysis and Control of Discrete Event/Hybrid Systems" (with A. Giua).

Journal Review Activities

Members of the SCT-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.*

5. Teaching Activities

5.1. Systems Engineering and Cybernetics

Most of our teaching activity is related to a 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 I** (1st semester, 2 hours/week)
- **Cybernetics II** (2nd semester, 2 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)
- **Hybrid Systems** (8th semester, 3 hours/week)

5.2. Other Courses

Courses which are not part of the regular curriculum include:

- **Systems Theory and Coding Theory** (with W. Willems, summer 2001, 8th semester students in mathematics, 2 hours/week)
- **Sequential and Parallel Logic Control Systems** (with J. Ihlow, summer 2001, 6th semester students in electrical engineering, 2 hours/week)
- **Dynamics of Discrete Event Systems** (with H. Wehlan, at Stuttgart University, winter 1998/99 and 1999/2000, 3 hours/week)
- **Supervisory Control Theory** (at Technical University of Hamburg-Harburg, summer 1998, 1 hour/week)

5.3. Teaching Related Activities

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.

In cooperation with the University of Ploiesti, Romania, and funded by the European Union, we organise an ERASMUS/SOCRATES student exchange program in the general area of systems and control.

5.4. Ph.D Theses

J. Raisch supervises the following Ph.D projects:

- U. Vollmer: Control of crystallisation processes, to be submitted in 2003
- E. Mayer: Scheduling and control of cyclic discrete-event systems, in preparation
- C. Conradi: Analysis of biochemical reaction networks, in preparation

A. Itigin: Hierarchical hybrid control systems, to be submitted in 2003

- 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
- B.V. Mishra: Control of multiproduct batch plants, in preparation

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

- E. Klein (Universität Stuttgart): Discrete-event modelling, specification and control synthesis for process engineering problems, 03/2001
- T. Moor (Universität der Bundeswehr Hamburg): Approximation-based synthesis of discrete controllers for hybrid plants, 12/1999

A. Trontis (University of Strathclyde): Control synthesis for hybrid systems, 01/2003

6. Awards, Fellowships, Appointments

During the period covered by this report, J. Raisch was offered the following C4-professorships (chairs)

- Chair for Control Systems, Department of Mechanical Engineering, University of Duisburg, March 1999.
- Chair for Systems Theory in Engineering, Department of Electrical Engineering, Otto-von-Guericke University Magdeburg, January 2000.
- Chair for Control Systems, Department of Computer Science, Carl-von-Ossietzky University Oldenburg, May 2000.
- In September 2000, he accepted the Chair for Systems Theory in Engineering.
- In Feb./March 2001, he held a visiting research fellowship at the Australian National University.
- In February 2002 he was appointed External Scientific Member of the Max Planck Institute for Dynamics of Complex Technical Systems.
- Since September 2002, he has also been managing director of the Institut für Automatisierungstechnik (Institute of Automatic Control) at the Otto-von-Guericke University Magdeburg.

7. References

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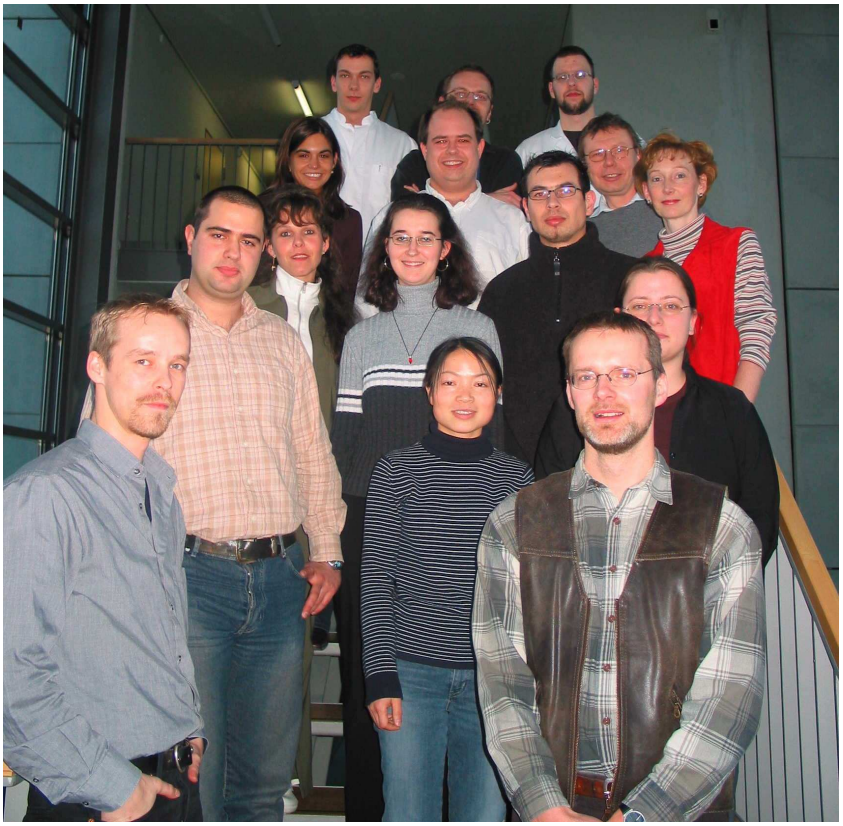
[21] *T. Schauer, F. Previdi, K. J. Hunt, N.-O. Negård, E. Ferchland, and J. Raisch:* Online Identification of the Electrically Stimulated Quadriceps Muscle Group. Accepted for *5th IFAC Symposium on Modelling and Control in Biomedical Systems,* Melbourne, 2003.

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

Research Group:

Physical and Chemical Foundations of Process Engineering (PCF)

Prof. Dr.-Ing. Andreas Seidel-Morgenstern



This report covers the period between August 1998 and April 2003

1. PCF Group Introduction

The activities of the research group “Physical and Chemical Foundations of Process Engineering” started in August 1998 with the appointment of Prof. A. Seidel-Morgenstern as an External Scientific Member of the Max Planck Society. With this appointment, the basis was laid for a good cooperation of the MPI with the Otto-von- Guericke-University (OvGU) in Magdeburg and in particular with the Faculty of Process and Systems Engineering where A. Seidel-Morgenstern is the head of the Chair of Chemical Process Engineering.

The main activities in the busy initial period of building up the MPI were focused on the recruiting of suitable co-workers for the whole institute and for the PCF group and the planning of research laboratories for the first temporary location in the ZENIT building and in parallel for the new building. In 1999 Dr. H. Lorenz and J. Kaufmann joined the group. With their help, the laboratories were equipped and first scientific projects were initiated. Since several groups at the MPI identified the investigation of various types of crystallization processes and of population balance systems as a challenging and integrating project area for joint research, the PCF group began to develop a research program in this field. The focus was set on the experimental and theoretical study of crystallization processes that can be used for the isolation and purification of pharmaceutical drugs (in particular, enantiomers). In 2000 our lab was capable to measure reliable solubility data for enantiomeric systems. When A. Perlberg and M. Kaspereit joined the group as the first Ph.D. students, new activities were initiated devoted to quantifying the rates of crystal growth and the equilibria of adsorptive and chromatographic separation processes. Further activities devoted to systematically investigating reaction processes supported by membrane separation were started at the end of 2000. To investigate this research area, a major project proposal was elaborated. Since the beginning of 2001 the German Research Foundation (DFG) has supported 8 different subprojects at the Magdeburg University and at the MPI within the framework of the DFG Research Group “Membrane Supported Reaction Engineering”. After the start of a second major joint project focused on combining chromatography and crystallization for the separation of enantiomers (in cooperation with the company Schering in Berlin, financed by the German Research Ministry), further co-workers joined the group. At this time, our research work also became increasingly interesting for students from the OvGU as documented by a growing number of diploma and master thesis projects. Thus, the last months in the ZENIT building were characterized by significant space problems and the end of 2001 was the right time to move into the new building. Here again, several months were needed to reinitiate and expand the experimental work, however, this time there were many more possibilities. In particular the experimental work on crystallization was intensified. A significant catalyst for this development was Dr. A. Mahoney who joined us as a postdoc

introducing profound expertise in the analysis of population balance systems. The possibilities in the new building also triggered joint projects with other groups at the MPI. Examples are the analysis of new types of simulated moving bed processes in cooperation with the PSD group (A. Kienle) and the evaluation of the potential of confocal laser microscopy for investigating electrochromatographic processes in cooperation with the BPE group (U. Reichl). The latter activities are part of a larger research project which is devoted to quantifying electrokinetic phenomena and the dynamics of capillary electrochromatography conducted in collaboration with U. Tallarek (OvGU).

In July 2002 A. Seidel-Morgenstern became a Scientific Member of the Max Planck Society and a director at the MPI. To promote the excellent cooperation between the MPI and Otto von Guericke University he continued as the head of the Chair of Chemical Process Engineering.

In recent months further co-workers have joined the group (e.g. Y. Shan, M. Elsner, E. Rapp) expanding our range of activities in the fields of crystallization and chromatography. Also, the experimental basis has been further improved, e.g. a powerful mass spectrometer was recently acquired in cooperation with the BPE group (U. Reichl). The acquisition of an X-ray diffractometer is also in progress, in cooperation with the PCP group (K. Sundmacher), which will allow us to study, for example, crystal structures and phenomena of polymorphism in more detail.

2. Members of the PCF Research Group

As of April 30, 2003, the group of Prof. Seidel-Morgenstern consists of 5 scientists with a Ph.D. (including 4 postdocs) and 8 graduate students working on their Ph.D. (2 of them in joint projects with a foreign university). The scientific and technical staff is summarized below:

Dr. rer. nat. H. Lorenz	(Staff scientist, permanent, Particulate systems, since 01.10.1998)
Dr. A. W. Mahoney	(postdoc, Population balance systems, from 03.07.2001 to 28.11.03)
Dr. R. Wu	(postdoc, Capillary Electrochromatography, since 15.08.2002)
Dr. Y. Shan	(postdoc, Gradients in liquid chromatography, since 01.10.2002)
Dipl.-Ing. M. Elsner	(postdoc, Ph.D. exam pending, Crystallization by entrainment, since 01.01.2003)
Dr. J. Yang	(postdoc, Mass transfer through porous media, since 01.01.2003)
Dipl.-Ing. A. Perlberg	(Ph.D. student, Kinetics of crystallization, since 01.11.1999)
Dipl.-Ing. M. Kaspereit	(Ph.D. student, Competitive Adsorption and preparative chromatography, since 17.01.2000)

Dipl.-Phys. D. Hlushkou	(Ph.D. student, Hydrodynamics in capillaries, since 01.05.2002)
Dipl.-Ing. M. Paces	(Ph.D. student, Prague, Czech Republic, Theory of Capillary Electrochromatography, since 01.07.2002)
Dipl.-Chem. A. Seebach	(Ph.D. student, Chiral membranes, since 15.07.2002)
Dipl.-Chem. P. Viberg	((Ph.D. student, Lund, Sweden, Chromatography and Time of flight- Mass spectrometry, since 12.09.2002)
Dipl.-Ing. C. Hamel	(Ph.D. student, Membrane reactors, since 01.11.2002)
Dipl.-Chem. E. Rapp	(Ph.D. student, Capillary Electrochromatography and mass spectrometry, since 01.02.2003)
J. Kaufmann	(Technician, since 01.02.1999)
T. Wolff	(Technician, since 01.11.2001)
J. Protzmann	(Technician, since 01.01.2002)
A. Raasch	(Secretary, since 15.07.2002)
K. Mewes	(Trainee, since 24.03.2003)

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

Juniorprofessor U. Tallarek, Dipl.-Ing. D. Beltcheva, Dipl.-Chem. G. Chen, Dipl.-Ing. K. Gedicke, Dipl.-Ing. L. Gueorguieva, M.Sc. M. Joshi, Dipl.-Chem. F. Leinweber, M.Sc. M. Phong, Dipl.-Ing. D. Sapoundjiev, Dipl.-Ing. S. Thomas, Dipl.-Ing. A. Tota, Dipl.-Ing. B. Vollbrecht, M.Sc. T. Vu Dinh

3. Survey of Research Projects

The current research projects are summarized below in tabulated form. Since most of them 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 (the names of the corresponding scientists are indicated with *).

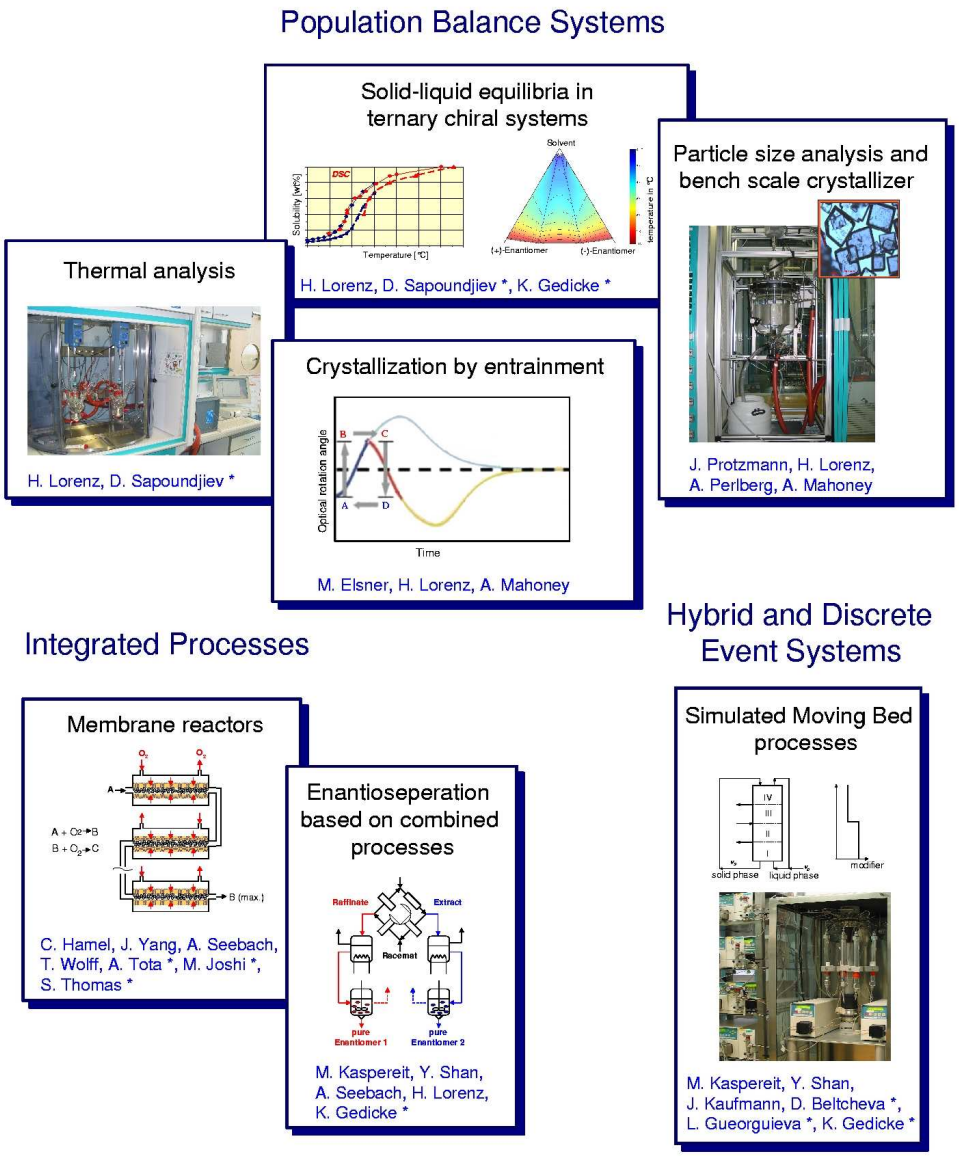


Fig. 50: Survey of research areas and projects of the PCF group

Project Area: Population Balance Systems

Title	Scientists	Funded by	Start	Partners
Project: **Crystallization**	Our work in the area of crystallization is currently focused on the theoretical and experimental study of the separation of enantiomers applying several techniques. A bench scale unit is under construction that can also be used by other MPI groups to study the dynamics of continuous crystallization.			
Subproject: Thermal analysis	H. Lorenz D. Sapoundjiev*	Pro-3 MPI	1999	OvGU IIT Chicago Prof. Myerson
Subproject: Solid-liquid equilibria in ternary chiral systems	H. Lorenz, D. Sapoundjiev*	BMBF MPI	1999	OvGU Schering AG
Subproject: Particle size analysis	A. Perlberg A. Mahoney H. Lorenz	MPI	2000	MPI
Subproject: Crystallization kinetics of enantiomers	A. Perlberg A. Mahoney H. Lorenz	MPI	2000	OvGU
Subproject: Crystallization by entrainment	H. Lorenz M. Elsner A. Mahoney	MPI	2002	Uni Rouen Prof. Coquerel
Subproject: Bench scale crystallizer	J. Protzmann H. Lorenz A. Perlberg	MPI	2001	MPI [SCT, PSD]

Project Area: Hybrid and Discrete Event Systems

Title	Scientists	Funded by	Start	Partners
Project: **Simulated moving bed (SMB) processes**	Chromatographic separations can be performed in a continuous manner using the simulated moving bed process. Our research work in the area of SMB is focused on exploiting gradient concepts and on studying the potential of modulating certain process parameters during the shifts.			
Subproject: Determination of adsorption isotherms	M. Kaspereit J. Kaufmann K. Gedicke*	MPI	2000	OvGU, Uni Belgrad Prof. Petkovska
Subproject: Gradient chromatography	Y. Shan D. Beltcheva* L. Gueorguieva*	Sachsen/ Anhalt MPI	2000	Uni Rzeszow Dr. Antos
Subproject: SMB concepts based on modulations during shifts	M. Kaspereit	Pro-3 MPI	2000	OvGU Uni Veszprem Prof. Szanya MPI ^{PSD}

Project Area: Integrated Processes

Title	Scientists	Funded by	Start	Partners
Project: **Membrane reactors**	The work is focused on studying the potential of membrane reactors for dosing reactants in order to enhance the selectivity in complex reactions. In the subprojects, the rates of chemical reactions and mass and heat transfer processes are studied experimentally and theoretically. Currently, partial oxidation reactions are main objectives. Porous membranes are applied in various configurations to supply oxygen in an optimized manner.			

Subproject: Characterization of Catalysts and determination of reaction rates	C. Hamel M. Joshi*	DFG MPI	2000	OvGU MPI [PCP, PSD] FHI (MPG) Prof. Schlögl
Subproject: Mass and heat transfer through porous media	J. Yang A. Seebach D. Hlushkou U. Tallarek*	DFG MPI	1998	OvGU Czech Ac. Sci. Dr. Uchytil MPI [BPE]
Subproject: Tubular reactors with porous walls	C. Hamel T. Wolff A. Tota*	DFG MPI	2001	OvGU Inocerm GmbH MPI [PSD]
Project: **Enantioseparation based on combined processes**	This projects attempts to combine different processes for enantioseparation in an efficient manner. There are theoretical and experimental research activities for three individual processes (chromatography, crystallization, and membrane separation) and for various possible combinations.			
Subproject: Chromatographic chiral resolution	M. Kaspereit Y. Shan K. Gedicke*	BMBF	1998	OvGU Schering AG MPI [MF]
Subproject: Crystallization of industrial samples	H. Lorenz K. Gedicke*	BMBF	2001	OvGU Schering AG Axiva GmbH
Subproject: Chiral membranes	A. Seebach	MPI	2002	Technical Uni Berlin Dr. Brüggemann
Subproject: Chromatography and subsequent crystallization	M. Kaspereit H. Lorenz K. Gedicke*	BMBF	2000	OvGU Schering AG
Subproject: Membrane separation and subsequent crystallization	H. Lorenz A. Seebach	MPI	2002	OvGU

Project: **Combining electro-chromatography and mass spectrometry**	Capillary electrochromatography (CEC) and modern TOF-mass spectrometry (MS) possess a large resolution poten-tial. CEC is studied in the project experimentally and theo-retically. Using the MS in direct combination with CEC offers the potential to efficiently analyze complex mixtures of larger molecules (e.g. proteins).			
Subproject: Analysis of the dynamics of electro-chromatography	E. Rapp D. Hlushkou M. Paces R. Wu U. Tallarek*	DFG MPI	2000	OvGU Uni Prague Prof. Marek E. Merck MPI [BPE]
Subproject: Coupling CEC and TOF-MS	P. Viberg, E. Rapp, U. Tallarek*	MPI	2002	OvGU, E. Merck MPI [BPE]

Further projects

Title	Scientists	**Funded by**	**Start**	**Partners**
Project: **Nonlinear Chromatography**	A. Seidel-Morgenstern	NATO (Linkage grant)	2001	Uni Ferrara Uni Pardubice Uni Veszprem Uni Knoxville OvGU

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. To understand, to quantitatively analyze and to optimize the under-lying processes, a large number of physical and chemical data and parameters has to be known. Although there are data banks available and theoretical concepts allow the prediction of certain physical and chemical parameters, their experimental determination is of immense importance. This is particularly true for complex molecules currently isolated in large diversity from natural products or synthesized daily by organic chemists. To characterize such molecules and to design processes that involve these molecules, the measurement of numerous

thermodynamic and kinetic data is required. Thus, one goal of the PCF group is to determine physical and chemical data and parameters that are related to the chemical engineering and bioengineering processes investigated at the MPI. Due to their importance in the understanding and design of separation and reaction processes there are currently activities to determine 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, there are different experimental techniques and equipment in use. Besides the application and improvement of established techniques, the goal is, in particular, to develop new concepts that allow the determination of reliable data in less time and with lower requirements concerning the sample amounts. One project is concerned with the elaboration of a new method allowing the measurement of the relation between the solubility of a certain substance, the type of solvent and the temperature. The method is based on heating a saturated solution of the substance of interest in a reaction calorimeter, at a sufficiently small heating rate, ensuring the attainment of equilibrium. The thermal effect resulting from the dissolution process is recorded continuously and applied to determine the solubility temperature. In Fig. 51, heat flow curves measured for different mixtures of a pharmaceutical compound in acetonitrile as solvent are shown. The solubility temperature can be taken from the curve offset (T_{off}) as indicated. Further development of the calorimetric method for solubility determination was directed toward the investigation of the “solubility curve” over a broad range of temperatures from a single calorimetric run to significantly shorten the experimental time effort. The principle is illustrated in Fig. 51 (right), where the measured heat flow is presented together with the derived solubility curve. For comparison, independently obtained solubility data are given. Results covering different chemical systems and an evaluation of the potential of the promising new method are summarized in [1-3].

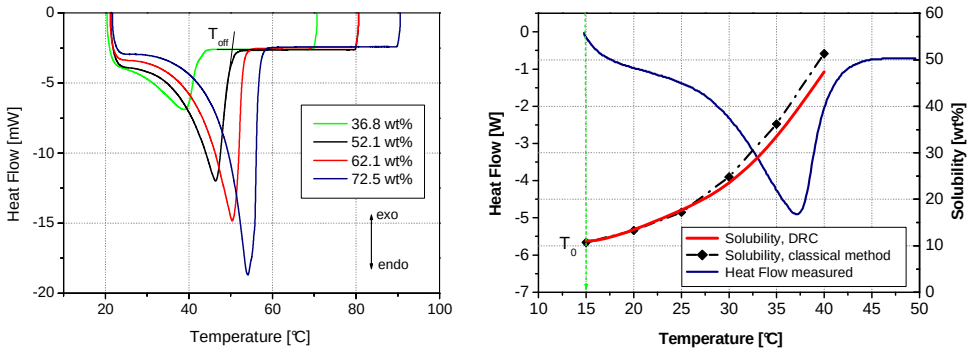


Fig. 51: Left: Differential Scanning Calorimetry (DSC) curves for solutions of different concen-tration of a pharmaceutical intermediate in acetonitrile (DSC 111/Setaram, 68-78 mg sample mass, heating rate 1 K/min). Right: Determination of the solubility curve from a single calorimetric experiment (reaction calorimeter DRC/Setaram, 40 wt% rac. mandelic acid in water, total sample mass 70 g, heating rate 0.5 K/min) [1, 3].

In another project, the growth of crystals in a solution was observed using laser optical techniques. Focused beam reflectance measurements (FBRM, Lasentec®) were used for inline size determination in particulate systems. The measurement principle allows the determination of chordlength distribution data, which cannot readily be compared with results from other particle size measurement techniques such as microscopic image analysis or laser diffraction. This technique is therefore an object of research activities in the field of measuring particle size distributions. Fig. 52 (left) shows the application of a FBRM probe in an isothermal crystal growth experiment using mandelic acid in water.

Fig. 52 (right) demonstrates results regarding a calibration of the FBRM. The cube weighted median chordlength was used as an indicator for the size increase of initially added seed crystals. The expected particle size distribution was obtained using parallel microscopic image analysis. The reconstructed particle size distribution was extracted from the chordlength distribution data of the same sample using a calibrated kernel [4]. The transformation shows good results at particle populations > 200 µm.

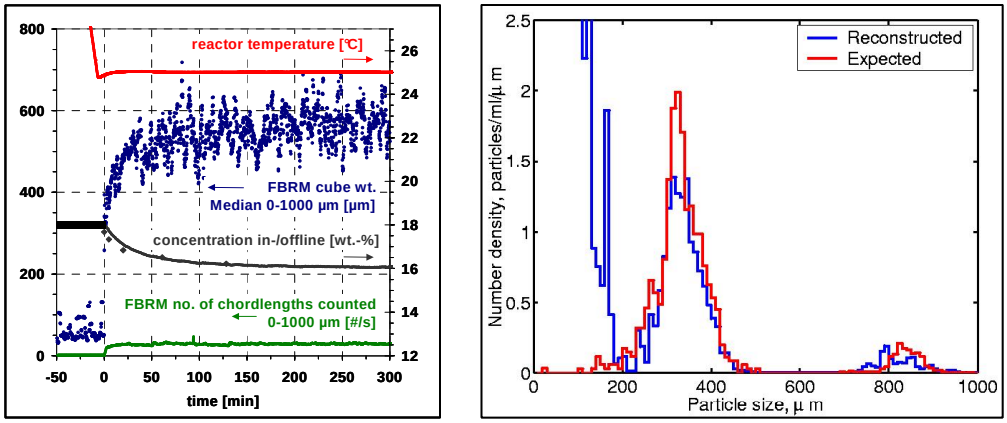


Fig. 52: Left: Isothermal crystal growth experiment for determination of growth kinetic parameters, time = 0 min: seed crystals of a specific size fraction are added to a supersaturated solution, FBRM no. of chordlengths counted: confirms pure growth without spontaneous nucleation, concentration (offline): density measurements, concentration (inline): acoustically determined. Right: Comparison of expected and reconstructed particle size distribution based on FBRM measurements [4].

To understand the chromatographic separation of enantiomers it is essential to know the adsorption isotherms that form the driving force for the separation process. Since in the process of developing new drugs the amount of pure substances is usually very small, we are trying to develop methods that generate reliable data with a minimum amount of sample material. Typical results of applying a perturbation method [5,6] are summarized in Fig. 53. In collaboration with the University of Belgrade (Prof. Petkovska) a method was developed which is based on the frequency response analysis of a fixed-bed filled with the adsorbent. The inlet concentrations are periodically altered between two constant levels and the responses are recorded using suitable detectors. From these responses the adsorption isotherms can be extracted [7].

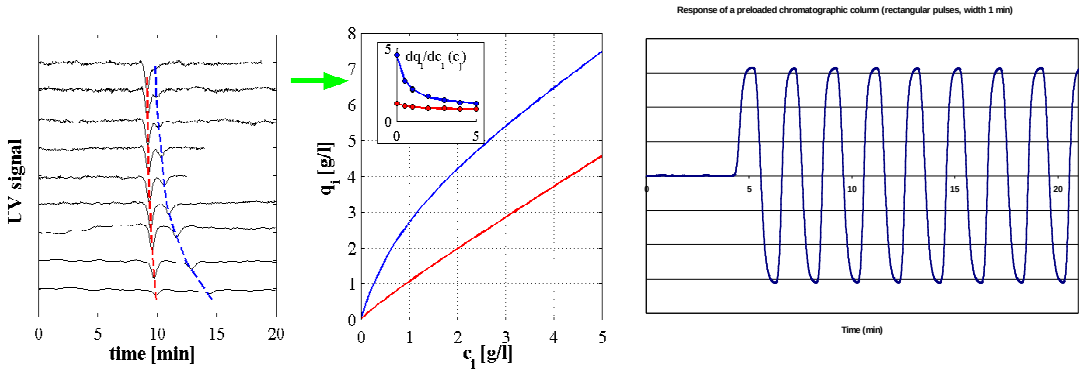


Fig. 53: Left: Determination of isotherm parameters by perturbation method. The retention times of small perturbations applied to a column equilibrated on different concentration levels can be related to the local derivatives of an isotherm model (centre, inset) [5, 6]. Right: Primary data for a frequency response analysis of a chromatographic column [7].

Several projects are devoted to quantifying and analyzing concentration changes in reacting systems in order to determine and model rates of chemical reactions. As an important basis for the project “Membrane Supported Reaction Engineering” in cooperation with the PSD group (A. Kienle) the rate of the oxidative dehydrogenation of ethane to ethylene was studied experimentally by applying a $VO_X/\gamma\text{-}Al_2O_3$-catalyst (1.37 % V, 167 m^2/g). By analyzing fixed-bed experiments performed in a wide temperature and residence time range the reaction network given in Fig. 54 (left) was postulated and the individual reaction rates r_1-r_5 were quantified [8]. In Fig. 54 (right) experimental and predicted conversion data for a fixed-bed reactor validating the derived kinetic equations are given [9].

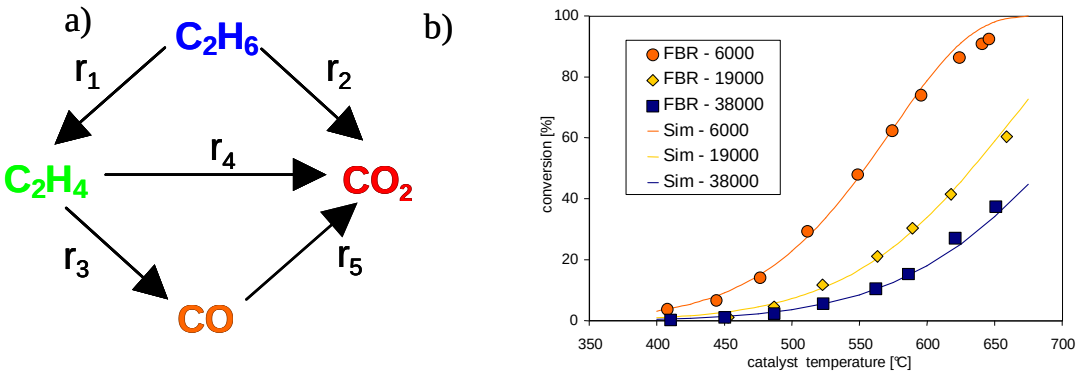


Fig. 54: Quantified reaction network of the oxidative dehydrogenation of ethane and predicted (Sim) versus measured conversions in a fixed-bed reactor (FBR) for several residence times (in s^{-1}) [8, 9].

4.2. Analysis and Design of Separation and Reaction Processes

The PCF group is currently investigating several separation and reaction processes in detail. A main topic is the development and design of processes capable of isolating and purifying fine chemicals. A particularly difficult task in this area is the separation of enantiomers. These are pairs of molecules which are, like our hands, mirror images of each other. To produce certain drugs, the pharmaceutical industry frequently needs the pure enantiomers. In order to isolate the desired species, special crystallization processes, membrane separation and preparative chromatography are investigated.

Mandelic acid has been chosen in several projects as a model system. Studies of the solid liquid equilibira revealed that this acid belongs to the compound forming systems, i.e. the racemate cannot be resolved by crystallization procedures alone [10]. However, an asymmetric mixture with an initial enantiomeric composition exceeding the eutectic one, may be used to obtain the enantiomer in excess with high purity by applying a suitable

crystallization procedure. Fig. 55 shows the ternary solubility phase diagram determined for the mandelic acid/water system [11,12]. The region that can be used to gain the (+)-enantiomer is indicated by the yellow triangle bordering on the 60℃-isotherm. A typical experiment is also presented. An aqueous solution of mandelic acid with an enantiomeric excess of about 59% of the (+)-species was subjected to a cooling crystallization procedure. The separation process was performed in a batch of 2 liters and initiated by seeding. The on- and offline measured process data shown, clearly describe the course of the crystallization process. The purity of the (+)-mandelic acid obtained was 99.3% [13].

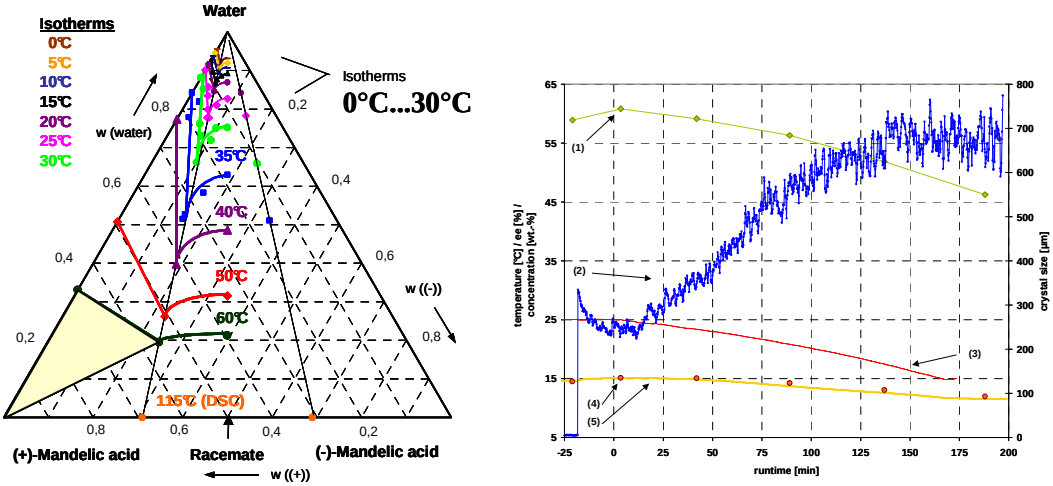


Fig. 55 Left: Ternary solubility phase diagram of the mandelic acid enantiomers in water [10 – 12]. Right: Batch crystallization experiment for purification of an asymmetric mixture of mandelic acid in water ((1) enantiomeric excess of solution (ee) , (2) median crystal size (FBRM), (3) temperature profile in the crystallizer, (4) solute concentration (offline, density measurements), (5) solute concentration (inline, acoustically determined)) [13].

An attractive alternative to performing conventional crystallization in the two phase region is to produce pure enantiomers using crystallization by entrainment in the three phase region. The applicability of the process is restricted to conglomerate forming enantiomeric systems. The principle of the "preferential crystallization" process is illustrated in Fig. 56.

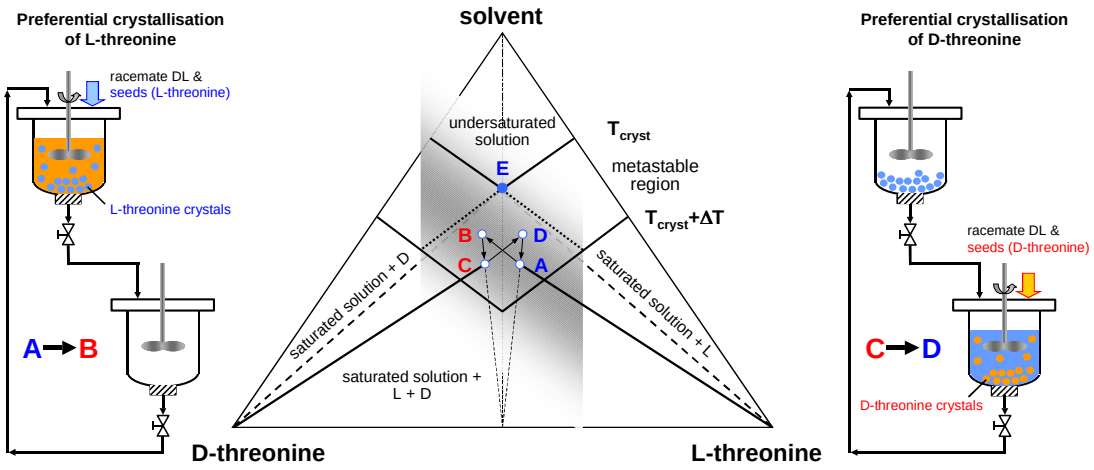


Fig. 56: Principle of the preferential crystallization and a possible quasi-continuous operation mode.

In equilibrium the liquid phase will have racemic composition (point E) and the solid phase will consist of a mixture of crystals of both enantiomers. However, as the system approaches equilibrium under special conditions it is possible to preferentially produce just one of the enantiomers after seeding with homochiral crystals. The process is based on the specific driving forces due to the different supersaturations and initial surface areas of each enantiomer. The goal of our work is to study the preferential crystallization process systematically and to develop a new quasi-continuous operation mode. In the first experiments, the amino acid threonine was used as a model system. Reliable thermodynamic data (like the metastable zone width and the ternary solubility phase diagrams of threonine in the used solvents) and knowledge of the temporal concentration changes of the enantiomers during the process are required for a successful operation and for a mathematical description of the process. Preliminary experimental results using a newly developed on-line polarimetry technique in combination with refractometry proved the general applicability of this process [14]. The technique developed enables us to follow the resolution process directly and to recognize the limit of the region of "safe" resolution (Fig. 57).

In order to study crystallization processes on a larger scale, a 20 liter mini-plant unit was set up. Besides performing enantioselective crystallization processes this unit will also be used by the PSD group (A. Kienle) and the SCT group (J. Raisch) to study issues related to crystallization dynamics and control of particle size distributions.

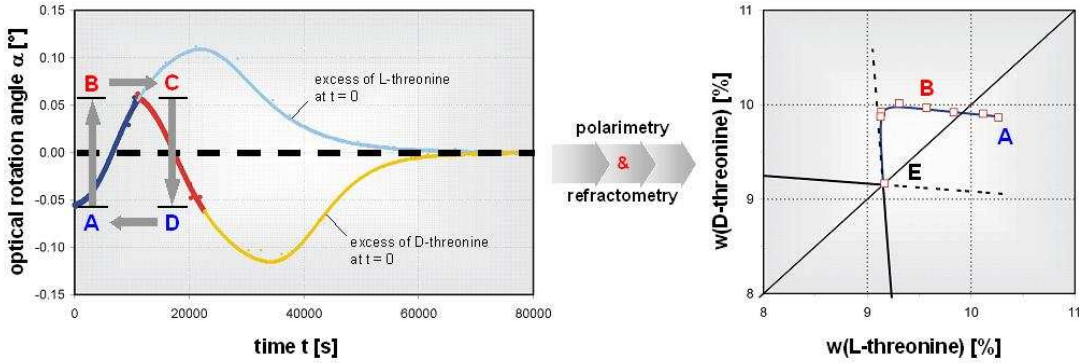


Fig. 57: Left: Polarimetric signal for the resolution of both enantiomers. Right: Phase diagram for the preferential crystallization process with an excess of L-threonine at the beginning (point A) [14].

As a powerful alternative to enantioselective crystallization, simulated moving bed (SMB) chromatography is being investigated. This is a periodically operated multi-column countercurrent process which possesses several interesting features. In our group we are interested in improving the performance of conventional isocratic SMB processes with constant operating parameters. One concept under investigation is the introduction of streams with different solvent strength. These gradient concepts possess the potential to reduce the overall solvent amount required for the separation and to deliver more concentrated product streams [15-17]. In collaboration with the PSD group (A. Kienle) a new operation mode was developed which is based on a periodic variation of the feed concentration during the shift period. This mode exploits the concentration dependence of the migration speeds of concentration fronts in fixed-beds under nonlinear conditions. Compared to the conventional technology using constant feed concentrations, a higher productivity can be achieved and the solvent consumption can be reduced [18-21]. Fig. 58 shows that under the influence of a forced feed concentration variation the concentration fronts in the unit change their position allowing the operation of the process under different conditions. The task of optimizing these more sophisticated SMB processes is currently being studied in cooperation with Profs. Tobiska and Weismantel (Magdeburg University, Faculty of Mathematics) in the framework of a DFG research group. For experimental investigations, a SMB mini-plant unit has been set up at the MPI.

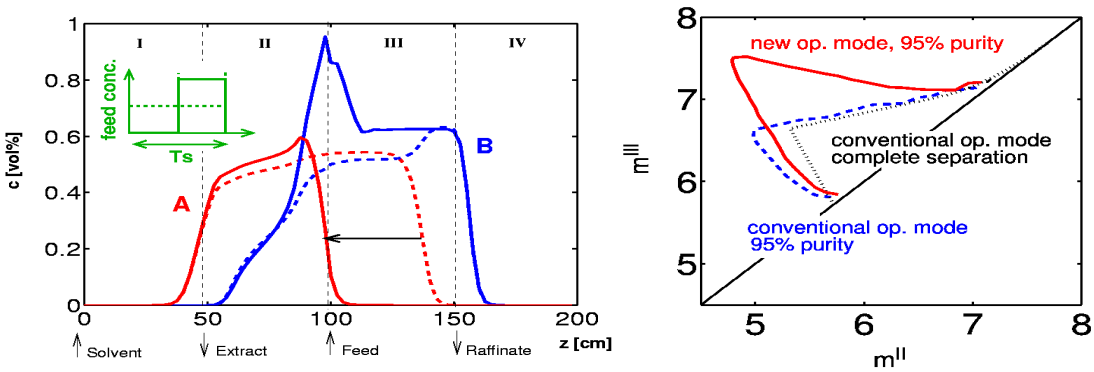


Fig. 58: Left: Effect of a non-constant feed concentration on the internal concentration profiles in a SMB unit. Right: Corresponding changes of the area of possible operation parameters ("separation region") [18 – 21].

In cooperation with U. Tallarek (OvGU) in recent years, several aspects of chromatographic separation have been investigated: the application of smaller column dimensions (capillaries) to reduce sample amounts and time for analysis, monolithic stationary phases to reduce pressure drops, and electric fields to increase separation efficiencies. In all these innovative areas, cooperations have been established (e. g. with Prof. Marek in Prague and the company E. Merck in Darmstadt) and initial experimental and theoretical results have been obtained [22-25]. In cooperation with the BPE group (U. Reichl) the effects of diffusion, electroosmosis and electrophoresis have been studied using Confocal Laser Microscopy. Fig. 59 illustrates the observed pronounced differences of the concentration profiles of charged and uncharged analytes in a porous sphere during desorption under the absence and presence of an external field [26]. The results demonstrate the large potential of driving the flow in an optimized manner by electric fields and/or pressure.

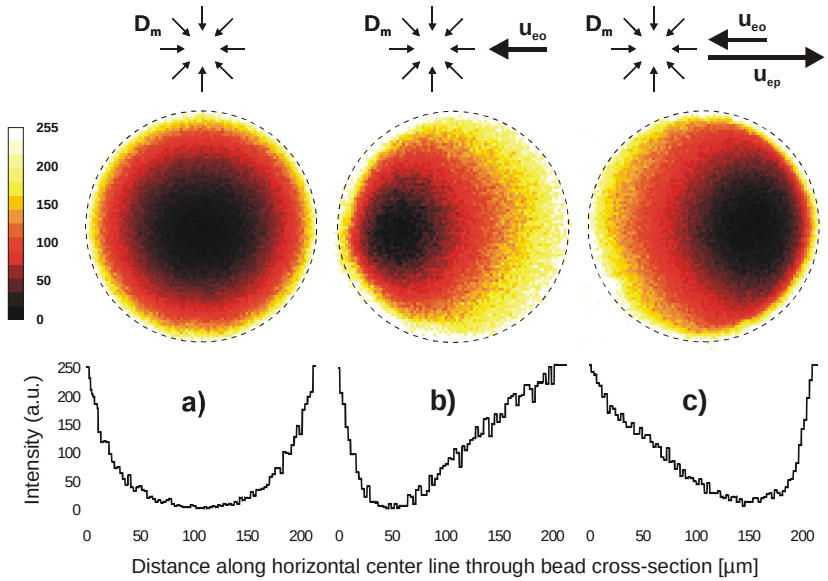


Fig. 59: Distribution of fluorescent molecules in a porous glass bead during intraparticle transport by diffusion (left) diffusion and electroosmosis (center) and diffusion, electroosmosis and electrophoresis (right) [26].

4.3. Integration and Combination of several Processes

At the MPI, several types of process integration are being investigated. This offers the possibility for various cooperations. It is a future goal to develop, based on several examples, a more comprehensive and general understanding of such processes.

One example studied in our group is the combination of reaction and adsorptive separation in a chromatographic reactor. In this area, together with the university group, the reaction rates of several heterogeneously catalyzed hydrolysis reactions are determined based on calorimetric measurements. Complementary, adsorption isotherms on the same catalysts are determined using the methods described above. Initial results of studying the combined process prove the necessity of a careful adjustment of the two key process [27].

Another area of interest for us is to apply possible techniques for enantioseparation in a coupled manner. An example is illustrated in Fig. 60 where continuous SMB chromatography is used first to deliver partially enriched products [28]. The desired final purity is then achieved through enantioselective crystallization. This arrangement improves the overall performance compared to the exclusive application of the expensive chromatographic step [29].

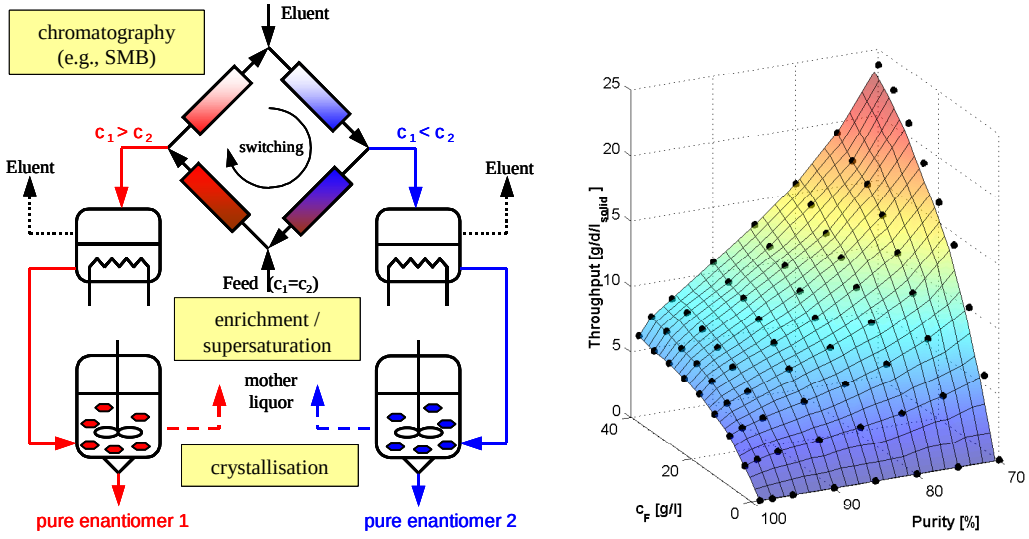


Fig. 60: Example for two coupled separation processes. A racemic feed is partially resolved by SMB-chromatography and then split into the pure enantiomers by subsequent enantioselective crystallization (left). Numerical simulation for a pharmaceutical compound reveal the possibility of substantially increased productivity of the chromatographic step (right) [28, 29].

A larger research project is devoted to use membranes in reactors. Initially the focus was the selective removal of a certain product through a porous reactor wall [30,31]. Currently, intensive activities are devoted to studying the possibility of dosing one or more reactants into the reactor via membranes. These types of membrane reactors possess the potential to improve the selectivity with which a certain intermediate product can be obtained. The concept is, in particular, interesting for performing partial oxidation reactions or selective hydrogenations. In cooperation with membrane producers and the group of Dr. Uchytil (Prague) the mass transfer properties of various porous ceramic composite membranes have been studied and quantified [32].

Important questions that need to be answered in order to develop and evaluate the membrane reactor concept are currently being investigated in several groups at the MPI in close cooperation with several groups at the Otto von Guericke University and funded by the German Research Foundation (Forschergruppe “Membranunterstützte Reaktionsführung”). Joint issues that are studied experimentally and theoretically are, for example, heat transfer and cooling problems, mathematical problems related to a proper formulation of boundary conditions at porous walls, and the comparison of fixed-bed and fluidized-bed reactors.

In the PCF group in particular the application of a series connection of several fixed-bed reactor segments is being analyzed. Based on the determination of the reaction rates for the

ethane oxidation on supported VO_x catalysts and a developed mathematical model for this type of reactor, optimal dosing profiles were calculated. The results obtained deliver some generally applicable rules for a successful reactor operation. The applicability of the reactor concept has also already been proven experimentally [33]. Typical results of experiments carried out in a one stage membrane reactor (PBMR) and in a fixed-bed reactor (FBR) are shown in Fig.61. The oxygen dosing in the PBMR led to significant improvements in the ethylene selectivity in comparison to the FBR operation where all reactants were fed together at the reactor inlet. In cooperation with Prof. Pushpavanam (IIT Madras) it was further shown theoretically that besides adjusting local oxygen concentrations also the residence time behavior of the different reactants has to be carefully analyzed [34]. Fully optimised, the reactor concept is capable of delivering highly favorable selectivity-conversion characteristics (Fig. 61 b) [35].

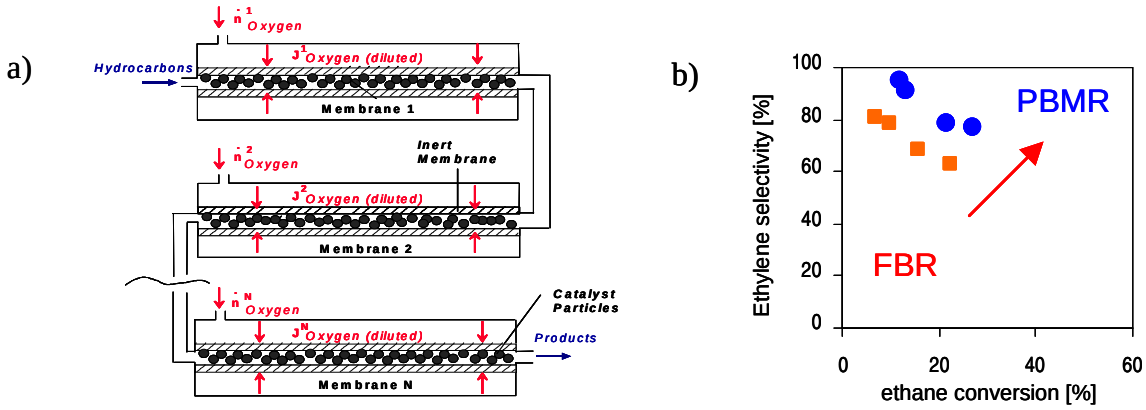


Fig. 61: a) Experimental setup of a packed bed membrane reactor (PBMR), b) Performance of fixed bed reactor (FBR) and PBMR [33, 35].

At the MPI there is intensive cooperation within the membrane reactor project with the PCP group (K. Sundmacher) which is studying electrochemical membrane reactors and the PSD group (A. Kienle) which is studying reaction kinetics and developing modular models for various types of membrane reactors.

5. Selected Teaching Activities, Ph.D. Projects

5.1. Lectures of Prof. A. Seidel-Morgenstern:

- Chemical Reaction Engineering (OvGU, summer term, in German and in English)
- Chemical Process Technology (OvGU, summer term, with Prof. H. Rau and Dr. H. Lorenz, in German)
- Adsorption and Heterogeneous Catalysis (OvGU, winter term, in German)
- Numerical Methods in Chemical Process Engineering (OvGU, winter term, in German)
- Safety Analysis of Chemical Reactions (OvGU, winter term, in English)

5.2. Lectures of Dr. H. Lorenz:

- Chemical Process Technology (OvGU, winter term, with Prof. H. Rau and
- Seidel-Morgenstern, in German)
- Technical Chemistry (OvGU, winter term, with Prof. H. Rau, in German)
- Technical Chemistry in Chemical and Process Engineering (OvGU, winter term, in English)
- Solid-Liquid Equilibria (University of Rouen, France, summer term 2002, in English)

5.3. Selected Ph.D. Projects

- Perlberg, “Growth rates in enantioselective crystallization”
- M. Kaspereit, “Analysis of competitive adsorption equilibria”
- Seebach, “Chiral membranes”
- Hamel, “Analysis of a multistage membrane reactor”
- P. Hamera, “Removal of aromatic components from water by adsorption on immobilized
- β-cyclodextrines”, 1998
- H. Kniep, “Comparing different concepts to perform preparative liquid chromatography“, 1998
- Tuchlenski, “Characterization of membranes and their application in membrane reactors“, 1999
- O. Schramm, “Performing reversible reactions in membrane reactors“, 2000
- K. Mihlbachler, “Enantioseparation via SMB chromatography: A study of Tröger’s base unique adsorption behaviour and the influence of heterogeneity of the column set on the performance of the SMB process”, 2002
- T. Falk, “Analysis of a chromatographic reactor”, submitted

- Schlinkert, “Determination of reaction rates from chromatographic responses”
- N. Emberger, “Selective oxidation of butane”
- S. Thomas, “Determination of optimal dosing profiles for membrane reactors”
- Vollbrecht, “Kinetics of the methanol synthesis under transient conditions”
- Tóta, “Membrane reactors for partial oxidations”
- F. Leinweber, “Monoliths in chromatography”
- M. Joshi, “Reaction rates in catalytic-partial oxidation”
- D. Beltcheva, “Experimental study of gradient simulated moving bed chromatography”
- L. Gueorguieva, “Gradient Elution chromatography”
- G. Chen, “Experimental investigation of capillary electrochromatography”
- K. Gedicke, “Coupling crystallization and chromatography for enantioseparation”
- M. Phong, “Reaction calorimetry to determine reaction rates”
- T. Vu Dinh, “Hydrolysis reactions in a chromatographic reactor”
- D. Sapoundjiev, “Determination and analysis of solid-liquid equilibria”

5.4. Habilitations

- H. Lorenz, ”Particulate systems in combustion and crystallization processes“, in preparation

6. Selected Memberships, Appointments and Awards

6.1. Andreas Seidel-Morgenstern

08 / 1998	Appointment as a 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,	Award of Faculty of Process and Systems Engineering (OvGU)
2000	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

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

10 / 2002 Chairman of the International Symposium of Preparative and Industrial Chromatography (SPICA) in Heidelberg

6.2. Heike Lorenz

1998 Grant of state of Sachsen Anhalt to support Habilitation

1999 Award for Young Researcher in Technical Chemistry (DECHEMA)

6.3. Christof Hamel

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

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Research Group:

Bioprocess Engineering (BPE)

Prof. Dr.-Ing. Udo Reichl

This report covers the period between July 1999 and April 2003.

1. BPE Group Introduction

The activities of the BPE Group began in Summer 2000 with the appointment of U. Reichl as Director and Scientific Member of the Max Planck Society. Until September 2001 laboratories in the Zenit building (Magdeburg) were shared with researchers of the newly established Chair of Bioprocessing at the OvGU. The focus during this period of time was to structure and organize research activities, select and order laboratory equipment such as bioreactors, cell cultivation systems, instruments for on- and off-line analysis, and coordinate the prerequisites for safety levels S1/S2 with local authorities. The main emphasis was on the establishment of animal cell culture technology and virology, set-up of first experiments in microcarrier cultures at 4 to 20 L working volume, downstream processing e.g., crossflow-filtration or chromatography, and method validation. In parallel, several course lectures, special lectures, laboratory courses and seminars at the Faculty for Process and Systems Engineering in Magdeburg were prepared. Due to the restrictions in laboratory (50 m^2) and office capacity, the number of scientists (2) and non-scientific staff (4) increased slowly and totaled 6 employees in September 2001.

With the completion of the new Institute building in September 2001, the spatial conditions improved significantly. Today the BPE Group shares about 400 m^2 of laboratory space at safety levels S1 and S2 with the SBI Group. An additional 100 m^2 of S2 laboratories are available for research of the Chair of Bioprocessing. Start-up in the new laboratories took only a few weeks and the first experiments with animal cell cultures and viruses started in November 2001. Since then we have realized a major expansion of our experimental and analytical methods for studying animal cell culture processes in detail. The main focus is on the analysis of growth of adherent cells (primary and transformed cell lines) in various static systems and bioreactors up to 20 L, detailed studies of virus replication in animal cell culture for vaccine production, microscopical investigations of viral infections in single cells and cell populations, mathematical modeling of relevant aspects of the bioprocesses at the bioreactor and the cellular level, and optimization of downstream processing methods, in particular preparative chromatography.

2. Members of the BPE Research Group

As of April 30, 2003, the research group BPE consisted of 3 scientists with PhDs, 5 PhD students, several diploma students, and technical assistants.

Composition of BPE Group as of 30 April 2003

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.D. Prasad Nayak	Post doc	Chemical Engineering	01.02.2002
L. Antoniukas, MA	PhD student	Biology	01.01.2003
Dipl.-Ing. A. Bock	PhD student	Process Engineering	01.03.2003
Dipl.-Ing. R. Danova	PhD student	Chemical Engineering	01.01.2002
Dipl.-Ing. (FH) J. Schwarzer	PhD student	Analytical Chemistry	15.01.2003
I. Sidorenko, M.Sc.	PhD student	Mathematics and Physics	01.08.2001
Technical Staff			
Dipl.-Ing. (FH) I. Behrendt	Technican	Biotechnology	01.07.2001
S. König	Technican	Analytical Chemistry	01.08.2001
Dipl.-Ing. S. Lehmann	Technican	Biotechnology	01.11.2002
F. Hasewinkel	Worker		01.08.2002

At the Chair of Bioprocess Engineering at the OvGU the head of the research group, Prof. U. Reichl, supervises 6 PhD students (H. Sommer, J. Schmidt, B. Hundt, L. Möhler, M. Pohlscheidt, D. Holtmann) and several diploma students.

3. Survey of Research Projects

The current research projects of the BPE Group are illustrated in Fig.62. More detailed information is collected (see next page) where the projects are classified in correspondence to the project area structure established by the MPI. Projects in collaboration with the Chair of Bioprocess Engineering at the OvGU and with industrial partners are presented at the end of this table.

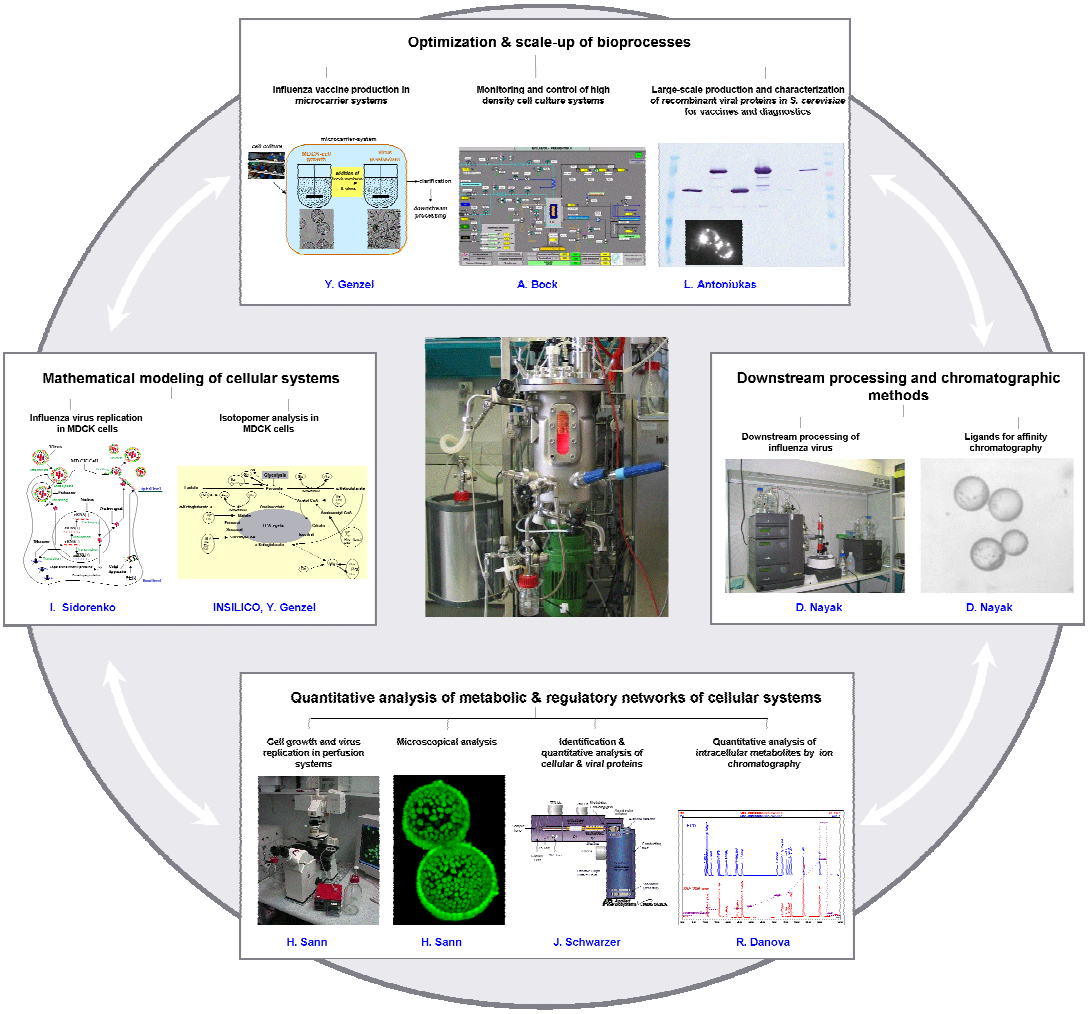


Fig. 62: Survey of BPE research areas and projects.

Survey of research projects of BPE Group

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
Subproject: Large-scale production and characterization of recombinant viral proteins in *S. cerevisiae* for vaccines and diagnostics	L. Antoniukas	MPI	01/2003	Institute of Virology, Charitè, (Berlin), Institute of Biotechnology (Vilnius, Litauen)
Subproject: Monitoring and control of high density cell culture systems	A. Bock	MPI	03/2003	Chair of Bioprocess Engineering
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			

Subproject: Downstream processing of influenza virus	D. Nayak	MPI	02/2002	Chair of Bioprocess Engineering
Subproject: Ligands for affinity chroma-tography	D. Nayak	MPI	02/2002	
Project: Quantitative analysis of metabolic and regulatory networks of cellular systems	• Microscopical 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			
Subproject: Cell growth and virus replication in perfusion systems	H. Sann	MPI	07/2000	
Subproject: Microscopical analysis	H. Sann	MPI	07/2000	
Subproject: Quantitative analysis of energy metabolism of animal cells	R. Danova	MPI	01/2002	
Subproject: Identification & quantitative analysis of cellular & viral proteins	J. Schwarzer	MPI	01/2003	

Project Area: Hierarchical Structures

Project: Mathematical modeling of cellular systems	• Detailed mathematical models for influenza virus replication in MDCK cells • Metabolic flux analysis • Population balances for virus host interactions			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject: Influenza virus replication in MDCK cells	I. Sidorenko	MPI	08/2001	Institute of Numerical Mathematics (Russian Academy of Science)

Projects: Chair of Bioprocess Engineering (OvGU)

Project: Process analysis and process optimization 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: DF
Project: Dynamics of microbial communities J. Schmidt (Start: May 2002)	Mathematical modeling of microbial growth dynamics in batch and continuous culture, use of T-RFLP analysis for identification and quantification of microbial communities, bacterial species of Cystic Fibrosis patients
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: SBI Group.

Projects: Cooperation with other Institutions and Industry

Project: Development of an on-line sensor for the determination of the metabolic activity of microorganisms in biological wastewater treatment plants D. Holtmann (Start: Jan. 2001)	Karl Winnacker Institut der Dechema, Frankfurt, Germany
Project: Isotopomer analysis in MDCK cells Y. Genzel (Start: Sept. 2002)	INSILICO biotechnology GmbH, Stuttgart, Germany
Project: Development of serum free cultivation methods for primary chicken embryo fibroblasts in microcarrier systems B. Hundt (Start: February 2002)	OvGU, Chair of Bioprocess Engineering; Impfstoffwerk Dessau Tornau GmbH, Germany
Project: Development of cultivation methods for large scale pro-duction of mink enteritis vaccines B. Hundt (Start: August 2002)	OvGU, Chair of Bioprocess Engineering; Impfstoffwerk Dessau Tornau GmbH, Germany
Project: Cultivation methods for manufacturing of recombinant HIV vaccines B. Hundt (Start: March 2003)	OvGU, Chair of Bioprocess Engineering; Impfstoffwerk Dessau Tornau GmbH, Germany
Project: Development and establishment of a procedure for virus production in animal cells under suspension conditions M. Pohlscheid (Start: July 2002)	OvGU, Chair of Bioprocess Engineering; Bayer AG, Leverkusen, Germany

4. Research Highlights

4.1. Optimization and Scale-up of Bioprocesses: Influenza Vaccine Production in Microcarrier Systems

Using animal cells in biotechnology requires detailed research to find the right cell for each specific product and process. One can select between primary or transformed cells growing in suspension or on surfaces. After opting for one cell line, cultivation methods (Fig. 63), process conditions and parameters as well as downstream processing methods have to be selected and optimized. Decision criteria for optimization strategies are mostly quantitative data on different aspects of the process in question. Based on a detailed understanding of the biological mechanisms of cell growth and product formation, together with mathematical models of all relevant steps of a bioprocess, an increase in product yield and purity should be achieved. As an example we have started to implement this for a process of equine influenza vaccine production that was previously set up according to an industrial production scheme.

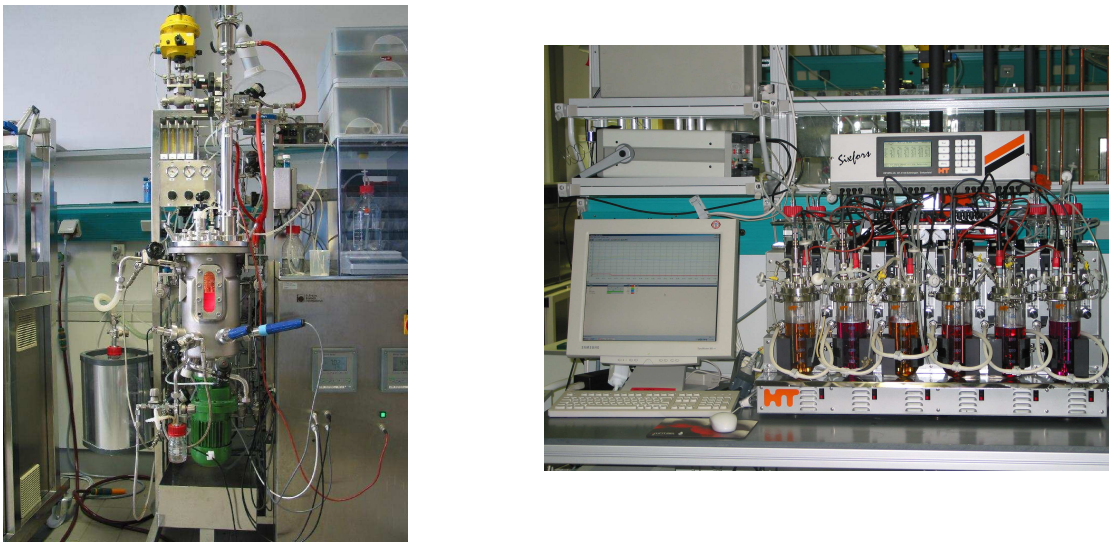


Fig. 63: Two possibilities for controlled cultivation using microcarrier systems in our lab (5 L bioreactor (B. Braun Biotech, Melsungen, Germany) and 6 parallel reactors of 0.5 L (Infors, Basel, Switzerland).

In this case, the host for the influenza virus is an adherent Madin Darby Canine Kidney cell (MDCK), which prefers serum addition during growth, whereas during virus infection, a serum-free medium should be used [1,2]. Dealing with cells growing on a surface in bioreactors, requires the use of microcarriers for scale-up and a short exponential growth phase followed by contact inhibited growth until confluency. At this point the process is stopped to wash the cells and to remove serum constituents that interfere with virus infection.

Fresh serum-free medium is added together with virus-seed and the process is continued. The end of the virus production is the release of viruses, apoptosis and cell breakage.

Using this process, we have set up and validated standard on-line analytics as well as numerous off-line analytical methods (Fig. 64, Fig. 65). In view of using these data for mathematical modeling, we selected new methods that need little sample preparation and are easy to standardize. Monitoring and control is done by PCS7 software (Siemens, Karlsruhe, Germany). As an example for a typical cultivation, the uptake and release of the two major cellular carbon and energy sources, glucose and glutamine, as well as the corresponding metabolites lactate and ammonia are shown in Fig. 64. Different immunological assays are used for the determination of virus yield (HA, $TCID_{50}$, PFU). The cells are counted and the concentrations of most amino acids in the medium are determined (Fig. 65). Additional information like osmolality of the medium as well as phosphate, protein and pyruvate concentrations are collected for specific questions.

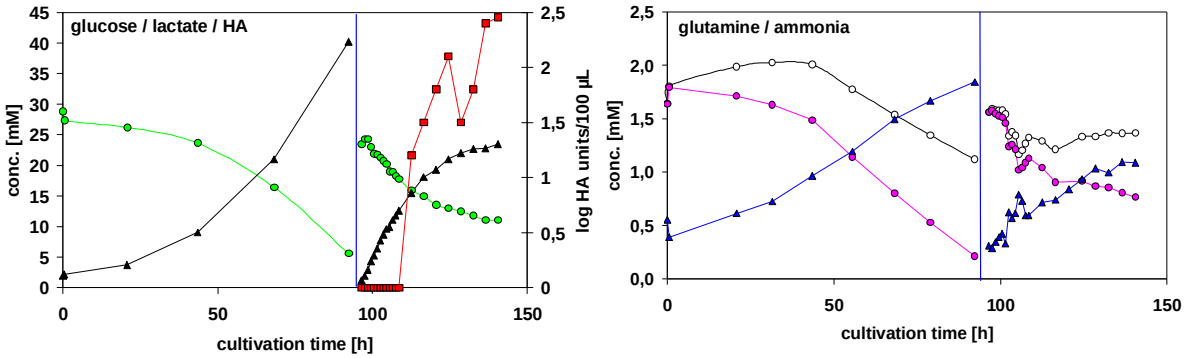


Fig. 64: Profiles of metabolites (left: glucose ●, lactate ▲ and HA ■; right: total glutamine ●, glutamine without chemical decomposition ○ and ammonium ▲) during growth of MDCK cells on microcarriers in a 5 L stirred bioreactor (left side of blue vertical line) and during influenza virus production after medium exchange (right side of blue line); biochemistry analyzer YSI 7100 (YSI, Yellow Springs, USA) and Vitros DT60-II (Ortho Clinical Diagnostics, Neckargemünd, Germany).

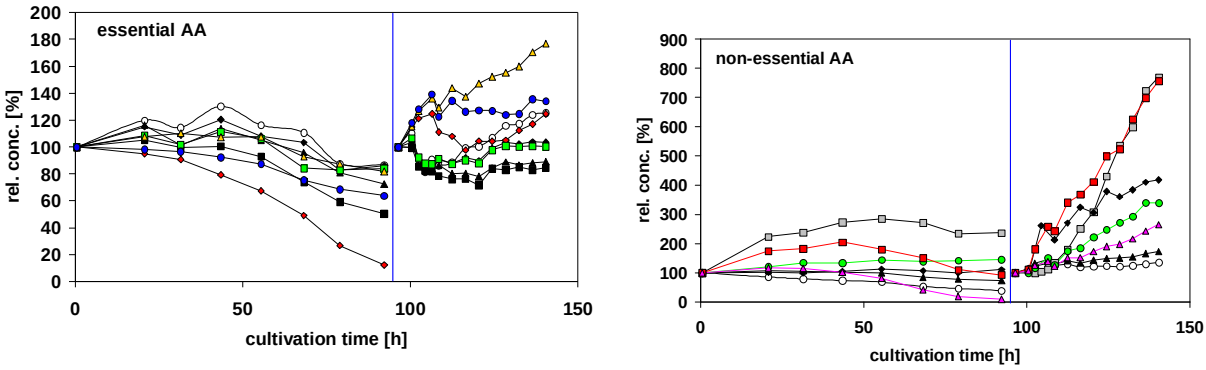


Fig. 65: Profiles of extracellular essential amino acids (○ val ■ leu ▲ ile ● trp ■ phe◆ thr ◆ met ▲ his) and non-essential amino acids (○ cys ■ asn ▲ tyr ● gly ◆ ala ▲ ser ■ pro) (relative concentrations: 100 % = starting concentration at t= 0 h and t= 95 h) during growth of MDCK cells on microcarriers in a 5 L stirred bioreactor (left side of blue vertical line) and during influenza virus production after medium exchange (right side of blue line); anion exchange chromatography & integrated pulsed amperometric detection (Dionex, Idstein, Germany).

These detailed data allow us then, to develop strategies to improve productivity and yield for such a process acting on different levels by:

- optimization of medium composition (glucose, glutamine, amino acids, growth factors, salts, vitamins, etc.) for cell growth and virus replication
- reduction of inhibitor concentration (lactate, ammonia)
- finding optimal carrier and cell densities
- definition of infection strategies (time point of infection, multiplicity of infection)
- determination of process parameters (aeration, stirring, temperature, etc.)
- comparison of different cultivation methods (roller bottles, microcarriers, suspension, perfusion, wave bioreactors®, etc.)
- investigation of scale-up possibilities
- development of monitoring and control strategies (feeding, perfusion, etc.)

4.2. Quantitative Analysis of Metabolic and Regulatory Networks of Cellular Systems: Microscopical Analysis

In viral vaccine production a single mammalian host cell (MDCK) is the smallest production unit. For optimization of the virus production processes we are investigating the host cell growth and the replication of the virus using microscopes.

4.2.1. Growth of MDCK Cells on Microcarriers and in Static Systems

MDCK-cells grow as monolayers on surfaces and are growth limited by contact inhibition. To better understand the growth dynamics in different culture systems and to support mathematical modeling of cellular growth, we quantitatively characterize the growth behavior and describe cellular morphology on the surface of microcarriers both in the bioreactor systems and in static cultures such as T-flasks and roller bottles (Fig. 66).

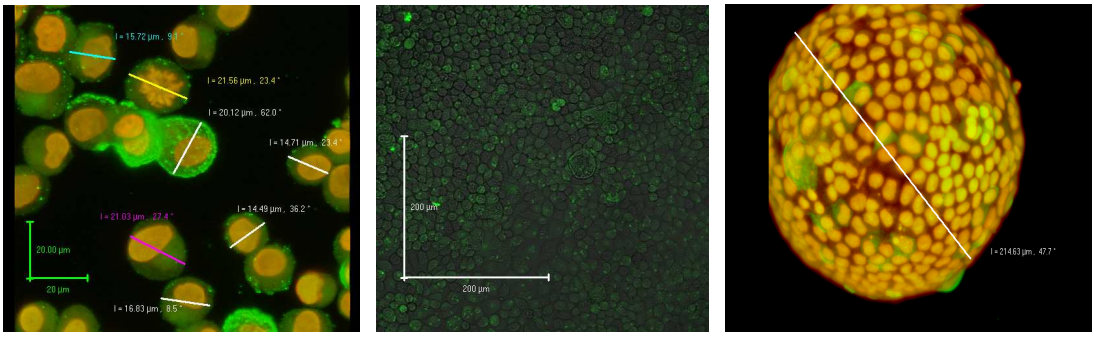


Fig. 66: left: Trypsinated MDCK cells in suspension, mean diameter is 15 µm (Sytox orange nucleic stain); middle: MDCK cells on the surface of a culture flask; right: MDCK cells on a microcarrier, sample from a stirred 5 L bioreactor.

4.2.2. Cell Cultivation Monitored under the Microscope

In addition to the examination of bioreactor or culture bottle samples, it is inter-resting to study the development of host cells under controlled growth conditions directly under the microscope. An inverted microscope equipped with a video camera coupled to an image processing system and an incubator allows us to cultivate cells with controlled atmospheric CO_2, temperature and medium (Fig. 67). Depending on the culture chambers used, several batch and perfusion cultivation strategies are possible.

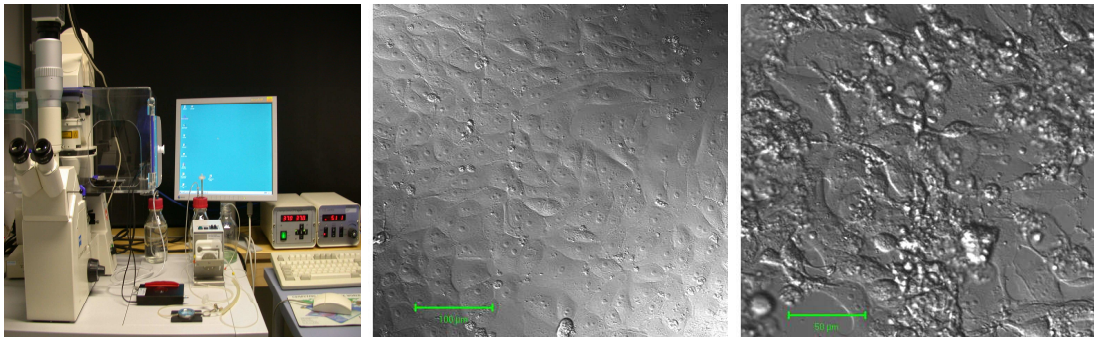


Fig. 67: left: Cultivation equipment for microscopic visualization; middle: MDCK cells grow on the culture chamber surface as monolayer (DIC); right: MDCK cells 24 h after infection with influenza virus (DIC).

4.2.3. Virus Replication in Microcarrier Culture

Typically, qualitative aspects (e.g. virus attachment mechanism, molecular biology and general timing of events) are well established to describe influenza virus replication in host cells. To support our modeling activities, quantitative information on replication dynamics is required. Therefore, we will extend our investigations of the interactions between influenza virus and host cells which will allow us to follow the time course of virus development in different cellular compartments (GFP-mutants, endocytosis, transcription of the viral genome, expression of virus proteins) and the cell specific response to viral infections (apoptosis, flow cytometry).

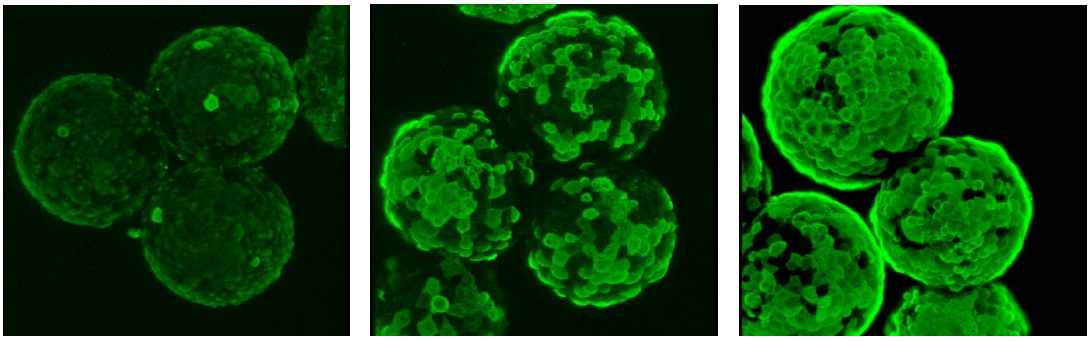


Fig. 68: MDCK cells on microcarrier, time course of influenza infection and development, cells stained with poyclonal anti-influenza antiserum and Alexa 488 (Molecular probes); left: 5 h after infection; middle: 10 h after infection; right: 22 h after infection.

Taking bioreactor samples at regular intervals after infection allows us to get information about the real infection dynamics and the infectivity of the virus in populations of cells (Fig. 68). Samples were stained immunologically and analyzed with a confocal laser scanning microscope [3]. The results were compared with other data obtained during the production process e.g. from hemagglutination (HA) and infectivity assays (Fig. 69). Furthermore, we are trying to develop a reliable virus quantification assay based on the agglutination activity of the influenza HA protein. In collaboration with the electron microscopy group at the Robert Koch Institute Berlin (Dr. M. Özel) we are investigating several microscopical methods to differentiate between virus particle numbers and virus infectivity.

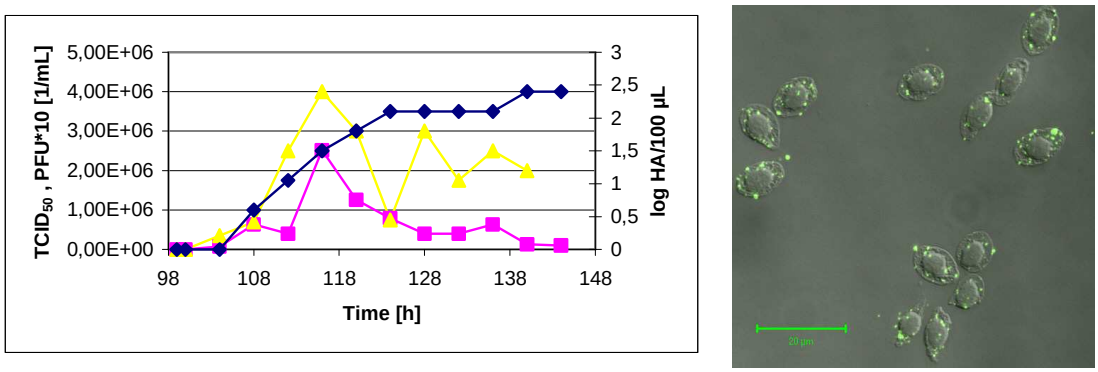


Fig. 69: left: Time course of virus infection in microcarrier culture (4.5 L wv) analyzed by HA (-◊-), TCID50 (-□-) and PFU (-?-); right: resuspended erythrocytes, influenza virions immunologically stained.

4.3. Mathematical Modeling of Cellular Systems: Influenza Virus Replication in MDCK Cells

Mathematical modeling plays a crucial role in analyzing and understanding bioprocesses. Even in most of the well-established animal cell culture systems there is much to be learned about the dynamics of cell growth, kinetics of product formation, stoichiometry of cellular metabolism and the complex interaction between observed state variables in a bioreactor under study. Combined with results from extensive experimental investigations at the cellular and bioprocess levels, adequate mathematical models not only allow the detailed analysis of the system under investigation, but also the design of optimization strategies.

At present, our work focuses on the dynamics of virus replication in single cells and populations of cells. The aim is to reveal basic laws that control the replication of viruses in animal cells, to investigate the interaction of viruses with their host in bioprocesses and to use this knowledge to optimize vaccine production processes. The simplest models of virus dynamics can be formulated by applying either structured or unstructured approaches [4]. An unstructured model does not consider intracellular phenomena. In the case of the virus infection cycle, a system of three differential equations describe how the numbers of uninfected cells, infected cells and free virus particles change over time. In a structured model, different state variables are used to model virus replication in different cellular compartments such as membrane, endosome, cytosol or nucleus. Based on genetic and molecular mechanistic data, rate equations are expressed for viral transcription, translation, protein expression and for reactions catalyzed by virus-encoded enzymes.

As a model system we focus on the replication of influenza virus in adherent MDCK cells.

Mathematical models for influenza virus infection of animal cells take only the first steps of infection, virus binding and endocytosis, into account. No model has been formulated which describes the entire infection cycle and the overall growth dynamics. Our model considers the individual steps of the process such as attachment, internalization, genome replication and translation, and progeny virion assembly (Fig. 70). Based on this model and a set of initial conditions, it is possible to predict the system's behavior at any moment in time, to analyze its sensitivity with respect to parameter changes, to identify possible targets for molecular engineering or to develop strategies for improving yields in vaccine production. Furthermore, detailed insight into the interactions of viruses and host cells might help to improve our understanding of virus-related diseases and to develop therapies.

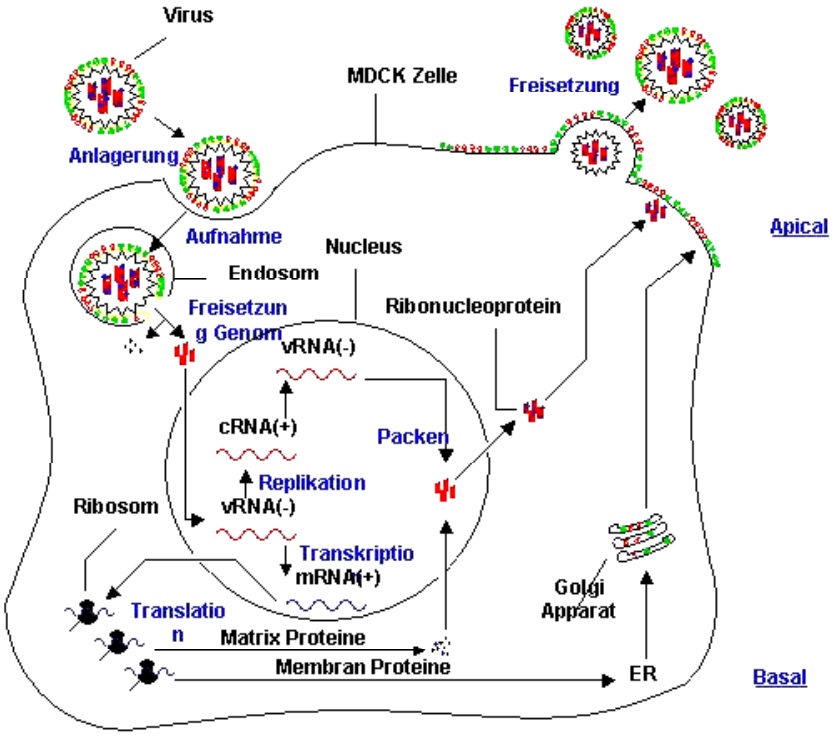


Fig. 70: Influenza A - virus replication.

In the model, an average cell surrounded by a small quantity of medium and infected by a certain number of virus particles is considered. We assume that each virus participates in only one replication cycle - the progeny virus particles released do not reinfect the cell. The model is represented by a system of 39 nonlinear ordinary differential equations which are solved numerically by means of algorithms provided by ProMoT/DIVA, a software package developed by the SBI and PSD Group in our institute to build structured dynamic simulation models.

The model reveals the factors that limit the growth rate of progeny virus and its release. The viral genome is stored in the virion as viral ribonucleoprotein (vRNP) complexes. When a new vRNP complex is being formed in the nucleus it binds to M1 protein - a matrix protein which stabilizes the viral membrane. Among all proteins making up a virus particle, this is the most abundant and simulations show that the total amount of M1 limits virus replication (Fig. 71 left). Other newly synthesized viral proteins (nucleoprotein NP, viral polymerases) and viral RNAs are also incorporated into vRNP complexes, but accumulate in the nucleus and their numbers increase linearly with time. A similar situation takes place in the budding stage, when newly synthesized vRNPs represent a limiting factor.

Simulations also help to understand factors required for the optimization of the overall growth rate of influenza virus. One attractive idea to obtain more progeny virus particles is speeding up transcription of viral RNAs by improving viral polymerase activity or translation efficiency at cellular ribosomes. Fig. 71 right shows that increasing the transcription rate by a factor of two results in an increase in the number of released virons of slightly more than 100% after 12 h.

The model allows us to estimate the cellular resources consumed by virus replication. Simulation results show that the number of cellular surface receptors and endosomes as well as other resources such as the number of free nucleotides or amino acids are not significantly influenced by influenza virus propagation.

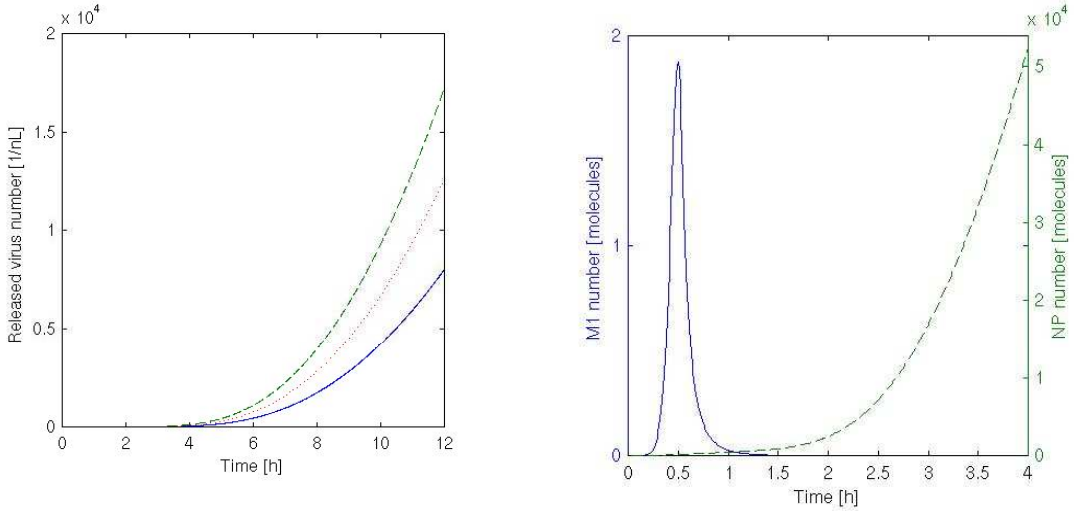


Fig. 71: left: Viral components in the nucleus. M1 protein (() is limiting at the stage of vRNP formation, whereas viral capsid proteins and vRNA accumulate in the nucleus, e.g. nucleo protein NP (---); right: Number of virions released from the cell with increase of polymerase transcription rate by factors of 1.0 (()), 1.5 (((((() and 2.0 (---).

Our further activities focus on obtaining kinetic information on basic replication steps for parameter estimation and model validation. Using different methods of microscopical

analysis of virus infection (see 4.2) we want to quantify several rate coefficients, overall dynamics and cellular events such as the switch from viral protein production to RNA genome replication or cellular defense mechanisms. Furthermore, work is in progress to better characterize changes in cellular metabolism during viral infection by means of metabolic flux analysis using tools developed by SBI Group and the use of flow cytometry to investigate cell-virus interactions during cultivations in bioreactors.

4.4. Downstream Processing and Chromatographic Methods: New Matrices and Ligands for Affinity Chromatography

For the production of pharmaceuticals using microorganisms or cell cultures, product purification (downstream processing), next to the actual biosynthesis, is often the most expensive and time-consuming step. Based on the physical and bio/chemical properties of the desired product and contaminating molecules in the cultivation broth, a broad range of separation methods can be applied (Fig.72). For most applications, chromatographic methods are the key steps during the processing of bioactive components. Among these are classical gelfiltration, ion-exchange, hydrophobic interaction and affinity chromatography which are operated in a packed or fixed bed mode.

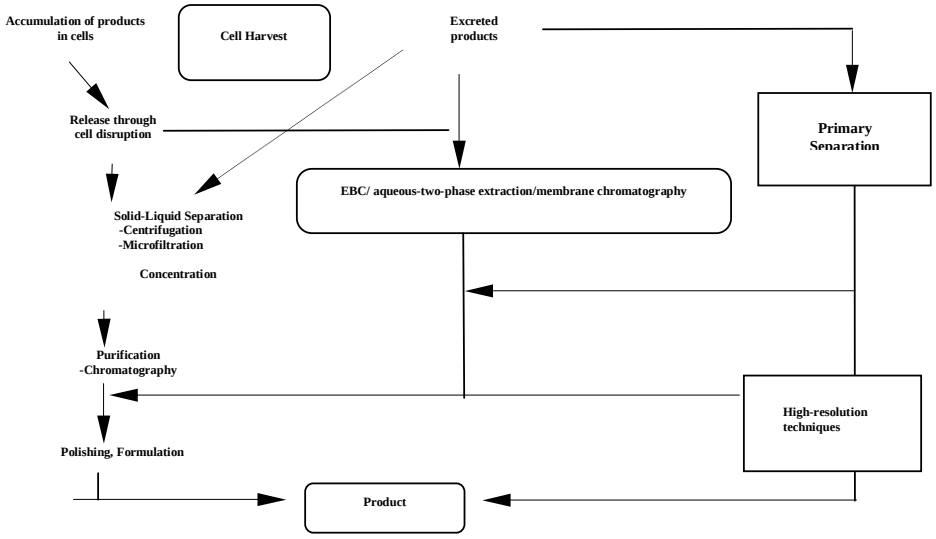


Fig. 72: Overview on downstream processing methods.

We have chosen the influenza virus as an example for optimizing downstream processing methods in vaccine production. So far, the commercial production of inactivated human influenza vaccines relies on the cultivation of the virus in embryonated hen's eggs. In a next step, filtration followed by continuous centrifugation of the allantoic fluid is used to purify viral

antigens. However, to overcome limitations in production and to improve existing influenza vaccines, many companies are currently establishing animal cell culture based upstream processes. With the additional need to further reduce possible negative side effects on humans or animals such as allergic or autoimmune reactions, new downstream processing schemes also have to be developed. In a recently established industrial process [2] virus particles are clarified with a combination of depth filters, inactivated with binary ethyleneimine (BEI), concentrated by ultra filtration (UF, 20-50 fold, 100 kDa MW cut off) and subsequently purified on a gel filtration column (Sepharose CL-2B). While this process is robust enough for industrial applications, recovery and purity of the final product as well as overall process economics could probably be improved considerably by optimizing individual steps. As an example, effluent concentration profiles of the two virus membrane proteins hemagglutinin (HA) and neuraminidase (NA) from a gel filtration column are shown in Fig. 73.

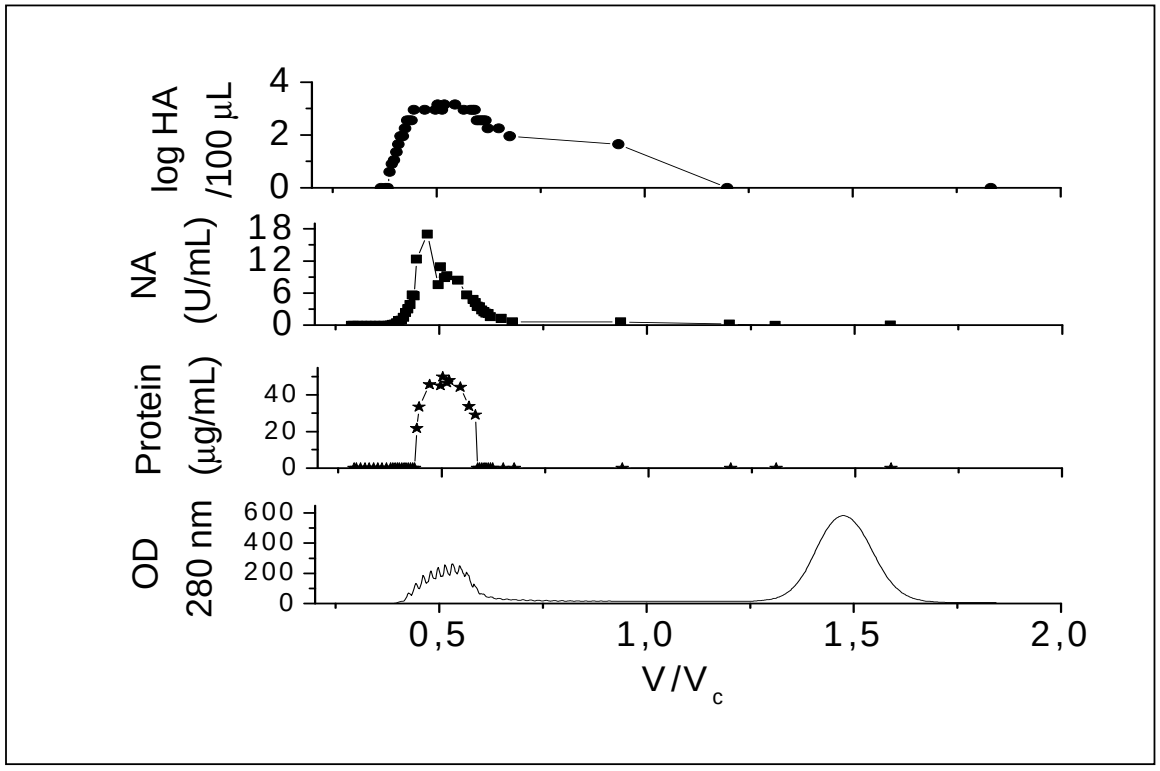


Fig. 73: Elution profile of HA, NA and protein of equine influenza virus from gel filtration chromatography. V and Vc are the effluent and column volume, respectively.

The overall yield of the process for HA is only 38% while NA remains at its activity level during purification. Contaminating protein is reduced by more than 95%. Chromatography plots show a broad HA peak and sharp NA as well as protein peaks. This is either related to the release of single HA molecules or HA bound to cellular membranes during virus replication or it indicates the destruction of intact viruses due to the high shear stress

involved in UF. Experimental work is in progress to further characterize individual processing steps and develop methods to analyze virus size distributions. Besides detailed investigations on how to improve the performance of existing technologies, we also focus on the development of Expanded Bed Affinity Chromatography (EBAC) to purify virus particles and viral antigens. At present we are investigating the use of several base matrices [5] and ligands (e.g. polyclonals, lectins) required for the specific purification of whole virions or viral surface membrane proteins based of specificity. Furthermore, matrix properties, kinetics of binding, ligand-virus and non-specific interactions as well as elution characteristics, recovery and purity of the harvests are characterized in detail (Fig. 74).

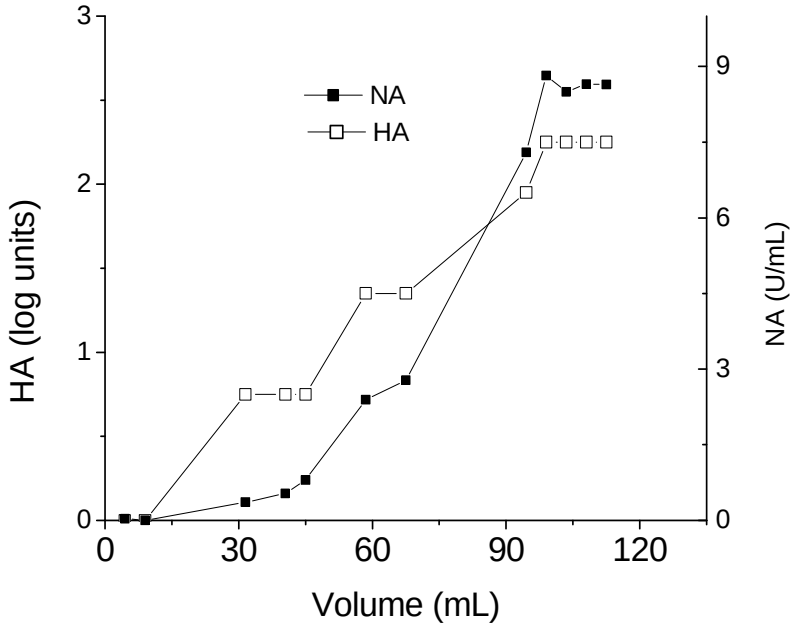


Fig. 74: Breakthrough curve of inactivated equine influenza virus showing HA and NA activities from affinity hromatography in a packed bed. V and C denote volume and concentration of the effluent where as C_0 and V_C are the feed concentration and column volume, respectively.

The experimental work will be supported by mathematical modeling of relevant aspects of the process to optimize EBAC on a preparative scale. Additionally, the physical and chemical parameters involved in this adsorption process will be evaluated in collaboration with PCF Group. Eventually, this information will not only allow us to develop an EBAC for virus purification but also to compare different downstream processing methods and to evaluate recovery, purity and process efficiency for various options.

5. Selected Teaching Activities, PhD Projects and Habilitations

5.1. Lectures at OvGU (Prof. U. Reichl):

- Biochemical engineering
- Modeling of bioprocesses
- Laboratory course biochemical engineering
- Biochemical engineering II (mammalian cell culture)
- Laboratory course biochemical engineering II
- Modeling of cellular systems

5.2. PhD Projects (started summer 2000)

At present there are 5 PhD students at the BPE Group and 6 PhD students at the OvGU, ten supervised by U. Reichl, and one by Y. Genzel.

5.3. External Evaluations

PhD Projects

2002

- Falkner-Tränkle, K.: Untersuchungen zum Zelltod in eukaryotischen Zellpopulationen und Einzelzellen mittels Videomikroskopie und digitaler Bildanalyse, Uni Stuttgart

2001

- Kendelbacher, T.: Trajektorienoptimierung von Fermentationsprozesses, Uni Stuttgart
- Kremling, A.: Strukturierung zellulärer Funktionseinheiten - ein signalorientierter Modellierungsansatz für zelluläre Systeme am Beispiel von *Escheria coli*, Uni Stuttgart

Habilitations

2003

- Dr. E. Müller: Evaluation process: Polymere Oberflächenbeschichtungen - eine Methode zur Herstellung von Träger-materialien für die Biochromatographie, Fakultät Verfahrens- und Systemtechnik der OvGU, Germany
- Appointment committee: Professor (C3) of polymer mechanics (Max Planck Institute for Polymer Research, Main, German Institute for Polymers Darmstadt, Technical University Darmstadt)

2000/2001 Scientific council: "code of conduct"

6. Selected Memberships, Appointments and Awards

Reichl, U.

- start 2002 Consultant to the biochemical industry, Bayer AG
- start 2003 Managing Director of the Institute for Process Engineering, OvGU

7. References

[1] Genzel, Y., Voges, L. and Reichl, U. (2001): Development of bioprocess concepts on vaccine production: influenza virus as an example, Animal cell technology: from target to market; Proceedings of the 17 ESACT meeting - 17th ESACT meeting, Lindner-Olsson, E., Chatzissavidou N., Luellau, E., pp. 344-346, Tylösand, Sweden.

[2] Reichl, U. (2000): ISCOMs - Antigen production and downstream processing, Proceedings of the 4th International Congress on Biochemical Engineering - International Congress on Biochemical Engineering; 4, Brunner, H., pp. 314-318, Stuttgart.

[3] Sann, H. and Willhardt, I. (1996): Measure of calpain activation in epithelial cells by laser scanning fluorescence microscopy, Biol. Chemistry, pp. 377.

[4] Möhler, L., Flockerzi, D. and Reichl, U. (2002): Mathematical model of virus replication in animal cells, Chemie-Ingenieur-Technik, 74,5, pp. 661-662.

[5] Nayak, D. P., Ponrathnam, S., Rajan, C.R. (2001): Macroporous copolymer matrix: IV. Expanded bed adsorption application., J. Chromatogr. A, 922, pp. 63-76.

[6] Tallarek, U., Rapp, E., Sann, H., Reichl, U., Seidel-Morgenstern, A. (2003): Quantitative Study of Electrokinetic Transport in Porous Media by Confocal Laser Scanning Microscopy, Langmuir, 19, pp. 4527-4531.

[7] König, B., König, W., Reichl, U., Trotha, R.; "Methods for the qualitative and quantitative detection of microbes in a sample" (applied for on 23-April-2002).

[8] Sann, H., Bock, A., Reichl, U.; "Vorrichtung und Verfahren zur Entnahme von flüssigen Proben" (applied for on 2-October-2002).

Research Group:

Systems Biology (SBI)

Prof. Dr.-Ing. Ernst-Dieter Gilles

This report covers the period between June 1998 and April 2003.

1. SBI Group Introduction

Research in modern molecular biology is mainly descriptive and qualitative. It is focused on the understanding of molecular details. Thus, it concentrates on the study of single components such as genes and proteins and on the individual interactions between these molecules. However, the analysis of the overall holistic behavior determined by the interactions of a high number of cellular components has been paid little attention in the past. To understand the complex structure and behavior of metabolism, signal-transduction and regulation requires an overall holistic analysis. Due to the multitude of interacting components, an understanding of these processes just by reflection is not possible. Here, the aid of mathematical modeling is absolutely essential to combine the available biological knowledge with a system-theoretical way of thinking. In combination with recent results in developing new measurement technologies of intracellular components, the system-theoretical approach opens the way to a quantitative description of cellular systems.

As an emerging field of interdisciplinary research, *Systems Biology* is based on a system-theoretical approach. It studies the interplay of all interacting components that are relevant for a specific cellular system. From an abstract point of view, Systems Biology aims at transforming structural and topological characteristics of a cellular system into functional dynamics. It can be expected that this approach will allow better and faster solutions to medical and biotechnological problems.

Research in Systems Biology will only succeed if interdisciplinary cooperation between biologists, engineers and computer scientists is established. Above all, model analysis must be linked very closely to experimental studies. In experiments, a systematic stimulation of a biological system can be achieved by quantitative changes in the experimental conditions (substrate, composition, temperature, etc.) or by constructing well-defined isogenic mutant strains. To analyze a systems response, parallel measurements of the transcriptom, the proteom and the metabolom must be taken distributed over time. These measurements can then be used to validate the model structure and to identify the model parameters. Model based experimental design as well as formulation and testing of hypotheses will allow a very strong interlocking of theory and experiments. Research in the field of Systems Biology requires powerful computing tools for modeling and simulation as well as for system analysis and system design.

The Systems Biology group at the MPI started its research activities in June 1998, continuing a longstanding cooperation on catabolite repression in *Escherichia coli* with the group of Prof. Lengeler, University of Osnabrück. This cooperation was initiated several years ago at the University of Stuttgart and then transferred to Magdeburg in 1998.

The activities in developing a very general tool (ProMoT) to set up mathematical models for cellular functional units were also transferred from Stuttgart to Magdeburg in 1998. This tool is based on a modular modeling concept reflecting the natural modular structure of biological systems. It is important to stress that the modeling concept underlying ProMoT assigns elementary modeling objects to elementary cellular components. This assignment guarantees a high level of biological transparency and facilitates the interdisciplinary cooperation between biology and systems engineering. It also encourages the acceptance of mathematical modeling in biology because it allows scientists to perform virtual experiments on computers that are analogous to experiments in a real biological laboratory.

After starting research work in Magdeburg, the Systems Biology group has continuously extended its activities by taking up studies on a number of additional aspects of metabolic regulation and signal-transduction including both prokaryotic and eukaryotic systems. Although the research group itself is composed of researchers from different disciplines, all activities are based on a close cooperation with external biological groups, with the main focus of their work on the specific research area of cooperation. The group has built up a well-equipped fermentation laboratory to perform experiments with isogenic mutant strains of *E. coli* and other microorganisms. The quantitative determination of important parameters, such as metabolite concentrations in fermentation experiments is a major task for the set up and validation of the mathematical model. Here, experimental methods for sampling, sample preparation and sample analysis are being developed through the combined effort of the research groups SBI and BPE (Prof. Reichl). The functional units under investigation are mainly focused on global control and signal-transduction systems.

Examples of functional units in prokaryotes are: catabolite repression, general stress response and two components signal-transduction in *E. coli*, redox control in *Rhodospirillum rubrum* and phototaxis in Halobacteria. The EGF induced MAP kinase cascade and the TNF induced apoptosis in mammalian cells as well as cell cycle regulation in yeast are examples of signal-transduction units in eukaryotic cells under investigation. Together with the PSD group of Prof. Kienle, the modeling and simulation environment ProMoT/Diva is being developed and adapted for cellular systems. The models set up by the Systems Biology group are rather large. With the group of Prof. Flockerzi (MF), new strategies to structure and to reduce the models are under investigation. Several methods for experimental design are also being analyzed together with Prof. Raisch (SCT) and Prof. Doyle (UC, Santa Barbara, USA).

2. Members of the SBI Research Group

Composition of Systems Biology group as of 30 April 2003:

Group Member	**Status**	**Joined SBI**
Prof. Ernst Dieter Gilles	Head of Group	
Project team: *Signal-transduction and regulation in bacterial cells*		
Dr. Katja Bettenbrock	Postdoc	09/1998
Dr. Hartmut Grammel	Postdoc	03/1998
Dr. Andreas Kremling	Postdoc	03/1998
Tobias Backfisch	Ph.D. Student	03/2000
Steffen Klamt	Ph.D. Student	05/1998
Group Member	**Status**	**Joined SBI**
Torsten Nutsch	Ph.D. Student	01/2000
Sophia Fischer	Ph.D. Student	03/2001
Project team: *Signal-transduction and regulation in eukaryotes*		
Birgit Schöberl	Ph.D. Student	04/1999
Jörg Stelling	Ph.D. Student	08/1998
Julio Saez Rodriguez	Ph.D. Student	03/2002
Project team: *Computer-aided modeling*		
Martin Ginkel	Ph.D. Student	11/1998
Technical staff:		
Britta Laube	Laboratory Coworker	04/1999
Helga Tietgens	Laboratory Coworker	07/2001
Ruxandra Rehner	Laboratory Coworker	10/1999

Group at Stuttgart University:

Michael Ederer	Ph.D. Student	
Christine Kammerer	Ph.D. Student	
Soenke Mannal	Ph.D. Student	
Thomas Sauter	Ph.D. Student	

Visiting Scientists:

Prof. Doraiswami Ramkrishna	Purdue University, West Lafayette, USA	2002
Prof. Francis Doyle	University of California, Santa Barbara, USA	2002
Prof. John Doyle	California Institute of Technology, USA	2003
Prof. Joseph Lengeler	University of Osnabrück	2003

3. Survey of Research Projects

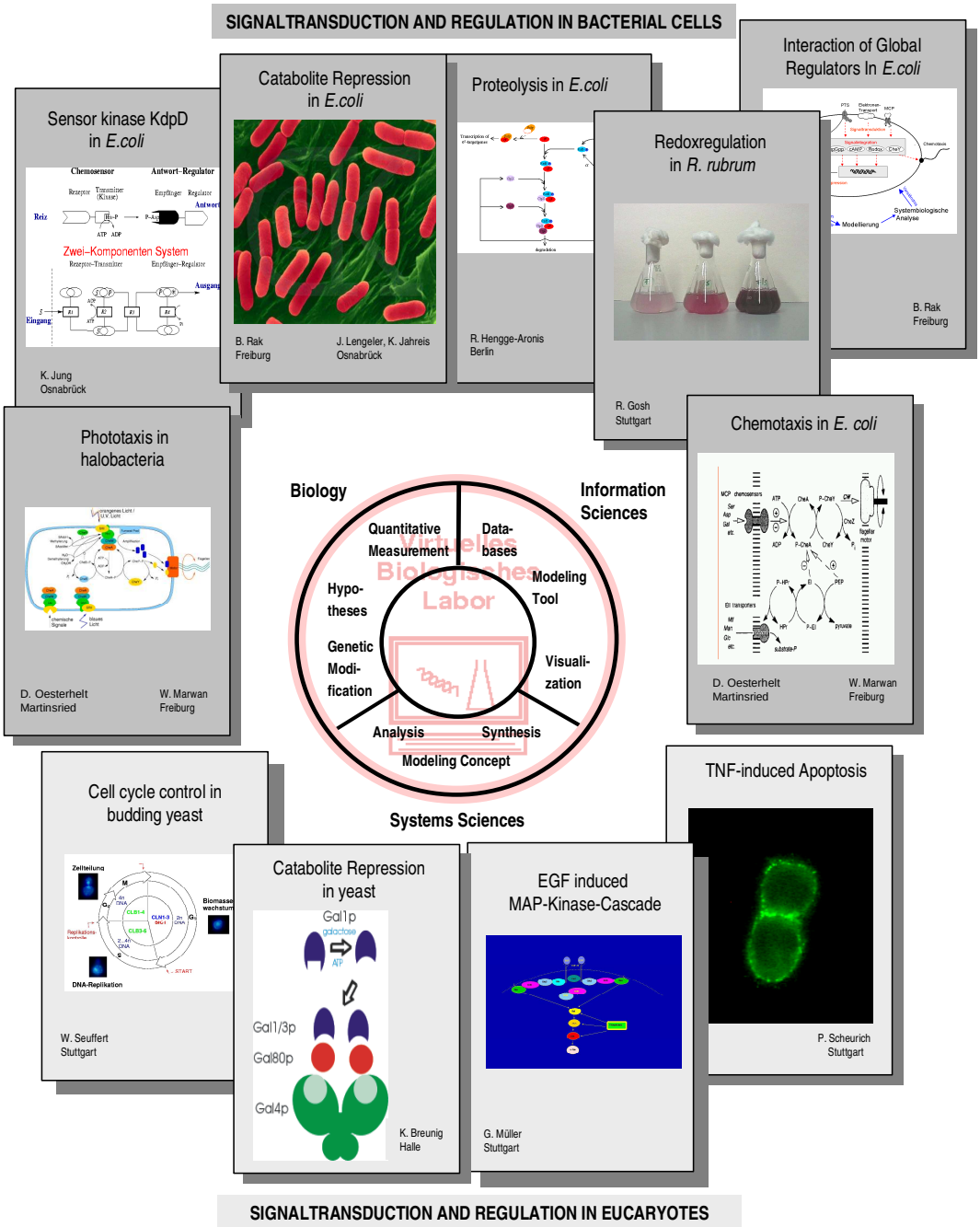


Fig. 75 Survey on the cellular functional units studied by the Systems Biology Group; Network of cooperation.

Survey of research projects of *Systems Biology* group:

Project Area: Hierarchical Structures

Project: Signal-transduction and regulation in bacterial cells	The structural analysis of regulatory processes is the key to a better understanding of the behavior of cellular systems. Cellular systems are able to respond very efficiently to changes in the environmental conditions. Focusing on *E. coli* and *R. rubrum*, a number of regulatory processes and signal-transduction networks are under investigation. The group activities are focused on: • set up of detailed mathematical models • experimental investigations to stimulate the biological system in different ways (nutrient limitation, mutations) • analysis of structural properties of the network			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject: Redox control in photosynthetic bacteria	Grammel, Klamt	MPI, Land Baden-Württemberg	03/98	Stuttgart Univ. (Prof. Ghosh; ISR), OvGU Magdeburg (Prof. Reichl)
Subproject: Mathematical Modeling of Catabolite Repression in *E. coli*	Bettenbrock, Fischer, Kremling	MPI, Land Baden-Württemberg	03/98	Osnabrück Univ. (Prof. Lengeler),
Subproject: Regulation of stress sigma factor σ^S	Backfisch	MPI	01/01	FU Berlin (Prof. Hengge-Aronis)
Subproject: Two-component signal-transduction in *E. coli*	Kremling	MPI DFG	07/02	TU Darmstadt (Prof. Jung)
Subproject: Phototaxis in Halobac-terium salinarium	Nutsch	MPI	01/01	MPI Biochemie (Prof. Oesterhelt), Freiburg Univ. (Dr. Marwan)
Subproject:				

Chemotaxis in *E. coli*	Nutsch	MPI Land Baden-Württemberg	01/03	Freiburg Univ. (Dr. Marwan)
Subproject: Interaction of global regulators in *E. coli*	Bettenbrock, Kremling	MPI, Land Baden-Württemberg	01/03	Stuttgart Univ. (ISR), Freiburg Univ. (Prof. Rak)

Project: Signal-transduction and regulation in eukaryotes	Signal-transduction in mammalian cells is characterized by a high number of interconnected components. These projects focus on EGF and TNF-induced signal-transduction pathways as well as cell cycle control in S. cereviseae. Activities are concentrated on: • modular structuring of signal-transduction networks • model analysis with system-theoretical methods • model reduction of cell cycle regulation			
Title	Scientists	Funded by	Start	Partners
Subproject: EGF-induced MAP kinase cascade	Schöberl, Saez-Rodriguez	MPI, SFB 495, Land Baden-Württemberg	04/00	Stuttgart Univ. (Prof. Pfizenmaier), MIT Boston (Prof.Lauffenburger)
Subproject: TNF-induced apoptosis	Schöberl, Saez-Rodriguez	MPI, SFB 495, Land Baden-Württemberg	04/00	Stuttgart Univ. (Prof. Pfizenmaier), MIT Boston (Prof.Lauffenburger)
Subproject: Mathematical modeling of cell cycle regulation in eukaryotes	Stelling	MPI, SFB 495, Land Baden-Württemberg	03/98	Stuttgart Univ. (Prof. Seufert), SCT group (MPI), MF group (MPI)
Subproject: Catabolite repression in budding yeast	Stelling	MPI, Land Sachsen-Anhalt	01/01	Halle Univ. (Prof. Breunig)

Project Area: Network Theory

Project: Computer Aided Modeling and ana-lyses 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	Scientists	Funded by	Start	Partners
Subproject: Modular modeling concept	Kremling, Saez-Rodriguez	MPI	03/98	Osnabrück Univ. (Prof. Lengeler), PSD group (MPI), MF group (MPI)
Subproject: Modeling and simulation tool ProMoT/Diva for biological systems	Ginkel	MPI	01/99	Donezk Univ. (Prof. Svjatnyi), PSD group (MPI), PCF group (MPI)
Subproject: Virtual Biological Laboratory	Kremling, Ginkel, Fischer	MPI	01/01	BPE group (MPI)
Subproject: Stoichiometric Network Analysis	Klamt, Stelling	MPI	01/01	MDC Berlin (Dr. Schuster), MF group

				(MPI), SCT group (MPI), BPE group (MPI)
Subproject: Methods for model discrimination and reverse engineering	Kremling, Fischer	MPI	07/02	California Univ. (Prof. F. Doyle)
Subproject: Robustness analysis in circadian clocks	Stelling	MPI	07/02	California Univ. (Prof. F. Doyle)

4. Research Highlights

4.1. Bacterial Signal-Transduction and Regulation

4.1.1. Introduction and Objectives

Bacteria have to face drastic changes in their surroundings. To cope with these changes they have to respond and adapt quickly. Adaptation requires the ability to sense signals, to process them and to respond in an appropriate way. Sensors for external stimuli are often membrane proteins like the methyl chemotaxis proteins that mediate chemo- and phototaxis. Often one or more sensor proteins are linked to a single signal-transduction system that then allocates the information from these sensors to the various regulatory systems. The bacterial phosphotransferase system can be seen in such a way. It integrates information from a number of sensors specific for a certain carbohydrate but it also integrates information about the internal state of the cell by measuring the concentrations of the metabolites PEP and pyruvate. Facultative photosynthetic bacteria like *Rhodospirillum rubrum* integrate different environmental stimuli such as the availability of O_2 and light apparently by sensing the redox state of electron transfer chain components to control photosynthetic and respiratory gene expression.

In most cases the response is the activation or inactivation of a transcriptional regulator that controls a defined set of genes, but there are also other responses like regulation of flagellar movement. A certain signal will only affect one or a small group of regulators and thereby a defined number of genes. According to the number and specificity of genes, affected regulations can be designated as specific or global. 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. For the setup of mathematical models, different strategies can be pursued starting either with basic analysis of the metabolic network or with a detailed reproduction of existing knowledge.

4.1.2. Redox Control in Photosynthetic Bacteria

This project uses the strategy of basic analysis of network capabilities. The facultative phototrophic bacterium *Rhodospirillum rubrum* offers unique opportunities to study redox control of gene expression and membrane differentiation in prokaryotes. The biosynthesis of intracytoplasmic photosynthetic membranes (PM) is hierarchically dependent on different environmental stimuli, such as O_2, light and C-source. There is evidence that these stimuli affect gene expression via a signal-transduction system that uses the redox state of the respiratory and photosynthetic electron transport chain components (ubiquinone, cytochromes, cytochrome oxidases) as molecular signals (Fig. 76).

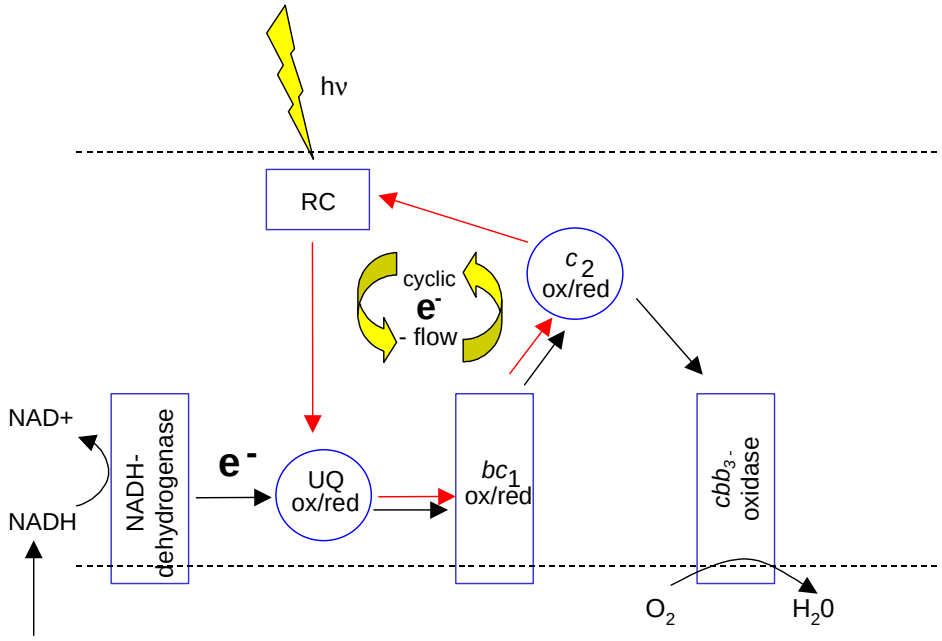


Fig. 76: Electron transport chain components of *R. rubrum.*

We study the formation of PM in bioreactor cultures under aerobic, semi-aerobic and anaerobic photosynthetic conditions. To adjust semi-aerobic growth, a unique process control strategy was developed that uses the pH of the culture to adjust the dissolved oxygen to values below 0.5%. A metabolic profile of the central carbon metabolism of these cultures was obtained by the determination of key enzyme activities. This information was then used to perform metabolic flux and pathway analysis of the redox metabolism of *R. rubrum* [1]. Under semi-aerobic conditions, succinate and fructose were utilized simultaneously, but not by diauxic growth, with succinate being regenerated by reactions of the reductive TCA-cycle. Fructose was utilized solely via the EMP-pathway. High pyrophosphate-dependent phosphofructokinase activities were found to be specific to the semi-aerobic state. The oxidative pentose phosphate pathway does not contribute to fructose breakdown, as no glucose-6-phosphate dehydrogenase activity could be detected under any condition. We demonstrated that, under oxygen-limited conditions, NADPH is supplied mainly by the pyridin-nucleotide transhydrogenase. We also confirmed that the tricarboxylic acid cycle enzymes are present at significant levels during semi-aerobic growth, albeit at lower levels than under fully aerobic growth. We showed that during photosynthetic growth on distinct substrates the net CO_2 fixation and maximal biomass yield is a global stoichiometric constraint despite a large degree of freedom in the network [2]. Furthermore, the phenomenon that the Calvin cycle for CO_2 fixation is needed as a redox sink, even in the case where a net CO_2 release occurs, could be predicted correctly. A dynamic model of the electron transport chain was developed which allows the testing of different hypotheses for redox-mediated regulation by simulating the redox state of electron carriers. The simulations show that: (i) there is strong coupling between redox states of ubiquinone and NAD/NADH and (ii) ubiquinone is more reduced under low-light conditions than under high-light conditions. We hypothesize that the redox state of ubiquinone controls PM formation in addition to other signals and that semi-aerobic growth with succinate/fructose as C-sources affects the ubiquinone pool in a way essentially identical to light signaling, thus yielding maximal expression of PM in the dark [1].

4.1.3. Mathematical Modeling of Catabolite Repression in *E. Coli*

Another strategy was applied in the project “Mathematical Modeling of Catabolite Repression in *E. coli*.” In this project, it was possible to start with a quite detailed model describing molecular interactions because many physiological and molecular details were already available. The term catabolite repression describes the phenomenon that some carbohydrates are able to repress the uptake of other carbohydrates. This effect is most pronounced in the presence of glucose. The system that is responsible for most effects is the

bacterial phosphoenolpyruvate-dependent phosphotransferase system (PTS). The PTS represents a group translocation system that mediates uptake and concomitant phosphorylation of a number of carbohydrates. It consists of the sugar specific enzymes and the general components EI and HPr. A special task is assigned to $EIIA^{Crr}$. Although this protein can be considered to be a protein specific for the Glc-PTS, it is coded within the *pts*-operon together with the genes for EI and HPr. If $EIIA^{Crr}$ is in its phosphorylated state, indicating no PTS mediated transport, it activates the adenylate cyclase. This enzyme produces cAMP that acts in a complex with Crp as a transcriptional activator for all genes subject to catabolite repression. In addition to the regulation by cAMP.Crp, these genes are also subject to specific regulation. If $EIIA^{Crr}$ is in its unphosphorylated state, indicating uptake of glucose or another PTS substrate, it is able to complex with certain permeases or catabolic enzymes thereby inactivating them.

The model that was set up describes the reactions of the PTS, the uptake of the PTS substrates glucose and sucrose, and the uptake and metabolism of lactose, a non-PTS substrate, whose uptake and metabolism is repressed by glucose according to the two mechanisms described above. Glycolysis and drains into monomer synthesis are described in a simplified form. The regulation of gene expression and the control of enzymatic activities are also considered. To reduce the model, the hierarchy of transcriptional regulation with the sigma factor of RNA polymerase representing the top level, cAMP.Crp the medium level and the specific regulators the lowest level of the hierarchical organization was implemented in such a way that signals are transduced from the top to the bottom only [3]. The model was set up with data and parameters from literature and predictions were compared with measurements. To get these measurements that allow for parameter estimation with system level methods, a set of experiments was performed with the wild-type strain, which was grown under varying but well-defined experimental conditions. Because these data allowed only a small subset of the parameters of the model to be estimated, the experiments were complemented by the construction and analysis of a set of isogenic mutants and the establishment of further measurements that allowed measuring intracellular variables like the phosphorylation state of $EIIA^{Crr}$. These experiments allowed the estimation of more parameters, which enabled a good reproduction of measurements by the model. But the model still deviated from reality. These deviations were analyzed and demanded the consideration of additional regulations or alternative metabolic pathways in the model. Some of these regulations had not been described previously, like the existence of a specific regulator for the gene for $EIIBC^{Glc}$ which was characterized a few months later. Other effects had not been recognized before. It was known that lactose, a non-PTS substrate, is able to provoke some catabolite repression. Our experiments showed a substantial dephosphorylation of $EIIA^{Crr}$ during growth with lactose and the time course of this

phosphorylation state during diauxic growth. We assume that glucose produced intracellular from lactose is phosphorylated by the PTS. This reaction was previously ascribed to glucokinase but the characterization of strains mutated in glucokinase showed that this enzyme is not essential for lactose metabolism [4].

As the PTS is central to the model, it is obvious that kinetic parameters of the phosphotransfer reactions and of the central metabolism are important for system behavior. To analyze these parameters, other types of experiments had to be conducted. Fermentations with limiting amounts of PTS substrates were carried out and the equilibrium was disrupted by pulses. In another type of continuous experiment, the concentration of carbohydrates was varied from saturating to limiting amounts. These experiments showed the relationship between extra- cellular carbohydrate concentration and the PTS phosphorylation state. Measurements of glycolysis intermediates and the phosphorylation state of $EIIA^{Crr}$ in pulse experiments allowed the modeling and validation of the dynamic response of the PTS and the central metabolism. The analyses showed that there are defined time hierarchies in the system [5].

The current model that was extended to describe growth with additional carbohydrates comprises 85 ODEs and uses about 300 kinetic parameters. Smaller sub-models exist, that allow more detailed analysis, e.g., of the PTS reactions. In the future the validated model will be used to discriminate between alternative hypotheses and it will be subjected to system level analysis.

4.2. Modeling Tool and Concept

4.2.1. Introduction and Objectives

Research in the field of systems biology requires powerful computing tools for modeling, simulation, system analysis and synthesis. The tools developed are based on a general modeling framework that was introduced for chemical process engineering and is now being adapted for biological systems. The developed software tools were applied to different subprojects of the Systems Biology Group. Further applications will include modeling of virus dynamics in cooperation with the BPE group (Prof. Reichl).

The overall aim is to provide a framework for modeling cellular systems that will serve as a basis for software tools that support model setup and model analysis. ProMoT provides a large library with sub-models for the description of all cellular processes. The simulation environment DIVA allows simulation as well as parameter analysis, parameter estimation and bifurcation analysis.

4.2.2. Modular Modeling Concept

The modeling concept is based on the analysis of the available knowledge on metabolism, signal-transduction, and cellular control and the combination of these with system-theoretical methods. The modeling procedure thus has to be based on the molecular structure of the functional units in such a way that a cellular unit is represented by an equivalent mathematical sub-model. This modular approach is a new feature in the mathematical modeling procedure and guarantees a high transparency for biologists and engineers.

The basis of the framework is the definition of a complete but finite set of elementary modeling objects (Fig. 77). They should be disjunct with respect to the biological knowledge they comprise to prevent overlapping. The modeling process proceeds along two coordinates: a structural and a behavioral coordinate. The structural coordinate represents a progressive combination and linkage of elementary modeling objects to higher aggregated model structures. Higher aggregated model structures are called “functional units.” Modeling along the behavioral coordinate means that equations have to be assigned to each of the elementary modeling objects.

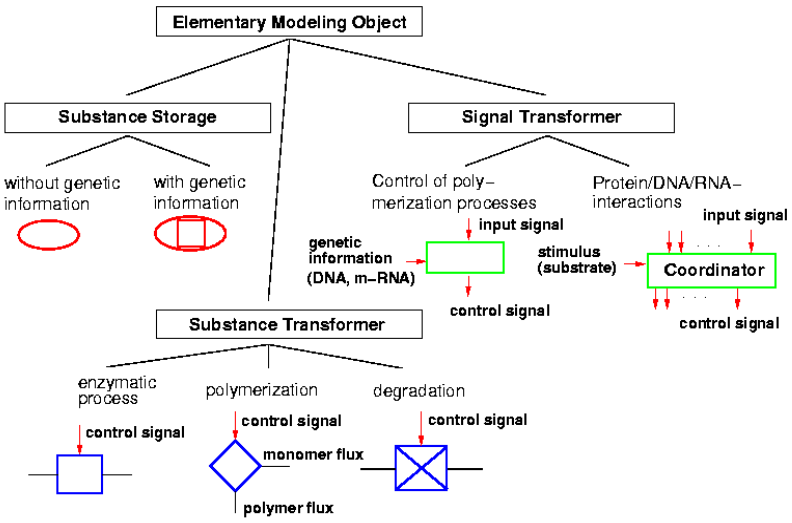


Fig. 77: Overview elementary modeling objects.

Functional units are defined according to three biologically motivated criteria.

- A common physiological task. All elements of a functional unit contribute to the same physiological task. Easily recognizable examples are the specific catabolic pathways for individual carbohydrates, or the biosynthetic pathways for the different amino acids, nucleotides and cofactors from their precursors.
- Common genetic units. The genes for all enzymes of a functional unit are organized in genetical units and in a hierarchical structure. These are at the lowest level the operons and regulons. A regulon is a group of operons that is controlled by a specific regulator. Regulons are typical for more complex metabolic pathways that contain too many genes (enzymes) for one operon, or contain genes (enzymes) expressed in different amounts or under different conditions. More important for our considerations are, however, genetic units at a higher hierarchical level, in particular, modulons. These are groups of operons and regulons, which are controlled by global regulators that respond to more general physiological states. Control by these global regulators is epistatic, i.e., superimposed and dominant over the specific control systems mentioned before.
- A common signal-transduction network. All elements of a functional unit are interconnected within a common signal-transduction system. The signal flow over the unit border (“cross-talk” or “cross-regulation”) is small compared to the information exchange within the unit, such that the coordinated response to a common stimulus (“stimulon”) helps to identify the members of a unit [6]. How modules should be delimited from a theoretical point of view is still an open question. However, decomposing a network as far as possible into units with non-retroactive signal transfer is desirable since this allows a straightforward analysis by means of system-theoretical tools. In the project, a number of signal-transduction pathways – from a “simple” two-component system in *E. coli* up to the complex mitogen-activated protein kinase (MAPK) – are analyzed with respect to their role in physiology, their dynamics, and their interaction with other signal-transduction units. Once modules are found, they can be systematically analyzed and classified, creating a library of units that could be reused. This will simplify the set-up of models, since many parts of signal networks, e.g. the MAPK cascade, are found in several signal-transduction pathways. his research is done in close cooperation with Prof. Flockerzi. His MF group also gives us continuous support in model reduction techniques and the analysis of structural properties of biochemical networks.

4.2.3. Modeling and Simulation Tool ProMoT/Diva for Biological Systems

Modular models are implemented in the equation-based and object-oriented modeling tool ProMoT [7] that is being developed and maintained together with the group of Prof. Kienle (PSD). ProMoT supports the development of modules as classes in an object-oriented inheritance hierarchy. This concept from computer science is especially used to build extensible libraries of reusable modules. ProMoT is therefore used by a number of research groups at the MPI for biological models as well as for models used in chemical engineering. Models in ProMoT can be developed graphically, as a flow-chart of connected modules within a graphical user interface (GUI), or using a modeling language (Fig.78).

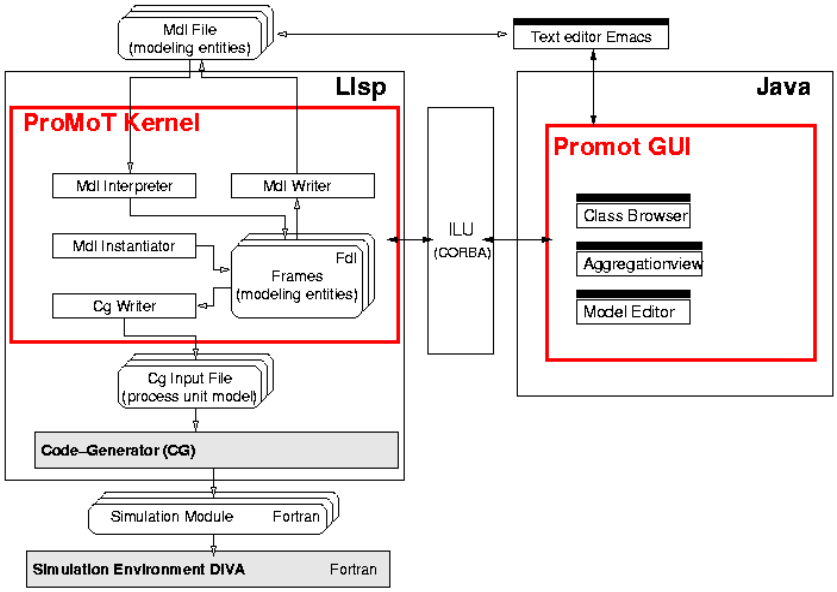


Fig. 78: Structure of ProMoT.

The tool supports model development and debugging through different views of model structures and with algorithms for handling the resulting differential-algebraic equation system. With these algorithms, the equations can be checked for structural consistency and are optimized symbolically to achieve good simulation performance. The resulting models are computed as compiled subroutines in the simulation environment DIVA, which allows for the efficient numerical solution of large-scale systems.

A collaboration with the PCF group (Prof. Seidel-Morgenstern) focuses on establishing new methods of parameter estimation in DIVA, employing mathematical models both from chemical engineering and systems biology.

4.3. Control of Cell Proliferation in Eukaryotes

4.3.1. Introduction and Objectives

Cells continually sense their surrounding environment and make decisions based on the information received via nutrients, growth factors, hormones and/or chemokines. These extracellular signals are transmitted into the nucleus, inducing gene expression, thus controlling essential cellular processes such as cell proliferation, differentiation, or apoptosis (programmed cell death). Since it is related to basic properties of the cell, defective signal processing is responsible for a variety of diseases, for instance, cancer and diabetes.

One essential response governed by signal-transduction is cell proliferation. The division cycle of eukaryotic cells is divided into discrete phases: mass growth (G1 phase), replication of the genetic material (S phase) and finally chromosome separation, chromosome distribution and cytokinesis (G2/M phase). This sequence is controlled by “checkpoints”, ensuring that each cell cycle phase is initiated only after successful completion of the preceding phase. Cyclin dependent kinases (CDKs) – forming distinct kinase complexes with phase-specific cyclins to provide different functionality – are at the heart of cell cycle control.

Both signal-transduction and regulation of cell proliferation are too complex to be understood intuitively. In signal-transduction, the high number of components involved, the complex crosstalk phenomena among the different pathways and the crucial role played by the dynamics form a picture that is difficult to grasp. In cell cycle regulation, furthermore, all regulators are embedded in a highly interconnected network including positive and negative feedback loops, with many different regulatory mechanisms at the DNA, mRNA and protein level.

As a first step towards an understanding of this entanglement, several signal-transduction pathways in mammalian cells as well as the cell cycle regulation in yeast have been analyzed. Dynamic mathematical models were structured as a set of sub-models according to the modular modeling approach.

4.3.2. EGF-induced MAP Kinase Cascade

The EGF (Epidermal Growth Factor), TNF (Tumor Necrosis Factor) and Insulin signaling pathways are of great interest since they play a key role in tumor growth, arthritis and rheumatism. Understanding cell decision processes requires the analysis of the crosstalk mechanisms between survival and death receptors such as the TNF receptor or Fas receptor. For this reason, we have developed independent models of the survival pathways (EGF and insulin induced MAP kinase cascade) and the apoptotic TNF pathway, which can then be combined into a full model in the future.

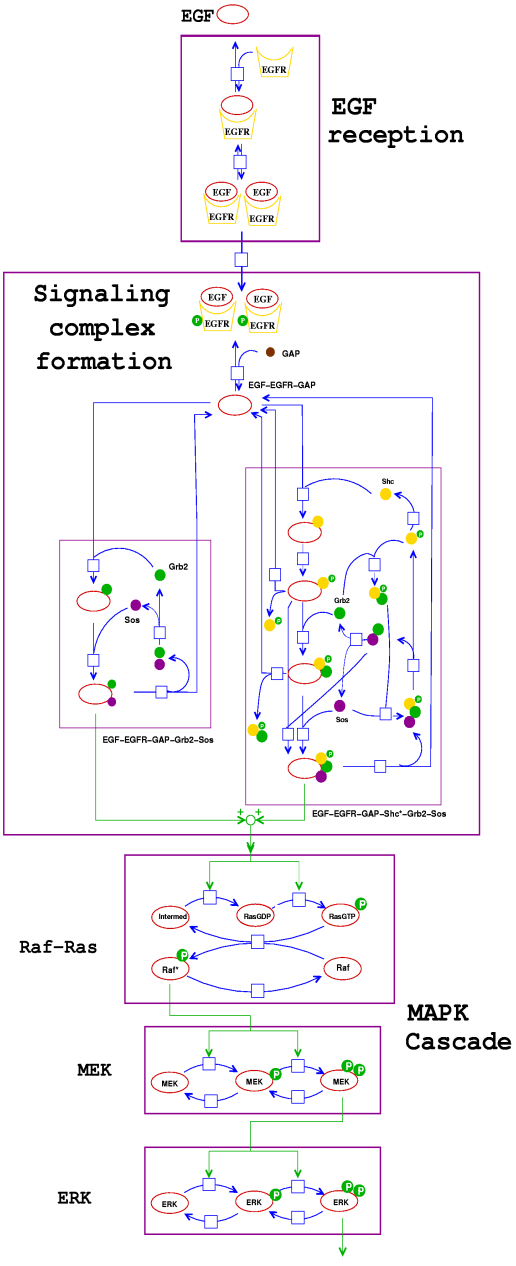


Fig. 79: Modular representation of the EGFnetwork.

The EGF receptor is expressed in all mammalian organs. EGF receptors play a complex role during embryonic and postnatal development and in tumor progression. A mathematical model of the mitogen-activated protein kinase (MAPK) cascade activated by the EGF receptor has been recently published [8]. The model includes the binding of EGF, receptor internalization and trafficking, the signal complex formation, the resulting activation of Ras-GDP/GTP, and the MAPK cascade. The model suggests interesting properties: the ligand concentration might be of marginal importance over a 100-fold range, whereas the initial speed of receptor activation is a crucial parameter. By separating the signal triggered by the internalized receptors from the signal triggered by receptors remaining on the cell surface, the possible role of the receptor internalization can be elucidated: at high EGF concentration internalization leads to signal attenuation and at low EGF concentration internalization amplifies the signal.

4.3.3. TNF-Induced Apoptosis

Tumor necrosis factor (TNF) induces a broad spectrum of cellular responses such as differentiation, immune response or apoptosis via a highly complex signaling network. TNF induced signal-transduction is controlled by two distinct membrane receptors, TNFR1 and TNFR2. While it is known that TNFR1 on its own is capable of triggering either apoptosis or gene induction, the role of TNFR2 still remains unclear. Our model [9] describes the experimental data of different stimulation protocols. Several hypotheses could be obtained from the model; regarding the crosstalk between the two TNF receptors, for example, that the binding of TRAF2 to TNFR2 is not sufficient to induce almost complete depletion of TRAF2 from the cytosol that was observed. During the model development it was shown that cIAP1 ubiquitinates TRAF2.

4.3.4. Mathematical Modeling of Cell Cycle Regulation in Eukaryotes

For the field of cell cycle regulation in eukaryotes, systematic development and validation of a modular, system- and signal-oriented mathematical model was first carried out for the budding yeast *Saccharomyces cerevisiae* as a model organism. Several sub-models have been developed, which, when connected, are able to represent the major aspects of the complete system of cell cycle regulation in yeast [10, 11, 12]. In particular, as exemplified by the analysis of a sub-model describing the G1/S-transition [10,11] mathematical modeling can lead to direct conclusions on the biological system under consideration. Here, major conclusions include (i) biological knowledge on the regulatory network under consideration is sufficient to explain the observed behavior, (ii) the seemingly complex behavior results from the interplay of regulatory circuits, which have to be viewed in a quantitative way to begin understanding the entire network's function and (iii) mathematical modeling gives hints that this network constitutes a relatively robust regulatory module.

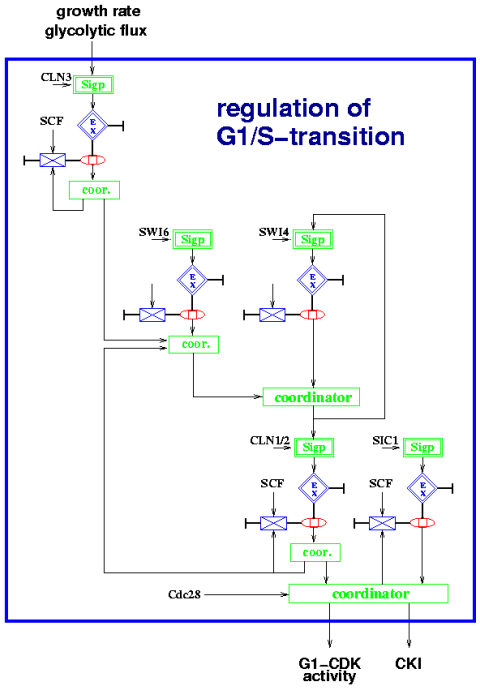


Fig. 80: Modular model structure for G1/S-control in budding yeast.

Robustness – qualitatively stable functionality despite uncertainty – seems to be a general, essential feature of cellular control circuits. The same property, however, provides a challenge to the investigator because it hinders the estimation of kinetic parameters and thus the quantitative understanding of cellular regulation. Using the control of mitosis as an example, the value of mathematical modeling in the elucidation of cellular control circuits under these constraints was investigated [12]. Parameter estimation accuracy gives a quantitative measure for robustness, which in this case strongly supports the concept of highly optimized tolerance, i.e. of the co-existence of robustness and fragility in cellular control. Similar observations concerning robustness of most parameters (but sensitivity towards flaws in network structure) were made for signal-transduction, namely the TNF, EGF and insulin models. A differentiated view on robustness and identifiability is thus required, but realistic models of cellular control are possible despite limited quantitative data.

4.4. Structural Network Analysis

4.4.1. Introduction and Objectives

A major current challenge in systems biology is to clarify the relationship between structure, function and regulation in complex cellular networks. However, dynamic mathematical modeling of large-scale networks is difficult, as the necessary mechanistic detail and kinetic parameters are rarely available. In contrast, structure-oriented analyses only require network topology, which is often well known. Projects in the field of structural network analysis therefore aim at directly gaining a better understanding of – predominantly metabolic – networks, but also at identifying constraints that could be exploited for the development of more detailed dynamic mathematical models.

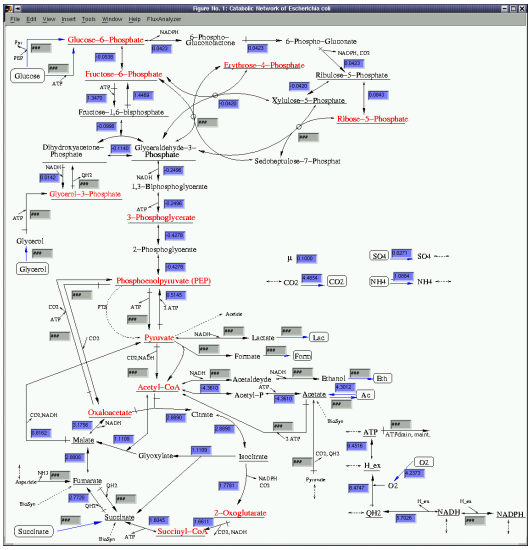
4.4.2. Stoichiometric Network Analysis

Stoichiometric network analysis has become an important approach for understanding the functionality of metabolic networks. Specifically, metabolic pathway analysis serves to study the complete space of admissible steady-state flux distributions, also taking into account the reaction reversibilities. A promising approach is the concept of elementary flux modes. These structural elements are unique for a given metabolic network and can be considered as non-decomposable steady state flux distributions using only a minimal set of reactions. For a very similar theoretical concept (extreme pathways), we showed that it yields identical results for most realistic applications, and that, hence, pathway analysis could be unified

[13].

For computer-based modeling of cellular systems, analysis of metabolic network stoichiometry has been considered only to a minor extent. Therefore, we developed the FluxAnalyzer, a user-friendly package for MATLAB® facilitating integrated pathway and flux analysis for metabolic networks within a graphical user interface [14]. It serves as modeling tool for our own projects [2,15], industrial corporations and academic research groups worldwide. Arbitrary metabolic network models can be composed and linked with network graphics leading to interactive flux maps. They allow for user input, control of a powerful collection of tools and algorithms, and display of calculation results. Pathway analysis in larger networks is hampered by the combinatorial explosion of possible routes. We derived a theoretical upper bound for the number of elementary modes, depending on network size [16]. The FluxAnalyzer has been applied to complex networks with more than 500,000 elementary modes, which far exceeds other published pathway studies.

Applying the elementary-mode analysis to the central metabolism of *E. coli*, we showed that an integrated analysis of elementary modes can be used to reconstruct key aspects of cellular behavior from metabolic network topology, namely to reliably classify mutant phenotypes, to analyze network robustness and flexibility, and to quantitatively predict functional features of genetic regulation. More generally, we conclude that robustness of metabolic networks is linked to redundancy, and that hierarchical genetic control supports this robustness by finding a trade-off between network efficiency and flexibility [15].



Elementary-mode analysis also proved suitable for metabolic flux analysis, which is often difficult because the metabolite balancing equation is underdetermined. For a network model of *R. rubrum*, we demonstrated that elementary modes enable one to identify fixed, additionally required, and never observable fluxes [2].

The concept will be also applied to analyze a model for infected MDCK cells (BPE group of Prof. Reichl).

Fig. 81: FluxAnalyzer: E. coli central metabolic network.

4.4.3. Discrete Abstractions

In the process of developing a dynamic mathematical model, one often faces uncertainty with respect to network topology and reaction mechanisms. This usually implies the existence of several plausible reaction schemes and, hence, basically leads to the development of families of differently structured models followed by a model discrimination step. When developing accurate continuous models, this process is severely impeded by the time-consuming task of parameter identification. Purely discrete models are much easier to establish, but are often “too coarse” to completely distinguish between competing hypotheses.

Together with the SCT group of Prof. Raisch the strength of both approaches were combined. We related sets of continuous models associated with a reaction scheme to individual discrete models. Discrete models (reaction networks) that are not able to explain available experimental data are discarded in a first step. This reduces the number of competing hypotheses and, hence, greatly facilitates the remaining discrimination task. Obviously, it is of utmost importance not to discard any continuous model that conforms to experimental data during the first step. We were able to prove that the behavior of any discrete model covers the quantized behaviors of all associated continuous models. In hybrid systems terminology, we construct finite automata, each representing a conservative abstraction of an infinite set of ordinary differential equation models [17]. The approach has been tested for smaller networks in intracellular signaling. Future work will include its refinement and application to complex regulatory networks in signal-transduction and genetic regulation.

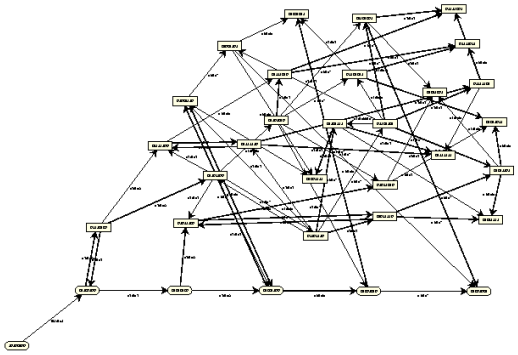


Fig. 82: Automaton for the MAP kinase cascade.

5. Selected Teaching Activities, Ph. D. Projects

5.1. Lectures

Dynamik verfahrenstechnischer Systeme, Univ. Stuttgart (E. D. Gilles)
Mathematical methods in ecological technologies, FH Magdeburg (A. Kremling)
Umweltbiotechnologie/biologische Grundlagen, OvGU Magdeburg (H. Grammel)

Ph. D. projects

Grammel, H.	Untersuchungen zur Regulation der Antibiotikaproduktion in Fermentationskulturen von *Streptomyces tendae* und *Amycolatopsis mediterranei*	1999
Kremling, A.	Strukturierung zellulärer Funktionseinheiten - ein signalorientierter Modellierungsansatz für zelluläre Systeme am Beispiel von *Escherichia coli*	2002
Kreth, J.	Untersuchungen zum Einfluss des Phosphoenolpyruvat zu Pyruvat Verhältnisses auf den Kohlenstoff-Katabolismus von Enterobakterien	2002
Kendelbacher, T.	Trajektorienoptimierung von Fermationsprozessen	2001
Falkner, K.	Untersuchungen zum Zelltod in eukaryotischen Zellpopulationen und Einzelzellen mittels Videomikroskopie und digitaler Bildanalyse	2003

Supervision of Ph.D. Theses (in preparation):

Backfisch, T.	Proteolysis in Prokaryotes	since 2001
Ederer, M.	Modellierung und Analyze der Interaktion globaler Regulationssysteme in *E. coli*	since 2003
Fischer, S.	Mathematische Modellierung und Analyse des Stoffwechsel von *E. coli*	since 2001
Kammerer, C.	Modellierung des Wachstums- und Produktbildungsverhaltens von Actinomyceten	since 1998
Klamt, S.	Modellierung metaboler und regulatorischer Netzwerke am Beispiel des Redox-Stoffwechsels und der redox-gesteuerten Regulation in Purpur-	since 1999

	bakterien	
Mannal, S.	Modellierung von Kernfunktionen des Hepatozyten zur modellgestützten Überwachung von Leber-ersatzsystemen	since 2003
Nutsch, T.	Mathematische Modellierung von Amplifikation, Ex-citation und Adaption in der Photo- und Chemotaxis	since 2000
Saez Rodriguez, J.	Modeling and Analysis of Signal Transduction Pathways in Mammalian Cells	since 2002
Sauter, T.	Die bakterielle Signalverarbeitung am Beispiel des Sucrose Phosphotransferasesystems in *E. coli* – Modellierung und experimentelle Überprüfung	since 1998
Schöberl, B.	Mathematical Modeling of Signal-transduction in Mammalian Cells at the example of the EGF induced MAP Kinase Cascade and TNF Receptor Crosstalk	since 1999
Stelling, J.	Robustness in cellular metabolic and regulatory networks	since 1998

6. Selected Memberships, Appointments and Awards

Gilles, E.D.

1993 - 2002 German Editor of Chemical Engineering Science
1997 - 2002 Managing Director at the MPI
1998 Member of Heidelberg Academy of Science
1999 Honorary Professor at Otto-von-Guericke-University Magdeburg
1999 Honorary Doctorate of University Ploesti, Romania
2000 Corresponding Member of Scientific Society Braunschweig
2002 External Member of Berlin Brandenburg Academy of Sciences and Humanity

Schöberl, B.

2001 Schloessmann Fellowship

Stelling, J.

1999 –2001 Fellowship of Peter-und Traudl-Engelhorn Stiftung zur Förderung der Biotechnologie und Gentechnik

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Research Group:

Mathematical Foundations of Dynamical Systems (MF)

Prof. Dr.rer.nat. Dietrich Flockerzi

This report covers the period from May 2001 to April 2003

1. MF Group Introduction

Given limited resources, how is it possible to render complex modern production processes more efficient while improving upon economic and ecological standards? In answering this question it is obviously crucial to have detailed knowledge of the fundamental principles governing the underlying technical processes and a precise framework for their formulation.

The engineering sciences have traditionally been restricted to the application of scientific knowledge. The modern engineering sciences are increasingly forced to bridge the apparent gap between fundamental research and industrial application. Tackling today's problems cannot be done by relying on mere computing power. New means are required. The need to focus on the development of new models, methods and tools, typically stated in mathematical terms, becomes more and more apparent. This shift of paradigm is reflected in our Max Planck Institute where engineers are pushing research forward together with mathematicians, biologists and computer scientists within a highly interdisciplinary research concept. The common aim is to improve the analysis of dynamic processes so that – based on their newly discovered properties – such processes can be run in the desired controlled way.

The formulation of appropriate mathematical models based on the fundamental relationships in the natural sciences and the experience from experiments is a major task in tackling the projects investigated by the research groups of the MPI. Detailed mathematical modeling of technical processes or cellular systems offers a rather precise approximation of the real processes but will inevitably lead to models of high dimension and high structural complexity. Consequently, such detailed models may be too complicated for a rigorous analysis of their dynamical behavior and for a practical design and implementation of efficient control strategies. Thus, reduction methods on a firm mathematical basis are urgently needed to arrive at mathematical models, which, on the one hand, still describe the relevant features of the underlying real process and, on the other hand, can be investigated analytically or numerically at acceptable computational costs. Of course, synthesis and control strategies derived from a reduced model need to work reliably for the real process.

The Research Group *Mathematical Foundations of Dynamical Systems* was founded in May 2001

- to assist in the mathematical formulation of models,
- to do model reductions and modularization on a rigorous mathematical basis,
- to offer alternative mathematical approaches to applied problems,
- to help with the validation of a *successful* numerical routine,
- to do fundamental research on topics that are connected to the applications put forth at the Max Planck Institute,
- to restate plausible or formal arguments in mathematically precise terms,
- to *translate* publications from the mathematics community, thereby narrowing the gap between the languages used by mathematicians, engineers and biologists.

Another important function of the MF group is to provide any kind of service or help requested by the staff of the Max Planck Institute in many fields of mathematics (analysis, algebra, geometry, topology, stochastics, etc.) – individually and in intensive courses.

2. Members of the MF Research Group

Dietrich Flockerzi

- at the MPI since July 2000
- head of research group since it was founded in May 2001

The group is to be a small one with only two or three further members (one funded by the MPI, one or two by a third party). A graduate of mathematics and cybernetics at the University of Stuttgart is a promising candidate for joining *Mathematical Foundations of Dynamical Systems*. He possesses the prerequisites to tackle the mathematical problems in the new projects on Population Balance Systems.

3. Survey of the Research Projects

Project Area: Reduced Models

Project: Invariant Manifolds	The geometric theory of *Invariant Manifolds* for systems of differential equations in finite or in infinite dimensions offers a precise reduction mechanism to lower dimensionality since the reduced system will be an exact subsystem of the given system. In case such an invariant manifold is attractive, the long-time behavior of the reduced system presents a reliable approximation of the asymptotic behavior of the original system. This is of particular use since algorithms exist for computing approximations of invariant manifolds with high accuracy.			
Title	**Scientists**	**Funded by**	**Start**	**Partners**
Subproject: Model Reduction via Center Manifolds and Singular Perturbation Theory	D. Flockerzi	MPI	05/2001	MPI groups, OvGU Magdeburg
Subproject: Model Reduction in Population Balance Systems	D. Flockerzi, N.N.	MPI	02/2003	MPI groups, OvGU Magdeburg

Project Area: Integrated Processes

Project: Nonlinear Dynamics and Control of Integrated Processes	The integration of different process units in multifunctional processes very often gives rise to synergetic effects that can be technically exploited. Such integrated processes are modeled by systems of nonlinear differential equations and can, in the beginning, be investigated by general mathematical methods. But typically, the performance requirements pose novel challenges for a mathematician as well as for an engineer. New concepts for process integration are being developed; their efficiency and their technical applicability are being examined.

	Scientists	Funded by	Start	Partners
	D. Flockerzi	MPI	01/2002	

Project Area: Coupled Processes

Project: Nonlinear Dynamics of Coupled Processes	From a mathematical point of view, systems of equations for coupled and integrated processes can be approached by using similar methods. From the chemical engineering side, the questions posed are more specific to the system class. So for coupled processes, the discussion is concentrated on the new effects generated by coupling different units, e.g. reactors and separators. In Systems Biology the decomposition of coupled systems is of primary interest for answering the manifold open problems concerning metabolic, regulatory and signal transduction pathways.			
	Scientists	**Funded by**	**Start**	**Partners**
Subproject: Nonlinear Dynamics and Control of Coupled Processes	D. Flockerzi	MPI	01/2002	

Moreover, the MF group assisted and cooperated with all of the other research groups at the Max Planck Institute on a variety of research projects not listed above.

4. Research Highlights

4.1. Invariant Manifolds

The local geometric theory of dynamical systems concerning bifurcations via center manifolds and the global geometric theory referring to homoclinic and heteroclinic bifurcations are advanced with respect to the specific applications from chemical engineering. In addition, results – partly known, partly to be developed – concerning Singularity Theory and Inherent Structures (such as symmetry and monotonicity) are employed for solving the specific problems from the application side. Quite often, phenomena that are generic in applied problems are mathematically non-generic. As an example we mention that chemical equilibrium curves originate from non-generic vertical bifurcations (cf. section 4.1.4 below and [10]).

The design of safe reduction algorithms is of utmost importance in ordinary and partial differential equations as well as in integro-differential and functional-differential equations showing dominant sub-dynamics. The detection of suitable scales of time, variables and parameters – justifying a generalized quasistationarity assumption – is of particular interest in many applications since it leads directly to reduced models. Hereby, the decomposition into slow and fast variables, into masters and slaves, may vary within phase space. Thus, in a nonlocal setup, the quasistationarity can, in general, not be checked by examining pointwise linearizations. The nonlocal case presents a tough problem for theorists, and there are many pitfalls on the way. In [6] we present a series of counterexamples to the method of Intrinsic Low Dimensional Manifolds as it is frequently employed in combustion theory[1].

The derivation of quantitative statements is a *conditio sine qua non* for any kind of approximation. Here, it is essential to know *how distinctive* the dichotomies within the underlying system really are in order to establish bounds on

- *how slow* and *how fast* certain dynamics need to be for proving the applicability of abstract theorems and
- *how accurate* a chosen approximation needs to be for achieving reliable numerical solutions.

Such error bounds are necessary for the validation of the reduced models and their numerically computed solutions. For example, in finite dimensions, the closeness of the

[1] Warnatz J., Mass U., Dibble W.: Combustion, Springer Verlag 2000

reduced model and the original model cannot be measured by the respective vector fields – a fact that is sometimes overlooked (cf. [5], [6]). A challenging goal of the project *Invariant Manifolds* is the identification of system classes (in chemical engineering and systems biology) that allow a simple detection of dichotomies via the spectral properties of linearized systems. Of course, any concept for synthesis and control that is obtained from the reduced finite dimensional model needs to be proven so efficient that it can be applied to the underlying real process safely and successfully.

Systems biology tries to explain the complex functionality of metabolic and regulatory networks, cell cycles and signal transduction pathways. Based on systems theory and interdisciplinary cooperation, mathematical models of amenable size and structure have been, and still need to be, established. The decomposition (*modularization*) of a network and the analysis of the building blocks (*modules*) and their interconnections present a promising approach for answering the manifold open problems in biological reaction networks. For special classes, the geometric theory of Invariant Manifolds in conjunction with Stability Theory can be applied with success. So, the problem of localizing and analyzing dominant sub-dynamics and of detecting hidden hierarchies within a complex network can sometimes be solved by the definition of appropriate coordinates and suitable scales. Invariant Manifold Theory then constitutes one way to take advantage of inherent hierarchies, e.g.,

- to describe the attractor containment, the transition phase, the switches and the input-output relations,
- to offer computable approximations,
- to understand the robustness of inherent network structures,
- to analyze the sensitivity with respect to parameter variations.

Important aspects of modularization are the definition and the structural investigation of single modules, the analysis of the interconnections of several modules (e.g. as shown in a synchronization process) and finally their synthesis and control.

- Which interconnections of which modules generate a model that reflects the dynamics of the given network?
- Which interconnections of which modules lead to a model showing the behavior that the underlying system is to be designed for?

Such questions are investigated in cooperation with the SBI research group of Prof. Gilles. Also, sensitivity issues in biological networks have been addressed in collaboration with Prof. Gilles' group.

4.1.1. Reduced Models

There are many cases where simplified models of the underlying process can be helpful. Always having in mind the specific problem formulation, for example,

- to detect multiple steady states and switching surfaces (cf. section 4.1.4 and Fig. 83),
- to establish oscillations or bursting phenomena (cf. section 4.1.3, Fig. 84 and Fig. 85),
- to analyze the pathways in signal transduction and in metabolic or regulatory networks,
- to improve the process design, e.g. to optimize biological processes like the virus dynamics (cf. section 4.1.2)
- to design a robust control scheme in the presence of uncertainties,
- to detect and compensate for disturbances,

such simplified or *reduced models* should still be capable of reflecting the essentials of the dynamical behavior and should allow the construction of effective and reliable control strategies.

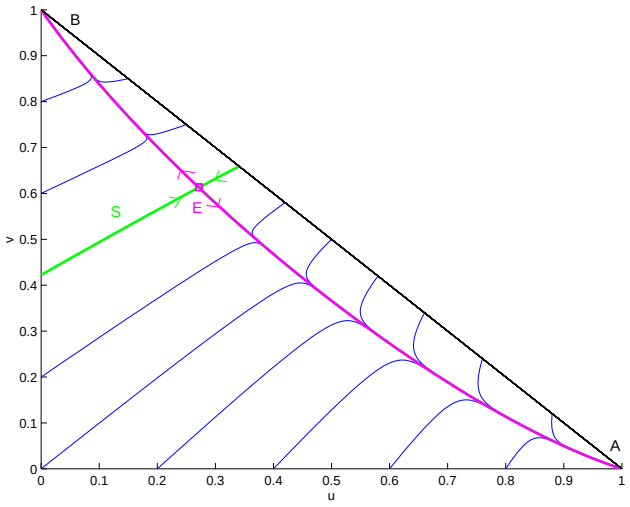

Fig. 83: Bistability with a switching curve S and pure products.

For initial values below S the concentrations of the products A and B tend towards the concentration of the pure product A, for initial values above S towards the one of the pure product B.

Proposed reduction mechanisms include:

(a) The restriction of the dynamical process to an attractive invariant manifold of desirably small dimension and the discussion of the detailed model on it – or more roughly – the restriction to an approximation of such an attractive invariant manifold and the discussion of an approximation of the induced detailed model on it (cf. approximate center, slow and inertial manifolds and quasistationary approximations).

(b) Finite expansions with respect to eigenfunctions or empirical eigenfunctions (Karhunen-Loève method) leading to finite-dimensional substitute systems in the case of partial differential equations, the method of moments in the case of population balance systems.

For example, given a slow/fast decomposition in a reaction-diffusion or a transport-reaction system of parabolic partial differential equations, a Galerkin-type reduction or a more general reduction based on empirical eigenfunctions often allow the derivation of a finite dimensional ordinary differential equation on an approximate inertial manifold (cf. Prof. Kienle's PSD and Prof. Sundmacher's PCP group).

(c) The assumption of special structures for the sought solutions like wave-form solutions in separator systems, reactive distillations or in chromatography (cf. Prof. Kienle's PSD group).

(d) The abstraction of the detailed model within a more general framework, e.g., within the theory of hybrid systems or automata, exploiting hierarchical structures and additional properties like symmetry and monotonicity (cf. the *behavioral system theory* promoted by Prof. Raisch's SCT group).

Qualitative and, if possible, quantitative error bounds need to demonstrate the success of any model reduction. Within the project area Reduced Models at the MPI the Research Group *Mathematical Foundations of Dynamical Systems* develops methods and tools that lead to reduced models possessing the necessary precision for the specific task. So, model reduction can be validated in a series of applications.

4.1.2. Virus Dynamics

In developing bioprocess concepts for vaccine production, one of our main interests is the presentation of a, not too complex, mathematical model, that describes the cell growth and replication of influenza viruses in MDCK cells (cf. [2]). Based on experiments on cell metabolism, on virus replication in fermenters and single-cell cultures and based on the determination of industrially relevant on- and off-line values for glucose, ammonium, lactate, aminoacids and virus titer, this model allows us to develop concepts for process monitoring

and control. These concepts then help to analyze the sensitivities of the process, for example, the yield variations, and facilitate the validation of these processes. This research is performed in cooperation with Prof. Reichl's groups at the MPI and the OvGU Magdeburg.

4.1.3. Bursting and Coding in a Hemin-Oscillator

Oscillatory behavior in the *pH*-value was observed during the oxidation of sulfite by hydrogen peroxide mediated by hemin in a continuous stirred tank reactor. With increasing flow rate the oscillations evolve from relaxation oscillations to more complex bursting behavior.

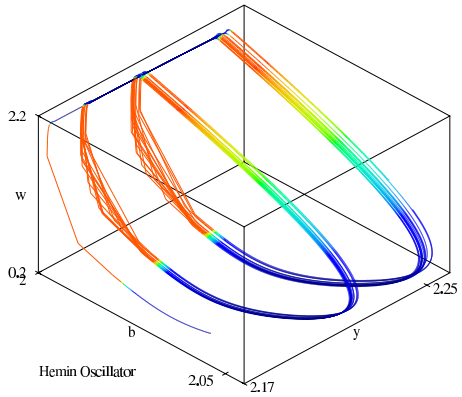

Fig. 84: A typical solution for the 3D-Hemin-system .

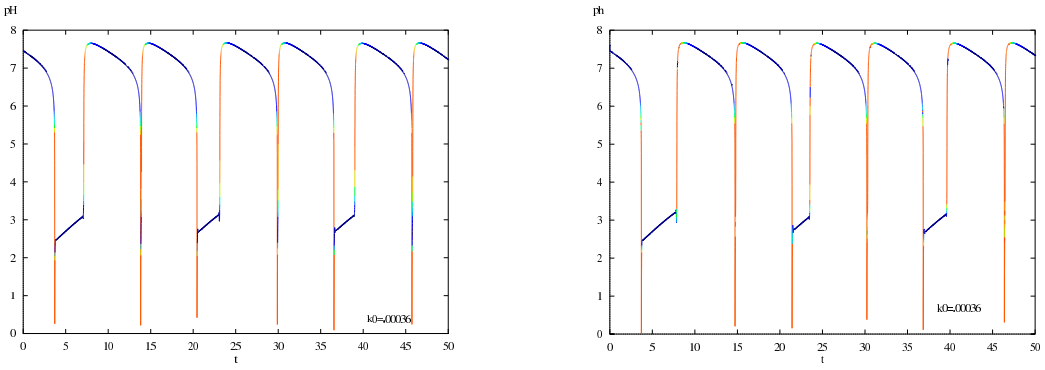

Fig. 85: pH(t) for 3D- and 6D-Hemin-system

For the 6D-Hemin-system a 3D reduced model is defined on an attractive and slow invariant manifold. Fig. 85a shows a typical solution for the reduced model, Fig. 85b compares the pH-value of the reduced model (left) and of the full model (right).

The proposed relaxation mechanism involves the autocatalytic oxidation of HSO_3^- by H_2O_2. Equilibria between *pH*-dependent forms of hemin account for the consumption of protons and provide the feedback steps that give rise to oscillatory dynamics.Numerical simulations show that two *pH*-dependent reactions suffice to obtain bursting oscillations which resemble those observed in the experiments (cf. Figures 2, 3 and [9]). The small amplitude oscillations between the bursts refer to the possible coding of biological information. This research is performed in cooperation with the Biophysics Department of the OvGU Magdeburg.

4.1.4. Singularity Analysis of Reactive Separations

Singular points like pure components, azeotropes, reactive azeotropes or pinch points of reactive reboiler and reactive condenser models are analyzed. Five typical one-reaction systems with different liquid nonidealities, two of them involving liquid phase splitting, illustrate the bifurcations of singular points for the reactive reboiler as well as for the newly introduced reactive condenser. This research towards the conceptual design of continuous counter current reactive distillation processes is performed in cooperation with Prof. Sundmacher's PCP group (cf. [10]). Fig. 83 presents one of the typical residue curve maps for a reactive condenser.

4.2. Nonlinear Control

The work on *Nonlinear Control* is concerned with fundamental principles of disturbance attenuation in nonlinear control problems. It is based on the theory of integral manifolds for differential games and has no specific application in mind. In *Dissipation Inequalities and Nonlinear H$^\infty$-Theory* ([8] and [1]) we consider smooth control systems which are influenced by an exogeneous input $t \to v(t) \in \mathbb{R}^d$, e.g. by a disturbance signal. The dynamics are given by a smooth ordinary differential equation

$$\dot{x} = f(t, x, u, v) \tag{1}$$

with $x \in \mathbb{R}^n$ where $u \in \mathbb{R}^m$ is the control variable that is to be chosen as a function of *t* or of *(t, x).* Given a scalar instantaneous pay-off $f_0(t, x, u, v)$ and a time interval $[t_0, t_e]$ we are looking for mappings *(t, x)* $\to$ *u (t, x)* and a scalar function *V (t, x)* such
that the dissipation inequality

$$\int_{t_0}^{t_e} f_0(t, x(t), u(t, x(t)), v(t))dt \le V(t_0, x(t_0)) \tag{2}$$

holds true for rather arbitrary *v(t).* In [8] we describe various ways of constructing feedback control laws that give rise to such dissipation inequalities. Usually, one speaks of H^∞-control laws or worst-case strategies. Here, the state *x(t)* of our system may vary significantly from equilibria so we do not resort to linear H^∞-theory. There is however one hypothesis *(ℋ)* which we impose on f and f_0 and that is always satisfied in the affine-quadratic scenario.

The dissipation inequality (2) can be viewed as the minmax-half of the saddle-point condition for the two-person zero-sum differential game

$$\min_u \max_v \overset{!}{=} \max_v \min_u \overset{!}{=} \int_{t_0}^{t_e} f_0(t,x,u,v)dt$$
$$\text{subject to} \quad \dot{x} = f(t,x,u,v), \quad x(t_0) = x_0, \tag{3}$$

with fixed terminal time t_e. In fact, if *u(t, x), v(t, x)* is a saddle-point of this game (3) then (2) holds true with the value $V(t_0, x_0)$ of the game as a function of the initial data. With the Lagrangian function

$$L(t,x,y,u,v) := y^T f(t,x,u,v) + f_0(t,x,u,v). \tag{4}$$

Hypothesis (*ℋ*) requires that

$$H(t,x,y) := \min_u \max_v L(t,x,y,u,v) = \max_v \min_u L(t,x,y,u,v) \tag{5}$$

is well defined and smooth. The main result of [8] for differential games satisfying hypothesis (*ℋ*) is a precise version of the principle that the following three facts are shown to be equivalent:

(a) The Isaacs problem admits a solution.

(b) The Hamilton-Jacobi partial differential equation

$$V_t + H(t,x,V_x^T) = 0 \tag{6}$$

is solvable given the appropriate terminal condition.

(c) The Hamiltonian ODE-system, also called canonical equation,

$$\dot{x} = \frac{\partial H}{\partial y}^T (t,x,y), \qquad \dot{y} = -\frac{\partial H}{\partial x}^T (t,x,y) \tag{7}$$

has an integral manifold of the form *y = S(t,x)* that achieves the appropriate terminal values.

The Hamilton-Jacobi equation (6) plays a central role since any solution *V(t,x)* gives rise to an inequality similar to (2), namely

$$\int_{t_0}^{t_e} f_0(t,x(t),u_H(t,x(t),V_x^T(t,x(t))),v(t))dt \le V(t_0,x(t_0)) - V(t_e,x(t_e)) \tag{8}$$

where $u_H(t, x, y)$ is the *u*-component of the saddle-point of the Lagrange function *L*. (8) holds true for any *v(t)* if *x(t)* is a solution of

$$\int_{t_0}^{t_e} f_0(t,x(t),u_H(t,x,V_x^T(t,x))),v(t)), \qquad x(t_0) = x_0. \tag{9}$$

Thereby it is clear that the problem of finding control laws which give rise to dissipation inequalities can be reduced to the problem of solving (6) locally, i.e., on a neighborhood of the solution curve $\{(t,x(t)) : t_0 \le t \le t_e\}$ of (9). Such local solutions are provided by characteristics of the Hamilton-Jacobi equation (6) which are embeddable into local integral manifolds. A characteristic is a curve $t \to (t,\tilde{x}(t),\tilde{y}(t))$ such that $(\tilde{x}(t),\tilde{y}(t))$ is a solution of the canonical equation (7) with terminal value prescribed by the integral manifold *y = S(t,x).* A characteristic can locally be embedded if the associated nonautonomous Riccati matrix differential equation does not possess a conjugate point.

When does a control law *u = u(t, x)* exist that gives rise to a dissipation inequality and how can it be established in concrete situations?

Roughly summarizing [8] the answer runs as follows: Consider for every $\hat{t} \in [\, t_0, t_e \,]$ – with the system (9) being in the state $x(\hat{t})$ – all characteristics $(t,\tilde{x}(t),\tilde{y}(t))$ with $\tilde{x}(\hat{t}) = x(\hat{t})$ and make sure that none of them has a conjugate point in the time interval $[\hat{t}, t_e]$. Then there is a scheme for computing the control law by repeatedly solving boundary value problems.

This answer is based on the tacit assumption that one has manageable criteria for the absence of conjugate points. Since such criteria are hard to establish due to the indefiniteness of the Riccati equations we present alternative approaches for the affine-quadratic scenario that partly avoid these difficulties. The price to be paid is exhibited in certain disturbance restrictions.

5. Teaching Activities and Ph.D. Projects

Teaching:

- *Dynamik nichttechnischer Systeme*
  Block Course ([3] and [5]), MPI Magdeburg (02 and 03, 2000)
- *Dynamische Systeme und Chaos*
  Block Course ([4]), MPI Magdeburg (07, 2000)
- *Monotone Dynamical Systems*
  Block Course, MPI Magdeburg (11, 2000)
- *Dynamik nichttechnischer Systeme*
  Course at ISR ([3]), University of Stuttgart
- *Nichtlineare Systeme*
  Course at the Institute of Automatic Control, OvGU Magdeburg

Topics in Linear Algebra [7] was written for the biology groups SBI and BPE. Emphasis was placed on the geometric aspects, in particular on the Singular Value Decomposition and the associated Principal Component Analysis as needed in *Stoichiometric Network Analysis*.

Organization of the mini-course *Delay Equations* by Prof. B. Lani-Wayda (11/2002).

Referee of Ph.D. Theses by G. Dirr (University Würzburg) and B.J.L. Brown (University of Cape Town, South Africa).

6. Selected Memberships, Appointments and Awards

Member of Deutscher Hochschulverband (DHV)
Referee for

- Automatica
- Chemical Engineering and Processing
- Chemical Engineering Sciences
- Systems and Control Letters

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Research Group:

Integrated Navigation Systems (INS)

Prof. Dr.-Ing. Ernst Dieter Gilles

This report covers the period from June 1998 to April 2003.

1. INS Group Introduction

The research group *Integrated Navigation Systems* (INS) is actively involved in the development of state of the art navigation systems for inland and coastal navigation. The integrated navigation system that has been developed in cooperation with German waterway authorities is intended to improve the safety of navigation in difficult situations like night and foggy weather and relieves the pilot of the routine work usually involved with navigation.

The project started more than 20 years ago at the Institute of System Dynamics and Control at the University of Stuttgart. Prof. Gilles has been the head of the project since its inception. As a result of the long development time, the *Integrated Navigation System* has reached a mature state and is used today on many ships. Fig. 86 shows a typical navigation situation on the river Rhine as displayed on the navigation screen.

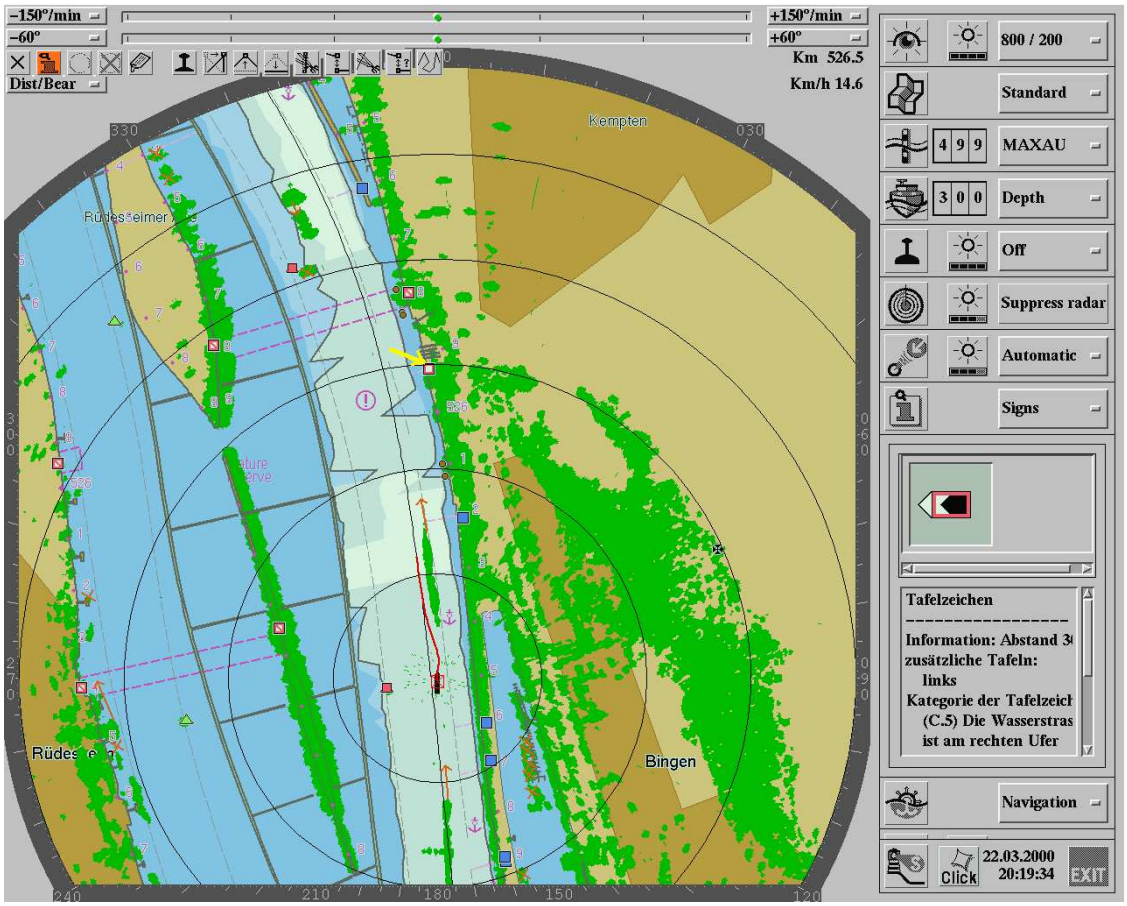


Fig. 86: Navigation display.

The research group at the MPI is currently addressing a couple of problems that have not been successfully solved up to now. The open problems are mainly in the areas of modeling the dynamic behavior of ships, sensor fault detection, sensor integration, and automatic track keeping for vessels of different sizes in narrow bends.

2. Members of the INS Research Group

As of April 15, 2003 the group consists of 2 scientists with PhDs and 3 PhD students.

Group Member	Status	Joined INS
Prof. Ernst Dieter Gilles	Head of group	
Dr. Arne Driescher	Postdoc	08/1998
Jan Blumschein	PhD Student	09/2002
Emil Petersky	Electrical Engineer	01/2000
Adrian Derscanu	PhD Student	09/2002

Group at Stuttgart University: Jörn Beschnidt, Ralph Bittner - PhD Students

3. Survey of Research Projects

Project Area: Network Theory

Title	Scientists	Funded by	Start	Partners
Project: Virtual navigation environment	The project focuses on the development of a simulation tool that can handle complex traffic scenarios for inland navigation. Its primary use is the detailed simulation of the ship dynamics of a single ship including realistic sensor data generation for real-time testing of the integrated navigation system.			
	Beschnidt Driescher	ISR Stuttgart MPI	2001	
Project: Dynamic ship models	Accurate modeling of ship dynamics is required for simulation, testing and controller design. The project currently concentrates on the drift dynamics of large ships in current.			
	Blumschein	MPI	09/02	ISR Stuttgart, SCT

Project Area: Hierarchical Structures

Title	Scientists	Funded by	Start	Partners
Project: Automatic chart generation	Availability of electronic navigation charts is the most important obstacle for wide spread use of modern inland navigation systems. The process of chart generation can be partly automated by using radar image processing techniques. [5]			

	Derscanu	MPI	2002	ISR Stuttgart
Project: High performance radar interface	Radar is the single most important sensor for inland navigation. Besides the direct impact on image quality on the navigation display, radar is used for radar-map-matching, object tracking and automatic chart generation. The project currently focuses on developing hardware for interfacing radar systems with standard PC systems.			
	Driescher Petersky	MPI	2001	ISR Stuttgart

4. Research Highlights

4.1 Integrated Data Processing

Knowledge of the ship's position and course is an essential requirement for navigation. One of the major characteristics of the Integrated Navigation System is the integration of different sensors with complementary error characteristics. Measurements from various sensors are combined into one *state estimate*. Blending of the different sensor signals is done based on a model of the ship's dynamics by the well-known Kalman filter approach.

4.1.1 Kalman filter techniques

Kalman filter techniques based on a *linear* state space model of the form

$$D_t \mathbf{x} = \mathbf{A}\mathbf{x} + \mathbf{B}\mathbf{u} + \mathbf{G}\mathbf{w}$$

$$\mathbf{y} = \mathbf{H}\mathbf{x} + \mathbf{R}\mathbf{v}$$

with state vector **x**, known inputs **u**, and measurements **y** have been popular since the early 1960s. The family of Kalman filters (the general structure is applicable both to continuous-time models where $D_t \equiv \frac{\partial}{\partial t}$ and to discrete-time models where D_t is a time-difference operator) yield *optimal* estimates of the system state **x** and its covariance matrix **C** at some given time *t*. The properties of Kalman filters hold for a linear model under the assumption that the noise processes **v** and **w** are independent Gauss-Markov processes. (In practice, and especially in navigation applications, both assumptions are often violated; the dynamics are non-linear, and the noise isn't Gaussian.)

The problem of linear filter design is generally solved by the Kalman filter provided that

- the underlying dynamics are linear and exactly known, and
- any noise or uncertainty is Gaussian with known characteristics.

This means that the difficulties of filter design are actually moved into modeling. For the nominal model (the one without noise parameters) one can benefit from the rich variety of models whose development has been forced by the needs of control applications. In addition, a detailed description of noise characteristics is needed which is an often underestimated problem.

4.1.2 Application Demands

Apart from the common theoretical foundations, different applications impose completely different demands on the processing of sensor data. These different kinds of applications clearly call for different models to be used.

The *safety of navigation* requires reliable information about the ship's position and course under all conditions. The detection of sensor failures plays an important role here, whereas the precision of data is only a secondary issue.

Control applications generally require the state estimates to be continuously available, as predictions may, under certain conditions, be substituted for unavailable measurements. The data processing must not introduce additional delays of a kind that could affect the dynamics of the closed-loop system. It can be assumed that a detailed model of the ship's dynamics is available.

Measurements for *model identification* and *model validation* are usually carried out under "optimal" conditions where the effects of unwanted disturbances can be kept to a minimum. The measurement precision to be achieved exceeds the demands of usual navigation applications; it can be increased by repeated experimentation. As the goal of data grabbing is to obtain a model, the data processing itself cannot be based on that model. Noise reduction plays an important role, but it is limited to simple filtering related to models that represent basic physical constraints (e.g., kinematic behavior and bounded energy).

Recently, an extensive comparative analysis of several model structures was carried out with respect to their fitness for state estimation (data filtering and prediction) as needed by control applications [6].

4.1.3 Nonlinearities

The ship's dynamics to be modeled are basically nonlinear due to three different reasons:

1. Essential nonlinearities are introduced by the rotational motion of the ship. The structure of these is simple, and the nonlinearities can easily be compensated for if the rotation is sufficiently known.
2. The hydrodynamics yield forces that are mainly nonlinear functions of the ship's velocity relative to the water. The effects involved are very complex (e.g. transitions from laminar to turbulent flow patterns), and therefore these will be modeled by rather simple approximations. Precise modeling of the hydrodynamic forces requires exact knowledge of the stream velocity field around the ship that cannot be measured in practice, the model will be based on an estimate of that velocity.
3. The usage of geographic coordinates for the ship's position involves non-linear coordinate transforms. The handling of these is easy as it is sufficient in practice (especially in the case of inland shipping) to replace them with a constant linearization.

As the nonlinear hydrodynamic models are just being established, the question of whether the linearizations currently in use are sufficient will be addressed in the near future.

4.1.4 Non-uniform Sampling

For the sake of simplicity, the representations of dynamic model and Kalman filter equations are usually given in continuous time (preferred for the model) and/or sampled at equidistant points in time (preferred for the measurements).

The sensor equipment used on board enforces a different situation: measurements may be provided at different sample frequencies, and due to varying levels of disturbance there may be some samples missing. This means that the measurements are provided at non-uniform sample intervals, and in general there will be only a subset of the measurements provided at each of these. The Kalman filter can easily (and without loss of exactness) be extended to this situation; the approximations used for the discretization of the continuous problem require the sample times to be bounded.

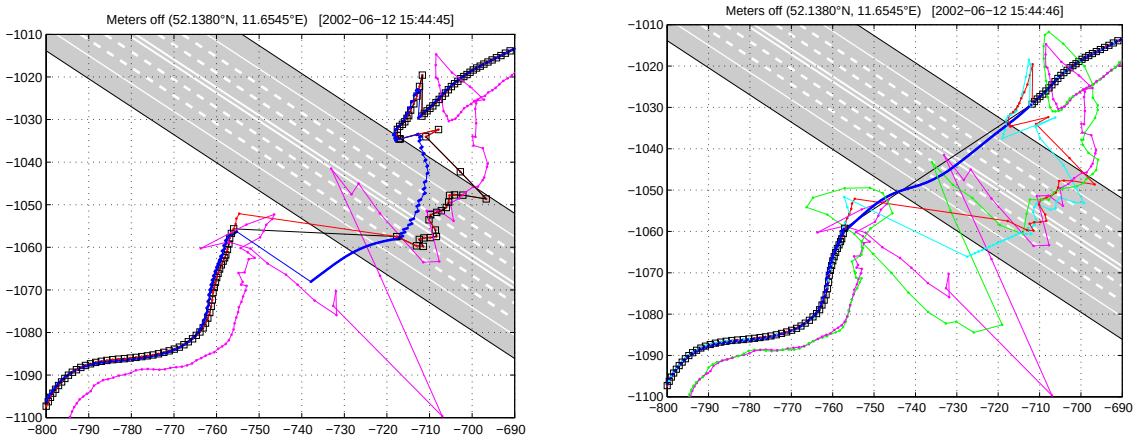
The key issue in the application of Kalman filters to a complex navigation system is a robust implementation that handles different sources of data in an asynchronous manner. The implementation done in our Integrated Navigation System supports not only the usage of arbitrary sample frequencies, but even allows measurements affected by varying transport delays to arrive in time-reversed order, triggering a roll-back mechanism.

4.1.5 Model Uncertainties

The theoretical Kalman filter approach requires the underlying dynamic model to be known exactly. A quite common approach consists of including the effects of model errors in the system noise parameters. As far as unmodeled causal effects are concerned, it is clear that these errors are in some sense deterministic, and the Gaussianness of noise is lost. While this procedure is unsatisfactory from a theoretical point of view, increasing the system noise level leads to filters with reduced sensitivity to model parameters, which are preferred in practice (the so-called “sub-optimal filtering”).

4.1.6 Signal Validation

Faulty sensors may produce disturbed signals that have to be detected and ignored. From the Kalman filter point of view, there is a probability distribution assigned to each of the expected sensor values - when very unlike values occur, the sensor will be regarded as faulty.



Original situation: GPS multipath reflections around the bridge confuse the controller.

Simulated correction: Suspicious data is discarded; the position is predicted based on a model of the ship’s dynamics.

Fig. 87: GPS failure detection and compensation during bridge crossing.

Especially in the case of GPS measurements there are various fault mechanisms to be handled separately. Commercial receivers do their best to reject faulty measurements but cannot completely achieve that without knowledge of the ship's dynamics. As they tend to filter the measurements on their own, disturbances are attenuated and hard to detect.

The current work focuses on that point, especially on the effect of multipath reflections caused by metal constructions like bridges, etc. The disturbances produced by these effects are usually very small, – measured in meters – and fall below the limit of the GPS overall precision. They may be detected by the corresponding changes in velocity that are a violation to the underlying ship dynamics. Fig. 87 demonstrates the rejection of GPS data disturbed by multipath reflections using a comparison against predicted positions.

The switching of sensors may lead to transients in the filtered signal. While applications like chart display must receive any information as soon as possible, control applications need special handling to suppress these transients.

4.1.7 Noise Modeling

Until now, many of the noise parameters involved were taken only as raw approximations of their "true" values. The filtering of data works sufficiently well in practice with somewhat "overestimated" noise parameters, though there may be better results attainable. Signal validation, in contrast, requires the noise estimates to be as sharp as possible.

To obtain reasonable values for the noise parameters requires a thorough investigation of the noise properties of the disturbances one can expect. The question of how the non-Gaussian noise, e.g., resulting from stream influence or nonlinear hydrodynamic forces, can effectively be approximated by a Gaussian noise process still has to be addressed.

4.2 Modeling of Ship Dynamics

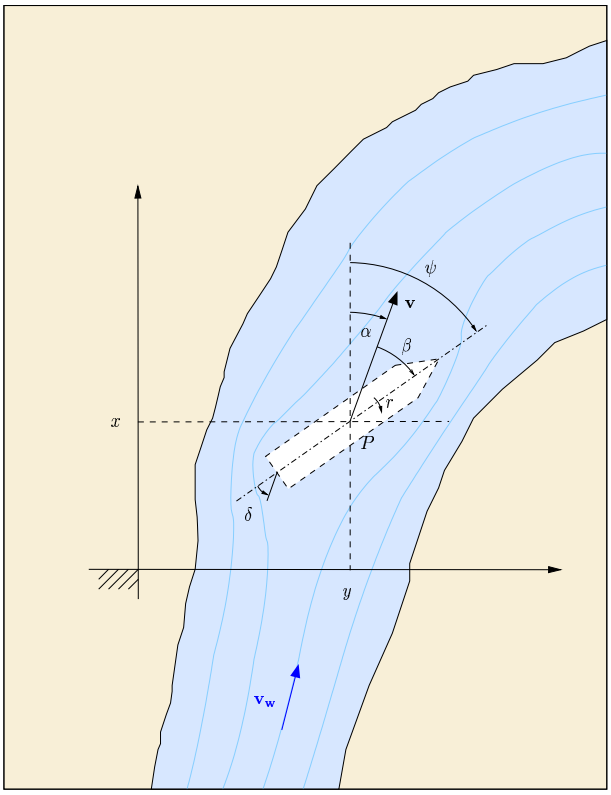
Unlike in open sea, a continuously changing course and reduced space availability characterize navigation on inland waterways. In order to achieve the required performance, ship models, as a mathematical representation of the available knowledge about the ship's behavior, are included in several modules within the *Integrated Navigation System*. This is particularly the case with the sensor signal processing and the track keeping modules. Their performance strongly depends on the accuracy of the model representing the ship dynamics.

During navigation, several variables characterizing the ship's movement have to be monitored as well as influenced by the *Integrated Navigation System*. These variables, shown

in Fig. 88, are the linear and angular positions and velocities, which describe the ship's translational and rotational movements respectively. These variables can be influenced by means of the propulsion system and the rudder angle δ. A dynamic ship model generally represents the interdependencies between the described variables with a set of differential equations.

Several ship models have been developed in the past and are available in the literature. Although the use of some of them in the *Integrated Navigation System* has led to acceptable results, they have failed to appropriately represent the dynamics of inland vessels under certain conditions. The particular characteristics of inland navigation demand the following model features:

- High precision, because of the reduced space availability in inland navigation.
- A low number of well identifiable parameters that can be determined despite the restricting conditions on many inland waterways.
- Robustness against water current, i.e., the required precision should be met for upstream and downstream navigation, in spite of the water current present in rivers.



ψ : Heading [rad]

r : Turning rate (yaw) [rad/s]

α : Course over ground [rad]

β : Drift angle [rad]

δ : Rudder angle [rad]

P: Reference point of the model

$\mathbf{v}$: Velocity vector at P [m/s]

$\mathbf{v_w}$: Water current vector [m/s]

Fig. 88: Variables involved in the modeling problem.

The most accurate available models have an excessive number of unknown parameters. For those that do meet the structural simplicity requirements, the necessary accuracy is not achieved under particularly difficult conditions, such as big ships navigating downstream through tight curves. The considered models fail to properly reproduce the drift behavior, which is strongly present in the described situation. The drift implies the presence of a sway (lateral) velocity component, causing the direction of movement to differ from the ship's length axis by a "drift angle" β, as shown in Fig. 88. The impact of the water current on this effect can be observed by comparing the small drift angles in upstream navigation with the much larger angles needed when navigating downstream.

As the described restrictions in the use of the available models in the *Integrated Navigation System* are a limiting factor in the performance of the system, efforts are being made to develop dynamic ship models that meet the special requirements for inland navigation. Based on the following aspects, a physically motivated approach has been chosen:

- The requirement of high accuracy in spite of simplicity can only be achieved by selecting a reduced number of effects to be included in the model. This is only possible starting from relationships that have a physical interpretation.
- Analyzing robustness against water current requires the explicit consideration of the effect of the current on the model variables. This property is not met by any of the available models. It can be achieved at a physical level, by considering that the hydrodynamic drag forces depend on the relative velocity between ship and water, while the inertial forces are affected by the velocity relative to ground.
- A physical interpretation of model parameters makes it possible to estimate their values based on physical ship properties like mass and geometry. This could be helpful given the restricted identification conditions.

Based on Newton's second law, and the consideration of nonlinear hydrodynamic drag force components and added masses, recent work [7] has led to the following drift dynamics model for the simpler case of still water:

$$\dot{\beta} = -\frac{\|v\|}{L_\beta}|\beta|\beta + K_\beta r$$

The parameters L_β and K_β are velocity independent. Although it results from the consideration of the relevant physical aspects, the structure is still remarkably simple and contains only two parameters. As compared to former models used for inland vessel control, experimental results based on turning circle maneuvers confirmed improved performance in

describing the drift behavior in still water. Current efforts concentrate on the extension of the developed model, accounting for the effect of water current, as well as the application of the model to the different tasks of the *Integrated Navigation System*.

4.3 Model Based Ship Control

The integrated navigation system includes a feature for automatic track keeping of inland vessels. The control task is defined as keeping a well-defined location of the ship (e.g. the bow) on a given track along the river. The track is usually defined by the pilot beforehand and saved as part of the electronic navigation chart. Moreover, for many situations it is appropriate to allow for an offset to the predefined track, e.g., to make way or to pass other ships on the same track. This offset can be adjusted online by the pilot by means of a joystick.

The control algorithm has to calculate an appropriate rudder movement based on the current position of the ship, the desired position and the offset to the guiding line. While keeping a ship sailing along a straight line is already a difficult task due to significant unknown disturbances (current, wind) and model uncertainties (changing and unknown load), following a narrow bend in the river requires a much greater effort. To achieve the smallest possible deviation from the given track, the controller has to anticipate the required ship movement and compensate for the curvature in the given guiding line. The necessary calculations for the rudder angle require an accurate model of the ship dynamics and therefore falls into the framework of model based control. The approach to the control problem is illustrated in Fig. 89 and consists of two basic parts: the feed-forward controller and the feedback controller. The feed-forward controller is designed to be a good approximation of the inverse ship dynamics. Ideally, the series connection of feed-forward controller and ship model would result in perfect track keeping in the absence of disturbances. However, due to the physical limitations of the rudder system and possible non-minimum phase systems (depending on the reference system chosen) perfect track keeping control is not possible. Interestingly, the non-minimum phase behavior can be removed by an appropriate choice of the controller reference point so that the major performance limitation is due to the limits of the rudder system.

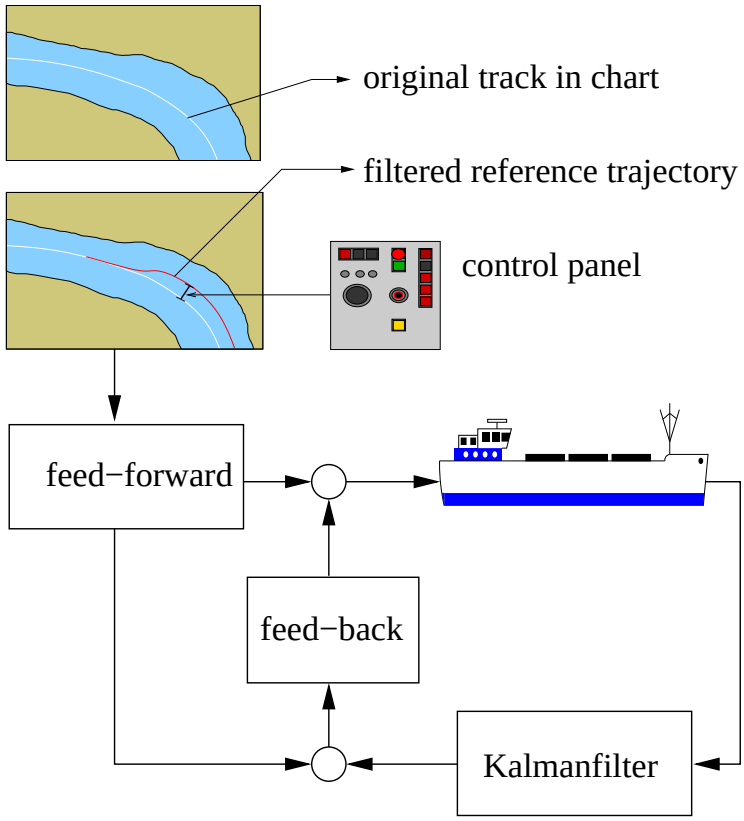


Fig. 89: Control loop

The current research follows two approaches for the design and implementation of the feed-forward controller: a predictive control strategy to invert the ship dynamics in the least square sense (see Fig. 90), and alternatively an analytic inversion of the differential equations. Both approaches have their merits and the insight gained by applying one method usually helps improve the other as well. The major argument for a predictive solution is the easy integration of constraints into the control problem. Besides the obvious physical constraints of the steering gear, a good controller is supposed to work with small and slowly changing rudder angles. Moreover, human pilots have certain expectations about how the ship should behave that usually translate into a stronger emphasis on the turn rate while position accuracy is only secondary. All that can easily be handled in the predictive control framework. However, it comes at the cost of a significant computational burden that makes real-time implementation a big challenge. Although the average computation time is, due to the receding horizon approach, relatively small (good start value from last optimization run); a typical course change, as introduced by the pilot for giving way to other vessels, still requires more than one second of computation time. Immediate reaction to pilot commands is essential for safe and reliable navigation, so that the predictive control approach is currently not suitable for day-to-day usage.

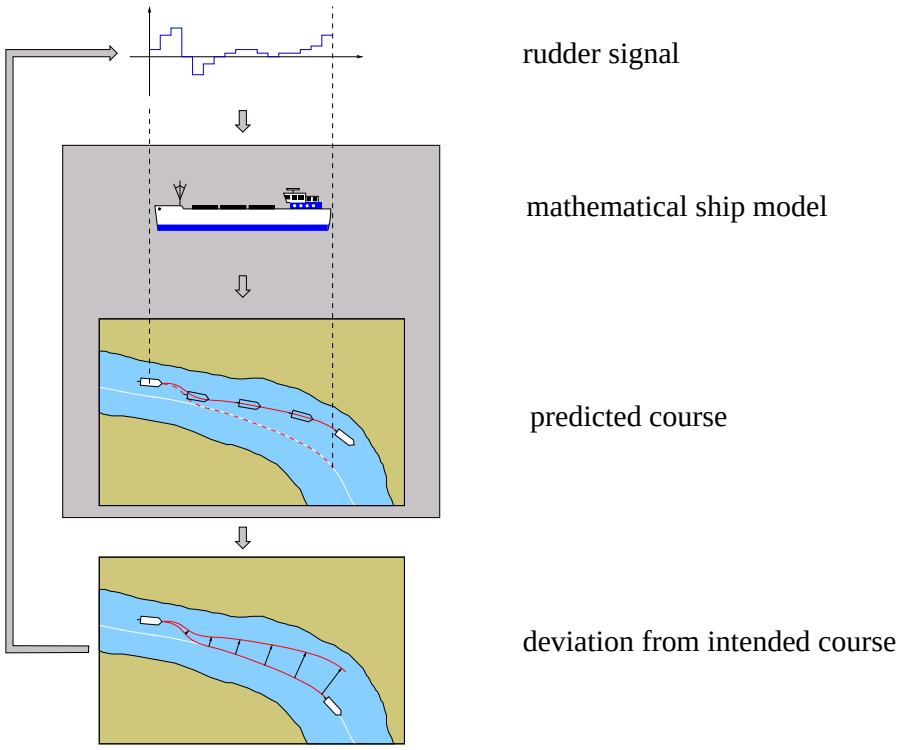


Fig. 90: Predictive control strategy.

In comparison to the predictive control approach, the use of the analytic inversion of the differential equation system describing the ship dynamics results in a very small computational load. However, there is no inherent guarantee that the solution is in any way suitable for the application if the given trajectory is infeasible for the given constraints. This problem can be indirectly approached by imposing certain restrictions on the reference trajectory. Because the second and third order derivatives of the reference trajectory correspond to turn rate and turn rate acceleration respectively, limiting them to reasonably small values is sufficient for the purpose at hand. From an application point of view, this means that the user interface for editing tracks on the navigation system restricts the possible curvature of a track to feasible values. The track is internally represented as a Spline function so that the calculation of the required derivatives is very simple.

5. Selected Teaching Activities and PhD Projects

PhD Projects:

Kabatek, U.	Leitlinienplanung bei Binnenschiffen	1999
Zimmermann, R.	Repräsentation dynamischer Schiffsmodelle in einem Navigationssystem für die Binnenschifffahrt	2000
Gern, T.	Automatische Flusskartengenerierung	2000
Wahl, A.	Einsatz optimaler Regelverfahren zur automatischen Bahnführung von Binnenschiffen	2001
Sandler, M.	Integrierte Messdatenverarbeitung in einem Navigationssystem für Binnenschiffe	2003

Supervision of PhD Theses (in preparation):

Blumschein, J.	Automatic docking and lock entering for inland vessels	since 2002
Derscanu, A.	Sensor fusion and error detection in an integrated navigation system	since 2002
Bittner, R.	Automatic Track-Keeping of Inland Vessels Using Inversion of the Ship Dynamics	since 2000
Beschnidt, J.	Virtuelle Wasserstraße	since 1998
Faul, M.	Hochgenaue Positonsbestimmung zur automatischen Schiffsführung	since 1998

6. Selected Memberships, Appointments and Awards

The research group is a member of the international "Inland-ECDIS Expert Group" and is actively involved in the standardization of inland navigation systems. Memberships and awards of Prof. Gilles: see group report of the Systems Biology research group (SBI).

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