MAX PLANCK INSTITUTE
FOR DYNAMICS OF COMPLEX
TECHNICAL SYSTEMS
MAGDEBURG

Annual Report 2014

+ **Miroslava Varnicic**
Ph.D. candidate in the *Process Systems Engineering group*.

The experimental setup is used to investigate the chemical conversion of the sugar glucose, a renewable platform chemical, into the valuable product gluconic acid. The salts of gluconic acid are called gluconates. They are very useful for treating diseases such as anemia. In the investigated process redox enzymes are used as catalysts which provide a very high selectivity. Thus they help to avoid the formation of undesired by-products and thereby simplify the subsequent separation of the desired product gluconic acid. The redox enzymes are directly immobilized on the surface of metal electrodes in order to regenerate the enzymatic cofactors via electron transfer. The general goal of this research is a better understanding of the reaction mechanisms taking place at the electrodes during the enzymatic conversion of renewable substances into useful products.

FREQUENTLY USED ABBREVIATIONS

Research Groups headed by MPI Directors

BPE	Bioprocess Engineering
CSC	Computational Methods in Systems and Control Theory
PCF	Physical and Chemical Foundations of Process Engineering
PSE	Process Systems Engineering

Research Groups headed by External Scientific Members

PSD	Process Synthesis and Dynamics
SCT	Systems and Control Theory

Max Planck Research Groups headed by Senior Scientists

ARB	Analysis and Redesign of Biological Networks
MSD	Molecular Simulations and Design
NDS	Numerical Linear Algebra for Dynamic Systems

Others

BMBF	German Federal Ministry of Education and Research
BMWi	German Federal Ministry of Economy
CDS	Center for Dynamic Systems: Biosystems Engineering (Magdeburg)
COST	European Cooperation in Science and Technology
CPTS	Chemistry, Physics and Technology Section of MPG
DAAD	German Academic Exchange Service
DFG	German Science Foundation (Deutsche Forschungsgemeinschaft)
FVST	Faculty of Process and Systems Engineering at OVGU Magdeburg
GAMM	(International Association of Applied Mathematics and Mechanics) Gesellschaft für Angewandte Mathematik und Mechanik
IMPRS	International Max Planck Research School
LSA	German Federal State of Saxony-Anhalt
MaCS	Magdeburg Center for Systems Biology
MPG	Max Planck Society (Max-Planck-Gesellschaft)
MPI	Max Planck Institute for Dynamics of Complex Technical Systems Magdeburg
OVGU	Otto von Guericke University Magdeburg
PDE	Partial Differential Equation
SAB	Scientific Advisory Board
SFB	DFG-funded Collaborative Research Center (Sonderforschungsbereich)
SIAM	Society for Industrial and Applied Mathematics
TU	Technical University (Technische Universität Berlin, Technische Universität Dortmund)
UCL	University College London

Annual Report 2014

MAX PLANCK INSTITUTE
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MAGDEBURG

+ Research Groups

Introduction

Research Groups

Directors

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Intense and Highly Productive Research in the Systems Area – A View Back

It has been an honor and a distinct pleasure to have been associated with MPI as member of the Scientific Advisory Board for ten years (2002–2012). Those years were marked by very intense and highly productive research in the Systems area at the Institute, which is continuing today as witnessed by the present Annual Report.

The Founding director, Ernst-Dieter Gilles, was convinced, in the mid-nineties, that a dynamical systems approach is fundamentally important in the analysis, synthesis and control of modern production systems, that consist of interacting process units. Tighter economic and ecological constraints demanded better understanding of the dynamic interactions in these complex systems. So while the Institute was to have a clearly defined focus in the area of bio-chemical processes, research would not be confined to such applications only. Indeed, over the years, other exciting projects have developed ranging from biomedical systems, to transportation networks, to energy systems. To cope with the inherent challenges of complex large-scale dynamics, it was vital to further develop the available set of mathematical, computational and control theoretic methods underpinning the various applications studied at the Institute. This has led to a truly interdisciplinary research environment, where chemical engineers, biologists, physicists, mathematicians and control engineers cooperate.

The success of the Institute, as of any organization, is due to the caliber of its people who have defined its research and have made the Institute a world force. In addition to the Founding Director Ernst-Dieter Gilles, now retired, Directors Kai Sundmacher, Udo Reichl, Andreas Seidel-Morgenstern, Peter Benner and External Scientific Members Achim Kienle and Jörg Raisch have been a superb motivating force of the world class research at MPI. I have interacted with these outstanding individuals and I have been impressed by their professionalism and abilities to collaborate and lead teams of highly competent researchers. Congratulations!

Panos Antsaklis

Prof. Dr. Panos J. Antsaklis
Department of Electrical Engineering, University of Notre Dame, USA
MPI Scientific Advisory Board 2002 to 2012
Chair 2008 to 2012

Introduction

The Max Planck Institute for Dynamics of Complex Technical Systems in 2014

When I wrote the introduction to the Annual Report 2013, we had gone through a year of ups and downs, the downs not really in the area of our influence, with the hundred year Elbe flood, and the discussion on budget cuts in education and research planned by the state of Saxony-Anhalt. The latter was resolved at the end of 2013 in the "Bernburger Frieden", and constructive discussions among the academic institutions and the state government led to a development plan for our main scientific partner, the Otto von Guericke University (OVGU) Magdeburg, that all parties could, maybe not happily, but without losing their faces, agree upon in 2014. As the Elbe also was quite peaceful in 2014, we could focus almost completely on scientific aspects, and thus I can joyfully report on a very successful year!

Starting my report on the positive developments in 2014, I would like to mention that one of our graduates, Dr. Tobias Breiten from the CSC group, was awarded one of the prestigious Otto Hahn Medals of the Max Planck Society for his outstanding Ph.D. thesis on "Interpolatory Methods for Model Reduction of Large-Scale Dynamical Systems". Dr. Breiten now is a tenure track assistant professor at the Karl Franzens University of Graz (Austria). With mixed feelings, I can report on another great loss for the institute: Dr. Richard Hanke-Rauschenbach of the PSE group was appointed full professor for Electric Energy Storage Systems at the Leibniz University of Hanover. Richard Hanke-Rauschenbach is not only an excellent scientist whose inspiration and passion for science will be missed at the institute, but also his involvement as co-organizer of the "Fête de la Musique" in Magdeburg and his many other cultural and social activities will be hard to replace. We wish him, and all others who left the MPI Magdeburg in 2014, all the best for their future careers.

New Research Projects

2014 marks a year of substantial success for the MPI Magdeburg in acquiring research grants of great international visibility. On the European level, the MPI Magdeburg participates in three COST (European Cooperation in Science and Technology) networks launched in 2014: CM 1402: "From molecules to crystals – how do organic molecules form crystals?", CM 1305 COST Action ECOSTBio and TD 1307: "EUropean MOdel Reduction NETwork (EU_MORNET)". MPI scientists play leading roles in both: Dr. Matthias Stein leads a working group in CM 1305, and Prof. Peter Benner serves as co-chair of TD 1307. Both are also the national representatives of Germany in these networks.
The MPI-funded project "Continuous synthesis and purification of artemisinin-derivatives" in collaboration with Prof. Dr. Peter Seeberger from the MPI of Colloids and

+ from left to right

The now president of the Max Planck Society, Prof. Dr. Martin Stratmann, awarded the Otto Hahn Medal to Dr. Tobias Breiten during the Max Planck Society's Annual Assembly 2014 in Munich.

Prof. Dr.-Ing. Kai Sundmacher, Prof. Dr.-Ing. Andreas Seidel-Morgenstern, Prof. Dr.-Ing. Achim Kienle, Prof. Dr.-Ing. Jörg Raisch, Prof. Dr. Peter Benner, Dr. Steffen Klamt, Dr. Matthias Stein, Prof. Dr.-Ing. Udo Reichl, Dr. Martin Stoll

Visit of Dr. Hartmut Möllring, Minister of Science and Economic Affairs of the state Saxony-Anhalt, at MPI Magdeburg on January 9, 2014.

Interfaces in Golm led to a breakthrough in developing new production methods for antimalarial drugs. For this work, Andreas Seidel-Morgenstern, head of our PCF group, and Peter Seeberger received the "Humanity in Science" Award in March 2015!

Apart from a number of other projects funded by the German Research Foundation (DFG) and the German Ministry for Education and Research (BMBF), two new collaborative projects stand out in their importance for current societal challenges. Both are conducted in cooperation of several Max Planck Institutes, and both are funded by the Max Planck Society as so called Max Planck Research Networks "MaxNet". "MaxNet Energy" (2014 – 2018), coordinated by the MPI for Chemical Energy Conversion in Mühlheim, aims at obtaining a deeper understanding of basic processes in chemical energy conversion and the rational design of novel catalysts, materials and techniques, thereby contributing to developing new sustainable energy systems, a major challenge in the energy transition currently taking place in Germany. The PSE group participates by investigating the dynamics of water electrolysis processes for hydrogen production on multiple time and length scales. "MaxSynBio" (2014 – 2020) is coordinated by Prof. Dr. Kai Sundmacher from our PSE group, together with Prof. Dr. Petra Schwille from the MPI of Biochemistry in Martinsried, and co-funded by the BMBF within their "Biotechnology 2020+" initiative. The goal of this interdisciplinary cooperation of nine Max Planck Institutes and one university partner is the better understanding of minimal requirements for living cells. This is a key aspect of synthetic biology, which itself plays a fundamental role in future biotechnological processes. The development of protocells using a bottom-up approach is the ultimate goal of MaxSynBio. This approach involves creating entirely new modules and systems based on fundamental biological principles, drawing on a combination of natural, modified and synthetic biomolecules as building blocks. In a unique manner, this network not only builds upon classical expertise in biosystems and biotechnology, but also aims at employing ideas from process systems engineering in the assembly of the functional building blocks, eventually leading to the "minimal cell".

Exchanging Ideas With Decision Makers

2014 also was a year with a remarkable number of politicians visiting the MPI in Magdeburg. We invited the new Minister of science and economic affairs of Saxony-Anhalt, Dr. Hartmut Möllring, to our institute, and he happily accepted. Dr. Möllring visited the MPI on January 9, 2014. We had an open discussion on several aspects of the research landscape in Saxony-Anhalt, and the minister showed great interest in our research work and facilities.

After the elections of the German Bundestag in 2013, the then president of the Max Planck Society, Prof. Dr. Peter Gruß, invited all elected members of the Bundestag to visit the Max Planck Institutes in their electoral districts. Magdeburg is happy to send three representatives to the Bundestag, all of which gladly accepted our invitation. So we could welcome (in chronological order) Burkhard Lischka (SPD) on March 7, Dr. Rosemarie Hein (Die Linke) on April 14, and Dr. Tino Sorge (CDU) on June 18 at the MPI. In all cases, we had interesting, fruitful, and constructive discussions, and regardless of their political color, the members of Bundestag expressed their highest appreciation of the research conducted at MPI Magdeburg, and assured us of their strong support.

Journalists represent a second important class of people in decision making, as they significantly influence the reception of science in the public view. A particular event for journalists reporting on science took place in Magdeburg, November 24 – 26, 2014. The annual conference "WISSENSWERTE" (freely translated as "the values of science", though the pun of the German conference title cannot easily be transported to another language) brings together science journalists and communicators. Originally always taking place in Bremen, the event in Magdeburg was the first "WISSENSWERTE" out of town. It attracted 350 participants, and the MPI joined with exhibitions describing our current research projects.

Women Career Day

On November 11, 2014, the coordinators of the International Max Planck Research School (IMPRS) and the Graduate School of the OVGU organized the first Women Career Day for (Ph.D.) students of the engineering sciences and mathematics in the Lukasklause Magdeburg (Otto von Guericke Center). The focus was on different career paths, on the possibilities and difficulties for the students after graduating, and on how to find a reasonable balance of career and family. Four successful women working in both, research and industry, presented their own career paths and experiences. These invited guest speakers were Prof. Ulrike Krewer (TU Braunschweig), Prof. Frauke Gräter (Klaus Tschira Stiftung), Prof. Gabriele Sadowski (TU Dortmund), and Dr. Jana Bohne (Salutas Pharma GmbH). All Ph.D. students and Postdocs of the MPI and the OVGU, regardless of their gender, were welcome to join the presentations of the speakers and the afterwards discussion. The participants also had the chance to interview the speakers one-to-one. Due to the great success and the positive feedback, it is planned to offer such Women Career Days on a regular basis.

Many other events took place at the MPI Magdeburg, or were co-organized by researchers of our institute; see also the section on "Events" in this annual report. As every year, we offered one-week student labs in spring and fall, both oversubscribed as usual. The 9th Science Night in Magdeburg took place May 17, 2014, and with 1.500 visitors at the MPI, set a new record. Our scientific approach to "molecular

+ from left to right

MPI demonstration at the "WISSENSWERTE", a conference for journalists and communicators in science, held in Magdeburg, November 24–26, 2014.

Science Night. Lab scientist Melanie Fachet and molecular cook Lars Ginsberg explain the chemical processes in molecular gastronomy.

Impressions from the Women Career Day in the Otto von Guericke Center Magdeburg, November 11, 2014.

Peter Benner handing over the Managing Director's position to Andreas Seidel-Morgenstern, symbolized by a baton, during the MPI's Christmas Party 2014.

gastronomy" was particularly well received – our lab scientist Melanie Fachet and the molecular cook Lars Ginsberg produced ice cream from eatable wallpaper paste!

In conclusion, at the end of my term as the Managing Director of the institute, I am happy to say that the MPI in Magdeburg is in good standing, scientifically and otherwise. The new collaborative research projects that started in 2014 show a great involvement in current societal challenges, like the development of new biomedical processes, and the questions about future energy systems. Our firm belief is that the combination of mathematical methods and well-designed lab experiments, using a system-theoretic understanding of complex technical processes, provides a unique way to face many of the challenges in these highly relevant areas. We will continue to do our best in providing answers to the related fundamental research questions encountered, and thereby hope to help paving the way to new solutions! My last words (as Managing Director) and best wishes go to Andreas Seidel-Morgenstern who takes over as Managing Director for the period 2015–2016, and who will guide us through the upcoming comparative evaluation of the MPI Magdeburg in December 2015.

Magdeburg, April 2015,

Prof. Dr. Peter Benner
Managing Director 2013–2014

Peter Benner studied Mathematics (major) and economics (minor) at RWTH Aachen and obtained his diploma in 1993. After he finished his Ph.D. thesis at Technische Universität of Chemnitz-Zwickau in 1997 he worked as an assistant professor at the Zentrum für Technomathematik of the University of Bremen, a lecturer at the Institute for Mathematics, Technische Universität Berlin, a Visiting Associate Professor at Technische Universität Hamburg-Harburg and a Full Professor for Mathematics in Industry and Technology, Chemnitz University of Technology. In 2010, he became a Scientific Member and Director at the Max Planck Institute for Dynamics of Complex Technical Systems, Magdeburg.

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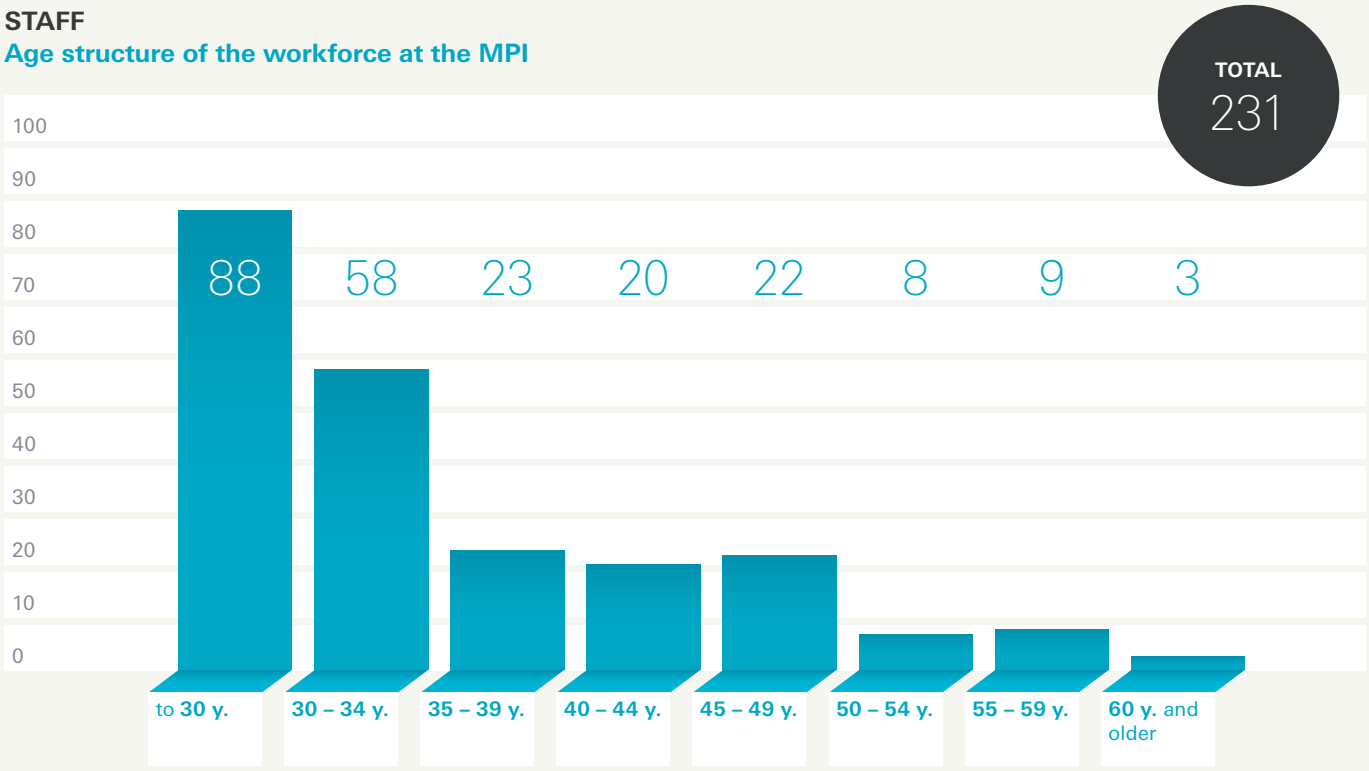
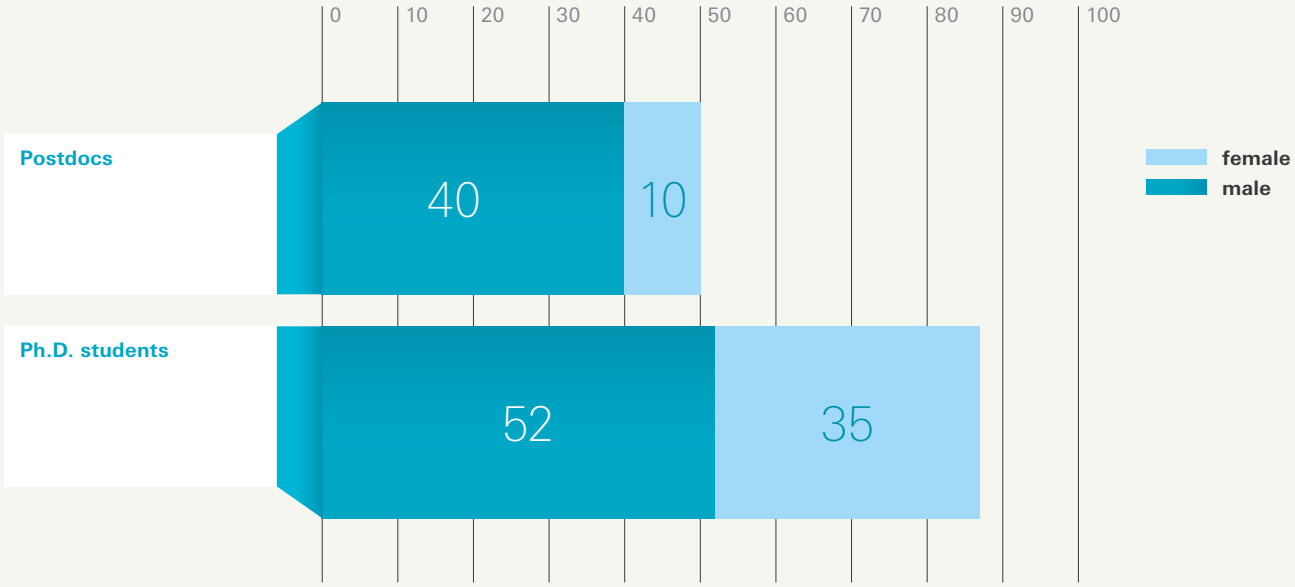
Facts and Figures

STAFF
Age structure of the workforce at the MPI



STAFF
Distribution of scientists by gender

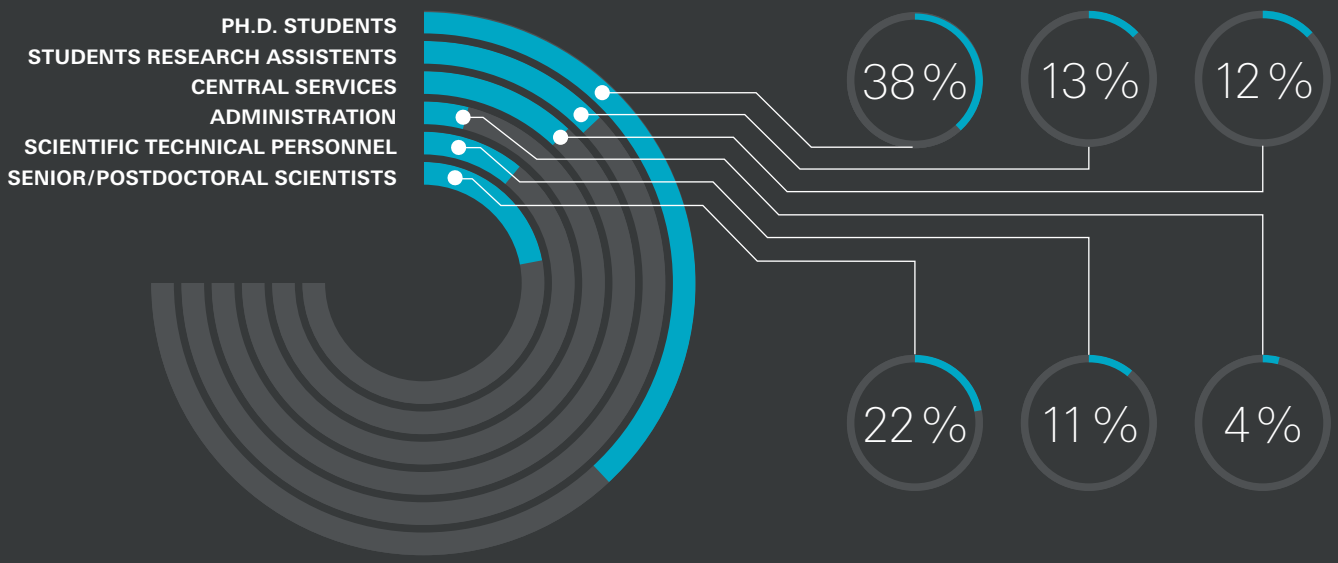
Female employees: 20% Postdocs and 40% Ph.D. students



The two graphs above show show the age structure and the gender balance among the institute's scientists on the Postdoc and Ph.D. levels, respectively. As Max Planck Institutes are run with very few permanent scientists, the average age of employees is quite low as the majority of scientists consists of Ph.D. students and young Postdocs.

STAFF

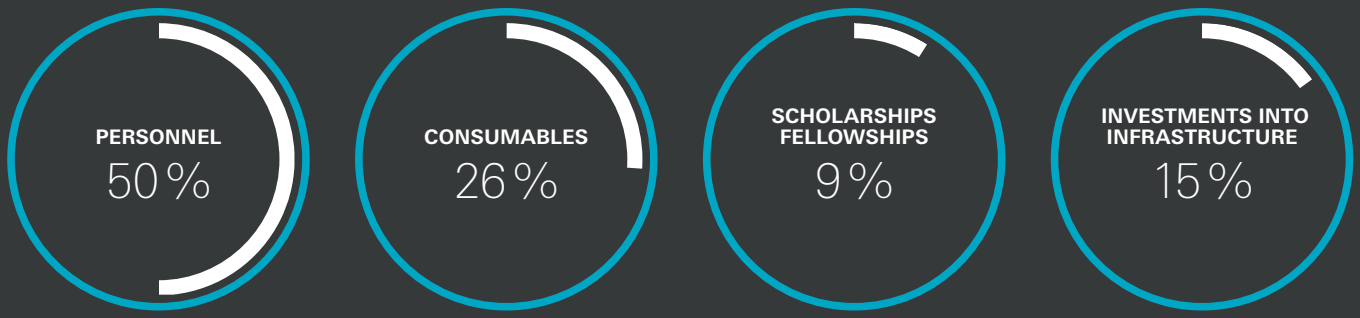
2015: 231 Employees 137 Scientists: 50 Postdocs, 87 Ph.D. students



At the beginning of 2015, the MPI employed 231 persons. The majority are scientists and student researchers as illustrated by the pie chart above. As can be seen, the institute is run by a lean administration, while running the labs and technical facilities accounts for the rest of the employees.

EXPENDITURE PATTERN IN 2014

Total Expenses in Fiscal Year 2014: 14.92 million Euro



The total budget of the MPI in the fiscal year 2014 was 14.92 Mio. Euro, an increase of approximately 9 % compared to 2013. The pie chart above shows how this was distributed to the major budget categories. As can be seen, nearly 60 % of the budget was used for salaries and scholarships.

MPI-GENERAL BUDGET 2014

Total Revenue: 14.92 million Euro Third-party funds: 2.4 million Euro

The second pie chart related to the budget shows the distribution of the budget sources. As usual for Max Planck Institutes, the main source is institutional funding provided by the Max Planck Society.

Sparse Matrix Computations and the Prediction of Customer Preferences

In April, the joint workshop of the International Association of Applied Mathematics and Mechanics (GAMM) activity groups for Applied Numerical Linear Algebra and Mathematical Signal and Image Processing was held at the Technische Universität Berlin (TU) Berlin. This three-day workshop on Matrix Computations for Sparse Recovery was co-organized by Gitta Kutyniok (TU Berlin) and Peter Benner from the CSC group. About 40 participants were joined by MPI researchers Ulrike Baur, Jonas Denißen, and Jan Heiland.

The workshop was aimed at bringing together two communities: one concerned with numerical linear algebra – a main field of research for Peter Benner and his CSC group – and the other concerned with signal processing and compressed sensing, which has developed a rich theory at a fast pace over the last few decades. Once a subfield of compressed sensing, this is now a vibrant research topic in its own right. One of the two main foci of the workshop was sparse recovery which is, broadly speaking, concerned with the question of how gaps in data sets with a sparse structure can be closed using mathematical methods. One main application area is the prediction of customer preferences, but the possibilities for also applying these techniques to problems from science and engineering involving gappy data are evident. Researchers have only recently started to employ approximating numerical algorithms for sparse recovery problems. These are the joint to research on matrix computation in the field of numerical linear algebra.

The benefits of this symbiosis became strikingly apparent when David Gross (University of Freiburg) interpreted the concept of low-rank recovery as applying the concept of sparsity to the eigenvectors of a matrix. Based on this observation, many algorithms from sparse recovery become easier to handle when considered from the point of view of linear algebra.

The workshop included introductory talks of tutorial value and presentations on state-of-the-art results. The presence of experts from different backgrounds created a discursive atmosphere with plenty of questions after each talk throughout the whole three days and during a beautiful conference dinner onboard a boat on the River Spree. | **Dr. Jan Heiland**

+ Entrance to "Ringberg Castle", a conference facility of the Max Planck Society. Overlooking the Tegernsee, it is a splendid meeting place for workshops and scientific gatherings. The CSC and NDS groups held their joint annual workshop 2014 in Ringberg Castle, June 25 – 28.

CSC/NDS Ringberg Workshop

In July, the CSC and NDS Research Groups initiated a workshop at Castle Ringberg, which is in the Bavarian Alps overlooking beautiful Lake Tegernsee.

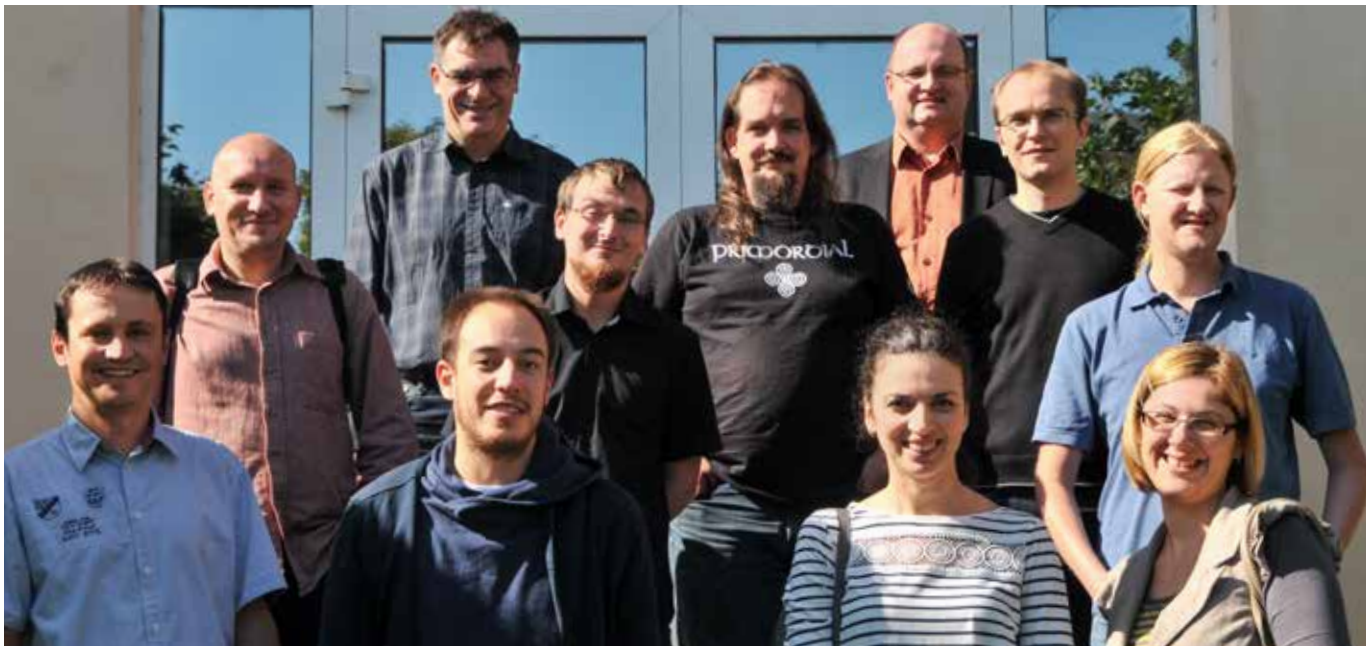
Several internationally renowned experts from various backgrounds and institutions were invited to this meeting. Their areas of expertise range from model order reduction and optimal control to more general topics in optimization.

Together with several talks from members of both groups we had a varied, interesting, and stimulating scientific program throughout the three-day meeting, which started in the afternoon of 25 June with a gathering and initial discussions over coffee and ended on Saturday 28 June after breakfast. The scientific part of the meeting ended on the Friday evening with a two-hour poster session in which all members of the CSC and NDS groups who had not given an oral presentation presented their work.
With over 20 talks and more than 15 poster presentations, the meeting allowed for a fruitful exchange of results and ideas and also gave younger researchers a chance to talk to established scientists from around the globe. While the scientific program was packed, there was still plenty of time for social interaction across the ping pong table or during the Bavarian evening, for example. The highlight was certainly the Friday afternoon hike which some topped with a swim in the castle pool. While this was the second time that the groups have met at Castle Ringberg, the group spirit combined with the fantastic location certainly means that the participants will want to return.
I Dr. Sara Grundel I Dr. Martin Stoll

DAAD Workshop on Optimal Damping of Vibrating Systems

From 7 to 10 October 2014, after nearly two years of joint work, a workshop was held at the J. J. Strossmayer University of Osijek, Croatia, in cooperation with the Max Planck Institute for Dynamics of Complex Technical Systems Magdeburg (MPI Magdeburg), Germany. The workshop was part of the joint German Academic Exchange Service (DAAD) project *Optimal Damping of Vibrating Systems*[1] sponsored by the German Federal Ministry of Education and Research (BMBF), the Department of Mathematics at the J. J. Strossmayer University of Osijek and the Zeidler-Forschungs-Stiftung.

The workshop was aimed at bringing together researchers and users of damping optimization techniques in vibrating systems such as multiple mass-spring-damper chains, finite element discretizations of bridges and earthquake models. Workshop topics ranged from the eigenvalue behavior of excited systems, attainability, uniqueness and passivity of



+ Participants of the DAAD Workshop 2014

optimization criteria, weighting of the total energy and the H_2-norm to low-rank perturbation methods and its relative bounds in the context of external damping. The 15 participants came from universities and research institutes in Germany and Croatia.

Overall, the workshop succeeded in showing the practicability of and need for optimization techniques for external damping, particularly when applied to vibrating systems. The fruitful cooperation on damping optimization with the University of Osijek has been strengthened by a newly approved two-year joint DAAD project on *Mixed Integer Nonlinear Programming for Damping Optimization* starting in January 2015.

I Jonas Denißen

[1] http://www.mpi-magdeburg.mpg.de/1590589/Optimal_Damping_of_Vibrating_Systems

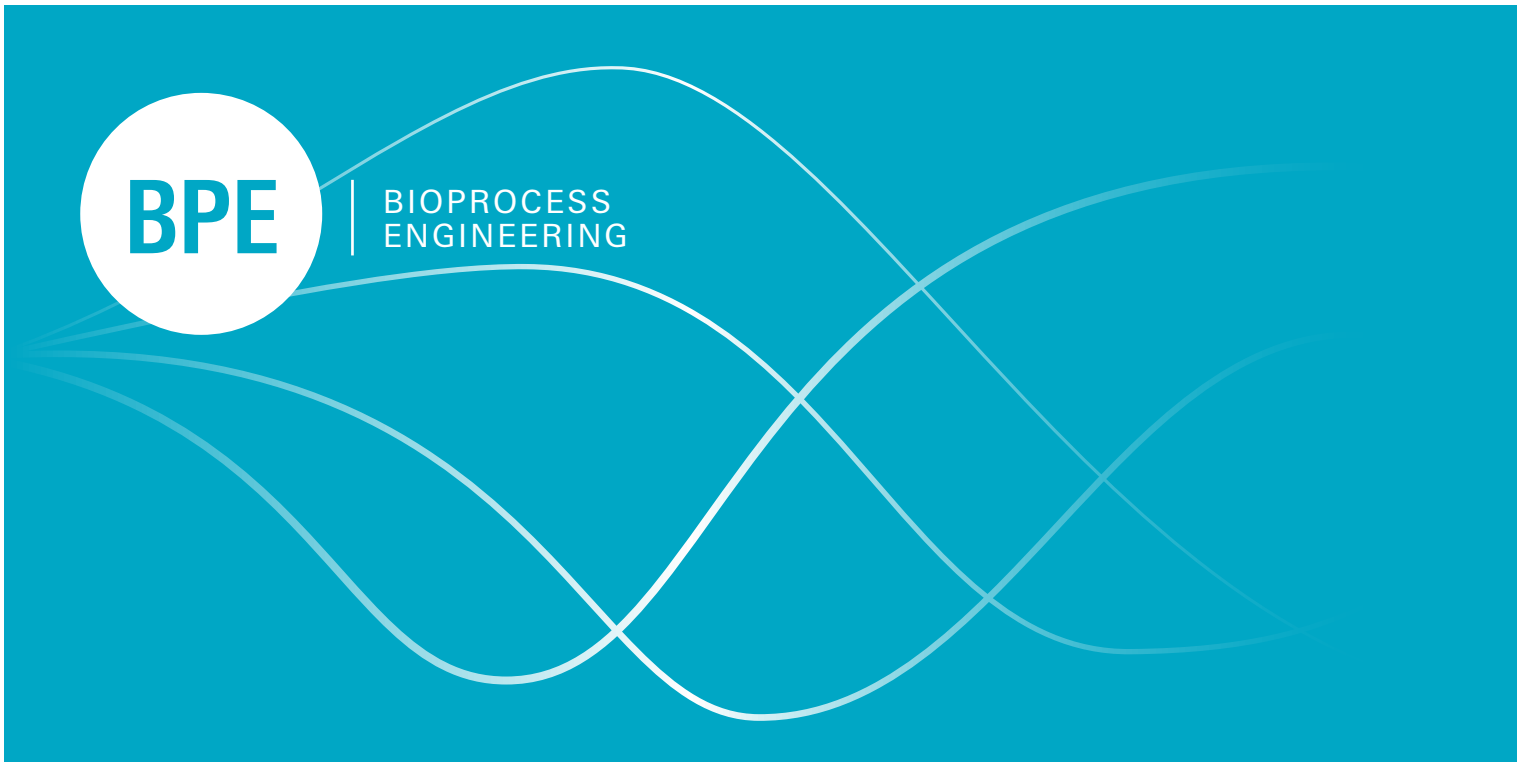
PSE Workshop 2014

From 24 to 26 September 2014, the MPI Process Systems Engineering (PSE) research group organized a workshop in Wernigerode, Germany. Besides knowledge exchange, the goal was to critically evaluate achievements in the group's research projects and to strengthen the team spirit of the group members. Upon arrival and after lunch, the head of the group Prof. Kai Sundmacher officially welcomed group members with an introductory presentation regarding the current status and future direction of all research activities. Each project group then presented their research results to the other participants, informing them about recent scientific breakthroughs and challenges. A discussion followed each presentation, giving valuable input to the presenters.

On the second day, all researchers had the chance to present their work individually on posters prepared ahead of the workshop. Previously selected teams of fellow researchers evaluated the posters and the accompanying presentations according to predefined criteria. A team-building exercise followed in the afternoon when the group went to the peak of the Wurmberg in the Harz Mountains to ride downhill on "monster rollers" (scooters with oversized wheels). In the evening, the poster evaluations were summarized. A relaxed get-together at a local bar completed this eventful day. Overall, participants will look back fondly on their stay at the Harz cultural and conference center, which was marked by a fruitful and informative exchange between group members. The poster session evaluation, including individual, constructive criticism as well as concluding remarks by Prof. Sundmacher, rounded off the last day of the excursion. **I Marcus Wenzel**

+ PSE research group members in Braunlage at the foot of the Harz mountains.

+ Research Groups



PROF. DR.-ING. UDO REICHL I DIRECTOR

Bioprocess engineering covers the use of microorganisms in the production of industrial bulk products and in manufacturing of specialized biopharmaceuticals. In addition, bioprocess technology plays an important role in biofuels production, waste water processing, and solid waste treatment. The design and optimization of bioprocesses from the engineering and biological point of view requires the integrated use of dedicated equipment, software tools, and molecular biology techniques. Additionally, a wide range of assays for process monitoring and a comprehensive set of analytical "omic" technologies need to be applied. The increase in specific product yields, process intensification, improvement of the efficacy and safety of drugs as well as the reduction of "time to market" is part of today's challenge.

The Bioprocess Engineering group headed by Prof. Udo Reichl studies various key aspects of cell culture-based bioprocesses for the production of viruses. These processes are currently seeing a renaissance with a high increase in market share due to the development of new viral vaccines, options for gene therapy, and the treatment of cancer or autoimmune diseases. Due to its relevance as a respiratory pathogen and the complexity involved in virus-host interactions, influenza virus propagation in animal and human cell lines was chosen as a model system. Five teams bring together their expertise covering different aspects of the overall process.

The **Upstream Processing team** (PD. Dr. Yvonne Genzel) characterizes growth and product formation of several host cells in combination with different viruses to optimize virus production in bioreactors including stirred tanks, hollow fiber-based systems, and disposable units. In addition, advanced cultivation strategies are being developed to further optimize process performance and to increase virus yields. The experimental data obtained are used by the **Mathematical Modelling team** (Prof. Udo Reichl) to quantitatively analyze fundamentals of cell metabolism and cell growth. In addition, models are being used to simulate intracellular virus replication and to investigate infection dynamics in bioreactors. On the experimental side, virus-host cell interactions are studied in detail by the **Molecular Biology team** (Jun.-Prof. Timo Frensing) to identify bottlenecks in virus production. Virus replication dynamics are investigated by a combination of classical virus quantification assays and state-of-the-art methods such as quantitative real-time PCR and imaging cytometry. With a focus on proteomics, glycomics, and glycoproteomics, the **Bio/Process Analytics team** (Dr. Erdmann Rapp) is developing a set of bioanalytical tools for the in-depth analysis of protein expression levels and post-translational modifications of proteins. Finally, the design

+ Scientists of the Bioprocess Engineering group monitoring growth and morphology of animal cells used for influenza A virus production.

and optimization of process trains to purify virus harvests, guaranteeing high yields at low contamination levels of the final product, is performed by the **Downstream Processing team** (Dr. Michael Wolff). While consideration of the influenza vaccine manufacturing process links all teams, each team has a range of further projects. These include Modified Vaccinia Ankara (MVA) virus production in designer cell lines, cell line development using systems biology approaches or establishing a platform for in vitro *N-glycosylation* of therapeutic proteins, to name a few.

In 2014, the Upstream and Downstream Processing teams continued their efforts towards process intensification by establishing perfusion and pseudo-perfusion one-stage cultivation strategies. In addition, semi-continuous two-stage bioreactor set-ups are being developed for MVA production. In collaboration with the Robert Koch Institute (Berlin), first steps were taken towards cell-culture based yellow fever production. Supported by the German Federal Ministry of Education and Research (BMBF), new analytical devices have been put into operation to characterize virus particle aggregation for process optimization. In addition, a magnetic separation technology based on chemically synthesized ligands has been submitted for patenting. To improve cell-specific productivities by genetic modification of virus strains and production cell lines, the molecular biology laboratories were extended and lentiviral vectors are now being used for cell line engineering. These activities are being supported by simulation studies performed by the Mathematical Modeling team to identify the most promising cellular targets and to estimate the overall impact of changes on virus yields. Eventually, Bio/Process Analytics could extend their glycoanalytical portfolio by acquiring a new carbohydrate analysis system and a high resolution "Orbitrap" mass spectrometer to strengthen research activities in glycomics and glycoproteomics, i. e. projects funded by the European Commission and the BMBF.

Prof. Dr.-Ing. Udo Reichl
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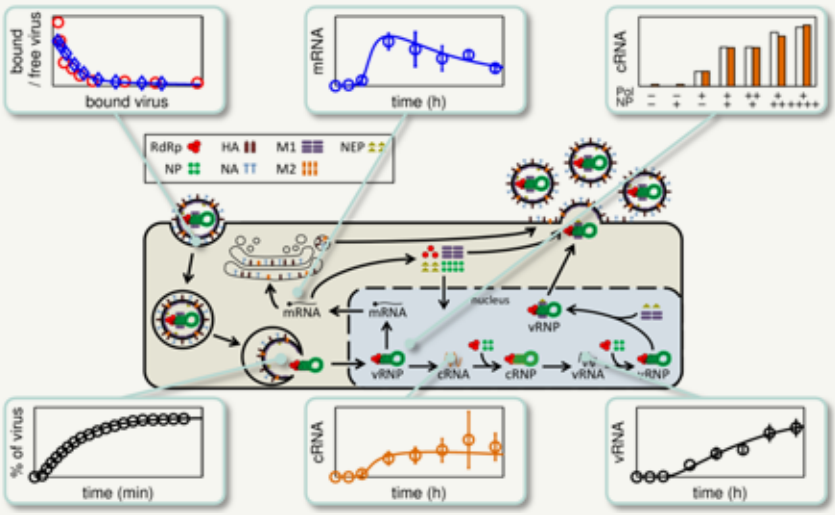


+ Figure 1:
Model for influenza A virus infection in an individual cell. The agreement of simulation results (closed bars and lines) with experiments (open bars and symbols) is shown.

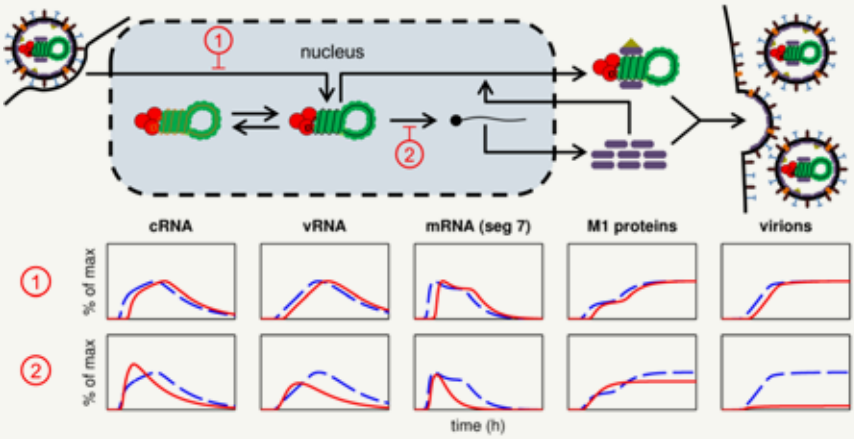
Discovering New Targets for Anti-influenza Drugs

Influenza A viruses are human respiratory pathogens that cause a highly contagious disease characterized by high fever, dry cough, myalgia, headache, sore throat, and rhinitis. According to the World Health Organization (WHO), the virus infects 5–15% of the world's population in annual epidemics causing 3–5 million cases of severe illness and up to 500,000 deaths. In addition, it can rapidly evolve and generate virus variants with the potential to start pandemics, like the "Spanish Flu" of 1918 with an estimated 50 million victims worldwide. Antiviral drugs are the first line of defense against such outbreaks. However, there are currently only two classes of antivirals licensed for influenza treatment and drug-resistant viruses are on the rise.

In an effort to identify new targets for influenza therapy, the Bioprocess Engineering group follows a highly interdisciplinary approach combining state-of-the-art experimental techniques with mathematical modeling. As a first step, Dr.-Ing. Frank Stefan Heldt of the Mathematical Modeling team headed by Prof. Dr.-Ing. Udo Reichl reconstructed an individual cell *in silico* to simulate its fate upon viral infection. A scheme of the resulting model is presented in Figure 1. The simulation accounts for key mechanisms of influenza A virus infection from the moment the virus enters its host cell until the cell releases progeny virions that can spread the disease. While developing the model, special attention was paid to the synthesis of viral genome copies and proteins. These components are of particular interest in antiviral therapy as they are foreign to the host cell and can therefore be targeted with only minor side effects.

To investigate whether the established model can faithfully reproduce influenza A virus infection, the Molecular Biology team under Timo Frensing conducted experimental infections in cell culture. In particular, they used a novel PCR method specifically designed to quantify the three viral RNA species and to distinguish between the different segments of the influenza A virus genome. In addition, a variety of literature sources were harnessed to compare their data with the model. The experimental results and simulations were in excellent agreement, confirming that the model can capture both the qualitative and quantitative aspects of the intracellular viral life cycle (see Figure 1). This facilitated a detailed analysis of influenza A virus infection revealing that, inside an infected cell, viral proteins are present in excess. By contrast, the amount of virus particles that a cell can produce heavily depends on the synthesis rate of viral polymerases and on virus particle assembly. These processes are thus ideal targets for antiviral drugs that aim at reducing peak virus titers.

Encouraged by these results, the model was extended to not only account for an individual infected cell but also to consider how the virus would spread throughout a cell population. This scenario resembles the situation in the lung tissue of an infected patient. Since the improved model accounted for an additional scale of the infection process, it called for a new



+ Figure 2:
Simulated effect of drugs that target virus entry (1) and viral mRNA synthesis (2). Time courses of selected viral components in the absence (dashed line) and presence (solid line) of specific inhibitors are shown.

type of experimental data. Thus, the Upstream Processing team headed by Yvonne Genzel set out to analyze influenza A virus infection using virus-specific flow cytometry. Again, the model not only reproduced the measurements successfully but also provided further insights into potential targets for antiviral therapy. In particular, it predicted how specific inhibitors of the intracellular viral life cycle would affect virus production and spreading (see Figure 2). As observed before, blocking the viral polymerase, either at the step of viral mRNA synthesis or genome replication, is the most promising strategy to impair virus growth. By contrast, virus entry inhibitors, a class of drugs currently in use for treatment, performed poorly in the simulations (see Figure 2, right column). These antivirals delayed the spread of infection but did not reduce peak virus titers in *vitro*. This may explain why entry inhibitors frequently lead to resistant mutations when used to treat patients. In particular, since an infected cell produces similar amounts of virus particles in the presence and absence of such drugs, a virus variant that overcomes the block can rapidly reproduce and outgrow the wild-type strain. Based on these and other modeling results, a ranking of potential drug targets was created enabling future studies to focus their attention on the most viable strategies for influenza treatment.

In summary, the Bioprocess Engineering group has developed a powerful mathematical model that describes influenza A virus infection across multiple scales. This model provides the unique opportunity to test antiviral agents *in silico* before time and resources are invested in their development. It can thus help to speed up the development process, eventually leading to more potent antiviral drugs that can fight future pandemics and mitigate the impact of seasonal influenza.

I Dr.-Ing. Frank Stefan Heldt

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Author **Dr.-Ing. Frank Stefan Heldt**

Stefan Heldt studied Biosystems Engineering at the Otto von Guericke University in Magdeburg specializing in the reconstruction of biological systems by mathematical models. In 2009, he received his degree after completing a diploma thesis at the University of Aberdeen. He then joined the Bioprocess Engineering Group at the Max Planck Institute where he recently finished his Ph.D. thesis on modeling approaches to the analysis of infectious diseases.

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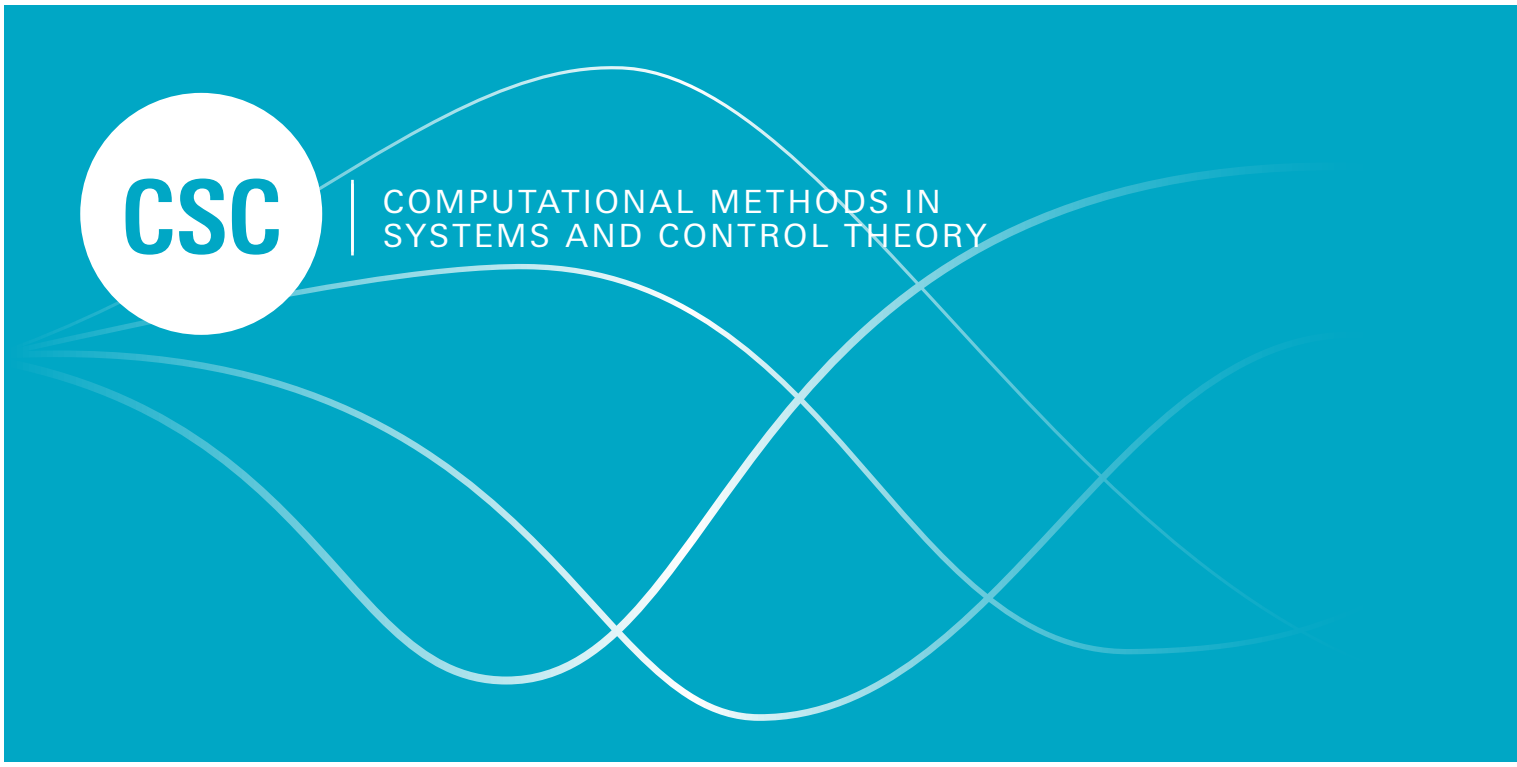
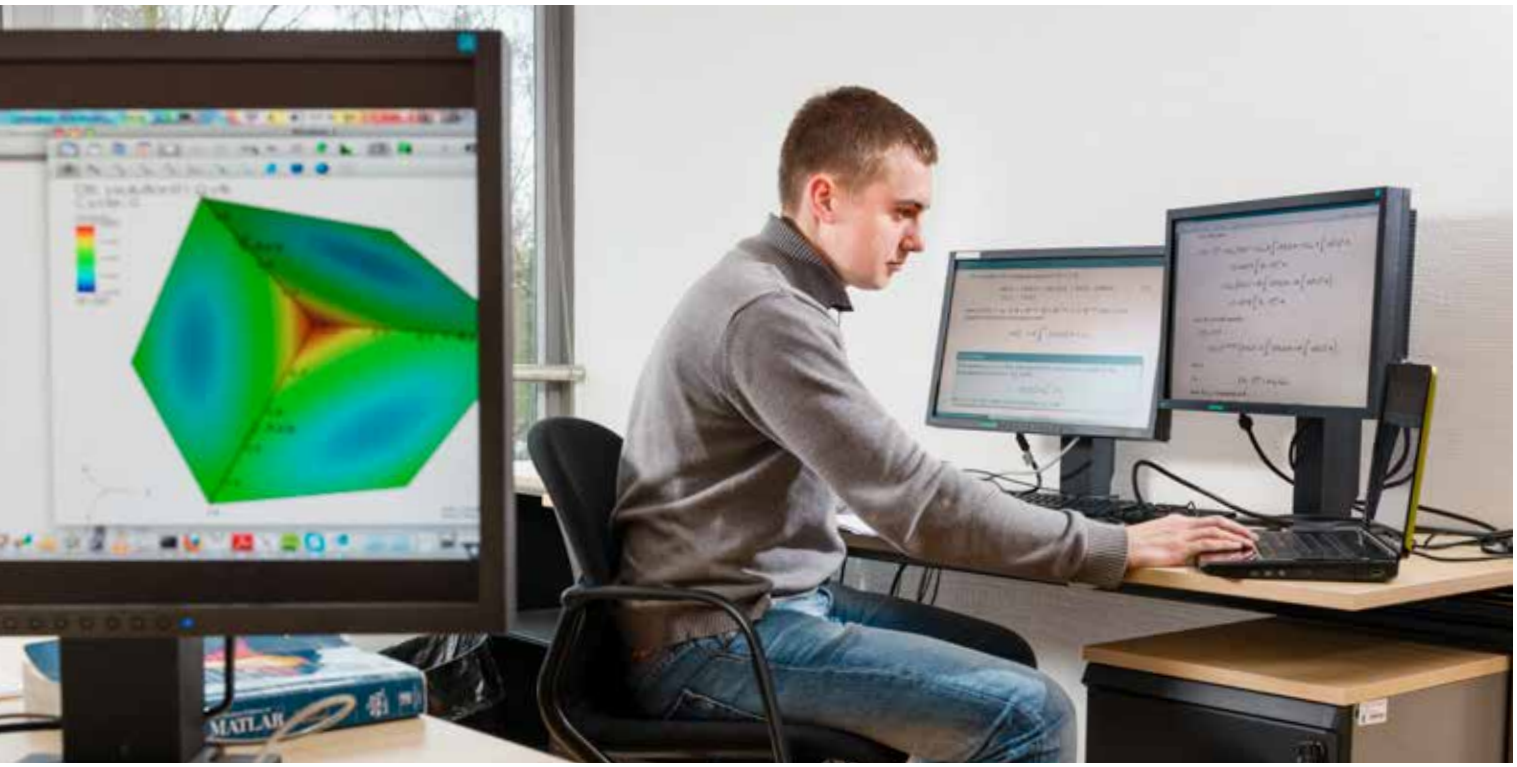


PROF. DR. PETER BENNER I DIRECTOR

The CSC group is concerned with mathematical ideas and concepts to develop new methods in the context of *in silico* design or experiments – the third pillar of scientific research besides theory and lab experiments – for complex technical systems as investigated in the engineering departments at MPI Magdeburg, but also in a number of other areas. In particular, we consider the efficient simulation and optimization, as well as feedback control, of dynamical systems, i. e., of mathematical models described by systems of ordinary or partial differential equations. The application areas of our methods range from various complex technical processes considered in the engineering groups at MPI Magdeburg, i. e., chemical and biotechnological process engineering, to microsystems design and nanoelectronics to fluid dynamics and machine tool manufacturing. Our work flow often starts with the mathematical model provided by or developed together with engineers, physicists, chemists, etc., followed by an analysis of the goals of the desired computer experiments. Based on this, we either try to adapt and optimize existing algorithms, or we develop new ones for the target computations. Promising approaches are implemented, tested and benchmarked, before the best variants are turned into user-friendly mathematical software to be used by practitioners. This often includes sophisticated programming strategies for modern multicore computer architectures and clusters, including hardware accelerators like GPUs. For this, we use different hardware platforms, including our Linux cluster "otto" with 1000+ cores.

Teams within the CSC group

Our work is currently organized in six teams. The biggest of them, Model Order Reduction (headed by Dr. Lihong Feng), deals with mathematical methods to algorithmically reduce the number of degrees of freedom in mathematical models in order to accelerate their simulation, to facilitate their optimization, and to enable control design. The Computer Aided Control System Design unit (Dr. Jan Heiland) deals with various aspects of computational methods for control systems. A very important aspect here is that many of these computational techniques rely on solutions of certain matrix equations, like Lyapunov, Sylvester and Riccati equations. The team Matrix Equations (Dr. Jens Saak) focuses on efficient algorithms to solve them numerically. These algorithms are based on efficient techniques of Numerical Linear and Multilinear Algebra, a core mathematical technique percolating almost all aspects of the CSC research work. The corresponding team, led by Prof. Dr. Peter Benner, deals with linear and nonlinear eigenvalue problems, preconditioning techniques, matrix function evaluation, and tensor techniques as often needed in multiparametric problems. The efficient implementation of the algorithms for matrix equations



+ Besides developing mathematical theory, daily work in the CSC group often comprises writing computer code, running numerical experiments, and visualizing them. The picture shows Martin Redmann, one of the CSC Ph.D. students, working in the area of stochastic differential equations.

and eigenvalue problems, as well as of linear system solvers, on modern computing platforms is the task of the Scientific Computing team (Dr. Jens Saak). A new team on Simulation of Energy Networks (Dr. Sara Grundel) was established in 2014. Its focus is on modeling and numerical simulation of power, gas, and water networks.

Research Trends and Highlights in 2014

A main trend in CSC research 2014 was the increased activity in model reduction of nonlinear and parametric systems. This concerns new algorithmic developments, but also the use of such techniques in application areas like batch chromatography (jointly with the PCF group) and crystallization (in cooperation with the PSD and PCF groups). Within the EU project "nanoCOPS – Nanoelectronic Coupled Problems Solutions", efficient methods for model order reduction of coupled parametric nonlinear differential-algebraic systems are developed. Another area of growing importance is related to incorporating uncertainties and stochastic effects in general into the models. As one branch of research, we develop UQ (Uncertainty Quantification) methods for partial differential equations with random (uncertain) parameters. On the other hand, we have started to investigate optimal control and model order reduction of dynamical systems driven by noise (e.g., Wiener, Levy) processes.

Other highlights in 2014 were the workshops (co-)organized by the CSC group, including the joint CSC/NDS Workshop at Ringberg Castle, the GAMM Workshop on "Matrix Computations for Sparse Recovery" held at TU Berlin, and the DAAD project meeting on "Optimal Damping of Vibrating Systems" in Osijek (Croatia), all described in the "Events" section of this annual report. We also observe an increasing interest of collaborating scientists to visit us in Magdeburg, resulting in a nearly constant flow of national and international cooperation partners.
The increasingly important topic of parametric model order reduction, playing its role in many of the projects conducted by the CSC group, is the topic of the CSC research highlight on the following pages.

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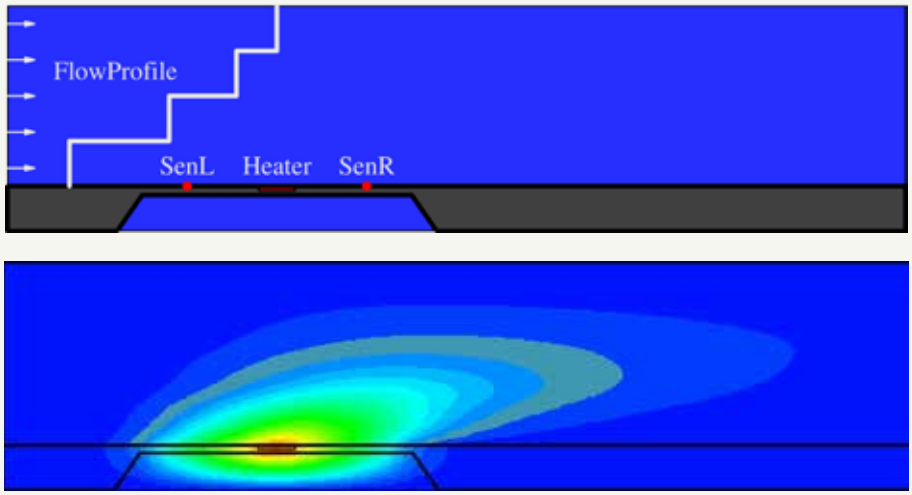


+ **Figure 1:**
2D model of an anemometer by courtesy of IMTEK, University of Freiburg, Germany.

+ **top:**
schematics

+ **bottom:**
calculated temperature profile

The anemometer is part of the benchmark collection in the Model Order Reduction Wiki: http://www.modelreduction.org.

Efficient Numerical Simulations by Parametric Model Order Reduction

The importance of numerical simulation has steadily increased during the past couple of decades across virtually all scientific and engineering disciplines. In many application areas, e. g. in mechanical engineering, fluid dynamics, control, design of integrated circuits and systems, microelectromechanical systems (MEMS), and in uncertainty quantification, experiments have been largely replaced by numerical simulation in order to save on design and development costs. Numerical simulation requires a mathematical description of the system considered as a first step.

The resulting mathematical models are usually in the form of partial differential equations. To simulate such models, spatial (-time) discretization is necessary, which results in large-scale, complex systems with an enormous number of equations. The number of (differential and algebraic) equations easily reaches a multiple of 10^5. The numerical simulation of such a high-dimensional system of differential equations, i. e. the iterative procedure of solving or integrating a system, becomes very time-consuming. This is especially the case in control and optimization, where the underlying system has to be solved many times. The resulting demands on computational resources can be overwhelming with respect to both, storage requirements and computing time.

Model Order Reduction

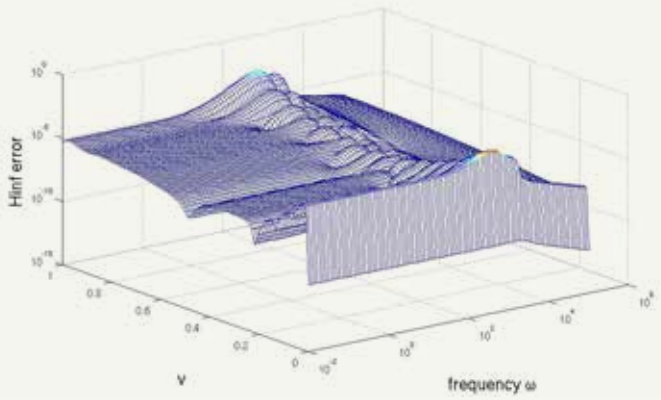
Model order reduction (MOR), which has been developed from well-established mathematical theories and robust numerical algorithms, has been recognized as an efficient tool for the creation of compact, efficient, and high-fidelity dynamical system models.
Using MOR, the original high-dimensional system is substituted by a compact system of far less equations, which approximates the response to external forcing of the original system to high accuracy. As a result, the simulation can be sped up by several orders of magnitude. See [3] for a recent survey on MOR.

However, standard techniques for MOR cannot be applied if the system incorporates parameters such as geometric variations, changes in material properties or alterations in boundary conditions, and when the system has to be solved for different values of these parameters. This can be particularly onerous in design optimization, where parameters are changed in each optimization cycle. These parameters should be preserved in the reduced-order system; a task that motivated the development of new approaches to MOR referred to collectively as parametric model order reduction (PMOR).

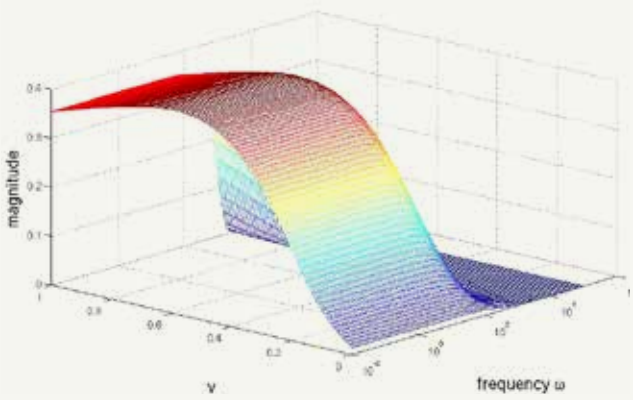
A MEMS Example

The application considered here is a flow sensor (anemometer), a device for the measurement of flow which consists of a heater and temperature sensors before and after the heater (see Figure 1).

When discretized in space using e. g. the finite element method, this leads to a system of 29,008 (implicit) ordinary differential equations. A simulation of the original system in the frequency domain requires 32.13 seconds on a workstation with a constant



+ **Figure 2:**
Error plot for the anemometer example.



+ **Figure 3:**
Frequency response of the reduced-order anemometer system.

fluid velocity v=1. In practice, the (normalized) fluid velocity is supposed to vary between 0 and 1, and the computational costs increase to approximately 1 hour for evaluating the original system for 100 different velocities. For the more realistic case, a system which includes 10 parameters, the simulation would require 10^{14} years by the exponential growth of complexity.

Parametric Model Order Reduction

It is thus necessary to reduce the large dimension of the system by preserving v as parameter in the reduced-order system. To this end, we developed a new approach for PMOR called transfer function interpolation [2].
The method uses standard MOR techniques at selected values in the parameter space and takes the local information for the construction of a (parameter-dependent) interpolant. Different kinds of interpolation can be applied, e. g. piecewise polynomial interpolation, rational interpolation [4].
Especially suitable is the use of balanced truncation for the local reduction since a global error bound can be derived by a combination of the balanced truncation error bound at the interpolation points and error estimates for the interpolation error. Furthermore, a more sophisticated choice of interpolation points (sparse grid points) can help to deal with the curse of dimensionality in the case of higher-dimensional parameter spaces [2]. We also developed approaches which are especially suitable for systems with special parameter dependence [1].

Simulation Results

We reduced the anemometer locally at 16 parameter sampling points in [0,1]. The (local) reduced order is set to 10, which leads to an order of 160 in the parameterized reduced-order system. To illustrate the quality of the reduced system, the absolute error between the original system and the reduced-order one in frequency domain is computed on a 100 x 100 grid of the parameter interval times the frequency range considered. This error plot is shown in Figure 2.
It can be seen that the reduced-order system approximates the full-order system very well with a maximum error of 0.0048. The simulation time of the reduced system on 100 parameter values in Figure 3 takes 18 seconds in contrast to 53.55 minutes for evaluating the original system 100 times.

I Dr. Ulrike Baur

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Dr. Ulrike Baur studied mathematics at the Technische Universität Berlin, where she received her Ph.D. in 2008.
After some years at the Technische Universität Chemnitz and a research visit at the VirginiaTech, Blacksburg, US, she works in the CSC research group at the Max Planck Institute Magdeburg since 2011. Her research interests are parameter preserving model order reduction and model reduction for large-scale systems using hierarchical matrices.

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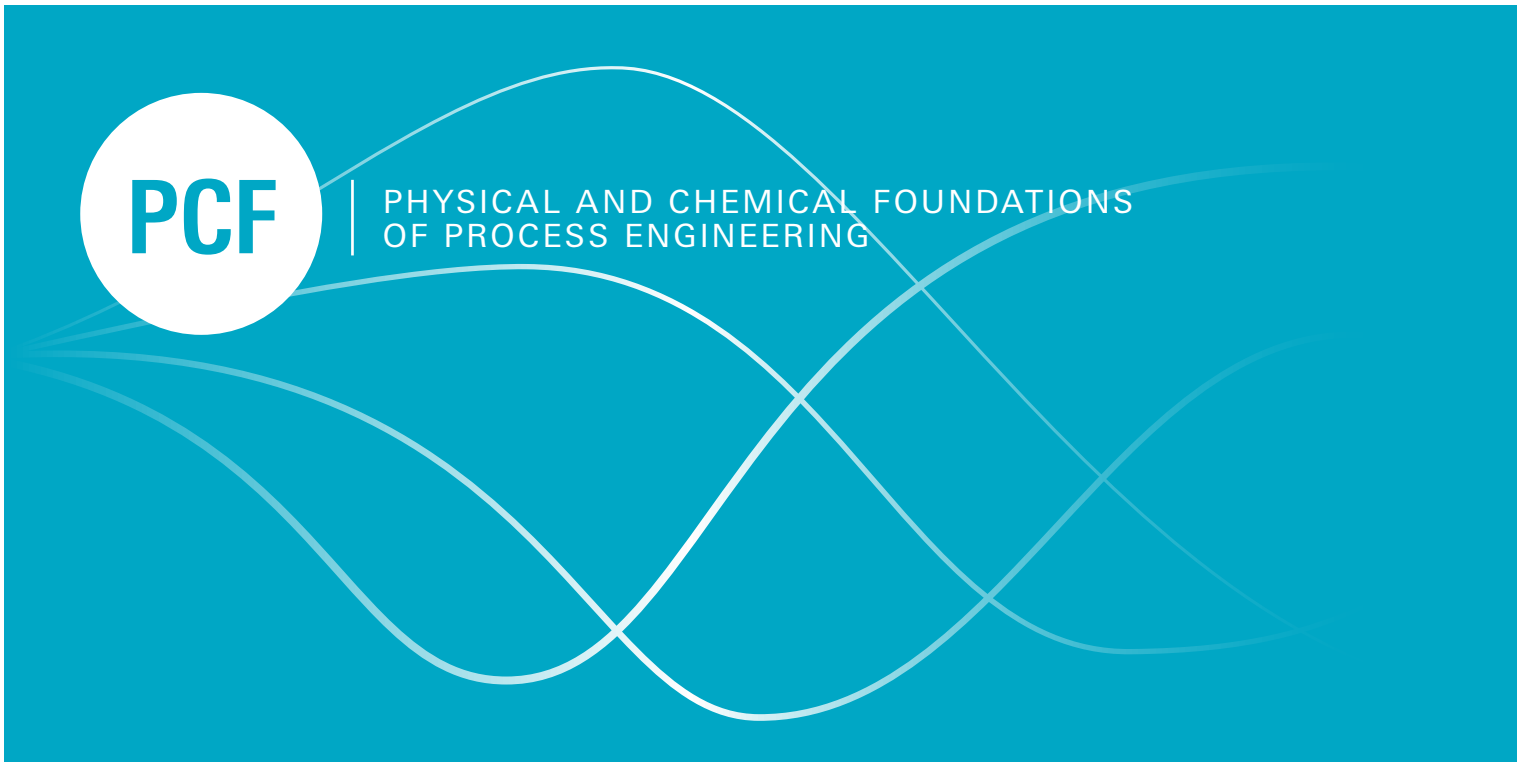


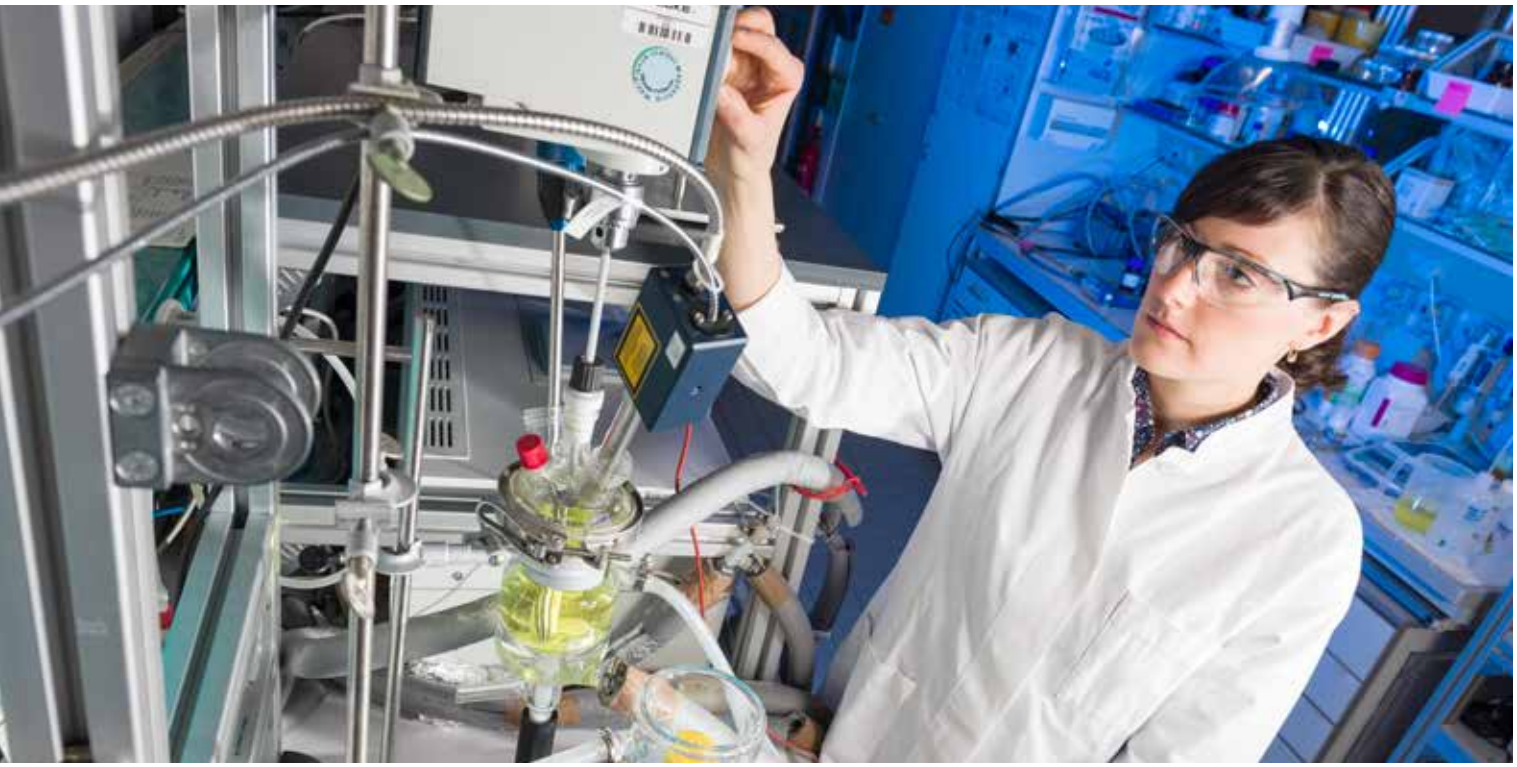
PROF. DR.-ING. ANDREAS SEIDEL-MORGENSTERN |
DIRECTOR

The development and production of new products with improved or hitherto unknown properties increasingly requires the application of advanced and often complex technologies. To understand, to analyze quantitatively, and to optimize the underlying processes, profound knowledge of a large number of physical and chemical data and parameters is of key importance.

Related to this, there are currently three main research directions being investigated within the PCF group.

The **Chromatography Research team** is working on discontinuous and continuous separations of complex mixtures in order to provide pure enantiomers or biomolecules. Applying batch chromatography, essential physical and chemical properties are measured experimentally. These properties are then used for the design and simulation of chromatographic separation processes. Advanced innovative continuous chromatographic separations, e. g. different configurations of simulated moving bed (SMB) technology, are studied to separate binary or more complex mixtures. Coupled processes of SMB and continuously operated reactors, or SMB in combination with subsequent crystallization processes, are designed to improve performances compared to conventional operation concepts.

The **Crystallization Research team** is studying different crystallization processes such as e.g. isothermal and polythermal batch crystallization or new continuous crystallization concepts. Various types of compounds are being investi-



+ Elena Horosanskaia carries out a crystallization experiment in a batch crystallizer to isolate a target component from a solution containing several solutes.

gated, e. g. different conglomerate or compound-forming chiral systems. For a better understanding of the underlying mechanisms of crystallization, the growth rates of crystals and the solid liquid phase equilibria are quantified based on experimental investigations. Recently, the group started to investigate options to isolate and purify natural products exploiting both chromatographic and crystallization based separation methods.

The **Reaction Engineering Research team** is working on the development of new reactor concepts. Of particular interest at present are direct combinations of reactions with separation processes such as applied e.g. in membrane reactors and in chromatographic reactors, and periodic operation of reactors, e. g. the application of a forced modulation of input parameters such as feed concentrations or flow rates.

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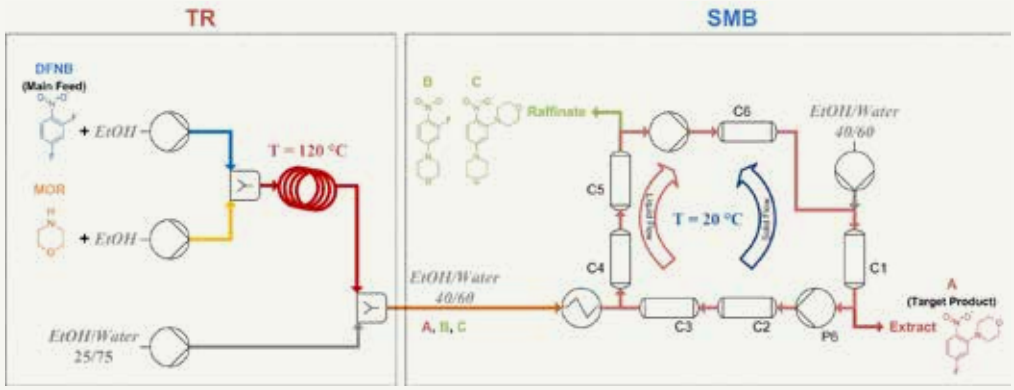


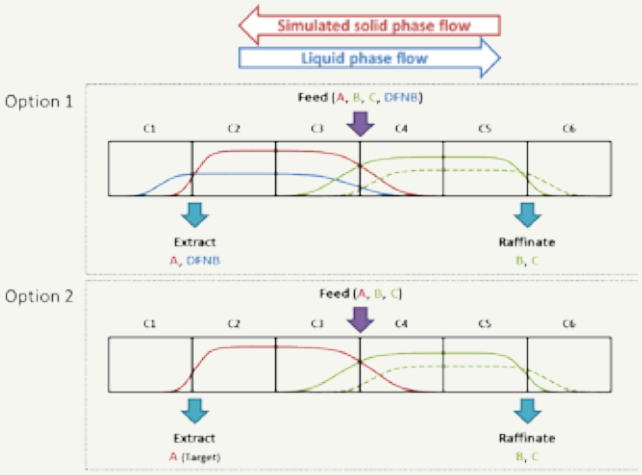
+ Figure 1:
Schematic illustration of the coupled system of a tubular reactor (TR) and a chromatographic separation process (carried in a simulated moving bed, SMB) for continuous production.

Continuous Production by Coupling of Upstream and Downstream

A chemical plant can be classified into two sections called *upstream* and *downstream*. In *upstream* operations, the desired target compounds are produced by chemical reactions with reagents. The produced target compounds are transferred toward *downstream* operations to remove unwanted byproducts and impurities and to polish the desired target compounds. These *upstream* and *downstream* operations are interconnected in a chemical plant in various ways. If the production is carried out batchwise, the product of a prior operation step is stored, and then a certain amount of the product is transferred to the next operation at a time. In this way, both operations can be carried out continuously. In a fully continuous production process, all operations are continuous and directly connected. Thus, there is no delay in transferring reactants and products between different operation steps. Historically, continuous processes have been developed mainly for the production of bulk chemicals needed in large quantities. This is due to the fact that continuous production tends to be more efficient at reducing costs and controlling product quality. For small production scales, e. g. in the pharmaceutical industry, batch production has been considered more efficient and easier to implement compared to continuous production. Continuous production is currently attracting the attention of the pharmaceutical industry. This is also because the regulatory authorities have recognized that continuous production has the potential to improve product quality.

In a research project carried out by the PCF group and Peter Seeberger's group at the MPI in Potsdam-Golm, it was investigated whether a continuous reaction capable of producing a target compound A in a tubular reactor (TR) from the two reactants morpholine (MOR) and 2,4-difluoronitrobenzene (DFNB) can be directly coupled with continuous chromatographic separation isolating the product from the side products B and C that are formed. Figure 1 illustrates schematically the process configuration suggested. The reactor outlet is directly connected to the feed inlet of continuous chromatography called a simulated moving bed (SMB). The target and waste components are continuously separated and collected in the extract and the raffinate streams respectively. It was experimentally validated that this process can be continuously operated and provides the target component with high purity and without delay between two unit operations. The compositions and concentrations at the reactor outlet change as a function of the reactor conditions such as residence time, feed concentrations and compositions, and temperature. In the SMB unit, six columns (C1 to C6) are connected in a ring. The liquid phase flows clockwise and the columns switch their positions counterclockwise to simulate a desired countercurrent flow of the liquid and the solid phases. Components that have strong affinity to the liquid phase move preferably with the liquid flow, and vice versa. In the example case studied, the target component could be collected at the extract stream because it had strong affinity to the solid phase selected for separation. Waste components (B and C) that have strong affinity to

+ **Figure 2:**
Schematic changes of the reactor outlet concentrations as a function of residence time.



+ **Figure 3:**
Schematic illustrations of the concentration distributions of the components in chromatographic SMB separation for two different possible options.

the liquid phase could be collected at the raffinate stream. Figure 2 schematically shows concentration changes at the reactor outlet as a function of residence time. It can be seen that the concentrations of the two reactants MOR and DFNB decrease as the target compound and the waste components are formed. The target component concentration is maximized for a certain residence time, and it drops if the reactions continue to produce component C. One of the reactants, DFNB, can be seen as the main feed (it is more valuable than MOR) and thus in the SMB effluent is also treated as waste. To maximize the productivity of the TR, two different options could be realized as described in Figure 2. Option 1 is preferable here. However, in this option DFNB remains in the reactor effluent. To consume all DFNB in the TR, the other option (Option 2) is preferable. Figure 3 shows the schematic concentration distributions of the components within the SMB separation process. As mentioned above, DFNB can be seen as a possible waste component that has stronger affinity to the solid phase than the product. Further treatment is therefore required to remove DFNB contaminating the target component in Option 1. By contrast, when all DFNB is consumed in the TR in Option 2, SMB can produce the pure target component.

As a result of the project briefly described above, a conceptual approach was developed to combine in a rational manner reaction and separation processes in continuous production processes directly. The approach is based on analyzing and optimizing all unit operations systematically based on a detailed understanding of each unit. For the example considered, the systematic design method applied could improve the performance of the coupled system by up to 19 % compared to a traditional sequential design.

I Dr. Ju Weon Lee

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In September 2007, Dr. Ju Weon Lee obtained a Ph.D. from Inha University (Incheon, South Korea). He continued his studies of the separation process as a post-doctoral associate in Purdue University (IN, USA) until November 2009. Since December 2009, he is a member of the Max Planck Institute in Magdeburg as a post-doctoral associate. His research is devoted to design, optimization, and control of separation processes with a focus on continuous operation modes.

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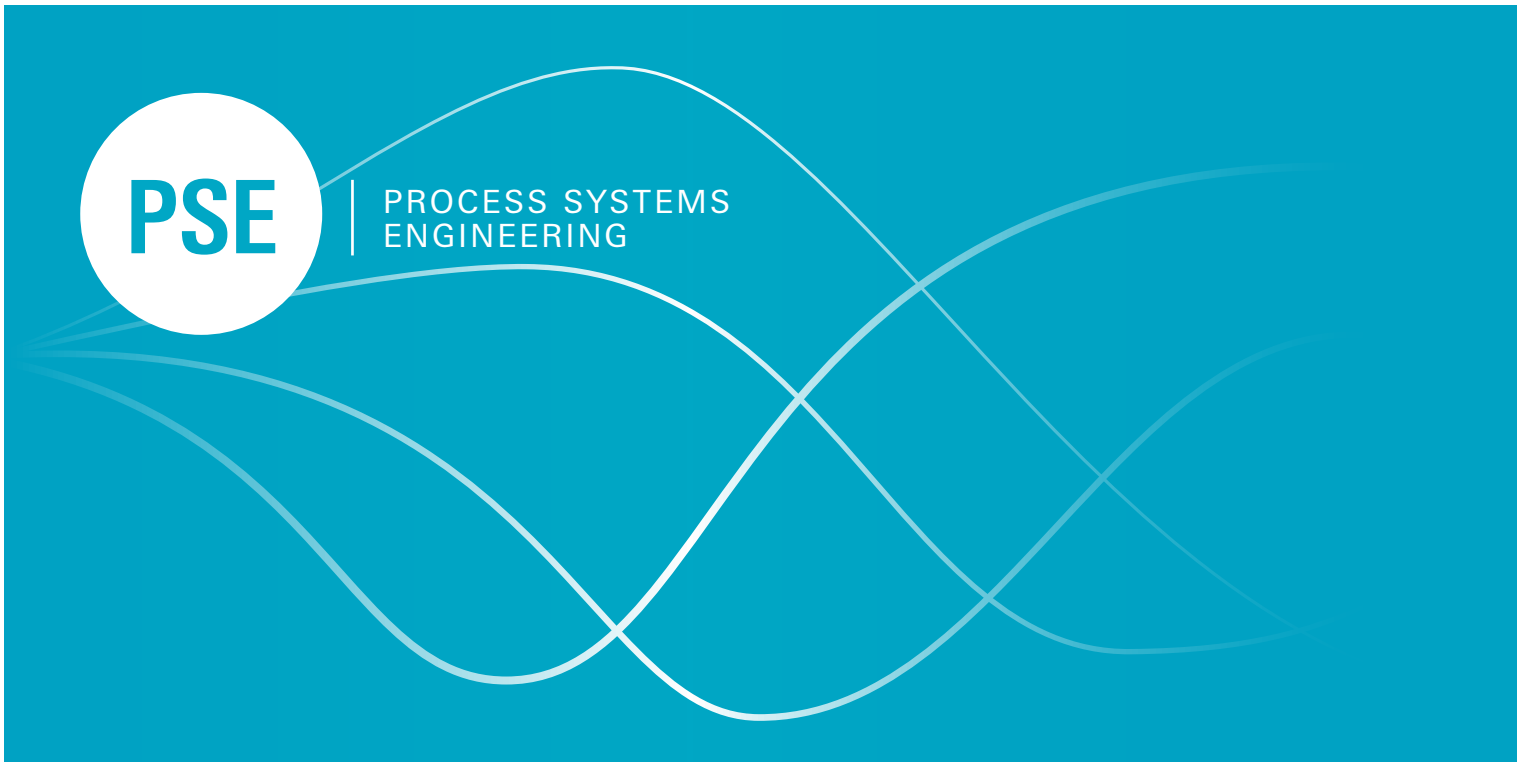


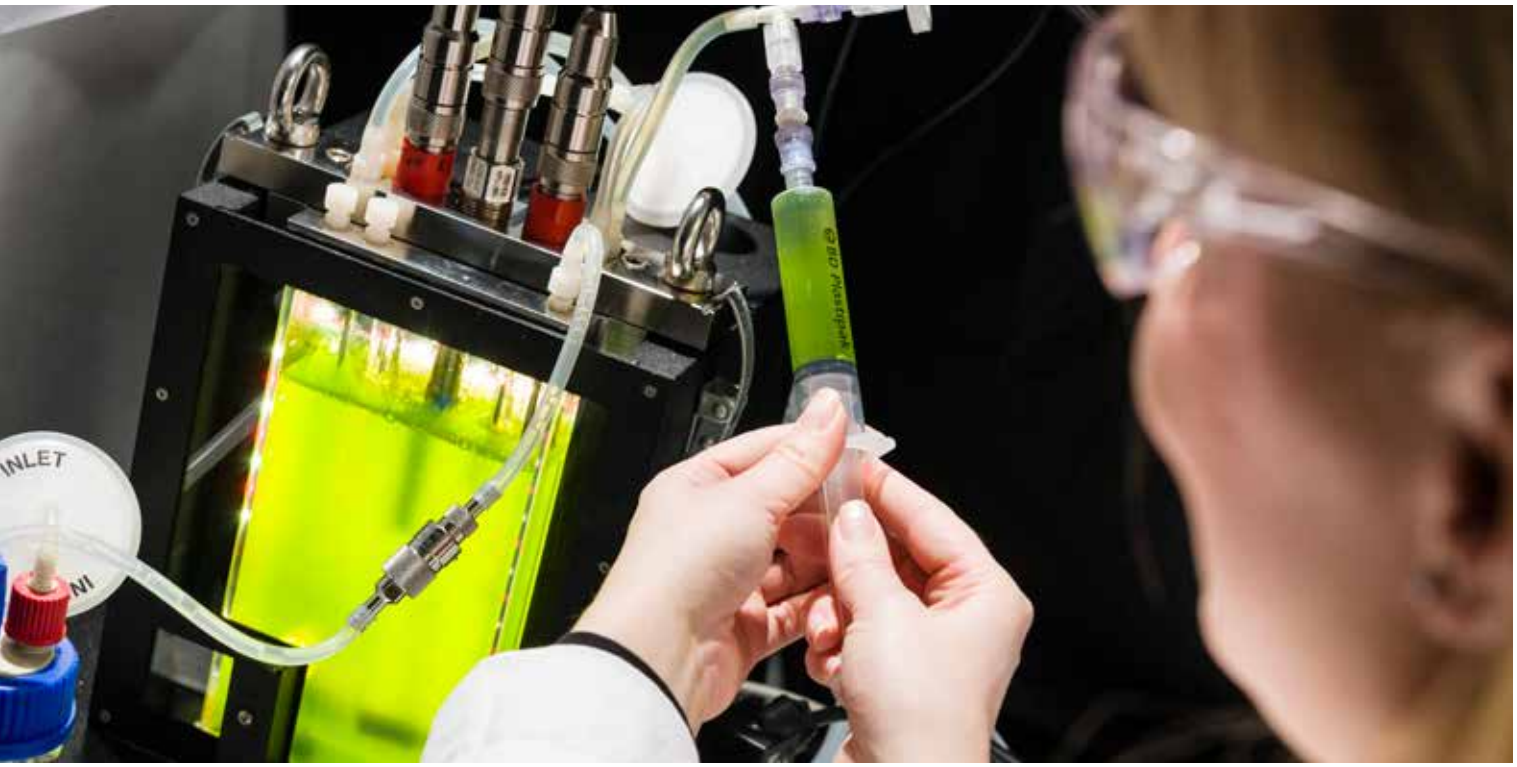
PROF. DR.-ING. KAI SUNDMACHER | DIRECTOR

Over the past decades, continuous progress has been made in increasing the productivity, selectivity, and sustainability of chemical and biotechnological production processes. Nevertheless, to cope with the challenges of the future, breakthroughs in **Process Systems Engineering** are necessary in order to find "dream processes" for synthesizing chemicals and transforming energy to enable the transition from fossil fuels and petrochemical feedstock to renewable materials and energy, to close carbon dioxide cycles, to enhance efficiency significantly, and to incorporate new functionality into materials and products.

For this purpose, new scientifically based process engineering approaches need to be developed, which are able to deal with the inherent multi-level structure of production systems. Very efficient process systems might be designable if engineers succeed in considering all hierarchical levels involved in a process system simultaneously, i. e. from the molecular level up to the plant level. However, a multi-level design strategy will be successful only if the underlying submodels are validated by using reliable experimental data obtained at different levels of the process hierarchy.

Experimental data are an indispensable element required to discriminate between rival models and to identify model parameters with small uncertainties. For this reason, only by closely combining mathematical process models and experimental data can an advanced quantitative understanding of complex process systems be attained to open up new ways of translating fundamental science into practical solutions.

This vision statement forms the background for the PSE group research strategy. Our group closely combines **mathematical modeling** of complex process systems with theoretical methods for **process analysis, identification, synthesis,** and **optimization** as well as with experimental validation techniques. In recent years, we have developed a multi-level strategy which is aiming at the synthesis of production systems from elementary process functions. This methodology



+ Cultivation of *Dunaliella salina* in a flat-plate photobioreactor

supports process design decisions on different levels of the process hierarchy (molecular level, phase level, process unit level, plant level).

We have used the methodology as the basis for the rational derivation of innovative process technologies in different areas. In the field of **Chemical Production Systems**, our current research focus is on multiphase reactions performed in solvent mixtures whose properties are tunable by temperature or pressure. This research is being carried out in cooperation with TU Berlin, TU Dortmund and the Otto von Guericke University in Magdeburg under the umbrella of the DFG-funded Collaborative Research Center SFB/TR 63 "InPROMPT". With regard to **Energy Systems**, we develop new process designs for the efficient conversion of electrical power into different chemicals, including hydrogen, synthetic methane, and liquid fuels. The key step in the energy conversion chain is the electrochemical splitting of water in membrane cells, which we are investigating in detail with colleagues from Leibniz University of Hanover and the Max Planck Institute for Chemical Energy Conversion in Mülheim an der Ruhr. In the field of **Biological Production Systems**, we initiated a new Max Planck Research Network in Synthetic Biology supported by the Max Planck Society and the German Federal Ministry of Education and Research (BMBF Biotechnology 2020+ program). The long-term goal of this network is the modular bottom-up assembly of protocells from functional biomolecules.

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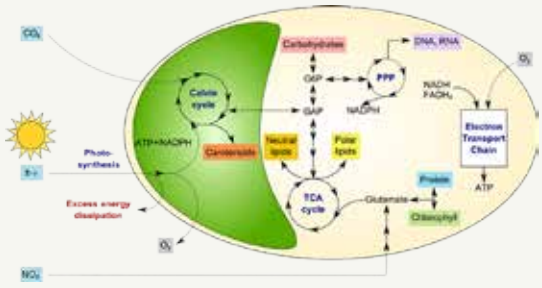
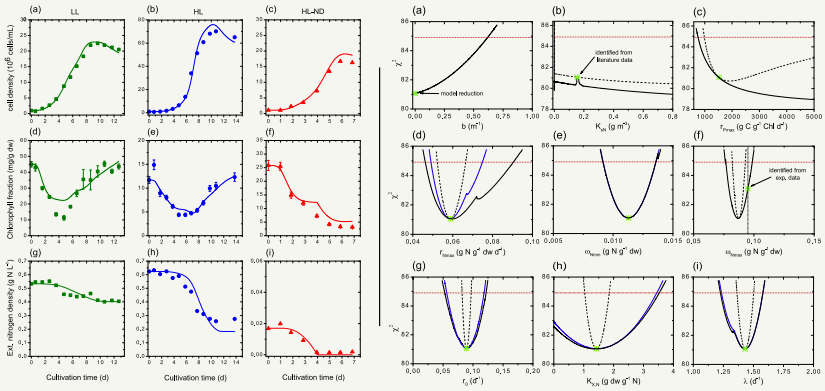


+ Figure 1:
Scheme of an algal cell in light. The main metabolic processes are shown, including the production of carbohydrates, chlorophyll and carotenoids. Adopted from Kliphuis *et al. J. Appl. Phycol. 2012.*



+ Figure 2:
Growth model of *Dunaliella salina.*

Left: Model Simulation for low light (LL), high light (HL), and high light/nutrient depletion (HL-ND) scenarios compared to experimental data. Solid lines represent model simulations, markers the data.

Right: Identifiability analysis of the 9 model parameters (for details see: Fachet *et al. Bio. Res. Tech. 2014*) based on the profile likelihood (black solid lines χ^2). Blue solid lines is the profile likelihood level at fixed $\omega_{N,max}$. The red dotted line represents the critical χ^2 value at significance level $\alpha = 0.05$. The green asterisk indicates the best parameter estimate.

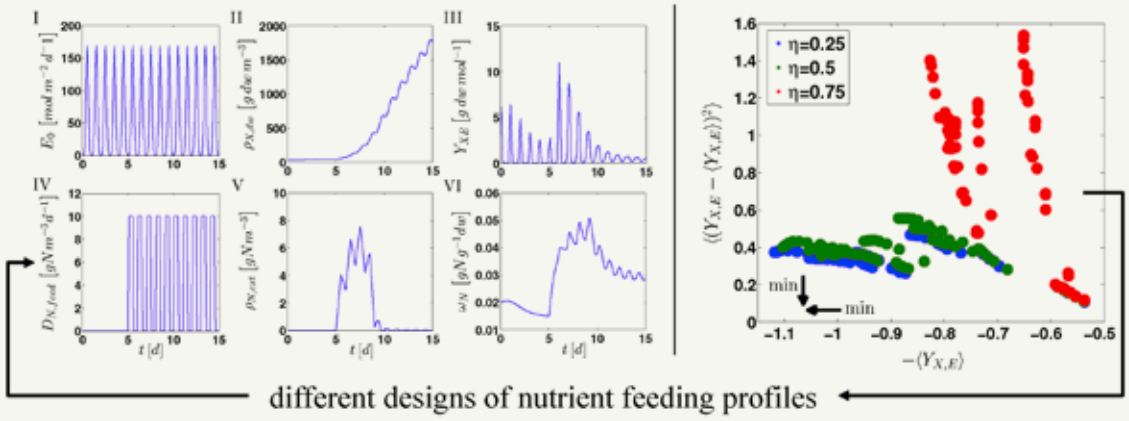
Robust Process Design for Production of Carotenoids in Green Microalgae

+ Photosynthetic microorganisms such as cyanobacteria and microalgae are innovative cell factories for the light-driven and sustainable production of chemicals from renewables. These microorganisms are capable of carrying out photosynthesis which allows the synthesis of a wide range of compounds from sunlight and carbon dioxide at higher volumetric and areal productivities compared to land-based crops. The broad scope of applications for microalgal products spans the feed, food, bioenergy, and chemical sectors.

Microalgae photosystems harbor light-harvesting pigments including chlorophylls, carbohydrates, and carotenoids (Figure 1). From a commercial perspective, carotenoid pigments of natural origin are of great industrial relevance. For the production of such natural carotenoids, the microalga *Dunaliella salina* is among the most promising organisms as it can be cultivated in open sea farms avoiding competition for valuable cropland. Furthermore, resistance to bacteria and other contaminants is increased by its *halotolerance*. Large-scale systems for mass cultivation of *D. salina* have been operated in Australia, Israel and in the US for more than 25 years but on a rather empirical basis. Here mathematical models of laboratory-scale cultivations can support the operation, control, and design of large-scale cultivation systems. In combination with targeted experiments, new details can be identified of the metabolism for economically feasible production of added-value compounds.

During the modeling process of such biosystems, scientists have to cope with numerous challenges. Often there is limited or even contradicting knowledge about the underlying mechanisms, and experimental limitations in combination with measurement noise and biological variability hamper reproducible probing of the system. As a result, identified model structures and parameters are highly uncertain as are model-based predictions, including optimized bioprocess designs. Here the PSE group delivers methodological contributions to robustify model-based predictions, including experimental and bioprocess designs, against the aforementioned uncertainties. These methodologies are applied to real-life cases ranging from biotechnological to biomedical applications.

Within the field of biotechnology, the PSE group worked on the optimal design of bioreactors based on the green alga *D. salina*. As a first step, a computational growth model of *D. salina* was identified and validated using experimental data of *D. salina* cultivated in a flat-plate photobioreactor under stressed and non-stressed conditions (Figure 2, left). Subsequently, an identifiability analysis was performed to evaluate the predictive power of the growth model. Three out of nine model parameters were initially non-identifiable. These non-identifiabilities were removed by incorporating additional knowledge and by reducing the complexity of the model (Figure 2, right). In a second step, the PSE group developed a new approach to predict a robust process design for the



+ Figure 3:
Robust design of nutrient feeding profile.

Left: Illustration of the influence of a day/night profile (I) on cell density (II), biomass yield (III), extracellular nitrogen density (V) and intracellular nitrogen fraction (VI) for a deterministic nutrient feeding profile (IV).

Right: *Criterion space average biomass yield on absorbed light energy* $\langle \bar{Y}_{X,E} \rangle$ and its *variance* $\langle (\bar{Y}_{X,E} - \langle \bar{Y}_{X,E} \rangle)^2 \rangle$ for several designs. Profile likelihood samples and three different process noise levels (0.25, 0.5, 0.75) are considered.

production of carotenoids in *D. salina* based on the growth model. Robustness is referred to as the consideration of model and process design uncertainties. The robust design approach is based on a hybrid uncertainty propagation strategy using profile likelihood and sigma point samples. The approach makes it possible to efficiently sample the confidence region of the typically high-dimensional model parameter space for estimating the uncertainties of model predictions. Additionally, variability of the process in the form of process noise, e. g. varying feeding profiles or fluctuations in operating conditions, can be described efficiently.

On the left side of Figure 3, we illustrate a typical cultivation scenario using our growth model. The influence of the periodic day/night light profile is clearly visible, as is the influence of the nutrient feeding profile. The right side of Figure 3 illustrates a possible criterion space for different nutrient feeding profiles, which was derived using our robust design approach. The criteria are average biomass yield on absorbed light energy $\langle \bar{Y}_{X,E} \rangle$ and its *variance* $\langle (\bar{Y}_{X,E} - \langle \bar{Y}_{X,E} \rangle)^2 \rangle$ While the former is to be maximized, the latter should be minimized to obtain a design prediction which is robust against uncertainties about the model parameters and also fluctuations in the design itself. As our analysis shows, a robust process design approach enables the engineer to trade-off expected performance and its fluctuations, which is especially important for large model parameter uncertainties and design variability. In our future work, we will focus on the experimental analysis and validation of the optimized bioprocess designs.

In conclusion, the combination of robust experimental design, experiments, and mathematical modeling allows efficient robust bioprocess design under uncertainties, including model identification. The strength of such an iterative approach has also been demonstrated by the PSE group in the field of biomedicine. Using our robust experimental design methodologies, we identified a dynamic model for DNA damage signaling in cancer cells, which could be used to understand the impact of specific inhibitors on gamma irradiation therapy.

I Dr.-Ing Robert Flassig

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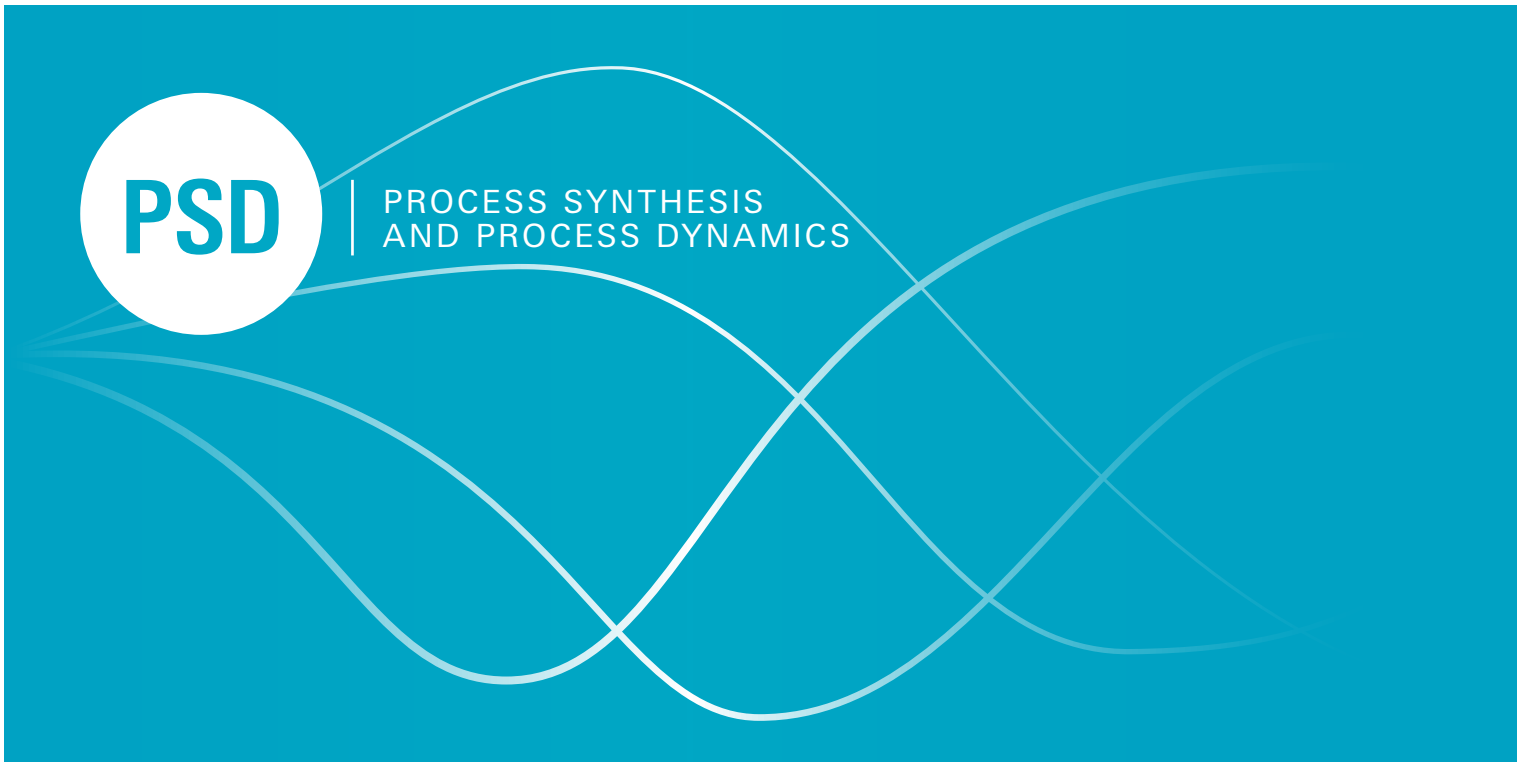
Author **Dr.-Ing. Robert J. Flassig**

Dr.-Ing. Robert J. Flassig obtained his diploma in 2008 in Physics on Saturnian dust dynamics at the University of Potsdam. In 2014 he received his Ph.D. degree from the University of Magdeburg. Within the PSE group, Robert J. Flassig currently develops and applies process design methodologies for robust bioproduction systems with a team of Ph.D. students. At the PSE chair of the University Magdeburg, he works as an assistant lecturer for optimal experimental design.



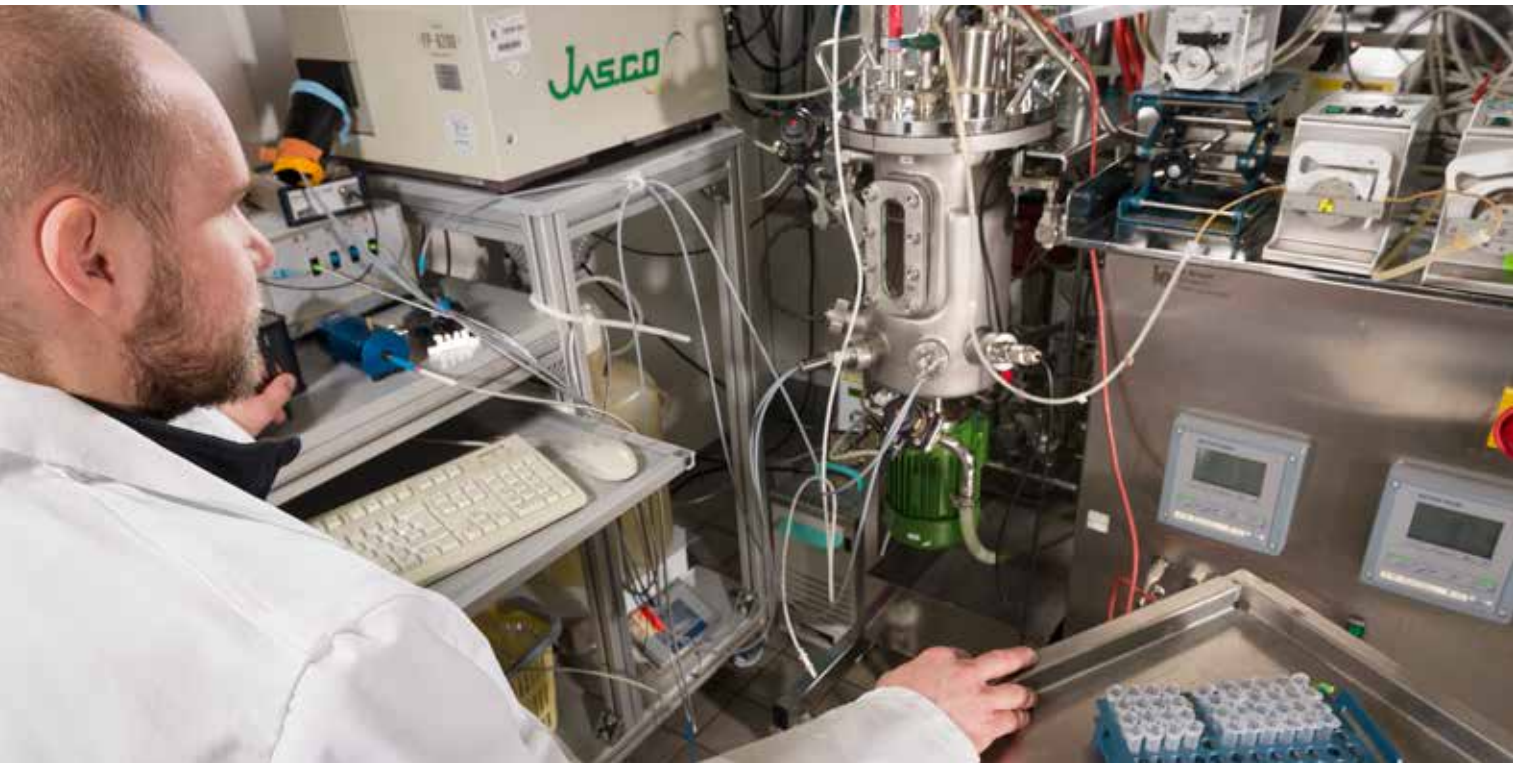
PROF. DR.-ING. ACHIM KIENLE |
EXTERNAL SCIENTIFIC MEMBER

The Process Synthesis and Dynamics (PSD) group is headed by Achim Kienle who is an external scientific member of the MPI. He also holds a professorial position at the Otto von Guericke University. The MPI and university group are collaborating closely.

The PSD group develops methods and tools for the synthesis, analysis, and control of complex process systems. It combines physical chemical insight with theoretical concepts from systems and control as well as applied mathematics. Process insight guides the way to suitable problem formulations, and feasible as well as efficient solution strategies.
Theoretical concepts are validated experimentally. This is often done in cooperation with the experimental groups at the MPI.

Process control has developed as a major field of research for the PSD group in recent years. Currently, the focus is on control of particulate processes, control of advanced chromatographic processes, and plantwide control strategies. Particulate processes are described by nonlinear partial differential equations and represent a particularly challenging class of distributed parameter systems. Important topics which are addressed by the PSD group include nonlinear model reduction as well as new approaches to robust and nonlinear control of particulate processes. Novel crystallization and fluidized bed spray granulation processes are considered to be interesting application examples. The particular focus of the PSD group is on adaptive cycle to cycle control and plantwide control of integrated chromatographic processes leading to hybrid separation and/or hybrid reaction/separation processes. Chromatographic processes are switched systems with cyclic behavior.

In the field of **Process design**, the PSD group develops computational methods for systematically designing complex process systems. Approaches range from shortcut methods



+ Biopolymers are produced by many microorganisms under unbalanced growth conditions. They are made from renewable resources. They are biodegradable and biocompatible and can be used for example for the manufacture of biomedical implants. For better understanding and optimization of biopolymer production, Ph.D. candidate André Franz has developed a joint theoretical and experimental approach.

based on analytical insight through to rigorous simultaneous mixed integer nonlinear optimization (MINLP) of process configurations and operating conditions. One area of special interest is new methods for deterministic global MINLP optimization being developed in cooperation with partners from mathematics. Some innovative multiphase reaction systems and integrated processes for the production of pure enantiomers are considered to be interesting fields of application.

Biosystems engineering has been identified as a research area of common interest for the Max Planck Institute and the Otto von Guericke University. Important contributions by the PSD group to biosystems engineering lie in the fields of novel methods for optimal experimental design, nonlinear dynamics, and multidimensional population balance modeling. Vaccine and biopolymer production processes are considered to be interesting fields of application.

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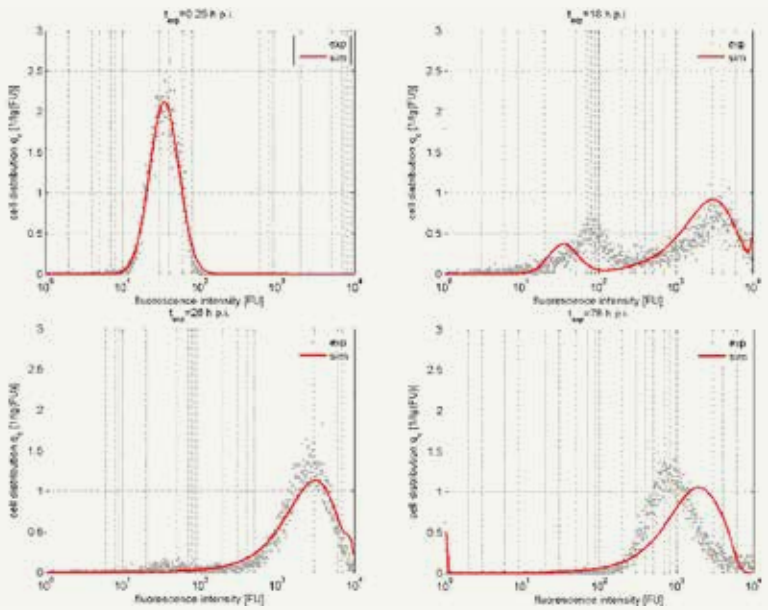


+ Figure 1:
Temporal evolution of fluorescence distribution for influenza virus replication in MDCK cells. Comparison of model predictions and experimental results according to [2].

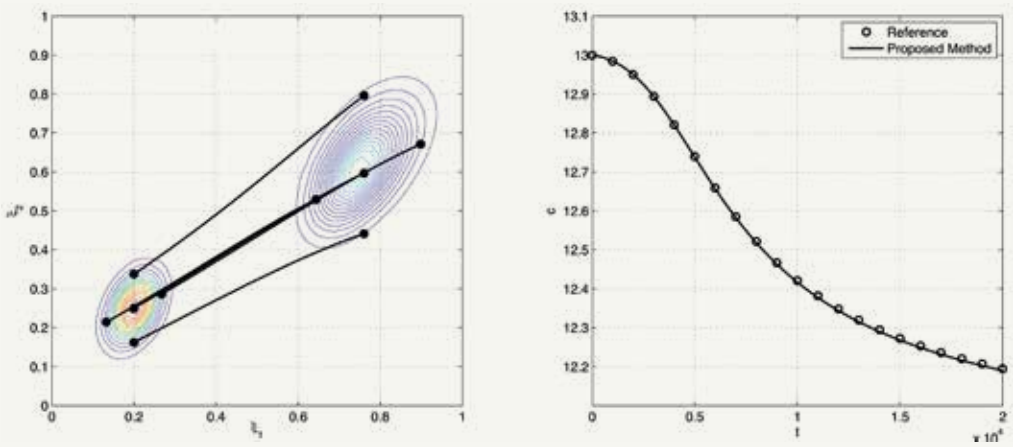
Modeling and Simulation with Multidimensional Population Balances

+ Particulate processes like crystallization, granulation, or precipitation play an important role in process engineering. They comprise a large number of particles, which are typically nonuniform and differ in view of characteristic properties like size, morphology, and composition.

Cellular production systems in bioprocess engineering have an analogous structure. They consists of a large number of cells differing in view of characteristic physiological properties. Often cell to cell variability needs to be addressed explicitly to provide a deeper understanding of the underlying biological processes. Application examples considered in the PSD group are processes for biopolymer production [1] and influenza virus replication in vaccine production processes [2]. The latter is studied in cooperation with the Bioprocess Engineering group. Preliminary results based on a one-dimensional unstructured model with some global kinetics for infection, virus replication, and release are shown in Figure 1. The figure shows fluorescence intensity distributions of the cells at different time points with interesting dynamic features including transient bimodality and a characteristic backshift at later time points. Fluorescence intensity in this figure is proportional to the amount of intracellular viral nucleoproteine NP. Comparison between theoretical predictions and experimental data shows only qualitative agreement. For quantitative agreement, more structured models are required leading to multidimensional distributions.

Mathematically, the above processes can be described by population balances. They represent nonlinear partial differential equations. Their dimension is equivalent to the number of characteristic properties also termed “internal coordinates”. The number of internal coordinates can be high, especially in the case of cellular systems.
Often population balances are coupled to integro differential equations describing the medium. Analytical solutions are only possible in extremely special cases. Usually, therefore, a numerical solution has to be applied.
Established numerical solution strategies comprise discretization techniques like finite differences, finite volumes, finite elements or Monte Carlo methods. Due to high computational effort, these approaches are usually limited to problems with a few internal coordinates. However, from a practical point of view, often the full multidimensional distribution is not required but only some characteristic properties like mean, variance or skewness, which represent the moments of the distribution. Only in special cases can these moments be calculated from a closed set of ordinary differential equations and approximate closures have to be applied. In this approach, the multidimensional integrals are evaluated with a cubature, which is a weighted sum of so-called abscissas.
Classical approaches based on Gaussian cubatures have been applied successfully to one and two-dimensional problems. Extension to higher dimensional problems is straightforward, but involves great computational effort as the number of abscissas and weights, and thus the corresponding number of differential equations, increases exponentially with dimension.

+ **Figure 2:**
Two dimensional crystal growth: (a) Contour plots of the temporal evolution of two dimensional crystal size distribution and corresponding abscissas. (b) Predicted solute concentration in the medium. Taken from [3].



To overcome this problem, a new approach was developed based on monomial cubatures [3]. In contrast to classical Gaussian cubature formulas, the computational effort increases only polynomially with the dimension of the problem. In the case of a Gaussian initial distribution, a particularly efficient monomial cubature formula can be found. This formula is known as the Sigma-Point rule for which the number of abscissas increases linearly with dimension. Thus even high dimensional problems become tractable with reasonable accuracy.

Application was demonstrated in [3] for multidimensional growth processes including two-dimensional crystal growth and a theoretical benchmark problem with five internal coordinates. The results of the new approach showed good agreement with some reference solutions obtained from more rigorous and computationally much more expensive numerical approaches or analytical solutions.

More recently, application to a generic model for virus replication in cell cultures with five internal coordinates was presented where the synthesis of essential viral components is analogous to multidimensional growth processes [4]. In addition, infection was taken into account corresponding to a nucleation process in process engineering. Future work aims at a quantitative multidimensional population balance model for influenza virus replication in vaccine production processes based on more detailed single cell kinetics developed in the Bioprocess Engineering group. In addition, possible extensions to particulate processes with agglomeration and/or breakage will be studied. I **Robert Dürr**

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Robert Dürr is a Ph.D. candidate in the group of Prof. Kienle. He studied Systems Engineering and Engineering Cybernetics at the Otto von Guericke University in Magdeburg and received his diploma in 2009. Since 2011 he is member of the International Max Planck Research School Magdeburg for Advanced Methods in Process and Systems Engineering (IMPRS ProEng). Currently, he is working on modeling, simulation and parameter estimation of population balance systems with applications in process and bioprocess engineering.

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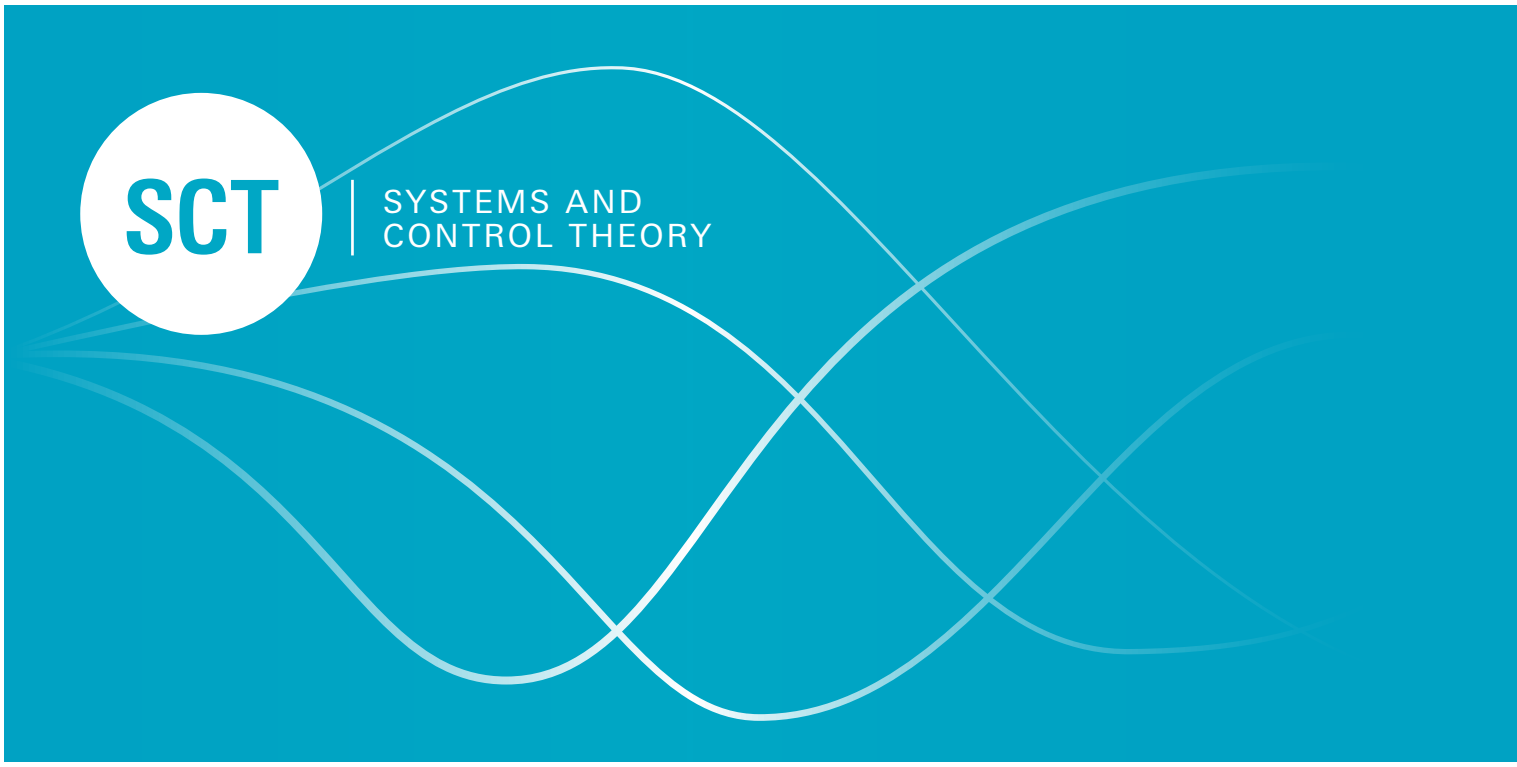

"There is nothing as practical as a good theory"

(K. Lewin)

PROF. DR.-ING. JÖRG RAISCH |
EXTERNAL SCIENTIFIC MEMBER

The SCT group is led by Jörg Raisch who has been an External Scientific Member of the MPI since 2001. Jörg's primary affiliation is with the Technische Universität (TU) Berlin where he heads the Control Systems group within the Department of Electrical Engineering and Computer Science. In practice, both groups operate as a unit and there are currently 21 Ph.D. students, three postdoctoral researchers, and two senior researchers.

Our research is carried out in close cooperation with other research groups from the MPI and/or other national and international cooperation partners.

We investigate theoretical aspects but also work on a number of exciting application projects. Our theoretical interests are mostly concerned with developing new methods to synthesize feedback control for discrete event and hybrid systems. The former are dynamical systems that can be adequately characterized by the occurrence of discrete events; the latter are systems exhibiting nontrivial interaction between discrete event dynamics and "standard" continuous dynamics modeled by differential equations.

Our application projects are predominantly in the areas of biomedical engineering, electrical distribution networks, and process and manufacturing systems. Most of our biomedical projects are related to the use of functional electrical stimulation in the context of the rehabilitation of stroke patients. The control of electrical networks has re-emerged as a challenging

+ Testing an adaptive drop-foot stimulator intended for stroke patients. The underlying control concept is based on ideas from Iterative Learning Control (ILC). Left and right: Dr. Thomas Schauer (TU Berlin), Prof. Dr.-Ing. Jörg Raisch. (Healthy) test person in the middle: former Ph.D. student Thomas Brunsch.

problem since an increasing number of distributed renewable energy sources are connected to distribution grids. We try to keep a good balance between methodological and application projects; we also attempt to match projects in the sense that results obtained from theoretical work are transferred into specific application projects as rapidly as possible.

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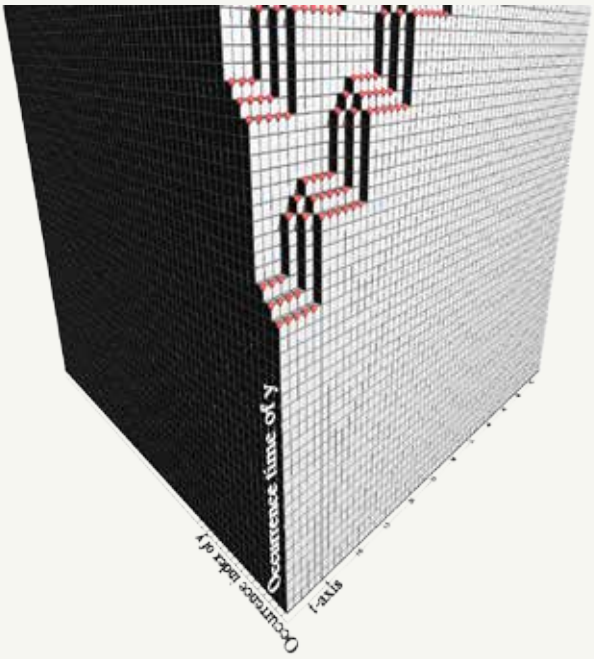


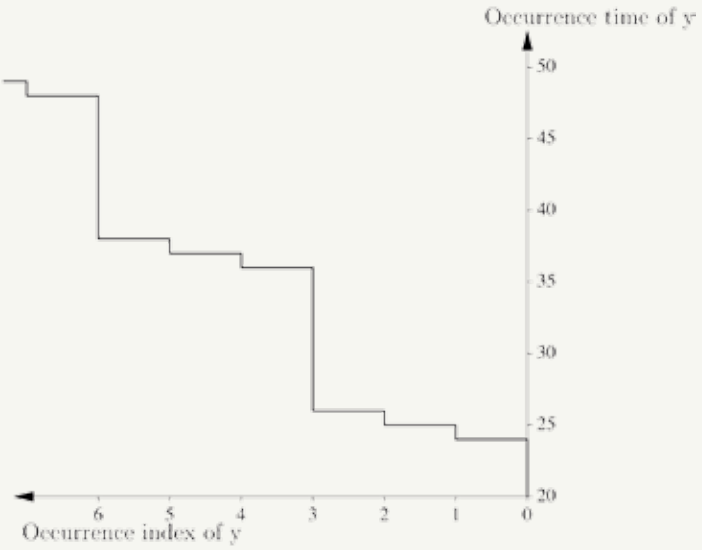
Figure 1:
Transfer function of a simple road network with traffic lights, providing the timing pattern of the output event y, if the input is an impulse (i. e., an infinity of occurences at the same time) at time t.

Event-based Modeling and Control of Transportation Networks

In standard control theory, models are usually time-driven and often expressed as differential or difference equations over time. However, to capture the interesting dynamics of some man-made systems such as transportation networks, it is often useful to work on an abstraction level where only the occurrence of discrete events is considered. Such abstractions are called discrete event systems (DES) (e. g. [1]) and have been a fruitful research area during the past decades. In a discrete event system, two basic elements are distinguished: the event set and the rule describing the behavior of the system. Various formal approaches such as finite-state automata and Petri nets have been investigated to express this rule. In particular, discrete event systems with a rule composed of standard synchronizations have been thoroughly investigated (standard synchronization refers to conditions of the form "occurrence k of event A is at least t units of time after occurrence k-l of event B"). Such systems are convenient to model transportation networks functioning under a predefined schedule, as standard synchronization captures phenomena such as travel durations and capacity constraints. Discrete event systems ruled by standard synchronizations are linear in specific algebraic structures such as the so-called max-plus algebra, and are therefore often called max-plus-linear systems. Many modeling and control approaches available for standard linear systems (e.g. transfer function matrix model and optimal control) have been successfully extended to max-plus-linear systems (e. g. [2]).

The novel aspect of our work lies in considering not only standard but also partial synchronizations. Partial synchronization requires simultaneity between events. Formally, the partial synchronization of event A by event B is defined by "event A can only occur when, not after, event B occurs". Many phenomena in transportation networks are naturally modeled by partial synchronization (e.g. a car can cross an intersection only when the traffic light displays green). We consider a particular class of discrete event systems ruled by standard and partial synchronization which can be decomposed into a main subsystem and a secondary subsystem such that there exist only standard synchronizations between events in the same subsystem and partial synchronizations of events in the secondary subsystem by events in the main subsystem. Such systems are referred to as max-plus-systems with partial synchronization. The main system is a max-plus-linear system as the synchronizations affecting an event in the main system are standard synchronizations by events in the same subsystem. However, due to partial synchronization, some events in the secondary system can occur only when, not after, associated events in the main system occur. Therefore, the modeling and control methods developed for max-plus-linear systems cannot be directly extended to max-plus-systems with partial synchronization.

In practice, max-plus-systems with partial synchronization can be interpreted in the following way. The main system offers a service to the secondary system during a time window.



+ Figure 2:
Section of the transfer function corresponding to an impulse at t = 0.

Furthermore, while obtaining this service is essential for the secondary system, the secondary system does not affect the main system. An intuitive example is a road network with traffic lights. The traffic lights solve the resource allocation problems at intersections and give permission to vehicles to cross intersections during time windows. This is expressed by partial synchronizations: a vehicle can cross an intersection only when the associated traffic light displays green. Furthermore, while the color of a traffic light affects the behavior of the vehicles, the presence or absence of vehicles at an intersection is – in the absence of a control policy – irrelevant for the associated traffic lights. In this example, the main system corresponds to the traffic lights and the secondary system corresponds to the road network.

In our work, we propose a max-plus-algebraic model for max-plus-systems with partial synchronization and extend optimal control [3] and model predictive control [4] to such systems. Furthermore, by considering a predefined behavior of the main system, we manage to obtain a transfer function matrix model (see Figure 2) for the secondary system and synthesize appropriate model reference control for this subsystem. Applying this to the above example allows traffic conditions to be improved by delaying as much as possible the entrance of vehicles into the transportation network without degrading its input-output behavior. **I Xavier David-Henriet**

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Author **Xavier David-Henriet**

After a two-year intensive programme in Advanced Mathematics and Physics, Xavier David-Henriet was accepted at Supélec – Ecole Supérieure d'Electricité – in France specializing in Electrical Engineering and Computer Science. In 2011, he obtained a dual degree with the TU Berlin in Electrical Engineering with a major in Control Theory. He then joined the Max Planck Institute in Magdeburg as a Ph.D. student jointly supervised by Prof. J. Raisch from the Control Systems Group at the TU Berlin and by Prof. Hardouin from the LARIS at the Université d'Angers (France).

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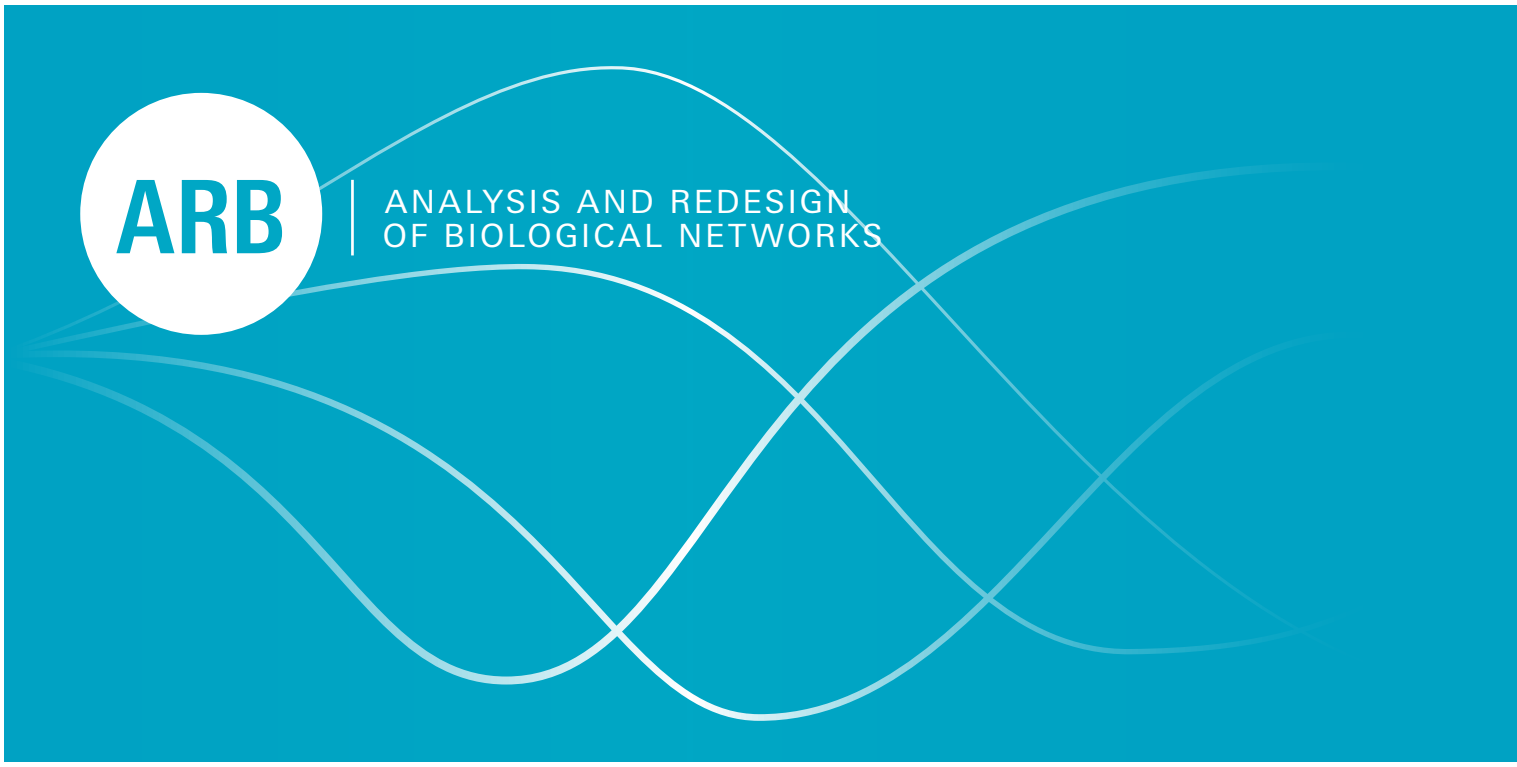

DR.-ING. STEFFEN KLAMT | SENIOR SCIENTIST

It is nowadays widely accepted that understanding the complexity of life at the cellular level requires mathematical and computational tools. In particular, the unbiased integration of ever-increasing factual biological knowledge with rapidly accumulating experimental data from novel measurement technologies seems impossible without mathematical approaches. This gave rise to interdisciplinary research fields such as Systems Biology and Computational Biology, which combine wet lab (experiments) and dry lab (mathematical modeling and analysis) investigations to obtain a holistic understanding of cellular processes and networks.

Along this line, the primary research interests of the ARB group lie at the intersection of biology, mathematics, and engineering sciences and a key goal is to obtain a network and systems view of the cell. On the theoretical side, we develop computational methods for modeling, analysis, and data-driven inference of bio-molecular networks. From an engineer's perspective, we are also interested in using models to calculate suitable intervention strategies that change the behavior of a cell towards a desired response. Furthermore, our group develops software for modeling biological systems, including *CellNetAnalyzer*, a widely used MATLAB package for biological network analysis. We employ our methods and tools in collaborations with biological partners to study realistic networks of cellular signal transduction and metabolism. Application examples include the data-driven elucidation of changes in the topology of cellular signaling networks under certain disease states or the rational (re)design of bacterial metabolic networks towards bio-based production of certain chemicals. The ARB group has also an experimental research team studying aspects of metabolic regulation and metabolic engineering in the model bacterium *Escherichia coli.* As a long-term goal, with our research we want to help pave the way for the routine use of mathematical modeling and network analysis in biology, biotechnology, and biomedicine.

+ The ARB group develops and applies computational methods for the analysis, identification, and targeted modification of biological networks. Here we see Dr. Oliver Hädicke studying a computer model of the metabolism of a bacterium.

In 2014, research results achieved and published by our group included novel algorithms for computational strain design, a systems-level description of how *Escherichia coli* responds to oxygen, and new criteria for the emergence of bistability in signaling networks induced by protein phosphorylation cascades. Results were presented at several international conferences, for example the Metabolic Engineering Conference in Vancouver (the biggest symposium in this field), the Conference on Systems Biology of Mammalian Cells in Berlin, the SIAM Conference on the Life Sciences in Charlotte (US), and the European Conference on Mathematical and Theoretical Biology in Gothenburg where two mini-symposia were organized by members of the ARB group.

For our group, one particular research topic deals with the design principles of bacterial regulatory circuits, specifically with two-component systems which are modular signal transduction systems employed by bacteria to mediate adaptation to changes in diverse environmental conditions such as pH, osmolarity or the presence of anti-microbial peptides. Ronny Straube presents results of this study in our highlight section, illustrating how mathematical modeling helps to gain a deeper understanding of regulatory mechanisms in the cell.

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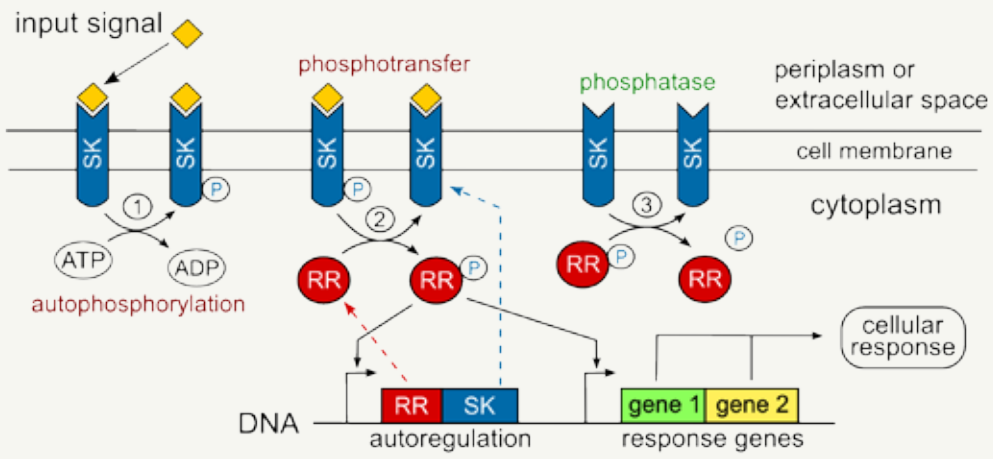


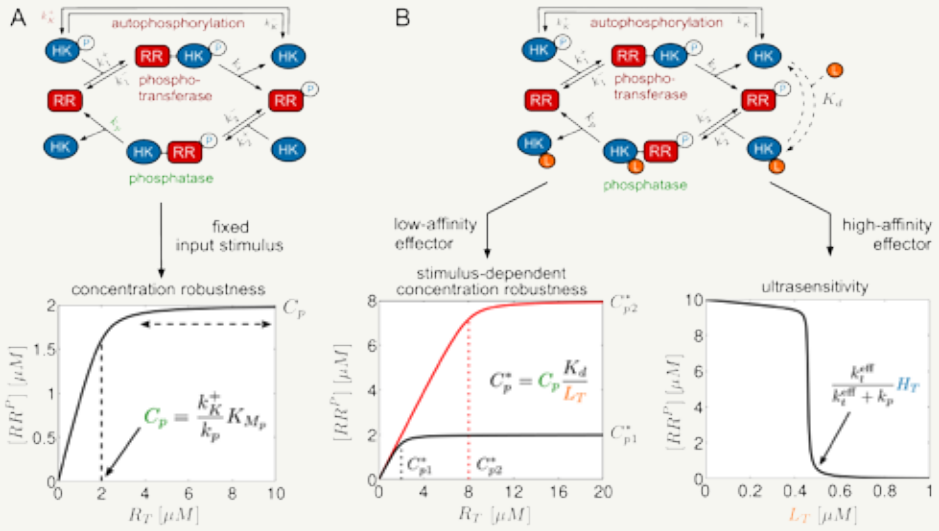
Figure 1:
Signal flow in two-component systems: Upon activation the sensor kinase (SK) undergoes autophosphorylation and phosphotransfer to a response regulator (RR) which then activates a set of response genes including those of the SK and RR themselves (autoregulation). Often, the SK is bifunctional, i. e. it not only phosphorylates the RR, but it also exhibits phosphatase activity towards the RR.

Regulatory Properties of Bacterial Two-Component Systems

Two-component systems (TCSs) are modular signal transduction systems which are employed by bacteria to mediate adaptation to changes in diverse environmental conditions such as pH, osmolarity or the presence of anti-microbial peptides. Since they regulate many aspects of bacterial physiology, analyzing their regulatory properties is essential for understanding the design principles of bacterial genetic circuits. The knowledge gained may then be used to control the behavior of bacterial strains in biotechnological applications or for the development of antibiotic drugs. Due to their modular architecture, TCSs also represent an attractive source for the construction of regulatory circuits with novel functionality in the context of synthetic biology.

As the name suggests, two-component systems consist of only two components (proteins): a sensor kinase (SK) and a cognate response regulator (RR). Typically the SK is a transmembrane protein with an outwardly directed sensor domain and an inwardly directed kinase domain. Upon stimulation by an input signal the SK becomes activated through a process called autophosphorylation (step 1, Figure 1) in the course of which a phosphoryl group is transferred to the cytosolic domain of the sensor protein. Subsequently, this phosphoryl group is transferred to the receiver domain of the cognate RR (step 2, Figure 1) which, thereby, itself becomes activated. The activated form of the RR then binds to specific promoter sites at the DNA in order to enhance or repress the transcription of certain genes whose protein products eventually mediate the cellular response to the input signal. In addition, RR activation often leads to an increase in the SK and RR concentrations due to autoregulation.

Apart from autokinase and phosphotransferase activity, many SKs also exhibit a distinct phosphatase activity (step 3, Figure 1) through which the RR becomes dephosphorylated (inactivated) in the absence of an input signal. Such SKs are called bifunctional and TCSs with a bifunctional sensor protein have the remarkable property that under steady state conditions the RR phosphorylation level does not depend on the SK concentration, i. e. they exhibit concentration robustness with respect to the SK. Intuitively, under steady state conditions the rate of RR phosphorylation equals that of RR dephosphorylation and, since both rates are proportional to the SK concentration, the latter simply drops from the steady state equations. Interestingly, TCSs with a bifunctional SK may also exhibit concentration robustness with respect to the RR, provided that SK autophosphorylation is rate-limiting for the activation of the RR. The latter property can be quantitatively understood within a mathematical model proposed by Batchelor and Goulian (Figure 2 a). Even though the key predictions of this model have been experimentally confirmed, it is still unclear why concentration robustness would be a desirable property for TCSs. One general idea is that it might be advantageous if the output of a regulatory system (here the phosphorylation level of the RR) is independent of the concentrations of the network components (SK and RR). In the case of TCSs, this would allow every bacterium in a heterogeneous cell population to respond in a similar manner to an input signal despite naturally existing cell-to-cell fluctuations in protein abundances.



+ Figure 2:
(A) Concentration robustness in the Batchelor-Goulian model (1).
(B) Extended Batchelor-Goulian model (2): Depending on the strength of the input signal the system may either exhibit stimulus-dependent concentration robustness or ultrasensitivity.

Within the Batchelor-Goulian model it is difficult to quantitatively predict how the RR phosphorylation level would change with respect to an input signal because the model essentially focuses on the description of the three activities of a bifunctional SK, but does not explicitly account for a signal-sensing mechanism. Moreover, it has been argued that input signals (such as small allosteric effectors) are likely to affect multiple enzyme activities. For example, in the PhoQ/PhoP TCS binding of Mg^{2+} to the PhoQ sensor kinase inhibits the enzyme's autokinase activity while, concomitantly, activating its phosphatase activity. We have recently proposed an extension of the Batchelor-Goulian model which implements this regulatory scheme in its simplest form (2). The analysis of this model shows that the input-output behavior of the system now crucially depends on the affinity of the effector, i. e. on the strength of the input stimulus. If the effector affinity is low (weak input signal) the system is predicted to exhibit concentration robustness similar to the original Batchelor-Goulian model, but with the difference that the maximum RR phosphorylation level now depends on the input stimulus. In contrast, a high-affinity effector (strong input signal) may lead to a switch-like (ultrasensitive) change in the RR phosphorylation level in response to the input signal. In conjunction with autoregulation a high-affinity effector may also generate a bistable induction of response genes where induced and uninduced cells would coexist for a range of input stimuli. It is generally believed that such behavior might be an advantageous survival strategy in uncertain environments. Next we will analyze how concentration robustness is affected by transcriptional feedback through autoregulation and how these two features combine to allow for differential gene regulation in response to input signals. Also, in recent years it became apparent that there exists substantial cross-talk between different TCSs and we would like to gain a better quantitative understanding of the underlying mechanisms.

I Dr. Ronny Straube

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Dr. Straube studied physics at the Friedrich Schiller University Jena. After receiving his diploma in 2001 he moved to the University of Magdeburg where he obtained a Ph.D. in Biophysics in 2006. Starting in mid 2005 he spent 18 month at the Hahn Meitner Institute Berlin before he joined the Systems Biology Group at the MPI Magdeburg in 2007. Since 2011 he has been leading a research team in the research group Analysis and Redesign of Biological Networks (headed by Dr.-Ing. Steffen Klamt) with a focus on the functional analysis of regulatory biological networks. For the winter term 2015/2016 he has been appointed as a deputy professor for biomathematics at the University of Erlangen.

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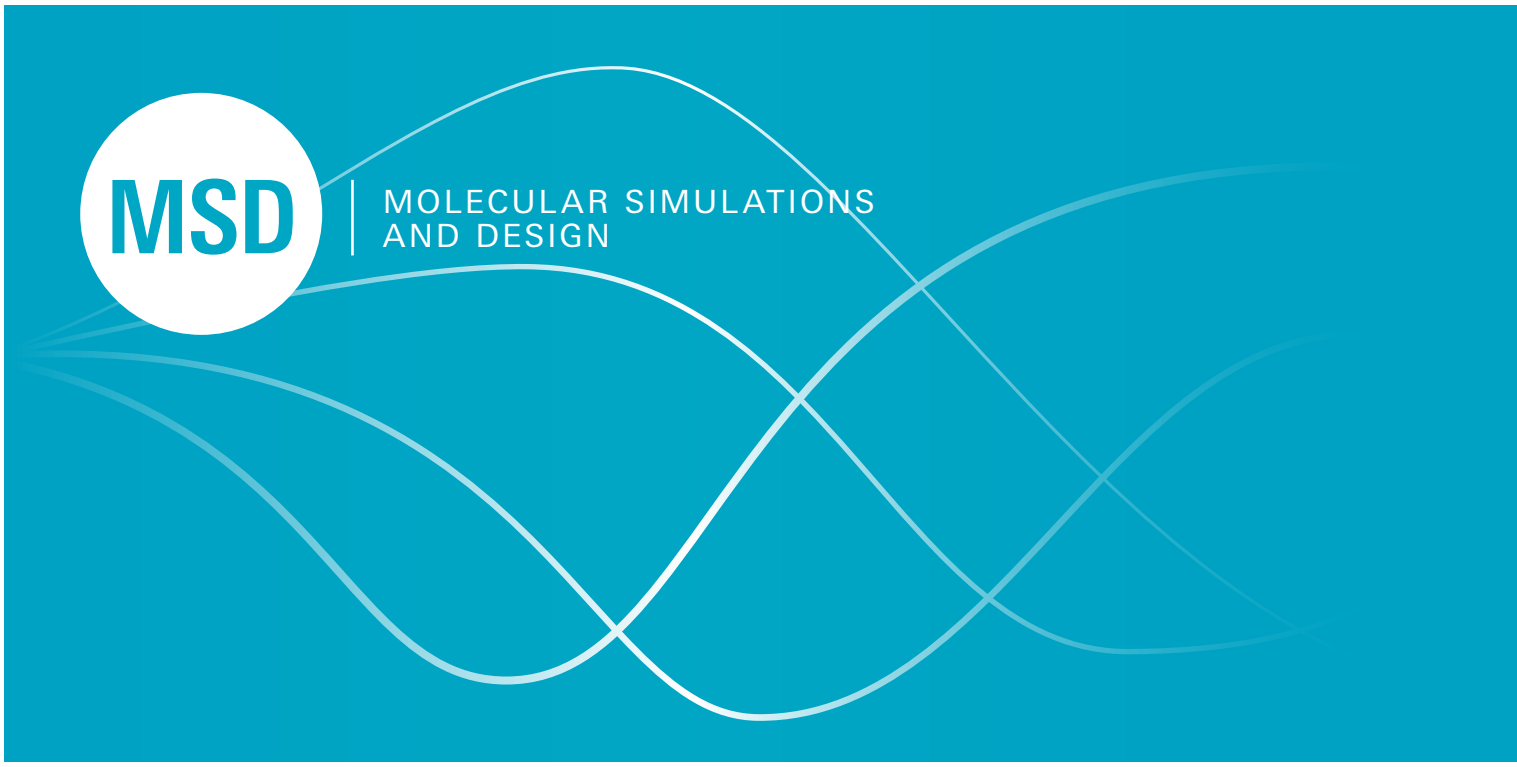

DR. RER. NAT. MATTHIAS STEIN I SENIOR SCIENTIST

The Molecular Simulations and Design (MSD) group is a Max Planck Research Group (MPRG) led by Dr. Matthias Stein. The interdisciplinary work of the MSD group is reflected by the range of tools from bioinformatics, protein structural modeling, different molecular simulation techniques, and quantum chemistry that the MSD group develops and applies to different problems from biology and chemistry.

During this year, Prof. Sandeep Kaur-Ghumaan from the University of Delhi (India) spent her second period of stay as a DST-MPS Fellow with the MSD group. She electrochemically and theoretically examined some of the new chemical compounds synthesized in-house in terms of their hydrogen-producing capabilities. The question of how close the synthetic 'bioinspired' models come to the enzymatic active sites in terms of structural, electronic, and catalytic features was described in a review article in 2014.

In 2014, the MSD group commenced working on homogeneous catalysis in complex reaction media in the framework of the Collaborative Research Centre (CRC) SFB/TR 63 "InPROMPT" with partners from universities in Dortmund, Berlin, and Magdeburg. Emilija Kohls joined the MSD group to do her Ph.D. in this field of reactive mechanisms and microkinetics of large-scale processes. The CRC offers scientific exchange and regular meetings between Ph.D. students and scientists from all three sites but also a training program for Ph.D. students to acquire additional qualifications. Two European networks, in which the MSD participates, were positively evaluated during the last year. In the CM1402 (Crystallize, 2014 – 2018) network, the molecular organization of organic

+ Chemistry on the computer. A molecular catalyst releasing H_2 in acid media is visualized.

molecules during the phase transition from liquid to solid will be investigated. The Ph.D. project by Rebecca Hylton (joint student with UCL) covers this area.

Dr. Stein is the national representative, management committee member, and also working group leader of the new CM1305 COST Action ECOSTBio (2014-2018). In this network, the role of electron spin as a determinant of reaction rates and mechanisms in chemical and biological systems will be elucidated. Transition metal containing systems can exist in different spin states and may interconvert between those. The reactivity of various spin-state potential energy surfaces may be different and there may be a change between different spin-states during a process.

In the second period of funding of the IMPRS for Advanced Methods in Process and Systems Engineering, our new IMPRS student Md Bin Yeamin will continue the work that Eileen Edler initiated during her Master thesis. Eileen investigated the influence of the spin state of an Fe(III) central metal in a mononuclear thiolate on the complex structural parameters, the favored electronic ground state and preferred ligand orientation.

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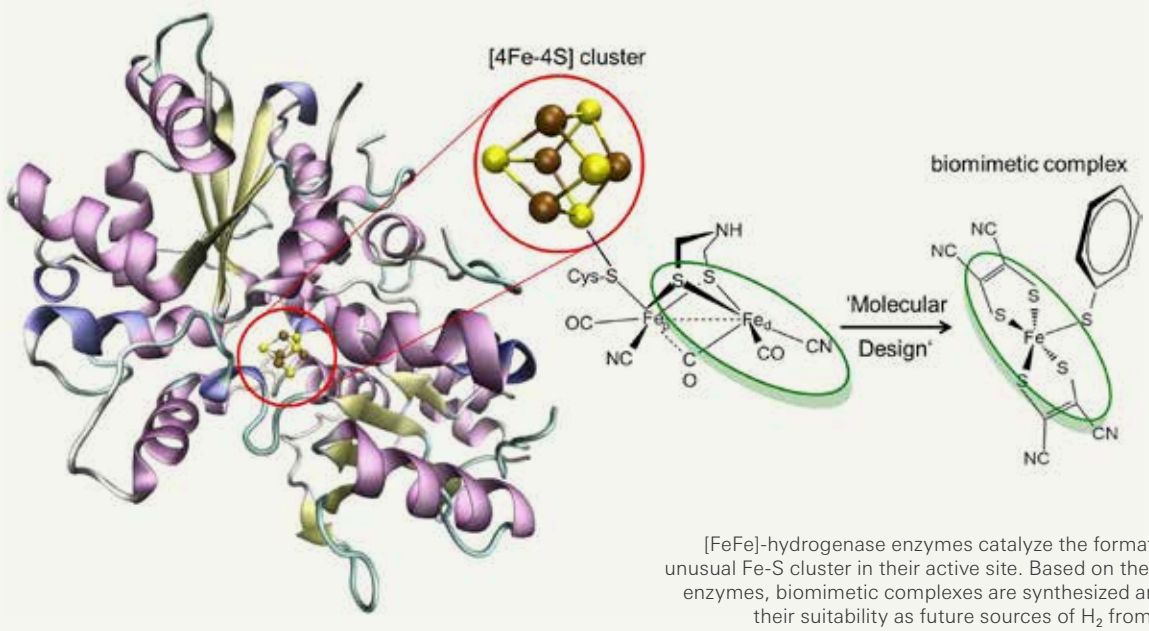


Figure 1:
[FeFe]-hydrogenase enzymes catalyze the formation of H_2 using an unusual Fe-S cluster in their active site. Based on the structure of these enzymes, biomimetic complexes are synthesized and investigated for their suitability as future sources of H_2 from proton reduction.

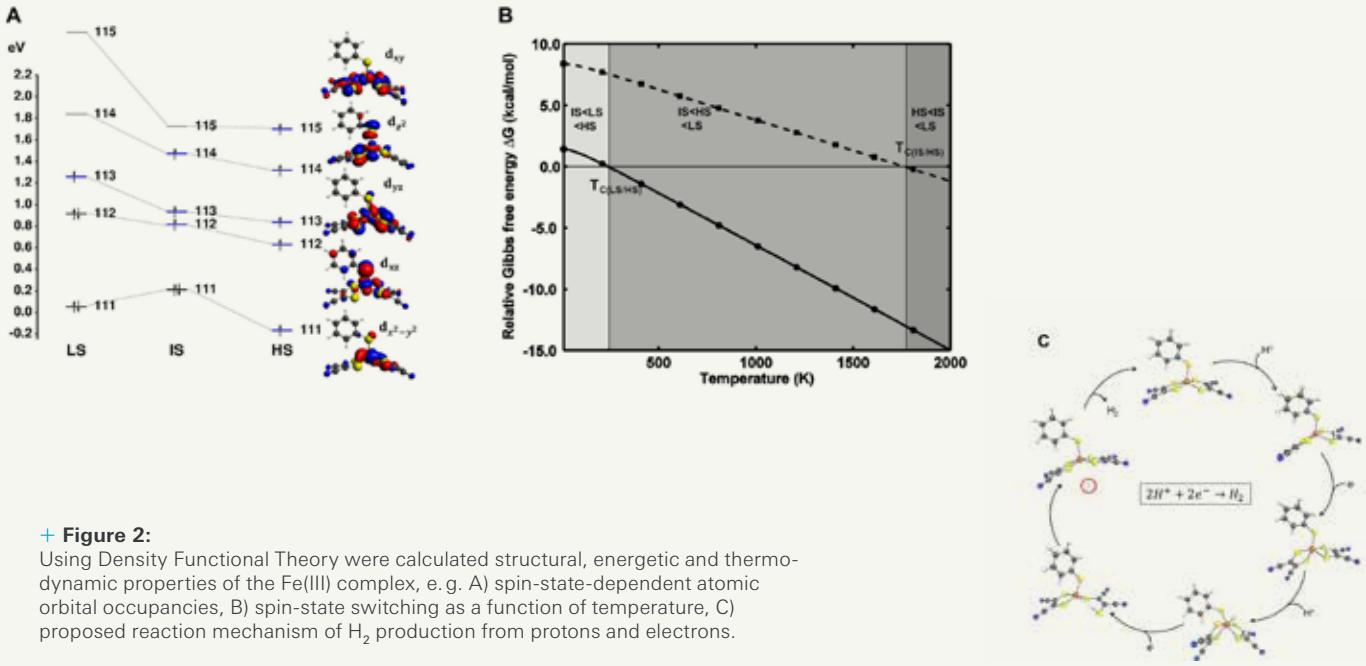
Magnetic Mononuclear Fe(III) Complex: High, Low or Intermediate-Spin?

Over billions of years nature has developed concepts used as an inspiration for our modern inventions and technologies. Materials and methods adopted from biological systems, so-called biomimetics, are an indispensable part of our everyday life. Nature also provides valuable inspiration regarding power generation. Increasing global energy consumption along with imminent exhaustion of fossil resources requires the development of alternative energy sources. Molecular hydrogen (H_2) is considered a potential future energy carrier. In nature, enzymes called hydrogenases produce molecular hydrogen from protons and electrons in archaea, bacteria, and eukaryotes and use the cheap and abundant metal iron (Fe) to accomplish this task. Based on the model of their active sites, biomimetic chemical complexes were synthesized which act as catalysts for H_2 conversion [1] (Figure 1).

Structural biomimetic complexes try to rebuild an enzyme's active site. A series of heterobimetallic complexes taking up biological structural design principles of hydrogenase active sites was investigated [2]. Functional mimics go one step further, abstract functional principles, and by "molecular design" suggest a new type of catalyst. In test tube experiments, molecular hydrogen can also be generated from mononuclear complexes with either a penta-coordinate Fe(II) [3] or Fe(III) atom surrounded by five sulfur atoms in square-pyramidal coordination [4]. In many cases, experiments cannot provide the required temporal or spatial resolution to characterize the catalytic mechanism of hydrogen evolution and, consequently, computational chemistry and biology are challenged.

Fe(III) as a transition metal can exist in different spin states, i.e. the electrons can be distributed in different ways among the atomic orbitals (Figure 2A). We tested the performance of different "functionals" in the framework of Density Functional Theory and found structural properties and energies to be considerably dependent on the choice of functional [4]. In particular, hybrid functionals performed rather poorly for our complex. It turned out that the admixture of Hartree-Fock exchange had to be reduced in order to obtain structural properties in excellent agreement with experimental data. We validated the performance of this new functional using additional iron complexes with experimentally or theoretically verified properties as benchmarks.

The intermediate-spin (S=3/2) state was shown to be the preferred electronic ground state in agreement with experimental data. The energetic ordering of subsequent spin states was highly dependent on the computational method.
In addition, we found that the properties of the catalyst such as structural (bond lengths, bond angles, and dihedral angles) and conformational preferences are heavily influenced by the spin state. For intermediate (S=3/2) and high-spin (S=5/2)



+ Figure 2:
Using Density Functional Theory were calculated structural, energetic and thermodynamic properties of the Fe(III) complex, e. g. A) spin-state-dependent atomic orbital occupancies, B) spin-state switching as a function of temperature, C) proposed reaction mechanism of H_2 production from protons and electrons.

states, the preferred conformation of the axial thiophenolate ligand corresponded to that of the crystallized form whereas for the low-spin (S = 1/2) state rotation of the complex axial ligand is possible at room temperature and yielded a rotated global minimum. Spin-state-dependent properties and energetics are associated with the concept of "multi-state reactivity".

Since the energy differences between the spin-dependent conformations were small, we investigated the complex behavior with regard to a possible spin-crossover, i. e. a change in electronic ground state. Spin-crossover compounds can change their spin state due to an external stimulus, e.g. temperature or pressure. This is accompanied by a modification of the physical properties. For the Fe(III) complex, three regions of different spin state ordering can be observed (IS<LS<HS; IS<HS<LS; HS<IS<LS) with two switching temperatures at 240 K and 1700 K (Figure 2B). The switching of magnetic properties by temperature potentially opens up the possibility of related Fe(III) complexes being used as single molecule magnets with a binary ability to store information and data.

Following the electronic and structural property analysis of the complex, we investigated possible reaction pathway scenarios for H_2 formation. In an acidic environment, the complex releases molecular hydrogen produced from protons and electrons in a two-step reduction process. The formation of a negatively charged hydride is an essential intermediate step, which allows the release of H_2 from a hydride-proton reaction (Figure 2C). This reflects the reaction mechanism occurring in nature: [FeFe]-hydrogenases involve terminal hydrides in their catalytic pathway as well. Since the present complex is able to produce H_2 from protons and electrons it is also a candidate for artificial photosynthesis when coupled with suitable photo-sensitizers. The overall objective is to mimic the energy delivering processes of photosynthesis from green plants, i. e. to split water molecules using sunlight and generate molecular hydrogen as a liquid fuel. However, such an application remains challenging due to potential difficulties regarding catalyst stability (e. g. oxygen tolerance), solubility in solvents as well as a fast and efficient turnover. We will focus on a detailed elucidation of the reaction mechanism in our future work including the application in artificial photosynthesis. **I Eileen Edler**

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Author **Eileen Edler**

Eileen Edler studied Biosystems Engineering and received her Master of Science degree from the Otto von Guericke University in Magdeburg in 2013. She started her Ph.D. in the Molecular Simulations and Design research group at the Max Planck Institute Magdeburg. Eileen Edler is also taking part in the COMETiN Program of coaching and mentoring excellent young female scientists. Her Ph.D. project focuses on multiscale modeling and analysis of protein-membrane interactions in particular the membrane recruitment of endocytotic proteins of the early endosome. She is an associated member of the CRC/TR 63 InPROMPT.

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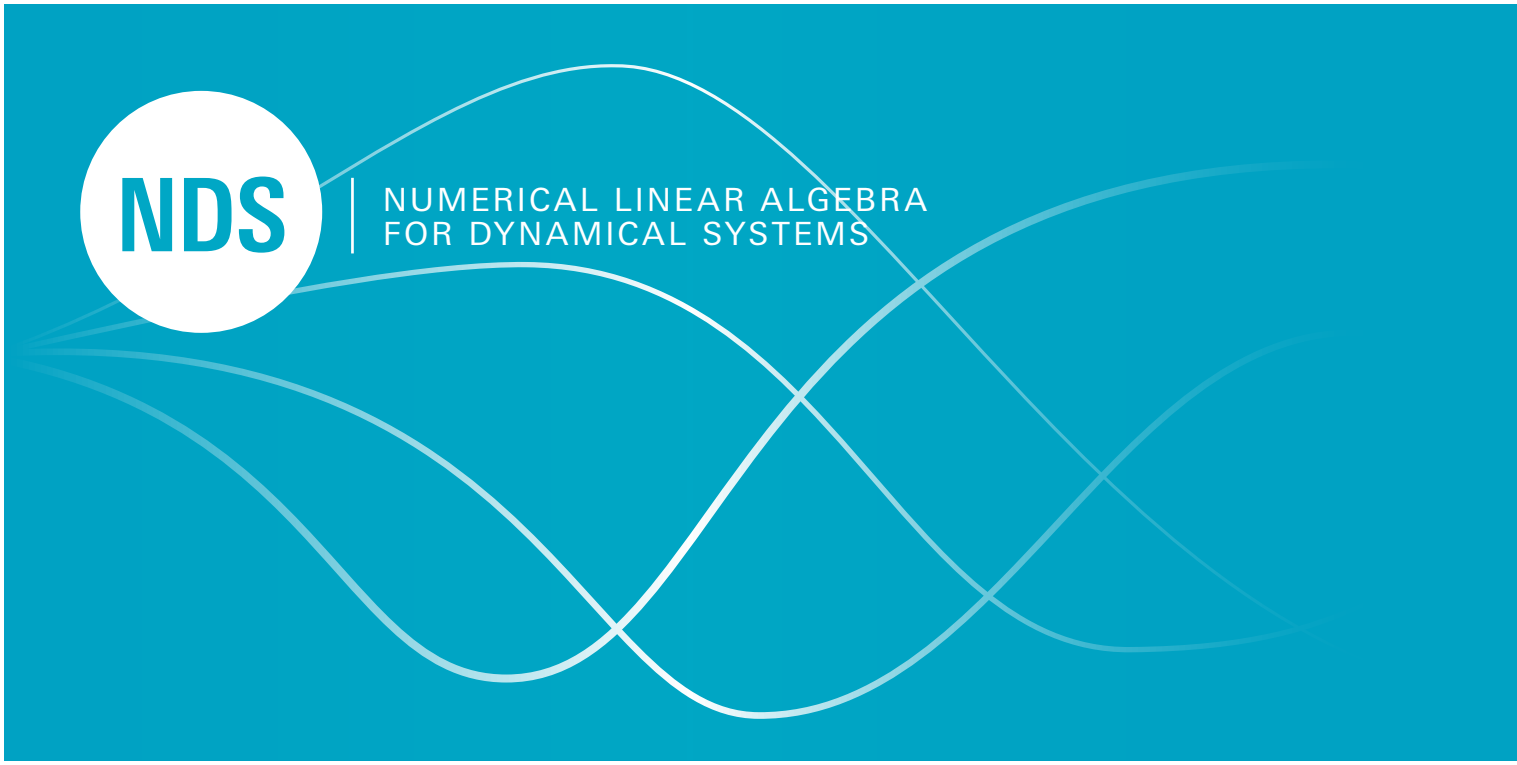

DR. MARTIN STOLL I SENIOR SCIENTIST

Our group was established in 2013 under the name Numerical Linear Algebra for Dynamical Systems and enjoyed its first year of being up and running in 2014.

In addition to the daily routine of writing and polishing papers and software, we also had many changes in the setup of our group. While Dr. Andrew Barker, a former Postdoctoral Researcher working on high performance computing approaches for PDE-constrained optimization, was leaving for a permanent job at the Lawrence Livermore Laboratory in California, we have seen the arrival of Wei Zhao who started her Ph.D. on nonlocal differential equations and the arrival of Dr. Sergey Dolgov. Sergey moved to Magdeburg coming from the Max Planck Institute for Mathematics in the Sciences, where he recently finished his doctorate, and is currently working on high dimensional problems for nonlocal operators. Additionally, he is one of the main developers of the Tensor Train Matlab toolbox, which is used around the globe.

Much of our research effort has again gone into what can be described as efficient simulation techniques for complex models. These models are often of a complicated structure inherited from the differential equations needed to describe particular phenomena. While such equations are found everywhere ranging from financial markets to the design of airplanes, we have focused our efforts on the solution of problems from material science, image processing, and pattern formation in biological systems.
The governing equations in all these fields often share similar features that our methodologies are able to exploit. Our goal is to allow computational algorithms to run faster or, even more importantly, to enable the solution of previously intractable simulations.

In particular, our phase-field models highlighted in last year's issue, which we have previously used for simulations of prob-

+ Martin Stoll and colleagues discussing the numerical solution of partial differential equations that come from the modeling of real world phenomena. The white or black board are main tools for developing numerical methods and strategies within the group.

lems from material science, have been adapted and applied to problems from image inpainting – a technique to restore missing information in images that is also discussed in our Research Highlight this year.

One of the very many good things happening in 2014 was a first prize for Jessica Bosch in a Ph.D. student competition at the 13th Copper Mountain Conference on Iterative Methods in Copper Mountain, Colorado, USA. Jessica won the prize for her paper on Preconditioning for Vector-Valued Cahn–Hilliard Equations, which she then presented at the meeting in the Rocky Mountains. Additionally, Dr. Martin Stoll was invited to give a plenary lecture at the Householder Symposium in Spa, Belgium. This meeting is one of the most prestigious and long-standing meetings in Numerical Analysis. He presented his work with Tobias Breiten (Graz) and Valeria Simoncini (Bologna) on fast solvers for fractional differential equations.

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+ **Figure 1:**
Cahn-Hilliard inpainting applied to an image

+ **Figure 1a:**
Destroyed image.

+ **Figure 1b:**
Reconstructed image.

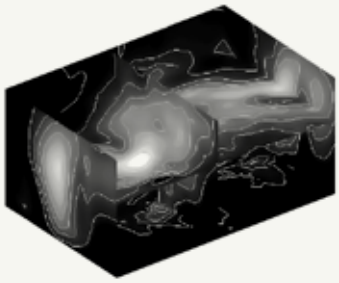
Inpainting Techniques and Solvers

Inpainting is the art of modifying parts of an image such that the resulting changes are not easily detectable by an ordinary observer. Applications include the restoration of damaged paintings and photographs, the replacement of selected objects or the reduction of artifacts in medical images. Due to the large number of applications much effort has gone into the development of digital techniques.

In the following we concentrate on gray images. In the case of RGB color images one could solve the inpainting problem for each color channel separately. Given a gray image, the parts that are going to be modified are denoted by the inpainting domain. These parts are often called missing or damaged portions, since the observer is (usually) unfamiliar with the original image. The target is to reconstruct the inpainting domain in an undetectable way, whereby the lines of equal gray values arriving at the boundaries are extended inside. Figure 1a shows an example image where the inpainting domain is given in form of the unicolored grid (which could be seen as cracks or scratches). Figure 1b illustrates the inpainted reconstruction using a Cahn-Hilliard model explained later.
The derivation of inpainting models takes specific goals and features of the requested reconstruction into account. These include among others the preservation of sharp image features, the degree of smoothness of the fill-in or the connection of edges over large distances. For example, an image of mostly straight lines should not be treated in the same way as an image of mostly curved lines. One model, which is suitable for the latter type and able to connect lines over large distances, is based on the so-called Ginzburg-Landau energy functional. The motivation for using this energy is as follows. One of the model's characteristics is the existence of an interface of small width between the pure gray values. However, the size of these smooth transitions can be controlled by the user via a model parameter. The evolution of the interface is driven by an interfacial energy whose minimization penalizes interfaces with high curvatures. This forms the first part of the Ginzburg-Landau energy functional. The second part is given by a free energy that incorporates a so-called multi-well potential with distinct minima for each gray value. Hence, its minimization penalizes all values away from the specified gray values. The study of the Ginzburg-Landau energy functional is known for the modeling of coarsening and phase-separation processes (see last year's Annual Report). The Cahn-Hilliard equations form a well-known model that can be derived from the minimization of this energy functional. For its application to the inpainting problem, an additional energy term is taken into consideration. This so-called fidelity term acts on the regions outside the inpainting domain and penalizes values that are too far away from the original image. All in all, one obtains a system of evolution equations, the so-called system of modified Cahn-Hilliard equations, and the inpainted version of a given image is constructed by following this system to steady state.

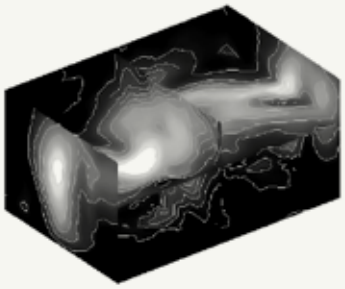
The system of equations is described by partial differential equations including nonlinear terms. This makes these equations typically hard to solve and one has to carefully devise

+ **Figure 2:**
Cahn-Hilliard inpainting applied to a 3D image.
80% of the data were randomly removed.



+ **Figure 2a:**
Original 3D image.

+ **Figure 2b:**
Corrupt plane.



+ **Figure 2c:**
Reconstructed 3D image.

algorithms that take the structure of the model into account. The finite difference or finite element method are standard approaches that allow the discretization of operators such as the ones describing the modified Cahn-Hilliard equations. Besides, fractional models, in which a standard differential operator is replaced by a corresponding fractional differential operator, are becoming increasingly used as a modeling tool for processes with spatial heterogeneity. It is known that fractional diffusion models lead to thinner interfaces that allow for smaller pure regions and a much more heterogeneous structure. In our work we compare the standard and fractional Cahn-Hilliard inpainting model in terms of the temporal evolution and sharpness of the inpainted image.
Another crucial point is the choice of the multi-well potential within the Cahn-Hilliard energy functional. Smooth functions can be handled using available fast computational techniques. Nondifferentiable functions typically show sharper visual results but require additional caution and pose a challenging numerical problem. The resulting discrete problems are typically of very large size and cannot be tackled using naive approaches as these require vast amounts of time and storage. Our aim is to develop efficient and robust solvers that enable the solution in a reasonable time. The development of effective solvers also allows us to perform three-dimensional experiments which typical lead to much larger problems. Figure 2 shows the results of a Cahn-Hilliard inpainting model applied to a 3D image. I **Jessica Bosch**

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Jessica Bosch received a Bachelor of Science degree in mathematics from the Georg-August University Göttingen in 2010 and a Master of Science degree from the Otto von Guericke University Magdeburg in 2012. After that, she completed a three month research visit at the Oxford Centre for Collaborative Applied Mathematics (OCCAM) at the University of Oxford (UK). Since 2013, she is a Ph.D. student within the NDS research group at the Max Planck Institute Magdeburg.

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Publications 2014

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