



MAX PLANCK INSTITUTE
FOR DYNAMICS OF COMPLEX
TECHNICAL SYSTEMS
MAGDEBURG

Annual Report 2013



+ Kamila Galan

Ph.D. candidate in the *Physical and Chemical Foundations of Process Engineering* group

The experimental setup is used to perform crystallization based separations in a continuous manner. Pairs of enantiomers (two compounds which are mirror images of each other) cannot be easily separated due to their identical physical and chemical properties in an achiral (symmetric) environment. So far only the batchwise crystallization has been applied. The investigated chiral substance is threonine, which is an example of an enantiomeric system. The goal of this research is to find new ways to carry out resolutions.

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Message by the Chairman of the Board of Trustees

Today the state capital of Magdeburg is an important administrative centre with a highly-productive economy, but above all it is an extremely dynamic centre of scholarship. Traditionally, alongside medicine, the engineering sciences are a cornerstone of the city's research profile. For this reason it is especially pleasing that with the Institute for the Dynamics of Complex Technical Systems (MPI) the Max Planck Society has chosen to establish its first engineering institution in Magdeburg.

240 members of staff, including many international guests, are conducting fundamental research here into questions such as how biological processes can be transferred to technical applications and how increasingly complex processes can be optimised. This demands a high degree of interdisciplinary cooperation and close collaboration with other scientific institutions.

Indeed it is this close scientific integration and cooperation that is one of the strengths of the location. The state capital is doing its utmost to support this, as the development of Magdeburg as a centre of scholarship is one of the city's most important strategic objectives. For this reason I am delighted to have taken on the role of chairman of the board of trustees of the MPI.

In addition to excellence in research, in close cooperation with the Otto von Guericke University, the MPI is also making a key contribution to the high quality of education here. That is why I am particularly pleased that the International Max Planck Research School will continue in the years to come.

The MPI is a hugely important asset to the scientific landscape in Magdeburg. I wish the institute continued great success in the years ahead. The MPI can be certain of the full support of the state capital.

A stylized handwritten signature in black ink, consisting of a large 'L' followed by a series of loops and a long horizontal stroke.

Dr. Lutz Trümper
Mayor

+ **Intro**duction





The Max Planck Institute for Dynamics of Complex Technical Systems in 2013

✚ 2013 marked an eventful year for the Max Planck Institute for Dynamics of Complex Technical Systems in Magdeburg (MPI Magdeburg, for short). This was not at all anticipated. When I started my two-year term as Managing Director on January 1, 2013, I actually expected a smooth and calm period as we just had successfully gone through the evaluation by our Scientific Advisory Board (SAB) in 2012. We had managed the re-structuring following the retirement of Prof. Dr.-Ing. Ernst Dieter Gilles, the founding director of our institute, and my appointment as the fourth director at the institute.

My own group had basically reached its expected size and had been well integrated, so I was ready for taking on my new administrative duties. As will be detailed below, expectations had been overtaken by reality, though, but at writing this text, I think we are back to a smooth operation mode with promising prospects.

As you read this text now, you may already have realized that this is our first Annual Report in a format attractive for the interested public. It uses our novel Corporate Design (CD), including the newly designed logo, and is a result of

the process of developing a new Corporate Identity for the MPI Magdeburg, starting mid-2013. Like the events described below, this was not on the agenda when I took office, but in the process of our web relaunch (see below, too), we realized that our old presentation to the public did not at all live up to the standards of modern CD's. The process is still going on at this writing and can hopefully be completed successfully before Andreas Seidel-Morgenstern takes over as Managing Director on January 1, 2015.

In the following, I report on a few important events in 2013. The first one actually is not a single event, but a sequence of events that pulled the institute into a political debate in the state of Saxony-Anhalt, caused by the need to present a balanced state budget in the coming years. This led to the suggestion to cut down the budget for the universities and for research significantly in the years to come. It also led to the demission of Minister for Economy and Science, Prof. Birgitta Wolff, who had different ideas how to realize these budgets cuts than the rest of the state government, to numerous demonstrations by students and employees of universities and research institutes (including the MPI) in Magdeburg and Halle,



+ from left to right

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

and a number of supporting activities where we got involved. A joint statement of the research institutes in Magdeburg in support of an adequate funding for education and research was released and was cited in an article reviewing the situation in Saxony-Anhalt in the *Süddeutsche Zeitung* (May 6, 2013). It seemed the state government was quite surprised by the level of protest and the solidarity among all research and higher education institutions. At the end of 2013, a compromise ("Bernburger Frieden") could be reached that led to much smaller budget cuts than planned, and was based on a proposal of the state universities to reduce budgets where they seemed reasonable.

The debate on the budget cuts took a back seat in June 2013 when yet another Elbe flooding took place. Though it looked not severe at first predictions, it turned out to break all records in Magdeburg. We had to establish a crisis squad (the leading of which was also quite a new experience for me) as it became clear very quickly that part of our premises would be flooded. As the institute's main building sits high enough above the Elbe banks, it was not endangered of getting flooded (though a power outage would have cau-

sed severe damage in the labs), but we had no chance to save the basement of one of our guest houses sitting on the level of the Elbe banks. Eventually, we had to evacuate both guest houses since we had to shut down all their infrastructures. The solidarity among the employees at the institute was amazing and within a day, we could find shelter in guest rooms or on couches of our employees for all our guests. Also, our institute staff helped with clearing out the basement of Guest House II and cleaning up after the flood. A report on this appeared in the *Max Planck Journal* (no. 4/2013), and the figure on the next page shows our staff hauling sandbags during the preparations for the flood.

At the end, we were quite lucky – the damage was little and constrained to the basement of Guest House II. The renovation of which was supported by the Max Planck Society, and we hope to be very well prepared for the next flood to come, hopefully far in the future. Unfortunately, not all our employees came out that well, some had to leave home, and some reported massive damage of their houses. As yet another sign of solidarity, donations for their support were collected during our summer party in July.



+ MPI Magdeburg's members preparing protection of the guest houses with sandbags



But there were also many very good news in 2013: Our International Max Planck Research School (IMPRS) got the approval for a second period 2013–2019. Under its new name “ProEng – Advanced Methods in Process and Systems Engineering” we currently educate 46 Ph.D. students from 16 countries. There were also a number of successful grant applications on all levels (DFG – the German Research Foundation, BMBF – the German Ministry for Education and Research, and the EU), of which I will only name a few: in the new DFG Priority Program SPP1679 “Dynamische Simulation vernetzter Feststoffprozesse”, researchers from Magdeburg are involved in almost one Third of the projects. The MPI also becomes official partner in the DFG Collaborative Research Centre TR63 “InPROMPT” for the second funding period 2014–2017.

In the BMBF research network “HYPOS: Hydrogen Power Storage & Solutions East Germany” of 90 partners, MPI researchers are involved in topics related to the process of storing renewable energy and making efficient use of the stored energy. The MPI is also taking part in the BMBF research network “GECKO: German-Canadian Cooperation on Kinetics and Mass Transport Optimization in PEM Fuel Cells” (2013-2016). MPI researchers take a lead in the BMBF research network “CellSys: Cell Line Development by Systems Biology” and are partners in the EU FP7 Health project “HighGlycan – Methods for high-throughput analysis of protein glycosylation” as well as the EU FP7 Strep project

“Nanoelectronic Coupled Simulation (nanoCOPS)”, all launched in 2013. Numerous smaller projects complete a very successful year in acquiring third-party funding and in summary will lead to a further growth of the institute's staff of 235 employees at the end of 2013.

With Dr. Martin Stoll's new research group “Numerical Linear Algebra for Dynamical Systems” and Dr. Timo Frensing's new junior research group “Cellular Systems in Bioprocess Engineering”, we could also establish two new research directions supporting the established research on mathematical methods for complex dynamical systems and biotechnology.

As already mentioned, since last year our institute now presents itself in a new web design (with a Go Live on November 28, 2013), following the one the Max Planck Society itself and many of its institutes are now using. This will be accompanied by a new Corporate Design as already explained above.

2013 also saw a number of regular events like the 8th Long Night of Sciences in Magdeburg with again more than 1.000 visitors to the MPI, a Girl's Day, our student labs for high-school students, as well as a number of workshops and conferences (co-)organized by MPI researchers in Magdeburg and elsewhere, see also the reports on pages 14 to 16. Last but not least, we also enjoyed our MPI summer and Christmas parties!



+ Over 1.000 visitors attended the Long Night of the Sciences at the MPI Magdeburg on June 1, 2013.

The research success of MPI researchers is documented by again a high number of journal publications; see the list at the end of this Annual Report. This certainly is the cornerstone to the successful collaboration in international research groups and to third-party funding, but it also shows in individual prizes. In 2013, we were happy to learn that Christian Borchert won one of the Otto Hahn medals for his Ph.D. thesis on crystal shape dynamics. The Otto Hahn medal is the prestigious Ph.D. prize of the Max Planck Society and is annually given for the 30 best dissertations finished by Max Planck researchers in the preceding year.

In summary, I see the MPI Magdeburg in good standing with excellent prospects for the future. We look forward to a year 2014 in which we will continue our path to systematically analyze, design and control complex dynamical systems using mathematical tools as well as well-designed lab and computer experiments, and in which we hopefully will not see more political quarrels and expect the Elbe to stay where it is supposed to flow!

Magdeburg, April 2014

Peter Borchert

Prof. Dr. Peter Benner
Managing Director 2013–2014



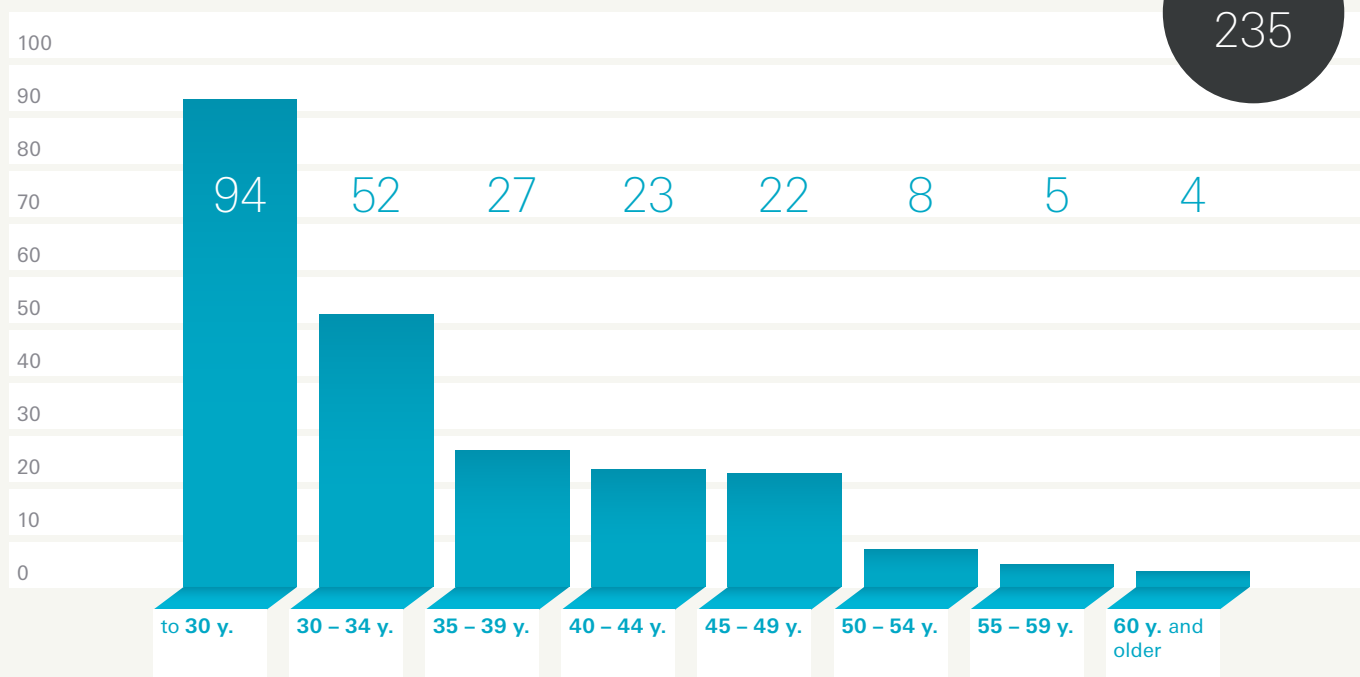
Peter Benner studied Mathematics (major) and economics (minor) at RWTH Aachen and obtained his diploma in 1993. After he finished his Ph.D. thesis at Technische Universität of Chemnitz-Zwickau in 1997 he worked as an assistant professor at the Zentrum für Technomathematik of the University of Bremen, 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

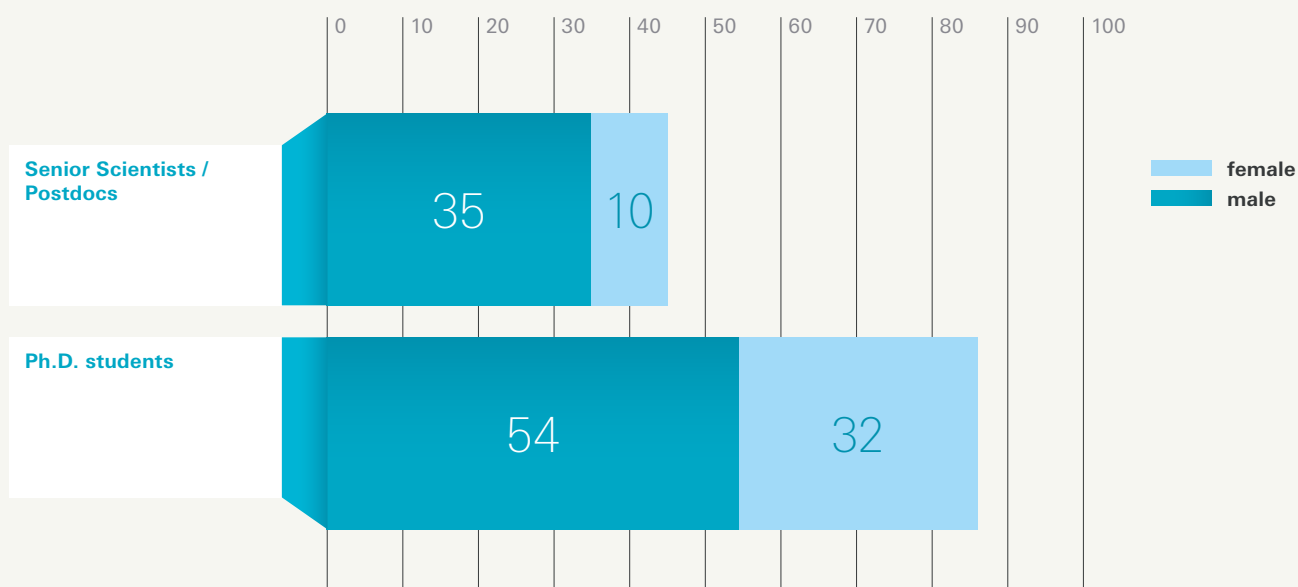
Age structure of the workforce at the MPI



STAFF

Distribution of scientists by gender

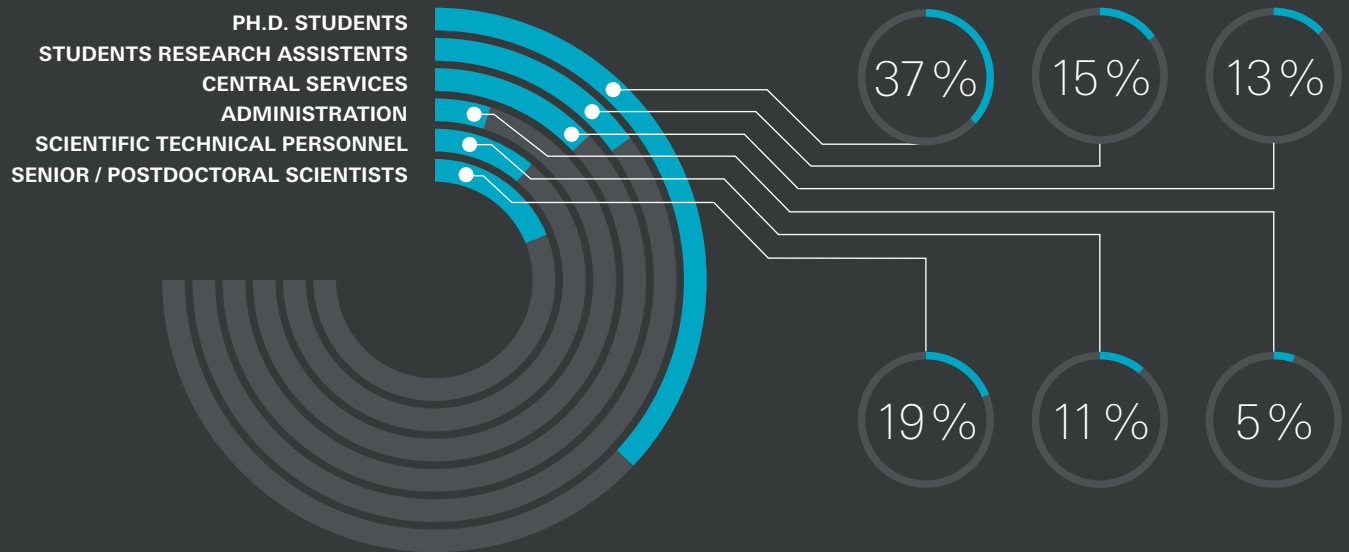
Female employees: 22% Postdocs and 37% Ph.D. students



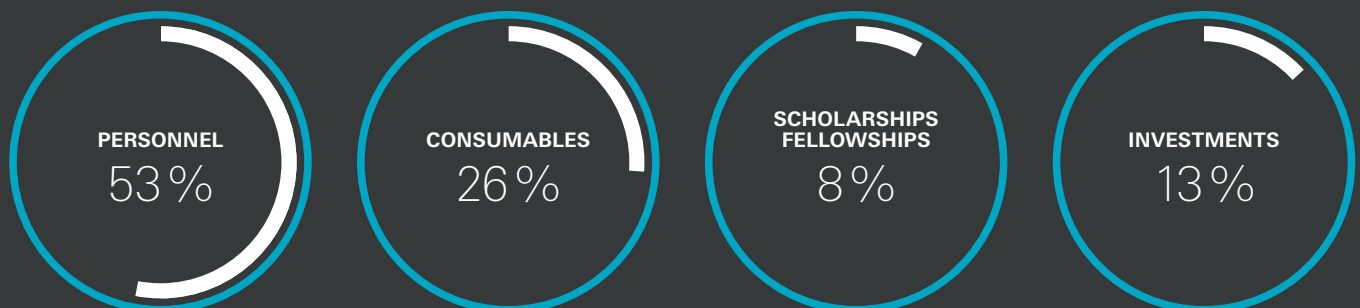
The two graphs above show the gender balance and age structure among the institute's scientists on the Postdoc and Ph.D. levels, respectively. As Max Planck Institutes are run with very few permanent scientists, the average age of employees is quite low as the majority of scientists consists of Ph.D.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

STAFF**2014: 235 Employees**

131 Scientists: 45 Postdocs, 86 Ph.D. students



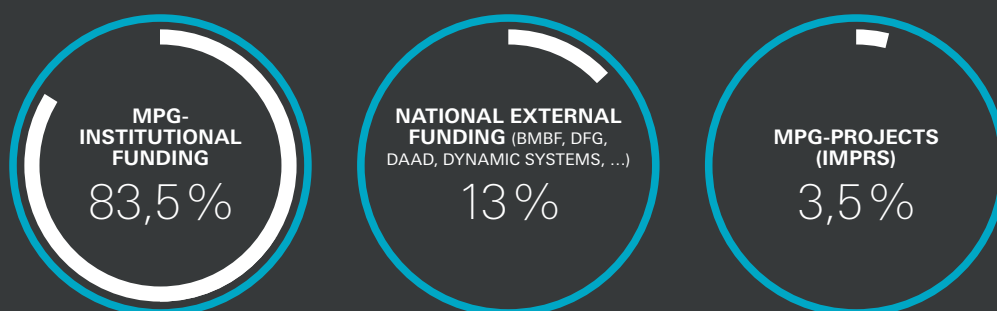
At the end of 2013, the MPI employed 235 persons. The majority are scientists and student researchers as illustrated by the pie chart above. As can be seen, the institute is run by a lean administration, while running the labs and technical facilities accounts for the rest of the employees.

EXPENDITURE PATTERN IN 2013**Total Expenses in Fiscal Year 2013: 13.72 million euro**

The total budget of the MPI in the fiscal year 2013 was 13.72 Mio. euro. The pie chart above shows how this was distributed to the major budget categories. As can be seen, more than 60% of the budget was used for salaries and scholarships.

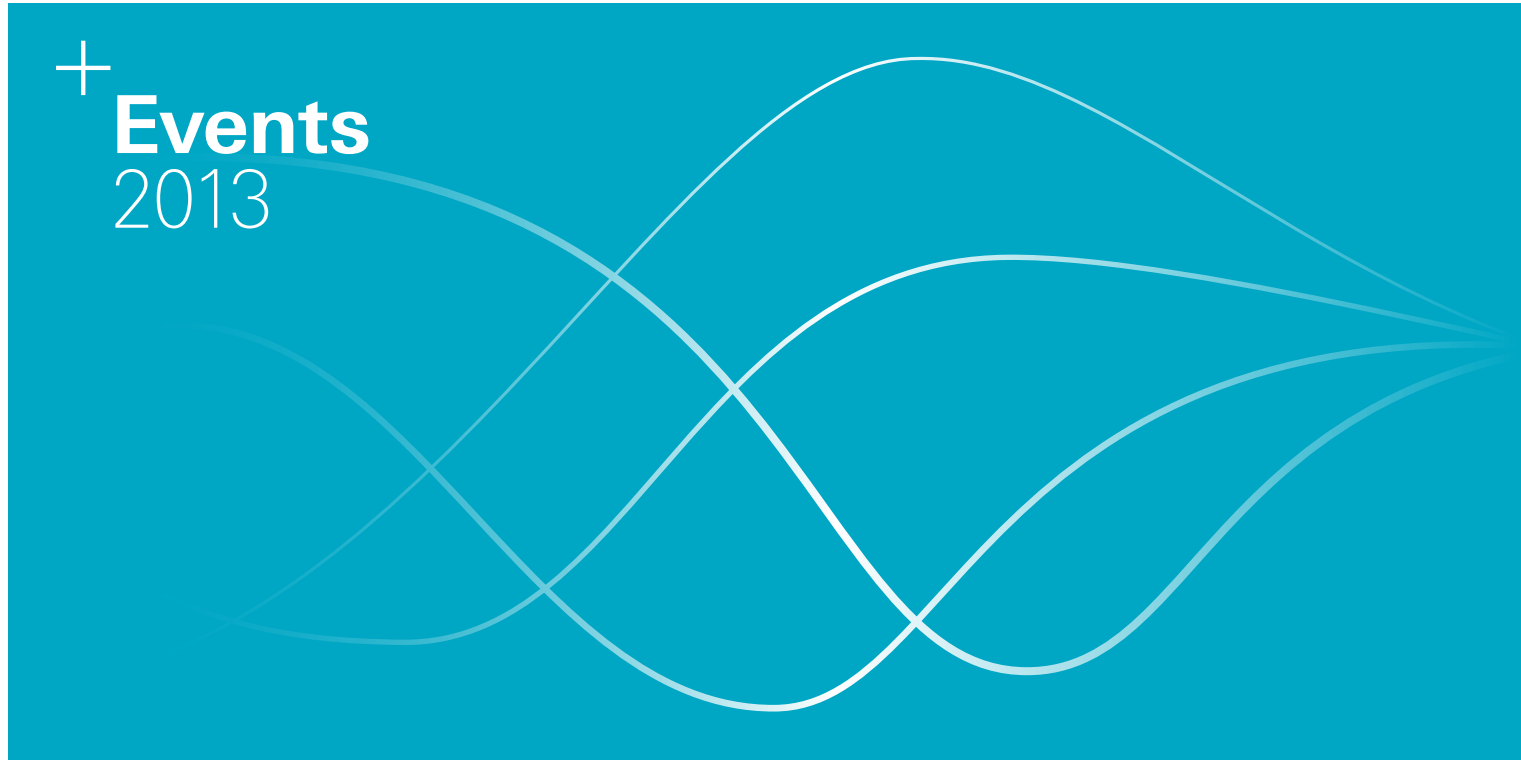
MPI-GENERAL BUDGET 2013**Total Revenue: 13.72 million euro**

Third-party funds: 1.8 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. Third-party funding in 2013 was lower than usual as some large-scale external projects terminated the year before and new ones only started in the second half of 2013, including two EU grants.

+ Events 2013



ProcessNet – Annual Symposium on Crystallization 2013

In March 2013, the ProcessNet colloquium, initiated by DECHEMA and VDI-GVC, invited to the annual symposium on crystallization. With around 90 participants from research and industry, the conference took place in Magdeburg. On the basis of lecture and poster contributions and afterwards fruitful discussions we profited from direct exchange to the topics of the current research as well as field reports from the industry.

After welcoming the participants by the organizing committee, to which belonged apl. Prof. Dr. Heike Lorenz of the MPI for Dynamics of Complex Technical Systems, Magdeburg, as well as on Dr. Wolfgang Beckmann, from Bayer Technology Services in Leverkusen, opened the conference with a talk to different ranges of application of the continuous crystallization in the chemistry of fine chemical products. Afterwards, the lecture program was continued with eight other contributions from research and industry. In the foreground were such topics as specific production of polymorphs, influence of impurities on crystallization, application of crystallization for coating of tablets as well as application of the glaze crystallization for the material separation. The first conference day was closed with a poster session and their discussion.

The second day of the colloquium contained four talks, mainly on the current research at the universities. Thereby, basic aspects to process development and product design on concrete practical examples were introduced.

A lecture given by Günter Hoffmann (VDI, before engineer with the GEA Messo GmbH) to the „insights into a 40 years working life of the plant engineering and construction“ was in particular interesting for the audience.

With three lectures (Holger Eisenschmidt, Sebastian Wloch, Daniel Binev) and four poster contributions (Elena Horosanskaia, Kamila Galan, Erik Temmel, Matthias Eicke) our Physical and Chemical Foundations of Process Engineering group at the Max Planck Institute of Magdeburg could present itself very well at this conference. With the poster award for Erik Temmel the colloquium found its successful end for the institute team. | **Elena Horosanskaia**

Multi Scale Simulations – about the 3rd Summer School of the IMPRS

The Summer School of the IMPRS took place from September 2 to 6, 2013. The objective of the school was to introduce basic concepts and theoretical foundations of multiscale research and to bridge the gap between mathematics and various application disciplines, including biology, chemistry and engineering.

The focus was on the students of the IMPRS. Furthermore, we invited Ph.D. students and advanced Master students from the above mentioned disciplines in Europe. In the end, we had over 50 participants, 18 of them female. Apart from

the 13 different nationalities of the IMPRS students, we had visitors from all parts of Germany, from the UK, Italy, Czech Republic and Slovak Republic.

We invited leading experts in the field of Multi Scale Simulations from abroad e.g. Richard Braatz from the Massachusetts Institute of Technology (MIT) and Daniele Marchisio from Politecnico di Torino in Italy as well as from Germany, e.g. Frauke Gräter from the Tschira Labs and Frerich Keil from the University Hamburg-Harburg.

Our speakers introduced applications in different scientific areas as well as the possible connection between some of these areas. This year tutorials played a strong part as they allowed the participants to complete the theoretical knowledge about multiscale simulations by practical issues for a better understanding of the underlying ideas. In the run-up of the Summer School bootable USB-sticks with the Linux operation system and all necessary applications were prepared to provide an equal basis for all participants. The sticks could be taken home to reproduce the programs and results during the school.

In such a broad scientific field with such multidisciplinary participants, topics and applications, it is not easy or nearly impossible to find a program that satisfies everyone. The evaluation of the school showed that we managed this issue pretty well. 70% of the students stated that they could follow the talks completely though the schedule was quite dense and over 85% said that the school gave a good survey of the topic. One of the students put it in a nut shell "The



schedule was fine. The content is quite broad and it should be expected that most of the people were not able to follow all the talks, but in my opinion that was unavoidable in a school in which the last objective was to change some paradigms in modeling and simulation." Anyway, next time maybe it would be good to think about a less broad topic.

In the end, one could say this was a very successful week where many inspiring discussions evolved across the borders of the various disciplines not only during the talks but also during coffee and lunch breaks and of course during the social gatherings in the evening.

The next Summer School will take place in 2015, preparations will start in fall 2014. | **Dr. Jürgen Koch**

Otto Hahn Medal awarded to Dr.-Ing. Christian Borchert

More than 70% of all products of the chemical industries are processed or sold as solids. In nearly all cases, solids are handled as dispersed systems, e.g. as powders, granules or crystals. The quality requirements for dispersed phase products (catalysts, pharmaceuticals, etc.) steadily increase. Particularly for a more efficient utilization of available material and energy resources, the understanding and control of solids processes is required.

In his dissertation thesis, Christian Borchert, a former Ph.D. student of the PSE group supervised by Professor Kai Sundmacher, focused on a highly important problem in the above mentioned field: The production of crystals of a desired shape. This is highly relevant, e.g. for the production of pharmaceuticals and agrochemicals whose separation by filtration is massively influenced by their crystal shape.

In industrial practice, the crystal shape is changed by altering the chemical environment, i.e. by substituting the solvent or adding surface active substances. These additives can contaminate the product and must subsequently be separated, which is an expensive operation. Christian Borchert has demonstrated that the growth of crystal facets is a function of supersaturation and that for each facet this kinetic function is different in many cases. Hence, the supersaturation can be employed as control variable for the shape-selective growth of crystals without using additives. The technical application of crystal shape control via supersaturation requires dynamic balances and kinetic laws that track not only the evolution of one single crystal but of a whole crystal population. Beside the description of the movement of a population in the shape space, this information must be made available from the observation of real processes.

The Otto Hahn Medal was awarded to Christian Borchert for his outstanding contributions to the field of shape-selective crystallization. His achievements include the development of generalized models that describe the evolution of arbitrarily complex convex single crystals and populations, the reconstruction of shape distributions from 2D projections of crystals in suspension recorded in a flow-through microscope, the estimation of face-specific growth rates from measured shape distributions, and the experimental validation of the proposed approach. | **Prof. Dr.-Ing. Kai Sundmacher**

2. Workshop on Model Reduction for Complex Dynamical Systems MODRED 2013

Only two weeks before Christmas, December 11–13, 2013, the Workshop on *Model Reduction for Complex Dynamical Systems (MODRED)* was held at the Max Planck Institute for



+ Participants of the ModRed conference

Dynamics of Complex Technical Systems Magdeburg (MPI Magdeburg), Germany. This workshop followed MODRED 2010, held at TU Berlin in December 2010.

The topics of the workshop ranged from model order reduction for various applications to optimization and uncertainty quantification (UQ), with a particular emphasis on model order reduction in computational nanoelectronics and electromagnetics. But also a wide range of other applications was discussed; thereunder gas networks, antennas, filters and transonic flows.

The workshop aimed at bringing together researchers and users of model order reduction technique. There were participants from industry as well as scientists from universities and research institutes. The 64 participants came from Germany, the United States of America, Belgium, the Netherlands, France, Austria and Switzerland including 3 invited speakers. The choice of the invited speakers was also motivated by this diverse audience. Romanus Dyczij-Edlinger from the Universität des Saarlandes, an electrical engineer, showed the application of model order reduction methods to various real world problems. Jan Hesthaven from the École Polytechnique Fédéral de Lausanne, a mathematician, discussed reduced basis methods for systems with many parameters. Karl Meerbergen from the Katholieke Universiteit Leuven, a mathematician who also has worked in industry, showed reduction methods for vibration problems such as the damping of a bridge.

MODRED 2013 was also held as the dissemination workshop of the research network Model Reduction for Fast Simulation of New Semiconductor Structures for Nanotechnology and Microsystems Technology (MoreSim4Nano) funded by the German Federal Ministry of Education and Research (BMBF) within the program “Mathematics for Innovations in Industry and Services”. Together with five partners from universities in Hamburg, Braunschweig, Augsburg and Darmstadt as well as from the Fraunhofer Institute ITWM in Kaiserslautern, Peter Benner and Judith Schneider from the MPI Magdeburg developed model reduction methods for

the simulation of new semiconductors with uncertain parameters, see www.moresim4nano.org for more information. After three years of joint work, the project partners collectively organized the second MODRED. The first MODRED 2010 had also served as dissemination of the predecessor BMBF network, SyreNe. One session of talks was reserved for the results obtained within MoreSim4Nano. Besides that, 23 contributed talks on different model order reduction techniques and applications were held.

Additionally to the conference, model reduction related satellite meetings were held. On the one hand, a meeting with a particular focus on model reduction for mechanical systems was held for researchers working in this area. Additionally, the model order reduction wiki was presented to potential users. The wiki serves as a database for benchmark problems, a description of model reduction algorithms and collects links to relevant software frameworks. It is maintained by Peter Benner’s group at the MPI Magdeburg and can be accessed via www.modelreduction.org.

The European Union funded COST action EU-MORNET was introduced by Wil Schilders (TU Eindhoven / NXP Semiconductors). It is set up as a European model reduction network with a four year plan. A first meeting is planned for mid-2014 after which additional members can join the network.

Overall, the conference achieved to show how the often theoretical methods developed by mathematicians in the model reduction field made its way into engineering applications. The newly starting research networks like the EU-MORNET¹ or nanoCOPS² and the various satellite projects like MORwiki show the growing relevance of model reduction techniques in not only nanotechnology and microsystems technology, but all kinds of engineering applications. Due to the success of the conference, the MODRED conference series is supposed to continue in a three year rhythm. | **Judith Schneider**

¹ http://www.cost.eu/domains_actions/TDP/Actions/TD1307

² <http://fp7-nanocops.eu/>

+ **Research** Groups



BPE

BIOPROCESS
ENGINEERING

PROF. DR.-ING. UDO REICHL | DIRECTOR

+ Bioprocess engineering covers the use of microorganisms and eukaryotic cells not only for the production of industrial bulk products but also for manufacturing of specialized biopharmaceuticals. In addition, bioprocess technology plays an important role in biofuels production, waste water processing, and solid waste treatment. Optimization of such processes from the engineering as well as from the biological point of view using a wide range of assays and all available analytical “omic” tools is part of today’s challenge. Increase in specific product yields, reduction of “time to market” together with process intensification needs to make up with the pressure of global markets.

The bioprocess engineering group headed by Prof. Dr.-Ing. Udo Reichl has chosen cell culture-based processes to tackle fundamental challenges in viral vaccine production. These processes see currently a renaissance with a high increase in market shares due to the development of new vaccines and the

establishment of advanced production strategies. Due to the complexity involved, 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 and disposable bags. In addition, advanced process strategies are developed to further increase virus yields. The obtained experimental data are used by the **Mathematical Modelling team** (Prof. Dr.-Ing. Udo Reichl) to quantitatively analyze fundamentals of cell metabolism and growth as well as intracellular virus replication and infection dynamics in bioreactors. Virus-host cell interactions are studied in detail by the **Molecular Biology team** (Jun.-Prof. Dr. Timo Frensing) to identify bottlenecks in virus production. Therefore, virus replication dynamics is investigated on the RNA level and by flow cytometry-based assays. With a focus on glycomics and glycoproteomics, advanced bioanalytical tools are developed for



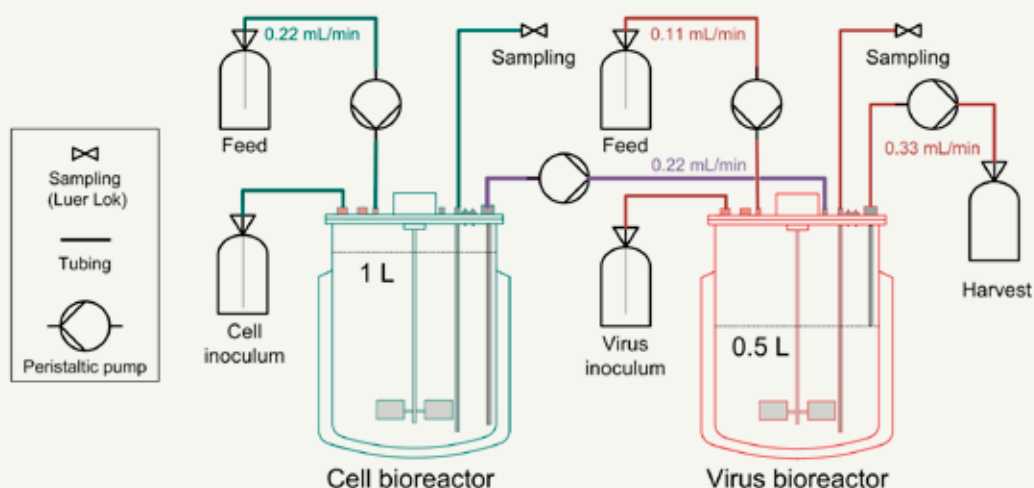
+ For the optimization of production processes using mammalian cells one aim is to increase the cell concentration in bioreactors. Such high cell density cultivations require novel techniques to continuously provide nutrients for cell growth. Here, Ph.D. candidate Daniel Vázquez Ramírez is testing different perfusion systems such as the depicted *alternating tangential flow* (ATF) system.

in-depth analysis of post translational modifications of proteins by the **Bioprocess Analytics team** (Dr. Erdmann Rapp). Finally, design 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 the considered vaccine manufacturing process links all teams, each team has a range of further projects. This includes Modified Vaccinia Ankara (MVA) virus production in designer cell lines, cell line development by systems biology approaches or establishment of a platform for in vitro N-glycosylation of therapeutic proteins to name a few.

In 2013 up- and downstream processing has focused on process intensification by moving towards continuous manufacturing. Hollow fiber-based cell retention devices are used, for example, to cultivate and infect cells at very high concentrations to maximize virus yields in bioreactors. Together with the research group of Prof. Dr.-Ing. Andreas Seidel-Morgenstern, simulated moving bed (SMB) chromatography was established for separations allowing continuous virus purification. Improving cell-specific productivities by genetic modification of virus

strains and production cell lines is aimed for by the molecular biology team. Based on a multiscale model for virus replication vaccine production can be optimized and development of novel antiviral drugs supported. Finally, to dig deeper into cellular proteomes regarding the adaptation of cell lines to grow in suspension and specific aspects of virus-host cell interaction, gel- and label-free LC-MS/MS-based proteomic approaches were developed by the bioprocess analytics team.

Overall, new strategies for design and optimization of cell culture-based processes are envisaged. Bringing fundamental research knowledge into industrial manufacturing of biologicals could thus have an enormous social impact.



+ Figure 1:
Scheme of the bioreactor
setup for continuous
influenza virus cultivation.

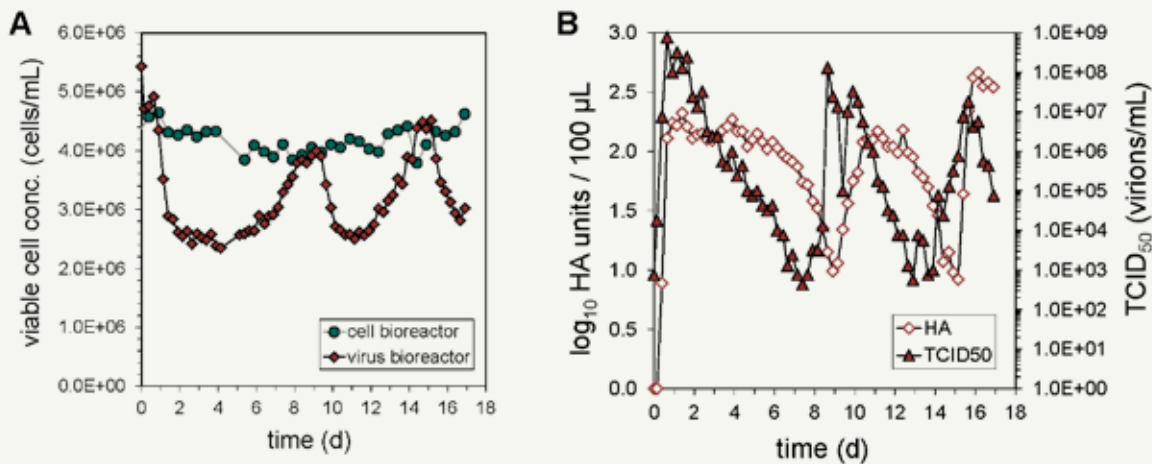
Continuous influenza vaccine production

+ Most people already experienced that a real influenza is much more severe than a common cold. Influenza is an acute respiratory disease that is transmitted by virus particles entering the respiratory tract via small droplets. Worldwide it affects millions of people every year, and up to 500,000 people die due to these infections. The best protection against influenza is provided by annual vaccination using vaccines which protect against the three most prevalent circulating strains of a particular influenza season. For the production of these vaccines the three virus strains need to be propagated in large quantities, and historically embryonated chicken eggs have been used as a susceptible host system for virus cultivation. However, millions of embryonated eggs are required to produce influenza vaccines (approximately one egg per dose). Thus, the conventional production process is very laborious and not very flexible to meet the demands. Nowadays, the cultivation of influenza virus in continuous animal cell lines using large-scale bioreactor systems has become an important alternative.

The Bioprocess Engineering group at the MPI Magdeburg tries to design and optimize cell culture-based influenza vaccine production by establishing a long-term continuous virus cultivation system. Therefore, a set up of two bioreactors was used by the Upstream team of PD Dr. Yvonne Genzel. In the first bioreactor (cell reactor) animal cells were continuously grown and fed continuously into the second bioreactor (virus reactor), where virus replication took place (see figure 1). Hence, a constant supply of fresh host cells for virus propagation was provided, and the same volume that was introduced into the second bioreactor was continuously harvested to keep the working volume

constant. The system was successfully operated for 17 days and represented the first long-term continuous influenza virus cultivation process. During the run time, the viable cell concentration in the first bioreactor fluctuated only slightly, which indicated that stable continuous cell production was achieved. In contrast, both the virus titer and the viable cell concentration showed periodic fluctuations in the virus reactor (see figure 2). Variations were most pronounced for the infectious virus titer (TCID₅₀) that fluctuated by six orders of magnitude. This was a quiet surprising result since calculations had shown that continuous virus cultivation should yield constant titers. Therefore, the experiment was repeated using a new batch of seed virus. However, the same periodic fluctuations of cell concentrations and virus titers were observed.

The unexpected results obtained called for a detailed molecular analysis that was subsequently performed by the Molecular Biology team of Jun.-Prof. Dr. Timo Frensing. He had the idea that these fluctuations might be caused by so called defective interfering particles (DIPs). DIPs are viruses with a deletion in their genome. In the case of influenza A viruses, their DIPs carry at least one internal deletion in one of the eight viral genome segments so that no functional protein can be produced from this gene. However, with one protein missing DIPs cannot complete the virus replication cycle on their own. Instead, DIPs depend on a co-infection with a complete standard virus. During the co-infection the standard virus will synthesize all required viral proteins enabling the replication of both the standard genome and the DIP genome. Due to the shorter length of the DIP genome, however, it will accumulate more rapidly than a full-



+ Figure 2:

Cell concentrations and virus titers during the continuous virus propagation.

(A) Concentrations of duck-derived AGE1.CR cells (ProBioGen, Berlin) in the cell and virus bioreactor. (B) Titers of influenza virus A/Puerto Rico/8/34 determined by HA and TCID₅₀ assay, which measure the concentration of total virus particles and infectious viruses, respectively.

length genome. Thus, co-infected cells produce more DIPs than infectious standard viruses. Therefore, DIPs can be regarded as parasites of standard viruses that steal viral proteins they cannot produce on their own leading in turn to the interference with the replication of standard viruses.

Using a conventional PCR assay we were able to show that at the beginning of the continuous virus cultivation the standard viruses were present and efficiently replicated in the cell population. Indeed, virus titers of 10^9 infectious virions per mL were reached at that time. However, with so many virions in the virus reactor fresh cells become infected by multiple virus particles. These conditions increase the chance of co-infections of standard viruses and DIPs that can be generated as an error during standard virus replication. As soon as DIPs are present they can rapidly accumulate under conditions that favor co-infections and the PCR confirmed the increase of defective genomes during the continuous virus cultivation. The accumulation of DIPs is the reason why infectious titers dropped dramatically. As a consequence, however, DIPs that rely on co-infection with standard viruses cannot replicate anymore. Hence, without replication virus particles are out-diluted in a continuous cultivation. Subsequently, with less DIPs in the reactor the standard viruses are able to restore their replication as co-infections are less likely under these conditions. With increasing amounts of standard viruses, however, the chance for co-infections rises again and DIP accumulation is favored once more. Consequently, these dynamics of replication and interference by DIPs cause periodic fluctuations in long-term continuous virus production processes.

Finally, Dipl.-Ing. Stefan Heldt of the Mathematical Modelling team supervised by Prof. Dr.-Ing. Udo Reichl, confirmed that DIPs were the reason for titer fluctuations with a mathematical model that clearly shows that without DIPs we could have expected to see constant virus titers in the virus reactor. But as soon as we introduce DIPs into the system, the system becomes unstable and virus titers start to fluctuate periodically.

Model simulations also indicate that the system would only lead to constant virus yields in the complete absence of DIPs since they rapidly accumulate even from smallest starting quantities. Therefore, DIPs represent a severe challenge for the success of continuous virus cultivation as they significantly reduce the productivity of these systems.

Still, the established continuous influenza virus propagation represents a valuable novel tool to study aspects of virus evolution. This might also lead to a better understanding of the generation and replication of DIPs. In addition, it needs to be analyzed if DIPs have an impact on the yield of other influenza virus cultivation systems as well. Finally, continuous virus production might be an attractive process strategy for those viruses that do not tend to generate DIPs, e.g. large DNA viruses. Therefore, we are just at the beginning of exploring the possibilities of using continuous virus cultivation systems for vaccine production.

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Author Jun.-Prof. Dr. Timo Frensing

Timo Frensing studied biology at the University Bielefeld and obtained his diploma in 2003. Afterwards he became a Ph.D. student there and finished his Ph.D. thesis in 2007. Since August 2007, he is a scientist at the Max Planck Institute Magdeburg leading the Molecular Biology team in the department Bioprocess Engineering. In addition, Timo Frensing became a Juniorprofessor at the Otto von Guericke University Magdeburg in September 2013.

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CSC

COMPUTATIONAL METHODS IN
SYSTEMS AND CONTROL THEORY

PROF. DR. PETER BENNER | DIRECTOR

Though maybe overly stressed already, computer experiments have long since become the third pillar of scientific research besides theory and lab experiments. Also often called *in silico* design or experiments, they rely on efficient and reliable algorithms for computer simulations. In the CSC group, we are concerned with using mathematical ideas and concepts to develop new methods in this context. In particular, we consider the simulation, optimization and control of dynamical systems, i.e., of mathematical models described by systems of ordinary or partial differential equations. The application areas for which we develop and adapt our methods range from the various complex technical processes considered in the engineering groups at the MPI Magdeburg over Microsystems Technology

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 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 in applications. This often also includes sophisticated programming strategies for modern multicore computer platforms and clusters, including hardware accelerators like GPUs. For this, we use different hardware platforms, including our Linux cluster "otto" with 1000+ cores.

The work in the CSC group is currently organized in five teams. The biggest of them is **Model Order Reduction**, dealing with

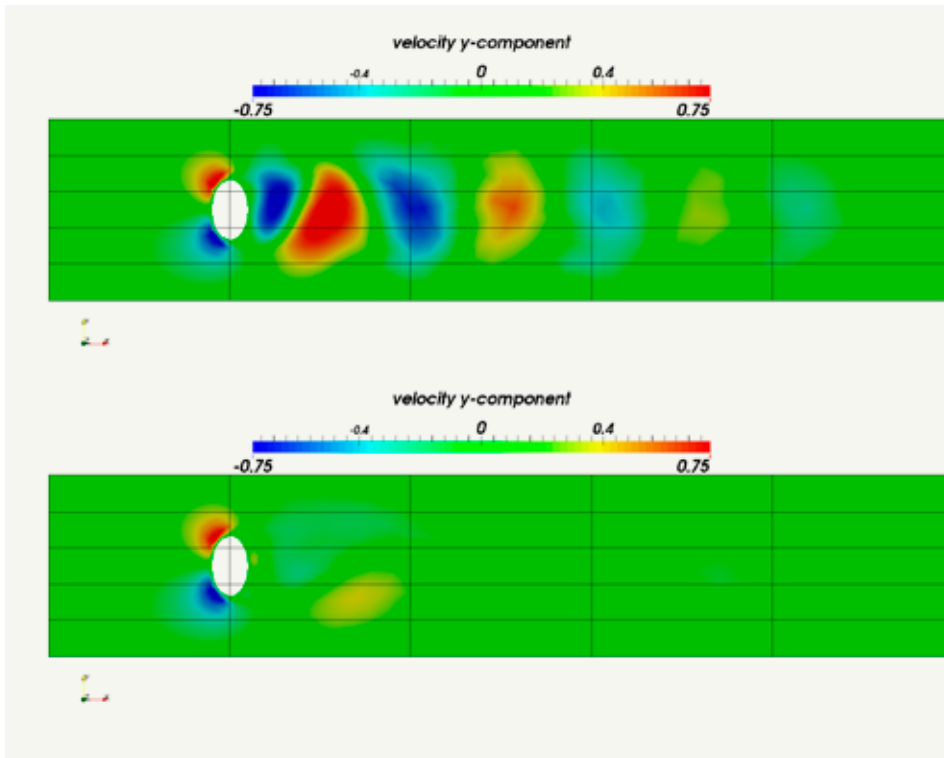


+ Dr. Lihong Feng explaining principles of model reduction for dynamical systems to Yongjin Zhang and Martin Hess (Ph.D. students in the CSC group). Pen and white (black) board or paper are still main utilities in developing numerical methods before they are implemented as computer algorithms.

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 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** focuses on efficient algorithms to solve them numerically. These algorithms rely on efficient techniques of Numerical Linear Algebra, a core mathematical technique percolating almost all aspects of the CSC research work. It is also a main topic for the **Scientific Computing** team, dealing with algorithms for High-Performance Computing, particularly for the areas considered in the other teams and groups at the institute. We are also in the process of establishing a **Uncertainty Quantification** unit to address

the increasing need of assessing the influence of uncertain parameters in mathematical models of technical processes.

The computational design of stabilizing controllers for flow problems touches upon the research work of almost all CSC teams. In this regard, a just concluded research project within the DFG Priority Programme 1253 is described on the following pages.



+ **Figure 1:**

Vertical components of velocity field within “von Kármán vortex street” and Reynolds number 300. Top: without feedback; Bottom: with LQR feedback

Feedback stabilization of multi-field flow problems

+ In many areas of engineering, chemical, and biological research, the motion of fluids, such as liquids or gases, is considered. The construction and development of aerial, maritime, and land transportation vehicles involves complex flow models of the surrounding media to increase efficiency and safety. In chemical and biological research, fluids are often a carrier medium for other substances that will react and interact with each other. In both cases, the knowledge of the particle movement is necessary and in many cases one wants to modify and control the behavior of the fluid to steer the system towards a desired state. Examples include the stable flying of an airplane, efficient driving of a car, and explicit steering of chemical or biological substances in reactors.

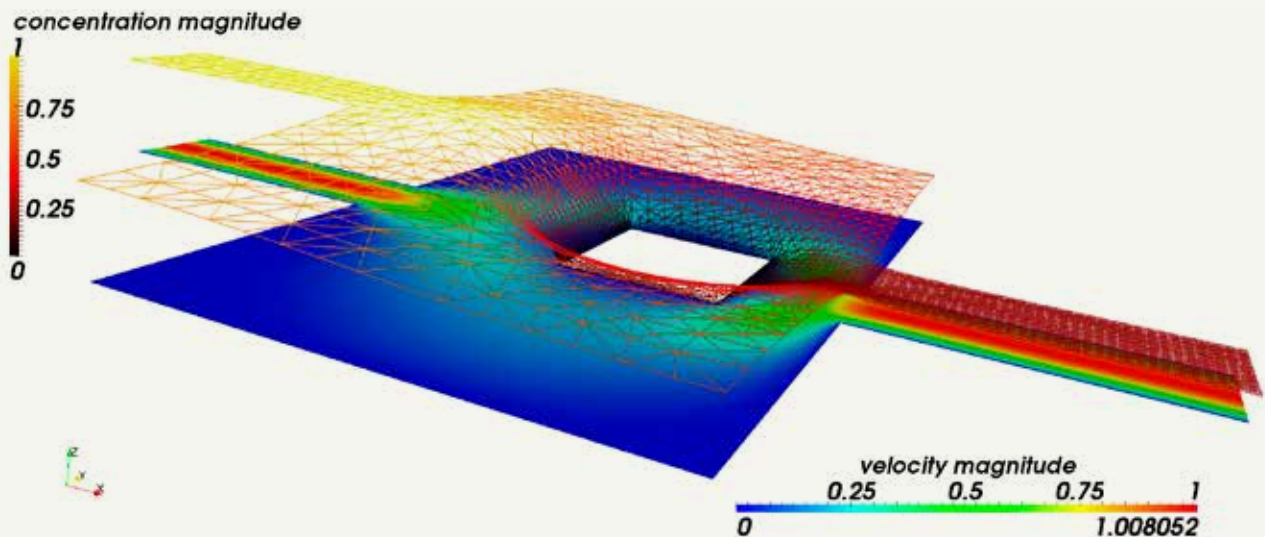
The flow models considered in this project describe the motion of a fluid induced by interaction of convection, diffusion, and pressure variances. The important parameter that describes the ratio of inertial and viscous forces inside the fluid is the Reynolds number. For higher Reynolds numbers, the flow is dominated by convection and the physical behavior gets harder to predict, because the forces between the particles inside the fluid get weaker and the behavior gets more chaotic. For example, the Reynolds number for honey is smaller than for water and much smaller than for gases. To ensure that we have no fluid sources or sinks inside the domain, the mass conservation law has to be fulfilled in our domain at every time.

Our research is focused on incompressible flow models, where the fluids' density does not change in time. We investigate methods to control and stabilize an incompressible fluid flow inside

a bounded area that can be described by the so called Navier-Stokes equations. These non-linear partial differential equations contain two distinguished parts. The first is the dynamical equation that models the evolution of velocity and pressure in time. The second is an algebraic equation that guarantees the mass conservation and is often called divergence-free condition. Besides liquids, gases that move at a low velocity can be described via these models.

We introduce a feedback stabilization approach for the incompressible Navier-Stokes setting using the “von Kármán vortex street” as a benchmark that can be described as follows: if one puts an obstacle inside a channel flow, vortices occur due to friction and convection processes behind the obstacle if the Reynolds number is at a certain level. This phenomenon can be seen in nature on a river, where a pier of a bridge is an obstacle for the running water. Observing the motion of clouds via satellites, the same phenomenon occurs if clouds flow around high and steep mountain peaks. The main goal is to predict or prevent such vortices within certain test assemblies, for example, vortices produced by a vehicle moving through a fluid.

To illustrate the concept we consider a rectangular flow channel of one unit width and five units length and we place an elliptic obstacle at one fifth of the length. The described domain is illustrated in Figure 1, where the occurring vortices are visualized in the upper part of the picture. The vertical component of the velocity field is depicted with a color range from blue (maximal negative velocity) to red (maximal positive velocity). By controlling the boundary conditions on two small parts



+ Figure 2:
2D velocity field within simplified reactor model.
Spread of reactive substance depicted as lifting grid
over the domain.

located on the back of the obstacle, we manage to reduce these vortices. In detail, a linear-quadratic regulator (LQR) approach is used to determine the optimal control that describes blowing or exhausting fluid into or out of the domain. The bottom part of Figure 1 illustrates the influence of the LQR feedback within a forward simulation.

When dealing with biological and chemical problem settings, we consider a simplified reactor model, where the fluid movement is responsible for the spread of the concentration of a substance. In this case, it is necessary to consider a diffusion-convection equation coupled to the Navier-Stokes system. We assume that the concentration expands within the reactor due to natural diffusion and convection that is driven by the velocity field of the Navier-Stokes system. In addition, we suppose a fast reaction of the substance with the surface of an obstacle inside the reactor such that the concentration vanishes as soon as the substance reaches the obstacle.

We control the velocity inflow condition to stabilize the reaction process at the obstacle, so that we stabilize the flux rate of the concentration via the surface of the obstacle regarding perturbations of the inflow conditions. Figure 2 shows the velocity field inside the two-dimensional reactor assembly. Furthermore, the concentration of the reactive substance is shown like a lifting grid, with the height depicting the scalar concentration in each domain point.

The main mathematical difficulty of applying the Riccati-based LQR approach is the efficient solution of large-scale, projected, and quadratic matrix equations, also known as algebraic Riccati equations. We investigate various methods to solve these

matrix equations efficiently. More detailed information about the project as well as a variety of videos of the simulations can be found at the project web page: www.mpi-magdeburg.mpg.de/1024214/spp1253

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Dipl.-Math. techn. Heiko K. Weichelt obtained his diploma in *Technomathematik* from the Technical University in Chemnitz in 2010. He completed a research visit at the Oxford Center for Collaborate Applied Mathematics (OCCAM) at the University of Oxford in 2011. After that, he started his Ph.D. under the supervision of Prof. Dr. Peter Benner in the research group Mathematics in Industry and Technology (MiIT) at the Technical University in Chemnitz. Since 2013, he is a Ph.D. student within the CSC research group at the Max Planck Institute Magdeburg.

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PCF

PHYSICAL AND CHEMICAL FOUNDATIONS
OF PROCESS ENGINEERING

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

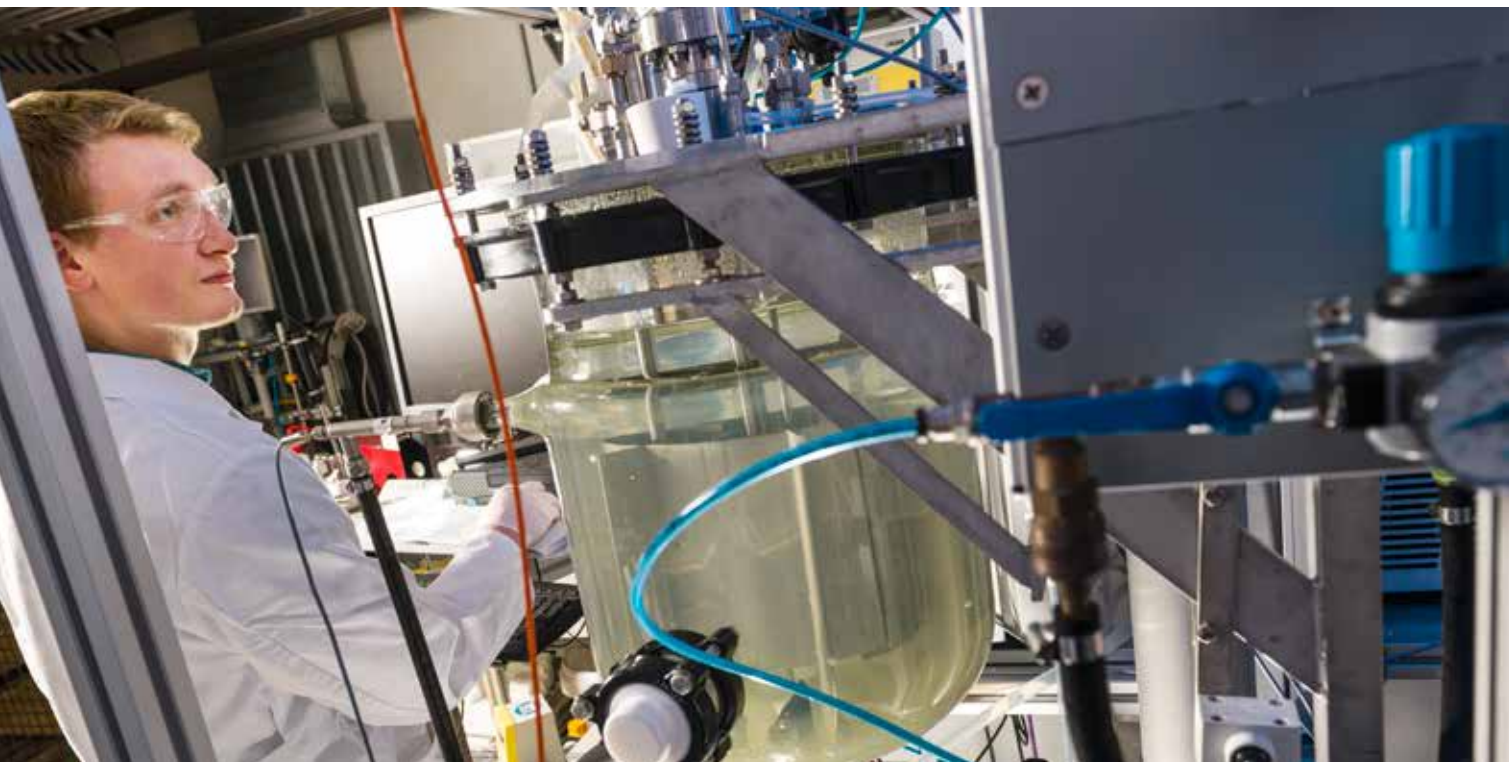
✚ The development and production of new products with improved or hitherto unknown properties increasingly requires the application of advanced and often complex technologies. To understand, to analyze quantitatively and to optimize the underlying processes, a profound knowledge about a large number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

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

The **Chromatography Research team** is working on discontinuous and continuous separations of complex mixtures,

to provide pure enantiomers or biomolecules. Applying conventional batch chromatography, essential physical and chemical properties are experimentally measured. These properties are used for the design and simulation of chromatographic separation processes. Advanced innovative continuous chromatographic separations, e.g. different configurations of the 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 standalone operation concepts.

The **Crystallization Research team** is studying different concepts of crystallization processes, as e.g. isothermal and polythermal batch crystallization or new continuous crystallization concepts. Hereby various compounds are investigated,



+ A reactor with a volume of 20 Liters is used in the “Pilot Plant Hall (Technikum)” of the MPI, to study crystallization processes – here, by Ph.D. candidate Erik Temmel. A main point of interest is to produce particles with an optimal size distribution. Therefore, the research focuses on the quantification of the rates of the underlying mechanisms such as crystal growth and the birth of new particles by nucleation. After determining essential kinetic parameters, mathematical-based process design and control approaches can be applied to achieve the required product quality.

e.g. different conglomerate or compound forming chiral systems. For better understanding of the underlying mechanisms of crystallization, the growth rates of crystals and the solid liquid phase equilibria are quantified.

The **Reaction Engineering Research team** is working on the development of new reactor concepts. Of particular interest are currently direct combinations of reactions with separation processes, 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, as the feed concentrations or flowrates.

+ **Figure 1:**
Principle of preferential crystallization in one vessel to obtain pure enantiomer E1.

+ **Figure 2:**
Two crystallizers at different temperatures are coupled via the liquid phase. E1 crystallizes in tank 1 and selectively dissolves from the supplied solid racemate in tank 2.

Separating enantiomers by crystallization

+ Certain molecules, occurring in nature, possess the property of chirality and are called enantiomers. Like the human hands, they cannot be aligned with their mirror image but are, apart from that, identical. Nature usually uses only one of the two molecules of an enantiomeric pair. Proteins, for example, are built almost exclusively from L-amino acids, not from their mirror image, the D-form. Since two enantiomers are essentially identical, they share the same physical and chemical properties, which makes it particularly difficult to distinguish them from one another. The human body and any other biological system is, however, capable to differentiate. For this reason, a chiral active pharmaceutical ingredient can have unwanted metabolic effects if both of its enantiomers are administered. As a result of the thalidomide tragedy, regulations have been imposed demanding enantiopure drugs.

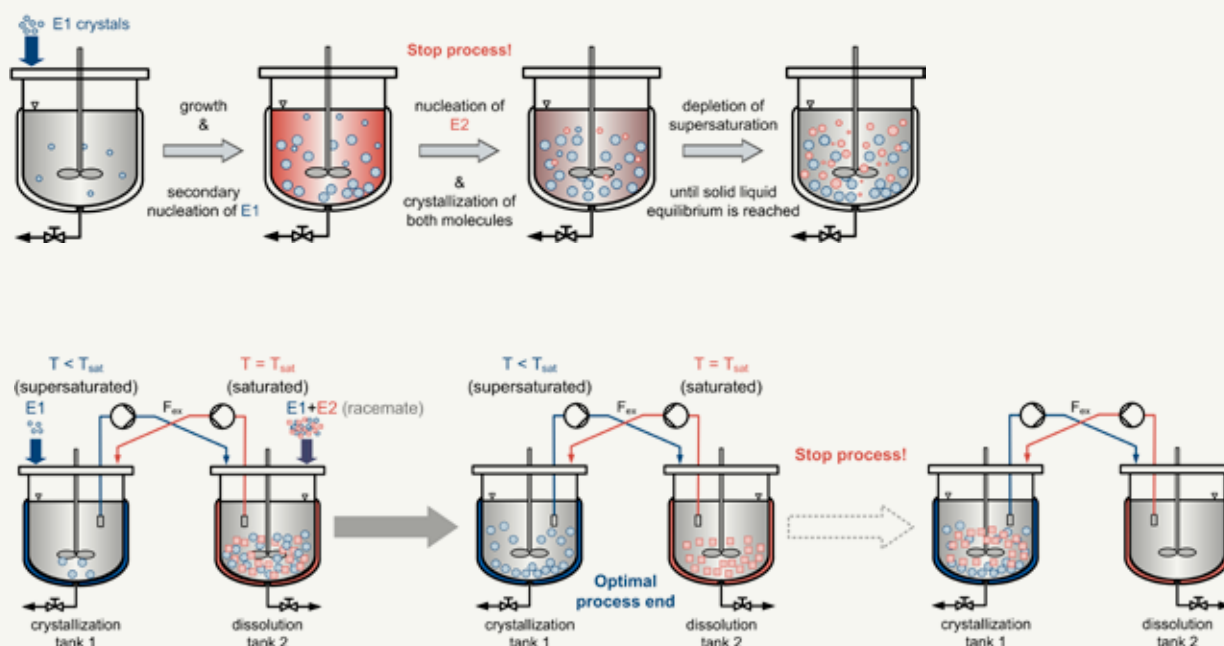
In many cases the production of a chiral drug initially yields the racemate, which contains both enantiomers at equal proportion. Subsequently, the preferred molecule has to be separated from its mirror image. Chromatography, for example, is a very reliable technique to do so but yields a dilute product stream, which has to be further processed. Since many drugs are sold in solid form, a final crystallization step is usually necessary. An alternative to chromatographic methods is preferential crystallization (PC). It combines separation and solid formation in a single step and has a much higher space-time yield while equipment costs are commonly lower.

The principle of PC is shown in Figure 1 in its simplest implementation. The process starts with a racemic solution, which is subcooled below saturation temperature yielding a super-

saturated state. Since it is now thermodynamically unstable, immediate crystallization of both enantiomers should be the result. The solution remains, however, clear for a certain period of time because solid formation is kinetically inhibited. This property is called metastability, which is the key for applying preferential crystallization. Pure crystals of the preferred enantiomer are then added to the metastable liquid resulting in their growth and possible formation of new crystals by secondary nucleation.

The greatest challenge during PC is the appearance of the unwanted enantiomer in the solid phase. As it remains dissolved, its supersaturation stays at a high level, which eventually leads to its nucleation after some time. From that point onwards, the solid phase, consisting so far only of the preferred species, is gradually contaminated until the solution has again reached equilibrium. In order to meet purity demands, the process has to be stopped before. Pure crystals of the preferred type can then be harvested by filtration.

With this implementation of PC, product yield is, however, quite low and because of the stochastic nucleation of the counter enantiomer, it is not a very robust process. A significant improvement can be achieved, when two crystallizers are connected via the liquid phase. The continuous exchange of crystal free solution between both tanks allows for two different process strategies. In the first case, both crystallizers are operated at the same temperature. After cooling below saturation temperature, the racemic solutions are seeded with opposite pure enantiomers. It is thus possible to obtain increased amounts of both molecules at nearly 100% purity since nucleation of



the respective unseeded enantiomer is circumvented due to its crystallization in the other tank.

The second process strategy is depicted in Figure 2. It makes use of a temperature difference between both crystallizers. Tank 1 is operated below saturation temperature and seeded with one pure enantiomer (here E1). Tank 2 is kept exactly at saturation temperature and contains a racemic suspension, consisting of the same solution as in tank 1 and solid racemate. As the seeded enantiomer crystallizes in the left tank, a transient undersaturation of E1 occurs in the right crystallizer. This leads to a selective dissolution of E1 from the solid racemate and results in a gradual purification of the supplied material with respect to E2. The optimal process end is reached, when tank 2 contains only pure solid E2. Crystallization of E1 in the left tank will continue, until supersaturation is depleted, however, nucleation of E2 is also possible. When this happens, the pure enantiomer in tank 2 will start to dissolve as well, until only racemic solution is left. At equilibrium the entire solid phase will have been transported to tank 1 via dissolution and liquid exchange. Naturally, the process needs to be stopped before E2 nucleates but within this time frame, solid racemate can be purified in the dissolution tank.

Given this operating mode, one has the option to either produce the desired enantiomer in the left tank by preferential crystallization or in the right tank by selective dissolution of the respective impurity. The first option results in a higher productivity, because of the higher driving force but suffers from the possible nucleation of the counter enantiomer. The second option yields a very robust process, since it is operated at satura-

tion temperature. Therefore, any nucleation is impossible. In the worst case, the pure enantiomer in tank 2 would start to dissolve, which can be stopped by turning off the liquid exchange.

The connection of PC and selective dissolution is a powerful alternative process strategy for the separation of conglomerate forming, enantiomeric systems. Compared to the simplest implementation (Figure 1), productivities can be more than six times higher at increased process robustness.

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In 2005, Matthias Eicke obtained a diploma in engineering (FH) from the University of Applied Sciences in Hamburg. He then pursued his studies of Bioprocess Engineering there until 2008 and graduated with a Master of Science degree. Since 2008, he is member of the Max Planck Institute in Magdeburg where he is currently holding a Ph.D. position.

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**PSE****PROCESS SYSTEMS
ENGINEERING****PROF. DR.-ING. KAI SUNDMACHER | DIRECTOR**

+ In the past decades, continuous progress in increasing the productivity, selectivity and sustainability of chemical and biotechnological production processes has been made. Nevertheless, in order to cope with the challenges of the future, breakthroughs in process systems engineering are necessary 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 founded process engineering approaches need to be developed, able to deal with the inherent multi-level structure of production systems.

Very efficient process systems might be designable if engineers succeed to consider all hierarchical levels involved in a process system simultaneously, i.e. from the molecular level up to the plant level. But a multi-level design strategy will be successful only if the underlying sub-models are validated by use of reliable experimental data obtained at different levels of the process hierarchy.

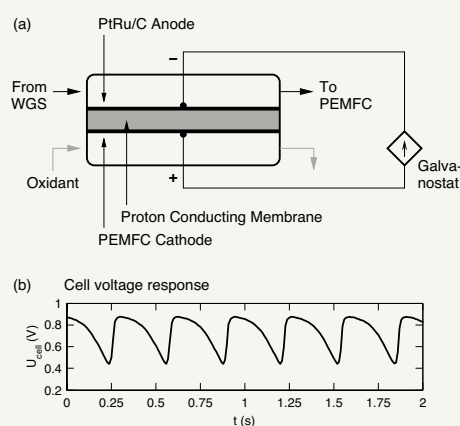
Experimental data are an indispensable element required to discriminate between rival models and to identify model parameters with small uncertainties. Hence, only by closely combining mathematical process models and experimental data, an advanced quantitative understanding of complex process systems can be attained for opening new paths to translate fundamental science into practical solutions.

This vision statement forms the background for the PSE group research strategy. Our group closely combines mathematical

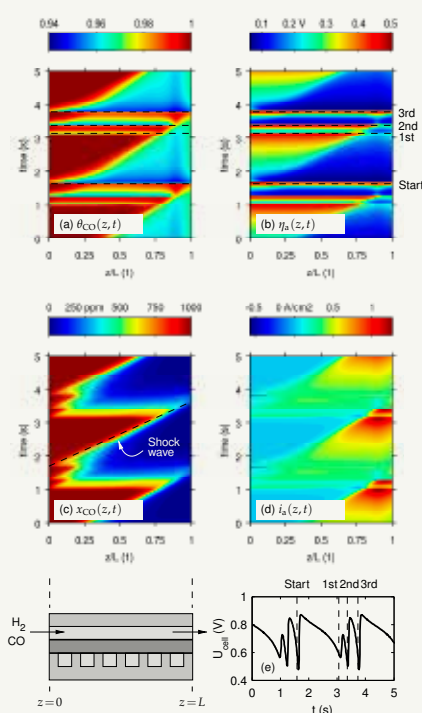


+ Photosynthetic organisms such as marine microalgae are tiny cell factories. They produce numerous interesting substances for food and energy applications from sunlight and carbon dioxide as precursors. To fully exploit the commercial potential of a certain organism, they need to be cultivated in a sterile environment to avoid contaminations from outside. Ph.D. candidate Melanie Fachet is in charge of that.

modeling of complex production processes with theoretical methods for process analysis, design and optimization as well as with experimental validation techniques. Understanding and modeling the dynamics of complex process systems is the core competency of the PSE group. In recent years, we have continued to expand our competence in this direction by integrating new theoretical concepts and challenging process examples, including chemical production systems, energy conversion systems, and biological production systems.



+ Figure 1:
(a) Scheme of an ECPrOx reactor and (b) oscillatory response of the system under galvanostatic control.



+ Figure 2:
Oscillatory behaviour of the system in case of strong influence of the channel dynamics: (a)-(d) spatio-temporal evolution of the CO surface coverage θ_{CO} , the anode overvoltage η_a , the channel CO mole fraction x_{CO} and the local anodic current density i_a ; (e) temporal evolution of the cell voltage U_{cell} .

Spatiotemporal pattern formation during deep CO-removal from H₂-rich gases for fuel cells

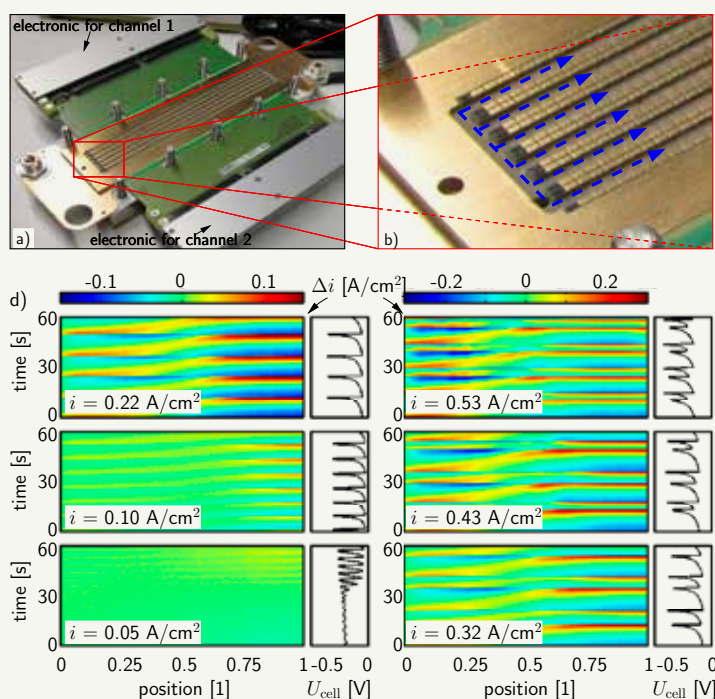
+ Polymer electrolyte Membrane (PEM) fuel cells are expected to play an important role in a future hydrogen-based energy system. As electrochemical energy converters, they allow a direct and efficient conversion of hydrogen and oxygen into electricity. Fuel cells in automobile applications will be fueled with hydrogen produced by means of electrolysis utilising excess electricity from renewable resources. In contrast, stationary fuel cells are typically fueled with hydrogen being produced on-site from natural gas. During the conversion of natural gas into hydrogen, large amounts of carbon monoxide (CO) occur as an undesired by-product. This CO acts as a strong poison for the catalysts used in the PEM fuel cell. Therefore, CO is removed from the feed gas in a process consisting of several steps. In the last of these steps, called deep CO removal, the CO content has to be brought down from 1–3% into the ppm-range (ppm = parts per million).

The researchers from the PSE group are investigating a fascinating system, which involves the electrochemical preferential oxidation (ECPrOx) of the CO. The ECPrOx system might serve as alternative to classical approaches for deep CO removal. Currently, the most important classical approach is the preferential oxidation of CO. In this concept the gas to be cleaned is mixed with a small amount of oxygen and sent over a noble catalyst bed. The main disadvantage is that a part of the hydrogen contained in the feed gas is inevitably burned during this process and lost as fuel for the adjacent fuel cell. In contrast,

in the ECPrOx concept under investigation, an electrochemical membrane reactor is utilized. Also here some of the hydrogen is consumed within the reactor. However, it is not converted into heat, but partially into electricity.

What makes the ECPrOx system so fascinating is the fact that it shows an interesting oscillatory behaviour, i.e. when applying a constant reactor current the reactor voltage oscillates between an upper and a lower value (Fig. 1 (b)). The frequency of these oscillations lies in the range of some 100 mHz up to a few Hz. The origin of this behaviour lies in a cyclic self-cleaning process of the reactor, which allows for the selective oxidation of CO from the gas mixture to be cleaned. The ultimate goal of our research on this system is to suggest an optimal design for such an ECPrOx reactor, i.e. to determine the optimal cell geometry, to choose the optimal catalyst composition and to define optimal operating conditions, such as temperature and reactor current.

Our first effort aimed at a mechanistic understanding of the system's complex nonlinear behaviour, which is essential for the design of a technical reactor. In two initial studies the behaviour of a spatially distributed model was analyzed in detail. In addition to the oscillatory behaviour, complex spatiotemporal patterns have been predicted for a wide range of technical relevant operating conditions (Fig. 2). To explain the observed behaviour, the system can be understood as a cluster of coupled



+ **Figure 3:**

a) The segmented anode flow field with 80 segments per channel (channel length: 14.4 cm). The both inner channels are used for current distribution measurement, while the outer channels serve for homogenization. Each segment consists of two sub-segments that face across the channel. d) Collected experimental results for a current scan during H_2 , CO electro-oxidation: Spatio-temporal plots of the measured spatially distributed current signal (corrected for its temporal space dependent average) starting with the current value given in the plots.

oscillators. The electrical coupling appears in terms of global and migration coupling and was found to be influenced by the electrolyte conductivity and the geometry of the reactor. Furthermore, the system features coupling by means of the anode gas channel dynamics. Depending on the characteristic time for CO transport in the channel, two limiting cases exist. In the first case, for large feed flow rates, the channel dynamics is fast and plays a secondary role. The spatial profile of the channel CO mole fraction does not change in time significantly. It basically determines the intrinsic oscillation frequency of each of the oscillators. Depending on the electrolyte conductivity, coupling/synchronization or decoupling can be observed. In the second case, for small feed flow rates, the channel dynamics dominates the oscillatory behaviour of the system and leads to more complex behaviour. The spatiotemporal evolution of the CO surface coverage is governed by shock waves traveling through the channel. Depending on the fraction of covered cell area and on the electrolyte conductivity a series of sub-sequent pre-ignitions during each main oscillation period can be observed. They manifest themselves in characteristic patterns in the cell voltage (Fig. 2e), which has been observed at that time experimentally by other researches.

In order to verify the predictions made within the theoretical studies, afterwards experiments were carried out. For this purpose a prototype reactor with a special instrumentation was designed (Fig. 3a,b). It allows for the measurement of the current density distribution along the reactor coordinate. The experimental results confirmed most of the predictions. For galvanostatic operation and high feed flow rates well expressed globally coupled oscillations are found. For decreasing feed flow rate the predicted shock fronts and the characteristic voltage

patterns were observed (Fig. 3d). Further experiments were carried out under potentiostatic control. These conditions provoke the breakage of the strict phase relation between adjacent oscillators and the appearance of pulses as well as turbulence was seen. The turbulence is enhanced if an oxygen reducing cathode is introduced instead of a hydrogen evolving cathode.

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Author **Dr.-Ing. Richard Hanke-Rauschenbach**

Dr.-Ing. Richard Hanke-Rauschenbach obtained his diploma in Energy Engineering from the Leipzig University of Applied Sciences. In 2007, he received a Ph.D. degree from the University of Magdeburg. Hanke-Rauschenbach leads a team of Ph.D. students within the PSE group and works as an assistant lecturer for Fuel Cell Technology, Process Dynamics and Process Optimization at the PSE Chair of the University of Magdeburg. His research focus is on the analysis, design and operation of renewable energy systems.

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PSD
**PROCESS SYNTHESIS
AND PROCESS DYNAMICS**

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

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

The PSD group develops methods and tools for synthesis, analysis and control of complex process systems. It combines physical chemical insight with theoretical concepts from systems and control as well as applied mathematics. Process insight guides the way to suitable problem formulations and feasible as well as efficient solution strategies. 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 of the PSD group during the last years. New methodologies have been introduced in the areas of nonlinear model reduction for particulate processes with nonideal flow fields, model based measurement and control of particulate processes, the synthesis of robust plant wide control strategies and nonlinear model based control of various types of fuel cell systems. In the field of particulate processes, besides crystallization, fluidized-bed spray granulation processes are considered, which also play an important role in process industries. Control of these processes, however is difficult and has hardly been studied before.

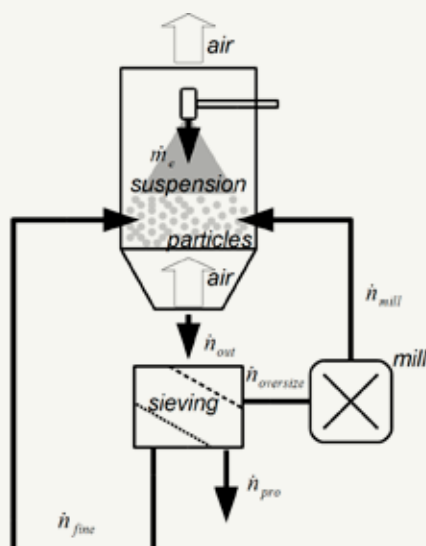
In the field of **process design** the PSD group develops computational methods for a systematic design of complex process systems. Approaches range from shortcut methods based on analytical insight up to rigorous simultaneous mixed integer nonlinear optimization (MINLP) of process configurations and



+ The PSD group follows an interdisciplinary research approach. Developing mathematical process models and tailored process design methods requires a continuous communication between theorists and experimentalists. The picture shows Dr. Michael Mangold and Ph.D. candidate André Franz discussing a problem from Systems Biology.

operating conditions. Special interest is on 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 have evolved as interesting fields of application.

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



+ **Figure 1:**
Flowsheet of fluidized bed spray granulation with external product classification

Control of particulate processes

+ Particulate products like crystals, granules, powders play a major role in process industries. Typical examples are pharmaceuticals, detergents, pigments, polymers etc. They represent about 60% of the produced value in the chemical industry. Typical production processes comprise crystallization, granulation, polymerization etc. Function and effectiveness of particulate products often depend on particle properties – such as size, porosity, morphology or composition. Main objective of our research in this field of application is to devise new methods and tools to control particulate processes and thereby adjust the desired product properties.

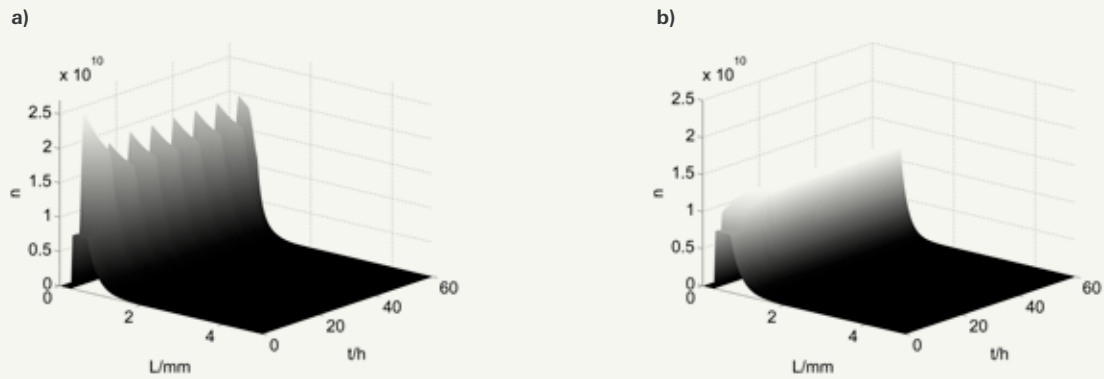
This is a challenging issue due to nonuniformity of particle systems, where particles differ with respect to individual properties, and product properties are represented by the collective behavior of the particle population. From the theoretical point of view particulate processes belong to a special class of distributed parameter systems, so called population balance systems. They are described by nonlinear partial differential equations often coupled to integro-differential equations describing the surrounding medium.

A typical example that has been studied in some detail is fluidized bed spray granulation with external product classification as illustrated in Fig. 1. Core of the plant is the granulation chamber, where the particles are fluidized through an air stream. The injected solid solution or suspension is deposited on the particle surface, where it leads to particle growth through subsequent drying. In this process, product particles are continuously removed and classified with some screens. The oversize fraction is

grinded in a mill and fed back together with the undersize fraction to the fluidized bed for further processing. At high milling grades, after startup a stable steady state with constant particle properties is achieved. In contrast to that, at lower milling grades the system becomes unstable resulting in a cyclic change between particle growth and particle formation through grinding. Particle properties, in particular particle sizes, are also varying periodically, which is usually not acceptable. Such patterns of behavior are characteristic for many particulate processes involving crystallization or also some polymerization processes.

To stabilize the process, feedback control can be applied. Control variables are typically integral quantities of the particle population like overall number or overall surface of particles, which can be measured comfortably with available equipment. A suitable manipulated variable is the milling grade. In control, automatic process manipulation has to be linked to process observations by a suitable control algorithm. The algorithm has to be designed in such a way, that stability of the overall system comprising the process and the controller can be achieved. This is a challenging issue for the present class of system which was tackled in two different ways.

The first type of approach is based on a finite dimensional approximation of the process in combination with methods from robust control. The controller has to be designed conservatively to account for approximation errors and/or parameter variations occurring during startup. Consequently, the performance is limited [2, 3].



+ Figure 2:
Temporal evolution of the particle size distribution
a) without control
b) with control

Alternatively, a new method was developed, which is based directly on the nonlinear distributed model and exploits a special Lyapunov stability theory. The control law is designed guaranteeing stability a priori only in a generalized, here integral, sense circumventing problems found in classical late lumping approaches. It is further argued, that stability in the integral sense implies pointwise convergence if the zero dynamics of the system is stable. For systems with unstable zero dynamics, a parallel compensator is designed leading to a new system with stable zero dynamics which admits the previous approach [4].

The new method is relatively simple, and intuitive and applies to a large class of technical systems. Application to fluidized bed spray granulation with external product classification is illustrated in fig. 2. Besides, feasibility of this approach has also been shown for granulation process with internal nucleation and product classification as well as continuous crystallization processes [2].

Besides an extension of the control methodology, current research is focussing on multi chamber granulation processes with increased complexity in cooperation with Prof. Heinrich from Technical University Hamburg Harburg and Prof. Tsotsas from Otto von Guericke University Magdeburg and on fluidized bed crystallization in cooperation with the Seidel-Morgenstern group at MPI.

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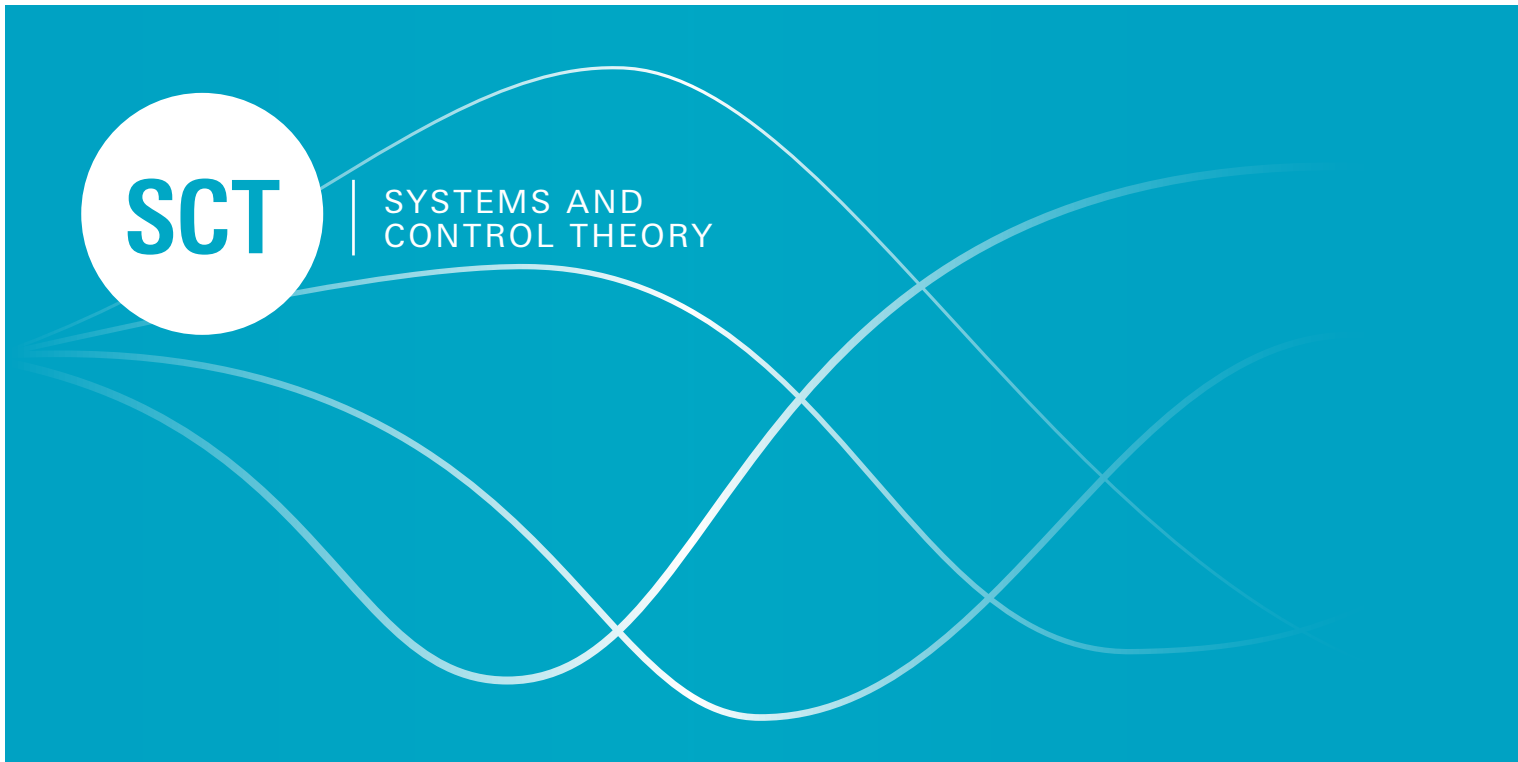
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Dr. Stefan Palis is senior researcher in Professor Kienle's group. He received his Ph.D. in 2012 from the Otto von Guericke University Magdeburg. Among others, his Ph.D. thesis was awarded with the price for the best dissertation by the International Association of Automation Engineering in Process Industry (NAMUR). His research focus is on control of distributed parameter systems.

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“There is nothing as practical as a good theory”

(K. Lewin)

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

✚ According to the psychologist Kurt Lewin, “there is nothing as practical as a good theory”. He was right. The field of Systems and Control Theory (SCT) nicely illustrates this observation, which has also been attributed to T. Karman and G. Kirchhoff.

SCT has been recognized as a research area in its own right for several decades. Roughly speaking, its subject is the analysis and synthesis of dynamical systems, in particular the design of feedback control systems. In its evolution, SCT has developed an array of methods and tools which have been successfully applied to solve a great number of problems. One of the most spectacular examples is the control of spacecraft.

Other, equally important examples are the control of large chemical plants and power stations, and various control problems in the automotive and the biomedical sector. The Internet and other communication networks now provide a new generation of complex challenges for SCT.

In addition, SCT has served as a bridge between a variety of application areas, e.g. chemical engineering, mechanical and manufacturing engineering, economics, biology, etc.: by translating specific application problems into a unique mathematical framework, SCT provides a common language that allows scientists and engineers with extremely diverse technical backgrounds to communicate and hence to generate considerable synergetic effects.

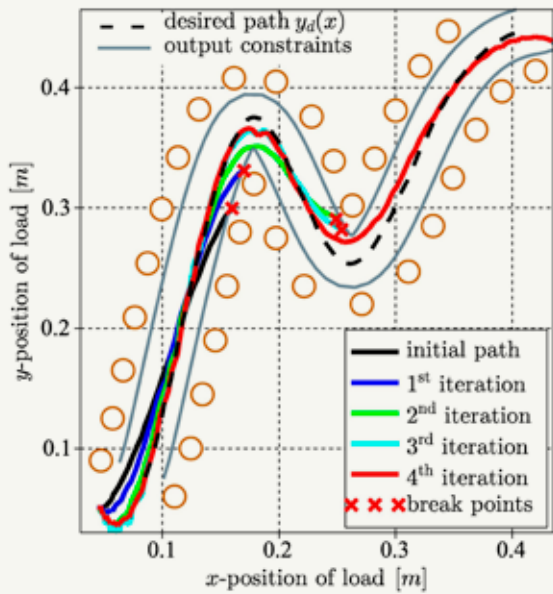
This general perspective of SCT is reflected in the group’s research interests. It addresses both challenging problems from



+ 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.

the “core domain” of SCT and from a number of application areas. Within the group, there is a good balance between theoretical and application projects; the group also attempts to match projects in the sense that results obtained from theoretical work are transferred into specific application projects as rapidly as possible.

The group is headed by Jörg Raisch, who is an External Scientific Member of the MPI. His primary affiliation is 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. Their research is carried out in close cooperation with other research groups from the MPI and/or further national and international cooperation partners.



+ **Figure 1:**

Variable pass length ILC algorithm on a lab-scale gantry crane. The load of the crane shall follow a desired path without hurting the obstacles. When the output constraints are infringed, the rope is wound up and the algorithm needs to learn from incomplete trial information. In the experiment, the path is followed after four iterations.

Iterative learning control for variable pass length systems

+ Iterative Learning Control (ILC) is a control strategy which aims at improving the performance of systems that execute the same task repeatedly. It somehow teaches robots to get better from trial to trial. The often used analogy to human learning is the example of a child who learns how to walk for the first time. ILC tries to imitate this behavior by learning from past trials. In classical ILC, it is assumed that the system can finish a whole task before the learning is made. However, for some applications, constraints may lead the system to stop the trial before it is finished. A child must first learn to not fall before he learns how to run. In this case, for automated systems, a new type of ILC is needed, which is Iterative Learning Control with Variable Pass Length. I work on new theoretical concepts which guarantee stability and monotonic convergence of such algorithms.

Humans can learn by repeatedly performing tasks, e.g. a basketball player can improve his hand and arm movement from throw to throw and a rally driver can try to get closer to the optimal trajectory from lap to lap. Technical systems that have to repeat the same task over and over again can be equipped with a controller that allows it to imitate human learning.

Iterative Learning Control (ILC) is a control method which enables technical systems to improve their performance. To this end, an input trajectory, which is typically applied in a feed-forward fashion during an iteration, is updated from trial to trial based on error information from the last iteration. ILC has been successfully used in many applications such as robotics, biomedical systems, chemical processes, steel production systems and many more. In the vast majority of these applications though, it

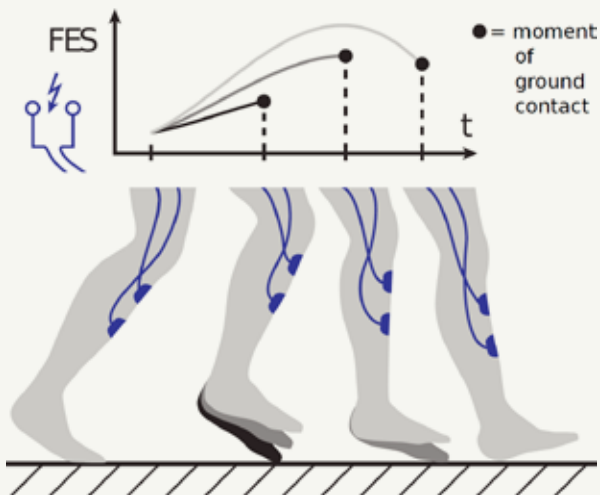
is assumed that, even before the first learning step, the system is able to complete a trial and that the complete output trajectory of that first trial can be obtained.

However, for some ILC application systems, the initial input, i.e., the input that is applied in the first trial, drives the system to violate constraints before the trial has been completed and, consequently, that trial is aborted before it is finished. For such systems, the incomplete output information must nonetheless be used to improve the input trajectory such that, in the second trial, the constraint is not violated, or at least violated at a later time.

It is not clear under which circumstances a learning algorithm leads to completion of a trial in a finite number of learning steps. Besides this, the evolution of the tracking error in such systems from pass to pass is of primary importance. This kind of control problem is called ILC with variable pass length (VPL) [3], since the time interval on which information is available may vary from iteration to iteration.

Recent results on variable pass length dynamics have been applied to analyze VPL systems, to demonstrate how an ILC algorithm might learn from the incomplete information of a disrupted trial and still converge even in the presence of large disturbances. These results provide conditions which guarantee monotonic convergence of the resulting error, but many other results are yet to be found.

This type of ILC has already been successfully applied to trajectory tracking on a laboratory-scale gantry crane with output



+ **Figure 2:**

Influence of stimulation intensity on the duration of swing phase. When stimulation is too weak, the foot touches ground early. The measurement data acquired until that point must be used to improve the stimulation intensity profile for the next step.

constraints [1]. In this system, a load is placed at the end of a rope, which is attached to the crane's cart. The rope can be wound up and down, thus allowing the load to move in a three-dimensional space. The latter feature introduces the idea of switching during a trial. Instead of disrupting the trial, is it possible to wind up the rope of the crane to a secure distance and keep learning? What are the consequences in terms of theoretical concepts? How can one prove stability, monotonic convergence and robustness when switching occurs while learning? Could a new concept of Switched Iterative Learning Control (SILC) be of use? It seems like a challenging problem with many potential applications.

Standard ILC, i.e., ILC without switching, has already been successfully applied to many practically important problems, e.g. in biomedical engineering. In fact, Functional Electrical Stimulation (FES) and ILC have helped stroke patients in their rehabilitation process [2–3]. Stroke can cause hemiplegia, which is paralysis of one side of the body, and rehabilitation involves practicing to regain motor functions. A common symptom in stroke patients is the drop foot syndrome, which is characterized by insufficient dorsiflexion of the foot and can be treated by FES. To this purpose, a predefined foot movement can be produced via electrical stimulation of the respective muscle through skin electrodes. This way, stroke patients walking on a treadmill can be supported, for example, by controlling the ankle joint angle via electrical stimulation of the tibialis anterior muscle. Due to the repetitive nature of gait, ILC was successfully used to learn the stimulation profile for the swing phase within a small number of steps. However, the hip joint and the knee joint are actuated by the patients themselves. Thus, depending on their strength and abilities, the steps are usually cut short by suddenly putting the foot down. Assuming that up to this point the movement of hip and knee was hardly different from the movement in a full-length step, the data gathered in these aborted steps should be used for learning. Therefore, a VPL ILC algorithm could be used [3].

In recent related work [4], FES and ILC have also been shown to help patients regaining lost motor functions of the upper limb. Indeed, after some rehabilitation sessions with FES and ILC, the voluntary muscle activity increased and therefore less electrical stimulation was needed for the task to be performed by the patient.

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Author Mickaël Guth

After a two-year intensive programme in Advanced Mathematics and Physics, Dipl.-Ing. M.Sc. Mickaël Guth was accepted at Supélec – Ecole Supérieure d'Electricité – in France specializing in Electronics and Computer Sciences. In 2013, he obtained a dual degree with Technical University Berlin, in Electrical and System Control Engineering. He then joined the Max Planck Institute in Magdeburg as a Ph.D. student, working with the Control Systems Group at the TU Berlin.

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ARB

ANALYSIS AND REDESIGN
OF BIOLOGICAL NETWORKS**DR.-ING. STEFFEN KLAMT | SENIOR SCIENTIST**

+

The primary research interests of our group lie in the area of Systems Biology, at the intersection of biology, mathematics and engineering sciences. We develop theoretical and computational methods for the analysis, inference, and targeted modification of biomolecular networks and employ these methods in interdisciplinary collaborations with biological partners. A long-term goal of our research is to help paving the way for routine use of mathematical modeling in biology, biotechnology, and biomedicine.

The group is divided into four teams, three dealing with theoretical and one with experimental aspects of Systems Biology. The experimental work focuses on the regulation of the metabolism

in the model bacterium *Escherichia coli* and is embedded in an iterative cycle between “dry lab” (mathematical modeling provides predictions and hypotheses) and “wet lab” (experiments provide data and observations to be evaluated by the dry lab).

In 2013, several new BMBF-funded projects have taken off in which the ARB group is involved as a contributing partner. These projects deal with different topics such as metabolic engineering of cyanobacteria for photosynthetic production of biofuels (CYANOSYS II) or the computer-aided elucidation of mechanisms underlying the misbalanced and pathophysiological action of a human signal transduction pathway (JAK-Sys).

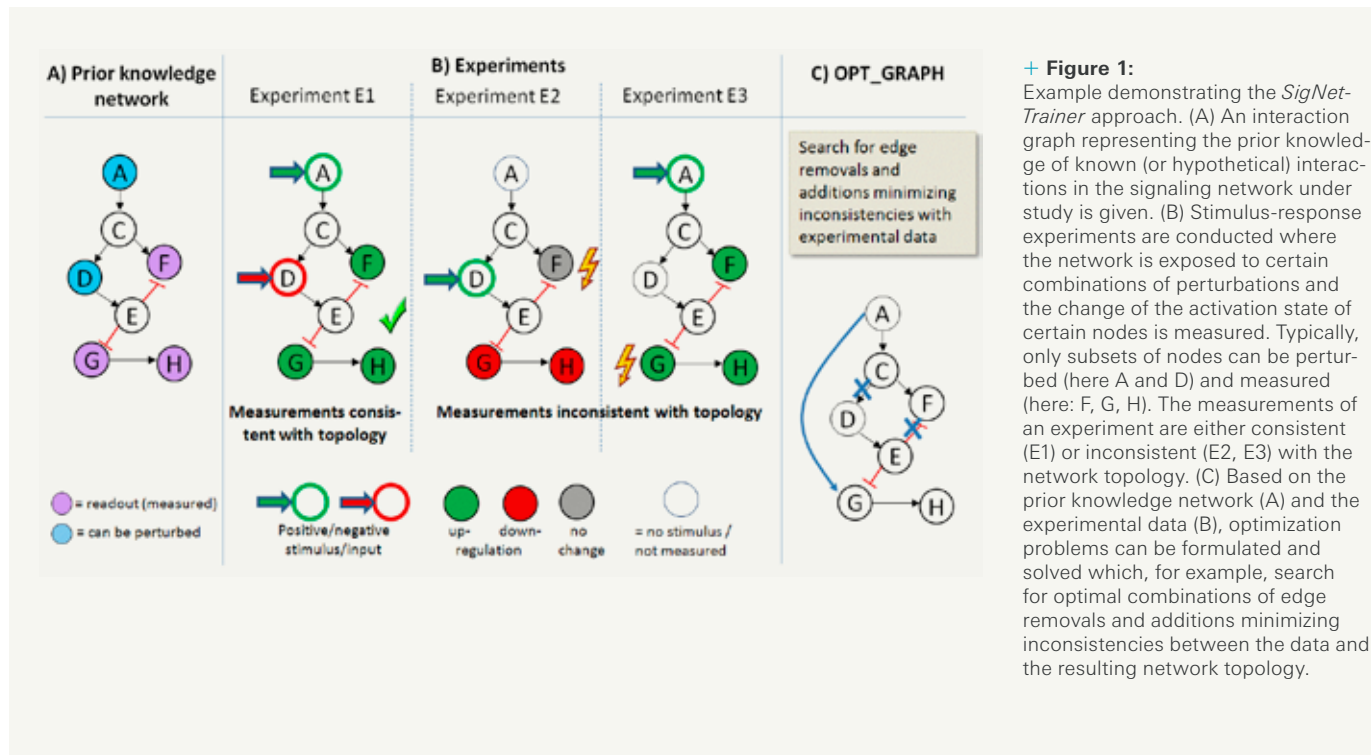
In September, we welcomed two Humboldt scholarship holders: Prof. Martin Schuster (Oregon State University) and Prof. Radhakrishnan Mahadevan (University of Toronto). Both stayed several months at the MPI giving us the opportunity to establish



+ Many processes in the cell are controlled by large-scale and complex networks of interacting biomolecules. The ARB group develops and applies computational methods for the analysis, identification, and targeted modification of biological networks. Here we see Ph.D. candidate Philipp Erdrich studying a computer model of the metabolism in cyanobacteria. The ultimate goal of his project is to use such models for the identification of suitable genetic intervention strategies by which these photosynthetic organisms produce biofuels with high yield from sunlight, carbon dioxide, and water.

fruitful collaborations with distinguished experts in the fields of bacterial communication (Prof. Schuster) and computational strain design (Prof. Mahadevan).

A very successful event for the group was the participation in a community-based effort for reconstructing biomolecular networks from experimental data on which we report in the highlight section on the following pages.

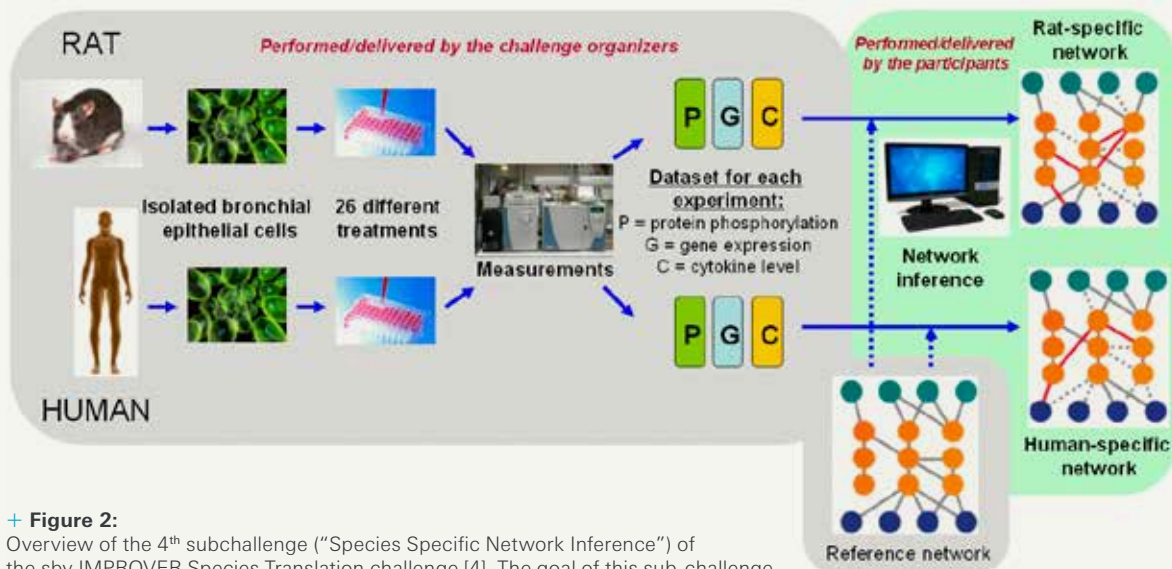


Computer-aided elucidation of cellular signaling networks

One research focus of the ARB group is the computer-aided inference (or *reverse engineering*) of cellular signal transduction networks based on experimental data. Signaling and regulatory networks allow the cell to receive and process intra- and extracellular signals and to respond appropriately by adjusting the expression of certain genes. Signal transduction networks are spanned by “communicating” proteins which may activate or inactivate each other (e.g., by phosphorylation). Prominent examples are signaling cascades triggered by the hormone insulin or by certain growth factors. Signaling networks are commonly depicted as “canonical” pathway maps in text books and online databases. However, each cell type may have distinct variants of signaling pathways, and wiring diagrams are often altered in disease states like cancer. Moreover, several signaling pathways are still not fully elucidated. The computer-aided identification of active topologies of cellular signal transduction networks based on experimental data is therefore one key challenge in systems biology and is greatly facilitated by the rapidly evolving measurement technologies.

Our group has been developing several inference methods (e.g., [1,2]) with *SigNetTrainer* [1] being the most recent approach developed in collaboration with partners from the Technical University in Athens. *SigNetTrainer* starts with an interaction graph (IG) capturing prior knowledge about the network structure. The IG depicts known activating and inhibitory influences between the signaling proteins as positive ($\rightarrow$) and negative ($\rightarrow$) edges (Figure 1A). Network inference always requires experimental data from stimulus-response experiments where different combinations of nodes are perturbed (e.g., by triggering external signals

or by adding inhibitors blocking certain proteins) and where the activation states (e.g., phosphorylation level) of some readout nodes are then measured. In the example in Figure 1, we have three experiments (E1-E3) where nodes A and D are stimulated in different combinations; nodes G, H, F are the measured readouts and C and E can neither be measured nor perturbed. We assume that the data are discretized to indicate whether an up-regulation (+1), down-regulation (-1) or no activity change (0) was measured in the node when compared to the initial (unperturbed) state. Although an IG is a very simple model of a signaling network, it constrains the potential qualitative behavior implying that some experimental findings may be inconsistent with the network structure. As a *sign consistency rule*, we expect that a change in the steady-state level of a species must be explained by an appropriate change of at least one of its predecessors. Experiment E1 in Figure 1 complies with this rule: up-regulation of F can be explained by (non-measured) up-regulation of C induced by external activation of A whereas up-regulation of G and H follows because inhibition of D lowers activation of E which leads to a reduced inhibition (thus up-regulation) of G and H. In contrast, experiments E2 and E3 are not consistent with the network structure: in E2, node F should be down-regulated when D is activated and, in E3, G and H should be down- instead of up-regulated because of the path $A \rightarrow C \rightarrow D \rightarrow E \rightarrow G$ transducing a negative signal from A to G. As a key result of our work, we showed that the sign consistency relationships imposed by the IG can be encoded by linear inequalities over integer variables. Based on these inequalities, certain optimization problems can be formulated to detect inconsistencies and to minimize them by correcting the network structure via removal



+ **Figure 2:**

Overview of the 4th subchallenge ("Species Specific Network Inference") of the sbv IMPROVER Species Translation challenge [4]. The goal of this sub-challenge is to infer human and rat signaling networks given phosphoprotein, gene expression and cytokine data and a reference network provided as prior knowledge. Data and reference network were provided by the challenge organizers, the network inference had to be conducted by the participants.

and addition of certain edges. Figure 1C shows one such optimal solution: deletion of edges C→D and E→F and adding the edge A→G leads to a network topology being fully consistent with all experiments. We also devised methods to enumerate multiple optimal solutions for underdetermined problems. All algorithms have been implemented in a toolbox *SigNetTrainer* which uses CPLEX as solver for the posed Integer Linear Programming (ILP) problems. In [1] we applied the proposed methodology to derive a cell-type specific network of the Epidermal Growth Factor (EGF) signaling network in hepatocytes – the major cell type of the liver – and came to conclusions regarding possibly inactive or missing edges. These results provide hints for further targeted experiments.

The rapidly increasing number of algorithms proposed for biological network inference led to the establishment of platforms for a rigorous and unbiased testing of the different approaches. DREAM [3] and sbvIMPROVER [4] are two such collaborative efforts. Using our *SigNetTrainer* approach we took part in a recent challenge of the sbvIMPROVER platform, more precisely in the 4th sub-challenge of the Species Translation Challenge. Here, the goal was to infer species-specific signaling networks for bronchial epithelial cells in rats and in human based on a given reference network and a large-scale dataset for each of the two species targeting major signaling pathways (Figure 2). With some adaptations, we were able to apply the *SigNetTrainer* approach to this large-scale problem (the reference network comprised more than 200 nodes and 500 edges) and determined for each organism a network minimizing the inconsistencies with the data. Our analysis revealed that many interactions in the reference pathways were not active, especially those linking proteins with gene regulation. With the presented method and obtained results, our MPI-team (with members from ARB and PSE group) was ranked first, together with another team. This successful application gives us confidence that our approach holds promising potential for network reconstruction problems in Systems Biology.

SigNetTrainer uses steady-state data to characterize and analyze the effects of perturbations and we are currently studying how far also transient and more quantitative data can be integrated in such a framework. We also developed algorithms to reconstruct regulatory networks without any prior knowledge on their topology [2] and established new collaborations with biologists to further test and employ these methods in concrete applications.

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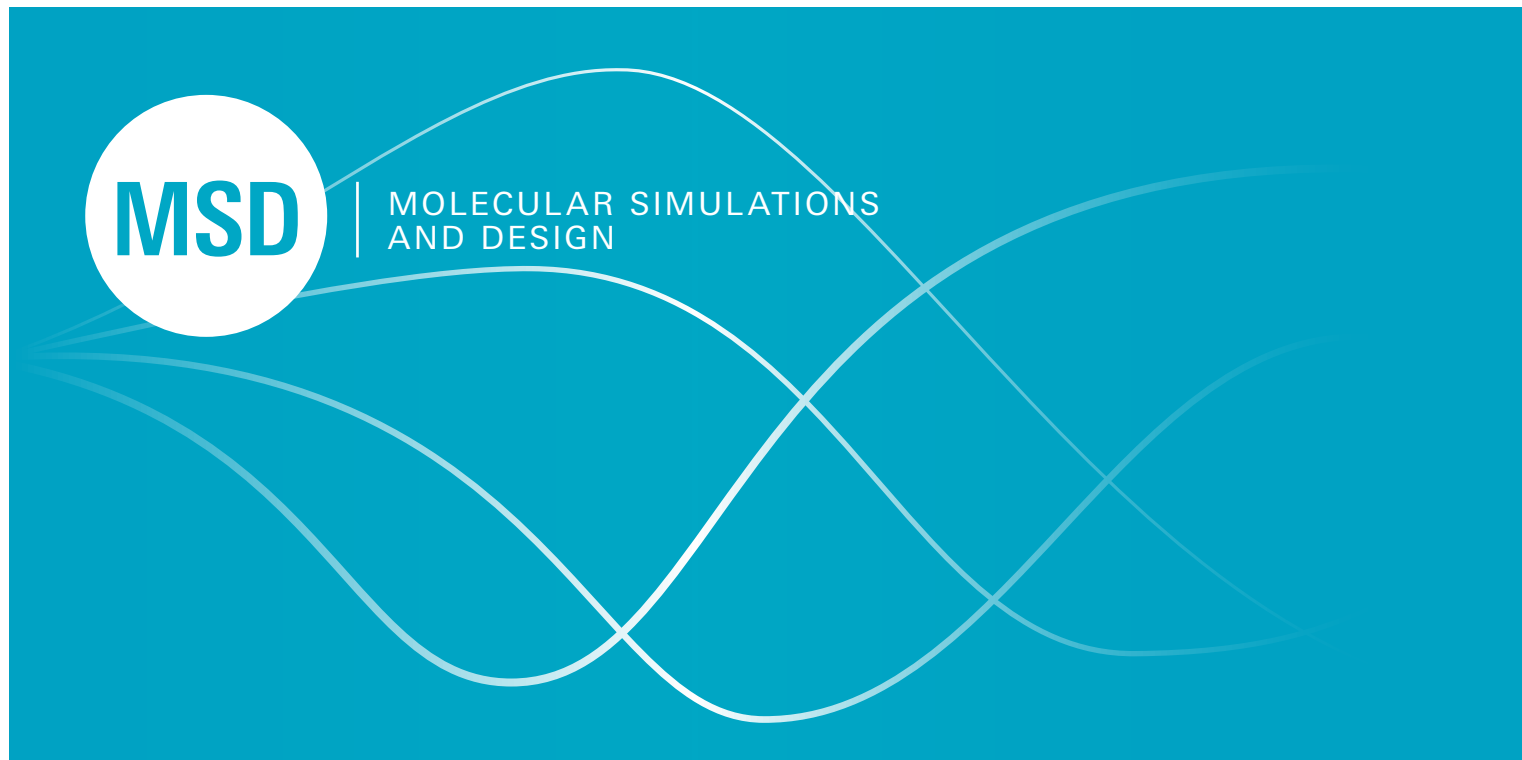
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Author **Dr.-Ing. Steffen Klamt**

Steffen Klamt studied *Applied Systems Science* at the University in Osnabrück and received his diploma in 1998. In the same year, he started working in the Systems Biology group of Prof. Dr.-Ing. Ernst Dieter Gilles at the MPI in Magdeburg and obtained his Ph.D. degree in 2005. In 2009, he became head of the research group *Analysis and Redesign of Biological Networks* at the MPI.

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DR. RER. NAT. MATTHIAS STEIN | SENIOR SCIENTIST

+ The Molecular Simulations and Design Group (MSD) is a Max Planck research group (MPRG) which is closely integrated into the institute's research activities.

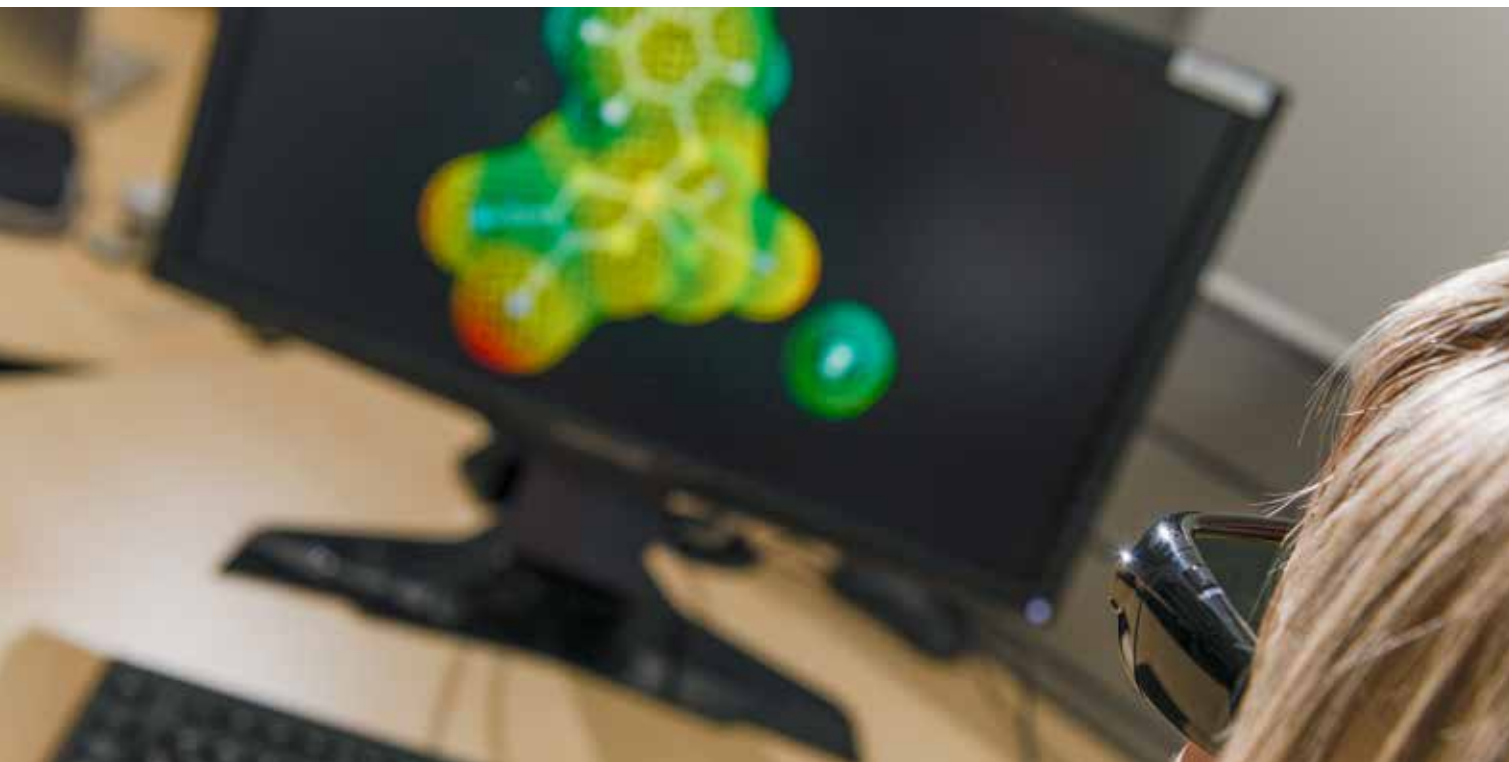
The MSD group performs interdisciplinary research at the interface between chemistry, biology, physics and the group members have diverse academic backgrounds. The MSD group develops and uses computational approaches to investigate problems in bioinformatics, molecular systems biology, structural biology, biotechnology and various areas of chemistry.

Computational approaches to modern biology and chemistry can yield insights into the molecular interaction properties of proteins and molecules, their reaction mechanisms and identify

intermediates which are sometimes difficult to obtain experimentally.

In 2013, Prof. Sandeep Kaur-Ghumaan from the University of Delhi (India) spent her first residence as a guest scientist with the MSD group as a DST-MPG Fellow, which is a joint project between the Indian Department of Science and Technology and the Max Planck Society (MPG). As a result from the collaboration two scientific publications have already appeared. Prof. Kaur-Ghumaan has excellent complementary expertise and common research interest to the MSD group regarding developing bio-inspired and biomimetic complexes for the generation and activation of molecular hydrogen. She will come and visit again during the following three years.

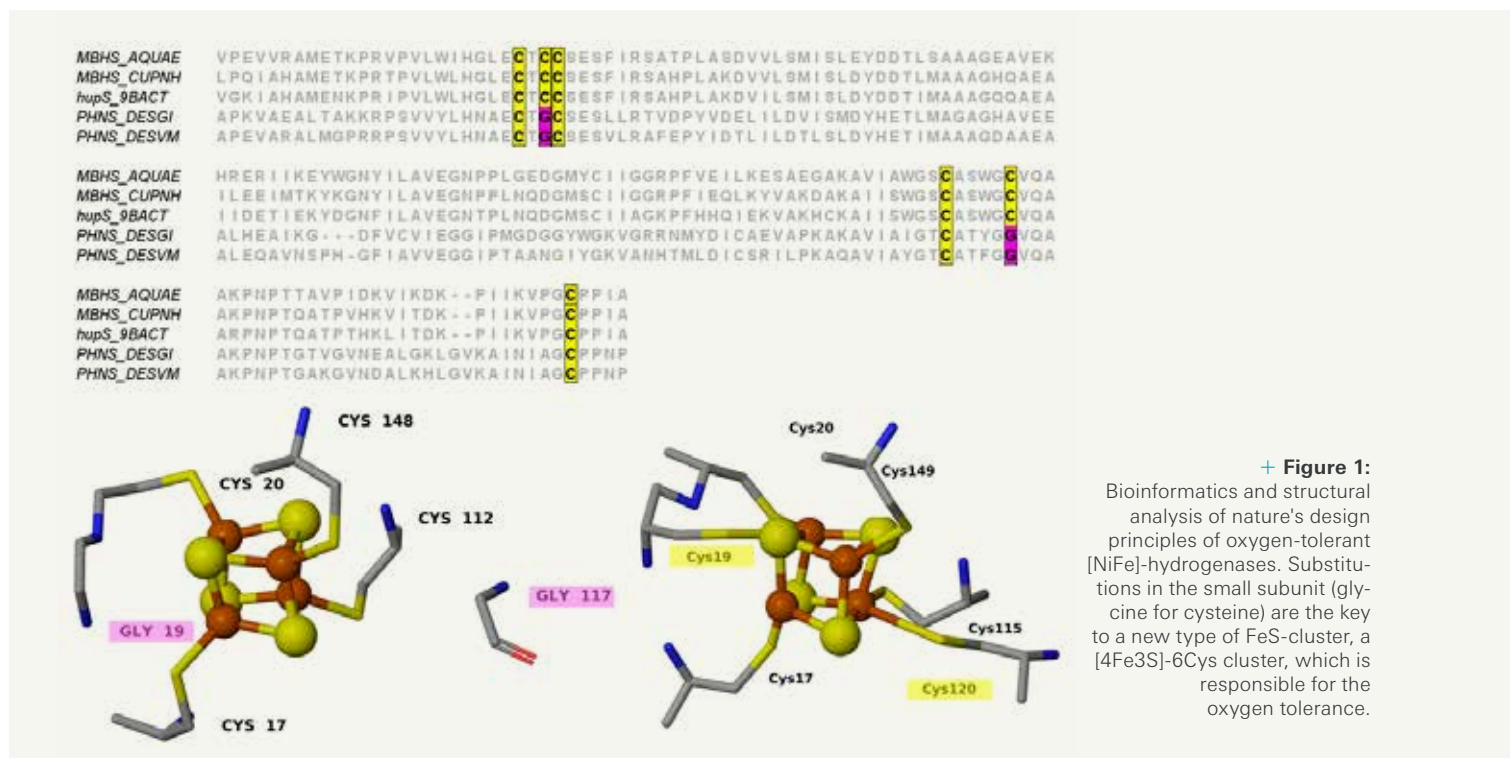
Dr. Serdar Durdagi, a postdoc from the MSD group, was appointed as Associate Professor in the Medical Faculty by the



+ The computer is the most important technical tool for the MSD group. Computational methods are developed and applied to study processes and systems from chemistry and biology. Here, Ph.D. candidate Eileen Edler is inspecting the calculated structure of an iron model complex which is able to generate hydrogen from acidic solutions. The complex takes up design principles from nature and acts as a bio-inspired catalyst. As such it is an interesting alternative to produce one of the most prominent energy carriers of the future.

Bahcesehir University in Istanbul, one of the strongest places for science in Turkey. A scientific collaboration between the MSD group and Serdar Durdagi will continue.

One of the areas of research is the investigation of biological hydrogen turnover and model systems inspired by nature's design principles. Detailed insight at the atomic level is very difficult to obtain experimentally and challenging to interpret sometimes. Here, computational investigations are necessary to model and understand experimental results.



Hydrogen and oxygen turnover without explosion-put the enzyme into the tank

+ Burning petroleum to drive automobile devices produces 3.5 billions of tons of carbon dioxide emissions plus other exhaustive fumes per year. CO₂ is termed a climate dangerous gas ('greenhouse gas'); its concentration has increased by 30% during the last 40 years.

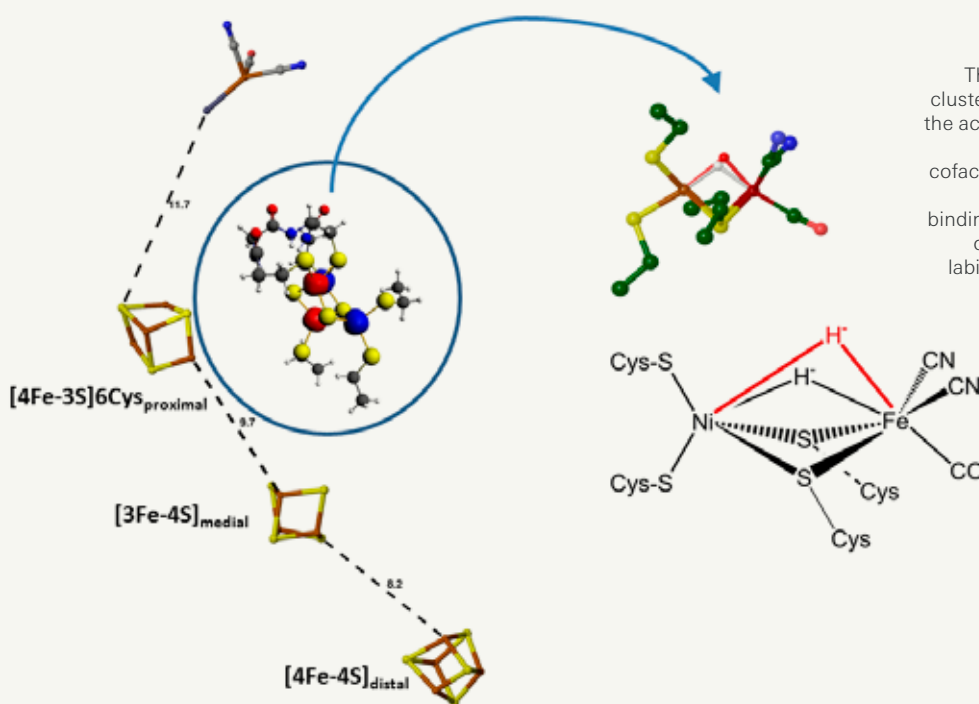
Hydrogen, on the other hand, is a climate-friendly gas since it burns emission-free and only water is released as a product (H₂O). The energetics of the most stable, homonuclear chemical single bond are a sake and a curse at the same time: molecular hydrogen (H₂) is a suitable energy storage compound and combustion compound but the production of molecular hydrogen requires large amounts of energy as well. Today, H₂ is industrially generated by electrolysis of water or by biomass degradation but then also CO₂ is released. Activation of hydrogen requires, again, precious noble metal catalysts and elevated temperatures.

Nature has found a way to generate molecular hydrogen at ambient temperature (room temperature) and normal pressure with the aid of a class of enzymes, called 'hydrogenases'. The hydrogenases are classified according to their active site composition as [FeFe]-, [NiFe]- or [Fe]-hydrogenases. They all use cheap and abundant metals to either generate/produce molecular hydrogen from protons and electrons, or to activate and split molecular hydrogen both at room temperature. These catalysts have evolved over billions of years and were present on

earth a long time before plant photosynthesis and then oxygen in the atmosphere appeared. The hydrogenase enzymes provide highly efficient catalysts. For example, one molecule of the [FeFe]-hydrogenase can produce 9,000 molecules of hydrogen per second at 30 °C!

Due to their evolution in an atmosphere without oxygen, an anaerobic setting, care has to be taken to avoid the presence of oxygen when isolating, purifying and characterizing these enzymes in the laboratory. Oxygen acts as an inhibitor of the enzymes and also leads to oxygenic destruction of the proteins. A particular strand of the hydrogenases, however, has evolved that is able to cope with the presence of oxygen. This class of O₂-tolerant [NiFe]-hydrogenases retains its catalytic activity in an atmosphere of oxygen and can even resist oxygenic destruction.

Together with our experimental collaborators, we investigated the molecular basis for this oxygen tolerance. To our surprise, the oxygen-tolerance was not due to modifications or changes at or in the vicinity of the active site where the catalytic reactions occur. Spectroscopically there were no differences between the oxygen-sensitive and tolerant enzymes detectable. It was thus concluded that the active site composition and the structural arrangement of protein in its surrounding are identical. Rather, changes in the nearest iron-sulphur cluster which is at a distance of 11 Å from the active site made the difference.



+ **Figure 2:**

The new type of proximal [4Fe-3S]6Cys cluster is the source of oxygen tolerance of the active site at 11 Angstrom distance. The unusual electronic structure of this cofactor has an effect on the catalytic turnover at the active site. For example, binding in the catalytic intermediate Ni-C in oxygen-tolerant hydrogenases is more labile (red hydride) compared to standard hydrogenases (black hydride).

In the O₂-tolerant enzymes this FeS-cluster is strikingly different from that of standard hydrogenases. In standard hydrogenases, this iron-sulphur cluster is a 'cube' in which the corners are occupied by alternating iron and sulphur atoms. This cluster is different in oxygen-tolerant enzymes. It contains two additional cysteine amino acid residues which also coordinate directly or indirectly to the iron atoms. This is a new type of particular 'signature' in the hydrogenase enzymes amino acid sequence. It can now be used to functionally annotate unknown or not characterized [NiFe]-hydrogenases as being either 'standard' or 'oxygen-tolerant'.

This is a new type of iron-sulfur cluster which was not observed before in any protein structure. The peculiarity of this arrangement lies in the electronic transitions that this cluster may undergo. Compared to 'standard' hydrogenases this new type of iron-sulfur cluster may donate an extra electron to its nearest neighbours, i.e. the active site at a distance of 11 Å. The fast electron donation may serve as a protectant against the otherwise inhibitory or destructive oxygen when it approaches the active site. Thus, oxygen, as coming close to the active site, is immediately reduced once or twice to a harmless and easy to destroy species. The new FeS-cluster therefore serves as a fast reductive protectant of the enzyme's active site. The new ability of electron donation due to the electronic structure of this new iron-sulphur cluster was investigated in detail by quantum mechanical calculations. Due to the large number of unpaired electron spins, different pairing 'coupling' schemes are possible. The most plausible is shown in Figure 2.

Nature's design principles are more complex but also more imaginative than people could have thought beforehand. The

localization/positioning of a reductive protectant at a medium distance from the enzyme active site to protect it from oxidative damage may not be obvious. Now chemists and engineers are to consider this oxidative-protectant strategy and incorporate its principles when developing bio-inspired or biomimetic catalysts with a similar functionality and oxidative stability.

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**NDS**NUMERICAL LINEAR ALGEBRA
FOR DYNAMICAL SYSTEMS**DR. MARTIN STOLL | SENIOR SCIENTIST**

+ The year 2013 has seen the introduction of an additional research group to the institute. Our official title is Numerical Linear Algebra for Dynamical Systems.

In short, we focus on the fast solution of equations that come from the modelling of real world phenomena. In more detail, we are very much interested in the study of differential equations that can come in various flavours to model chemical processes, fluid dynamics or human interactions.

These equations often are of very complicated structure and it is typically not possible to explicitly write down a solution. This

then creates the need to find efficient ways to approximate the solution using computers and fast algorithms. In order to provide accurate answers to the questions asked by engineers or biologists, the size of the problems the computer has to work with are often vast. Only efficient computational techniques are able to give satisfactory results.

For this purpose, we develop fast and robust solvers that are supported by theory and have to then be efficiently implemented in mathematical software. Our application areas are often found in fluid dynamics, image processing and chemical engineering but due to the universality of the mathematical models many of the techniques can be carried over to other sciences.

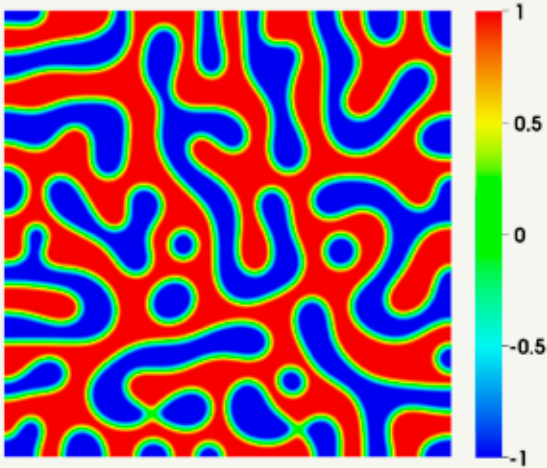
Due to the increasing dimensionality of mathematical models, where space-time formulations are combined with uncertainty



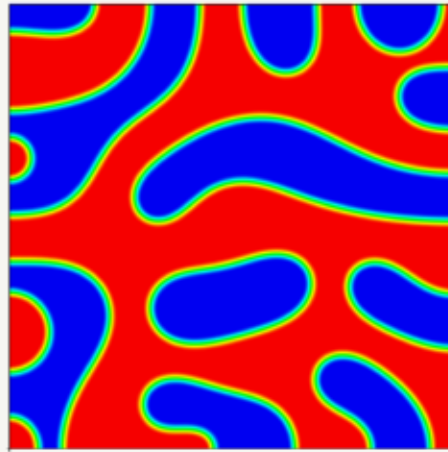
+ Martin Stoll and colleagues discussing the numerical solution of Cahn-Hilliard equations. The screen shows the adaptive refinement of the computational domain to represent regions of interest in more detail.

or nonlocal derivatives are used, we need to consider finding the solution within a lower-dimensional space that is tractable on a computer. For this we have developed algorithms fully working on these low-rank manifolds. Typical examples for these setups are questions based in uncertainty quantification or fractional differential equations.

One of our core research areas in the last year has been the solution of so-called coarsening or phase-field problems that are discussed on the following pages – in our article on Solvers for Phase-field problems.



+ **Figure 1a:**
Phase separation modeled with a Cahn-Hilliard equation; earlier time.



+ **Figure 1b:**
Phase separation modeled with a Cahn-Hilliard equation; later time.

Solvers for phase-field problems

+ The process of coarsening or phase separation is important in many application areas. One of the easiest ways to understand the meaning of coarsening can easily be tried at home. Take a mixture of oil and vinegar just as in your favorite vinaigrette. A good shake will mix both the vinegar and oil droplets but as soon as you stop shaking those tiny droplets are starting to grow and we see a coarser mixture until all the oil will sit on top of the vinegar.

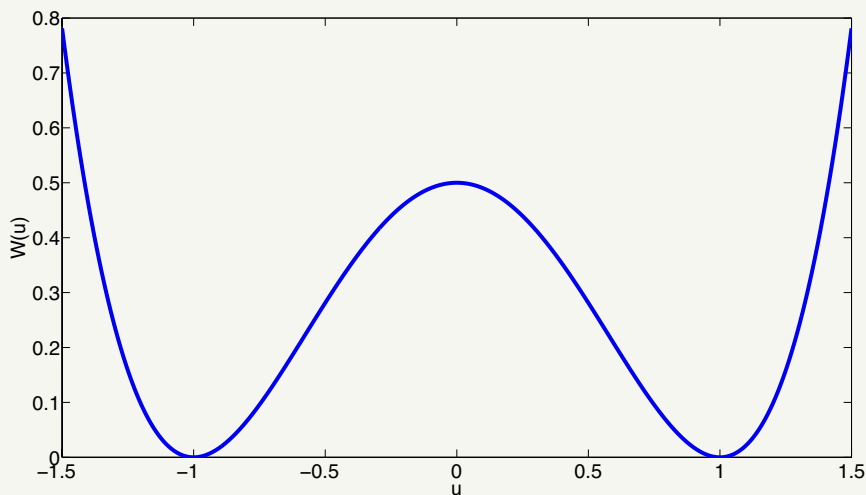
Such coarsening procedures are observed throughout all application areas and we only give a short list of some famous and not so famous ones. John von Neumann among being a brilliant mathematician and quite the party thrower observed that when you have a two-dimensional foam certain bubbles grow while others disappear. Von Neumann's law¹ as it is called today states that all cells with fewer than 6 neighbors shrink while all with more than 6 neighbors grow. Coarsening is also frequently observed in molten iron or molten rocks. Figure 1a shows the computation of an intermediate coarsening step using a Cahn-Hilliard model explained later. Figure 1b shows a later step of this coarsening procedure.

Due to the extreme conditions that one would need to create in a lab to observe molten rocks or iron it is desirable to perform adequate virtual experiments using accurate and sophisticated simulations. For this it is necessary to derive models that can capture most properties of the physical real-world system. For the process of coarsening or phase-separation the study of the so-called Ginzburg-Landau energy

$$\mathcal{F} = \int_{\Omega} \frac{\varepsilon}{2} |\nabla u(x)|^2 + \frac{1}{4\varepsilon} W(u(x))$$

is crucial. The motivation for using this energy is as follows. One replaces the assumption of only two phases by a slightly weaker one where we allow an interface of small width $(\sim \varepsilon)$ to exist between the two pure phases. For this we use the phase-field variable $u(x)$. This now allows us to explain the energy $\mathcal{F}$. The function $W(u(x))$ is a so-called double well potential shown in Figure 2, which is used in the minimization of this energy to penalize all values away from one and minus one, the pure phases. The first term $|\nabla u(x)|^2$ is large whenever u changes rapidly and hence a minimization of $\mathcal{F}$ is avoiding just these too rapid changes in u .

The minimization of these energies follows the well-known concept of gradient flows. Such gradient flows are based on the fact that $\mathcal{F}$ decreases fastest if one goes from a point in the direction of the negative gradient. Depending on the definition of the gradient taken one can now obtain different models that describe the evolution of our mixture. Two of the most well-known methods that can be derived in such a way are the Allen-Cahn and Cahn-Hilliard equations. Both of them are described by partial differential equations including nonlinear terms. This makes these equations typically hard to solve and one has to carefully devise algorithms that take the structure of these models into account. The finite element method is a classical method that allows the discretization of operators such as the ones describing the Allen-Cahn and Cahn-Hilliard equations. This method splits the domain into a large number of smaller well-studied subdomains such as quadrilaterals or triangles. The unknown solution u describing the evolution of the phases (think of this as your vinaigrette) can then be obtained by solving this equation for the collection of u values on all the corner points of the subdomains assuming that we use a certain type of quadrilateral element.



+ **Figure 2:**
Double well potential.

As the number of corner points tends to be large we store them in one large one-dimensional array called a vector. The relation between these points as induced by the partial differential equations are stored in a two-dimensional form called a matrix. The goal of all fast and accurate methods is to obtain the vector of unknowns by efficiently inverting the associated matrix. For realistic scenarios it is never feasible to use naive approaches as these require vast amounts of time and storage. In our work we develop fast solvers that iteratively solve for the unknowns by only using one sweep through the matrix with every iteration and one inversion of a simpler operator called the preconditioner. This allows us to solve for an almost arbitrary number of unknowns and different geometries.

Typically, a very large number of unknowns is necessary to provide accurate predictions that help laboratory-based scientists to make experimental decisions.

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¹ <http://de.wikipedia.org/wiki/Von-Neumann-Gesetz>



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