MAX PLANCK INSTITUTE
FOR DYNAMICS OF COMPLEX
TECHNICAL SYSTEMS
MAGDEBURG

Report 2015–2016

+ PD Dr. Yvonne Genzel
head of the *Upstream Processing team* in the *Bioprocess Engineering group*.

In the analytical laboratory, supernatant samples from bioreactor experiments are analyzed for their amino acid composition.

FREQUENTLY USED ABBREVIATIONS

Research Groups headed by MPI Directors

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

Research Groups headed by External Scientific Members

PSD	Process Synthesis and Dynamics
SCT	Systems and Control Theory

Max Planck Research Groups headed by Senior Scientists

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

Max Planck Fellow Group

DRI	Data-Driven System Reduction and Identification

Others

BMBF	German Federal Ministry of Education and Research
BMWi	German Federal Ministry for Economic Affairs and Energy
CDS	Research Center Dynamic Systems: Systems Engineering
COST	European Cooperation in Science and Technology
CPTS	Chemistry, Physics and Technology Section of MPG
DAAD	German Academic Exchange Service
DECHEMA	Expert Network for Chemical Engineering and Biotechnology in Germany (Gesellschaft für Chemische Technik und Biotechnologie e.V.)
ERC	European Research Council
DFG	German Science Foundation (Deutsche Forschungsgemeinschaft)
FVST	Faculty of Process and Systems Engineering at OVGU Magdeburg
GAMM	(International Association of Applied Mathematics and Mechanics) Gesellschaft für Angewandte Mathematik und Mechanik
IMPRS	International Max Planck Research School
LSA	German Federal State of Saxony-Anhalt
MaCS	Magdeburg Center for Systems Biology
MPG	Max Planck Society (Max-Planck-Gesellschaft)
MPI	Max Planck Institute for Dynamics of Complex Technical Systems Magdeburg
OVGU	Otto von Guericke University Magdeburg
SAB	Scientific Advisory Board
SFB TR	DFG-funded Transregional Collaborative Research Center (Sonderforschungsbereich)
SIAM	Society for Industrial and Applied Mathematics
TH	University of Applied Sciences (Technische Hochschule)
TU	Technical University (Technische Universität Berlin, Technische Universität Dortmund)

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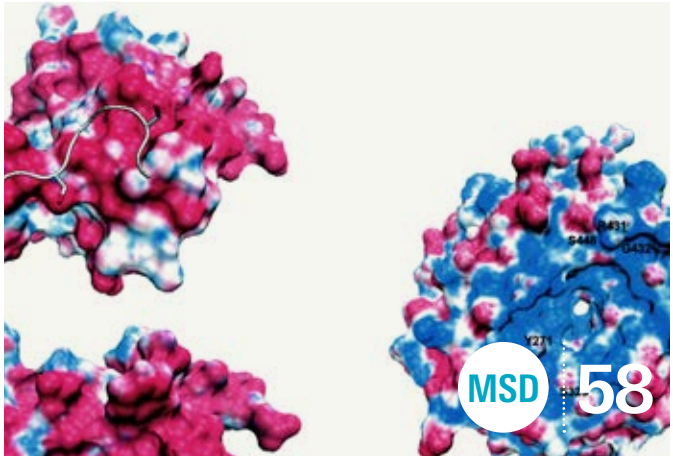
+ Research Groups

Introduction

Research Groups

Directors



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„Wie sollte man leben? In lebendiger Offenheit gegenüber allen.“

“How should one live? Showing lively openness towards all.”

(Mechthild von Magdeburg, ~ 1210 – 1283)

Mechthild of Magdeburg was a bold, well educated woman in her time. About 750 years later, in 1998, a bold team of scientists started the MPI for Dynamics of Complex Technical Systems in Magdeburg. Their mission was “To analyze, design, optimize and control advanced chemical, biological and energy conversion systems – driven simultaneously by theory and experiments.”

It's a decade since I was invited to watch and guide them as well as their dedicated colleagues as member of their Board of Trustees. I always felt very close to them in manifold ways – perhaps because I gained my chemistry degrees by calculating Dynamic-NMR-Experiments. All research group leaders “show lively openness towards all”, and thus have been following Mechthild’s advice in a dynamic and pragmatic way with confidence.

This report covers their work and achievements during 2015 and 2016. It was a very important period as the institute under the leadership of Andreas Seidel-Morgenstern had to prepare and undergo the “Extended Evaluation” by the Scientific Advisory Board and the Rapporteurs in December 2015. They passed this examination with flying colours. Congratulations to all!

The institute and its people showed stamina and have been open for new team members from many nations, high school students through lab courses, the general public during spectacular “Long Nights of Science”, as well as for new topics, new funding programs, complex interdisciplinary global projects, and new responsibilities within regional as well as international communities.

I would like to thank all members of the institute very much for their diverse initiatives and wish them a good deal of continuity. This is an important ingredient for coping with all dynamic matters ahead of all of us.

Dr. Eva E. Wille
Vice President, Executive Director, Wiley-VCH Verlag

Introduction

+ **Figure 1:**
Mostafa Mangal, Ph.D. student in the Process Systems Engineering group is supporting refugees in Magdeburg by accompanying them to public authorities and as an interpreter.

+ **Figure 2:**
Poster discussion with the Scientific Advisory Board on December 1, 2015. Professor Georges Belfort (Rensselaer Polytechnic Institute, Troy, USA) visiting our pilot scale lab and discussing research results.

Milestones of our Max Planck Institute in 2015 and 2016

With this report I would like to offer insight into some of our activities in the past two years, which were very successful for the Max Planck Institute (MPI) for Dynamics of Complex Technical Systems.

After the transition of the Presidency of the Max Planck Society from Professor Peter Gruss to Professor Martin Stratmann in 2014, several improvements related to the status and financial situation of young researchers were introduced. It is the goal of the society and our institute to substitute the provision of grants for Ph.D. students by support contracts, which offer more social benefits and security. After graduation, extensions are now possible in the frame of a so-called "Postdoc wrap up phase". In the process of implementing these changes, there are currently also several attempts to reduce the number of short term contracts for non-scientific staff.

In contrast to 2013, in 2015 and 2016 the Elbe River as our closest neighbor was luckily peaceful and very enjoyable. However, in the last two years we unfortunately witnessed an ongoing loss of political stability all over our planet. In Germany and also in Magdeburg, the demonstrations and activities of Pegida and Magida indicated an increasing xenophobia. As an internationally connected research institute with about 40% foreign Ph.D. students, we observe these developments with much concern. The "Max Planck Foundation" provided within the initiative "People for people" substantial resources for unconventional projects. These were of direct help to refugees and helped establishing sustainable supporting structures. Several of our MPI employees were and are active in projects devoted to support refugees in our city, as e.g. Mostafa Mangal (Fig.1). At the MPI, we all strive rendering Magdeburg into an even more cosmopolitan city.

The mission of our institute is to perform basic research in order to support solving difficult global problems. Thus, our work complements the activities of other research institutions, which are more devoted to applied research. To be successful both creativity and patience are needed and there is always the risk of failing. Reaching breakthroughs requires basic research to be embedded in the world-wide connected scientific community.

International recognition

I can joyfully report that the international visibility of our institute has further grown in the last two years. We will summarize selected results of our research in this report. In a couple of areas, we have acquired leading positions as confirmed just recently by our international Scientific Advisory Board (SAB). This board consists of eleven renowned scientists from five countries and is currently headed by Prof. Michael Doherty (University of California, Santa Barbara, USA). During its fifth visit from November 30 to December 2, 2015, the SAB critically evaluated our work. The triannual evaluations are always important events for us and keep the whole institute very busy for quite some period. This time the visit of our SAB (Fig. 2) was even extended and connected with

+ **Figure 3:**
Almost fourty of the 100 participants of the International Workshop on Industrial Crystallization (BIWIC) at the MPI in Magdeburg, September 6 to 8, 2016 took part in an international football tournament.

a joint comparative evaluation of three other institutes of the Max Planck Society. The report, which we received in January, 2016 and the very positive outcome of the major meeting with Professor Stratmann in the Headquarter of the Max Planck Society in Munich in September 2016, made us very happy and proud. The concluding section of the report states: "The SAB was impressed by outstanding world-class research that is performed at the institute and for the continuing development of new areas of research that evolves the institute in important new directions. The research groups are outstanding and some are among the world leaders in their fields".

New research projects and grants

The positive evaluation by our SAB was partly also due to the fact that the institute was successful in securing several new projects and research grants of significant national and international visibility. New research projects which we started in the last two years and which are funded by various sources are e.g. the Max Planck Research Network in Synthetic Biology "MaxSynBio", "MathEnergy-Mathematical key technologies for energy nets", "Production of biofuels with cyanobacteria", "Vaccine purification and formulation with magnetic sulfated cellulose particles", "Golgi Glycan Factory", "Anti-malaria drugs based on artemisinin", "Chiral polymorphism" and "Continuous Resolution of enantiomers-CORE". One highlight was that one of the highly competitive Consolidator Grants of the European Research Council (ERC) was given just recently to Dr. Steffen Klamt in order to support his research on the model-driven design of microbial cell factories in the next five years with two million Euro.

Awards and appointments

We are very proud that members of our institute received several scientific awards in the last two years. Examples are the Ph.D. Faculty Awards given in 2015 by the Otto von Guericke University to Matthias Voigt (Faculty for Mathematics), Philipp Rumschinski (Faculty for Electrical Engineering and Information Technology) and Philipp Berg (Faculty for Process and Systems Engineering). All three are graduates of our International Max Planck Research School (IMPRS). Stefan Heldt received the "Award for Medical Systems Biology" of the MTZ Foundation and Andreas Seidel-Morgenstern was honored together with Peter Seeberger from the MPI for Colloids and Interfaces in Potsdam-Golm with the "Humanity in Science Award" (issued by Phenomenex and Analytical Scientist). In 2016, Martin Stoll obtained the "Richard von Mises Award" of "Gesellschaft für Angewandte Mathematik und Mechanik (GAMM)". Furthermore, in the period of this report several of our Ph.D. students received Poster and Best Lecture Awards during major scientific conferences.

An important sign of the recognition of the work performed in our institute is also the fact that the following three of our Team Leaders received attractive offers from other research institutions and left our institute: Carsten Conradi (now Professor at the University of Applied Sciences in Berlin), Michael Mangold (now Professor for Engineering Mathematics at TH Bingen) and Michael Wolff (now Professor for Isolation and Purification of Biomolecules at TH Mittelhessen). We wish them, and also all other colleagues who left the MPI in 2015 and 2016, all the best for their future careers.

Scientific and non-scientific events

The number of scientific meetings which were organized under the active participation of members of our institute is very large. Here, I can just mention a few selected examples. Already the third Indo-German Workshop on the "Advances in Materials, Reactions & Separation Processes" was jointly organized by the Department of Chemical Engineering of the Indian Institute of Technology Guwahati and our MPI in Guwahati between February 23 and 26, 2016. This workshop was a platform to strengthen the collaborative research activities between Indian and German colleagues.

The International Workshop on Industrial Crystallization (BIWIC), chaired by Heike Lorenz, took place in the facilities of our institute

+ **Figure 4:**
4th Summer School of the IMPRS on Theory of Process Systems Engineering, August 31 to September 4, 2015.

between September 6 and 8, 2016. A highlight was the traditional football tournament with participants from more than twenty countries (Fig. 3).

The International Max Planck Research School (IMPRS) for "Advanced Methods in Process and Systems Engineering", which is jointly organized with the Otto von Guericke University, had its highlight with the 4th IMPRS Summer School on "Process Systems Engineering" between August 31 and September 4, 2015. Excellent speakers from many countries gave in our institute an overview regarding the current state of the art in this quickly developing field (Fig. 4).

The Conference on "Numerical Algebra, Matrix Theory, Differential-Algebraic Equations, and Control Theory" took place from May 6 to 9, 2015 in Berlin and brought together experts in these fields. It was dedicated to Volker Mehrmann, who is a leading expert in the areas of the conference. The 3rd "Ladies' Night for Women in the Engineering Sciences", organized by the Faculty of Process and Systems Engineering in cooperation with the IMPRS Magdeburg, was held on April 19, 2016. It provided for students and doctoral candidates an insight into the variety of academic and industrial scholarships, funding instruments and career paths.

The Magdeburg Science Night attracts thousands of visitors to open universities and research institutes every year. In 2016, 1,400 visitors came and took part in guided tours through our labs – including highly frequented special tours for children aged six to ten.

More events that took place in 2015 and 2016 will be introduced in a later section of this report.

Further activities at our institute

The first "MPI Health Day" dedicated to occupational health problems took place on October 6, 2015. Hereby, back pain is currently the number one health complaint. Musculoskeletal complaints and disorders cause a quarter of all days of incapacity to work. The program of the "Health Day" included presentations and practical exercises. Our MPI coworkers had the possibility to test yoga and back therapy training.

In January 2016, we opened our "Parent Child Office" in the MPI guest house. Two fully equipped PC workstations are available, on which parents can work while supervising their children. A baby cot and a diaper changing table complete the interior. Furthermore, there is a rest room for pregnant and nursing women. Our "Sustainability Group", newly founded in 2015 by MPI staff members, meets regularly to discuss possible ways to make the work at the institute ecologically more sustainable. The group initiated the installation of a beehive in the MPI garden (Fig. 5). The first honey was already highly appreciated.

Our now already traditional "Summer Party" is organized every year in our facilities for the staff and their families. A performance of the MPI band "MuMPItz" is always one of the party highlights. MuMPItz is a jazzband, wherein scientists are exchanging their lab or computer workplace with the rehearsal room in the MPI basement and the stage. The band performs every year also on occasion of the worldwide organized "Fête de la Musique" (Fig. 6).

Celebrations and anniversaries

On May 16, 2015, our institute had the opportunity to congratulate our Founding Director Prof. Ernst Dieter Gilles on the occasion of his 80th birthday. Due to his groundbreaking activities devoted to investigate metabolic and regulatory networks in cells and his tremendous contributions to support integrated projects between biologists, mathematicians and engineers, he is one of the pioneers of Systems Biology.

Prof. Dietrich Flockerzi celebrated his 65th birthday on August 1, 2016. With his profound knowledge in all fields of mathematics, his very broad interest and his openness to coope-

+ **Figure 5:**
Members of the MPI Sustainability Group in the garden on MPI grounds next to the guest house in spring 2016.

+ **Figure 6:**
Summer Party 2016 with MPI band MuMPItz performing live.

rate with colleagues from other disciplines, Dietrich was and is an extremely important integrator in our institute. We are happy that there is an opportunity to prolong our successful cooperation.

In August 2016, the PCF group of our institute organized a Colloquium "Trends in Chemical Process Engineering", where we could meet again many of our alumni and former colleagues working now in industry and academia either in Germany or abroad. This colloquium also gave me the chance to thank everyone for the numerous congratulations, which I received on the occasion of my 60th birthday. Finally, I would like to mention the 10th anniversary of the "Center of Dynamic Systems (CDS)", that we could celebrate on December 13, 2016. This activity was initiated by Prof. Gilles. It is now one of the research pillars of the Otto von Guericke University characterized by a strong cooperation with our institute.

Outlook

We are very happy that in 2017 our new Max Planck Fellow Prof. Dr. Athanasios C. Antoulas will start working in the institute. His research group "Data-Driven System Reduction and Identification" will deal with problems of model reduction to treat very large systems of equations and parameters.

The IMPRS will organize the next Summer School dedicated to "Decision making and uncertainty" between August 28 and September 1, 2017. We already received numerous confirmations of internationally well-known experts in this field and can guarantee an excellent program.

Due to the necessary maintenance of an old sewage channel, which was built in the 19th century and is located beneath our property, we will probably face several disturbances next summer. We hope for a rapid and reliable construction work. However, various experiences teach us (see e.g. the Airport in Berlin-Schönefeld), that also such activities carry significant uncertainties.

Altogether, we are much aware that the political situation appears to be not at all in steady state. I am convinced that in the future all of us need to be attentive, cooperative and use our common sense. At the end of my term as the managing director of the institute, I am happy to say that the MPI for Dynamics of Complex Technical Systems in Magdeburg is in good standing, scientifically and otherwise. There are still numerous large research problems open. We will tackle several of them with our interdisciplinary scientific approach. I would like to thank all members of our Scientific Advisory Board and the Board of Trustees headed by the Lord Mayor of our city, Dr. Lutz Trümper, and the Chairman of DECHEMA, Prof. Kurt Wagemann, for their strong continuous support, and of course our whole staff for its commitment and contribution to further develop the MPI.

Finally, I wish our new Managing Director Kai Sundmacher all the best for his term in 2017 and 2018.

Magdeburg, April 2017

Prof. Dr.-Ing. Andreas Seidel-Morgenstern
Director

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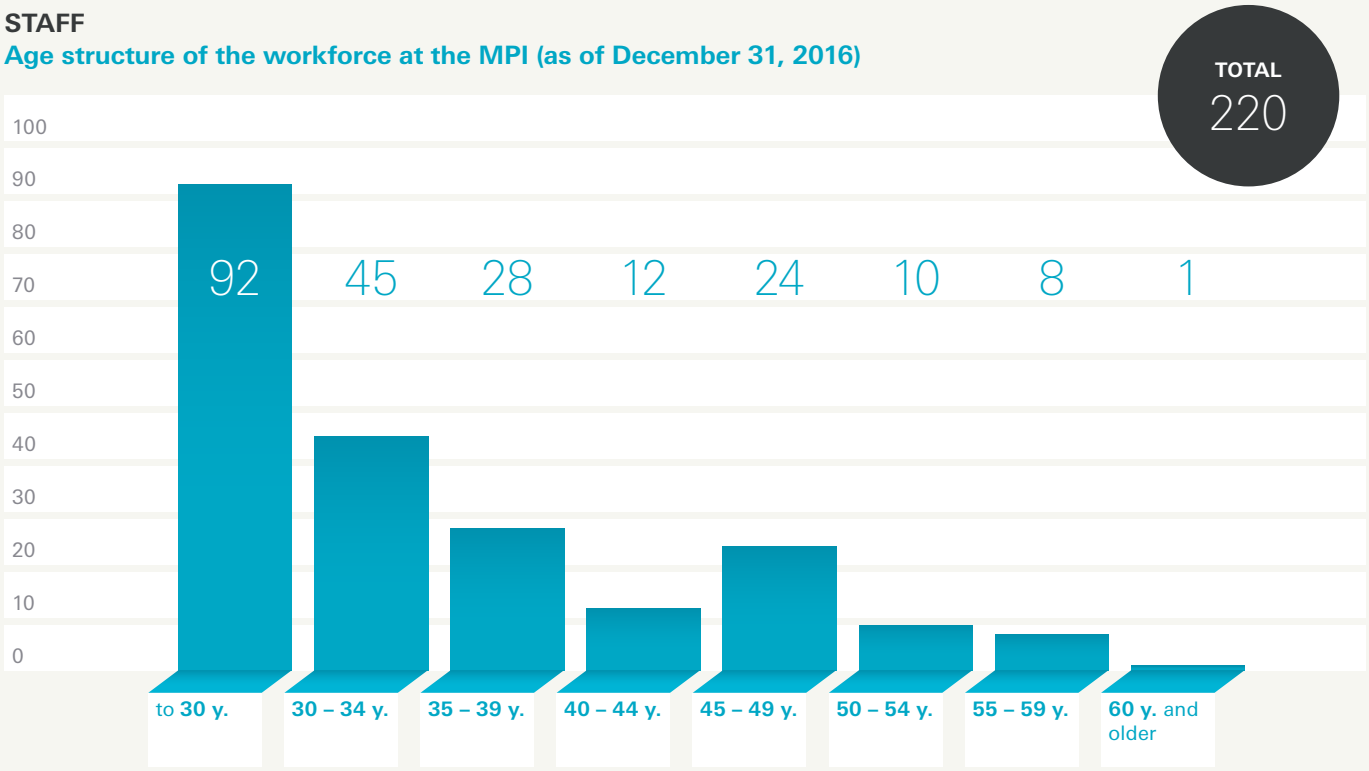
Facts and Figures

STAFF

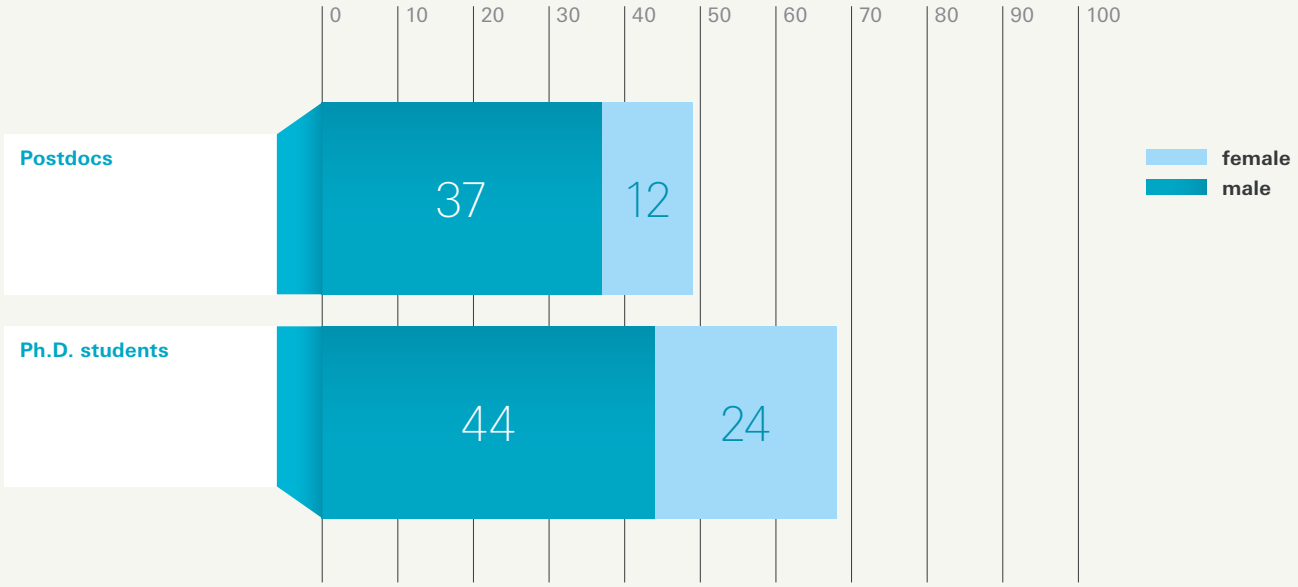
Age structure of the workforce at the MPI (as of December 31, 2016)



STAFF

Distribution of scientists by gender

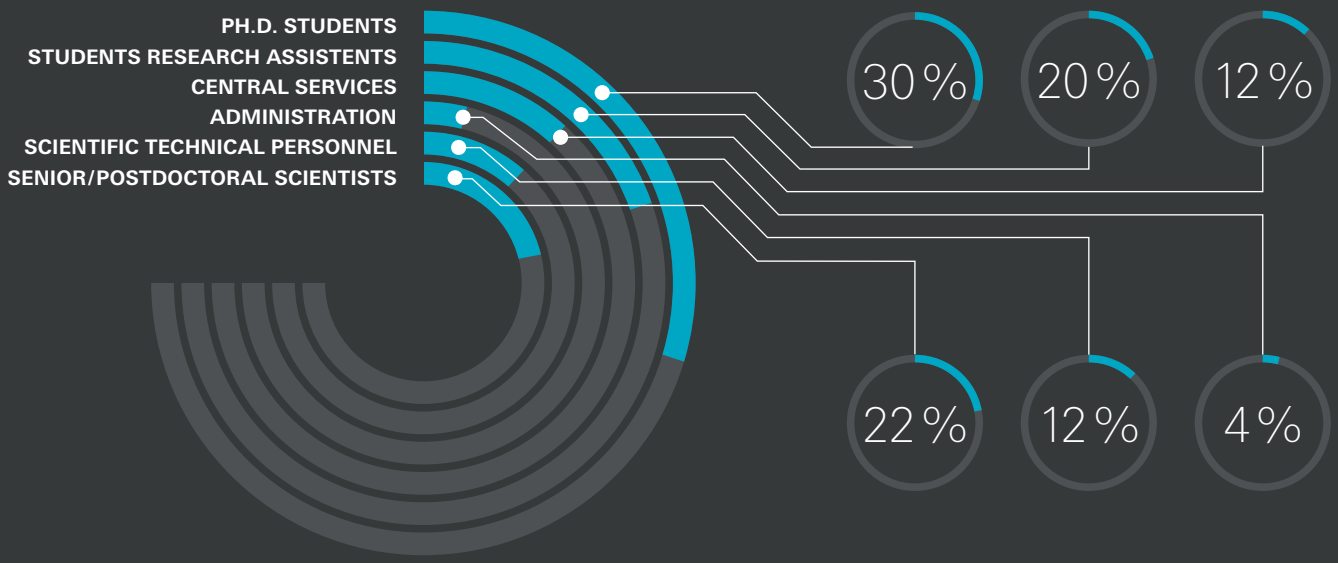
Female employees: 20% Postdocs and 40% Ph.D. students



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

STAFF

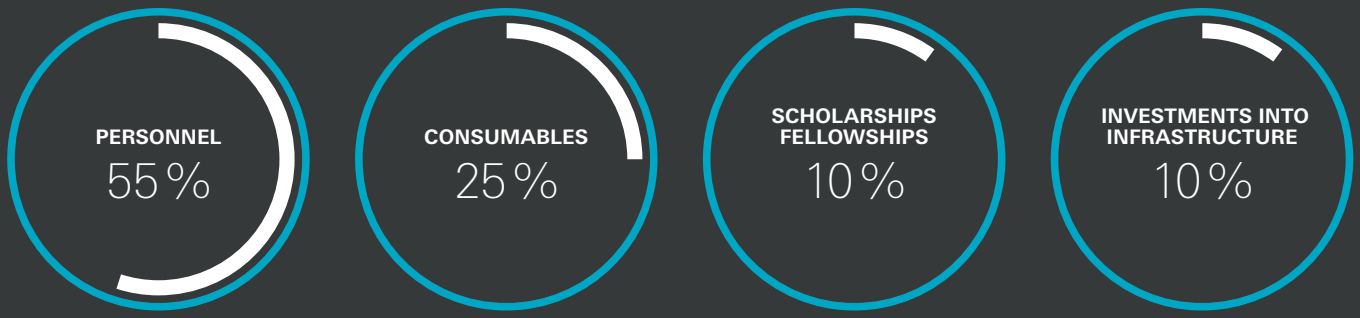
December 31, 2016: 220 Employees 117 Scientists: 49 Postdocs, 68 Ph.D. students



At the beginning of 2017, the MPI employed 220 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 2016

Total Expenses in Fiscal Year 2016: 14.77 million Euro



The total budget of the MPI in the fiscal year 2016 was 14.77 million Euro. The pie chart above shows how this was distributed to the major budget categories. As can be seen, nearly 60 % of the budget was used for salaries and scholarships.

MPI-GENERAL BUDGET 2016

Total Revenue: 14.77 million Euro Third-party funds: 1.9 million Euro

This 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.

Selected Events 2015 – 2016

A New Series of Workshops on "Power-Aware Computing"

In 2015, the CSC group established a new series of workshops. The first Workshop on Power-Aware Computing was held at the institute in July 2015. It was funded by the German Federal Ministry of Education and Research (BMBF) as part of a two-year project supporting the scientific exchange with researchers at Universidad de la República in Uruguay. Thanks to the additional support from the industrial partner MEGWARE, the workshop could be offered free of charge to all participants. One of the goals of this two-day event was to bring together the colleagues from Uruguay with German researchers who also work in the field. Additionally, it allowed the CSC researchers to strengthen on-going collaborations with researchers in Spain, Austria and Germany.

The keynote program started with an introduction to white-box modeling for the software optimization with respect to both, performance and energy consumption, given by Georg Hager. It continued with a survey on energy-saving techniques in linear algebra computations by Enrique Quintana-Ortí. The program ended with a very practical presentation on the first steps towards the realization of a low-power HPC computing center exclusively powered by renewable energies given by Markus Geveler. The remaining contributions had a similarly broad topical range, and were continued in many fruitful discussions mingling the theoretical and practical experiences. The second workshop in the series will take place at the Max Planck conference center Ringberg Castle in July 2017. It will feature four keynote and three invited speakers with remarkable contributions in the area (More info at http://www.mpi-magdeburg.mpg.de/csc/events/paco17). **I Dr. Jens Saak**

Hybrid Modeling Summer School

The second Hybrid Modeling Summer School, jointly organized by members of the BPE research group and the New University of Lisbon, was held from 7th to 9th of September 2015 at the Max Planck Institute (MPI) Magdeburg. PD Yvonne Genzel, leader of the Upstream Processing team at the BPE group, welcomed the participants to the Summer School, the MPI and the city of Magdeburg.

In total, 26 participants from 7 European countries attended this theoretical and practical course. Attendees comprised Ph.D. students, postdoctoral researchers and professionals from industry and academy, seeking for methods to improve the modeling of complex (bio)processes. During the three-day

+ Hybrid Modeling Summer School 2015 in Magdeburg

+ GAMM Workshop on "Applied and Numerical Linear Algebra" 2015 in Magdeburg

course, hybrid modeling fundamentals and their application were presented by leading experts from industry (e.g. Dr. Thomas Mrziglod, Bayer Technology Services GmbH, Leverkusen, Germany) and academia (e.g. Prof. Rui Oliveira, New University of Lisbon, Portugal). Furthermore, participants were able to apply hybrid modeling for typical bioprocess engineering during the 3 + 3 h practical course. An important focus of the "hands-on" section was the application of hybrid modeling within the "Quality by Design" framework, as promoted by the Process Analytic Technology initiative (PAT).

Participants were able to introduce themselves and their research work in form of short pitch-presentations. To incentivize the networking and additional discussions, coffee breaks, lunches and BBQ were provided at the MPI. Participants could also appreciate the historical heritage of the City of Magdeburg with a short tour through the "Straßen der Romanik" around the Magdeburg Cathedral and a closing dinner nearby.

As a closing wrap-up, a panel discussion was led by the co-organizer Dr. Moritz von Stosch and Dr. Thomas Mrziglod, around the perspectives of hybrid modeling and the creation of a tighter community. A very positive feedback was obtained from the participants, who were willing to build up a community for future information, discussion and collaboration within the field. **I Daniel Vazquez Ramirez**

GAMM Workshop on "Applied and Numerical Linear Algebra"

The GAMM activity group on Applied and Numerical Linear Algebra continued its long tradition of annual workshops in July 2015 at the Max Planck Institute for Dynamics of Complex Technical Systems. The theme of the workshop was large-scale network computations, a topic relevant to fields ranging from systems biology to recommender systems.

The three invited speakers were Michele Benzi (Emory University, USA), Ernesto Estrada (University of Strathclyde, UK), and Caren Tischendorf (Humboldt University, Germany), all world-renowned experts that shared their latest research in keynote presentations with the international audience attending the workshop. With over 50 attendees and more than 25 talks coming from both experienced researchers to young Ph.D. students, the workshop was an exciting opportunity to learn about the state of the art in numerical linear algebra.

Professor Benzi and Professor Estrada discussed communicability and geometry of complex networks with applications found in areas such as molecular structures. Caren Tischendorf from the Humboldt University in Berlin discussed aspects of differential algebraic equations in structured networks.

In addition to these three execellent lectures, the contributed talks discussed numerical aspects of problems, such as the curse of dimensionality, eigenvalue problems from control theory or the reduction of model complexity in various application areas. Besides the great research presented the workshop allowed for vibrant discussions after talks and over coffee. And additionally, we shared a beautiful conference dinner overlooking the cathedral and the Hundertwasserhaus (Grüne Zitadelle). **I Dr. Martin Stoll**

+ MaxSynBio Symposium 2015 in Potsdam

MaxSynBio Symposium

"Synthetic Biological Systems: From Molecules to Functional Modules" was the title of the first Symposium of the Max Planck research network MaxSynBio which took place on 24/25 September 2015 in Potsdam. MaxSynBio is a research network of the Max Planck Society jointly funded by the Bundesministerium für Bildung und Forschung (BMBF, Federal Ministry for Education and Research of Germany). In MaxSynBio, scientists from nine Max Planck Institutes work together to build modules for synthetic cells following the bottom-up approach of synthetic biology. The research on synthetic life is monitored by a group of scientists working in the field of Responsible Research and Innovation (RRI) at the Friedrich Alexander University in Erlangen-Nuremberg.

The symposium took place roughly one year after the start of MaxSynBio in summer 2014 and was hosted by the Max Planck Institute of Colloids and Interfaces which also participates in the research network. Over sixty scientists from all collaborating institutes participated in the meetings. Several international speakers were invited including Prof. Stephen Mann from University Bristol, David Weitz from Harvard University and Bartosz Lewandowski from ETH Zurich. The first day of the meeting focused on the question which microcompartments would be suitable as a platform to build modules for synthetic cells, how to manipulate and analyze them. Related topics such as protein expression in synthetic compartments and light controlled organization of biomolecules were discussed on the second day. The Max Planck Institute for Dynamics of Complex Technical Systems was represented by 13 scientists and contributed two presentations on "Bringing the parts together – Steps towards an in-silico protocell" by Prof. Michael Mangold and "Bottom-up synthesis of energy and metabolism pathways" by Dr. Ivan Ivanov. The symposium was organized by the members of the MaxSynBio coordination office (Jeannette Helbing, Dr. Jakob Schweizer, Prof. Kai Sundmacher) which is located at the Max Planck Institute in Magdeburg. **I Dr. Jakob Schweizer**

1st Symposium on "Advances and Applications in Metaproteomics"

In February 2016, the Bioprocess Engineering Group at the Max Planck Institute Magdeburg organized the 1st Symposium of Advances and Applications in Metaproteomics.

Microbiomes are essential for human health and global nutrient cycles as well as for the production of renewable energy from biomass. Meanwhile, the progress of mass spectrometry allows the taxonomic and functional description of microbiomes on protein level supplementing metagenomic approaches. After ten years of research in the fields, fifty scientists from Europe and USA used the symposium for an inspiring scientific exchange. Paul Wilmes (Luxemburg), a pioneer of metaproteomics, pointed in his presentation to synergies of combining metaproteomics with other multi-omics approaches. Further presentations dealing with the microbiome of human gut, rumen, soil and biogas plants confirmed this trend. The importance of reproducible strategies for data aquisition was underlined by Robert

+ Sino-German Symposium on "Modelling, Model Reduction, and Optimization of Flows" 2016 in Shanghai

Hettich (Tennessee). Martin von Bergen (Leipzig) presented protein-SIP applying stable isotopes for elucidation of metabolic interactions. All speakers agreed that the high complexity of samples is a major challenge in metaproteomics. Thus, Lennart Martens (Gent) requested the development of adequate bioinformatic tools for metaproteomics.

The new MetaProteomeAnalyzer software integrates a complete bioinformatic workflow in a graphical user interface and meets some of these expectations. The software developed by the Max Planck Institute Magdeburg in collaboration with the Otto von Guericke University Magdeburg was presented in a post symposium workshop.

Finally, all attendees agreed to collaborate and to promote metaproteomics as an essential tool in microbiome research. A follow-up symposium is scheduled for June 2017 in Sardinia.

I Dr. Dirk Benndorf

Sino-German Symposium on "Modelling, Model Reduction, and Optimization of Flows"

In September 2016, a workshop on "Modelling, Model Reduction, and Optimization of Flows" was organized by the Shanghai University and the Max Planck Institute Magdeburg. The joint idea and realization of the workshop was a result of the close ties between Magdeburg and Shanghai established by the former MPI postdoc Dr. Xin Du. Supported by the *Chinesisch-Deutsches Zentrum für Wissenschaftsförderung* (CDZ), 14 scientists, mainly from Germany (including the MPI Researchers Peter Benner, Jan Heiland, and Yue Qiu) and 25 from China gathered in Shanghai, China, to discuss various aspects of the simulation of flow phenomena.

The four days of the workshop started with an opening ceremony that comprised welcome speeches by Prof. Min Wang (vice president of the Shanghai University), Prof. Lesheng Chen (vice director of the CDZ), and Prof. Peter Benner (MPI). Just like the participants, the presented topics were diverse.

Within the four days of the workshop, the full range of modelling, model reduction, simulation, optimization, and industrial applications was covered. Nevertheless, the common divisor – fluids and flows – ensured that every talk was well perceived in the audience. Every single talk triggered at least a few questions, while certain talks ignited discussions that went well over the coffee break. The presented works also gave bases for the search for common ground and a possible cooperation. Apart from the scientific aspects, the participants from Europe obtained general and valuable insights into the Chinese academic ecosystem.

A glimpse on the cultural heritage of China was taken during an excursion to the ancient water town Zhouzhuang on the last day of the workshop. First results of the new Chinese-German cooperation may well be presented at the second edition of the MMOF that is planned for 2019 in Germany.

I Dr. Jan Heiland

+ Reduced Basis Summer School 2016 in Hedersleben

23rd International Workshop on "Industrial Crystallization (BIWIC 2016)"

From September 6 to 8, 2016, we hosted the 23rd International Workshop on Industrial Crystallization (BIWIC 2016) at the Max Planck Institute in Magdeburg. The annual meeting, held in the last years in Delft, Tianjin, Odense, Rouen and Daejeon, brings together scientists and engineers from academia and industry to present and discuss the current work and also to identify challenging fields of research of both fundamental and industrial interest.

It was our pleasure to organize it for the 2nd time after 2008 and to welcome almost 100 participants from 22 countries all over the world. 78 contributions were given as oral or poster presentations addressing topics that reflect key applications and recent trends of crystallization as 1) fundamentals of crystallization, 2) separation and formulation in life-science industries with applications in food, pharmaceuticals and agrochemical sectors, 3) monitoring and modeling of crystallization processes and 4) crystallization for sustainability.

Beside the scientific sessions, the traditional football match (40 players, Ph.D. students as well as professors) and a conference dinner in the historic walls of the "Festung Mark" offered plenty of opportunities to exchange experiences, initiate collaborations and, for the Ph.D. students, to meet international experts in an informal atmosphere. With this 23rd event, we bid farewell and thanked Prof. Joachim Ulrich, the initiator of the BIWIC conference in 1990, for shaping and evolving it into a real international forum of the crystallization community. Overall, it was again a successful BIWIC fruitful and enjoyable both from the scientific and the social point of view. I **apl. Prof. Dr. Heike Lorenz**

Reduced Basis Summer School

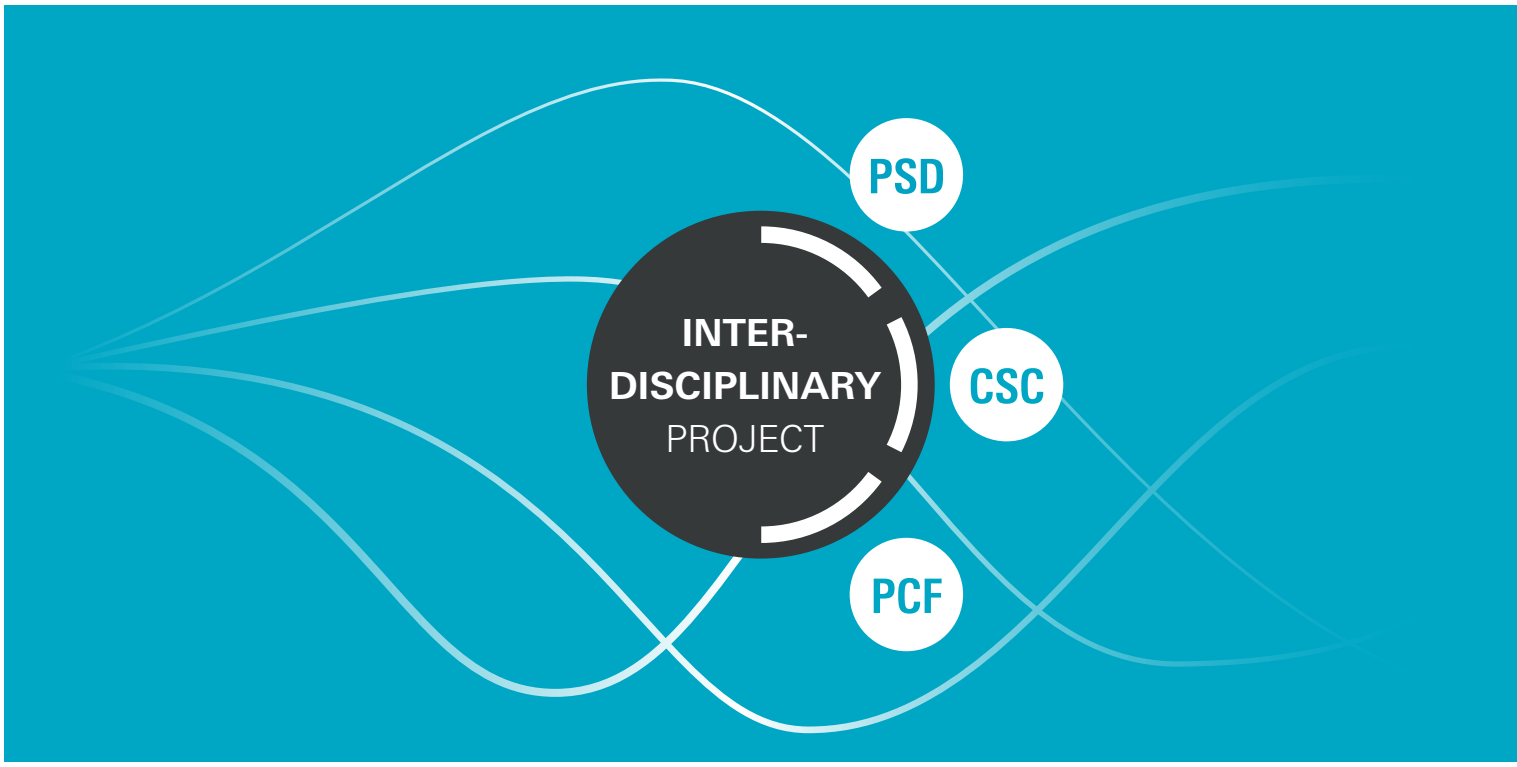
The 6th Reduced Basis Summer School, organized by the CSC research group, was held from 4 to 7 October 2016 in Kloster Hedersleben (Hedersleben, Germany). It aimed at Master and Ph.D. students working in the field of model order reduction (not limited to reduced basis methods). As the main purpose was getting to know each other, participants were encouraged to give talks about their research. There were 31 participants: 20 of them came from Germany (including 6 Ph.D. students from the CSC group), while the other 11 participants came from India and 7 European countries.

On Tuesday morning, Lihong Feng welcomed the participants and officially opened the event. In the following days, almost all participants presented their latest research results and open problems, stimulating plenty of discussions. On Thursday, Serkan Gugercin (Virginia Tech) gave a tutorial talk on interpolatory model order reduction methods for linear and nonlinear systems. Peter Benner closed the event with concluding remarks on Friday before lunch.

To promote social interactions, an excursion was organized to the nearby city of Quedlinburg for Wednesday afternoon, where students saw the sights and went for coffee and cake in one of the local cafés. On Thursday evening, a campfire was prepared at the Kloster, where participants made bread on a stick, baked marshmallows, and prepared s'mores.

In conclusion, the participants will remember fondly the time they spent with other students sharing similar interests and they are looking forward to meeting again in the next Reduced Basis Summer School. I **Petar Mlinarić**

+ Research Groups



MATHEMATICAL CONTROL THEORY FOR HIGH-PERFORMANCE SEPARATION TECHNIQUES

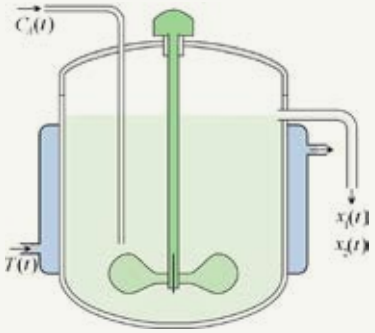
The project "Control and Stabilization of Distributed Parameter Systems with Application to Crystallization Processes and Chromatography as High-Performance Separation Techniques" was launched in May 2015 under the support of the Strategic Innovation Fund of the Max Planck Society. The goal of this project is to develop new mathematical methods for process control and to solve the stabilization problem for a class of prototype processes in chemical engineering.

The class of systems under consideration includes mathematical models of crystallization processes and a moving bed chromatography for the production of high-purity products. The scientific importance of this research is underpinned by the development of a new research field in the intersection of the partial stability theory for distributed parameter systems and the process control in chemical engineering. As for the science organization added value, this project aims to establish a new link between the research groups on Computational Methods in Systems and Control Theory (CSC), Process Synthesis and Process Dynamics (PSD), and Physical and Chemical Foundations of Process Engineering (PCF).
A mathematical model of a moving bed chromatographic process is considered by using the material balance of the solutes in both liquid and solid phases. This model is represented as a control system of first-order quasilinear partial differential equations with respect to the concentrations of the components. We have analyzed the reachable sets for such a system by using the volumetric flow rate ratio of both phases and concentrations at the inlet of the column as controls. This study also results in a solution of the steering problem for quasilinear hyperbolic systems by using a family of finite-dimensional optimal controls and spillover analysis of the residual dynamics[1]. From a practical viewpoint, this investigation is motivated by the requirement to estimate the quality of separation depending on parameters of the operating envelope of a chromatographic process. The theoretical outcome of this work comprises sufficient controllability conditions and the construction of a family of open-loop controls that solves the steering problem.

In this project, we also consider a class of quasilinear partial differential equations that represent the dynamics of particulate processes. We represent these equations as an abstract differential equation in a suitable Hilbert space. This abstract differential equation admits an equilibrium which is not asymptotically stable in the general case. To stabilize the equilibrium, we apply a finite-dimensional control in the right-hand side of the abstract differential equation. We use a quadratic Lyapunov functional to construct a bounded feedback law provided that the state of the system is fully observable. Then, the limit behavior of the trajectories is analyzed by means of LaSalle's invariance principle. In particular, it is shown that the equilibrium of the closed-loop system is asymptotically stable under additional assumptions concerning the Fourier transform of the control coefficients.

The computational aspects of this project are illustrated by solutions of the stabilization problem for reduced models of continuous crystallization processes. We study the class of reduced models governed by nonlinear ordinary differential equations under the assumption that the controllability rank condition is ensured by the first order Lie brackets[3]. We exploit a natural analogue between nonlinear hyperbolic equations and finite-dimensional systems of nonlinear oscillators. For this class of ordinary differential equations with

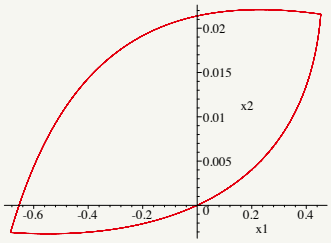
a)



+ Figure 1 a:
Schematic representation of a CSTR with two periodic inputs:
C_A – inlet concentration of A;
T – inlet temperature.

+ Figure 1 b, c, d:
Periodic trajectories satisfying the necessary optimality conditions:
x_1 – dimensionless outlet concentration of A,
x_2 – dimensionless temperature [6].
The point $x_1=x_2=0$ corresponds to a steady-state operation with constant controls.

b)



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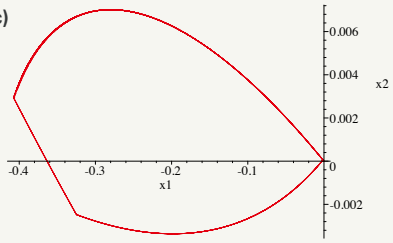

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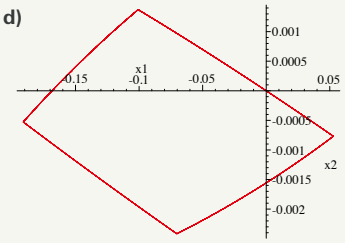

strong nonlinear effects, the problem of defining a stabilizing feedback law remained challenging.
To overcome this difficulty, we have proposed an extension of Lyapunov's direct method by using the Volterra series representation of solutions instead of using the time-derivative of a Lyapunov function [2], [4]. Then a family of trigonometric controls is used to approximate the gradient flow associated with such a Lyapunov function. These controls are applied for the derivation of a time-varying feedback law under a sampling strategy. An advantage of this approach lies in the reduction of the stabilization problem to solve a certain system of algebraic equations with respect to the control parameters. The solvability of these algebraic equations is proved by employing fixed point theorems in the general case [5]. Furthermore a numerical scheme is proposed for a particular class of prototype systems. These theoretical results of fundamental importance in systems and control theory are applied for the control design of a continuous crystallization process.

As part of this project, we have studied the optimal control problem for a continuous stirred tank reactor (CSTR) that represents a reaction of the type "A → product". The reactor dynamics is described by a nonlinear system of ordinary differential equations controlled by two inputs: the inlet concentration and the inlet temperature (Figure 1). We formulate the problem of maximizing the average product of this reactor for a fixed consumption of the input component over a period of time. This kind of isoperimetric optimal control problem is analyzed by using the Pontryagin maximum principle with Lagrange multipliers. We show that the optimal controls are bang-bang and propose an upper bound for the number of switchings for the linearized problem with periodic boundary conditions [6]. Numerical simulations confirm that our control strategy can be used to improve the reactor performance over a specified period of time in comparison to the steady-state operation. **I Dr. Alexander Zuyev**

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Alexander Zuyev received his Diploma with Honors in Mathematics from Donetsk National University in 1997 and a Ph.D. degree in 2000 from the Institute of Applied Mathematics and Mechanics, National Academy of Sciences of Ukraine (IAMM NASU). He was a visiting scientist at the Abdus Salam International Centre for Theoretical Physics under the aegis of UNESCO and IAEA in Trieste and received the Alexander von Humboldt Research Fellowship at TU Ilmenau and the University of Stuttgart. Since his habilitation in 2008, he has been working as a Professor at Donetsk National University and a Leading Researcher/Department Head at IAMM NASU. Alexander Zuyev joined the CSC Group at the MPI Magdeburg in November 2014.

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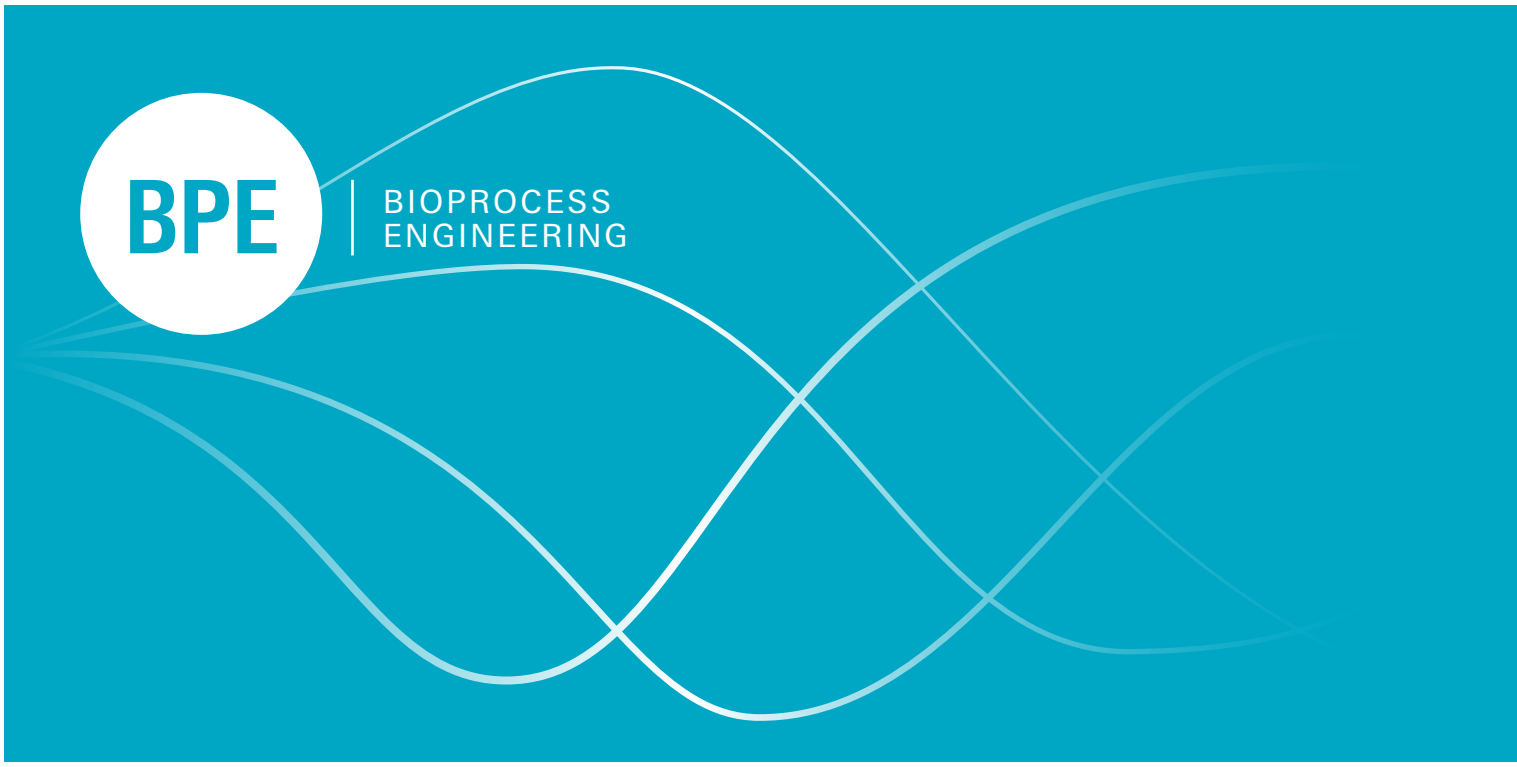

PROF. DR.-ING. UDO REICHL I DIRECTOR

Bioprocess engineering covers the use of microorganisms in the production of industrial bulk products and in the manufacturing of specialized biopharmaceuticals. In addition, bioprocess technology plays an important role in biofuels production, waste water processing, and solid waste treatment. The design and optimization of bioprocesses from an engineering as well as from a biological point of view requires the integrated use of different biological systems and in their chemical background, dedicated equipment, software tools, and molecular biology techniques. Additionally, a wide range of assays for process monitoring and a comprehensive set of analytical "omics" technologies need to be applied. The challenge we are facing today: How to achieve an increase in product yields, establish new methods for process intensification, and reduce time to market while warranting efficacy and safety of drugs.

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

The **Upstream Processing team** (PD. Dr. Yvonne Genzel) characterizes growth and product formation of several cell lines (adherent and suspension growth) in combination with different viruses (influenza, Modified Vaccinia Ankara, attenuated yellow fever, Japanese encephalitis, Zika) to optimize vaccine production in bioreactors including stirred tanks, hollow fiber-based systems, and disposable units. In addition, advanced cultivation strategies are being developed to further improve process performance and to increase virus yields. The experimental data obtained are used by the **Mathematical Modeling team** (Prof. Udo Reichl) to quantitatively analyze fundamentals of cell metabolism and cell growth. In addition, models are being used to simulate intracellular virus replication and to investigate infection dynamics in bioreactors. On the experimental side, virus-host cell interactions are studied in detail by the **Molecular Biology team** to identify bottlenecks in virus replication. Virus replication dynamics are investigated by a combination

+ A Ph.D. student is monitoring data measured with a cross-flow system to design and optimize a process for virus particle purification.

of classical virus quantification assays and state-of-the-art methods such as quantitative real-time PCR and imaging cytometry. With a focus on proteomics, glycomics, and glycoproteomics, the **Bio/Process Analytics team** (Dr. Erdmann Rapp) is developing a set of bioanalytical tools for the in-depth analysis of protein expression levels and post-translational modifications of proteins. Finally, the design and the optimization of process trains to purify virus harvests, guaranteeing high yields at low contamination levels of the final product, are performed by the **Downstream Processing team** (Dr. Michael Wolff).

In 2016, the Upstream Processing team continued its efforts towards process intensification by optimizing perfusion strategies for high cell density cultivations and by developing options for continuous vaccine production in tubular bioreactors. To complement these activities, simulated moving bed processes using membrane adsorbers were established by the Downstream Processing team. In addition, as a new tool for the fast screening of new vaccine candidates, the use of sulfated magnetic beads for the immunization of mice against influenza was demonstrated successfully. Within the scope of the CellSys project (BMBF funding) numerous cell lines were generated to investigate options to improve the virus replication in animal cells by overexpression and knock down of targets identified in a large screen for influenza A virus propagation. To support these activities and to characterize virus dynamics of promising cell lines, comprehensive simulation studies were performed by the Mathematical Modeling team. Assisted by substantial third party funding from the European Commission and the BMBF, Bio/Process Analytics could further extend their glycoanalytical methods portfolio to mass spectrometry based peptide- and glycopeptide-mapping. Further, a longitudinal study of the human plasma N-glycome (running over six years) could be published. Here, for the first time the big potential of longitudinal glycobiomarker discovery studies could be demonstrated, which is an important step towards personalized diagnostics.

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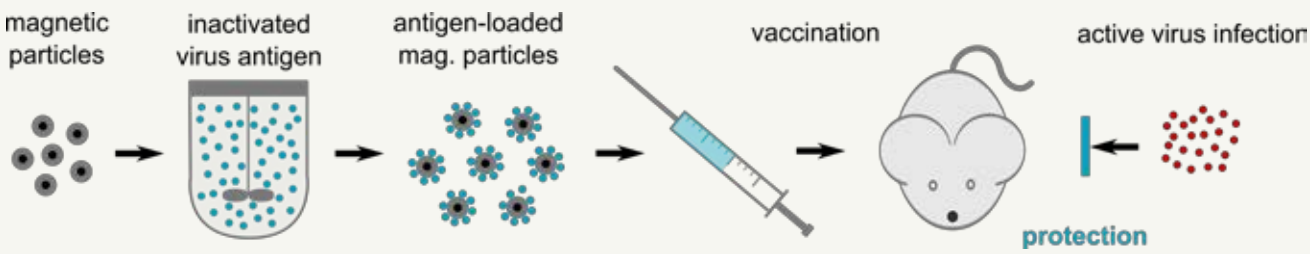


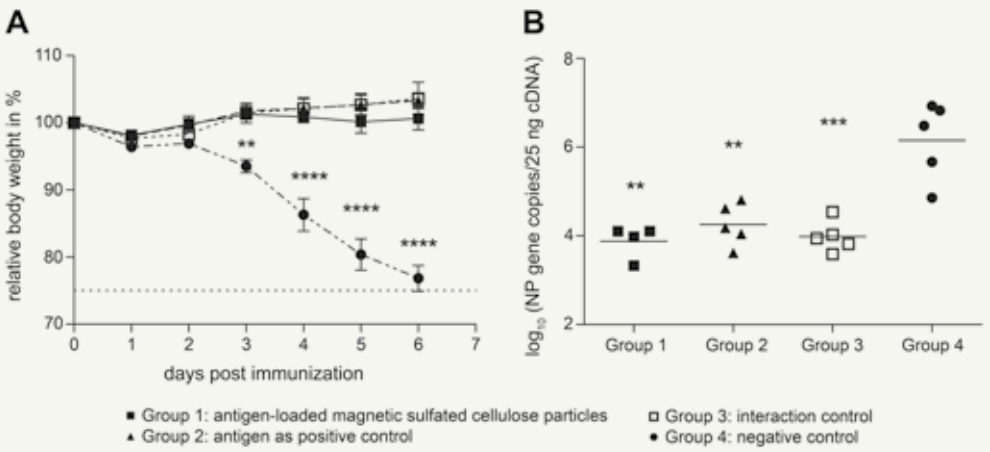
Figure 1:
Experimental scheme for the immunization of mice using a newly developed magnetic sulfated cellulose particle vaccine system. The inactivated antigen (influenza A virus particles) is bound to magnetic sulfated cellulose particles and directly used for the formulation of vaccine candidates.

Purification of Influenza Virus Vaccines Using Magnetic Sulfated Cellulose Particles

The production of viral vaccines usually employs a set of different unit operations where formulation and filling are the final steps of the so-called downstream processing. However, downstream processing can be highly complex, expensive, and hard to realize in research laboratories focusing on the development of novel vaccine candidates. Moreover, there are no real ready-to-use tools for high-throughput screening to speed up the development of downstream processing of whole virus particles. Because of these needs, we developed a new platform based on magnetic sulfated cellulose particles[1] for easy and straightforward whole virus particle purification that can additionally be used for the formulation of vaccine candidates.

Proof of concept was carried out with an influenza A/Puerto Rico/8/1934 (H1N1) whole virus vaccine for the immunization of mice (Figure 1). The virus particles were produced in suspension Madin Darby canine kidney cells, harvested, clarified, chemically inactivated, and concentrated using an in-house standard protocol. After diafiltration to low salt buffer, the virus was bound to the magnetic sulfated cellulose particles. In a next step, these antigen-loaded particles were washed and resuspended in formulation buffer to obtain the ready-to-use influenza vaccine. The immunization experiment consisted of four groups: Group 1: immunization with antigen-loaded magnetic sulfated cellulose particles; Group 2: positive control, Group 3: magnetic sulfated cellulose particles with separate antigen as particle antigen interaction control; Group 4: negative control. The injection scheme involved a first injection followed by a booster injection to induce a potent immune response. After immunization, the mice were challenged with a lethal virus dose to verify the protective features of the influenza vaccine based on the antigen-loaded magnetic sulfated cellulose particles (Figure 2).

The results obtained showed similar high anti-influenza antibody levels in mice immunized with antigen-loaded magnetic sulfated cellulose particles (Group 1) and antigen-containing controls (Group 2 and 3). All three groups did not show any weight loss after the challenge. The untreated mice showed no antibody levels and a significant weight loss after the challenge (Figure 2a). In addition, the mice's lungs of the negative control (Group 4) showed a 400-fold increase of influenza nucleoprotein gene copies, indicating a high virus load, when



+ Figure 2a:
Relative body weight changes in mice after a lethal challenge (n = 4–5 mice/group, mean ± SEM, ** $p < 0.001$, **** $p < 0.0001$).

+ Figure 2b:
Estimation of viral load at day 6 post infection by real-time PCR (** $p \leq 0.002$, *** $p \leq 0.0009$).

compared to mice immunized with antigen-loaded magnetic sulfated cellulose particles (Group 1, Figure 2b).

In summary, the use of magnetic sulfated cellulose particles for purification and formulation of influenza vaccines proved to be practicable and showed excellent protection after a lethal virus challenge. Besides, such a process has the potential to be implemented directly after the virus production for a single step purification of virus particles and formulation of vaccines. Because of these advantages, possible applications range from studies in research and development to manufacturing of veterinary vaccines. In addition, optimized magnetic sulfated cellulose particle systems could be of interest for applications in the medical field including vaccine delivery and gene therapy.

This project was carried out in collaboration with Sarah Frentzel (University Hospital of the Otto von Guericke University Magdeburg) and Dunja Bruder (University Hospital of the Otto von Guericke University Magdeburg and Helmholtz Centre for Infection Research), who designed and carried out the immunization studies. **I Michael M. Pieler**

Reference:
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Author **Michael M. Pieler**

Michael M. Pieler studied Biotechnology at the University of Natural Resources and Life Sciences in Vienna/Austria. In 2012, he received his Master degree after completing a thesis on real-time high resolution melting analysis of surface immobilized nucleic acids at the Austrian Institute of Technology. He then joined the Bioprocess Engineering Group at the Max Planck Institute where he conducts his Ph.D. thesis on virus particle aggregation and downstream processing of vaccines.

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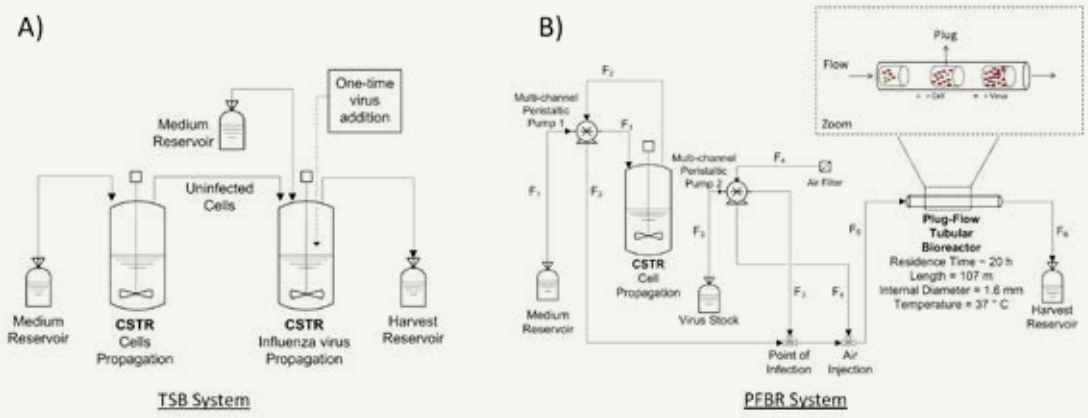


+ Figure 1:
Diagrams of the two continuous bioreactor systems that have been used for influenza virus production.

+ Figure 1 a):
The two-stage stirred tank bioreactor (TSB) system consists of a continuous stirred tank reactor (CSTR) for cell production linked to a CSTR for influenza virus propagation. At the beginning of the production phase the virus seed is added once in the second vessel where it continuously replicates (residence time: 25 h, production rate: 0.33 mL/min).

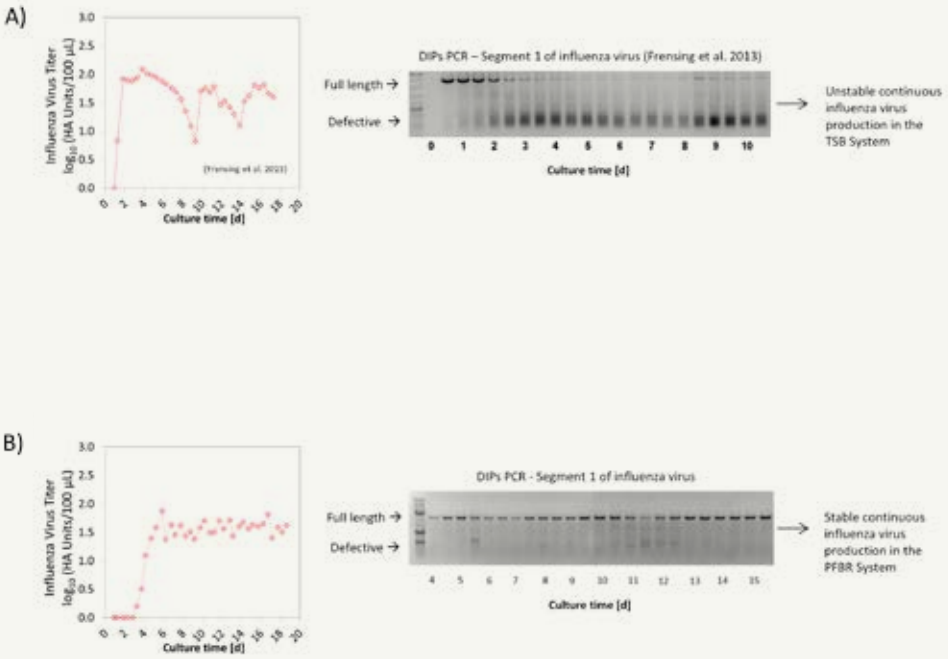
+ Figure 1 b):
Plug-flow tubular bioreactor (PFBR) system developed at the MPI Magdeburg. This bioreactor consists of a CSTR for cell production linked to a plug-flow tubular bioreactor for virus propagation. The PFBR has a length of 107 m and an internal diameter of 1.6 mm (residence time: 20 h; production rate: 0.20 mL/min).

A Novel Tubular Bioreactor for Stable Continuous Production of Influenza Virus Vaccines

According to the World Health Organization, an estimated number of 1.4 billion doses of seasonal influenza vaccines are produced each year to protect high risk human populations against the disease [1]. These vaccines are traditionally produced in fertilized chicken eggs, but cell culture-based batch processes are being established since several years as an alternative [2]. In particular, these new processes offer a more flexible production technology in an aseptic environment and help to overcome problems related to the adequate supply of eggs and the lead time in case of influenza pandemics. Nevertheless, the challenge in influenza vaccine production for the next decades will be to further increase the global production capacity, ensure easy and fast access to seasonal and pandemic vaccines to low-income regions [1], and to develop more efficient and flexible viral vaccine production platforms.

One approach that can significantly increase the productivity and reduce costs of viral vaccine manufacturing is the establishment of continuous processes. Vaccine production in continuous mode can be faster than today's batch-operated systems because they do not require cleaning and sterilization steps between batches. In addition, continuous processes have only a small footprint due to smaller bioreactor sizes, and they can provide more consistent and higher product quality.

One bioreactor system that has been proposed for continuous virus production is a cascade of two stirred tank bioreactors (TSB system; Fig 1a). In this system, cells are propagated under steady-state-conditions in the first stirred tank bioreactor (CSTR), and continuously transferred to a second CSTR where virus infection, propagation and continuous harvest take place. Although continuous virus replication in this system is possible, major drawbacks involve the risk of unwanted antigenic variations over process time, and the accumulation of defective interfering viral particles (DIPs) in the virus population. In particular, DIPs can accumulate in the bioreactor, and cause oscillations in virus titers resulting in low productivity levels, known as "von Magnus effect". This phenomenon was observed recently over 18 days of continuous influenza virus propagation using a duck cell line and the influenza A/Puerto Rico/8/1934 (H1N1) virus strain. Influenza virus titers oscillated over several orders of magnitude, and a polymerase chain reaction (PCR) analysis showed unstable segment patterns confirming DIPs accumulation (Fig. 2a) [3].



+ Figure 2:
Comparison of continuous influenza virus production using the TSB and the PFBR bioreactor system.

+ Figure 2a):
In the TSB system, influenza virus titers oscillated during production time (left). This oscillation was due to the accumulation of defective interfering particles (DIPs), as confirmed with a polymerase chain reaction (PCR) analysis specific for influenza virus (right).

+ Figure 2b):
With the PFBR system, stable influenza virus titers were obtained (left). A DIPs PCR analysis (right) showed a stable DIPs and full-length RNA segment pattern, demonstrating that the von Magnus effect was avoided.

To solve these drawbacks, we have developed a multi-stage bioreactor system for continuous production of influenza virus that avoids back-mixing. Therefore, the accumulation of unwanted antigenic variations and the von Magnus effect are avoided. The bioreactor consists of a CSTR connected to a plug-flow tubular bioreactor (PFBR; Fig 1b) with a production capacity of 0.20 mL/min [4]. In this system, animal cells are continuously produced in the CSTR and transferred to the PFBR. The cells are infected at the entry of the PFBR with a virus stock of a defined virus passage number, and moved in a plug-flow mode through the tube without back-mixing. The residence time was about 20 h, which is sufficient for virus replication. First cultivation runs showed that the virus titers were stable, and the oscillations previously observed with the TSB system were avoided. In addition, PCR analysis demonstrated stable RNA segment patterns. The PFBR system was evaluated with two different cell lines, Madin-Darby Canine Kidney and AGE1.CR.pIX cells, and the production of high influenza virus titers was achieved for up to three weeks.

In summary, the Bioprocess Engineering group developed a powerful bioreactor technology that allows the stable production of influenza virus in a continuous mode. This platform opens the possibility to develop highly efficient cell culture-based processes for the production of live attenuated and inactivated influenza vaccines, and can help to reduce the cost of vaccine manufacturing worldwide. Furthermore, this bioreactor concept can be expanded for the continuous production of other viruses that are a public health concern.

I Felipe Tapia

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Felipe Tapia received a Diploma in Chemical Engineering from Universidad Técnica Federico Santa María in Valparaíso, Chile, with focus in process engineering, and a Master of Sciences (w. Hons) in Advanced Materials and Processes from Friedrich-Alexander-Universität Erlangen-Nürnberg, Germany, with focus in biomaterials and tissue engineering. In 2012, he joined the International Max Planck Research School (IMPRS) in Magdeburg, where he conducts a Ph.D. thesis in continuous production of cell culture-derived viral vaccines in the Upstream Processing team of Dr. Yvonne Genzel.

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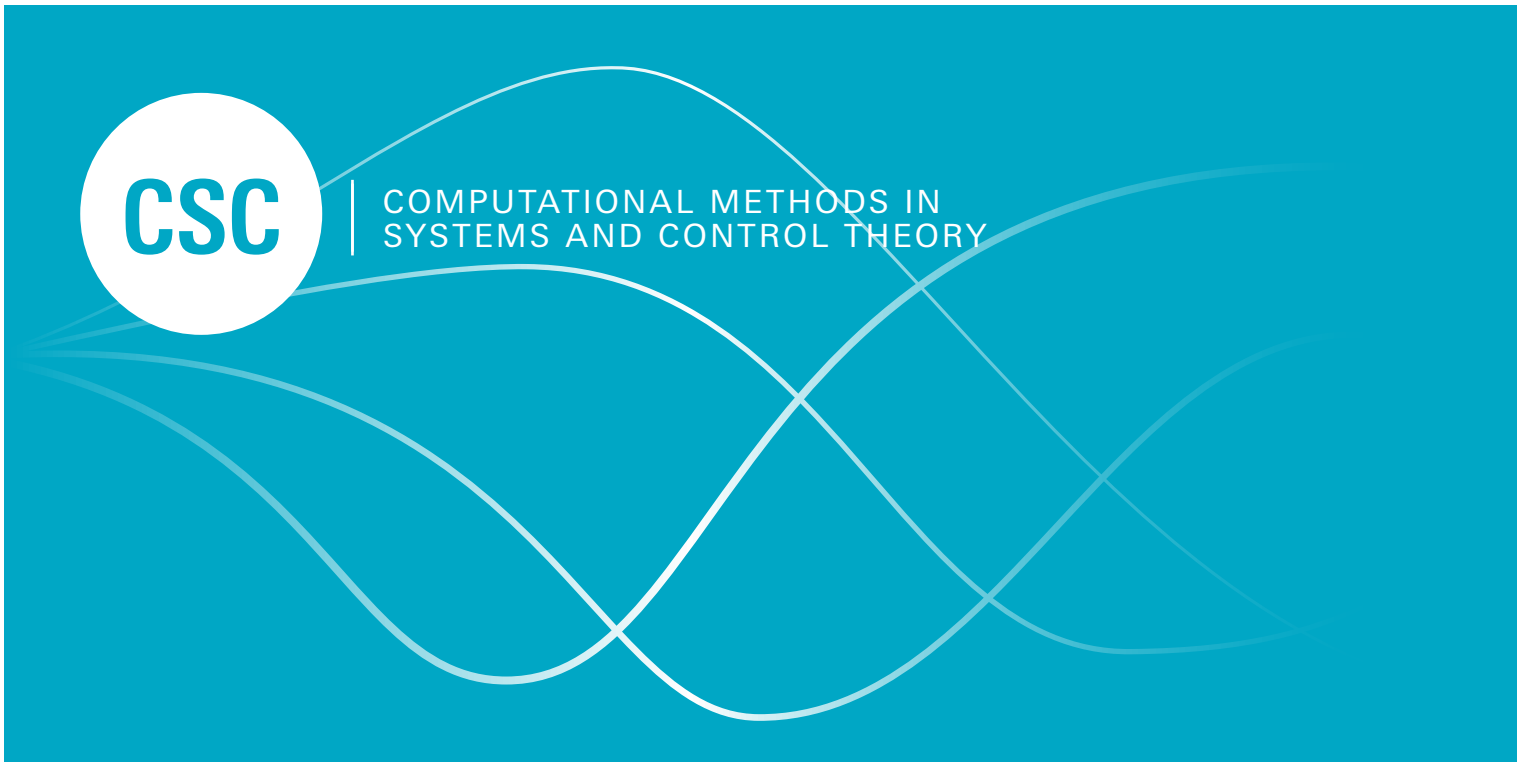

PROF. DR. PETER BENNER | DIRECTOR

Research in the CSC group is concerned with mathematical ideas and concepts to develop new methods in the context of *in silico* design or experiments for complex technical systems as investigated, e.g., in the engineering departments at the MPI Magdeburg. Particularly, we consider efficient simulation and optimization, as well as feedback control, of dynamical systems, i.e., of mathematical models described by systems of ordinary or partial differential equations. Our application areas range from chemical process engineering to nano-electronics to energy networks. Our work flow often starts with a mathematical model provided by or developed together with engineers, physicists, chemists, etc., followed by an analysis of the goals of the desired computer experiments. We then either try to adapt and optimize existing algorithms, or to develop new ones for the target computations. Promising approaches are implemented and benchmarked, before the best variants are turned into user-friendly mathematical software to be used by practitioners. This often includes sophisticated programming strategies for modern computer architectures and clusters, including hardware accelerators like GPUs. For this, we use different hardware platforms, including our Linux cluster "otto" with 1,000+ cores, and we also study their energy efficiency.

Teams within the CSC group

The current CSC structure comprises 6 teams. The biggest is **Model Order Reduction** (headed by Dr. Lihong Feng). It deals with mathematical methods to algorithmically reduce the number of degrees of freedom in mathematical models in order to accelerate their simulation, to facilitate their optimization, to enable control design, and to quantify uncertainties. The **Computer Aided Control System Design** unit (Dr. Jan Heiland) deals with various aspects of computational methods for control systems. A very important aspect here is that many of these computational techniques rely on solutions of Lyapunov, Sylvester and Riccati equations. The team **Matrix Equations** (Dr. Jens Saak) focuses on efficient algorithms to solve them numerically. These algorithms are based on efficient techniques of **Numerical Linear and Multilinear Algebra,** a core mathematical technique percolating almost all aspects of the CSC research work. The corresponding team, led by Prof. Dr. Peter Benner, deals with eigenvalue problems, preconditioning techniques, matrix function evaluation, and tensor techniques. The efficient implementation of the developed algorithms on modern computing platforms is the task of the **Scientific Computing** team (Dr. Jens Saak). The **Simulation of Energy Systems** team (Dr. Sara Grundel) focuses on modeling and numerical simulation of power, gas, and water networks, and their coupling.

+ Besides developing mathematical theory, daily work in the CSC group often comprises writing computer code, running numerical experiments, and visualizing them. Numerical experiments are run on various computing platforms, including the CSC compute cluster "otto", a 12 TFlop system consisting of more than 100 nodes with more than 1,200 cores. Martin Köhler is the main administrator of "otto".

Research Trends and Highlights in 2015/16

We have increased our research on networked (control) systems, including multi-agent systems. A particular application is the simulation and control of energy networks. In the BMWi funded "MathEnergy" project (start: October 1, 2016) we investigate a new hierarchical modeling approach for the German gas and power networks and their couplings as part of the German energy transition program.

Furthermore, we have continued and strengthened our cooperation with several groups at the MPI Magdeburg investigating dynamical reactor models for processes like methanation, crystallization, and chromatography. The development of novel model reduction and control techniques for these often highly nonlinear processes remains a challenge for further research.

In recent years, low-rank tensor techniques had a breakthrough as computational method to solve high-dimensional science and engineering problems. We have applied these techniques to a number of problems concerned with the propagation of uncertainties in dynamical systems described by unsteady partial differential equations. In cooperation with the MPI for Mathematics in the Sciences in Leipzig, we have also developed new approaches to solve problems from theoretical physics and chemistry based on low-rank (tensor) approximations.

Other highlights in 2015/16 were the workshops (co-)organized by the CSC group, including the joint CSC/NDS Workshop at Ringberg Castle 2016, the GAMM Workshop on "Applied and Numerical Linear Algebra" held in Magdeburg in 2015, and in particular the conference "Numerical Algebra, Matrix Theory, Differential-Algebraic Equations, and Control Theory" held at the TU Berlin on the occasion of Volker Mehrmann's 60th birthday.

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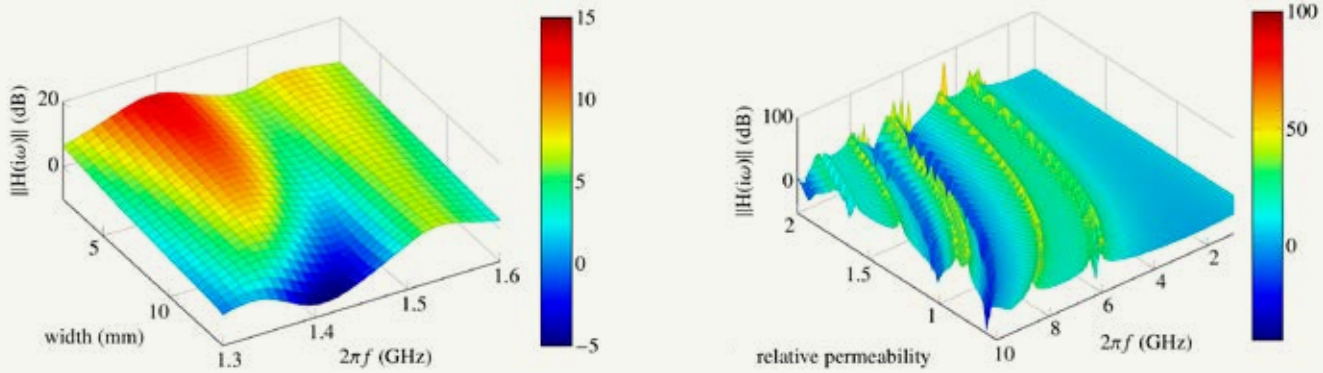


Figure 1:
Transfer function of a coplanar waveguide with parametric variations in frequency and geometry (left) and transfer function of a branch-line coupler with parametric variations in frequency and relative permeability (right).

Simulation and Model Reduction in Electromagnetics

The simulation of wave propagation provides insight and understanding of complex physical phenomena and is desired in many scientific and industrial areas. An example is optics, where the design and construction of lenses can be significantly improved, when it is aided by computer simulations. The underlying partial differential equations (PDEs) for wave propagation, such as light or radio waves, are Maxwell's equations. A computer simulation of Maxwell's equations in a realistic geometry, taking into account material properties, reflection and refraction, boundary layers and realistic sources, is still largely a future endeavor. Current research develops efficient and reliable methods to allow such simulations. Mathematical theory asserts the accuracy of simulations with respect to the real-world wave propagation and numerical algorithms and software are developed to perform increasingly complex computations.

A typical task in the engineering context is to determine the precise configuration at which a device works best. This is in the sense of lowest energy consumption or highest throughput, for instance. Mathematically, this poses an optimization or inverse problem, whose solution easily exceeds currently available computational resources.

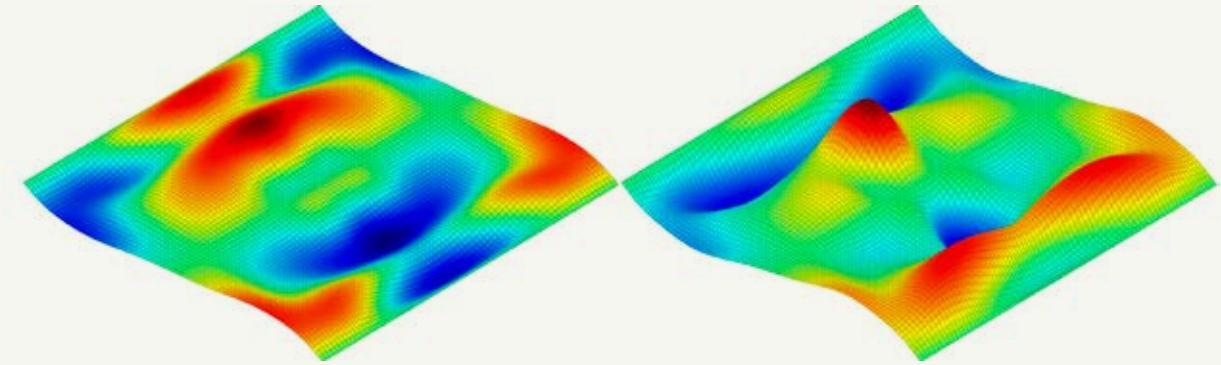
The starting point of computational electromagnetics is always a mathematical model given by Maxwell's equations, but in complex media, additional equations can come into play. Two examples shall be highlighted, the temporal dispersion[3], which is a material property, present in many media other than air, and microwave applications.[2] In contrast to other areas like solid mechanics or fluid dynamics, electromagnetics is linear in nature. Due to linearity, electromagnetic applications are easily converted to frequency domain, which is a common approach in microwave applications. The application is represented as a mathematical model with several millions of equations and naturally parametrized in the frequency. Evaluating the model for many frequencies of interest is a time-consuming task.

Model Reduction

Model order reduction (MOR) is a tool to remedy the obstacle of very time-consuming and complex simulations. It replaces a high-dimensional model of several millions of equations, with a reduced order model, typically containing just a few hundreds of equations. As a result, the compute time reduces from several hours to just a few minutes. Developing efficient numerical methods and a theory behind the model reduction process is an active research area for all types of partial differential equations. Of particular importance is parametric model order reduction (PMOR, [1]), which allows to find optimal parameter configurations using a parametrized reduced order model.

Parametric Model Reduction

Parametric PDEs occur naturally in optimization tasks and inverse problems. MOR is particularly useful in this context to cope with the computational complexity. A central idea is to use information obtained at some parameter locations to derive



+ **Figure 2:**
Relaxation polarization (left, normalized) and electric field strength (right, normalized) in a unit square with zero tangential boundary condition after a simulation time of 2.4 ns. A Gaussian pulse provides a broadband input source.

predictions of the model behavior at other parameter locations. In this process, care must be exercised to preserve the parametric dependence in the reduced order model. We work with a multitude of approaches to fulfill this task, some of them are: Transfer function interpolation uses polynomial or rational interpolation to generate a reduced order model, or the balanced truncation technique uses theorems from system theory to obtain error bounds on the approximation error. The moment matching and reduced basis techniques are also equipped with a variety of error estimators and error indicators, which have been developed in recent years. Tensor methods potentially allow to break the so-called curse of dimensionality by using algorithms whose complexity does not depend exponentially on the parameter dimensionality.

Example: Microwave Devices

Microwave devices typically operate at frequencies of a few gigahertz (GHz). The transfer functions, i.e., the input-to-output mapping, of two models, a coplanar waveguide and a branch-line coupler, are shown in Figure 1. The PMOR for these devices was carried out with the reduced basis method [2]. In particular the branch-line coupler poses a challenge for the model reduction due to multiple resonance configurations in the parameter domain.

A comparison of different PMOR methods could show that methods taking the underlying PDE structure into account are much more able to resolve the transfer function than interpolating methods.

Example: Temporal Dispersion

When electromagnetic waves travel through media other than vacuum or air, a number of additional physical effects come into play. One such effect is temporal dispersion, which in water for instance causes an exponential damping of the wave amplitudes. The mathematical modeling takes a time-dependent relative permittivity into account, which depends on the electric field strength at previous time steps. A relaxation polarization is defined by the convolution of electric field strength and electric susceptibility. This can be visualized in a computer simulation by comparing the polarization with the electric field strength, see Figure 2. In contrast to free space, the polarization and the electric field are not exactly in sync. I **Dr. Martin Hess**

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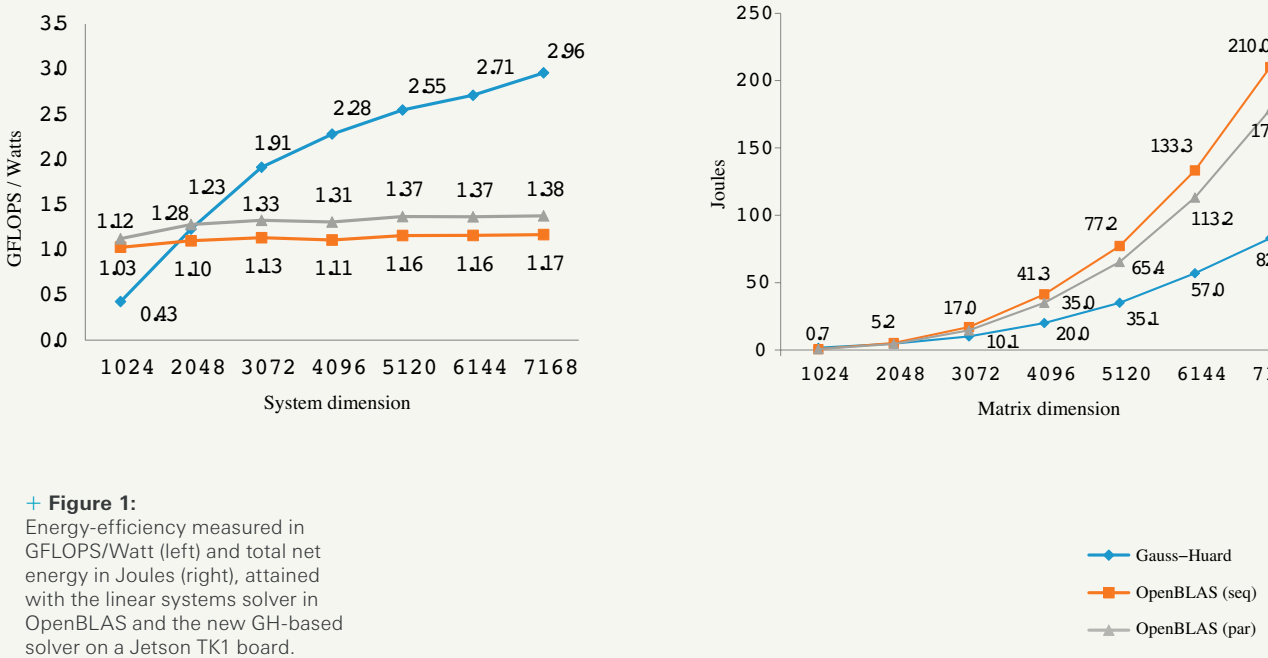

Figure 1:
Energy-efficiency measured in GFLOPS/Watt (left) and total net energy in Joules (right), attained with the linear systems solver in OpenBLAS and the new GH-based solver on a Jetson TK1 board.

High Performance and Power-Aware Computing

Energy-aware computing aims to reduce the energy required to perform a computation. It has become increasingly relevant in the recent years. For example, in addition to the usual Top500[1] list of the most powerful computers worldwide, the Green500[2] lists the most resource efficient high performance computers. Current supercomputers exhibit a power consumption that makes their operating at least as costly as their acquisition. The Tianhe-2 supercomputer (NSC in Guangzhou, China) that has dominated the TOP500 list over the recent years, consumes about 24MW (17.6MW for the supercomputer and 6.4MW extra for cooling). This means that it requires as much power as a 20,500 inhabitants city in Germany.

There are three major reasons that motivate the utilization of energy-saving techniques:

- Reduction of the power consumption of a supercomputer results in a lower electricity bill and also may have a positive impact on the cooling expenses.
- Portable devices represent an important motivation for energy-aware computing. Society always demands for more powerful portable devices (e.g. cell-phones, tablets or laptops) that are powered with limited batteries. Here, reducing the power consumption means not only to enlarge the device autonomy but also to increase their usability.
- Power-consumption has become a design limitation in new hardware architectures. In the past, the new families of processors always presented a larger clock-rate than their predecessors, but a larger clock-rate means more power and also more heating. The problem is that overheating can damage the hardware components. To overcome this problem, the hardware manufacturers have increased the number of computational units instead of their clock-rate. As power is increased linearly with the number of computational units and exponentially with the clock-rate, this strategy provides more powerful platforms and a limited increase in the power-consumption.

Additionally, experts[1] agree that energy is currently the limiting factor for performance. Hardware manufacturers have performed several efforts to reduce the power consumption in newer platforms, e.g. by developing accelerators for specific tasks or power-efficient storage. But energy-aware computing is not only about hardware, it is also about software. There are a number of techniques that can reduce the energy required by a computational kernel, e.g. exploiting communication avoiding algorithms, the use of mixed-precision techniques or reducing the usage of power-hungry components.

The CSC group actively participates in the development of energy-efficient computational solutions. Its researchers have been working in two main areas, the development of energy-efficient software and the design of low-power hardware platforms.

The "Power-Aware High Performance Computing" project[2] aims to develop a set of energy-aware linear algebra computational kernels that can be employed in the solution of a collection of scientific and engineering problems. Those kernels are often computationally intensive. Therefore, they require the use of high performance and energy-aware computing techniques. The project started in 2015 and is funded by the

+ **Figure 2:**
Computational nodes (left) and storage subsystem (right) of the I.C.A.R.U.S. Server. This low-power server has been developed by TU Dortmund and MPI Magdeburg and it is entirely powered with solar energy.

German Federal Ministry of Education and Research (BMBF). It is a collaboration with researchers from the Universidad de la República (Uruguay). As part of this project, several modern hardware platforms have been evaluated (among them GPUs and the Intel Xeon Phi processor) in order to select the most suitable regarding computational power and power consumption. In a second stage of the project, several high performance energy-aware computational kernels were developed on a Nvidia Jetson TK1 board. This included a review of the algorithms, e.g. the Gauss-Huard (GH) algorithm for the solution of linear systems. The GH algorithm was presented in 1979 but has been abandoned for 2 decades as LU-based solvers show a better performance in traditional platforms. Our experiments demonstrated that it provides a reliable and competitive alternative to traditional solvers under certain circumstances, delivering important time and energy savings[3]. Currently, we face the last stage of the project, which is the use of the developed kernels to solve complex scientific problems, as the solution of Lyapunov equations.

Some of the results obtained in the project have been published in international conferences and journals. Among them, we can remark the development of a linear systems solver that exhibits a 50 % less energy consumption with respect to previous solvers, or the extension of the GH method for the solution of delayed systems.

A different but complementary approach is the I.C.A.R.U.S. project. This project lead by TU Dortmund aims to build a supercomputer based on low-power components and powered exclusively with renewable energies. The CSC group participates in this project and has designed the necessary data storage subsystem. While the computational part of I.C.A.R.U.S. relies on Jetson TK1 boards, Banana-Pi boards connected via a Gbit ethernet form the storage system. It presents a capacity of 10TB and low power requirements, of well below 50W.

Besides, in collaboration with researchers in Spain, the group has applied energy-aware techniques to hyperspectral unmixing algorithms. This research includes the evaluation of different hardware platforms and algorithms, and the subsequent development of an efficient and energy-aware final solution. I **Dr. Alfredo Remon**

[1] www.top500.org
[2] www.green500.org

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[2] *Power Aware High Performance Computing project.* http://www.mpimagdeburg. mpg.de/csc/projects/pahpc
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Alfredo Remon received his Diplom in computing at the Polytechnic University of Valencia (UPV), Valencia, Spain, in 2001. Afterwards he joined the Department of Systems Engineering and Control (at UPV) as an assistant researcher. From 2005 to 2013 he worked at University Jaume I, Castellón, Spain, where he received his Ph.D. in Computing in 2008. Since 2013 he is a researcher at the Max Planck Institute Magdeburg. His research interests are in the field of high performance computing with special focus on linear algebra applications and novel hardware architectures. Additionally, he is interested in power-aware computing techniques and platforms.

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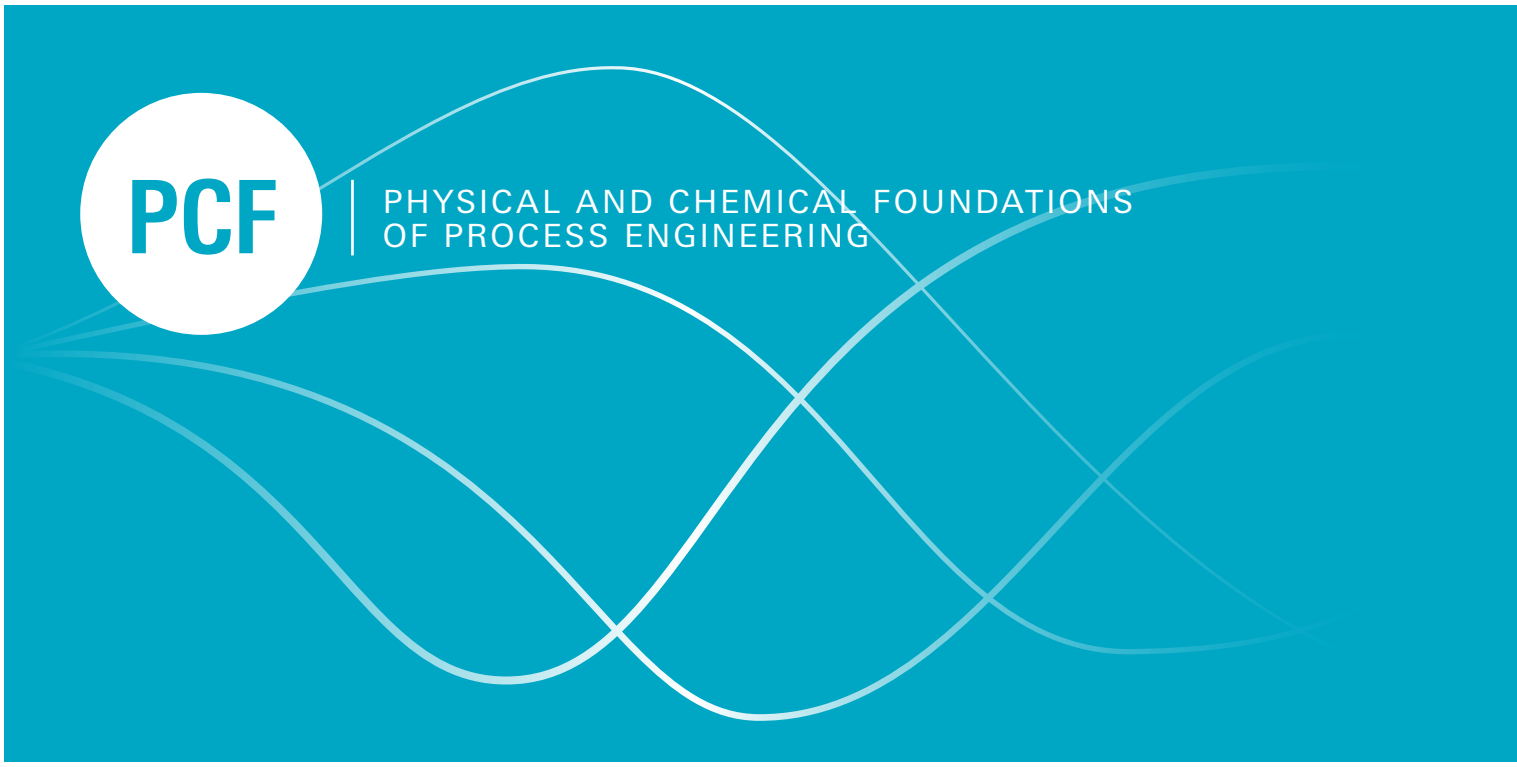

PROF. DR.-ING. ANDREAS SEIDEL-MORGENSTERN |
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The development and production of new products with improved or hitherto unknown properties require the application of advanced and often complex technologies. Besides realizing transformation steps exploiting chemical reactions, there is a growing need in advanced separation processes to provide the required product purity. Currently, there are three main research directions being investigated within the PCF group.

The **Crystallization Research team** is studying crystallization processes capable to provide very pure products, as needed e.g. in the pharmaceutical industry. Under development are for example isothermal and polythermal batch crystallization or new continuous crystallization concepts. Various types of compounds are being investigated, for example different conglomerate or compound-forming chiral systems. To quantify and understand the underlying mechanisms of crystallization, the growth rates of crystals and the solid liquid phase equilibria are quantified based on systematic experimental investigations and correlated with mathematical models.

The **Chromatography Research team** is working on discontinuous and continuous chromatographic resolution methods capable of separating complex mixtures in order to provide pure enantiomers or biomolecules. Essential physical and chemical properties are determined experimentally. These properties are then used for the design and simulation of various types of chromatographic separation processes. Advanced innovative continuous chromatographic separations are studied, e.g. different configurations of simulated moving bed (SMB) technology. SMB processes directly combined with reaction and crystallization processes are also investigated in order to provide alternatives to conventional operation concepts. The group investigates new options to isolate and purify natural products exploiting jointly chromatographic and crystallization based separation methods.

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

+ Knowledge regarding the solubility of a specific target molecule is crucial for the design of purification processes using chromatography and crystallization. Stefanie Leuchtenberg carries out static equilibrium measurements to determine this property.

In the last two years, members of the group participated in numerous national and international conferences. We are happy that several of our presentations received prestigious Poster Awards as a sign of international recognition. To honor the results achieved by our group in the field of Separation Science, Andreas Seidel-Morgenstern received in 2015 the "Humanity in Science Award" (together with Peter Seeberger from the MPI for Colloids and Interfaces) and in 2016 the Emil Kirschbaum Medal.

In 2016, members of our group chaired the organization committees of two major international meetings, namely Heike Lorenz the "International Workshop on Industrial Crystallization (BIWIC)" and Andreas Seidel-Morgenstern the conference "Fundamentals of Adsorption (FOA)", which takes place only every nine years in Europe.

Recently, the Innovative Training Network "CORE" was granted by the European Union and the PCF group looks forward to work in the next four years within an international consortium on the "Continuous resolution of chiral Components".

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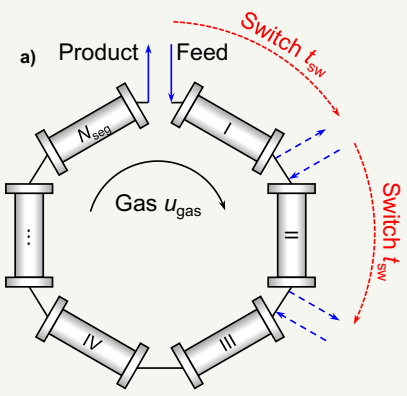
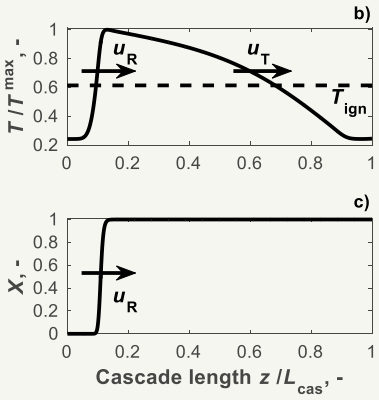
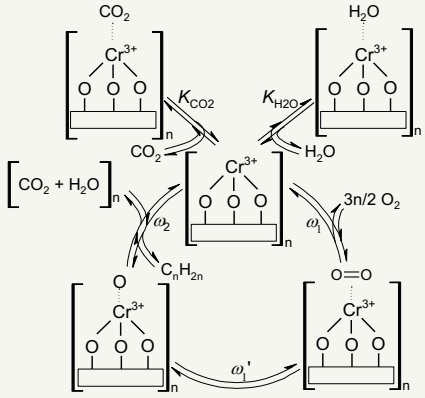


+ **Figure 1 a:**
Principle Simulated Moving Bed Reactor scheme of a periodic operated reactor cascade of N_{seg} catalytic fixed beds based on switching in- and outlet port positions in gas flow direction



+ **Figure 1 b:**
Temperature profile including the traveling exothermal reaction (u_R) and temperature (u_T) front in the middle of switching period in a reactor cascade

+ **Figure 1 c:**
Conversion profile including the traveling exothermal reaction (u_R) front in the middle of switching period in a reactor cascade



+ **Figure 2:**
Postulated catalytic cycle of the total oxidation of a hydrocarbon based on an *Eley/Rideal* mechanism on a $CrO_x/\gamma\text{-}Al_2O_3$ catalyst, which coordinative unsaturated Cr^{3+} species catalyze the reaction [3]

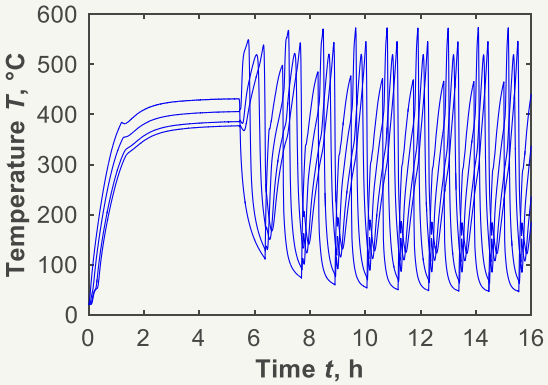
Simulated Moving Bed Reactor Operation

The purification of industrial volatile organic compound (VOC) exhaust streams requires special attention in order to observe new stricter emission standards. Frequently, harmful environmental components are diluted in air or nitrogen. Thus, the total oxidation of these components needs thermal energy to preheat the whole stream including inerts to the ignition temperature T_{ign}. The idea of an autothermal process, using the exothermal energy release to preheat the reactants, was investigated in the last century. Inspired by well-known countercurrent movement separation processes, a promising innovative concept is the Simulated Moving Bed Reactor (SMBR).

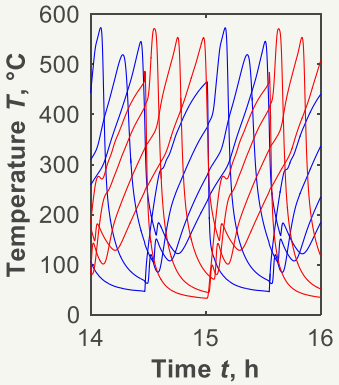
For a successful process, an adiabatic reactor cascade of at least two reactor segments ($N_{seg} \geq 2$) has to be assumed (Figure 1a). If cold feed gas enters the first hot reactor segment I, the reactants heat up to ignition temperature and total oxidation occurs. The formed exothermal reaction front moves in flow direction by the shift of cold feed gas. After passing completely the segment I, the feed and outlet port position is shifted into flow direction following the reaction front. Thus, the formerly cold first segment is switched at the end of the reactor cascade and the hot exhaust gas can heat up the segment again. This periodic process attempts to trap a self-sustained exothermic front, and allows an autothermal operation. At steady-state conditions, two fronts are formed: the exothermal reaction front and the leading thermal front (u_R and u_T in Figure 1b-c). Based on the catalytic fixed bed, gas phase properties (e.g. heat capacities) and the adiabatic temperature rise, different front velocities can be observed.

To predict cyclic stable ignited conditions in the SMBR concept, several aspects have to be considered. For this purpose, the theoretical determination of the front velocities and the corresponding effect on the switching time t_{sw} is required. Additionally, unexpected ignition behavior as well as front dynamics, especially in reaction mixtures, have to be investigated. To reduce the computing effort for reactor behavior prediction, a simplified SMBR model was presented by Zahn et al.[1], based on a countercurrent continuous movement of the solid catalyst phase. To increase the model significance, the determination and quantification of the reaction kinetic is given special importance as well.

As representative VOC model system, the total oxidation of ethylene and propylene on a $CrO_x/\gamma\text{-}Al_2O_3$ catalyst is studied experimentally and model based. Depending on the type of the catalyst, different reaction mechanisms are preferred. In the present work, the oxidation reactions of the hydrocarbons were described via an *Eley/Rideal* mechanism, where the hydrocarbons are assumed to react directly from the gas phase with dissociated oxygen. By means of the corresponding postulated catalytic cycle (Figure 2) and the *Christiansen* methodology[2], global kinetic rate approaches can be determined. In this connection, it is obvious that the adsorption behavior of the reactants and products are a relevant part of the kinetic description. To increase the



+ **Figure 3a:**
Temperature signals of reactor 1 for start-up behavior and periodic operation



+ **Figure 3b:**
Temperature signals of reactor 1 (blue lines) and reactor 2 (red lines) within two cycles

physical meaning of these parameters and to reduce the model additional individual adsorption measurements were performed. To quantify the adsorption isotherms on experimental data, a multiplicity of different procedures are available. The most used is the analysis of dynamic concentration fronts moving through the reactor after a perturbation. At these obtained experimental single gas data, adsorption parameter can be estimated and afterwards transferred in kinetic rate approaches. Based on this model reduction using the additional adsorption information, the kinetic constants were estimated with increased accurateness. A good agreement of the model with a large set of experimental data was achieved[3].

For the experimental investigation of the SMBR concept, a pilot plant was designed and constructed at the Max Planck Institute in Magdeburg. This test facility consists of two adiabatic segments controlled by a multiplicity of thermocouples in each reactor and several valves. Thus, the temperature dynamic front behavior can be studied in detail. In Figure 3a, the time dependent temperature signals along the catalyst bed of the first segment are shown. After a general experimental start-up procedure of six hours, the periodic operation is initiated. The cyclic steady-state operation is maintained using a closed loop control concept. In this case, the switch of the in- and outlet ports is triggered, if a certain temperature set-point at the end of the segment has been reached from top to down. Using this robust controller concept, the cyclic steady-state is attained approximately after seven cycles. Thereby, the controller-based switching time is decreased from 55 to 32 minutes at an almost constant maximum temperature. Thus, stable ignited operation could be experimentally demonstrated for at least 120 hours. Based on the constructed SMBR pilot plant, the determined simplified reactor model as well as the quantified reaction kinetic can be analyzed and if required improved.

Future studies will be devoted to apply these models to predict the front velocities, the maximum temperatures and the reactant conversion of single and multi-component feed gases characterized by different ignition temperatures. Furthermore, the development of more stable control concepts is in focus to address challenges of industrial applications. The SMBR operation exploiting multiple segments seems to be a promising reactor concept which offers large potential for efficient VOC exhaust stream purification.

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Gregor Kiedorf studied Process Engineering at the Otto von Guericke University in Magdeburg and received his Diploma degree as best alumnus of the faculty in 2011. In the same year, he started his Ph.D. in the Physical and Chemical Foundations of Process Engineering research group at the Max Planck Institute Magdeburg. His research focuses on mechanistic reaction kinetic analysis in homogeneous, heterogeneous and enzyme catalysis and their model application in innovative dynamic reactor concepts. He is associated member of the Collaborative Research Center/Transregio 63 InPROMPT.

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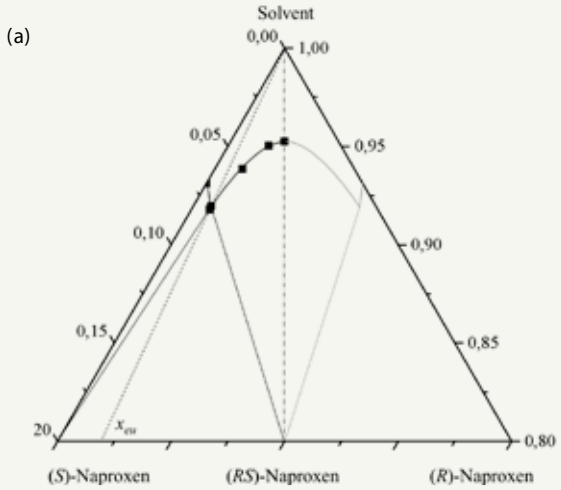
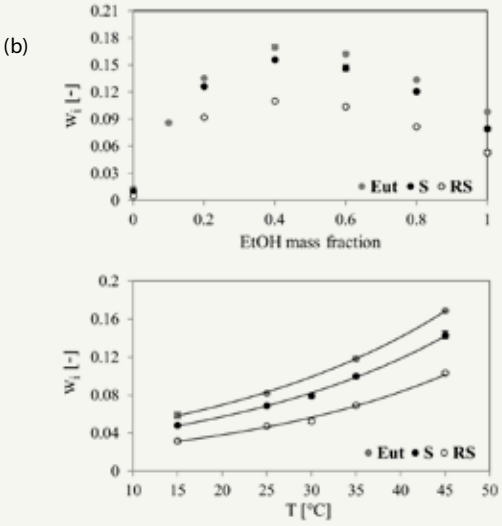


+ **Figure 1a:**
The ternary phase diagram of (*S*)- and (*R*)-naproxen in the solvent ethanol given in weight fractions, w_i at 25 °C (*RS*)-naproxen is the racemic molecular compound. The eutectic composition, $x_{eu}=x_S/(x_S+x_R)$, is a key quantity for the crystallization process design. Lines are guides to the eye.



+ **Figure 1b:**
Dependency of the solubility of (**S**) (*S*)-naproxen, (**RS**) the racemic molecular compound (*RS*)-naproxen and (**Eut**) the eutectic composition on (b, top) the solvent at 30°C (exemplarily shown for an ethanol / toluene solvent mixture) and (b, bottom) the temperature in pure ethanol.

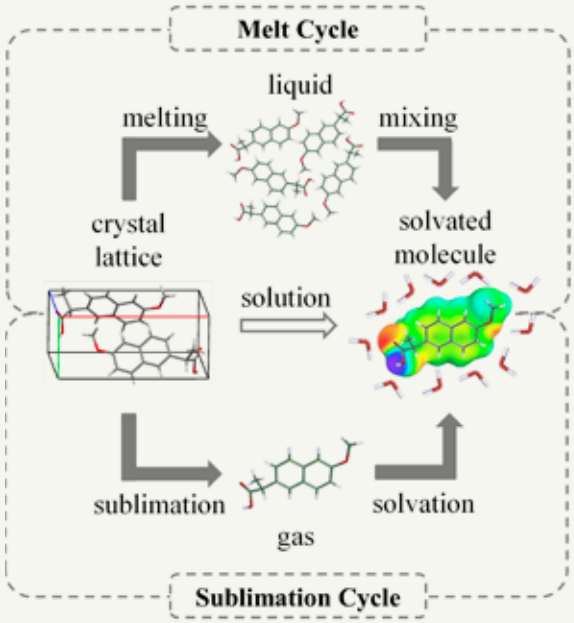
Calculating Solubilities for Enantioseparation Process Design

A significant number of molecules are chiral which means they exist in two possible conformations that are non-superimposable mirror images of one another. The two opposite counterparts are called enantiomers. Apart from their different spatial arrangement, they are identical and have the same physical and chemical properties in an achiral environment. In most cases nature favors one of two enantiomers to build living organisms which is commonly referred to as homochirality of life. As a consequence the human body contains biological receptors that can discriminate between enantiomers which result in different pharmacological and toxicological properties. Therefore the U.S. Food and Drug Administration (FDA) now requires that drugs have to be marked as pure enantiomers or the mixture has to be proven to be harmless.

Pure enantiomers can be provided by either preferentially synthesizing only one enantiomer or by separating the synthesis mixtures, which usually consists of a 50:50 'racemic' mixture of the two enantiomers, in a downstream process. Separation by preferentially crystallizing only one enantiomer is a downstream process possibility which is comparably cheap in an industrial scale. This is especially true if a product is marked as a solid and a crystallization or precipitation step is required anyhow [1].

The thermodynamic feasibility and productivity of a crystallization process depends on the solubilities of the pure enantiomers and their mixtures which are often illustrated in a ternary phase diagram (TPD). Of special importance is the solubility and enantiomeric composition of the eutectic mixture as it defines the areas where pure enantiomer can be crystallized. Figure 1a exemplarily shows the measured TPD of the anti-inflammatory chiral drug naproxen in ethanol at 25°C. As many chiral substances, naproxen can crystallize as an enantiopure crystal or, for certain mixtures, as a racemic molecular compound, (*RS*)-naproxen. Each point within a TPD is depending on the solvent (see Figure 1b, top) and the temperature (see Figure 1b, bottom). From a thermodynamic perspective, the solubilities describe the phase equilibria between the crystal (solid phase) and the saturated solution (liquid phase) which can be complicated if the substance can crystallize in different solid state forms, e.g. polymorphs or solvates [2].

In early stages of process design, for example during the development of a pharmaceutical, the amount of a substance available for experimental work is usually limited, and computational methods are of value to support, or possibly replace, substance and time-consuming experimental investigations to determine a TPD. For that, the free energy of solution, ΔG_{sol}, has to be determined by computational methods. It is beneficial to use a thermodynamic workaround, a so called thermodynamic cycle, that divides ΔG_{sol} into computationally accessible quantities. ΔG_{sol} can be expressed by i) transferring the molecule from the crystal via the sub-cooled melt to the solution or by ii) transferring the molecule from the crystal via the vapor to the solution (see Figure 2). The



+ Figure 2:
Two thermodynamic approaches to model solubilities: The commonly used *Melt Cycle* and the suggested *Sublimation Cycle* which is exploiting computational quantum chemistry.

first approach, the "melt cycle", is nowadays often used to calculate solubilities. It uses the melting properties of a crystalline substance which are only accessible precisely enough by experiment. The second approach is called the "sublimation cycle". It uses the lattice energy which is accessible by quantum chemical methods and can be calculated with an increasing accuracy nowadays. It is defined as the energy to separate the static perfect lattice into infinitely separated molecules in their lowest energy conformation. The static crystal lattice does not incorporate any vibrational contributions, not even vibrations at zero Kelvin (zero-point vibrations). As solubilities are relevant at around ambient temperatures, there is a large temperature gap which needs to be closed.

In a joint project with a research group of the University College London (UCL) and the MSD group all relevant quantities of the sublimation cycle have been determined for naproxen and other chiral molecules to study the accessibility of ternary phase diagrams by purely predictive methods. The sublimation cycle has been evaluated against solubility measurements and the results using the second thermodynamic approach, the melt cycle (see Figure 2). This however relies on experimental melting enthalpies and temperatures and is therefore not solely predictive.

In the course of this project experimental sublimation thermodynamic quantities have been determined experimentally from measured vapor pressures[3] and by computational methods which are based on density functional theory (DFT). To adjust calculated lattice energies to solution temperature thermal corrections have been determined using computed lattice and molecular vibrational frequencies[4]. The calculation accuracy has been contrasted against the thermal corrections obtained from experimental solid-state heat capacities which were measured in a large temperature range (-271 °C to ~ 150 °C). To study the effects of the solvent on the solubilities and the ternary phase diagram the solvation free energies have been investigated using the quantum chemistry based thermodynamic method COSMO-RS.

It was shown that the sublimation cycle is competitive for predicting the eutectic composition using the calculated energy differences between the enantiomer and the racemate. Hereby, besides the main energy contribution, the lattice energy, differences in the thermal corrections between the enantiomer and the racemate were shown to be of significance for the predictions. However, even using state-of-the-art computational methods it is still a big challenge to access the absolute thermodynamic quantities precise enough to reliably calculate solubilities of organic crystalline solids. **I Hannes Konrad Buchholz**

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Hannes Konrad Buchholz joined the research group of Prof. Seidel-Morgenstern as a Ph.D. candidate by the end of 2012. He studied Chemical Process Engineering at RWTH Aachen University where he received his diploma in 2012. From 2008 to 2009 he studied at the Norwegian University of Science and Technology Trondheim as an exchange student. His main focus within the PCF group is on predictive determination of solid-liquid equilibria (SLE).

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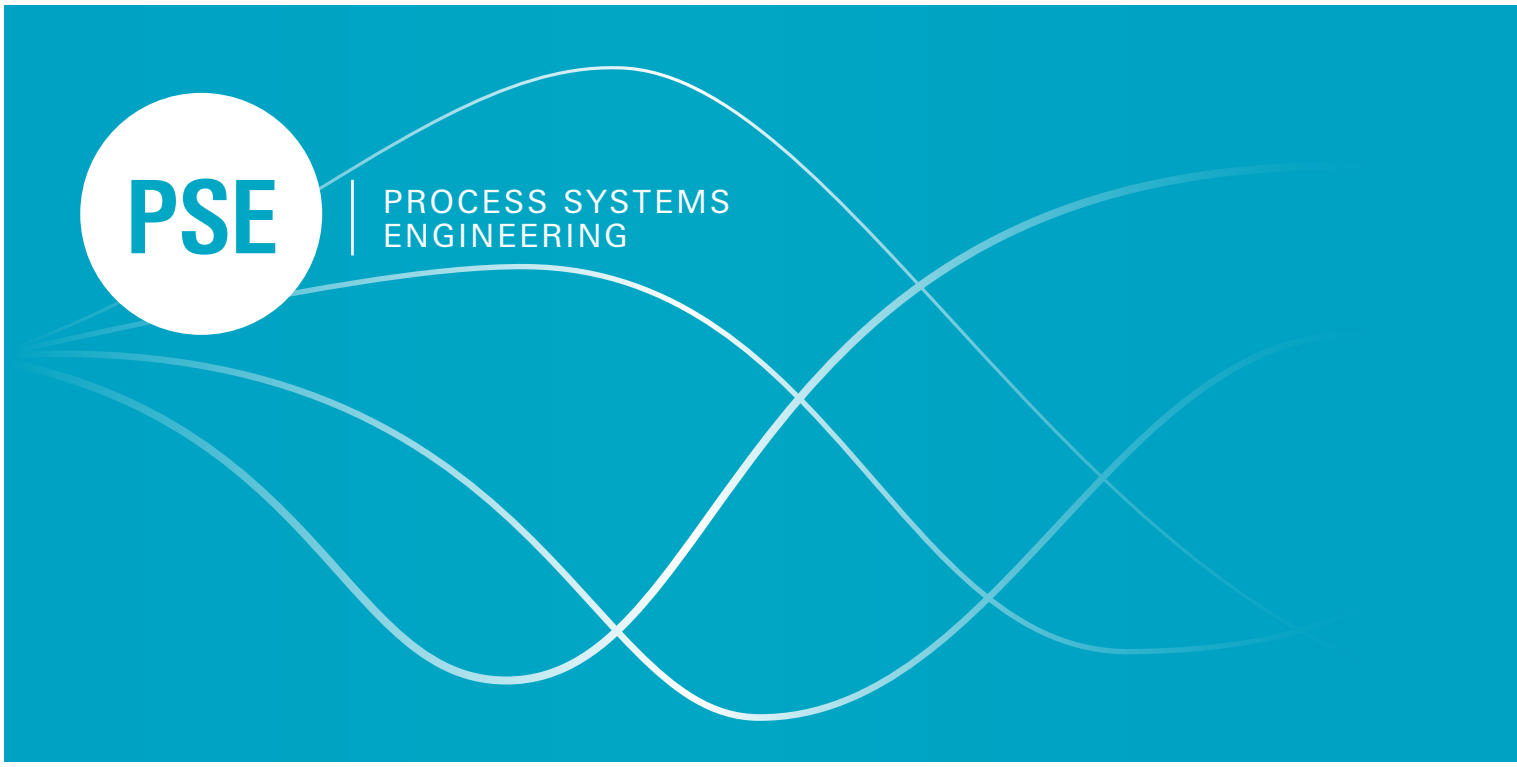

PROF. DR.-ING. KAI SUNDMACHER | DIRECTOR

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

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

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

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

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

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

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

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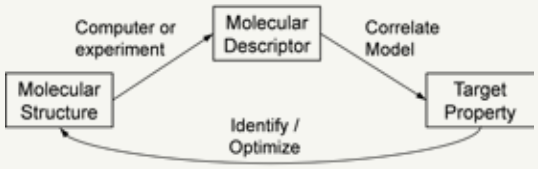
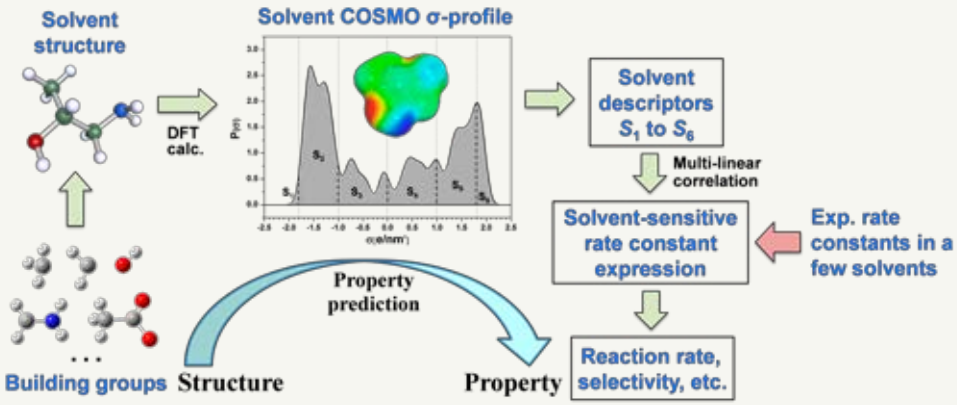


+ **Figure 1:** Computeraided molecular design (CAMD) methodology.



+ **Figure 2:** Framework of the proposed solvent design methodology.

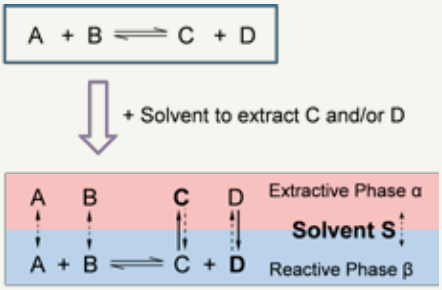
Computer-Aided Molecular Design of Solvents for Chemical Reactions

Solvents are widely used as reaction media in liquid phase reactions. It has been proven that the variation of the type of solvent can dramatically change the reaction rate and equilibrium conversion. Despite that, so far there have been only few works addressing the optimal selection or design of solvents for chemical reactions. Since solvents can influence the reaction kinetics and thermodynamics, the PSE group developed two Computer-Aided Molecular Design (CAMD) approaches: a) a method for the optimal design of solvents to increase reaction rates for irreversible reactions and b) a method for improving equilibrium conversions of reversible reactions. The two methods are briefly described in the following.

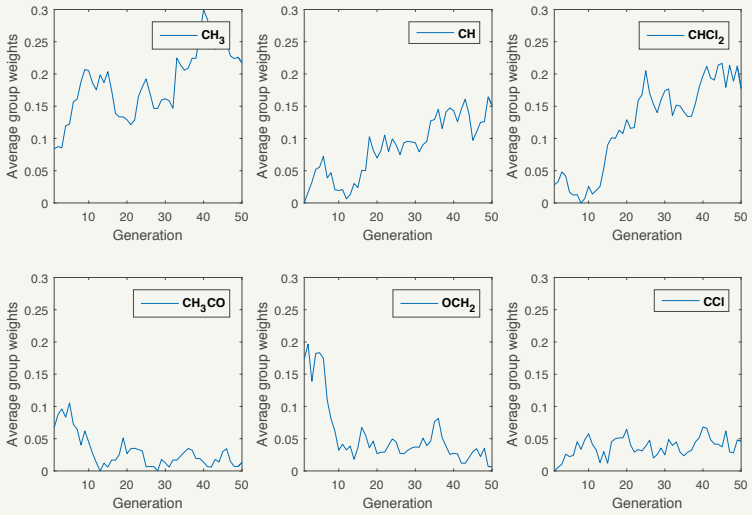
The task of CAMD is to design molecules possessing specific and desirable properties. As depicted in Figure 1, a standard CAMD procedure consists of two subproblems. The forward problem relates molecular structures to molecular properties through certain molecular descriptors. The reverse problem determines molecular structures that possess the optimal properties based on the established structure-property relationship models.

For CAMD of reaction solvents, we introduced a new type of solvent molecular descriptor and used these descriptors for correlating the effect of solvents on chemical reaction rates. Later, we formulated and solved an optimization-based molecular design problem to identify the best solvent structure. As illustrated in Figure 2, starting from a given set of molecular building groups, different solvent structures were generated. Through DFT calculations based on the COSMO solvation model, we obtained the σ-profile, i.e. the screening charge density distribution, of each solvent molecule. Due to its molecule-specific nature, the σ-profile can be regarded and used as a molecular fingerprint. Consequently, we partitioned the σ-profile into six sections and used the areas underneath the curve sections as solvent molecular descriptors. By correlating experimental reaction rate constants measured in few known solvents with their descriptors, we parameterized a QSPR (Quantitative Structure Property Relationship) model which describes the solvent effect on the rate of the investigated reaction. Based on this model and an additionally developed group contribution method for estimating the descriptors from solvent molecular building blocks, one can reversely optimize solvent structures in terms of the combination of groups for identifying an optimal solvent featuring the highest reaction rate or another best rate-related property, such as the reaction selectivity. The solvent design method has been applied successfully to two Diels-Alder reactions [1], [2].

Due to the fact that solvents as reaction media can change the equilibrium of a chemical reaction, the PSE group developed a CAMD methodology for finding optimal solvents to the equilibrium conversion via a "extractive reaction" strategy. Therein,



+ Figure 3:
Scheme of solvent-aided extractive reaction.



+ Figure 4:
Evolution of average group weights over many generations.

a suitable solvent is added to the reaction mixture to selectively extract products into a separate phase, thus allowing for higher product yields. The concept of a solvent-supported extractive reaction is depicted in Figure 3. The design problem can be described as follows: Given a liquid reaction mixture composed of a known amount of reactants A and B under a specified temperature and pressure, determine which solvent and by which amount it should be added to the mixture in order to achieve a maximum equilibrium conversion of the reaction.

The above-mentioned solvent design task leads to a challenging optimization problem containing continuous and binary decision variables. For a given solvent structure and composition, we used a rate-based dynamic method for calculating the combined chemical and liquid-liquid phase equilibria. A genetic algorithm (GA)-based CAMD method was developed to optimize the solvent structure and composition for maximizing the reaction equilibrium conversion. The method has been applied successfully on an esterification reaction where 1,1-dichloro-2-methylpropane and 1,1-dichlorobutane were found to be the best solvents.[3]. In this GA-based molecular design approach, the structural groups can be regarded as genes that constitute the molecules. Just as promising genes have more chances of being retained while non-promising genes are gradually eliminated in natural selection, the appearance frequency of a group in a generation behaves in a similar way. Figure 4 shows the evolution of average group weights in a generation. As can be seen, favorable groups (such as CH_3, CH, and $CHCl_{2)}$ accumulate in the evolution. The weights of unfavorable groups (such as CH_3CO and OCH_2) generally decrease with increasing number of generations. Some group weights (such as CCl) do not change much at all during the evolution. These observations are consistent with the final solvent design results.

I Dr.-Ing. Teng Zhou

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Author **Dr.-Ing. Teng Zhou**

Dr.-Ing. Teng Zhou obtained his master degree in 2012 from East China University of Science and Technology in Shanghai, China. In 2016 he received his Ph.D. degree from Otto-von-Guericke University Magdeburg. Within the PSE group, Teng Zhou is developing systematic methods for reaction solvent design and integrated solvent and process design. He published five first-author articles and earned several important awards, including the CAST Directors' Award 2015 granted by the American Institute of Chemical Engineers (AIChE). At the PSE chair of Otto-von-Guericke University Magdeburg, he works as an assistant lecturer for the graduate course Advanced Process Systems Engineering (APSE).

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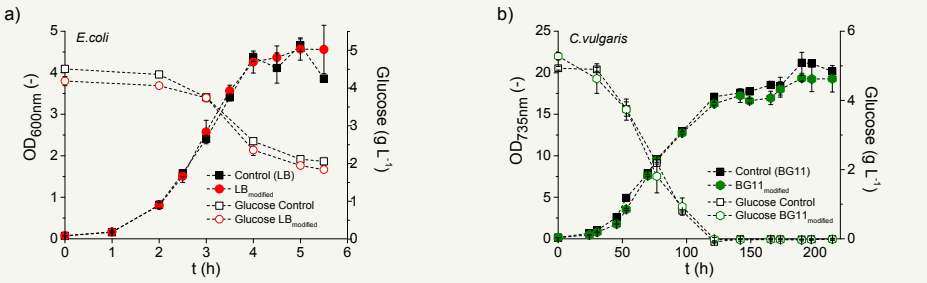
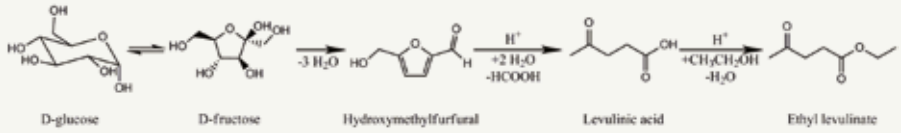


+ Figure 1:
Growth and glucose consumption of (a) *E. coli*, and (b) *C. vulgaris* on standard culture medium. The glucose concentration was adjusted by the addition of the aqueous phase of liquefied *D. salina* (100 C, 0 min) (reprinted from [2]).



+ Figure 2:
Hydrolysis and subsequent dehydration chain of storage carbohydrates, here: D-glucose.

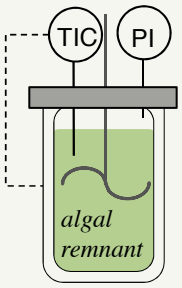
Valorization of Renewable Platform Chemicals from Algal Remnant

+ Photosynthetic microalgae are producers of valuable compounds, e.g. pigments. The main product obtained from the green microalgae *Dunaliella salina* is natural β-carotene, a light protecting pigment used as food and feed colorant, nutrient supplement or antioxidant. Due to the high halotolerance, the alga *D. salina* is one of the few green algae species which is industrially cultivated in saline open ponds and sea farms without competition of arable land. Over the years, the cultivation and harvesting technologies have been developed experienced-based having the goal to maximize the pigment yield. A systematic modeling approach based on dynamic flux balance analysis (DFBA) with detailed regulatory models could identify unexplored potentials for the accumulation of pigment molecules – an idea which was successfully demonstrated by the PSE group [1]. However, not only the optimization of the cultivation conditions is critical. The maximal valorization of all ingredient fractions of the algal cell is of high importance for the economics, too. The main product pigment and triglycerides are typically extracted by nonpolar solvents, whereby an algae residue is obtained. The maximal valorization of the remnant is one of the key factors for improving the overall profitability. Hydrothermal liquefaction under severe reaction conditions is an established thermochemical treatment method for the conversion of algal biomass into fuels. Our idea for capitalizing the remnant biomass is to apply a mild treatment with the goal to valorize the algal carbohydrates and other valuable biomolecular ingredients separately.

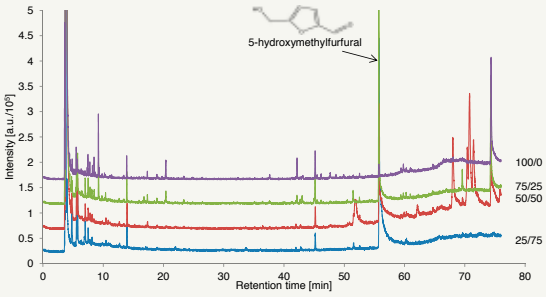
In the PSE group, two approaches have been followed to explore the potential of valorizing the remnant fraction after pigment extraction. Firstly, the aqueous phase solubles obtained in the mild hydrolysis of *D. salina* remnant were used as a carbon source in the cultivation of various micro-organisms. The decomposed remnant, consisting mostly of glucose, was successfully used for the cultivation of the bacteria *E. coli* and the alga *C. vulgaris* (Figure 1). No visible inhibitory effect by possible toxic decomposition products on the mixotrophic growth was observed [2].

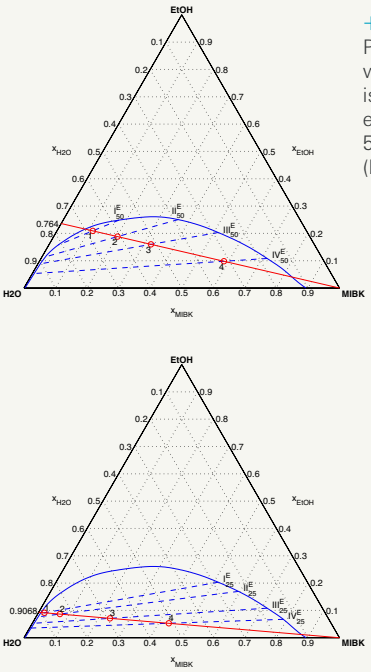
The second approach investigated in the PSE group was to explore and identify functionalized compounds formed from the algal remnant under mild treatment in an ethanol/water mixture [3]. The molecules in the liquefaction effluent are formed by the hydrolysis and subsequent dehydration of the storage carbohydrates following a dehydration chain (Figure 2). Our study demonstrated that the one-step conversion of the algal remnant direct to hydroxy methyl furfural, 5-HMF, was successful (Figure 3). No prior purification or separation of the carbohydrates from the biomass was required.

Today, computational chemistry is an important supporting tool for experimental analysis. Sophisticated computational methods are able to estimate thermodynamic properties in the absence of empirical data or other information. The Conductor like Screening Model for Real Solvents (COSMO) can be used



+ Figure 3:
Analysis of the reactor effluent after mild liquefaction at different ethanol/water ratios (v/v).





+ Figure 4:
Phase diagram of the system water/ethanol/MIBK (methyl isobutyl ketone) at 298 K at the ethanol/water mixing ratios 50/50 v/v (top) and 25/75 v/v (bottom).

to determine the surface charge densities of molecules which can be used to predict thermodynamic properties of pure liquids or liquid mixtures. The COSMO-RS approach was applied here to estimate the solubility and partitioning of the target compound 5-HMF during the extraction. An efficient separation of the product compounds by extraction from the reaction effluent is essential, because the liquefaction reactor effluent contains not only desired chemical compounds but also water soluble nutrient residues, salts, partially decomposed proteins and carbohydrates. In our study, we selected MIBK (methyl isobutyl ketone) as extraction medium. The solubility of 5-HMF was estimated computationally at the ternary composition points along the binodal curve (Figure 4). The recovery is influenced not only by the solubility, but also by the phase ratio. As predicted by COSMO-RS, 5-HMF was highly concentrated in the MIBK rich phase. The high partition ratio indicates that the 5-HMF was extracted foremost into the MIBK rich phase and only a small fraction was lost in the aqueous phase. The computational predictions of the 5-HMF recovery from the D. salina remnant by MIBK extraction were verified experimentally after mild liquefaction in an ethanol/water mixture. During the extraction, as expected, the ternary mixture split into aqueous and MIBK-rich phases at room temperature according to the miscibility gap in the phase diagram. 5-HMF was the main compound in the MIBK extract and the overall yield increased according to the MIBK concentration in the extract.

In conclusion, the proof-of-principle for a direct conversion of the algal remnant to chemical compounds by mild thermal treatment without any separation or purification of the biomacromolecules, e.g. starch or sugars, was demonstrated successfully. So far, the quantitative yields of this biogenic platform chemical 5-HMF are moderate. However, the applied liquefaction operating conditions are far from optimal, thus offer large optimization potentials. In view of an integrated biorefinery, we see that the valorization of the remnant algal biomass fraction for chemicals and/or fuel purposes could essentially enhance the economic potential of algae-based bioproduction processes [4].

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Dr. Techn. Liisa K. Rihko-Struckmann studied chemical engineering at the Helsinki University of Technology and obtained her diploma in 1989. Parallel to her first industrial position in Catalysis Department at Neste Oil Refinery in Finland, she started scientific research in the field of reaction engineering and modeling at Helsinki University of Technology, where she received her Ph.D. in 1997. After a two-year post-doctoral position in Helsinki, she joined the PSE group in Magdeburg in 2001. Her main scientific interest fields are the design of chemical and biochemical processes involving renewables and CO2 as raw materials as well as the progress in biofuels and renewable platform chemicals production. Since 2009, she is lecturing at the Otto-von-Guericke University Magdeburg in the field of biofuel production and sustainability.

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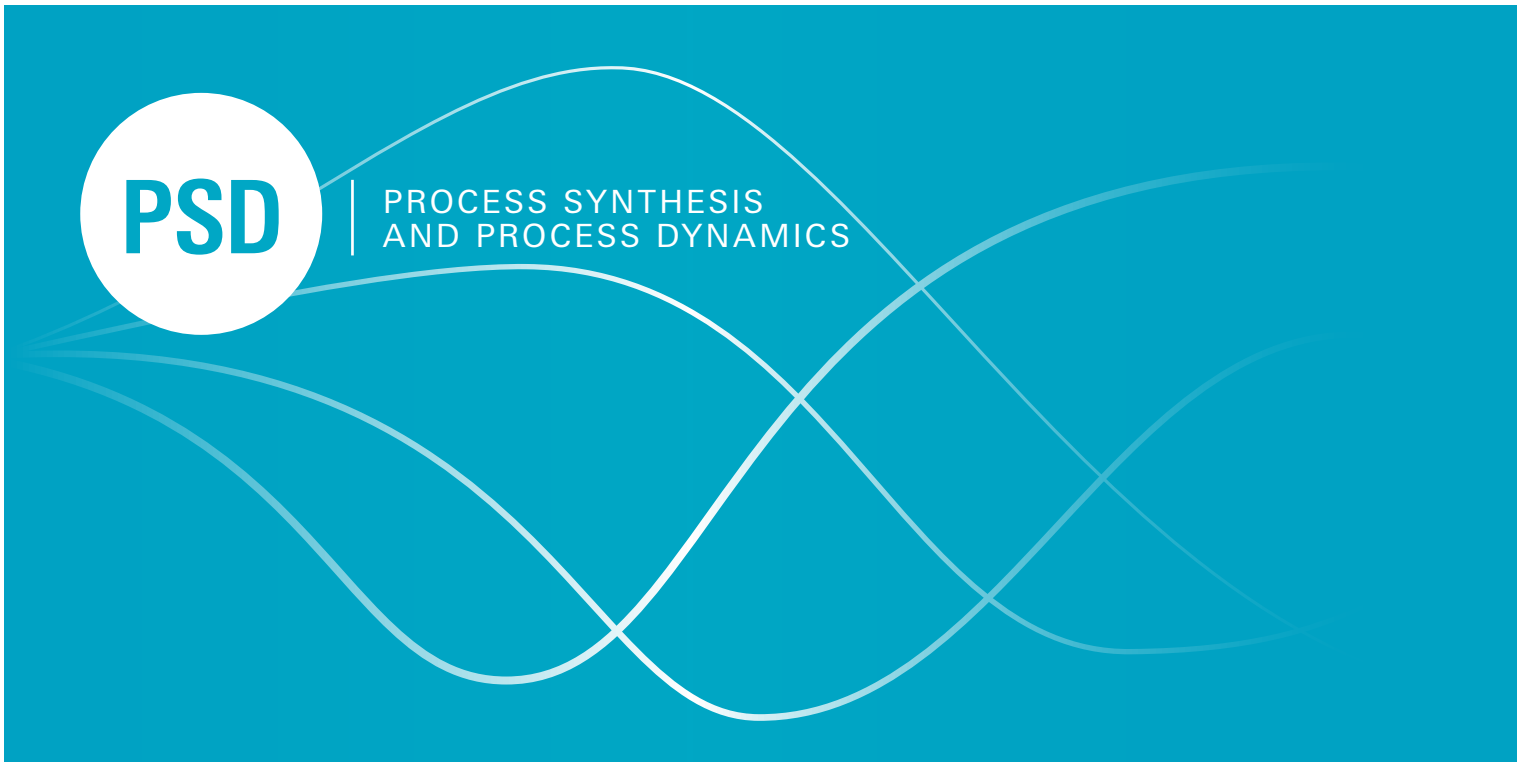

PROF. DR.-ING. ACHIM KIENLE |
EXTERNAL SCIENTIFIC MEMBER

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

The PSD group develops methods and tools for the synthesis, analysis and control of complex process systems. It combines physical and 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. Currently, the focus is on the control of particulate processes and the control of advanced chromatographic processes. Particulate processes are described by nonlinear partial differential equations and represent a particular challenging class of distributed parameter systems. Important topics which are addressed by the PSD group comprise predictive mathematical modeling, the development of computer tools for the automatic nonlinear model reduction as well as new approaches to the robust and nonlinear control of particulate processes. Interesting applications are concerned with some novel crystallization, fluidized bed spray granulation and agglomeration processes.

Chromatographic processes are switched systems with cyclic behavior. Particular focus of the PSD group is on the adaptive cycle to cycle control and the plantwide control of integrated chromatographic processes leading to hybrid separation and/or hybrid reaction/separation processes. Some details are given in the research highlight section.

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 operating conditions. Special interest is on new

+ A simulated moving bed pilot plant, which was used among others for the experimental validation of the control concepts described on the next two pages.

methods for deterministic global MINLP optimization being developed in cooperation with partners working in the field of mathematics. Applications are concerned with some innovative multiphase reaction systems and integrated processes for the production of pure enantiomers.

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 modeling. Process applications are concerned with vaccine production processes and the biopolymer production in microorganisms.

During the period of this report, the PSD group has been involved in a number of highly visible larger joint research projects with external funding, among others the joint research center Transregio SFB 63 on integrated chemical processes in liquid multi phase systems, which involves about 15 other partners mainly from the TU Berlin and the TU Dortmund. Furthermore, the group has been involved in a national priority program SPP 1679 on dynamic flowsheet simulation of particulate processes, the MaxSynBio initiative of the Max Planck society on synthetic biology and a joint research project in the field of biosystems engineering funded by the Federal Ministry of Education and Research (BMBF) with partners from academia and industry.

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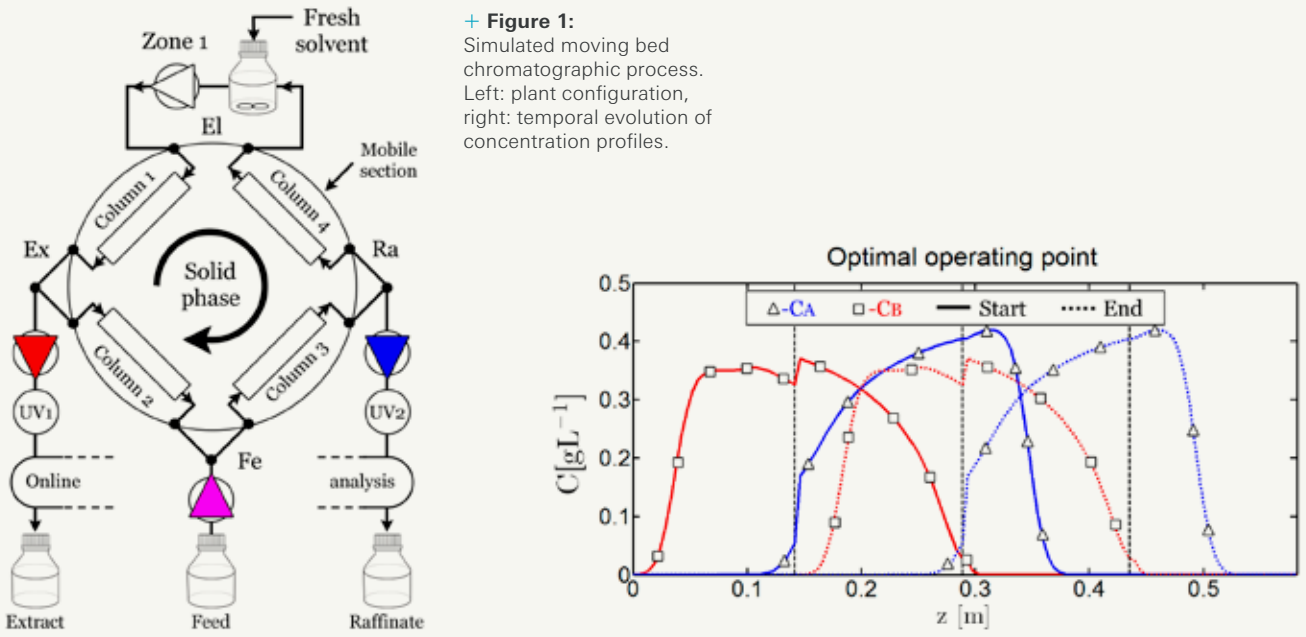


Figure 1:
Simulated moving bed chromatographic process. Left: plant configuration, right: temporal evolution of concentration profiles.

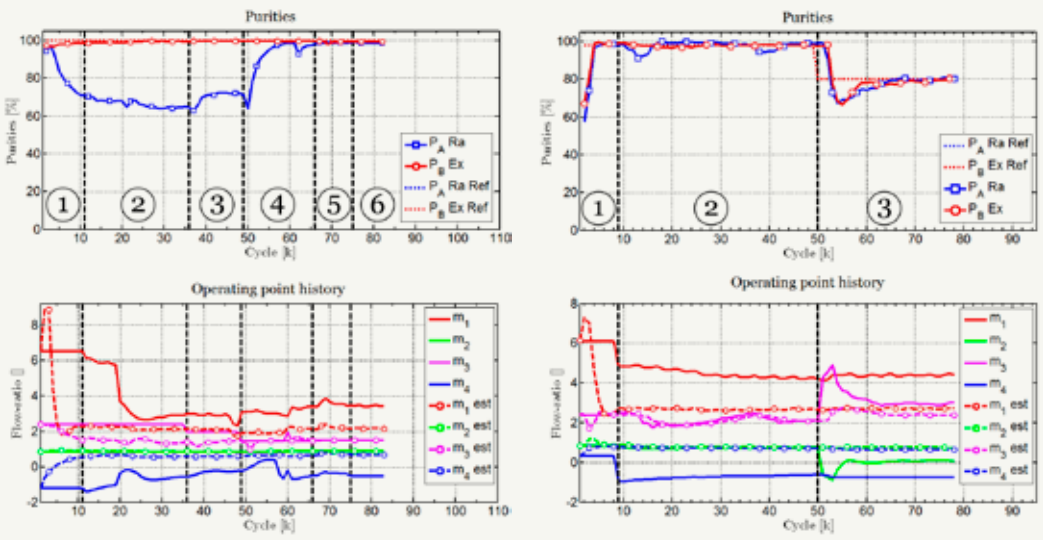
Parameter Estimation and Adaptive Control of Simulated Moving Bed Processes

Simulated moving bed (SMB) chromatographic processes are frequently applied for the continuous separation of isomers including stereo isomers like enantiomers, which play an important role in pharmaceutical production. The standard process configuration is illustrated in Fig. 1 for a classical binary separation problem. It consists of a series of chromatographic columns connected to a ring. The dynamics of the cyclic process is characterized by travelling concentration fronts (Fig. 1, right), where the component with the higher affinity to the fluid phase (concentration c_A in Fig. 1) is travelling ahead and the component with the higher affinity to the solid phase (concentration c_B) is lagging behind. The movement of fronts is illustrated in Fig. 1 with the profiles at the beginning (solid line) and the end (dashed line) of one cycle. Due to the limited capacity of the solid phase, the in- and outlets of this process have to be repositioned from time to time to maintain the desired separation

Standard application is for total separation to gain both components with high purity. Under optimal operating conditions with maximum productivity and minimum solvent consumption, the process shows a maximum sensitivity to disturbances. In practice, this is often handled by using suboptimal operating conditions to introduce some robustness against disturbances. Alternatively, feedback control can be applied to automatically reject disturbances under optimal operation conditions. This however, is a challenging task due to the system properties. The process represents a nonlinear system with distributed parameters, which is described by partial differential equations, and includes discrete events due to the switching of the in- and outlets.

Some powerful control concepts were developed during the last years. Most of them were based on model predictive control. These, however, are computationally very expensive due to repetitive online optimization. Therefore, we followed a different approach which is based on a fundamental process insight and exploits characteristic moving concentration fronts as illustrated in Fig. 1. Theoretical concepts were developed by Marco Fütterer [1] during his Ph.D. studies in the PSD group. More recently, concepts were extended and put to practice during the Ph.D. studies of Paul Suvarov [2],[3],[4],[5], which was a cotutelle with the University in Mons/Belgium. Experimental validation was done in cooperation with Ju-Weon Lee from the MPI's PCF group.

An important component of the control concept is a parameter estimator, which estimates online the optimal operating conditions for total separation from retention time measurements with UV sensors and some basic discrete time model for the movement of the concentration fronts based on characteristic velocities. Experimental results for the open loop operation of the parameter estimator are illustrated in Fig. 2, left. Application was demonstrated for the separation of the enantiomers of Bicalutamide - an interesting pharmaceutical compound. During phase 1 in Fig. 2, the process was started



+ Figure 2: Experimental evaluation of the developed concepts. Left column: Validation of the online parameter estimator, right column: Validation of the control concept.

up with wrong operating conditions leading to a cyclic steady state with very low purity of the raffinate as indicated by the blue line in the upper left diagram of Fig. 2. In parallel, the parameter estimator determines optimal operating conditions for total separation during the first ten cycles of phase 1. Afterwards, the crucial m_3 value is applied to the process in two steps during the phases 3 and 4 in Fig. 2 leading indeed to the desired high product purities of both components in the upper left diagram.

In the standard design approach for SMB processes, optimal operating conditions are calculated *offline* from adsorption isotherms. These, however, are often not so well known or may even change over time due to degradation of the solid phase. In addition, the separation is influenced by unknown dead volumes introduced by the tubes and fittings. All of these effects are automatically compensated by the proposed *online* estimator using available measurement information. The estimator is therefore also a powerful tool for process design. It requires only rough initial estimates of the adsorption isotherm as illustrated above.

The application of the parameter estimator for closed loop control is illustrated in the right column of Fig. 2. The control strategy is relatively simple. It comprises some feedforward action based on the estimated parameters and some feedback control with standard PI control. As illustrated in Fig. 2, the strategy can be used to adjust the product purities also at some given lower values. This can be attractive from the practical point of view, because reduced product purities admit higher productivity.

Ongoing research is concerned with more advanced control strategies and an application to more advanced separation processes including ternary separation problems, which play an important role, for example for the isolation of natural products. **I Dr. Paul Suvarov**

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Author **Dr. Paul Suvarov**

Paul Suvarov is currently working as a researcher at the University of MONS (UMONS), Belgium. He has studied at the Faculty of Electrical and Electronic Engineering of the Dunărea de Jos University in Galaţi, România where he received his master degree in Telecommunications in 2008. Since 2011, he was involved in the research project 'Robust control methods for Simulated Moving Bed Chromatographic processes' at the Max Planck Institute in Magdeburg and UMONS, following a cotutelle program involving the Otto von Guericke University in Magdeburg and UMONS. He completed his dissertation and received the Ph.D. in 2016.

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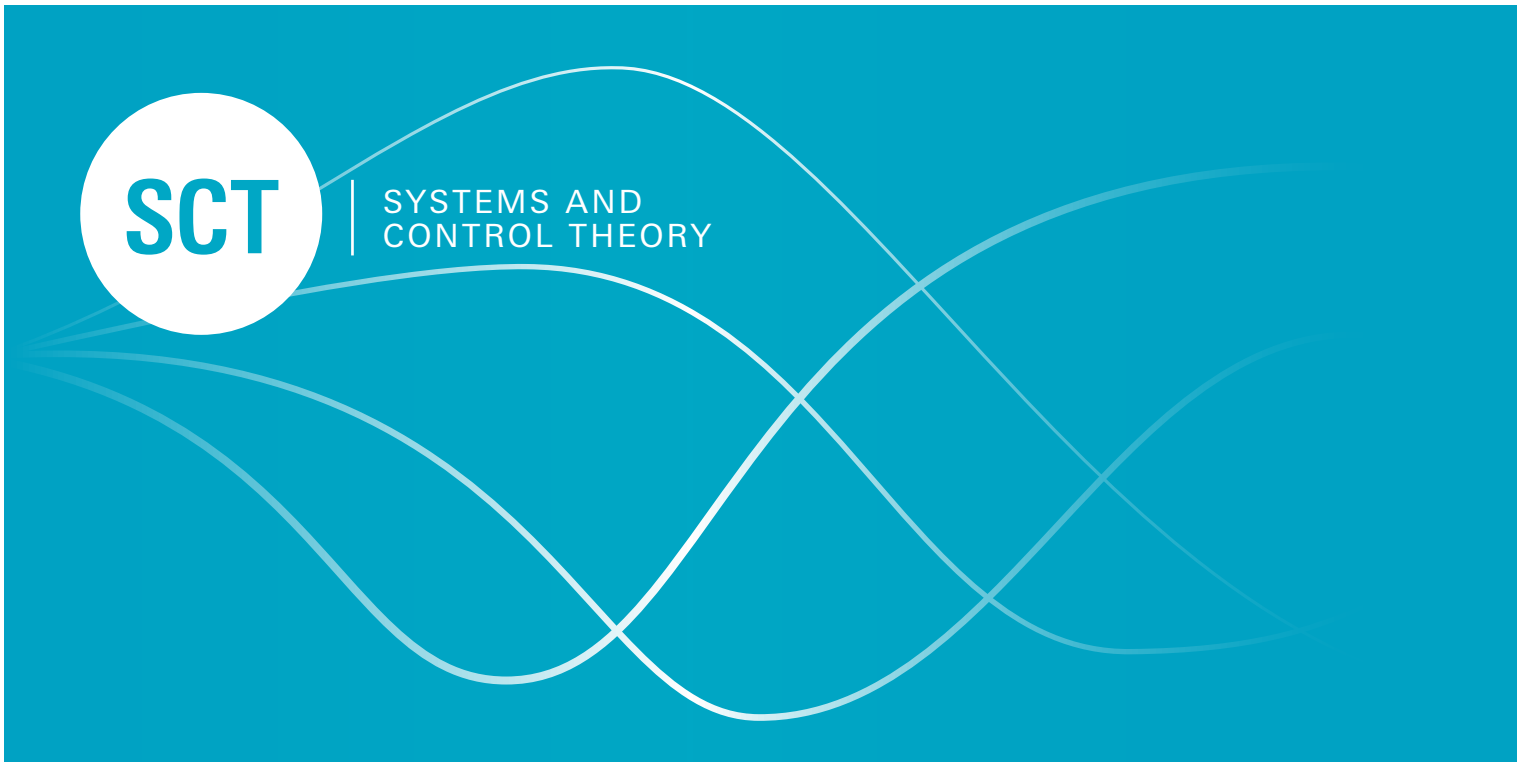

"There is nothing as practical as a good theory"

(K. Lewin)

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

The SCT group is led by Jörg Raisch who has been an External Scientific Member of the MPI since 2001. Jörg's primary affiliation is with the Technische Universität (TU) Berlin where he heads the Control Systems group within the Department of Electrical Engineering and Computer Science. In practice, both groups operate as a unit and there are currently 20 PhD students, three postdoctoral researchers, and two senior researchers.

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

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

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

+ Dr. Thomas Schauer (TU Berlin) and Prof. Dr.-Ing. Jörg Raisch assessing a new omni-directional drive concept for a rehabilitation robot.

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

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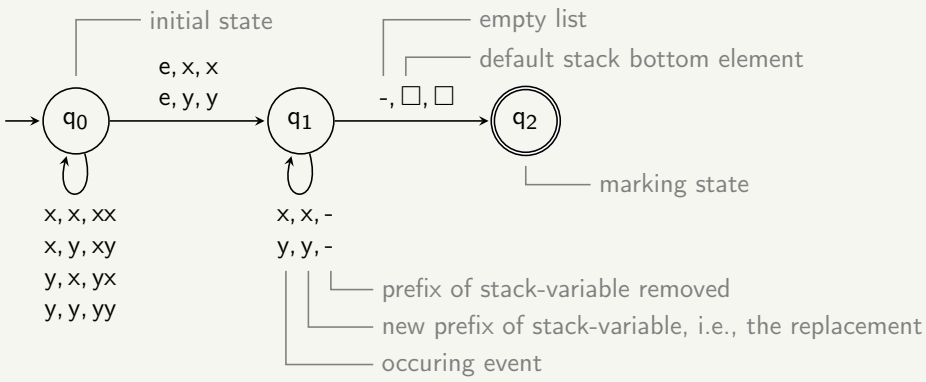


+ Figure 1:
Deterministic Pushdown Automaton marking all sequences of events x, y, and e where (1) event e occurs precisely once and (2) the sequence that occurs before event e occurs is repeated in reversed order after event e.

Automatic Controller Synthesis for Discrete Event Systems

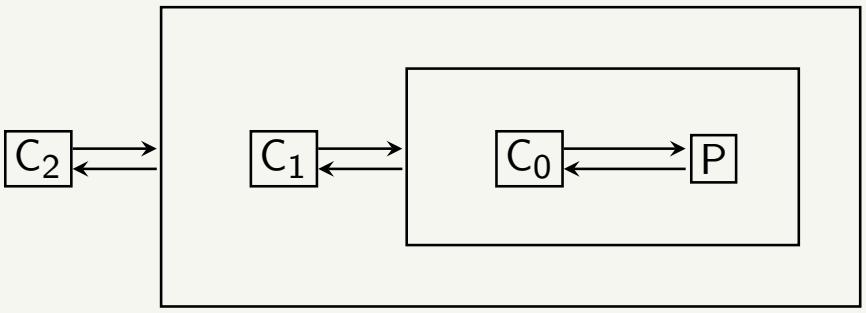
+ Many technical processes, e.g., in manufacturing and traffic engineering, are characterized by the occurrence of discrete events and are modelled by discrete event systems. The fully automated synthesis of controllers for such systems is an important field in the domain of control theory. Based on a description of the system to be controlled (plant) and a description of the desired behavior (specification), a controller is to be synthesized by applying a suitable algorithm. This controller, via appropriate interaction with the plant, restricts the plant behavior to enforce the specification.
Events may be preventable or non-preventable by a controller. Non-preventable events are often associated with sensor information, and can then be interpreted as inputs to the controller. Preventable events, however, are associated with information that is sent from the controller via actuators to the plant.

In practice, there are often multiple controllers interacting with a single plant to simultaneously enforce multiple specifications. In this case, the individual controllers are composed to provide an overall controller. In the context of such a compositional controller construction, it is important that each individual controller only restricts the plant behavior to an extent where its associated specification holds. Controllers satisfying this requirement are called minimally-restrictive. Stated differently, a minimally restrictive controller may only prevent an event if its occurrence would lead to a violation of the specification. Thus, the individual controllers minimally restrict the set of preventable events resulting in a closed-loop system with maximal freedom.

A further requirement is that every task started by the plant can eventually be completed. Controllers satisfying this requirement are called nonblocking. This property also ensures the absence of deadlocks, where the controller would not allow any further events to occur. Finally, the controller to be synthesized must respect the partition of the event set into preventable and non-preventable events.
Standard controller synthesis algorithms modify initial controller candidates by iterative minimal restriction until a controller candidate is obtained satisfying all the above requirements.

Ramadge und Wonham [1] developed a controller synthesis procedure where finite automata are used as realizations for the involved plant models, specifications, and controllers. The constructions used within the controller synthesis procedure are then based on algorithmic constructions on finite automata, which can be easily implemented. Furthermore, controllers represented by finite automata can (in principle) be easily composed to provide an overall controller as discussed above.

In our work we have structured, formalized, and verified this well-established approach on an abstract level to allow for subsequent instantiations to concrete domains [3]. Ramadge



+ **Figure 2:**
Several controllers (C_i) interacting with a plant (P).

und Wonham's controller synthesis procedure based on finite automata is then an instantiation of this abstract controller synthesis procedure. This instantiation is given by instantiation of building blocks for the abstract controller synthesis procedure. These building blocks, taken together, enforce the specification in a minimally restrictive way, while guaranteeing nonblockingness and respecting the (non-)preventability property of events.

Additionally, we have introduced a more powerful instantiation where the specification and the constructed controller are modelled by deterministic pushdown automata (partially published in [2]). Deterministic pushdown automata are a standard extension of finite automata obtained by integrating a so-called stack variable. Past behavior is not only stored in the current automaton state, but also recorded in a theoretically unbounded stack. The use of deterministic pushdown automata for describing specifications allows for a broader class of specifications than obtained by using finite automata. In particular, deterministic pushdown automata allow to state properties based on the data stored in the stack variable. Hence, it is possible to compare current sequences of events to previously recorded sequences (of arbitrary length), or to count the number of occurences of events.

This extension of controller synthesis for discrete event systems to a more expressive formalism is also provided by an instantiation of our abstract controller synthesis algorithm. However, due to the existence of the stack variable, the instantiation of the basic building blocks proved to be much more complex than in the standard case.

We have formalized and verified the abstract synthesis procedure as well as the instantiation based on deterministic pushdown automata in the interactive theorem prover Isabelle/HOL to ensure maximal confidence with respect to our results.

I Sven Schneider

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Author **Sven Schneider**

After participating in research and teaching activities for various professors at the Technische Universität Berlin he obtained his diploma in 2008. Aftwerwards, he joined the the group of Uwe Nestmann at the Technische Universität Berlin as a Ph.D. student working on models for concurrency and control theory. In 2014, he joined the Max Planck Institute in Magdeburg to continue the work on control theory as presented here. In mid 2016 he joined the Hasso-Plattner-Institute for Software Systems Engineering in Potsdam working additionally on theory and applications of graph transformation systems.

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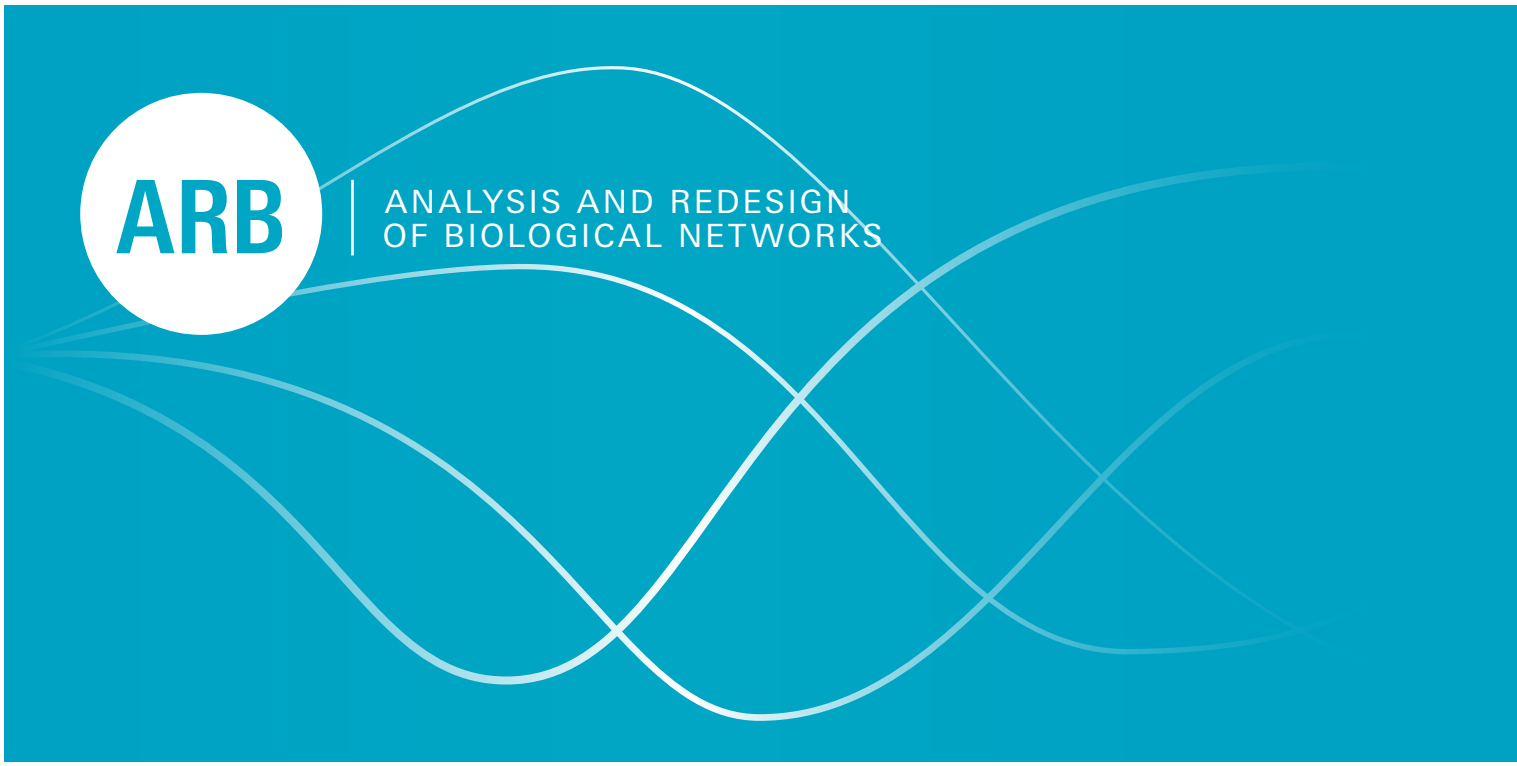

DR.-ING. STEFFEN KLAMT | SENIOR SCIENTIST

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

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

Highlights and trends in 2015/2016

As one important highlight in 2016, the ARB group became a funded partner of *de.NBI*, the German network for bioinformatics infrastructure. *de.NBI* is supported by the Federal

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

Ministry of Education and Research (BMBF) and provides comprehensive bioinformatics services to users in life sciences research and biomedicine. Together with Prof. Ursula Kummer (Heidelberg University), our group will be responsible for providing support and tools for modeling in systems biology. Another new BMBF-funded project ("Z-Fuels") deals with acetaldehyde production by *Zymomonas mobilis*. Within a larger consortium, our group will be responsible for bioreactor cultivations and in depth characterization of *Z. mobilis* strains designed for this process.

In 2015/2016, the research of the ARB group resulted in more than 20 publications reporting, for example, advances in computational strain design or new insights in the HGF signaling network in hepatocytes. Further, in collaboration with the BPE group, we have started activities in the exciting field of mathematical modeling of microbial communities and presented a new conceptual approach for modeling metabolic interdependencies in those communities with applications for the biogas process. As a major trend within the ARB group, several new methods and strategies for the rational design of microbial cell factories have been developed and partially experimentally tested in our lab with *E. coli* as host organism. Key results of these developments were presented by an invited talk at the "Metabolic Engineering" conference (the major symposium in this field) in Kobe (Japan) in June 2016. One particularly successful example of these research activities concerns the model-based design of an *E. coli* strain for the high-yield production of itaconic acid, an important platform chemical for polymer synthesis. Our IMPRS student Björn-Johannes Harder reports about this project on the next two pages demonstrating the power of rational metabolic engineering approaches.

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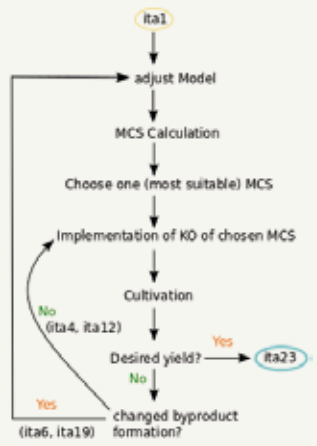
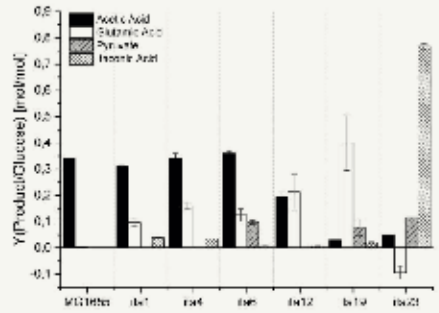
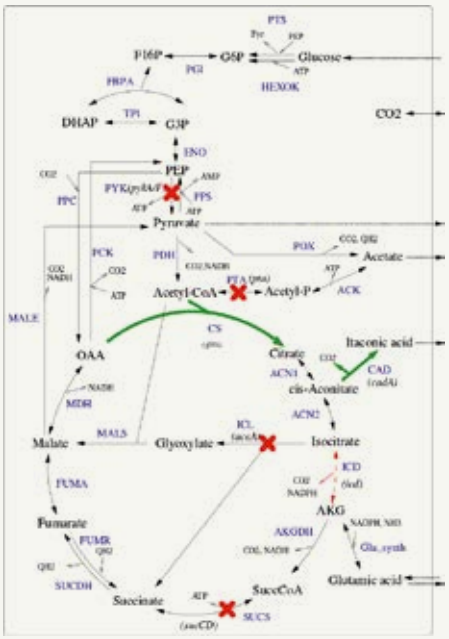






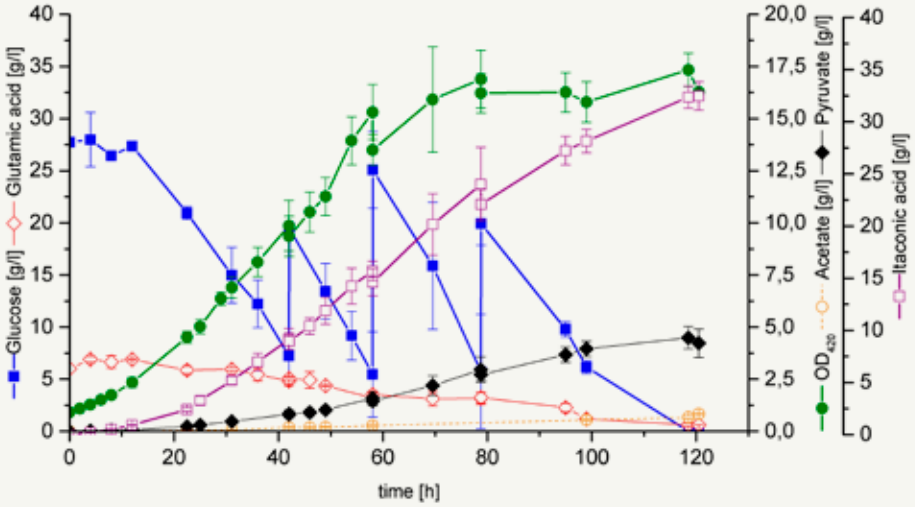
Strain	ita1	ita4	ita6	ita12	ita19	Ita23
Genotype	MG1655 *pCadCs*	MG1655 Δ*aceA* *pCadCS*	MG 1655 Δ*aceA* Δ*sucCD* *pCadCS*	MG1655 Δ*aceA* Δ*sucCD* Δ*pykA* Δ*pykF::Cam* *pCadCs*	MG1655 Δ*aceA* Δ*sucCD* Δ*pykA* Δ*pykF* Δ*pta* *pCadCs*	MG1655 Δ*aceA* Δ*sucCD* Δ*pykA* Δ*pykF* Δ*pta* Δ*Picd::Cam_P2* pCadCs

Model-based Design of an *Escherichia coli* Itaconic Acid Cell Factory

One major goal of industrial (white) biotechnology is to develop bio-based and sustainable production processes that can replace traditional routes to chemicals based on petroleum. An established workhorse for bio-based production processes is *Escherichia coli*, a well-characterized and fast growing bacterium. It has been successfully engineered to produce organic acids (lactic acid; succinic acid), alcohols (ethanol; 1,3-propanediol) and amino acids (L-lysine; L-threonine). In this project we aimed to engineer *E. coli* for high yield itaconic acid production. Itaconic acid, which was classified by a DOE-report as one of the top twelve value-added compounds derived from biomass, is industrially used for the production of polymers, coatings, lattices and detergents. Itaconic acid is currently synthesized in fermentation processes with the natural producer *Aspergillus terreus*, a filamentous fungus [1]. However, this organism grows slowly and has a high oxygen demand. Using instead an engineered *E. coli* strain would help to overcome these problems.

We started by introducing the heterologous (non-native) enzyme for itaconic acid production (cis-aconitate decarboxylase (CAD) from *Aspergillus terreus*; Figure 1) in the wild type *E. coli* strain MG1655 [2]. The respective gene *cadA* from *Aspergillus terreus* was codon-optimized and co-expressed with the citrate synthase (CS) of *Corynebacterium glutamicum*, which is insensitive to regulation by NADH increasing the flux through the tricarboxylic acid cycle (TCA). Itaconic acid was indeed produced by the derived strain ita1, however, the yield was quite low (0.04 mol/(mol glucose)). Therefore, we aimed to use techniques of computational strain design to rationally modify this strain for maximal itaconic acid production. We used our developed framework of constrained minimal cut sets [3] to identify, within a stoichiometric model of the central metabolism of *E. coli*, all minimal gene knockout strategies that guarantee a high itaconic acid yield ($Y_{(Itaconic\_acid/glucose)} > 0.7$ mol/(mol glucose)) while still allowing some minimum growth ($\mu \geq 0.01$ h^{-1}). Each minimal cut set (MCS) represents one intervention strategy that results in stoichiometric coupling of growth and product synthesis, that is, itaconic acid becomes a mandatory byproduct of growth. When implementing the knockouts of a calculated cut set, as a conceptual novelty, we pursued an adaptive approach allowing changes in the model (and in the initially calculated cut sets), if a genetic modification induced significant changes in byproduct formation in the constructed strain [2]. Initially, one out of the 945 cut sets calculated was selected for strain ita1 and the first gene (*aceA*; isocitrate lyase (ICL)) suggested by this cut set was removed from the chromosome of *E. coli*. The derived strain (ita4) was analyzed in shake flask cultivations (Figure 1). Since ita4 showed a similar phenotype as ita1, we went on by deleting the next gene (*sucCD*; succinyl-coA ligase (SUCS)), contained in the cut set resulting in strain ita6. This strain excreted pyruvate, which had to be considered by enabling the export of pyruvate in the model. Consequently,

+ **left: Figure 1:**
Iterative model-based design of a high-yield itaconic acid producer strain of *E. coli*. The figure on the left illustrates how the phenotype changes observed in the different strains affected the strain design process (adaptation of model and minimal cut sets (MCSs)). The bar diagram shows the performance (metabolic yields) of those strains and the metabolic interventions in the final producer strain ita23 are summarized in the map on the right-hand side (green arrows: upregulation; red arrows: downregulations; red crosses: reaction/gene deletions).



+ **right: Figure 2:**
Fed-batch cultivation of *E. coli* strain ita23.

we recalculated the intervention strategies and identified the pyruvate kinase (PYK) as essential target to reduce pyruvate excretion. The deletion of the two isoforms of the pyruvate kinase (*pykA/pyk*F genes) showed reduced acetate formation and slightly increased glutamate production, but no longer pyruvate excretion (strain ita12). To directly affect the acetate formation, we next inactivated the main acetate synthesis pathway (PTA) as suggested by the cut sets resulting in a sharp reduction of acetate formation in strain ita19. Because of the significantly increased glutamate formation in ita19, we updated the model by allowing glutamate excretion. Since glutamate is essential for growth, no intervention strategy (cut set) can exist which blocks or reduces glutamate excretion while still allowing growth. When glutamate consumption was allowed, the deletion of the isocitrate dehydrogenase (ICD) was found as a suitable strategy. We tried to reduce the activity of the ICD by replacing the natural promoter by a synthetic promoter with low activity (strain ita23) to enable growth without supplementation of glutamate. Unfortunately, the flux to glutamate was not high enough to enable growth. We therefore added (as also suggested by cut set analysis) glutamate to the medium. The strain ita23 now grew with a maximum growth rate of 0.09 h^{-1} and produced 2.27 g/l itaconic acid with an excellent yield of 0.77 mol/(mol glucose (figure 1). The uptake of glutamate was low since, due to the interrupted TCA cycle, it cannot be further degraded and only be used for biomass synthesis. In a fed-batch bioreactor process (Figure 2), this strain produced itaconic acid with a high titer of 32 g/l and with an overall yield of 0.68 mol/(mol glucose) and a peak productivity of 0.45 g/l/h [2]. The reported yields and titers are by far the highest values that have ever been achieved for heterologous itaconic acid production and indicate that realistic applications come into reach. Furthermore, this study demonstrated the great potential of rational metabolic engineering based on computational strain design methods such as minimal cut sets. I **Björn-Johannes Harder**

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Author **Björn-Johannes Harder**

Björn-Johannes Harder studied Biotechnology at the Technical University Braunschweig, where he received his Master of Science degree in 2013. Since 2014, he is PhD student in the International Max Planck Research School Magdeburg for Advanced Methods in Process and Systems Engineering (IMPRS ProEng) and member of the ARB group. In his Ph.D. project he implements model-based metabolic engineering strategies for *Escherichia coli*.

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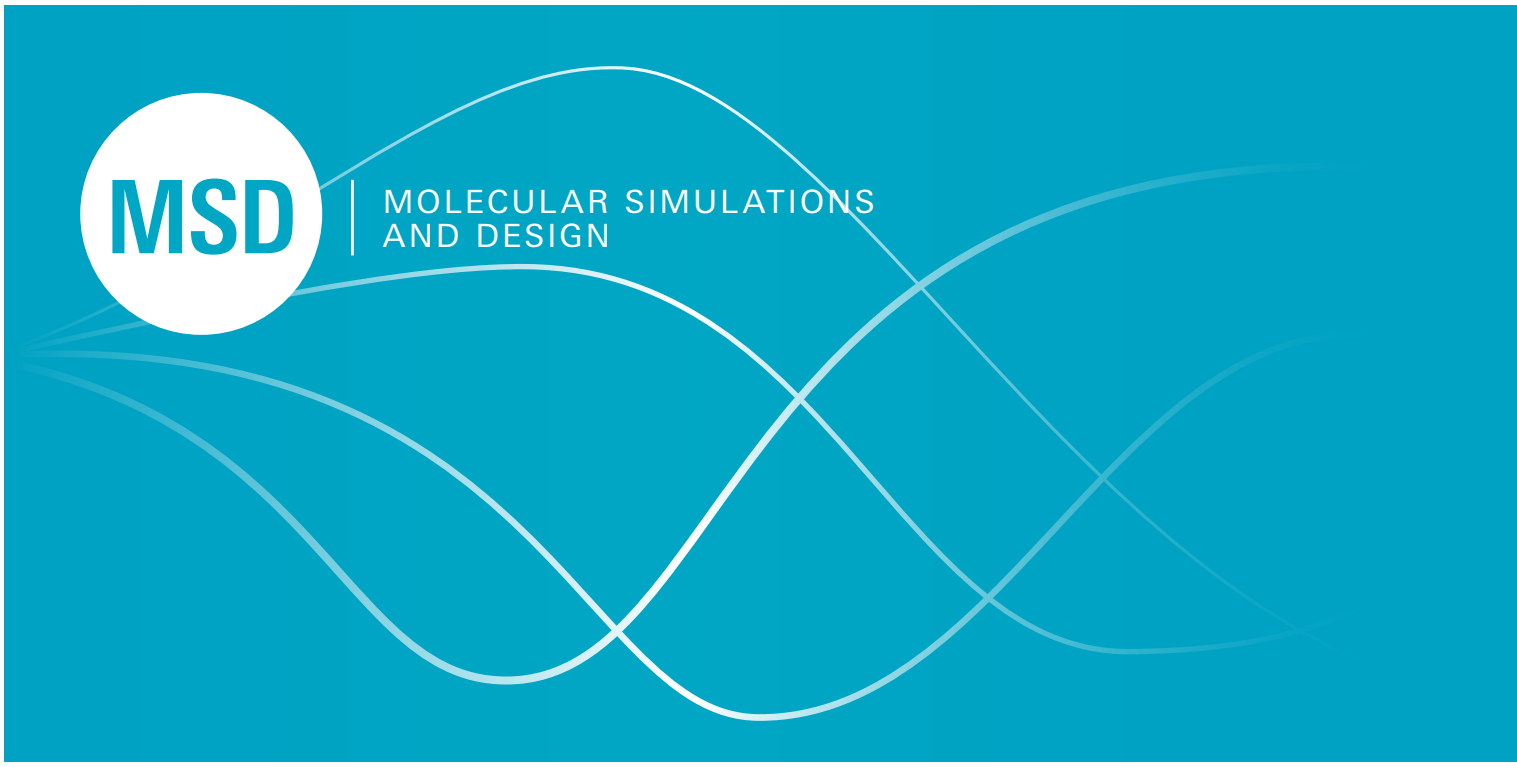


DR. RER. NAT. MATTHIAS STEIN I SENIOR SCIENTIST

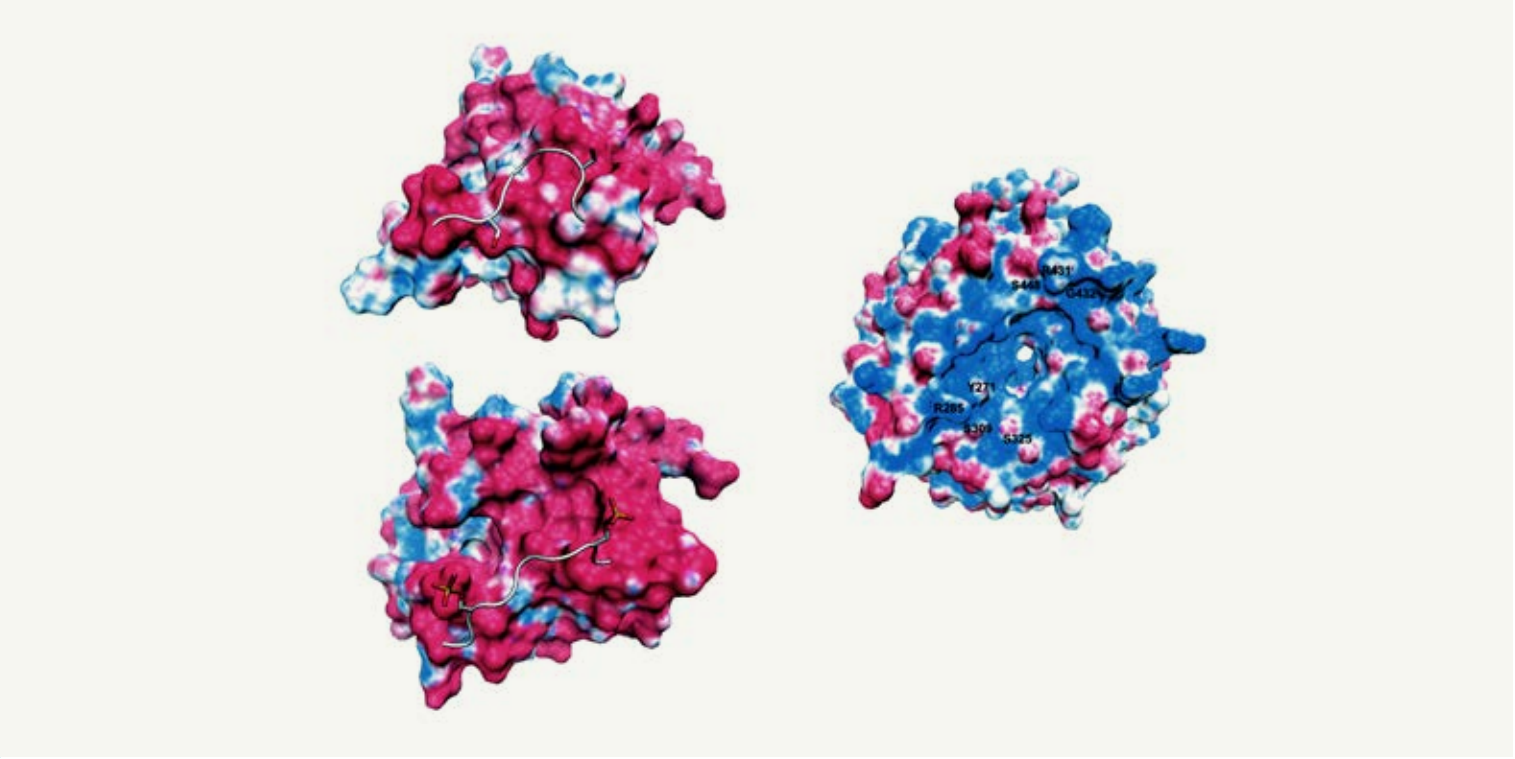
The Molecular Simulations and Design (MSD) group is a Max Planck Research Group (MPRG) at the MPI Magdeburg led by Dr. Matthias Stein. The MSD group performs multi-scale computer simulations in order to elucidate complex phenomena from biology and chemistry. The areas of expertise comprise a wide range of computational approaches, ranging from quantum chemistry, atomistic and coarse-grained molecular dynamics to Brownian dynamics. It is the combination of these methods which allows investigating chemical and biological processes across many time and spatial scales.

In close collaboration with experimental partners in the institute, in Germany and worldwide, challenging projects which range from homogeneous catalysis to protein signaling are being addressed.

As one example for such a successful collaboration, the medical faculty of the Magdeburg University (OvGU) can be mentioned. With partners from experimental internal medicine, the structure, stabilization and post-translational modification of a protein-protein complex made up of the nuclear growth factor NF-κB and its inhibitor IκBα was simulated. Incorrect physiological regulation of NF-κB has been linked to cancer, inflammatory and autoimmune diseases. By use of tools from bioinformatics, protein threading and molecular dynamics simulations, it was possible to investigate the protein-protein complex between NF-κB and IκBα. According to our extensive simulations, the N-terminal signal receiving domain (SRD) is by no means disordered as previously suggested but displays stable secondary structure elements closely related to that of the ankyrin repeat unit. Phosphorylation by the kinase IKK at two serine residues of the SRD unexpectedly leads to a stabilization of the protein-protein complex and an increase in local order descriptors. Understanding the regulation and control of NF-κB activity in its signaling pathway is a pre-requisite for the development of new therapeutic approaches in relevant medical areas such as cancer and cardiovascular diseases.

As part of the Collaborative Research Centre (CRC) **SFB/TR 63 InPROMPT**, the MSD group computationally elucidates the reaction mechanisms, calculates thermodynamic and kinetic parameters of large scale industrial chemical processes. Today, fine-tuned catalysts are able to generate high-level chemical products at high yield and selectivity. By choosing appropriate conditions, the productivity and selectivity of such processes can be controlled according to the choice of solvent and external parameters such as temperature and pressure. This work is performed in cooperation with partners from universities in Magdeburg, Berlin and Dortmund.

The MSD group is part of two large European networks: COST Actions **CM1305 ECOSTBio** and **CM1402 Crystallize** which promote the exchange of students and foster



+ Electrostatic potential maps of unphosphorylated NF-κB (top left) and doubly phosphorylated NF-κB (bottom left) which can be recognized by the complementary WD40 domain of beta-TrCP (right).

international collaborations in the field of spin catalysis and molecular organic crystals, respectively.

Esra Boz from Istanbul Technical University (ITU) joined the MSD group in her final year of PhD as a guest scientist with a scholarship from the Turkish Science Council TÜBITAK. Due to an unstable political situation in her home country, Esra had to return and her scholarship terminated immediately. She is now back and financed by a German third party grant and is going to receive financial support from the president of the Max Planck Society in the coming year

Dr Serdar Durdagi, former postdoc in the MSD group and now Associate Professor at the Bahcesehir University Istanbul, has received The Scientific and Technological Research Council of Turkey (TUBITAK) 2016 Incentive Award in Health Sciences. This is the most prominent prize for young scientists in Turkey and awarded to those who have made already significant contributions in their work at an international level.

As an international guest scientist, Prof. Sandeep Kaur-Ghumaan from the University of Delhi (India) spent two periods in 2015 and 2016 with the MSD group on the basis of a Max Planck India Mobility Grant. Being a synthetic bioinorganic chemist, her work on bio-inspired redox active catalysts is supported by computational work of the MSD group. The biomimetic complexes perform the same reaction as transition metal containing enzymes in nature. By designing these model compounds accordingly, their reactivity and stability for the electrochemical proton reduction to molecular hydrogen (H_2) is investigated.

Molecular hydrogen is one of the global mobility energy carriers of the future. In a fuel cell, chemical energy (energy stored in molecular bonds) is converted into electrical energy. The products of the reaction in the fuel cell are water (H_2O) and electricity. It is possible to also have enzymes perform the catalytic processes in a biological fuel cell. Bacteria with non-noble metals are able to synthesize or split hydrogen (H_2). Molecular simulations provide an in-depth insight into the protein-electrode association and binding which is not accessible by experiment.

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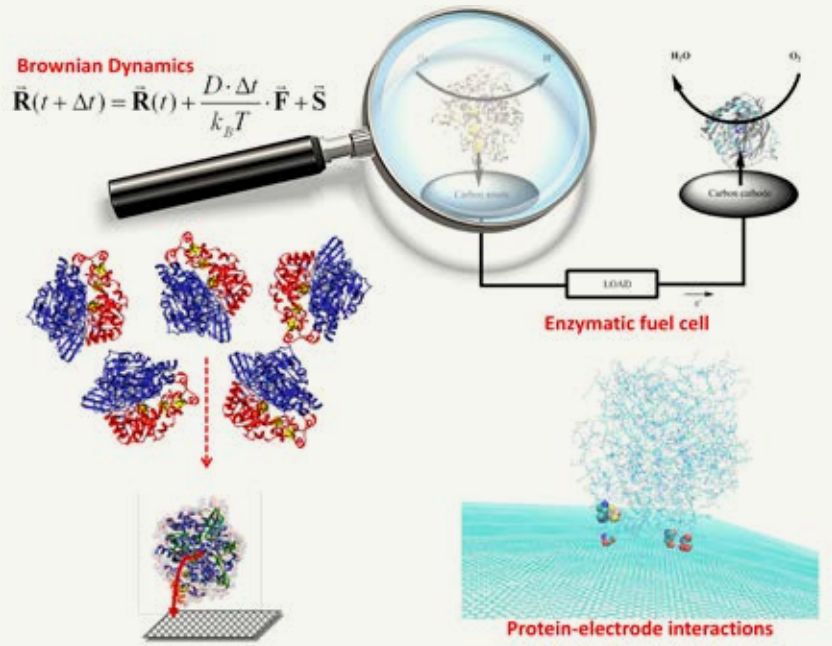


+ Figure 1:
Schematic design of an enzymatic fuel cell (top right). Molecular hydrogen (H_2) is oxidized and oxygen (O_2) is reduced to water. By Brownian Dynamics (left), the association and orientation of the hydrogen splitting hydrogenase enzyme on the anode were simulated. Amino acid residues that make contact with the graphite electrode surface were identified (bottom right).

Multiscale Simulation of Protein-Electrode Association and Electron Transfer in Enzymatic Fuel Cells

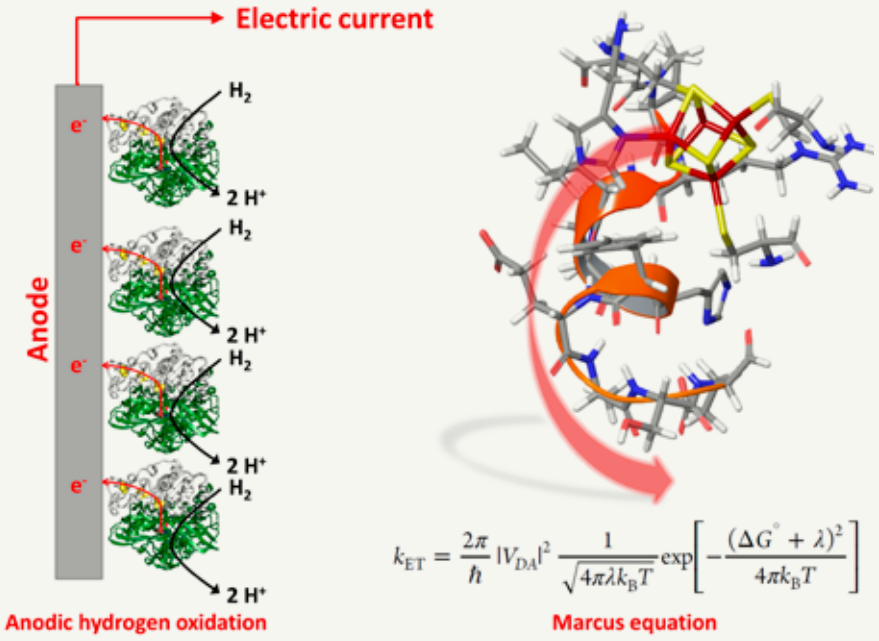
The development of usage of alternative energy sources is a global responsibility in terms of the consequences of global climate changes. Molecular hydrogen (H_2) is one of the future energy carriers and an efficient energy storage. In nature, enzymes called hydrogenases produce or split molecular hydrogen at ambient temperature by using earth-abundant cheap metals in their active sites. They serve as inspiration and example for the design of catalytically active biomimetic complexes which may then be used as alternative hydrogen activating materials.
The hydrogenase enzymes themselves can be also combined with a different class of enzyme (for example a laccase) to make up an 'enzymatic fuel cell' and generate an electric current from oxidizing hydrogen and reducing oxygen. In such a fuel cell, molecular hydrogen is split to yield protons and electrons. At the other (cathodic) side oxygen may be reduced and thus an electric current is generated and only harmless water (H_2O) is the final product. This makes H_2 the cleanest energy carrier of all.

Hydrogenase enzymes with a heterobimetallic nickel and iron active site can do the hydrogen splitting very efficiently. They perform the reaction up to 10.000 times per second. The generated protons wander along some protein amino acids as proton transfer pathway into the aqueous environment. The released electrons take a different route: they flow along a well-aligned chain of iron-sulfur clusters to the electron acceptor. In nature, the physiological electron acceptor is a cytochrome c3. In an enzymatic fuel cell, a graphite electrode can take the role of the electron acceptor and the hydrogenase enzyme adsorbs on its surface.

The overall rate of electron transfer from the active site to the electron acceptor can be measured experimentally but details of the protein-electrode interaction and the preferred orientation of the enzyme at the electrode surface is still beyond experimental resolution.

Brownian dynamics (BD) simulations are named after the British botanist Robert Brown who observed an apparently random motion of grains of plant pollen in water under the microscope. The laws and physical principles of this motion, however, were only explained by Albert Einstein 100 years later. The Brownian particle diffuses in solution and collides with a large number of small water molecules and thus performs an apparent stochastic motion. In molecular simulations, BD transport and diffusion can be simulated using the Ermak-McCammon algorithm.

A large number of computer simulations of the stochastic Brownian motion of a hydrogenase enzyme diffusing towards a graphite electrode surface were performed. They revealed details about possible protein orientations upon binding to the surface. The BD simulation approach allows an efficient sampling of rotational and translation orientations. Upon elec-



+ Figure 2:
Different electron transfer pathways upon hydrogen oxidation at the anode from the distal [4Fe4S]-cluster to the electrode surface were investigated. The rates of electron transfer of these plausible pathways were calculated according to the Marcus equation. Only the through-bond or through-space electron transfer pathway via histidine and phenylalanine amino acid residues to the terminal serine led to electron transfer rates in excellent agreement with experiments.

trode association, amino acids at the protein surface were identified which are critical for establishing the protein-electrode interaction.

Electron transfer is a quantum mechanical (QM) effect and requires a different computational approach. The overall rate determining step of electron transfer in an enzymatic fuel cell is that from the most distal iron-sulfur cubane cluster to the electrode or any other electron acceptor. The exact routes the electrons take from the distal [4Fe4S] cluster towards the electron acceptor are not known. The Marcus equation allows calculating the rate of electron transfer from a donor (D) to an acceptor (A). In this case, the distal FeS-cluster is the donor and a molecular representative of the graphite electron acceptor was chosen to be the acceptor (a coronene or circumcoronene molecule). The parameters in the Marcus equation that influence the rate of electron transfer are the donor-acceptor distance, the reorganization energies of the cofactors and the electronic coupling matrix between their respective HOMO and LUMO orbitals. All of these can be calculated quantum mechanically.

The BD simulations were used to identify protein-electrode interactions and snapshots from the trajectories were used to construct possible routes of electron transfer from the distal FeS-cluster to the electrode. The calculated rate of electron transfer between the distal FeS-cluster and the electrode acceptor was in excellent agreement with experimental measurements. In addition, it could be revealed that it is the unusual coordination of the distal iron-sulfur cluster by a histidine amino acid ligand that is responsible for this efficient electron flow [1].

When this amino acid histidine is substituted by a cysteine, like in standard [4Fe4S] cubane clusters, the rate of electron transfer decreases by three orders of magnitude. This is also in agreement with experimental observations but could not be rationalized so far. These findings also explain why hydrogenase enzymes from cyanobacteria cannot be used in enzymatic fuel cells. Their iron-sulfur cluster does not allow a directed flow of electrons from the active site to a fuel cell anode electrode [2].

The identification of details of spontaneous protein-electrode binding in an enzymatic fuel cell can be used to modify and stabilize this interaction. The stability of this biological fuel cell can thus be improved. Likewise, the efficient natural rate of electron transfer can serve as an inspiration for the design of novel, synthetic electron donors to be used in future fuel cells.

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Dr. Alexander Petrenko studied physics and applied mathematics; he did his PhD in chemical physics at the Academy of Sciences in Novosibirsk. He obtained his habilitation from the National Academy of Sciences in Ukraine. His professional scientific career led him to many different stays in the UK, US and Korea. Computing of intermolecular interactions, ab initio electronic structure calculations and the design of nanostructures and devices for molecular electronics and solar energy conversion are at the core of his research interests.

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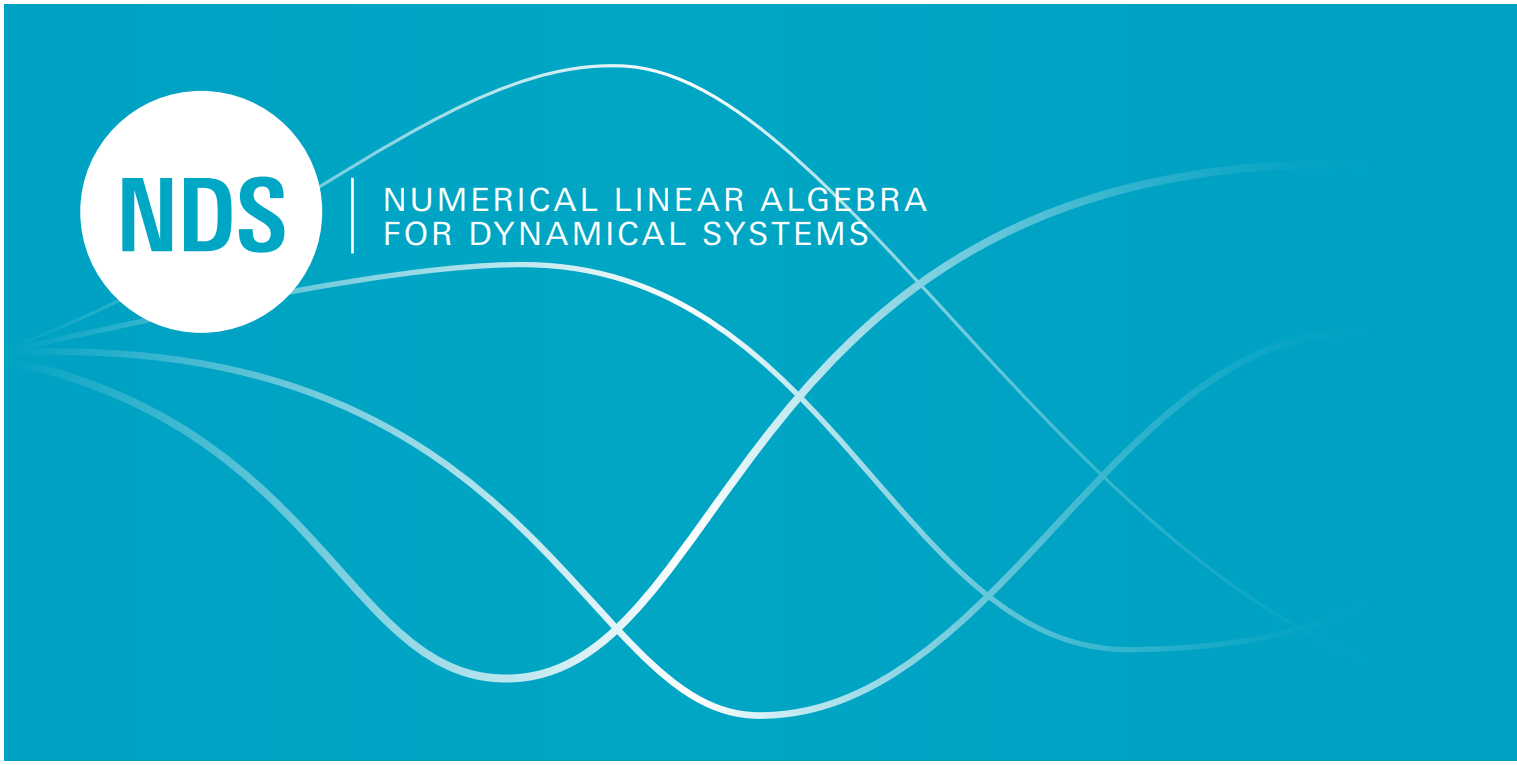

DR. MARTIN STOLL I SENIOR SCIENTIST

Our group was established in 2013 under the name Numerical Linear Algebra for Dynamical Systems, and has now seen three years at our institute.

In addition to a daily routine of writing and polishing papers and software, we also had many changes in the setup of our group. We unfortunately had to say farewell to Dr. Sergey Dolgov who won a prestigious EPSRC fellowship with the opportunity to work at the University of Bath. We are still collaborating with Sergey and wish him a fantastic time in the UK. Two of our Ph.D, students, Jessica Bosch (NDS) and Akwum Onwunta (CSC / NDS), successfully defended their doctoral dissertations in the summer of 2016. While Akwum is staying for a postdoctoral position to continue working on the quantification of uncertainty, Jessica left Magdeburg to take up a postdoctoral position at the University of British Columbia. She joined the group of Prof. Chen Greif and also became a fellow of St. Johns College at UBC. There were not only people leaving the group: Dr. Yue Qiu arrived with a Ph.D. from the University of Delft to work as a postdoctoral researcher in Prof. Benner's group and the NDS group. His work is focusing on aspects of statistical inverse problems in combination with the study of efficient solvers for energy systems.

Martin Stoll was very honored when he was awarded the 2016 Richard-von-Mises prize of the GAMM awarded at the GAMM annual meeting in Braunschweig. The prize came with the fantastic opportunity to give a plenary lecture in front of almost all applied mathematicians in Germany. In the summer of 2016, Martin Stoll also defended his habilitation at the University in Magdeburg which was titled *Fast iterative solvers for time-dependent PDE-constrained optimization problems*.

Much of our research effort has gone into what can be described as efficient simulation techniques for complex models. These models are often of a complicated structure

+ Solving phase field models using adaptive finite elements

inherited from the differential equations needed to describe particular phenomena. One of the particularly challenging problems comes from the curse of dimensionality that we wanted to lift in the area of PDE-constrained optimization and uncertainty quantification. The fruitful period over the last two years has seen many successful results by us and other groups.

This work mainly utilizes the structure of the corresponding equations and allowed us to dramatically reduce the complexity of the problems, see the research highlight for a more detailed discussion.

Our group was also involved in the organization of the meeting of the GAMM Activity Group on Applied and Numerical Linear Algebra here at our institute. This meeting brought together a fantastic mix of researchers both international and local as well as very experienced scientists and also scientists at the beginning of their careers.

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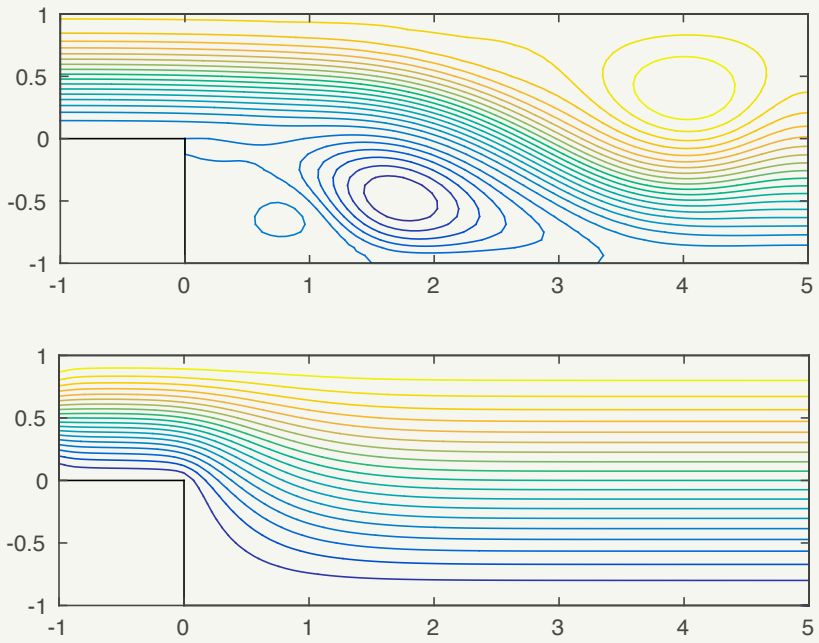
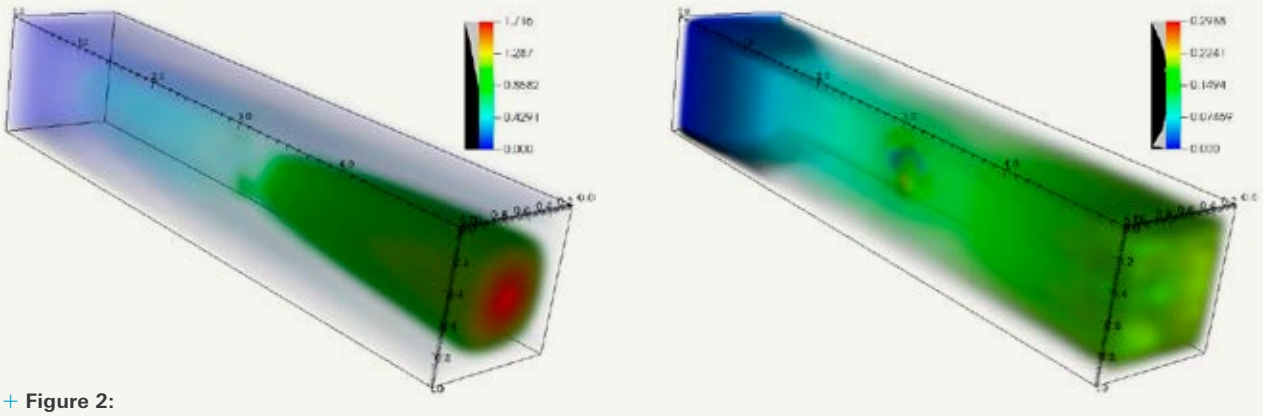


Figure 1: Controlled (bottom) vs. uncontrolled (top) Navier-Stokes flow over a backward facing step.

Breaking the Curse of Dimensionality

The concept of the *curse of dimensionality* is quite a challenging and ubiquitous issue in the fast-growing fields of computational science and engineering. The term was originally coined by Bellmann in 1961 when discussing the complexity of dynamic optimization problems. The discretization of infinite-dimensional problems defined on a d-dimensional hypercube is probably one of the common examples of the curse of dimensionality. More precisely, consider, for example, a unit square or a unit cube. If we cover the square with a mesh of constant width and then evaluate the infinite dimensional problem at every mesh-point on this grid, then we obtain a finite dimensional problem of size n. The width of the grid is an indicator to the accuracy of the numerical solution. In other words, the smaller the grid size, the more accurate the solution that one typically obtains. For a two-dimensional problem, this means that when we halve the width of the mesh, the number of points goes up by a factor of 4 as this is the result of a doubled number of grid points in both the x and the y directions. Similarly, in a three-dimensional space where we cover the unit cube with a mesh of equal width, the resulting increase in halving the mesh width is now 8 as a result of 2*2*2; that is, a two for each dimension. Proceeding in this fashion, this problem increases more and more as we consider higher dimensions. This means that for an arbitrary d-dimensional problem, halving the mesh size results in a corresponding increase in the complexity increase by 2^d. Even though we live in a three-dimensional world, higher dimensional problems occur on a very frequent basis.

In our current research, one of the problems that has posed a significant challenge with respect to the curse of dimensionality is the optimization of functions that are constrained by complex partial differential equation models [1]. To perform the necessary optimization, one essentially obtains a coupled system of complex equations that typically have the dimensionality of three spatial dimensions plus an additional temporal dimension. In order to obtain satisfactory numerical results, one then has to solve a very large linear system of equations that suffers from the curse of dimensionality. While many efficient techniques exist to solve the full (3+1)-dimensional problem, the reduction in complexity is necessary if one wants to tackle real-world scenarios. One of the key observations of our approach is that, quite often, the problems are fortunately endowed with a lot of mathematical structure. More specifically, using the mathematical language we say that the problems enjoy (tensor product) Kronecker product structure. This special structure allows us to rewrite the unknowns, typically given as a gigantic vector, into a matrix whose dimension is n_x times n_t, i.e., the spatial times the temporal dimension. So far nothing is gained! However, we next employ the well-known singular value decomposition (SVD) that is an indispensable tool in applied mathematics. Note that SVD occurs in many disciplines, but is often disguised under different names such as the principal component analysis (PCA), Karhunen-Loeve expansion (KLE), etc [2]. The SVD allows us to put the high-dimensional problem in *low-rank format*; that is, to optimally represent the matrix of large dimensions by a small number of vectors from the spatial and a small number of vectors of



+ **Figure 2:**
Mean velocity (left) and mean control (right) for a 3D Stokes-Brinkman optimal control problem with random data

the temporal dimension. This means the storage of a time-dependent problem reduces to a problem which is not much more expensive than a steady-state formulation. Crucially, the obtained low-rank form is the chief corner stone of our numerical algorithms; in fact, the low-rank form is then used within iterative solvers for the solution of the linear systems . In particular, a well-known iterative solver which we use is the minimal residual scheme (MINRES). Indeed, with an optimal complexity, the MINRES allows us to maintain the low-rank form throughout the iteration process. This comes at very little additional cost – mainly the need to re-compress to the smallest possible low-rank form.

While this process has proven extremely efficient for optimization problems with linear constraints, nonlinear differential equations pose a significant challenge to numerical algorithms. The question as to whether the low-rank approach extends to the nonlinear case is difficult to answer. We have taken first steps to show that for the Navier-Stokes equations such a strategy can work well and reduce the storage requirements to a small fraction of the full problem [3]. Another very challenging case comes from the optimization of differential equations that include random or uncertain coefficients. Numerical techniques for such problems typically suffer from the fact that our preferred method, i.e., the stochastic Galerkin method, requires vast amounts of storage due to the presence of Kronecker structure of the resulting equations. Hence, many people refrain from using this method. We have shown again a low-rank technique can efficiently reduce the computational complexity and for this we have employed recent methods designed for the numerical treatment of tensor valued equations. In these problems, the solution is sought in a high-dimensional space where the use of matrices is typically not sufficient. The basis for our techniques is the very successful tensortrain format and the corresponding Matlab toolbox [4]. We have used these tensor techniques for the optimization of PDEs with random coefficient starting from the simple Poisson problem to the Stokes-Brinkman equation which is widely used in fields such as oil recovery and porous media flow [2]. There are many problems that are yet to be tackled by tensor techniques. Our group is looking forward to playing a significant role in establishing efficient methods that enable the solution of these problems. I **Dr. Akwum Onwunta**

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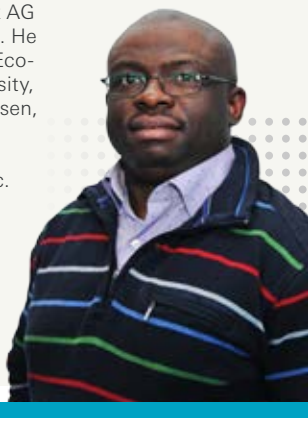

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