MAX PLANCK INSTITUTE
FOR DYNAMICS OF COMPLEX
TECHNICAL SYSTEMS
MAGDEBURG

Report
2017–2018

+ A long-term vision of the *Analysis and Redesign of Biological Networks* (ARB) research group is to help pave the way for routine use of advanced mathematical modeling approaches in (micro)biology and biotechnology. The picture shows the fermentation lab of the ARB group. Here, various genetic and experimental techniques are used to verify predictions of mathematical models on metabolic and regulatory processes in *E. coli* and other microorganisms.

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
EEC	Electrochemical Energy Conversion
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	Federal Ministry for Economic Affairs and Energy
CDS	Center for Dynamic Systems (Magdeburg)
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 TRR	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)

Report
2017 – 2018

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TECHNICAL SYSTEMS
MAGDEBURG

+ Research Groups

Introduction

Research Groups

Directors

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External Scientific Members

Senior Scientists

World-class Powerhouse Working on Systems-oriented Subjects

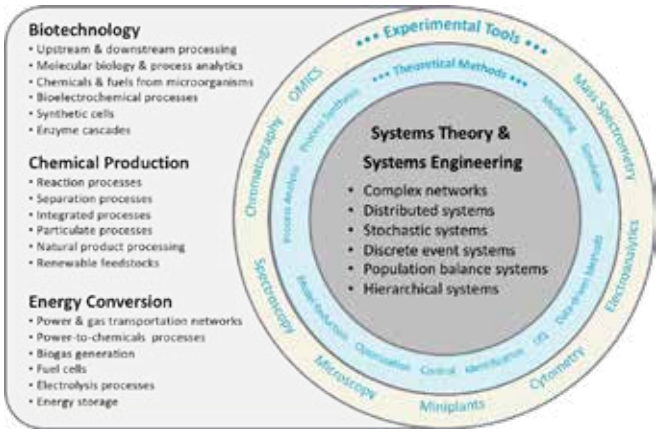
Process systems engineering is the holistic study of chemical, biochemical and energy systems. This research field was formally launched by the late 1960s with the goal of developing systematic methods to invent, simulate, optimize and control chemical processes, while simultaneously including realistic constraints to satisfy health and safety, environmental impact, etc. World class centers grew that were dedicated to particular aspects of this field; one of them was led by Prof. Dr.-Ing. Ernst Dieter Gilles at the University of Stuttgart. In time he realized that it is too big a subject with so many interconnected moving parts for any one team to conquer. His solution to this difficulty was uniquely German – he must create a Max Planck Institute dedicated to all aspects of process systems engineering. Only with the resources of the Max Planck Society, coupled with the formation of a Max Planck Institute would it be possible to create an organization big enough and good enough to match the size of the new challenge. Thus, during the 1990s he set on the formidable journey to establish a new Max Planck Institute dedicated to the Dynamics of Complex Technical Systems in Magdeburg.

His choice of Directors and subject areas was brilliant, and led to the meteoric rise of the Institute in both Germany and internationally. The four permanent Directors (Prof. Dr. Benner, Prof. Dr.-Ing. Reichl, Prof. Dr.-Ing. Seidel-Morgenstern, and Prof. Dr.-Ing. Sundmacher) are ably complemented by an outstanding cast of external scientific members (Prof. Dr.-Ing. Achim Kienle, Otto von Guericke University, and Prof. Dr.-Ing. Jörg Raisch, TU Berlin, a Max Planck fellow (Prof. Dr. Athanasios C. Antoulas, Rice University) as well as internal members, including senior scientist group leaders, Drs. Steffen Klamt, Matthias Stein, and Tanja Vidaković-Koch; team leaders, postdocs, doctoral students as well as outstanding people in central services, scientific technical staff and administrative staff. The Institute benefits greatly from the continued strong collaborative relationship with the local Otto von Guericke University which has created an upward spiral of excellence that benefits both institutions enormously.

Overall, the Max Planck Institute Magdeburg is a world-class powerhouse working on systems-oriented subjects that are vital to the future well-being of human society globally. An organization of this size, quality, openness, and longevity could not have been born anywhere else in the world but Germany. Both the Max Planck Society and the Max Planck Institute(s) are an inspiration to all. Looking forward to the next years, the challenge for the Institute will be to adapt to meet the needs of the future. I am absolutely confident it will continue to succeed.

Michael F. Doherty
Duncan & Suzanne Mellichamp Chair in Process Systems Engineering, and
Professor of Chemical Engineering
University of California, Santa Barbara

+ Introduction



+ **Figure 1:**
Research Concept of our Institute

+ **Figure 2:**
6th Meeting of the Scientific Advisory Board in November 2018.

The Max Planck Institute in Magdeburg – Our Mission and Recent Developments

The global challenges associated with the ever-increasing world population, the depletion of natural resources and climate change make the development of sustainable production technologies essential. The development of advanced processes for more efficient production of chemicals, transportation fuels, food and pharmaceuticals as well as the transformation and storage of renewable energies is a formidable task for the current and future generations. Achieving breakthroughs in providing solutions to these issues requires tremendous joint international efforts across several scientific disciplines. In this broad context the main goals of the research activities carried out at our Max Planck Institute are to develop mathematical models capable of describing complex chemical, biotechnological and energy-related processes, and to analyze the system properties and dynamic behavior of these processes using the models. After validation, these models are used for design, optimization and control. The objectives of the MPI do not only require the development, application and experimental validation of process and systems engineering approaches, but also the establishment of new computational methods and approaches in systems and control theory. Our systems-oriented approach serves as an umbrella for all activities in the different research groups. This approach, together with the tight integration of theoretical and experimental investigations, is the key factor in the success of our institute.

New research groups

As of December 2018, the MPI consists of nine research groups: four groups headed by MPI Directors (Professors Benner, Reichl, Seidel-Morgenstern and Sundmacher), three groups headed by Senior Scientists (Dr. Klamt, Dr. Stein, Dr. Vidaković-Koch), one group headed by an External Scientific Member (Professor Kienle) and one group headed by a Max Planck Fellow (Professor Antoulas). The Max Planck Fellow group was established in early 2017, supported by the Max Planck Fellowship program of the MPG. It deals with data-driven modeling, reduction and large-scale computing. The second new research group was started in October 2018, headed by Dr. Tanja Vidaković-Koch. Her group is focusing on electrolysis processes, fuel cells, electroanalytical methods, and bio-electrochemical conversion processes. This group is closely collaborating with the PSE group (Professor Sundmacher), thereby strengthening the institute's scientific workforce in the field of energy systems.

+ **Figure 3:**
Otto von Guericke Award winning Prof. Achim Kienle in the middle of Prof. Dr. Monika Brunner-Weinzierl, Vice President, and Prof. Dr.-Ing. Jens Strackeljan, President of the Otto von Guericke University.

+ **Figure 4:**
Dr. Jessica Bosch receives the Otto Hahn Medal in June 2018 in Heidelberg, handed over to her by Prof. Dr. Ferdi Schüth, Vice President of the Max Planck Society.

New research projects and grants

In the period 2017-2018, important achievements were accomplished, and new projects were initiated in the four major scientific clusters illustrated in Figure 1. Many of these projects were set up within strong international, national or local partnerships. Particularly important projects in the Biotechnology research cluster are "StrainBooster" (ERC Consolidator Grant of Steffen Klamt, ARB), the DARPA-funded project "DIA_TIP" (BPE group), and the big collaborative network "MaxSynBio" (PSE, EEC, PSD groups). In our Chemical Production research cluster, the Collaborative Research Center CRC/TR 63 "InPROMPT" (MSD, PCF, PSE, PSD groups) has been approved for extended funding by the DFG until 2021, and two new EU research projects were acquired by the PCF group ("UNRAVEL" and "CORE"). In our Energy Conversion research cluster, we continued to participate in the Max Planck Research Network on Energy Systems (MaxNet Energy) dealing with low-temperature water electrolysis cells, and we created a larger consortium of six MPI research groups "Altmark Energy" (ARB, BPE, CSC, MSD, PCF, PSE) with regional partners (Biogas Gardelegen, Avacon), supported by the EFRE-program of the federal state of Saxony-Anhalt, to develop new conceptual designs and operating strategies for Power-to-Gas systems. Moreover, the CSC group together with several industrial and academic partners attracted the BMWi-funded project "MathEnergy", the aim of which is to devise a new simulation platform for fast scenario analysis of the gas transport networks in Germany. Last but not least, in our Systems Theory and Systems Engineering research cluster the new DFG Research Training Group "Mathematical Complexity Reduction" (OVGU with CSC group) was established and the Max Planck Network BiGmax ("Big-Data-Driven Materials Science", coordinated by the CSC group) was initiated, whose objective is to devise new machine learning tools and algorithms addressing the 4V challenge (volume, variety, veracity of data, velocity at which data arrive).

Visit of the Scientific Advisory Board (SAB)

The quality of our research activities is assessed every three years by an International Scientific Advisory Board (SAB). It consists of twelve renowned scientists from four countries and is headed by Professor Michael Doherty (University of California in Santa Barbara, USA). After its sixth visit on November 28-29, 2018, the SAB submitted a report wherein they came to

+ **Figure 5:**
The MPI Choir is performing on occasion of the treble of 20 – 70 – 100, 20 years MPI Magdeburg, 70 years Max Planck Society and 100 years Nobel Prize for Max Planck.

the conclusion: "The Scientific Advisory Board was impressed by the outstanding world-class research that is performed at the Institute and for the continuing development of new areas of research (e.g., molecular simulation & multi-scale modeling, breaking the curse of dimensionality, data-driven modeling, bottom-up and in vitro synthetic biology) that steer the Institute in important new directions. All the research groups are first class, and some are among the world leaders in their fields". Naturally, we are delighted by this extremely positive evaluation result.

Appointments and awards

We are very proud that three of our senior scientists received offers for positions at other academic institutions: Oliver Hädicke (now Professor for Modeling and Simulation at Biberach University of Applied Sciences), Jan Heiland (now Junior Professor for Numerical Methods for Descriptor Systems at OVGU and team leader within the CSC group), and Robert Flassig (now Professor for Energy Systems Engineering at Brandenburg University of Applied Sciences). We wish them, and all other former colleagues who left the MPI in 2017-2018 the very best for their future careers.

For their excellent research work and achievements, several members of the MPI received prestigious scientific awards or became members of scientific societies and panels: Matthias Stein (Fellow of the Royal Society of Chemistry, 2018), Patrick Kürschner (Dr.-Klaus-Körper Prize awarded by GAMM, 2017), Peter Benner (SIAM Fellow 2017), Jessica Bosch (Otto Hahn Medal of the Max Planck Society, 2017), Robert Flassig (DECHEMA Award for Up- and Coming Lecturers in Higher Education, 2017), Achim Kienle (OVGU Research Prize, 2017), and Thilo Muth (Ph.D. Dissertation Award, German Society for Proteome Research, 2017).

20 years MPI Magdeburg

In 2018, the MPI celebrated 20 years of scientific work in Magdeburg, together with the 70th anniversary of the foundation of the Max Planck Society (MPG), and the Nobel Prize awarded to Max Planck exactly 100 years ago. This "treble" of anniversaries is a unique opportunity for the MPI and the Max Planck Society as a whole to reach out to the public and say: *"We are Max Planck!"* By declaring the 14th September 2018 to be Max Planck Day, all Max Planck Institutes together directly addressed the public and presented the science community

+ **Figure 6:**
Creative people and crowded house: 200 guests visited our entertaining science slam evening in September 2018, vividly presented by thirty scientists and members of technical staff.

in all its diversity. Under this headline, the MPI dedicated this day to informing the public in Magdeburg about science and the people behind it, the importance of science for the future development of society, and specific research projects pursued by groups at the MPI in Magdeburg. It was organized by taking a bottom-up approach by a team of Ph.D. students, postdoctoral scientists, and technical employees. This team did a really brilliant job and presented Science Slam talks on Energy, Production, Industry & Innovation, Climate and Health, they organized a Max Planck exhibition and designed a new communication area within the entrance hall of our institute.

Finally, I wish my successor as Managing Director, Professor Udo Reichl, a very successful time during his term from 2019 to 2020.

Magdeburg, March 2019

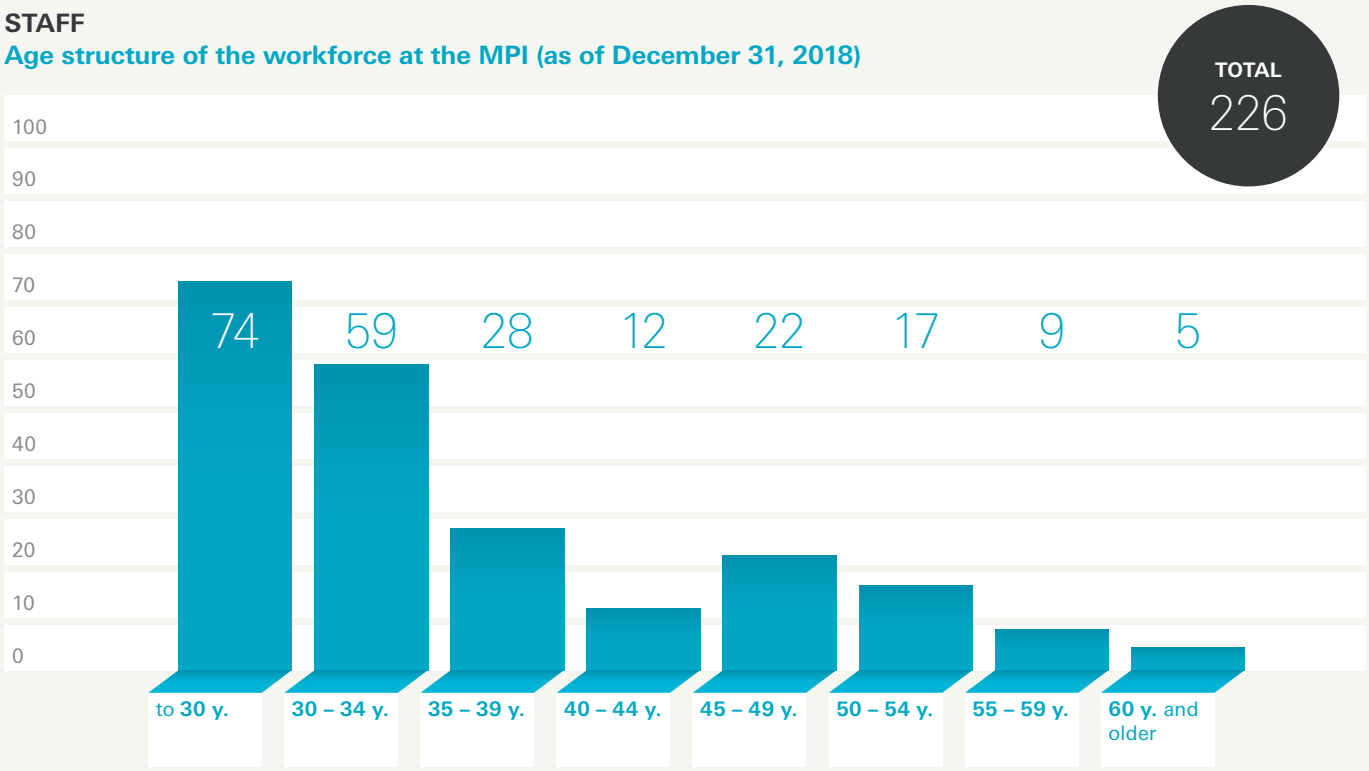
Prof. Dr.-Ing.
Kai Sundmacher
Director

sundmacher@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/pse

Facts and Figures

STAFF

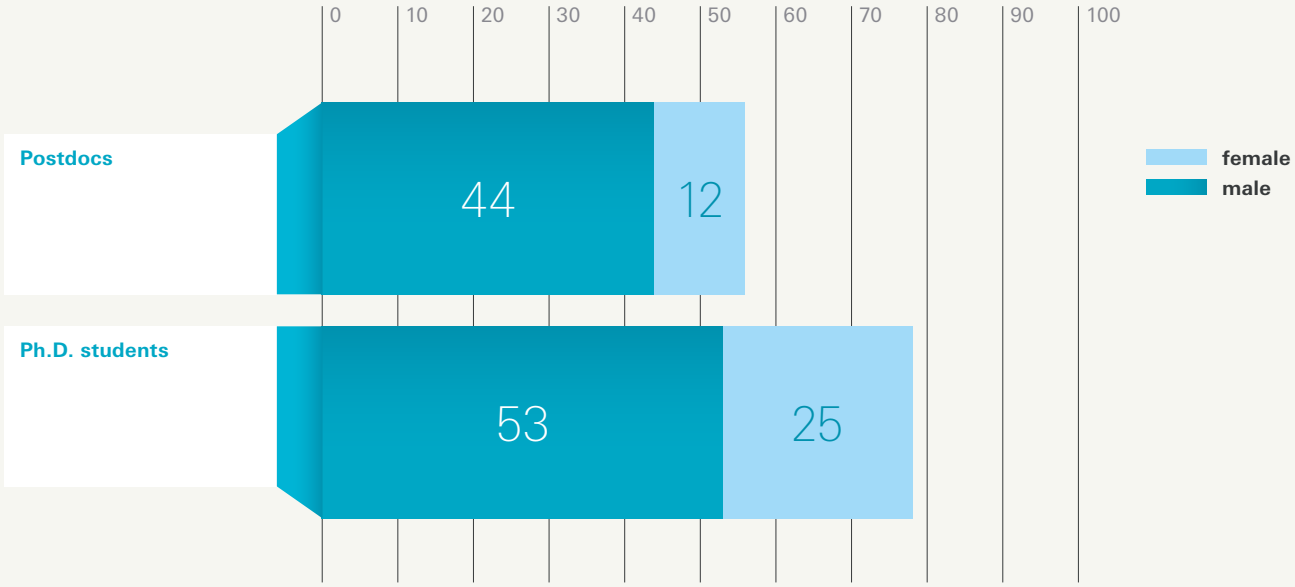
Age structure of the workforce at the MPI (as of December 31, 2018)



STAFF

Distribution of scientists by gender

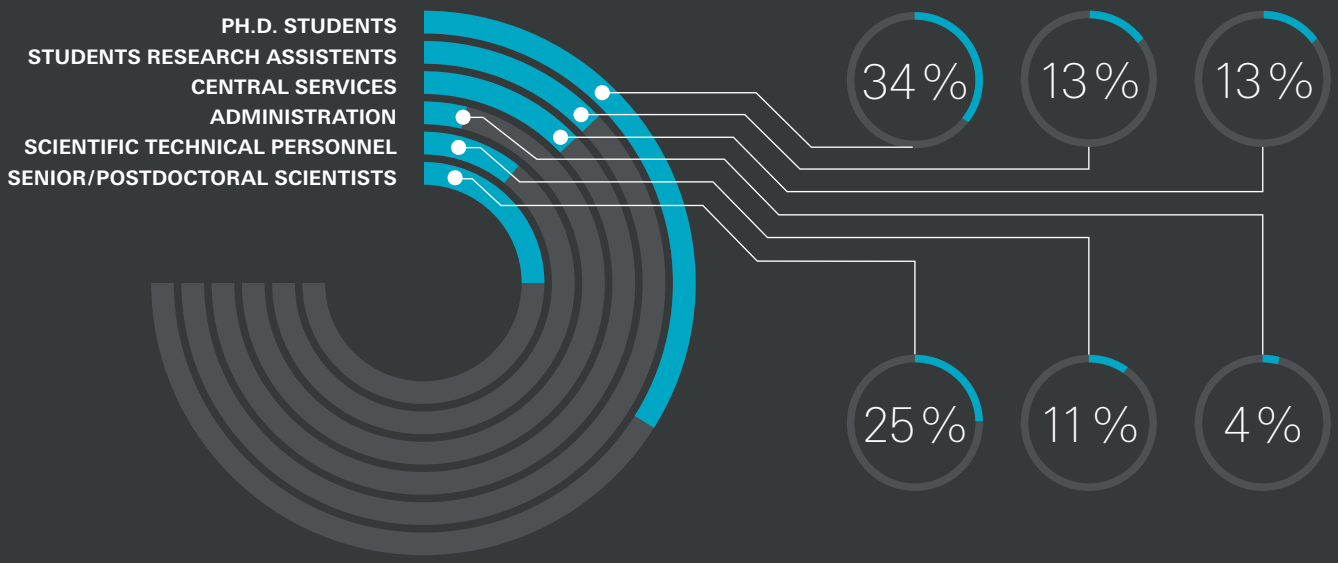
Female employees: 21 % Postdocs and 32 % Ph.D. students



The two graphs above 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

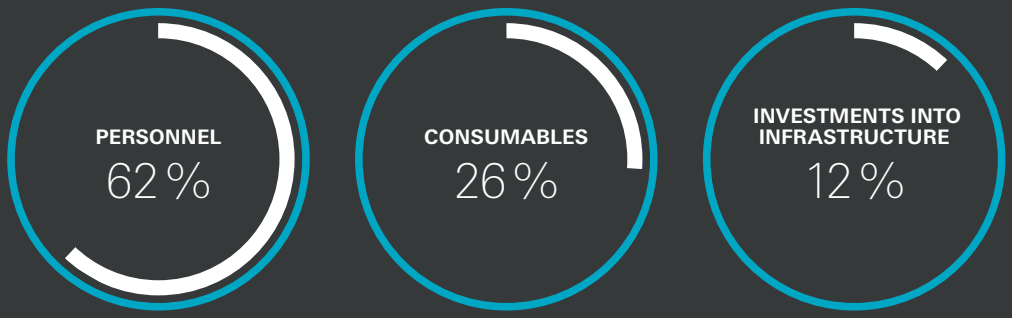
December 31, 2018: 226 Employees 134 Scientists: 56 Postdocs, 78 Ph.D. students



At the beginning of 2019, the MPI employed 226 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 operating the labs and technical facilities accounts for the rest of the employees.

EXPENDITURE PATTERN IN 2018

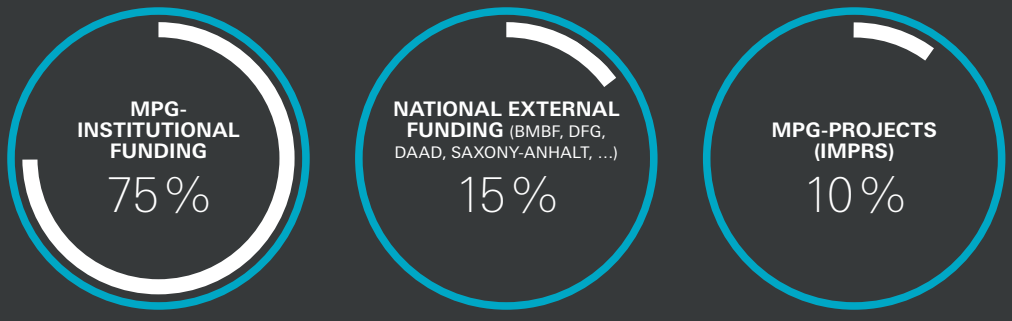
Total Expenses in Fiscal Year 2018: 15.85 million Euro



The total budget of the MPI in the fiscal year 2018 was 15.85 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.

MPI-GENERAL BUDGET 2018

Total Revenue: 15.85 million Euro Third-party funds: 2.3 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.

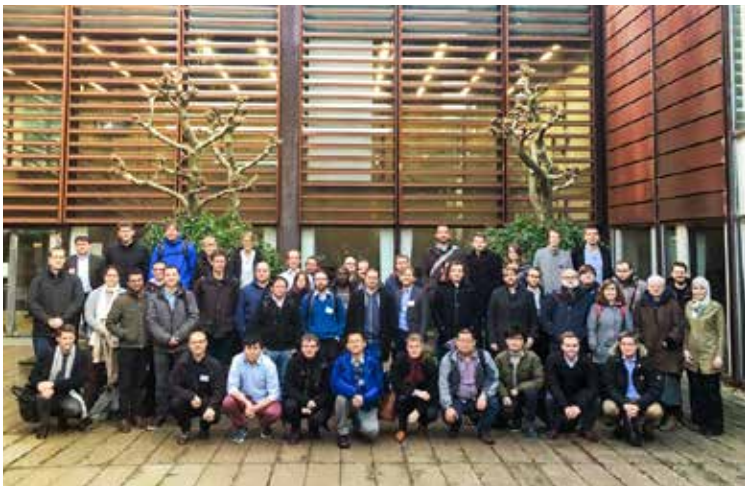
Selected Events 2017 – 2018

3rd Workshop on Model Reduction of Complex Dynamical Systems (MODRED)

In 2017, January 11th to 13th, the 3rd Workshop on Model Reduction of Complex Dynamical Systems was co-organized by the MPI Magdeburg (MODRED, http://www.mpi-magdeburg.mpg.de/csc/events/modred2017). It was funded in part by the European Model Reduction Network (EU-MORNET, http://eu-mor.net) and hosted by the University of Southern Denmark, Odense. The third edition of this workshop, which is approximately organized every three years, focused on recent advances in the field of model reduction, which encompasses the dimensionality reduction of differential equation models with the aim of enabling or accelerating numerical simulations. Overall, 55 international scientists participated and current research results were presented in five plenary lectures and two parallel tracks spanning 37 contributed talks with topics ranging from system-theoretic to reduced basis methods for parametric, nonlinear or descriptor systems. The committed involvement and discussion between the participants, as well as the thorough organization, made the MODRED workshop a great success. Selected results presented at the meeting are published in a special issue of the SpringerNature journal "Advances in Computational Mathematics" (Volume 44, Issue 6, 2018). In addition, the third Model Order Reduction Wiki (MORwiki, http://modelreduction.org) user meeting was also held during this workshop. The MORwiki is a community-driven web resource on model reduction initiated by the MPI Magdeburg. The wide range of advances for different model reduction methods underlined the vibrancy of this field of research with an upcoming fourth workshop in 2019, which will continue the tradition of a highly focused meeting for developers and users of model reduction techniques on various academic levels. **I Dr. Christian Himpe**

GlycoBioTec2017

The Max Planck Institute for Dynamics of Complex Technical Systems Magdeburg, Department of Bioprocess Engineering, was pleased to welcome 170 international participants to GlycoBioTec2017. The first international conference on Glycobiotechnology took place at the newly renovated Harnack House, the conference venue of the Max Planck Society, from 7th – 9th February, 2017. Current trends in the field of modern Biomedical/Biopharmaceutical Glycobiotechnology, ranging from fundamental theory to method and technology developments relevant to biopharma, health, medicine and functional food areas, were presented and discussed by academics and professionals. The conference successfully created an interactive forum for discussing cutting-edge research and for



+ 3rd Workshop on Model Reduction of Complex Dynamical Systems (MODRED) in Odense

+ Lively discussion during the workshop "From Academia to Industry: Applied Research and Career Challenge" in March 2017

networking in the course of lecture hall sessions and informal dine & discuss sessions.

The conference, organized by Professor Udo Reichl, Dr. Thomas Rexer and Dr. Erdmann Rapp, proved to be very beneficial and valuable to MPI scientists in the field of glycobiotechnology. Moreover, the results of an ambitious joint project between the MPI Magdeburg and Martin Luther University Halle-Wittenberg, in the very dynamic field of synthetic glycobiotechnology, were presented comprehensively to a wider research audience for the first time and were met with very positive resonance.

Due to highly encouraging feedback, the second edition of the "GlycoBioTec2019" conference took place in January 2019 and will be held biennially in future. | **Dr. Thomas Rexer**

+ 1st GlycoBioTec Conference 2017 in the Harnack House Berlin

From Academia to Industry: Applied Research and Career Challenge

In mid-March 2017, the open event *"From academia to the industry"* took place at the Max Planck Institute in Magdeburg. Its aim was to promote interaction between academia and industry and bring to light future challenges and opportunities for recent graduates. These topics were addressed from the perspectives of industrial guest speakers from different fields presenting their career paths, past and current work, and life experiences.

The event was jointly organized by the MPI external PhD representative and the SIAM student chapter Magdeburg, together with volunteer MPI doctoral researchers. Among the 7 speakers, there were former PhD students from our institute and from the International Max Planck Research School (IMPRS), and many companies, both multinational (Bayer, BASF, Evonik, Bosch) and local (Thorsis, icubic) were represented. The speakers, who came from diverse backgrounds and were in different stages of their careers, shared interesting experiences with the audience from different points of view.

The day started with a welcome from the managing director, Prof. Dr. Sundmacher, and the talks were presented in morning and afternoon sessions. Discussions were extended to the coffee breaks and dinner in a stimulating and friendly environment. Over 100 participants attended the talks, mainly PhD candidates and Master's students from the MPI and Otto von Guericke University. Both attendees and speakers gave very positive feedback, and the format of the event will be repeated in 2019. | **Thiane Carneiro**

+ The participants of the 5th Summer School, taking place in September 2017 in Magdeburg, could test newly acquired scientific knowledge during practical exercises and exchange ideas for current and future implementation in their own scientific projects.

2nd Workshop 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 2-years project that supported scientific exchange with researchers at Universidad de la República in Montevideo (Uruguay). For the second workshop we successfully applied for the Max Planck conference site, "Schloss Ringberg", at lake Tegernsee in the beautiful Bavarian alps.

The primary goal of the series of workshops is to bring together researchers from all parts of high-performance computing (HPC) whose methods potentially make it possible, or have proven, to save energy in large computations.

The 2017 workshop featured an outstanding list of invited and keynote speakers, and had strong contributed presentations, with researchers coming from Germany, Uruguay, Spain, France, Poland, the UK, and the US. Keynote presentations on topics ranging from hardware surveys and the energy wall to communication avoidance were given by Jack Dongarra (ICL University of Tennessee), Laura Grigori (INRIA Paris), Ulrich Rüde (FAU Erlangen-Nürnberg) and Axel Klawonn (University of Cologne). Due to the financial support from our long term technical/hardware partner MEGWARE we were also able to feature three invited lectures from younger colleagues in the field. Matthias Bolten (University of Kassel), Hartwig Anzt (University of Tennessee) and Markus Geveler (TU Dortmund University) discussed multigrid efficiency, the trade-off between floating point operations and communication, as well as the co-design of hardware and software for power-aware computations.

The third workshop in the series will be held in Magdeburg in November 2019 and the fourth workshop will be hosted by our partner group in Uruguay in 2021. **I Dr. Jens Saak**

5th Summer School of the International Max Planck Research School Magdeburg

The Summer School of the International Max Planck Research School for Advanced Methods in Process and Systems Engineering Magdeburg (IMPRS) attracted more than fifty participants from August 28th to September 1st, 2017 to the Max Planck Institute for Dynamics of Complex Technical Systems Magdeburg. The focus was on the current hot topic of "Decision making and uncertainty". Thus, several renowned experts from industry and the academic fields of Applied Mathematics and Process Systems Engineering from Pittsburgh, Toronto, London, Zurich, Berlin and Magdeburg offered the participants a glimpse of how the industry applies theoretical models in decision making, such as in medical research or engine design.

For example, in order to precisely predict the efficiency of an industrial process, the uncertainties of model parameters and process input variables must be taken into consideration. Quantifying these uncertainties is a major challenge in Process Systems Engineering, mainly when more complex structures and systems are to be designed. For this purpose, the Ph. D. students gained insight into modern theoretical concepts and received valuable stimuli during the Summer School.

Not only throughout the lectures, but also during practical exercises the participants were able to test newly acquired scientific knowledge in practise and exchange ideas for current and future implementations in their own scientific projects.
I Gabriele Ebel

+ 3rd Annual MAXNET Energy Workshop in 2017 in Magdeburg

3rd MAXNET Energy Workshop

MAXNET Energy, the Max Planck Research Network, brings together key competencies from eight Max Planck Institutes and two international partners, the Cardiff Catalyst Institute in Great Britain and the University of Virginia in the United States. They work on understanding the fundamental principles and finding new ways of converting chemical energy, with the aim of achieving a better understanding of how to make use of renewable energy for chemical production and transportation. Their work ranges from research on new catalyst materials to the application in water splitting electrolyzer test sets, from the chemistry of small molecules up to understanding the interplay of materials and operating conditions in technical devices.

Around thirty scientists exchanged latest information about their research as part of the 3rd MAXNET Energy Workshop at the Max Planck Institute Magdeburg on October 26 – 27, 2017. They discussed their recent results on novel materials, investigations on elementary reaction steps, and the performance of system components under reaction conditions.

Renowned guest speakers included Professor Bouzek, Department of Inorganic Technology at the University of Chemistry and Technology in Prague, and Professor Dr. Richard Hanke-Rauschenbach, Professor for Electric Energy Storage Systems in the Institute of Electric Power Systems at Gottfried Wilhelm Leibniz University Hannover, who reported on their progress in research into water electrolysis.

I Gabriele Ebel

EU Horizon 2020 COST Action 'ECOSTBio'

European Cooperation in Science and Technology (COST) Actions form networks to promote and spread excellence among top research groups from all European countries, to foster interdisciplinary research for breakthrough science, and grow ideas.

In the COST Action CM1305 'Explicit Control of Spin States in Technology and Biochemistry' (ECOSTBio) 28 countries plus one near neighbor country participated to exert explicit control of spin states of transition-metal compounds through rational design of the nature of metal, oxidation state and coordination environment. The interactions of theorists and experimentalists created a synergy, enabling theoreticians to validate their suggested models and experimentalists to design and improve the performance of novel materials with desired properties.

After seven scientific workshops, the COST Action concluded with a final scientific meeting in Berlin in April 2018. Successes of this Action include the publication of more than 200 peer-reviewed journal articles plus the hosting of 25 short-term scientific missions to exchange students between different labs in different countries.

Dr. Matthias Stein was the national representative of Germany in the Managing Committee from 2014-2018 and working group leader of activities regarding 'Enzymatic Spin States'.

One immediate outcome of this Action is the foundation of the 'Quantum Bio·Inorganic Chemistry Society' QBICS (www.qbicsoc.org) which is a non-profit organization whose goal is the advancement of science and research in theoretical

+ Experts from MaxSynBio and guests debated in a public panel discussion about the question "Synthetic Nature – what is synthetic, what is natural?" in the framework of the MaxSynBio Symposium in July 2018 in Magdeburg.

and computational chemistry as applied to inorganic and bioinorganic chemistry. Dr. Matthias Stein is one of the founding members of QBICS and an elected member of the Board.
I Dr. Matthias Stein

International MaxSynBio Symposium on Synthetic Biology in Magdeburg

"From so far to here – from here so much further" – taking this motto as their theme, 120 international scientists met from 2 to 4 July 2018 in Magdeburg to present achievements and perspectives of bottom-up synthetic biology and discuss the potential of this new research discipline. The motto which was taken from an art installation that is a familiar landmark in Magdeburg, blazed the trail for this symposium: Since MaxSynBio started in 2014, it has become the world´s largest bottom-up synthetic biology consortium. Researchers from the network work together in an interdisciplinary manner to build modules for synthetic living systems. At annual symposia, the scientific community is invited to debate the state of the art, actual projects and latest achievements. The top-class program was thus composed of 20 panel talks by outstanding international guest speakers and MaxSynBio researchers, poster and satellite sessions.

Since the word "synthetic" in synthetic biology is an emotive term in public discussions, the symposium also included a panel discussion that was open to the public to consider the question "What is synthetic and what is natural?". Five panel speakers, all experts in their field, discussed philosophical, sociological, ethical, political and specialized perspectives of the scientific disciplines involved.

During the debate the panelists outlined the field of synthetic biology as the impulse for creating artificial cells, and as a certain way of understanding the origins of life by finding additional dualisms such as "unregulated vs. regulated" or "existing vs. created". **I Ulrike Papajewski**

3rd International Metaproteome Symposium

In December 2018, about 80 scientists from 14 countries participated in the 3rd International Metaproteome Symposium. The leading event in the field of metaproteomics was organized by the Helmholtz Centre for Environmental Research – UFZ and the German Network for Bioinformatics Infrastructure - de.NBI (de.NBI partner project MetaProtServ, Otto von Guericke University Magdeburg).

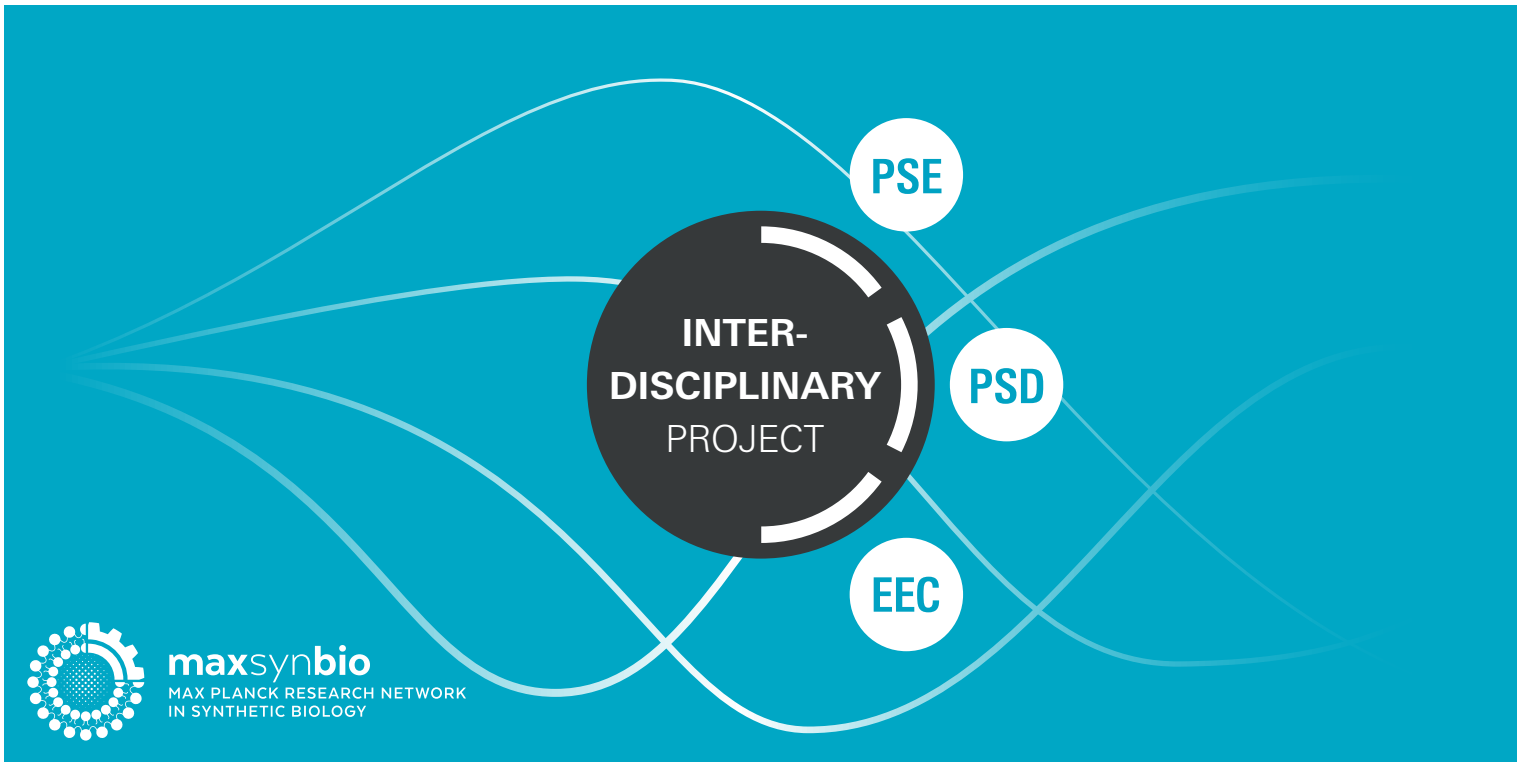
The number of publications examining microbiomes is currently exploding and results are providing new perspectives on human health and global nutrient cycles as well as on the technical application of microbial communities in biotechnology. Multi-omics analysis is accepted as the gold standard for assessing the microbiome samples, but the data integration is still challenging. The symposium offered a great opportunity to broaden the discussion on the integration of different datasets. In addition to results from all areas of microbial ecology, initial results from a collaborative multi-omics study of a human gut microbiome sample and of a defined microbial community were presented. Early insights demonstrated the reliability of metaproteomics for the assignment of major phyla and functions. The ongoing analysis of data from multiple labs will provide more detailed knowledge on the reliability of metaproteomic data obtained with different experimental and bioinformatic pipelines, and will reveal aspects for further improvement of the different workflows.

The symposium provided a good platform for oral and poster presentations by passionate young scientists in the interdisciplinary field of microbiome research.

The scientific committee of the symposium agreed to continue this symposium series at eighteen-month intervals. The next symposium will be held in summer 2020 in Luxembourg (organized by Paul Wilmes, University of Luxembourg).

Microbiome researchers interested in the emerging field metaproteomics are invited to join the Applied Metaproteomics Workshop in Magdeburg in June 2019. **I Dr. Dirk Benndorf**

Research Groups

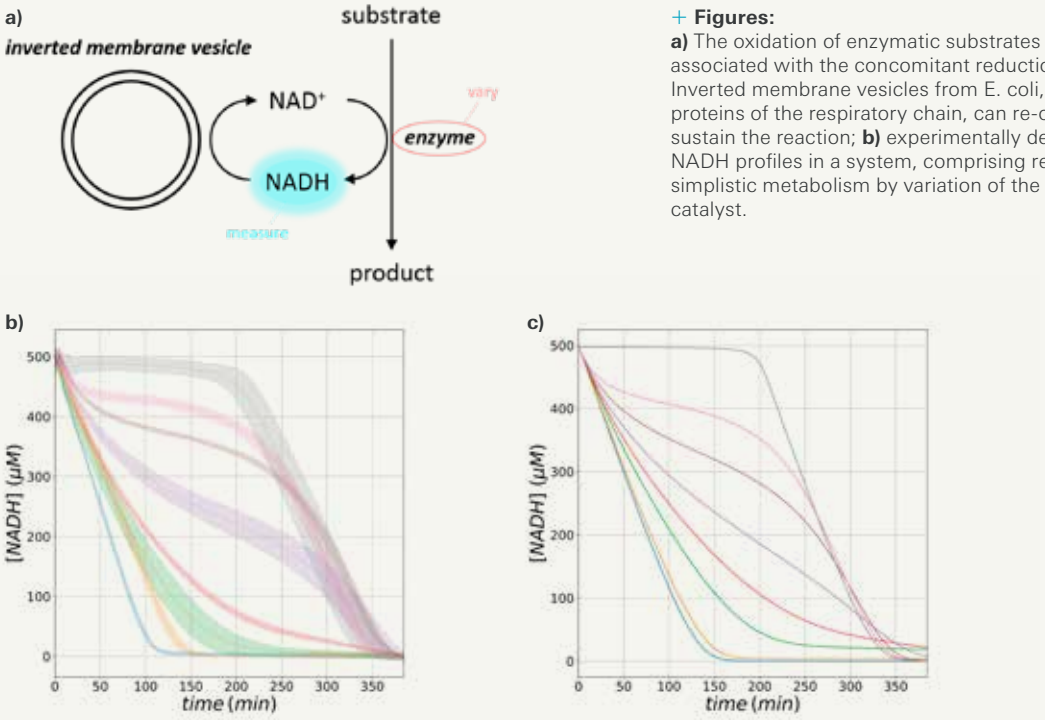


BOTTOM-UP SYNTHESIS OF ARTIFICIAL CELLS FROM FUNCTIONAL MODULES

Synthetic biology holds great promise for the future of biotechnology, the advance of which is hindered by the complexity of living organisms. This complexity is caused by the large number of components involved, some of which are redundant or exercise ambiguous functions. In this context, synthetic biology aims to implement life in much simpler and more predictable systems in order to increase the efficiency for production of valuable chemicals and conversion of energy. The quest for minimal cells has relied for many years on the so-called *top-down approach*. Here, a living organism is minimalized by cutting out the parts, that are presumed to be expendable. This genetic engineering strategy results in functional cells but even after identifying the key knockouts, it is often difficult to attribute underlying mechanisms to the observed behavior due to the aforementioned complexity. This major disadvantage is addressed by the *bottom-up approach*, whose goal is the understanding of essential life processes via the stepwise and modular synthesis of cells, using well-characterized functional modules, parts and molecular entities. Ultimately, a whole organism could be synthesized from non-living matter.

In 2014 the Max Planck Society, supported by funds from the Federal Ministry of Education and Research in Germany, launched the MaxSynBio network that is dedicated to the bottom-up approach. The interdisciplinary research consortium involves nine Max Planck institutes and two university research groups (Erlangen, Bordeaux). The MPI for Dynamics of Complex Technical Systems has a leading role in MaxSynBio, as Professor Kai Sundmacher has responsibility for coordinating the whole network. Scientifically, MaxSynBio links the activities of several project partners with the Process Systems Engineering (PSE), Process Synthesis and Process Dynamics (PSD) and the recently established Electrochemical Energy Conversion (EEC) research groups. In this way, not only does the project streamline our core expertise in the engineering of complex systems, it also adds further value by establishing new collaborations within the Max Planck Society. The MaxSynBio consortium focuses on selected life processes of fundamental importance, such as metabolism, energy supply, morphogenesis, signaling, motility, and reproduction, summarized under the umbrella term "proliferome" [1]. Our institute deals specifically with compartmentalization and growth, energy and cofactor regeneration, and metabolic modules for the processing of matter and its exchange with the environment. Moreover, we are devising a general methodology for the integration of functional parts and modules, both experimentally and theoretically.

Compartmentalization is a landmark of life and serves to spatially segregate processes and to establish non-equilibrium conditions. Therefore, we are developing various methods for production of compartments, including microfluidic tools [2]. To elucidate the role of confinement, we encapsulate biochemical reactions such as the recent artificial CO_2 fixation cycle, CETCH. Such active metabolic processes need a continuous supply of energy. Thus, we functionalize the interfaces of compartments with the biochemical machinery for energy conversion in order to create minimal cellular organelles, such as artificial mitochondria [3], powered by chemical energy carriers or by light. We mainly focus on phospholipids to mimic the architecture and function of natural membranes. However, the bottom-up approach opens the door to synthetic alternatives, allowing us not only to mimic life processes, but



+ Figures:
a) The oxidation of enzymatic substrates by dehydrogenases is associated with the concomitant reduction of the cofactor NAD. Inverted membrane vesicles from E. coli, which contain essential proteins of the respiratory chain, can re-oxidize the cofactor and sustain the reaction; **b)** experimentally determined and **c)** simulated NADH profiles in a system, comprising regeneration module and simplistic metabolism by variation of the amount of metabolic catalyst.

possibly also obtain new functions and behaviors. In this context, we reconstitute membrane proteins in amphiphilic copolymers, whose properties allow for further tailoring for specific applications[3]. To further substantiate the chemical aspect of synthetic biology, we establish the regeneration of encapsulated cofactor by a synthetic molecule, which mediates electron transfer across the membrane. This allows us to shortcut and emulate part of the respiratory chain without the involvement of membrane proteins[4]. In parallel, we extract natural counterparts of the bottom-up-assembled modules and employ them to sustain a simple metabolism in droplets[5].

Based on our systems engineering expertise, we also apply a system-wide theoretical perspective on artificial cells. In the long term, we aim to produce a computer-aided design toolbox to assemble life-like cell constructs using a standardized library of functional modules. To this end, we are analyzing unstructured whole-cell models to identify the essential functional modules and replace them with real biochemical systems. Here, we are combining experimentally validated parts to create a fictitious cell-like entity working synchronously, which is able to grow and divide after doubling its length[6]. In parallel, we start with subsystems, studied in isolated experiments, and aggregate them by defining interfaces for information exchange. For instance, we describe the active cytoskeleton dynamics (spatial clustering and wave propagation), which play pivotal roles in cell motility, division and morphogenesis[7]. In addition, we are developing a kinetic model for the coupling between proto-metabolism and cofactor regeneration, which reveals possible mass transport limitations and provides a quantitative framework for the integration of modules[5]. I **Dr. Ivan Ivanov**

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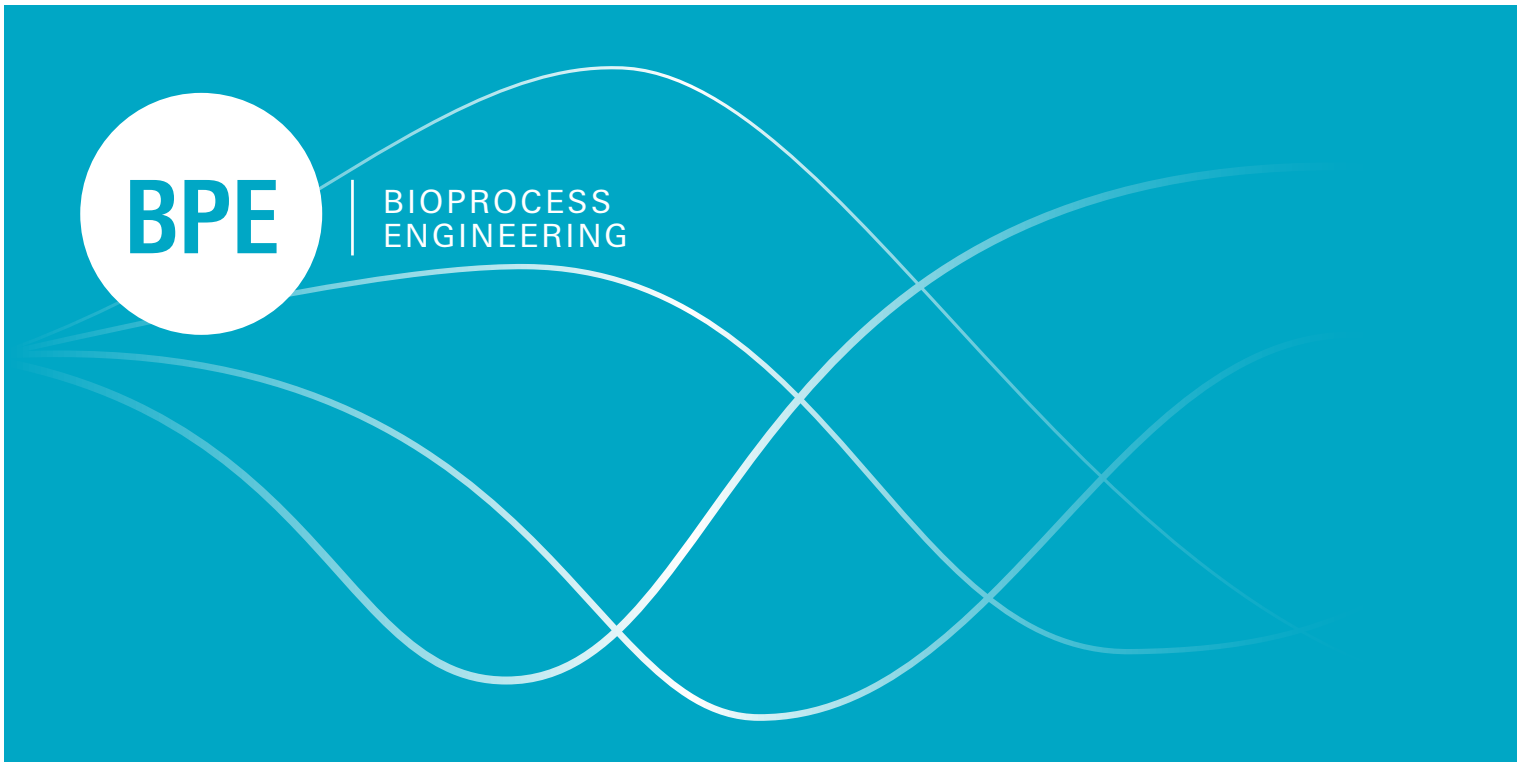
Author **Dr. Ivan Ivanov**

Ivan Ivanov studied organic chemistry at the University of Chemical Technology and Metallurgy in Bulgaria and in 2012 obtained his Ph.D. at the Max Planck Institute in Magdeburg in the field of enzymatic fuel cells. He then spent two years as a postdoc at Penn State University, working in the area of microbial electrochemical technologies. In 2014 he rejoined the PSE research group, where he is currently a Team Leader working in the field of bottom-up synthetic biology. His research interests include biological electron transfer and electrocatalysis, biomimetics, multi-phase systems and compartmentalization.

ivanov@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/pse



PROF. DR.-ING. UDO REICHL I DIRECTOR

Bioprocess engineering covers the use of microorganisms in the manufacturing of industrial bulk products, food, and biopharmaceuticals. In addition, bioprocess technology plays an important role in biogas and biofuels production, wastewater processing, and solid waste treatment. The design and optimization of bioprocesses from both an engineering and a biological point of view requires the integrated use of complex biological systems and in-depth understanding of (bio) chemical reactions, dedicated equipment, and modeling and software tools. Additionally, a wide range of assays for process monitoring and a comprehensive set of analytical and "omics" technologies need to be applied. The challenge we are facing today is how to achieve an increase in product yields, establish new methods for process intensification, and reduce time to market while guaranteeing efficacy and safety of drugs.

In the context of biologics production, the Bioprocess Engineering group, headed by Professor Udo Reichl, studies key aspects of cell culture-based production of virus particles. These processes are currently seeing a renaissance with a strong increase in market share of vaccines due to the emergence of new diseases, the growing use of viral vectors in gene therapy, and emerging options for viral therapy to cure cancer or autoimmune diseases. Influenza virus propagation in animal and human cell lines is considered to be a model system due to its relevance as a respiratory pathogen, the complexity involved in virus-host interactions, and its frequent mutation including gene reassortment. The group combines the expertise of five teams covering different aspects of the overall process. Many years' experience from design and optimization of cell culture-derived influenza manufacturing provides the basis for tackling other challenging virus production processes for vaccination and therapeutic use.

The **Upstream Processing team** (PD. Dr. Yvonne Genzel) characterizes growth and product formation of a large number of adherent and suspension cell lines in combination with different viruses (influenza, Modified Vaccinia Ankara, Zika, attenuated yellow fever, and Japanese encephalitis virus) to optimize vaccine production in stirred and orbital shaken bioreactors, hollow fiber-based systems, and disposable units. In addition, advanced cultivation strategies using online sensors for feeding control are 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** in order to identify bottlenecks in virus replication. Virus replication dynamics are investigated on the single cell and the cell population level by a combination of classical virus quantification assays and state-of-the-art methods such as quantitative real-time PCR and imaging cytometry. With a focus on proteomics, glycomics,

+ Gwendal Gränicher and Juliana Coronel are introducing sensors into small scale bioreactors in preparation for a new experiment.

and glycoproteomics, the **Bio/Process Analytics team** (Dr. Erdmann Rapp) is developing a comprehensive set of bioanalytical tools for the in-depth analysis of protein expression and post-translational modifications of proteins. Finally, the design and optimization of process trains to purify virus harvests, guaranteeing high a recovery of the final product at low contamination levels, are performed by the **Downstream Processing team** (Dr. Michael Wolff).

Over the last two years, the Upstream Processing team continued its efforts towards process intensification by optimizing perfusion strategies for high cell density cultivations, by developing options for continuous vaccine production in tubular bioreactors, and by characterizing cell and virus retention using hollow-fibers, settlers and acoustic filters. Also, we successfully initiated the project "Dynamics of Influenza A Virus Defective Interfering Particle Replication – From Single Cells and Tissues to the Host Level (DIA-TIP)" in DARPA's "INTERfering and Co-Evolving Prevention and Therapy" (INTERCEPT) program. To support these activities and to characterize virus dynamics of promising cell lines, comprehensive simulation studies were performed by the Mathematical Modeling team. The Downstream Processing team focused on the further improvement of membrane-based methods including steric exclusion chromatography for virus particle purification. Efforts will be continued within the USP team towards process integration, as the DSP team will phase out its activities with the appointment of Dr. Wolff as professor at the Institute of Bioprocess Engineering and Pharmaceutical Technology (Technische Hochschule Mittelhessen, Gießen). The Bio/Process Analytics team further extended its glycoanalytical methods portfolio regarding mass spectrometry-based peptide- and glycopeptide-mapping, and acquired funding, from the DFG as part of the research unit FOR 2509: "The Concert of Dolichol-Based Glycosylation - from Molecules to Disease Models". The overall focus of this project is on congenital disorders of glycosylation (CDG) to investigate the glycosylation machineries in the endoplasmatic reticulum, and the implications of hypo-glycosylation on the molecular, cellular and organismal level. Finally, the **Synthetic Glycobiotechnology** team headed by Dr. Thomas Rexer was also established. Efforts will be directed towards the development and application of an *in vitro* enzyme platform technology to characterize structural and functional aspects of *N*-glycosylated proteins, in particular antigenicity and immunogenicity of viral antigens.

Prof. Dr.-Ing. Udo Reichl
Director

ureichl@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/reichl

+ **Figure 1:**
Columns and materials used for steric exclusion chromatography (SXC). (A) Computer-aided design of a filter housing. (B) Assembled column. (C) Electron micrograph of cellulose membranes used as stationary phase.

+ **Figure 2:**
Chromatographic separation of biomolecules by steric exclusion chromatography (SXC). (A) Molecules are captured proportionally to their hydrodynamic size. (B) Typical SXC chromatogram: virus particles are captured while impurities of smaller size are washed away. The target product, in this case influenza virus particles, is traced by light scattering.

A Purification Platform for Viral Vaccines and Gene Therapy Vectors

+ Viral vaccines are considered to be amongst the most successful achievements in modern health science. In addition, the use of viral vectors for gene therapies has shown the promise to become the next medical revolution for combating a wide variety of currently untreatable diseases.

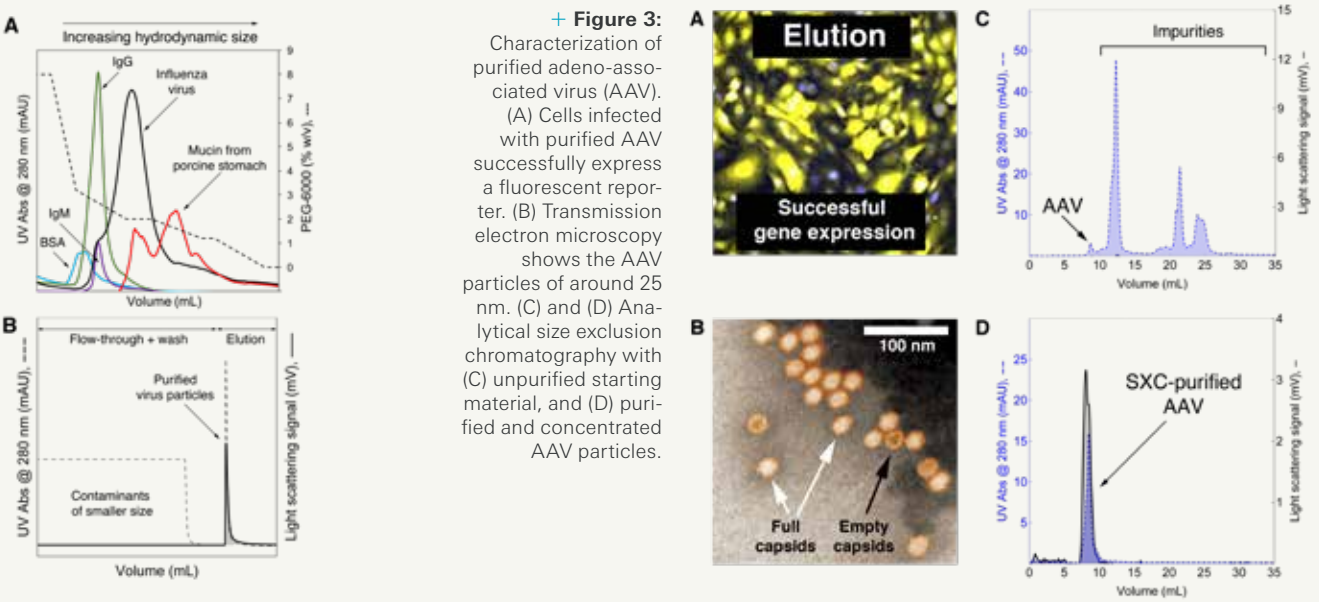
At their dawn, viral vaccines were mostly crude preparations of tissues and cells, but they have become more complex as their manufacturing processes and requirements have evolved. The wide range of existing viruses, their production methods, and the emergence of new public health threats make it extremely difficult to standardize viral vaccine manufacturing. These challenges are also true for gene therapy, in which billions of viruses are needed to administer treatments costing several hundred thousand US dollars.

To ensure the potency and safety of these products, viruses need to be isolated from complex mixtures (for example animal cell cultures) and purified to extremely high standards. This can be a considerable challenge for the process engineer. Additionally, there might be the need to generate virus products extremely quickly, as in the case of pandemic influenza outbreaks, or it may be necessary to concentrate several hundred liters of a virus-containing solution down to a few milliliters, as in the case of gene therapy treatments.

Purification operations are typically individually tailored to each particular virus species and production system, making process development slow and expensive. Furthermore, industrial purification methods are frequently limited to particle-based chromatography and filtration operations, which can become very expensive and inefficient at commercial scale.

To address these drawbacks, we have developed a new purification method for viruses, named steric exclusion chromatography (SXC)[1, 2]. In SXC, an unpurified sample that contains viruses is mixed with a polymer such as polyethylene glycol (PEG) and fed into a chromatography column made from low-cost cellulose membranes (Figure 1). The viruses are captured in the column without a direct chemical interaction thanks to the PEG while impurities are washed away. The purified virus particles are recovered by flushing the column with a solution not containing PEG (Figure 2).

The results obtained so far with laboratory-scale devices[1, 3, 4] show nearly full recovery (>98%) for a wide range of virus species relevant in both vaccine and gene therapy applications, including influenza virus, yellow fever virus, Vaccinia virus, and adeno-associated virus (AVV) (Figure 3). Depletion of host cell DNA and proteins with SXC is commonly >85%.



+ Figure 3: Characterization of purified adeno-associated virus (AAV). (A) Cells infected with purified AAV successfully express a fluorescent reporter. (B) Transmission electron microscopy shows the AAV particles of around 25 nm. (C) and (D) Analytical size exclusion chromatography with (C) unpurified starting material, and (D) purified and concentrated AAV particles.

SXC is performed under physiological conditions, unlike other techniques where often harsh conditions such as very acidic environments are needed, which can compromise the biological effectiveness of the viruses. With SXC, it is possible to purify different virus strains and serotypes using the same process conditions, which is very hard to achieve using other methods. The narrow operational range of SXC makes it possible to purify even unknown viruses with a high probability of success and the low cost of the membranes allows single-use operation, which avoids expensive and time-consuming cleaning and sanitization steps. Scale-up of SXC is simple, as it requires only a linear increase in membrane surface, and the use of devices of up to 20 m^2 would enable industrial-scale virus purification.

In summary, SXC allows the single-use purification of virus particles with almost no product losses. This technology concentrates the virus product without compromising its biological effectiveness and allows different strains and serotypes to be purified using very similar process conditions, which significantly accelerates process development time. For these reasons, SXC offers the potential for becoming a platform technology for virus purification for both vaccine and gene therapy applications. In particular, it can contribute to making gene therapies widely available at significantly lower cost.

This project was carried out with the kind assistance of external partners: Federal University of Rio de Janeiro, Heidelberg University Hospital, the Max-Planck-Institute for Biophysical Chemistry, and the European Molecular Biology Laboratory (EMBL). Project development and commercial implementation will continue with the support of an "EXIST Transfer of Research" grant from the German Federal Ministry for Economic Affairs and Energy (BMWi).

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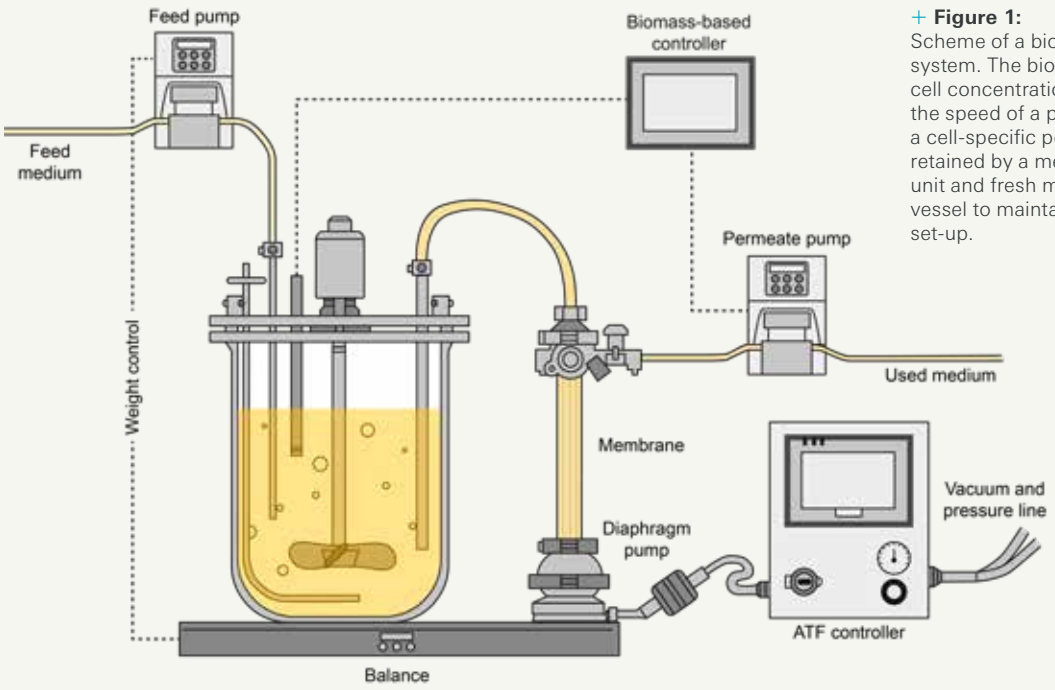
Author **Pavel Marichal-Gallardo**

Pavel Marichal-Gallardo studied Biotechnology Engineering at the Tecnológico de Monterrey in Mexico. In 2014, he received his Master's degree in Process Engineering from Hochschule Offenburg in Germany. He has worked on the purification of several recombinant proteins and was head of Downstream Processing at UGA Biopharma before joining the Bioprocess Engineering Group at the Max Planck Institute in 2015. His Ph.D. thesis focuses on downstream processing of viral vaccine candidates and gene transfer vectors.

marichal-gallardo@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/bpe



+ Figure 1:
Scheme of a bioreactor with perfusion system. The biomass probe monitors the cell concentration and a controller adjusts the speed of a permeate pump to maintain a cell-specific perfusion rate. Cells are retained by a membrane in the perfusion unit and fresh medium is added to the vessel to maintain a pre-set weight of the set-up.

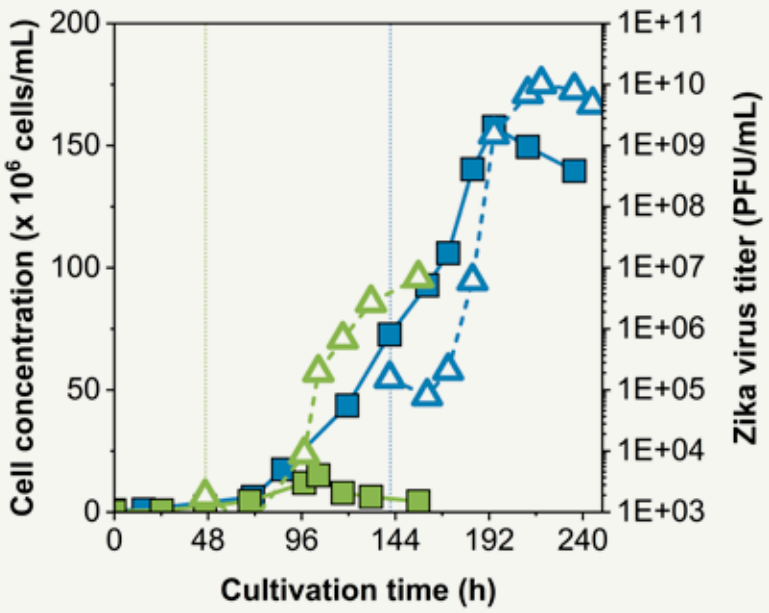
Zika and Yellow Fever Virus Production at Very High Yields

+ Since the rapid spread of Zika viruses in South America shortly before the 2016 Olympic Games in Brazil, everyone has been aware of the serious threat such viruses pose. Sporadic Zika virus infections were first reported in Africa from the 1950s onwards, and specific mosquitos were identified as the main transmission vector. Due to the lack of vaccines and antivirals, disease control proved to be particularly difficult. Zika virus was regularly encountered in Africa, where it circulated between jungle and urban regions. Constant infections resulted in natural population immunity. Symptoms were typically mild or not reported and thus no further attention was paid to the virus. This changed, when the Zika virus rapidly spread from Brazil to more than 60 other countries throughout a population without native immunity. The link between infection and severe microcephaly in newborns and other congenital defects prompted the World Health Organization to declare a global health emergency. The outbreak quickly abated, presumably due to the population acquiring immunity. However, although the epidemic seems to be over, the need for an effective vaccine to protect the population against emerging and re-emerging viral threats remains.

In an effort to establish efficient production processes for such viruses, the Bioprocess Engineering group focuses on technologies using animal suspension cell lines and perfusion systems for reaching very high cell concentrations in fully controlled and closed bioreactors. Compared to a standard batch process, where all nutrients are present at high concentrations only at the beginning of a cultivation, fresh medium is constantly added and spent medium withdrawn in perfusion mode while specific cell retention devices enable the accumulation of cells (Fig. 1).

In a first step, Alexander Nikolay of the Upstream Processing team headed by PD Dr. Yvonne Genzel attempted to propagate Brazilian Zika virus (ZIKV) in adherent baby hamster kidney (BHK-21) cells. To this end, he tested various ZIKV isolates from Brazilian patients in close collaboration with the working groups headed by Professors Amilcar Tanuri and Leda Castilho at the Federal University in Rio de Janeiro, Brazil. Further experiments in Brazil identified one isolate, which propagated to low but stable virus titers in cell culture. In order to increase virus yields, BHK-21 cells were adapted to grow in suspension and cultivated in a 3 L benchtop bioreactor with a membrane-based, manually controlled perfusion system. A higher cell concentration was achieved, but infections resulted only in a minor increase in titers. Subsequent virus quantification indicated an intracellular accumulation of viral RNA and therefore possible limitations in virus maturation or release [1].

Back at the MPI and motivated by this hypothesis, further studies were conducted with a duck embryo-derived suspension cell (EB66®) in collaboration with Valneva SE, France. The promising ZIKV isolate from Brazil was sub-cultured



+ **Figure 2:**
Batch and perfusion cultivation for Zika virus production. EB66® cells were cultivated either at conventional cell concentrations in batch mode (green squares) or at high cell concentrations in perfusion operation (blue squares). Cells were subsequently infected (indicated by vertical lines) with Zika virus (triangle).

over five passages in the new cell substrate leading to significantly increased virus yields. As a result, the virus potentially adapted and reached titers about 100-fold higher than before. To increase the yield even further, an online biomass probe was now used to monitor cell concentration and automatically fed a specific medium volume in a 1 L perfusion culture. This enabled a controlled cultivation without manual interventions and higher reproducibility. The cell-specific perfusion rate was adjusted to 34 pL/cell/day, which made it possible to achieve a cell concentration of 1.6×10^8 cells/mL – ten times higher than with conventional batch cultivations. Infection with the well-adapted ZIKV seed resulted in titers of up to 1×10^{10} infectious particles per mL (PFU/mL) (Fig. 2).

This set-up was then also challenged for the production of yellow fever virus (YFV), which also belongs to the flaviviruses. Yellow fever is an equally serious disease, which fortunately can be prophylactically countered with available vaccines. However, since the vaccine is still produced in embryonated chicken eggs and manufacturing capacities cannot simply be increased, the vaccine supply is chronically close to shortages. As for Zika virus, propagation of YFV in EB66® cells at high cell concentrations resulted in very high titers of up to 7.3×10^8 PFU/mL in less than two weeks of production time (data not shown). Considering the bioreactor volume of 1 L, this virus harvest equates to raw material for ten million live-attenuated vaccine doses [2].

In summary, the Bioprocess Engineering group has developed a highly efficient and robust perfusion process to produce ZIKV and YFV at very high virus yields. The new production method can support rapid availability of vaccines in case of outbreaks, and help to avoid future vaccine shortages. In addition, this technology can also be utilized for the production of other viruses such as modified vaccinia Ankara virus (MVA), which is a promising viral vector for gene therapies.

I Alexander Nikolay

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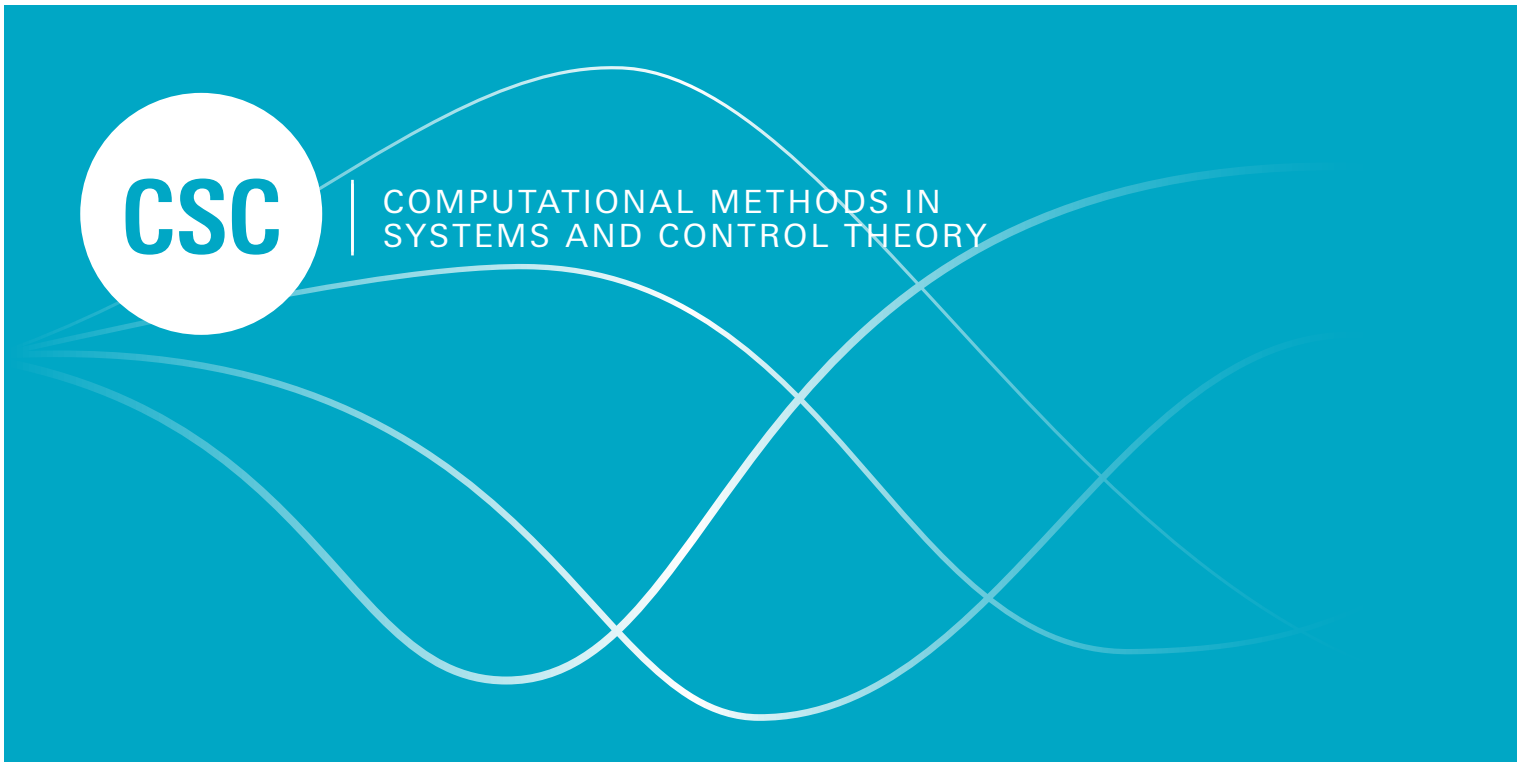
Author **Alexander Nikolay**

Alexander Nikolay studied Biotechnology at the Technische Universität Braunschweig specializing in the field of Bioprocess Engineering. In 2014, he received his Master of Science degree after completing his thesis in the Bioprocess Engineering Group at the MPI in collaboration with IDT Biologika GmbH. In the same group he then continued to pursue his Ph.D. thesis on intensified processes for cell culture-derived flavivirus production.

nikolay@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/bpe



PROF. DR. PETER BENNER | DIRECTOR

Research in the CSC group employs mathematical ideas and concepts to develop new methods for *in silico* design or experiments for complex technical systems as investigated, for example, in the engineering departments at the MPI. Specifically, we consider efficient simulation and (feedback) control of dynamical systems, i.e., of mathematical models described by systems of ordinary, differential-algebraic or partial differential equations. Our application areas range from chemical and biotechnological processes to nano-electronics and energy networks. Our work flow often starts with a mathematical model provided by or developed with engineers, physicists, chemists, etc., followed by analyzing the goals of the desired computer experiments. We then either adapt and optimize existing algorithms, or 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, such as hardware accelerators like GPUs, as well as energy-awareness in the algorithm design. We use different hardware platforms, including our new Linux cluster, *mechthild*[1], with 2000+ cores, which replaced the previous compute cluster, *otto*, in 2018.

CSC Teams

Since 2015, the CSC structure has comprised 6 teams. **Model Order Reduction** (headed by L. Feng) deals with mathematical methods to algorithmically reduce the number of degrees of freedom in mathematical models in order to accelerate their simulation, facilitate their optimization, enable control design, and quantify uncertainties. The **Computer Aided Control System Design** unit (J. Heiland, who also became a *Juniorprofessor* at OVGU in 2018) considers computational methods for control systems. A very important aspect here is that many of these techniques rely on the solutions of Lyapunov, Sylvester and Riccati equations – their efficient numerical solution is the focus of the **Matrix Equations** team (J. Saak). Efficient techniques of **Numerical Linear and Multilinear Algebra** percolate almost every aspect of the CSC research work. The corresponding team, led by P. Benner, deals with eigenvalue problems as well as preconditioning and tensor techniques. Efficiently implementing the developed algorithms on modern computing platforms is the task of the **Scientific Computing** team (J. Saak). The **Simulation of Energy Networks** team (S. Grundel) focuses on the modeling and numerical simulation of power, gas, and water networks, and their coupling.

Research Trends and Highlights in 2017/18

A particularly important field of application is the simulation and control of energy networks. In the BMWi[2] funded "Math-Energy" project (2016-2021) we are accelerating the scenario

+ In the BMWi-funded project MathEnergy, researchers of the CSC group are simulating coupled energy networks in order to investigate scenarios for energy supply systems using electrical power, gas and heat. Here, Christian Himpe is studying a gas transportation network, for which fast simulation tools are developed as one of the core tasks of the CSC group within MathEnergy.

analysis of the (coupled) German gas and power networks as part of the German energy transition program for real-time operation.

We have also continued our cooperation with several MPI groups investigating dynamical reactor models for 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, where, for example, the optimal periodic operation of chemical reactors is currently of particular interest.

Low-rank tensor techniques have become a new paradigm for tackling high-dimensional scientific and engineering problems. We have applied these techniques to a number of uncertain dynamical systems described by unsteady nonlinear partial differential equations. In cooperation with the MPI for Mathematics in the Sciences in Leipzig and the Lawrence Berkeley Labs, we have also developed new approaches to solving problems from computational chemistry and (bio-)physics based on low-rank tensor approximations. A particular highlight in using the low-rank tensor paradigm was the solution (in cooperation with NDS) of an optimality system for control of an uncertain flow problem, comprising 10^{15} unknowns, – this has to be compared to the largest linear systems of equations currently being solvable on the world's top supercomputers: with conventional methods, the current limits lie in the range of 10^{13} to 10^{14} unknowns!

Another highlight in 2017/18 was the establishment of the Max Planck network BiGmax[3] on big-data-driven methods in materials science (co-chaired by P. Benner and M. Scheffler from the Fritz Haber Institute and funded 2017-2022), where we leverage machine learning methods to explore the materials configuration space.

[1] Named after "Mechthild von Magdeburg" (c.1207- c.1282/94), a Beguine and the first mystic to write in German.

[2] Bundesministerium für Wirtschaft und Energie (German Ministry for Economics and Energy)

[3] See https://www.bigmax.mpg.de/

Prof. Dr. Peter Benner
Director

benner@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/benner

+ **Figure 1:**
Symbolic picture
of a gas pipeline

The Gas Network Challenge

The MathEnergy Project

The green energy revolution affects all energy supply networks, including the gas transport and distribution networks. Consequently, the volatile nature of renewable energies and the complementary quick response of gas-fired power plants makes operation and control of gas networks increasingly more complex due to often changing supply and demand situations.

The aim of the BMWi-funded *MathEnergy* cooperation project (http://mathenergy.de) is the research and development of novel methods for fast and efficient numerical simulation of gas and power network behavior. The associated sub-project, investigated at the MPI Magdeburg, is concerned with accelerating the simulation of dynamical gas network models by means of model reduction techniques.

From Pipelines to Networks

The standard transient model for gas transport is the Euler equations[1, 2]. These equations, in mathematical terms a hyperbolic and nonlinear partial differential equation system, can be formulated to describe the flow of gas in a pipeline. In a second step, models for many pipes are connected to a network. Due to the transportation of gas (pressure and mass-flux) from one pipe to the next, this equation system has to be solved holistically, which presents the computational challenge for large networks.

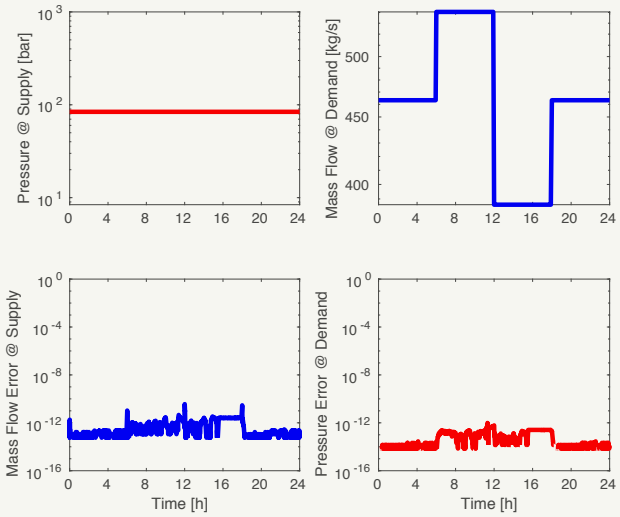
Fortunately, engineers and controllers of gas networks are not interested in exact simulation results at every meter of a pipeline system, but only at points where actual measurements are made. This includes the inlets and outlets of the network as well as additional stations spread throughout the network. The task in the model reduction sub-project is to simulate these measurements without simulating the network as a whole.

Data-Driven Model Reduction

The basis for the developed model reduction method is mathematical system theory. This discipline of applied mathematics established in its modern form in the 1960s, separates the model into three parts: inputs, states and outputs. In the gas network setting, the inlets and outlets (and measurement stations) correspond to inputs and outputs, while the pipelines are identified by states. The idea behind system-theoretic model reduction is to determine the simplest mapping from inputs to outputs with regard to the states, but without preserving them. Due to the nonlinear nature of the model describing the gas network, a data-driven approach to determine this mapping is employed[3]. In a training phase, the network behavior of the original model is simulated for various generic input-output situations over short periods of virtual time (for example one hour). From this data a so-called projection operator is extracted, which transforms the original network model to a tiny surrogate model, which in terms of inlets and outlets corresponds to the original up to a small error but is valid for a longer virtual time period (such as 24 hours). An important

+ Figure 2:
Map of the Yamal-Europe gas pipeline runing across four countries: Russia, Belarus, Poland and Germany

+ Figure 3:
Upper row: **Input** time series of pressure at the pipeline inflow (left), and mass flow at the outflow (right).
Lower row: Error between the original and reduced model **output** time series of mass flow at the pipeline inflow (left) and pressure at the outflow (right).



aspect is the careful design of training inputs, as the actual supply and demand situation at inlets and outlets is unknown at the time of training. Furthermore, the internal reduced states have no physical meaning any more.

An Illustrative Example

To illustrate this approach, a reduced model for a part of the Yamal-Europe pipeline connecting Siberian gas fields with Germany is presented (Figure 2). On the one hand, a pipeline is a very simple network as there are no junctions or cycles, yet, from the point of view of model reduction, a pipeline can be more complicated than a network with complex topology since there is little redundancy in a pipeline model to be reduced.

As described above, based on simulations of the pipeline for generic inlet-outlet behavior a projector is computed and applied to the model. The resulting reduced pipeline model is compared in Figure 3 to the original pipeline model in terms of inlet-outlet changes for a scenario of intra-day supply and demand. The figure shows a mean error of less than 0.001% between the original and reduced models, while the reduced model can be computed 84 times faster.

Outlook

Initial results for model reduction of long pipelines and smaller networks are very promising: The utilized data-driven method resolves the nonlinearity of the gas transport to a suitable degree of accuracy. In the coming years, this method will be applied to larger networks with more complicated components such as compressors.

Overall, model reduction is a front runner in accelerating simulation for systems with known physics. Compared to other methods, data-driven system-theoretic model reduction combines information from the empirical data with the analytic model and hence creates reduced models based on the selected input-output filter and the underlying physics.

| Dr. Christian Himpe

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Author **Dr. Christian Himpe**

Dr. Christian Himpe holds a doctoral degree in applied mathematics from the University of Münster. Since 2016 he has been a postdoctoral researcher in the Simulation of Energy Systems team within the Computational Methods in Systems and Control Theory group at the Max Planck Institute for Dynamics of Complex Technical Systems Magdeburg, where he is working on the efficient numerical simulation of gas networks via model reduction.

himpe@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/csc

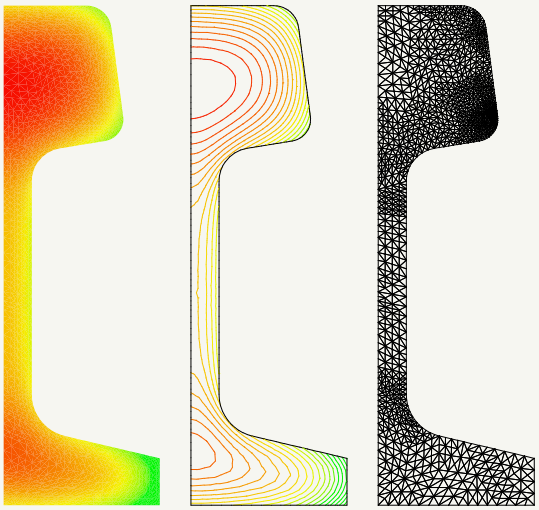

Figure 1a:
The temperature distribution within a cross-section of a steel rail (left) and a contour plot of the same (middle). Also shown is a finite element discretization (right), which gives rise to the matrices defining the differential Riccati equation.

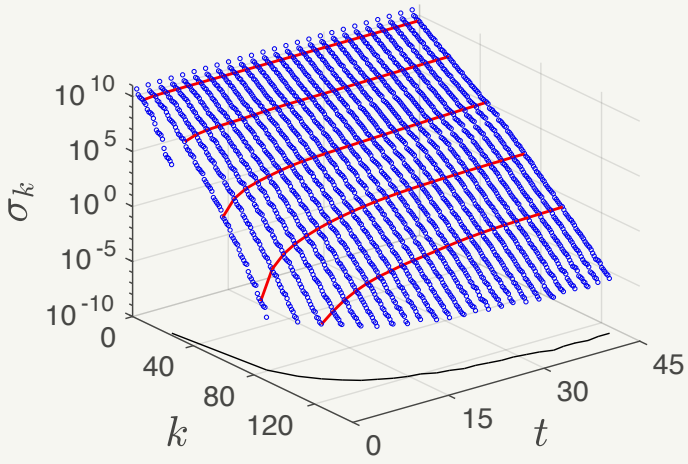

Figure 1b:
The singular values of the solution to the differential Riccati equation. The rapid decay of these shows that the solution has low numerical rank at each point in time. The solution matrix is of size 20209, but its numerical rank does not exceed 135.

Differential Riccati Equations

Minimizing the production costs for obtaining a desired output of a process is a key challenge in industry. To achieve this, the system must be controlled. By using sensors to gather information about the current state, actuators can influence it in the desired direction. This is called feedback control, and the mathematical tools for solving such problems may be found within the field of control theory.

A particular kind of feedback control is the linear quadratic regulator (LQR). Here, the underlying model of the system is linear, which can always be achieved through linearization around the desired state. The cost which should be minimized is modeled as a quadratic function of the necessary actuator effort (the input) and of the deviations from the desired state (the output). Because of the relatively simple structure of the problem, it has an explicit solution where the optimal input is given in terms of the state of the system.

While this relation is explicit, evaluating it requires us to solve a so-called Riccati equation. These come in two flavors; differential Riccati equations (DRE), which arise when optimizing over a finite time interval, and algebraic Riccati equations (ARE), which arise when the time interval is infinite. A typical industrial process runs in finite time, and DREs are therefore the natural choice. Nevertheless, the focus until recently was mostly on AREs, because they are easier to solve and since their solutions may give reasonable approximations to the finite-time situation. The feedback control law corresponding to the DRE solution is, however, superior. In the last few years, much effort has therefore been spent on developing competitive numerical methods for this class of problems as well.

Numerical methods. A DRE is a differential equation where the right-hand side is the sum of an affine (linear + constant) part and a quadratic part. The main difficulty lies in the fact that it is matrix-valued, and the number of unknowns in the DRE will be the square of the number of unknowns in the system to be controlled. If the latter is large, as is often the case, the former becomes extremely large. Any naive approach to solving the DRE, for example based on vectorization, therefore immediately fails. The main idea for overcoming this is to utilize structural properties of the problem. In particular, the solutions will, under common assumptions, exhibit a low numerical rank [5]. This allows us to approximate the solution well by a low-rank factorization, which drastically decreases the number of unknowns and changes the problem from untreatable to merely difficult.

In the Matrix Equations team, we are working on several different types of numerical methods using this feature. The first of these are low-rank versions of "classical" methods for the integration of ordinary differential equations, such as BDF and Rosenbrock methods [2], and recently also so-called PEER methods [3]. The common theme here is that in each time step an algebraic matrix equation has to be solved. The specific forms of these equations depend on the method, but in every case, they may be solved efficiently by methods previously developed by the team. Recent and future work in this area includes proper initialization of higher-order BDF methods, and support for time-varying problems.

We also work on low-rank versions of splitting schemes applied to DREs. The main idea here is to split the problem into one affine and one purely quadratic problem. Then, alternate

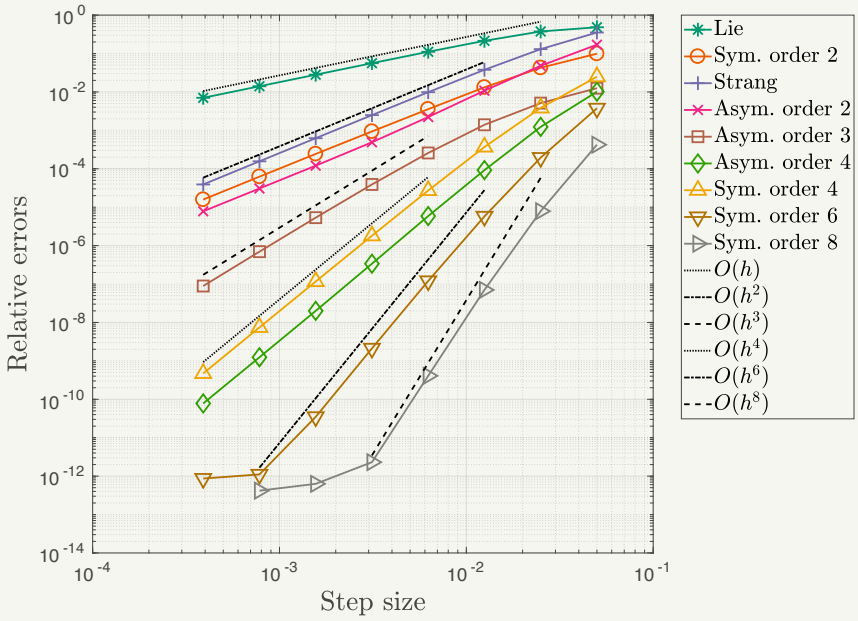

Figure 2:
Error vs. time step size for splitting schemes of different method orders, when applied to a small-scale differential Riccati equation. Higher order is generally better, as it results in smaller errors, but each step also requires more effort.

between solving these subproblems in a well-chosen manner. The subproblems both have closed-form solution formulas. The evaluation of these constitutes the main effort and requires the computation of matrix exponential actions on tall, skinny matrices. For details, see[4] and the references therein. Recent and future work in this area includes automatic error control of all computations within a time step, as well as support for time-varying problems.

Finally, we work with Krylov subspace methods. These project the DRE onto a lower-dimensional subspace, which yields a DRE of much smaller size that may be solved efficiently with traditional time stepping methods after vectorization. The main work here consists of computing a suitable Krylov subspace. In the autonomous case, it is possible to show that the same space works for every point in time, and it may essentially be computed by solving one ARE. Compared to the previous two approaches, this is more recent, but promising, work. For details, see[1].

We are considering all these different methods because they work well in different situations. Basically, the classical methods excel when applied to unstable but stabilizable problems and are generally robust. The splitting schemes can easily achieve high method orders and are typically more efficient in the stable case, if their parameters are carefully chosen. Finally, when applicable, the Krylov methods are vastly more memory-efficient than either of the two other types of methods.

Numerical example. A test problem which is often used in this context comes from a real industrial process, where a newly manufactured steel rail should be cooled down evenly by spraying cooling fluid onto its surface. This can be formulated as a 2D LQR problem, since the rail (Fig. 1a) is essentially infinitely long compared to its cross-section. Fig. 1b demonstrates that the solution to the corresponding DRE has low numerical rank, which means that low-rank methods may be applied for approximating it. | **Dr. Tony Stillfjord**

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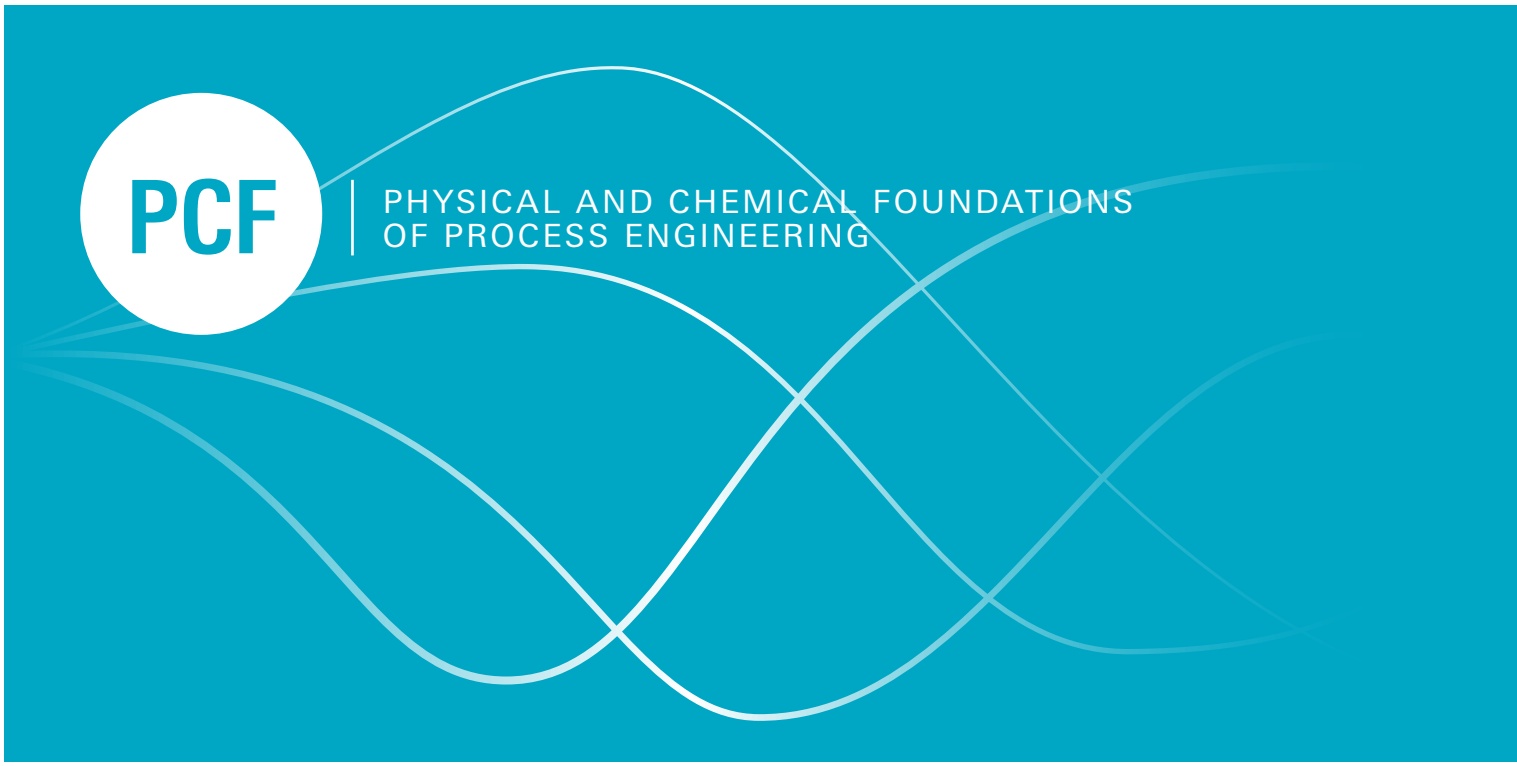
Author **Dr. Tony Stillfjord**

Tony Stillfjord studied mathematics at Lund University, Sweden, where he also obtained his Ph.D. in Numerical Analysis in 2015. After two years as a postdoc at Chalmers University of Technology and the University of Gothenburg, he became a member of the CSC research group at the Max Planck Institute Magdeburg in 2017. His research concerns the construction, analysis and implementation of numerical methods, mainly for partial differential equations. In particular, he has done much work on splitting schemes.

stillfjord@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/csc



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

The development and production of new products with improved or hitherto unknown properties require the application of advanced technologies. As well as realizing transformation steps exploiting chemical reactions, there is a growing need in separation processes to provide target compounds with the required purity. For isolating specific target molecules out of complex mixtures, the Physical and Chemical Foundations of Process Engineering (PCF) group develops and applies crystallization-based and chromatographic separations and, more recently, solid-liquid extraction processes. To identify and develop new generic process options, we undertake systematic experimental and theoretical investigations, with both model systems and industrially-relevant compounds. Directly connecting continuous reaction and separation steps, and the application of forced dynamic operation, are also objects of current investigations. Rational development and optimization of separation and reaction processes require numerous thermodynamic and kinetic parameters. Since many of these parameters are not readily available, one significant area of activity for the PCF group is the identification and application of suitable experimental methods capable of determining specific physical and chemical data. These data are then applied in appropriate mathematical models in order to quantify and evaluate new process options. However, most of our efforts are clearly devoted to implementing and experimentally validating promising process options.

Over the period covered by this report, significant progress has been achieved in the PCF group in developing efficient enantioseparation processes, i.e. processes that can separate mixtures of optical isomers. In this field, 15 Ph.D. students form 8 universities are currently collaborating within the larger European project "CORE (COntinuous REesolution of Chiral Components)". A recent highlight of our research in Magdeburg is the analysis and successful exploitation of a process exploiting a continuous fluidized bed principle.

A second difficult separation problem, which is currently being investigated thoroughly by our group, consists in isolating a specific target component with high purity from a complex mixture containing many other components, e.g. specific natural products present in plant extracts or a biomolecule present in a fermentation broth. In these cases, the target components are frequently present only in low concentrations. Based on systematic investigations

+ Jacqueline Kaufmann and Heike Lorenz are discussing the results of thermo-analytical studies of a fine chemical. To deeper understand its phase behavior temperature-modulated differential scanning calorimetry (DSC/TMDSC) and combined DSC-microscopy are used.

of the underlying thermodynamic equilibria, within the period of this report it was possible to develop and successfully validate new purification concepts for three different natural products (curcumin, rutin and the anti-malaria drug artemisinin). A highlight was the recent discovery of the potential for exploiting chlorophyll, extracted from plant leaves together with the target molecules, as an efficient and literally green photocatalyst. In another project, in close cooperation with the Fraunhofer Center for Chemical-Biotechnological Processes in Leuna, the controlled continuous precipitation of lignin from black liquors was successfully transferred from laboratory to pilot scale. The patented process will be further developed and extended in the coming years in conjunction with several other partners in the European project "UNRAVEL (UNique Refinery Approach to Valorise European Lignocellulosics)".

A growing focus of the work of the PCF group is currently set on studying theoretically and experimentally the potential of a forced periodic operation of separation units and reactors, which are exposed to modulations of certain operating parameters, as e.g. the inlet concentrations and/or flowrates.

Within the period of this report Susann Triemer received the DECHEMA Student Award (in the Category "Chemical Process Engineering" and Andreas Jörke received the Ph.D. Dissertation Award (Faculty of Process and Systems Engineering) of the Otto von Guericke University. The PCF group presented the results achieved very successfully at numerous international conferences, where several Ph.D. students won prestigious Poster Awards.

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

seidel-morgenstern@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/seidel-morgenstern

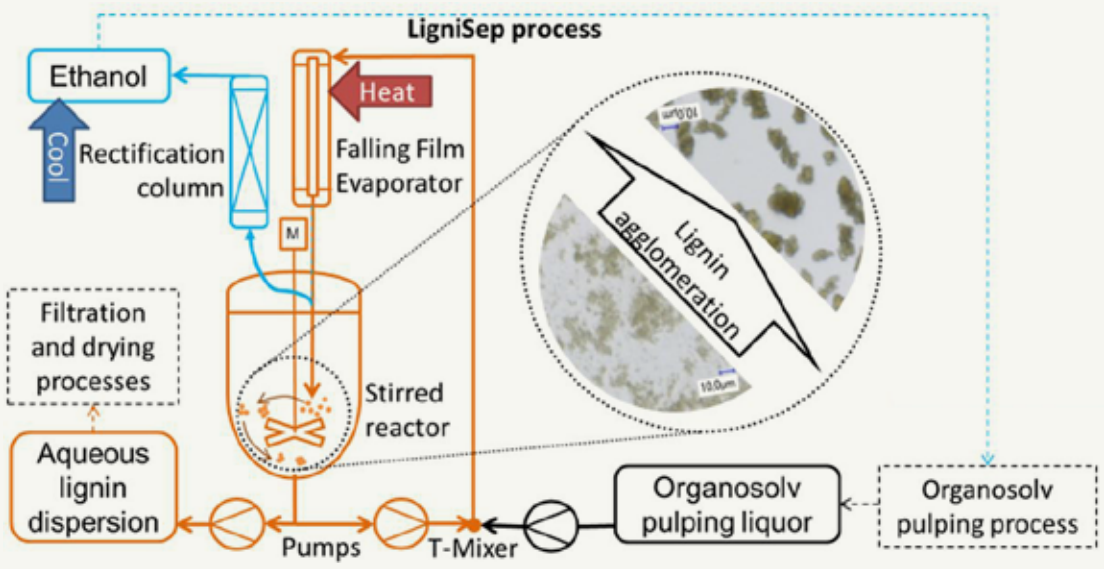


Figure 1:
Simplified scheme of the new "LigniSep" process embedded in a lignocellulose biorefinery[4]

Separation of Lignin from Solvent Pulping Liquors

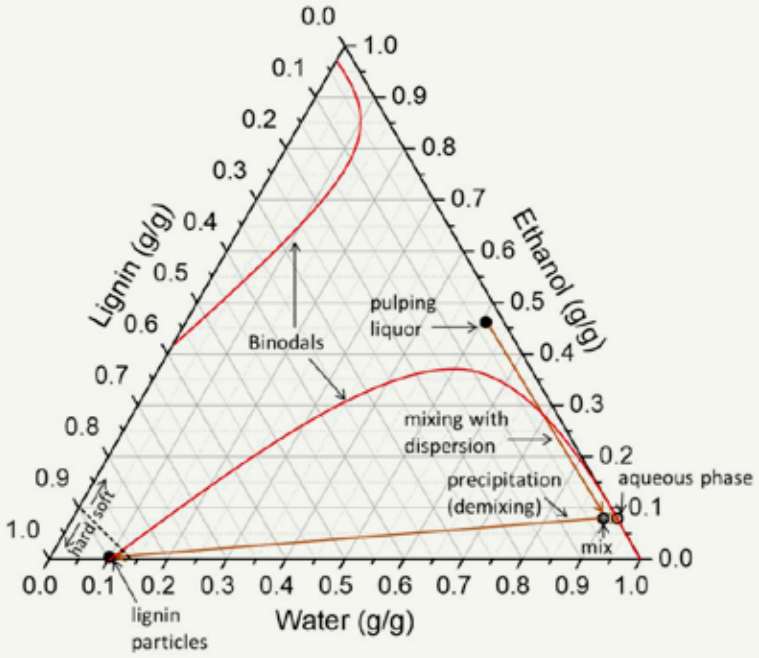
Humanity still relies predominantly on fossil-based resources for materials, chemicals and energy. The exploitation of fossil carbon resources exhibits disadvantages, like carbon dioxide enrichment in the atmosphere and approaching shortage of finite resources. Thus, improved methods for the efficient and sustainable utilization of renewable carbon resources, like straw and wood residues, has been the focus of research for decades.

Since the end of the 19th century, most conservative pulping mills apply processes that exploit wood to produce mainly cellulose fibers. Globally, the other two main constituents of woody biomass, lignin and hemicellulose, are incinerated to the tune of many million tons per year to recycle pulping chemicals and provide energy. Only a small fraction of the lignin processed in these mills is utilized as a material or chemical.

Organosolv (OS) pulping was invented nearly a century ago but is still underexploited[1]. It performs almost complete fractionation of woody biomass and provision of its main constituents, cellulose, lignin and hemicellulose, as products. Furthermore, the organic solvent used (e.g. ethanol) can be easily recycled. Thus, OS lignocellulose (LC) biorefineries (BR) that provide sustainable platform chemicals and materials are promising objects of research. However, efficient separation processes are essential for economic viability. In particular, the organic solvent recycling and accompanying lignin separation processes that have a significant impact on the energy consumption of the refinery are of great importance. Commonly applied processes for the separation of lignin from OS pulping liquors (solutions containing lignin and hemicellulose) exploit simple dilution of the pulping liquor with water or another aqueous process stream leading to lignin dispersions with poor filterability and low lignin yield. Less utilized direct evaporation of the solvent from the pulping liquor leads to undesired fouling by a soft lignin phase.

A joint project with the Fraunhofer Center for Chemical-Biotechnological Processes (CBP) developed an improved lignin separation process from ethanol OS pulping liquors based on a fundamental understanding of the lignin phase behavior[2]. The advanced process (Figure 1) was developed on the lab scale at MPI and successfully up-scaled by a factor of 210 (with respect to feed) to the pilot LC BR plant at the Fraunhofer CBP[3, 4].

In the course of this project, solubility, softening and agglomeration of particulate lignin in aqueous dispersions with different ethanol contents have been studied to determine the conditions (temperatures and ethanol contents) where lignin separates from solution and tends to soften/agglomerate and to form incrustations. The suitable oper-



+ **Figure 2:**
Illustration of the process trajectories (brown) in the qualitative pseudo-ternary phase diagram of the lignin-ethanol-water system at 40 °C. The miscibility gaps between water-lignin and ethanol-lignin are drawn as red Binodals.

ation window found for the range of investigated pulping liquors is 38-44 °C (at 80-120 mbar) and 6-9 wt. % ethanol content in the lignin dispersion. When the pulping liquor is mixed with the dispersion cycle under these conditions, the lignin is practically insoluble in the aqueous phase and it precipitates according to the miscibility gap illustrated in Figure 2. The precipitated lignin phase behaves as solid but can be easily softened by slight increases of temperature or ethanol content. Thus, agglomeration can be regulated by the heating temperature in the falling film evaporator, the pressure (boiling temperature) or the ethanol content (e.g. feed rate). However, if the particles are too soft, they tend to form undesired incrustations. The desired ethanol content is maintained by continuous evaporation and rectification of ethanol that was fed in with the pulping liquor. Product dispersion is constantly removed from the system to keep the desired liquid level in the system.

The lab and pilot plants were equipped with particle analytics and ethanol content monitoring for optimized process control. Lignin yields close to 100 % and dispersions of good filterability (filter cake resistances between 10^{11} and 10^{13} m^{-2}) were achieved by controlled agglomeration of slightly softened lignin particles.

We are confident that the "LigniSep" process brings the concept of LC BR closer to commercialization because it offers full lignin and solvent recovery, continuous operation and good filterability of lignin particles.

In 2018, applicability of the separation process to acetone-water solvent systems generated by the FABIOLA process[5] began to be studied as part of the European project "UNRAVEL-UNique Refinery Approach to Valorize European Lignocellulosics".

I Dr.-Ing. Peter Schulze

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Author **Dr.-Ing. Peter Schulze**

Peter Schulze joined the group led by Professor Seidel-Morgenstern as a Ph.D. candidate in 2013 and defended his Ph.D. project "Lignin Separation from Ethanol Water Pulping Liquors" in the middle of 2018. He studied Chemical Engineering at Otto von Guericke University Magdeburg and received his diploma in 2010. From 2010 to 2013, he was employed as a project engineer in the soda ash industry. Currently, he works as a postdoctoral researcher within the European project "UNRAVEL" focusing on lignin separation from various pulping liquors.

schulzep@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/pcf

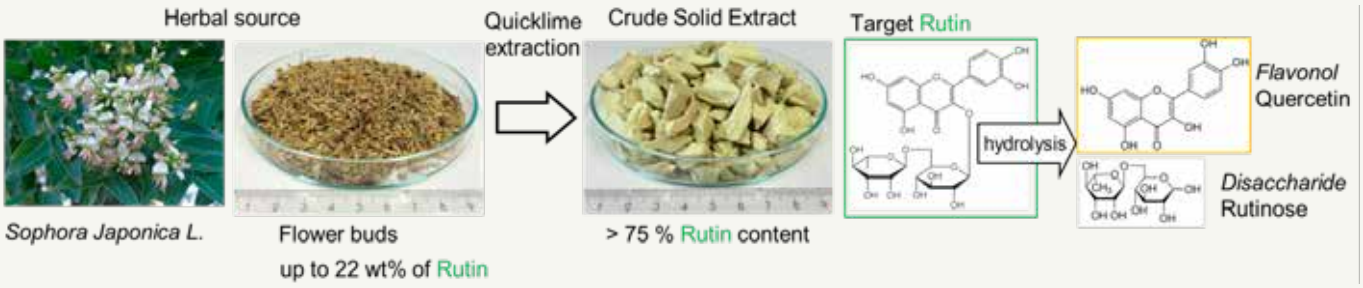


Figure 1:
The pathway from *Sophora japonica* L. to the crude extract containing target rutin.

Isolation of Natural Products via Crystallization exemplified on Rutin

Secondary plant metabolites, also called natural products, are bioactive ingredients. They are stored in plants, at usually low concentrations (0.01 - 3 wt %), and can be isolated from the vegetable source only by an extraction process. The product of the plant extraction commonly represents a multicomponent mixture of the targeted natural compound with a great variety of structurally very similar undesired rarely identified by-products. In order to provide the target component of desired purity in crystalline form, crystallization as a highly selective separation technique is often applied as the final purification step. In particular, the application of cooling crystallization with the addition of seed crystals of the component to be purified into the supersaturated solution enables the selective separation of the target compound from the mixture.

Rutin, with more than 40 therapeutic properties, is a typical representative of a pharmaceutically relevant, plant-produced bioactive molecule[1]. An extraordinarily high rutin content of 22 wt % was found in dry flower buds of Vietnamese *Sophora japonica* Leguminosae, also known as the "pagoda tree" (Fig 1)[2]. As a result, the plant extraction provides a crude solid mixture containing > 75% rutin.

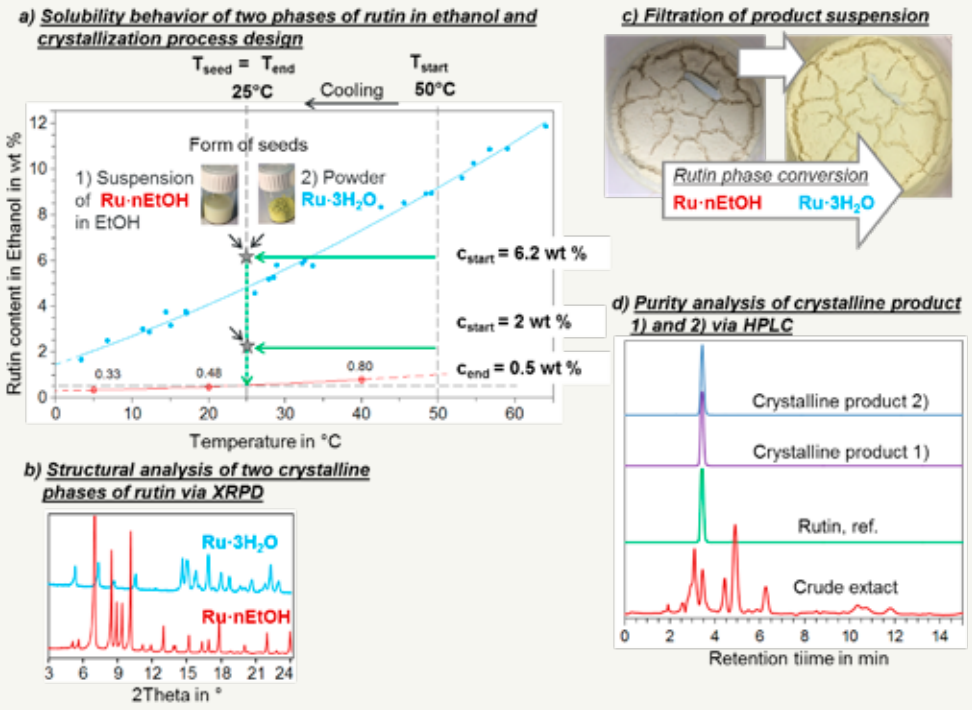
Nevertheless, the possible presence of undesired toxic alkaloids as by-products in the crude extract underlines the necessity of further processes for rutin purification, before utilization for pharmaceutical manufacturing[3].

Design and implementation of a crystallization process for rutin purification from the plant extract as a successive step after the extraction is presented below. A seeded cooling crystallization from ethanol solution was considered. Knowledge of the solubility, recrystallization and solid phase behavior of rutin in ethanol is essential for crystallization process development.

Solubility and phase behavior of rutin

Rutin trihydrate ($Ru{\cdot}3H_2O$), the crystalline phase of rutin, which is stable under ambient conditions, was utilized as the initial solid for solubility studies. Solubility of $Ru{\cdot}3H_2O$ in ethanol (Fig. 2 (a), blue data points and curve), which represents the so-called apparent solubility, was obtained by applying a polythermal method on prepared $Ru{\cdot}3H_2O$-in-ethanol suspensions. Isothermal agitation of suspensions containing initially $Ru{\cdot}3H_2O$ and ethanol provided the saturation solubility curve of rutin ethanolate (Ru·nEtOH) in ethanol (Fig. 2 (a), red data points and curve). Obviously, Ru·nEtOH is noticeably less soluble in ethanol in comparison to $Ru{\cdot}3H_2O$. The results of the structural analysis of two crystalline phases of rutin, the initial trihydrate phase (blue XRPD pattern) and the phase formed in ethanol at thermodynamic equilibrium (red XRPD pattern), are shown in Fig. 2 (b).

Stability studies of the two rutin phases demonstrated that Ru·nEtOH is only stable in ethanol. During filtration of



+ Figure 2:
a) Polythermal (blue curve) and isothermal (red curve) solubility behavior of rutin trihydrate initial phase in ethanol; **b)** X-ray powder pattern of initial trihydrate phase of rutin (blue curve) and the equilibrium phase of rutin formed in ethanol (red curve); **c)** observation of a solid-solid phase transformation from in ethanol crystallized Ru·nEtOH to Ru·3H$_2$O stable under ambient conditions during a filtration step; **d)** analytical HPLC chromatogram of crude extract (red), rutin reference sample (green) and crystalline product 1) and 2).

Ru·nEtOH-in-ethanol suspensions (Fig. 2 (c)), due to the air humidity, Ru·nEtOH crystals come into direct contact with water molecules and a solid-solid phase transformation to Ru·3H$_2$O occurs within a short time. The latter remains stable at ambient conditions.

Crystallization process design and implementation

Considering the solubility and phase behavior of rutin, the crystallization process was implemented in two steps. The 1st step served to provide a highly concentrated rutin-in-ethanol solution to gain a high product mass. Two equal clear unsaturated solutions from crude extract, each of 6.2 wt % rutin in ethanol, were prepared at 50°C. The 2nd step was the crystallization step. Here each solution was cooled to 25°C and seeded with a suspension containing Ru·nEtOH crystals in ethanol (Fig. 2 (a), 1)), or Ru·3H$_2$O powder (Fig. 2 (a), 2)). Due to the particular weak temperature dependency of Ru·nEtOH solubility, further cooling of the seeded solution would not increase the process yield and hence was not applied.

The obtained product suspension was of very high suspension density and almost impossible to agitate. After solid-liquid phase separation the purity of the solid products was analyzed via HPLC, Fig. 2 (d) (blue and violet line).

Both crystallization experiments provided satisfactory results with product purities >99% and overall process yields of about 95%. Further, to enable a semi-continuous process performance, the initial rutin content in the solution was set to 2 wt %. The crystallization process operated in a semi-continuous mode finally provided >99% pure crystalline Ru·3H$_2$O with a yield of 87% from the crude extract within a single separation step.

In conclusion, the developed crystallization-based separation process represents an attractive perspective for production of pure crystalline rutin from a plant extract of Vietnamese *Sophora Japonica L.*, which can be operated on-site as a successive step after the extraction procedure. The full manuscript is published in [4] and the purification approach has been patented by the authors [5].

| Dr.-Ing. Elena Horosanskaia

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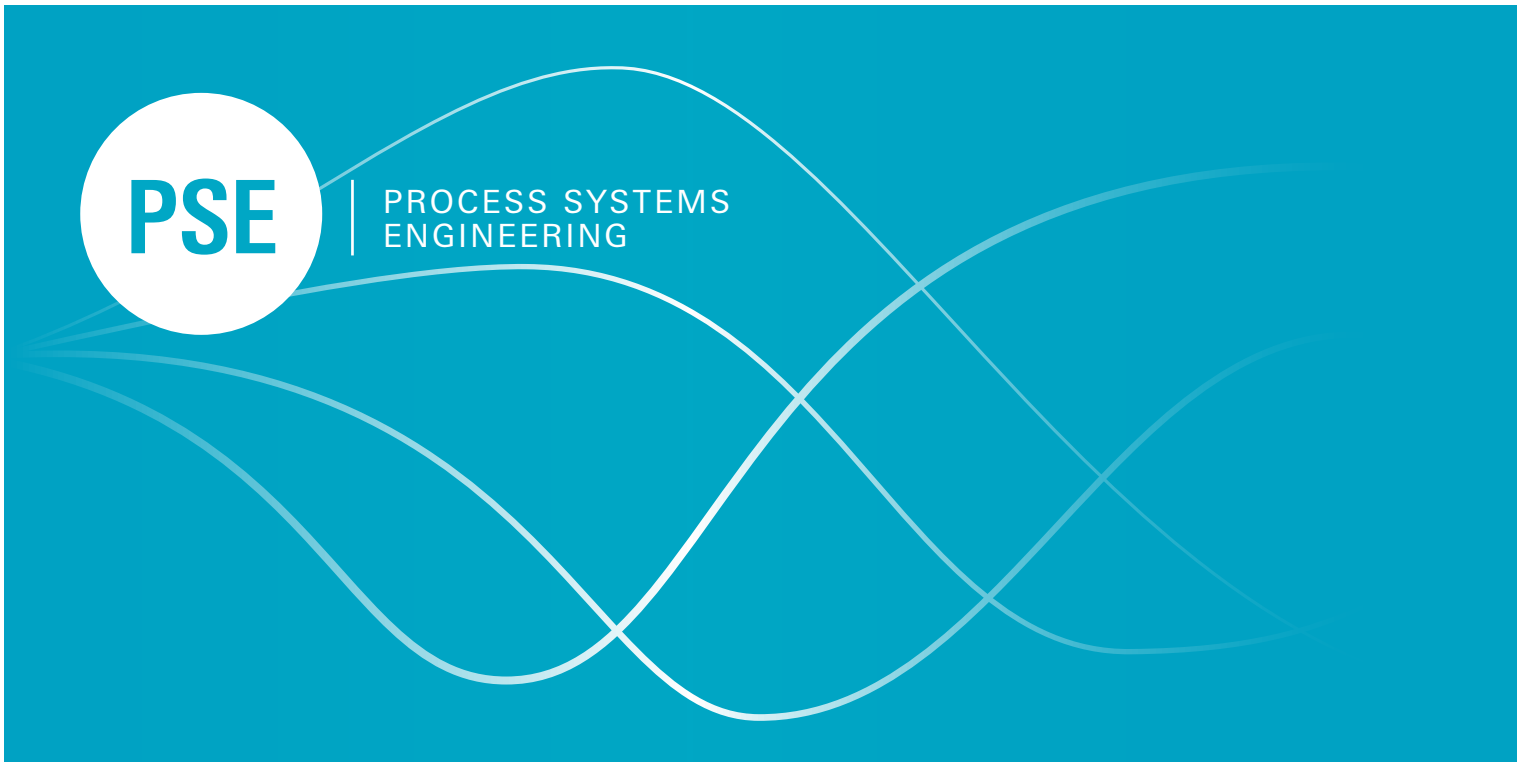
Author **Dr.-Ing. Elena Horosanskaia**

Elena Horosanskaia studied Chemical Process Engineering from 2005 to 2010 at Otto von Guericke University in Magdeburg where she received her degree in 2010. From January 2011 to May 2012 she worked as a project engineer with consulting engineers at Industrieberatung Umwelt GmbH & Co. KG in Wistedt i.d. Nordheide. From June 2012 to January 2019 she successfully worked on her Ph. D. degree for which she focused on crystallization-based isolation of natural products from multicomponent mixtures, plant extracts or product solutions of organic synthesis.

horosanskaia@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/pcf



PROF. DR.-ING. KAI SUNDMACHER | DIRECTOR

Over recent 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 to 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, the aim of which is to synthesize production systems from **elementary process functions**. This methodology supports process design decisions on different levels of the process hierarchy (molecular level, phase level, process unit level, plant level). More recently, we have extended our methodology to be able to deal with complex production systems ("FluxMax" approach) and successfully applied the same to industrially relevant examples.

In the field of **Chemical Production Systems**, our current research focus is mainly on multiphase reactions performed in different innovative solvents systems, in particular ionic liquids, thermomorphic multicomponent mixtures, micellar solvents and deep eutectic solvents. This research is being carried out partly in cooperation with TU Berlin, TU Dortmund and Otto von Guericke University in Magdeburg un-

+ In the MaxSynBio research consortium we follow a bottom-up approach for mimicking the fundamental structural and functional principles of cells towards their better understanding. For example, we produce phospholipid vesicles by microfluidics and stain them with dyes in order to observe their behavior with a fluorescence microscope. These vesicles, seen as orange spheres on the screen, serve as minimal models of biological cells.

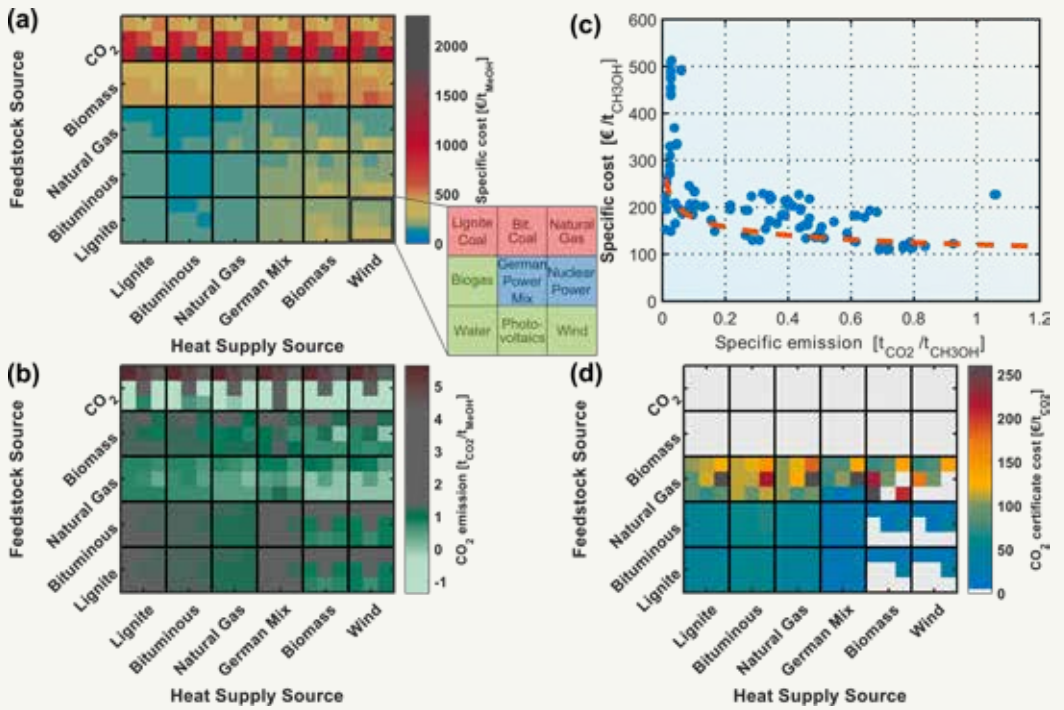
der the umbrella of the DFG-funded Collaborative Research Center SFB/TR 63 "InPROMPT". Regarding molecular solvent design, we collaborate closely with our Max Planck Partner group at the East China University of Science and Technology in Shanghai/China, headed by Professor Zhiwen Qi.

Concerning **Energy Conversion Systems**, we develop novel Power-to-X processes for the efficient conversion of electrical power into different chemicals, including hydrogen, synthetic methane, methanol and liquid fuels. A 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 Max Planck Institute for Chemical Energy Conversion in Mülheim and the Fritz Haber Institute in Berlin. Due to the volatility of renewable energies, the dynamic operation and optimal control of catalytic reactors, for example for the methanation of hydrogen, is becoming increasingly important. For this purpose, we have started to investigate novel reactor-catalyst concepts both via mathematical modeling and via targeted experiments at both lab and miniplant scale, partly supported by the new DFG-funded priority program SPP 2080.

In the field of **Biological Production Systems**, since 2014 we have been coordinating 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 consortium is the modular bottom-up assembly of artificial cells from functional biomolecular modules. In the past two years, several joint articles with other Max Planck Institutes (Mainz, Martinsried, Potsdam, Stuttgart, etc.) have been published in high impact factor journals. The realization of a synthetic ATP regeneration module for energy supply in synthetic cells is one of the success stories, that we have achieved together with the EEC group.

Prof. Dr.-Ing. Kai Sundmacher
Director

sundmacher@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/sundmacher



+ Figure 1:
Systematic evaluation of the influence of different sources for feedstock, heat, and power supply on the specific production cost (a) and on the specific CO_2 emissions (b); Pareto curve of conflicting objectives – costs and CO_2 emissions – for natural gas-fed processes (c); and evaluation of required CO_2-certificate cost to support low emission processes (d)

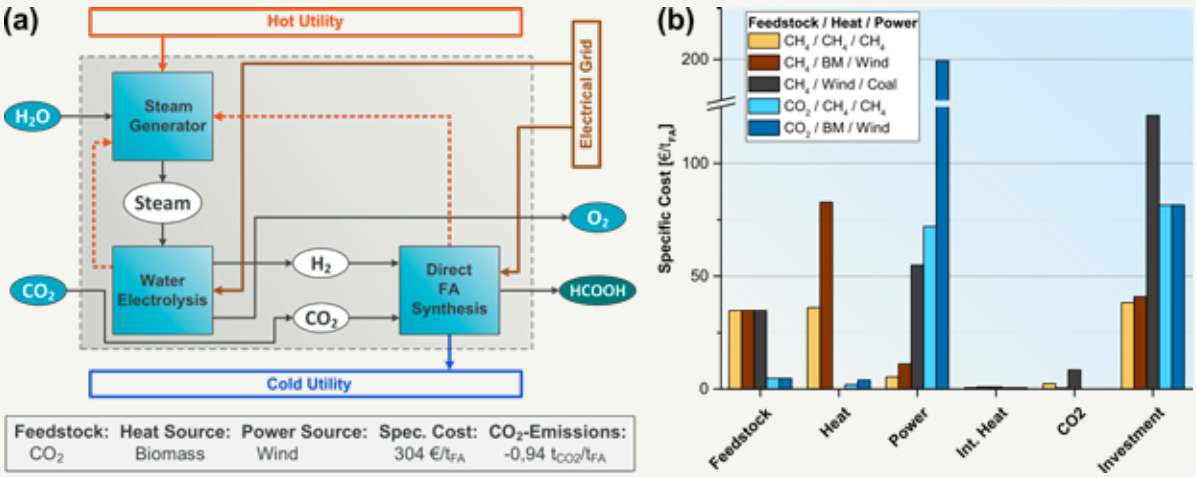
R2Chem: Renewables to Valuable Chemicals and Fuels

+ In recent years, the awareness of a more sustainable use of available resources in research and industry, as well as in politics and society, has increased significantly. There is common agreement about the need to replace fossil feedstock and energy carriers with renewable resources in order to reduce CO_2 emissions. However, an expansion of renewable power plants, e.g. wind farms or photovoltaic systems, and the simultaneous removal of base load plants will inevitably lead to major challenges due to the high volatility of renewable energy sources (wind, solar). The fluctuating supply of renewable energy to the grid can result in an electrical surplus usable for chemical processes. In this context, Renewables-to-Chemicals (R2Chem) processes are a very attractive option for future chemicals production. A key step in the R2Chem context is the electrochemical splitting of water into hydrogen and oxygen by electrolysis and the subsequent utilization and/or storage of hydrogen. Since in many areas, for example the transportation sector, (synthetic) hydrocarbons will still be needed in the future, sustainable carbon sources must also be identified. There are several different approaches to gaining or recycling carbon. The most prominent is the conversion of biomass by anaerobic digestion into (bio-)methane, but carbon capture and utilization (CCU) technologies are also key areas of research. CCU seems to be very attractive as it offers the possibility of closing the carbon cycle by recycling the bounded carbon atom in the carbon dioxide (CO_2) molecule.

However, in order to transition successfully towards a more sustainable system of producing chemicals, industry will need not only to utilize renewable feedstocks and energy, but also to increase the energy efficiency of existing fossil-based technologies. For a fair assessment of the economic and ecological impacts, a systematic comparison of all combinations of feedstock and energy sources as well as process technologies is necessary. Due to the multitude of alternative raw materials and process technologies, there are many different potential pathways to converting renewables into valuable target products.

In [1] we introduced an elegant problem formulation in terms of continuous process extent variables to avoid binary decision variables. All constraints (equalities, inequalities) as well as the objective function are formulated as linear expressions in terms of the (purely continuous) decision variables, namely mass, heat and work fluxes as well as the extent variables. The objective function contains the Total Annualized Costs (TAC) and penalty terms for direct and indirect CO_2 emissions.

For the target product methanol, we systematically evaluated the specific cost and specific CO_2 emissions of a multitude of fossil and renewable-based feedstocks as well as energy sources (see Figure 1a, b). By applying the method presented in [1], we identified the cost-optimal process structure and the associated CO_2 emissions for each combination of feedstock and energy source considered. A net consumption of CO_2 by the overall production system is possible if renewable energy sources are exploited and CO_2 is used as a feedstock source at the same time. If fossil energy sources are used, a significant carbon footprint is unavoidable due to the high indirect CO_2 emissions from the energy supply (electricity,



+ Figure 2:
Schematic illustration of the optimal process configuration to convert CO_2 and renewables into formic acid by applying the electrochemical processes water electrolysis and the direct synthesis technology (a); and the single contributions to the total production costs for five selected process configurations (b)

heat). Thus, not only the economic challenge of using CO_2 as a raw material, but also the ecological impact depends strongly on the energy source used.

We have shown that using natural gas or biogas as a feedstock source leads to a very good trade-off between production cost and emissions, especially if the required energy comes from renewable sources. A multi-objective optimization of the two conflicting objectives – costs and emissions – for natural gas-fed processes resulted in the Pareto plot shown in Figure 1c. It becomes obvious that it is possible to significantly reduce the CO_2 emissions while costs increase only slightly. Only if almost emission-free configurations are desired do the costs rise drastically. Therefore, we further analyzed the theoretical price of CO_2 certificates, which would be required to make almost emission-free configurations cost-optimal (see Figure 1d). Depending on the energy source used, we calculated certificate prices in the range of 50 to 150 EUR/t_{CO_2} (current price: 20 EUR/t_{CO_2}).

In a similar study, we evaluated the formic acid production network [2] in which we evaluated CO_2 and natural gas-fed processes. Figure 2a shows a simplified scheme of a process configuration that converts CO_2 directly into formic acid using hydrogen from electrolysis. Also here a net CO_2 consumption is reached by the use of renewable energy sources, however, the production costs are very high. Figure 2b shows the single contributions to the total production costs. It can be seen that the main cost drivers for CO_2-fed processes are the costs of power supply and the investments. The reasons, respectively, are the high costs of electricity generated from renewable energies, and the low technology readiness level of the process technologies applied, which result in high investment costs.

Both case studies presented, show the main advantage of the proposed methodology, that is its ability to quickly determine an optimal process system within a superstructure in which many alternative process configurations are embedded. The main outcome is the fact that a net consumption of CO_2, and thus a real reduction of atmospheric CO_2, is only possible if the energy is provided entirely by renewable energies. However, due to the high economic challenges posed by high electricity prices and a low technology readiness level, a combination of fossil-based natural gas and renewable energy supply is an economically viable alternative in the transition period that can drastically reduce CO_2 emissions.

| Dominik Schack

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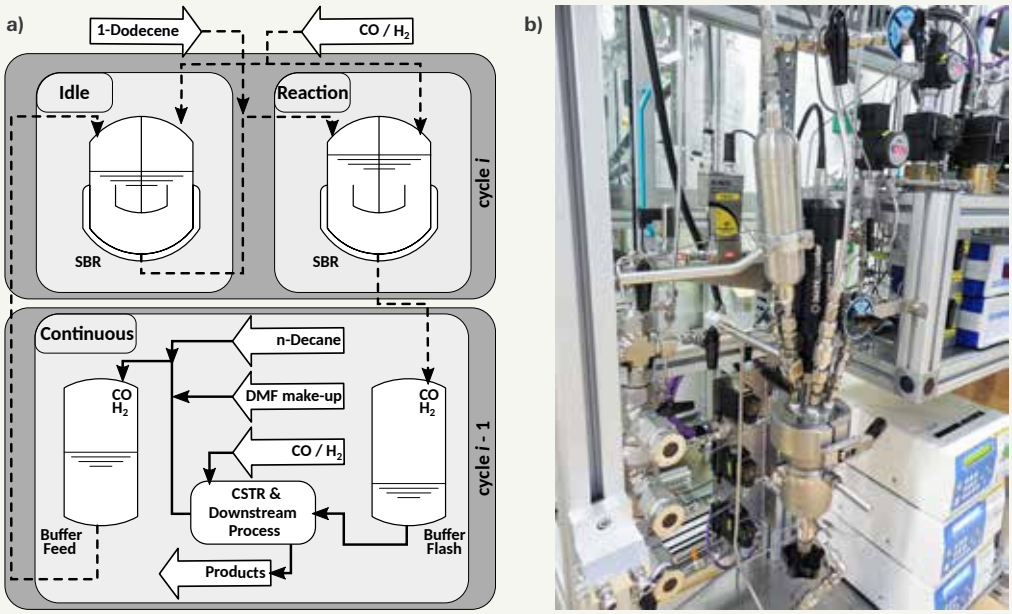
Author **Dominik Schack**

Dominik Schack received his Bachelor's degree in Environmental and Energy Process Engineering from Otto von Guericke University in 2012. He then studied Sustainable Energy Systems and graduated in 2014 with a Master's degree. Since then, he has been a Ph.D. student in Professor Sundmacher's PSE group at the Max Planck Institute. His research focuses on the optimization of Renewable-to-Chemical process networks for the conversion of renewable energies into valuable chemical products and the synthesis of chemical processes across different length scales. His work helps to identify strategies for the economically and ecologically sustainable use of renewable energies.

schack@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/pse



+ **Figure 1:**
Repeatedly operated semi-batch reactor (RSBR) process. a) Dynamic model formulation [1]1 and b) experimental setup.

1 please see imprint

Reactor Design for Green Chemical Production Processes

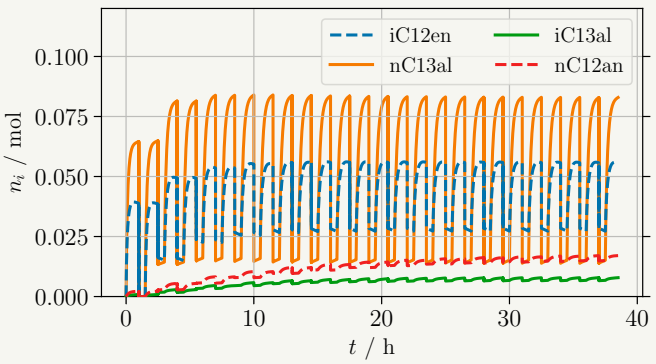
+ Modern chemical production relies heavily on fossil feedstocks as a source of raw materials. The simple structure of natural gas and crude oil molecules make it possible to develop highly specialized and optimized processes for increasing conversion and selectivity towards desired products. However, in order to achieve the necessary level of efficiency and performance, tight bounds on the raw material quality are critical. Biomass-based feedstocks generally contain complex and highly functionalized molecular structures which cause fluctuations in the feedstock quality and prevent their direct utilization in established plants that are often continuously operated. The challenge for future chemical production processes therefore lies in combining process flexibility with robust process operation while maintaining adequate production capacities.

Within this context, the PSE group focuses on the fast, model-based synthesis of innovative and efficient processes on different scales. Generally, process synthesis in chemical engineering refers to a multi-step process in which a flowsheet is designed in accordance with a predetermined objective. This objective may vary between processes and might be subject to external factors like geographical aspects or the economy. Generally, performance measures like conversion, selectivity, energy demand, production capacity and economic aspects are incorporated into the overall objective. In the face of the transition towards sustainable raw materials, flexibility, and therefore the choice of operational mode, is a criterion which deserves higher priority in the process design task.

By utilizing the *Elementary Process Functions* (EPF) methodology [2], the process design is represented in terms of functional modules leading to an optimal sequence of operational tasks independent of conventional process units. Using the homogeneously catalyzed hydroformylation of long-chain olefins with Rhodium as catalyst and specialized ligands in a thermomorphic multiphase system (TMS) as an example process, the PSE group developed two process designs which differ in terms of operational mode. Besides a continuously operated process, the integration of a repeatedly operated semibatch reactor (RSBR) in a continuous overall process is proposed [3]. Both of the concepts share a similar performance in terms of conversion and selectivity but the quasi-continuous process excels with regard to controllability because of its simple construction and flexible operability.

Due to its inherent dynamic behavior, the assessment of the RSBR process requires detailed simulations and experimental investigations. In a first step, the PSE group proposed a modeling procedure for the complex interaction of a batch-wise operated semi-batch reactor and the continuously operated downstream process [1]. Circumventing any integer decisions, the process model in Fig. 1a is formulated as a nonlinear program (NLP) and solved cycle-wise with reasonable

a)



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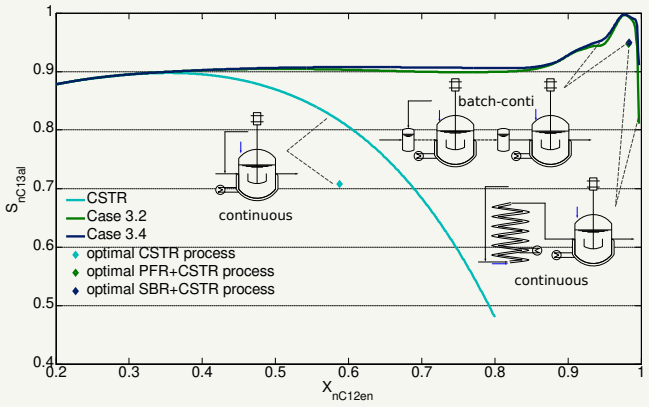

+ Figure 2:
Simulative investigation of the hydroformylation of 1-dodecene. a) Simulated start-up behavior of a RSBR and subsequent CSTR with catalyst and isomer recycle[1]1. b) Predicted selectivity-conversion behavior of different reactor designs[3]2.

2 please see imprint

computational effort. In addition to a prediction of the process performance in steady-state which matches previous steady-state simulations, the dynamic process model allows for the investigation of discrete events like set-point transitions or fluctuations in the feed stream. Of particular interest, the simulation of the start-up process allows for an estimate of the time required to reach steady-state. Here, the simulation reveals different time constants for each species (see Fig. 2a) with the accumulation of the hydrogenation product being the rate determining process.

To validate the predictions, the quasi-continuous process was investigated experimentally at mini-plant scale. Two long-term campaigns with a total operation time of over 180 h were conducted: one with and one without side-product recycling[4]. In order to better compare our results to the literature, the predetermined total residence time needed to be distributed between the various reaction zones. By using the dynamic process model for this task, not only the residence time distribution but also the expected flow rates in the process were estimated and used in the preparation of the experiments. In addition to an excellent agreement between the simulations and the experimental results, the experiments confirm the predicted increase in conversion and product yield (see Fig. 2b) although the process potential was not fully exhausted in the experimental evaluation.

| Karsten Hans Georg Rätze

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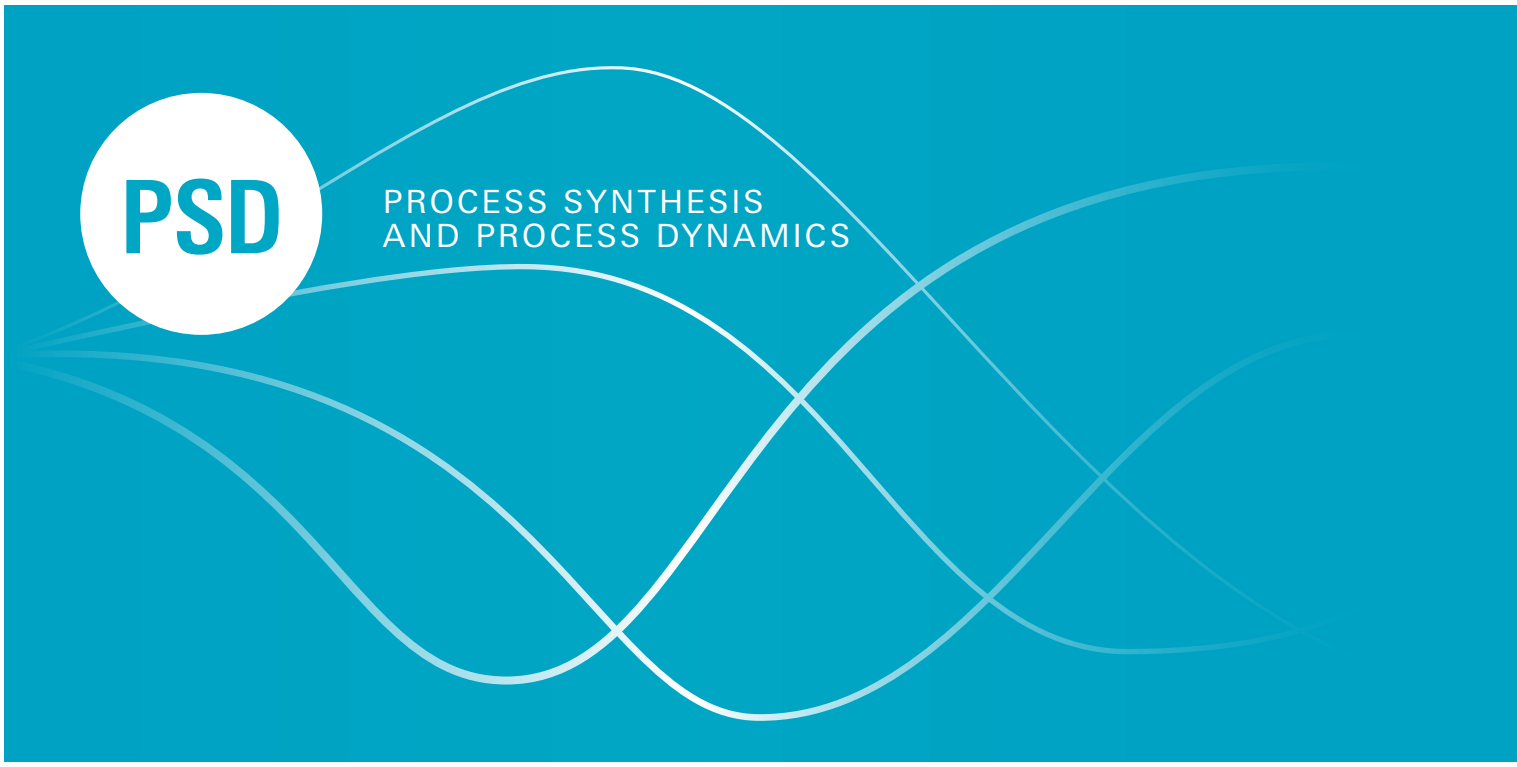
Author **Karsten Hans Georg Rätze**

Karsten H. G. Rätze embarked upon his academic career in 2011 when he started his Bachelor's degree in Process Engineering at the Otto von Guericke University in Magdeburg. After undertaking an internship and finishing his Bachelor's thesis at BASF SE in Ludwigshafen, he commenced his Master's degree at OvGU with the particular focus on Process Systems Engineering. In 2015, he joined the Process Systems Engineering group of Professor Kai Sundmacher as a student assistant and received his Master's degree after completing his Master's thesis in the Biegler Research Group at Carnegie Mellon University. Since October 2016, he has been pursuing his Ph.D. in the group headed by Professor Sundmacher on the topic of process synthesis of liquid multiphase systems.

raetze@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/pse



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 Otto von Guericke University. The MPI and university group collaborate closely.

The PSD group develops methods and tools for the synthesis, analysis and control of complex process systems. It combines physical chemical insight with concepts from systems and control theory as well as applied mathematics. Process insight guides the way to suitable problem formulations and to feasible, efficient solution strategies. If possible with reasonable effort, theoretical concepts are validated experimentally. With its approach the PSD group helps to bridge the gap between theory and application.

Process control has emerged as a major field of research for the PSD group during recent years. Currently, focus is on control of particulate processes, advanced chromatographic processes and methanol synthesis as one example of a challenging reaction system. Particulate processes are described by nonlinear partial differential equations and represent a highly challenging class of distributed parameter systems. Important topics addressed by the PSD group include mathematical modeling, non-linear model reduction, and new approaches to robust and nonlinear control of particulate processes. Novel crystallization, fluidized bed spray granulation and agglomeration processes were investigated as interesting application examples. Chromatographic processes are switched systems with cyclic behavior. A particular focus of the PSD group is adaptive cycle-to-cycle control of simulated moving bed chromatographic processes, which play an important role for difficult separation problems in fine chemistry including the pharmaceutical industry. Novel challenges for the control of methanol synthesis are posed by new applications for chemical energy storage under randomly fluctuating conditions. Furthermore, new modes of forced periodic operation are being developed together with the Seidel-Morgenstern group from the MPI and the Petkovska group from Belgrade University.

In the field of **Process design** the PSD group is developing computational methods for a systematic design of complex process systems. Approaches range from shortcut methods based on analytical insight to rigorous simultaneous mixed integer nonlinear optimization (MINLP) of process configurations and operating conditions. During the period covered

+ Robert Dürr, Stefanie Duvigneau, and Christian Kunde are discussing with Prof. Kienle (left) about the biopolymer project.

by this report, particular interest was given to new methods for deterministic global MINLP optimization of multiphase reaction and separation systems being developed in cooperation with partners from mathematics, and on novel analytical and numerical methods for chromatographic processes with complex adsorption isotherms.

Biosystems engineering has been identified as a research area of common interest at the Max Planck Institute and the Otto von Guericke University. The PSD group makes important contributions to biosystems engineering in the fields of modeling, nonlinear dynamics and control of biotechnological processes with special emphasis on cell-to-cell heterogeneity. Vaccine and biopolymer production processes were investigated as interesting application examples. Further, the group has commenced activities in the innovative field of conceptual modeling and analysis of synthetic biological systems.

The PSD group has been involved in a number of highly visible larger joint research projects with external funding, including the joint research center Transregio SFB 63 on integrated chemical processes in liquid multi-phase systems, which involves about 15 other partners, mainly from TU Berlin and TU Dortmund, the national priority program SPP 1679 on dynamic flowsheet simulation of particulate processes, the national priority program SPP2080 on catalysts and reactors under dynamic operating conditions for energy storage and transformation, 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.

Prof. Dr.-Ing. Achim Kienle
External Scientific Member

kienle@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/kienle

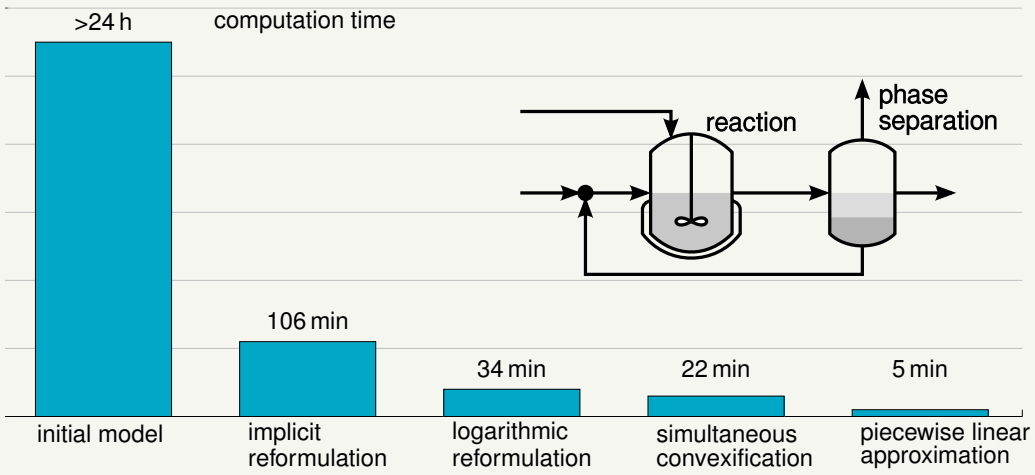


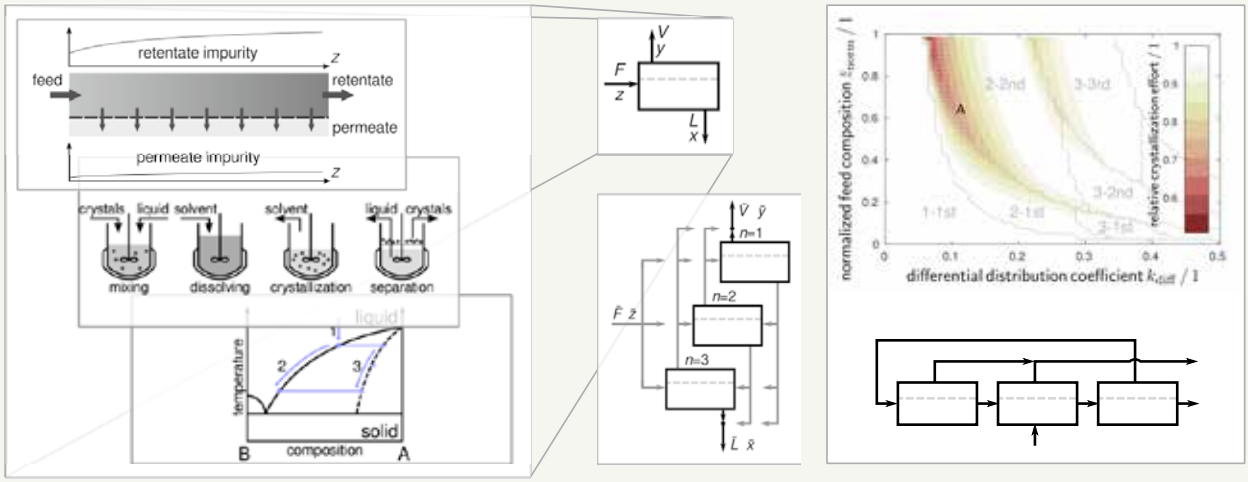
Figure 1:
Deterministic global optimization of a novel hydroformylation process. Influence of model formulation, relaxation strategies and model approximation on computational effort.

Global Optimization of Multiphase Systems

Optimal design of chemical processes often leads to mixed integer nonlinear optimization problems (MINLP). In practice, often local or stochastic optimization methods are applied to solve them. However, due to the presence of multiple local minima, such methods cannot guarantee that a global optimum will be reached. To overcome this problem powerful methods for deterministic global optimization were developed during recent years based on convex relaxations. Convex relaxations are mathematical model approximations, which contain the solution of the original problem. They are easier to solve and can be refined successively. However, the computational effort for solving even relatively simple problems from the engineering point of view can be tremendous. In this project we aim to reduce the computational effort by suitable model (re)formulation, bound tightening and relaxation strategies. Physical process insight guides the way to efficient solution strategies.

The project is embedded in the joint research center SFB/TR 63 with partners from TU Dortmund and TU Berlin. From the application side, focus is on the development of novel chemical processes from renewable resources in integrated liquid multiphase systems. So far, the main focus of our research has been on hydroformylation of long chain olefines using thermomorphic solvent systems. These solvent systems establish a homogeneous liquid phase under reaction conditions and separate into an organic product phase and a catalyst containing aqueous phase when cooled down. This allows high reaction rates and easy separation and recycling of the expensive noble metal catalyst. Suitable methods for global optimization have been developed for this type of processes as illustrated in Fig. 1 [3]. The methods include some problem-specific mathematical model reformulation, simultaneous convexification of different nonlinear terms in the constraint set, and a piecewise linear approximation of the activation functions of an artificial neural network, which is used to describe the complex solubility of the synthesis gas in the liquid phase. Overall, it has been possible to reduce computational costs by orders of magnitude as illustrated in the figure.

For the overall process concept also separation processes play an important role. Their main tasks are the efficient separation of the products, and the recycle of the excess reactants, the expensive catalyst, catalyst ligands and solvents. Among the separation processes, distillation columns have a large impact on flowsheet optimization, because of the high energy costs for this type of separation processes. Using monotonic reformulations, tailor-made bound tightening or surrogate models with iterative refinement, global optimization of distillation columns has become feasible for the first time with moderate computational effort in the order of minutes up to a few hours depending on the specific process (number of components, 'difficulty' of separation) [7, 2, 1]. It has been shown that even for ideal mixtures under certain conditions global optimization can improve the design significantly compared to traditional approaches ([6]).



+ Figure 2:
Global optimization of multistage separation processes involving melt and solution crystallization and membrane separation (left): Influence of network structure (middle) on process performance (right).

Furthermore, global optimization was also applied to other multistage separation processes including membrane separation, melt and solution crystallization, leading to novel insights (see Fig. 2). Comprehensive optimization studies were performed for binary separations with different feed compositions, different separation factors and different objective functions to gain the complete picture. It was found that all of these processes share the common feature that, in particular for low numbers of required stages, traditional countercurrent cascades are suboptimal. The physical explanation is that the overall amount of processed material can be significantly reduced by generating as much product as possible in a first stage such that purity specifications are met after mixing with a small amount of highly purified product from other stages. Substantial improvements in total costs up to 35 % were found for the novel process configurations compared to classical countercurrent cascades and some simple design rules were derived from the rigorous global optimization results [5, 6, 4].

I Christian Kunde, Tobias Keßler

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Author **Christian Kunde**

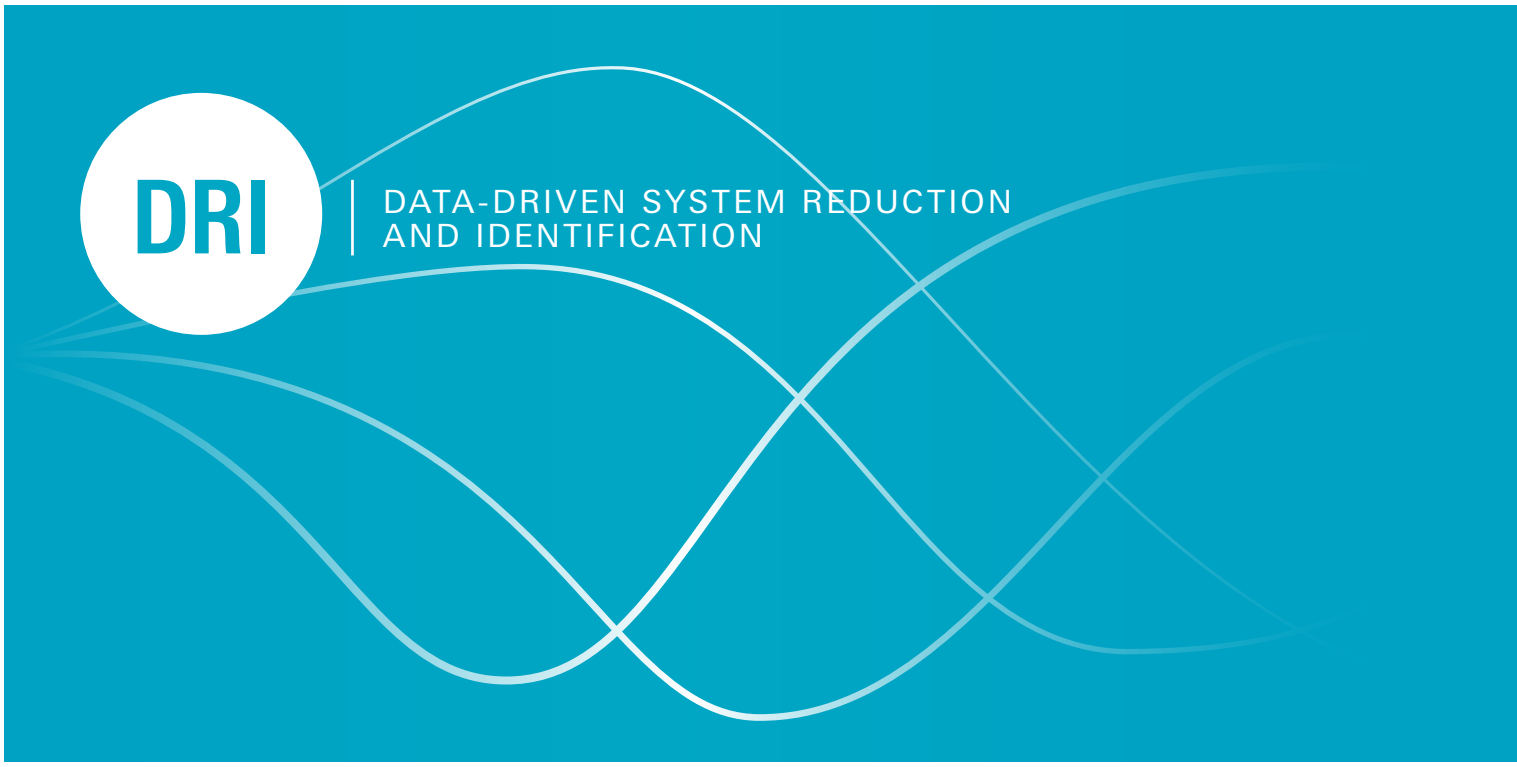
Christian Kunde studied 'Systems Engineering and Engineering Cybernetics' at Otto von Guericke University Magdeburg and received his diploma in 2009. He then joined the PSD group, where he worked on deterministic global optimization of multistage separation processes, and completed his Ph.D. with honors in 2017. His current research in the PSD group includes data-based surrogate modeling and its application to global optimization. He is associated member of the TRR63-InPROMPT collaborative research center.

kunde@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/psd

Author **Tobias Keßler**

Tobias Keßler studied 'Systems Engineering and Engineering Cybernetics' at Otto von Guericke University Magdeburg and received his M.Sc. in 2015. In the same year, he started his Ph.D. in the PSD group. His research focuses on the optimization of thermomorphic multicomponent systems and separation processes for the efficient recovery of homogeneous catalysts and solvents. He is a member of the TRR63-InPROMPT collaborative research center.

kesslert@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/psd



PROF. DR. ATHANASIOS C. ANTOULAS |
MAX PLANCK FELLOW

The Max Planck Fellows Program aims to strengthen cooperation between Max Planck Institutes and universities. Following an application by Professor P. Benner in February 2016, in July 2016 Professor A.C. Antoulas was appointed by the Max Planck Society as Max Planck Fellow for a three-year term starting January 1, 2017. The two other members of the group, namely the post-doctoral researcher Dr. I.V. Gosea and the doctoral student D.S. Karachalios were hired in February and July 2017, respectively.

The thrust of the research activities of the DRI group concentrates on data-driven model reduction, with the Loewner pencil and the Hankel pencil as primary tools. These are direct data-driven model identification and reduction approaches. They construct models for which the (appropriately defined) input-output mappings approximate well those of the original system. Originally developed at Rice University in the last decade, these approaches have since been refined and extended to more complex situations. Moreover, these methodologies have steadily sparkled the interest of research groups around the world and have been successfully applied to a multitude of problems.

The research activities also included a number of collaborations within the MPI in Magdeburg, for instance with the CSC group (led by Prof. Benner) that resulted in several research papers. The main topic of interest that linked the two groups is model reduction of switched and hybrid systems. Additionally, in 2018, the DRI group initiated common research with the PSE group (led by Prof. Sundmacher) and with the EEC group (led by Dr. Vidaković-Koch).

The Loewner Framework – one Main Tool of our Group

The Loewner Framework is a data-driven interpolation-based identification and reduction technique that uses measured or computed data to construct surrogate models of low complexity. In practice, the data consists of frequency response measurements for linear systems or of generalized types of frequency response measurements in the nonlinear case. The core of the method for the case of linear systems, has recently appeared in the tutorial paper[1]. One attribute of the Loewner framework is that it can construct a model from a set of measured or computed data in a direct and automated way (with basically no computational cost). Another is that it offers a trade-off between accuracy of fit and complexity of the model. The numerical tool that allows this is the singular value decomposition (SVD).

The Loewner framework has been extended and applied to classes of nonlinear systems, such as bilinear systems and quadratic-bilinear (QB) systems. It has also been applied to systems with non-rational transfer functions (which represent

+ Nowadays, many processes in engineering and natural sciences can be modeled, studied and optimized based on large collections of measured data. The goal is to use the available resources to devise reliable and efficient data-driven reduction methods. Dr. Ion Victor Gosea and Dimitrios Karachalios are here discussing on different choices of interpolation grids for implementing the model reduction method for bilinear control systems.

infinite dimensional linear systems), e.g., a clamped Euler - Bernoulli beam. As an example of applying the Loewner framework to nonlinear systems, consider Burgers' equation with Robin boundary conditions. The dynamics is characterized by partial differential equations with quadratic nonlinearity. After performing a spatial discretization using piecewise linear finite elements on a uniform grid, a QB system results. We approximate this original system with a smaller QB system constructed by interpolating certain generalized transfer functions in the Loewner framework. The reduced order model provides similar output response as the full order model. The approximation error depends on the selected truncation order of the Loewner model after computing the SVD of an appropriately defined Loewner pencil. For an overview see[1] and the book[2].

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Prof. Dr. Athanasios C. Antoulas
Max Planck Fellow

antoulas@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/dri

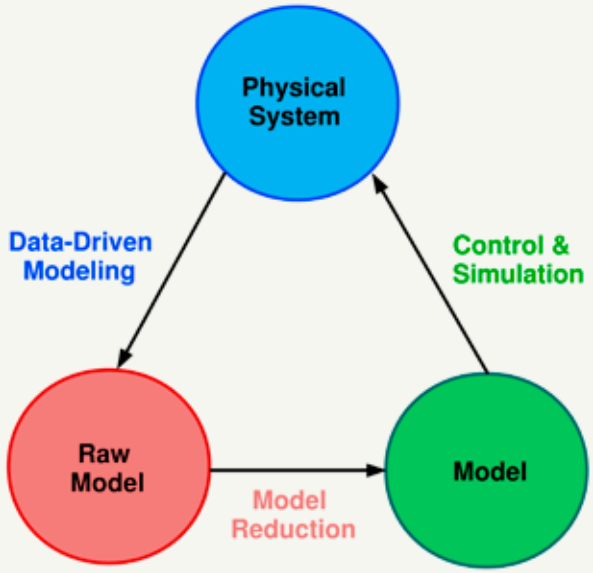


Figure 1:
The scope of the DRI research group is to use real-time analysis of measured data to construct models that can accurately identify the underlying dynamics. The figure besides summarizes the group's approach to model identification and reduction.

Gene Oscillations

The circadian (or daily) rhythm allows organisms to anticipate environmental changes and to prepare accordingly. The 24-hour circadian cycle has been well understood and described over the years and is involved in many metabolic processes. Consequently, distortions of the 24-hour cycle may have profound impacts on health. The goal of this research (joint with colleagues from the Baylor College of Medicine, Houston) was to find other cycles, in particular 12-hour cycles, of gene transcription.

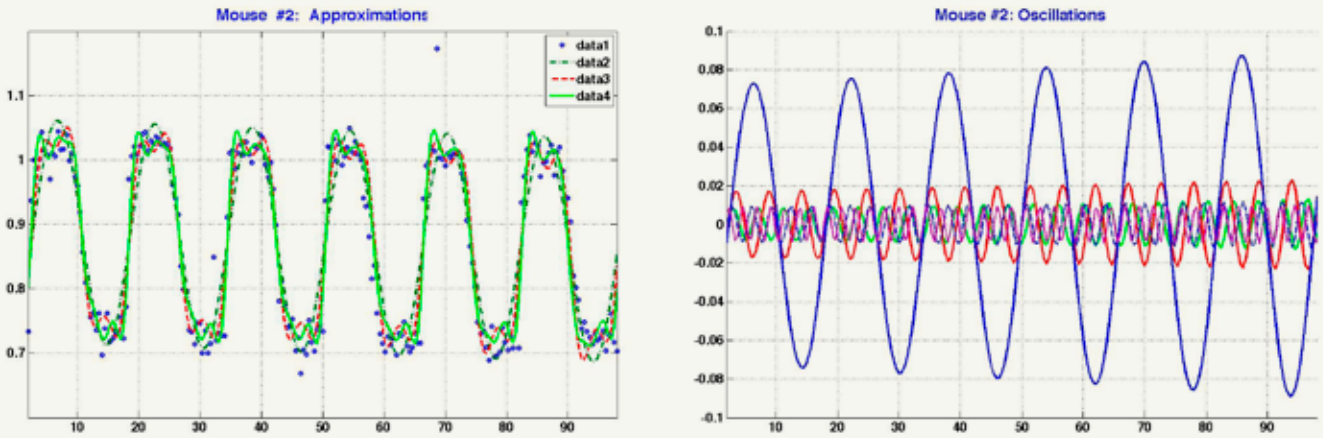
A novel mathematical approach has uncovered that some animal cells have robust 12-hour cycles of genetic activity, in addition to circadian or 24-hour cycles. The method, published in the journals Cell Metabolism [1] and PLOS ONE [2], assessed the periodicity of gene expression data and compared the results with those obtained with other computational methods. As opposed to the other methods, this novel approach showed not only the existence of unsuspected biological cycles, but also that the 12-hour cycles work independently from the 24-hour cycles, which has been confirmed by laboratory experiments (reported in [1]). These findings open a new area of study of how gene functions influence health and disease over time.

Circadian rhythms are physical, mental and behavioral changes that follow a 24-hour cycle driven by environmental light and darkness. One of the best known circadian cycles is sleeping at night and being awake during the day. These biological rhythms reflect complex interactions at the molecular level that occur among the paths mediating the expression of genes into active proteins carrying functions in the cell.

There is evidence, however, that other biological cycles exist in addition to 24-hour rhythms. Blood pressure, body temperature, cognitive performance, some circulating hormones, reaction to stress and responses to drug therapy, for instance, appear to follow a 12-hour rhythm, but little is known about their biological basis. Together with colleagues from Baylor we set out to find answers.

Other mathematical methods approached this type of problem by asking, does a specific waveform exist in the data? They were already biased to find a particular type of wave. On the other hand, the method that we proposed asked an unbiased question: what type of wave is present in the data, if any? We applied a mathematical method used to analyze different types of data, in order to analyze the biological phenomena at hand, specifically gene expression data that had been collected every hour for 36 or 48 hours. More than 18,000 mouse liver genes involved in a variety of cellular processes, including metabolism, cell stress, cell cycle and cellular respiration, were analyzed.

Our method revealed the fundamental cycles present in each data set collected for each gene. We confirmed the 24-hour



+ **Figure 2:**
The response of the models (left) and the main oscillations (right) for one of the data sets.

circadian cycles and uncovered genes whose expression over time followed a 12-hour cycle that was not evident when using other computational methods. The matrix pencil method that we used revealed that these cycles were independent, and this was subsequently confirmed by laboratory experiments showing that knocking down genes that follow a 24-hour cycle does not affect the expression pattern of the 12-hour genes [1].

By looking at the function of genes over time, as opposed to looking at a single moment, we have uncovered that fundamental cell functions, such as inflammation, stress response, protein quality control and energy supply, follow certain cycles. This finding has implications for redefining aspects of human health as controlled by genes.

It has been shown that disturbing the 24-hour clocks may lead to diseases of metabolism. For instance, experimental evidence shows that night-shift workers who periodically change their night and day shifts or people who travel overseas often alter their sleep cycles, and this seems to make them prone to gain weight and develop diabetes and other alterations of metabolism that may lead to disease. Its not a good idea to disturb the circadian rhythm on a regular basis. We anticipate that disturbing the other cycles may also affect health and disease.

I Prof. Dr. Athanasios C. Antoulas

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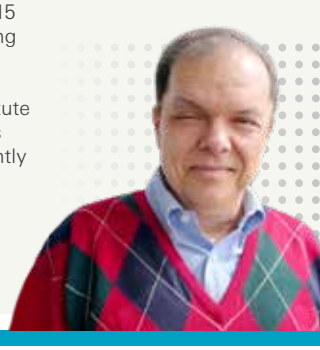
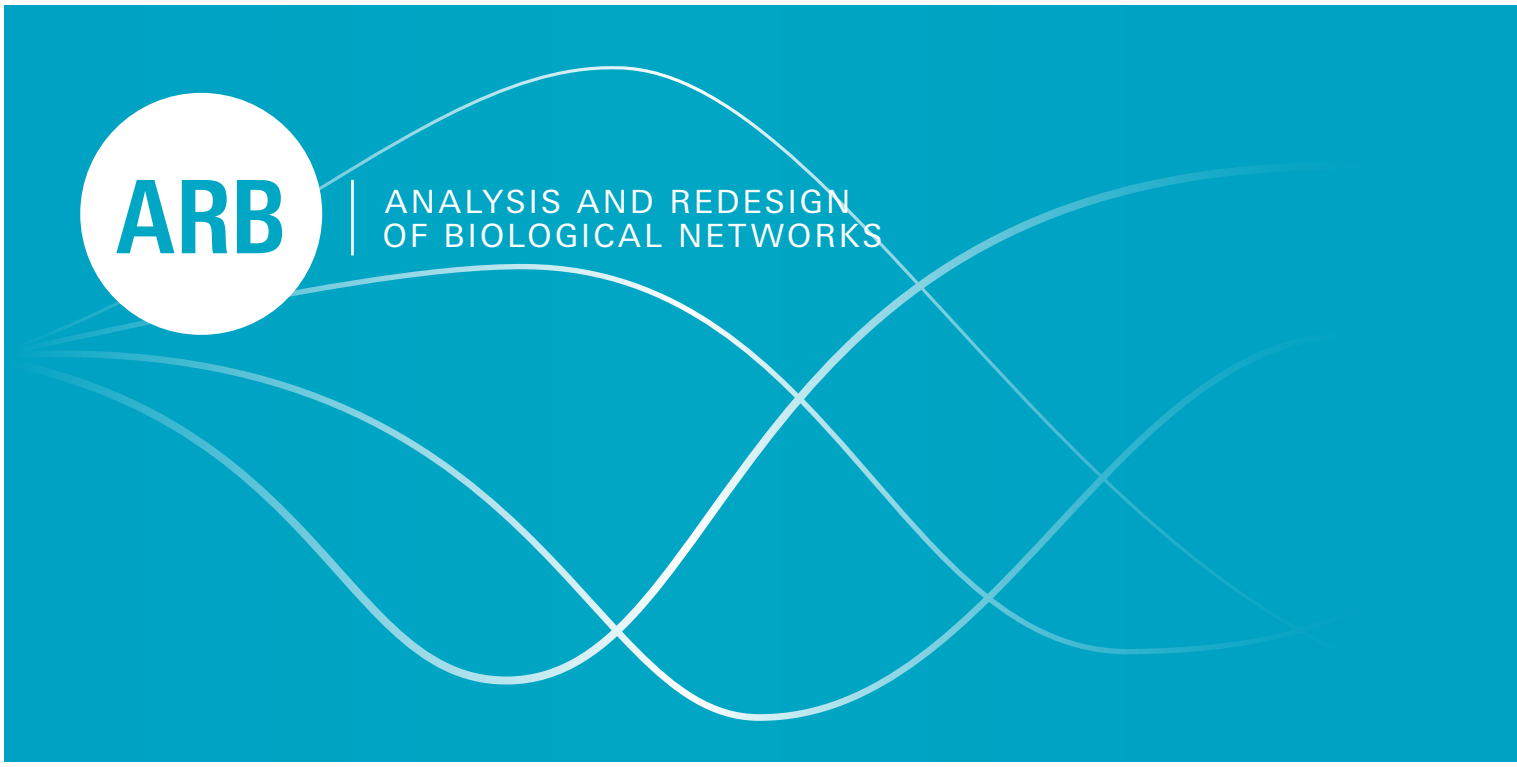
Author **Prof. Dr. Athanasios C. Antoulas**

Athanasios Antoulas obtained the Diploma of Electrical Engineering in 1975, the Diploma of Mathematics in 1975, and the Ph.D. Degree in Mathematics in 1980 at the ETH Zürich. Since 1982 he has been with the Department of Electrical and Computer Engineering, Rice University, Houston, Texas, USA, where he is currently a Professor. Between 2002 and 2015 he was Professor at the School of Engineering and Science at the Jacobs University in Bremen. He has been named a Max Planck Fellow associated with the Max Planck Institute for Dynamics of Complex Technical Systems Magdeburg by the beginning of 2017. Currently he is also Adjunct Professor of Molecular and Cellular Biology at the Baylor College of Medicine, Houston.

antoulas@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/dri





DR.-ING. STEFFEN KLAMT I SENIOR SCIENTIST

Nowadays it is widely accepted that understanding the complexity of life at the cellular level requires mathematical and computational tools. With this in mind, the W2 research group *Analysis and Redesign of Biological Networks* (ARB) develops and applies methods from systems and computational biology and combines dry-lab and wet-lab investigations to infer, analyze, and rationally modify cellular (biomolecular) networks. One central focus of our research is methods for the modeling and computational design of metabolic networks in microorganisms with applications in metabolic and biosystems engineering. Other research areas include systems analysis of microbial communities, data-driven inference of signaling and regulatory networks, and the development of a comprehensive MATLAB toolbox for the computer-aided analysis of biological networks (*CellNetAnalyzer*).

Apart from theoretical developments, we use various genetic engineering and bioreactor cultivation techniques to study the physiology of microorganisms under controlled conditions. The experimental studies focus mainly on *Escherichia coli*, one of the most important model organisms that also serves as host in many biotechnological production processes. The tight integration of wet-lab and dry-lab investigations under one roof enables us to promptly verify model-based predictions.

Research in our group is thus highly interdisciplinary at the intersection of biology, informatics, mathematics, and engineering sciences, and a long-term goal of our activities is to help pave the way for routine use of advanced mathematical modeling approaches in the life sciences.

Highlights and trends in 2017/2018

One important highlight for our group was the ERC (European Research Council) Consolidator Grant awarded to the group leader Steffen Klamt for conducting a comprehensive research project entitled *StrainBooster*. The project is funded with two million euro over a period of five years and will combine innovative theoretical and experimental techniques to establish a new generic principle to rationally engineer microbial cell factories. The project started in May 2017 and has become a major pillar of the groups's activities. Several new scientists joined the ARB group and three Postdocs and

+ In our interdisciplinary research we develop and apply methods from systems and computational biology and combine dry-lab and wet-lab investigations to infer, analyze and rationally modify cellular (biomolecular) networks. Here, Giulia Slaviero and Philipp Schneider discuss how to intervene in a metabolic network of an microorganism to maximize the production of a chemical.

two PhD students are currently funded by and jointly working for *StrainBooster*.

Another development, *CellNetAnalyzer*, our MATLAB package for biological network analysis, became an official part of *de.NBI* at the end of 2016. *de.NBI* is the German Network for Bioinformatics Infrastructure and aims to provide high-quality bioinformatics tools and services to users in life sciences research. Due to the financial support of the BMBF over the last two years we could extend user services and organize dedicated training courses for *CellNetAnalyzer* and other systems biology tools (together with Prof. Ursula Kummer, Heidelberg University). One such workshop took place here at the MPI in Magdeburg in April 2018.

In 2017/2018, our group published 15 papers reporting, for example, on new theoretical developments in metabolic network and pathway analysis, on experimental evidence for the bistable behavior of the lac operon in *E. coli*, on experimental findings clarifying the roles of the three quinone pools in *E. coli,* and on the further development of an *E. coli* itaconic acid producer strain for its use in a two-stage process to increase its productivity. Furthermore, two papers have been published in the high-impact journal *Nature Communications* on computational methods and studies related to the model-driven rational design of microbial strains for the production of chemicals. On the following two pages, Axel von Kamp summarizes the major results of these publications, which are of fundamental importance for the field of metabolic engineering and also of high relevance for the *StrainBooster* project.

Dr.-Ing. Steffen Klamt
Senior Scientist

klamt@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/klamt

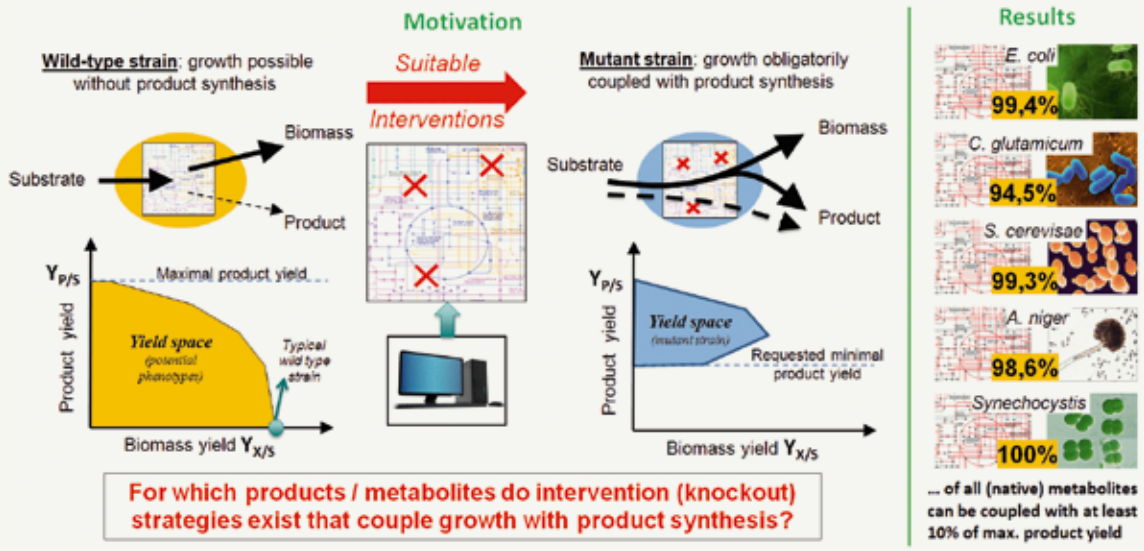


Figure 1:
Growth-coupled product synthesis: principle and results of a large-scale feasibility study with 5 major production organisms. The yield spaces show which combinations of product and biomass yields are possible in the wild-type (yellow) and the mutant strain (blue). The right panel shows the percentages of metabolites for which an intervention that enforces growth-coupled production could be computed for the five organisms.

New Computational Approaches and Principles for Metabolic Engineering

The interest in bio-based production processes has greatly increased as they open up the possibility of synthesizing various chemicals in a more sustainable manner compared to petro-chemical methods. Typically, bio-based production relies on fermentation processes involving micro-organisms that are often genetically modified to enhance their output. This has led to the emergence of the field of metabolic engineering, which develops theoretical and experimental methods for the design of such production organisms.

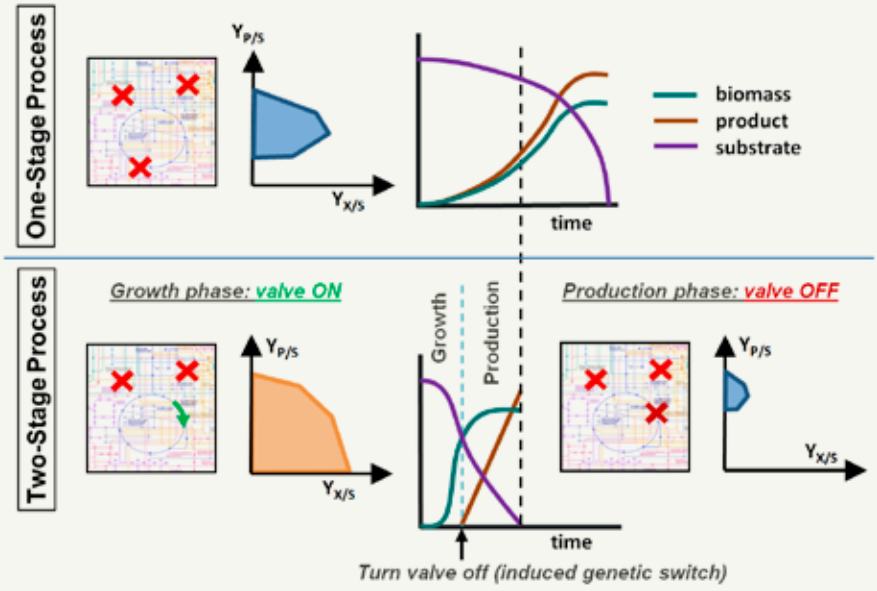
Feasibility of growth-coupled strain designs

One key principle of metabolic engineering that is frequently used to guide the rational design of microbial cell factories is the stoichiometric coupling of growth and product synthesis, which makes production of the desired compound obligatory for growth (Figure 1). Various methods from constraint-based modeling have been developed to calculate intervention strategies that couple growth with the production of a desired compound, including our approach of *minimal cut sets* [1]. A successful example where we applied coupling of growth and production was the model-driven construction of a modified *Escherichia coli* strain that produces itaconic acid with high yield [2]. However, despite its practical relevance, coupling of growth and product synthesis may not necessarily be feasible for every metabolic compound.

This motivated us to perform a systematic computational study to analyze the feasibility of growth-coupled product synthesis in five microorganisms frequently used in biotechnological production processes (*E. coli, Corynebacterium glutamicum, Saccharomyces cerevisiae, Synechocystis sp. PCC 6803, Aspergillus niger*) [3]. In order to perform this large-scale study with metabolic models comprising hundreds or even thousands of reactions and metabolites, it was necessary to develop a scaleable computational framework enabling the calculation of intervention strategies (minimal cut sets) for growth-coupled product synthesis in very large networks [3]. For each metabolite (= potential product) of the five organisms, a mixed-integer linear program (MILP) was formulated and solved by a dedicated solver. By solving thousands of such MILPs on the MPI compute cluster we were eventually able to show that coupling of growth and production is, in principle, feasible under appropriate conditions for almost all metabolites in all five considered organisms (Figure 1). Since the chosen organisms comprise prokaryotes and eukaryotes we could thus prove a fundamental result for metabolic engineering, namely that growth-coupling as a strain design principle is widely applicable.

Strain design with dynamic interventions for two-stage processes

Although coupling of growth and production has several advantages, there is a well-known trade-off between fast growth (and higher productivity but lower product yield) and high product yield (with low biomass yield and therefore low volumetric productivity). This effect was also evident in our itaconic acid producer strain [2]. Such limitations can be overcome by employing a two-stage process (Figure 2) separating growth from production, which we successfully implemented for an



+ Figure 2:
Comparison of one-stage processes (growth-coupled product synthesis; see also Figure 1) and two-stage processes (with separated growth and production phase). Because of the increased volumetric productivity of the two-stage process, the time needed to complete the fermentation is reduced compared to the one-stage process. The yield space (orange) of the constructed strain during the growth phase of the two-stage process differs only slightly from the (yellow) yield space of the wild type in Figure 1, but primes the organism for a switch in the production phase. In the latter, the valve is switched off leading to strongly reduced (or even zero) growth but high product yield.

itaconic acid strain[4]. The search for suitable interventions for a two-stage process requires a generalization of the minimal cut sets approach, since the latter involves only static interventions. Together with the Mahadevan group in Toronto we developed the **M**etab**o**lic **V**alve **E**numerator (MoVE) algorithm, which identifies combinations of static interventions (e.g., knockouts of metabolic genes) together with metabolic valves which must be controlled dynamically[5]. The valves are chosen such that they enable operation of a two-stage process (Figure 2). In the first phase the valves are active allowing a high growth rate (while the introduced static interventions prime the strain for the second phase). When sufficient biomass has been accumulated, the valves are switched off (e.g., via temperature-dependent gene regulation[4]) which then enforces production in the second phase (with low or no growth). We used this algorithm to compute intervention strategies for the production of diverse compounds and obtained solutions for two-stage processes for over 70% of the products with a relatively small number of highly represented valves. MoVE offers a systematic approach to identifying metabolic valves, providing insights into the architecture of metabolic networks and accelerating the implementation of dynamic flux redirection.

Outlook: StrainBooster project

Even two-stage processes may suffer from low volumetric productivity: due to the reduced or even zero growth rate in the production phase, the amount of substrate taken up by the cells also often decreases and is mainly used to produce a some amount of ATP required for cellular maintenance processes[4]. When ATP synthesis is coupled with product synthesis this suggests the use of an "ATP wasting" mechanism to further increase the productivity in the production phase. A proof of principle for such a design strategy was established in[6] where an inducible ATP wasting futile cycle was shown to increase the lactate production rate in a modified *E. coli* strain. In the recently started ERC project "StrainBooster", we investigate the broader applicability of ATP wasting as a powerful strategy for metabolic engineering. | **Dr. Axel von Kamp**

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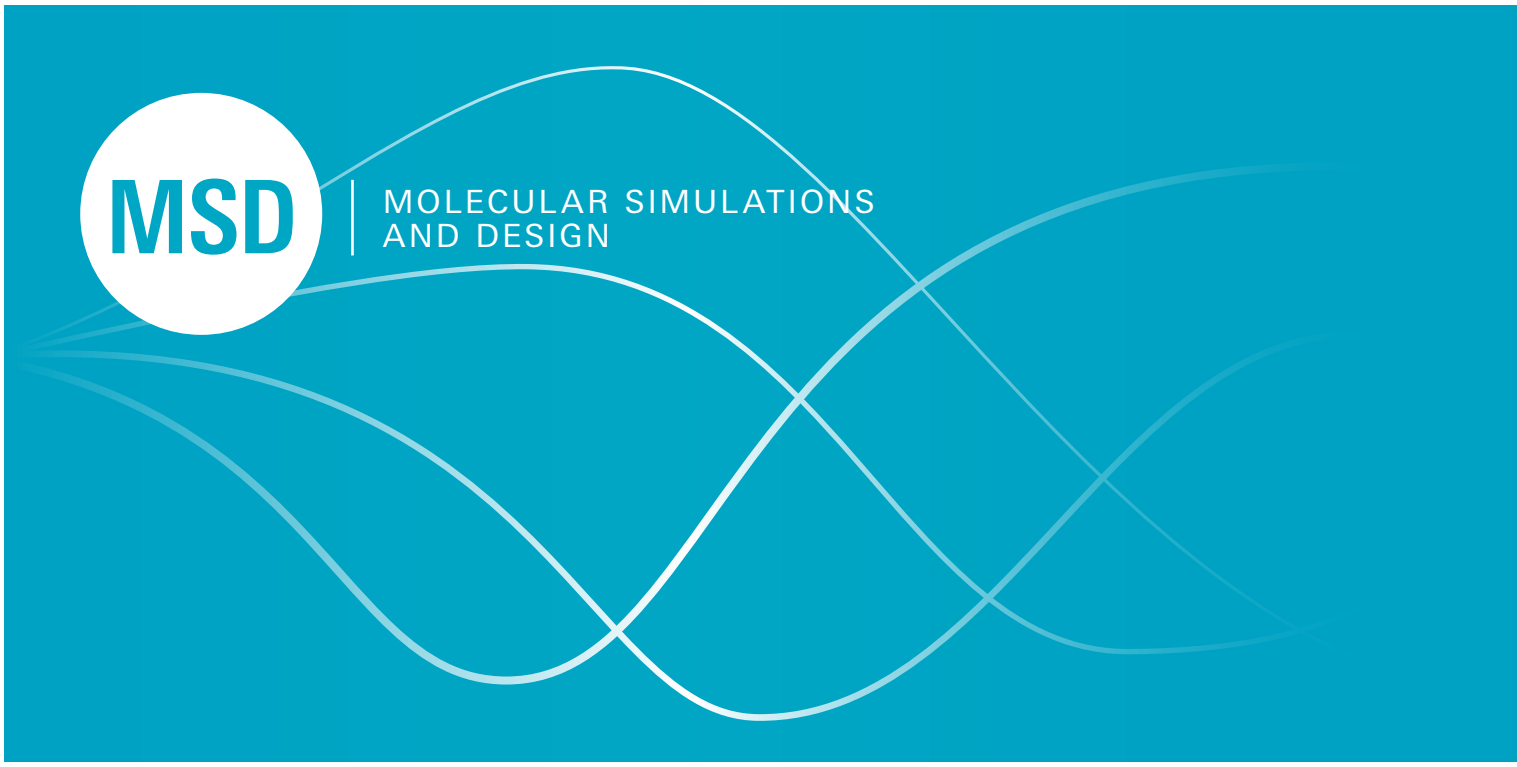
Author **Dr. Axel von Kamp**

Axel von Kamp studied Biology and Computer Science at the University of Bielefeld. After his PhD at Dublin City University he joined the Bioinformatics department at the University of Jena in 2003. Since 2007 he has been working as a researcher in the ARB group at MPI Magdeburg. His research focuses on the development and implementation of algorithms for the analysis and targeted modification of biological networks.

vonkamp@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/arb



"Our knowledge can only be finite, while our ignorance must necessarily be infinite." (Sir Karl Popper (1902-1994), philosopher)

DR. RER. NAT. MATTHIAS STEIN I GROUP LEADER

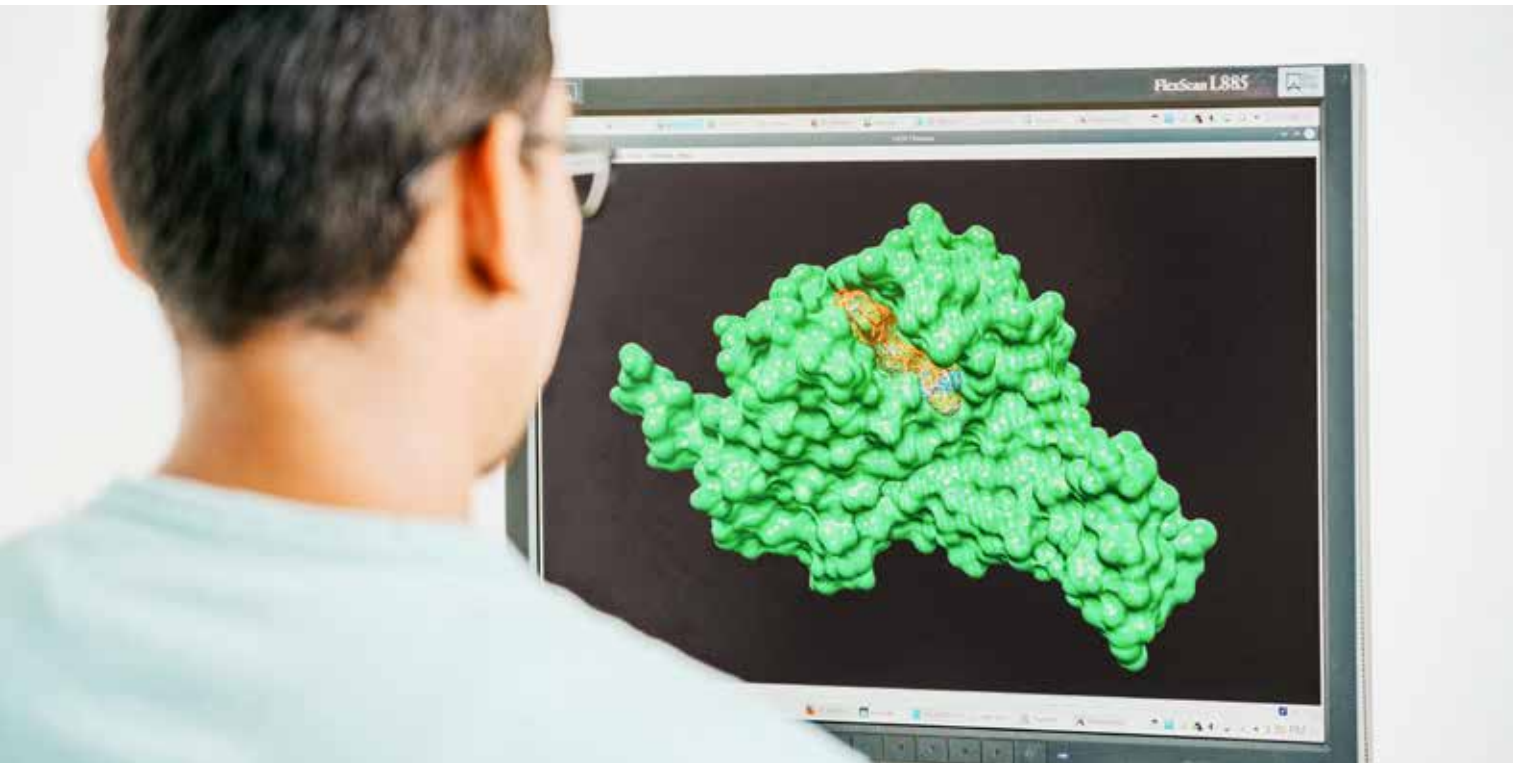
The MSD group performs structure-based simulations across multiple orders of magnitude in temporal and spatial dimensions. Molecules, proteins and large complexes are treated at full atomic resolution and as three-dimensional objects. Computer simulations give insight into complex processes from biology and chemistry which may be otherwise very difficult or impossible to obtain.

The portfolio of computational methods in the MSD group was extended to also be able to address larger and largest e.g. infinite systems, in particular large enzymatic systems (with QM/MM) and the crystalline state of molecular compounds (with periodic DFT). For enzymes, the active site is treated quantum mechanically since here catalysis occurs and electrons are shuffled around: substrate chemical bonds are broken and new bonds are being formed that constitute the product. The protein surrounding is a highly-developed, specifically-tailored environment for the active site to efficiently perform the enzymatic function but can be treated with classical mechanics and a forcefield energy expression.

The solid state of molecular organic compounds is of infinite dimension and characterized by directed and non-uniform weak intermolecular interactions between molecules within a unit cell but also with neighboring cells. Electrostatic, van-der-Waals and hydrogen bonding are difficult to calculate accurately. The use of atom-centered Gaussian basis functions of high quality, however, gives calculated lattice energies to within 4-8 kJ mol^{-1} of experimental results. The feasibility of discriminating between enantiopure and racemic crystal forms of chiral compounds was demonstrated for a set of example molecules. The computational quest for possible alternative crystal forms of the same compound (polymorphs) is of great relevance for the pharmaceutical industry and will be intensified in the MSD group.

Four co-supervised PhD students received their doctoral degrees in 2017/2018: Sonja Pullen (w Uppsala University, Sweden), Rebecca Hylton (w University College London, United Kingdom), Esra Boz (w Istanbul Technical University, Turkey) and Hannes Buchholz (w PCF Group, MPI Magdeburg).

During the period from 2017 to 2018, the MSD research in the **Collaborative Research Centre/TR63 'InPrompt'** was successfully evaluated enabling us to continue our work



+ The focus of our research is on 3D structure-based molecular simulations of complex phenomena in biology and chemistry. Dr. Vikash Kumar is analyzing the results of Molecular Dynamics simulations of a protein which will be targeted by computer-designed small molecules.

on solvent effects on the thermodynamics and kinetics of green chemistry reactions. As the only project at the Max Planck Institute, it entered its second period of funding from 2018-2021. At the end of 2018, the group's research activities were assessed by the Scientific Advisory Board of the institute. The MSD group left a strong impression with the Board and a positive statement is expected at the beginning of 2019.

Saxony-Anhalt and the European Regional Development Fund are supporting the Center for **Dynamic Systems 'Altmarkenergie'** project. Carbon dioxide (CO_2) is the major source for global warming. Biogas fuel is an economic and environmentally friendly energy carrier and outperforms many other biofuels. When biogas is generated from the anaerobic fermentation of organic waste, it is a mixture of methane, carbon dioxide and to a lesser content of other gases. Before the biogas can be fed into the gas pipeline system, removal of CO_2 is required to meet the strict raw gas standards. Computer simulations of some novel CO_2-binding molecules provide a useful insight into the behavior of the mixed solvents. The results guide the design and development of novel carbon dioxide sequestrating compounds.

Information about the three dimensional protein structure is a guide to the computer-aided design of novel drug molecules. They can be tested on the computer if they are binding to a protein and inhibit its malfunction and thus be potentially used as a therapeutic. In an iterative process between initial hits *in silico* and experiments *in vitro* in the lab, properties of the candidate compound can be further refined.

Dr. Matthias Stein
MSD Group Leader

matthias.stein@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/stein

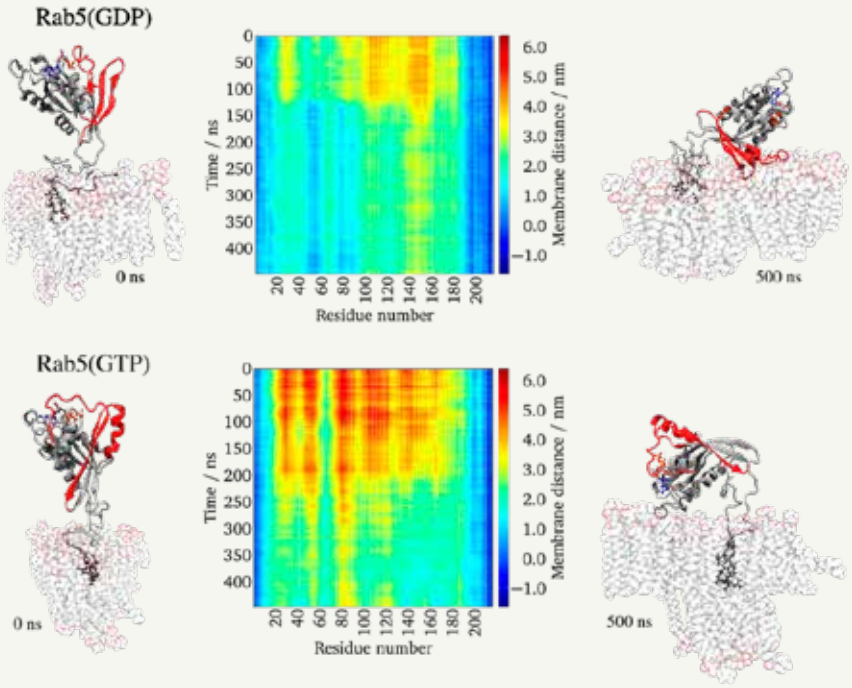


Figure 1: Starting from an orientation perpendicular to the membrane (left), membrane-bound Rab5 tilts towards the surface of the negatively charged membrane of the early endosome. Top right: Rab5(GDP) adopts a conformation with partially inaccessible switch regions (red). Bottom right: The Rab5(GTP) switch regions remain fully accessible to binding partners.

Switch Proteins as Regulators of Cellular Processes

Some small proteins are so-called *'switch'* proteins since they exist in an 'off' and an 'on' state. The functional state of the protein is recognized and also controlled by other binding proteins which can then initiate an entire signalling cascade and control cellular processes.

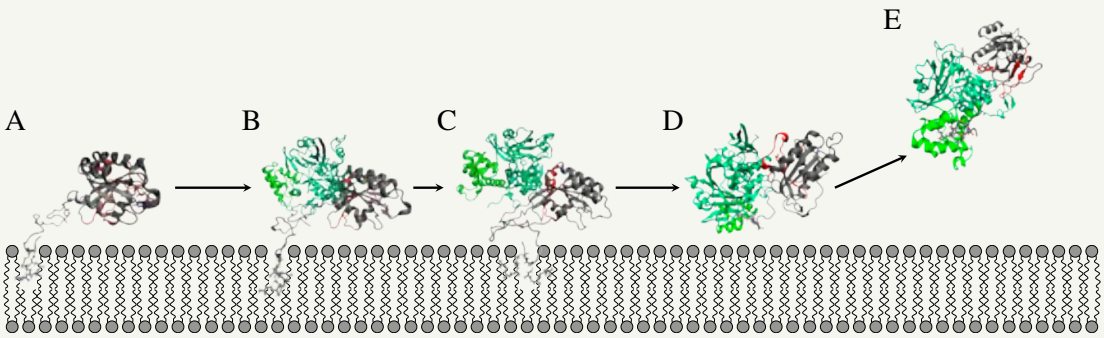
The protein Rab5 is one of these 'switch' proteins. It is the key regulator of endocytic cargo transport in cells and its malfunction is involved in a range of diseases. Based on its central role in cellular transport processes, Rab5 dysfunction is often associated with bacterial and viral infections, Alzheimer's and Parkinson's diseases as well as tumor cell dissemination. Thus, the pharmaceutical exploitation of Rab5 as a therapeutic target is of great interest.

The central, structurally conserved and catalytically active GTPase (G) domain is common to all members of the small GTPase family and able to bind guanosine di- or triphosphate (GDP/GTP; off/on). The inactive, GDP-bound and active, GTP-bound states are structurally distinguished by different conformations of the so-called 'switch' regions. The small protein is anchored to the early endosome membrane via two post-translational geranylgeranyl modifications covalently attached to a long hypervariable region (HVR) at the protein C-terminus. Rab5(GTP) is exclusively membrane-associated where it regulates endosomal trafficking by recruiting and binding effector proteins. In contrast, Rab5(GDP) shuttles between the membrane surface and the cytoplasm in a Rab GDP dissociation inhibitor (GDI)-dependent manner.

A profound understanding of Rab5 structure, membrane-associated dynamics and recognition by binding partners provides the basis for the development of Rab5-specific therapies.

In order to gain insight into Rab5 function and dynamics, full-length Rab5 protein structure models for both nucleotide states were anchored to model membranes of increasing complexity and subjected to multiple long-term full-atomistic molecular dynamics (MD) simulations. These simulated systems consist of a large patch of a phospholipid double layer of different lipid compositions, the membrane-bound protein, water as a solvent and ions to neutralize the system. In total, 400,000-1,000,000 atoms were simulated for microseconds.

Specific protein-membrane interactions were observed between the negatively charged signaling lipid phosphatidylinositol 3-phosphate (PI(3)P) head group and a basic arginine residue of the protein.[1] Simplified model membrane systems fail to reproduce relevant structural parameters of protein orientations at the membrane. Only when a realistic membrane composi-



+ **Figure 2:**
The Rab5(GDP) membrane extraction process is facilitated by RabGDI. Approaching RabGDI first recognizes the Rab5 switch regions, followed by a slight re-orientation to allow RabGDI binding to the Rab5 HVR and position the prenyl binding pocket in close proximity to the membrane surface. The accommodation of the geranylgeranyl chains in the binding pocket induces the detachment of the Rab5(GDP):RabGDI from the bilayer and the formation of a tightly bound soluble complex.

tion is chosen, differences between full-length Rab5(GDP) and Rab5(GTP) become apparent. (Figure 1). In case of Rab5(GDP), a simultaneous rotation of the G domain leads to an orientation in which the switch regions are partially buried between protein and bilayer, and thus hardly solvent accessible. In contrast, the switch regions remain fully accessible to effector and regulatory proteins in the GTP-bound state. The observed nucleotide-dependent orientations offer an approach to exploiting an overexpressed Rab5(GTP) as a drug target.[2]

Inactive Rab5(GDP) extraction from the membrane requires assistance from RabGDI, which accommodates the geranylgeranyl chains in a hydrophobic pocket and transfers the small GTPase to donor membranes. Based on a model from yeast, the protein-protein interactions between human Rab5(GDP) and RabGDI in cytoplasm as well as when membrane-bound were investigated by MD simulations. A mechanism of the physiological Rab5(GDP):RabGDI extraction process (Figure 2) can be suggested based on our simulations. RabGDI first contacts the switch regions of membrane-associated Rab5 via its Rab binding platform (RBP). As RabGDI re-orients, it establishes more contacts with the protein while positioning its prenyl binding pocket in close proximity to the membrane surface. Hydrophobic patches in vicinity of the binding pocket can be identified, which guide the geranylgeranyl chains into the cavity. Subsequently, the tightly bound Rab5(GDP):RabGDI complex is able to diffuse from the membrane.[3]

I Dr. Eileen Münzberg

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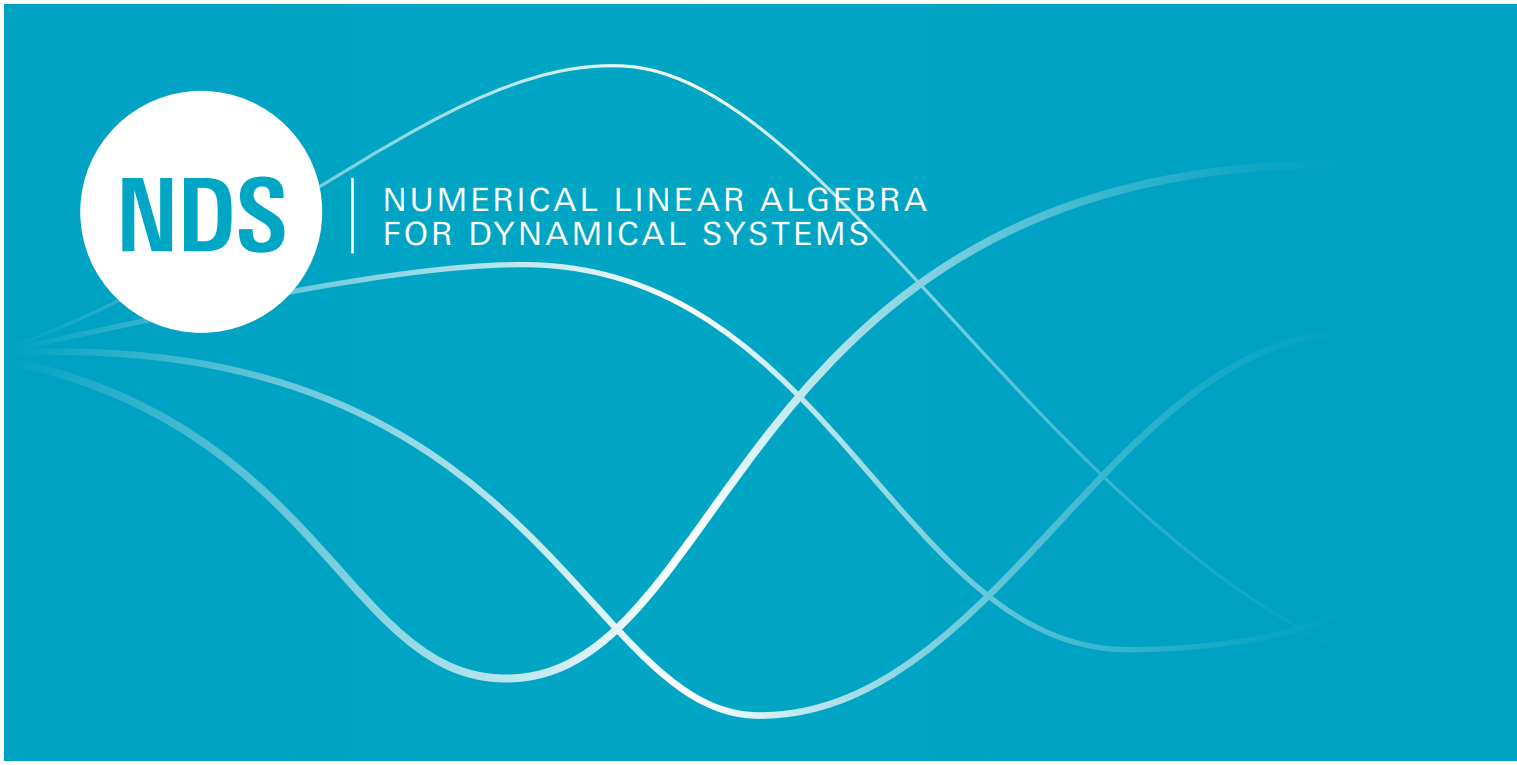
Author **Dr. Eileen Münzberg**

Eileen Münzberg studied Biosystems Engineering and received her Master of Science degree from the Otto von Guericke University in Magdeburg in 2013. After that, she started her Ph.D. in the Molecular Simulations and Design research group at the Max Planck Institute which she successfully completed in 2019. Eileen Münzberg is also taking part in the COMETiN Program for coaching and mentoring excellent young female scientists. Her Ph.D. project focused on multiscale modeling and analysis of protein-membrane interactions, in particular the membrane recruitment of endocytotic proteins of the early endosome. She is an associated member of the CRC/TR 63 InPROMPT.

edler@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/msd



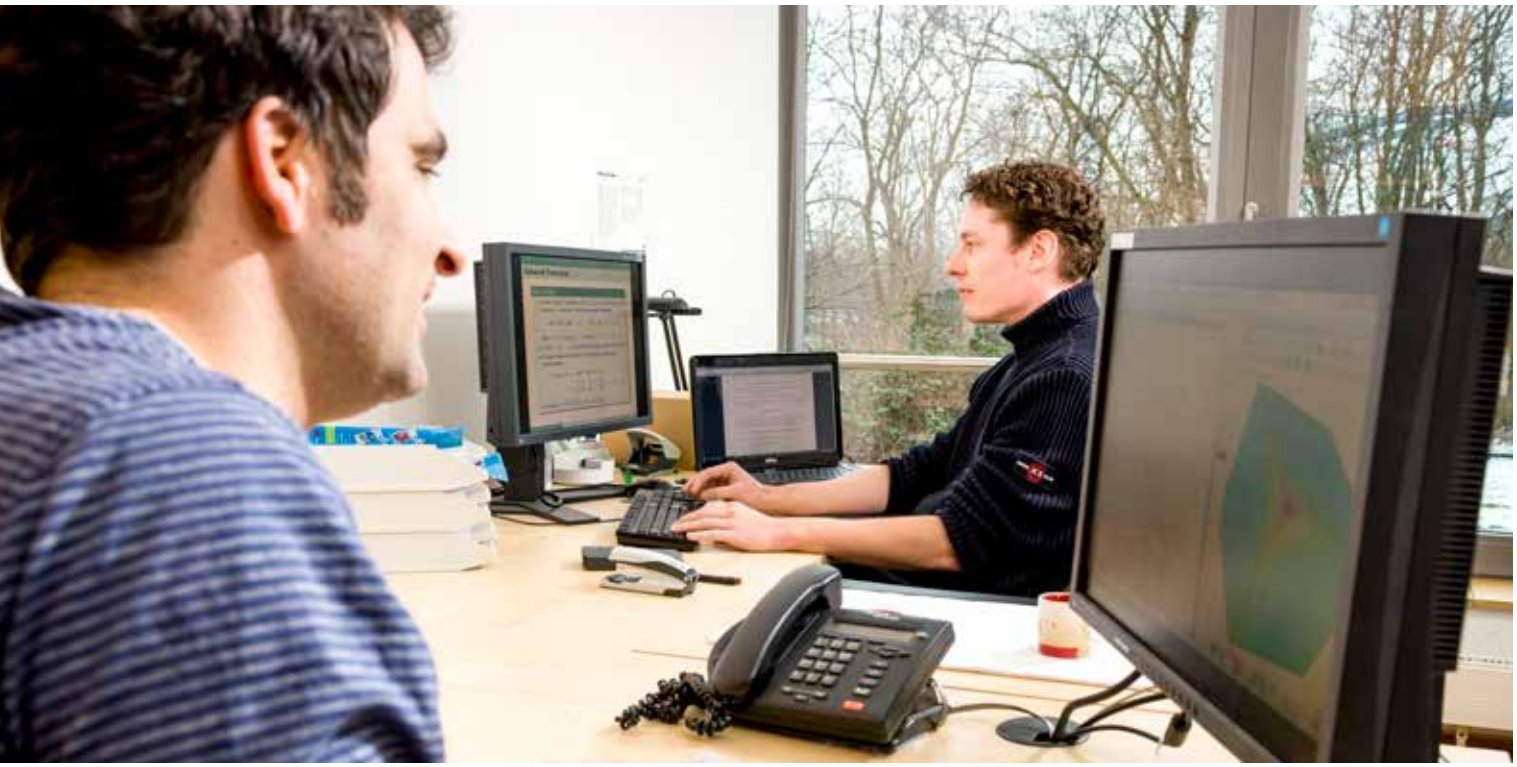
PROF. DR. MARTIN STOLL I SENIOR SCIENTIST

The group was established in 2013 under the name Numerical Linear Algebra for Dynamical Systems, and has seen four years at our institute. Martin Stoll left the Max Planck Institute in October 2017 and became a professor in the Mathematics Department at Chemnitz University of Technology in Chemnitz (Germany). Since the group has left the institute, this will be their last report in this brochure.

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. 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. She was awarded the *Otto Hahn Medal for Junior Scientists of the Max Planck Society* during the 69th Annual Meeting of the Max Planck Society in June 2018 in Heidelberg. The prize was given for her work on the development of fast and robust solvers for phase field problems from many application areas in materials science, biology, image processing or machine learning.

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 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*



+ Novel algorithms and techniques are introduced within numerical linear algebra that enable the efficient solution of mathematical equations coming from a variety of challenging applications.

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 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.

Although the group has left the institute, strong ties will remain with the MPI, for instance indicated in joint work with Dr. Steffen Klamt (ARB), Prof. Peter Benner (CSC) and Prof. Kai Sundmacher (PSE).

Prof. Dr. Martin Stoll
Senior Scientist

martin.stoll@mathematik.tu-chemnitz.de

+ **Figure 1:** Classification into four classes (left) and two classes (right).

Computational Data Science Inspired by Differential Equations

+ Phase separation plays an important role in many applications. One do-it-yourself example is given by mixing oil and vinegar just as in your favorite vinaigrette. A good shake will mix both the vinegar and oil droplets but as soon as you stop shaking, those tiny droplets are starting to grow and we see a coarser mixture until eventually all the oil is sitting on top of the vinegar.

We have reported on a coarsening procedure of this nature before in this report and feel that it is relevant to mention the famous von Neumann's law. John von Neumann, as wells being a brilliant mathematician and quite the party animal, observed that when you have a two-dimensional foam certain bubbles grow while others disappear. Von Neumann's law states that all cells with fewer than six neighbors shrink while all those with more than six neighbors grow.

We want this complex process to be reflected in a mathematical model. The so-called Ginzburg-Landau energy is crucial to this. The minimization of this energy will result in a separation in the pure phases with a minimal interface length.

The minimization of these energies follows the well-known concept of gradient flows. Such gradient flows are based on the fact that the energy formula decreases fastest if one goes from a point in the direction of the negative gradient of the functional. Depending on the definition of the gradient taken, different models can be obtained that describe the evolution of our mixture. Two of the best-known methods that can be derived in this way are the Allen-Cahn and Cahn-Hilliard equations. Both of them are described by partial differential equations including nonlinear terms. This makes these equations typically hard to solve and care must be taken to devise algorithms that take the structure of these models into account. The finite element method is a classical method that allows the discretization of operators such as those describing the Allen-Cahn and Cahn-Hilliard equations.

A similar procedure based on the same equations can be used when one wants to perform inpainting in an image. In this instance, we assume that there is a damaged region in an image that we want to fill in with sensible information. Here the Allen-Cahn or Cahn-Hilliard equations are augmented by a fidelity term that penalizes if the filled image deviates from the original image in the undamaged parts. In order to reflect the complexity of the task one usually has to rely on a large number of degrees of freedom that turn the image into one large one-dimensional array called a vector. The relation between these points as induced by the partial differential equation, e.g. the Cahn-Hilliard-equation, is stored in a two-dimensional form called a matrix. The goal of all fast and accurate methods is to obtain the vector of unknowns by efficiently inverting the associated matrix. For realistic scenarios, it is never feasible to use naive approaches, as these require vast

amounts of time and storage. In our work, we develop fast solvers that iteratively solve for the unknowns by only using one sweep through the matrix with every iteration and one inversion of a simpler operator called the preconditioner. This allows us to solve for an almost arbitrary number of unknowns and different geometries. Typically, a very large number of unknowns is necessary to provide accurate predictions that help laboratory-based scientists to make experimental decisions.

Recently, we have taken this approach further by considering the application of Allen-Cahn equations for data science applications. In many learning tasks, it is crucial to separate the data into several classes. We represent the data as nodes in a graph and then the process of phase separation corresponds to cutting the graph into several groups where the connection within the group is strong and the edges across different groups only carry a small edge weight. The setup we consider is semi-supervised learning where a part of the data is already labeled and the remaining data needs to be classified based on the given training data. The modeling approach is similar to the one used in image inpainting. The training data correspond to the undamaged image part and we want to compute the value in the damaged/unknown regions.

The computational challenge here comes from the underlying sparse and very large matrix, the graph Laplacian. Its eigenvalues and eigenvectors provide essential information about the nature of the data. To efficiently compute the eigenvectors, we combine a Krylov subspace solver with a non-equispaced fast Fourier transform so we never need the full data information.

We extended this technique to more complex graph structures such as the hypergraph Laplacian and the signed graph Laplacian, which models friend and foe relationships in complex societal structures. I **Prof. Dr. Martin Stoll**

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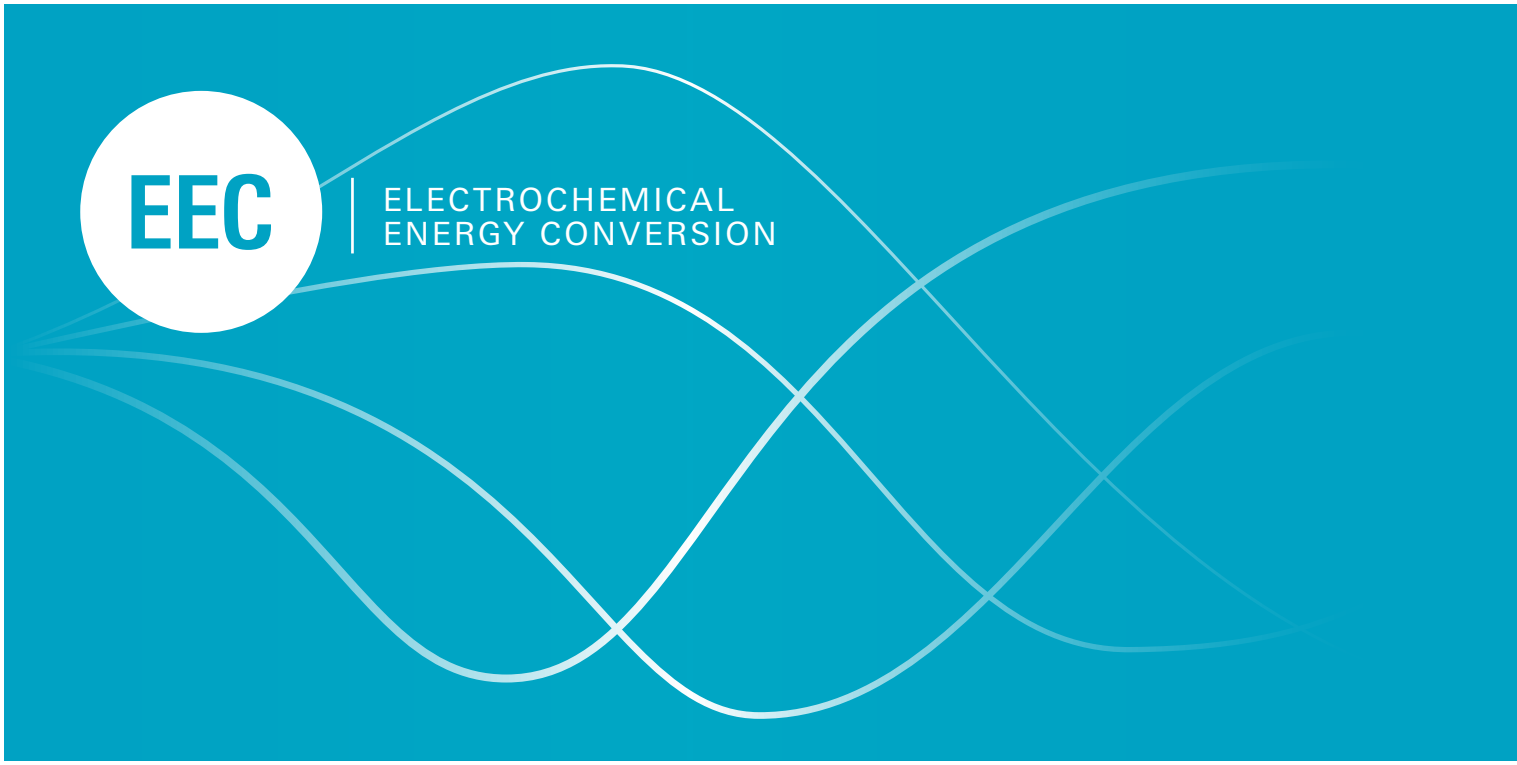
Author **Prof. Dr. Martin Stoll**

Martin Stoll is a professor in the Mathematics Department at Chemnitz University of Technology (Germany). From 2005 to 2008 he obtained his Ph.D. in Numerical Analysis at the University of Oxford. In 2008 he joined the OCCAM Centre for Applied Mathematics at the University of Oxford as a postdoctoral researcher. In 2010 he joined the Max Planck Institute Magdeburg as a postdoctoral research fellow in the CSC group of Professor Peter Benner. From 2013 to 2017 he headed the Numerical Linear Algebra for Dynamical Systems research group at MPI Magdeburg. Furthermore, Martin Stoll is a member of three GAMM Activity Groups and a Faculty Advisor of the SIAM Student Chapter (Society for Industrial and Applied Mathematics, SIAM).

martin.stoll@mathematik.tu-chemnitz.de



DR.-ING. TANJA VIDAKOVIĆ-KOCH | SENIOR SCIENTIST

The Electrochemical Energy Conversion (EEC) group is the youngest group in the institute having only been established in October 2018. Before my appointment as a research group leader of the EEC group, I headed the Electrochemical Energy Conversion Systems team in the PSE group. The focus of the EEC group's research is on the important area of energy conversion related either to efficient electricity generation or chemical production. In this respect we are trying to understand the limitations of existing electrochemical processes using advanced electrochemical methods, as well as to develop new electrochemical processes based on biological catalysts. Furthermore, the EEC group is working on conceptually new process designs. In this respect we are extending (bio)electrochemistry toolboxes with synthetic biology tools. Our aim is to design and reconstitute the energy conversion infrastructure of an artificial cell following a bottom-up synthetic biology approach.

The EEC group has made a significant contribution to the development of two advanced electrochemical methods. Together with Professor Petkovska at the University of Belgrade in Serbia and the PSE group we have developed the theoretical backgrounds and experimental routine of a so-called nonlinear frequency response analysis (NFRA). We are currently applying the NFRA method to understanding the limitations in oxygen reduction reaction (ORR) under strong alkaline conditions. This is a research focus of DFG Research unit 2397, where the EEC works with six other partners throughout Germany. While with NFRA electrical periodic input is applied, in another method so-called concentration-alternating frequency response analysis (cFRA), we apply concentration as a periodic input. We worked with the PSE group on this novel method. Our current example is a polymer electrolyte membrane (PEM) fuel cell, and more details are described in the research highlights report by Antonio Sorrentino. Since frequency response spectra are too complex for intuitive understanding and the theoretical backgrounds give clear guidance for the design of experiments, Antonio Sorrentino successfully established

+ We aim to find solutions for the storage of renewable energies with the help of electrochemical processes. Our major interest is in dynamics of electrochemical processes as in water electrolysis and electroenzymatic processes. In the experimental setup shown here, the performance of different catalysts to enhance the electrolysis of hydrogen chloride in a polymer electrolyte membrane electrolyzer were investigated.

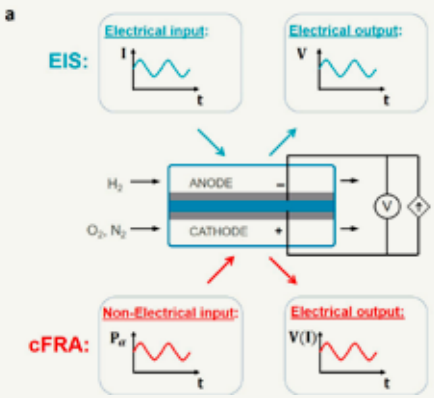
both, theoretical backgrounds of this novel method and an experimental proof of concept. The EEC group is proud that his poster was awarded the best poster prize at last year's Annual Meeting of the International Society of Electrochemistry in Bologna.

In the area of novel electrochemical processes based on biological catalysts, in December 2018 Dr. Tanja Vidaković-Koch defended her habilitation entitled "Bioelectrochemical systems for energy and materials conversion".

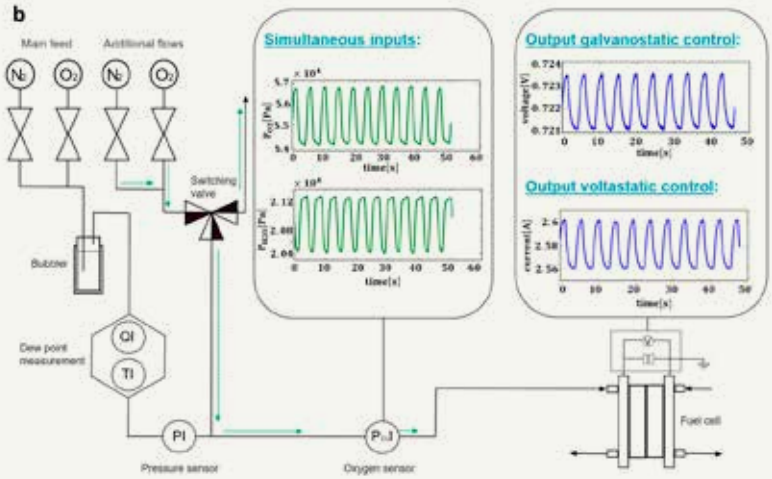
In the area of synthetic biology, the EEC group is involved in the MaxSynBio initiative and has major responsibility for energy conversion. This highly interdisciplinary project is very challenging, but it opens up possibilities for conceptually new process designs, and the EEC group is extremely excited about the future impacts of synthetic biology in the energy field. We focus on chemically- and light-driven energy regeneration systems and integration approaches.

Dr.-Ing. Tanja Vidaković-Koch
Senior Scientist

vidakovic@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/eec



+ **Figure 1a:**
Schematic representations of periodic inputs and outputs applied in electrochemical impedance spectroscopy (EIS) and concentration alternating frequency response analysis (cFRA) experiments



+ **Figure 1b:**
Simplified scheme of the experimental setup designed to perform cFRA experiments.

Fuel Cell Dynamics at a Glance

+ Considering that almost 23% of CO_2 emissions are caused by the transportation sector[1], the development of vehicles based on zero CO_2-emission technologies will be crucial for combating the global warming. In this respect, polymer electrolyte fuel cells (PEMFC) are being targeted as one of the most promising clean alternatives to replace the internal combustion engine. The main reasons are their high-power density, relatively fast dynamic and the use of hydrogen as fuel. However, efficiency and operating life will need to be significantly improved to make the performance of PEMFC comparable to that of other technologies.

The performance losses in PEMFCs are mainly due to dynamics occurring on the cathode side of the cell. In this regard physical phenomena like mass transport of oxygen in the cathode flow field and catalyst layer, charging of the electrochemical double layer, and sorption of the produced water in the Nafion membrane are the most influential. The impact of each of these phenomena on the global performance depends on parameters related to properties of the cell component materials, as well as on operating conditions. Therefore, a deep understanding of the mechanisms governing each of these underlying processes is necessary in order to optimize the characteristics of the components, operating modality and reduce the performance losses.

Frequency response analysis techniques are often used successfully to separate different phenomena acting in parallel in a system and to evaluate their single contributions to the total efficiency losses. Electrochemical impedance spectroscopy (EIS) is the most commonly used frequency response methodology applied to PEMFC. It consists in exciting the cell by a periodic electric input (current or cell potential) at different frequencies, measuring the complementary electric output, and analyzing the input/output correlation in frequency domain (fig. 1a). However, EIS often fails to separate the contributions of different phenomena due to the coupling in the frequency spectra of the effect of dynamic phenomena with similar time constants. For this reason, in many instances, it is difficult to identify the mechanism which dominates the performance of a PEMFC system through EIS experiments. The use of specific nonelectrical inputs instead of electrical ones to excite the cell could generate a response containing only the contribution of a single or few specific processes minimizing the coupling issues. Following this strategy, we have developed a frequency response methodology applied to PEMFC based on concentration inputs, so called concentration alternating frequency response analysis (cFRA).

During cFRA experiments on a PEMFC, a feed characterized by a periodic concentration of oxygen and/or water is sent to the cathode side of the cell at different frequencies (fig. 1a). A periodic current or cell potential is obtained as output depending on the electric control applied to the cell, respectively voltastatic or galvanostatic. Since two different inputs and outputs are used, it is possible to analyze four distinct input/output correlations in frequency domain containing different information on performance losses in the system.

Initially, a model-based analysis of the cFRA experiments was performed to investigate theoretically the potential of the new technique. In the figures 2b-c, simulated magnitude spectra

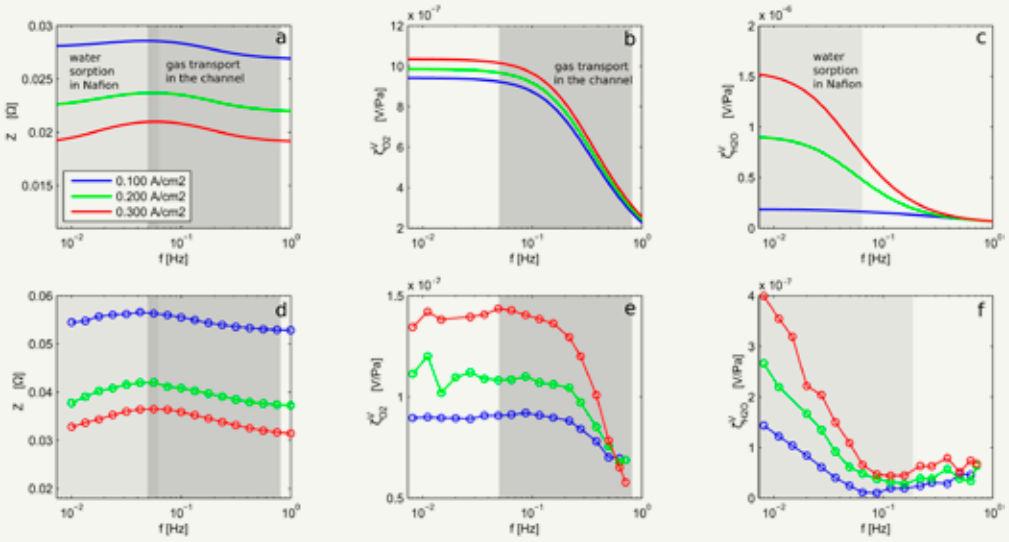


Figure 2: Comparison between experimental (symbol-solid line) and simulated (solid line) EIS and cFRA spectra under galvanostatic conditions at three different steady state conditions: a-b EIS magnitude plot, c-d cFRA magnitude plot obtained by oxygen pressure input, e-f cFRA magnitude plot obtained by water pressure input.

in frequency domain related to cFRA experiments using oxygen and water concentration as input, and cell potential as output are displayed under three different operating conditions and compared to classic EIS spectra (fig. 2a). EIS spectra detect the contributions of all the main dynamic processes occurring in cell, i.e. charging of the double layer due to the electrochemical reactions, mass transport of oxygen in the cathode channel and electrode, and water sorption in the Nafion membrane. In contrast, cFRA separately reveal the contribution of the oxygen mass transport or water sorption to the Nafion using respectively concentration of oxygen (fig. 2b) and water (fig. 2c) as input [2].

An ad-hoc experimental setup was designed in order to perform cFRA experiments and validate the theoretical results [3]. As shown in the setup scheme in fig. 1b, a small flow of pure dried oxygen or nitrogen is periodically added to the main humidified feed direct to the cathode by using a switching valve able to switch the flow to the cathode inlet or to the outlet. By regulating the speed of the switching valve, a feed with simultaneous periodic concentration of oxygen and water is obtained at the desired frequency. The generated periodic electric output is due to both the concentration perturbations at the same time. A procedure has been developed to determine the contributions of the two inputs to the electric response and to evaluate the theoretical frequency spectra.

The experimental results (fig. 2d-f) show a good agreement with the theoretical predictions confirming the capability of the cFRA technique to selectively analyze specific dynamic phenomena.

In conclusion, cFRA allows clear identification of the processes which dominate the performance of the operating cell. Moreover, it makes it possible to estimate specific parameters using a simpler dynamic model accounting for only transport in a single layer of the cell rather than complex global PEMFC models. This decreases computational costs and unfavourable parameter correlation effects. | **Antonio Sorrentino**

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Author **Antonio Sorrentino**

Antonio Sorrentino studied Industrial Chemistry at the University of Naples Federico II, Italy with a focus on material sciences and mathematical modelling of physicochemical processes. In 2013, he received his Master 's degree after completing his thesis on the modeling of the calcium looping process for capture of CO_2 generated in thermo-conversion plants. In the same year, he joined the Process System Engineering group at Max Planck Institute Magdeburg where he is undertaking his Ph.D. on the development of dynamic perturbation methods for system identification of polymer electrolyte fuel cells. Since 2018, he has been affiliated to the Electrochemical Energy Conversion group headed by Dr. Ing. Tanja Vidaković-Koch.

sorrentino@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/eec

+ Publications 2017

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MAX PLANCK INSTITUTE FOR
DYNAMICS OF COMPLEX TECHNICAL SYSTEMS
MAGDEBURG

Sandtorstrasse 1
39106 Magdeburg
Germany
P +49 391 6110 0
F +49 391 6110 500
info@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de