MAX PLANCK INSTITUTE
FOR DYNAMICS OF COMPLEX
TECHNICAL SYSTEMS
MAGDEBURG

Report
2019–2020

+ **Frania Zuñiga**
Ph.D. candidate in the Bioprocess Engineering group

With a focus on proteomics, glycomics and glycoproteomics, the Bio/Process Analytics team is developing a comprehensive set of bioanalytical tools for the in-depth analysis of protein expression and post-translational modifications of proteins, such as glycosylation. Glycosylation is the biological process of creating a sugar chain (glycan) attached to proteins. Even though it is so far unpredictable, the glycan composition can reflect the cellular homeostasis. In the picture, Frania Zuñiga inspects the inner structure of the MALDI-TOF (matrix-assisted laser desorption/ionization-time of flight) mass spectrometer. This instrument is capable to accurately measure the molecular mass of both free glycans and glycans attached to small fragments of proteins. The molecular mass is a powerful evidence for supporting the identification and validation of novel glycan compositions.

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

Research Groups headed by Senior Scientists

ARB	Analysis and Redesign of Biological Networks
EEC	Electrochemical Energy Conversion
MSD	Molecular Simulations and Design

Max Planck Fellow Group

DRI	Data-Driven System Reduction and Identification

Others

ATP	Adenosine triphosphate, organic compound that provides energy to drive many processes in living cells
BMBF	German Federal Ministry of Education and Research
BMWi	German Federal Ministry for Economic Affairs and Energy
CDS	Center for Dynamic Systems: Biosystems Engineering (Magdeburg)
CORE	European project: Continuous Resolution and Deracemization of Chiral Compounds by Crystallization
COST	European Cooperation in Science and Technology
CPTS	Chemistry, Physics and Technology Section of MPG
DAAD	German Academic Exchange Service
DARPA	Defense Advanced Research Projects Agency (United States)
DECHEMA	Expert Network for Chemical Engineering and Biotechnology in Germany (Gesellschaft für Chemische Technik und Biotechnologie e.V.)
ERC	European Research Council
ERDF	European Regional Development Fund (Europäischer Fonds für regionale Entwicklung (EFRE)
EXIST	University-Based Business Start-Ups (support programme of the BMWi)
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
MLU	Martin Luther University Halle-Wittenberg
MPG	Max Planck Society (Max-Planck-Gesellschaft)
MPI	Max Planck Institute for Dynamics of Complex Technical Systems Magdeburg
Omics	Various disciplines in biology whose names end in the suffix -omics, such as genomics, proteomics, metabolomics and glycomics
OVGU	Otto von Guericke University Magdeburg
SAB	Scientific Advisory Board
SFB CRC 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)
UNRAVEL	European project: A Unique Refinery Approach to Valorise European Lignocellulosis

Report
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MAGDEBURG

+ Research Groups

Introduction

Research Groups

Directors

External Scientific Members and Max Planck Fellows

Senior Scientists

+ Download as PDF: www.mpi-magdeburg.mpg.de/mpi_annual_report

The Dawning of a New Era

Did the beginning of 2020 mark the dawning of a new era - “before Covid” and “after Covid”?

Indeed, many changes will endure, and the perception of the importance of the health system and the vulnerability of our society will also change.

There will, of course, also be a lasting impact on our travel habits. A multitude of events have had to be canceled or postponed. Thanks to our experience with web-based events, the virtualization of workshops, symposia and even to an extent the larger conferences - of the DECHEMA as well as the MPI Magdeburg - went off without any appreciable problems. However, this required a great deal of effort and placed heavy demands on the flexibility of our employees and colleagues.

How will the sharing of scientific knowledge look in future and what are the measures that we will need to develop to assist in this? Can we return to the conferences and conventions of the past, or will we find ourselves living in a virtual world in future? The latter sounds great if you already know one another and when the answers to the unresolved questions that are discussed do not cause too much controversy. Getting to know new people or building consensus, however, requires face-to-face interaction, an understanding of one’s counterpart, and not just as a face on a screen.

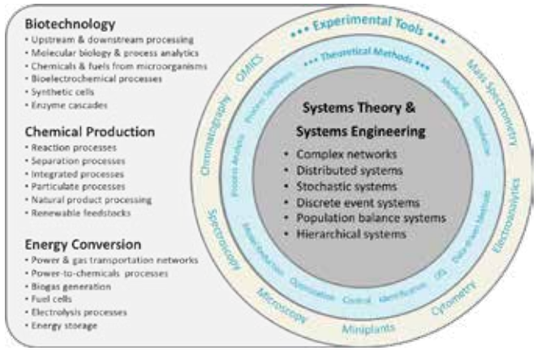
The key topics for science, industry and society, however, remain unchanged. 2019 was the year of climate protection and the “Fridays for Future” movement. While the methods of agitation may change due to the Coronavirus, the central message remains, and I fully endorse it: we must combine our forces and develop technologies to become carbon neutral by 2050. For this reason, here at the MPI we can actually say that it is “business as usual”, when you consider the important contributions that have already been made on the subjects of energy and raw materials efficiency, the use of batteries and fuel cells, and energy system research.

And even though, of course, there are many other important contributions that would also have been worth mentioning, it is entirely appropriate to highlight the fact that in the year of the Coronavirus the Bioprocess Engineering group at the MPI Magdeburg has focused its efforts on vaccine production processes. This work, in an area that has now been recognized as being of systemic importance, has been underway for many years. I think that it is greatly to be welcomed that since 2018 two of our young researchers have set out to establish their own company for the efficient continuous production of vaccines. I would like to wish them every success!

And in what are at present somewhat difficult times, I am certain that the MPI will, in future, continue to make important contributions to research topics of truly vital relevance to our industrial society.

Prof. Kurt Wagemann
Executive Director, DECHEMA e.V.

+ **Intro**duction



+ Figure 1:
Research Concept of our Institute

+ Figure 2:
Prof. Dr.-Ing. Kai Sundmacher is the new spokesperson of the International Max Planck Research School Magdeburg. After six years, Prof. Dr.-Ing. Andreas Seidel-Morgenstern finished his term on August 30, 2019 with a symbolic passing of the baton.

+ Figure 3:
Companions, friends and colleagues of Prof. Ernst Dieter Gilles met on the occasion of the Commemorative Colloquium in honor of the scientific achievements of Prof. Dr.-Ing. h.c. mult. Ernst Dieter Gilles on November 14, 2019, at our institute.

+ Figure 4:
Prof. Jennifer Wilcox, Professor at Pennsylvania University, was awarded with the Max Planck Sabbatical Award. She is shown here with Prof. Dr.-Ing. Kai Sundmacher during her visit in Magdeburg in September 2019.

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 continuing climate change make the development of new and sustainable production technologies essential. This concerns, in particular, the establishment of advanced processes for a more efficient production of chemicals, transportation fuels, pharmaceuticals, and biologics. In addition, the transformation and storage of renewable energies is a formidable task for the current and future generations. Achieving breakthroughs in providing solutions to these challenges requires close collaboration across several scientific disciplines both on a national and international level. In this broad context, the main goals of the research activities carried out at the Max Planck Institute Magdeburg are to develop mathematical models capable of describing highly complex chemical, biotechnological and energy-related processes and to analyze their system properties and dynamic behavior. Model validation and testing of new concepts are carried out in extensive experimental studies *in silico* and both at the laboratory and at the pilot scale level. In return, the establishment of new processes in chemical and biochemical engineering and the implementation of state-of-the-art analytical tools also stimulates the development of new computational methods and approaches in systems and control theory. Overall, our systems-oriented approach serves as an umbrella for all research groups. Together with the tight integration of theoretical and experimental investigations, it is the key factor in the success of the MPI Magdeburg.

New Research Groups

As of December 2020, 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). An extension for a further three years of the Max Planck Fellow group has been granted and will finish by the end of 2022. Moreover, a partner group on *Efficient Heterogeneous Computing* headed by Dr. Ezzatti at the Universidad de la Republica in Montevideo, Uruguay, was established in 2018.

On June 12, 2019, Prof. Dr.-Ing. Ernst Dieter Gilles, the founding Director of the institute sadly passed away at the age of 84. Ernst Dieter Gilles served as director from 1997 to 2008 and headed the Systems Biology research group until 2011. As a scientist and professor, he contributed strongly to the theoretical, basic and applied research of the MPI, where he supported and mentored many prospective scientists. An essential characteristic and merit of his work was advancing the state of the art in methods in the domain of systems and control theory and then applying these new techniques to actual problems in engineering and the natural sciences. His research interests comprised topics ranging from the control of chemical engineering processes and the automatic navigation of inland water vessels to applications in systems biology and biotechnology. His outstanding theoretical expertise, his ability to identify new trends and developments in the engineering sciences, and his prudence as an administrative director all laid the foundations for the extremely successful development of our institute. In recognition of his scientific achievements, a colloquium was organized on November 14, 2019, with contributions covering his research activities from the early years at the University of Stuttgart to his years as a Scientific Member of the Max Plank Society, his collaborations with external academic partners and industry, and his networking activities. In addition, in the year 2020, an Ernst Dieter Gilles postdoctoral fellowship was established to support promising junior scientists in the early stage of their career who plan to develop and implement an independent research project within the scope of activities of the MPI Magdeburg.

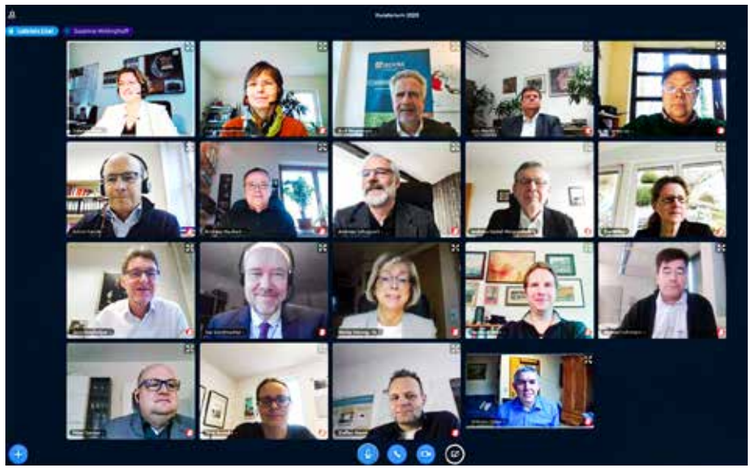
New Research Projects and Grants

In the period 2019-2020, 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 include "StrainBooster" (ERC Consolidator Grant of Steffen Klamt, ARB), the DARPA-funded project "DIA_TIP" for the development of a new class of therapeutic antibodies, the spin-off project "ContiVir" (a two-year EXIST-Transfer of Research project to advance gene therapy manufacturing, BPE group), and the large collaborative research network "MaxSynBio" (PSE, EEC, PSD groups, and eight other Max Planck Institutes) dealing with bottom-up synthetic biology.

In our *Chemical Production* research cluster, the Collaborative Research Center CRC/TR 63 "InPROMPT" (MSD, PCF, PSE, PSD groups) will be funded by the DFG until 2021. As in the previous years, investigations in two EU research projects ("UNRAVEL" and "CORE") are being carried out by the PCF group. The US-American chemical engineer Professor Jennifer Wilcox received the Max Planck Sabbatical Award 2019. The prize was given to her by the end of October 2020. Established by the Max Planck Society, the award offers renowned scientists a research stay at and close cooperation with one of the Max Planck Institutes. Caleb Woodall, chemical engineer and member of the group of Jennifer Wilcox, started research in this context at our institute in November 2020. He is collaborating with a team of the PSE group on ways of capturing and storing CO_2 from mining operations.

In our *Energy Conversion* research cluster, we are continuing to participate in the Max Planck Research Network on Energy Systems (MaxNet Energy) where we are dealing with low-temperature water electrolysis cells. We have also created a larger

+ **Figure 5:**
At the beginning of 2020, Dr. Matthias Stein was appointed as Honorary Professor for Computational Chemistry in the Department of Chemistry at OVGU, shown here with Prof. Dr.-Ing. habil. Dominique Thévenin and President Prof. Dr.-Ing. Jens Strackeljan.



+ **Figure 6:**
The 15th meeting of our Board of Trustees was, for the first time, completely held virtually on December 10, 2020.

+ **Figure 7:**
The DECHEMA Colloquium on "Forced Periodic Operation" on November 4, 2020, with 70 participants, including from the United States, Canada, Switzerland and Saudi Arabia, was only possible using modern video techniques.

+ **Figure 8:**
Ph.D. defense under pandemic conditions - with face masks, keeping distance, and a hybrid doctoral defense presentation. Dr.-Ing. Jens Bremer (pictured right with Prof. Kai Sundmacher) successfully defended his dissertation in November 2020.

consortium of six MPI research groups "Altmark Energy" (ARB, BPE, CSC, MSD, PCF, PSE) with regional partners (Biogas Gardelegen, Avacon, etc.), supported by the EFRE-program of the federal state of Saxony- Anhalt to develop new conceptual designs and operating strategies for Power-to-X systems. Moreover, the CSC group together with several industrial and academic partners have initiated the BMWi-funded project "MathEnergy", the aim of which is to devise a new simulation platform for fast scenario analysis of gas transport networks in Germany.

In our Systems Theory and Systems Engineering research cluster, the DFG Research Training Group "Mathematical Complexity Reduction" (OVGU with CSC group), which was established in 2017, requested a second funding period (2021-2025, to be decided in spring 2021) and the Max Planck Network BiGmax ("Big-Data-Driven Materials Science", coordinated by the CSC group) continues to devise new machine learning tools and algorithms addressing the 4V challenge (volume, variety, veracity of data, velocity at which data arrive).

Finally, the MPI Magdeburg is also active in the German National Research Data Infrastructure Initiative (NFDI), in which 900 million Euro will be spent this decade to establish the FAIR (findable, accessible, interoperable, reproducible) principles for handling scientific research data. The bottom-up approach of the NFDI allows for the development of measures for FAIR research data handling in 30 topical consortia. The MPI Magdeburg also contributes as a co-applicant institution in the NFDI4Cat (Digital Catalysis, funded 2020-2025) and MaRDI (Mathematics, submitted) consortia.

Appointments and Awards

We are very proud that many of our senior scientists have received offers of positions at other academic institutions: Tobias Breiten (now full professor at the Institute for Mathematics, TU Berlin); Andres M. Escorcia (now professor at the Universidad Icesi Colombia); Robert Flassig (now Professor for Energy Systems Engineering at Brandenburg University of Applied Sciences); Erdal Aydin (now Assistant Professor at the Bogazici University in Istanbul, Turkey); Chayan Bhawal (now Assistant Professor at IIT Guwahati, India); Martin Redmann (now Assistant Professor at the Institute for Mathematics, MLU Halle-Wittenberg); Yue Qiu (now Assistant Professor at ShanghaiTech University, P.R. China); Teng Zhou (now Junior Professor, W1 Professor in the Faculty of Process & Systems Engineering, OVGU Magdeburg and team leader within the PSE group). We wish them, and all other former colleagues who left the MPI in 2019-2020, all the best for their future careers.

As in previous years, several members of the MPI have received prestigious scientific awards or became members of scientific societies and panels for their excellent research work and achievements. These include Marcus Wenzel (Otto Hahn Medal of the Max Planck Society and best Ph.D. student by the Department of Process and Systems Engineering at OVGU in 2019); Matthias Stein (Honorary Professor for Computational Chemistry at OVGU); Andreas Seidel-Morgenstern (President of the *International Adsorption Society* (IAS), 2019-2022); Pawan Goyal (Dr. Klaus Körper Award of the Gesellschaft für Angewandte Mathematik und Mechanik (GAMM) and Honorable Mention related to the Householder Prize); Steffen Werner and Jens Saak (Best Paper Award from the "at – Automatisierungstechnik" journal; 2019).

Challenges of COVID-19

With the advent of the Coronavirus in 2019, a long-standing concern regarding the risks of the international spread of new, virulent pathogens became a reality and had a significant impact not only on our societies but also on our daily lives as researchers at the MPI. For many of us there has been a contraction of the world and a turn towards the smaller aspects of life, where travelling and visiting conferences are largely on hold. Personal contacts with colleagues, even members of the same team, have been restricted to video conferences for months. Recruitment of doctoral candidates and post-docs has become increasingly complicated, for many countries almost impossible. While it has been possible to quickly establish options for working from home and there are now solutions for organizing hybrid conferences, communication and the exchange of ideas are still suffering. On the other hand, many new research projects and ideas have been stimulated by this challenge, including research at our MPI in Magdeburg, and the intense worldwide efforts towards vaccine development will hopefully pay off. Nevertheless, the long-term damage to science is difficult to assess. This concerns not only the prioritization of research activities and the possibilities for future funding but also the detrimental impact of COVID-19 on the global economy as well as ethical questions, i.e. the living conditions and health of those living in poverty.

Finally, I wish my successor as Managing Director, Professor Peter Benner, a very successful time during his term from 2021 to 2022.

Magdeburg, November 2020

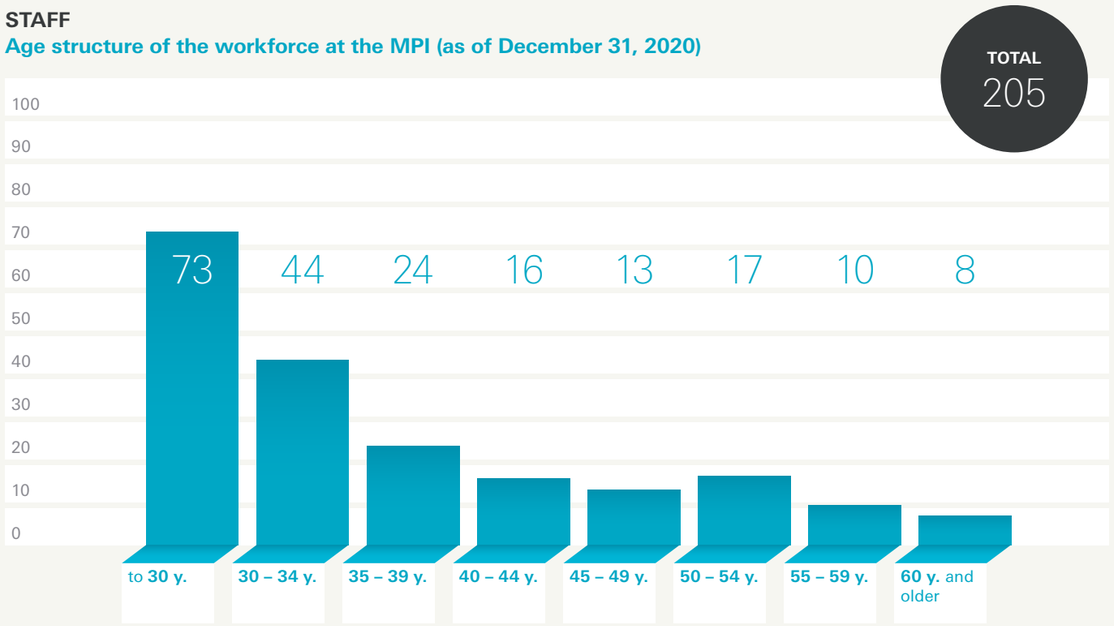
Prof. Dr.-Ing. Udo Reichl
Director

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

Facts and Figures

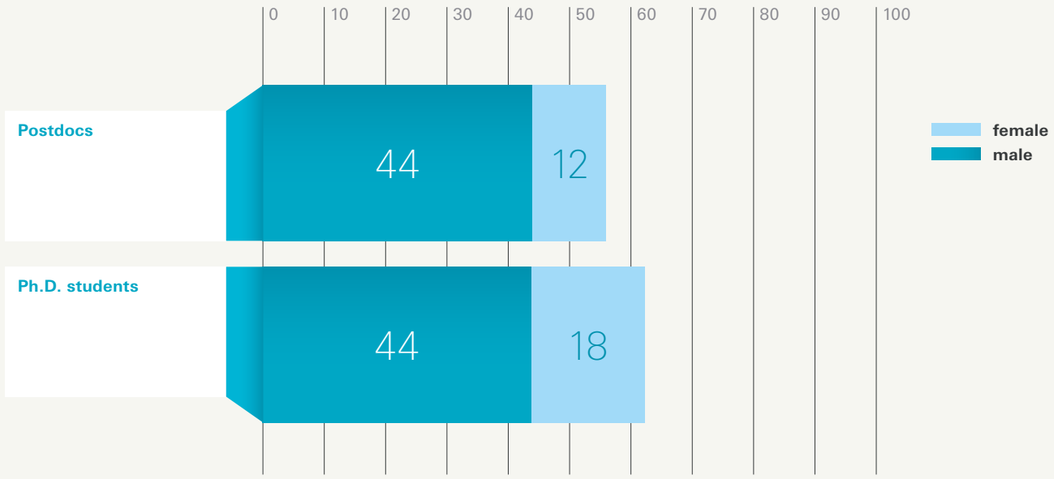
STAFF

Age structure of the workforce at the MPI (as of December 31, 2020)



STAFF

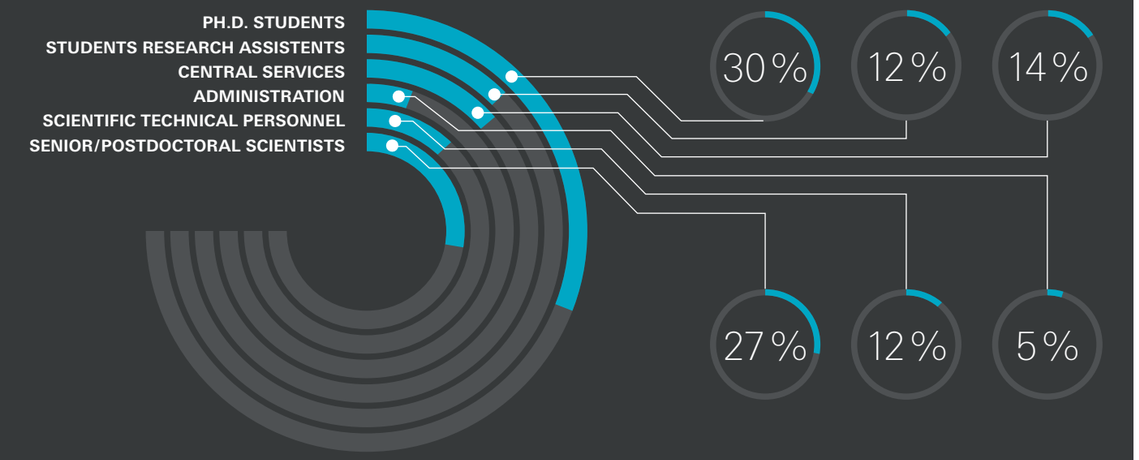
Distribution of scientists by gender Female employees: 21 % Postdocs and 29 % Ph.D. students



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, 2020: 205 Employees 118 Scientists: 56 Postdocs, 62 Ph.D. students



At the end of 2020, the MPI employed 205 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 2019

Total Expenses in Fiscal Year 2019: 16.14 million Euro

The total budget of the MPI in the fiscal year 2019 was 16.14 million Euro. The pie chart above shows how this was distributed to the major budget categories. As can be seen, more than 60 % of the budget was used for salaries.

MPI-GENERAL BUDGET 2019

Total Revenue: 16.14 million Euro Third-party funds: 2.4 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 2019 – 2020

+ The 6th IMPRS Summer School was held from 26 to 30 August 2019 at the Max Planck Institute in cooperation with the Otto von Guericke University Magdeburg. The participants gathered here in front of the entrance to our institute.

1st International Young Professionals Conference on Process Engineering

Current challenges, future trends and the intersection between industry and academia were in the spotlight during the first International Young Professionals Conference on Process Engineering (YCOPE), hosted by the International Max Planck Research School (IMPRS), from March 18 to 20, 2019 in Magdeburg.

Bright young minds discussed the latest news from process engineering with a view to contributing to the ongoing debate on how to find cutting-edge solutions for the process industry and dealing with several key questions of our time. For instance, how to store renewable energy and how to produce better active pharmaceutical ingredients more sustainably, using less energy and generating less waste.

It was the first time that an international conference had been completely conceived, planned and executed by IMPRS students. The initiative reached impressive numbers: 83 participants from 17 institutes in eight countries came to Magdeburg and mingled during the six keynote lectures, 23 talks and 37 poster presentations.

For the students, it was a great opportunity to network with colleagues from different backgrounds in a small and intimate atmosphere - something that is more difficult at larger international events. “We were able to come to an agreement on future directions in light of the challenges currently posed, for example, by climate change, machine learning and even the diverse language adopted across professions,” said Jennifer Uebbing, IMPRS student and YCOPE Chair of External Affairs. The general reception of the new conference format was surprisingly good, and the organizers observed quite a high level of engagement not only at the conference itself but also on social media. They are confident of being able to successfully repeat the event in future, making it even more visible to young researchers.

I Renata Malkes

1st Workshop “Sustainability in the Max Planck Society”

Sustainable industrial processes and renewable energies constitute major research fields at our institute. However, through their research efforts scientists also contribute to the global anthropogenic emission of greenhouse gases and to other environmental impacts. Back in 2015, employees of our institute established a sustainability group, or local think tank for sustainable research. Example topics include the reduction of CO_2 emissions resulting from conference travel, the use of recycling paper for printers and copy machines, and the ecological management of our green spaces. As pioneers in this field within the Max Planck Society, the sustainability group organized the 1st Workshop “Sustainability in the Max Planck Society” from 16 to 17 May 2019 which was open to employees from the entire Max Planck Society. 65 colleagues, scientific and non-scientific staff, from 30 Max Planck Institutes as well as representatives of the General Administration in Munich took part. The workshop program featured keynote presentations by directors from our institute and other MPI as well as small working groups to discuss potential measures and their implementation for sustainable research. This workshop finally resulted in the collective decision of the participants to establish an MPG-wide Sustainability Network. The conference organizers also made efforts to make the meeting itself sustainable, which included the integration of a virtual keynote presentation, reusing old conference posters by using the blank sides for the working groups, and a vegan dinner. In 2020, the entire Max Planck Sustainability Network Meeting was organized in virtual format, not only due to the COVID-19 pandemic but also to serve as a best practice example for climate-friendly scientific conferences. Today, the Max Planck Sustainability Network has become a significant platform for sustainable research with sustainability groups in more than thirty Max Planck Institutes and members in more than 60, including Max Planck Institutes abroad.

I Dr. Jakob Schweizer

https://www.nachhaltigkeitsnetzwerk.mpg.de/

+ The IMPRS hosted the first International Young Professionals Conference on Process Engineering (YCOPE) between March 18 to 20, 2019, in Magdeburg.

+ Max Planck colleagues discussing ideas how to make research more sustainable.

6th Summer School of the International Max Planck Research School

Producing tailor-made particles for a wide variety of applications in chemistry, medicine and the environment and optimizing the processes involved were the central topics of the 6th Summer School of the International Max Planck Research School for Advanced Methods in Process and Systems Engineering (IMPRS Pro Eng). The Summer School, which had around fifty participants, was held from 26 to 30 August 2019 at our institute in cooperation with Otto von Guericke University Magdeburg.

For a whole week, the large seminar room at the MPI was transformed into a computer laboratory. Where usually there are only chairs in rows, during this period there were 20 computers and monitors ready for the participants of the Summer School to use. The presentations, tutorials and software workshops revolved around the smallest particles - particles such as those that occur during crystallization, granulation, fermentation or polymerization processes.

+ The participants of the Symposium on "Insights into Gas Diffusion Electrodes" in September 2019 assembled on the premises of the Festung Mark, an event and conference venue in Magdeburg.

+ The 8th Workshop on "Matrix Equations and Tensor Techniques" was held in November 2019 at MPI Magdeburg.

+ The participants of the 4th Indo-German Workshop on "Advances in Materials, Reaction and Separation Processes" assembled in the garden of the Harnack House, the conference venue of the Max Planck Society in Berlin-Dahlem.

Various different methods of process optimization and their mathematical modeling were part of the Summer School's agenda. The speakers, among others from Politechnico Torino, Italy, Hamburg University of Technology and Massachusetts Institute of Technology, USA, provided very good insights into the numerical methods that are used currently for this and that should be used more fully in future. Interesting information about applications in industry and a look at possible future careers in their companies were provided to the doctoral students by speakers from BASF SE and CiT Wulkow GmbH.

The passing of the baton within the leadership of the IMPRS was a further highlight of the Summer School. Professor Dr.-Ing. Kai Sundmacher has been the new spokesperson since 30 August 2019. **| Gabriele Ebel**

International Symposium on Functional Materials for Electrolysis, Fuel Cells and Metal-Air Batteries

Materials scientists, electrochemists and process engineers met from 23rd to 25th September 2019 in Magdeburg during the first International Symposium on "Insights into Gas Diffusion Electrodes". The event was organized by our Max Planck Institute (Tanja Vidaković-Koch) and TU Clausthal (Thomas Turek) within the framework of the DFG Research Unit 2397 "Multiscale Analysis of Complex Three-Phase Systems", with the aim of gaining new insights into the complex processes within gas diffusion electrodes.

Gas diffusion electrodes are functional materials used in various technically important electrochemical processes such as fuel cells and metal-air batteries. Considering the challenges of the energy transition in particular, the further development of these materials is of major importance.

More than 100 scientists from 18 nations, as well as representatives and speakers from various industrial companies such as Covestro and C3 Prozess- und Analysentechnik GmbH (Process and Analysis Technology), discussed the latest developments in the research field. It became clear that only through joint efforts in the fields of materials science, electrochemistry and process engineering will it be possible to better understand gas diffusion electrodes and develop innovative processes that are based on them.

The event was supported by the German Research Foundation (DFG), the Society of German Chemists (GDCh), the International Society of Electrochemistry (ISE) and Otto von Guericke University Magdeburg.

| Professor Thomas Turek / Dr.-Ing. habil. Tanja Vidaković-Koch

DECHEMA Colloquium on "Circular Economy"

In order to obtain a broader overview of the research activities in Germany looking at the "Circular Economy", the Max Planck Institute and DECHEMA organized a colloquium that took place on 12 November 2019 at the institute. More than 70 participants from academia and industry discussed various aspects of plastics recycling, metal recovery, phosphorus from wastewater, and nutrients from biogas digestate. Motivated by the colloquium's results, in 2020 the MPI initiated a new research project on the chemical recycling of plastics.

| Prof. Dr.-Ing. Kai Sundmacher

METT VIII - 8th Workshop on Matrix Equations and Tensor Techniques

In November 2019, the 8th Workshop on Matrix Equations and Tensor Techniques (METT VIII) was held at our institute. This 3-day workshop (6-8/11/2019) was the 8th in a series of itinerant workshops on matrix equations, and the 5th - since the 4th workshop - to also deal with tensor techniques. METT takes place in a different location every two years, with previous workshops having been held in Germany (Leipzig, Chemnitz, Braunschweig and Aachen), Switzerland (Lausanne) and Italy (Bologna, Pisa).

As in the previous meetings, the focus of the workshop was on the latest developments in the theory, computation and applications of linear and nonlinear matrix equations, and tensor formulations. The efforts of many outstanding researchers are currently devoted to these topics and matrix equations and tensor techniques are certainly some of the most active research areas in numerical analysis. The scientific program of the workshop included 19 contributed talks and 10 notable poster presentations, whose contents ranged from error bounds for low rank tensor approximation to the exploitation of the tensor-train format in image classification, and from the efficient solution of large-scale algebraic and differential Riccati equations to the design of novel matrix equation techniques in parametric model order reduction.

Many scientists, from well-known experts in the field to Ph.D. students new to the topic, took part in METT VIII. Forty-seven researchers from all over Europe (Germany, Italy, UK, Czech Republic, France, Belgium, Switzerland) as well as from the US and Asia attended METT VIII, and thanks to the generous sponsorship of the MathCoRe Graduate School, the attendance of three Ph.D. students was fully supported.

The informal, friendly atmosphere of the workshop along with the facilities of our institute (e.g., many rooms for discussions and brain storming) contributed to creating a very fruitful and successful meeting. We are all looking forward to the 9th Workshop on Matrix Equations and Tensor Techniques that will be held in Perugia, Italy, on 9-10 September 2021.

| Dr. Davide Palitta

Advances in Materials, Reaction and Separation Processes

The 4th Indo-German Workshop on "Advances in Materials, Reaction and Separation Processes" successfully took place from 24th to 26th February 2020 in Berlin. The latest developments in the specified areas of materials, reactions and separations were the focus of the workshop.

Reaction and separation are two critical unit operations in chemical process industries. Unconverted reactants are to be separated from the final product along with other non-desirable side products. A complete understanding of the processes occurring in these units is essential for safe and efficient operation of any plant. During the workshop, recent experimental and theoretical work was discussed.

This workshop series started in 2008 at the IIT Madras followed by an event in 2012 in Bad Herrenalb and another in 2016 at the IIT Guwahati. It works as a platform for strengthening collaborative research activities between Indian and German colleagues, for introducing senior doctoral students to the research currently being undertaken in the specified areas, and for visits by scientists from one country to the other. The success of the collaboration can be gauged from numerous publications in internationally reputed journals which have been co-authored by scientists from both countries. **| Professor Andreas Seidel-Morgenstern**

SAMM 2020: Learning Models from Data

The 7th GAMM Juniors' Summer School on Applied Mathematics and Mechanics (SAMM) took place in July 2020 with the theme "Learning Models from Data: Model Reduction, System Identification and Machine Learning". This event continued the series of SAMMs, which are organized by GAMM Juniors and held almost yearly in different locations focusing on recent research topics in applied mathematics and mechanics.

Originally planned as an in-person meeting at the Max Planck Institute in Magdeburg, it was converted into an online event due to the restrictions caused by the COVID-19 pandemic. Nonetheless, this transformation became a great opportunity for an exceptional international experience. From a high number of applications, 75 young researchers from 17 different countries covering 10 different time zones were selected to participate.

Each day, the participants, mainly Ph.D. students, but also post-doctoral researchers, undergraduate students, and participants from industry, followed the live online lectures and tutorials given by Feliks Nüske (Paderborn University), Benjamin

+ Virtual GAMM Juniors' Summer School on Applied Mathematics and Mechanics in July 2020

+ Prof. Andreas Seidel-Morgenstern (right) and Prof. Achim Kienle are hosting the virtual DECHEMA Colloquium on "Forced Periodic Operation".

Peherstorfer (New York University), and J. Nathan Kutz (University of Washington). The focus of the summer school was to study recent developments in the field of learning models from data including topics such as, among others, data-driven approximation for stochastic systems, learning reduced-order models from data, and utilizing neural networks for learning a flow map of a dynamical system.

In addition, almost all participants presented posters on their own research in three virtual poster sessions, which allowed a fruitful exchange of ideas. | **Dr. Carmen Gräßle/Dr. Petar Mlinarić**

Foundation of the QBIC Society

Dr. Matthias Stein is a founding member and member of the Board of the QBIC Society. The Quantum Bio-Inorganic Chemistry Society (www.qbicsoc.org) was founded in 2018 and started its activities in 2019 with the purpose of bringing together scientists from academia and industry who are working in the broad fields of theoretical and computational inorganic, bioinorganic, and biological chemistry. Its aim is to enhance the visibility and recognition of the contributions that computational chemists make to important problems in inorganic and bioinorganic chemistry. Membership of the QBIC Society is open to all scientists and currently has more than 50 members

The QBIC Society organized the 5th QBIC Meeting from 8th to 10th July 2019 in Marseille (www.qbicv.cnrs.fr) and is now preparing for the 6th meeting in Groningen in 2022.

+ 5th Quantum Bio-Inorganic Chemistry Conference in Marseille in July 2019, with more than 70 participants from all over the world.

The QBIC Society is awarding the Quantum Bio-Inorganic Chemistry Society Award for the years 2020 and 2021 to young scientists. The aim of the award is to recognize outstanding contributions in the field of inorganic and bioinorganic chemistry that were achieved with theoretical, quantum chemical or other computational methods. | **Dr. Matthias Stein**

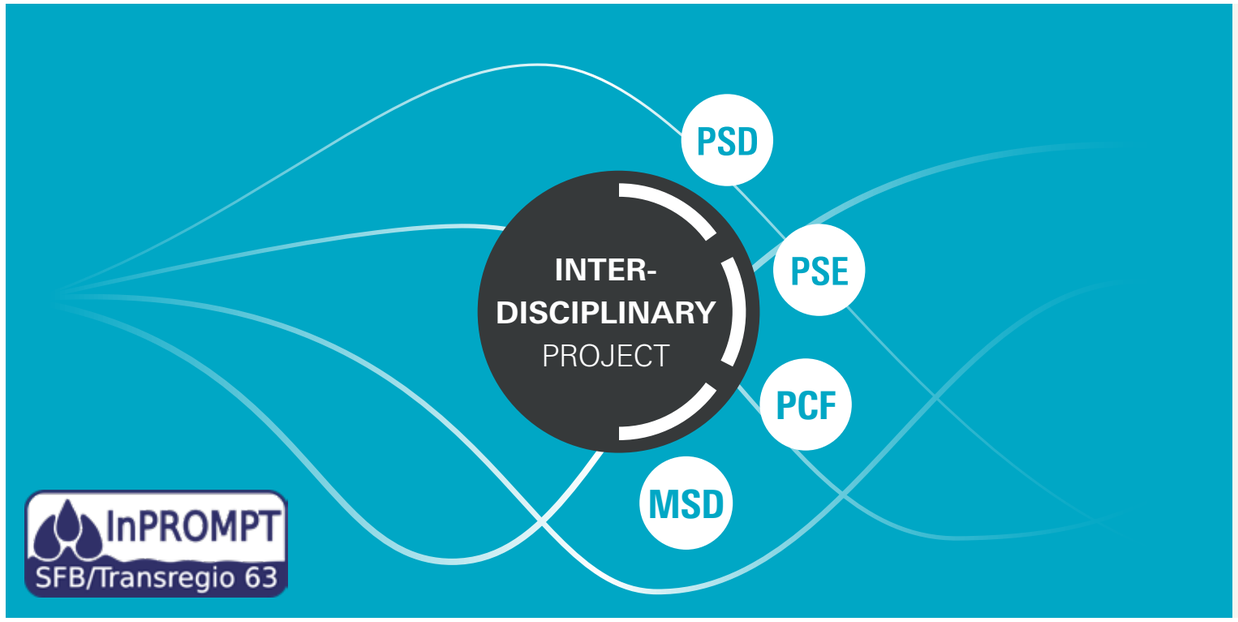
DECHEMA Colloquium "Forced Periodic Operation"

Continuously operated chemical reactions are not always at their best when in steady state; in fact, some benefit remarkably from forced periodic operation. At this DECHEMA Colloquium, which was held virtually at the Max Planck Institute in Magdeburg on November 4, 2020, experts from academia and industry - from the University of Belgrade (Serbia), Linde AG Munich, BASF SE Ludwigshafen and from Otto von Guericke University Magdeburg - showcased the promising concept of forced periodic operation of reaction and separation processes and discussed how it can be further exploited.

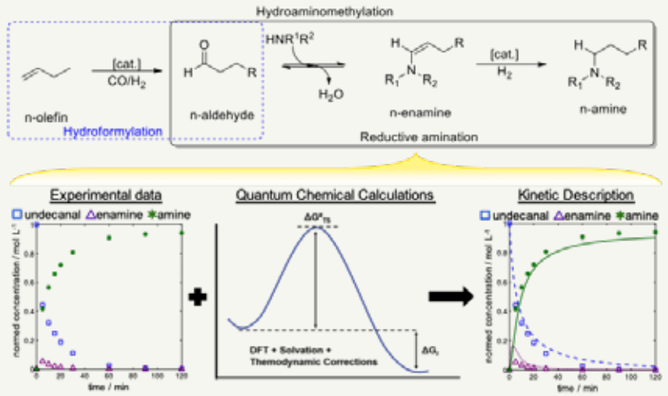
Most reaction and separation processes that are carried out continuously are operated under steady state conditions. This is due to robustness and simplicity of operation. However, due to process nonlinearity, the average performance in a periodic process can exceed that of the optimal steady-state operation. Recently, remarkable progress has been achieved in the development of straightforward and simple-to-apply prediction methods based on using the concept of nonlinear frequency analysis. Equipment and control systems for periodic processes have also become more widely available. A number of processes that can only work in a periodic regime are nowadays applied successfully in industry. Separation processes exploiting adsorption principles are an example.

The colloquium was organized by DECHEMA e.V., Max Planck Institute Magdeburg and Otto von Guericke University Magdeburg, and it was hosted by Professor Andreas Seidel-Morgenstern. Seventy participants, including from the United States, Canada, Switzerland and Saudi Arabia, joined in the online event. | **Professor Andreas Seidel-Morgenstern**

+ Research Groups



+ Figure 1:
Constructed rigs of the helically coiled tubular reactor (left) and repeatedly operated semibatch reactor (right). Adopted from [2] published under CC BY-ND 2020).



+ Figure 2:
Working steps for the derivation of mechanistic reaction network models by combination of experiments, quantum chemical calculations and parameter estimation.

INTEGRATED PROCESS DESIGN FOR FINE CHEMICALS FROM RENEWABLE FEEDSTOCKS

+ Since the industrial revolution, the chemical industry has provided us with an almost uncountable number of synthetic materials and products, which have boosted our economies and made our everyday lives much easier and more comfortable. However, this advancement was only possible thanks to the wide and cheap availability of fossil resources. Nowadays, we are all feeling the negative side effects of this boom in terms of global warming and climate change. To reduce our carbon footprint, switching to renewable feedstocks is essential. Since the structures of bio-based molecules are much more complex than those based on fossil fuels, new concepts for chemical production processes have to be developed. Furthermore, these new processes need to be developed in accordance with green chemistry guidelines, which require the use of harmless solvents, highly selective catalysts and advanced process intensification methods. To comply with all of these requirements, every process level, from the molecule up to the production plant, has to be considered during process design. This requires close interdisciplinary cooperation between experts from the fields of chemistry, industrial catalysis, reaction engineering and process systems engineering. The collaborative research center, Transregio 63 (CRC/TRR 63) "Integrated Chemical Processes in Liquid Multiphase Systems" (InPROMPT) funded by the German Research Foundation (DFG), was established in 2010 to address this. Within this consortium, researchers with a STEM background are working hand in hand to develop new process design methodologies and validate them through the construction and operation of pilot plants. Currently, researchers from seven German universities (Berlin, Darmstadt, Dortmund, Karlsruhe, Köthen and Magdeburg) as well as four research groups from the MPI for Dynamics of Complex Technical Systems are involved in this center. The researchers from Magdeburg are primarily addressing the selection of catalysts and solvents (MSD, PSE), the development of mechanistic models of the reaction kinetics (PCF, MSD), reactor synthesis and validation (PSE), and overall process optimization (PSD, PSE).

In the first and second funding periods (2010-2017) of the CRC/TRR 63, the homogeneously catalyzed hydroformylation reaction of long chained olefins was studied in depth. In industry this reaction is carried out on megaton scale per year to produce aldehydes that are mostly used as intermediates for the synthesis of alcohols, carboxylic acids and amines for manufacturing body care products, solvents and plasticizers. Today, these aldehydes are mostly produced from fossil fuels. However, the olefin feedstock can also be obtained from renewable resources in the form of unsaturated fatty acids from plants such as sunflower or colza. To make the hydroformylation process economically feasible, the expensive homogeneously dissolved rhodium catalysts have to be recovered after the reaction. To do this, a thermomorphic multiphase system (TMS) is used. It enables the catalyst to be recovered by means of a simple liquid-liquid separation step. An optimal tailored reactor design for highly selective aldehyde production was derived using the mechanistic reaction kinetic model developed in the PCF group and the Elementary Process Functions (EPF) methodology of the PSE group [1]. As the optimal reactor design consists of two sections with different mixing and reaction conditions, two consecutively connected reactors are required. For the pilot plant study, two design approaches with different operation modes were constructed: i) a helically coiled tubular reactor (HCTR) connected to a continuously stirred tank reactor (CSTR) and ii) a repeatedly operated semibatch reactor (RSBR) followed by a CSTR. To maximize selectivity with respect to the desired aldehydes, these two reactor tandems enable the target-orientated manipulation of the reaction conditions in a discrete (HCTR-CSTR) and continuous manner (RSBR-CSTR). Both tandems were operated in the pilot plant hall of the MPI for more than 500 hours with continuous catalyst recycling. Compared to the existing benchmark process, where a single CSTR has been used, the conversion and aldehyde yield were enhanced by 25% using the tailored reactors and, additionally, a higher space time yield was achieved [2].

Since 2018, the CRC/TR 63 has focused on the synthesis of amines from long chained olefins. These amines can be synthesized directly in one step from olefins via the hydroaminomethylation reaction or consecutively via hydroformylation and reductive amination (RA) reactions. To achieve high productivity, suitable reaction pathways need to be identified for the selective production of amines. For this purpose, the reaction mechanism and kinetic descriptions for the RA [3,4] and hydroformylation reaction [5] are to be combined and utilized within the process methodologies developed so far. In addition to the methodologies for process synthesis, a systematic screening approach for TMS solvent selection has also been developed within the CRC/TRR 63, which also considers the important aspect of catalyst leaching. Recently, this quantum chemical screening approach was extended, as a result of which it becomes possible to identify environmentally friendly solvents and solvent systems [6]. The identified green solvent candidates were evaluated in an economic overall process optimization. It was found that the replacement candidates perform similarly to the state-of-the-art substances but lead to a much more sustainable process technology [7]. **I Dr.-Ing. Michael Jokiel**

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[4] Kirschtowski et al. (2021): *Kinetics of the reductive amination of 1-undecanal in thermomorphic multicomponent system.* Chem. Eng. Sci. 230,pp 116187, DOI: 10.1016/j.ces.2020.11618

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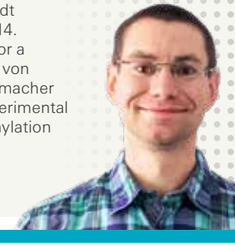
[6] Linke et al. (2020): *Systematic Green Solvent Selection for the Hydroformylation of Long-Chain Alkenes.* ACS Sustainable Chem. Eng., 8, 10795–10811, DOI: 10.1021/acssuschemeng.0c02611

[7] Kessler et al. (2019): *Systematic Selection of Green Solvents and Process Optimization for the Hydroformylation of Long-Chain Olefines.* Processes, 7, 882; DOI: 10.3390/pr7120882

Author **Dr.-Ing. Michael Jokiel**

After an apprenticeship as a car mechanic, Michael Jokiel studied Chemical Technology at Darmstadt University of Applied Sciences from 2010 to 2014. Afterwards, he moved to Magdeburg to study for a Master's degree in Process Engineering at Otto von Guericke University. In 2015 he joined the Sundmacher group for his Ph.D. on the construction and experimental evaluation of tailored reactors for the hydroformylation of 1-dodecene, which he finished in 2020.

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



BPE | BIOPROCESS ENGINEERING

+ Preparation of a sample for mass spectrometry-based protein identification and characterization.

PROF. DR.-ING. UDO REICHL | 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 an integrated view of complex biological systems, in-depth understanding of (bio) chemical reactions, dedicated equipment and modeling tools. Additionally, a wide range of assays for process monitoring and a comprehensive set of analytical and "omics" technologies should be utilized. The challenges we are facing today in bioprocess engineering relate not only to the increase in product yields, but also to the establishment of new methods for process intensification and a reduced time to market while guaranteeing the quality and safety of drugs.

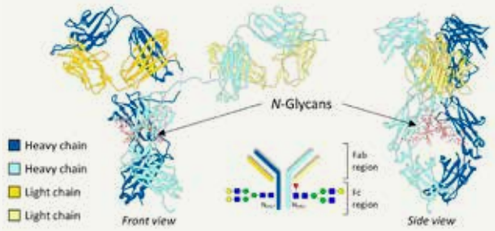
In the context of biopharmaceuticals production, the **Bioprocess Engineering group**, headed by Professor Udo Reichl, studies key aspects of the cell culture-based production of virus particles, viral vectors and other biologicals. Virus production processes are currently seeing a strong increase in market share due to the emergence of new diseases and a steady increase in general demand. This concerns, in particular, the recent outbreak of Zika virus in Latin America and the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic. Furthermore, the growing use of viral vectors in gene therapy, and promising options for viral therapy to cure certain types of cancer or autoimmune diseases demand significant efforts. As in previous years, influenza virus propagation in animal and human cell lines is considered a model system in bioprocess development due to its enormous relevance as a respiratory pathogen, the high complexity involved in virus-host cell interactions, its frequent mutations including gene reassortment, and options for using influenza virus-derived defective interfering particles (DIPs) as a new class of antivirals.

The group combines the expertise of five teams covering different aspects of biologics production, analytics and modeling. The **Upstream Processing team** (PD. Dr. Yvonne Genzel) focuses on virus and viral vector production processes. Therefore, the propagation of influenza virus, Zika virus, attenuated yellow fever virus and modified vaccinia Ankara virus is characterized in various adherent and suspension cell lines. Studies involve the design and optimization of processes performed in stirred and orbital shaken bioreactors, hollow fiber-based systems and disposable units. In addition, advanced cultivation strategies using online sensors and cell retention devices are being developed to further improve process performance and optimize productivity. Details of virus-host cell interactions are studied by the **Molecular Biology team** (Dr.-Ing. Sascha Kupke) to identify bottlenecks in virus replication and to develop new strategies for antiviral treatment. Virus dynamics are investigated on the single cell and 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. The experimental data obtained from both groups are used by the **Mathematical Modeling team** (Prof. Udo Reichl) to elucidate fundamentals of cell growth, metabolism and virus replication. Multiscale models are established to simulate the spreading of infections and the accumulation of virions in bioreactors starting from the single cell level. With a focus on proteomics, glycomics 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 posttranslational modifications of proteins. Finally, the **Synthetic Glycobiotechnology team** (Dr. Thomas Rexer) is concerned with the development of enzyme-based process platforms for efficient in-vitro glycosylation of proteins and peptides.

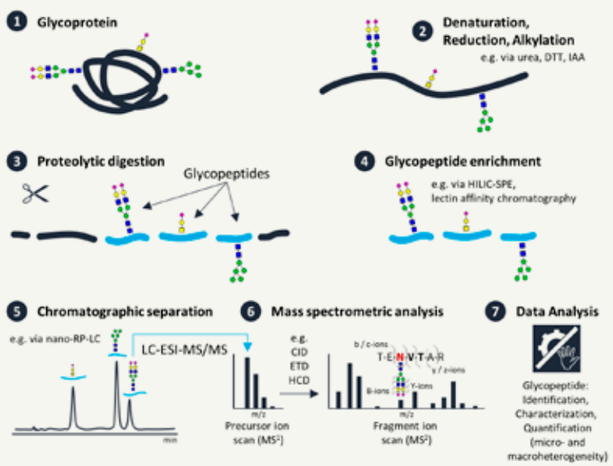
Over the last two years, the Upstream Processing team has continued its efforts towards process intensification and process integration by optimizing perfusion strategies for high cell density cultures, and by exploring options for cell and virus retention using hollow-fibers, settlers and acoustic filters. With the recent challenges of the SARS-CoV-2 pandemic, collaborations with several research groups and commercial partners have been initiated to tackle various aspects of vaccine development. The spin-off project "ContiVir" was initiated successfully to continue the development of a manufacturing platform for viral gene therapy vectors within a two-year funded "EXIST-Transfer of Research" project. Furthermore, processes have been established for high-yield DIP production. This involves not only conventional influenza A virus-derived DIPs, which are characterized by large deletions in their RNA segments, but also a novel interfering particle, OP7, which contains various nucleotide substitutions in its segment 7, that was recently discovered by our group. To test hypotheses regarding the DIP interference mechanism, multiscale models are being developed that quantitatively describe DIP and standard virus replication dynamics for a wide range of infection conditions in cell cultures and bioreactors. Finally, our efforts in synthetic glycobiotechnology have resulted not only in the filing of a patent family covering a group of multi-enzyme cascades for the generation of nucleotide sugars for synthesis of lipid-linked oligosaccharides and production of human milk oligosaccharides, but also in the generation of various forms of glycosylated coronavirus S proteins for animal trials. Finally, the Bio/Process Analytics team has further extended its portfolio of glycoanalytical methods for mass spectrometry-based peptide- and glycopeptide-mapping that are utilized not only for the in-depth analysis of viral antigens and synthetic glycosylated peptides but also in numerous collaborations in basic research.

Prof. Dr.-Ing. Udo Reichl
Director

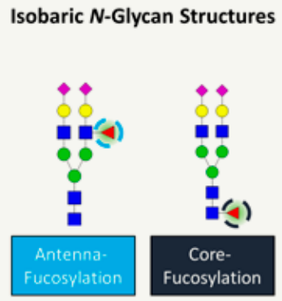
ureichl@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/reichl

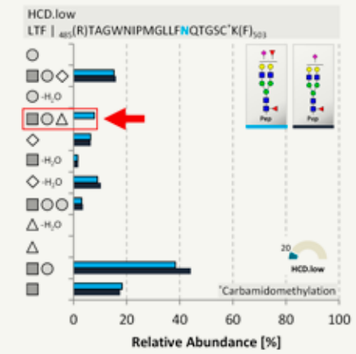


+ Figure 1:
Protein structure of human IgG. Highlighted: The Fc-gamma receptor binding site (N-glycosylation site N297) with core-fucosylation (red triangle, right).



+ Figure 2:
General workflow for MS-based glycoproteomic analyses.





+ Figure 3:
Differentiation of isobaric N-glycopeptides carrying antenna- or core-fucosylation (left) based on the detection of characteristic oxonium ions (right). Right: Oxonium ion plot showing the relative abundance of characteristic glycan fragment ions (oxonium ions) for two N-glycopeptides derived from human lactotransferrin (LTF; light blue and dark blue). The data were acquired by HCD.low fragmentation of the N-glycopeptides. The presence of a characteristic tri-saccharide oxonium ion (red arrow) makes it possible to discriminate the antenna-fucosylated (light blue) from the core-fucosylated (dark blue) form of the LTF N-glycopeptide. Symbolic representation of the monosaccharides: blue/dark gray square = N-acetyl-glucosamine, green circle = mannose, yellow circle = galactose, pink/white diamond = N-acetylneuraminic acid, red/white triangle = fucose, striped white circle = mannose/galactose.

Recent Advcances in Glycoproteomics

+ The production of biologicals, i.e. therapeutic monoclonal antibodies (mAbs), is currently the main driver of the pharmaceutical industry with a global sales revenue of about $94 billion in 2017, and an expected revenue of $139 billion in 2024. Due to their high target specificity and large number of effector functions, mAbs have a wide spectrum of applications including the treatment of various autoimmune diseases and types of cancer, and the treatment of infectious diseases. The potency, efficacy and immunogenicity of mAbs are heavily influenced by complex carbohydrates – so-called glycans – that are present in the Fc-gamma receptor binding site of their stem region (Figure 1). Depending on (I) the cellular target, (II) the desired effect (e.g. increased cytotoxicity), (III) the production cell line, and (IV) the process conditions, the Fc-gamma glycosylation of mAbs needs to be glycoengineered accordingly. For instance, mAbs with Fc *N*-glycans lacking α1,6-core-fucosylation exhibit an up to 100-fold higher antibody-dependent cellular cytotoxicity compared with their core-fucosylated variants – a characteristic that is crucial for cancer treatments.

As illustrated, glycans can modulate key functions of the proteins to which they are attached. These include, for instance, correct folding or binding specificity. Due to the omnipresence of this posttranslational modification, protein glycosylation is known or assumed to be involved in numerous physiological and pathophysiological processes in all higher cells. By providing structure-function relationships, the qualitative and quantitative analysis of glycans and their carrier proteins can therefore help to understand the implications of glycans during these processes. In turn, such knowledge can be used to understand and monitor the onset and progression of a disease, or to improve properties of therapeutic glycoproteins, such as immunoglobulin gamma (IgG)-based mAbs.

To comprehensively analyze *N*-glycosylation, mucin-type *O*-glycosylation and similar forms of protein glycosylation, the detailed characterization of the protein along with all glycans attached to the specific glycosylation sites is required. In particular, a glycoproteomic approach of this nature relies on the analysis of glycopeptides as intact subsets of the entire glycoprotein. This not only provides site-specific glycosylation information but also allows the elucidation of the micro- and macroheterogeneity of glycans (structural glycan variations per glycosylation site and variations in site occupancy).

The current state-of-the-art platform for glycoproteomic analyses is mass spectrometry – standalone or combined with liquid chromatography. Glycoproteomic analyses, however, are currently still limited with regard to the structural information that can be obtained from the glycan moieties of a glycoprotein. Despite recent advances such as the advent of fast-scanning ultra-high-resolution mass spectrometers equipped with various fragmentation modes, only compositional glycan information can be provided in most cases. This means that no direct information on the linkages or topology of the monosaccharides of which the glycan is composed can be retrieved. To overcome this limitation, orthogonal glycoanalytical approaches such as multiplexed capillary gel electrophoresis with laser-induced fluorescence detection (xCGE-LIF) and/or the use of selective glycoenzymes (e.g. exoglycosidases) or lectins is required.

Over the last four years, our group has developed a glycoproteomic workflow that enables an in-depth and site-specific analysis of different forms of protein glycosylation. This includes not only *N*- and mucin-type *O*-glycosylation but also *O*-mannosylation and *C*-mannosylation [1]. The workflow combines liquid chromatography with tandem mass spectrometry (LC-MS/MS) and is centered on the high-resolution mass spectrometric analysis of hydrophilic interaction liquid chromatography (HILIC)-enriched and C18-LC-separated tryptic and non-tryptic intact glycopeptides (Figure 2). The method takes advantage of the stepped collisional energy fragmentation capabilities of mass spectrometers and enables the unambiguous identification of both peptide moiety and glycan moiety alike. The developed workflow was verified using a set of selected and representative *N*- and *O*-glycoproteins, including the human IgG [1].

During this workflow development we identified and systematically evaluated the occurrence of unique and glycan-related fragment ion patterns (oxonium ions) that provide additional structural information on the *N*- or *O*-glycan moiety of the glycopeptides. Those patterns allow, for instance, the discrimination of core- and antenna-fucosylation among *N*-glycopeptides (Figure 3). Using these new insights can significantly increase the depth and reliability of glycoproteomic analyses.

Finally, the workflow was complemented by the development of an open-source software suite, named glyXtool^{MS} [2]. This software facilitates the semi-automated analysis of *N*- and *O*-glycopeptide mass spectrometry fragmentation data and thereby takes advantage of the aforementioned fragmentation signatures and pattern. Based on a transparent and flexible framework, glyXtool^{MS} provides a versatile software solution for a wide range of targeted and explorative glycoproteomic MS data. I **Dr.-Ing. Marcus Hoffmann**

References:

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[2] Pioch, M., Hoffmann, M., Pralow, A., Reichl, U., and Rapp, E. glyXtool(MS): *An Open-Source Pipeline for Semiautomated Analysis of Glycopeptide Mass Spectrometry Data.* Anal Chem, 90, 11908-11916, 2018.

Author **Dr.-Ing. Marcus Hoffmann**

Marcus Hoffmann studied Biosystems Engineering at Otto von Guericke University in Magdeburg. He received his diploma in 2010. After completing an internship at Leiden University Medical Center in the Netherlands, he joined the Bioprocess Engineering Group at the Max Planck Institute as a Ph.D. candidate in 2011. While working on his Ph.D. thesis he specialized in mass spectrometry-based *N*- and *O*-glycoproteomics. He finished his Ph.D. in 2020 and now works as a postdoctoral researcher in the BPE group.

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

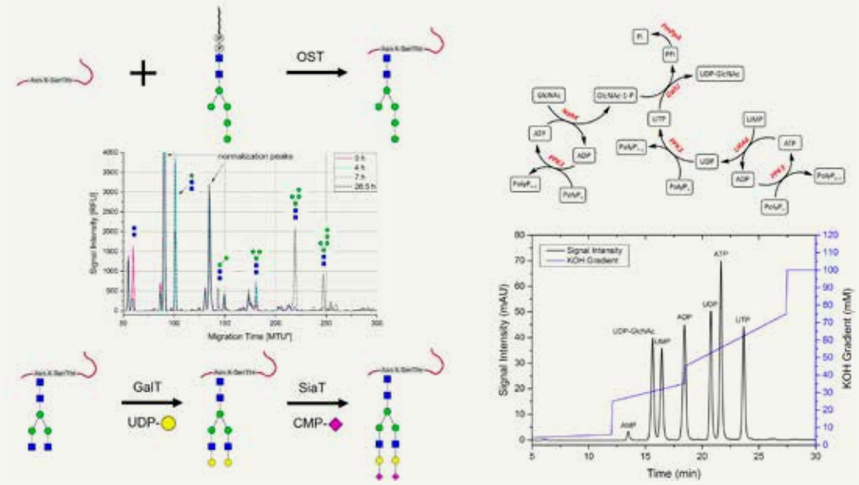

Figure 1:
Biocatalytic platform for the *in-vitro N*-glycosylation by a recombinant oligosacharyltransferase (OST) (upper right), the glycoengineering of proteins (lower right) and the scalable synthesis of nucleotide sugars (left) [1-4].

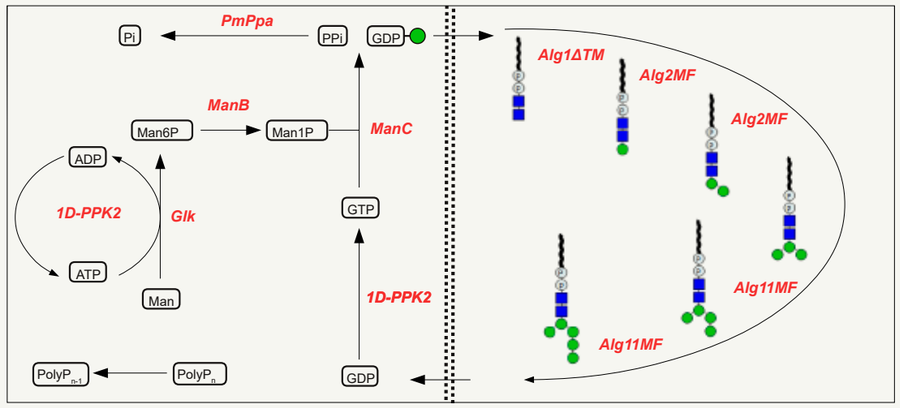

Figure 2:
Synthesis of lipid-linked glycans in compartmentalized multi-enzyme cascades for the *in-vitro N*-glycosylation of peptides [4].

Glycoengineering of the Recombinant SARS-CoV-2 Spike Protein

Worldwide, the COVID-19 pandemic is inflicting severe social and economic disruption. Most notably, due to the resulting recession, vulnerabilities and inadequacies in the global health and food system have been intensified. As of October 2020, 1.16 million people have died from COVID-19. In addition, the WHO estimates that as many as another 132 million people will suffer from malnutrition in 2020 (source: WHO website). It is widely assumed that the pandemic can only be contained, and economic recovery promoted, through the development of an effective vaccine and a broad vaccination campaign.

The COVID-19 outbreak was caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Along with other viruses that have caused pandemics associated with a significant death toll, SARS-CoV-2 is an enveloped virus. The viral envelope protects the genetic material of the virus and consists of glycoproteins along with other host cell-derived components. The glycoproteins on the viral envelope are major antigens and typically the target for vaccine development. Glycoproteins consist of a protein backbone and a number of covalently linked glycans of various sizes [2]. The major antigen of SARS-CoV-2, the viral envelope protein "spike" (S), is heavily glycosylated – at least more than two-fold higher than hemagglutinin, the major antigen of influenza vaccines. Viral vaccine manufacturing largely relies on growing viruses in eggs or in animal cell cultures. The latter is especially well suited to large-scale production in closed systems under highly defined cultivation conditions. Interestingly, the glycoform of viral envelope proteins can differ vastly among the various cell lines used. The effect of protein glycosylation, namely how the various glycostructures of the major antigens affect immune responses and, thus, the efficacy and safety of vaccines, is severely under-investigated. However, it is assumed that glycoengineering approaches can be exploited to enhance the immune response and, thus, increase vaccine efficacy.

Over the last few years, the Synthetic Glycobiotechnology team headed by Thomas Rexer has developed a comprehensive platform to glycosylate and glycoengineer peptides and proteins for therapeutic use and vaccination. The platform consists of a range of recombinant enzymes, expressed in *E. coli, S.cerevisiae* or insect cells that are combined in one-pot reactions to form multiple cascades. Through the enzymatic assembly of novel lipid-linked precursors by a linear cascade of glycosyltransferases, glycans can be transferred *in-vitro* on N-glycosylation consensus sequences of peptides in one-pot reactions [3, 4]. The cascade can also be coupled to an *in-situ* GDP-mannose synthesis and regeneration cascade in a compartmentalized one-pot setup (see Figure 2). This avoids the addition of very expensive GDP-mannose precursors (Figure 2). Accordingly, the cascade can be regarded as a synthetic copy of the glycosylation machinery of the Endoplasmic Reticulum of eukaryotic cells. The cascades for tailoring, i.e. glycoengineering, the glycoform on glycoproteins consist of a range of partly transmembrane-deleted recombinant glycosyltransferases. Recently, our team has successfully used these cascades to engineer and homogenize the glycoform of monoclonal antibodies and the SARS-CoV-2 viral membrane protein. In all cascades, nucleotide sugars serve as the building blocks for glycans. Their price significantly exceeds 1000 Euro per gram and, consequently, prevents the large-scale application of our platform. For this reason, scalable biocatalytic cascades for the synthesis of the most abundant nucleotide sugars have been developed [1]. The nucleotide sugars can be synthesized from inexpensive precursor materials and, typically, yields above 20 g/L are achieved. A common feature of the cascades is the effective regeneration of the co-factor ATP from low cost polyphosphate.

One of the most promising vaccine candidates against SARS-CoV-2 is recombinant S protein produced in insect cells, and at least one candidate is currently being investigated in clinical trials. In a joint project with Professor Dunja Bruder (Institute of Medical Microbiology, Infection Control and Prevention at Otto von Guericke University Magdeburg) initiated in 2020, our platform is being used to tailor insect-cell derived S protein glycosylation. Therefore, various glycan types are being generated and their effect on the immune response will be investigated in a mouse model. The MPI acknowledges funding from the DFG for this project.

In summary, we have developed a platform for the *in-vitro N*-glycosylation and glycoengineering of proteins. The latter is used to tailor predefined glycostructures on monoclonal antibodies and viral glycoproteins. In the future, the technology could help to generate more efficacious therapeutics and viral vaccines and, therefore, contribute to the health and well-being of millions of people.

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Author **Dr. Thomas Rexer**

Thomas Rexer studied Process Engineering (BSc) at the University of Stuttgart and Chemical Engineering (MSc) at the University of Manchester. He obtained a Ph.D. degree from Newcastle University. Since 2014, his and his co-workers' research at the MPI Magdeburg has focused on the development of multi-enzyme cascades for the synthesis of glycans and the glycoengineering of proteins.

rexer@mpi-magdeburg.mpg.de

www.mpi-magdeburg.mpg.de/bpe

CSC | COMPUTATIONAL METHODS IN SYSTEMS AND CONTROL THEORY

+ Mathematician Carolin Penke is discussing her approach and results. The exchange of ideas and methods is essential in everyday scientific work. She introduces her project on the following pages.

PROF. DR. PETER BENNER I DIRECTOR

+ The CSC group is concerned with modeling, simulation, optimization, control, and uncertainty quantification of time-dependent problems from the sciences and engineering. CSC researchers employ mathematical ideas and concepts to develop new methods for *in silico* design or experiments for complex technical systems such as those 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 areas of application range from chemical and biotechnological processes and electro-magnetic devices to energy networks and materials discovery. Our workflow 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 Linux cluster, *mechthild*[1], with 2000+ cores, and several GPU-powered workstations.

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 an assistant professor 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 **Numerical Linear and Multilinear Algebra** techniques 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. Recently, several efforts towards developing improved machine learning algorithms have started. Efficiently implementing the algorithms developed 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. In 2021, the team structure will change, placing more emphasis on novel research directions in Scientific Machine Learning. Furthermore, our activities in Research Data Management following the FAIR principles, will become increasingly visible.

Research Trends and Highlights in 2019/20

A particularly important field of application is the simulation and control of energy networks. In the BMWi[2]-funded "MathEnergy" project (2016-2021), we are accelerating the scenario analysis of the (coupled) German gas and power networks as part of the German energy transition program in order to enable real-time operation. To this end, the open-source software library, morgen, has been developed to allow the fast transient simulation of gas transportation networks.

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. This research track is incorporating more and more data-driven methods, including machine learning techniques, thus making use of the plethora of available measurement data. The development of numerical algorithms leveraging low-rank tensor techniques has steadily lowered the barrier to tackling high-dimensional scientific and engineering problems. Recently, we have applied these techniques to the control and optimization of incompressible flow problems. In cooperation with the MPI for Mathematics in the Sciences in Leipzig, the Lawrence Berkeley Labs, the University of Bath and our former group leader Martin Stoll – now full professor for Scientific Computing at TU Chemnitz - we have also developed new approaches to solving problems from computational chemistry, (bio-)physics, and machine learning (nonlinear classification) problems based on low-rank tensor approximations.

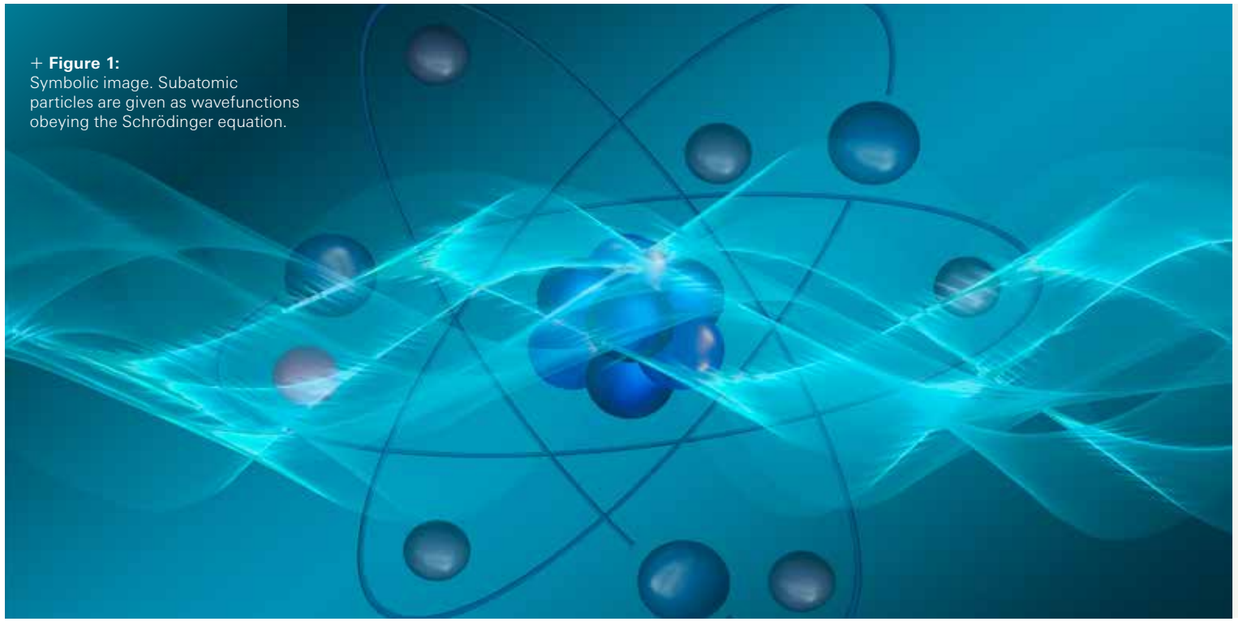
Of course, the Sars CoV-2 pandemic has also posed challenges for our group. Given our expertise in simulating and controlling dynamical processes, we initiated several COVID-19-related projects. These include the development of optimal testing strategies for medical care facilities together with University Hospital Magdeburg and the Children's and Youth Psychiatric Clinic Magdeburg as well as the development of age-aware compartment models for establishing optimal control strategies for contact reduction and vaccination schedules. On the other hand, several CSC members were invited to participate in the Spring 2020 semester program "Model and Dimension Reduction in Uncertain and Dynamic Systems," to be held January 27 – May 1, 2020, at the Institute for Computational and Experimental Research in Mathematics (ICERM) at Brown University in Providence, RI (USA). This semester program came to an unexpected early end in March 2020, due to the COVID-19-outbreak. Though several activities continued in virtual environments, many opportunities of informal interaction in the inspiring research environment provided by the ICERM certainly were missed!

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

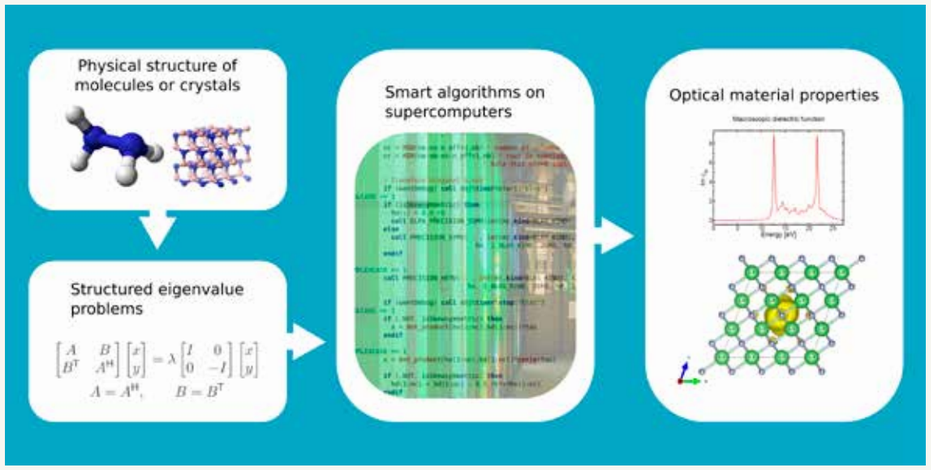
[2] Bundesministerium für Wirtschaft und Energie (German Ministry for Economics and Energy)

Prof. Dr. Peter Benner
Director

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



+ **Figure 1:**
Symbolic image. Subatomic particles are given as wavefunctions obeying the Schrödinger equation.



+ **Figure 2:**
Schematic view of the research process leading to insights about novel materials without the need for experiments. Results were generated by collaborators using the exciting software package.

Exciting Eigenvalue Problems

+ Max Planck started the era of quantum physics in 1900 when he presented his results on black-body radiation. 120 years later, quantum physics is not only an accurate description of nature, but also provides a powerful toolbox employed by material scientists and chemists.

In the subatomic world, the laws of classical mechanics fail to accurately describe the dynamics of involved particles, such as electrons. Quantum mechanics manage to do exactly that and is incredibly powerful and precise in its predictions. The state of a particle is described in the form of a wavefunction, not by its position and velocity in space. This state is a solution of the well-known Schrödinger equation.

Solving the Schrödinger equation in a straight-forward fashion is infeasible in most situations of practical interest. Approximative schemes such as the Hartree Fock (HF) approach and Density Functional Theory (DFT) are very successful in computing the ground state of physical systems. The Molecular Simulation and Design (MSD) group at MPI Magdeburg employs these approaches in their simulations. The techniques boil down complex physical questions to the simple mathematical form of symmetric eigenvalue problems. Computers may take an extremely long time to solve them when larger, more interesting, systems are considered. This is why supercomputers, such as the *mechthild* computing cluster at the MPI Magdeburg are used for this task.

A current research frontier becomes relevant as scientists and engineers are not only interested in the ground state of physical systems, but also in their excited states. We explore this frontier in collaboration with the solid-state theory group of the physics department at Humboldt University in Berlin, led by Prof. Claudia Draxl (see http://exciting-code.org/). Excited electrons play a key role in any optical phenomenon, such as light absorption and emission. Part of the motivation comes from the increasing importance of renewable energy, calling for more efficient photovoltaic technologies. The goal is to predict optical properties of novel composite materials and nanostructures *in silico*, without the need for empirical experiments.

New methods based on many-body perturbation theory (in particular the Bethe-Salpeter approach) or time-dependent DFT again manage to approximately describe complex physical realities in the form of mathematical eigenvalue problems. The resulting matrix structures, however, are more complex than the symmetry resulting from ground-state approaches (HF and DFT).

Structured Eigenvalue Problems

Our research focuses on developing and implementing algorithms that preserve and exploit the structures that arise, with the goal of computing eigenvalues and eigenvectors. This way, the physical reality encoded in the structure is respected and algorithms become more efficient and show better numerical stability. Similar structures arise in control theory and model order reduction, for example in the solution of algebraic Riccati equations. This is one core area of expertise of the CSC group, in particular the Numerical Linear and Multilinear Algebra (NLMA) team. This knowledge is now being applied and extended in the presented research direction. On the basis of new mathematical results, we have been able to improve state-of-the art algorithms with respect to computational effort and achieved accuracy [2]. Two interesting quantities that can be derived from the computed eigenvalues are the density of states and the optical absorption spectrum. Arising low-rank structures are exploited and tensor approximations used to accurately represent the density of states with lower computational costs and memory demands [1]. Ongoing work focuses on the development of new tools in the field of numerical linear algebra, that are tailored towards the mathematical structures that arise. This includes GR decompositions, Cholesky-like factorizations [3], generalized polar decompositions and spectral divide-and-conquer schemes.

High Performance Algorithms

In view of the ongoing massive increase in parallel computing power, the solutions to formerly unsolvable problems are now within reach. In order to unlock the full potential of a supercomputer, algorithms must be designed in a way, that takes into account the hardware they are supposed to run on. In the past, the computational effort was the key factor determining the performance achieved by an algorithm. Nowadays it is much more important for algorithms to be parallelizable and avoid communication. This refers to the amount of data transferred across the memory hierarchy as well as between compute nodes or processors. Often, communication bandwidth is the bottleneck and the full computing power is not exploited when a processing unit has to wait for data. Therefore, in modern algorithm development it can make sense to avoid communication even at the expense of more operations. The Scientific Computing (SC) team has abundant experience in navigating this trade-off. Our technical know-how concerning hard- and software technologies allows us to implement and optimize algorithms not only as theoretical prototypes but in the form of production-level code. Together with the Max Planck Computing and Data Facility (MPCDF), we extended the ELPA library [4], which contains widely used high-performance eigensolvers. These are now used to tackle some of the structured eigenvalue problems arising in the description of electronic excitation processes. I **Carolin Penke**

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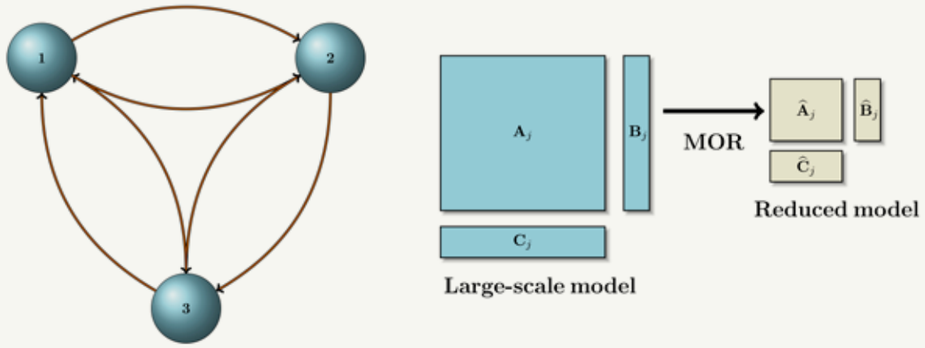
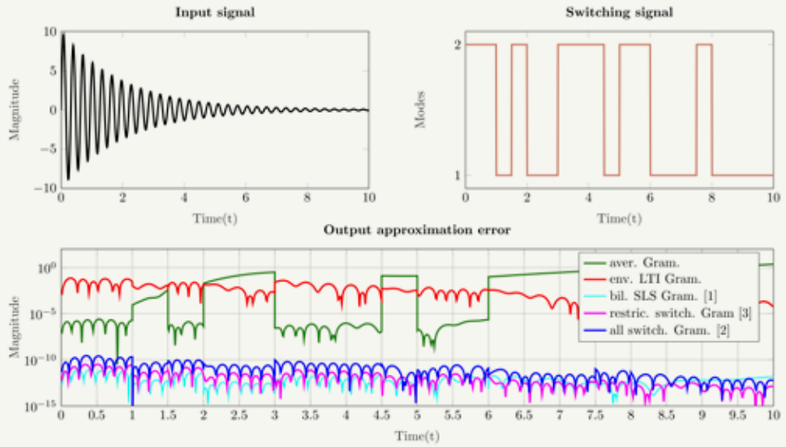
Author **Carolin Penke**

Since 2017, Carolin Penke is a Ph.D. student in the CSC group at the Max Planck Institute for Dynamics of Complex Technical Systems in Magdeburg. She develops new algorithms and tools for solving structured eigenvalue problems arising in quantum mechanical theories for describing electronic excitations. Her focus is on parallel high-performance implementations. In 2014, she started working in the group as a student assistant, while studying first for a Bachelor's and then for a Master's degree in applied mathematics at the Otto von Guericke University Magdeburg.

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



+ Figure 1:
Left: Scheme of a switched system having three operating modes.
Right: Illustration of an MOR method.



+ Figure 2:
Upper row: Input time signal exciting the switched systems (left), and switching signal determining the operating mode (right).
Lower row: Error between the original and reduced model simulations compared for different methods.

Switched Systems and Model Order Reduction

Introduction

+ Dynamical systems are the basic framework used for modeling, controlling and analyzing a large variety of engineering processes. In this context, the term "switched system" is used for processes whose time-evolution depends not only on continuous state variables (e.g., position coordinates, pressure, temperature…), but also on switching variables indicating the operating mode of the system. For a typical example of a switched system, one could consider the temperature control system consisting of a thermostat and a heater. For this example, the continuous variable is represented by the room temperature, while the switching variable is the heater's operating mode that can be alternated between on and off. Another typical example is the car gear system, where the operating velocity modes are switched using the gear stick.

A great variety of dynamical processes are likely to feature switching behavior: computers, electrical networks, airplanes and washing machines are some examples. Hence, in the design of a new product, one should take into consideration the switching behavior. Due to the increasing use of dedicated computer-based modeling design software, numerical simulation is now used more and more frequently to understand the dynamics of a complex system and shorten both development time and cost. However, the need for enhanced model accuracy inevitably leads to an increasing number of variables and resources that need to be managed and that entail a high numerical cost.

In this context, model order reduction (MOR) is a possible remedy for such complex simulations. Indeed, MOR aims at replacing the complex high-dimensional model with a reduced-order model that mimics the original behavior and preserves its main features. As a result, this alleviates the numerical burden and reduces the computational time.

Model Order Reduction for Switched Systems

One important tool in MOR is the framework of projection-based methods. In this setup, the dominant subspaces containing the main information about the dynamics are identified. Hence, the equations of the high-dimensional system are then projected onto the low-dimensional manifold, leading to reduced-order models. As a consequence, the reduced-order model that is obtained should feature similar behavior to the original system. MOR for dynamical systems has been formally developed since the 1960s. Since then, well-established methodologies have been proposed, such as the proper orthogonal decomposition, balanced truncation, interpolation based-methods. However, most of the literature on MOR is dedicated to systems having no switching behavior. One naive approach to reducing switched systems is to apply model reduction for each switched sys-tem's operating mode and then couple the resulting reduced systems together. However, this approach might not produce a satisfactory reduced-order model in many applications because it does not consider the subspaces activated by the switching. In the Simulation of Energy Systems team, in collaboration with the DRI group, we are working on developing suitable MOR techniques for switched systems. With this aim, we have focused on the class of switched linear systems, i.e., switched systems, where each operating mode is represented by a linear dynamical model. Our main philosophy is that all of the MOR approaches that are developed should be able to identify the right subspaces that encode the dynamics of such systems. Hence, they should include the dominant subspaces for each mode but also the activated subspaces by switching between the modes. One of our major mathematical contributions has been to show that those subspaces for switched linear systems are encoded by the solution of coupled Lyapunov matrix equations. Similar matrix equations also play a crucial role in MOR for stochastic and bilinear systems. Additionally, those equations can be solved efficiently in the high-dimensional context using low-rank methods. As a result, combining the low-rank solution of those matrix equations with projection-based methods leads to very accurate reduced-order switched models. We have developed MOR methods for switched linear systems based on those principles, allowing all types of switching between the modes [1, 2]. More recently, we have extended these methodologies for switched systems obeying restrictions on the switching behavior [3].

Numerical Example

To illustrate those results, a test large-scale switched linear system was reduced using the different proposed methodologies. Figure 2 depicts the output approximation errors for a given input signal and switching pattern. By inspecting this figure, we observe that our proposed methodologies [1–3] provide very accurate reduced models compared to other methods suggested in the literature. This is due to the fact that the proposed MOR methodologies are able to encode the right dominant subspaces for switched systems.

Outlook and Future Research

In this project, we have dedicated effort to new MOR methods for high-dimensional switched systems. The methodologies were successfully applied to benchmarks. Future research will be dedicated to incorporating nonlinear dynamics into the approaches. I **Dr. Igor Pontes Duff**

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Author **Dr. Igor Pontes Duff**

Dr. Igor Pontes Duff graduated from Ecole Polytechnique, Palaiseau, France, with a double degree in engineering from ISAE-SUPAERO in 2013. From 2014, he worked on his Ph.D. at Onera, the French aerospace lab, in Toulouse. He received his Ph.D. degree in January 2017 from the University of Toulouse and ISAE-SUPAERO. Since January 2017, he has held a postdoctoral position at the Max Planck Institute for Dynamics of Complex Technical Systems in Magdeburg, Germany. His research focuses on model order reduction, system theory, structured and switched systems, and system identification.

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

PCF | PHYSICAL AND CHEMICAL FOUNDATIONS OF PROCESS ENGINEERING

+ Chemist Francesca Cascella at the optical microscope in a lab in the Max Planck Institute. She is determining the morphology and size of crystals by directly observing the target molecule in the solid state. Her project is described on the following pages.

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

+ Profound changes in our energy and feedstock bases are required to address the many and enormous global problems that we are currently facing. There is a need to develop new transformation concepts exploiting dedicated chemical reactions combined with efficient separation processes to provide a multitude of target compounds with a high level of purity.

The Physical and Chemical Foundations of Process Engineering group (PCF) seeks to make a contribution to isolating certain components or fractions from renewable resources that can act as feedstocks for subsequent reactions. An example is the provision of lignin from the black liquors that originate from processing wood. A patented precipitation process is currently being studied with several other partners in the European UNRAVEL project (UNique Refinery Approach to Valorise European Lignocellulosics). Interesting building blocks that are attractive candidates for synthesizing aromatic bulk chemicals can be produced by depolymerizing the larger lignin molecules. In other projects the PCF group is investigating the extraction of valuable natural products from plants. Example target molecules are currently artemisinin (present in the plant *Artemisia annua* and of large relevance as a potent anti-malaria drug, see 38-39) and certain components of saffron (present in *Crocus sativus*). In our research we are currently striving to improve extraction methods by developing efficient continuously-operating countercurrent processes.

In order to support efficient usage of valuable feedstocks in chemical reactions, we are concentrating our efforts on developing new catalytic processes. This includes studying new solid catalysts, for example for the transformation of ethylene to propylene, or the application of innovative solvents and catalysts in homogeneous liquid phase reactions, such as for the hydroformylation of long chain olefins into aldehydes performed in thermomorphic solvents. The latter research is embedded in the larger DFG-funded SFB initiative, InPROMPT, in which colleagues at TU Berlin and TU Dortmund and several other MPI and OVGU groups are involved (see pages 20-21). An area of focus of the work of our PCF group that is currently growing is theoretically and experimentally investigating the potential of the periodic operation of reaction and separation processes. The corresponding reactors and separation units are exposed to forced modulations of certain operating parameters, such as non-constant inlet concentrations and flow rates. Since 2019 the DFG has supported a collaboration with the groups led by Achim Kienle and Menka Petkovska (University of Belgrade) to study responses to forced fluctuations of the inlet composition of a catalytic reactor designed to produce methanol at elevated pressure from CO_2, CO and hydrogen. The goal of the project is to provide and validate theoretical concepts for predicting mean values of relevant performance parameters and for exploiting dynamic operation in an optimal manner. Unfortunately, the coronavirus crisis has caused delays in finalizing our novel experimental set-up and experimental results are not yet available.

In the field of isolating specific target molecules out of complex mixtures, during the period of this report the PCF group has contributed by developing and applying dedicated crystallization-based and chromatographic processes. In this connection, the progress made with 15 other partners in the European CORE (COntinuous REesolution of Chiral Components) project related to the separation of enantiomers (see pages 36-37) and the demonstration of novel optimization and control concepts to more efficiently apply multi-column simulated moving bed chromatography (with the group led by Achim Kienle) are of note.

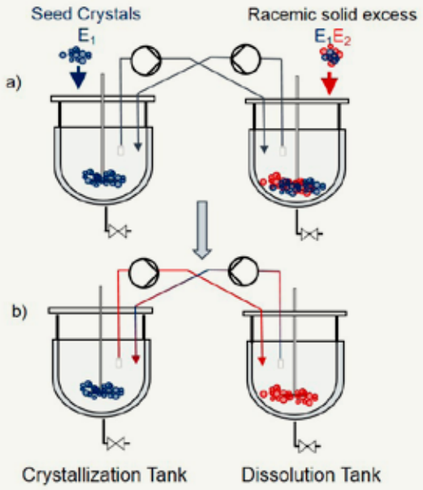
The PCF group was able to present its research results very successfully in 2019 and early 2020 at numerous international conferences. During the period of this report, the group members published a significant number of research papers. We were also able to finalize several larger projects, such as the publication of the third edition of "Preparative Chromatography", an Annual Review of Chemical and Biomolecular Engineering entitled "Separation Processes to Provide Pure Enantiomers and Plant Ingredients", and a chapter of a book entitled "Continuous Enantioselective Crystallization of Chiral Compounds".

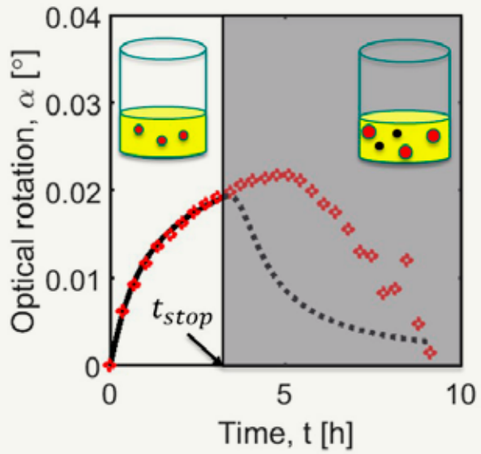
We consider ourselves to be extremely lucky to have been able, at the end of February 2020 and in conjunction with 25 participants from India, to hold our 4th Indo-German-Workshop, "Advances in Materials, Reaction & Separation Processes". This traditional and always fruitful event took place just a few days before the coronavirus crisis hit. Unfortunately, the recent DECHEMA Colloquium on "Forced periodic operation" was only possible using modern video techniques. Nevertheless, it was a great success, also thanks to the support of our IT group.

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

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

+ Figure 1 :
Schematic representation of the Coupled PC with Dissolution (CPCD) process. Initially, a supersaturated solution is created in the crystallization tank and the solid racemate is suspended in the dissolution tank (a). The preferential crystallization of the preferred enantiomer in the crystallization tank and the simultaneous activation of the exchange of the mother liquor triggers selective dissolution in the dissolution tank. (b)





+ Figure 2:
Comparison between short cut model (SCM) predictions and experiments. Red circles: Experimental profiles for an initial supersaturation of 1.24. Solid black curve: SCM results until t_{stop}, indicated with an arrow. Dotted lines: Extrapolation of SCM beyond stop time shown for illustration. Non-shaded area: Effective crystallization of preferred enantiomer (desirable region). Gray shaded area: Nucleation of counter enantiomer (undesirable irrelevant region).

Crystallization Processes to Separate Enantiomers: Design and Operation

At molecular level, the presence of an asymmetric center connected to four different groups or atoms generates two non-superimposable mirror-images, called enantiomers. As enantiomers exhibit different physiological effects and given that the majority of the pharmaceutical molecules are chiral, the ability to isolate a single enantiomer is of particular concern for the pharmaceutical, food and agrochemical industries. Of the methods used for the provision of pure enantiomers, preferential crystallization (PC) is a direct and cost-efficient technique. It is based on seeding a slightly supersaturated racemic solution with enantiopure crystals of the preferred enantiomer. With regard to industrial applications, the aim is to develop processes that provide high productivity, purity and yield. A reliable process model based on accurate experimentally determined thermodynamic and kinetic parameters can be used to find the optimum experimental conditions.

Although relatively straightforward, the PC process is known to be unstable due to the difficulty of avoiding the nucleation of the counter enantiomer and the contamination of the product. A coupled configuration, using two connected stirred tanks operated batch-wise makes it possible to keep the mother liquor close to racemic composition, which allows the avoidance of the nucleation of the unwanted enantiomer for a longer time. In a recent application, PC was successfully combined with selective dissolution (CPCD) using two coupled stirred tanks. While in one tank PC takes place, the mother liquor is pumped in the second tank where the selective dissolution of one enantiomer from a racemic suspension is triggered exploiting a higher temperature. At the end of the process, two solid phases with opposite chirality can be recovered. (Figure 1).

The active pharmaceutical ingredient (API) guaifenesin was investigated in an experimental case study. The results achieved highlighted that the selection of solvent for crystallization processes is crucial for the outcome of the enantioseparation. Batch operation in a single tank led to high productivity and purity above 95%.[1] For the same system, a successful resolution was also achieved using the CPCD process, which provided both pure enantiomers.[2] In an ongoing project, attention is being given to the continuous resolution of the two enantiomers of API guaifenesin applying a fluidized bed crystallizer (FBC). However, the low growth rate of the guaifenesin crystals limits the applicability of such an advanced configuration for resolution purposes. This is an example of why sometimes simple batch processes should be still preferred.

Quantitatively evaluating the essential kinetic mechanisms such as nucleation and growth, Population Balance Models (PBMs) are a powerful tool for describing the preferential crystallization process theoretically [3]. Due to its detailed form, the underlying equations often require efficient tools to solve them. Even with the significant efforts on model reduction techniques, it still requires many experiments to estimate process parameters. Therefore, there is a need to develop simpler models that provide estimates for the key performance indicators (KPIs) such as productivity, purity and yield more quickly. A shortcut model (SCM) has been developed for isothermal batch PC which is based on the principle of "total mass transfer" between the two phases assuming equal particle radii and quantifying only one lumped kinetic mechanism for crystal growth and nucleation [4]. For the components of interest, the SCM requires preliminary knowledge of solubilities and metastable zone widths.

For the chiral model compound DL-Asparagine monohydrate, the isothermal batch PC simulation was carried out using the shortcut model. Figure 2 illustrates a good level of agreement between the experiments (red circles) and SCM simulation (solid black curve) in the region of interest (non-shaded area). This confirms that the model is capable of quantifying PC process for enantiomers that crystallize as conglomerates. Recently, we have successfully extended the shortcut model for the simulation of continuous PC and PC coupled racemization. For the future, we plan to exploit the applications of the simple basic model for various other crystallizations processes.

It should be mentioned that this work is part of joint efforts with the academic and industrial partners of an EU-funded Marie Curie International Training Network (CORE, 722456). The overall project aims to deliver rules and methods for enantioseparation via crystallization processes in order to resolve a wide range of chiral molecules such as APIs and drug precursors. I **Francesca Cascella, Shashank Bhandari**

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Author **Francesca Cascella**

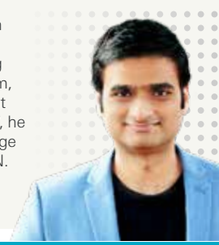
Francesca Cascella joined the research group at the MPI in May 2017 as Early Stage Researcher within the Marie Curie Project CORE-ITN. She holds a Master's degree in Chemistry from the University of Bari (Italy). Her main research activity consists in experimentally determining fundamental properties of pharmaceutically relevant molecules as well as the operation of enantioseparation processes via preferential crystallization.

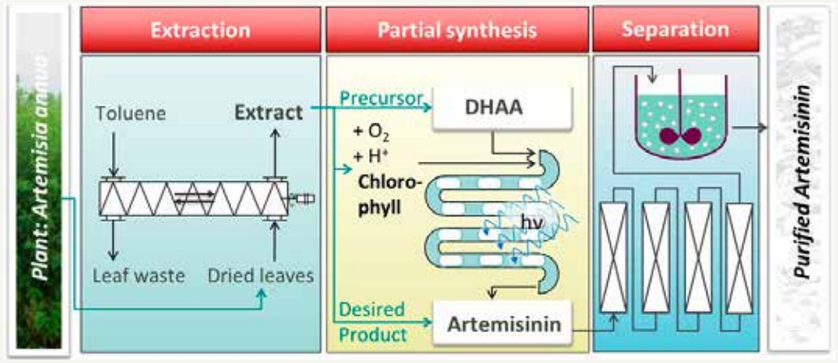
cascella@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de/pcf

Author **Shashank Bhandari**

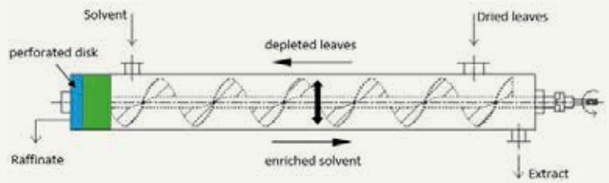
Shashank Bhandari received his Bachelor's degree in Chemical Engineering at the University of Mumbai, India in 2012. After working as a process engineer in a petrochemical company for a couple of years, he started his Master's degree in Chemical Engineering from KTH Royal Institute of Technology in Stockholm, Sweden in 2014. He concluded his Master's thesis at AstraZeneca in Sodertalje, Sweden, in 2016. In 2017, he joined the research group at the MPI as an Early Stage Researcher within the Marie Curie Project CORE-ITN.

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





+ Figure 1:
Illustration of the process for continuous artemisinin production using the plant *Artemisia annua*.



+ Figure 2a:
Principle of the continuous countercurrent extraction process using a rotating screw.

+ Figure 2b:
Continuous extraction process pilot plant

Towards Continuous and Efficient Production of Artemisinin

+ Combating malaria is a major aim of the United Nations' Millennium Development Goals. In 2018, approximately 228 million people were infected causing around 405,000 deaths. Artemisinin-based combination therapies (ACTs) are the most effective medications against malaria currently available on the market. However, due to the high price of the base compound, artemisinin, the availability of these medications is limited, especially in developing countries. Reducing the cost of artemisinin-based treatments and thus increasing the availability of medication, would be important steps combating malaria.

Artemisinin is mainly produced by extraction from *Artemisia annua L.* with a maximum content of 1.4 % based on dried weight. Our approach to making ACTs less cost-intensive is to increase the amount of artemisinin obtained from the plant by following three main research directions: 1) Maximizing productivity by developing a continuous counter-current extraction process; 2) Utilizing the co-extracted byproduct, dihydroartemisinic acid (DHAA), as an additional source of artemisinin and 3) Applying advanced technologies together with optimized conditions to the initial extraction and final purification steps to increase the efficiency of the overall process (Figure 1).

For decades, the state of the art in plant extraction has been batch processing. Less systematic activities, however, have been devoted to studying continuous extraction processes. To develop an efficient artemisinin extraction process, the influence of important parameters such as solubility, kinetics, distribution coefficients and residence time were quantified in batch experiments. Based on that understanding, a continuous process exploiting a screw extractor was designed and implemented (Figure 2). This extractor consists of a perforated disk at one end where the continuously transported plant material is compressed forcing the solvent in the opposite direction. As a result, the already enriched solvent is contacted at the other end with fully loaded *A. annua* leaves and exits the extractor in concentrated solution (Figure 2). This counter-current process results in reduced solvent waste and allows for the residence times of the leaves and solvent to be precisely controlled. Experimental studies of the continuous extraction process demonstrated a high recovery (95%) and five-fold increase in productivity (3.2 g/L/h) compared to the conventional batch operation.

In addition to artemisinin, the extract obtained contains a variety of other metabolites, e.g. dihydroartemisinic acid (DHAA), which is an important precursor of the active substance. This biological precursor can be converted into additional artemisinin via photooxidation followed by an acid-catalyzed reaction sequence [2]. Partial synthesis is performed continuously in a mini-channel tubular reactor, where the plant extract is contacted with oxygen and illuminated by high-intensity LED lamps. To initiate the photooxidation, a photoactive compound is required which transfers absorbed light energy to oxygen forming singlet oxygen. Chlorophyll, another available co-extracted byproduct of the extraction process, can be utilized to catalyze the formation of singlet oxygen making the addition of other, often toxic photosensitizers unnecessary [2]. We were able to successfully demonstrate that artemisinin can be synthesized out of crude extract of *A. annua* – which contains *both* the reactant and the photosensitizer – by treating it just with oxygen, visible light and acid. This enables 67 % of the byproduct dihydroartemisinic acid to be utilized.

The reactor effluent obtained from the synthesis step constitutes a complex mixture containing a wide range of metabolites extracted from the plant and the by-products formed in the partial synthesis. In an initial study, a process of continuous chromatography coupled with a crystallization step was developed to purify artemisinin from the reaction solution [3]. Recently, we were also able to show that pure artemisinin (>99%) can be obtained more easily from the reactor effluent after combined extraction and synthesis just by introducing a single cooling crystallization step [4].

I Truong Giang Vu, Susann Triemer

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Author **Truong Giang Vu**

Truong Giang Vu studied Chemical Engineering at Hanoi University of Science and Technology. He received his Master's degree in Chemical and Process Engineering from Otto von Guericke University Magdeburg in 2007. He is a lecturer in the School of Chemical Engineering at Hanoi University of Science and Technology since 2010. In 2014, he joined the group led by Professor Seidel-Morgenstern as a Ph.D. candidate. His research focuses on the continuous extraction of natural products.

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

Author **Susann Triemer**

Susann Triemer received her Bachelor's degree in Molecular and Structural Product Design from Otto von Guericke University Magdeburg in 2014. She then studied Process Engineering and graduated in 2016 with a Master's degree. In the same year, she joined the research group led by Professor Seidel-Morgenstern at the Max Planck Institute to pursue her Ph.D. on the coupling of extraction and partial synthesis for the continuous production of artemisinin.

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

PSE | PROCESS SYSTEMS ENGINEERING

+ Chemical technologist Michael Jokiel is supervising the reactors of a pilot plant in the pilot scale lab hall at the Max Planck Institute. He describes the interdisciplinary project on the integrated process design for fine chemicals from renewable feedstocks on pages 20-21.

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, **Process Systems Engineering** breakthroughs will be needed 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.

With this aim, new scientifically-based systems engineering approaches need to be developed that are able to deal with the inherent multi-level structure of production processes. It might be possible to design highly efficient process systems if systems 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 in discriminating between rival models and identifying 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.

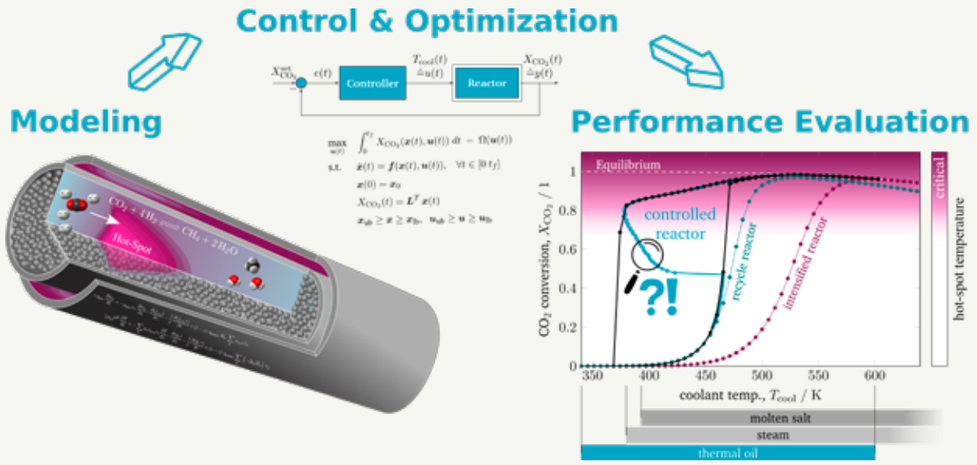
In the field of **Chemical Production Systems**, our current research focus is mainly on multiphase reactions performed in different innovative solvent systems, in particular ionic liquids, thermomorphic multicomponent mixtures, micellar solvents and deep eutectic solvents. This research is being carried out partly in cooperation with TU Berlin, TU Dortmund and Otto von Guericke University in Magdeburg under 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 are developing 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. To this end, we have started to investigate novel reactor-catalyst concepts both via mathematical modeling and targeted experiments at lab scale as well as at miniplant scale, partly supported by the new DFG-funded priority program SPP 2080 in collaboration with Karlsruhe Institute of Technology and the University of Leipzig.

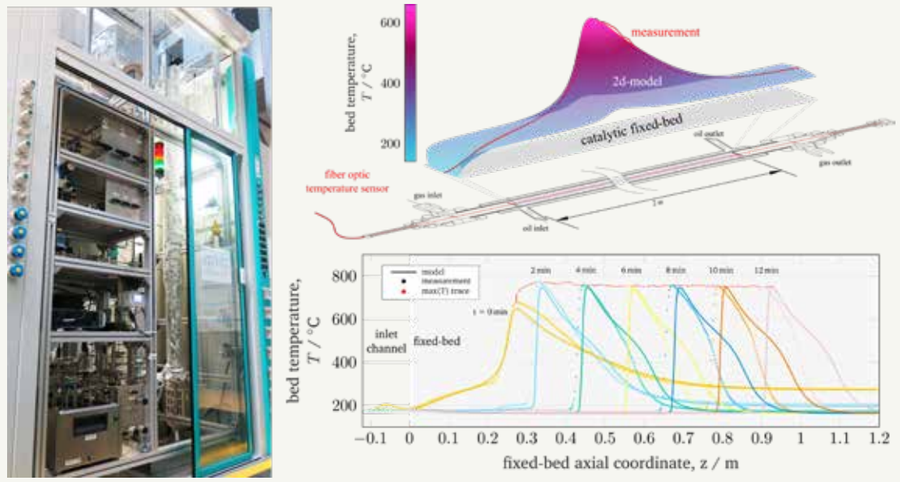
In the field of **Biological Production Systems**, since 2014 we have been coordinating the Max Planck Research Network in Synthetic Biology (MaxSynBio) supported by the Max Planck Society and the German Federal Ministry of Education and Research (BMBF, Biotechnology 2020+ program). The long-term goal of this consortium is the modular bottom-up assembly of artificial cells from functional biomolecular modules. Recently, several joint articles with other Max Planck Institutes (Potsdam, Martinsried, etc.) have been published in high impact factor journals. The construction of a fully functional artificial respiratory chain in synthetic polymer compartments is one of the great success stories that we have achieved in collaboration with the EEC group.

Prof. Dr.-Ing. Kai Sundmacher
Director

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



+ Figure 1:
Illustration of the cooled tubular reactor model (left), applied control and optimization techniques (center), and performance evaluation of recycle and intensified reactors in comparison to our novel controlled reactor concept.



+ Figure 2:
Reactor section of the methanation pilot-plant (left), comparison between model and experiment (top right), and reactor temperature excursion and subsequent creeping reaction front resulting from a cool-down perturbation (bottom right).

Advanced Operating Strategies for CO_2 Methanation Reactors

+ In December 2019, the European Council endorsed the objective of making the EU climate-neutral by 2050. To achieve the required reduction in CO_2 emissions, a massive expansion of renewable power generation, which ultimately will boost the demand for novel Power-to-X processes, is essential. Fuel syntheses from green hydrogen and carbon dioxide (CH_4, CH_3OH, Jet Fuel) are seen as an essential technological link transforming renewable energy into valuable, easy-to-distribute chemical energy carriers.

Catalytic fixed-bed reactors are the favored technical solution for performing cost-effective fuel synthesis on a large production scale. However, changing market environments and volatile process inputs (e.g., if renewable energies are involved) currently demand reactor and catalyst designs that perform well, not only at a fixed nominal load point but under varying partial loads. Furthermore, it is often unclear how load changes are to be performed, how much time the load change requires, and whether there is a risk of any material damage during the dynamic transition. Our research activities focus particularly on these aspects by making use of powerful computational tools to model, control, and optimize fixed-bed reactors [2,3,4,5]. From our theoretical observations, we have already been able to derive several, often non-intuitive, technical solutions, which are currently examined experimentally.

The digital backbone of this research project belongs to a detailed dynamic fixed-bed reactor model as illustrated in Figure 1 (left). This model considers an industrial-scale tubular reactor geometry surrounded by a cooling channel. The model involves detailed heat and mass transport correlations, as well as a quasi-stationary catalyst particle model [3]. All model components are represented by a large set of governing equations, which are solved numerically to simulate a multitude of realistic dynamic scenarios (e.g., load change, start-up, shut-down). In addition to simulations, rigorous control and optimization studies (Figure 1 top) enable us to identify promising operating policies and, moreover, novel reactor design concepts. In process systems engineering, such in-silico analyses are essential for building up profound knowledge and hypotheses that justify expensive technical realizations.

From our simulation studies, various state-of-the-art reactor concepts (e.g., intensified reactors, recycle reactors) are analyzed with respect to their expected operating range, including the occurrence of state-space multiplicity [1]. Stabilizing control has been found to be a very promising yet unexploited heat management approach, which allows for moderating the reactive zone (hot-spot) via adaptive coolant temperature variations [3]. This way, unconventional operating points in regions of steady-state multiplicity are attainable and enable reduced catalyst temperatures (< 550 °C) while maintaining elevated reactor performance (see Figure 1 right). When considering these additional operating points, a broader and more flexible operation of industrial reactors becomes feasible. Systematic sensitivity studies regarding relevant reactor and operating parameters indicate that a robust technical implementation of these operating points is possible, even with commonly available cooling fluids.

More advanced control concepts (e.g., optimal control) revealed reactor operating policies that ensure fast and safe transitions between different reactor loads. For instance, we demonstrated that the observed unconventional operating points are already attainable during reactor start-up without hazardous temperature excursions [4]. The applied methodology for optimal control is computationally demanding, but in combination with a moving horizon strategy, the problem becomes feasible. In accordance with the literature, the results confirmed that reactors are predestined for control purposes as they offer improved performance in closed-loop settings. Hence, advanced control concepts appear to be an essential link for making future reactors more flexible.

Motivated by our theoretical results, we designed and built an entire pilot-plant concept that enabled us to reproduce our in-silico results from above (showcased in Figure 2 left). The essential unit of the experimental setup is a reactor whose design was developed entirely based on the previous numerical results. Furthermore, the setup offers novel opportunities for studying the temperature field in real-time (via a fiber optic temperature sensor), and a unique heat transfer unit enables fast interactions with the reactor via coolant temperature changes. Steady-state experiments are conducted to capture significant reactor states, which are used for model validation and adjustment. Finally, the adjusted model is used to compare the computational dynamic reactor behavior with cool-down perturbation experiments (Figure 2 bottom right). Although a slight re-adjustment of the model is necessary, the model proves to be well suited for rigorous dynamic studies, underpinning the relevance of the results obtained in-silico.

In summary, we see that our findings are essential links to supporting chemical processes that transform renewable energy into valuable, easy-to-distribute chemical energy carriers. Further work will primarily focus on the experimental implementation and validation of our theoretical findings to minimize the barriers to industrial application.

I Dr.-Ing. Jens Bremer

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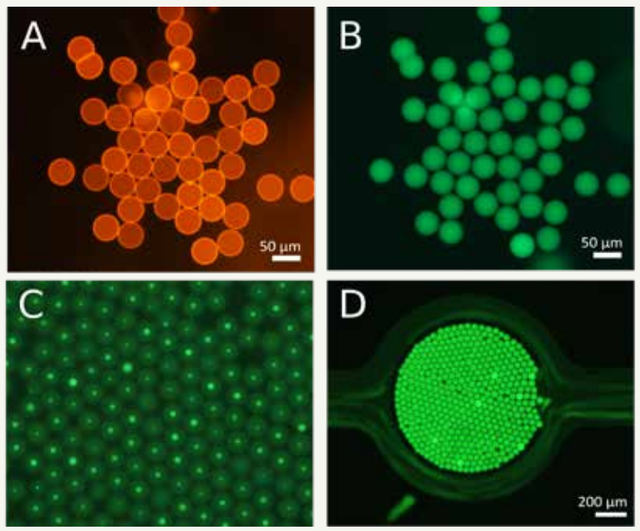
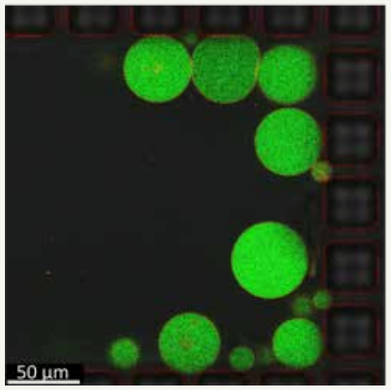
Author **Dr.-Ing. Jens Bremer**

Jens Bremer embarked upon his academic career in 2008 with his Bachelor studies in Energy and Process Engineering at TU Berlin. During this time, he worked as an intern and wrote his thesis with Daimler AG, Stuttgart focusing on hydrogen supply for fuel cell powertrains. He received his Master degree from TU Berlin in 2014 after completing his thesis in Professor Biegler's Research Lab at Carnegie Mellon University, Pittsburgh, USA. Since October 2014, he has been working in the PSE group headed by Professor Sundmacher and focuses on the advanced operation of fixed-bed reactors for Power-to-Gas applications. His aim is to build a bridge between modelling, numerical algorithms and experimental investigations.

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



+ Figure 1:
The microfluidic production of double emulsions and the subsequent oil separation results in uniform GUVs and efficient *encapsulation*: phospholipid compartments, whose membrane **(A)** is stained with rhodamine-labeled lipid (orange), while their lumen **(B)** is filled with fluorescein-labeled dextran (green). The phospholipids can be replaced with *amphiphilic polymers* for higher *stability*, which makes it possible to study the formation of artificial *membraneless organelles* over weeks **(C)**: in the minimal cytosol of PBd-PEO GUVs, the enzyme dextransucrase catalyzes the polymerization of sucrose to dextran, which in turn leads to *phase separation* from the encapsulated polyethylene glycol. Microfluidics also enables dense packing of the compartments in *tissue*-like structures to study *intercellular communication* **(D)**: phospholipid GUVs in a circular trap, equipped with inlet and outlet for exchange of the outer solution.



+ Figure 2:
Rectangular hydrodynamic trap for investigation of the *proton permeability* of GUVs made of PDMS-PEO, and the activity of bacterial *proton pumps*, reconstituted in their membranes. Flushing a solution (from left to right) with either a different pH or containing chemical activators of the enzyme results in a change to the inner proton concentration. The dynamics of this change are assessed via the encapsulated pH-sensitive dye, pyranine (green).

Bottom-Up Assembly of Functional Modules for Mimicking Cells

+ Synthetic Biology (SynBio) can be best understood by looking at the etymology of the Greek word synthesis (putting together, combining), which also reflects the gradual shift in biology from a descriptive science towards fully harnessing it to serve societal needs. In a manner that is consistent with the aim of manipulation rather than mere observation, SynBio has a pronounced engineering slant that is embodied in the interplay between the modular view and systemic perspective. Modularization and assembly can be accomplished by the genetic engineering of existing organisms via standardized pieces of DNA software. This approach has already had several success stories and promises to revolutionize biotechnology through an unprecedented degree of control. However, despite the multiple advancements in various omics, the complexity of life has not thus far been tackled to a satisfying degree; installing the software often does not lead to the expected outcome, while nearly one third of the genes in the simplest synthetic organisms are still of unknown function.

The hurdles posed by evolutionary clutter can be overcome through the bottom-up assembly of biological hardware. The modular and hierarchical building of organelles and cells from molecular building blocks enables much greater predictability but is also much more challenging. Nevertheless, the construction of ensembles that reproduce life phenomena aids the understanding of fundamental biological principles while generating emerging applications in parallel. The bottom-up assembly of cells is, in fact, extremely similar to the way that a process engineer puts together a chemical plant, namely by integrating reactors, separators, heat exchangers and pumps with defined performance parameters. In this way, the PSE department follows immanent engineering goals such as stability, efficiency, sustainability and economic production in the context of cell mimicking too.

Among the multitude of biological processes, we focus on 1) metabolic processing of matter, 2) growth as a step towards self-reproduction, and 3) energy supply, with the latter being pursued jointly with the EEC group. These lines of research are associated with compartmentalization, which is a universal living characteristic that enables segregation from the environment and establishment of gradients [1], in a similar fashion to membrane reactors. The most intuitive cell models are liposomes, which self-assemble in water thanks to the amphiphilic properties of phospholipids. However, traditional methods like the spontaneous or assisted hydration of lipid films suffer from low yield, uncontrolled size, and difficult encapsulation of larger biomolecules. We have addressed these shortcomings by adopting and optimizing the microfluidic production of w/o/w double emulsions, followed by osmotically assisted oil separation, to controllably produce giant unilamellar vesicles (GUVs) [2] (Figure 1). Through this automated assembly line, we are able to encapsulate phase-separation or cell-free transcription-translation systems as well as bundles of proteins like the artificial enzymatic cycle for CO_2 fixation, known as CETCH.

The SynBio molecular toolbox is not limited to natural molecules and often resorts to man-made building blocks. This concept has, for instance, enabled the expansion of the genetic code by additional base pairs or the incorporation of unnatural amino acids. In this respect, we use amphiphilic polymers like poly(butadiene)-poly(ethylene oxide) (PBd-PEO) to mimic natural lipids and create rigid and durable GUVs. Not only does the membrane of these compartments provide a physical border but it also acts as an interface for transporters, receptors and bioenergetic machineries. However, while some channels appear less sensitive to the membrane environment, complex membrane proteins like the bacterial proton pump bo_3 oxidase require exact matching of the mechanical properties. To this end, we have replaced the hydrophobic polymer block with a more flexible poly(dimethylsiloxane) (PDMS) chain and assessed the membrane fluidity, softness and permeability, next to the enzyme activity, in microfluidic traps [3] (Figure 2).

In order to multiply like cells, the model compartments first need to grow by volume and area. In this context, we are also investigating different mechanisms of vesicle fusion as a means of uptake of membrane material [1]. PDMS-PEO behaves similarly to lipids in this context as well, while conferring chemical resistance against oxygen radicals [3], and the membrane expansion can be triggered by salts, charge or proteins. Fusion can also be employed for signaling or integration of membrane and cytosolic machinery to assemble biochemical pathways. With respect to the latter, the PSE group has undertaken theoretical activities and applies methods from systems engineering to synthesize enzymatic reaction networks of intermediate complexity. One such network is the aforementioned CETCH cycle consisting of 17 enzymes, whose carbon conversion and energy efficiency we aim to increase by identifying optimal catalyst compositions and eliminating systemic bottlenecks. Overall, we seek to advance the exciting and slowly maturing research area of artificial life-like cells by complementing biology with new technological solutions derived from a process systems engineering perspective. **| Dr.-Ing. Ivan Ivanov**

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Author **Dr.-Ing. 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 Pennsylvania State University, working in the area of electromicrobial technologies. In 2014 he rejoined the PSE department, where he is currently a team leader working in the field of bottom-up synthetic biology. His research interests include biological electron transfer and catalysis, biomimetics, multi-phase systems and compartmentalization.

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

PSD

PROCESS SYNTHESIS AND PROCESS DYNAMICS

+ Systems Engineer Dr.-Ing. Christian Kunde working on computer-aided modeling and design of chemical processes in liquid multiphase systems.

PROF. DR.-ING. ACHIM KIENLE I
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, nonlinear model reduction, and new approaches to robust and nonlinear control of particulate processes. Novel crystallization, fluidized bed spray granulation and agglomeration processes have been investigated as interesting application examples. Chromatographic processes are switched systems with cyclic behavior. A particular focus of the PSD group has been on online parameters estimation, optimization and 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.

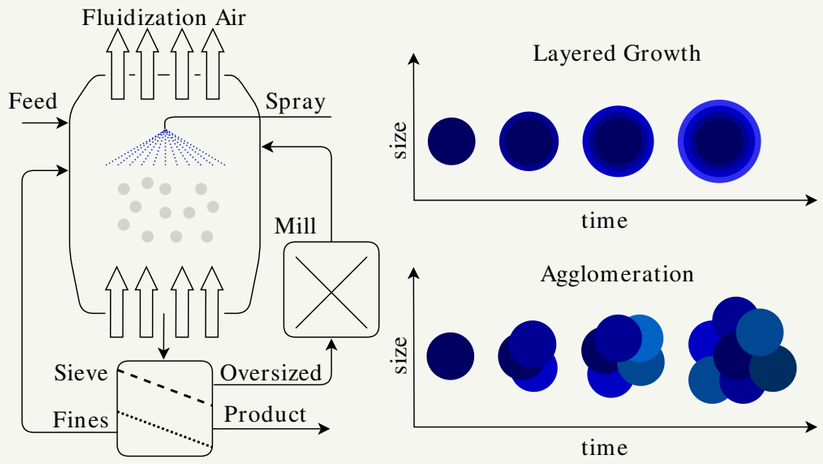
In the field of **Process design**, the PSD group is developing computational methods for a systematic design of complex process systems. Approaches range from shortcut methods based on analytical insight to rigorous simultaneous mixed integer nonlinear optimization (MINLP) of process configurations, operating conditions and auxiliary materials.. During the period covered by this report, particular emphasis was placed on new methods for integrated molecular and process design for liquid multiphase reaction systems using hierarchical MINLP optimization approaches and on novel analytical and numerical methods for chromatographic processes with implicit 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 in multi-cellular systems. Vaccine and biopolymer production processes have been investigated as interesting application examples. Furthermore, the group has contributed to the institute's activities in the innovative field of conceptual modeling and analysis of synthetic biological systems.

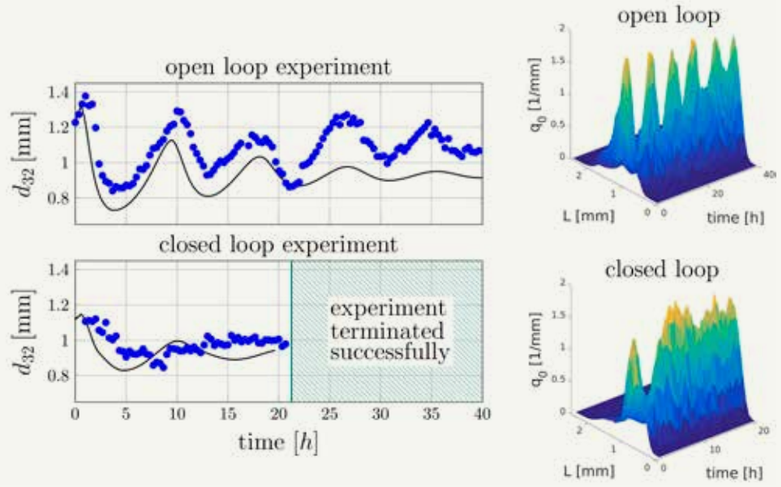
The PSD group has been involved in a number of highly visible larger joint research projects with external funding, including the joint research center Transregio SFB 63 on integrated chemical processes in liquid multi-phase systems, which involves about 15 other partners, mainly from TU Berlin and TU Dortmund, the national priority program SPP 1679 on dynamic flowsheet simulation of particulate processes, the national priority program SPP 2080 on catalysts and reactors under dynamic operating conditions for energy storage and transformation, and the MaxSynBio initiative of the Max Planck society on synthetic biology.

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

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



+ Figure 1:
Process scheme with sieve mill cycle and particle growth for layering granulation and agglomeration.



+ Figure 2:
Theoretical and experimental results for open loop and closed loop operation of a layering granulation process with sieve mill cycle according to [4].

Modeling and Control of Particle Formation in Continuously Operated Fluidized Beds

+ Particle formation in fluidized beds represents an important class of processes in the chemical, pharmaceutical, and food industry. The objective is the stable production of tailor made particles with given product properties. In general, due to the complex interaction between particle growth and also heat and mass transfer between the particle and the fluid phase, this is a challenging issue. In practice, product and process development is often dominated by expensive and time-consuming trial and error procedures. Our research aims to achieve a better understanding of the complex dynamics of these processes by using mathematical models and to improve the particle formation in fluidized beds by developing new methods for model-based control.

In the large-scale, fluidized bed particle processes are operated continuously as illustrated in Fig. 1. For this purpose, they are often equipped with a sieve mill cycle which facilitates product classifiction and milling of oversized particles. Milled particles are then fed back to the process chamber together with the undersized particles. Depending on the mode of operation, two different types of particle formation processes in the fluidized bed can be distinguished as illustrated in Fig. 1 on the right. For agglomeration processes, the injected liquid is a binder which supports the aggregation of particles. For layering granulation, the injected liquid is a solid solution or suspension, which is deposited on the surface of the particles and leads to a layerwise growth of the particles after drying. In granulation, aggregation of particles may also take place but is usually avoided by carefully adjusting the operating conditions.

In our research, the initial focus was on layering granulation. The main results relate to modeling, dynamics and control. A key feature of particle formation in fluidized beds is a certain variance in particle size leading to a particle size distribution that evolves over time. This has been modeled with so called population balances. The approach was systematically extended step by step to account for segregation into a spraying and a drying zone, the influence of the drying conditions on particle size and particle porosity, and nonideal particle milling, which depends strongly on the particle properties and operating conditions. For the latter, data driven on- and offline approaches were developed. The resulting models show good agreement with experimental data that were obtained in collaboration with our project partners from the Tsotsas group at Otto von Guericke University in Magdeburg and the Heinrich group from the Technical University in Hamburg. These kinds of models can also be used for the design of advanced particle processes in multistage granulation processes. A recent overview was given in [5].

A well known problem of continuous granulation processes with sieve mill cycle is the occurrence of self-sustained oscillations of the particle size distribution, which is illustrated in Fig. 2. This was also validated experimentally with the Heinrich group from TU Hamburg (upper row in Fig. 2). Furthermore, it was shown that feedback control can be applied to dampen these oscillations significantly (lower row in Fig. 2). With this, the startup time of these processes can be reduced significantly, e.g. from more than 40 hours in the upper diagrams of Fig. 2 without control to about 10 hours in the lower diagrams of Fig. 2 with control [4]. Again, theoretical predictions indicated by the solid lines and experimental results show good agreement. The concept has been extended recently to also adjust the desired particle porosity automatically by adding another control loop acting on the thermal conditions [3, 2]. Besides linear control concepts, more advanced and powerful robust and nonlinear approaches were also developed [5].

More recently, the focus has shifted to agglomeration processes. It turns out that mathematical modeling from first principles is much more challenging for this type of process. Therefore, we have followed a hybrid modeling approach which combines population balance modeling with datadriven kernel identification. Initial results look very promising and can be used in future for further work on process control [1, 6]. Collaboration partners in the field of agglomeration are the Bück group from Friedrich Alexander University in Erlangen Nuremberg and the Tsotsas group from Otto von Guericke University Magdeburg.

I Dr.-Ing. Robert Dürr, Dr.-Ing. Christoph Neugebauer

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Author **Dr.-Ing. Robert Dürr**

Robert Dürr studied Systems Engineering and Engineering Cybernetics at Otto von Guericke University Magdeburg and received his diploma in 2009. Afterwards, he joined the PSD group where he worked on population balance modeling and simulation of vaccine production processes. After finishing his Ph.D. with honors in 2016, he was a postdoctoral fellow at the Department of Chemical Engineering at KU Leuven (Belgium). In 2018, he returned to Magdeburg and is now a postdoctoral research associate in the PSD group. His recent fields of research comprise modeling and control of microbial biopolymer production, as well as granulation and agglomeration processes.

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

Author **Dr.-Ing. Christoph Neugebauer**

Christoph Neugebauer studied Systems Engineering and Engineering Cybernetics at Otto von Guericke University Magdeburg and received his diploma in 2013. He then joined the PSD group, where he worked on modeling, dynamics and control of fluidized bed spray granulation processes as a member of the DFG priority programm SPP 1679 on dynamic flowsheet simulation of particulate processes. He finished his Ph.D. with honors in June 2020.

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

DRI | DATA-DRIVEN SYSTEM REDUCTION AND IDENTIFICATION

+ Prof. Athanasios Antoulas and Prof. Anderson (foreground) in Canberra, Australia, in September 1985. The pictured meeting shows the beginnings of the method that Prof. Athanasios Antoulas made world-famous and which put the bases of data-driven modeling in systems and control theory. The Loewner framework is also used by other groups at the MPI on a regular basis – it is of great importance even nowadays.

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

+ The Data-Driven System Reduction and Identification (DRI) group has been supervised by Professor Antoulas since 2017. In addition, the DRI group consists of one post-doctoral researcher, Dr. Ion Victor Gosea, and one doctoral student, Dipl. Eng. Dimitrios Karachalios, M.Sc. The DRI group carries out mathematical research with the main focus on numerical linear algebra and system theory from a data-driven perspective.

Nowadays, one of the main challenges is the reliable information that can be extracted from data. In many engineering disciplines (e.g., mechanical or chemical engineering) the usual way of providing solutions is to linearize the derived theoretical models and test them for different sets of data. This approach has its own limitations. For instance, linear approximations to nonlinear problems are locally successful without being able to provide long-term predictions.

Moreover, the derived theoretical models sometimes have missing terms which cannot explain the data noise (undescribed physics). In the modeling stage, when more features are included, this inevitably leads to the curse of dimensionality. Therefore, one successful way of overcoming the dimensionality problem is to introduce model order reduction. Methods such as balanced truncation have made model reduction techniques popular and reliable by providing error bounds. These methods do not offer any solution when only input-output data are known, and the system acts as a black box or the model is too complicated to be constructed.

Recently, *machine learning* (ML) techniques have aimed to "learn" the black box. For specific tasks such as pattern recognition, ML has been able to achieve great success. The restrictions of ML methods begin when the interpretation of the derived models is under consideration. By combining learning from data, along with reduction techniques, we have introduced an approach that yields identification of reduced models from data (discovery of dynamical systems). It constitutes a non-intrusive method that deals with real data (engineering measurements such as frequency, velocity, current and concentration) able to identify linear and nonlinear systems and at the same time offer the opportunity for reduction that is crucial for simulation, design and control. One way to carry out model reduction is by employing interpolation. The method under consideration known as the *Loewner framework* (LF) is a non-intrusive interpolatory model order reduction technique that works towards the identification of the black box systems when only input-output in time or in frequency domain data are offered.

The Loewner framework (LF) is a data-driven interpolation-based identification and reduction approach that uses measured or computed data to construct surrogate models of low complexity introduced by Professor Antoulas and Professor Anderson in 1986 (in Fig.1). The activity of the DRI group has been mostly focused (although not entirely) on advancing and extending this framework to different problems and applications.

Internal and External Scientific Collaboration

The following are internal collaborations within the MPI Magdeburg:

1. Joint work with the CSC group led by Prof. Peter Benner (also collaborating with Dr. Igor Pontes Duff) on model reduction of switched systems, and on time-domain reduction of structured nonlinear systems.
2. Joint work with the EEC group led by Dr.-Ing. Tanja Vidaković-Koch (also collaborating with Mr. Antonio Sorrentino); the scope was applying the Loewner framework for the frequency response analysis of fuel cells, which will result in the master thesis of Mr. Bansidhar Patel (under preparation).

The following are external collaborations outside of the MPI Magdeburg:

1. Joint work with Prof. Matthias Heinkenschloss (Houston, USA) on various model reduction topics.
2. Joint work with Dr. Mihaly Petreczky (Lille, France), Dr. John Leth and Prof. Rafael Wisniewski (Aalborg, Denmark) on modeling switched and hybrid systems.
3. Joint work with Dr. Stefan Güttel on rational approximation for matrix-valued functions (additionally, an invited research visit was undertaken by Dr. Ion Victor Gosea to the University of Manchester (UK) from 14-19.05.2019).
4. Joint work with Prof. Serkan Gugercin on data-driven modeling of linear systems with quadratic outputs (additionally, an invited research visit was undertaken by Dr. Ion Victor Gosea to the Virginia Tech University (USA) from 02-17.11.2019).
5. Joint work with Dr. Charles Poussot-Vassal (Toulouse, France) on data-driven control.

Prof. Dr. Athanasios C. Antoulas
Max Planck Fellow

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

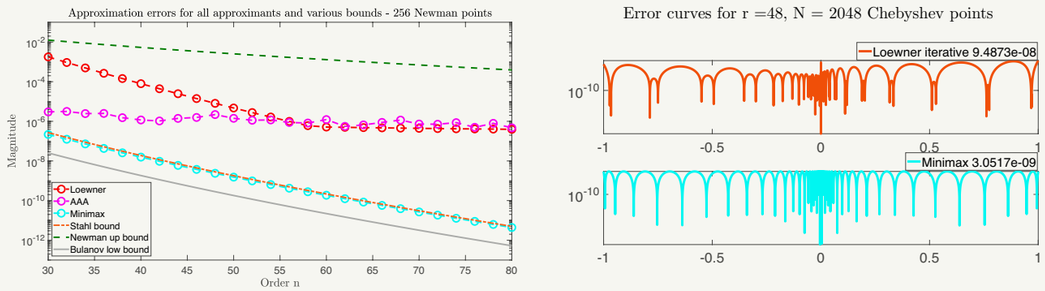

Figure 1:
Approximation errors

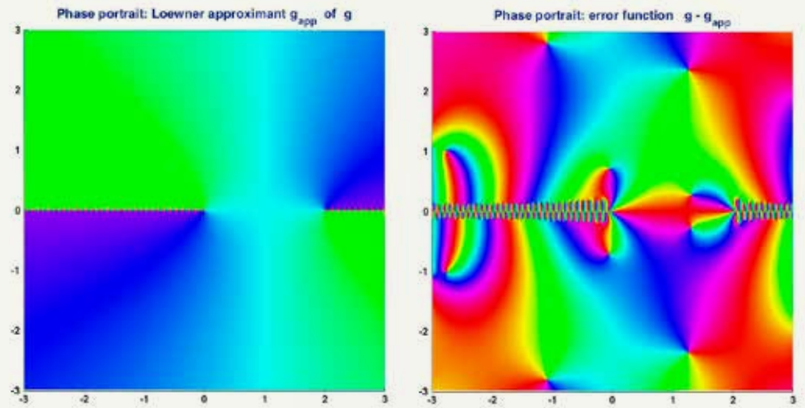

Figure 2:
Phase portraits `a la Wegert [6].

Error Bounds and Branch Cuts in the Loewner Framework

Introduction Approximation theory is a well-established field of mathematics that has applications in many areas of applied sciences. Examples include computational fluid dynamics, solution and control of partial differential equations, data compression, electronic structure calculation, systems and control theory (model order reduction of dynamical systems) and analysis of electro-chemical devices (fuel cells). In the work mentioned here, we are concerned with rational approximation, i.e., approximation of given functions by means of rational functions.

It is known that rational functions can approximate functions with singularities and with oscillatory behavior better than polynomials can. Furthermore, rational functions are extensively used in systems and control theory since the input-output behavior of linear dynamical systems is described in the frequency domain by the so-called transfer function (which is indeed a rational function). The poles of this function determine important system properties such as asymptotic stability, transient behavior or damping. The methods under consideration do not necessarily require access to the exact closed-form of the original function, but only to evaluations of it on a particular domain. Hence, these methods are data-driven, with the Loewner framework being the principal method under investigation. It has been successfully applied for approximating non-rational transfer functions in [1]. Here, a comparison with the adaptive Antoulas-Anderson (AAA) method is provided.

Error Bounds for Rational Approximation One challenge that arises in the development of interpolation-based rational approximation data-driven methods is to be able to enforce error bounds and conditions for optimality. This represents a difficult task and the reason for this is that the quality of the rational approximant strongly depends on the available data measurement. Moreover, when interpolation is enforced on a finite sample set, extrapolation is difficult to reach outside this boundary. Another challenge is approximating functions with discontinuities. Towards dealing with this challenge, the Loewner framework has been applied to approximating the sign function in [1]. Another example is the absolute value function, which is a continuous function, non-differentiable at the origin. Approximating this function by polynomials played a significant role in the early development of approximation theory.

In [2], we propose an extensive numerical study of approximating the absolute value function. The methods reviewed have been proposed relatively recently, e.g., the Loewner framework, the AAA and Minimax algorithms (iterative methods). The result presented by D. J. Newman in [3] is at the heart of this study; he showed that for the sign function, the speed of polynomial approximation is much slower than that of rational approximation, by giving explicit bounds of the decay for the latter (the first such results ever obtained). His work was successfully continued by other mathematicians in the second half of the 20th century (such as H. Stahl, who provided asymptotic bounds for the best approximant in [5]). In Fig. 1 (left pane), we depict the approximation errors for the three approximants under consideration (Loewner, AAA, and Minimax) as well as three approximation bounds by Newman, Bulanov and Stahl [5].

Another contribution of [2] was to propose a novel iterative correction approach for the Loewner framework to improve the overall approximation quality. By applying this modified Loewner-based method, we managed to compute data-driven rational approximants that were very close to the optimal ones (computed with the Minimax method); see Fig. 1 (right pane).

To summarize, a detailed comparison of best rational approximants has been provided by accounting for different results and bounds from classical approximation theory.

Approximation of Functions with Branch Cuts The Loewner framework has also been applied to functions with isolated singularities such as the inverse of the Bessel function and the sign function in [1]. In [4], we have investigated functions that possess branch cuts, such as the complex square root function. A branch cut is a curve in the complex plane across which a function is discontinuous. Branch cuts often appear as lines or line segments.

We have shown that approximating such functions by means of rational functions, with both AAA and Loewner methodologies, yields approximants with poles and zeros lying on the branch cuts of these functions. Furthermore, the zeros and the poles were observed to interlace In Fig 2, we display the phase portraits of the rational Loewner approximant to the function $g(z) = \sqrt{z(2-z)}$ (left pane). Additionally, the phase portrait of the error function is also depicted (right pane). The colors of the phase portraits in Fig 2 follow the specifications of [6], namely: red indicates angles around 0, green angles around $\frac{2\pi}{3}$ and blue angles around $\frac{-2\pi}{3}$. **| Prof. Dr. Athanasios C. Antoulas**

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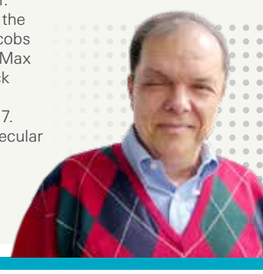
Author **Prof. Dr. Athanasios C. Antoulas**

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



ARB | ANALYSIS AND REDESIGN OF BIOLOGICAL NETWORKS

+ A deep understanding of bacterial metabolism and its regulation is vital for engineering bacteria for biotechnological applications. The picture shows the cultivation of several bacterial strains under controlled conditions in our experimental systems biology lab.

DR.-ING. STEFFEN KLAMT I SENIOR SCIENTIST

+ Nowadays it is widely accepted that understanding the complexity of life at the cellular level requires mathematical approaches 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 theoretical and experimental investigations to analyze and rationally modify cellular (biomolecular) networks. One central focus of our research is on 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 and design of microbial communities and of cell-free production systems, as well as 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 different microorganisms under controlled conditions. Our experimental studies have a particular focus on *Escherichia coli*, one of the most important model organisms that 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 the routine use of advanced mathematical modeling approaches in the life sciences.

Highlights and Trends in 2019/2020

In the reporting period we have added a new species to our zoo of microorganisms that we experimentally analyze in our lab: *Zymomonas mobilis*. This bacterium has some extraordinary capabilities. It can produce ethanol from glucose with an unprecedented rate and yield; the specific production rate is even 2-3 times higher than that of the well-known ethanol producer yeast. Despite its unique productivity, concrete biotechnological applications with *Z. mobilis* are still rare. One main reason is the lack of reliable genetic engineering tools, which could be used to redirect the metabolism of this organism towards an extended spectrum of substrates and products. In our new project, ZIP, which is funded by the German Ministry of Education and Research (BMBF), we aim to develop a new molecular toolkit for the genetic and metabolic engineering of *Z. mobilis* to eventually establish this organism as a new microbial platform strain for biological production processes. Together with computational strain design approaches we then want to demonstrate that this organism can be redesigned for the efficient synthesis of value-added products beyond ethanol.

The COVID-19 pandemic has also dominated our everyday lives in 2020 and led to severe restrictions on the scientific work carried out in our group. In particular, wet-lab activities had to be stopped for more than two months from March to May. Working from home in that time was nevertheless effective at least for theoretical and computational research, for planning and discussing new research activities via video meetings and – last but not least – for writing manuscripts. From the end of May, step by step, we resumed our work at the institute. We were very happy that, after postponing it from May to July and in compliance with sanitation and social distancing rules, we were able to successfully conduct our long-planned workshop "Tools and methods for rational engineering" at Schloss Ringberg (a Max Planck Society venue close to Lake Tegernsee). On the one hand, this workshop served as a group retreat, but it also provided a platform for discussing recent progress in our research with six prominent guest speakers and for initiating new collaborations with them.

Another workshop, organized by us in September 2020 with colleagues from the University of Heidelberg, had to be moved from the seminar room to a virtual (online) conference room. Within the framework of de.NBI (the German Network for Bioinformatics Infrastructure), in this training course we presented tools for systems biology modeling and data exchange including our *CellNetAnalyzer* toolbox for metabolic network analysis. The positive feedback from the participants showed us that this format is indeed a viable option, maybe even beyond the COVID-19 pandemic.

In 2019/2020, the ARB group published 19 papers in peer-reviewed journals. A major pillar of our current research activities is the *StrainBooster* project funded by the ERC Consolidator Grant awarded to the group leader Steffen Klamt. This project combines innovative theoretical and experimental techniques for establishing a new generic strategy for the rational engineering of microbial cell factories. On the following two pages, Simon Boecker will explain the key principle of this strategy and present experimental results demonstrating the high potential of this approach for optimizing the bio-based production of chemicals.

Dr.-Ing. Steffen Klamt
ARB Group Leader

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

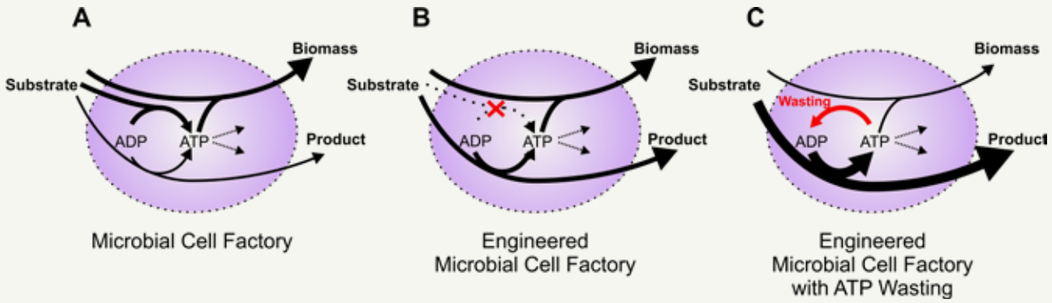


Figure 1:
Concept of enforced ATP wasting as metabolic engineering strategy. A microbial cell factory that produces a product of interest from a given substrate (A) is engineered by employing a suitable knock-out strategy that couples ATP synthesis to product formation (B). In this engineered strain, an ATP wasting mechanism is introduced forcing the cells to convert more substrate into product to keep up with the cellular ATP demand and thus increasing yield and productivity (C).

Enforced ATP Wasting as a Design Principle for Metabolic Engineering

The development of efficient bio-based production processes for fuels, commodity chemicals and therapeutics is coming into focus to turn industry away from fossil-based towards sustainable and CO_2-neutral manufacturing. However, to be able to compete with conventional petrochemical production, the three main performance measures of these bioprocesses - yield (product per substrate), titer (product per volume) and productivity (product per volume and time) - need constant improvement. In our group, the central goal of the ERC-funded project "StrainBooster" is to develop a novel generic strategy for rationally engineering microbial cell factories maximizing these performance parameters. The concept relies on a manipulation of the energy metabolism, called "enforced ATP wasting ", and consists of two steps. First, a microbial cell factory able to convert a given substrate into a product of interest (Figure 1 A) is engineered by a suitable knock-out strategy to mandatorily couple ATP synthesis to formation of the product of interest (Figure 1 B). Finding these strategies is supported by computational strain design methods, including the minimal cut set approach that our group has developed [1]. The engineered cell will then only be able to produce ATP for maintenance and growth processes when it synthesizes the product simultaneously. On top of this engineered strain, a mechanism is introduced that consumes ("wastes") an extra amount of ATP and thus forces the cell to convert even more of the substrate into ATP and product and less into biomass to keep up with the increased ATP demand. Therefore, product yield and productivity can be expected to increase (Figure 1 C).

In recent studies, using wild type strains of *E. coli* and the yeast *S. cerevisiae*, we were able to show that the cytosolic F1-ATPase subunit from *E. coli* is an efficient mechanism for targeted hydrolysis (wasting) of ATP to ADP. Moreover, as a first proof of principle of the ATP wasting strategy, its expression indeed led to enhanced production of natural fermentation products in these organisms under anaerobic conditions (ethanol, formate, lactate, acetate and succinate in *E. coli* and ethanol in *S. cerevisiae*) because their synthesis is coupled to ATP formation [2, 3].

Improvement of 2,3-butanediol Production in *E. coli* by Enforced ATP Wasting

As a realistic application example, in collaboration with the group led by Stefan Pflügl from Vienna University of Technology, we next applied the ATP wasting strategy to an *E. coli* strain that had been engineered to convert glucose to the alcohol 2,3-butanediol (2,3-BDO) – an important building block for the chemical industry. As 2,3-BDO production is coupled to ATP formation in this constructed strain, enforced ATP wasting can be applied and we expressed the F1-ATPase encoding genes *atpAGD* in the 2,3-BDO producer strain. We then compared the 2,3-BDO production performance of this "ATPase strain" with a "control strain" for various cultivation conditions [4]. During aerobic growth-coupled production, the substrate uptake and 2,3-BDO synthesis rate of the ATPase strain increased by more than 50% and the 2,3-BDO yield by 45%. Under growth-decoupled production, which is important for improving the volumetric productivity via two-stage fermentations, the ATPase strain exhibited an enormous sixfold and tenfold increase in the glucose uptake and 2,3-BDO production rate, respectively. However, relatively high amounts of the 2,3-BDO precursors pyruvate and acetoin were still excreted due to the unlimited supply of oxygen.

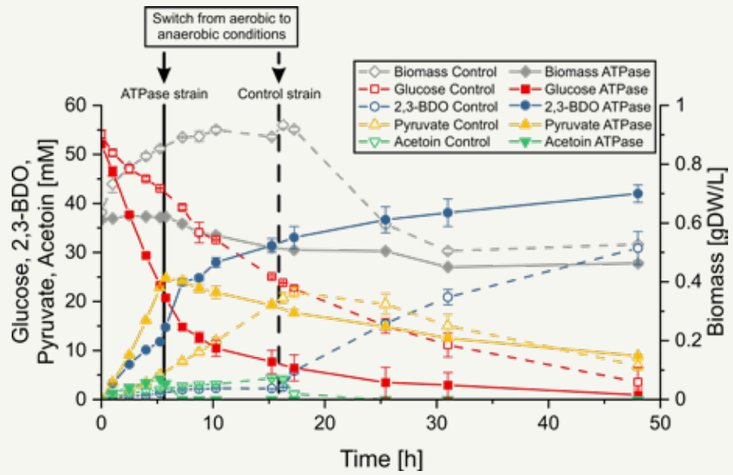


Figure 2:
Results for the second (aerobic, no growth) and third (anaerobic, no growth) phase of a three-stage cultivation strategy for 2,3-BDO production with the ATPase and the control strain (the first (growth) phase is not shown). The optimal point for switching from aerobic to anaerobic conditions was calculated beforehand and is reached when 60% of the glucose has been consumed. Overall, enforced ATP wasting in the ATPase strain led to a process with an increased yield (+23%) and an improved productivity (+125%) compared to the control strain.

To obtain higher 2,3-BDO yields, microaerobic conditions were then applied for the production phase, where 2,3-BDO serves as mandatory redox sink. This increased the 2,3-BDO yield by 100 % to 0.87 mol/(mol glucose), which is 87 % of the maximum yield. However, in turn the microaerobic conditions reduced the glucose uptake and 2,3-BDO synthesis rates. Based on all these findings and to circumvent microaerobic conditions, which are difficult to maintain in large bioreactors, we finally proposed and validated a three-stage process involving (i) an aerobic growth phase, (ii) an aerobic production phase followed by a switch (at an optimal, predetermined point in time) to (iii) an anaerobic production stage where the byproducts acetoin and pyruvate are co-consumed and further converted to 2,3-BDO (Figure 2, showing results from the aerobic and anaerobic production phase). In this novel cultivation approach, the ATPase strain exhibits a 2,3-BDO yield that is 23% higher than in the control strain and its productivity was even increased by more than 125%.

These results demonstrate that ATP wasting is a powerful tool for making bioprocesses more competitive in comparison with traditional fossil-based chemical production in the future.

I Dr. Simon Boecker

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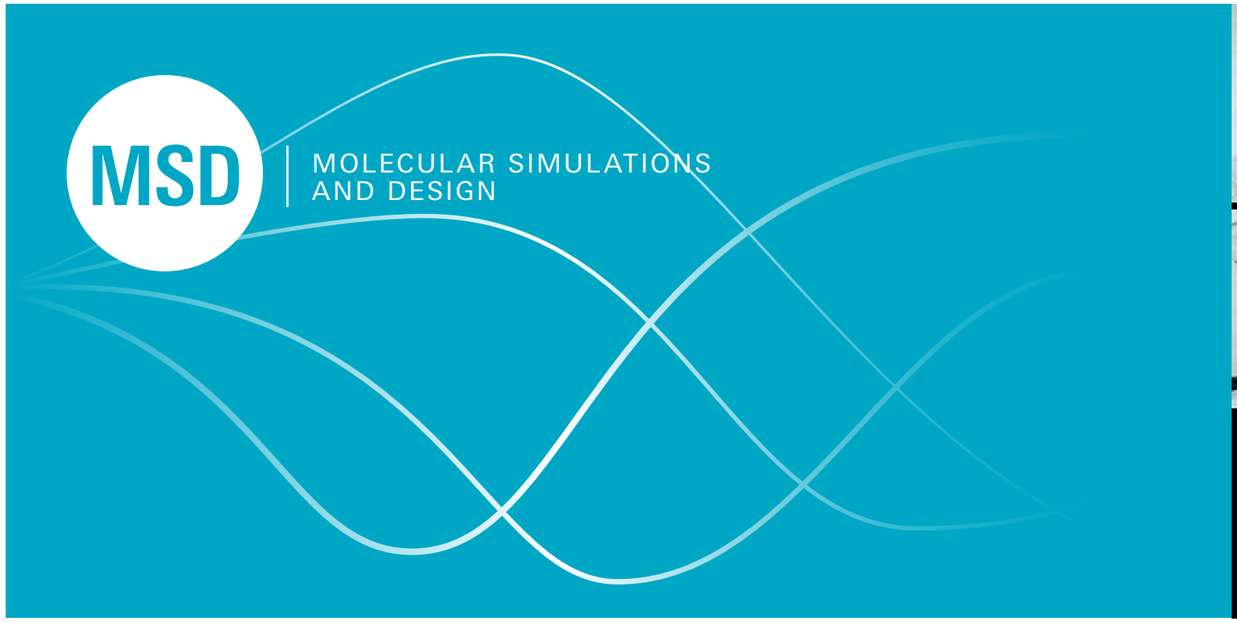
Author **Dr. Simon Boecker**

Simon Boecker studied Biotechnology at Berlin University of Technology and Dongseo University Busan (South-Korea) and received his Diploma in 2013. After an internship at Sandoz GmbH, he started his Ph.D. at Berlin University of Technology in 2013, focusing on the heterologous production of secondary metabolites in filamentous fungi. Since 2018 he has been working as a postdoctoral researcher in the ARB group at MPI Magdeburg. His research focuses on establishing and analyzing ATP wasting strategies as tools for metabolic engineering.

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



+ The Coronavirus epidemic in 2020 changed the way we work at the Max Planck Institute. Maybe it will be a long-term transformation. Here is a typical picture of an MSD video group meeting.

“I can't believe it. I can't believe it. Football. Bloody hell.”

(Sir Alexander Ferguson, CBE (*1941), football manager)

DR. MATTHIAS STEIN I GROUP LEADER

+ **Molecular Simulations** are the core of our research. It is the unique three-dimensional positional arrangement of atoms, molecules and large macromolecular complexes, such as proteins, that determine their properties and interactions. The MSD group makes use of and develops tools for simulating both the strength of interactions between those molecules and their dynamic behavior. The simulations are based on principles from physics and chemistry. In our work we address current global challenges such as the quest for novel innovative **Materials, Pharmaceuticals and Drugs, and Sustainable Chemistry**.

2019 was a particularly successful year for the MSD group. Science was strong and making good progress in the fields of controlling Rab protein signaling, sustainable catalysis using renewable feedstock and carbon dioxide sequestration (see **Research Highlight**). The CO_2 project originated from an interdisciplinary consortium of groups at the MPI funded by the ERDF (‘Altmarkenergie’) which came to an abrupt end.

Eileen Münzberg defended her Ph.D. thesis at the OVGU in Magdeburg. The focus of her Ph.D. project was on control and regulation of switchable membrane-associated proteins of the Rab family. An imbalance in their function is associated with several neurodegenerative diseases such as Alzheimer’s, Parkinson’s and Huntington’s. These Rab proteins switch between an “off” and an “on” state which is regulated and controlled by a number of effector and inhibitory proteins. They are prime examples of the complexity of protein signaling with various, spatially distinct positive and negative feedback loops.

The group hosted a bioinformatics student from Halle (Laura Isigkeit) and an **ERASMUS student** from Poland (Maria Bzwoka) for research stays.

At the beginning of 2020, Matthias Stein was appointed as **Honorary Professor** for Computational Chemistry in the Department of Chemistry at OVGU.

The year 2020 was marked by the SARS-CoV-2 virus pandemic and its severe consequences for working at the MPI and elsewhere. Between March and July, working from home was necessary and a challenge for all members of the MSD group. Maintaining **social coherence** within the group and finding operable working conditions for everyone required an individual adjustment to difficult times and a good deal of resilience. Full research work only re-started slowly after July.

It is clear that such a period of interruption and all subsequent restrictions have an influence on productivity and performance. Small steps in day-to-day work are also valuable and must be appreciated. During the shutdown period there were no new students in the MSD group, since they were not allowed to leave their countries, were locked down or had not managed to obtain a visa to come to Europe. Most of the scientific conferences were cancelled or replaced by smaller online events. Until the end of 2020, the global spread affected both international postdocs and international projects. With collaborators’ labs closed, universities shut down and scientists having to isolate, we will feel the effects for a long time.

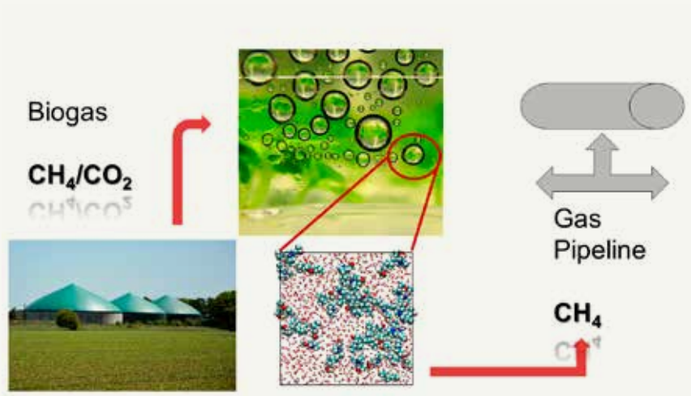
However, I am proud to see how strongly the MSD group members reacted and the way in which they continued to work or resumed their efforts after the first break. People have developed individual skills during the lockdown or when working from home. Some fantastic publications came out this year. We can even devote some of our expertise to the structural biology of the SARS-CoV-2 virus and suggest possible paths of intervention.

Now, as we move into the final stretch of 2020, the situation is more serious than ever. Regular activities at the institute are, again, restricted and working from home becomes the new “normal”. The virus spreads at fast speed and we will have to live with it for quite some time. We are going to feel its effects for a long time despite great scientific achievements in unmet global and cooperative efforts.

In the end, we will come back. It’s science, bloody hell. This is how Alex Ferguson put it when Manchester United turned around the Champions League final against Munich. He was overwhelmed by the spirit of his team and could not rationally explain the result of the match.

Dr. Matthias Stein
MSD Group Leader

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



+ Figure 1:
An example of a selective carbon dioxide sequestration process from biogas. Carbon dioxide is absorbed and methane fed into the gas pipeline system

Designing Innovative Novel Materials for Carbon Dioxide Sequestration

+ One of the grand challenges set in the Paris Agreement by the United Nations Framework Convention on Climate Change (UNFCCC) is a 40% reduction in greenhouse gas emissions in Germany by 2030 in comparison with 1990. Stabilizing atmospheric CO_2 levels requires a drastic reduction in emissions but also a circular economy that will lead towards a zero-emission scenario. However, global energy consumption and demand are continuously increasing, and the majority of the resources exploited, such as petroleum, natural gas, and coal are still from fossil sources and not sustainable.

One approach of working towards achieving the Paris Agreement goal is the removal of carbon dioxide from air or gaseous mixtures. This requires the temporary fixation of the CO_2 molecule to a solid or liquid material from which it can be recovered later as a chemical building block. Carbon dioxide can, on the one hand, be captured directly from air, but it can also be removed from gaseous mixtures before these are used in further processes. For example, CO_2 can be "washed out" from industrial flue gases or biogas from anaerobic fermentation.

The latter is a combination of methane (50-75%), CO_2 (25-50%), nitrogen (0-10%), and H_2S (0-3%) depending on the fermentation process (organic waste). For some applications, such as vehicle fuel or grid injection, it is necessary to fulfil strict specifications and therefore the natural gas needs to be upgraded. Since CO_2 is the major contaminant of biogas, its removal is the most critical step in terms of the economics of the entire process, e.g. for transport applications or satisfying pipeline specifications. Biogas can be upgraded to biomethane by removing CO_2 using different technologies, of which reversible chemical absorption in amine-based solutions can be considered the most advanced and promising technique.

From a large set of molecular compounds, a subset of candidate molecules was evaluated as to their thermodynamic and kinetic properties taking into account aspects of sustainability and toxicity. Molecular simulations are able to provide detailed insight into liquid solution behavior and give relevant compound-specific thermodynamic and transport properties for novel CO_2-absorbing compounds, which are not available in the literature and not accessible experimentally.

The liquid structure properties of a set of representatives of alkanolamines molecules in pure water and in the presence of CO_2 were investigated over a wide range of solvent alkanolamine/water mixture compositions and temperatures. By using in-house high-performance computing facilities (our Linux cluster, '*mechthild*'), a detailed assessment of the compounds' individual properties and features that need to be considered when designing novel CO_2-absorbing materials were addressed.

For example, when comparing today's standard CO_2-absorbing compound MEA (Figure 2) with the next generation compound DEAB, small but decisive differences become apparent. They have different reactivities towards CO_2 and a different amount of energy is required to regenerate the absorbing compound. Complex multi-component mixtures of charged and neutral intermediates form during CO_2 fixation.

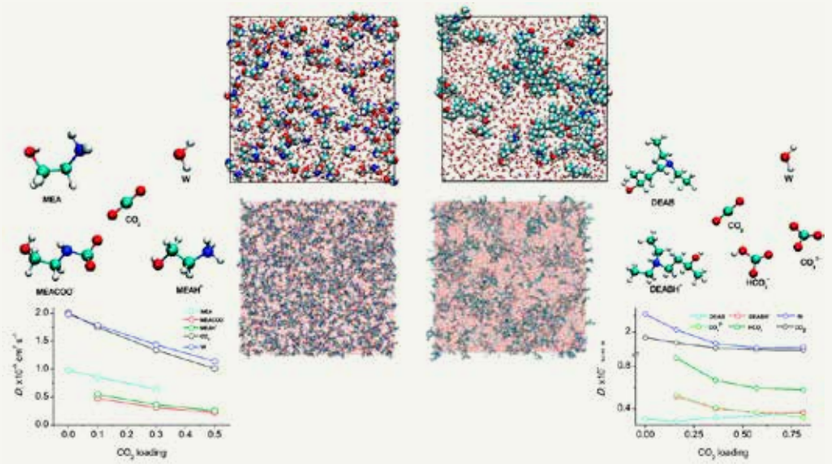
The MEA molecules and all charged product species are individually solvated (see Figure 2); CO_2 shows no preference for approaching either MEA or water molecules. Upon an increase of CO_2 loading in solution, the motion ('diffusion') of all species slows down and the viscosity of the mixture increases.

For the new tertiary alkanolamine DEAB, the opposite behavior is observed. Self-aggregation and clustering of hydrophobic DEAB molecules diminish in presence of the newly formed charged and hydrophilic absorbent species; the local concentration of CO_2 molecules decreases in proximity to DEAB molecules. Upon increasing CO_2 loading in the solution, the diffusion coefficients decrease for all species in solution except for unreacted DEAB. Its mobility increases and finally approaches that of the protonated $DEABH^+$ product. The change in the diffusion coefficient of CO_2 at increasing load is less prominent due to two compensating effects: the acceleration of mobility of the first solvation shell CO_2 molecules in close proximity to DEAB molecules at low loading and the disruption of DEAB self-aggregates at higher loadings.

A clear understanding of molecular processes during carbon dioxide sequestration in post-combustion capture is an important pre-requisite for designing and controlling novel CO_2-absorbing compounds. The results show that different, sometimes competing effects have an influence on the performance of amine scrubbers in reactors at different levels of CO_2 loading. The physical and organic chemistry of alkanolamines is not easy to rationalize and requires careful analysis of novel data from structure-based simulations.

The process of CO_2 absorption is a balance between the compound's solubility in water and desolvation, hydrogen bonding and hydrophobic interactions and is very sensitive to the exact composition of the solution. In most currently available compounds, the solvation and distribution of carbon dioxide are very similar. Novel materials, such as DEAB, were specifically designed for their high CO_2 binding affinity and predicted to have a lower degree of toxicity than MEA. Computer-aided molecular engineering can further assist the design of advanced materials for highly efficient absorptive CO_2 removal.

I Dr. Sergey M. Melnikov



+ Figure 2:
Details of computer simulation of carbon dioxide-absorbing compounds in aqueous solution. Left: the standard molecule monoethylamine (MEA). Right: the next generation absorber 4-diethylamino-2-butanol (DEAB). Alkanolamine molecules are displayed as spheres and water molecules as stick models. Simulated diffusion coefficients of reaction product species as a function of CO_2 loading are shown.

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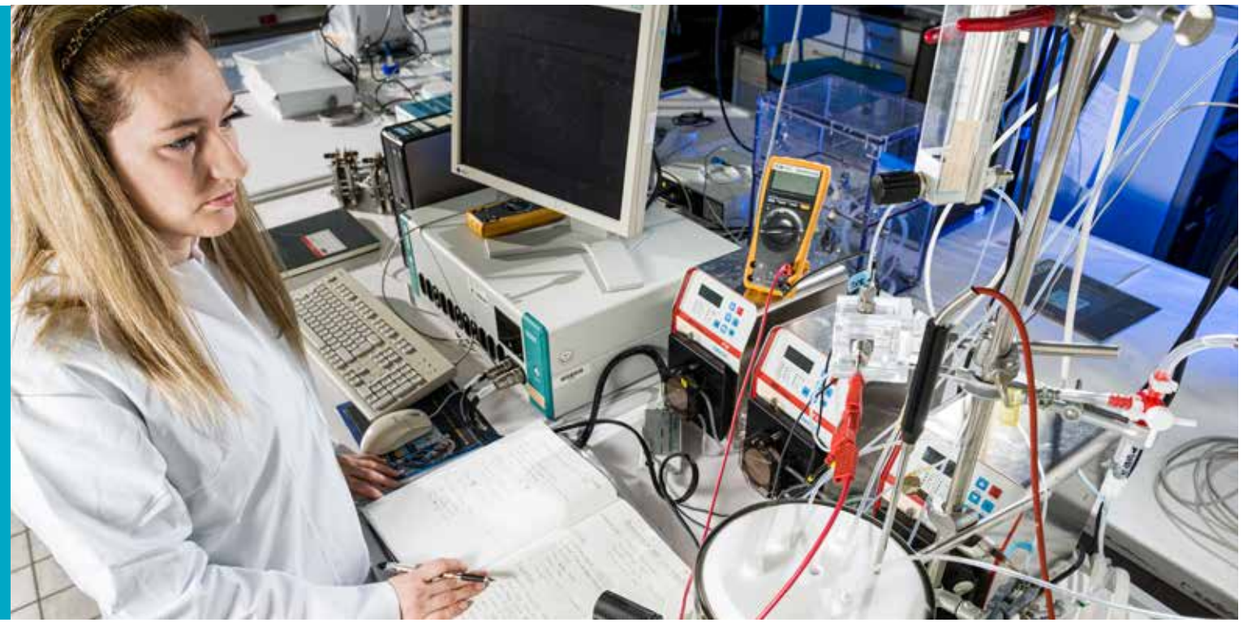
Author **Dr. Sergey M. Melnikov**

Dr. Sergey M. Melnikov studied Physics in Minsk (Belarus) where he also obtained his Ph.D. in single-photon detection and then worked as an academic docent. He was a postdoc in Leeuwen (Belgium), Marburg (Germany) and the MPI in Magdeburg. His expertise is in computer simulations of fluids in meso- and macroporous materials, chromatographic separation processes and liquid state properties. He is the author of more than 25 peer-reviewed scientific publications.

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

EEC | ELECTROCHEMICAL ENERGY CONVERSION



+ Efficient electrochemical regeneration of co-factors is a key to economically viable industrial-scale biotransformations with redox enzymes.

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

+ In 2019 and 2020 the Electrochemical Energy Conversion (EEC) group continued to work on the important area of energy conversion. This report briefly summarizes our major projects, directions, meetings and editing activities, and provides details of our new members over what have been, for many reasons, two exciting and productive years.

In our **"Dynamics of electrochemical processes"** project area, we use nonlinear frequency response analysis (NFRA) in order to study the kinetics of electrochemical reactions as well as the periodic operation of electrochemical reactors. With respect to electrochemical kinetics, our current examples are oxygen reduction reaction (ORR) under strong alkaline conditions and carbon dioxide reduction (CO_2RR) on silver. Both topics are very closely related to the activities of DFG Research Unit 2397, where the EEC group, together with partners from a total of seven universities and research institutes (Clausthal University of Technology, Karlsruhe Institute of Technology, University of Stuttgart, University of Bayreuth, Ruhr University Bochum, Helmholtz Center Berlin and MPI Magdeburg), is investigating the complex processes within gas diffusion electrodes (GDE). The research unit was successfully evaluated in 2019 and we are pleased to report that the second funding phase will go ahead from 2020. The main focus will be on CO_2RR. In 2019, in cooperation with partners from DFG Research Unit 2397, the EEC group organized an International Symposium on GDE in Magdeburg and had the pleasure of hosting many excellent plenary and invited speakers.

The "Dynamics of electrochemical processes" project area has been further strengthened by our new group member, Dr. Luka Zivkovic (since December 2019), whose main focus is on computer-aided nonlinear frequency response.

In 2019, the EEC group joined the International Max Planck Research School (IMPRS) and we are happy to welcome our first IMPRS Ph.D. student, Tamara Milicic, who has just joined us (in October 2020). Her arrival in Magdeburg was delayed for several months due to the Coronavirus, and we are grateful to the Max Planck Society for its flexibility and support during the prolonged visa application period. Her thesis topic is the periodic operation of water electrolyzers. We are cooperating on this project with Professor Tsotsas and Dr. Vorhauer-Huget from OVGU Magdeburg and have obtained some interesting results concerning the transport properties of porous transport layers in water electrolysis.

Water electrolysis is a high-interest topic, and Dr.-Ing. habil. Vidaković-Koch was invited by the MDPI "Processes" journal to serve as a Special Issue Editor on electrolysis processes. In her editorial dedicated to this special issue, she briefly summarizes different electrochemical technologies for utilizing excess electricity for intermediate energy storage such as water electrolysis and batteries, as well as further electrochemical technologies, for example wastewater treatment and even electromachining.

The dynamics of electrochemical processes was also a topic of Dr.-Ing. habil. Vidaković-Koch's keynote lecture at the 71st Annual Meeting of the International Society of Electrochemistry (30 August - 4 September 2020 in Belgrade, Serbia). Due to the Coronavirus, the meeting was held onlineand alltogether it was an interesting new experience. In her talk she discussed a generalized framework for the dynamics of electrochemical processes. Although it was unfortunate not to have the opportunity to meet and discuss in person, Dr.-Ing. habil. Vidaković-Koch appreciated the opportunity to stay in contact and discuss science with international colleagues via live chat sessions as well as interesting e-mail exchanges.

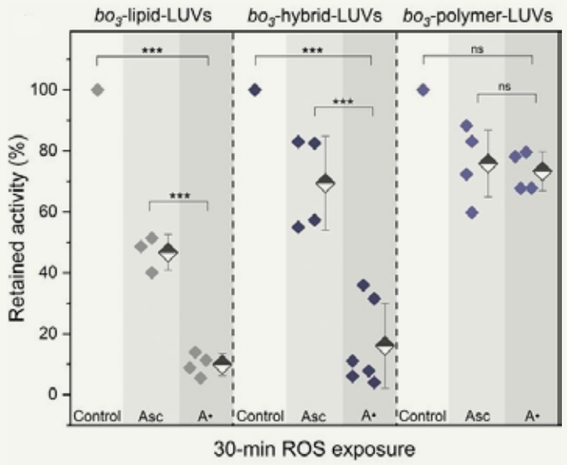
In the **"Bioelectrochemical processes"** project area, we are investigating the application of enzymatic cascades and electrochemical co-factor regeneration for synthesizing value-added products. In this respect, the EEC group participated in the DFG Priority Program "Bioelectrochemical and Engineering Fundamentals to Establish Electro-Biotechnology for Biosynthesis – Power to Value-Added Products (eBiotech) - SPP 2240", and our project proposal in collaboration with Professor Bornscheuer from the University of Greifswald on the development of a novel process for the regeneration of NAD(P)H cofactor was recommended for funding. We are excited to cooperate with the group led by Professor Bornscheuer on this topic.

As already mentioned, the 71st Annual Meeting of the International Society of Electrochemistry (30 August - 4 September 2020 in Belgrade, Serbia) was held online. As part of this meeting, Dr.-Ing. habil. Vidaković-Koch co-organized the Symposium 6 on "Advances in microbial electrochemistry for energy conversion biotransformation, bioremediation and electroanalysis", which attracted approximately 100 participants over 2 days of online meetings. On this occasion, the journal Electrochimica Acta published a Virtual Special Issue (VSI) collating the best of the papers presented, and she was happy to accept an invitation to be a guest editor for the VSI on Symposium 6.

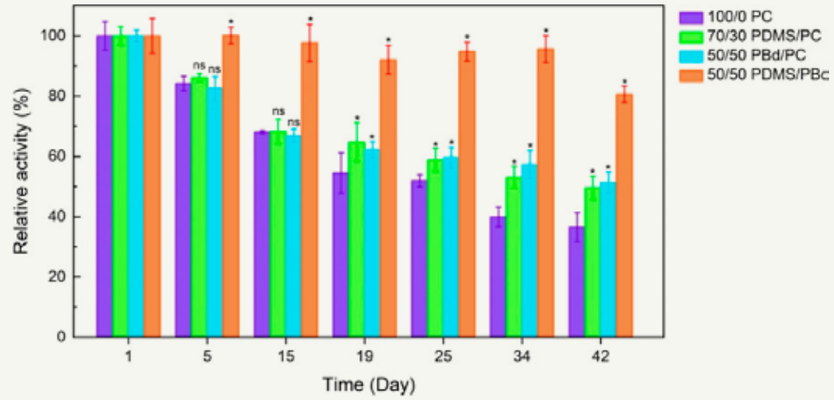
Finally, in our **"Electrochemistry meets synthetic biology"** project area, we continued with the development of different artificial organelles for energy conversion. Our publication on light-driven ATP regeneration was selected for the cover of the CHEMBIOCHEM Journal and our Ph.D. student, Christin Kleineberg, who was a first co-author of this publication will shortly submit her Ph.D. thesis. In cooperation with Professor Wegner (University of Münster, formerly of MPI Mainz) we have identified an interesting integration of an adhesion unit with the light-driven ATP regeneration module in one synthetic cell. It was demonstrated that this cell could adhere to locations that are optimal for ATP production and that it has the ability to self-position and carry out its functions in a selected location. Further research in this area was related to chemically-driven ATP production and more details on our research in the area of energy conversion for bottom-up synthetic biology are provided in our Research Highlights article by Lado Otrin.

Dr.-Ing.habil. Tanja Vidaković-Koch
Senior Scientist

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



+ Figure 1:
Protective function of PDMS-*g*-PEO against oxidative damage. Shown is the activity retention of bo_3 oxidase after incubation with ascorbate (Asc) and ascorbyl free radical (A•) for 30 min. For 100 % (control), activity of untreated bo_3-LUVs was measured.



+ Figure 2:
Hybrid vesicles improve long-term stability of the light-driven ATP regeneration module. Significantly enhanced functional lifetime of the coupled bacteriorhodopsin/ATP synthase was observed upon their insertion into PDMS-*g*-PEO/PBd-PEO hybrid vesicles (50:50, mol:mol).

Energizing Synthetic Biology

+ Synthetic biology encompasses the efforts of a broadly interdisciplinary scientific community to manipulate living matter on an unprecedented level of complexity. In this context, synthetic constructs, such as synthetic cells and organelles, are designed with certain desired functionalities in mind and are assembled from natural or man-made building blocks in a highly-controllable bottom-up manner. To a large extent, current efforts are focused on understanding the principles of life that govern the synergy between these building blocks. Therefore, unsurprisingly, present designs are mostly aiming to reproduce or mimic the essential processes of living matter, such as growth, motility, metabolism and reproduction. Commonly, these bottom-up replicated processes are built and developed as separate modules, which can then be integrated to form synthetic organelles and cells. Nevertheless, in their synthetic form as well as in nature, these processes are highly energy-intensive and require a continuous supply of adenosine triphosphate (ATP). Consequently, energy regeneration modules are an essential component of every and any synthetic construct.

In the EEC group, we design and construct energy regeneration modules based on photophosphorylation as well as oxidative phosphorylation, with the long-term vision of assembling an artificial chloroplast and an artificial mitochondrion [1]. In our modules, ATP is synthesized by a complex transmembrane enzyme ATP synthase inserted in membranes of nano-sized compartments in the form of vesicles. Synthesis is driven by the proton gradient, a difference in proton concentration between the inside and outside of said compartments, which is established and maintained via the proton translocation activity of proton pumps. The latter are complex transmembrane enzymes co-inserted in compartments along with the ATP synthase. In our constructs, we employ two types of proton pumps – those powered by light, such as in the case of bacteriorhodopsin, and those driven by reducing agents, like in the case of the respiratory enzyme bo_3 quinol oxidase.

A significant disadvantage of these synthetic constructs featuring vesicles functionalized with various membrane proteins is their low functional and structural stability and durability. In the absence of the repair and replacement mechanisms, the inserted enzymes are unstable and rapidly lose their activity. Furthermore, compartments as well as integrated enzymes are subjected to oxidative damage that leads to enzyme deactivation and compartment permeabilization, both of which have a strongly diminishing effect on the ATP regeneration. Hence, we are looking to replace traditionally used lipid compartments with more durable and versatile polymer ones.

With respect to this, we are exploring the integration of enzymes related to energy regeneration into polymer compartments comprising graft co-polymer PDMS-*g*-PEO, a polymer that is miscible with lipids as well as with block-co-polymers, thus enabling the formation of so-called hybrid vesicles. PDMS-*g*-PEO forms membranes with a thickness and fluidity similar to natural membranes, thus presenting an enzyme-compatible environment. In our recent work in collaboration with the PSE group [2], we integrated bo_3 oxidase and ATP synthase in said polymer as well as lipid/polymer hybrid compartments. We observed a high level of retained activity in the inserted bo_3 oxidase, which was reflected in the proton gradient established upon enzyme activation. Said gradient was maintained due to the low proton permeability of polymer compartments. Interestingly, enzyme insertion into hybrid vesicles caused a reorganization of the lipid fraction of hybrid membranes, which resulted in even lower membrane permeability. Astonishingly, the polymer protected bo_3 oxidase from the oxidative damage (Fig. 1), while maintaining high structural integrity, both being invaluable attributes for the construction of energy regeneration modules. Finally, with the enzyme integration into PDMS-*g*-PEO-based membranes, we were able to extend their functional lifetime, leading to retention of their activity for over 13 days.

In similar work [3], we investigated the insertion of bacteriorhodopsin and ATP synthase, enzymes of our light-driven energy module, into graft polymer/block polymer PDMS-*g*-PEO/PBd-PEO hybrid compartments. Remarkably, we observed significantly improved long-term stability, with over 80 % retained activity of said enzymes over the course of 42 days (Fig. 2). Furthermore, polymer/polymer hybrids featured proton permeability similar to that of lipid membranes.

Moreover, very recently we made our first attempts towards the integration of energy modules with modules mimicking other life functions [4]. We assisted in the construction of a minimal synthetic cell, which combined a multistimuli sensitive adhesion unit with a light-driven energy regeneration module. Integration of the adhesion unit with the ATP conversion module into a single synthetic cell allowed it to adhere to surfaces under blue light illumination, non-oxidative conditions, at neutral pH and in the presence of metal ions, which were the right conditions for ATP synthesis. Thus, the multistimuli responsive adhesion unit allowed self-positioning of the synthetic cell and execution of its functions. Meanwhile, our current work is focused on the integration of chemically-driven energy regeneration modules with metabolic modules with the aim of creating an artificial mitochondrion.

I Lado Otrin

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Author **Lado Otrin**

Lado Otrin studied Molecular Biology in the Biotechnical Faculty, University of Ljubljana, Slovenia. He received his MSc in 2014 in the field of Nanobiology and Nanotoxicology under the supervision of Professor Damjana Drobne. He discovered his passion for membrane proteins during a stay at the Laboratory of Biomolecular Research, Paul Scherrer Institute, Switzerland, under the supervision of Professor Rolf Jaussi. Currently, he is pursuing a Ph.D. at the Max Planck Institute for Dynamics of Complex Technical Systems, Germany, in the field of bottom-up synthetic biology, focusing on chemically-driven energy regeneration systems and integration approaches.

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

Journal Articles

Ahmad, A. G., **Qamar, S.**, & **Seidel-Morgenstern, A.** (2019). Linearized non-equilibrium and non-isothermal two-dimensional model of liquid chromatography for studying thermal effects in cylindrical columns. *Journal of Liquid Chromatography & Related Technologies, 42(13-14)*, 436-451. doi:10.1080/10826076.2019.1625370.

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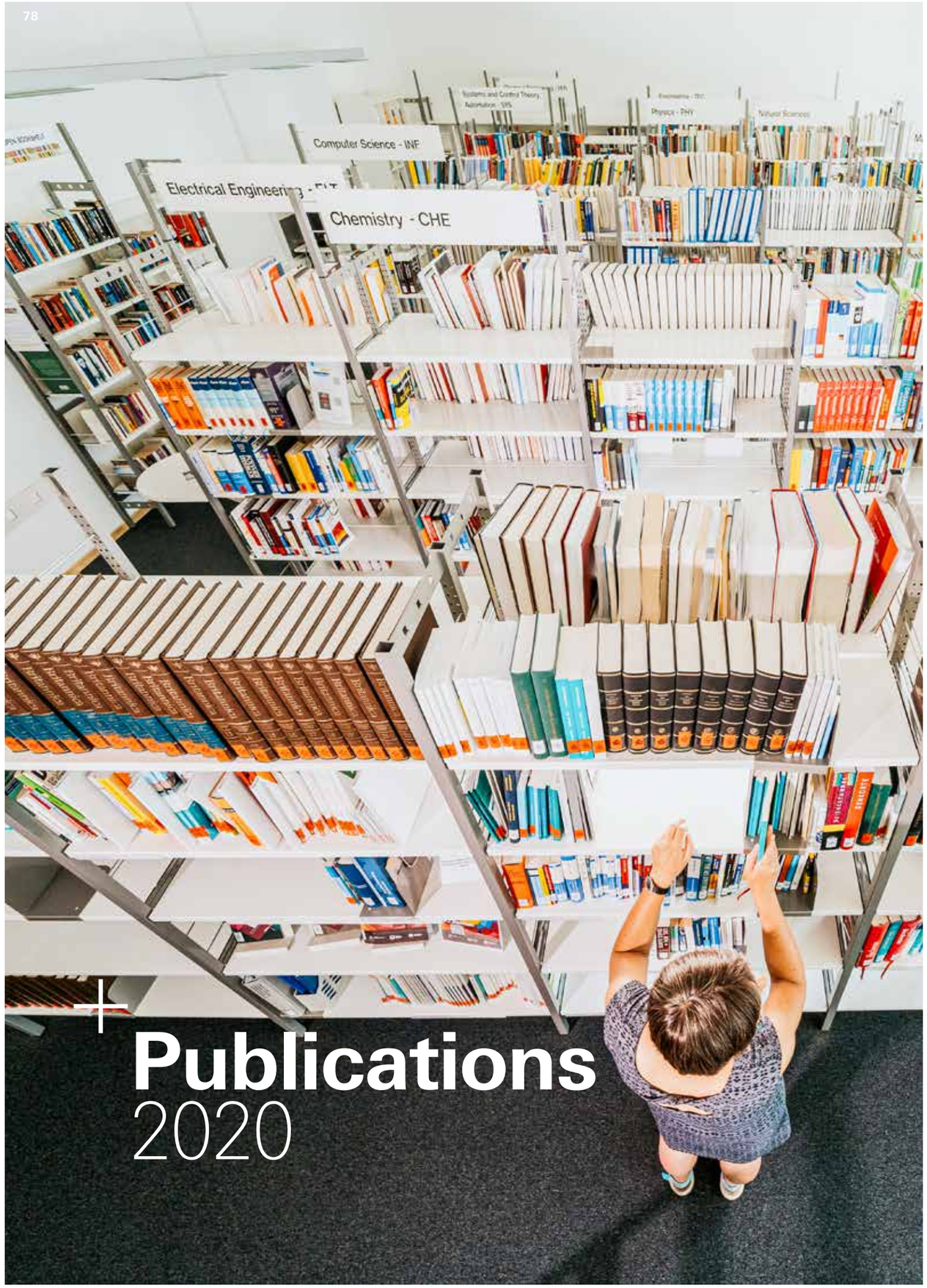

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Sandtorstrasse 1
39106 Magdeburg
Germany
P +49 391 6110 0
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info@mpi-magdeburg.mpg.de
www.mpi-magdeburg.mpg.de