Annual Report

Technical University of Munich

Institute for Advanced Study

2017

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TUM President's Foreword

Leverage. A good idea can move the world if it's grounded right and implemented with conviction. A prime example, one of many I could point to from our university's 150-year history, is the commitment we made – in our strategy for the second round of Germany's Excellence Initiative – to jump-start the nation's first globally competitive career system. The TUM Faculty Tenure Track pioneered a new academic career path where excellence and performance are rewarded. Strange as sounds when I state it so plainly, this approach was novel and unique in Germany just six years ago.

As 2017 drew to a close, TUM was well on the way to the goal of appointing 100 tenure track professors by 2020, having recruited 83 of the world's most promising young researchers from a pool of 2500 applicants. As intended, the new career system is helping TUM stay at the cutting edge across its entire research portfolio while shaping a faculty profile that is younger, more international, and more diverse. The TUM-IAS, of course, has played a special role in this by energetically recruiting Rudolf Mößbauer Tenure Track Professors, a push that has already brought 17 exceptionally innovative researchers and educators into the TUM community.

In the meantime, the federal and state governments have launched a "TT-1000" initiative inspired by our "TUM 100" – a billion-euro commitment to help universities nationwide create 1000 new tenure track positions over the next 15 years. Among the 34 universities that won support in the first round of this program, TUM has been granted 40 new tenure track professorships.

That's leverage. We did what we did for our own reasons and at our own risk; the positive impact has been amplified and reaches far beyond this university. The changes set in motion should make Germany, not just TUM, a more attractive destination in the international competition for talent: that vital resource needed to explore deep questions, address societal challenges, drive a vibrant economy, and educate the next generations.

The TUM Institute for Advanced Study is another example of how this kind of leverage works. The effort and resources that go into TUM-IAS collaborations and operations are multiplied many times over in terms of the Institute's scientific output and influence. The latest evidence is documented in this Annual Report.

Throughout 2018 the entire TUM community – including alumni, external partners, and our neighbors as well as faculty, staff, and students – will be celebrating our 150th anniversary with a focus on the future. Since 1868, when "tech fan" Ludwig II, King of Bavaria, founded the polytechnical school that would become TUM, our university has embraced its role as a servant of society.

We are proud of TUM's contributions to transforming Bavaria from a relatively poor agrarian land to a booming center of 21st-century industry, innovation, and discovery. And proud of the outstanding recognition TUM receives in every major international ranking.

At home in Bavaria, successful globally: To paraphrase Archimedes, "Give us a place to stand, and we can move the world."

Prof. Wolfgang A. Herrmann
President

TUM-IAS Director’s Message

Dear friends and members of the TUM-IAS,

Ten years of Fellows in the TUM Institute for Advanced Study – we were able to celebrate this milestone at our annual meeting in 2017. Ten years of Hans Fischer and Hans Fischer Senior Fellows – that means more than 70 leading figures in research from all over the world have blazed new trails in joint projects with their Hosts at TUM. Ten years of Carl von Linde Senior Fellows – 14 scientists from our university have had the opportunity, thanks to an extended period of freedom from everyday teaching and administrative duties, to initiate research with a forward-looking emphasis in collaboration with partners throughout the world. Ten years of Rudolf Diesel Fellowships have facilitated great advances in the exchange between academic and industrial research. In the first ten years of the TUM-IAS, nearly 1200 scientific papers were published in the best journals and proceedings of the respective fields, participation in countless conference sessions was supported, and – not to be forgotten – more than 200 doctoral candidates were financed in individual research projects. In addition, we can now look back on five years of Rudolf Mössbauer Fellowships. Already, this very successful tenure track program has enabled us to recruit 17 outstanding young scientists from around the world, who not only play a central role in the overall appointment strategy of TUM, but also lead the way in new directions with their innovative, often highly interdisciplinary research fields. Finally, five Anna Boyksen Fellowships have enabled scientists and scholars to investigate gender- and diversity-specific research questions.

Our 2017 General Assembly took place in the TUM Science and Study Center Raitenhaslach near Burghausen, which reopened after three years of extensive renovation. The prelate's wing of this former Cistercian monastery offers fantastic possibilities for small and medium-sized workshops and conferences. The unique atmosphere it exudes is due not only to the 200-year history of the building itself, with its wonderful Ceremonial Hall, but also to a sense of the more than 900-year history of the Cistercians. Founded in 1098 in Cîteaux (Burgundy), the Cistercian order arose through reforms of the Benedictine order. Today it's hard to believe that the order was able, under late medieval conditions, to establish 330 offshoots or “daughter houses” within roughly 50 years. Cistercian sites spanned Europe and beyond, from Scotland in the north to Tripoli in the south, and from Portugal in the west to the Baltic in the east. These monasteries were self-contained, but not isolated from each other. Because they were tightly interconnected spiritually, administratively, and economically, they were able to make an impact on Europe's development that is beyond comparison.

Out of these monasteries came the reclamation and cultivation of extensive tracts of land as well as pioneering work in the development of mining and metallurgy. A great many inventions and innovations in irrigation technology and water power, in the construction of canals and mills, can be traced back to the Cistercians. They built up what was for their time a very modern health system. And they established trade connections whose extent was unrivaled until the era of the Hanseatic League.

The Cistercians were able to exert this extraordinary influence because they put into practice a sophisticated network of mutual visits and “peregrinations” of monks as well as skilled artisans who worked in the monasteries. Today these visitors would be called Fellows. What was true in the 11th century holds true in the 21st: Progress in science and society is achieved through the exchange of ideas, and this exchange is most fruitful when it is based on personal encounters. In that, the core idea behind our Fellowship programs is anything but new, but just as effective as 1000 years ago.

Prof. Ernst Rank
Director

People

Board of Trustees

The Board of Trustees is formed by a group of international advisors from academia, research support organizations, and industry. It advises the director on general scientific, organizational, and technical issues. The Board also defines the general strategy and standards of the Institute.

Members

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Max Planck Institute of Neurobiology, Emeritus Research Group Leader,
Nobel Prize for Physiology or Medicine 1991
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Prof. Henry Tye The Hong Kong University of Science and Technology, Department of Physics, and Jockey Club Institute for Advanced Study, former Director

Advisory Council

The TUM-IAS Advisory Council consists of a member from the Max Planck Institute of Quantum Optics and TUM professors covering all major fields of the university. It functions as a standing advisory board to the TUM-IAS Director and his management team. One of its prime functions is advising on the suitability and ranking of Fellow nominations the institute receives for its various Fellowship programs. In addition, the Council advises on the scientific and technological course of the Institute, on the basis of an assessment of the potential and needs of the university. The Advisory Council meets regularly, typically three times a year.

Members

Prof. Martin Bichler
Decision Sciences and Systems
Prof. Dirk Busch
Institute for Medical Microbiology, Immunology and Hygiene
Prof. Hubert Gasteiger
Technical Electrochemistry
Prof. Ulrich Heiz
Physical Chemistry
Prof. Florian Holzapfel
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Prof. Katharina Krischer
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Plant Breeding
Prof. Daniel Straub
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Director

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Program Manager

Tatjana Steinberger
Program Manager

Dr. Susanne Wahler
Program Manager

Christin Seidel
Senior Event Manager

Annette Sturm
Senior Event Manager /
Web Coordinator

Anja Adler
Secretary / Guesthouse
Coordination

Isabella Schnekenburger
Secretary / Building
Coordination

Sigrid Wagner
Senior Event Manager /
Web Coordinator (on maternity leave)

Fellows

Carl von Linde Senior Fellows	2008	Prof. Horst Kessler
	2014	Prof. Martin Buss
	2015	Prof. Franz Pfeiffer
	2016	Prof. Hendrik Dietz
	2017	Prof. Daniel Cremers
Hans Fischer Senior Fellows	2009	Prof. Stanley Riddell
	2012	Prof. Stephen M. Goodnick
	2013	Prof. Josef P. Rauschecker, Prof. Jelena Vuckovic
	2014	Prof. John S. Baras, Prof. Dirk Bergemann, Prof. Gregory D. Hager, Prof. Tamas Horvath, Dr. Andreas Kronfeld, Prof. A. Lee Swindlehurst, Prof. Nicholas Zabaras
	2015	Prof. Carl P. Blobel, Prof. Klaus Kästner, Prof. Yannis Kevrekidis, Dr. Thierry Lasserre, Prof. Jane A. McKeating, Prof. Anca Muscholl, Prof. Ayyalusamy Ramamoorthy
	2016	Prof. Angela Casini, Prof. Krishnendu Chakrabarty, Prof. Johannes Lehmann, Prof. Bernhard Schrefler (awarded by the TÜV Süd Foundation)
	2017	Prof. Kelly Clifton, Prof. Paolo Giommi, Prof. Maya Schuldiner, Prof. Takao Someya
Hans Fischer Fellows	2013	Prof. Matthias Batzill
	2014	Prof. Yana Bromberg, Prof. Tsung-Yi Ho, Prof. Stuart Khan, Prof. Suljo Linic
	2015	Dr. Kaye Morgan, Prof. Alessandro Reali, Prof. Dominique Sugny
	2016	Prof. Jochen Blumberger, Dr. Marc Janoschek, Prof. Melike Lakadamyali
	2017	Prof. Camilla Hollanti, Prof. Hai (Helen) Li
Rudolf Diesel Industry Fellows	2013	Dr. Thomas Koehler, Dr. Peter Lamp
	2014	Dr. Heike Riel
	2015	Prof. Carlo Ratti
	2017	Prof. Michael Bronstein
Rudolf Mößbauer Tenure Track Professors	2013	Prof. Kathrin Lang, Prof. Bjoern Menze
	2014	Prof. Jia Chen, Prof. Matthias J. Feige, Prof. Franz Hagn, Prof. Michael Knap, Prof. Robert König
	2015	Prof. Job Boekhoven, Prof. Carlo Camilloni, Prof. Frank Johannes, Prof. Rolf Moeckel
	2016	Prof. Stephan Günnemann, Prof. Matthias Nießner, Prof. Menno Poot, Prof. Sebastian Steinhorst, Prof. Antonia Wachter-Zeh
	2017	Prof. Laura Leal-Taixé
Anna Boyksen Fellows	2014	Prof. Madeline Heilman
	2015	Prof. Giovanni Boniolo, Prof. Regina Ensenauer, Prof. Sarah de Rijcke
	2016	Prof. Nicola Lautenschlager
Amalie Baur Fellow	2017	Prof. Lena Henningsen

Alumni Fellows

Carl von Linde Senior Fellows	2007	Prof. Andrzej Buras, Prof. Arthur Konnerth, Prof. Reinhard Rummel	15
	2008	Prof. Claudia Klüppelberg	
	2009	Prof. Axel Haase	
	2010	Prof. Ulrich Stimming, Prof. Gerhard Abstreiter	
	2011	Prof. Ingrid Kögel-Knabner	
	2013	Prof. Annette Menzel	
Carl von Linde Junior Fellows	2007	Prof. Adrian Jäggi	
	2008	Dr. Martin Gorbahn, Dr. Ulrich Rant, Prof. Robert Stelzer	
	2009	Prof. Kolja Kühnlenz, Dr. Marco Punta, Prof. Ian Sharp, Prof. Julia Kunze-Liebhäuser	
	2010	Prof. Wilhelm Auwärter, Dr. Vladimir García Morales, Prof. Alexandra Kirsch, Prof. Miriam Mehl, Dr. Christian Stemberger, Prof. Dirk Wollherr	
	2011	Prof. Angelika Peer, Prof. Dongheui Lee	
	2013	Dr. Peer-Hendrik Kuhn	
Hans Fischer Senior Fellows	2007	Prof. Gerhard Beutler, Prof. Walter Kucharczyk, Prof. Bert Sakmann	
	2008	Prof. Anuradha M. Annaswamy, Prof. Yasuhiko Arakawa, Prof. Douglas Bonn, Prof. Mandayam A. Srinivasan, Prof. David A. Weitz	
	2009	Prof. Matthew Campbell, Prof. Richard Davis, Prof. Gino Isidori, Prof. Shuit Tong Lee, Prof. Wolfgang Porod, Prof. Peter Schröder, Prof. Zohar Yosibash	
	2010	Prof. Robijn Bruinsma, Prof. Markus Hegland, Prof. Michael Ortiz, Prof. Stefan Pokorski, Prof. Tim Sparks, Prof. Raman I. Sujith	
	2011	Prof. Silvio Aime, Prof. Polly Arnold, Prof. Daniel Gianola, Prof. Frank R. Kschischang, Prof. Christian Werthmann	
	2012	Prof. Dietmar W. Hutmacher	
	2013	Prof. Harald Brune, Prof. Zvonimir Dogic	
Hans Fischer Fellow	2012	Prof. George Biros, Prof. Franz Hagn	
	2013	Dr. Christian Hirt	
Hans Fischer Tenure Track Professors	2007	Prof. Thomas Misgeld	
	2010	Prof. Hendrik Dietz	
Rudolf Diesel Industry Fellows	2009	Prof. Khaled Karrai, Dr. Dragan Obradovic, Dr. Georg von Wichert	
	2010	Dr. Tsuyoshi Hirata, Prof. Gernot Spiegelberg, Prof. Matthias Heller, Dr. Chin Man W. Mok	
	2012	Dr. René-Jean Essiambre, Prof. Michael Friebe, Dr. Bruno Schuermans	
	2014	Dr. Norman Blank	
Rudolf Mößbauer Tenure Track Professor	2013	Prof. Alessio Zaccone	

Honorary Fellows 2017

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Alexander von Humboldt Professor

Prof. Marco Caccamo | University of Illinois at Urbana-Champaign

Alexander von Humboldt Research Awardees
Honorary Hans Fischer Senior Fellows

Prof. Martin Meyer | Université du Quebec
Prof. Oren Schuldiner | Weizmann Institute of Science

ERC Grantees

Prof. Johannes Barth | Molecular Nanoscience & Chemical Physics of Interfaces, TUM
Dr. Ante Bilandzic | Dense and Strange Hadronic Matter, TUM
Dr. med. vet. Rabea Hinkel | Internal Medicine, TUM
Dr. med. Simon Jacob | Neuroscience, TUM
Dr. med. Valentin Riedl | Neuroradiology, TUM
Dr. med. Hendrik Sager | Internal Medicine – Cardiology, TUM
Dr. med. Johannes Stigler | Biophysics, TUM

August-Wilhelm Scheer Visiting Professors

Dr. Bill Addis | University of Cambridge
Prof. Mark Balas | University of Tennessee Space Institute
Prof. Taryn Bauerle | Cornell University
Prof. Alexey Bulgakov | South Russian State Polytechnic University
Dr. R. Andrew Byrd | National Cancer Institute
Prof. Richard Connon | University of California, Davis
Dr. João Domingos Galamba Correia | Universidade de Lisboa
Prof. Dragan Djurdjanovic | The University of Texas at Austin
Prof. Nesim Kohen Erkip | Bilkent University
Prof. Pascal Fallavollita | University of Ottawa
Prof. Orfeo Fioretos | Temple University
Prof. Antonio Formisano | University of Naples Federico II
Prof. Stephen Glaser | University of California, Berkeley
Prof. Michael U. Hensel | Oslo School of Architecture and Design
Prof. Julia Hsu | University of Texas at Dallas
Prof. Mark Hughes | Aalto University
Prof. Md. Taohidul Islam | Bangladesh Agricultural University
Prof. Hamidreza Koofigar | University of Isfahan
Prof. Haris Koutsopoulos | Northeastern University
Prof. Fuxin Liu | Nanjing University of Aeronautics and Astronautics (NUAA)
Dr. Sam McColl | Massey University
Prof. Noa Marom | Carnegie Mellon University
Prof. Pierre Mertiny | University of Alberta
Prof. André Mischke | Utrecht University
Prof. Claudia Negulescu | Université Paul Sabatier / Institut de Mathématiques de Toulouse

Prof. Jarkko Niiranen | Aalto University
Dr. Gerhard E. Overbeck | Federal University of Rio Grande do Sul (UFRGS)
Prof. Piotr Parasiewicz | The Stanislaw Sarkowicz Inland Fisheries Institute
Prof. Wolfgang Porod | University of Notre Dame
Prof. Maria Prandini | Polytechnic University of Milan
Prof. Krithi Ramaritham | Indian Institute of Technology Bombay
Prof. Adrian Rodriguesz-Contreras | City College of New York
Prof. Patrick Rinke | Aalto University
Prof. Lorenz Schneider | EMLYON Business School
Prof. Marie-Therese Wolfram | University of Warwick
Prof. Eitan Yaakobi | Technion – Israel Institute of Technology
Dr. Shuguang Zhang | Beihang University
Prof. Ziyan Zhang | Civil Aviation University of China

Visiting Fellows 2017

Prof. Andreas Gerstlauer | The University of Texas at Austin
Prof. Gernot Kubin | Graz University of Technology
Prof. Jianping Li | Chengdu Aircraft Design and Research Institute

Activities and Events

TUM-IAS General Assembly

May 4–5, 2017

This year the General Assembly took place for the first time in the wonderful location of Raitenhaslach, providing a very special atmosphere and environment to celebrate ten years of TUM-IAS Fellows. We invited a few Alumni Fellows appointed in the very first years of the Institute for a special session celebrating the 10th anniversary of our Fellowship program. We were delighted to see the important role the TUM-IAS Fellowship played at the time in the development of their careers or in new connections and projects within the TUM academic environment, and how keenly they look back on the time spent at the Institute. From a young successful biotech entrepreneur to a world leader in satellite geodesy and a Nobel Prize winner, we are proud of our alumni!

Once again, there was enough time and plenty of opportunities to establish or strengthen connections among Fellows, Hosts, and in general all members of the TUM-IAS community across all disciplines. During two days they had the opportunity to engage in scientific discussions, whether during the talks and poster sessions or informally during coffee and lunch breaks.

The topics of the General Assembly mirror the current research done at the TUM-IAS. During the regular sessions, topics ranged from visual computing to quantum dynamics, from philosophy of science to biomedical humanities, and from medicinal inorganic chemistry to electromobility – underscoring once more the truly interdisciplinary nature of the Institute.

The conference dinner is always a good and festive occasion to announce new community members and to honor departing ones. This year we had the honor to welcome the Senior Executive Vice President for Human Resources, Administration and Finance, Albert Berger. In his speech he emphasized once more the uniqueness of the TUM Science and Residence Center Raitenhaslach, a science hub for international and interdisciplinary collaboration in a cultural heritage site, and underlined a very positive balance on the first ten years of the Institute's Fellowship program, whether on the top quality of the research performed, the high number of scientific events organized, or the role of the TUM-IAS building on the Garching campus as an intellectual center of TUM.

Program

Tracking human faces in real-time
Matthias Nießner | Rudolf Mößbauer Tenure Track Professor

Unraveling the mysteries of collective quantum dynamics
Michael Knap | Rudolf Mößbauer Tenure Track Professor

Philosophy of science and biomedical humanities at TUM-IAS
Giovanni Boniolo | Anna Boyksen Fellow

From single cells and single columns to cortical networks – coincidence detection and synaptic transmission in brain slices and brains
Bert Sakmann | Nobel Prize winner, Alumnus Hans Fischer Senior Fellow and Member of the TUM-IAS Board of Trustees

Biomolecular and social interactions
Ulrich Rant | Alumnus Carl von Linde Junior Fellow

What satellite gravimetry tells us about the Earth
Reinhard Rummel | Alumnus Carl von Linde Senior Fellow and Member of the TUM-IAS Board of Trustees

Delineation of hydrogeologic heterogeneity by hydraulic and geophysical tomography
Chin Man W. Mok | Alumnus Rudolf Diesel Industry Fellow

A thermogenic concept for brain regulation of behavior and systemic metabolism
Tamas Horvath | Hans Fischer Senior Fellow

Aging mechanisms in high-energy cathode materials for Li-Ion batteries
Peter Lamp | Rudolf Diesel Industry Fellow

Metal-based chemical entities: new tools to study disease mechanisms and for biomedical applications
Angela Casini | Hans Fischer Senior Fellow

Closing Remarks
Ernst Rank | TUM-IAS Director

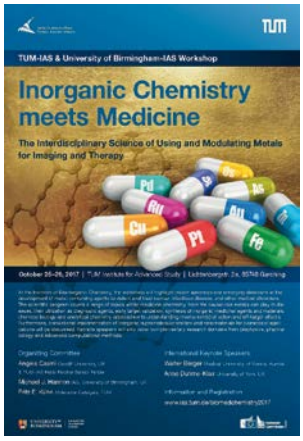

electrical signals in sensory cortex S1
bird eye view
blood vessels

International Workshop: Inorganic Chemistry Meets Medicine

October 25–26, 2017
Organization: Focus Group Medicinal and Bioinorganic Chemistry & The Institute of Advanced Studies, University of Birmingham, UK

As a highlight of the activities of the Focus Group Medicinal and Bioinorganic Chemistry during 2017, we organized a workshop titled “Inorganic Chemistry Meets Medicine: The interdisciplinary science of using and modulating metals for imaging and therapy.” The workshop, co-sponsored by the Institute of Advanced Studies of the University of Birmingham (IAS-UoB), took place at the TUM-IAS. The goals were to bring together researchers working in different areas of metallodrugs development and to define the future trends in bioinorganic chemistry. More than 40 participants attended the event from different countries in Europe and also from the United States. In total, the workshop program featured 24 oral contributions, delivered by plenary, keynote, and invited speakers, which provided the basis for vivid and stimulating discussions. Of note, 33% of these oral contributions were delivered by women. In addition, nine selected early career scientists delivered oral presentations of very high quality. A poster session featured contributions from postdoctoral researchers and doctoral candidates.

The scientific program covered a range of topics, including the causal role metals can play in diseases and disorders, the synthesis of inorganic medicinal agents and materials, their utilization as diagnostic agents, early target validation for metal complexes, chemical biology and analytical chemistry approaches, and understanding mechanism(s) of action and off-target effects. Furthermore, translational implementation of inorganic supramolecular entities and nanomaterials for biomedical applications was discussed. Debate was stimulated around outstanding papers from different research fields in bioinorganic chemistry with the aim of developing new research areas and collaborations among participants. Several collaborations were established between scientists from TUM and the University of Birmingham. Of note, following his participation in the workshop, Dr. Alexander Pöthig (Faculty of Chemistry, TUM) was awarded the IAS-UoB Vanguard Fellowship to deepen collaboration with the group of Prof. Mike Hannon – a member of the TUM-IAS Board of Trustees – and other scientists at UoB.



From the discussions that took place during the workshop, a number of key points and recurring themes emerged. The complexity of cancer disease necessitates the use of innovative solutions (therapies) at different levels. In terms of chemotherapy approaches, there is a need for more selective and targeted anticancer agents to be used alone or in combination therapy. In this context, metal-based compounds (coordination and organometallics) are ideal to design novel chemical entities with multiple functionalities, for example to achieve multimodal imaging and therapeutic agents ("theranostics"), to exploit photo-induced reactivity for drug activation at the cancer site, or to take advantage of two different metal fragments that display a synergistic or cooperative anticancer effect.

The development of a variety of metallodrug delivery systems to target tumors, including metal nanoparticles, was highlighted during the workshop. In addition, the possibility of exploiting targeted caged-drug release with self-assembled metallacages was found to be particularly attractive. At the end of the workshop, following the enthusiastic feedback on the theme of the bio-applications of supramolecular coordination chemistry, Prof. Angela Casini agreed to be the guest editor of a special issue of the journal Frontiers in Chemistry, entitled "Supramolecular Metal-Based Entities for Biomedical and Biological Applications," which will be published in September 2019. Several of the participants in the workshop will be among the contributors to this thematic issue.

Simulation for Additive Manufacturing SIM-AM 2017

An ECCOMAS Thematic Conference

October 11–13, TUM-IAS, Garching, Germany
Chairperson(s): Ernst Rank, Ferdinando Auricchio, Paul Steinmann, Stefan Kollmannsberger
Number of participants: 187

In the past few years, additive manufacturing (AM) has evolved to one of the most promising techniques for creating solid structures of virtually any shape using a large variety of different materials. Applications for AM products range across many fields in engineering, from design models to lightweight components for the automotive or aerospace industry, or to medical applications such as patient-specific implants. Yet AM can only realize its complete technological potential if it is fully integrated in the digital design and production process and if the involved physical phenomena are understood in detail and controlled by a predictive numerical simulation.

The objectives of the 1st ECCOMAS Conference on Simulation for Additive Manufacturing, with more than 180 participants from 24 countries, were therefore to present and discuss the state of the art, mathematical models, numerical methods, and computational techniques for simulating processes and products generated by additive manufacturing. The goal of the conference was to make a step forward in the formulation, solution, prediction, and optimization of these processes and products. All these issues were discussed against the background that simulation for AM is often much more complex than for classical manufacturing techniques. AM processes involve multi-physics and multi-scale phenomena, where relevant spatial scales range over many orders of magnitude; important time scales start at microseconds for physical processes and reach to hours or even days for production of full parts.

Physics involved include mechanical, thermal, radiation, and phase change problems. Validation and verification are of utmost importance, and these are in many cases more difficult for AM than for other manufacturing processes. A final important difficulty is that, for a long time in the past, a lack of appropriate manufacturing technologies hindered the realization of designs as obtained, e.g., by shape and/or topology optimization. Therefore, many discussions concentrate on optimization, where the AM technology allows realizing very complex shapes of optimized structures. Furthermore, AM itself poses new demands for mathematical optimization, for instance through reduction of support structures or limitation of overhangs, that other manufacturing technologies would not require.

Five plenary lectures gave a broad overview of the main research areas associated with simulation for additive manufacturing. Further, the conference was structured in six topical minisymposia on AM process simulation, product simulation, multi-physics and multi-scale problems, material modeling, optimization, and innovative applications.

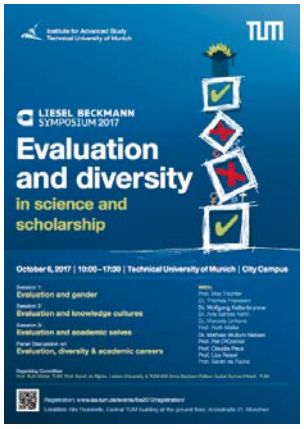
The feedback on the conference was very positive. In particular, participants pointed out the multidisciplinary background of attendees, which strongly supported discussions on the many facets of the general topic. Last but not least, the suggestion was made (which was fully supported by the organizers of SIM-AM 2017) that this conference should be a starting point for a biannual series of symposia on this important topic. ECCOMAS (the European Community on Computational Methods in Applied Sciences) and IACM (the International Association for Computational Mechanics) have agreed in the meantime to fully support such a series.

Proceedings: http://www.eccomas.org/spacehome/1/10

Post-Conference publication:
Special issue in the Journal of Computers and Mathematics with Applications, Elsevier, 2018

Liesel Beckmann Symposium: Evaluation and Diversity in Science and Scholarship

October 6, 2017
Organization: Focus Group Gender and Diversity in Science and Engineering



In 2017, the Liesel Beckmann Symposium, which generally aims to generate new ideas and concepts for gender- and diversity-related research at TUM and to help promote internal and external networking, focused on the topic of evaluation and diversity in science and scholarship.

Current evaluation mechanisms have established accountability and performance measurement as the gold standard route to productivity and (cost-)efficiency in academia. While there are numerous informal discussions about the increasing role of assessments in science and scholarship, it is only recently that considerable research interest is being directed toward the manifest and more intricate effects that assessments might have on the organization and production of knowledge. This is important, because first results indicate that academic assessment systems do not necessarily comply with central ideals and goals of European, national, and institutional research policies: to foster diversity-relevant and socially responsible science.

In this symposium, we explored some of the ways in which evaluations have become pivotal to academic work. We examined how evaluation mechanisms and gender issues become intertwined, how certain notions of “good performance” affect knowledge cultures across fields, and how performance metrics may have become woven into the very socio-material fabric that shapes academic selves. The program included keynotes by internationally renowned scholars, as well as a panel discussion between researchers and decision makers. In between, presenters and participants used the breaks to connect with each other and exchange their views on and experiences with evaluation and diversity in science and scholarship.

After the welcome by Prof. Sarah de Rijcke (Leiden University, TUM-IAS Anna Boyksen Fellow) and Prof. Ruth Müller (MCTS, TUM), the introductory address was delivered by Prof. Claudia Peus, Senior Vice President for Talent Management and Diversity at the TUM.

The first lecture in the session on Evaluation and Gender was delivered by Dr. Mathias Wullum Nielsen, Aarhus University, who focused on scientific performance assessments through a gender lens. Thereafter, Dr. Marcela Linkova, Czech Academy of Sciences, discussed institutional responses and solutions to gender bias in assessment. Prof. Liudvika Leisyte, TU Dortmund, wrapped up the session with a discussion of the main issues addressed.

The second session focused on the topic of Evaluation and Knowledge Cultures. Prof. Max Fochler, University of Vienna, gave a lecture on why fostering the diversity and sustainability of what we know needs diversity in what counts as good science. His talk was followed by a presentation on valuing in and against epistemic capitalism by Dr. Thomas Franssen, Leiden University. Dr. Wolfgang Kaltenbrunner, TUM, wrapped up the session with a response in which he brought together key dilemmas in evaluating multivarious knowledge cultures in academia.

The first lecture in the third session on Evaluation and Academic Selves was delivered by Dr. Christine Teelken, Vrije Universiteit Amsterdam, and Dr. Inge van der Weijden, Leiden University. The talk focused on publication and grant pressures, and the tactics scientists use to cope with competition in science. In the second lecture, Prof. Sarah de Rijcke presented collaborative work performed with the MCTS and the TUM-IAS on metrics, merit, and academic identity work. Prof. Pat O'Connor, University of Limerick, Dublin, provided a thought-provoking response to both lectures.

The ensuing panel discussion on Evaluation, Diversity, and Academic careers included panelists from academia and science policy: Prof. Max Fochler, Dr. Mathias Wullum Nielsen, Dr. Marcela Linkova and Prof. Liza Reisel from the Institute for Social Research, Oslo as well as Dr. Ana Santos Kühn, TUM Vice President for International Faculty Recruiting and Career Programs and TUM-IAS Managing Director. The panel was moderated by Prof. Ruth Müller, TUM.

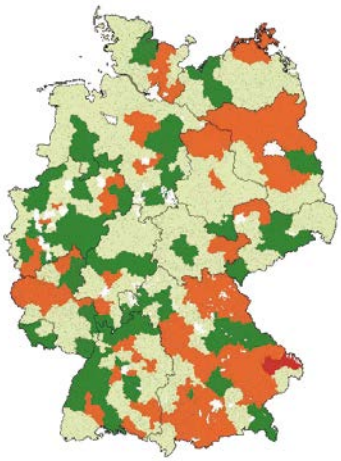
The TUM-IAS “Neighbors in Garching” Lecture Series: So what exactly is it that you do in Garching?

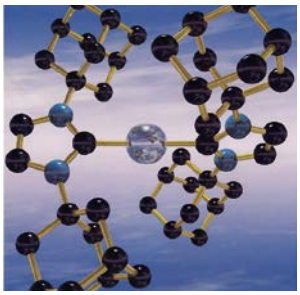
A peek behind the scenes at the work being done by researchers in Garching

It all started 2013 with a question former Institute director, Prof. Gerhard Abstreiter, was always getting form the area locals: “So what exactly is it that you do at the Garching campus?” As a reaction to this, he came up with the new concept of the TUM-IAS “Neighbors” series, aimed at getting the local community and neighbors living around TUM’s Garching campus more involved in the exciting research happening next door – and to encourage a real dialogue with them.

In this spirit, several times a year the TUM-IAS opens its doors to interested neighbors from the region for a “science Sunday matinee.” At this event we feature an informal talk by a well known scientist from the university or from one of our campus neighbors with the aspiration of making their work accessible for the diverse, general-public audiences in attendance. In around 45 to 60 minutes, the listeners – consisting of a diverse mix of people from nearby communities ranging in age from grade school to retirement age – are taken on a scientific journey during which they can get an insight into the fascinating world of research and scientific advances. After the talks, audience members (usually a respectable crowd of around 80) have the possibility of asking follow-up questions and talking directly with the experts over a cup of coffee and fresh-baked pastries.

In 2017 the scope of topics within the context of the TUM-IAS “Neighbors” event series ranged from catalysis as a future technology – personally presented by TUM President Prof. Wolfgang A. Herrmann – through the investigation of novel therapeutic approaches against the hepatitis B virus and issues to be addressed regarding automatic driving to the question of how mathematics can help us to understand (political) decision-making processes.





January 22 — Lecture Series Neighbors in Garching
Catalysis – technology of the future
Organization: TUM-IAS
Speaker: Prof. Wolfgang A. Herrmann (President of TUM)

May 7 — Lecture Series Neighbors in Garching
Viruses – the growing significance of the smallest germs
Organization: TUM-IAS
Speaker: Prof. Ulrike Protzer (Institute of Virology, TUM)

July 9 — Lecture Series Neighbors in Garching
Automatic driving – how? where? when? really?
Organization: TUM-IAS
Speaker: Prof. Markus Lienkamp (Automotive Technology, TUM)

November 12 — Lecture Series Neighbors in Garching
The discrete mathematics of democracy
Organization: TUM-IAS
Speaker: Prof. Peter Gritzmann (Applied Geometry and Discrete Mathematics, TUM)

Fellows' Lunches

An essential characteristic of the TUM-IAS is that it has Fellows, Honorary Fellows, Host professors, and other community members from all research areas in the TUM portfolio. With the aim of bringing our large community of talented people with many different specializations together, we regularly (typically once a month) host the TUM-IAS Fellows' Lunch. As the name already indicates, this event offers the possibility of getting to know each other at an informal lunch in connection with a talk by one of the members. This year, presentations covered a variety of fascinating topics including learning techniques for networks, cyber-physical system architectures, the Internet of Things, and data science in Earth observation – always explicitly addressed to an audience of scientists who are experts in fields other than the speaker's. When, after the lunch, we see vivid discussions and the formation of new, perhaps unexpected acquaintances, we know that once again, the Fellows' Lunch has fulfilled its purpose!

February 6 **Beyond independence: Efficient learning techniques for networks and temporal data**
Prof. Stephan Günnemann | Rudolf Mößbauer Tenure Track Professor

March 8 **Coding theory: "Old" concepts for "new" applications**
Prof. Antonia Wachter-Zeh | Rudolf Mößbauer Tenure Track Professor

June 1 **Cyber-physical system architectures and the Internet of Things – decentralization inevitable?**
Prof. Sebastian Steinhorst | Rudolf Mößbauer Tenure Track Professor

July 19 **In control of molecular motion**
Prof. Ben Feringa | Nobel Prize winner and Honorary Hans Fischer Senior Fellow



October 9 **Optomechanics: Measuring tiniest motion with light on a chip**
Prof. Menno Poot | Rudolf Mößbauer Tenure Track Professor

November 9 **Data science in Earth observation**
Prof. Xiaoxiang Zhu | Signal Processing in Earth Observation, TUM

December 11 **The opening of the multi-messenger era – the case of extragalactic sources**
Prof. Paolo Giommi | Hans Fischer Senior Fellow

Scientists Meet Scientists – Wednesday Coffee Talks

Since their introduction in 2013 by former director Gerhard Abstreiter, the Wednesday Coffee Talks seem to have become one of the most popular activities of the TUM-IAS. The event takes place every week after lunch in the spacious atrium on the first floor of the building and gives outstanding TUM publications a platform by allowing their authors to present their work in a short, simple presentation that would be understandable to non-experts too. The audience, made up of scientists on all career levels from the various research fields of TUM, in turn profits from the possibility to gain insight into exciting projects currently happening at TUM and to get to know each other in a relaxed, informal atmosphere.

Again in 2017, we had very interesting talks with topics ranging from the 3-D printing of live cells to the load bearing capacities of older bridges, followed by inspiring discussions and lively conversations. The Wednesday Coffee Talks are thus certainly adding to the TUM-IAS's standing as a center for intellectual exchange and discourse on campus.

January 11	Prof. Arne Skerra and Andreas Reichert on "bio(t)INK", a new concept for the 3-D printing of live cells
January 18	Prof. Liqiu Meng on "how much seeing is believing?"
January 25	Prof. Katharina Krischer on chimera states in dynamical systems
February 1	Prof. Florian Seitz on geodetic reference systems enabling highly accurate positioning
February 8	Dr. Eva Rath on mitochondria controlling stem cell fate
April 26	Prof. Carlo Bottasso on new control methods to optimize wind farm performance
May 3	Florian Praetorius on genetically encoded nanostructures that self-assemble from DNA and proteins
May 17	PD Dr. Christoph Hugenschmidt on positrons as a new tool for lithium ion battery research
May 24	Prof. Anja Rammig on self-amplified forest loss in the Amazon region caused by increased periods of drought
May 31	Dr. Eva-Maria Huber on the biological function and medicinal potential of the immunoproteasome in autoimmune diseases
June 16	Dr. Friedemann Reinhard on holography with the wi-fi router
June 21	Dr. Katharina Aubele on powering the energy revolution with heat from the Earth
July 5	Prof. Dr. med. Rainer Burgkart on unlocking the secrets of the Achilles' heel

July 12	Dr.-Ing. Jürgen Rauleder on realistic training methods for extreme flight conditions
October 18	Prof. Michael Knap on a quantum particle that shows a surprising behavior
October 25	Prof. Oliver Lieleg on the physical principles that make bacterial biofilms so tough
November 8	Prof. Matthias Rief on the use of “optical tweezers” to unveil the secret behind the cohesion of muscles
November 15	Dr. Tingying Peng and Prof. Nassir Navab on gaining a clear view on stem cell development with a new image correction program
November 22	Prof. Job Boekhoven on supramolecular materials with a time switch
November 29	Prof. Sherry Suyu on peeking around cosmic corners
December 6	Prof. Christoph Lütge on whether programmers should decide who lives and who dies
December 13	Prof. Steffen Glaser and Prof. Dominique Sugny on how classical mechanics helps control quantum computers
December 20	Prof. Oliver Fischer on whether old bridges last longer than expected

Events 2017

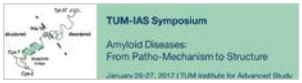
January 9–12

International Symposium **Machine Learning Challenges in Complex Multiscale Physical Systems**
(TUM-IAS Focal Period 2017)
Organization: Prof. Phaedon-Stelios Koutsourelakis (Continuum Mechanics, TUM), Prof. Nora Brambilla (Theoretical Particle and Nuclear Physics, TUM), Prof. Katharina Krischer (Nonequilibrium Chemical Physics, TUM), Prof. Oliver Junge (Numerics of Complex Systems, TUM), Dr. Andreas Kronfeld | Hans Fischer Senior Fellow, Prof. Yannis Kevrekidis | Hans Fischer Senior Fellow

January 16

Inaugural Lecture **Climate Smart Soils**
Speaker: Prof. Johannes Lehmann | Hans Fischer Senior Fellow

January 26–27



Symposium **Amyloid Diseases: From Patho-Mechanism to Structure**
Organization: Prof. Bernd Reif (Solid-State NMR, TUM), Prof. Ayyalusamy Ramamoorthy | Hans Fischer Senior Fellow

January 30

Inaugural Lecture **List Decoding of Errors in Arrays**
Speaker: Prof. Antonia Wachter-Zeh | Rudolf Mößbauer Tenure Track Professor

February 1

TUM Water Cluster Lecture Series **WASH in Slums: Access to Water, Sanitation and Hygiene – Challenges and Solutions in Periurban Informal Settlements**
Speaker: Dr. Ulrike Pokorski da Cunha (Deutsche Gesellschaft für internationale Zusammenarbeit)
Organization: TUM Water Cluster, IGSSE, TUM-IAS

February 8

Talk **Die Entstehung von Masse**
Speaker: Dr. Andreas Kronfeld | Hans Fischer Senior Fellow

March 13–14

Munich Battery Discussions **All Solid State Batteries - An Option for Future E-Mobility?**
Organization: Dr. Peter Lamp | Rudolf Diesel Industry Fellow, Prof. Hubert A. Gasteiger (Technical Electrochemistry, TUM)

March 15

Inaugural Lecture **Design of Decentralized Cyber-Physical System Architectures Considering Resource Constraints**
Speaker: Prof. Sebastian Steinhorst | Rudolf Mößbauer Tenure Track Professor

March 23–24

International Conference **Selection Theory and Breeding Methodology**
Organization: German Plant Breeding Society, Chair of Plant Breeding, TUM
Speaker: Prof. Daniel Gianola | Alumnus Hans Fischer Senior Fellow, et al.

April 3-5

Workshop **Quantum Control Theory: Mathematical Aspects and Physical Applications**
Organization: Prof. Dominique Sugny | Hans Fischer Fellow, Prof. Steffen J. Glaser (Organic Chemistry, TUM), Prof. Gero Friesecke (Global Analysis, TUM)

April 24 — Talk **Cellular Protein Folding: From Insight to Engineering**
Speaker: Prof. Matthias Feige | Rudolf Mößbauer Tenure Track Professor

May 2 — Talk **Nature and the Science in Moravian Instrumental Meteorological Observations from Late-18th Century Labrador**
Speaker: Prof. Dianne Newell | Visiting Fellow

May 4–5 — **TUM-IAS General Assembly**






May 8–10 — Symposium **Selected Topics in Science and Technology** (in the framework of the selection process regarding the Rudolf Mößbauer Tenure Track Professorships)
Organization: TUM-IAS

May 17 — Speakers Series on New Frontiers in Battery Science and Technology **Progress in High-Capacity Gradient Cathode Materials for Lithium-Ion Batteries**
Speaker: Prof. Yang-Kook Sun (Hanyang University)
Organization: Dr. Peter Lamp | Rudolf Diesel Industry Fellow

May 22–23 — Workshop **Coherent Neutrino Scattering**
Organization: Dr. Thierry Lasserre | Hans Fischer Senior Fellow

June 7 — TUM Water Cluster Lecture Series **What Shall We Measure Tomorrow? Needs and Trends in Future Water Analysis**
Speaker: Prof. Torsten C. Schmidt (University of Duisburg-Essen)
Organization: TUM Water Cluster, IGSSE, TUM-IAS

June 26–July 7 — Summer School **Methods of Effective Field Theory & Lattice Field Theory**
Organization: Prof. Nora Brambilla (Theoretical Particle and Nuclear Physics, TUM), Dr. Andreas Kronfeld | Hans Fischer Senior Fellow, et al.

July 3 **Munich Workshop on Coding and Applications (MWCA 2017)**
Organization: Prof. Antonia Wachter-Zeh | Rudolf Mößbauer Tenure Track Professor, Dr. Vladimir Sidorenko (Communications Engineering, TUM)

July 3 **TUM-IAS Summer Faculty Day**

July 18 Award Ceremony **TUM Distinguished Affiliated Professorship**
Awardee / Speaker: Prof. Ben Feringa | Nobel Prize winner and Honorary Hans Fischer Senior Fellow

July 31 Workshop **Microfluidic Large-Scale Integration Design Automation**
Organization: Prof. Tsung-Yi Ho | Hans Fischer Fellow, Prof. Krishnendu Chakrabarty | Hans Fischer Senior Fellow, Prof. Ulf Schlichtmann (Electronic Design Automation, TUM)

September 29 Speakers Series on New Frontiers in Battery Science and Technology **Towards Fundamental Understanding of Electrochemical Interfaces in Li-Ion Battery Electrolytes**
Speaker: Dr. Dusan Strmcnik (Argonne National Laboratory)
Organization: Dr. Peter Lamp | Rudolf Diesel Industry Fellow

October 6 Liesel Beckmann Symposium **Evaluation and Diversity in Science and Scholarship**
Organization: Prof. Sarah de Rijcke | Anna Boyksen Fellow, Prof. Ruth Müller (Science and Technology Policy, TUM)

October 6 Speakers Series on New Frontiers in Battery Science and Technology **Li-Ion Conductors and Solid-State Batteries: Status of Current Developments**
Speaker: Prof. Olivier Guillon (Forschungszentrum Jülich and RWTH Aachen University)
Organization: Dr. Peter Lamp | Rudolf Diesel Industry Fellow

October 11–13 ECCOMAS Thematic Conference **Simulation for Additive Manufacturing (Sim-AM 2017)**
Organization: Prof. Ernst Rank (TUM-IAS Director and Chair for Computation in Engineering, TUM), Prof. Ferdinando Auricchio (University of Pavia), Prof. Paul Steinmann (University of Erlangen-Nürnberg), Dr. Stefan Kollmannsberger (Computation in Engineering, TUM)

October 19 Inaugural Lecture **Modern Technology to Support Cognitive and Mental Health**
Speaker: Prof. Nicola T. Lautenschlager | Anna Boyksen Fellow

October 21

Tag der offenen Tür
Talk **Das Internet der Dinge – Was macht die Kaffeemaschine im Internet?**
Speaker: Prof. Sebastian Steinhorst | Rudolf Mößbauer Tenure Track Professor
Talk **Nanoelektronik und Nanophotonik**
Sprecher: Prof. em. Gerhard Abstreiter
(former TUM-IAS Director)

October 25–26

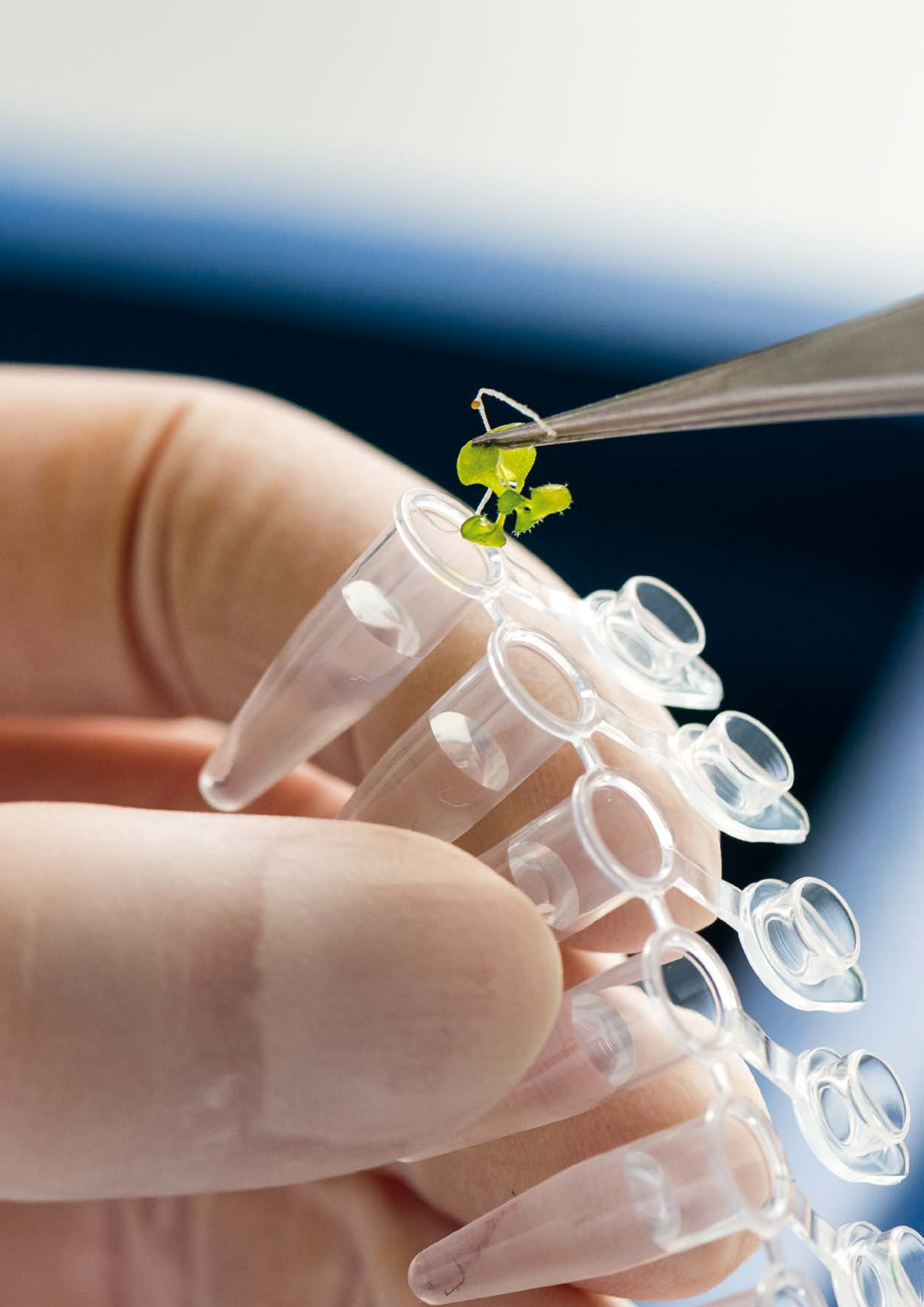
TUM-IAS UoB-IAS Joint Workshop **Inorganic Chemistry meets Medicine**
Organization: Prof. Angela Casini | Hans Fischer Senior Fellow,
Prof. Fritz E. Kühn (Molecular Catalysis, TUM), Prof. Michael J. Hannon (University of Birmingham and TUM-IAS Board of Trustees Member)

November 14

Award Ceremony **TUM Distinguished Affiliated Professorship**
Awardee / Speaker: Prof. David Baker | Honorary Hans Fischer Senior Fellow

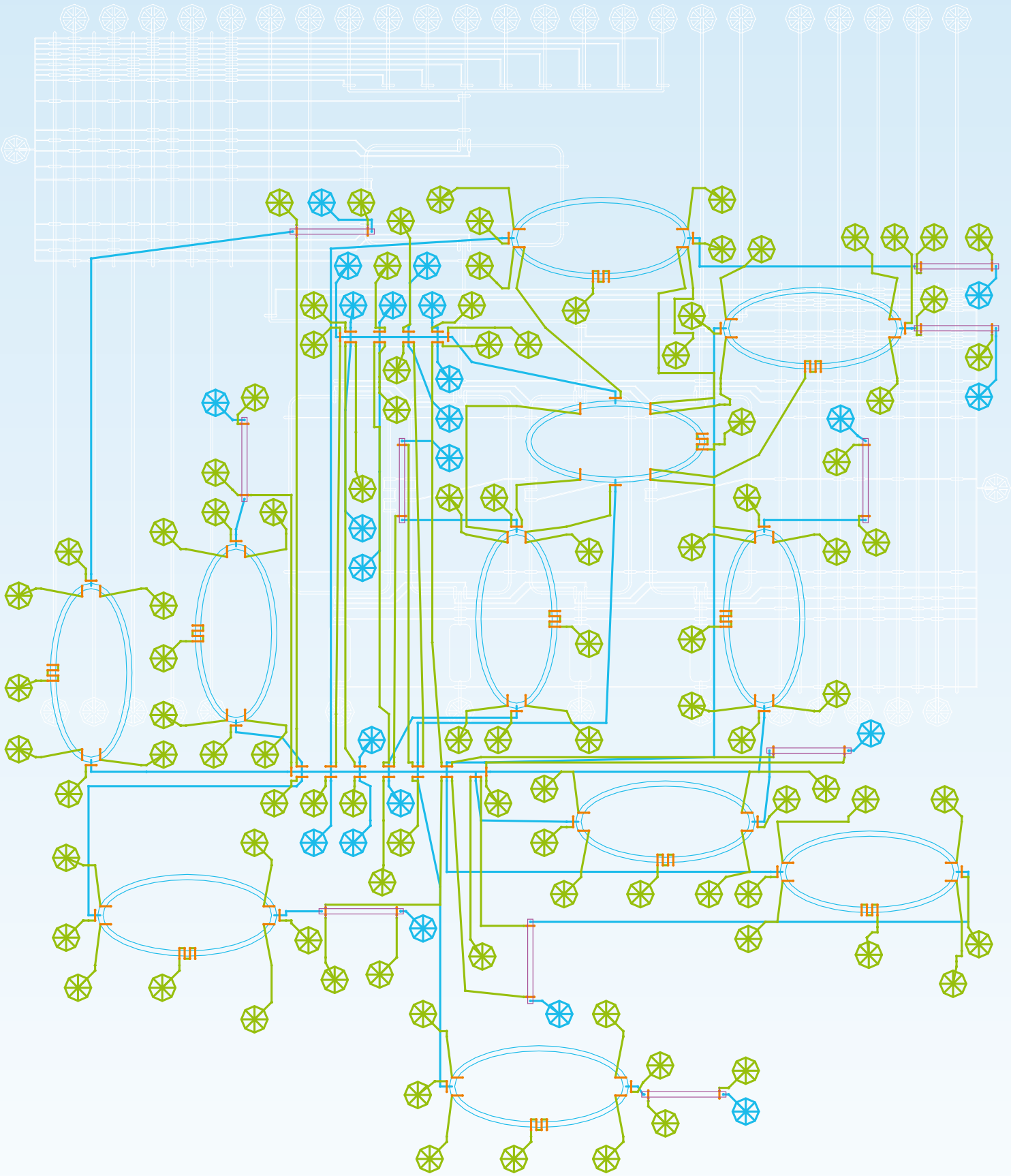
November 20–21

Workshop **Molecular Approaches to Heterogeneous Catalysis and Electrocatalysts**
Organization: Prof. Suljo Linic | Hans Fischer Fellow, Prof. Karsten Reuter
(Theoretical Chemistry, TUM)



In Focus

Microfluidic Design Automation and Neuromorphic Computing



Microfluidic biochip layout from Columba automated design tool.

Microfluidic Design Automation and Neuromorphic Computing




An emphasis on building new bridges between electronics and biology unites two TUM-IAS Focus Groups: Microfluidic Design Automation (MDA) and Neuromorphic Computing.

Both are hosted by Prof. Ulf Schlichtmann of the Department of Electrical and Computer Engineering at TUM. The principal collaborators in the MDA Focus Group are Prof. Krishnendu (Krish) Chakrabarty from the Department of Electrical and Computer Engineering at Duke University in the USA, a Hans Fischer Senior Fellow of the TUM-IAS, and Prof. Tsung-Yi Ho from the Department of Computer Science at National Tsing-Hua University in Hsinchu, Taiwan, who is a Hans Fischer Fellow. This Focus Group is also supporting two doctoral candidates, Yasamin Moradi and Chunfeng Liu. The Focus Group Neuromorphic Computing was established more recently in collaboration with Hans Fischer Fellow Prof. Hai (Helen) Li, who also is a member of Duke University's Department of Electrical and Computer Engineering.

The MDA Focus Group is addressing critical issues that could limit both the versatility and impact of microfluidics technology, best known as the basis for the rapidly growing "lab on a chip" market segment. Microfluidic biochips, microarrays, biosensors, and microreactors can be used in a range of applications including DNA sequencing, clinical diagnosis, drug discovery, and environmental monitoring. One of the keys to unlocking the technology's full potential will be computer-aided design tools similar to those that have helped the microelectronics industry master huge increases in the density and complexity of integrated circuits while also keeping reliability high and costs low. That is the main focus of the MDA collaboration.

In a way, it is the very success of modern computing that allows creative minds to imagine applications that expose its limitations – and that is where the emerging field of neuromorphic computing comes in. Interconnected trends in big data, embedded systems, and communications are giving rise to expectations that traditional computing architectures and devices seem unlikely to meet. Research in the Focus Group Neuromorphic Computing is aimed at providing an alternative inspired by the human brain and nervous system, through the investigation of novel devices and architectures that remove barriers between computer memory and processing.

The TUM-IAS conducted an interview on these two lines of research – as well as some areas where they intersect – with Tsung-Yi Ho (TH), Helen Li (HL), and Ulf Schlichtmann (US) in Munich and Krish Chakrabarty (KC) in North Carolina, who took part via videoconference.

Tsung-Yi Ho

Q: The promise of the “lab on a chip” has been heralded for many years already. What’s the status of real-world applications?

TH: There are several applications now, ranging from small-scale to large-scale. One of the key applications would be next-generation DNA sequencing. Companies are already using microfluidics for preparation of samples. There is even progress on “organ on a chip” technology. It is possible to simulate an organ on a microfluidics chip, and this has been used already in a clinical test. It shows a lot of promise.

KC: I would say, though, that we still are in the age of unrealized potential. There’s been a lot of hype and excitement, a lot of activity. But most of the work that these chips do is still the tedious work that people used to do on the benchtop, things such as pipetting into a test tube, shaking the test tube, doing mixing, transferring the sample to other media. Those things have been automated and have been demonstrated. There are many research labs that are using lab-on-chip to do these things, and there are a few scenarios in commercial practice, though not a lot, where this is done. But these chips still do not have intelligence in them. You still have a lot of human intervention, in making the decisions on how to interpret the data and what to do next. And I think this is where the next-generation lab on a chip can be very powerful, because we can embed real-time intelligence and decision-making capabilities into the systems.

Q: Is that something design automation can help achieve?

KC: That is one activity of our MDA Focus Group. We are looking at going beyond the regular tedious things that people do right now on the lab on a chip.

Q: And a prerequisite for that is reducing the human effort involved in designing the chips?

TH: We know a PhD candidate at EPFL who spent almost one month to design a microfluidic chip by hand, with 918 valves, the fundamental element. So think about it, if you have more than 10,000 valves – you can put that many elements on a chip, but it’s impossible to design it manually. You must go to automation.

US: Design automation for integrated circuits got started when they became more complex, so that the human designer had difficulties in handling the complexity in the first place and in getting anywhere near optimal solutions. Today in microelectronics we are dealing with systems that have billions of components. In microfluidics, we’re not there yet, but they are getting more complex, in terms of the number of operational units that you have on such a chip, how they are interconnected, and the assays that you want to perform. We’re getting to the point where, once you have a certain assay and want to design a specific biochip for that, you get there faster using automation techniques, and I think in many instances you will get a better solution than the human would get.

TH: We also want to do additional optimizations – to minimize the area or minimize the volume of fluid used – and these things all require design automation. Also, most microfluidic chips currently handle very basic operations, steps that traditionally need to be done separately. To do sample preparation, cell lysing,

Tsung-Yi Ho, Helen Li and Ulf Schlichtmann

extraction, and amplification, for example, and transfer the result of each step to the next, you might need at least three separate chips, or three components, or three robotic devices, and there may be some loss of material along the way. With microfluidics it is possible to integrate them so all the procedures can be performed on only one chip. But designing more highly integrated biochips by hand is impractical.

Q: An obvious difference between electronic integrated circuits and microfluidic chips is that you're dealing with different physics. What kinds of knowledge, technology, and experience can be successfully transferred from microelectronics to microfluidics?

KC: The similarities are more in terms of the fabrication. The lithography techniques are common. We make chips in pretty much the same way, using masks and lithography as in electronic circuits. Even bottom-up self-assembly has been attempted for both types of technologies.

US: Another similarity is that you have operations that need to be executed in a certain sequence, and the result of one operation sometimes feeds into the next operation. You need to decide when you do these operations, and on which of your chip's functional units you do them.

TH: The properties of fluid samples are totally different, of course. So there is a different delay, and fluid dynamics, when you design a lab on a chip. That's the big difference. And currently these chips are still designed bottom-up. That means that every component is designed by hand, and they can put it together, integrate the components, and then realize it doesn't work. They will iterate many times. For integrated circuits, the design automation framework is already very mature, and it's more top-down. So that means given the specification and the goal, we can design for the result using customization globally.

KC: When you look at electronic circuits, you have to first ask the question of what is the science, how do you explain electronic behavior. And it comes down to electrons and holes, the physics of the devices, and it has been very well explained and understood over many years. In microfluidics, that is not the case. There

Tsung-Yi Ho, Helen Li and Krishnendu Chakrabarty

are still a lot of open questions, and a lot of gaps in explaining how these devices work. The physics is much more complicated. It involves fluidics, sometimes optics, mechanical parts. And also in semiconductor physics, the underlying science is the same for most of the technologies. In microfluidics, you have different physics for different technologies. So we have continuous flow in channels using pumps and osmotic magnetics; that's one set of physics. Then you also have dielectrophoresis, where you have very high voltages and cages, which are being moved around under electrical control. There's electrowetting, and many other types of esoteric mechanisms. So that makes it very difficult.

I would also point to a problem that requires automation in microfluidics, something I call volume management, which we don't see in electronics. If you look at semiconductor integrated circuits, the carriers are effectively infinite. You can take as many electrons and holes from the substrate as you want, you can get your currents, and you can send them back to the substrate. It's a closed loop. In microfluidics, we're dealing with a finite amount of liquid volume. The stock volume is limited. We talk about having a reservoir with a certain milliliter volume. So any reaction that you do, any chemistry, you must be aware of the volume limitations. You can't set it up so you run out of one reagent while you have other media left over that you can't do anything with. So a lot of the design automation involves looking at how you can optimally utilize these volumes and finish the required chemistry in the shortest possible time.

Q: Where do you see microfluidics technology heading, and what are the other critical hurdles?

US: As Krish mentioned earlier, we are very interested in this fusion between microfluidics and microelectronic intelligence, cyber-physical systems as they are called. You have the microfluidic chip on the one hand, and you have electronics on the other hand monitoring the outcome of steps that are happening on the chip. What we're dealing with on the chip, after all, is chemistry and biology, and the outcomes of certain reactions depend on variables such as temperature and cannot be completely predictable. So you need to observe them using, for example, some optical system, and then decide whether you repeat an experiment or what is the next step. And if you do

that using electronic intelligence, you might be able to handle fairly complex biochemical assays and analyses on a single chip, without human intervention. That potentially might bring us closer to the promise of doing complex analyses at the point of care, even if there is no doctor or trained technician present, for example in a rural village in Africa.

KC: So clearly the challenges also come down to the cost of the products. These are mostly throw-away devices. You don't use them over and over again. And anything that you throw away must be cheap. If you do not have design automation, you really cannot explore the entire space of implementation, and you won't get to the lowest cost point very easily. If you have the tools, as Tsung-Yi was saying, you can use your mouse on your computer, click on different options, and get different layouts. And you can do it in a loop, considering larger numbers of possibilities, or use some mathematical frameworks for doing optimization – down to the smallest form factor, the smallest package, the lowest cost. It's very important.

We worked with a start-up company that came out of Duke, founded by one of my postdocs. They were selling to hospitals in Illinois. Their initial chip was manually designed. It was done by hand. They had come up with a layout with a small number of input/output pins, but the pins were a problem, because they took up a lot of the package area. Using mathematical tools and design automation techniques, we were able to decrease the number of pins by a very big number. The second version of the chip used our optimized layout, and they were very pleased.

Q: Has the framework of the TUM-IAS Focus Group helped you bring together complementary areas of expertise, extend your own capabilities, or expand your reach?

TH: Definitely. When we formed this Focus Group and started doing research on microfluidics, of course we started by focusing on reliability, because we have relevant expertise here. Ulf is the expert in designing integrated circuits for reliability. And very quickly we were able to publish findings on automated design for microfluidics, particularly considering reliability,

Ulf Schlichtmann

at a very good conference and also in a very good journal in our area. We have research results, and we also have a plan for a business. And in July 2017, thanks to the TUM-IAS funding, we had the first Munich Workshop on Large-Scale Microfluidics Design Automation. We've reached out to people designing biochips and also applications, in industrial as well as university research, including the European Microbiology Laboratory in Heidelberg. So we have already expanded this collaboration.

US: I'm in some sense the new kid on the block here, because Krish and Tsung-Yi started on microfluidics much earlier. Krish is the father of design automation for microfluidic biochips. And I was introduced to this topic first by Tsung-Yi when he was here as a Humboldt Fellow. When we realized that some of the techniques we have been using for electronic chips are also applicable for microfluidic biochips, that got me and my team really interested in this topic, specifically in terms of reliability. Some biochips are throw-away, as Krish was saying, but some of them might be used repeatedly, and the valves used in these chips are mechanical in nature, so they have a tendency to wear out. Traditional biochip designs were using the

valves very unevenly, and we had some ideas about how we could even out the usage of valves to increase the lifetime of the chip. This is one area where we brought some specific research that originated in electronics into the microfluidics field.

KC: Ulf is being extremely kind. I don't want to be the father of too many things. I have my own kids at home, I'm their father, and that's it. But otherwise Ulf has put it very well. We share the same excitement.

In the past I have looked at a whole range of design automation problems, from synthesis to placement, layout, routing, and chip design, also looking at failure mechanisms, how these chips fail, what kinds of faults they exhibit, how we can test them properly at low cost, make them reliable. But of late I have started moving more toward the biology. I want to understand the applications better, and what are the various biochemistries that we can run on these chips. So the motto that I follow now is "realistic microbiology on simple chips." I would love to see these chips simple enough that the user isn't intimidated, but the applications that would run on these chips would be complex, would be realistic. And that's where design automation is key, because it can allow complex chemistries to run on chips that are, by themselves, pretty dumb. But we have software, we have intelligence layered on top of the actual circuitry, that allows realistic chemistry to run.

So I think that is the complementarity. Tsung-Yi is one of the most respected persons I know in the design automation space. And I'm now looking more at how can I bring that to the biologists, what is the bridge we can form.

Q: How would you describe the bridge that connects these two TUM-IAS Focus Groups, Microfluidic Design Automation and Neuromorphic Computing?

HL: It is a two-way street. My research, especially where it concerns novel electronic devices, can benefit directly from both their design tools and their expertise. In the long run, I hope what I bring in terms of machine learning and a new computing paradigm might also contribute to advances in microfluidic design automation.

Essentially, neuromorphic computing aims to utilize what we know as VLSI, very-large-scale-integration circuits and systems, to mimic biological nerve systems and then to achieve more functionalities – including cognitive functionalities – and even further, to enable the system to learn by itself and maybe achieve some self-awareness in the future.

Neuromorphic computing is different from traditional computing. In the architectural perspective, traditional computing separates the processing from the memory. Processing can go really fast, but memory becomes the bottleneck. Essentially what we have in our human brains is a large volume of nerves and synapses that form network structures. We want to reform the computing architecture by mimicking that structure and then realizing it with VLSI circuits and systems. For about 30 years, efforts to mimic biological systems have focused mainly on the software level. Neural networks, machine learning, so-called deep learning – the main emphasis in these areas is on making algorithms functional and executable on existing computing systems. What we are trying to do is to put it completely into the hardware levels, so that execution and implementation will be more efficient.

Q: What role does the so-called memristor play in this?

HL: It lets you do away with the wall between processing and memory at the most basic hardware level. The memristor device was originally predicted by Leon Chua back in 1971. Stan Williams, at HP Labs, led the group that was first to realize a physical device representing the expected characteristics. HP's device is an oxide-based device. It's a thin-film structure. When you apply voltage or current through the device, charge across the device – which can serve as a basic unit for computational logic – is represented by its resistance states. And the good thing is when you remove the charge, the resistance states will remain. This behavior is very similar to the synapse in biological systems.

Another very important similarity between the two is the potential for large connectivities. So even though, as I said, 30 years ago people were talking about neural networks, the huge volume of connections is an essential requirement if you'd like to get useful applications from it. What we can do with the memristor, since it's only

two-terminal thin films, is form what we call crossbar structures. Essentially you have horizontal wires and vertical wires, and at each crosspoint we are able to make one device. So you can see the connection density is extremely high.

Q: Potentially billions on a chip?

HL: Potentially billions on a chip is not a problem. We might have to partition that into small arrays or groups in order to get flexibility in the design, in the functionality.

Q: Is this still purely a research topic, or are there products based on memristors?

HL: I do not think there are memristor-based neuromorphic computing system products yet. The technology itself, which is often called ReRAM or resistive memory technology, has been under development for several years. In general, any memory technologies using resistance states to represent logic for information can be categorized as resistive memory. One of Leon Chua's recent efforts in fact is to prove that many materials, including spintronics and phase change, are part of the memristor technology umbrella. Memory products based on these technologies are available now. And we have devoted a lot of effort to developing a new computing platform and realizing reasonable applications using memristor technology.

Q: Where do you see the biggest advantages this approach might offer?

HL: By bringing information storage and computation together, simultaneously, a neuromorphic computing system is expected to be especially good at handling perceptions, cognition, and learning, and at capturing and maybe extrapolating from existing conditions. For some applications, such as scientific computation for instance, existing computers might still be more advanced than a human being or a system that mimics a biological system.

In the Neuromorphic Computing Focus Group we are primarily working on the architecture but also circuit design, and working to bring those design concepts to the point where they can be implemented and realized.

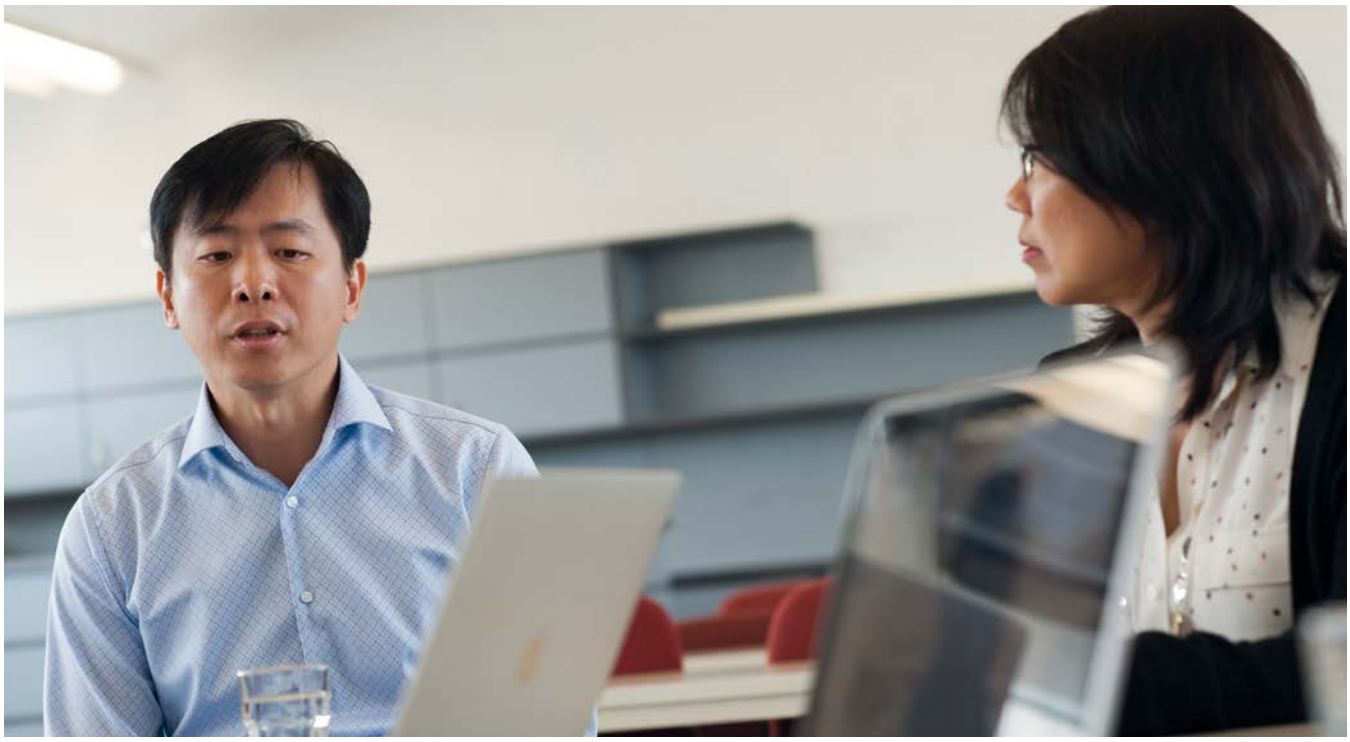
Helen Li

We put a lot of effort on the design side, and we also put a lot of effort into trying to connect with application levels. Initially we were working on the design concepts and a simple demonstration. But right now we're trying to move to larger-scale systems and make the approach really useful to potential users or customers.

Q: How would you define large-scale in this context?

HL: The demonstration originally is only dealing with very small things, like recognizing characters, for instance, to tell whether this is A or B or C or D or something else. But when we progress toward really useful applications, this actually requires a lot of computing resources. We have to make the hardware bigger and bigger to accommodate our requirements. This is what I meant by large-scale systems. But when we eventually shift toward commercialization, we will face the quality and reliability problems.

Tsung-Yi and I already had several interactions in these areas several years back, dealing with a lot of placement and routing issues. In that case we borrowed Tsung-Yi's intelligence to solve the problem. And it went really really well. We actually reduced the design size more than 50 percent, and the routing sizes more than 40 percent. That work was published in 2015 and was nominated for a best paper award. In addition to the design automation, we would further need reliability controls. All emerging technologies such as nanotechnology-enabled neuromorphic



Tsung-Yi Ho and Helen Li

computing will have significant reliability issues, for example defects, huge variations, temperature and ageing effects, and so on. We'd really like to work with Ulf on these reliability controls. And further, once we are getting ready to deliver a product, we will need to get it validated and tested, one of the special strengths Krish brings to the group. Thanks to our collaboration, I feel free to focus entirely on the neuromorphic computing.

KC: Helen's work is very exciting. She's a new faculty member at Duke, and we're very excited that she has joined us. Now Helen is going to tear down the memory wall that has been such a long-standing problem in computer architecture, where the processor is starved and waiting for data. I can only cheer her on: Professor Li, tear down that wall!

Q: There, in a nutshell, is one breakthrough you'd like to see. What are some other major outcomes you have in mind?

HL: I am hopeful about the computer's ability to learn by itself. We are already in the big data era, and if the computing systems could be able to learn from those huge amounts of data and extract information targeted for different applications or customers, I think there will be a very dramatic improvement in this area.

US: I personally am not looking for one big breakthrough because, as they say, it's hard to make predictions, especially about the future. What I'm hoping is that our research will be used by other people to advance their fields, whether that means understanding biology, curing diseases, or something else.

TH: Currently, most of the people using microfluidic chips use them for just one dedicated purpose. They may not think it is even possible to create multipurpose integrated microfluidic chips. But with our tool, it is possible. I hope with our technology they can have a general chip that can integrate everything together.

KC: I'm hoping that in a few years time, we can make fundamental breakthroughs in cancer research, with customized drug regimes for individual patients. We can do that through using microfluidic biochips as a key enabler for large-scale distributed experimentation, collaborative experimental research. I can envision a large group of labs and scientists running experiments in a very collaborative fashion, helping each other through microfluidic-enabled biochips and

the cloud infrastructure such that, let's say, two plus two would be five, not four. So that they can realize treatments, pathways for disease, in a distributed, collaborative manner.

Q: All of you have traveled widely and have spent significant time in various visiting positions at leading international universities. How does your TUM-IAS experience compare to other visiting stays?

TH: Krish is the real world traveler, but I have spent the most time here, starting from 2011. I first came here and met Ulf, and we started collaborating with support from the Humboldt Foundation. I think Humboldt provided a very good start for us to initiate this project, and it went well, so we applied for support from TUM-IAS to continue it. The main difference is that the Hans Fischer Fellowship here provides support for one doctoral candidate. I don't need to worry about any internal financial issues during my stay at TUM, and this is very good. Our doctoral candidate is doing very well, and he is learning about working in different cultures, Taiwan and Germany. That's something very special about this program.

KC: I would add that my experience has been that in many places where I visit, I am more like an outlier, in that there isn't much of an internationalization effort at the host university. I am brought in on the initiative of a professor there, my collaborator, and it's mostly inward-looking. At TUM there is a structure and an organized effort to reach out, and I am no longer an outlier. There are many people like me on campus and in the TUM-IAS who are from other countries and who are working closely with other researchers. So I find that internationalization is in the genetic code of TUM and the TUM-IAS, and that comes through all the time.

US: In science, often you meet somebody, you think you have some great ideas, then you get back to your office and there's tons of the usual stuff to do, and the cooperation never really happens. But here there really is quite a bit of common work, not just with jointly supervised doctoral candidates, but also extending beyond that. There is collaboration with a top PhD candidate of Krish's, who by the way took the opportunity of another TUM program, the Research Opportunities Week, to come here last spring and to interact with people here. Tsung-Yi has been very generous in giving advice to quite a few other doctoral candidates, and this has resulted in a very significant number of papers. And we have really been successful in targeting the top venues with our publications.

KC: There's also the opportunity of bilateral exchange visits. In the other places, it's one-way. So I visit, but there isn't much opportunity to invite researchers back to Duke. In the TUM-IAS it's much easier, because there are programs and funding to facilitate that. I think it's also very good, and possibly unique, that our doctoral candidates are expected to travel and spend time at the other institution. It's also easier to do research here because English is very widely used and very widely spoken. In many places you run into a language barrier, beyond the immediate close circle. Of course Munich itself is a very international place, so that makes it easier for visitors to stay here and to work here.

HL: I would stress one thing Krish and Tsung-Yi already highlighted, that doctoral candidates hired at TUM are expected – and supported – to go to Duke and join our groups for a period of time. Such a two-way communication will really help them learn the culture in the United States and then bring that back to TUM. Also, they are able to build a solid connection with my team. Extensive communication across TUM is also a big advantage. I've never seen such "luxury" situations in other universities.

US: I think the Alexander von Humboldt Foundation, which Tsung-Yi mentioned, is one of the really great science institutions that we have in Germany, and very few countries have anything comparable. They're really great at bringing scientists together and getting international scientists to Germany. And the TUM-IAS was built on the model of the Humboldt Foundation, but they actually went beyond that – I'll say it again – by providing support for a doctoral candidate, and also by making an effort within TUM, across the different disciplines, to bring the Hosts and Fellows together through things like the General Assembly and many other events. I think Krish put it very nicely. It's in their genetic code to foster this bilateral and cross-disciplinary international research.

Scientific Reports

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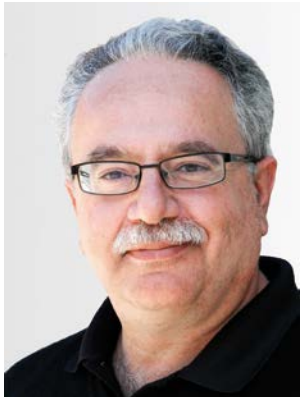
Focus Group **Complex Systems Modeling and Computation**

Prof. Yannis G. Kevrekidis (Johns Hopkins University and Princeton University)
Hans Fischer Senior Fellow
Sindre Haugland, Felix Kemeth, Maximilian Patzauer (TUM) | Doctoral Candidates

Scientific Reports



Yannis G. Kevrekidis

Hosts

Prof. Katharina Krischer
Nonequilibrium Chemical Physics, TUM

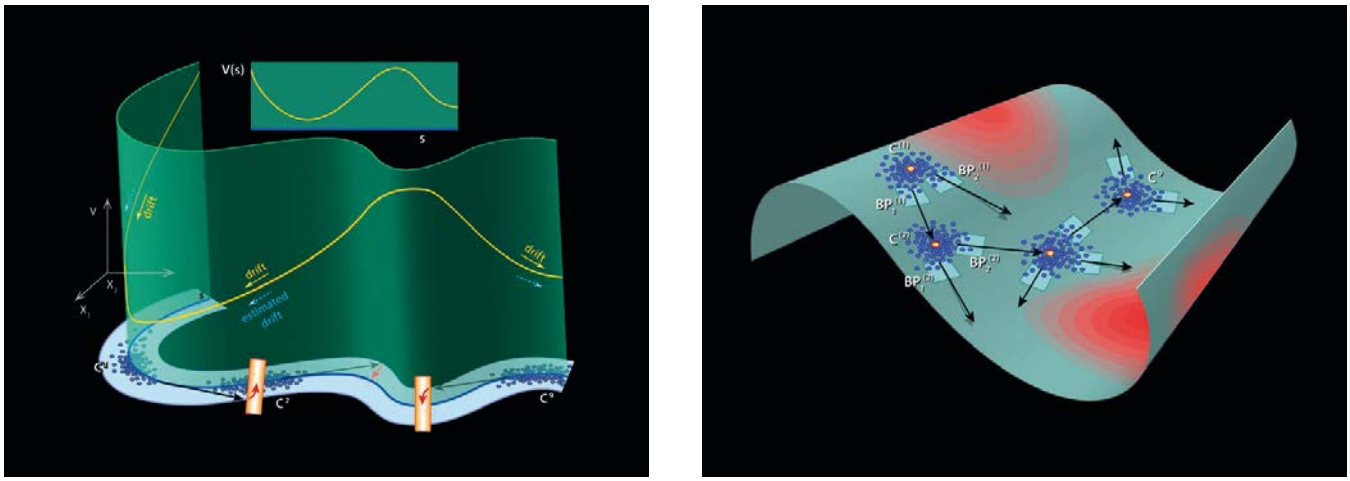
Prof. Oliver Junge
Numerics of Complex Systems, TUM

Machine learning and the modeling of complex systems

Our work focuses on complex systems modeling which, based on established mathematics and assisted by machine learning, appears to "sidestep" some elements of physical understanding. Thomas Kuhn, we claim, did not think big enough in his *Structure of Scientific Revolutions*. In the Middle Ages, an apprentice became a master of a craft not through understanding a set of laws and equations, but rather through amassing a giant set of experiences (many of them failures), what we now call a database, over a period of ten to fifteen years. "Science" consisted of manipulating large data sets painstakingly acquired over many years without real understanding. Galileo, followed triumphantly by Newton, collapsed this enormous database into a concise set of three equations, which we admiringly called "understanding." Outside of quantum mechanics, which is still not understood, modern science, in particular biology, rests on such a Newtonian approach in principle, but not in practice. While we claim we have understanding because of Newton (and later Maxwell), biology becomes an intensely data-rich enterprise at an accelerating rate. In many respects, things are now again not much different from the way they were in the Middle Ages: Experts become experts once again by amassing a giant set of experiences (many of them failures), in one tiny corner of biology: building a database, over a period of ten to fifteen years. While "paradigms" are used to describe the emergent new models of viewing the data, we can never again collapse huge data sets as compactly as Newton did. It is not lack of brilliance – it is just not possible.

Scientific "understanding" must then take on a new meaning, different by necessity from that which emerged from Newton, because of the impossible complexity and interconnectedness of biological systems at the ecological and evolutionary level. The problem facing us now is how to find global solutions of integrated biological processes when a detailed understanding in the Newtonian sense is beyond the grasp of the human mind. The main missing ingredients are (1) a mathematical structure for quantification and understanding of precision, a crucial limitation in the utility of mathematics for the life sciences and medicine, via computational algorithms that do not aim for a human Newtonian understanding, and (2) a close coupling of algorithms with experimentation on complex systems, which utilizes the algorithms for experimental design as well as for making predictions, going directly from queries to predictions and thus sidestepping human understanding.

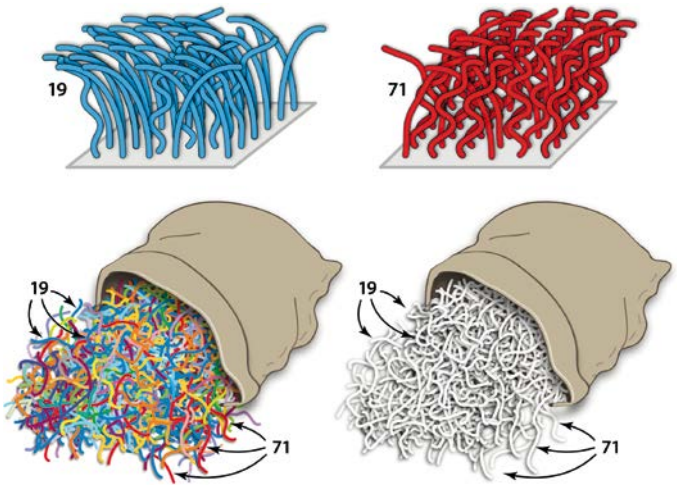
In mathematical modeling of biological systems, one typically progresses from observations of the world (and some serious thinking!) to equations for a model, and then to the analysis of the model to make predictions. Good mathematical models give good predictions (and inaccurate ones do not), but the computational tools for analyzing them are the same: algorithms that are typically based on closed-form equations. We want to turn that procedure around. While the skeleton of the process remains the same, today we witness the development of mathematical techniques that operate directly on observational data and circumvent the serious thinking that goes into selecting variables and parameters and writing equations. The process then may appear to the user like looking into a crystal ball: queries to predictions without human understanding. Yet the serious thinking is still there, and it uses the same and some new mathematics: It goes into building algorithms that



1 | Pictorial illustration of the iMapD exploration procedure with (left) 1-D and (right) 2-D effective free energy surfaces (FESs). In left inset, a good collective coordinate is already available – the collective coordinates in left and right are not known *a priori*.

jump directly from data to the analysis of the model (which is never explicitly available) so as to make predictions. We have worked on the close integration of such "present and future" crystal ball algorithms with "present and future" experiments, feeding back into the algorithms and advancing their oracular powers.

In the spirit of this modeling philosophy, work in our group this year had three noteworthy accomplishments: the use of machine learning to bias molecular dynamics simulations that accelerate folding computations for proteins (figure 1 and [1]); the extraction of evolution equations from agnostic data (figure 2 and [2]); and the discovery of "good" embedding spaces for data without apparent internal structure announced in last year's report [3].



2 | We observe an ensemble of short trajectories in what we call a trial from a fixed, yet unknown, dynamical regime. For example, one trial is labeled 19 and another trial is labeled 71. We store the short trajectories ("bag" them), and we only keep the label of the trial. Our goal is to empirically derive the dynamical regime information associated with each trajectory (labeled by the color in this case), by (a) deducing the state variables and the associated phase portraits and then (b) organizing the phase portraits of all the trials, so as to (c) derive (a tabulated form of) the evolution equation governing the dynamics.

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Focus Group **Computational Mechanics: Geometry and Numerical Simulation**

Prof. Alessandro Reali (Università degli Studi di Pavia) | Hans Fischer Fellow
Davide D'Angella (TUM) | Doctoral Candidate

Scientific Reports

Alessandro Reali

Host
Prof. Ernst Rank
Computation in Engineering, TUM

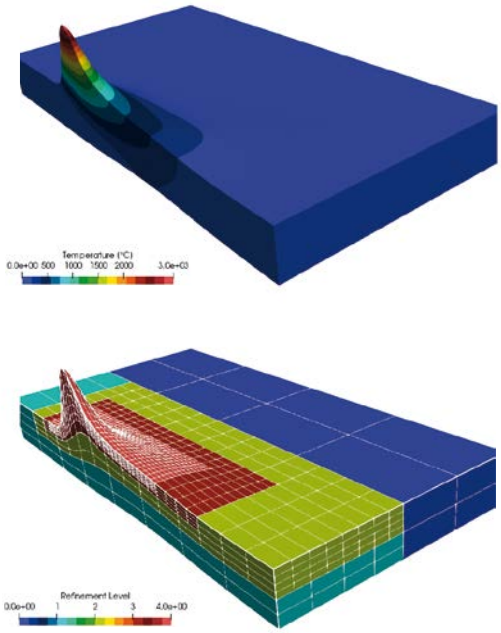
The main aim of this Focus Group is to take advantage of the unique approximation and geometric features of modern computational mechanics techniques, such as isogeometric analysis and the finite cell method, as the way to go for creating efficient analysis tools for the effective simulation of complex problems like those related to additive manufacturing.

Historically, finite element analysis (FEA; i.e., the main engineering numerical analysis tool) was developed well before the advent of computer-aided geometric design (CAGD; i.e., the main geometric design tool). The connection between the two worlds relies on interfaces often far from efficient. As a result, building analysis-suitable geometries is estimated to take up to 80% of the overall analysis time for complex CAGD-based engineering designs. Moreover, typically most FEA geometries are composed of simple objects, such as tetrahedra or hexahedra, which may not be able to represent highly sophisticated geometries with sufficient accuracy. This typically translates to very expensive simulations (and in some cases even to modeling errors and misleading results), and such a gap definitely has to be dealt with.

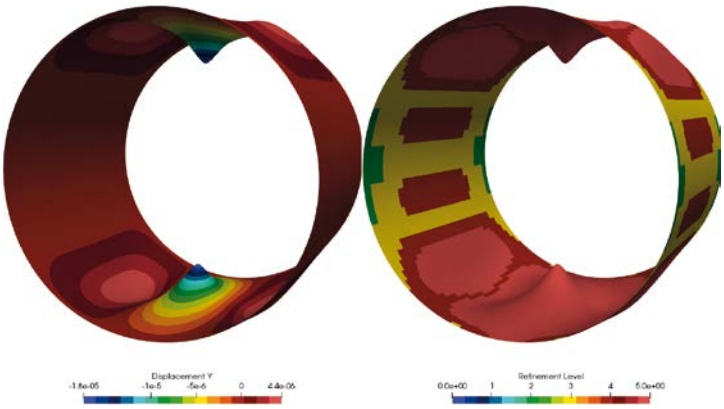
Isogeometric analysis (IGA) was introduced in 2005 with the idea of performing analysis with splines, which are the basic ingredient of CAGD geometries, in order to make the construction of analysis-suitable geometries much simpler and more efficient. Another relevant and promising simulation framework is the recently developed finite cell method (FCM), which makes it possible to deal with very complex and/or evolving geometries in a simple and effective way via the "immersed" concept. Both methodologies have been proven to be successfully applicable to practical problems, and we use a combination of them to create efficient analysis tools for additive manufacturing problems, which constitute one of the most interesting modern challenges of computational mechanics.

In the second year of the Focus Group's active work, we concentrated on various aspects of the methodological basis of the numerical methods to be applied. In particular, a new approach on how to implement local refinement within IGA was developed. To this end, we considered one of the best state-of-the-art local refinement techniques for IGA, and we proposed a novel implementation strategy consisting of a generalization of a well established way to implement IGA without local refinement, presenting various advantages. This work resulted in a publication [1] involving all members of the Focus Group. The concept will serve us to integrate adaptive IGA into the existing software for simulation of additive manufacturing developed at the TUM Chair for Computation in Engineering.

Furthermore, we proved that the above implementation strategy is suitable for a different family of applications, including elastoplastic and thermal problems. Moreover, this refinement was also applied to shells, i.e., special structures where one dimension is very small compared to the others.



1 | Temperature on a moving laser problem.



2 | Displacement of a pinched cylinder.

In addition, our collaboration with the Focus Group Regenerative Medicine continued to investigate phenomena governed by nonlinear mechanics. Specifically, nonlinear material models, solution techniques, and associated problematics were studied and tested in the context of the simulation of mechanical response of fiber-reinforced hydrogel. This project resulted in two publications [2]–[3]. In general, the nonlinear behavior is of fundamental importance for accurately capturing effects of complex geometries and materials in practical engineering problems. Therefore, this will also constitute an important building block for the simulation of additive manufacturing.

We finally highlight the collaboration with other TUM-IAS Focus Groups, namely, Computational Transport Oncophysics, Phase-Contrast Computed Tomography, and Image-Based Biomedical Modeling, which led to the (successful) proposal for a Focal Period entitled Advanced Computational Modeling for Tumor Growth Prediction, which will be organized in 2018.

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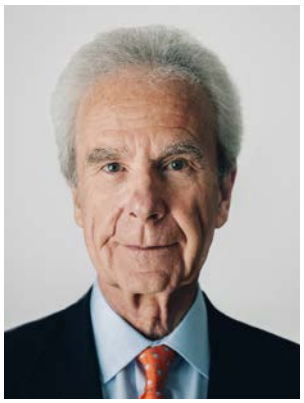
Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Computational Transport Oncophysics**

Prof. Bernhard Schrefler (University of Padova) | Hans Fischer Senior Fellow
funded by TÜV Süd Foundation
Johannes Kremheller (TUM) | Doctoral Candidate

Scientific Reports



Bernhard Schrefler

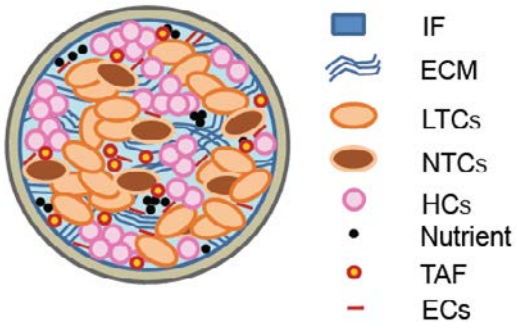
Host
Prof. Wolfgang Wall
Computational
Mechanics, TUM

Toward a patient-specific model for tumor growth and drug delivery

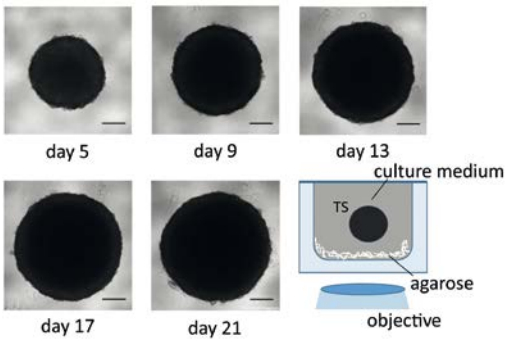
Cancer is a complex disease involving primarily uncontrolled cell proliferation and migration to distant regions of the body. Nowadays, it is clear that a combined effort from biology, oncology, and all the physical sciences is necessary to advance our understanding of the disease and promote the discovery of new cures. Over the last 40 years, various mathematical models have been developed to investigate the basic principles underlying cancer progression. One of the most advanced predictive tumor growth models has been proposed by the group of Bernhard Schrefler [1]–[2]. It is based on first principles according to the concepts of transport oncophysics. The individual components considered in this computational model are sketched on the left-hand side of the figure below. The different cell populations are treated as fluid phases, moving together with the interstitial fluid in a deformable extracellular matrix, i.e., a mesh-like, porous structure. Within the interstitial fluid, chemical species such as nutrients and therapeutic agents are transported. The model encompasses, among other processes, growth, hypoxia, necrosis, lysis, invasion of tumor cells into the healthy tissue, transport of therapeutic agents and signaling molecules, and exchange of substances between the interstitial fluid and the cell populations. To validate the model and study the impact of transport properties on tumor progression, a collaboration with the Houston Methodist Research Institute (HMRI) has been established. A very good agreement with experiments has been shown, e.g., for glioblastoma multiforme spheroids (cf. middle and right-hand side of figure). However, the model is also suitable for simulating the evolution of other cancer types and setups.

The tumor growth model has been implemented in the in-house research code BACI at TUM's Institute for Computational Mechanics and has been developed further within the past year. One important extension was to allow for an arbitrary number of phases and species in the model. Due to the modular design of BACI, the model can now also be easily extended to include additional relevant phenomena. Besides, a considerable speed-up and improved stability of tumor growth predictions has been achieved by employing a so-called monolithic coupling scheme (see [3]). Recently, modeling of the vascular phase of tumor growth has also been improved. In this case, tumor cells recruit new blood vessels from the host vasculature through tumor angiogenesis, a phenomenon that is known to be of fundamental importance in tumor progression [4].

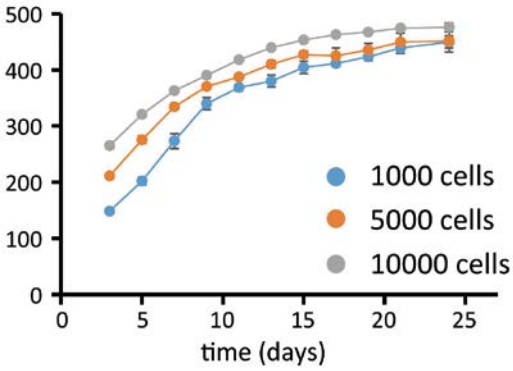
Ongoing work is concerned with coupling our model consistently with a patient-specific representation of the host vasculature (similar to [5]–[6]). Furthermore, we are currently introducing the effect of temperature on tumor progression into the model to investigate the efficacy of hyperthermia. This relatively new cancer treatment is based on exposing body tissue to high temperatures (up to 45°C), which can damage and kill cancer cells, usually with minimal injury to normal tissues [7]. Experimental data for validation of this extended model is available from our clinical partners.



1a | Components of the computational tumor growth model (IF: interstitial fluid; ECM: extracellular matrix; LTCs: living tumor cells; NTCs: necrotic tumor cells; HCs: healthy cells; TAF: tumor angiogenic factor; ECs: endothelial cells).



1b | Optical images of the growth of a tumor spheroid culture (U-87 MG MTS cells).



1c | Growth curves for different initial conditions (i.e., number of seeded tumor cells). Points represent experimental data; solid lines are model-based predictions. Figure reproduced from [2].

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Data Mining and Analytics**

Prof. Stephan Günnemann (TUM) | Rudolf Mößbauer Tenure Track Professor
Jan Böttcher, Oleksandr Shchur (TUM) | Doctoral Candidates*

Scientific Reports

Stephan Günnemann

Robust machine learning for non-independent data

The Focus Group Data Mining and Analytics conducts research in the area of machine learning and data analytics. Specifically, our group aims to develop machine learning methods able to handle erroneous and non-independent data.

In most real-world applications, the collected data is rarely of high quality but often noisy, prone to errors, or of varying reliability. Corrupted sensors, errors in the measurement devices, or adversarial user inputs are only a few examples. Since applying standard learning methods to such erroneous data leads to completely unreliable results, our goal is to design robust techniques that handle various forms of errors in an automatic way.

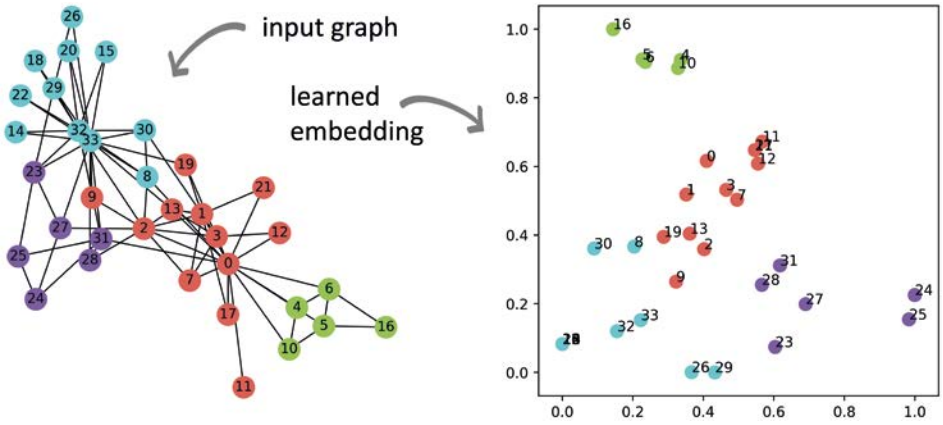
In this regard, our Focus Group is especially interested in designing techniques for non-independent data: While one of the most common assumptions in many machine learning and data analysis tasks is that the given data points are realizations of independent and identically distributed random variables, this assumption is often violated. Sensors are interlinked with each other in networked cyber-physical systems, people exchange information in social networks, and molecules or proteins interact on the basis of biochemical events. In our research, we exploit these dependencies by developing learning methods for, e.g., graphs and network data, thus enabling more effective analysis.

Robust graph embeddings

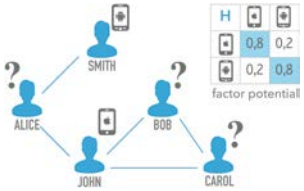
One of our recent advances is in robust graph embedding techniques. The aim of graph embedding techniques is to learn a mapping from a graph to a vector space while preserving important properties of the data, such as the graph's topology or the nodes' individual features (see figure 1). While graph embeddings have shown extreme success in many tasks (e.g., predicting missing links between entities and clustering similar entities), classical approaches are still very sensitive to erroneous data: If the underlying graph is corrupted, the resulting embedding gets distorted as well.

In our research, we developed a robust graph embedding technique, extending the idea of spectral embeddings [1]. We proposed a sparse and latent decomposition of the input graph, to jointly recover the clean graph and its embedding. Solving this formulation is algorithmically highly challenging, since finding the underlying clean graph leads to an NP-hard discrete optimization problem. In this regard, we proposed a scalable algorithm exploiting eigenvalue perturbation theory in combination with a reduction to the multidimensional Knapsack problem, leading to a runtime complexity that is linear in the number of edges in the graph. Our results have shown that our technique clearly leads to improved embeddings and outperforms state-of-the-art competitors in many clustering tasks.

** TUM-IAS-supported doctoral candidates in a group of a total of 10 doctoral candidates and postdoctoral researchers.*



1 | Illustration of a graph embedding. Each node of the input graph corresponds to a vector in the learned embedding that captures, e.g., the graph's topology. The learned representations can be used for downstream analysis tasks. If the input graph is noisy or corrupted, the embedding gets distorted as well. Therefore, we derived robust embedding principles.



2 | Node classification in graphs. Given prior information for a few nodes in a network (e.g., some users' preferences), what can we infer about the remaining nodes? The task can be treated as probabilistic inference in networks based on specific factor potentials. In our research, we derived novel inference techniques that are highly scalable and have provable convergence.

Efficient probabilistic inference in networks

In a second research direction, we developed techniques for efficient probabilistic inference in networks. Belief propagation, an inference algorithm for graphical models, marked the beginning of principled node classification in graphs when class labels for a subset of nodes are provided; and it has been used successfully in numerous settings, such as fraudulent entity detection in online retailers and classification in social networks (see figure 2). However, belief propagation also shows various limitations that make it impractical for real applications: It neither provides convergence guarantees in general nor takes uncertainty during the learning process into account.

In our research, we developed methods for inference in undirected heterogeneous networks with provable convergence guarantees [2]. The core idea lies in a clever approximation of the belief propagation update scheme, reducing it to a sparse linear algebra system. This approach not only gives us a closed-form solution and convergence guarantees, but also ensures linear runtime in the number of edges. In collaboration with a large e-commerce provider, we used this technique to identify fraudulent users, leading to near-perfect precision and running on graphs with 3.3 million edges in only a few seconds. Moreover, to take into account the uncertainty inherent in learning tasks, we proposed a generalized belief propagation principle based on Dirichlet distributions [3].

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Uncertainty Quantification and Predictive Modeling**

Prof. Nicholas Zabaras (University of Notre Dame) | Hans Fischer Senior Fellow
Markus Schöberl (TUM) | Doctoral Candidate

Scientific Reports

Nicholas Zabaras

Host
Prof. Phaedon-Stelios Koutsourelakis
Continuum Mechanics, TUM

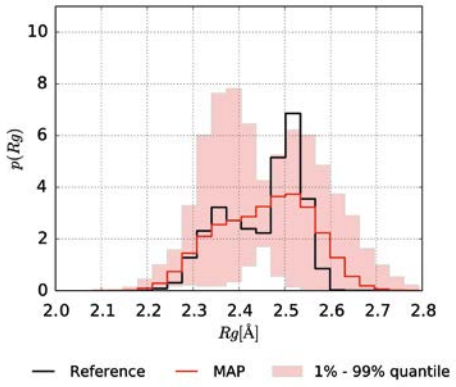
Bayesian coarse-graining and uncertainty quantification

This project seeks to advance computational physics simulations by employing concepts and developing tools from machine learning. Molecular dynamics (MD) simulations are nowadays commonplace in physics, chemistry, and engineering and represent one of the most reliable and accurate tools at our disposal to analyze complex physical processes and to design new materials. In contrast to top-down models of continuum thermodynamics, which are plagued by phenomenological assumptions (e.g., in the form of closures or constitutive equations), atomistic models enable the analysis of matter from first principles particularly when coupled with quantum-mechanical descriptions. The unparalleled accuracy and resolution that they offer comes at a significant computational price. Direct simulations are hampered by: a) the gigantic number of degrees of freedom, b) the extremely small time scale of molecular interactions in relation to the engineering scales of interest, and c) complex, potentially long-range and high-order interactions between the atoms or molecules that need to be accounted for at each time step. As a result, brute-force MD simulations are limited to small spatiotemporal scales, not just with current, but also with foreseeable computational resources. The challenge is to retain as much as possible the superior predictive ability of MD while extending the range of spatiotemporal scales that can be modeled.

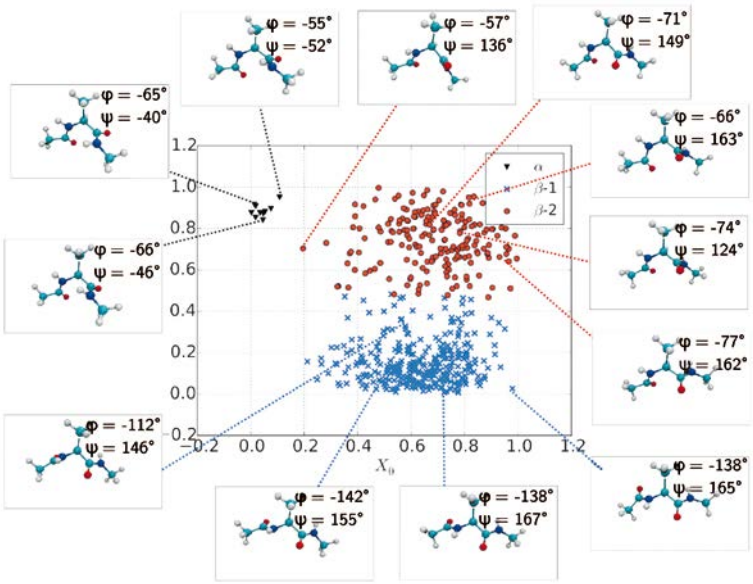
An approach toward this goal is coarse-graining (CG). Coarse-graining methods attempt to summarize the atomistic detail in significantly fewer degrees of freedom, which in turn leads to shorter simulation times with potentially larger time-steps and enables the analysis of larger ensembles with a moderate number of degrees of freedom. The pivotal question is how one can construct such a CG model, especially in the absence of physical insight. One promising avenue is simply based on data obtained from MD simulations.

Previous developments addressed the missing connection between the scales by employing a Bayesian CG formulation relying on generative probabilistic models. The proposed model comprises two main components: a probabilistic coarse-to-fine mapping that implicitly defines the CG variables and a coarse description accounting for the interactions between CG variables. The Bayesian formulation makes it possible to address questions with regard to model selection and validation rigorously. Furthermore, it enables a probabilistic reconstruction of the fine-scale picture and predictions of properties defined on the fine scale, while also accounting for the induced uncertainties due to dimensionality reduction and limited data.

Hand-tuned CG variables become impractical for complex systems, e.g., those originating from biochemistry. Moreover, nonintuitive coordinates could potentially lead to more compact CG descriptions with equal predictive quality. We have investigated parametrized, general classes of probabilistic coarse-to-fine mappings in conjunction with coarse descriptions that are refined sequentially.



1 | Probabilistic prediction of statistics of the deviation of the radius of gyration from a reference configuration.



2 | Representation of the training data in the reduced (two-dimensional) latent space. Three clusters, corresponding to the characteristic configurational modes, arise naturally.

Probabilistic predictions by a CG model for alanine dipeptide still convey the reference properties within the credible intervals, as shown in figure 1. Figure 2 depicts the configurational similarities between the fine scale and its latent coarse representation [1]–[3]. Our Focus Group contributed to the Focal Period PROMISe (Predicting Macroscopic Behavior from Microscopic Simulators. The collaboration brought together three Focus Groups jointly addressing challenges in multiscale modeling and quantification of uncertainty. Scientists from the fields of complex systems modeling and computation, effective field theory physics, and predictive modeling and uncertainty quantification made collaborative advances in predictive simulations in the presence of parameter uncertainties.

The International Symposium on Machine Learning Challenges in Complex Multiscale Physical Systems in January 2017 concluded the Focal Period [4]. Renowned scientists presented cutting-edge research and initiated subsequent informal discussions. The presentations were complemented by panel discussions on challenges in multiscale modeling, uncertainty quantification, and machine learning, which we hope will serve as the starting point for further collaborations.

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Human-Machine Collaborative Systems**

Prof. Gregory D. Hager (Johns Hopkins University) | Hans Fischer Senior Fellow
Christian Rupprecht (TUM) | Doctoral Candidate

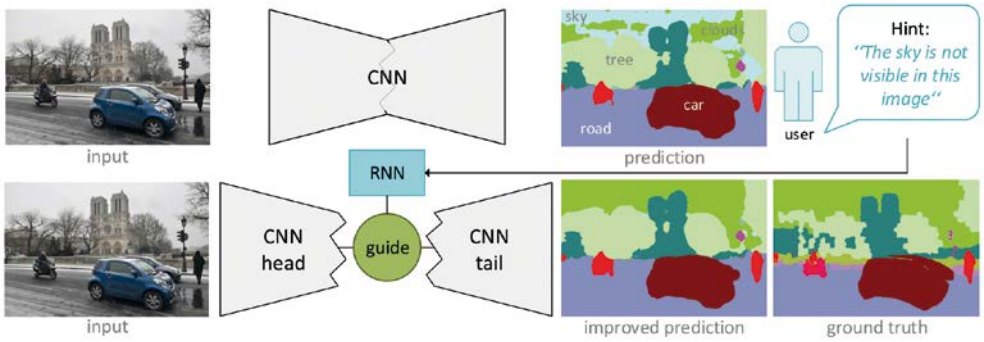
Scientific Reports

Gregory D. Hager

Host
Prof. Nassir Navab
Computer-Aided Medical Procedures & Augmented Reality, TUM

Improving machine learning for real-life interactions with people

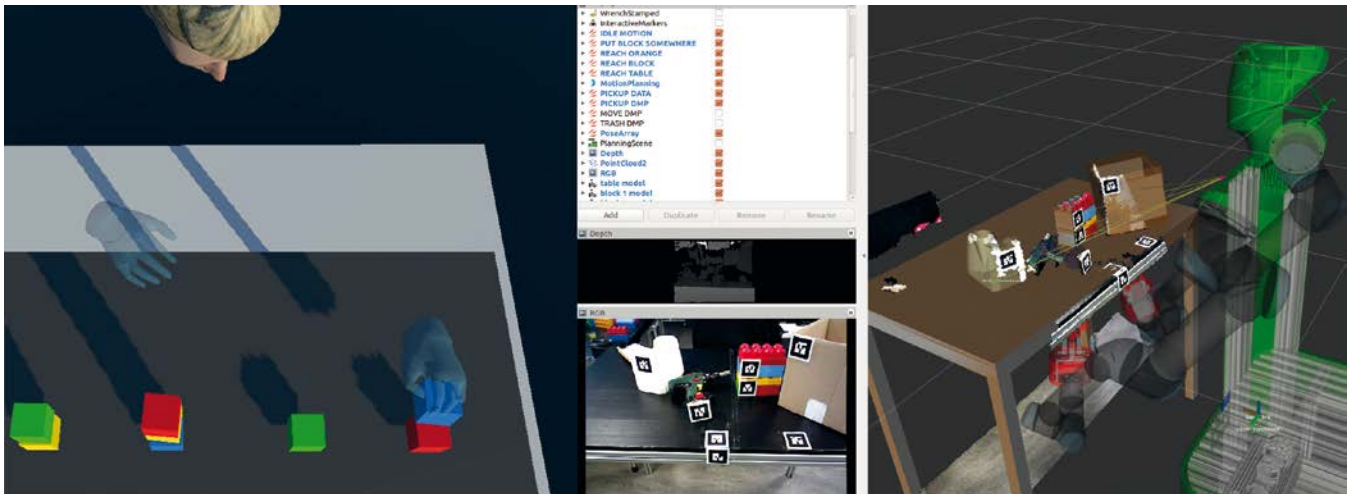
Interaction and collaboration between humans and intelligent machines is gaining importance as machine learning methods move into real-world applications involving end users. In our project, we have recently studied ways to handle interactions that involve uncertain or ambiguous problems. In one area of investigations [1], we give the system the option to suggest multiple answers when it is uncertain about its predictions. In addition, when our models are not perfect, we would have investigated ways to interact with the system to correct its mistakes. In [2] we explore methods to flexibly guide or improve the performance of a trained convolutional neural network through user input (see figure 1). While prior work at the intersection of language and vision has studied the problem of generating language output from vision, or vision output from language, much less research has focused on the use of language to guide or improve the performance of a learned visual processing algorithm. We do so by inserting a layer that acts as a spatio-semantic guide into a neural network. This guide is trained to modify the network feature maps either directly, via an energy minimization scheme, or indirectly through a recurrent model that translates human language to network interaction weights. Learning the verbal interaction is fully automatic and does not require manual text annotations. We can show that guiding a pre-trained network improves performance, and we have gained extensive insights into the interaction between the guide and the neural network.



1 | In our most recent work [2], we present a method to add human interaction to an already trained deep neural network. Simply typing textual hints to the network allows the prediction to be improved.

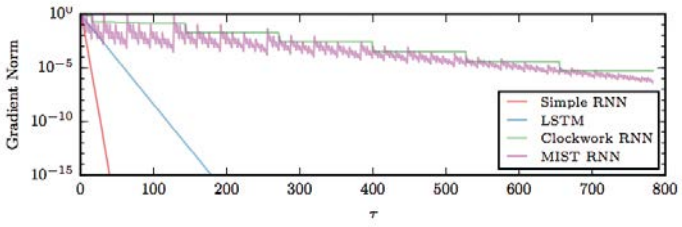
Ordinary end users must also be able to instruct collaborative robots to perform complex multi-step tasks. In our recent work, we use virtual reality environments to build semantic models of tasks, as shown in figure 2. Trajectory information is automatically segmented and used to build a set of policies corresponding to manipulation actions. This allows us to construct complex task models that translate from natural human demonstrations to the real world.

State-of-the-art neural network-based models lie at the core of many modern human-machine collaborative systems, with recurrent neural networks (RNNs) being especially well suited and successful for sequence-based modeling. In recent work, we analyzed the long-standing problem of learning long-term dependencies with RNNs. The problem is that gradient-based learning fails to capture very long-term dependencies, because gradients fall off exponentially fast as a function of delay, even for long short-term memory (LSTM), currently the most successful and widely used RNN architecture. We introduced a new architecture called MIST RNNs [3], which we showed to exhibit gradient properties superior to LSTM both theoretically and empirically (figure 3).



2 | Training using demonstrations of complex tasks performed in virtual reality. Left: virtual reality block-stacking task performed by a human user. Right: instantiation of a complex scene as perceived by the ICS TOM robot.

3 | Empirically observed gradient magnitudes as a function of delay for various recurrent neural-network architectures. Gradient magnitudes are directly related to the signal-to-noise ratio of our learning signal. Hence simple RNNs and LSTM have no hope of learning extremely long-term dependencies.



Finally, we showed that these superior gradient properties translate to performance boosts in practice: MIST RNNs outperformed LSTM on three sequence-modeling tasks and matched LSTM on two other tasks, where the diverse tasks ranged from fall detection using mobile-phone data to phoneme recognition using speech data.

Another model that lies at the core of many human-machine collaborative systems is the Kalman filter. However, Kalman filters require a motion model and a measurement model to be specified *a priori*, which is difficult if not impossible for many tasks. In [4], we introduced long short-term memory Kalman filters (LSTM-KFs), which learn dynamic representations of the motion and noise models from data, and we showed that LSTM-KFs achieve state-of-the-art performance on three of the most common pose-estimation tasks in computer vision.

In close collaboration with Gregory Hager's doctoral candidate, Robert DiPietro, from Johns Hopkins University, Maryland, USA.

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Focus Group **Image-based Biomedical Modeling**

Prof. Bjoern Menze (TUM) | Rudolf Mößbauer Tenure Track Professor
Esther Alberts, Jana Lipkova, Markus Rempfler (TUM) | Doctoral Candidates*

Bjoern Menze

Host
Image-based Biomedical Modeling, TUM

Image-based biomedical modeling

Our Focus Group develops computational algorithms that analyze biomedical images using statistical, physiological, and biophysical models. The work strives toward transforming the descriptive interpretation of biomedical images into a model-driven analysis that infers properties of the underlying physiological and patho-physiological processes by using models from biophysics and computational physiology. A related effort is the application of such models to big clinical databases in order to learn about correlations between model features and disease patterns at a population scale. In this, the main focus is on applications in clinical neuroimaging and the personalized modeling of tumor growth.

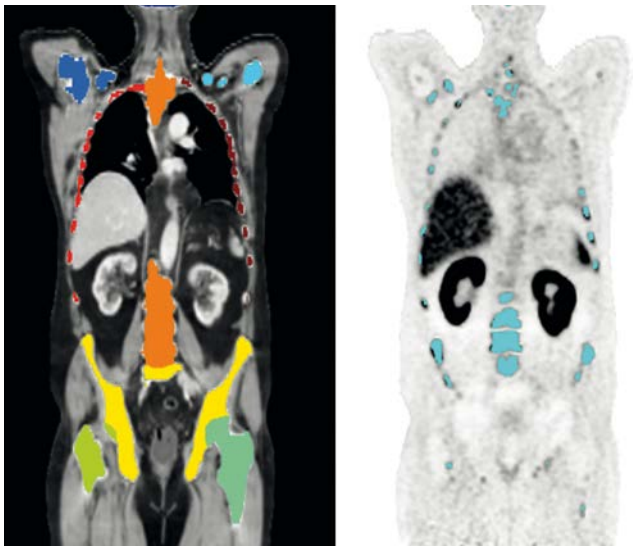
Clinical neuroimage analysis

The first direction is the modeling of processes underlying images acquired in common diseases of the brain. The focus is on the analysis of images acquired in glioma and stroke patients, including the development of algorithms for the analysis of brain lesions, and on new computational techniques for extracting vascular networks from angiographic images. The main sources of information are multimodal and multi-parametric clinical image data featuring magnetic resonance, position-emission-tomography, and computer tomography scans. Using these data we started exploring correlations between imaging phenotype and genetic subclasses of the disease. We were able to identify genetic tumor subtypes using only regular clinical MR imaging data [1]–[2]. In a generalization of similar geno-phenotype correlation studies, we also presented a deep learning approach for predicting patient survival using CT image of liver cancer patients as input, outperforming regular “radiomics” feature-based approaches by a wide margin [3].

Disease progression models

The second direction deals with the task of optimal oncological staging. It includes the anatomical annotation of images with a large field of view, such as abdominal scans or whole body images, the detection of lesion across modalities and in repeated scans, and the analysis of individual lesions using pathophysiological models. Emphasis is put on clinical applicability, and the algorithms are supposed to scale well to large data sets to enable the development of population-wide disease progression models. To this end, we are developing new methods for the automated annotation of organs and tumor lesion visible PET CT volumes acquired in cancer patients [4]–[5], illustrating the use of this technique for multimodal PET data analysis, and presenting a new volumetric biomarker to be used in the staging of patients with advanced prostate cancer [6].

** TUM-IAS-supported doctoral candidates in a group of a total of 26 doctoral candidates and postdoctoral researchers.*



1 | **Parsing PET CT images of cancer patients.** We developed algorithms for the automated annotation of anatomical structures in CT scans (left), also being able to detect and segment tumor lesions in the corresponding PET scans (right) [3]–[4]. These algorithms allow us to better quantify tumor progression patterns in prostate cancer patients [5].

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Optimal Control and Medical Imaging**

Prof. Dominique Sugny (University of Bourgogne) | Hans Fischer Fellow
Quentin Ansel, Wolfgang Kallies, Bálint Koczor (TUM) | Doctoral Candidates

Scientific Reports

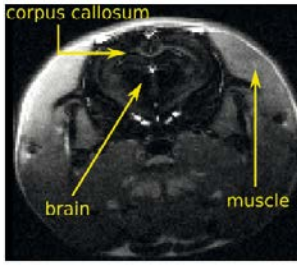
Dominique Sugny

Host
Prof. Steffen J. Glaser
Organic Chemistry, TUM

Our Focus Group aims to develop and apply innovative mathematical tools coming from optimal control theory (OCT) to improve theoretical and experimental techniques in magnetic resonance imaging (MRI), nuclear magnetic resonance (NMR) spectroscopy, and quantum information science. This approach allows us to explore and to experimentally reach the physical limits of the corresponding spin dynamics in the presence of typical experimental imperfections and limitations. Dominique Sugny was in Munich in August 2017. During this stay, the focus group pursued several research projects. The main results are briefly summarized below.

The tennis racket effect: Classical and quantum aspects

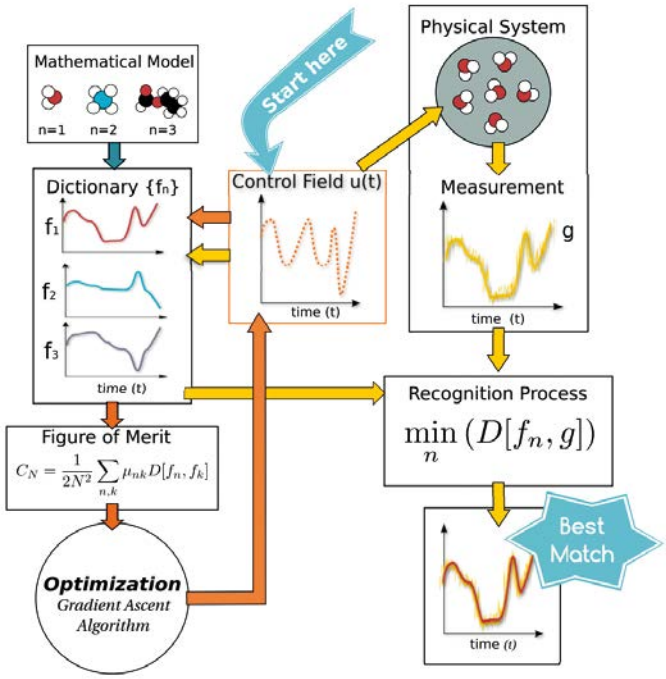
The tennis racket effect is a classical mechanical phenomenon that describes what happens when a tennis racket is tossed into the air while imparting a rotation about one of its axes. If we spin the racket about its transverse axis (the transverse axis lies in the plane of the head of the racket and is orthogonal to the handle), a surprising effect is observed. In addition to the intended 2π- rotation about its transverse axis, the racket will almost always perform an unexpected π-flip about its handle. In other words, when the racket is caught, the initial bottom side will be facing up. A complete theoretical description of the classical tennis racket effect is proposed in [1]. Using the analogy between the Euler and the Bloch equations, we show in [2] that the dynamics of a rigid body plays a fundamental role in the control of two-level quantum systems and can be used to design specific fields for state-to-state transfers or quantum gate implementations. The quantum analog of the tennis racket effect can also be defined and was demonstrated experimentally using techniques of NMR. A popular paper has been published on this subject.



1 | *In vivo* contrast experiment: Transverse section of a rat brain showing the result of the optimal pulse. The aim of the control is to saturate the brain while maximizing the intensity of the surrounding muscle tissues. The experiment was performed at CREATIS (Lyon, France).

Optimal control techniques for *in vivo* magnetic resonance imaging

We investigate in [3] and [4] the use of optimal control techniques in magnetic resonance imaging (MRI). We study image contrast optimization in [3]. We validate the optimal control sequences for the first time in both *in vitro* and *in vivo* experiments on a small-animal 4.7T magnetic resonance system. These results suggest that the theoretical benefit of optimal control pulses can be transferred to practical MRI acquisitions. An example in given in figure 1. In [4], we show how the magnetization phase can be actively controlled in MRI. An application to magnetic resonance elastrography (MRE) is also demonstrated. MRE is aimed at measuring the mechanical properties of soft tissues by imaging the propagation of shear waves with MRI techniques. In the MRE experiment performed in [4], the wave propagation is directly encoded in the phase image produced by the optimal sequence. This pioneering work opens a new research domain for the application of optimal control theory. We have applied for a patent on this subject. Finally, an invited review paper about the use of optimal control methods in MRI was published in PJMI [5].



2 | The optimal fingerprinting process is composed of two different loops. The first loop in yellow is the standard fingerprinting process. A control field is designed at the starting point of the loop. This field is applied to a physical system, which returns a specific response. On the other side, the response is computed numerically for an ensemble of physical systems with different values of the parameters. These simulations define a dictionary. The recognition process allows us to find the best match between elements of the dictionary and the result of the measurement. The second loop in orange describes the dictionary optimization. The optimization is performed for an ensemble of *N* systems with different values of the parameters. An optimization algorithm is used to maximize the figure of merit.

Optimizing fingerprinting experiments for parameter identification

The fingerprinting method is a well known technique generally used for determining the identity of a person. The overall process can be decomposed into three different steps, going from a fingerprinting recording of an ensemble of subjects to the creation of a database and finally to a recognition process. This idea has been recently adapted to magnetic resonance imaging for the identification of tissue parameters. In this study, each element of the database corresponds to the time evolution of some observables under the action of an external magnetic field. This approach increases the complexity of the fingerprintings and therefore the precision of the estimation. On this basis, we have introduced in [6] the concept of an optimal fingerprinting process (OFP) in which the field is designed by optimal control theory to maximize the efficiency of the recognition process. This concept is schematically illustrated in figure 2. As an illustrative example, we consider the estimation of the relaxation parameters of a spin 1/2 particle.

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Focus Group **Phase-Contrast Computed Tomography**

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Regine Gradl (TUM) | Doctoral Candidate

Kaye S. Morgan

Thomas Koehler

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Hosts
Prof. Franz Pfeiffer
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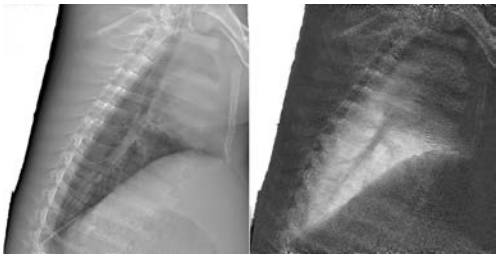
Using the Munich Compact Light Source, further progress toward clinical implementation

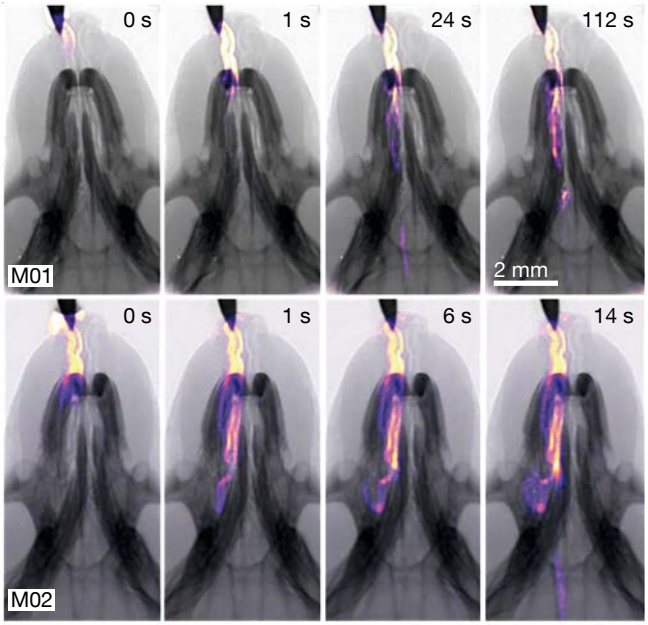
In conventional X-ray imaging, the image contrast is formed by X-ray attenuation and reflects the physical interactions of photoelectric absorption and Compton scattering. Both of these interaction processes are modeled conveniently by interpreting X-rays as photonic particles. If, on the contrary, X-rays are described as electromagnetic waves, other (wave-optical) interaction effects occur, and these yield to diffraction, refraction, phase-shift, and scattering. Our Focus Group aims at exploiting the latter mentioned wave-optical interactions of X-rays with matter for biomedical research and clinical applications. So far, preclinical results obtained in living mice indicate that the scattering signal, also called the dark-field signal, generated by lung tissue may provide very important additional information for the assessment of structural diseases of the lung tissue, for instance chronic obstructive pulmonary disease (COPD) [1].

A major achievement in 2016 was demonstrating that the technology works in the parameter range that is relevant for medical X-ray imaging, in particular at X-ray energies in the range from 70 to 120 kVp and for human-sized objects [2], see figure 1. During 2017, the focus moved forward toward clinical implementation of the technology. A prototype clinical dark-field X-ray (DAX) system was set up at the University Hospital Klinikum rechts der Isar and is now awaiting regulatory approval for the worldwide first clinical DAX study. In parallel to this activity, continuous effort was spent on the implementation of dark-field functionality on a clinical computed tomography (CT) system installed at the campus in Garching.



1 | Conventional X-ray image of a pig thorax (left) and a simultaneously acquired dark-field image (right). While in the conventional image attenuating material (bones, soft tissue) shows up, the dark-field image shows highly scattering, i.e., highly structured material, in particular lungs and bones.

In parallel to preclinical studies, we have been developing fast phase-contrast X-ray imaging in the laboratory as a biomedical research tool. Until now, this kind of imaging was only possible at synchrotron research facilities, which are hundreds of meters in diameter and have limited availability. Using the high flux provided by the Munich Compact Light Source (MuCLS), the world's first inverse-Compton-based source, we can now conduct high-speed imaging in the laboratory. This year marked the first *in vivo* dynamic imaging at the source, capturing treatment deposition (figure 2), the motion of the lungs during the breath cycle, and the clearance of inhaled debris along the airway surface.



2 | *In vivo* phase-contrast imaging at the Munich Compact Light Source captures the delivery of treatment to the nasal airways of mice, directly visualizing how the deposition depends on delivery speed and volume.

3 | A mini off-site workshop was held in Sudelfeld in July, bringing together almost 30 physicists, mathematicians, engineers, and physicians from TUM Physics, University Hospital Klinikum rechts der Isar, and Philips.

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Subcellular Dynamics in Neurons**

Prof. Maya Schuldiner (Weizmann Institute of Science) | Hans Fischer Senior Fellow
Prof. Melike Lakadamyali (University of Pennsylvania) | Hans Fischer Fellow
Dr. Shabab bin Hannan (TUM) | Postdoctoral Researcher
Antoneta Gavoci (TUM) | Doctoral Candidate

Scientific Reports

Maya Schuldiner

Melike Lakadamyali

Host
Prof. Thomas Misgeld,
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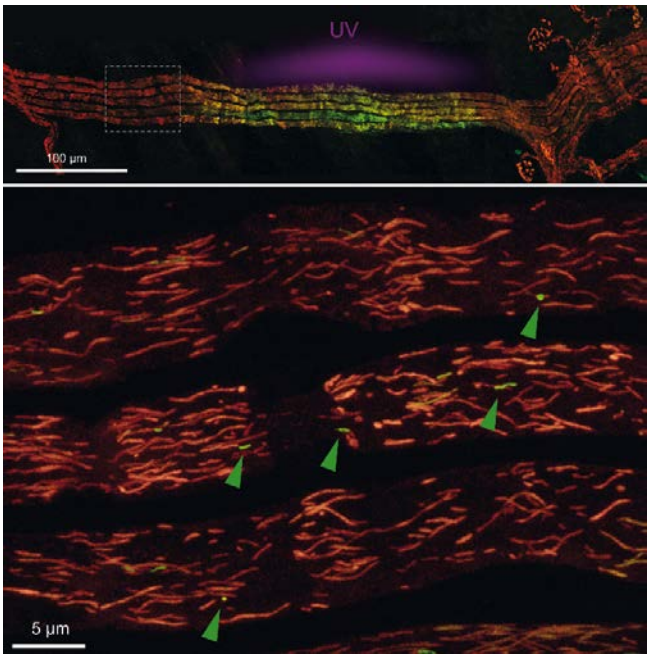
Life in a crowded place: How organelles travel and talk inside nerve cells

Cells are crowded places: Organelles of different kinds are densely packed in between strands of cytoskeletal cables, busy vesicles rushing in all directions making house calls, local dumpsites of broken proteins, and membranes avidly removing what cannot be fixed by the repair machinery, which steadily tries to get things back on track where they are stuck or tangled. All this cellular hubbub is immersed in an incredible density of molecules of all denominations – from small metabolic intermediates that need to meet their enzymes at the right place and in right numbers to gigantic protein machines that keep the entire place churning and moving. So how do cells organize all this chaos?

Two central principles have emerged: first, that cellular components are shuffled around by molecular motors along cytoskeletal tracks, in a fashion that is tightly controlled and imbued with specificity by combinatorial pairings of cargoes and motors via a variety of regulated adaptors. New observations suggest that a further layer of regulation affects the modification of the cytoskeletal tracks themselves, both in their surface composition – which can attract or repel certain motors or roadblocks – as well as in track length and directionality. Thus, an ingenious railroad system has emerged that allows cellular components to traffic in the right numbers to the right places. The second principle appears to be the polar opposite: Rather than being allowed to mix freely and rely on chance encounters to meet other organelles for metabolic collaborations in a “speed-dating” pattern, organelles are bound by molecular tethers into lasting marriages. Such contact sites impart organization onto the seemingly random marketplace of the cell – in effect creating combinatorial “super-organelles.”

Recognizing these principles has been a major achievement in our quest to understand how cells work – but they raise at least as many questions as they provide answers. Indeed, as cells differentiate their shape to match their specific tasks in the organism, new challenges arise. As of now, it is not clear how the principles of regulated traffic and tethered contact sites translate to the specific needs of highly differentiated cells in mammals. Consider the special case of a nerve cell: Extending from the cell body is an enormously long tunnel – the axon – which connects to the cell’s business end, a branched arbor decorated by synapses, where vesicles are released in an activity-dependent and highly energy-intensive cycle of synaptic exo- and endocytosis. Most supplies to keep this remote outpost of the neuron going, and to maintain the organellar superstructures that fuel and resupply it, need to be exported by a special version of cellular traffic, called axonal transport, and require subsequent assembly at the synapse. Obviously, such a complex system sounds like a potential Achilles heel of neuronal cell biology, and indeed, many neurological diseases affect it. However, we do not even know how this works normally – and this is the question at the heart of the TUM-IAS Focus Group Subcellular Dynamics in Neurons.



1 | Photoconversion assay to visualize moving mitochondria in fixed nerve tissue of a transgenic mouse in which a combination of red-to-green photoconvertible fluorescent proteins in mitochondria is expressed. Single mitochondria that moved out of the photoconversion area ("UV" schematic, top panel; image taken 30 minutes after illumination) can be identified by color and measured in detail (green arrowheads, lower panel). Image taken by Natalia Marahori on a specialized high-resolution setup in Melike Lakadamyali's lab at the University of Pennsylvania.

Our Focus Group reached full strength in 2017, and we initiated our research program aimed at understanding how the general principles of subcellular organization – which we know from model cells (such as yeast or immortalized cell lines) – are implemented in the more challenging cellular environment of neurons *in vivo*.

In a first line of work ("Team Transport"), we are studying one especially fascinating and complex organelle, the mitochondrion, which plays central roles in energy provision and metabolism and is affected in many neurological diseases, such as Parkinson's disease. Using new transgenic mice, time-lapse and superresolution imaging (figure 1), and ultrastructural methods, we are deconstructing the mitochondrial "life cycle" inside a synapse. We are trying to understand how new mitochondria are delivered from the cell body – due to their complex structure, they cannot be made *de novo* and likely derive in synapses from the remote somatic pool – as well as how such new mitochondria relate to the "old" ones already present at the synapse, and where and how old organelles are degraded.

In a second line of work ("Team Contact Sites") – which is in its preparatory *in silico* phase of data mining – we are initially focusing on the organellar contacts between mitochondria and another kind of organelle called peroxisomes, which share some features with mitochondria (e.g., a specialized degradation pathway) but are quite different in other regards (e.g., in membrane structure). Moreover, mitochondria and peroxisomes cooperate closely in certain metabolic pathways, e.g., those related to lipid metabolism. On the basis of information derived from large-scale analysis of mitochondrial proteomes in neurons and other neural cells, as well as genetic screens done in yeast, we are exploring which contact-mediating proteins might be present in neurons. In parallel, we are breeding mice to visualize both organelles *in vivo* in synapses, and to adapt biosensors that have been generated to indicate organelle proximity in cellular assays to this specific organelle pair and the *in vivo* applications we plan to pursue next year.

In collaboration with medical doctoral candidate Natalia Marahori, Neuronal Cell Biology, TUM

Focus Group **Coding for Communications and Data Storage (COD)**

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Prof. Camilla Hollanti (Aalto University) | Hans Fischer Fellow
Dr. Ragnar Freij-Hollanti (TUM) | Postdoctoral Researcher
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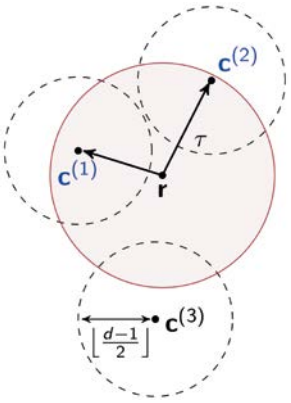
Antonia Wachter-Zeh

Camilla Hollanti

The COD Focus Group, headed by Rudolf Mößbauer Tenure Track Assistant Professor Antonia Wachter-Zeh, studies coding for communications and data storage. This includes theoretical and methodological aspects as well as the application to data storage, security, and network coding.

List decoding

One aspect of our work is list decoding, which is a powerful technique for increasing the error correcting capability of codes (see figure 1). A list decoder returns not only a unique decoding result, but all codewords in a certain radius around the received word. In pratical applications, list decoding is frequently used in concatenated coding schemes. In the last year, we have investigated list decoding of different types of errors: crisscross errors [1], insertions and deletions [2], and locally repairable codes [3].



1 | The principle of list decoding: All codewords within radius τ are returned.

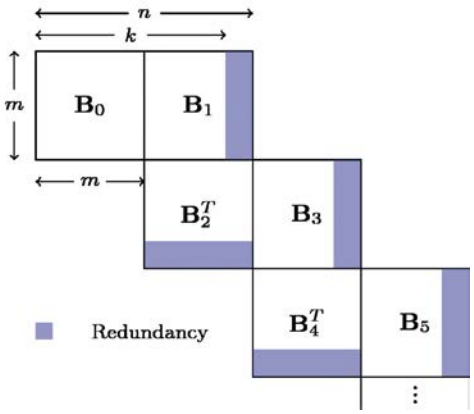
Coding for distributed data storage

In cloud storage systems (such as Dropbox) with distributed data storage (illustrated in figure 2), it is necessary to design coding solutions in order to cope with failures of data servers. Additionally, it is frequently important that only a few servers are contacted to repair a failed server. This number is called the code locality, and codes that consider locality constraints are called locally repairable codes (LRCs). Our research on LRCs in the last year was focused on list decoding. We have thereby shown that LRCs can be list decoded up to a larger fraction of errors than the corresponding Reed-Solomon code, and we have given an explicit list decoding algorithm [3].

2 | Distributed data storage: cloud data is stored on multiple distributed servers.

Staircase codes

Staircase codes are a powerful code construction based on a spatially coupled binary Bose–Chaudhuri–Hocquenghem (BCH) component code, designed for error correction in optical communication systems. Their construction is shown in figure 3. The dominating part of errors to the error floor consists of so-called stall patterns. In [4], we have developed a low-complexity method for resolving stall patterns when decoding staircase codes. The approach effectively lowers the error



3 | Structure of staircase codes: encoding is done in row and column direction.

floor for decoding staircase codes. This allows for a new range of block sizes to be considered for optical communication at a certain rate or, alternatively, a significantly decreased error floor for the same block size. Further, we have provided an improved analysis of the error floor behavior.

Insertions/deletions and DNA storage

The increasing demand for high density and long-term data storage and recent progress in biotechnological methodology have motivated the storage of digital data in DNA. However, the data is corrupted by errors during the replication of DNA, and therefore an adequate error-protection mechanism has to be found. Typical errors include insertions, deletions, substitutions, and tandem or palindromic duplications. While the correction of substitutions is well studied, the knowledge about correcting insertions/deletions and duplications is relatively limited.

The focus of our work is on code constructions for these types of errors, bounds on the size of such codes, and efficient decoding algorithms. We are also verifying our constructions in simulations with actual DNA storage data. In [5], our goal was to determine the minimum redundancy needed to correct tandem and palindromic duplications. Further, some code constructions were given. In [2], we have investigated list decoding of insertions/deletions and provided an efficient decoding algorithm for single-insertion/deletion correcting codes.

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Exploiting Antenna Arrays for Next-Generation Wireless Communications Systems**

Prof. A. Lee Swindlehurst (University of California, Irvine) | Hans Fischer Senior Fellow
Hela Jedda (TUM) | Doctoral Candidate

Scientific Reports

A. Lee Swindlehurst

Hosts
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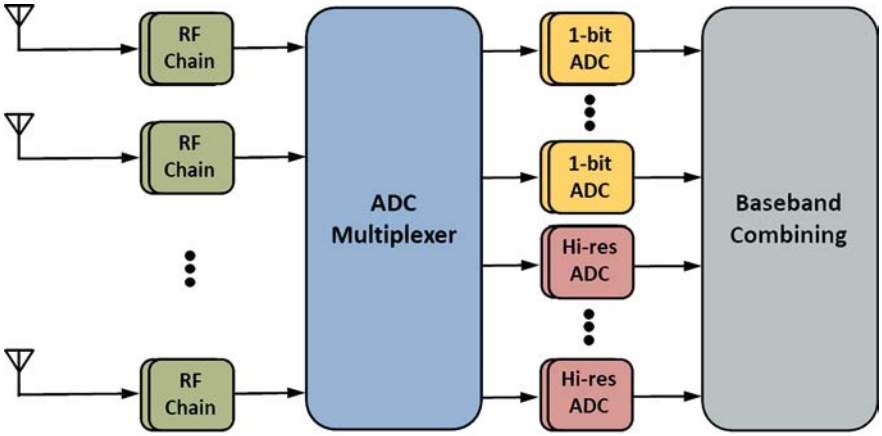
Prof. Wolfgang Utschick
Signal Processing Methods, TUM

Transmit precoding for quantized massive MIMO communication systems

For the next generation of mobile communication, where massive multiple-input-multiple-output (MIMO) systems are foreseen as one of the key technologies, power consumption is a crucial concern due to the deployment of a large number of antennas and corresponding radio-frequency (RF) chains. So-called “green” communication aims at minimizing the energy footprint of wireless systems while guaranteeing a certain quality of service. One aspect consists in reducing the hardware power consumption mainly of the power amplifiers (PAs) that are considered to be the most power-hungry devices on the transmitter side. When the PAs are run in the saturation region, high power efficiency is achieved. However, in the saturation region strong nonlinear distortions are introduced to the signals. To avoid the PA distortions in the saturation region, one can resort to constrained PA input signals. The most common type of constraint is a per-antenna power constraint, in which the amplitude of the signal cannot exceed a certain value corresponding to the PA saturation level. In other situations, to maximize the energy efficiency of the PA, one may wish to constrain the transmit signal to have a constant modulus. Another example that has recently gained attention is the use of a low-resolution (e.g., one-bit) digital-to-analog converter (DAC), which limits the transmit signal to one of only a finite number of possibilities.

The deployment of one-bit DACs at the transmitter ensures the constant envelope property at the input of the PA. In addition, the power consumption of the DAC itself is minimized. Therefore, the power-efficiency goal is achieved: power-efficient PAs due to the constant envelope signals and less power-consuming DACs due to the low resolution. The use of one-bit DACs is also beneficial in terms of reduced cost and circuit area and can further simplify the surrounding RF circuitry, leading to very efficient hardware implementations [3]. However, the coarse quantization causes nonlinear distortions that degrade the performance. Therefore, mitigating the quantization distortions has to be dealt with in multiuser (MU) MIMO systems.

Linear precoding schemes are not directly compatible with constant-envelope or one-bit DAC constraints, since the precoder output will in general not satisfy them. A simple approach to dealing with this situation is to use a linear precoder anyway, and then project its output onto the nearest constrained signal. This approach has recently been used for the case of one-bit DACs in [1]–[3]. Its performance was analyzed in [3] for the zero-forcing precoder, and was found to perform reasonably well as long as the ratio of the number of antennas to the number of receivers was large enough. However, direct nonlinear design methods that take the one-bit constraint into account when designing the transmit signal vector have been shown to perform considerably better. Some examples include [4]–[6] for one-bit DACs and [5], [7]–[13] for constant modulus signals. For per-antenna power constraints, most prior work has focused on linear precoders, although direct design of the transmit vector has recently been considered for this problem as well [14].



1 | Mixed-ADC massive MIMO scenario: The RF outputs are multiplexed to ADCs with different resolution levels prior to baseband digital combining.

Our work in 2017 focused on transmit precoding under the types of constraints discussed above, covering two primary areas of study. We have proposed new nonlinear precoders to transmit phase-shift keyed (PSK) signals in one-bit quantized MU-MISO systems with frequency-selective channels. The design of the transmit vector is based on maximizing the safety margin to the decision thresholds of the PSK modulation. Designs are presented for symbol-wise processing, block processing, and block processing with a cyclic prefix. The simulation results show a significant improvement compared to linear precoder designs. Block processing with larger block lengths achieves better performance, but the computational complexity increases cubically with the block length. The cyclic prefix additionally improves the performance, but proportionally decreases the throughput.

The primary drawback of direct nonlinear design approaches like these is their computational complexity. First, they are symbol-level precoders, which means that an entirely new precoding must be designed for each set of transmit symbols; this is in contrast to linear precoders, which remain fixed during the coherence time of the channel. Second, they require iterative algorithms in a search space of a dimension equal to the number of antennas, which can be very large in the case of massive MIMO systems. We have been studying the massive MISO downlink in which a base station with a large number of antennas transmits phase-shift keyed (PSK) symbols to a number of single-antenna users. The method that we have developed also requires symbol-level precoding, but it operates in a space whose dimension is equal to the number of users, which is typically much smaller than the number of antennas. The algorithm operates like the methods above that simply project the output of a linear precoder onto the constraint space, but it attempts to predistort the signals in order to find a better linear precoder output before the constraints are applied. In particular, the algorithm adjusts the input to the linear precoder to minimize the worst-case bit error rate (BER) at the receivers, where the minimum BER criterion is achieved by maximizing the “safety margin” described in [6].

Mixed-ADC massive MIMO systems

One of the main causes of performance degradation in purely one-bit massive MIMO systems is the error due to the coarse quantization that occurs during the channel estimation phase. While at low signal-to-noise ratio (SNR) the loss due to one-bit analog-to-digital conversion (ADC) is only about 2 dB, at higher SNRs performance degrades considerably more and leads to an error floor. The degradation can be reduced by improving the quality of the channel estimation prior to signal detection. One approach for doing so is to exploit so-called mixed-ADC architectures during the channel estimation phase, in which a combination of low- and high-resolution ADCs are used side-by-side. This architecture is depicted in figure 1.

Most existing work in the mixed-ADC massive MIMO literature has assumed either perfect channel state information (CSI) or imperfect CSI with “round robin” training. However, estimating all M channel coefficients with only a few (say, N) pairs of high-resolution ADCs requires longer training signals. More precisely, in the single-user scenario, M/N pilot signals are required to estimate all M channel coefficients with high-resolution ADCs. This training overhead will be exacerbated in the multi-user scenario where orthogonal pilot sequences should be assigned to the users. In this case, the training period becomes $(M/N)\eta$, where η represents the length of the pilot sequences (at least as large as the number of user terminals), which could be prohibitively large and may leave little room for data transmission in each coherence interval. Hence, it is crucial to account for this fact in any performance analysis of mixed-ADC massive MIMO systems.

Therefore, contrary to existing work that attempts to enhance the performance of one-bit massive MIMO systems using mixed-ADC architectures in the data transmission phase, we focus on the effect of using mixed-ADCs in the channel estimation phase by using a more accurate model for the quantization noise based on the Bussgang decomposition. We consider channel estimation using only the small number of N high-resolution ADCs. We address the impact of the aforementioned training duration overhead on the performance of the system for both maximum ratio combining (MRC) and zero-forcing (ZF) detection. Then, to further improve the mixed-ADC-aided channel estimation, we propose and study the performance of a true mixed-ADC approach that uses both high-resolution and one-bit ADCs jointly in estimating the channel. We demonstrate that joint channel estimation can improve the channel estimation accuracy and in turn the spectral efficiency for low SNRs.

On the basis of the channel estimate obtained by the mixed-ADC architecture, we designed mixed-ADC-adapted MRC and ZF detectors. We first considered the case in which high-resolution ADCs are connected to a set of N arbitrary antennas. Then we analyzed an antenna selection algorithm to improve the sum spectral efficiency that connects the N high-resolution ADCs to a subset of antennas with the highest channel gain. We analytically derived the performance of the antenna selection algorithm for MRC detection and numerically studied its performance for ZF detection. The results show that antenna selection is beneficial for high signal-to-noise ratios where accurate channel state information is available, while it has less impact on the spectral efficiency for low signal-to-noise ratios.

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Information, Interaction and Mechanism Design**

Prof. Dirk Bergemann (Yale University) | Hans Fischer Senior Fellow
Florian Brandl (TUM) | Doctoral Candidate

Scientific Reports

Dirk Bergemann

Hosts

Prof. Martin Bichler
Decision Sciences & Systems, TUM,
Prof. Felix Brandt
Algorithmic Game Theory, TUM

Auctions, Markets, and Voting

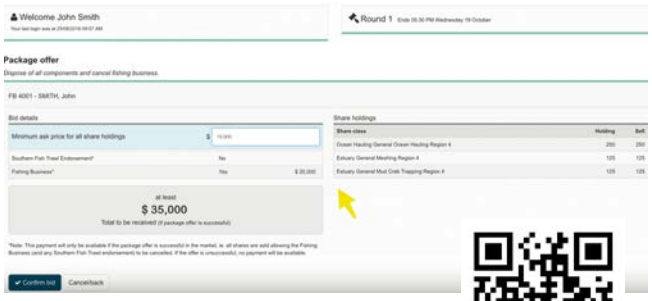
The Focus Group Information, Interaction and Mechanism Design aims at new types of models for the design and analysis of economic mechanisms and preference aggregation. Understanding and modeling markets and economic interactions can be described as the central theme in economics. Rather than modeling markets from a bird's-eye view, mechanism design models incentives of individual decision makers explicitly. A number of recent Nobel Memorial Prizes in Economic Sciences document the success of this stream of research and this specific way of modeling economic interactions. In recent years, the formal study of mechanism design has found concrete applications in the real world. It led to market designs in various fields such as spectrum auctions, procurement tenders, and kidney exchanges, where multiple independent decision makers need to be coordinated such that the outcome is economically efficient and the mechanisms are robust to various forms of manipulation.

A central activity in our research this year was the design and organization of a fishery exchange in New South Wales [1]. The market was organized in spring 2017 by the government and provided a market-based response to a substantial policy problem in fisheries worldwide: the allocation of catch shares to fishers in a cap-and-trade system designed to prevent overfishing.

The market solved a long-standing policy problem in New South Wales. For at least six years there was a political struggle between fishers and the government about the correct way to reallocate catch shares. The proposed market design addressed all key concerns and was decisive to finally get all stakeholders on board and facilitate the reallocation of catch shares. With around 600 participating fishers, 100 share classes, and 1300 bids in each round, this was the largest combinatorial exchange that we are aware of.

The market completely reshaped the fishing industry in New South Wales. Close to 600 fishing businesses registered for the market and placed 740 buy bids, 432 sell offers, and 107 package offers. Importantly, previously underutilized shares were transferred to active fishers: 86% of their buy bids were matched, and their overall share deficit was reduced by 75% to 95%. In addition, 60% of the package offers were matched. In total, 62 businesses successfully sold all their shares and exited the industry, receiving $10.1 million for their shares. Around $5.9 million went to sellers who just sold part of their endowment of catch shares. Overall, the government paid $14.8 million in subsidies to facilitate the transfer of shares from inactive to active fishers.

Similar reallocation problems arise in fisheries with catch-share systems worldwide. The market illustrates how computational optimization and market design can provide new policy tools, able to solve complex policy problems that were considered intractable only a few years ago.



1 | Bid submission screen and QR code for online video.

The project led to a number of challenging theoretical questions. Combinatorial exchanges such as the market for fishery access rights generalize traditional market models and allow participants on both sides to have complex preferences for combinations of objects. They often employ linear and anonymous prices because these are considered simple and fair. Despite their prevalence, linear anonymous prices are not well understood. In our research, we analyzed the effect of different pricing rules on the efficiency of combinatorial exchanges, using both analytic models and numerical experiments. We found that when linearity and anonymity are only required for one side of the market, the average efficiency loss is negligible. In contrast, with a single linear price vector for both sides the efficiency loss is substantial, especially when the market is small. In a formal model, we show that efficiency losses decrease when the number of buyers grows or the size of the submitted packages decreases.

The project is also an example for the research done in the context of the DFG Research Training Group (RTG) in which Dirk Bergemann and Martin Bichler serve as principal investigators. The RTG started in October 2017 with a three-day kick-off meeting, many presentations, and lively discussions in Bernried.
In other work, initiated while Felix Brandt's doctoral candidate Florian Brandl was visiting Dirk Bergemann at Yale, we re-examined Arrow's famous impossibility theorem under the assumption that the outcome space is the convex hull over some finite set of alternatives.

We provided characterizations of both the domains of preferences and the social welfare functions that allow for Arrovian aggregation. The domains allow for arbitrary preferences over alternatives, which in turn completely determine an agent's preferences over all outcomes. The only Arrovian social welfare functions on these domains constitute an interesting combination of utilitarianism and pairwiseness. When also assuming anonymity, Arrow's impossibility turns into a complete characterization of a unique social welfare function, which can be readily applied in settings that allow for lotteries or divisible resources such as time or money.

We have also used computer-aided solving techniques to prove a sweeping impossibility for randomized mechanisms. In particular, we have shown that every efficient aggregation mechanism can be manipulated for all expected utility representations of the agents' preferences. This settles an open problem and strengthens a number of existing theorems, including statements that were shown within the special domain of assignment. Our proof is obtained by formulating the claim as a satisfiability problem over predicates from real-valued arithmetic, which is then checked using an SMT (satisfiability modulo theories) solver. In order to verify the correctness of the result, a minimal set of unsatisfiable constraints returned by the SMT solver was translated back into a proof in higher-order logic, which was automatically verified by the interactive theorem prover Isabelle/HOL.

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Automated Controller Synthesis**

Prof. Anca Muscholl (LaBRI, University of Bordeaux) | Hans Fischer Senior Fellow
Dr. Denis Kuperberg, Dr. Edon Kelmendi (TUM) | Postdoctoral Researchers

Anca Muscholl

Hosts
Prof. Samarjit Chakraborty
Institute of Real-Time Computer Systems, TUM
Prof. Javier Esparza
Foundations of Software Reliability and Theoretical Computer Science, TUM
Prof. Matthias Althoff
Cyber-Physical Systems, TUM
Prof. Majid Zamani
Hybrid Control Systems, TUM

The research of the Focus Group concentrates on algorithmic techniques for the design and validation of complex controlled systems. Cars, planes, power grids, manufacturing plants, robots, and many other systems are increasingly controlled by software and require formal certification. Controller synthesis techniques produce correct-by-construction solutions that do not need heavy *post-factum* testing or verification.

Many modern systems rely on communication over a network connecting multiple devices (networked control systems). As an example, contemporary automotive in-vehicle architectures consist of hundreds of electronic control units, sensors, controllers, and actuators connected via shared buses. Designing these networks is a fundamental challenge.

From idealized controllers to implementations

The current state of the art in controller design is based on a number of idealistic assumptions about the network, such as zero delays and no signal losses. We investigate techniques supporting joint design and verification of controllers and their implementation infrastructure.

We have studied how to incorporate the characteristics and constraints of implementation platforms in the control algorithm design. We have shown that to be able to do this, different controller strategies are required – for example by switching between two different controllers with high- and low-resource usage phases [1].

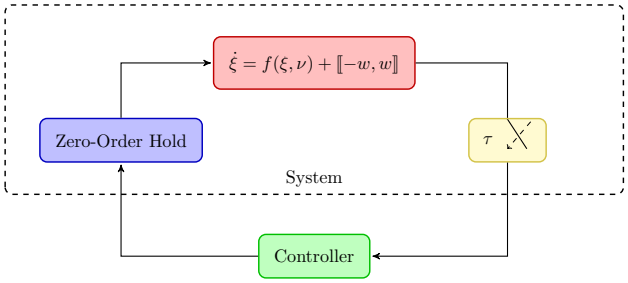
Automated verification techniques for distributed systems

We explore automatic techniques for checking that the implementation of a controller satisfies its specification.

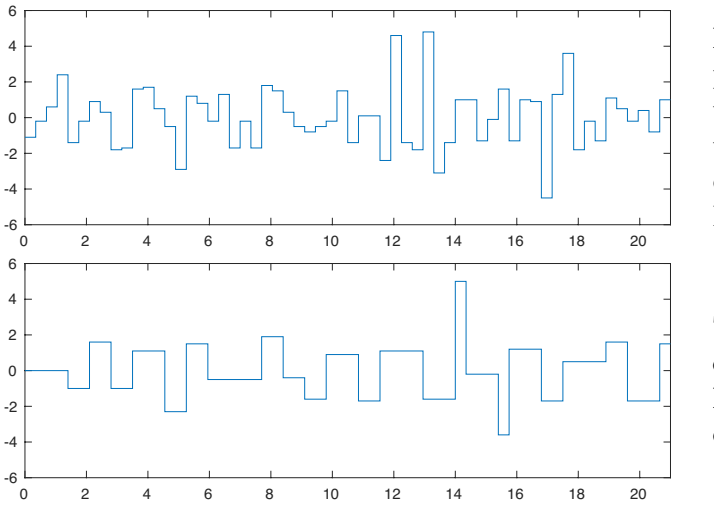
In 2016, the first year of the Focus Group, we started to study algorithmic verification techniques for a distributed model based on multi-party synchronization, called negotiation diagrams. In 2017 we have extended this research with a generic algorithm that allows us to verify a large variety of properties of negotiation diagrams in a uniform way. Using this algorithm, we can solve some game-theoretical problems in polynomial time, which leads to very efficient techniques for the synthesis of controllers satisfying safety objectives. The results of this research have been published in [2] and [3].

Distributed controllers

It is often unrealistic or impossible to design a monolithic controller for the complete network. We are investigating techniques to automatically transform a centralized controller into a collection of distributed controllers offering the same guarantees.



1 | Scheme of a generic control loop.



2 | Plots showing the input signal produced by the controller over time. The time intervals where the input signal can be held constant are shown by straight horizontal lines. The upper plot shows the un- optimized controller, while the lower plot shows the optimized controller.

Optimal controllers

The characteristics of a network introduce additional functional and quantitative constraints for the design of a controller. For example, due to bandwidth limitations or package losses one can be interested in controllers that communicate with the plant as little as possible, or in controllers that are as fault-tolerant as possible. We investigate techniques for the automatic design of optimal controllers with respect to these requirements.

We have studied the automatic synthesis of controllers for both safety and liveness specifications. We have proposed a symbolic technique applicable to perturbed, nonlinear systems. In [4] we provide a general construction of symbolic models for networked systems. In [5] we propose a quantitative strategy based on game theory to deterministically and optimally choose the control value to be applied to the plant. For example, our strategy allows us to synthesize controllers that communicate with the plant as little as possible. Figure 2 shows the actuation pattern of a controller before and after the optimization step.

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Embedded Systems and Internet of Things**

Prof. Sebastian Steinhorst (TUM) | Rudolf Mößbauer Tenure Track Professor
Ege Korkan, Emanuel Regnath, Philipp Weiss (TUM) | Doctoral Candidates

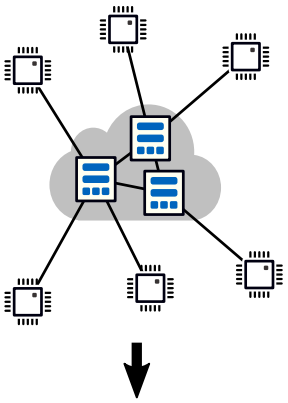
Scientific Reports

Sebastian Steinhorst

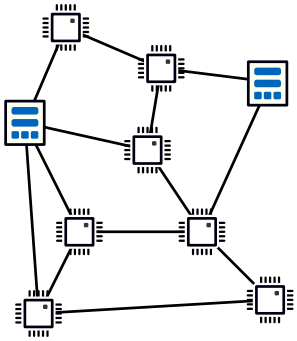
Decentralized system architectures

This Focus Group, newly established at the end of 2016, addresses the design challenges for resource-constrained embedded and cyber-physical system architectures, which are entering further areas of our everyday life with the advent of the Internet of Things (IoT). For such connected devices, conventional centralized system architectures are reaching their limits regarding manageability, scalability, and efficiency. Hence, design approaches are required where centrally coordinated networks of these devices are developed toward self-organizing architectures, as illustrated in figure 1. Here, smart algorithms will enable system-level functionality and achievement of common goals in a distributed fashion without central coordination. When properly designed, such fully decentralized architectures will provide scalability, modularity, efficiency, and robustness beyond the capabilities of centralized architectures. However, when considering resource-constrained embedded applications from the automotive, energy storage, or IoT domain, several challenges arise when attempting to design such decentralized architectures. Strong resource limitations regarding computation, communication, and energy require advanced methodologies for co-design of hardware/software architectures, distributed algorithms, and secure communication such that the goals of safety, security, efficiency, and scalability can be reached.

Cloud-based IoT



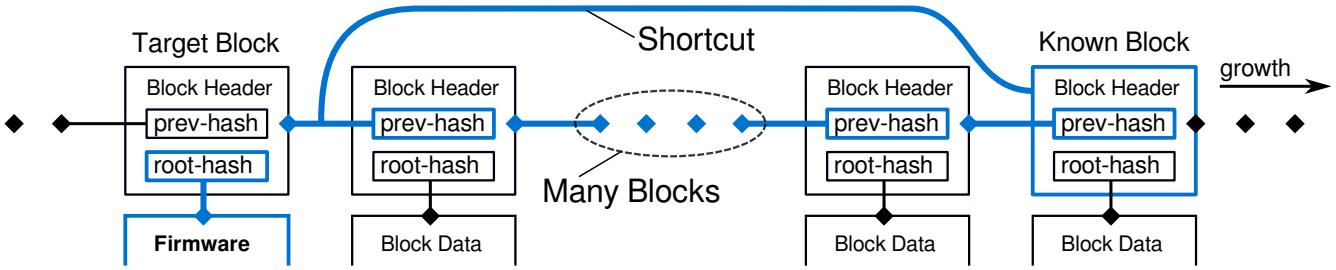
Decentralized IoT



1 | Many existing IoT applications are based on a centralized cloud service. We want to enable a decentralized IoT environment, which establishes efficient communication directly between end devices and results in a more robust infrastructure.

Within this line of research, we are investigating how to achieve efficient self-organization by reaching a common agreement – called consensus – on system states. One such system state, e.g., could be the current firmware that each embedded device is running. Traditionally, a trusted cloud server sends firmware updates to each such connected device, which must verify the authenticity of the data using intensive cryptography. For this problem, a promising approach would be a decentralized and trustless firmware distribution by reaching consensus among the network participants about the latest firmware and verifying that every device is running the same version.

While the consensus problem has been solved for a small number of network nodes, conventional solutions cannot be scaled to the large open networks of applications in a decentralized IoT. When the currency Bitcoin was invented in 2008,



2 | Each new block of a Blockchain stores the hash of the previous block (prev-hash). Verifying the hash of a firmware (stored in a certain target block) requires traversing the blockchain backwards (to the left) block by block. We introduce additional links as a shortcut to reach the target block with fewer intermediate blocks.

it solved the consensus challenge on a global scale by using a distributed ledger called a blockchain. The blockchain is a distributed data structure that enables consensus in large open networks without any central authority. Blocks containing agreed data are appended to an ever-growing chain that can be verified by every device. For embedded devices, however, we need to reduce the resource requirements for storing and verifying the growing blockchain without losing its benefits. Hence, in our Focus Group, we investigate how blockchain technology can be transferred from cryptocurrencies to embedded devices in decentralized IoT environments.

In our research, we have reduced the memory requirements that are necessary to verify that a certain block, which could certify a device firmware, is part of the blockchain and thus accepted consensus. For this purpose, we proposed a new block structure that allows efficient verification of blocks as illustrated in figure 2. With our approach, we were able to extract a subset of blocks from the blockchain that provides the same evidence as the original chain but is significantly smaller than the entire chain. Instead of several megabytes of chain data, only a few kilobytes are necessary to verify any block in the blockchain. The developed approach will extend blockchain application to the class of highly constrained embedded devices for the IoT. A paper detailing the approach has been submitted for publication.

Beyond the aforementioned research activities on IoT architecture decentralization, we have continued our lines of research both in the automotive and smart energy domains, e.g., by contributing decentralized automotive security approaches [1] and algorithms for efficient decentralized charge equalization for smart battery cells [2], respectively.

References

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Networked Cyber-Physical Systems**

Prof. John S. Baras (University of Maryland) | Hans Fischer Senior Fellow
Touraj Soleymani (TUM) | Doctoral Candidate

Scientific Reports

John S. Baras

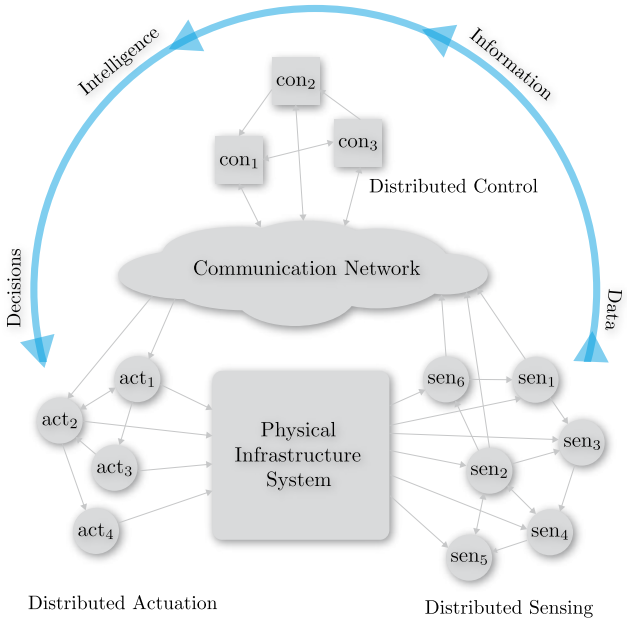
Host
Prof. Sandra Hirche
Information-Oriented Control, TUM

The Focus Group on Networked Cyber-Physical Systems was established by John Baras and Sandra Hirche in October 2014, and with doctoral candidate Touraj Soleymani research was initiated on the important topic of “value of information.” The purpose of our research is the development of fundamental principles for the design, manufacturing, and operation of cyber-physical systems that collaborate under various networking arrangements and constraints. Cyber-physical systems are technological systems where physical components and cyber components are tightly integrated (see figure 1). Examples abound, ranging from smart phones, smart sensors, smart homes, and smart cars to smart power grids, smart manufacturing, integrated transportation systems, and human robotic teams.

Most modern cyber-physical systems are actually networked, typically via the Internet or the cloud, or via special logical or physical networks. Examples include modern factories, modern enterprises, heterogeneous wireless networks, heterogeneous wireless sensor networks, social networks over the Internet, the Industrial Internet Consortium (IIC), and the Internet of Things (IoT). When networks are under consideration, new fundamental challenges emerge, as the network semantics and characteristics must be modeled and taken into account. The Focus Group's research is addressing fundamental challenges on two fronts: on the interface between the cyber and physical components, including their joint design and performance evaluation; and on the implications of the networked interfaces and the collaborative aspects of these systems, including their design and performance evaluation.

Recently, we studied the problem of controlling of a dynamical system using a wireless sensor node that is connected to the controller through a wireless communication channel. Wireless sensor nodes, following recent advances in micro electromechanical systems (MEMS) technology, have been attracting a lot of interest because of their promising and innovative applications in the context of Internet of Things (IoT). In general, a wireless sensor node is very small and requires very low power, but it is often equipped with a limited power source that is not replaceable due to application-related constraints. Therefore, following the fact that the power of a wireless sensor node is mainly consumed for communication, energy-efficient wireless communication for control purposes is vital.

One effective technique to conserve energy in a wireless sensor node is transmission power control (TPC). Intuitively, a power control mechanism should adjust the transmit power such that a high level of transmit power is used whenever a measurement contains valuable information and the wireless channel is in good condition. Nevertheless, the transmit power directly influences signal-to-noise ratio and subsequently the rate of packet dropouts. Packet dropouts have negative effects on the performance of the overall system and can even make the closed-loop system unstable. This interconnection between transmit power and control motivates us to jointly design a controller and a power control mechanism that satisfy our specifications.



1 | A schematic view of a networked cyber-physical system.

We developed a framework for achieving the minimum transmit power required for a specific performance level in linear quadratic Gaussian (LQG) control over a block-fading additive white Gaussian noise (AWGN) channel. We assumed that the state of a dynamical system is observed by a wireless sensor node that is supposed to transmit its noisy observations to a controller. In our study, we considered a lossy wireless channel between the sensor and the controller, which is proper for applications in which the controller is collocated with the actuator, or where the controller is remote but is connected to the actuator via an ideal channel.

For this setting, a power control mechanism and a controller are to be jointly designed. We used dynamic programming to characterize the optimal policies and showed that there exists a separation between the designs of the optimal estimator, optimal controller, and optimal power control mechanism. In addition, to save more power we designed a self-triggering mechanism that, whenever suitable, puts the sensor node into sleep mode until the next transmission time.

Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Safe Adaptive Dependable Aerospace Systems (SADAS)**

Prof. Matthias Heller (Airbus Defence and Space) | Rudolf Diesel Industry Fellow
Prof. Gernot Spiegelberg (Siemens AG) | Rudolf Diesel Industry Fellow
Prof. Klaus Schilling (University of Würzburg) | Visiting Fellow

Scientific Reports

Matthias Heller

Gernot Spiegelberg

Host
Prof. Florian Holzapfel
Flight System Dynamics, TUM

Successful first flight mission for unmanned jet aircraft SAGITTA

The main objective of our Focus Group is to investigate innovative methods to provide safe, highly reliable, and affordable automation for aerospace systems. To this end, the research and results of the former Focus Groups Aircraft Stability and Control (ASC) and Diesel Reloaded are being merged and advanced toward a novel common approach for future aerospace, vehicle, and multi-vehicle systems featuring a bidirectional transfer of concepts: from aerospace systems to vehicle systems – and back.

In aerospace applications, besides challenging systems dynamics that must be controlled and mastered, the highest safety requirements are mandatory and must be met. Promising new results from control theory research and progress in automation technology suggest highly attractive approaches and solutions to achieve robust, survivable, and reconfigurable unmanned aerial vehicles (UAVs). Nevertheless, due to the specific strict safety, reliability, and integrity requirements that are obligatory in the aerospace business, these new methods are far away from application.

Hence it is our vision and mission to bring novel control approaches to maturity (e.g., those featuring robust stabilization and flight envelope protection along with reconfiguration methods) so that they can be applied in real flying systems. We aim to overcome the so-called “certification collapse” by developing certifiable autoflight systems featuring guaranteed stability, robustness, and performance properties that comply with the rigid requirements for safety, accuracy, availability, and survivability that are common in the aviation sector. In order to bridge the gap between theory and real flight applications, the Focus Group SADAS integrates complementary fields of competence in mechanical engineering, flight system dynamics, robust and adaptive control, and embedded computers to achieve innovative results at aerospace system level.

Our project represents a research collaboration between TUM, Airbus DS, Siemens, and the University of Würzburg.

Major activities and achievements in 2017

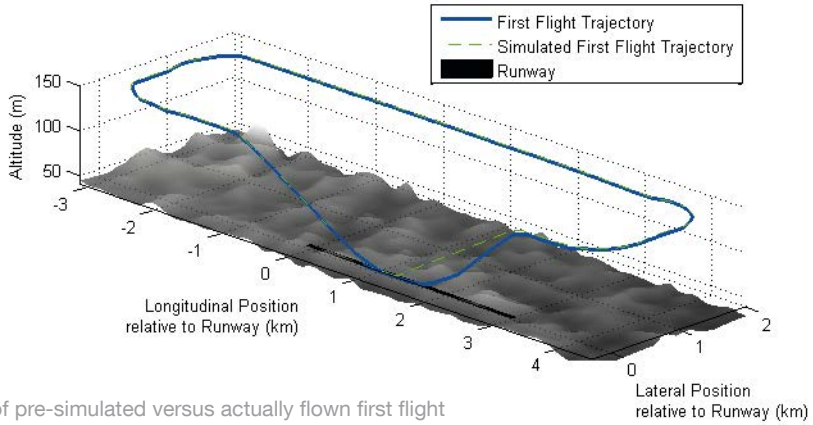
SADAS activities in 2017 were dominated by the final preparations, testing, and execution of the SAGITTA demonstrator`s first flight campaign. In the success of this campaign, we see our vision becoming reality. The SAGITTA demonstrator is a jet-propelled unmanned aerial vehicle developed by an initiative called Open Innovation – SAGITTA, with major contributions by the TUM-IAS Focus Group Aircraft

1 | The SAGITTA Demonstrator on the taxiway to its first flight (left) and airborne (right) at Overberg Test Range, South Africa.

2 | SAGITTA on final approach (left) and just after touchdown (right) within its fully automatic landing on the first flight mission.

3 | SAGITTA in front of South African mountains, and the TUM-IAS/FSD first flight mission support team (Markus Geiser, Martin Kügler, and David Seiferth) immediately after the successful first flight.

Stability and Control (now SADAS), On July 5, 2017, SAGITTA successfully accomplished its first flight mission at the Overberg Test Range in South Africa (figures 1–3). The innovative SAGITTA UAV flew completely autonomously for around seven minutes over the test site on a pre-programmed course (figure 4). The innovative diamond-shaped flying-wing design demonstrated excellent flying characteristics during the test, allowing for a second flight with additional mission segments after just one day of data analysis. These flights marked the successful completion of the first verification phase, which also comprised an extensive series of on-ground trials (including low/high-speed autonomous taxi tests).

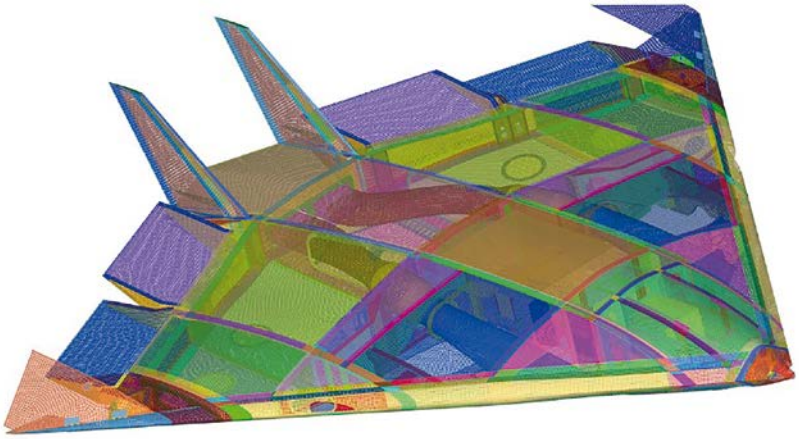


4 | Comparison of pre-simulated versus actually flown first flight mission trajectory of SAGITTA demonstrator.

Within the national Open Innovation – SAGITTA initiative launched by the aircraft manufacturer Airbus Defence and Space in 2010, the completely new SAGITTA research demonstrator UAV was developed in collaboration with a broad range of high-profile academic and research partners. Designed as an innovation and technology demonstration platform, the diamond-shaped flying wing UAV features a wingspan of three meters and a maximum take-off weight of 150 kilograms; it is jet-propelled by two 300 N turbines (see figure 5). The SAGITTA demonstrator embodies our vision of proving the validity and feasibility of the novel approaches and UAV technologies via in-flight demonstration.

In the context of the Open Innovation research partnership, the former TUM-IAS Focus Group Aircraft Stability and Control (and now the successor Focus Group SADAS), led by TUM-IAS Rudolf Diesel Industry Fellow Matthias Heller and hosted at the TUM Chair for Flight System Dynamics (Florian Holzapfel), developed the absolutely vital and safety-critical autoflight system (AFS) of the SAGITTA demonstrator. This system enables fully automatic flight missions from take-off to standstill after landing. This innovative AFS comprises – among other things – flight guidance and control allowing for waypoint navigation along a predefined flight plan, the automatic take-off and landing (ATOL) system, and the on-ground controller ensuring runway alignment, centerline tracking, and automatic braking during ATOL. Additionally, the responsible flight operator monitoring the aircraft from a ground control station can interrupt and/or alter the waypoint navigation reference mission and is able, therefore, to guide the aircraft in various control modes on different authority levels. Moreover, when the aircraft is in line of sight, external pilots can take over (for example, in emergency situations) and remotely control the aircraft as well.

The major challenge of the AFS development was to ensure a safe flight of the UAV, as there is no pilot on board who could react to unexpected behavior, e.g., due to model uncertainties or errors, external disturbances (turbulence, gusts) and system/equipment failures.



5 | SAGITTA demonstrator structural/inner life transparency drawing.

Since the novel aircraft configuration had never flown before, design, analysis and testing of the AFS were conducted exclusively with simulation models (in a so-called model-in-the-loop simulation environment). Unfortunately, such models inevitably represent the behavior of the real aircraft only up to a certain degree of accuracy; they exhibit a broad band of multiple uncertainties. It was thus a major design driver for the automatic flight control algorithms to ensure sufficient flight performance even if the aircraft would behave much differently in reality than in simulation. That means that the AFS is capable of coping with the widest possible spectrum of model deviations or errors.

The researchers' efforts were rewarded with extremely successful flight tests. The first flight of the SAGITTA demonstrator was accomplished fully automatically and exactly as planned, and the aircraft behaved as well as expected during the test. Since the aircraft and the flight control system performed so well throughout the whole first-flight mission, we were able to conduct a second flight in the identical configuration after just one day of data analysis. This second flight on July 7, 2017, tested additional high-level flight operator superposition commands including altitude and speed changes, as well as a holding pattern.

The SAGITTA First Flight has been recognized by a broad public. Almost all relevant media (such as *Flug Revue*, *Aviation Week*, *Welt/N24*, *UAS Weekly*, *DGLR Luft- und Raumfahrt*) reported with various impressive photos about the achievements of the first flight campaign and the “Open Innovation – SAGITTA” project.

Three doctoral candidates associated to our Focus Group – Stanislav Braun, Markus Geiser and David Seiferth – worked in close collaboration with us on all of these projects.

Focus Group **Climate Flows**

Prof. Carlo Ratti (Massachussetts Institute of Technology & Carlo Ratti Associati)
Rudolf Diesel Industry Fellow
Daniele Santucci (TUM) | Doctoral Candidate

Scientific Reports

Carlo Ratti

Host
Prof. Thomas Auer
Building Technology and Climate Responsive Design, TUM

The quality of urban spaces is fundamental to make cities livable. In the last decades many studies at different scales have developed methodologies to evaluate comfort conditions in public spaces, as this aspect is essential for making cities more walkable. Moreover, pedestrian activity can be considered significant for health.

In this context, our research group has developed a methodology for evaluating quality using data sets that include anonymous human trace data, Google Street View (GSV), and Open Street Map (OSM) data [1]. The anonymous human trace data were collected from an activity-oriented mobile phone application and include about one million trips of more than 60,000 anonymous users from May 2014 to May 2015. The data reveal patterns of how people use public spaces for walking in a high spatiotemporal resolution. Presence is used as an indicator for walkability by relating it to additional layers – such as density, canyon size, and proximity to recreational areas – and, more generally, to estimate the quality and the characteristics of the urban environment. The GSV data were used to measure and estimate the geometries of street canyons and the amount of street greenery. Since GSV panoramas are distributed discretely along streets, we first created samples every 100 meters along the streets in the study area. On the basis of those created samples, we further downloaded the GSV images based on the Google Street View API [2]–[3]. The GSV images and the walking trajectories matched with the OSM street segments have a complete correspondence in space, since they are both located at the street centerline.

The data sets allowed us to generate a georeferenced occupancy study in relation to the sky view factor (SVF), which quantifies the degree of sky visibility and therefore the proportions of street canyons. The SVF is an index that makes it possible to determine a variety of parameters such as density, typological variety, and the exposure to the environmental conditions [4]. We use it as an indicator of the urban morphology to relate walking behavior to form and its effects.

In an upcoming phase, the results will be validated by microclimatic simulations of outdoor comfort conditions using the Universal Thermal Climate Index (UTCI) and by using different techniques [5]–[6] to relate the results to people's presence. The remaining question is to which extent those indices are able to predict occupancy patterns in public outdoor spaces, due to the resolution that they are able to depict [7]. In fact, these studies show some limitations in terms of scale, since the increase of scale corresponds to a decrease in terms of accuracy: Either the granularity is very high – up to one meter – and the model scale is limited to a few blocks or, with an enlarged observation scale, the resolution drastically decreases.

The novelty of this study is to evaluate the dependency between walking activity and climatic conditions at a micro-level using the SVF as a fundamental indicator. SVF variability corresponds to the diversity of the built environment and therefore to the diversity in terms of microclimatic conditions: Variant urban environments generate varying comfort conditions in space at the street level. To further investigate people's response to microclimatic conditions and to find correlations between varying weather conditions and trajectories' length and location, a streetscape variable was selected – street enclosure by buildings – to identify a parameter that corresponds to diverse outdoor comfort conditions.

1 | Pedestrian activity in the Greater Boston area gathered from GPS-tracking apps [6].

Numerous studies have already demonstrated that the SVF can be a representative indicator for urban building density and layout. Several others have related the effects of SVF to thermal comfort in the urban environment [8]–[11]. Under this premise, the SVF is considered to be a fundamental parameter for evaluating microclimate in urban space, as it has been demonstrated that the correlation between SVF and outdoor thermal comfort (mean radiant temperature) is particularly strong, in particular for dense urban environments [12]. The present study provides a global mapping that illustrates to what extent pedestrians respond to the variability of the urban environment. The correlation between the SVF and the frequency of pedestrian activity along a street segment shows strong relations between the variability of urban spaces and their attractiveness for pedestrian use.

This result can be associated to the concept of diversity of cities that Jane Jacobs [13] considered one of the most important indicators for urban vitality. Furthermore, a higher variance of the SVF corresponds to a higher variability of the microclimatic conditions, producing frequent differences and variations in terms of outdoor comfort conditions: People walk preferably where the urban morphology determines variant microclimatic conditions. This tendency is valid under highly different climatic conditions, both for cold periods as well as for hot ones. The large number of trajectories and the urban scale allow us to consider this relation as an effective indicator for planners and policy makers with potentially extensive design implications.

Publications by this Focus Group can also be found in the section Publications of this report.

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Focus Group **Environmental Sensing and Modeling**

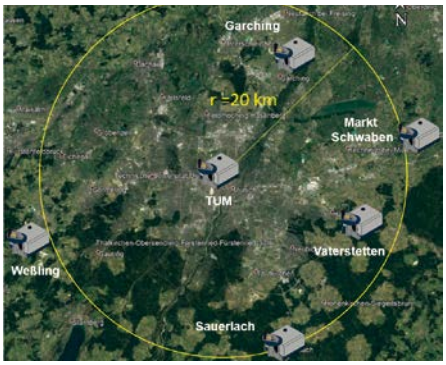
Prof. Jia Chen (TUM) | Rudolf Mößbauer Tenure Track Professor
Dr. Shrutilipi Bhattacharjee, Dr. Francisco Toja Silva, Dr. Yin Bai (TUM)
Postdoctoral Researchers
Florian Dietrich, Lijuan Lan (TUM) | Doctoral Candidates

Scientific Reports

Jia Chen

Host
Environmental Sensing and Modeling, TUM

Urban greenhouse gas (GHG) emission monitoring and methodology development

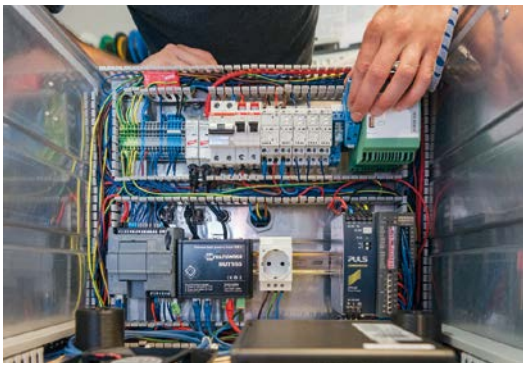


1 | Measurement sites during the Munich campaign 2017

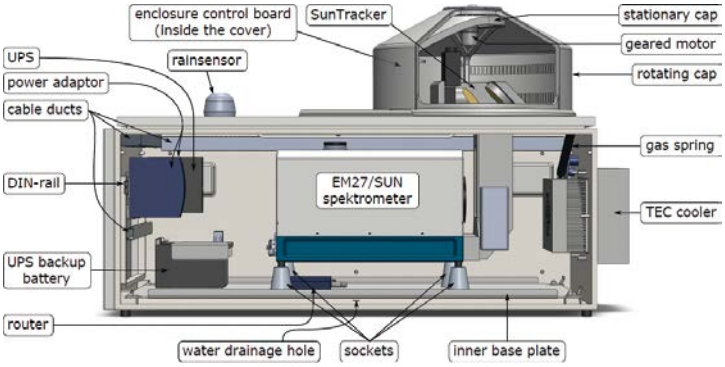
The majority of anthropogenic greenhouse gas (GHG) emissions originate from cities, therefore monitoring emissions in cities is essential to fight climate change. In addition to GHG, nitrogen oxides (NO_x) also play an important role in the urban climate. Recently, NO_x levels exceeding the limits in many German and other European cities have led to vigorous discussions on the banning of diesel vehicles in cities. Munich has a population of about 1.5 million and the highest population density in Germany. The city set up an ambitious emission reduction goal to cut CO_2 emissions by 10% every five years and to be carbon-neutral by 2050. The city's reports are based on software that employs a (non-measurement) bottom-up method. The natural gas pipeline system in Munich dates back to the 1960s, and power plants and heating plants are mostly based on natural gas. Both could be sources of unwanted CH_4 emissions that cannot be detected using the bottom-up method. In addition, Oktoberfest, the world's largest Volksfest, is held annually in Munich. There have been no GHG/NO_x measurements for Oktoberfest reported so far.

In Sept./Oct. 2017, we deployed six solar-tracking spectrometers (EM27/SUN) measuring column-averaged concentrations of CO_2 and CH_4 based on the differential column measurements principle [1]. Five stations were placed at the edges of the city to capture the inflow/outflow column amounts under arbitrary wind conditions. Additionally, one inner-city station was used for better partitioning of the city emissions (see figure 1). Four of the spectrometers were also utilized to monitor the column-averaged concentrations of CO, which will benefit source identification and apportionment. Further, we deployed two MAX-DOAS (multi-axis differential optical absorption spectroscopy) instruments for mapping the NO_x concentrations in a mobile setup on several days and capturing the differential column concentrations in a stationary setup for the rest of the campaign.

Initial analyses indicate Oktoberfest as a possible significant source for CO_2, CH_4 and CO. In addition, we detected a transient of a high CO plume passing the city on September 8th, 2017, observed from all CO stations. We have combined these data with HYSPLIT-STILT and WRF-STILT models to retrieve city and local emissions.



2 | Assembling the enclosure for a spectrometer measuring greenhouse gases



3 | CAD model of the enclosure

Our Munich campaign requires several spectrometers, leading to a significant increase in personnel costs. Therefore, to realize a long-term monitoring sensor network, it is essential to have automated protection enclosures that can undertake the tasks of the operators. This includes protecting the spectrometers against harmful weather conditions and maximizing the amount of measurement data. This is accomplished by opening the enclosure and starting the measurements automatically when it is sunny. The enclosure will close and measurements will stop when bad weather occurs or there is not enough sunlight. We have developed two generations of automated protection enclosures. The first enclosure has been deployed for a year and a half as a stationary measurement site for greenhouse gas monitoring in central Munich, and it has withstood all critical weather conditions [2]. Special features in the second generation are portability, increased safety and reliability, and cost reduction. Furthermore, it should be a preparation for small-scale production to also allow other institutes to use such an automated GHG measurement station. To that end, industrial components are used (cf. figure 2).

The functionality of the portable enclosure has been verified during the Munich campaign. It can be carried up easily to the measurement locations on rooftops, as it is lightweight (about 30 kg) and simple to transport. Thanks to the automated protection enclosures, multiple stations were operated at the same time by a single remote operator, while daily setup and dismantling efforts were reduced to zero.

A reliable enclosure has been developed that can serve equally well for stationary and mobile GHG measurement stations. It provides a foundation for a fully automated GHG observing system. The CAD model of this enclosure can be seen in figure 3.

In addition, we are also developing sensors for measuring concentrations of pollutant gases (CO_2, CO and CH_4) in the urban area. These compact sensors use the vertical-cavity surface-emitting laser (VCSEL) and are based on tunable diode laser absorption spectroscopy (TDLAS) and wavelength-modulation spectroscopy (WMS). The sensors are uniquely suitable for detection of trace gases, given their inherent characteristics: non-contact, high sensitivity, high precision, and rapid response. The measurement system has been built, and the precision reaches to 0.02 ppm with 10 minutes averaging time for CO_2 measurement.

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Modeling Spatial Mobility**

Prof. Rolf Moeckel (TUM) | Rudolf Mößbauer Tenure Track Professor
Prof. Kelly J. Clifton (Portland University) | Hans Fischer Senior Fellow
Dr. Ana Tsui Moreno Chou, Dr. Carlos Llorca Garcia,
Dr. Matthew Bediako Okrah (TUM) | Postdoctoral Researchers
Cat Silva, Qin Zhang, Shihang Zhang (TUM) | Doctoral Candidates

Scientific Reports

Rolf Moeckel

Kelly J. Clifton

Host
Modeling Spatial
Mobility, TUM

Transport modeling and travel behavior research

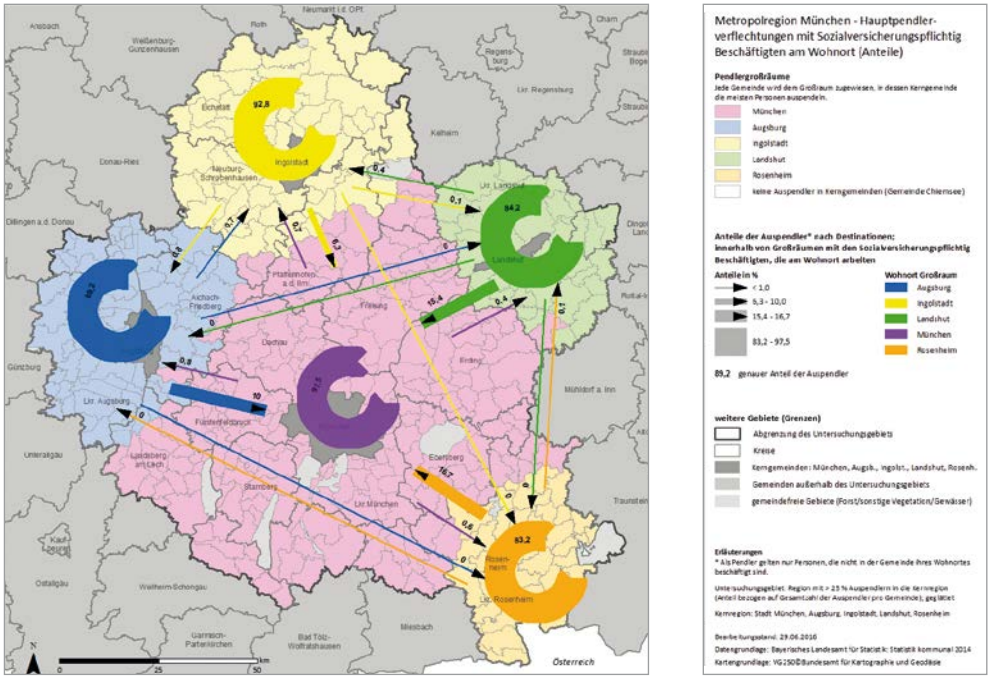
Our focus is on integrated modeling of land use and transport, together with travel behavior research. This includes model development of land use, transport, and related models, such as environmental impact models, health models, and fiscal impact models. This also includes the spatial analysis of travel behavior and location choice of households and firms. The interaction between land use and transport is of special interest. Ultimately, models and spatial analyses should improve policy analysis by extending scenario capabilities and by improving model sensitivities.

An integrated land use/transport modeling suite has been implemented for the Munich metropolitan area. The base year is 2011, and the model simulates land use and travel behavior through 2050. The study area consists of 444 municipalities with a population of 4.5 million. This area has been delineated on the basis of commuter flows and is shown in figure 1. The size of the study area was determined by the long distances many people commute to work, driven in part by the relatively high cost of living in Munich.

All models are built as microsimulation models. In aggregate models, the same level of aggregation of socio-demographic data is carried through the entire model. Relying instead on microdata allows every module to use different attributes of the microdata, or aggregations thereof. Model development follows the agile approach. In this paradigm borrowed from computer science, the simplest model possible is implemented at first, and it is improved gradually as necessary. In this concept, an operational model is maintained from the very beginning. At every step, the results are validated against observed data. The step that performs the least satisfactorily will be improved next. The agile approach applies both to model design and to data. In many cases, data may be borrowed from other models to speed up model implementation. Where borrowed data are found to work unsatisfactorily, they are replaced with local data.

Significant achievements over the last year include the development of an auto-ownership model that gradually adds or removes cars from individual households. The model also simulates the impact of autonomous cars, or self-driving cars, on personal auto ownership. Furthermore, a microscopic travel demand model called MITO has been significantly enhanced. The model includes a destination choice component that uses multinomial logit models to select destinations within a given travel time budget, and a nested mode choice model simulates the choice between auto, transit, walking, and bicycling for each trip. An incremental mode choice model has been specified to add the choice of traveling with an autonomous vehicle.

To assign travel demand to a transportation network, the open-source software MATSim is used. In such microscopic assignment models, it is common practice to scale traffic demand with the goal of saving on runtime. For example, the user may assign only 50 percent of all trips while cutting the network capacity in half.



1 | Munich metropolitan area delineated by commuter flows.

Theoretically, the level of congestion should be very similar to the full assignment on all links. We systematically analyzed, for the first time, the impact of network resolution and scaling factors, and we found that scaling in general has the tendency to underestimate congestion. Scaling below ten percent led to highly inconsistent traffic volumes.

The MSM group is very fortunate to host a Hans Fischer Senior Fellowship that was awarded to Dr. Kelly Clifton, an internationally recognized expert in pedestrian modeling. The goal of our collaborative research is to integrate her pedestrian model with the land use/transport model developed at TUM. In the last quarter of 2017, this model has been translated into Java to facilitate integration, and the integration has been developed in concept.

With funding from the DFG, the MSM Focus Group is currently implementing this modeling suite for the metropolitan region of Cape Town, South Africa. Special attention is given to townships that tended to be built in areas with rather low accessibilities. In particular, densification strategies and transit alternatives will be explored in this implementation in South Africa.

Last but not least, a long-distance person travel demand model was developed, implemented, and calibrated for the province of Ontario, Canada. The model simulates trips that are longer than 40 km or that include an overnight stay. A destination choice model applied Four Square social media data to significantly improve the performance of the destination choice model. Mode choice distinguished the transportation modes auto, regional bus, train, and air. This long-distance model has been fully integrated with the newly developed provincial travel demand model.

All models developed by this research group are open source under the GNU license and provided at https://github.com/msmobility free of charge. Interested users are welcome to download, use, and further develop these models. Data to run these models are shared as well, as long as no privacy considerations are affected.

Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Soil Architecture**

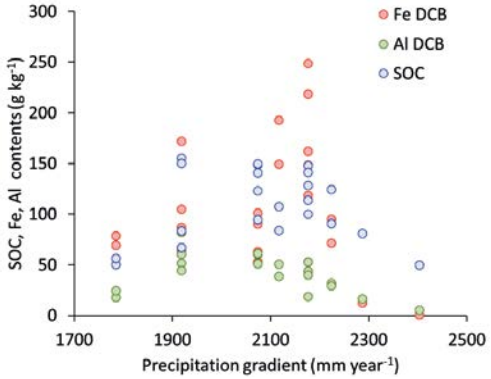
Prof. Johannes Lehmann (Cornell University) | Hans Fischer Senior Fellow
Thiago Massao Inagaki (TUM) | Doctoral Candidate

Scientific Reports

Johannes Lehmann

Host
Prof. Ingrid Kögel-Knabner
Soil Science, TUM

Soil organic matter is critical for global agricultural productivity, water quality and climate. Soil organic matter contains more organic carbon than global vegetation and the atmosphere combined. For this reason, the release and conversion into carbon dioxide or methane of even a small proportion of carbon contained in soil organic matter can cause quantitatively relevant variations in the atmospheric concentrations of these greenhouse gases. Moreover, organic matter retains nutrients as well as pollutants in the soil maintaining plant growth and water quality. Despite its recognized importance, our knowledge of its nature and cycling is still remarkably limited. Soil organic matter has recently been seen rather as a flow-through and transient conduit of carbon than a stable reservoir of recalcitrant carbon. We now recognize that plant residues are metabolized to ever smaller molecules whose persistence in soil relies on interactions with the minerals and not on the formation of stable molecules [1].

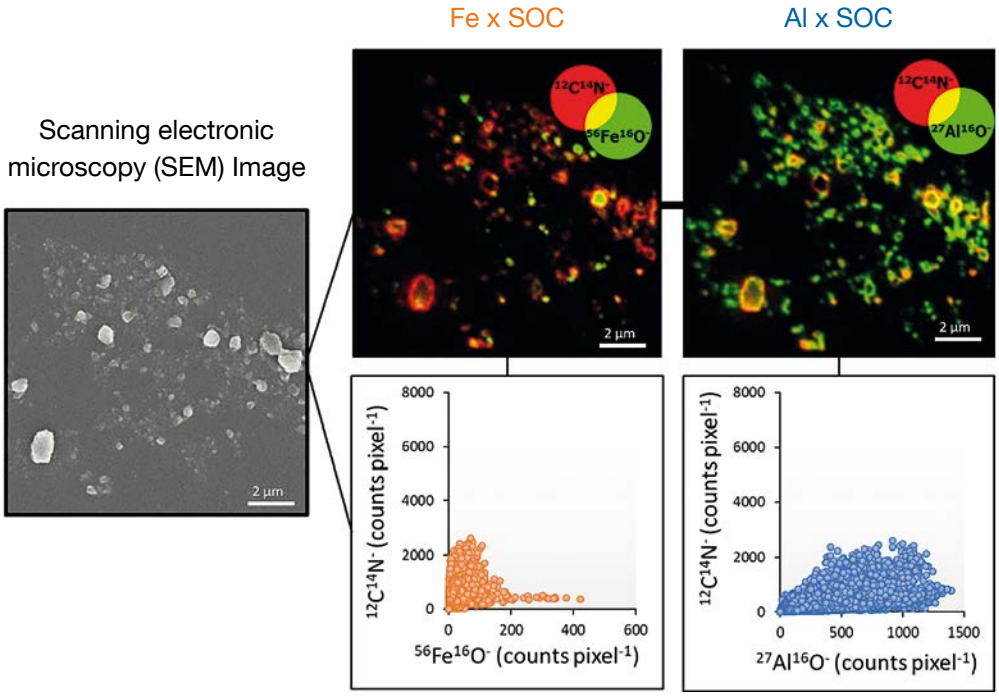


1 | Fe and Al (dithionite citrate extractable – DCB), and soil organic C at the depths of 0.4–0.9 m across the rainfall gradient.

Understanding carbon stabilization mechanisms in soils thus becomes increasingly important. We examined volcanic Andosols as they are recognized for their extraordinary capacity of storing organic carbon compared with other soils because of the specific type of minerals they contain. Utilizing a mineralogy gradient that formed as a result of rainfall varying from 1800 to 2400 mm year^{-1} [2] allowed us to examine how different soil mineralogy affects the mechanisms responsible for high soil organic carbon (SOC) storage.

Our results demonstrate a close relationship between SOC and short-range order minerals, especially aluminium oxides at the landscape scale (figure 1). Both SOC and short-range order minerals increase until precipitation levels of approximately 2200 mm year^{-1}, and they decrease at higher precipitation levels. Both the changes in short-range order minerals and the environmental conditions varying along the precipitation gradient (specifically redox conditions, leaching) are responsible for changes in SOC storage [3].

In support of the results found at the landscape scale, we also observed close relationships between Fe or Al and SOC at the microscopic scale (figure 2). This strong relationship at both scales highlights the role of short range order minerals for SOC stabilization [4]. Presently, we expand our studies to include incubation experiments with ^{13}C-labeled substrates to understand how different carbon inputs are stabilized in top and subsoils.



2 | Relationship of Fe and Al with SOC at the microscopic scale observed in the fine clay fraction (< 2µm) using nanoscale secondary ion mass spectrometry (NanoSIMS).

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Sustainable Water Cycles for Cities of the Future**

Prof. Stuart Khan (University of New South Wales) | Hans Fischer Fellow
Philipp Michel (TUM) | Doctoral Candidate

Scientific Reports

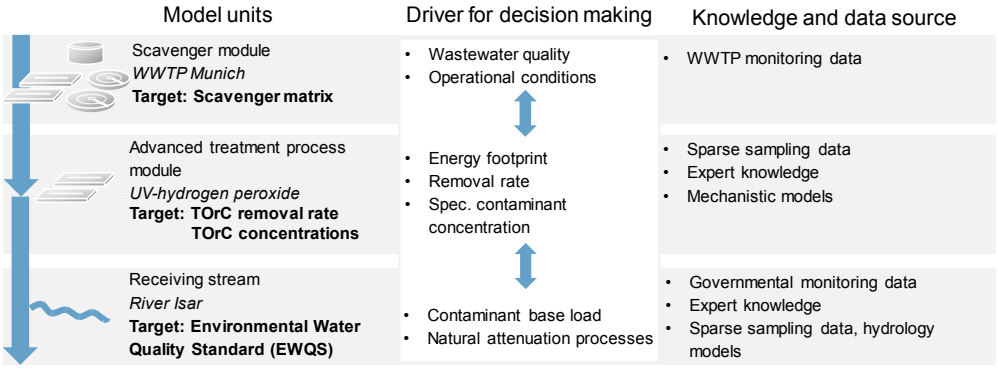
Stuart Khan

Host
Prof. Jörg Drewes
Urban Water Systems Engineering, TUM

Optimizing measurement, analysis, and decision making for water quality and ecology

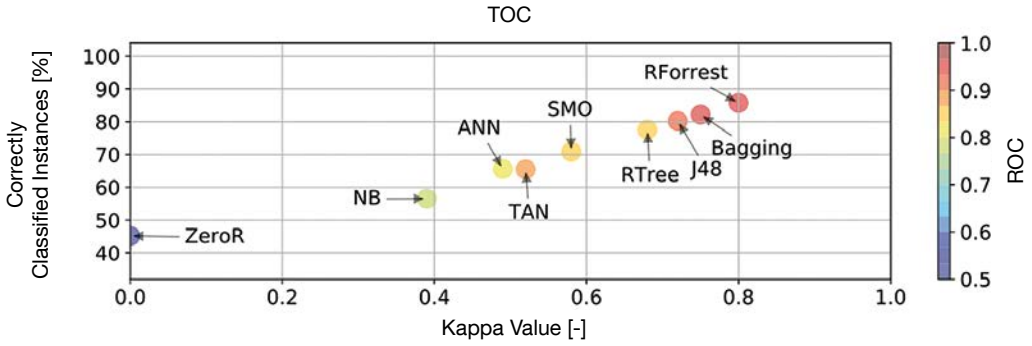
The principal objective of the EU Water Framework Directive (WFD) is to protect water quality and ecological attributes of Europe's rivers, lakes, groundwater, and coastal beaches. An important focus of the WFD is the control of chemical substances that may, when released into bodies of water, lead to detrimental ecological impacts. Priority chemical substances have been identified according to approaches outlined in the WFD. Advanced wastewater treatment technologies have been proposed to reduce contaminant loads from these point sources. However, these advanced treatment technologies are energy-intensive, operationally complex, and expensive. In light of these considerations, the investment in the implementation of advanced treatment technologies should balance the environmental benefits against environmental impacts and financial costs. The relationship between these costs and benefits will vary – both between locations and also over time.

The focus of our study is on the removal of trace organic chemicals and on surrogate parameters that correlate with their removal. Issues relating to data, model structures, incorporation of variability and uncertainty, calibration, potential surrogate parameters, and model validation will be investigated. The contributions of existing systems and parameters determining environmental contaminant concentrations (e.g., source variability, existing treatment, discharge dilution, environmental processing) will be accounted for.



1 | Model units for research investigations

As seen in figure 1, the research focuses on three different model units, the first two of which use data-driven machine learning strategies to model the different target parameters. The third model unit puts the developed models into an expert knowledge decision-making framework, which makes it possible to present central operational scenarios as well transparently show the individual uncertainties. Understanding and modeling of cause-effect relationships under uncertainty could provide a means for dynamic and more quantified decision making for advanced wastewater treatment, driven by machine learning approaches. This approach could result in significant savings in overall energy consumption, and thus lower costs and greenhouse gas emissions. Using state-of-the-art modeling approaches,



2 | Comparison of different machine learning algorithms for the classified prediction of total organic carbon (TOC). Different algorithms: ZeroR, Naïve Bayes (NB), Tree Augmented Naïve Bayes (TAN), Artificial Neural Network (ANN), Sequential Minimal Optimization (SMO), Random Tree (RTree), J48, Bagging (with J48), Random Forrest

this research will advance the predictive capacity for diverse contaminant concentrations in wastewater treatment and receiving environmental systems.

In 2017, we developed a program to preprocess data and further execute advanced multivariate analysis to evaluate the suitability and accuracy of several machine learning (classification) algorithms. The program allows predefined predictions, but also methodological transparency, which is central for these investigation because machine learning approaches have countless handles to adapt procedures and optimize so-called hyperparameters for multivariate analysis.

Figure 2 shows one small extract of results describing the analysis of different machine learning algorithms to predict a target variable, in this case total organic carbon (TOC). It can be seen that machine learning can show distinct performance differences. As shown in figure 2, multiple validation parameters need to be taken into account to produce a comprehensive performance comparison. This allows a distinct analysis for different data-set resolutions, target parameters, and classifiers.

Guido Carvajal Ortega visited TUM in September and October 2017. This visit was funded by the DAAD Australia-Germany Joint Research Cooperation Scheme. During this visit, doctoral candidate Philipp Michel and Guido Carvajal Ortega strengthened the collaboration and finalized the results a joint paper on “data-driven scavenger modeling,” submitted for publication in January 2018. In the context of this collaboration, Philipp Michel and Guido Carvajal Ortega co-authored “Robust evaluation of performance monitoring options for ozone disinfection in water recycling using Bayesian analysis” [1].

Throughout 2017, Jörg Drewes and Stuart Khan worked together on the organizing committee for the largest international water recycling conference, which took place in Long Beach, California, during July 2017. Prof. Drewes was the Chair of the conference. Moreover, Stuart Khan and Jörg Drewes co-authored a new chapter in an international handbook, *Advanced Oxidation Processes for Water Treatment*. Their chapter focuses on applications of advanced oxidation for potable water reuse. The book was published by the International Water Association (IWA) in 2017 [2].

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Biochemistry**

Prof. Horst Kessler (TUM) | Carl von Linde Senior Fellow

Scientific Reports

In 2017 we published 11 manuscripts with a total impact factor of 55.2.

Horst Kessler

Host
Chemistry, TUM

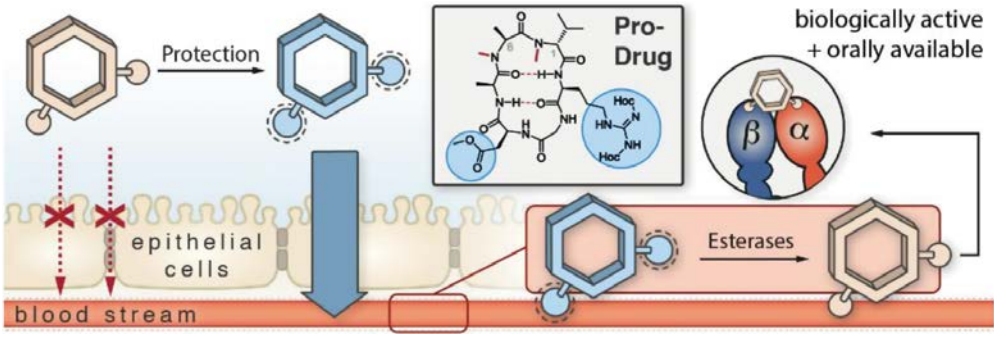
Oral bioavailability of peptides

Peptides are short pieces of proteins and consist of chains of two to 40 amino acids, the natural building blocks of proteins and enzymes. Longer chains are commonly known as proteins. Peptides are used, e.g., for communication between cells and tissues. In mammals, many peptides act as hormones through interaction with receptors found at the surface of other cells to signal for distinct functions.

To give an example: The peptidic hormone ACTH (adrenocorticotropic hormone) is produced in the brain and is transported in the blood stream to the adrenal gland. There it induces the excretion of adrenalin, which functions as a waking hormone. Hence, the well known “adrenalin rush” is in fact triggered by an ACTH rush. After transmitting their message, peptidic hormones are very rapidly degraded in the body as they no longer fulfill a function. Many peptidic hormones would be ideal drugs for many diseases in case of malfunctions. In addition, peptides are also able to mimic parts of proteins and thus to interfere with protein-protein interactions, which are related to many disorders.

In the last decade, there has been a renaissance of peptides and peptidic drugs in the pharmaceutical industry, and they are – next to biologics – the strongest rising drug market. Nevertheless, peptides are not considered good drugs, as they are not stable *in vivo* because they are degraded into smaller units or even into single amino acids. However, it has been discovered that the stability problem can be solved by peptide cyclization, e.g., from head to tail. In addition, incorporation of unnatural mirror-image amino acids (in D-configuration) as well as N methylation of peptide bonds can prevent enzymatic cleavage [1]–[3]. The remaining problem of peptidic drugs is their lack of oral availability, which is often dubbed “the holy grail in peptide chemistry.” Compared to the stability problem, it is even more difficult for peptides to be transported from the gut into the blood stream as there is a barrier of endothelial cells, which peptides usually cannot pass. In comparison, small molecular drugs are transported via the cell membranes or by distinct transporter systems [3]–[4].

In our recent publication in *Angewandte Chemie International Edition*, we reported a stepwise procedure to overcome this barrier [5]. The first step was the requirement of the correct backbone for permeability. This was explored by a large library of cyclic hexa-alanine peptides of the general formula *cyclo*(-D-Ala-Ala_5-) with almost all possible *N*-methylations in the different positions [6]. In the alanine peptides, all side chains are methyl groups. Out of this library, very few permeable peptides could be identified; these were used as templates to bring back biological activity by incorporating the required functional groups, in our case the tripeptide sequence RGD = Arg-Gly-Asp, in all positions of three permeable *N*-methylated hexa-alanine peptides (resulting in 3 x 6 = 18 RGD peptides). Only very few of them exhibited binding affinity to the integrin $\alpha v\beta 3$. After optimization by a few further Ala->Phe exchanges, a compound with extreme biological affinity was obtained. This compound was not orally available – obviously by the charge of the functional groups of Arg and Asp. However, when these functional charged groups were



1 | A selection of optimized cyclic hexapeptides – containing only alanines with a distinct pattern of *N*-methylation that showed high permeability from gut to blood (not shown here) – was "re-functionalized" with the RGD tripeptide sequence in all possible positions. The resulting peptide (pink model in the upper left corner) exhibited high affinity to its αvβ3 integrin receptor (upper panel, right). However, the charged residues, which were required for biological activity, prevented permeability (left side). Protection of the functional groups (highlighted in the insert in the middle in blue), which are easily cleaved by enzymes in the blood (lower panel, right), shielded the charge and formed a permeable prodrug (blue). After oral administration in mice the permeable protected peptide showed the desired biological effect, similar to intraperitoneal injection of the biologically active peptide without protecting groups.

protected with neutral residues that are easily cleaved by enzymes in the blood serum, permeability was observed, and the biological effect of the peptides was observed after oral administration in mice – similar to the effect of intraperitoneal injection of the unprotected peptide. This is the first time that an orally available functional peptide has been developed in a rational way. This is paving the way for the development of many novel peptidic drugs in the future.

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Biomolecular Design**

Prof. Hendrik Dietz (TUM) | Carl von Linde Senior Fellow

Scientific Reports

Hendrik Dietz

Host
Biomolecular
Nanotechnology, TUM

Advances in DNA origami: Building with proteins, building on the scale of viruses, and DNA mass production

Self-assembly of genetically encoded DNA-protein hybrid nanoscale shapes

We developed an approach to bottom-up fabrication that allows integration of the functional diversity of proteins into designed three-dimensional structural frameworks in the journal *Science* [1]. A set of custom staple proteins based on transcription activator-like effector proteins folds a double-stranded DNA template into a user-defined shape. Each staple protein is designed to recognize and closely link two distinct double-helical DNA sequences at separate positions on the template. We presented design rules for constructing megadalton-scale DNA-protein hybrid shapes; introduced various structural motifs, such as custom curvature, corners, and vertices; and described principles for creating multilayer DNA-protein objects with enhanced rigidity. We demonstrated self-assembly of our hybrid nanostructures in one-pot mixtures that include the genetic information for the designed proteins, the template DNA, RNA polymerase, ribosomes, and cofactors for transcription and translation.

Gigadalton-scale shape-programmable DNA assemblies

Natural biomolecular assemblies such as molecular motors, enzymes, viruses and subcellular structures often form by self-limiting hierarchical oligomerization of multiple subunits. Large structures can also assemble efficiently from a few components by combining hierarchical assembly and symmetry, a strategy exemplified by viral capsids4. *De novo* protein design and RNA and DNA nanotechnology aim to mimic these capabilities, but the bottom-up construction of artificial structures with the dimensions and complexity of viruses and other subcellular components remains challenging. In a paper published in *Nature* [2], we showed that natural assembly principles can be combined with the methods of DNA origami to produce gigadalton-scale structures with controlled sizes. DNA sequence information is used to encode the shapes of individual DNA origami building blocks, and the geometry and details of the interactions between these building blocks then control their copy numbers, positions, and orientations within higher-order assemblies. We illustrated this strategy by creating planar rings of up to 350 nanometers in diameter and with atomic masses of up to 330 megadaltons, micrometer-long, thick tubes commensurate in size to some bacilli, and three-dimensional polyhedral assemblies with sizes of up to 1.2 gigadaltons and 450 nanometers in diameter. We achieved efficient assembly, with yields of up to 90 per cent, by using building blocks with validated structure and sufficient rigidity, and an accurate design with interaction motifs that ensure that hierarchical assembly is self-limiting and able to proceed in equilibrium to allow for error correction. We expect that our method, which enables the self-assembly of structures with sizes approaching that of viruses and cellular organelles, can readily be used to create a range of other complex structures with well defined sizes, by exploiting the modularity and high degree of addressability of the DNA origami building blocks used.

1 | A 3-D printed model of a designed protein-DNA hybrid origami.

2 | A 3-D printed model of a 1.2 gigadalton defined-size dodecahedron that integrates the equivalent of 220 DNA origami.

3 | An artist's impression of future DNA-origami-containing medical tablets.

Biotechnological mass production of DNA origami

DNA nanotechnology, in particular DNA origami, enables the bottom-up self-assembly of micrometer-scale, three-dimensional structures with nanometer-precise features. These structures are customizable, in that they can be site-specifically functionalized or constructed to exhibit machine-like or logic-gating behavior. Their use has been limited to applications that require only small amounts of material (of the order of micrograms), owing to the limitations of current production methods. But many proposed applications, for example as therapeutic agents or in complex materials, could be realized if more material could be used. In DNA origami, a nanostructure is assembled from a very long single-stranded scaffold molecule held in place by many short single-stranded staple oligonucleotides. Only the bacteriophage-derived scaffold molecules are amenable to scalable and efficient mass production; the shorter staple strands are obtained through costly solid-phase synthesis or enzymatic processes. In the journal *Nature* [3], we showed that single strands of DNA of virtually arbitrary length and with virtually arbitrary sequences can be produced in a scalable and cost-efficient manner by using bacteriophages to generate single-stranded precursor DNA that contains target strand sequences interleaved with self-excising "cassettes," with each cassette comprising two Zn2+-dependent DNA-cleaving DNA enzymes. We produced all of the necessary single strands of DNA for several DNA origami using shaker-flask cultures, and we demonstrated end-to-end production of macroscopic amounts of a DNA origami nanorod in a liter-scale stirred-tank bioreactor. Our method is compatible with existing DNA origami design frameworks and retains the modularity and addressability of DNA origami objects necessary for implementing custom modifications using functional groups. With all of the production and purification steps amenable to scaling, we expect that our method will expand the scope of DNA nanotechnology in many areas of science and technology.

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Cellular Protein Biochemistry**

Prof. Matthias J. Feige (TUM) | Rudolf Mößbauer Tenure Track Professor
Nicolas Blömeke, Joao Coelho, Karen Hildenbrand, Susanne Meier, Yonatan Mideksa, Stephanie Müller (TUM) | Doctoral Candidates

Scientific Reports

Matthias J. Feige

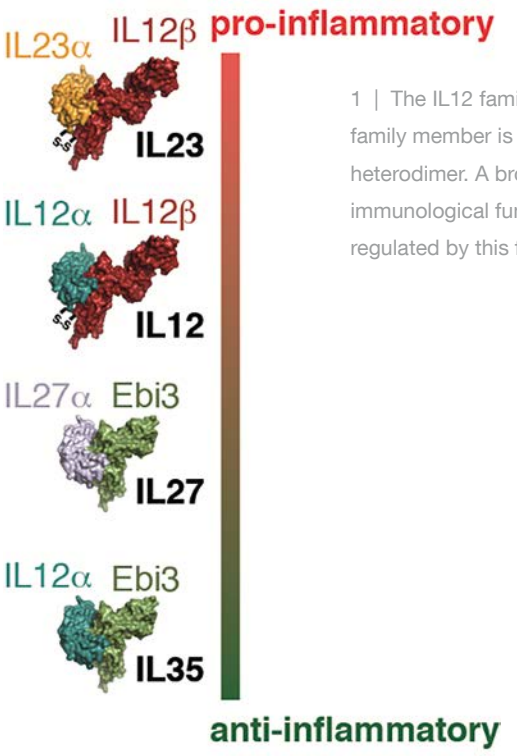
Host
Cellular Protein Biochemistry, TUM

Membrane protein quality control and interleukin biogenesis

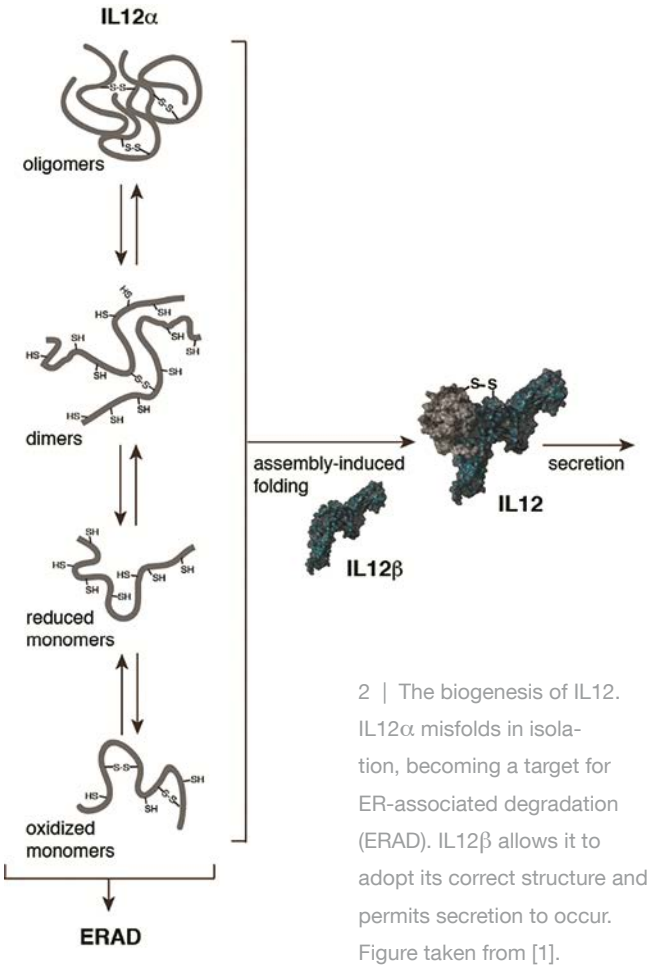
In complex organisms, cells need to communicate and interact with each other. Proteins secreted from cells or displayed on the cell surface allow cells to perform these tasks. Within a mammalian cell, a single subcompartment is responsible for the production of these proteins: the endoplasmic reticulum (ER), an extended net-like structure within the interior of the cell. Proteins are not only produced in the ER, but also controlled. Only proteins that have acquired their correct biologically active structure are allowed to leave the cell or to be displayed on the cell surface. Otherwise these faulty proteins are recognized by dedicated molecular quality control machinery and degraded. Insights into these processes are of immediate medical relevance for human pathologies including Alzheimer's and Parkinson's diseases – but may also inspire new approaches in biotechnology. In our lab, using an interdisciplinary approach from structural biochemistry to mammalian cell biology, we aim to understand and ultimately engineer the underlying processes.

Current work in the cellular protein biochemistry (CPB) lab focuses on two major topics. The first is the quality control of membrane proteins, where principles are still mostly unknown yet of immediate biomedical relevance. Failures in membrane protein biogenesis are associated with a large number of neurological disorders, and work from our lab is beginning to reveal some underlying principles.

A second research focus in our lab is the biogenesis of interleukins (ILs), which are key signaling molecules in our immune system. In humans, more than 40 different ILs exist, and these mount, sustain, or suppress immune reactions in health and disease. Understanding interleukin biogenesis in the cell in more detail will provide an avenue toward rationally optimizing these key immune molecules and should pave the way for novel approaches in immunomodulation. Our model system is the interleukin 12 (IL12) family, which comprises four members (IL12, IL23, IL27, and IL35) that span a broad range of biological functions – from activating immune responses to suppressing immunity (figure 1). Thus IL12 family members are involved in a large number of human diseases such as autoimmune disorders, cancer development, and sepsis. Of note, tight quality control measures act on all IL12 family members in human cells that safeguard correct heterodimerization within the family (figure 1). In a study on the founding member of the family, IL12, we have been able to reveal underlying principles [1]. The human IL12α subunit does not adopt its native structure in isolation, but instead forms wrong interactions. Only when its partner subunit is present, IL12β, does IL12α become correctly structured so that it can pass ER quality control, be secreted, and regulate immune responses (figure 2). Insights into these processes allowed us to engineer a simplified IL12 cytokine, which may be of future use in therapeutic approaches where IL12 is of interest, for example, to stimulate anti-tumor responses.



1 | The IL12 family. Each family member is an αβ heterodimer. A broad range of immunological functions are regulated by this family.



2 | The biogenesis of IL12. IL12α misfolds in isolation, becoming a target for ER-associated degradation (ERAD). IL12β allows it to adopt its correct structure and permits secretion to occur. Figure taken from [1].

Reference

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Focus Group **Chemical Catalysis, Photo-catalysis and Electro-catalysis**

Prof. Suljo Linic (University of Michigan) | Hans Fischer Fellow
Simon P. Rittmeyer (TUM) | Doctoral Candidate

Scientific Reports

Suljo Linic

Hosts
Prof. Ulrich Heiz
Physical Chemistry, TUM
Prof. Karsten Reuter
Theoretical Chemistry, TUM

Energy exchange at metal surfaces: Where does the energy go? Where does it come from?

Dynamical processes at the gas-solid interface lie at the heart of many industrial applications of great technological value such as heterogeneous catalysis. Here, different forms of energy are constantly converted into each other, and the intricate ways in which this happens ultimately influence not only reaction rates but also the corresponding specificity and yield.

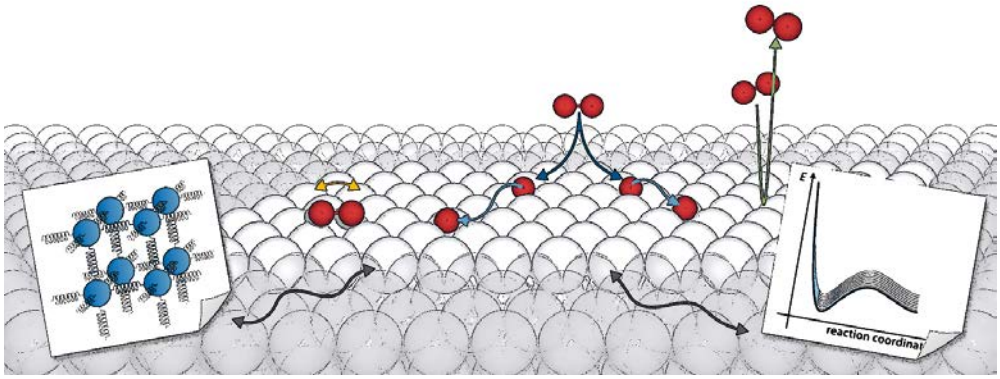
In 2017 our Focus Group was able to advance the fundamental understanding of these processes. In addition, we hosted an international workshop during which seven leading experts in the technologically critical fields of chemical catalysis and electrocatalysis presented two lectures each: one focusing on fundamental aspects of catalysis and another on potential applications in fields such as renewable energy and industrial chemistry.

Strengthening the basis for more detailed analysis

On insulating or semiconducting surfaces, the dynamical coupling to the surface can clearly be attributed to the excitation of and interaction with lattice vibrations, so-called phonons. On frequently employed metal catalysts, however, phonons are not the sole actor in terms of energy dissipation at the surface. An additional channel to be considered here is the adsorbate-induced excitation of typically low-energy electron-hole (*eh*)-pairs in the substrate. Supported by a rapidly increasing amount of experimental evidence, this suggests a breakdown of the ubiquitous and most fundamental Born-Oppenheimer approximation in many situations.

Our research aims at a deeper understanding of these different energy transfer processes and their relative importance for surface dynamical phenomena. While important steps toward a high-level explicit modeling of the phononic degrees of freedom have recently been achieved, the quest for an accurate and numerically efficient first-principles-based description of electronically non-adiabatic adsorbate dynamics on metal surfaces is still ongoing. A very popular candidate in this regard is the concept of electronic friction within the local density friction approximation (LDFA). However, a shroud of uncertainty remains over this effective model not only with respect to its validity, but also, in a broader context, regarding conclusions drawn from it on the role of the competing energy dissipation channels [1].

Aiming to improve on this situation, we recently demonstrated that the LDFA model yields reasonable results for the vibrational damping of high-frequency adsorbate vibrations on various metal surfaces [2]. We also suggested a simple and computationally very efficient strategy to extend the LDFA beyond the hitherto inherent independent-atom approximation, which compares quantitatively with experimental and theoretical reference data. With this confidence, we further scrutinized the role of *eh*-pair excitations in surface diffusion events [3]. Here, a comparison of respective LDFA-based simulations with experimental helium-3 spin echo measurements allowed us to decompose empirically obtained friction coefficients into electronic and phononic contributions. Consequently, for the thermal diffusion of Na on Cu(111),



1 | Adsorbate dynamics on a metal surface are intricately governed by energy exchange with the substrate. In this regard, interactions with lattice vibrations, so-called phonons (left inset) and electron-hole pair excitations (right inset), constitute two competing energy dissipation channels. Knowledge about their relative importance is scarce and inconclusive.

a surprisingly high degree of non-adiabaticity is found, suggesting that eh-pair excitations play a significant role in the rapid thermalization that adiabatic diffusion theories generally rely on.

As surprising and fundamental as our findings are, they simultaneously highlight one of the major issues of the electronic friction approach. Coarse-graining the electron dynamics up to an implicit Langevin treatment, it precludes a more profound understanding of the underlying *eh*-pair excitations. One of the prominent obscurities in this regard is that the non-adiabatic vibrational lifetimes for CO on Cu(100) and Pt(111) are virtually identical. Electronic friction theory reproduces these lifetimes rather accurately [2], which is a baffling finding given the pronounced band-structure differences of the underlying coinage and transition metal substrates. In our most recent work [4], we took a second look at these systems, this time however equipped with a time-dependent approach based on perturbation theory. By correlating resulting explicit *eh*-pair excitation spectra with respective electronic coherence times, we finally identified a pseudo-Markovian behavior of the electronic degrees of freedom to wash out effects of the differing band structures. Such an assumption is implicitly included in the electronic friction approach, which in turn explains its great success in this regard.

Altogether, our work has contributed significantly toward further establishing the electronic friction approach, and particularly the LDFA method, as a go-to-model for non-adiabatic gas-surface dynamics. Its performance has been validated on a sound basis through comparison to experimental benchmark observables, and crucial assumptions were tested using higher-level methods. This sets the stage to combine the latter with an accurate description of the substrate nuclear degrees of freedom in order to further address the importance of the competing energy dissipation channels at metal surfaces.

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Functional Metagenomics**

Prof. Yana Bromberg (Rutgers University) | Hans Fischer Fellow
Yannick Mahlich (TUM) | Doctoral Candidate

Scientific Reports

Yana Bromberg

Host
Prof. Burkhard Rost
Bioinformatics, TUM

Delivering innovative tools for the worldwide research community

In 2016 the Focus Group opened fusionDB [1] and mi-faser [2] resources to the public. The focus in 2017 was on the refinement and expansion of these services, as well as the release of their respective publications.

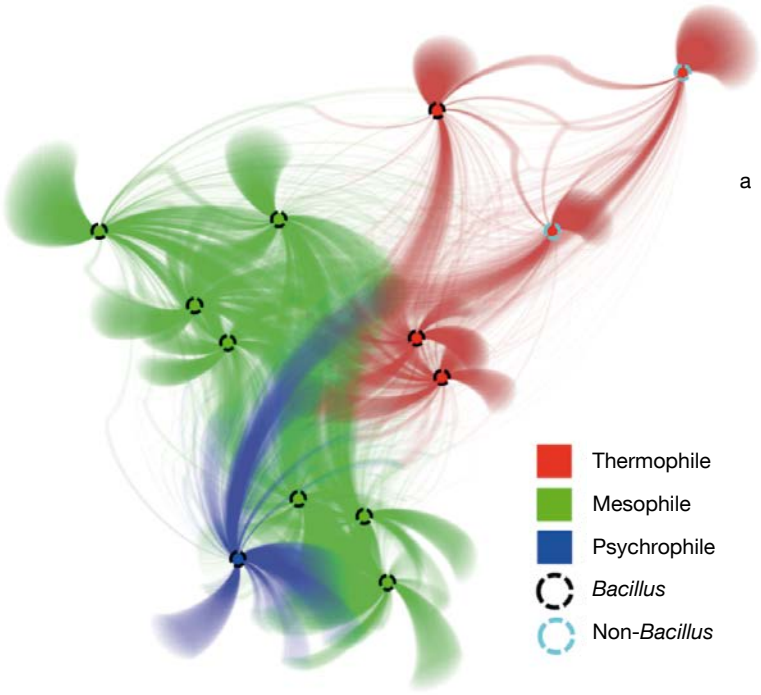
fusionDB, a database of functional similarities between organisms and their environmental placement, received an interface overhaul. Now the scientific community can explore microbial organisms of interest in the light of functional niches. We were able to successfully place previously unknown organisms into their corresponding functional spaces, highlighting functionally similar microbes (figure 1). We replaced BLAST (the alignment algorithm of choice up until now) with a new breed of much faster algorithms, which retain the high accuracy of functional annotations. This replacement will allow us to expand fusionDB's list of reference organisms by more than six-fold [3] and provide significantly shorter update cycles. Additionally, we validated key concepts in functional similarity annotation that were first described by Burkhard Rost over 25 years ago.

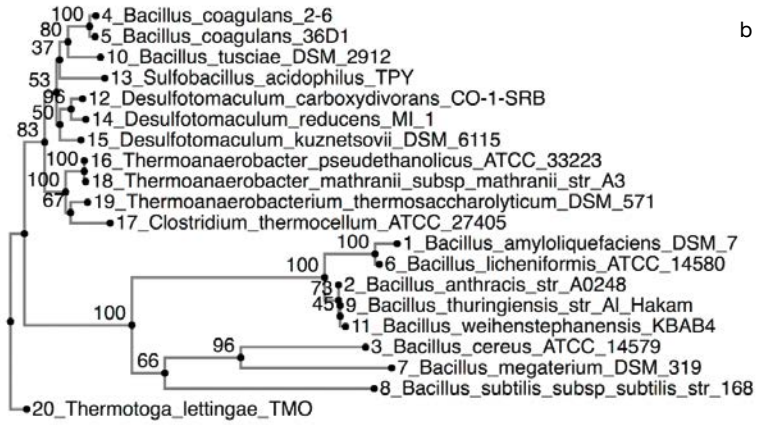
Mi-faser, an algorithm for assessment of metagenome functional capabilities directly from read data, has been steadily growing in usefulness to a broader community (paper in preparation). The service also received some refinements enabling easier processing of users' results and comparison of multiple metagenomic samples.

We made strides toward the development of a method for reconstructing the microbial composition of metagenomes, directly from sequencing reads, without relying on assembly or the information from 16s rRNA (in preparation). The algorithm will complement mi-faser functionality, such that we will be able not only to provide a functional profile of the microbial community, but also to give insight into its microbial composition.

Finally, clubber [4], a tool kit to simplify use of multiple high-performance computing clusters, has been described, published, and released to the public. Clubber facilitates and accelerates common computational biology experimental workflows through an automated cluster load-balancing system utilizing as many HPC resources as available to the user.

Piecing together all parts, we are expanding our tool kit for (meta-)genomic analyses focusing on the functional aspects of the microbial world. With the growing interest in issues including microbial communities' impact on human health and ecology, among many others, we hope to provide the means for fast and accurate analysis, leading to exciting biological discoveries and better scientific understanding.





1 | *fusion*DB reveals an HGT event between thermophilic *Bacilli* and thermophilic *Clostridia*. a) *fusion*+ visualization of Bacillus and thermophilc Clostridia. Large organism nodes are connected via small function nodes. The two thermophilic Clostridia are connected to the thermophilic Bacilli via functions that are possibly horizontally transferred; b) phylogenetic analysis of pyruvate, phosphate dikinase (PPDK) gene suggests HGT between thermophilic Bacilli and thermophilic Clostridia. The PPDK genes in thermophilic Bacilli are evolutionarily more related to those in thermophilic Clostridia than those in other Bacilli.

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Medicinal and Bioinorganic Chemistry**

Prof. Angela Casini (Cardiff University) | Hans Fischer Senior Fellow
Jens Oberkofler (TUM) | Doctoral Candidate

Scientific Reports

Angela Casini

Host
Prof. Fritz E. Kühn
Molecular Catalysis, TUM

Gold in drugs and drugs in cages: Frontier research in biology and medicine

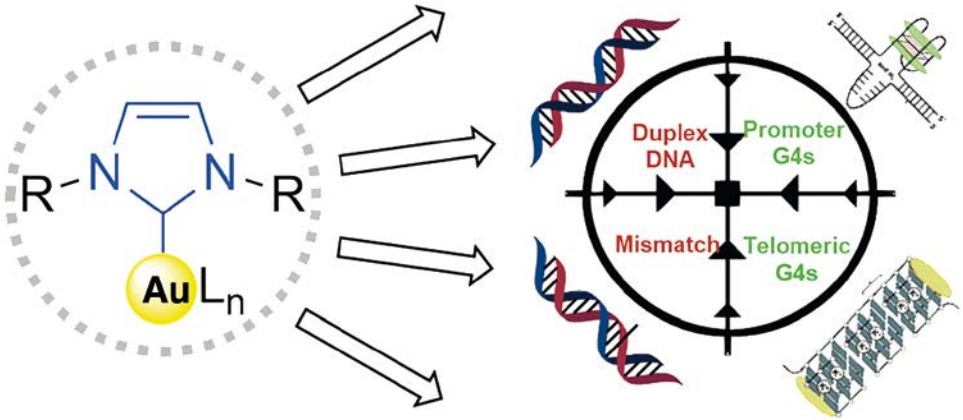
Our research interests relate to the study of the role of metal ions in biological systems. Specifically, one of the challenges is to discover the unique properties of metal compounds as inhibitors of the activities of proteins and enzymes or as selective DNA binders, and to exploit them for different therapeutic and imaging purposes.

In detail, our research focuses on the design of novel organometallic gold compounds. From wedding rings to stained-glass windows and Olympic medals, gold has been highly prized for millennia. Nowadays, organometallic gold compounds occupy an important place in medicinal chemistry due to their unique chemical and anticancer properties. The possibility of fine-tuning the stability of organometallic gold complexes while maintaining their biological activity and reducing their side-effects is extremely attractive. Notably, regulating the redox chemistry of gold compounds and their ligand exchange reactivity via the optimization of an appropriate organometallic scaffold may constitute a strategy to achieve selectivity for a particular pharmacological target, a feature that is not often guaranteed by purely organic molecules. Thus, gold complexes will be designed to be active against specific biomolecules with a great degree of target selectivity and innovative mechanisms of action.

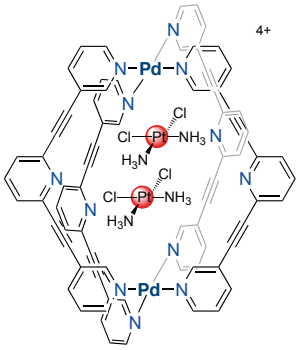
Moreover, novel applications for gold compounds are being explored in various domains of chemical biology, bio-analytical chemistry, and physiology. In fact, the use of selective protein inhibitors as chemical probes can complement genetic approaches to studying protein functions and can be valuable in elucidating the molecular mechanisms of diseases.

Besides synthetic inorganic chemistry and structural characterization of new metal compounds, we strongly focus on their intensive biological evaluation as possible therapeutic agents, and on the investigation of their mechanisms of action via the implementation of biophysical and analytical techniques coupled to pharmacological methods. The use of advanced computational methods such as molecular dynamics and metadynamics are also widely applied.

In the supramolecular chemistry field, coordination-driven self-assembly has provided the basis for tremendous growth across many subdisciplines, ranging from fundamental investigations regarding the design and synthesis of new architectures to defining different practical applications. In this area, our goal is to develop supramolecular three-dimentional “metallacages” as possible drug delivery systems. This is particularly relevant to cancer chemotherapy, where the success rate remains limited primarily as a result of inadequate selectivity of drugs for the tumor tissue, often leading to severe toxicity and the development of drug resistance. We recently reported on Pd_2L_4 cages (with L being exo-functionalized bipyridyl ligands) as drug delivery systems for the anticancer drug cisplatin (one of the most used anticancer drugs but presenting severe side-effects). The cages were shown, by NMR spectroscopy and X-ray diffraction studies, to encapsulate cisplatin and selectively kill cancer cells, while being non toxic in healthy rat liver and kidney tissues *ex vivo*.



1 | Schematic representation of organometallic gold(I) N-heterocyclic carbene compounds targeting different nucleic acids structures.



2 | Schematic representation of a supramolecular self-assembled Pd_2L_2 metallacage encapsulating two molecules of the anticancer drug cisplatin.

Ongoing work in our labs, and in collaboration with other TUM scientists in the Department of Chemistry, also aims at targeting these innovative drug delivery systems to tumor sites via bio-conjugation to peptides (Horst Kessler) or at the exploitation of supramolecular organometallic scaffolds as cancer therapeutics (Alex Pöthig).

Overall, the ambition of our Focus Group includes not only providing targeted metal-based prodrugs with unprecedented activity and control, but also an understanding of fundamental biological processes regulated by metal ions and their role in the development of diseases. Furthermore, we aim at developing the promising field of supramolecular coordination chemistry for biomedical applications.

As a highlight of the activities of this Focus Group during 2017, we organized a workshop, “Inorganic Chemistry meets Medicine: the interdisciplinary science of using and modulating metals for imaging and therapy,” which took place at the TUM-IAS on October 25–26 and was co-sponsored by the Institute of Advanced Studies of the University of Birmingham (UK). The goal of this workshop was to bring together researchers working in different areas of metallodrugs development and to define future trends in bioinorganic chemistry. The scientific program covered a range of topics, including the causal role metals can play in diseases and disorders, synthesis of inorganic medicinal agents and materials, their utilization as diagnostic agents, early target validation for metal complexes, and approaches from chemical biology and analytical chemistry to understanding mechanisms of action and off-target effects. Furthermore, participants discussed translational implementation of inorganic supramolecular entities and nanomaterials for biomedical applications. Debate was stimulated around outstanding papers from different research fields in bioinorganic chemistry, with the aim of developing new research areas and collaborations.

Doctoral candidate Jens Oberkofler presented a poster during the workshop. Furthermore, the research results of our Focus Group have been published in various international peer-reviewed journals and summarized in a number of review papers, as well as presented at national and international conferences and scientific meetings.

Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Physics with Effective Field Theories**

Dr. Andreas S. Kronfeld (Fermilab) | Hans Fischer Senior Fellow
Dr. Javad Komijani (TUM) | Postdoctoral Researcher

Scientific Reports

Andreas S. Kronfeld

Host
Prof. Nora Brambilla
Theoretical Particle and Nuclear Physics, TUM

Taming the strong force

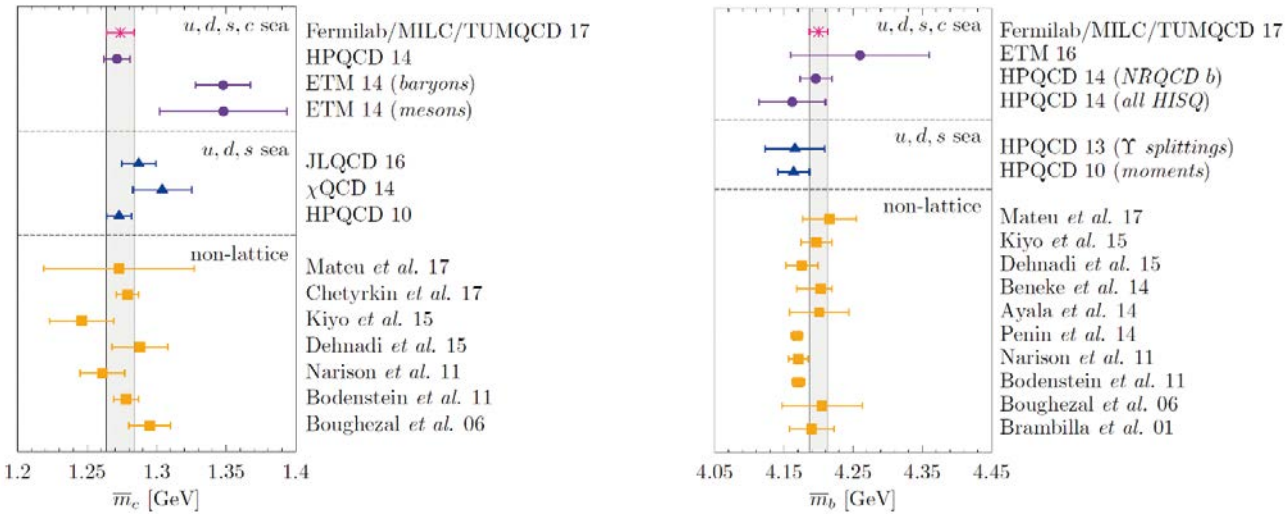
The main aim of elementary particle physics is to study fundamental interactions at the smallest distance scales, but the interpretation of experiments inevitably demands theoretical control over several length scales. A vital example lies in the search for new, as-yet unobserved interactions of quarks, which are the underlying building blocks of protons, neutrons, and many other particles known as *hadrons*. The strong nuclear force confines quarks into hadrons before they can be detected. Thus, whenever quarks are involved, it is crucial to understand physics at the distance scale of the proton radius, in order to examine physics at the microscopic frontier, which is found at distance scales at least 1000 times smaller than the proton.

An analogy for the way theoretical physicists treat such problems is a nest of Russian dolls. Open one up, and you find another one inside. The dolls in this case are *quantum field theories*: the mathematics for every particle is a quantum field – a concept that merges classical field theory and quantum mechanics. Nesting quantum field theories, à la Russian dolls, is known as *effective field theory*, which is one of the central elements of our Focus Group.

The other central element in our research is *lattice gauge theory*, which sets up quantum fields on a space-time lattice. Especially pertinent is the lattice gauge theory of the strong force, quantum chromodynamics (QCD). Lattice QCD uses high-performance computing to unravel QCD dynamics, which is needed to connect the intriguing world of quarks with the detectable world of hadrons.

In its third year, our Focus Group produced publications on a wide range of topics, including novel ideas in mathematical physics [1], ground-breaking lattice-QCD calculations for elementary particles physics [2], and a new understanding of molecular forces rooted in quantum electrodynamics (QED) [3].

The basic equations QCD and QED bear some similarity, but there are profound physical differences. Let us make the natural assumptions that the universe is electrically neutral and that it is color-neutral. Here, color is the quantum number in QCD analogous to electric charge in QED. That means if the (chromo)electric field emanates from some source, the field lines inevitably end at some sink. In QED, we can forget about this fact, because the field gets weaker and weaker: It is possible to measure the total energy of an isolated electron, that is, its mass, without knowing where the sink for electric field lines is. This is not so for QCD, because the chromoelectric field remains strong. The energy of an isolated quark depends on the sink. In fact, the field is so strong that it always “sparks” the creation of quark-antiquark pairs, so that eventually only color-neutral hadrons can be detected. Amazingly, this physics is encoded in an approximate power series for the total mass of a quark: The mathematics of such asymptotic series allows a reinterpretation of the approximate formula, but the reinterpretation is ambiguous. Somehow the formula knows more than we thought about QCD. Postdoc Javad Komijani examined the literature on this ambiguity and made two discoveries that had escaped attention. First [1], a new approach based on an asymptotic solution to a differential equation enabled a systematic calculation of the



1 | Comparison plots of m_c [GeV] and m_b [GeV] Comparisons of the Fermilab/MILC/TUMQCD results for charmed and bottom quark masses with other work [2].

strength of the long-range field. Second, we saw how this result makes it possible to snip off the ambiguous part of the chromoelectric field, so that it can be associated with the sink [2].

Komijani had turned his attention to these ambiguities because the TUMQCD Collaboration (an outgrowth of the Focus Group) was engaged, with the Fermilab Lattice and MILC collaborations, in determining the short-distance part of the quark masses. (A paper with the details has been submitted for publication, arXiv:1802.04248). The central idea is to trace out how the mass of a "heavy-light" hadron depends on the heavy quark's mass. To do so requires a good prescription for splitting the chromoelectric energy between the heavy quark and the rest of the hadron. After trying prescriptions in the literature, with unsatisfactory results, we saw that new theoretical ideas were needed (see above). With our new and unambiguous definition, we are now able to produce the most precise determinations of the (short-distance) quark masses, as one can see in figure 1. These results are important to elementary particle physics not only because they are fundamental constants of nature, but also because we believe they actually originate in the interactions of quark fields with the Higgs-boson.

Van-der-Waals-forces between two neutral but polarizable molecules are well known from chemistry. They are characterized by two length scales: the size of the molecules and the separation between them, which are typically very different. Such systems are thus natural candidates for a treatment with effective field theory. Indeed, we have set up a new effective field theory framework to define and systematically calculate the van der Waals interaction in electromagnetic systems [3]. We thus connect molecular physics directly to QED: We recover many standard results but also have a rigorous way to incorporate quantum effects. Van der Waals interactions reappear in nature in a broad sweep of problems, ranging from atomic, molecular, and condensed-matter physics to the strong interactions. For example, the nuclear force is one between two color-neutral but color-polarizable nucleons. Our framework, coupled with lattice QCD simulations, promises to treat the structure of nuclei in a genuinely *ab initio* way. Even in gravity, our methods can be used for a systematic understanding of tidal forces, for example the pull of our moon on the oceans.

In May 2016, our Focus Group hosted the "International Symposium on Effective Field Theories and Lattice Gauge Theory," bringing researchers from around the world to the TUM-IAS. The success of this event has led to a program, scheduled for November 2018, at the Munich Institute for Astro- and Particle Physics (MIAPP).

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Population Epigenetics and Epigenomics**

Prof. Frank Johannes (TUM) | Rudolf Mößbauer Tenure Track Professor
Dr. David Roquis, Dr. Amaryllis Vidali (TUM) | Postdoctoral Researchers
René Wardenaar (TUM) | Doctoral Candidate

Scientific Reports

Frank Johannes

Host
Population Epigenetics and Epigenomics, TUM

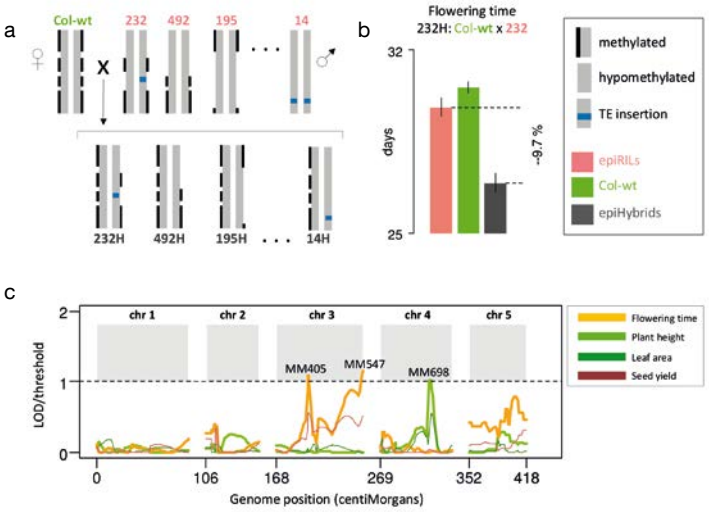
New evidence identifies the basis for superior performance in hybrid plants

DNA stores heritable information in the form of a four letter code: A, C, G and T. Textbook genetics tells us that the code can be mutated (e.g., letter A turns into letter G), and that such mutations alter the functions of genes. It is becoming increasingly clear that, in plants, heritable alterations in gene function can also be caused by meiotically stable epimutations, which arise independently of DNA changes. A well known example of an epimutation is the accidental gain or loss of DNA methylation, the chemical modification of a cytosine (the letter C in the DNA code) into 5-methylcytosine. We have previously shown that experimentally induced as well as spontaneously occurring epimutations can be remarkably stable across generations [1]–[2] and can even, in some cases, contribute to the heritability of important plant traits. Because of these observations, epigenetic modifications – such as DNA methylation – have emerged as potentially important factors in plant evolution [3]–[4], and as possible molecular targets for the improvement of commercial crops.

In 2017 our group was able to demonstrate that DNA methylation difference between parental plants can lead to superior offspring performance [5], a phenomenon called heterosis. Heterosis has been exploited extensively in agricultural breeding for decades and has improved crop performance tremendously. Despite its commercial impact, knowledge of the molecular basis underlying heterosis remains incomplete. Most studies have taken genetic approaches to try to delineate how the interaction between different parental DNA sequences can produce heterotic phenotypes in hybrid offspring, but such genetic explanations often neither sufficiently explain nor predict heterosis.

There is growing evidence that epigenetic factors also play an important role. Indeed, several recent studies have demonstrated that heterotic Arabidopsis thaliana hybrids have altered epigenetic profiles at genes regulating circadian rhythm. Moreover, heterotic hybrids in A. thaliana, maize, and tomato have also been shown to display shifts in the levels of small regulatory RNAs and/or DNA methylation (5mC) relative to their parental lines. It has been proposed that processes such as the transfer of 5mC between alleles (transchromosomal methylation), or a loss of 5mC at one of the alleles (transchromosomal demethylation) contribute to the remodeling of the epigenome. Nonetheless, it remains unclear whether the remodeling of hybrid methylomes is the direct result of “cross-talk” between the two parental epigenomes coming together in the zygote or whether it is simply a secondary molecular signature of classical genetic mechanisms, involving interactions between parental DNA sequence factors. Most studies have been unable to distinguish between these two possibilities, because the parental lines used for the hybrid crosses differed both in their genetic and epigenetic profiles, making it impossible to disentangle the two.

To address this problem, we generated a large panel of over 500 *A. thaliana* epigenetic hybrid plants (epiHybrids) [5], which we derived from near-isogenic but epigenetically divergent parents (figure 1a). This proof-of-principle experimental system



1 | (a) Selected epigenetic recombinant inbred lines (epiRILs) (pink labels, top) are each crossed to a single recurrent Col-wt female (green label, top) to obtain so-called epigenetic hybrid (epiHybrids) populations (black labels, bottom). For instance, a cross between the Col-wt female and epiRIL 371 produces epiHybrid 371H. Only one representative plant is shown for each epiHybrid population. Because the parental lines in each cross are virtually identical at the DNA sequence, except for rare *de novo* TE insertions, the epiHybrid populations differ only on the basis of the methylome profiles inherited via the paternal chromosome copy, the methylome contributions from the maternal copy being always the same. (b) Phenotypic analysis of the 19 different epiHybrid populations revealed substantial heterosis for a number of plant traits. Shown is one example of a heterotic phenotype observed in phenotypic screens: epiHybrid 232H shows a 9.7% reduction in flowering time relative to the earliest flowering parent. (c) We conducted an epigenome-wide search for parental differentially methylated regions (DMRs) that are predictive of heterosis in the epiHybrid offspring. This search revealed two regions (MM405 and MM547) that are associated with heterosis in flowering time and one region (MM698) that is associated with heterosis in plant height.

allowed us to quantify the contribution of parental methylation differences to heterosis. We measured a large number of different plant traits and observed several strong positive and negative heterotic phenotypes among the epiHybrids (figure 1b). Using a novel epigenetic quantitative trait locus mapping approach, we were able to identify specific differentially methylated regions (DMRs) in the parental genomes that are associated with hybrid performance (figure 1c). Sequencing of methylomes, transcriptomes, and genomes of selected parent-epiHybrid combinations further showed that these parental DMRs most likely mediate remodeling of methylation and transcriptional states at specific loci in the hybrids.

Taken together, our data suggest that epigenetic divergence between the parental lines can directly or indirectly trigger heterosis in Arabidopsis hybrids independent of genetic changes. These results add to a growing body of evidence that points to epigenetic factors as one of the key determinants of hybrid performance.

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Protein Misfolding and Amyloid Diseases**

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Hans Fischer Senior Fellow
Dr. Diana Rodriguez Camargo (TUM) | Postdoctoral Researcher

Scientific Reports

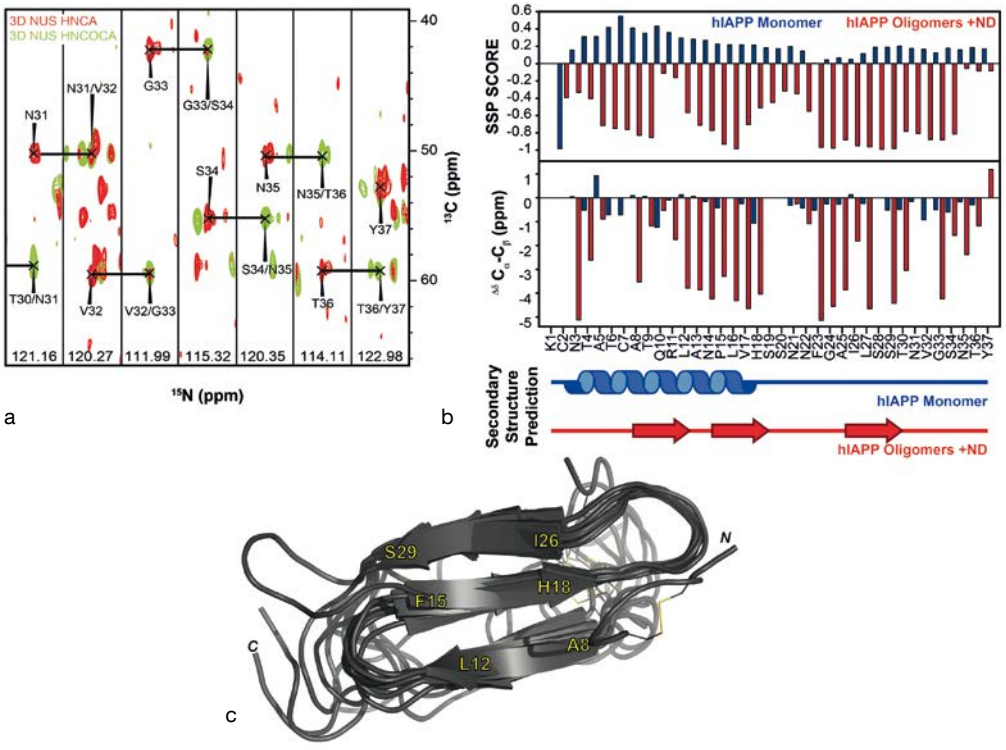
Ayyalusamy Ramamoorthy

Host
Prof. Bernd Reif
Solid-State NMR, TUM

We are using cutting-edge nuclear magnetic resonance (NMR) experiments to investigate the structure, dynamics, and aggregation of the hormone hIAPP (human islet amyloid polypeptide) in the presence of lipid membranes. Two different sub-projects are summarized below.

Oligomeric structure of human islet amyloid polypeptide in lipid nanodiscs determined by NMR

Membrane-assisted amyloid formation is implicated in human diseases, and many of the aggregating species accelerate amyloid formation and induce cell death. While structures of membrane-associated intermediates would provide tremendous insights into the pathology and aid in the design of compounds to potentially treat the diseases, it has not been feasible to overcome the challenges posed by the cell membrane. In this study, we used NMR experimental constraints to solve the structure of a type-2 diabetes-related human islet amyloid polypeptide intermediate stabilized in nanodiscs. ROSETTA and MD simulations resulted in a unique β-strand structure distinct from the conventional amyloid β–hairpin and revealed that the nucleating NFGAIL region remains flexible and accessible within this isolated intermediate. This suggests a mechanism by which membrane-associated aggregation may be propagated. The ability of nanodiscs to trap amyloid intermediates as demonstrated could become one of the most powerful approaches to dissect the complicated misfolding pathways of protein aggregation. Nanodisc preparations were done in collaboration with TUM-IAS Rudolf Mößbauer Tenure Track Professor Franz Hagn, and simulations were accomplished in collaboration with Professor Carlo Camilloni (TUM-IAS Rudolf Mößbauer Tenure Track Professor until April 2017). This study was published in Elife [1], and the discovery was covered in news media.



1 | NMR characterization of hIAPP-nanodisc interaction. (a) Triple-resonance experiments (HNCA and HNCOCA) of hIAPP oligomers in the presence of ND1 were utilized for resonance assignment and characterization of the secondary chemical shift. (b) Secondary structure prediction performed using both secondary structure propensity and the $\Delta\delta$ $^{13}C\alpha$-C_β secondary chemical shifts suggest a structure consisting of three β-strands. (c) The 10 lowest energy structures produced by CS-ROSETTA. The backbone RMSD of the lowest energy structures for residues 6-34 is 1.946 ± 0.521, and for all residues is 3.534 ± 0.489.

Native interactions of hIAPP: a correlation with metabolic and cardiovascular diseases

Diabetes, obesity, heart, and cardiovascular dysfunctions are pandemic in our modern world, braiding genetic factors with lifestyle. Metabolic disequilibrium and components imbalance such as oxidative stress, glucotoxicity, and lipotoxicity are important elements of this multifactorial mechanism. It is known that hyperamylinemia also affects the cardiovascular system. We have shown that glucose and lipids such as LDL directly interact with hIAPP and induce structural changes in hIAPP. This results in the formation of oligomers and colloidal structures that yield intrinsic fluorescence. The oligomers show increased β-cell toxicity and hemolytic activity correlating with the concentration of the complex. Our results provide insights toward a better understanding of off- and on-pathway oligomer formation of hIAPP in a native environment.

In collaboration with Prof. Franz Hagn (Structural Membrane Biochemistry, TUM), Prof. Axel Karl Walch (Analytical Pathology, Helmholtz Zentrum München), Prof. Martin Hrabě de Angelis (Institute of Experimental Genetics, Helmholtz Zentrum München), Prof. Erich Wanker (Max Delbrück Center for Molecular Medicine, Berlin), Prof. Carlo Camilloni (Computational Structural Biology, University of Milan; TUM-IAS Rudolf Mößbauer Tenure Track Professor until April 2017).

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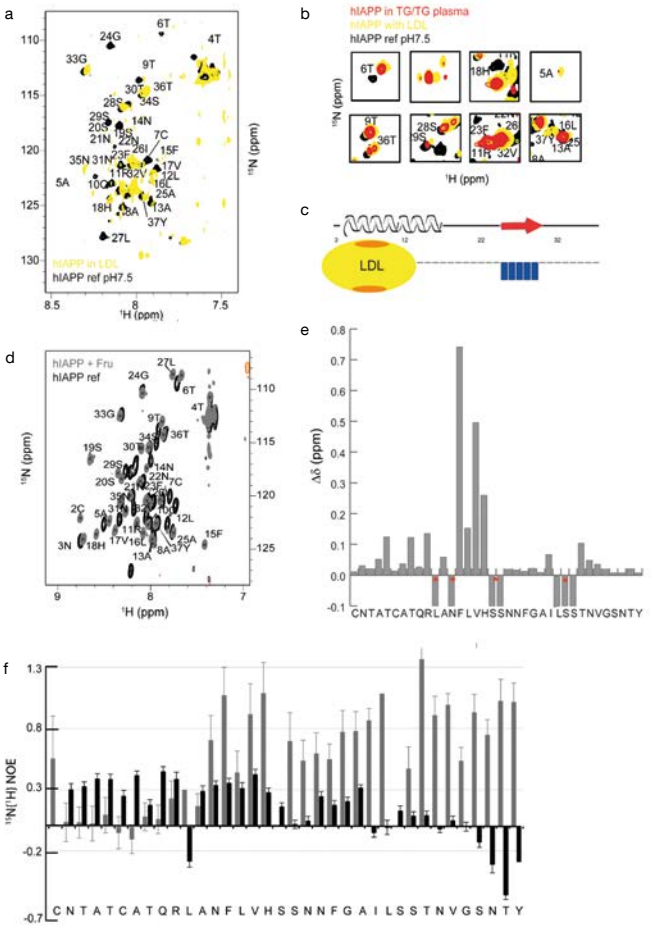

2 | Structural analysis of hIAPP with LDL and fructose. (a) ^{1}H-^{15}N-HMQC spectra of 100 µM hIAPP with 2 µM LDL (yellow) compared with spectra obtained from hIAPP dissolved into buffer (black). (b) Representative NMR peaks extracted from the ^{1}H-^{15}N-HMQC spectra of the hIAPP buffer sample and the hIAPP-LDL (hIAPP TG/TG plasma) sample show the similarity of two preparations. (c) Structural model based on secondary chemical shifts showing the interaction between hIAPP and LDL. (d) ^{1}H-^{15}N-HMQC spectra of 100 µM hIAPP in the presence of 35 mM fructose at pH 5.3 after 30 days of incubation at RT. (e) Residue-specific chemical shift perturbations (CSP) in ppm, obtained by comparison of spectra of hIAPP and 35 mM fructose, incubated for 30 days, compared with spectra of the peptide in buffer under the same conditions (pH 5.3 and RT). (f) Heteronuclear NOEs of hIAPP samples with 35 mM fructose incubated for 30 days. The hetNOE data confirms that the C-terminus of hIAPP has a high propensity to form a compact structure. By comparison, the peptide alone in buffer yields a high flexibility.

Focus Group **Sterile Neutrino and Dark Matter**

Dr. Thierry Lasserre (CEA, Saclay/APC, Paris) | Hans Fischer Senior Fellow
Konrad Altenmüller, Julia Sawatzki (TUM) | Doctoral Candidates

Thierry Lasserre

Host
Prof. Stefan Schönert
Experimental Physics and Astroparticle Physics, TUM

Sterile neutrinos

Neutrinos are neutral subatomic particles that rarely interact with matter. They are the most abundant matter particles of our universe. Three kinds of neutrinos are known, associated with the electron, muon, and tau particles. As an experimental fact, these neutrinos have a non-zero mass and oscillate – or change their type – as they travel in space and time. Beyond the Standard Model of particle physics, other types of neutrinos, which would not interact with matter, could exist. They are usually called sterile neutrinos. However, they would take part in oscillations with active neutrinos, leading to their possible detection. Our TUM-IAS Focus Group is among the worldwide leaders investigating the phenomenology and experimental perspectives for detecting sterile neutrinos at different mass scales.

Sterile neutrinos at the keV mass scale

The nature of dark matter is one of the major open issues in physics. Massive relic sterile neutrinos at the keV mass scale are well-suited candidates to explain the dark matter in our universe. In 2017 our Focus Group continued to develop methods to search for keV sterile neutrinos in a laboratory experiment. One approach is a future upgrade of the KATRIN experiment (called TRISTAN [1]), primarily designed to measure the mass of the known neutrinos by studying the high energy tail of the tritium beta-decay spectrum. For our purpose, a keV sterile neutrino would cause a distortion of the tritium beta-decay spectrum. For technical reasons this signature cannot be observed with the current KATRIN detector. Therefore, our group is developing a novel detector system in collaboration with MPP and HLL (Munich). The characterization of a small detector prototype with a readout system designed by CEA Saclay was finished in the beginning of 2017 and showed that the detector performance is limited only by the electronics, thus proving the suitability of the silicon drift detector technology for TRISTAN [2]. Newer prototype detectors were equipped with optimized custom readout systems by XGLab that unlocked the full potential of the detectors and delivered excellent results: The system has an outstanding energy resolution and is very fast, such that high-performance spectroscopy with high rates as needed for TRISTAN is possible. The design of the next larger prototypes has been completed, and they are now in production. The final TRISTAN detector will be unmatched in size and performance by any other system.

During two measurement campaigns in 2017, prototype detectors were successfully deployed at the Troitsk nu-mass spectrometer (INR RAS, Russia), which is a technological predecessor to KATRIN. This allowed for the full characterization of the detectors with electrons from different sources to study systematic effects and record first tritium spectra to develop analysis methods.

eV sterile neutrinos

Sterile neutrinos in the eV mass range could also exist. This hypothesis is supported by results of several short-baseline neutrino experiments reported in the last two decades. Our Focus Group has been contributing to the SOX experiment [3]

1 | (left) The Troitsk nu-mass experiment in Russia, where the Focus Group characterized detectors for the TRISTAN project. Electrons from the gaseous tritium source on the left are guided by a magnetic field through the large vacuum tank on the right, which houses an electromagnetic filter. Electrons that pass the filter are measured by our detector prototype (right picture), which was installed at the far-right end of the setup.

that aimed at deploying an intense ^{144}Ce-^{144}Pr neutrino generator in the vicinity of the Borexino neutrino detector, at the Laboratory Nazionali del Gran Sasso (LNGS), in Italy. The smoking-gun signal would be an oscillatory pattern of the neutrino interactions – in space and energy – inside the liquid scintillator detector, free of background.

A crucial part of the SOX experimental hardware is a thermal calorimeter to measure the source activity, i.e., the number of neutrinos produced by the source. This device was developed by the Focus Group and other TUM staff together with INFN Genoa. The characterization of the calorimeter was completed at LNGS with a final "blind" measurement under real conditions of an electrically simulated decaying heat source, where the set parameters were not known to the analysts. There we proved that the heat power can be measured with $<0.2\%$ accuracy, surpassing well the design goal of 1%. Another milestone for the experiment was reached in October 2017 with the successful simulation of neutrino source handling at the LNGS laboratory and insertion into the calorimeter under the surveillance of Italian nuclear safety authorities.

2 | K. Altenmüller next to the calorimeter developed by INFN and TUM and successfully commissioned at the LNGS laboratory.

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Structural Membrane Biochemistry**

Prof. Franz Hagn (TUM) | Rudolf Mößbauer Tenure Track Professor
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Laura Entenmann, David Goricanec, Elisabeth Häusler, Kolio Raltchev, Andrea Steiner (TUM and HMGU) | Doctoral Candidates

Scientific Reports

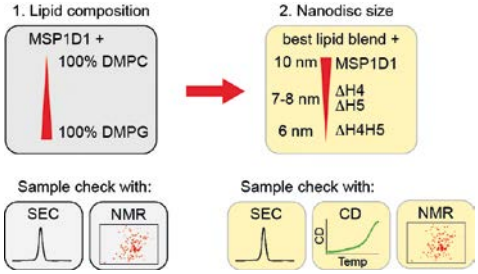
Franz Hagn

Host
Structural Membrane Biochemistry, TUM

Nanodiscs for structural studies of membrane proteins by solution-state NMR spectroscopy

Our Focus Group is dedicated to developing methods for determining the structure of membrane proteins, primarily by NMR spectroscopy but also using other techniques such as electron microscopy. Our focus in 2017 was the establishment of a robust protocol for the NMR-based structure determination of membrane proteins in so-called phospholipid nanodiscs. These represent a native lipid bilayer membrane system that consists of a patch of lipids encircled by a so-called membrane scaffold protein, which wraps around the lipids to form particles of defined size. This protocol was published in *Nature Protocols* [1].

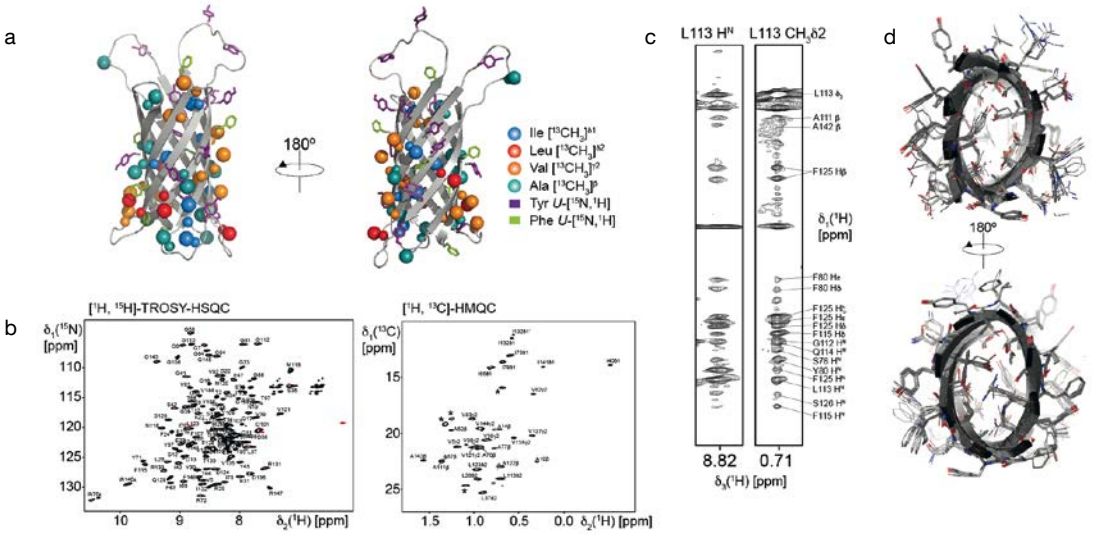
In that paper, we present a versatile method to incorporate membrane proteins into nanodiscs for a subsequent structural analysis with NMR spectroscopy. On the basis of our previously published paper where we presented nanodiscs of various sizes [2], we are able to adapt the nanodisc to the membrane protein under investigation. With this toolset, it is possible to screen for optimized size and lipid composition (figure 1) to obtain membrane protein-containing nanodiscs of homogenous size and native-like lipids, enabling a structural and functional investigation in a native environment. Such studies would not be possible in the more traditional and commonly used detergent micelles, as that system tends to alter the native membrane protein conformation and its function.



1 | Flow scheme for the optimization of nanodisc preparations for NMR spectroscopy. 1.) Any lipid that is required for protein stability and functionality can be used. 2.) The size of the nanodisc can be adapted to the size of the incorporated membrane protein. Initial screening can be done by size exclusion chromatography (SEC), circular dichroism (CD), and NMR spectroscopy. Taken from [1] with permission.

Furthermore, we were able to establish a robust protocol for the structure determination of membrane proteins in these optimized nanodiscs using selective isotope labeling of the membrane protein for subsequent multidimensional NMR experiments (figure 2) [3]. In addition, we introduced circular nanodiscs for structural studies that show exceptional size homogeneity suitable for high-resolution NMR and electron microscopy [4].

Together with the TUM-IAS Focus Group Protein Misfolding and Amyloid Diseases, we used our nanodisc methodology to characterize the structure of a folding intermediate of human islet amyloid polypeptide (hIAPP), whose aggregation in the pancreas leads to type-II diabetes [5]. The obtained structural insights will guide the way for the development of inhibitors of IAPP aggregation that specifically target the membrane-bound species.



2 | High-resolution structure determination of membrane proteins in nanodiscs. (a) Specific labeling of the membrane protein yields (b) high-resolution NMR spectra and (c) a large number of tertiary structure contacts in NOESY experiments, enabling efficient and high-resolution structure determination by NMR with quality comparable to X-ray crystallography (d). Taken from [1] with permission.

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Focus Group **Supramolecular Chemistry**

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Scientific Reports

Job Boekhoven

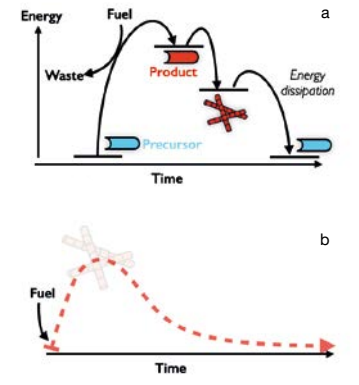
Host Supramolecular Chemistry, TUM

Temporary supramolecular materials with a tunable lifetime

Inspired by nature, our group is interested in translating the attractive properties of biological materials into fully synthetic analogs. In our second year at the TUM-IAS, we focused on the development of dissipative self-assembled materials with a finite tunable lifetime.

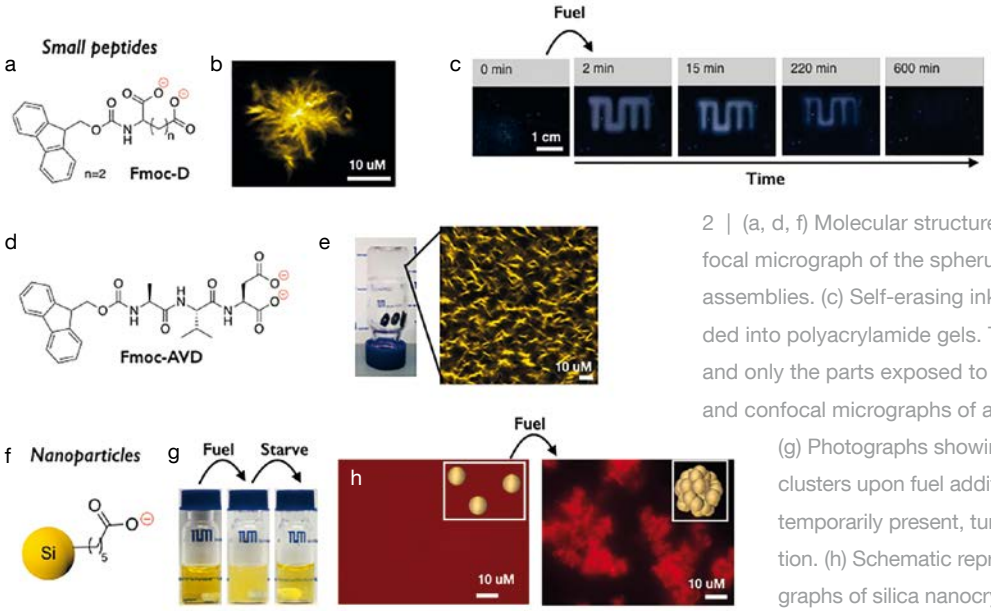
In supramolecular materials, molecules are assembled by non-covalent interactions into nanostructures with function. This strategy has been used in the last decades as a powerful tool to create functional materials. The success of this approach is exemplified by numerous examples ranging from liquid crystals (stacks of ordered molecules) in liquid crystal displays or smart amphiphiles that can release a drug exactly at the required location in the body.

Most of the supramolecular materials developed so far are in or close to equilibrium with their environment. That is a great feature; it implies the materials are stable. Moreover, in equilibrium, the processes involved are well understood, which allows scientists to design materials with entirely new functions. However, for some applications, temporary materials are preferred. As an example, biomedical implants that would autonomously degrade after performing their function would diminish the need for post-treatment surgery to remove the implant. Or, a detergent that would degrade hours after use would be less harmful to the environment. To that end, our group is pioneering man-made supramolecular materials that exist only out of equilibrium. Such structures are controlled kinetically rather than thermodynamically (figure 1a). Despite the promising features these materials are encoded with, their development is still in its infancy, most likely because of the lack of knowledge of the processes involved and missing design strategies. We have been working on a new strategy to develop dissipative supramolecular materials or structures based on the coupling of self-assembled structures to irreversible chemical reaction networks.



The chemical reaction networks we develop include an irreversible chemical reaction that forms an active molecule at the expense of a chemical fuel. This reaction converts a precursor into an active molecular building block that assembles with other active building blocks into a desired supramolecular material. The activated building

1 | (a) Energy landscape for assemblies out of equilibrium. Note that the assemblies formed due to energy consumption (red assembled bricks) are higher in energy than the original precursors (blue brick). Therefore, the thermodynamically unfavored assemblies will always revert back to the initial situation. (b) Scheme of the chemical reaction network for the fuel-driven formation of a transient product. The dicarboxylate precursor (blue brick) is converted into an anhydride product (red brick) by consumption of a carbodiimide (fuel). The aqueous anhydride is unstable and rapidly hydrolyzes back to the original precursor. Because of the loss of charges when anhydride is formed, the product self-assembles at a certain concentration. (c) Schematic representation of the temporary control over material formation and degradation achieved by using the energy-dissipating approach previously described.



2 | (a, d, f) Molecular structures of the tested precursors. (b) Confocal micrograph of the spherulites formed by Fmoc-D anhydride assemblies. (c) Self-erasing inks of Fmoc-D. Fmoc-D was embedded into polyacrylamide gels. The fuel was spread through a mask, and only the parts exposed to fuel turned turbid. (e) Photograph and confocal micrographs of a transient hydrogel from Fmoc-AVD. (g) Photographs showing the formation of silica nanoparticle clusters upon fuel addition. These assemblies were also temporarily present, turning back finally to the initial situation. (h) Schematic representation and fluorescence micrographs of silica nanocrystals before and after fuel addition.

block is thermodynamically unstable and reverts back to the original precursor by a spontaneous deactivation reaction, thereby closing the chemical reaction cycle. We found a chemical reaction network that fulfills all these requirements. It is based on the transient formation of anhydrides in aqueous environment at the expense of a carbodiimide fuel (figure 1b). The anhydride is designed to assemble in various supramolecular materials, but it is intrinsically unstable and hydrolyzes back to the initial precursor. The corresponding supramolecular material is, as a result of the continuous formation and degradation, dynamically formed and only present for as long as the fuel remains (figure 1c).

We have investigated small molecules, peptides, and nanoparticles as precursors for the chemical reaction network. All of them were able to form supramolecular materials upon the addition of fuel. Interestingly, their lifetimes could be tuned from minutes to hours simply by changing the components in the chemical network, such as the amount of fuel added. The different nature of the precursors translated into diverse type of assemblies, which we explored as temporary supramolecular materials. For instance, one amino acid self-assembled into spherulites upon fuel consumption (figure 2 a–b). The presence of these aggregates turned an initially clear solution into a turbid one.

With the help of colleagues in the Department of Physics, we used this feature to convert the concept in a temporary ink. Only where fuel was applied, the material turned turbid and a message could be written. However, since the formation of these messages was coupled to a chemical reaction network, they rapidly started disintegrating, and the message would disappear in a matter of hours (figure 2c). Such a material could be further developed as a reusable paper that self-erases after use.

The current chemical reaction network could also be easily adapted to work with nanoparticles as precursors. Gold or silica nanoparticles functionalized with carboxylic acids showed the formation of clusters when a batch of fuel was added (figure 2f–h). These nanoparticle clusters also turned back to solution and exhibited potential applications as self-erasing electronic circuits or as sensors for organic compounds. The reusability of all materials described was evidenced by sequential additions of fuel batches.

In the last year, our group has found a chemical reaction network that can be coupled to the formation of supramolecular materials. As a result, these materials turn into temporary materials with a tunable lifetime. We are currently exploring other materials as well as more diverse chemistry to further broaden the range of applications.

Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Synthetic Biochemistry**

Prof. Kathrin Lang (TUM) | Rudolf Mößbauer Tenure Track Professor
Marko Cigler, Maximilian Fottner, Susanne Mayer, Tuan-Anh Nguyen,
Marie-Kristin von Wrisberg, (TUM) | Doctoral Candidates

Scientific Reports

Kathrin Lang

Host
Synthetic Biochemistry
TUM

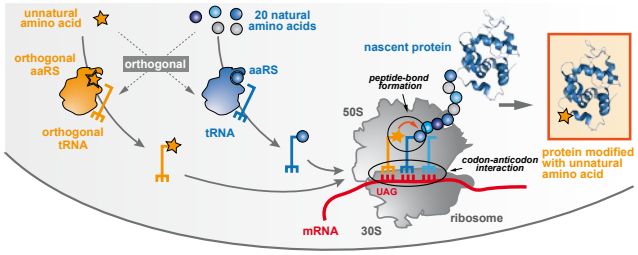
Studying protein-protein interactions via genetic code expansion

The research of the Focus Group Synthetic Biochemistry is based in the interdisciplinary area of chemical biology. We are especially excited about developing and designing new tools by endowing proteins with new functional groups to study and manipulate biological processes.

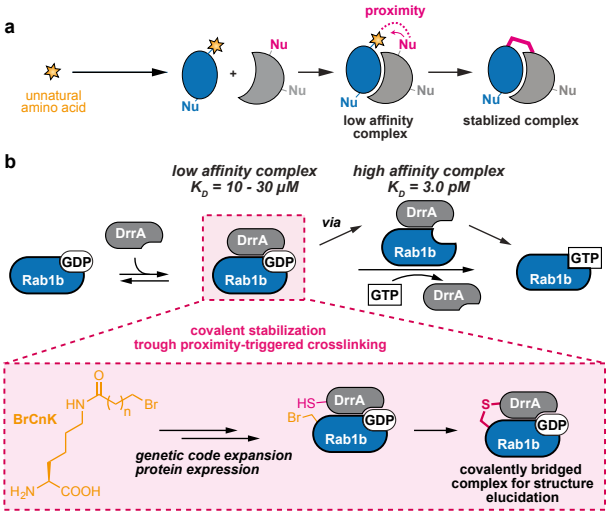
We do this by an approach called genetic code expansion. This allows the site-specific incorporation of designer amino acids (unnatural amino acids) with tailored physical and chemical properties into proteins in diverse cells and organisms. Genetic code expansion uses an expanded machinery of translation, consisting of an “orthogonal” aminoacyl-tRNA synthetase (aaRS) /tRNA pair that directs the incorporation of an unnatural amino acid (UAA) in response to an amber stop codon (UAG) placed at a user-defined site in a gene of interest (amber suppression, figure 1) [1]. By incorporating new UAAs bearing different functional moieties, it is possible to leverage genetic code expansion approaches to address unmet challenges in studying and controlling biological processes with a new level of spatial, temporal, and molecular precision [1].

Working at the interface of organic chemistry and biology, our Focus Group is especially interested in combining this amber suppression approach with carefully designed chemistries that are amenable to physiological conditions and applicable in living systems (*in vivo* chemistries). In the past we have developed new *in vivo* chemistries (inverse electron demand Diels Alder cycloadditions) [2] that allow the selective and rapid functionalization of proteins with biophysical probes and small molecules within their physiological context [3]–[4]. This has allowed us to visualize proteins and to modulate their enzymatic activity in live cells [5]–[6].

In 2017, we have concentrated on developing tools to study and elucidate protein-protein interactions within live cells. Protein-protein interactions serve pivotal roles in most biological processes and are indispensable for orchestrating different functions in live cells. In particular, the formation of transient and low-affinity protein complexes is essential in many signaling and regulatory pathways, where the requirement for dynamic association and dissociation events dictates affinities. The mapping and characterization of transient interaction networks remain major challenges, however, as transient protein-protein interactions are inherently dynamic in nature in order to enable quick adjustment to different stimuli and environmental conditions. In particular, high-resolution structural studies of low-affinity protein complexes represent a formidable challenge and are often elusive, as they typically require the generation of stable protein complexes. We have devised an approach that allows the chemical covalent stabilization of low-affinity protein complexes in vitro and in vivo [7]. For this, we have explored the genetic encoding of unnatural amino acids bearing chemical moieties that are able to undergo proximity-enabled reactions with adjacent nucleophilic residues (figure 2). The reactivities of these



1 | Amber suppression approaches using orthogonal aaRS/tRNA systems allow the *in vivo* production of proteins bearing unnatural amino acids.



2 | An unnatural amino acid (orange star) is site-specifically incorporated into a protein of interest (blue). The unnatural amino acid is inert under physiological conditions but can form a covalent linkage (pink bracket) with a target nucleophilic natural amino acid on an interaction partner due to proximity. This approach has been used to covalently stabilize a ternary Rab1b:GDP:DrrA complex.

groups are fine-tuned to be inert under physiological conditions, but to react with nucleophilic side chains when the local concentration of the nucleophile is dramatically increased through proximity. We have developed an efficient aaRS/tRNA pair that allows the genetic encoding of unnatural amino acids with such properties, bearing flexible bromoalkyl moieties with different alkyl chain lengths. These unnatural amino acids are inert under physiological conditions but react specifically with nucleophilic natural amino acids in a proximity-enhanced manner. We have used such reactions to trap and chemically stabilize biologically relevant protein-protein interactions in bacteria and mammalian cells and have demonstrated that these reactions can be used as a tool to aid the structure elucidation of a previously inaccessible transient, low-affinity GDP-bound ternary complex between a human small G-protein (Rab1b) and an effector protein from *Legionella pneumophila* (DrrA).

Looking ahead, our aims lie in understanding mechanisms of complex biological processes through the application of synthetic molecules with tailored functions and properties. In particular, we plan to extend approaches for endowing proteins with new chemical moieties and thereby re-engineer protein functions and design new ones. This will open up many possibilities for synthetic biology, drug design, biomaterials, and gene therapy.

Publications by this Focus Group can also be found in the section Publications of this report.

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Focus Group **Gender and Diversity in Science and Engineering**

Prof. Sarah de Rijcke (Leiden University) | Anna Boyksen Fellow
Isabel Burner-Fritsch (TUM) | Research Assistant

Scientific Reports

Sarah de Rijcke

Host
Prof. Ruth Müller
Munich Center for Technology in Society, TUM

The Focus Group Gender and Diversity in Science and Engineering analyzes the inclusion and exclusion mechanisms of evaluation procedures and indicators in science and engineering. Researchers are pulled in various, sometimes contradictory directions by the multiplication of performance metrics and new incentives to align with societal needs. Management structures, funding systems, and publication practices are increasingly influenced by pressures to promote only the highest quality science, and by models and incentives for academic advancement that would produce this highest quality. While some analysts welcome the possibility of increasing transparency through performance data, recent years have seen high-profile initiatives to improve current criteria for assessing academic achievements (e.g., the Leiden Manifesto, the Metric Tide, Science in Transition, DORA, METRICS, Reward Alliance). Concerns include both an erosion of the social in science – e.g., increasing competitive struggles, blistering "benchmark masculinity" [1], waning collegiality, and decreasing community service – and an erosion of epistemic diversity, e.g., cropping and tweaking the aims and contents of scientific inquiry to fit into the narrow confines of metric-based evaluation systems. Specifically, there are concerns that a growing focus on evaluation metrics might perpetuate gender bias in science as specific notions of what constitutes valuable scientific work or desirable academic biographies that are highly gendered become entrenched into seemingly neutral evaluation metrics [2].

The collaboration in the Focus Group is embedded in an emerging research agenda on the epistemic effects of indicators in academic settings [3]–[8]. From our previous projects in the life sciences, the social sciences, and law in the Netherlands, Austria, and Sweden we can extrapolate, first of all, that quantitative indicators feed into quite routine knowledge-producing activities (e.g., discussions over whom to collaborate with and when, how much time to spend in the laboratory producing data) [7]. Researchers are increasingly "thinking with indicators" at various stages throughout their research processes [9]. The Anna Boyksen Fellowship enabled the Focus Group to further chart these reification dynamics, and in- and exclusion mechanisms in evaluation systems. This research is crucial in order to develop more sophisticated policies and refined mechanisms for responsible research assessment in different fields that adequately address how evaluation practices might ameliorate or contribute to different forms of bias in academia.

Project on merit, metrics, and academic identity work

In 2016 and 2017, the Focus Group devised a project in collaboration with the senior management of the TUM-IAS (Ernst Rank, Ana Santos-Kühn). The purpose of this qualitative social science project was to analyze the application, review, and decision-making processes of the TUM-IAS Hans Fischer (Senior) Fellowship program [10]. To contribute to increasing gender equality in its programs, the TUM-IAS recently introduced a new requirement for the Hans Fischer (Senior) Fellowship

application procedure. From 2015 onward, the prospective TUM Host submits a joint proposal together with a Fellowship nominee, and this "tandem" should consist of at least one female researcher. Our Focus Group project set out to better understand: a) the work that goes into composing project applications and CVs of nominees and b) how the proposals and CVs were subsequently reviewed and processed by reviewers and selection committee members. This analysis also included contextual information on the specific funding program and evaluation criteria formulated by the TUM-IAS, and on the disciplinary background of Host and nominee.

Methodologically, the project consisted of a combination of document analysis and interviews. Document analysis is a systematic procedure for reviewing material recorded without the intervention of the researcher. It is often used in combination with other qualitative methods (in this case interviews) to triangulate empirical material. The triangulation yields data – excerpts, quotations, paragraphs – that are subsequently organized into larger themes and categories through coding and category construction. The document analysis included official documents from the TUM-IAS concerning the Fellowship call, nomination guidelines, templates used for the peer review by referees, and templates for rebuttals that candidates could fill in, as well as profiles from former Hans Fischer (Senior) Fellows; and from the nominees who were willing to participate in our study, we analyzed the CVs, letters of deans and Hosts, lists of suggested reviewers, statements of purpose, and the external reviews received. The research team interviewed applicants for both the Hans Fischer and Hans Fischer Senior Fellowship (2016 round), as well as external reviewers involved in this same application round. At the time of writing this annual report, the team is in the process of finishing the interviews with reviewers. We provided provisional observations from our analysis to the TUM-IAS senior management in December 2017. Presenting final conclusions in this report would be premature.

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Gender Stereotypes in Organizations**

Prof. Madeline E. Heilman (New York University) | Anna Boyksen Fellow

Scientific Reports

Madeline E. Heilman

Host
Prof. Isabell M. Welpe
Strategy and
Organization, TUM

Gender stereotypes in organizations

The Focus Group Gender Stereotypes in Organizations aims to understand how gender stereotypes affect impressions formed of men and women, particularly focusing on the context in organizations.

Research shows that men and women face stereotype-based biases in organizations. Independently from their individual characteristics, men are seen as more agentic and work-oriented than women, and women are seen as more communal and focused on relationships than men. Men and women not only are seen in different ways, but also are expected to comply with these stereotypic views. If they do not, they are socially penalized. For example, women who violate stereotypic expectations tend to be disliked and seen as interpersonally hostile.

Gender stereotypes and expressions of emotion

In a series of experiments, the Focus Group is examining how gender stereotypes and expressions of emotion jointly affect impressions formed about the emotion-expressing individuals, because emotion expressions – comparably to stereotypes – communicate social information about the emotion expresser.

We demonstrated in a 2016 publication that gender effects in agency (i.e., women are seen as less agentic than men) diminished when women and men expressed pride. Furthermore, the effect of expressing pride as compared to expressing happiness was more pronounced for women than for men.

In 2017, we continued this line of research by conducting further experiments to scrutinize if the effect holds under different conditions. Conditions under examination thereby included competitive situations, in which women may be scrutinized even more, and situations in which an achievement might be less clear and pride expressions, therefore, less warranted.

Gender stereotypes in STEM professions

In addition to continuing our work on gender stereotypes and expressions of emotion, we also started to work on the examination of gender stereotypes in STEM professions, i.e., professions in science, technology, engineering, and mathematics. Gender stereotypes in STEM professions have been under examination for decades, with research particularly focusing on the academic domain. Results have shown that gender stereotypes about mathematics in particular can keep women from studying and excelling in STEM professions.

Against the background of the digital transformation, stereotypes in STEM professions may become even more important in organizations. Technology-oriented professions, especially those in information technology, are increasingly central for organizations. Therefore, we aim to examine a) if gender stereotypes may prevent women from working in these fields, b) if gender stereotypes lower women's success in these fields, and c) how potential biases can be mitigated. Having just started to work on these new topics, the main steps in 2017 were to discuss research ideas and to identify first steps for their experimental examination.

In collaboration with Dr. Prisca Brosi, Chair for Strategy and Organization, TUM.

Focus Group **Modern Technology to Support Cognitive and Mental Health**

Prof. Nicola Teresa Lautenschlager (University of Melbourne) | Anna Boyksen Fellow

Scientific Reports

Nicola Teresa Lautenschlager

Host
Prof. Janine Diehl-Schmidt and
Prof. Hans Förstl
Psychiatry and Psychotherapy, TUM

RHAPSODY-plus: Online counseling for family caregivers of younger people with dementia

Our Focus Group Modern Technology to Support Cognitive and Mental Health was established in early 2017. As a central activity of our Focus Group we will conduct a two-year pilot study called RHAPSODY-plus. This pilot study builds on an Internet-based information and skill-building program called RHAPSODY specifically developed for family caregivers of care recipients with young onset dementia (YOD), which was funded by the EU and led by Alexander Kurz from the TUM Department of Psychiatry. YOD is defined by the emergence of clinical symptoms prior to the age of 65 years. The estimated prevalence of YOD is 1/1000 and the annual incidence is 5–20 per 100,000 in the population aged 45 to 64 in Europe, Japan, and the United States. YOD is associated with specific and particularly severe problems for patients, caregivers, and health-care professionals. While caring for a family member can offer rewarding experiences, caregivers are at increased risk of stress, depression, and sleep problems and often experience poor health outcomes with increased morbidity and mortality. Family caregivers of care recipients with YOD have specific needs due to common difficulties diagnosing the cause of dementia accurately and promptly, and also due to a significant burden borne by the caregiver. They therefore require YOD-specific information programs.

RHAPSODY was well received by the family caregivers (unpublished data), but feedback included their wish to be able to discuss what was learned via RHAPSODY in the context of their individual situations. We therefore will trial, as a next step in our pilot study RHAPSODY-plus, an offer for caregivers to participate in two additional individual support sessions provided by a social worker and a clinical psychologist via skype-like communication technology after they have explored and used RHAPSODY. The aims of this pilot study are to determine whether participating caregivers consider the intervention acceptable and useful and to investigate the potential benefits and barriers of using modern technology in this context.

There is a lack of resources targeted for informal caregivers of people with YOD. If successful, this pilot project will contribute new research knowledge to the important question of how practical support can be delivered effectively to caregivers via online communication technology, as an alternative to face-to-face or telephone contact. This approach might be of particular benefit to a diverse group of informal caregivers who cannot easily access face-to-face specialist support: for example, those who live in rural areas; those who cannot attend easily clinical appointments for other specific reasons such as work, being unable to leave the care recipient alone at home, or being responsible for children as well as the family member with YOD; or those who have a disability themselves. If successful, data from this pilot will provide a valuable foundation for a larger international translational research grant application.

During 2017, we worked on establishing our Focus Group and developing the research plan for our pilot study. We now have received ethics approval and secured research staff, and we are ready to commence recruitment for the study. An inaugural Anna Boyksen lecture was given in October at the University Hospital Klinikum rechts der Isar (by Nicola Lautenschlager), and we published an editorial in the scientific journal International Psychogeriatrics with the title “Modern technology to support carers of care recipients with dementia or functional mental illness: promising progress, but a long road ahead.” We anticipate that we will complete the pilot study in 2018 and hope to be able to report first results in the 2018 Annual Report.

In collaboration with Johannes Mayer, Maria Tensil, and Alexander F. Kurz

Focus Group **Preventive Pediatrics**

Prof. Regina Ensenauer (Heinrich Heine University Düsseldorf) | Anna Boyksen Fellow
PD Dr. Annette Wacker-Gußmann, PD Dr. Silvia Lobmaier | Research Associates

Scientific Reports

Regina Ensenauer

Host
Prof. Renate Oberhoffer
Preventive Pediatrics, TUM

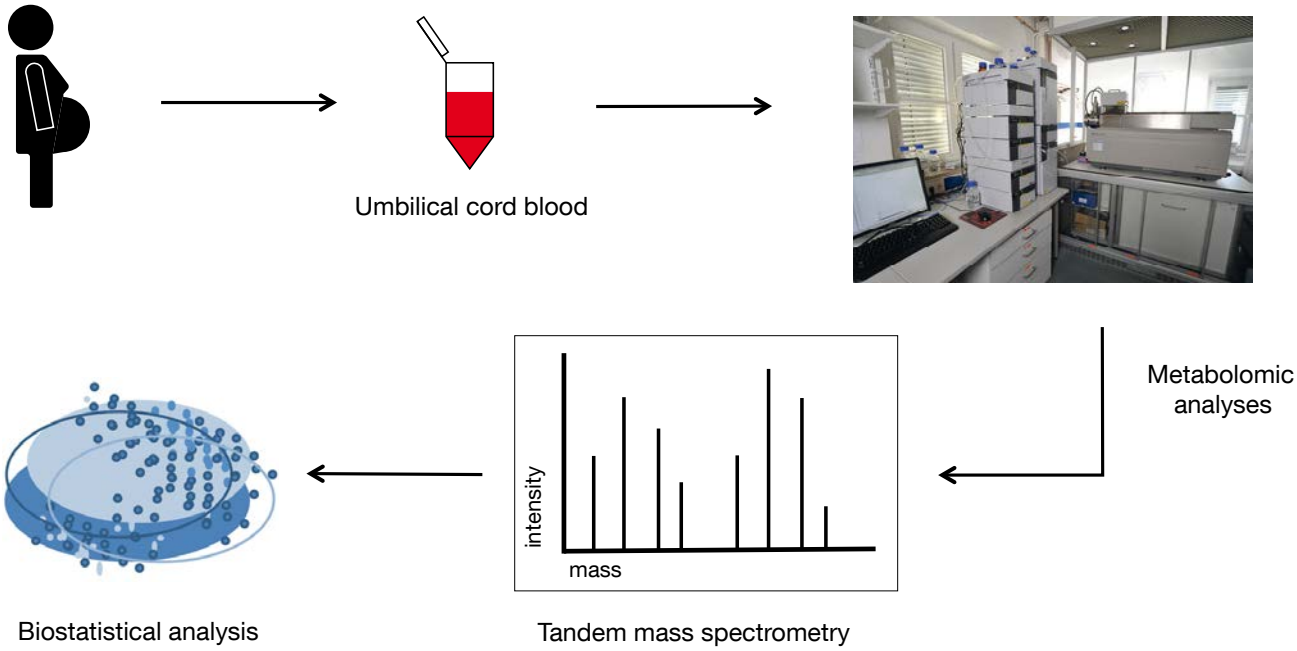
Gestational diabetes: Impact of metabolic dysregulation on the perinatal vascular health of mother and child

Gestational diabetes (GDM) is reported to be the most frequent metabolic disease in pregnancy: 16.2% of all pregnancies worldwide are complicated by GDM [1]. GDM is associated with adverse perinatal outcomes, such as large-for-gestational-age birth weight, fetal cardiac malformations, and neonatal hypoglycemia [2]–[3]. Moreover, GDM represents a significant risk factor for childhood overweight and metabolic disease [4]. However, the mechanisms and metabolic pathways underlying the relationship between maternal hyperglycemia, potentially early vascular alterations in pregnancy, and adverse offspring outcomes are largely unknown.

The GEDIVA (GEstational DIabetes and VAscular disease) Study was designed as a prospective controlled observational study of mothers with GDM and their children (test group) versus healthy mother-child pairs (control group). The aims of our Focus Group are to investigate the development of functional and structural vascular dysfunctions in pregnant women with GDM and their offspring and to identify associated metabolic dysregulations in offspring at birth. In cooperation with the Department of Obstetrics and Gynecology, University Hospital Klinikum rechts der Isar, women with singleton pregnancies have been included in the study if they are 18 years or older and have provided written informed consent. Excluded are women with a preexisting diagnosis of type 1 or 2 diabetes.

During 2017, our Focus Group continued with the recruitment of pregnant women with GDM to achieve the required sample size for final analyses. Using the expertise of our interdisciplinary team, we made significant progress toward fulfilling our goals. By year's end, 122 pregnant women with GDM and 92 healthy controls had been included in the study. Sample material is routinely obtained by midwives and study assistants according to the protocol for the standardized and optimized collection and handling of cord blood. Further, we performed quantitative measurements of functional versus structural vascular impairment in women and their fetuses during pregnancy and at follow-up 12 months post partum. Additionally, anthropometric parameters of the newborns and their development during the first six weeks of life were investigated. The data set includes data on additional prenatal risk factors for the development of childhood overweight, such as maternal preconception BMI, gestational weight gain, smoking during pregnancy, and nutritional status per trimester. Eventually, mass spectrometry (MS) and MS-based technology will be applied to the study sample to investigate global metabolic imbalances in cord blood of the exposed offspring (figure 1). Global metabolite profiling in cord blood will be performed in cooperation with the Helmholtz Zentrum München.

At the present stage of the study, we have investigated clinical phenotypes of the women diagnosed with GDM compared to age-matched healthy controls in whom GDM was excluded. We found that women with GDM had a higher BMI before pregnancy and a lower gestational weight gain, specifically in the third trimester. Additionally, offspring exposed to GDM had on average lower birth weights than controls, a finding that was unexpected considering the risk of macrosomia in offspring of those women. As GDM testing is performed at the end of the second trimester, we hypoth-



1 | Metabolite profiling by liquid chromatography-tandem mass spectrometry: quantification and interpretation of metabolite patterns from umbilical cord blood

esized that subsequent treatment of GDM may have an influence on maternal gestational and offspring phenotypes. Therefore, we analyzed outcomes separately according to their treatment modality (insulin therapy vs. therapy with diet only) and found that women with GDM who were treated with diet only had a high rate of inadequately low gestational weight gain, and their offspring had lower birth weights, compared to controls. Further, we prospectively studied metabolic outcomes in maternal and offspring samples at birth. Last-trimester glycemic control of women with diet-treated GDM was similar to the results of women with insulin-treated GDM but poorer than in controls, as indicated by higher maternal glycated hemoglobin (HbA1c) values at delivery. Cord blood parameters of glucose and lipid metabolism were comparable between offspring groups. Analyses of the effect of prenatal influences on metabolic offspring phenotypes including those of GDM treatment will be a focus in upcoming metabolomic investigations.

Results are expected to identify vascular dysfunctions in women with GDM and their offspring and to derive metabolite patterns in cord blood of offspring exposed to an altered milieu of GDM pregnancies that could be evaluated as risk indicators of adverse maternal and/or child health outcomes in longitudinal follow-ups.

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Publications by this Focus Group can also be found in the section Publications of this report.

In cooperation with doctoral candidates Alexandra Avrutina, Kristina Meyle, Jule Väth, and Maike Wagner.

Focus Group **Brain Temperature Control of Metabolic Diseases**

Prof. Tamas Horvath (Yale University) | Hans Fischer Senior Fellow
Tim Gruber (TUM) | Doctoral Candidate

Scientific Reports

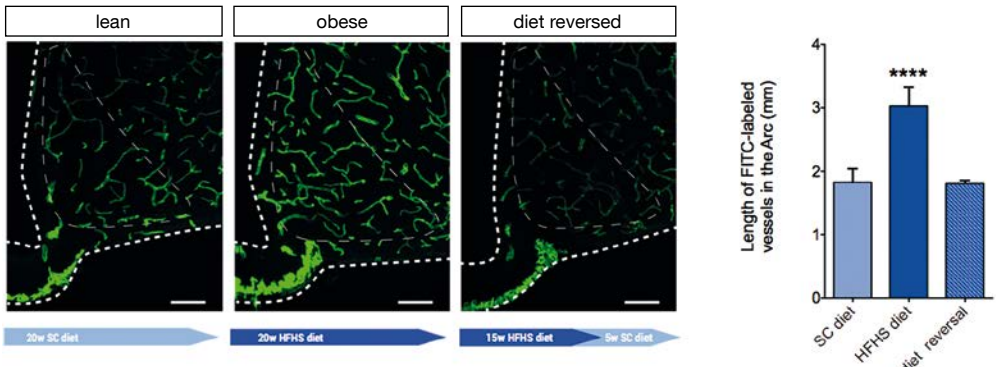
Tamas Horvath

Host
Prof. Matthias Tschöp
Metabolic Diseases, TUM

The brain vasculature in metabolic disease: Targeting the glia-vascular interface for the treatment of obesity

The worldwide prevalence of obesity and type 2 diabetes has kept on expanding at a concerning rate over the past decades. Despite considerable efforts aimed at prevention and treatment, the obesity epidemic is still on the rise. Especially in light of the multiple obesity-associated comorbidities, this development is predicted to become one of the biggest socio-economic burdens of the 21st century.

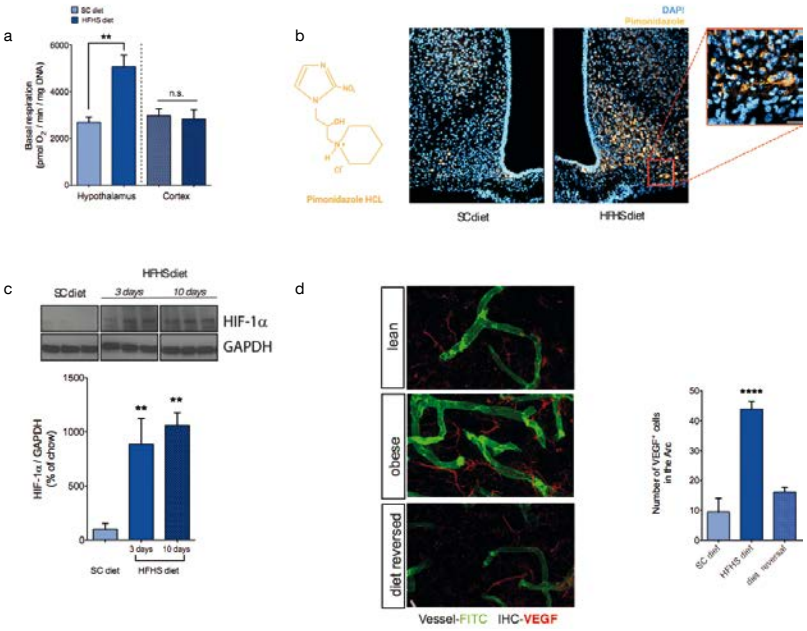
The control over body weight has historically been attributed to certain brain regions. Importantly, such brain regions as the hypothalamus are impacted by the consumption of a high-calorie diet and exhibit rapid structural changes. Some of those structural rearrangements even precede substantial body weight gain, suggesting their potential role in the pathogenesis of obesity [1]–[3]. We here report that chronic high-fat/high-sugar (HFHS) diet feeding induces hypervascularization of the hypothalamus in mice, presumably mediated by the HIF1a/VEGF pathway in astrocytes. This phenomenon is characterized by the excessive formation of new vessels, which exhibit higher permeability and altered integrity. This vascular remodeling was not found elsewhere in the brain and is reversible upon weight loss mediated by diet intervention.



1 | **High-fat/high-sugar feeding induces hypervascularization of the hypothalamus.** Lean, obese, and diet-reversed mice were transcardially perfused with a vessel tracer (lectin-FITC) in order to assess vascular density in different brain regions. As depicted in the representative confocal micrographs, a significant increase in vessel length is found in the hypothalamus of HFHS diet-fed mice compared to lean or diet-reversed formerly obese mice. SC diet = standard chow diet; HFHS diet = high-fat/high-sugar diet.

In order to identify which mechanisms are involved in the initiation of this pathologic vascularization during nutritional excess, we interrogated bioenergetic changes within the hypothalamus. We found evidence that the excessive intake of a high-caloric diet (overload of sugar and fat) increases cellular respiration while limiting local oxygen availability within affected brain regions. Such an imbalance between oxygen consumption and supply might trigger counter-regulatory mechanisms involved in promoting the formation of new blood vessels. The classical signaling pathway governing adaptation to hypoxia depends on the transcription factor known as hypoxia-inducible factor 1α (HIF1α), which mediates the expression of angiogenic factors such as vascular-endothelial growth factor (VEGF) [4]. Indeed, we found that mice exposed to a HFHS diet exhibit increased HIF1α as well as VEGF levels in the hypothalamus.

Interestingly, HFHS diet-induced VEGF expression was specifically observed in glial fibrillary acidic protein (GFAP)-expressing astrocytes in the hypothalamus, indicating



2 | **High-calorie diet induces bioenergetic adaptations and locally restricted oxygen availability in the hypothalamus triggering the induction of HIF1α and VEGF.** Basal rate of respiration was assessed in freshly isolated tissue of the hypothalamus and cortex from mice fed either SC diet or HFHS diet by using extracellular metabolic flux analysis. Hypothalamic tissue from HFHS diet-fed mice showed a significantly increased rate of oxygen consumption compared to mice fed SC diet while no such difference between the diet groups was observed in cortical tissue respiration (a). Mice were injected with the hypoxia marker pimonidazole, which binds to cells insufficiently supplied with oxygen. Binding of pimonidazole markedly increased in the hypothalamus of HFHS-fed mice (b) with concomitant increases of the angiogenic factors HIF1α (c) and VEGF (d) detected by western blot and immunohistochemistry, respectively.

astroglia as the primary source. Astrocytes are star-shaped glial cells that are situated at the interface between neurons and blood vessels and, being thus located, in a privileged position to sense diet-derived metabolic factors and remodel the local microenvironment in response to energy requirements [5].

On the basis of these findings, we generated a genetic mouse model to postnatally induce the ablation of HIF1α specifically in astrocytes to elucidate if these glial cells are involved in HFHS-induce hypothalamic angiopathy. Interestingly, we found that mice lacking HIF1α in astrocytes exhibit neither increased VEGF nor the overall angiogenic response to a HFHS diet. Therefore we are now performing experiments to further investigate the mechanism(s) by which astrocytes induce this phenomenon and to explore which HFHS-derived metabolic factors drive this response in astroglial cells. So far we conclude that HFHS diet-induced bioeneregetic changes in the hypothalamus trigger the astrocytic HIF1α-VEGF pathway, which is involved in the remodeling of vascularity in the hypothalamus during caloric excess.

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **MicroRNAs Regulating Diabetes and Obesity**

Prof. Klaus Kästner (University of Pennsylvania) | Hans Fischer Senior Fellow
Verena Ott (TUM) | Doctoral Candidate

Scientific Reports

Klaus Kästner

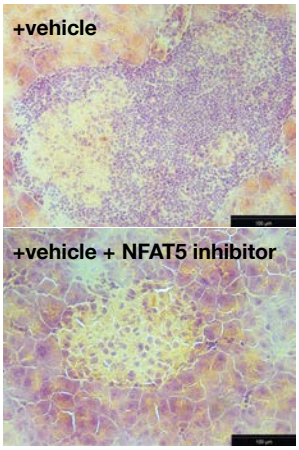
Host
Prof. Matthias Tschöp
Metabolic Diseases, TUM

MicroRNA-mediated control of immune activation in diabetes and obesity

The goal of our interdisciplinary Focus Group is to reveal the cellular and molecular mechanisms underlying the complex regulation of immune tolerance in diabetes and obesity. The incidence of type 1 diabetes (T1D), which is characterized by a breakdown of immunological self-tolerance to the insulin-producing islet beta cells, is increasing dramatically worldwide, especially in young children [1]. In conjunction with the increasing burden of type 2 diabetes (T2D) and obesity, it represents one of the most severe health threats of modern society.

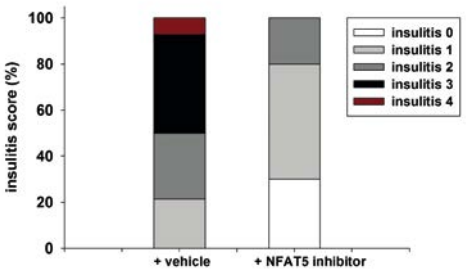
Recent studies, including work done by our group, have begun to reveal how multiple T cell subsets contribute to immune activation and autoimmunity during the onset of T1D islet autoimmunity as well as to inflammatory processes in the tissues [2]–[3]. For instance, we showed that children with a slow progression from islet autoimmunity to clinical T1D show high frequencies of insulin-specific regulatory T cells (Tregs), suggesting a crucial role for Tregs in preventing the progression of islet autoimmunity [2]. Tregs are well established key players for the maintenance of immune tolerance and the control of inflammatory processes, thereby maintaining tissue homeostasis [4]. Despite ongoing research efforts, the molecular mechanisms underlying Treg malfunction and the onset of autoimmunity remain poorly understood, a fact that hinders the development of innovative prevention and intervention strategies.

NOD mice with IAA$^+$ autoimmunity



1 | Representative hematoxylin and eosin-stained pancreas cryosections (left) and grading of insulitis (right) from IAA$^+$NOD mice treated with a miRNA181a or control antagomir for 14 days with 10mg/kg i.p. every other day (modified from I. Serr et al., Science Transl. Med., vol. 10, eaag1782, accepted).

Insulitis in NOD mice with IAA$^+$ autoimmunity



MicroRNAs (miRNAs) add an additional layer of complexity to the maintenance of immune homeostasis by controlling the expression of crucial regulatory proteins, and several studies have demonstrated a critical role of miRNA dysregulation in autoimmunity [5]. miRNAs are small, non-coding, single-stranded RNA molecules, and their mature transcripts bind to the RNA-induced silencing complex (RISC), guiding the RISC to target mRNAs, resulting in mRNA degradation or translational repression. Although recent studies provided considerable insight into the role of miRNAs in immune homeostasis, their direct targets and affected signaling pathways remain poorly understood, especially in T cells.

To address this knowledge gap, our group recently performed a next-generation sequencing (NGS)-based pilot screen to identify miRNAs differentially expressed in CD4$^+$ T cells of children with recent onset of autoimmunity compared to healthy controls. This analysis identified multiple differentially expressed miRNAs, with up to tenfold down- as well as upregulation. The detailed analysis of two miRNAs, miR181a and miR142-3p, and their respective signaling pathways provided considerable insight into their role for the activation of islet autoimmunity.

In a first study, we showed that elevated levels of miR181a during the onset of autoimmunity link increased expression of "nuclear factor of activated T cells 5" (NFAT5)

with impaired tolerance induction and autoimmune activation. This effect is mediated by increased signaling strength of the T cell receptor (TCR). We showed that enhancing miRNA181a activity increases NFAT5 expression while inhibiting Foxp3$^+$ regulatory T cell (Treg) induction *in vitro*. In contrast, the inhibition of miR181a as well as the specific blocking of its binding to NFAT5 can enhance *in vitro* Treg induction. To further support the notion of NFAT5 as a target of miR181a, we used T cells from NFAT5-null mice and showed an improved *in vitro* Treg induction capacity, while altering miRNA181a activity did not affect Treg induction in NFAT5-deficient T cells. Moreover, high co-stimulatory signals resulted in phosphoinositide-3-kinase (PI3K)-mediated NFAT5 activation, which interfered with Foxp3$^+$Treg induction. Inhibiting miRNA181a or NFAT5 increased Treg induction in murine and humanized models, and distinctly reduced murine islet autoimmunity in non-obese diabetic (NOD) mice [6].

The profiles of total miRNA abundance have been determined in multiple biological settings, including T cells [5], but the determination of which miRNAs are actively engaged in mRNA regulation and which mRNAs are specifically targets remains difficult. The HITS-CLIP technique (high-throughput sequencing of RNA isolated by cross-linking immunoprecipitation) offers a valuable tool to close this knowledge gap by directly investigating miRNA-mRNA pairs recruited to the RISC [7]. We applied this method to human CD4$^+$ T cells and identified miR142 as the most highly abundant miRNA in the RISC complex. Further analyses using CD4$^+$ T cells from children and NOD mice at an early stage of islet autoimmunity revealed enhanced levels of miR142-3p during islet autoimmunity. We showed that increased miR142-3p activity impairs *in vitro* Treg induction efficacy, resembling early stages of islet autoimmunity, while miR142-3p inhibition resulted in increased Treg induction capacity and phenotypical stability. Using our HITS-CLIP data, we identified an enzyme responsible for DNA demethylation, the methylcytosine dioxygenase Tet2, as a direct target of miR142-3p, linking high miR142-3p levels to epigenetic remodeling, impaired Treg induction, and the onset of islet autoimmunity.

Our recent discoveries improve our understanding of the mechanisms underlying impaired Treg induction and the onset of islet autoimmunity and suggest both miRNAs and the respective pathways as targets for the development of innovative strategies aiming at the reduction of islet autoimmunity.

This work was conducted in close cooperation with Dr. Carolin Daniel (Institute of Diabetes Research, Helmholtz Zentrum München).

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Proteases in the Brain**

Prof. Carl P. Blobel (Hospital of Special Surgery, Weill Cornell Medicine)
Hans Fischer Senior Fellow
Dr. Merav Shmueli | Postdoctoral Researcher
Johanna Tüshaus (TUM) | Doctoral Candidate

Scientific Reports

Carl P. Blobel

Host
Prof. Stefan Lichtenthaler
Neuroproteomics, TUM

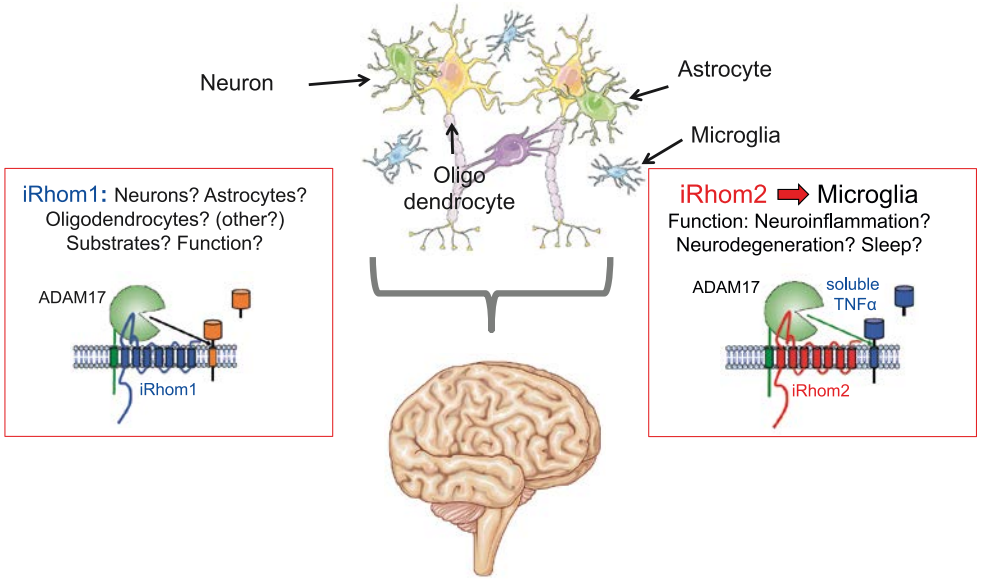
Probing molecular mechanisms in brain disease

Our Focus Group is dedicated to improving our understanding of the role of specific molecular signaling scissors (proteases) in the normal brain and their contribution to brain diseases such as Alzheimer's and traumatic brain injury. Specifically, we are studying molecular scissors termed ADAM17 (a disintegrin and metalloprotease 17, also referred to as TNFα converting enzyme or TACE) that are attached to most, if not all cells in the body. ADAM17 has generated a substantial amount of interest in biomedical research because it regulates two major signaling pathways with important roles in development and disease, signaling through the pro-inflammatory cytokine TNFα (tumor necrosis factor α) and the epidermal growth factor receptor (EGFR). TNFα is involved in the normal immune response, but when it is dysregulated, it causes serious inflammatory and autoimmune diseases, such as rheumatoid arthritis and inflammatory bowel disease and also, most likely, neuroinflammation in Alzheimer's disease and traumatic brain injury. The epidermal growth factor receptor has an essential role in protecting the skin and intestinal barrier but can cause cancer when it is dysregulated. Because ADAM17 is at the apex of both of these signaling pathways, it is considered an attractive target for treatment of diseases caused by dysregulated TNFα or EGFR signaling.

A potential concern in targeting ADAM17 for treatment of inflammatory diseases, including neuroinflammation, is the possibility of unwanted effects on the skin and intestinal barrier. The recent discovery that the signaling scissors ADAM17 have two separate regulators, termed inactive rhomboids 1 and 2 (iRhom1/2), offers an attractive opportunity to separate the pro-inflammatory functions of ADAM17 from its protective functions. iRhom1 and 2 can be thought of as two separate hands that control the scissors (ADAM17), and iRhom2 appears to be required for pro-inflammatory functions of ADAM17. iRhom1, on the other hand, can help ADAM17 protect the skin and intestinal barrier, even when iRhom2 is not present. Interestingly, iRhom2 is responsible for the function of ADAM17 in the microglia, the immune cells of the brain, whereas iRhom1 is important for the functions of ADAM17 in the rest of the brain.

We are taking two general approaches toward elucidating the role of iRhoms and ADAM17 in the brain.

Simone Scilabra, who is the recipient of a Marie Curie fellowship, is studying the contribution of iRhom2/ADAM17 to Alzheimer's disease, where iRhom2 acts as a risk factor. Using an Alzheimer's disease mouse model, Simone Scilabra has obtained promising preliminary data, in that genetic inactivation of iRhom2 slows neuroinflammation in the Alzheimer mouse brain. Together with Merav Shmueli, he is now investigating the detailed role of iRhom2/ADAM17 and related molecules in the neuroinflammatory process.



1 | Our main goal is to elucidate the substrates and functions of the signaling scissors ADAM17 and its regulators, the inactive Rhomboid proteins iRhom1 and iRhom2, in the brain. iRhom1 is the main regulator of ADAM17 in the brain (left box), and we are attempting to identify the cell types expressing iRhom1/ADAM17 and the relevant substrates and functions of iRhom1/ADAM17. We are also studying iRhom2 in the brain, which controls the pro-inflammatory function of ADAM17 in microglia, immune cells of the brain. These efforts could help provide a better understanding of neuroinflammation, for example in the context of Alzheimer's disease and traumatic brain injury.

Moreover, Johanna Tüshaus, a formerly TUM-IAS-sponsored doctoral candidate and recipient of a Boehringer Ingelheim PhD fellowship, is studying the function of iRhom1/ADAM17 in the brain. She has optimized the innovative secretome protein enrichment with click sugars (SPECS) method developed in the Lichtenthaler lab. This enabled her to perform an in-depth secretome analysis of minor amounts of primary cells in 2-D and 3-D cell culture models, thereby significantly improving the sensitivity of this approach. In addition, minute droplets of cerebrospinal fluid were analyzed to search for differences of iRhom-deficient mice compared to normal controls *in vivo*, an exciting and promising new direction for our group. Johanna Tüshaus has identified several novel substrates for the iRhom1/ADAM17 scissors in the brain, and she spent six months in Carl Blobel's lab in New York in 2017 to analyze the consequences of inactivation of iRhom1 and thus ADAM17 in the mouse brain.

The ultimate goal of our Focus Group is to improve our understanding of the role of the iRhom/ADAM17 signaling scissors in the brain in order to uncover new targets for treatment of neuroinflammation in Alzheimer's disease, traumatic brain injury, and other diseases that might depend on iRhom1/ADAM17.

In collaboration with postdoctoral researcher Dr. Simone Scilabra, DZNE.

Focus Group **Viral Hepatitis**

Prof. Jane A. McKeating (University of Oxford) | Hans Fischer Senior Fellow
Anindita Chakraborty, Lisa Wolff (TUM) | Doctoral Candidates

Scientific Reports

Jane McKeating

Host
Prof. Ulrike Protzer
Virology, TUM

Discoveries could lead to solutions for a global health problem

Chronic hepatitis B and C virus (HBV/HCV) infection is a global health problem with infected individuals at risk of developing liver disease that can progress to hepatocellular carcinoma [1]. The primary site of HBV and HCV replication is the liver, and developing novel therapies to prevent viral induced liver disease requires an understanding of the host factors that define susceptibility to infection.

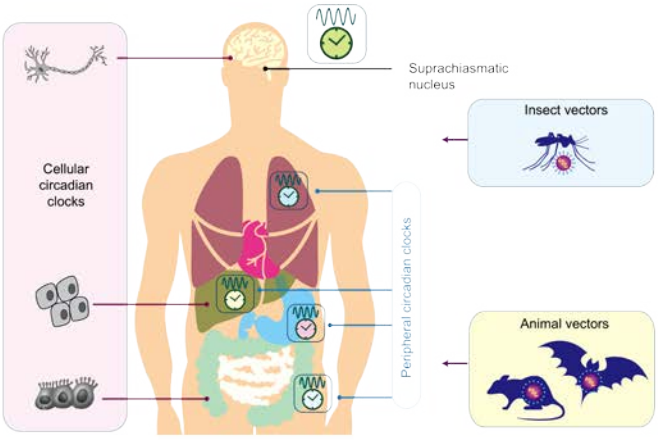
One option to prevent infection is neutralizing antibodies. We were able to identify a murine antibody with broad neutralization capacity and transformed this into a chimeric human antibody with no loss of efficacy or specificity [2]. Interferon-α (IFN-α) has been used for more than 20 years for treating chronic HBV and HCV infection, and its mechanism of action is complex and multifactorial. We demonstrated that the supernatant from IFN-α-treated cultured cells restricts HBV and HCV particle entry into hepatoma cells. The IFN-induced soluble factors compete with virus binding to heparan glycosaminoglycans and thereby inhibit viral binding [3].

We previously reported that activated macrophages promote HCV entry into polarized hepatocytes via a TNF-α-dependent process; however, the underlying mechanism was not defined. We have now shown that several TNF superfamily members, including TNF-α, TNF-β, TWEAK, and LIGHT, promote HCV entry via NF-κB-mediated activation of myosin light chain kinase (MLCK) and disruption of tight junctions. These observations support a model where HCV hijacks an inflammatory immune response to stimulate infection and uncovers a role for NF-κB-MLCK signaling in maintaining hepatocellular tight junctions [4].

New curative therapies for HBV are urgently needed, and current efforts are impeded by the lack of efficient model systems that support HBV replication. We found that hepatocyte-like cells (HLCs) derived from human pluripotent stem cells support robust HBV replication. This novel infection model offers a unique opportunity to advance our understanding of the molecular details of the HBV life cycle, to further characterize virus-host interactions, and to define new targets for HBV curative treatment [5]. In an effort to develop preclinical animal model systems, we discovered that expression of the HBV entry receptor, human sodium-taurocholate cotransporting polypeptide (hNTCP), on macaque primary hepatocytes facilitates HBV infection *in vitro*. Importantly, viral vector-mediated expression of hNTCP on hepatocytes *in vivo* renders rhesus macaques permissive to HBV infection. These macaque HBV infections are characterized by longitudinal HBV DNA in serum, and detectable levels of HBV DNA, RNA, and HBV core antigen in hepatocytes. Together, these results show that expressing hNTCP in macaque hepatocytes renders them susceptible to HBV infection and establishes a physiologically relevant model of HBV infection to study immune clearance and evaluate new therapeutic and curative approaches [6]. A thorough study of NTCP protein modification revealed that proper glycosylation is essential for NTCP localization to the cell surface but also for HBV infection [7].

The molecular mechanisms driving HBV liver disease and carcinogenesis are largely unknown, and gene expression profiling of HBV-infected primary human hepatocytes showed increased transcription of genes encoding for acute phase and anti-apoptotic proteins. This gene regulation was confirmed in liver tissue samples of patients with chronic HBV infection and in HBV-related hepatocellular carcinoma. Pathway analysis revealed activation of STAT3 to be the major regulator. Interleukin-6-dependent and -independent activation of STAT3 was detected in HBV-replicating hepatocytes. Preventing STAT3 activation by inhibition of Janus tyrosine kinases as well as small interfering RNA-mediated knockdown of STAT3-induced apoptosis reduced HBV replication and gene expression. These studies show that HBV activates STAT3 signaling in hepatocytes to foster its own replication and to prevent apoptosis of infected cells, supporting HBV-related carcinogenesis [8].

The circadian clock underpins most physiological conditions and provides a temporal dimension to our understanding of body and tissue homeostasis. Recent literature highlights a role for the circadian clock to regulate innate and adaptive immune functions that may prime the host response to infectious organisms. Viruses are obligate parasites that rely on host cell synthesis machinery for their own replication, survival, and dissemination. We reviewed the literature on how circadian rhythms impact viral infection and how viruses modulate molecular clocks to facilitate their own replication (see figure).



1 | Central and peripheral Circadian clocks. The mammalian circadian clock consists of the central oscillator, located in the suprachiasmatic nucleus (SCN) of the hypothalamus, and peripheral clocks present in virtually all cells of the body. Light activates photoreceptors in the retina that are connected to the central SCN clock, which synchronizes and entrains peripheral circadian clocks via neural and endocrine pathways. The interplay between the circadian clocks of man and vectors that carry viral pathogens may impact on their capacity to transmit viruses.

This emerging area of viral-clock biology research provides a fertile ground for discovering novel antiviral targets and optimizing immune-based therapies [9].

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Collective Quantum Dynamics**

Prof. Michael Knap (TUM) | Rudolf Mößbauer Tenure Track Professor
Dr. Johannes M. Oberreuter (TUM) | Postdoctoral Researcher
Annabelle Bohrdt, Alexander Schuckert, Simon Weidinger (TUM)
Doctoral Candidates

Scientific Reports

Michael Knap

Host
Collective Quantum Dynamics, TUM

Collective quantum dynamics: Teamwork of quantum particles

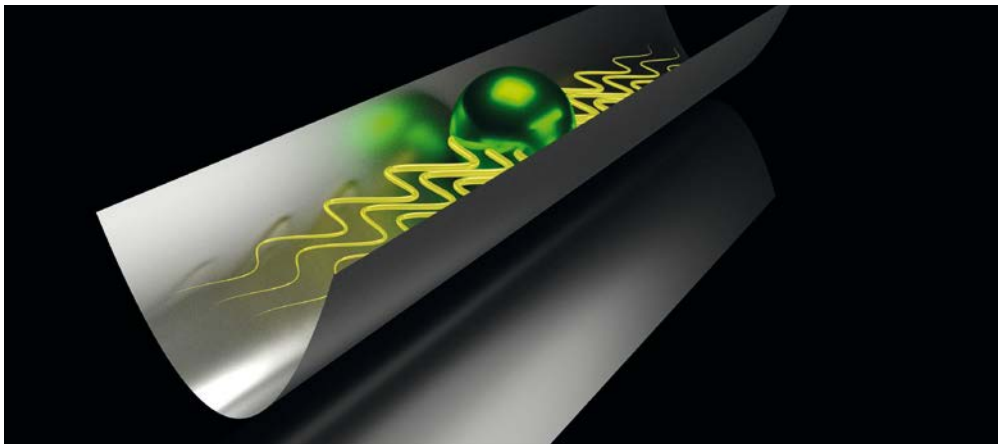
The research in our group aims at a broad range of questions from condensed matter theory such as exotic quantum materials, ultracold quantum gases, and light-matter systems. Interactions and correlations in condensed matter systems often manifest in striking and novel properties. These properties emerge from collective behavior of the quantum particles and cannot be understood from the perspective of a single particle alone. In that sense quantum particles can achieve new goals by forming teams. Many examples of collective quantum dynamics can be found in nature, including superconductors, quantum magnets, and superfluids. Our group develops both analytical and numerical techniques to elucidate the effects of strong interactions and emergent collective behavior. Another important factor of our research is its immediate relevance for experiments, which leads to close collaboration with experimental groups all over the world.

Correlated quantum systems out of equilibrium

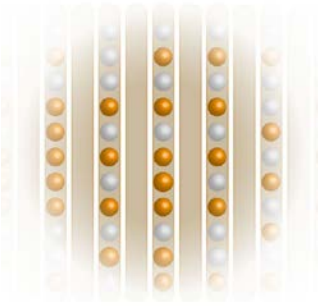
A ripe apple falling from a tree inspired Sir Isaac Newton to formulate a theory that describes the motion of objects subject to a force. Newton's equations of motion tell us that a moving body keeps on moving in a straight line unless any disturbing force changes its path. The impact of Newton's laws is ubiquitous in our everyday experience, ranging from a skydiver falling in Earth's gravitational field to the inertia one feels in an accelerating airplane and the orbit of our planet around the sun.
In the quantum world, however, our intuition for the motion of objects is strongly challenged and may sometimes even completely fail. In collaboration with Hanns-Christoph Nägerl's group in Innsbruck, we have shown that a quantum particle describes a completely unexpected behavior [1]. In a quantum gas the particle does not move like the famous falling apple; instead, it oscillates. At the heart of this surprising behavior is the phenomenon of "quantum interference," the fact that quantum mechanics allows particles to behave like waves, which can add up or cancel each other.

Disordered many-body systems

Disorder has a drastic influence on transport properties. In the presence of a random potential, a system of interacting electrons can become insulating; this phenomenon is known as many-body localization. Even beyond the vanishing transport, however, such systems have very intriguing properties. For example, many-body localization describes an exotic phase of matter that is robust to small changes in the microscopic Hamiltonian. Moreover, fundamental concepts of statistical mechanics break down in the many-body localized phase.



1 | A quantum particle performing an intriguing oscillatory back-and-forth motion in a one-dimensional atomic gas.



2 | Sketch of a many-body localized quantum system [2].

In recent work [2], we collaborated with Immanuel Bloch's group at the Max Planck Institute for Quantum Optics and studied the dynamics of a two-dimensional many-body localized quantum system. We started our system far from equilibrium (with atoms loaded into alternate columns) and observed if the system preserved the memory of this pattern. We found that beyond a critical disorder strength, the relaxation of local observables remains incomplete up to extremely long time scales, which hints at the existence of a many-body localized phase in two dimensions. Our work demonstrates absence of local thermalization in higher dimensions and paves the way for stabilizing exotic quantum phenomena, such as coherent quantum memories and topological phases, at temperatures at which they would be destroyed without disorder.

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[2] P. Bordia, H. Lüschen, S. Scherg, S. Gopalakrishnan, M. Knap, U. Schneider, and I. Bloch, "Probing Slow Relaxation and Many-Body Localization in Two-Dimensional Quasi-Periodic Systems," Physical Review X 7, 2017.

Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Computer Simulation of Charge Transport in Organic Semiconductors**

Prof. Jochen Blumberger (University College London) | Hans Fischer Fellow
Patrick Gütlein (TUM) | Doctoral Candidate

Scientific Reports

Jochen Blumberger

Hosts
Prof. Peter Müller-Buschbaum
Functional Materials, TUM
Prof. Karsten Reuter
Theoretical Chemistry, TUM

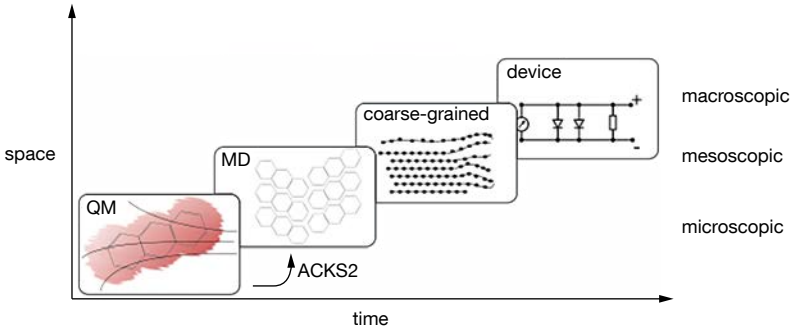
Toward accurate electronically polarizable force fields for simulation of charge transport in organic semiconducting materials

In a world where technology is pervasive, organic semiconductors are among the most intriguing materials discovered in the past decades. Lightweight, flexible, and relatively easy to produce from renewable fabrication resources, organic semiconductors combine many desirable properties for modern applications such as thin-film electronic devices. Important and disruptive state-of-the-art technologies include light sources, e.g., organic light-emitting diodes, and light-harvesting devices such as organic photovoltaics.

Unfortunately, the loss of electric conductivity – which is crucial for modern electronic devices – poses a serious downside for these newly found organic semiconductor materials compared to traditional inorganic compounds. The quest for new promising organic semiconductor compositions and the systematic improvement of their electric conduction properties require a proper understanding and accurate theoretical modeling of charge-carrier localization and transport. Despite recent progress, the current understanding of charge transport in organic molecular crystal and amorphous phases is still very limited. The motion and transient localization of charge carriers (excess electrons and holes) is subject to integral processes on very different time and length scales, which renders the theoretical representation a very difficult and expensive task. In classical multiscale modeling approaches, the microscopic charge-transport properties of organic molecules are upscaled to macroscopic electronic device setups and currents, with statistical coarse-grain methods bridging the mesoscale gap.

On an atomic or molecular level, organic semiconductors are subject to the non-negligible dielectric response of the surrounding environment. The presence of charge carriers induces polarization of nearby organic molecules, which in return influence localization and transport of charge carriers. These dynamical, many-body electronic rearrangements span over many molecules due to the small dielectric screening in organic semiconductors. This effect is particularly pronounced in densely packed materials like organic semiconductors, as the electronic states are strongly coupled to nuclear motion, while typical operation conditions of electronic devices at ambient (or elevated) temperatures lead to strong molecular vibrations.

In this situation, the recently proposed atom-condensed Kohn-Sham density functional theory approximated to second order (ACKS2) [1]–[2] approach could represent a computationally undemanding yet accurate technique to evaluate the



1 | Relevant length and time scales for modeling of charge transport in organic semiconducting materials. The focus of our research group is to bridge the electronic with the molecular scale by developing a novel force field based on the atom-condensed Kohn-Sham density functional theory approximated to second-order (ACKS2) approach.

electron density response to electric fields in organic semiconductor materials. Molecular electronic polarization is captured by a simple linear expansion of the density change in an atom-centered Gaussian-type orbital basis.

In 2017, our Focus Group wrote a computer program that calculates the ACKS2 electron density response due to an external electrostatic perturbation (static electric field, point charges) using ACKS2 parameters from density functional theory. We found excellent agreement for induced molecular dipole moments when compared to *ab initio* or experimental reference data. We also conceived and implemented a novel iterative ACKS2 algorithm for the self-consistent iteration of the electron density response of a molecule due to the electrostatic interaction with neighboring molecules, as is the case, for example, in a crystal lattice. This marked an important next step toward an accurate electronically polarizable ACKS2 force field to be used in combination with our recently developed non-adiabatic molecular dynamics method [3] for charge-carrier transport in organic semiconducting materials.

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Electrochemical Interfaces in Batteries**

Dr. Peter Lamp (BMW Group) | Rudolf Diesel Industry Fellow
Roland Jung (TUM) | Doctoral Candidate

Scientific Reports

Peter Lamp

Host
Prof. Hubert A. Gasteiger
Technical
Electrochemistry, TUM

Probing fundamental limitations of a critical technology

Electromobility is nowadays one of the greatest and most fascinating technological challenges. In order to extend the driving range of electric vehicles as well as to reduce the costs of lithium-ion batteries, novel materials and innovative battery systems need to be developed.

In the Focus Group Electrochemical Interfaces in Batteries, we have been developing a detailed understanding of the root causes of battery aging, showing that most of the degradation processes occur at the interface between the solid electrodes and the liquid electrolyte. The investigation of this interface is crucial to gain fundamental understanding of today's Li-ion batteries and to derive the necessary improvements for future batteries. Even though Li-ion batteries are already widely used, the various degradation mechanisms leading to capacity fading and a limited battery lifetime are still not fully understood. In this project, we analyze operando, i.e., during charge or discharge, the gas evolution occurring in battery cells from undesired side reactions. These reactions are due to electrode active material degradation and/or the decomposition of the electrolyte. Gassing in a cell not only has a detrimental impact on the lifetime and stability of the battery cell, but is also critical for the safety of Li-ion batteries.

We successfully showed that layered oxides, probably the most promising class of positive electrode materials, release reactive oxygen from the particle surface when they are overcharged. This not only causes a fast decay of the battery capacity, but also causes the decomposition of the electrolyte. This very detrimental mechanism has to be accounted for when designing a Li-ion battery cell; at the same time, it reveals the limits in capacity and stability for this class of cathode materials. We furthermore showed that these analyses are very well suited to explore the limits of various battery materials and to investigate strategies for extending these limits to yield materials with improved lifetime, capacity, and energy density.

Munich Battery Discussions

Peter Lamp co-organized, together with his group at BMW and the TUM-IAS, the 5th Munich Battery Discussions, which took place March 13–14, 2017. The focus of this year's Munich Battery Discussions was "All-Solid-State Batteries – an option for future e-mobility?" As in the years 2013–2016, this international conference brought together many renowned and leading scientists in the field of battery research, with many invited speakers from all over the world.

1 | Participants of the Munich Battery Discussions in March 2017: “All-Solid-State Batteries – an option for future e-mobility?"

Their presentations on the latest research advances provided a platform for very fruitful discussions on the challenges battery research is facing today. The interaction of many battery experts with highly motivated students and young scientists made the Munich Battery Discussions a great success, which will be continued with the 6th Munich Battery Discussions in 2018.

Also, as in previous years, the speakers series dedicated to New Frontiers in Battery Science and Technology was continued. The purpose of these invited seminars is to offer the research community a continuous update, aside from the annual Munich Battery Discussions, on the most exciting new findings in the field of battery research. By bringing together many academic and industrial researchers, it has developed into a platform for frequent exchange of ideas.

Focus Group **Nanophotonics and Quantum Optics**

Prof. Jelena Vuckovic (Stanford University) | Hans Fischer Senior Fellow
Armin Regler (TUM) | Doctoral Candidate

Scientific Reports

Jelena Vuckovic

Host
Prof. Jonathan Finley
Semiconductor Quantum Nanosystems, TUM

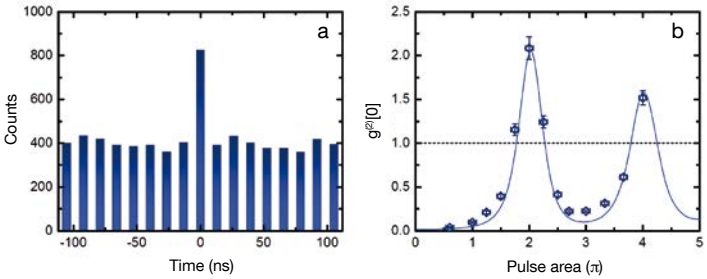
Splicing, splitting, and detecting quantum light using nanostructured materials

High-quality sources of single photons are one of the key elements needed for almost all photon-based technologies for quantum science and technology. The ideal single-photon source delivers identical pulses of light, in terms of the spatial and temporal shape of the wave packet emitted. Moreover, each pulse of light should contain precisely a single photon, and the rate at which the single photons are generated should be as high as possible, to process quantum information at a high rate.

To date most single-photon sources are based on a technique known as spontaneous parametric down-conversion (SPDC), where photons from a classical laser beam with a frequency ω_{pump} are spontaneously split into pairs of photons with frequencies ω_1 and ω_2, such that $\omega_{pump} = \omega_1 + \omega_2$. In such SPDC sources, the detection of one photon having a frequency ω_1 "heralds" the presence of the other with frequency ω_2 – photon pairs are emitted spontaneously with a low probability $P \ll 1$. While excellent in many ways, such sources are nondeterministic, making it very challenging to scale up to a more complex quantum photonic processor containing N photonic channels, since the probability of achieving the desired initial state decreases strongly with the number of channels as $\sim P^N$. As such, deterministic sources of quantum light are needed for which $P \sim 1$ and, moreover, the time at which single photons are generated in each of the N photonic channels should be well defined.

Semiconductor quantum dots (QDs) are "artificial atoms" in the solid state that can be controllably embedded within nanophotonic devices for various applications in quantum technologies. When individual QDs are resonantly optically excited with a picosecond (1 ps = 10^{-12} s) duration laser pulse, they can generate single photons on demand. Repeated optical excitation enables the generation of a stream of single photons, each having a wave packet that is spatially and temporally identical as required. Combined with nanoresonators, single-photon sources with high emission rates (~GHz) and collection efficiency ($P \sim 1$) have been demonstrated and are now being incorporated into quantum information processors. For example, high-quality QD sources were recently used in demonstrations to create a train of single photons, which were temporally multiplexed to the input of a photonic processor known as a boson sampler, one of the best experimental validations of optical quantum computing made to date.

Our Focus Group investigates the quantum interaction of light and matter at the nanoscale. Recently, we have investigated the dynamics of the interaction of a pulsed laser with a two-level transition in a single quantum dot [1]–[2]. Thereby, we have shown that in addition to the well known effect of single-photon generation, two-level systems are capable of generating two-photon pulses on demand for specific excitation pulses. The quantum character of light can be quantified by the measured degree of second-order coherence $g^{(2)}(0)$, where $g^{(2)}(0)=1$ corresponds

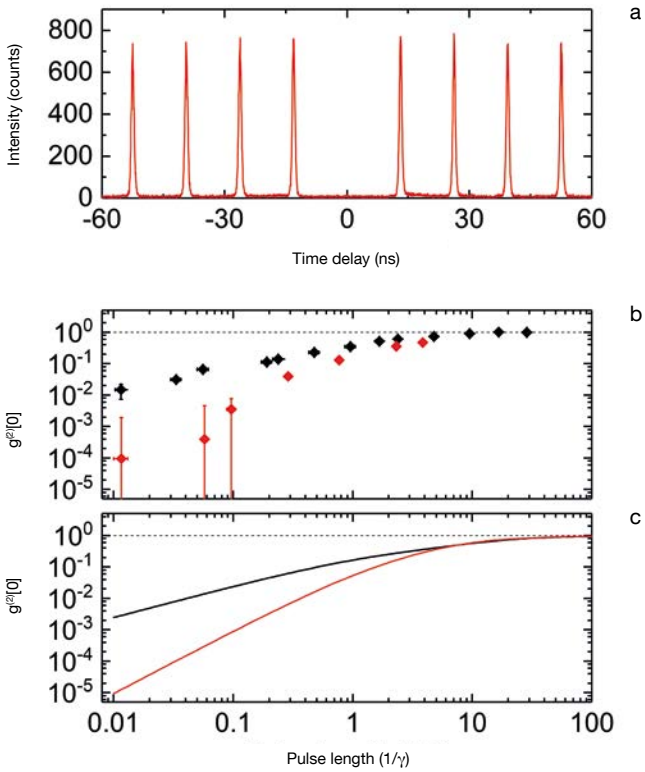


1 | $g^{(2)}(0)$ as a function of the pulse area for resonantly exciting an artificial atom with short laser pulses.

to coherent light, such as that provided by a laser, $g^{(2)}(0)=0$ to single photons, and values $g^{(2)}(0)>1$ to bunched emission. As an example, figure 1 shows $g^{(2)}(0)$ for a specific pulse length as a function of the excitation power and reveals clean oscillations between the generation of single photons and multi-photon pulses. Quantum optical simulations (blue line) are in excellent agreement with the measurements (black data points). In additional measurements and theory, we have identified the bunched emission to consist of two-photon pulses.

In related studies we have shown how, by exciting the QD at an energy corresponding to a two-photon optical transition, the performance of the quantum light source can be dramatically improved. Figure 2a shows the $g^{(2)}\,\tau$ of the light emitted by a single QD when excited via the two-photon resonance. It resembles a near-perfect source of single photons with the peak at zero-time delay (τ=0) entirely absent in the data. The lower panels of figure 2 show the measured (2b) and calculated (2c) values of $g^{(2)}(0)$ as a function of the duration of the exciting laser pulse. This data illustrates how the two-photon excitation method yields values of $g^{(2)}(0)$ that are up to 100 times better, as low as $g^{(2)}(0)\sim10^{-4}$, representing single-photon pulses with unprecedented purity. In the coming year, the quantum properties of these photons will be tested to assess their suitability for photon-based quantum information science and technology.

This work was conducted in cooperation with doctoral candidate Lukas Hanschke (Semiconductor Quantum Nanosystems, TUM) and postdoctoral researcher Dr. Kai Müller (Semiconductor Quantum Nanosystems, TUM).



2 | (a) High quality data recorded via two-photon excitation. The lower panels show the dependence on the pulse length for one (black) and two-photon excitation (red) in experiment (b) and theory (c).

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Quantum Matter**

Dr. Marc Janoschek (Los Alamos National Laboratory) | Hans Fischer Fellow
Franz Haslbeck (TUM) | Doctoral Candidate

Scientific Reports

Marc Janoschek

Host
Prof. Christian Pfleiderer
Topology of Correlated Systems, TUM

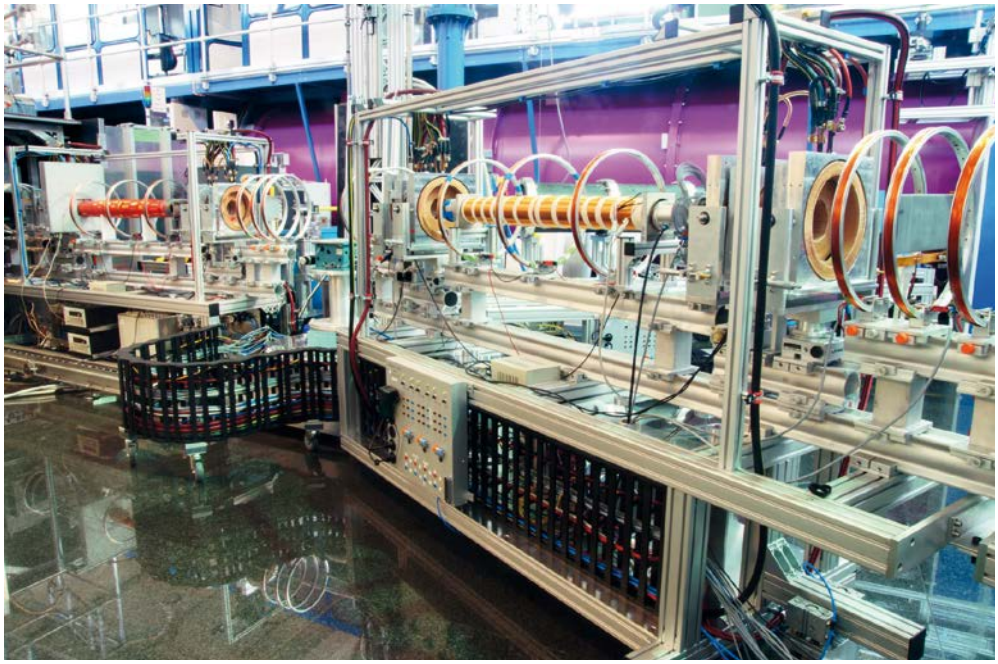
New frontiers of neutron spectroscopy in quantum matter

The properties of condensed matter emerge from the underlying atomic-scale interactions. For example, thermal conductivity in an insulator is governed by atomic-scale bonding forces that determine how strongly atoms may vibrate within a crystalline structure, and thus their ability to transfer energy or heat. Similarly, “quantum matter” is any novel phase of a solid with properties that are characterized by underlying interactions that are inherently “quantum” in nature. These quantum matter states are widely regarded as promising candidates to underpin future applications ranging from power management and transmission to quantum computation and novel versatile sensors [1].

Our Focus Group studies quantum matter that arises in metallic bulk materials in the vicinity of magnetic quantum phase transitions — that is, magnetic instabilities occurring at zero temperature and as a function of a non-thermal control parameter such as pressure. Decades of research have revealed a plethora of novel quantum matter phases near these quantum instabilities; the most prominent one is unconventional superconductivity, but more recently electronic nematic phases and topological order are also of interest. It is commonly believed that the strong quantum magnetic fluctuations at the instability drive this quantum matter potpourri. Their abundance generates a huge magnetic entropy that is “avoided” by the formation of a new quantum matter state. The quantum fluctuations also couple charge, magnetic, and structural degrees of freedom, which is the origin of exotic material properties.

While these quantum fluctuations arise at temperatures approaching zero, the resulting quantum matter exhibits profoundly altered properties at finite temperatures and, in some cases, up to room temperature. In turn, quantum phase transitions have developed from a zero-temperature oddity to one of the most important issues in solid-state physics. Simultaneously this highlights the relevance of quantum matter for future applications despite its low-temperature roots.

Although the importance of magnetic quantum phase transitions and the associated quantum fluctuations is widely appreciated, little quantitative information on the fluctuation spectrum is currently available. Because magnetic fluctuations sensitively couple to a neutron’s spin degrees of freedom, neutron spectroscopy is a powerful probe to study this issue. However, only very few studies have looked at quantum magnetic fluctuations, and these have been additionally hampered by two issues: All studies were performed near quantum phase transitions controlled by chemical substitution, which generally introduces disorder that strongly affects the behavior near quantum phase transitions [2]; and they were limited in energy resolution. The latter point is crucial for the study of zero-temperature instabilities. To extract the relevant quantum fluctuations spectrum, the measurements are carried



1 | The Neutron Resonance Spin-Echo (NRSE) Spectrometer RESEDA at the research reactor of the Heinz Maier-Leibnitz Zentrum (MLZ).

out at the extremes of low temperatures. The lowest temperature that is typically achieved in neutron experiments is about 50 mK, which corresponds to thermal energies of 4 μeV, an order of magnitude less than the resolution of conventional neutron spectroscopy.

In the Focus Group Quantum Matter we have made progress on both issues. Because pressure is known to be a clean tuning parameter for accessing metallic quantum phase transitions, we are developing new types of pressure cells for neutron scattering. More importantly, our effort has also reached new realms of energy resolution. Typically, better resolution is achieved by selecting neutrons that fulfill the desired scattering condition more rigorously. However, this strongly reduces the number of neutrons available for the experiment, and thus resolution is intensity-limited. We overcome this limitation by using a method called neutron resonant spin-echo (NRSE), which encodes the energy resolution in the neutron's spin degree of freedom. These measurements are carried out at the NRSE spectrometer RESEDA at the research reactor of the Heinz Maier-Leibnitz Zentrum (MLZ) at TUM (figure 1). Using this method, we have recently achieved 1 μeV energy resolution to study the magnetic fluctuation spectrum of the ferromagnet UGe_2. This breakthrough will enable us for the first time to study the quantum fluctuations that drive the emergence of quantum matter in metals.

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Semiconductor Nanowires**

Dr. Heike Riel (IBM Research - Zurich) | Rudolf Diesel Industry Fellow
Bernhard Loitsch (TUM) | Doctoral Candidate

Scientific Reports

Heike Riel

Hosts
Dr. Gregor Koblmüller
Semiconductor Nanostructures and Quantum Systems, TUM
Prof. Alexander W. Holleitner
Nanoscale Optoelectronics, TUM

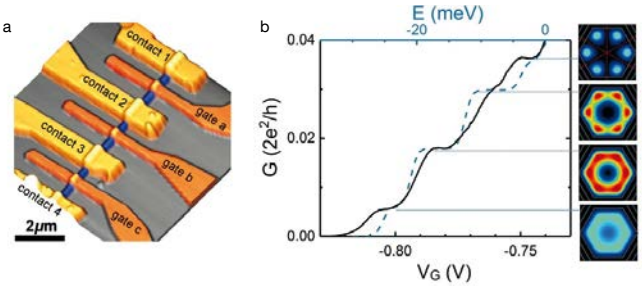
Novel nanowire heterostructures for advanced nanoelectronic devices

Semiconductor nanowires (NW) present an emerging platform for photonics and electronics research due to the ability to realize materials combinations and related devices not possible in conventional planar structures. Especially, the synthesis of complex hetero¬structures and the incorporation of III–V semiconductor materials directly on silicon facilitates the realization of various novel NW-based devices. Examples include high-performance lasers and transistors, as well as Esaki diodes and tunneling devices [1]–[4] – systems that are under intense investigation within and beyond our Focus Group.

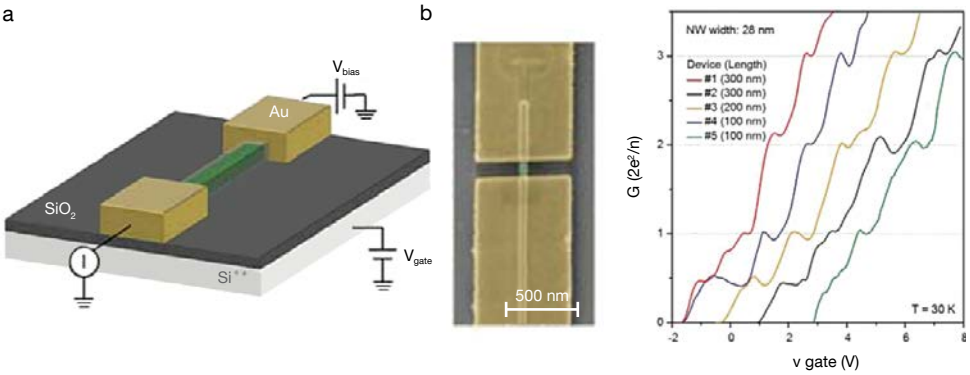
In nanoelectronics – one of the core themes within the Rudolf Diesel Fellowship between IBM Research Zurich and the Walter Schottky Institute at TUM – semiconductor NWs are nowadays deployed in high-frequency, low-energy transistors for future technology as well as for studies of quantum phenomena arising from the peculiar one-dimensional (1-D) nature of NWs. In this regard, there is significant interest in using quantum-confined NWs in several lines of research, including generation and manipulation of Majorana fermions, realization of ballistic transport, and enhancement of thermoelectric conversion efficiency by exploiting the discontinuity in the 1-D density of states.

These applications require, in general, high-purity, high-mobility conduction channels to ensure coherent 1-D transport. Therefore, development and improvement of high-mobility quantum-confined charge carrier systems in NWs are important goals for ongoing quantum electronics research. Thus the focus of this year's research aimed at the creation of quantum-confined and high-mobility NW channels and the exploration of their 1-D-like quantum transport properties. Two specific systems have been proposed through the concerted efforts enabled by the Rudolf Diesel Fellowship, on the one hand modulation-doped GaAs/AlGaAs NW heterostructures and on the other hand quantum-confined InAs NW channels.

A unique new system of modulation-doped (Si-delta doped) GaAs/AlAs core-shell NW heterostructures has been developed successfully, and their low-temperature transport properties have been investigated [5]. In particular, our studies were able to correlate transport signatures with quantized electronic subbands in the conduction channel. As shown in figure1, we observed characteristic 1-D-like



1 | (a) Typical GaAs/AlAs modulation-doped NW-FET device fabricated by electron beam lithography for four-terminal sensing with multiple Schottky gates; (b) Low-temperature measurements of the conductance G versus applied gate voltage showing discrete steps indicative of diffusive 1-D-transport. The experimental data shows good agreement with simulated data (blue trace) based on the successive depletion of the individual electronic states (sub-bands) of the confined electron gas in the NW channel (illustrated on the right) [5].



2 | (a) Schematic and false-color SEM image of a typical InAs NW ballistic device; (b) Electrical conductance as a function of gate voltage for five exemplary 28-nm-wide NWs with five different lengths (< 300 nm) as measured at 30 K. All devices exhibit quantized 1-D conductance plateaus.

conductance plateaus and determined that the plateaus correlate directly with singly and doubly degenerate sub-band levels generated by the rotational hexagonal symmetry of the NW. The investigations also provided insights into additional zero-dimensional-like confinement arising from disorder potentials due to background impurities. With support from complementary projects in NW electronics funded by the TUM International Graduate School of Science and Engineering (IGSSE), high-resolution structural analysis was performed using scanning transmission electron microscopy (STEM) and atom probe tomography (APT), to allow for accurate simulations and direct comparison with experiments [5].

Studies into the quantum transport properties have also been performed on InAs-based NWs, which are intrinsically a prominent system for 1-D-quantized ballistic transport. A novel template-assisted growth technology was employed to realize high-quality, surface-passivated InAs NWs with desired length, cross-section and position on a silicon platform. In quantum-confined NWs with cross-sections (diameter) of less than 40 nm, step-like 1-D conductance plateaus were observed in units of the quantum of conductance, $2e^2/h$ [6], indicative of ballistic transport. Length-dependent studies further revealed that ballistic transport for up to 300 nm and quasi-ballistic transport with mean free path of 470 nm are feasible at low temperatures [6]. These results are very promising for new generations of nanoscale transistors with negligible voltage drop.

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Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Theory of Complex Quantum Systems**

Prof. Robert König (TUM) | Rudolf Mößbauer Tenure Track Professor
Dr. Milán Mosonyi (TUM) | Postdoctoral Researcher
Martina Gschwendtner, Margret Heinze, Stefan Huber, Daniel Stilck França (TUM)
Doctoral Candidates

Scientific Reports

Robert König

Host
Theory of Complex
Quantum Systems, TUM

Manipulating quantum information

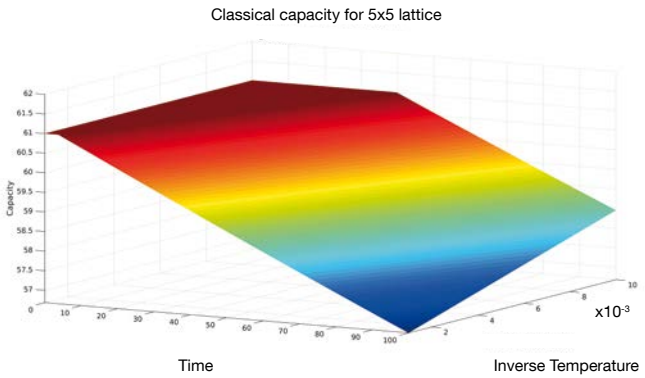
The Focus Group Theory of Complex Quantum Systems, established in 2015, pursues research at the intersection of physics, mathematics, and computer science. Our main objective is to develop quantitative methods applicable to quantum information processing. In particular, we seek to understand under what circumstances the use of quantum (instead of only classical) information provides significant operational advantages. To this end, we develop mathematical and information-theoretic tools that capture the essential features of quantum-mechanical systems.

Beyond the promise of quantum computers, quantum information theory is starting to play a central role in our modern approach to physical systems: Understanding the nature of quantum correlations in many-body systems provides significant structural insights and is key to exploiting these systems as platforms for information processing. A major challenge to be overcome is decoherence: Quantum information is intrinsically fragile and needs to be protected by suitably designed error-correction schemes. These introduce and maintain the redundancy required to protect against undesirable noise.

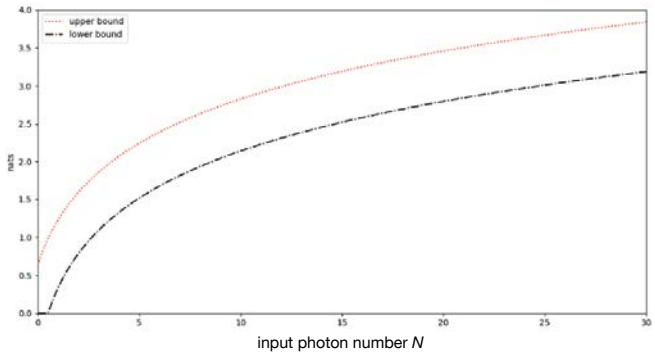
To harness certain quantum effects providing enhanced information-processing capabilities, a detailed quantitative understanding of the exact technological requirements is necessary. We study specific information-theoretic quantities of interest and investigate how they behave under typical dynamical processes. This can provide, for instance, information on the lifetime of an encoded qubit, giving an operational figure of merit for the comparison of different quantum memories.
A few areas of activity are the following:

Entropic inequalities for bosonic systems

Estimating the output entropy of a quantum channel is a central problem: Corresponding results can be used to characterize the classical capacity. The latter is a natural measure for the information-carrying capabilities of the channel. We have established bounds on the output entropy of non-Gaussian bosonic noise channels and applied these to communication. It is known that – for certain channels – the use of entanglement can increase communication capacities compared to the case where only classical correlations are used. Using our techniques, we have shown that this is not the case for the considered bosonic channels: any potential advantage resulting from the use of entanglement is negligible.



1 | **Preserving information in the toric code**
Quantum many-body systems can be used as quantum memories. A well-studied example is the toric code, a system of qubits arranged on a regular 2-D lattice. One may ask how long information stays encoded when the system is coupled to a thermal bath. The figure shows the classical capacity as a function of the inverse temperature and the storage time.



2 | **Communication capacities of non-Gaussian bosonic noise channels**
Bounds on the classical capacity of a beam-splitter channel with non-Gaussian environment: The maximal achievable rate (upper bound) resulting from the use of entanglement differs by at most an energy-independent constant from what is achievable with a coding strategy relying only on the use of classically modulated coherent states (lower bound).

Matrix analysis and entropies of finite-dimensional systems

One of the most fundamental statements in quantum information theory is the strong subadditivity or “data processing” inequality: It states – in a quantitative manner – the intuitive fact that information can only decrease under a given quantum evolution. Recently, a better quantitative understanding of this phenomenon has been obtained: A new inequality provides a bound on the amount of information that is lost. Closely related to these statements, we have developed a mathematical framework for the derivation of associated matrix inequalities: These are based on a generalized form a majorization, a certain fundamental relationship between density matrices of quantum states.

Quantum semigroups and their convergence rates

Estimating the convergence rate of quantum dynamical semigroups is central to the development of quantum algorithms based on Gibbs sampling ideas, and also to the study of the information-carrying capabilities of quantum systems under noise. We have developed technical tools to study the convergence rate of quantum dynamical semigroups under entropic distance measures and used them to estimate these rates for several cases of interest, such as quantum many-body systems coupled to a thermal bath. These include stabilizer Hamiltonians, a widely used class of models for quantum memories that encompasses important examples such as the toric code. From these convergence rates, it is then possible to estimate the lifetime of these memories depending on the temperature or how long it would take to prepare a quantum Gibbs state on a quantum computer.

Publications by this Focus Group can also be found in the section Publications of this report.

Publications

Publications

Advanced Computation and Modeling

Bio-Engineering and Imaging

Communication and Information

Control Theory, Systems Engineering and Robotics

Environmental and Earth Sciences

Fundamental Natural and Life Sciences

Gender and Diversity in Science and Engineering

Medical Natural Sciences

Surface, Interface, Nano- and Quantum Science

Advanced Computation and Modeling

Advanced Stability Analysis

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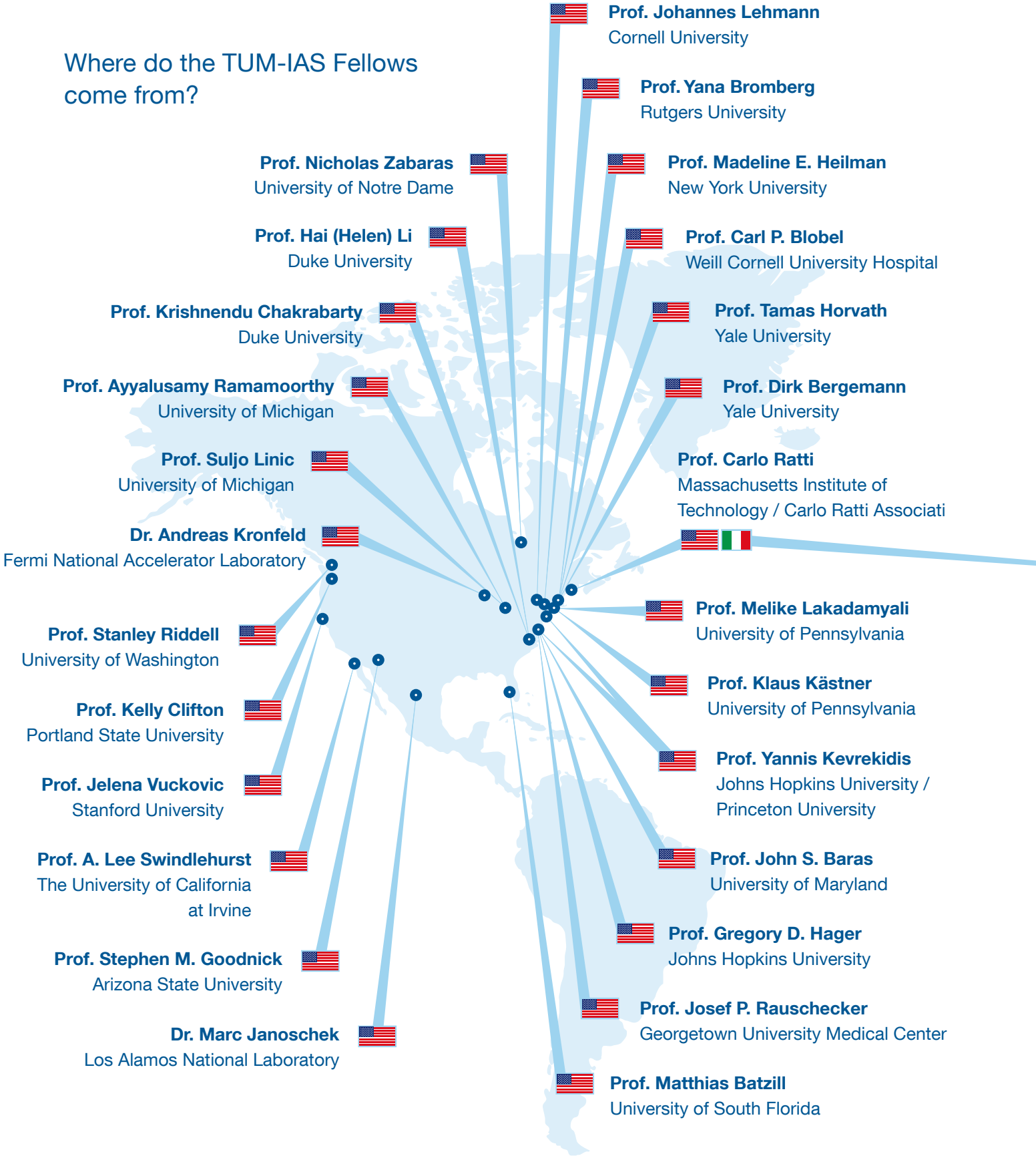
Facts and Figures

Where do the TUM-IAS Fellows come from?



Prof. Johannes Lehmann
Cornell University

Prof. Yana Bromberg
Rutgers University

Prof. Nicholas Zabaras
University of Notre Dame

Prof. Madeline E. Heilman
New York University

Prof. Hai (Helen) Li
Duke University

Prof. Carl P. Blobel
Weill Cornell University Hospital

Prof. Krishnendu Chakrabarty
Duke University

Prof. Tamas Horvath
Yale University

Prof. Ayyalusamy Ramamoorthy
University of Michigan

Prof. Dirk Bergemann
Yale University

Prof. Suljo Linic
University of Michigan

Prof. Carlo Ratti
Massachusetts Institute of Technology / Carlo Ratti Associati

Dr. Andreas Kronfeld
Fermi National Accelerator Laboratory

Prof. Melike Lakadamyali
University of Pennsylvania

Prof. Stanley Riddell
University of Washington

Prof. Klaus Kästner
University of Pennsylvania

Prof. Kelly Clifton
Portland State University

Prof. Yannis Kevrekidis
Johns Hopkins University / Princeton University

Prof. Jelena Vuckovic
Stanford University

Prof. John S. Baras
University of Maryland

Prof. A. Lee Swindlehurst
The University of California at Irvine

Prof. Gregory D. Hager
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Prof. Stephen M. Goodnick
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Prof. Josef P. Rauschecker
Georgetown University Medical Center

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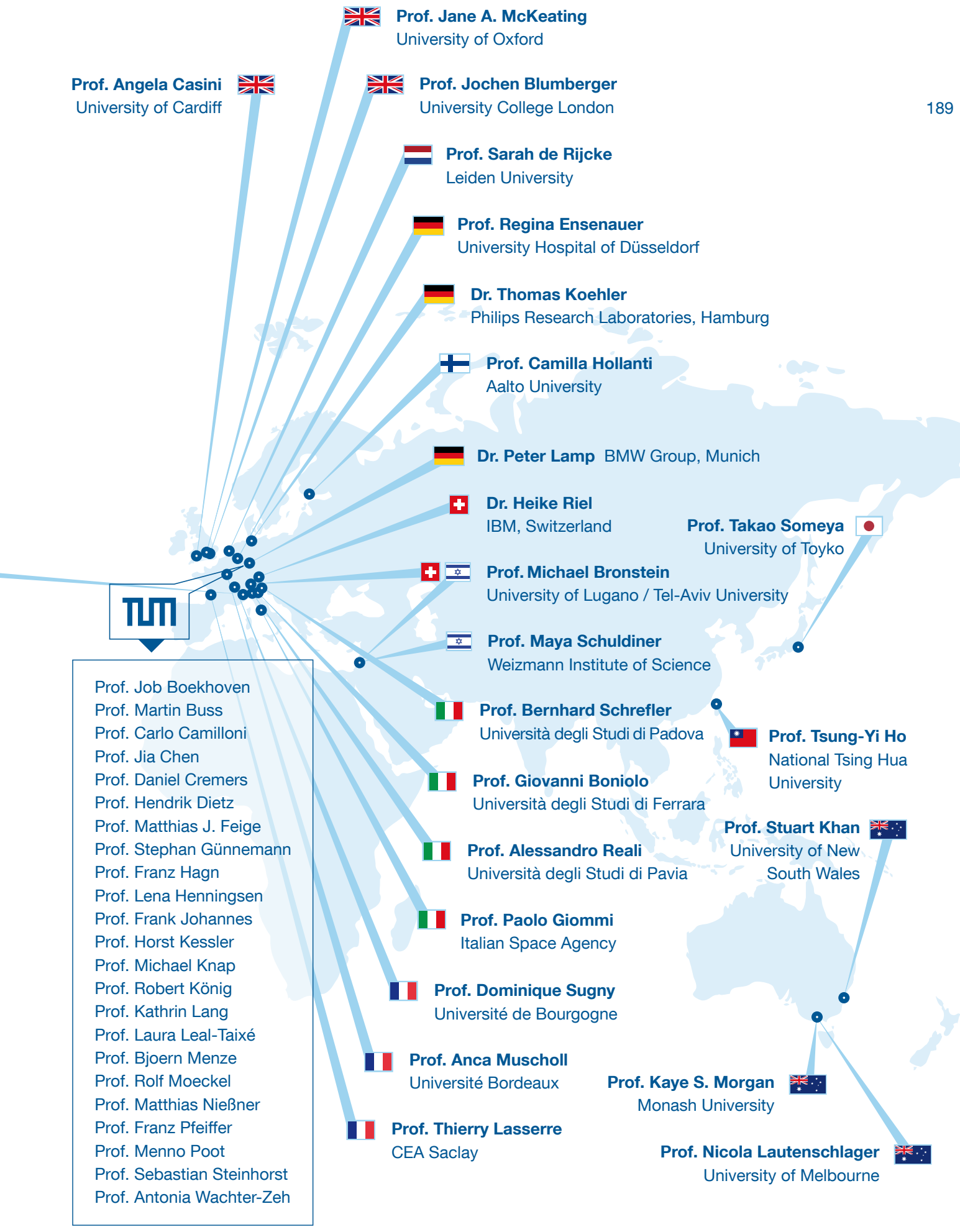
Los Alamos National Laboratory

Prof. Matthias Batzill
University of South Florida


Prof. Jane A. McKeating
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University Hospital of Düsseldorf
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Prof. Matthias Nießner
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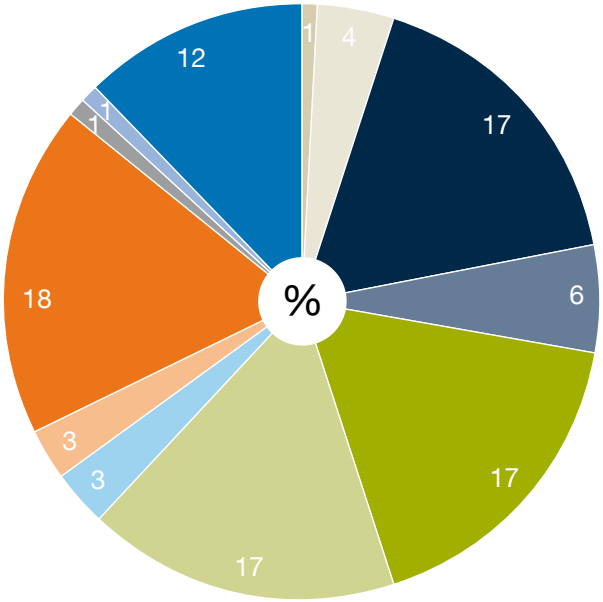
Prof. Antonia Wachter-Zeh

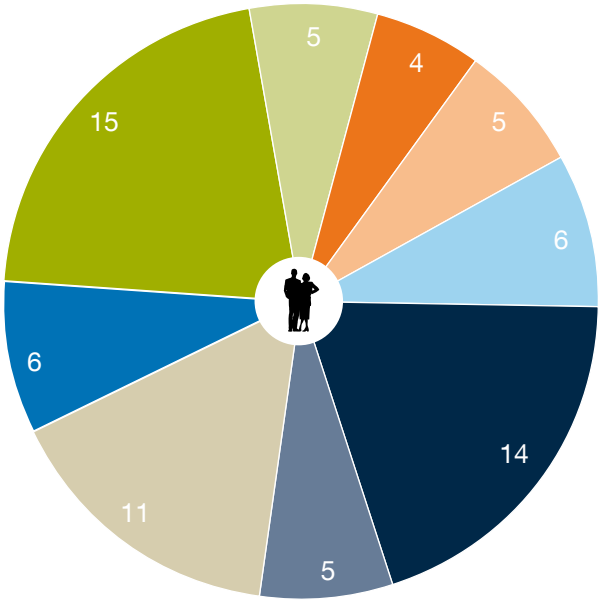
Fellow Distribution

Distribution of Active Fellows According to Faculties



- Architecture
- Center of Life and Food Sciences Weihenstephan
- Chemistry
- Civil, Geo and Environmental Engineering
- Electrical Engineering and Information Technology
- Informatics
- Mathematics
- Mechanical Engineering
- Physics
- Sports and Health Sciences
- TUM School of Management
- TUM School of Medicine

Distribution According to Research Areas



- Advanced Computation and Modeling
- Bio-Engineering and Imaging
- Medical Natural Sciences
- Communication and Information
- Control Theory, Systems Engineering and Robotics
- Environmental and Earth Sciences, Building Technology
- Fundamental Natural and Life Sciences
- Gender and Diversity in Science and Engineering
- Surface, Interface, Nano- and Quantum Science

Finances

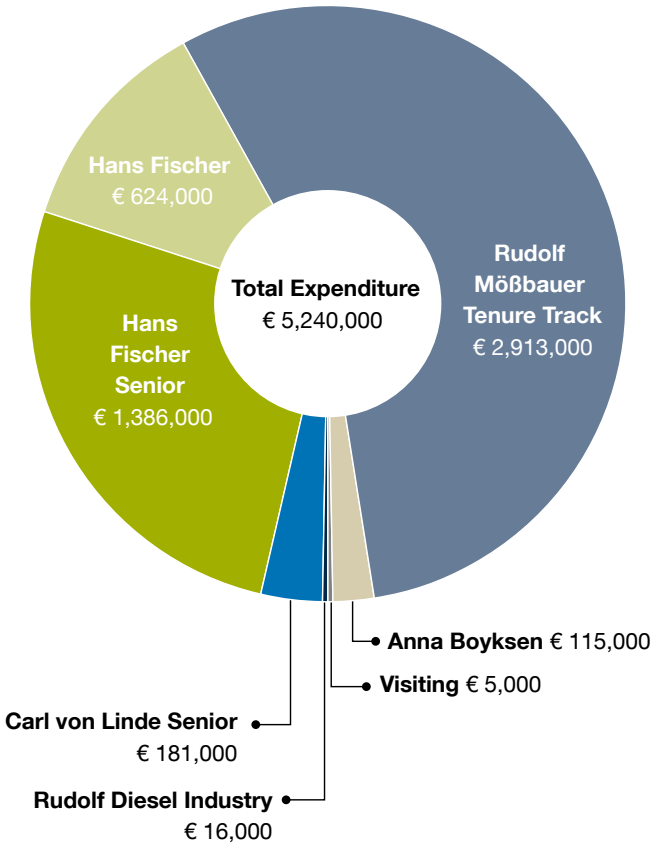
This section provides a brief overview of the financial data of the TUM-IAS. The expenditures are covered by the “third funding line” of the German Excellence Initiative, as well as by the European Union Seventh Framework Program (Marie Curie COFUND) and by the TÜV SÜD Foundation.

This chart illustrates the expenditure in 2017 for each Fellowship category. Most dominant in terms of costs (as has been the case since 2015) – with 55 percent of the total Fellowship expenditures – are the Rudolf Mößbauer Tenure Track Professorships. This program is devoted to the funding of outstanding, high-potential early-career scientists who have already achieved a major scientific or technological breakthrough, and who also have the ambition of developing a new field of endeavor when joining TUM (as a Tenure Track Assistant Professor). The program was only established in 2013 (five calls have been published between 2013-2017), and the financial data highlights the strong commitment to hiring these early-career talents as well as the significant investment the TUM-IAS makes in this Fellowship category.

The Hans Fischer Senior Fellowship comes in second in terms of costs and comprises 26 percent of the total expenditure for our Fellowship programs. These Fellowships represent an integral part of the TUM internationalization strategy and are immensely valuable in terms of the exchange of complementary expertise and the grooming of emerging fields.

In terms of costs, the Hans Fischer Fellowship remained at the same level as in 2016. The program was launched in 2013 as one of the latest additions to the TUM-IAS Fellowship program, and it has now attained a steady state. The fact that this program represents the third largest category of expenditures attests to its popularity and success.

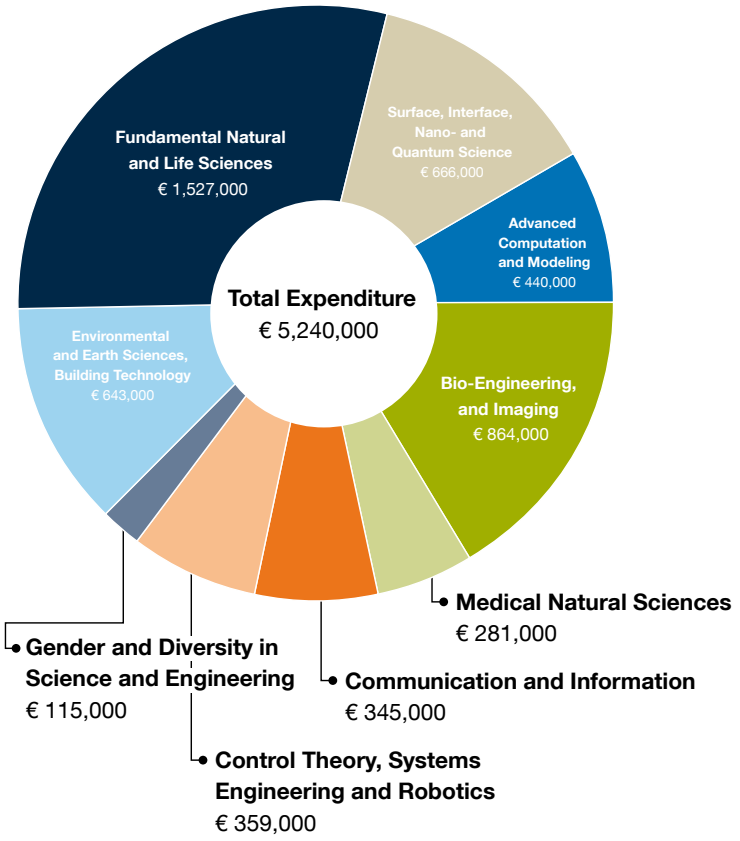
Expenditure per Fellowship Category in 2017



The Rudolf Diesel Industry Fellowship expenditures decreased in comparison to 2016, on the one hand because doctoral candidates are no longer financed in this category, and on the other hand because no Fellows were appointed in this category in the 2015 call and only one Fellow was appointed in the 2016 call.

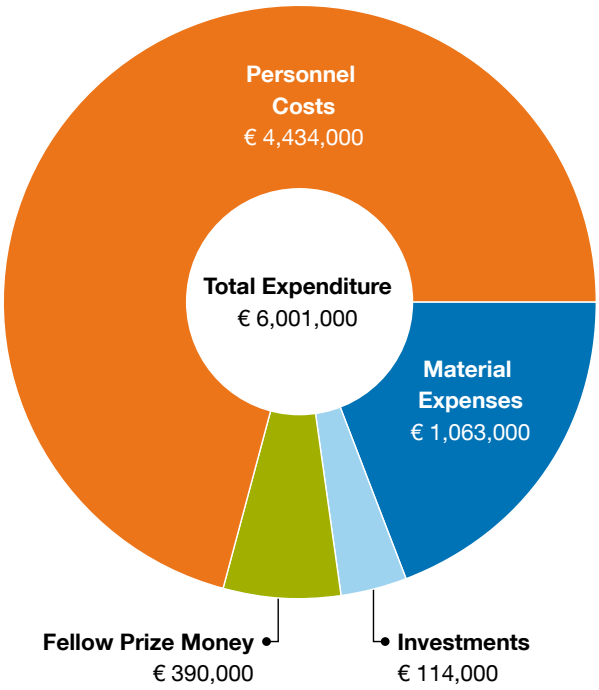
Expenditures in the Anna Boyksen Fellowship category, the newest addition to the TUM-IAS Fellowship roster when it was established in 2014, remain modest. Nevertheless, costs for this program have increased continuously and were twice as high in 2017 as in 2016.

Expenditure per Research Area in 2017



This chart shows the TUM-IAS Fellowship expenditures grouped into the TUM-IAS Research Areas, along with expenditures from the Start-up and Visiting Fellowship programs, which are also grouped according to Research Areas. Interdisciplinary projects were classified according to their most dominant field. The Research Area with the highest expenditures was Fundamental Natural and Life Sciences, reflecting a high number of Rudolf Mößbauer Tenure Track Professors and Hans Fischer Senior Fellows working in this field.

Total Expenditure in 2017



On this chart, total TUM-IAS expenditure is displayed, including Fellowships, Start-up funding, Visiting Fellowships, events, and management. The total expenditure increased in comparison to 2016 (€5,700,000) reflecting mainly the increase in the number of Rudolf Mößbauer Tenure Track Professors. The difference between the total expenditures per Fellowship category / Research Area and the total expenditure in 2017 is due to management and event expenses: €662,400 for management and €98,600 for event-related expenses.

Cover and inside cover: Pictures by TUM-IAS Carl von Linde Senior Fellow Prof. Hendrik Dietz (Biomolecular Nanotechnology, TUM).

4, 6, 10, 13 (Rank, Fischer, Steinberger, Adler, Schnekenburger), 21, 23, 27, 36, 39, 54, 76 (Wachter-Zeh, Hollanti), 84, 98 (Clifton), 118, 122, 132, 142, 148, 185: Astrid Eckert.

13 (Santos Kühn), 106 (Dietz): Astrid Eckert/Andreas Heddergott.

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13 (Seidel): Michel Buchmann.

13 (Sturm), 58, 68, 72 (Koehler, Pfeiffer), 78, 86 (Steinhorst), 96 (Chen), 97 (figure 2), 98 (Moeckel), 112, 124 (Hagn), 126 (Boekhoven), 130, 138, 146, 150, 158: Andreas Heddergott.

25 (poster): Brigitte Steinbüchler.

28 (poster), 30: Julie Rousset.

28–29 (pictures): Sarah de Rijcke/Leiden University.

31 (upper left): A. Brieden, P. Gritzmann, and F. Klemm, “Constrained clustering via diagrams: A unified theory and its application to electoral district design,” Eur. J. Oper. Res., no. 263, pp. 18–34, 2017.

31 (bottom left): Angewandte Chemie, WILEY-VCH.

31 (bottom right): Astrid Eckert/Andreas Heddergott.

38: TUM Corporate Communications Center.

42: Columba Microfluidic Biochip Tool/Tsun-Ming Tseng, Electronic Design Automation, TUM.

43–47, 49–50: Kurt Bauer.

59 (figures 1–2): Simulations by Chair for Computation in Engineering (TUM).

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Cover:
3-D printed model of a 1.2 gigadalton defined-size dodecahedron that integrates the equivalent of 220 DNA origami.

Inside cover:
3-D printed model of a designed protein-DNA hybrid origami.

Pictures by TUM-IAS Carl von Linde Senior Fellow Prof. Hendrik Dietz (Biomolecular Nanotechnology, TUM)

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