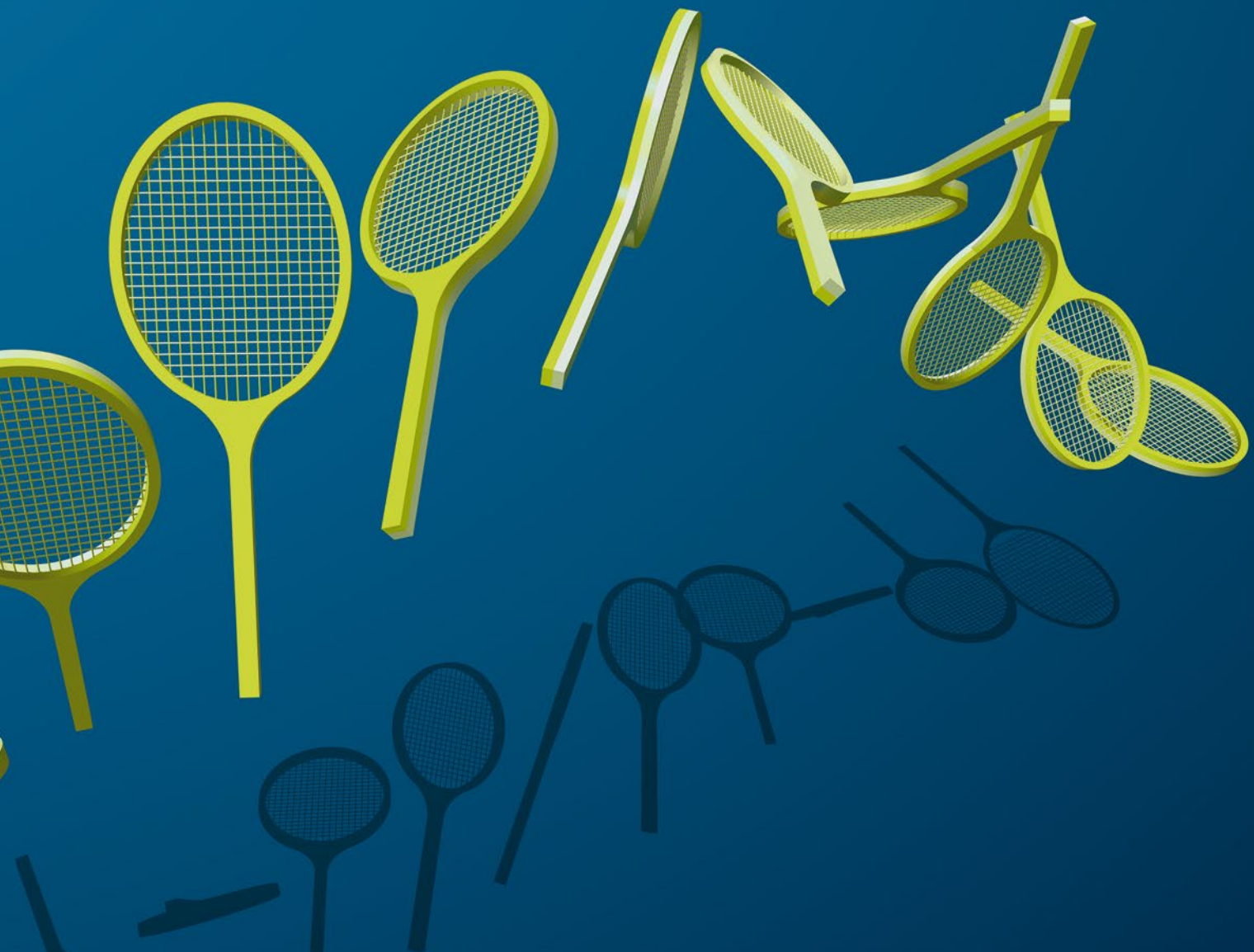
Annual Report

Technical University of Munich

Institute for Advanced Study

2018



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TUM President's Foreword

What a year 2018 was, full to the brim with events celebrating our university's 150th anniversary! Established on Easter Sunday(!) of 1868 by decree of the 23-year-old King Ludwig II, TUM is 150 years young, reinventing itself daily in the spirit of its initial impulse. That was, in the words of founding director Karl Max von Bauernfeind, "to bring the igniting sparks of science to the industrial and commercial world." As much as TUM and the times have changed, that devotion to education, innovation, and discovery in the service of society remains constant. The year 2018 was also marked by strenuous work above and beyond the usual, meaning practically around the clock, on our proposal for the third round of the Excellence Initiative of the federal and state governments.

It's a good thing that the TUM Institute for Advanced Study, founded as a central element of our strategy in the first round, has grown to be such a firm fixture in the landscape and life of the university. As TUM embarks on what may be the most profound transformation in its history – fortified, we hope, by a successful outcome in the Excellence Initiative competition – we can count on the TUM-IAS to serve as a steady hub amid the whirl of change. At the same time, it continues to serve as a beacon announcing the distinctive character of our university to the world: ever more international, diverse, interdisciplinary, and entrepreneurial.

Reform and growth have been the hallmarks of the past two decades, which brought us to an unquestioned position of leadership in Germany, prominence in Europe, and presence throughout the world. The international competition for talent and resources is merciless, though, and TUM is rising to the challenge with a new goal: to advance into the top league of elite universities worldwide.

In its broad outlines, our strategy for the coming years is guided by five objectives:

- further advances in gender- and diversity-equitable talent management
- a future-oriented, human-centered revitalization of "German Engineering" that will set new standards for responsible innovation
- promotion of dynamic scientific interactivity through interdisciplinary institutes – including new TUM-IAS Fellowships aimed at helping postdocs build up international networks, recruiting senior researchers with no previous TUM affiliation, and giving physicians more freedom to do research as "clinician scientists" – as well as powerful alliances, especially in and around Munich
- empowerment of our international network in teaching and research alliances that strengthen the university's profile, with renewed emphasis on the home continent of Europe and the often-neglected continent of the future, Africa
- renewal of university governance and administration, matching structures to strategy – for example, by organizing departments into an interwoven matrix system of schools – in the context of system integration, internationalization, and digitalization.

Since my time as President of TUM is drawing to a close, I will have to turn over the realization of this strategy to a new generation, and to a new leader in the tradition of Karl Max von Bauernfeind. Not only is my successor, Thomas Hofmann, a renowned scientist in his own right as well as our long-serving Vice President for Research and Innovation, but he also has a successful track record of championing and implementing reforms – notably the TUM Faculty Tenure Track and the comprehensive recruitment and career system introduced along with it. TUM's future is in good hands!

And just as the TUM-IAS has been a proving ground for many of the ideas that will now shape our future, I have no doubt that it will continue to provide leadership – as well as nurturing fellowship in the broadest sense – throughout the TUM community.

Prof. Wolfgang A. Herrmann
President

In December 2018, the funding period of the Marie Curie COFUND program of the European Commission drew to a close. For a total of six years (2012–2018), the COFUND program, intended to further education, mobility, and career development, has contributed 40% to the part of the TUM-IAS budget dedicated to its international incoming Fellows: Hans Fischer and Hans Fischer Senior Fellows, (international) Rudolf Diesel Industry Fellows, and Rudolf Mößbauer Tenure Track Professors. With these programs, the TUM-IAS seeks to attract researchers from industry as well as scholarly talent on senior and early-career levels from around the globe to establish intense international collaborations.

The Rudolf Mößbauer Tenure Track Professorship program was newly introduced with the beginning of the funding period and has proven to be a valuable tool to attract outstanding, high-potential early-career scientists to TUM, or, in a few cases, to keep them at TUM. This program offers merit-based academic career options that progress from the appointment as an assistant professor for six years through a permanent position as associate professor and on to full professor. Five calls for applications relevant for the funding period were published from 2012–2017, resulting in a total of more than 800 applications and 20 appointments. The Rudolf Mößbauer Tenure Track Professors were placed in eight different TUM departments; several of them hold joint appointments with a second TUM department due to the highly interdisciplinary character of their research. One of the first candidates (appointed in 2013) is scheduled for the tenure evaluation in 2019.

Furthermore, international teams (Focus Groups) were formed combining TUM competences (associated with TUM Hosts) with the external, international expertise of Hans Fischer (Senior) Fellows and with the industry knowledge of Rudolf Diesel Industry Fellows. Within the reporting period, six calls for applications were published, attracting a total of more than 150 applications and resulting in the appointment of 51 Fellows. These Fellows are hosted by 11 TUM departments and come from home institutions in 11 countries in Asia, Australia, Europe, Latin America, and North America, thus distinctively contributing to the internationalization of TUM. The newly appointed Fellows have not only strengthened research efforts on already existing research topics at the Institute, but also have established new fields of research including genomics, environmental sensing and modeling, multi-messenger astrophysics, biomarkers for prenatal stress, and data-driven dynamical systems analysis in fluid mechanics.

The number of scientific publications in high-impact international journals as well as contributions to conferences is often used as a measurement for the performance of a research institution. A great many research papers (more than 1800 for the years 2013–2018) have been published in journals such as Science and Nature, as well as in various other journals from the Science and Nature families, Cell, Advanced Materials, ACS Nano, Angewandte Chemie Int. Ed., Numerische Mathematik, Computer Methods in Applied Mechanics and Engineering, and many others.

In addition, the TUM-IAS organized exploratory workshops, international conferences, and summer schools, such as the annual “Munich Battery Discussions” (in cooperation with BMW Group, with around 150 participants each year) or various workshops on topics such as “Big Data and Predictive Computational Modeling” (2015), “Quantum Control Theory” (2017), “Rethinking Soil Carbon Modeling” (2018), and “Smart Skins” (2018), to name just a few of the roughly 400 events that were organized by TUM-IAS Focus Groups within the COFUND funding period. The TUM-IAS building offered a platform for scientific exchange and networking, serving as an intellectual center for TUM-IAS members who wished to organize top-class scientific events.

We cannot thank the COFUND program enough for its substantial contribution to the Institute’s development and success over the past six years, and we will certainly look out for further opportunities to collaborate once again with the European Commission.

Prof. Ernst Rank
Director

People


150 Jahre
culture of
excellence
150 Jahre
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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.

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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. Dr. med. Markus Schwaiger TUM, University Hospital Klinikum rechts der Isar, Medical Director
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

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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
Nonequilibrium Chemical Physics
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Max Planck Institute of Quantum Optics - Quantum Dynamics Group
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Electronic Design Automation
Prof. Chris-Carolin Schön
Plant Breeding
Prof. Daniel Straub
Engineering Risk Analysis Group
Prof. Barbara Wohlmuth
Chair of Numerical Mathematics, Director IGSSE

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Prof. Ernst Rank
Director

Dr. Ana Santos Kühn
Managing Director
(leave of absence since 04/2018)

Tatjana Steinberger
Acting Managing Director

Anna Kohout
Program Manager

Eva Pettinato
Program Manager

Dr. Susanne Wahler
Program Manager

Annette Sturm
Senior Event Manager /
Web Coordinator

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

Anja Adler
Secretary / Guesthouse
Coordination

Isabella Schnekenburger
Secretary / Building
Coordination

Dr. Agnes Limmer
Program Manager of IESP

Jessica Westermayr
Assistant of IESP

Fellows

Anna Boyksen Fellows

2016 Prof. Nicola Lautenschlager
2018 Dr. Sara Lucatello, Prof. Nina A. Mayr

Amalie Baur Fellow

2017 Prof. Lena Henningsen

Carl von Linde Senior Fellows

2016 Prof. Hendrik Dietz
2017 Prof. Daniel Cremers
2018 Prof. Bernhard Küster

Hans Fischer Senior Fellows

2013 Prof. Jelena Vuckovic
2014 Dr. Andreas Kronfeld
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
2018 Prof. Marta Cristina Antonelli, Prof. Leonidas Guibas, Prof. Noelle Eckley Selin, Prof. Henrik Selin

Hans Fischer Fellows

2014 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
2018 Dr. Angel X. Chang, Dr. Luca Magri, Prof. Robert Schmitz

Rudolf Diesel Industry Fellows

2015 Prof. Carlo Ratti
2017 Prof. Michael Bronstein
2018 Dr. Mirko Bothien, Dr. Filippo Maglia

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. 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, Prof. Kathrin Schumann
2018 Prof. Reinhard Heckel

Alumni Fellows

Anna Boyksen Fellows

2014 Prof. Madeline Heilman
2015 Prof. Giovanni Boniolo, Prof. Regina Ensenauer, Prof. Sarah de Rijcke

Carl von Linde Senior Fellows

2007 Prof. Andrzej Buras, Prof. Arthur Konnerth, Prof. Reiner Rummel
2008 Prof. Horst Kessler, Prof. Claudia Klüppelberg
2009 Prof. Axel Haase
2010 Prof. Ulrich Stimming, Prof. Gerhard Abstreiter
2011 Prof. Ingrid Kögel-Knabner
2013 Prof. Annette Menzel
2014 Prof. Martin Buss
2015 Prof. Franz Pfeiffer

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. Stanley Riddell, 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. Stephen M. Goodnick, Prof. Dietmar W. Hutmacher, Prof. Josef P. Rauschecker
2013 Prof. Harald Brune, Prof. Zvonimir Dogic
2014 Prof. John S. Baras, Prof. Dirk Bergemann, Prof. Gregory D. Hager, Prof. Tamas Horvath, Prof. A. Lee Swindlehurst, Prof. Nicholas Zabaras

Hans Fischer Fellows

2012 Prof. George Biros, Prof. Franz Hagn
2013 Prof. Matthias Batzill, Dr. Christian Hirt
2014 Prof. Yana Bromberg, Prof. Tsung-Yi Ho, Prof. Stuart Khan

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
2013 Dr. Thomas Koehler, Dr. Peter Lamp
2014 Dr. Norman Blank, Dr. Heike Riel

Rudolf Mößbauer Tenure Track Professor

2013 Prof. Alessio Zaccone
2015 Prof. Carlo Camilloni

Honorary Fellows 2018

Alexander von Humboldt Professor

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

Alexander von Humboldt Research Awardee

Honorary Hans Fischer Senior Fellow

Prof. George Em Karniadakis | Brown University

ERC Grantees

Prof. Matthias Althoff | Cyber Physical Systems, TUM
Prof. Andreas Bausch | Cellular Biophysics, TUM
Dr. Li Deng | Institute of Virology, TUM
Prof. Dr. Karl Duderstadt | Structure and Dynamics of Molecular Machines, TUM
Prof. Dr. Julijana Gjorgjieva | Computational Neurosciences, TUM
Prof. Dr. Danny Nedialkova | Biochemistry of Gene Expression, TUM
Prof. Matthias Nießner | Visual Computing, TUM
Prof. Andreas Pichlmair | Viral Immunopathology, TUM
Prof. Roland Rad | Institute of Molecular Oncology and Functional Genomics, TUM
Prof. Antonia Wachter-Zeh | Coding for Communications and Data Storage, TUM
Prof. Dr. Majid Zamani | Hybrid Control Systems, TUM

August-Wilhelm Scheer Visiting Professors

Dr. Bill Addis | University of Cambridge
Prof. Ayush Bhandari | Imperial College of Science Technology and Medicine
Prof. Jörg Bohlmann | University of British Columbia
Dr. Sirén Charlotta | University of St. Gallen
Prof. Subhasis Chaudhuri | Indian Institute of Technology Bombay
Prof. Gabor Csanyi | University of Cambridge
Prof. Nagwa Elkhafif | Theodor Bilharz Research Institute
Prof. Fabian Filipp | University of California
Prof. Melina A. Freitag | University of Bath
Prof. Shanti Gamper-Rabindran | University of Pittsburgh
Prof. Vidhan Goyal | The Hong Kong University of Science and Technology
Prof. Hongyun Han | Zhejiang University

Dr. Rianne Lord | University of Bradford
Prof. Dimitris Milakis | Technische Universiteit Delft
Prof. Mohamed Nour | Helwan University
Prof. Andrei Osterman | Sanford-Burnham-Prebys Medical Discovery Institute
Prof. Wolfgang Pantleon | Danmarks Tekniske Universitet
Prof. Thomas Pyszczynski | University of Colorado at Colorado Springs
Prof. Carlos Quesada | Instituto Nacional de Pesquisas da Amazonia
Prof. Alfons Schulte | University of Central Florida
Prof. Mathias O. Senge | Trinity College Dublin
Prof. Nic Shannon | Okinawa Institute of Science and Technology Graduate University
Prof. Yiyu Shi | University of Notre Dame
Prof. Jayant Sirohi | University of Texas at Austin
Prof. Raffaele Spinelli | National Research Council of Italy
Prof. Michael Strickland | Kent State University
Prof. Alejandro Tirachini | Universidad de Chile
Prof. Elaine M. Urbina | Cincinnati Children's Medical Hospital
Prof. Ramona Vogt | University of California, Davis
Dr. Tatjana C. Vollmer | Kopvol Architecture & Psychology
Prof. Peng Zhang | University of Connecticut
Prof. Shuguang Zhang | Beihang University
Dr. Zhenbin Zhang | Shandong University

Visiting Fellows 2018

Prof. Frank H. P. Fitzek | Technische Universität Dresden
Prof. Gernot Kubin | Graz University of Technology
Prof. Hideaki Yamamoto | Tohuko University

Activities and Events

TUM-IAS General Assembly

June 5–6, 2018

The venue for the General Assembly, which this year has already been held for the tenth time, was our beautiful headquarters on the Garching campus. For two days, our building was filled with Fellows and members of TUM-IAS who otherwise are spread all over the world. Over 100 participants from various disciplines took advantage of the opportunity to hear about progress in the Focus Groups and TUM-IAS projects, to engage in lively discussions, and to exchange experiences and ideas with new members and old acquaintances.

As always, the talks came from scientific areas that were as interdisciplinary as the TUM-IAS itself, including topics such as illegal entertainment fiction during the Chinese cultural revolution, challenges in post-quantum cryptography, air pollution and climate change, or the restless legs syndrome. A poster presentation in which most of our doctoral candidates took part offered a colorful overview of the work of our Focus Groups, giving participants and visitors alike the chance to meet scientists from related fields as well as to learn more about developments and results in wholly different areas of research.

During the General Assembly's conference dinner, which took place in the distinctive Faculty Club on the top floor of the TUM-IAS, TUM President and TUM-IAS Board of Trustees chair Prof. Wolfgang A. Herrmann used the festive occasion to hold a laudatory speech on our Alumnus Hans Fischer Senior Fellow Prof. Carl Blobel who was awarded the honorary title "TUM Distinguished Affiliated Professor." This award distinguishes leading international scientists who are working at other universities, advancing a scientific area, and developing long-term collaborations with their colleagues at TUM. Moreover, as has been tradition since the founding of the Institute, the new members of the TUM-IAS community were announced and their certificates were presented.


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TUM


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150

Program

Illegal Entertainment Fiction from the Chinese Cultural Revolution and the Rise of Science in Post-Mao China
Lena Henningsen | Amalie Baur Fellow

Senseable Cities
Carlo Ratti | Alumnus Rudolf Diesel Industry Fellow

Planning for Pedestrians in an Automated and Connected Future
Kelly Clifton | Hans Fischer Senior Fellow

Challenges in Post-Quantum Cryptography
Antonia Wachter-Zeh | Rudolf Mößbauer Tenure Track Professor

Understanding and Engineering How Cells Make Immune Proteins
Matthias Feige | Rudolf Mößbauer Tenure Track Professor

iRhoms and ADAM17: Molecular Scissors with Key Roles in Inflammation and Growth Factor Signaling
Carl Blobel | TUM Distinguished Affiliated Professor and Alumnus Hans Fischer Senior Fellow

Soft-Tissue-Sensitive X-ray Imaging: From the Synchrotron to the Laboratory
Kaye Morgan | Hans Fischer Fellow

Biomechanical Modeling of the Spine to Predict Back Pain: Challenges and Initial Results
Jan Kirschke | Neuroradiology, TUM

Decentralized Internet of Things and Cyber-Physical System Architectures – Disruption Ahead!
Sebastian Steinhorst | Rudolf Mößbauer Tenure Track Professor

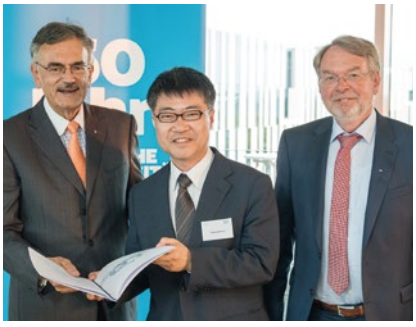
Can Computers Learn Physics by Example?
Nils Thuerey | Games Engineering, TUM

Air Pollution and Climate Change: A Sustainability Challenge
Noelle Eckley Selin | Hans Fischer Senior Fellow

Genetic Architecture of Widespread Diseases: Restless Legs Syndrome
Juliane Winkelmann | Neurogenetics, TUM

Closing Remarks
Ernst Rank | TUM-IAS Director


Online counselling for
dementia



First International Workshop on Smart Skins

November 19–20, 2018
Organization: Focus Group Artificial Electronic Skin

Smart skin is an emerging research field that realizes electronic functionalization of human skins and/or machine surfaces. By using newly developed stretchable and soft electronics, multiple electronic functions are being introduced on three-dimensionally curved surfaces and creating new applications ranging from health monitoring to the control of machines in human-machine interfaces such as a prosthetic hand. In particular, skin is the ultimate place to non-invasively introduce electronic functions, and therefore smart skin is an ideal solution to achieve non-invasive long-term monitoring of health conditions for personalized medicine and medical treatments in the future. On the other hand, an interactive surface of machines is one of the essential elements to equip robots to work cooperatively with people in their daily life. Thus, animal skin-like large-area sensors and actuators are needed to increase opportunities to use robots. Although great advances in smart skins have been reported recently, many challenges remain. These include system integration, reliability issues, and robust data analysis. Indeed, individual elements of smart skins have been intensively investigated, and it is time to emphasize more system-level integration and data analysis in identifying specific applications. Due to multidisciplinary features of smart skin, it is important to enhance collaboration among researchers in diverse research fields including electronics, mechanical engineering, computer science, materials science, chemistry, biology, medicine, and dermatology.

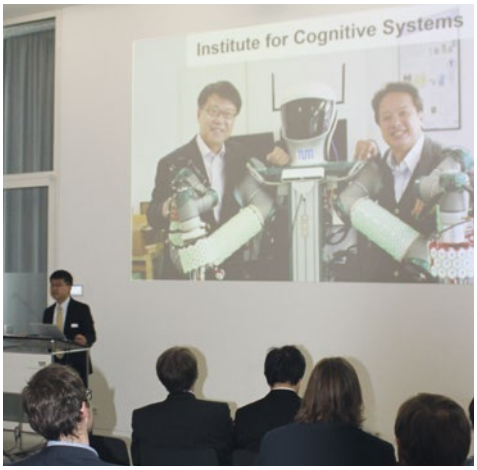
Following up on this idea, speakers at the event covered a broad range of topics: skin for robots, stretchable thin-film electronics, wearable sweat sensors, encoding and use of tactile afferent information in the control of manual dexterity, soft electronic and microfluidic systems for the skin, and so-called E-dermis to mimic the epidermis of the human skin. The First International Workshop on Smart Skins took place on November 19 and 20, 2018 in Munich, with around 30 participants from around the world.

Workshop program:
https://www.ias.tum.de/en/event-pages/smartskin2018/program/

The speakers of the Smart Skin Workshop, with TUM-IAS director Prof. Ernst Rank (fourth from the left).

Left: The consul general of Japan in Munich, Tetsuya Kimura, opened the workshop.

Right: TUM IAS Hans Fischer Senior Fellow Prof. Someya during his talk.



Poster session and discussion in the coffee breaks.

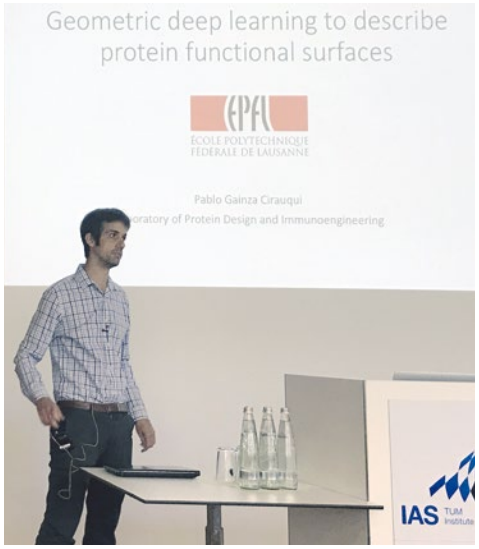
International Workshop: Machine Learning for 3D Understanding

July 2–4, 2018
Organization: Focus Group Computer Vision and Machine Learning

In the summer of 2018, the TUM-IAS hosted an interdisciplinary workshop on Machine Learning for 3D Understanding, bringing together some of the world's leading experts in both fields. The event was organized by Daniel Cremers (Professor at TUM and TUM-IAS Carl von Linde Senior Fellow), Michael Bronstein (Professor at Imperial College and USI Lugano, Principal Engineer at Intel, and TUM-IAS Rudolf Diesel Industrial Fellow), Leonidas Guibas (Professor at Stanford University and TUM-IAS Hans Fischer Senior Fellow), and Lourdes Agapito (Professor at UCL).

The program included invited talks from 23 speakers coming from all over the world, focusing on the interplay of geometry and machine learning and covering a broad range of topics, from large-scale point cloud analysis for autonomously driving cars and face modeling to protein design and structure prediction. A special emphasis in the workshop was placed on promoting young scientists, with about half of the talks delivered by early-career researchers (doctoral candidates, postdocs, and assistant professors). The workshop also tried to strike a balance between theoretical and applied research, and it included speakers from both leading academic institutions such as Stanford, Harvard, UCL, TUM, and Imperial College and industry (Google, Facebook, Intel).

The workshop was opened by Prof. Matthias Nießner (Rudolf Mößbauer Tenure Track Professor at TUM and TUM-IAS Fellow) who, together with a junior scientist, Angel Dai from Stanford, presented the recent progress on 3D scene analysis in computer vision using machine learning techniques. Hao Li (University of Southern California and Pinscreen) showed the use of deep learning techniques for photorealistic human digitization and rendering, and Stefanos Zafeiriou (Imperial College) gave an overview of past and present work on deformable models for human face analysis. Peter Claes (KU Leuven) presented the work of his group and his collaborators on facial genetics, culminating with a near-science fiction task of predicting facial features from genetic variations, or "face-from-DNA."



Dr. Pablo Gainza-Cirauqui from EPFL, Switzerland presenting on protein design using geometric deep learning at the TUM-IAS Workshop on Machine Learning for 3D Understanding held in July 2018 in Garching.

Among other highlights of the workshop, Mohammed AlQuiraishi (Harvard) showed the use of deep learning methods for predicting the 3D structure of protein molecules (“protein folding”), work that preceded the later highly publicized milestone result from DeepMind. Pablo Gainza-Cirauqui (EPFL) presented the use of geometric deep learning (developed together with the group of Michael Bronstein) for the construction of functional proteins that can target a broad number of therapeutic goals, potentially leading to a new generation of biologic drugs against cancer and other diseases.

The workshop was a success and saw attendance by TUM students and faculty. The relaxed and informal atmosphere of the TUM-IAS gave the participants an opportunity for high-quality interaction. The interdisciplinary nature of the gathering led to multiple insights across fields and sparked several successful collaborations.

International Workshop: Re-Thinking Global Soil Carbon Modeling

October 1–4, 2018
Organization: Focus Group Soil Architecture

During a beautiful Fall week in a spectacular retreat, 12 participants from Austria, France, Germany, Sweden, and the US critically examined the state of global carbon modeling. Against the scenic backdrop of TUM's conference center at Raitenhaslach monastery, ideas flowed freely throughout late-night sessions and morning walks along the river Salzach. The breadth of scientific expertise – ranging from forest ecologists to global ecosystem and soil carbon modelers, soil ecologists, biogeochemists, oceanographers, and environmental engineers – provided an unusual opportunity for cross-disciplinary insights. The group developed exciting new avenues to re-imagine global prediction of soil carbon changes in response to climate change and ever greater demand for food production with less negative environmental tradeoff. Borrowing concepts from microbial ecology and modeling of pollutant transport, the team identified ways to describe soil functional complexity for scaling.

The very generous and spacious rooms became plastered with drawings, sketches and graphics illustrating concepts about how to represent molecular changes and microbial ecology that occur at very small scale for a global model. Step changes in science do benefit from the type of intellectual collisions that long and uninterrupted conversations away from the office allow. Such collisions spark new ideas and allow participants to change their views. New perspectives and a chance to "reboot" were also provided by climbing the world's longest castle (or so the local advertisement promises) in nearby Burghausen. And while much work remains to be done toward defining a compelling concept and casting it in a high-impact publication, the face-time at Raitenhaslach was a catalyst that may also prove to be the most memorable and enjoyable part of doing interdisciplinary research.

Participants visiting nearby Burghausen.

Participants at a retreat on re-thinking soil carbon modeling in Raitenhaslach: Christina Kaiser, University of Vienna, Austria; Colleen Hansel, Woods Hole Oceanographic Institution, USA; Ingrid Kögel-Knabner, Technical University of Munich; Josh Schimel, UC Santa Barbara; Kate Maher, Stanford University; Johannes Lehmann, Cornell University; Margaret Torn, UC Berkeley; Markus Kleber, Oregon State University, Corvallis, USA; Markus Reichstein, Max Planck Institute for Biogeochemistry, Jena, Germany; Naoise Nunan, Centre National de la Recherche Scientifique, Grignon, France; Stefano Manzoni, Stockholm University, Sweden; Will Wieder, National Center for Atmospheric Research, Boulder, USA.

Liesel Beckmann Symposium: Technology, Cognition, and Dementia

December 12, 2018
Organization: Focus Group Modern Technology to Support Cognitive and Mental Health

The 2018 Liesel Beckmann Symposium was held on December 12 at the University Hospital Klinikum rechts der Isar, and in line with the central theme of this symposium series, we emphasized diversity. In line with the theme of our Focus Group, we were interested in coming together and discussing how the diverse needs of older people who experience cognitive changes could be supported by modern technology. Diverse local, national, and international speakers from various professional backgrounds exchanged their knowledge and ideas, ranging from research into theoretical and ethical concepts to the implementation of new technologies to support care and the quality of life. After a welcome from Prof. Janine Diehl-Schmid (TUM, Center for Cognitive Disorders at the Department of Psychiatry, University Hospital Klinikum rechts der Isar), Prof. Nicola Lautenschlager (University of Melbourne, TUM-IAS Anna Boyksen Fellow) chaired four diverse talks presented in English.

Prof. Gordon Cheng (TUM, Chair of Cognitive Systems) focuses in his research on humanoid robots. As an engineer he is interested in how robots can learn new skills to be able one day to support older people in their homes, potentially extending the length of time they can live independently. Alongside the practical challenges of developing a humanoid robot that can move, see, and communicate on a sophisticated level, Prof. Cheng's research uses semantic reasoning to investigate how best to teach a robot new skills (e.g., helping in the kitchen) via the steps of observing, interpreting, and replicating actions. Future scenarios in which humanoid robots could offer support in the health and age care sector are abundant.

The second presentation was by Dr. Henriëtte van der Roest (ZorgDNA Utrecht), a social psychologist whose research focuses on the quality of long-term care and assistive technology for people with dementia, as well as for their caregivers. She gave an overview on assistive technology for dementia, a rapidly growing research field where technologies including integrated systems such as smart houses, robots, mobile devices, applications, and sensors are investigated in the context of daily living, cognition, emotional and mental health, and physical mobility. This type of research needs to go through various steps focusing on development, usability, effectiveness, deployment, and ethics, adapting to address users' limitations and needs. It also has to get the "consumers" of assistive technologies involved in the research process from the outset. Much more research is needed to determine clinical benefits and cost-effectiveness.

Top left: Prof. Hans Förstl (Head of Department of Psychiatry and Psychotherapy at TUM)

Top right: Dr. Henriëtte van der Roest (ZorgDNA Utrecht)

After presentations from Prof. Hans Förstl (Head of Department of Psychiatry and Psychotherapy at TUM) and Prof. Alexander Kurz (Professor of Psychiatry at TUM and the University Hospital Klinikum rechts der Isar) on aspects of philosophy and ethics with regard to modern technology, the second part of the symposium was held in German and consisted of six short presentations showcasing research projects aiming at practical implementation of technology to improve quality of life and care for people with cognitive impairment and their caregivers. The symposium was well attended by a diverse audience including researchers, clinicians, and students. There were lively discussions throughout the symposium, as well as during the coffee break and the concluding get-together. This encouraged us, confirming that the theme of our Focus Group is of interest to many who are passionate about improving the lives of people with cognitive impairment and their caregivers.

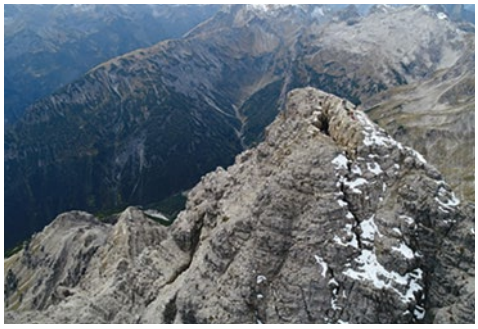
The TUM-IAS “Neighbors” Lecture Series: So what exactly is it that you do in Garching?

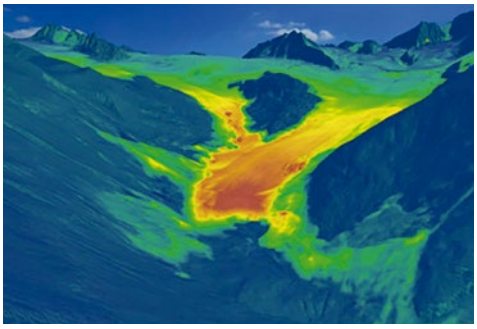
A peek behind the scenes at work being done by researchers in Garching

It all started in 2013 with a question the former Institute Director, Prof. Gerhard Abstreiter, was always getting from the area locals: “So what exactly is it that you do at the Garching campus?” In response to this, he came up with the new concept of the TUM-IAS “Neighbors” series, aimed at getting the local community and people 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 (in German) by a well known scientist from the university or from one of our campus neighbors, with the aspiration of making their work accessible to the diverse, general-public audiences in attendance. In around 45 to 60 minutes, the listeners – consisting of a 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 gain new 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 2018 the scope of topics ranged from harnessing nuclear physics for medicine to understanding natural hazards and their risks, as well as addressing timely issues such as fake news and pilotless aircraft.





January 28 — Lecture Series Neighbors in Garching
Magnetic Moments – Nuclear Spin in Research and Medicine
Organization: TUM-IAS
Speaker: Prof. Franz Hagn (Structural Membrane Biochemistry, TUM)

May 6 — Lecture Series Neighbors in Garching
Fake News: The Manipulation of Videos and the Role of Artificial Intelligence
Organization: TUM-IAS
Speaker: Prof. Matthias Nießner (Visual Computing, TUM)

July 15 — Lecture Series Neighbors in Garching
Alpine Natural Hazards and the Outlook for Prediction
Organization: TUM-IAS
Speaker: Prof. Michael Krautblatter (Landslide Research, TUM)

December 9 — Lecture Series Neighbors in Garching
Air Taxis and Pilotless Aircraft
Organization: TUM-IAS
Speaker: Prof. Florian Holzapfel (Flight System Dynamics, 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 ranged from biology and medicine to studies of our place and our practices on planet Earth – including not only discoveries enabled by new technologies, but also critical insights into the techniques themselves. As always, talks were pointedly geared toward communicating new ideas with an audience of 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 8
Computational Biochemistry - A Molecular Microscope for Biology
Prof. Ville Kaila | Computational Biocatalysis, TUM

March 8
Bits of Geography: Challenges of Geographic Information Science
Prof. Michael Frank Goodchild | Emeritus Professor of Geography, University of California, Santa Barbara

April 9
Elementary, My Dear Watson - Gene Detectives in Action
Prof. Maya Schuldiner | Hans Fischer Senior Fellow

July 9
Dynamic Vision and Learning
Prof. Laura Leal-Taixé | Rudolf Mößbauer Tenure Track Professor

October 8
A Model for Tumor Growth and Drug Delivery
Prof. Bernhard Schrefler | Hans Fischer Senior Fellow

November 5
Visualizing Biology at the Nanoscale Level
Prof. Melike Lakadamyali | Hans Fischer Fellow

December 13
Sustainability Transitions: Insights from 5000 Years of Human Use of Mercury
Prof. Henrik Selin | Hans Fischer Senior Fellow

Scientists Meet Scientists – Wednesday Coffee Talks

The Wednesday Coffee Talks seem to have become one of the best-known and most popular activities of the TUM-IAS: Under the responsibility of the Institute's Director Prof. Ernst Rank, the Coffee Talks are held weekly after lunch in the spacious atrium on the first floor of the building. They provide a platform for outstanding TUM publications, 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, profits in turn 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. What we especially like about this event, besides bringing together Fellows and guests who are currently in the area, is that it has brought in plenty of new faces with no prior relation to the TUM-IAS, often entering our building for the first time for this occasion. Again in 2018, we had very interesting talks with topics ranging from measuring the earth's rotational movement from the Bavarian countryside to producing sensors with an inkjet printer, 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 10	Prof. Michael Bader on new insights into the 2004 Sumatra megathrust earthquake
January 17	Prof. Ulrich Schreiber on measuring the earth's rotational movement from the Bavarian countryside
January 24	Prof. Gil Westmeyer on the new NeuBtracker open-source microscope
January 31	Dr. Hans-Gregor Hübl on a new spin on electronics
February 7	Prof. Tom Nilges on electrode materials from the microwave oven
April 11	Prof. Ernst Rank on computational structural analysis directly from photographs
April 18	Prof. Franz Pfeiffer on histology in 3D
April 25	Dr. Jan Christian Habel on insect die-off: even common species are becoming rare
May 2	Prof. Horst Kessler on a breakthrough for peptide medication
May 16	Prof. Ulrich Gerland on how bacteria adapt to different environments
May 23	Prof. Camilla Hollanti on private information retrieval
May 30	Dr. Ralph Gilles on the faster filling of lithium-ion cells

June 13	Prof. Thomas Brück on biotechnologically produced building blocks for chemistry and biodegradable synthetics
June 20	Dr. Klaudius Henke on 3D printing in concrete
June 27	Dipl.-Ing. Moritz Mungenast on custom building envelopes straight from the printer
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 2018

January 15 — **TUM-IAS Winter Faculty Day**

February 19–20 — Munich Battery Discussions **Next Generation of Li-Ion Batteries: Lifetime and Safety Perspectives of Achieving the Energy Targets?**
Organization: Dr. Peter Lamp | Alumnus Rudolf Diesel Industry Fellow,
Dr. Filippo Maglia | Rudolf Diesel Industry Fellow,
Prof. Hubert Gasteiger (Technical Electrochemistry, TUM)

April 10–11 — **Munich Workshop on Coding and Cryptography** (MWCC 2018)
Organization: Prof. Antonia Wachter-Zeh | Rudolf Mößbauer Tenure Track Professor,
Prof. Camilla Hollanti | Hans Fischer Fellow,
Dr. Ragnar Freij-Hollanti (Communications Engineering, TUM),
Dr. Vladimir Sidorenko (Communications Engineering, TUM)

April 16–17 — Symposium **Selected Topics in Science and Technology I**
(in the framework of the selection process regarding the Rudolf Mößbauer Tenure Track Professorships)
Organization: TUM-IAS

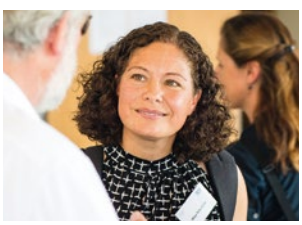
April 18 — TUM Water Cluster Lecture Series **Modeling of Urban Water Management Strategies in a Changing World - Why and How?**
Speaker: Prof. Karsten Arnbjerg-Nielsen (Technical University of Denmark)
Organization: TUM Water Cluster, IGSSE, TUM-IAS

April 23–25 — Symposium **Selected Topics in Science and Technology II**
(in the framework of the selection process regarding the Rudolf Mößbauer Tenure Track Professorships)
Organization: TUM-IAS

June 5–6 — **TUM-IAS General Assembly**





June 7–8

Symposium **Global University, Society, Labor Market – How to Shape Tomorrow's Talents**
(one of the key events amongst the 150th anniversary festivities of TUM)
Organization: TUM-IAS with support by the TUM International Center

June 13–14

Conference **Urban Mobility – Shaping the Future Together** (mobil.TUM 2018)
Organization: Prof. Rolf Moeckel | Rudolf Mößbauer Tenure Track Professor, et al.

June 14

Speakers Series on New Frontiers in Battery Science and Technology
Understanding Solid Ionic Conduction on the Route to Solid-State Batteries
Speaker: Dr. Wolfgang Zeier (Justus-Liebig-University Gießen)
Organization: Dr. Filippo Maglia | Rudolf Diesel Industry Fellow

June 25

TUM-IAS Summer Faculty Day

June 28

TUM Water Cluster Lecture Series **Water 2100: Innovating Now to Create Resilience Then**
Speaker: Prof. Craig Criddle (Stanford University)
Organization: TUM Water Cluster, IGSSE, TUM-IAS

July 2–4

Workshop **Machine Learning for 3D Understanding**
Organization: Prof. Michael Bronstein | Rudolf Diesel Industry Fellow, Prof. Daniel Cremers | Carl von Linde Senior Fellow

September 3–5

Symposium **Sino-German Frontiers of Chemistry**
Organization: Prof. Kathrin Lang | Rudolf Mößbauer Tenure Track Professor, et al.

September 8–14

European Conference on Computer Vision (ECCV 2018)
Organization: Prof. Daniel Cremers | Carl von Linde Senior Fellow, Prof. Bjoern Menze | Rudolf Mößbauer Tenure Track Professor, Prof. Matthias Nießner | Rudolf Mößbauer Tenure Track Professor, Prof. Laura Leal-Taixé | Rudolf Mößbauer Tenure Track Professor, Prof. Michael Bronstein | Rudolf Diesel Industry Fellow, et al.

September 10–12

Forum **Specification & Design Languages** (FDL 2018)
Organization: Prof. Sebastian Steinhorst
Rudolf Mößbauer Tenure Track Professor, et al.

September 24–25

Workshop **Advanced Computational Modeling for Tumor Growth Prediction**
(TUM-IAS Focal Period 2018)
Organization: Prof. Bernhard Schrefler | Hans Fischer Senior Fellow funded by TÜV Süd Foundation, Prof. Alessandro Reali | Hans Fischer Fellow,
Prof. Wolfgang A. Wall (Computational Mechanics, TUM)

October 1–4

Workshop **Re-Thinking Global Soil Carbon Modeling**
Organization: Prof. Johannes Lehmann | Hans Fischer Senior Fellow,
Prof. Ingrid Kögel-Knabner (Soil Science, TUM)

October 8

Talk **Sustainable Development: What Research Is Most Needed to Support Action?**
Speaker: Prof. William Clark (Harvard University)
Organization: Prof. Miranda Schreurs (Environment and Climate Policy, TUM),
Prof. Henrik Selin | Hans Fischer Senior Fellow,
Prof. Noelle Eckley Selin | Hans Fischer Senior Fellow

October 13

Tag der offenen Tür
Talk **FakeNews: Wie können Videos manipuliert werden?**
Speaker: Prof. Matthias Nießner | Rudolf Mößbauer Tenure Track Professor
Talk **Das Innenleben einer Nervenzelle**
Speaker: Prof. Thomas Misgeld (Neuronal Cell Biology, TUM)
Talk **Steht das antike Bauwerk noch stabil?**
Speaker: László Kudela, M.Sc. (Computation in Engineering, TUM)
Talk **Datensicherheit im Zeitalter von Quantencomputern**
Speaker: Dipl.-Ing. Julian Renner (Communications Engineering, TUM)

November 12–16

Autumn School **Proteostasis**
Organization: Prof. Matthias Feige | Rudolf Mößbauer Tenure Track Professor, et al.

November 19–20

Workshop **Smart Skins**
Organization: Prof. Takao Someya | Hans Fischer Senior Fellow,
Prof. Gordon Cheng (Cognitive Systems, TUM)

December 12

Speakers Series on New Frontiers in Battery Science and Technology
Some Simple New Experimental Methods for Studying Lithium-ion Batteries
Speaker: Prof. Jeff Dahn (Dalhousie University)
Organization: Dr. Filippo Maglia | Rudolf Diesel Industry Fellow

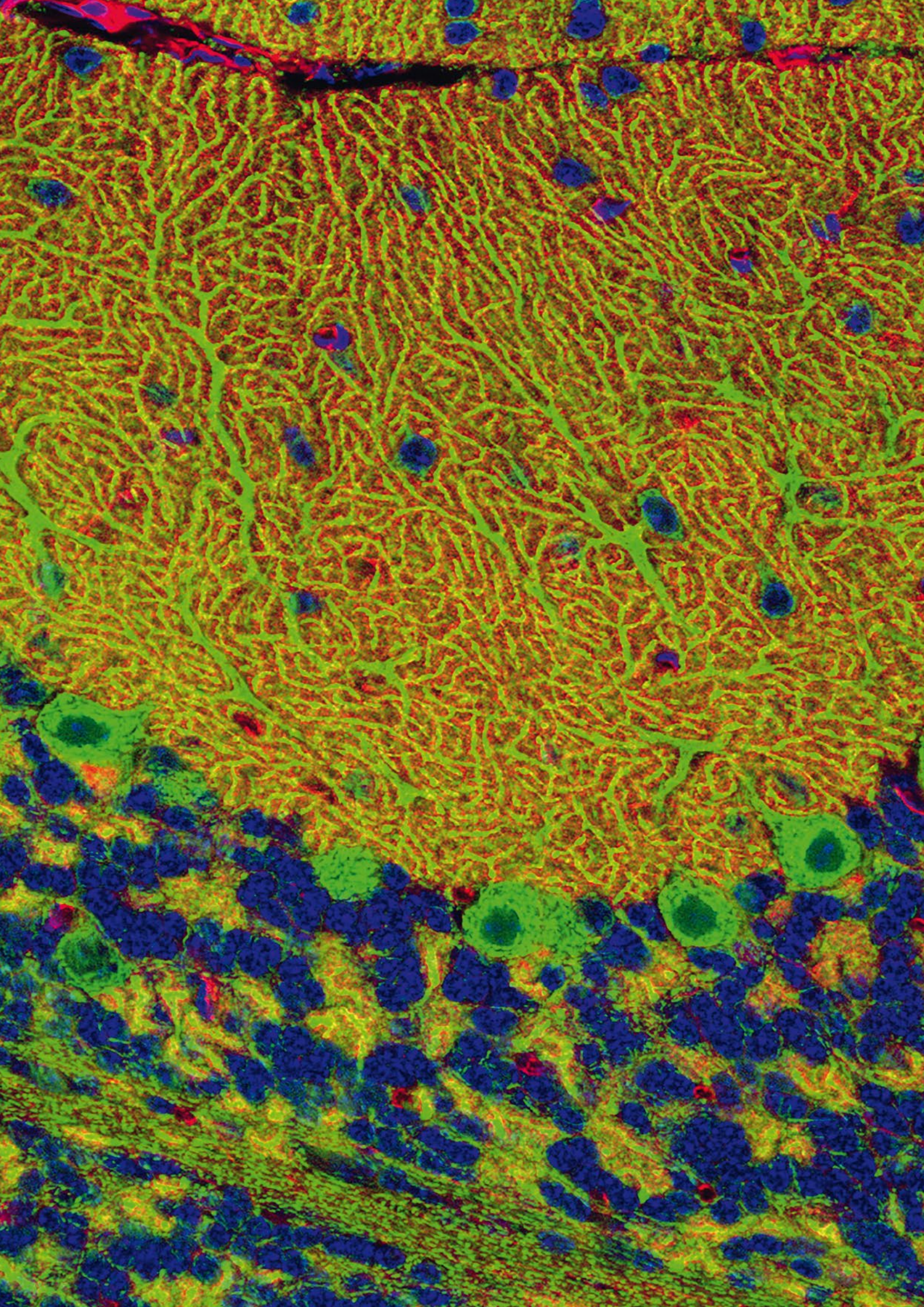
December 12

LIESEL BECKMANN SYMPOSIUM 2018
Technology, Cognition and Dementia

Liesel Beckmann Symposium **Technology, Cognition and Dementia**
Organization: Prof. Nicola Lautenschlager | Anna Boyksen Fellow,
Prof. Janine Diehl-Schmid (Center for Cognitive Disorders, TUM)

In Focus

Subcellular Dynamics in Neurons



Subcellular Dynamics in Neurons

Research probing mechanisms that organize vital processes in cells, from single-celled fungi to the human nervous system, advances our ability to understand – and potentially to diagnose, treat or cure – some of the most devastating illnesses, such as neurodegenerative diseases. At the same time, it sheds new light on some of the basic mysteries of life.

Hans Fischer Senior Fellow Maya Schuldiner is an Israeli biologist whose main research focus at the Weizmann Institute of Science is on organelles and protein functions in yeast, as revealed through a combination of genetic screening and imaging. Hans Fischer Fellow Melike Lakadamyali, originally from Cyprus, is a physicist in the Physiology Department of the University of Pennsylvania's medical school, where she too is investigating the molecular machinery at work inside cells – in her case, largely by pushing microscopy beyond what was considered possible just a few years ago. Gelsenkirchen native, TUM alumnus, and former Hans Fischer Tenure Track Fellow Thomas Misgeld heads the Institute of Neuronal Cell Biology in the TUM School of Medicine, with close, active ties to the German Center for Neurodegenerative Diseases (DZNE) and the Excellence Cluster SyNergy. His lab uses in vivo *imaging in mice and zebrafish to study what happens inside and between nerve cells in development and disease.*

They have joined forces in the Focus Group Subcellular Dynamics in Neurons to explore how mitochondria and other organelles travel and communicate in the crowded space of a cell – particularly in the neuron, with its extreme geometry and complex functions. How do the principles at work in the simplest cells – governing how cellular components are shuffled around by molecular motors along cytoskeletal tracks, and how the tracks themselves may be regulated – translate to neurons?

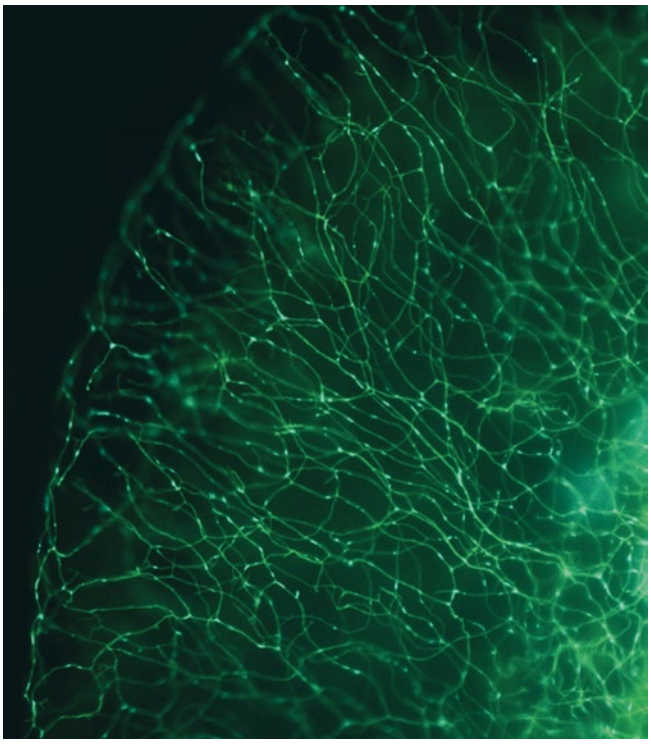
The TUM-IAS conducted an hour-long interview that spanned seven time zones: with Maya Schuldiner (MS) in Rehovot, Thomas Misgeld (TM) in Munich, and Melike Lakadamyali (ML) in Philadelphia.

Left: Purkinje neurons in the mouse cerebellum, where neuronal mitochondria (green), neuronal cell contacts (=synapses; red) and cell nuclei (blue) are labeled. Because synapses are packed with mitochondria, the synapses appear yellow.

Q: Your research interests, and the scientific tools you use to pursue them, seem to cover a broad spectrum. How would you characterize the work you typically do in your own labs, in relation to the collaborative interplay fostered by the TUM-IAS Focus Group?

TM: You could say we're trying to do ambitious things across long distances – biologically, between yeast and mice, and geographically as well.

MS: In my lab here in Israel, we try to understand how cells, the basic units that build up our bodies, are organized. All of our cells are compartmentalized into functional areas called organelles, which basically are membrane-enclosed compartments where specific biochemical reactions can take place. And they enable the cell to diversify the number and types of reactions or functions that can occur in parallel. This is an important aspect of how our cells are built, and I would like to understand how these organelles are organized in the three-dimensional space of the cell and how they communicate with each other. Because if you have these entities, and each performs several functions, in the end you also need to coordinate their functions with one another and make sure that it's all supporting this one big cellular community. We do this in a very simple cell. It's a model cell of the fungus called Saccharomyces cerevisiae, better known as baker's yeast or brewer's yeast. The wonderful thing about it is that the basic cellular functions of this fungus – even though we diverged in evolution about a billion years ago – are very similar to our own cells.

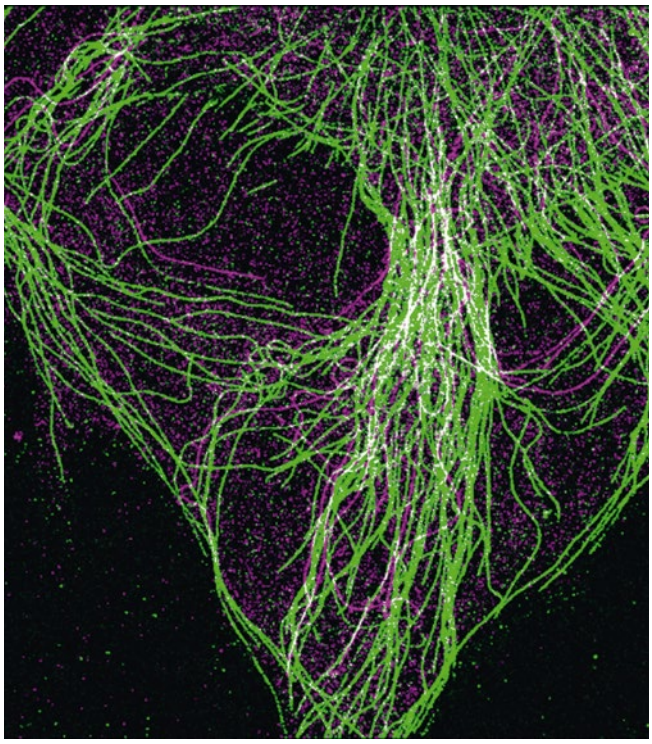


Nerve cell processes (green) with labeled mitochondria (blue) in the tail of a zebrafish larva.

»The wonderful thing about it is that the basic cellular functions of this fungus – even though we diverged in evolution about a billion years ago – are very similar to our own cells.«

The collaboration with Thomas allows us to explore how the principles that we find in yeast are conserved to mammals, such as mice and humans, and to try to understand how these principles are built on or diversified to sustain not only a basic cell but also the many different types of cells that we have in our bodies. On the one hand, we can look at the things that are similar between all cell types – because if it's similar in a neuron in a mouse brain, it means that every single eukaryotic cell will behave the same way. If this whole diversity still maintains the same basic functions, it's probably the same everywhere you look. And if we find cases or scenarios where unique differences between the yeast system and different mammalian cell types can be identified, this could help us recognize what types of functions have to be modified to support different types of functions, for example, in a brain.

TM: The neuron, in addition to being in a different organism and having a very different geometry, also has further levels of compartmentalization. There are some parts of the neuron where the organellar composition is what we conventionally associate with a cell in general, but there are other parts, like the axon and the synapse, that don't have the full complement. We're only starting to discover what is actually there, and given that everything has to be shuttled out there, it's actually quite interesting in which kinds of forms and interactions that happens, and whether the



Multi-color super-resolution image of tyrosinated (green) and detyrosinated (magenta) microtubules.

interactions between organelles are maintained during transport or whether the things are brought into the periphery of the cell separately and then re-formed in those contexts.

The starting point for doing these kinds of investigations is finding molecular definitions of these contacts. That's what Maya has spearheaded in the yeast, looking at pretty much any permutation of organelles you can think of and asking which molecules would mediate between them. These are typically pairs of molecules that tether together and create some kind of intracellular adhesion between organelles.

MS: For example, we discovered a couple of years ago that the mitochondrion, which is the organelle where we convert sugar to energy that can be utilized by the cell, and the peroxisome, which breaks down fats, also to provide an energetic source for the cell, are physically attached to one another through an area called a contact site. They literally contact each other, they are coupled, they move around the cell together. But it was not known what mediates this connectivity. So we devised a visual tool to look at only places where the mitochondria and the peroxisome are connected at this contact site. We coated all of the mitochondria with half a fluorescent protein, coated all of the peroxisomes with another half of the fluorescent protein, and only when they are in very close proximity, such as that which you find in contact sites, the two halves of the fluorescent protein come together and you see a signal. And now we could use this as a visual assay to look for proteins that affect this contact site.

So we screened genetically for proteins that affect the signal when overexpressed or deleted. And we found one protein – in yeast it's called Pex34 – that when you overexpress it, you can dramatically expand the amount of contact that these two organelles have. And we showed – with many different assays – that this Pex34 is really what holds the two organelles together and enables the transfer of the lipid breakdown product into the mitochondrion for conversion to ATP. Now it turns out that this Pex34 is conserved all the way to humans. Its human homologue is involved in a lot of very severe peroxisomal diseases, where the children who are born with mutations in this homologue have very bad neurological disorders, and they die at an early age. The question is: Is the same function that we found in yeast also conserved all the way to mammals, or to humans? So this is a place where we can really start to look. We've just finished making the same probes for a mouse cell, in collaboration with an Italian lab headed by Dr. Tito Cali.

TM: And so the starting point is to take what we know from yeast and try to find mammalian homologues and ask whether these mammalian homologues are in the nerve cells, and then to ask in which part of the nerve cell they are present, and ideally find ways to visualize them three-dimensionally. That is a forte of my lab, and here we can use the mouse as the model organism or use the zebrafish as an intermediate step. Some organelle contacts are fairly well characterized, like the ones between mitochondria and the endoplasmic reticulum. Both of these organelles not only play important roles in biosynthetic steps but also interact, for example, in terms of calcium-handling interactions and in lipid metabolism. It's very clear that these contacts, between mitochondria and the

Top research: Thomas Misgeld and Melike Lakadamyali in early discussions on the Wank summit near Garmisch Partenkirchen, 2009.

endoplasmic reticulum are disrupted in a lot of neurological disease settings like Alzheimer's. But there are many other organelle combinations that are unstudied.

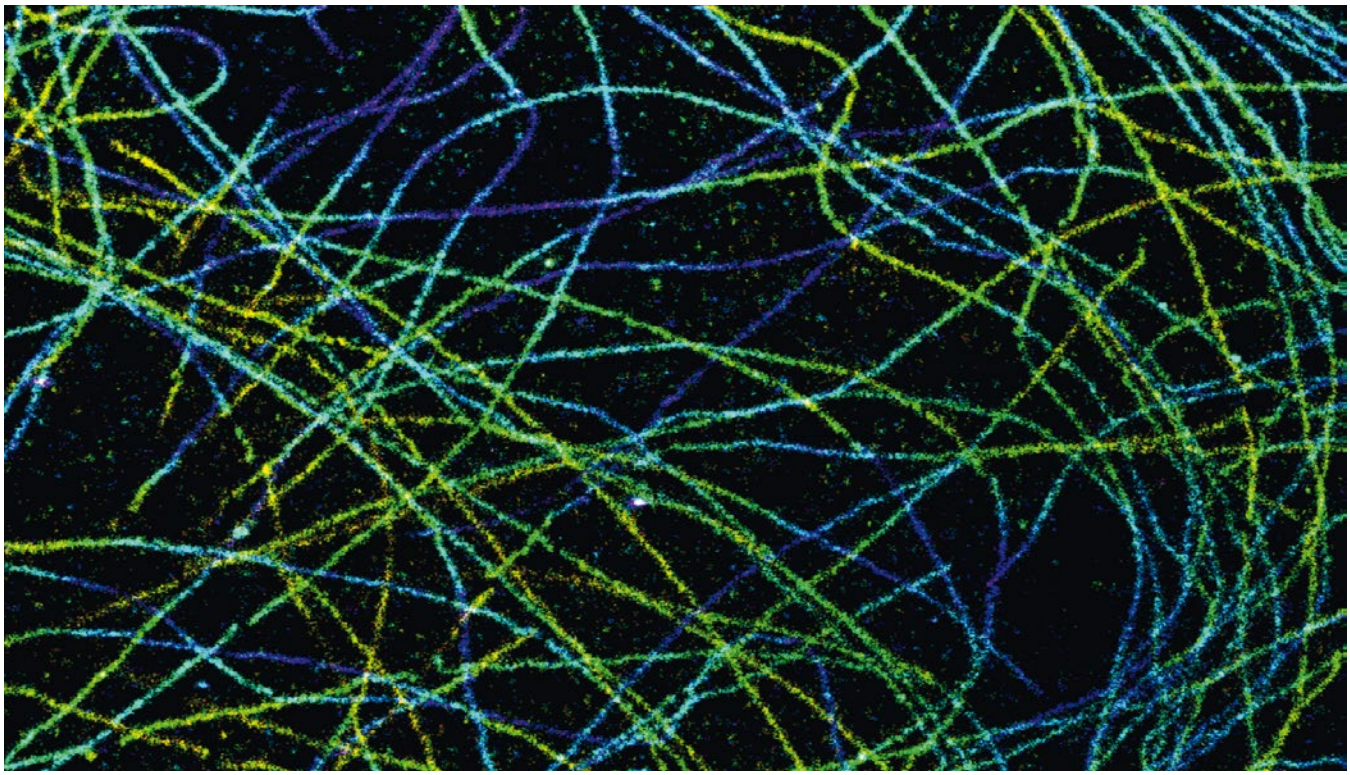
When you come from yeast to the brain, it gets a bit more complex. One way that we are approaching this is by using antibodies for this specific protein, the homologue of Pex34 called Pex11beta/gamma, to analyze mitochondria from neurons and from the neighboring cells, the glial cells. A defect in either can give you a brain disorder. To achieve this, we coated the surfaces of mitochondria with a full fluorescent protein, but in a way that allows us to decide, by breeding the animals, in which cell type that would happen, glial cells or neurons. Because there are very good antibodies for GFP, green fluorescent protein, you can not only see the mitochondria, but you can also grind up the brain and – with little iron beads and a big magnet – pull out only the mitochondria that came from either neurons or glial cells. Then you can ask: What is hanging onto my little iron beads? If something is strongly tethered to the mitochondria in this cell, that other thing should also be there. So you can ask: Do we ever pull out something that a mass spectrometer will tell us is, say, peroxisome instead of mitochondria? This happened – not in neurons, though, but in glial cells. This suggests that peroxisomes are attached to mitochondria very strongly in glial cells.

In the end you would want to target this protein in a way that is cell-type specific and ask: Will that change something about that relationship, and will it have functional consequences? The question might be that if you get this phenotype not in neurons but in glial cells, would that be compatible with the clinical picture of patients? Knowing the answer could play a role in how you make a model of a disease in an animal and how you target the underlying effect clinically. That shows how this combination of tools allows us to follow up on things we actually didn't anticipate.

Q: Melike, in addition to being based several hours west of Thomas and Maya, you're connecting to this from a different direction technically, aren't you?

ML: I'm especially interested in intracellular transport. Intracellular trafficking along the microtubule cytoskeleton is an important biological process in all cell types, but particularly in neurons, because they have very long structural projections and depend on long-range transport to get materials to the right place. We know the individual components that are involved in intracellular trafficking. We know proteins have to attach themselves to cargoes, subcellular compartments, and walk along microtubules to transport these materials from one place to another. But how these work in the complex environment of a living cell in the presence of obstacles – "roadblocks," if you will – is not clear because so far this has mostly been studied by reconstitution *in vitro*, that is on glass slides, where really high-resolution imaging tools can be used to probe the process. These *in vitro* reconstitution experiments are in an unrealistically simplistic environment that doesn't take into account the full complexity of the cellular environment. So the aim of my group is to bring these tools into the cell context and try to probe this process inside the cell at an unprecedented level of detail.

In my lab, we use and further develop microscopy and imaging tools, including super-resolution microscopy, that allow us to visualize processes inside a cell. Tools like two-photon microscopy or confocal microscopy are typically used to visualize cellular structures and compartments and molecular machinery by labeling them. These have taught us a lot, and they're great tools, but they're not so well suited to imaging the machinery that is involved in transport on the microtubule tracks. A microtubule is a long structure but very skinny, about 30 nanometers in diameter.



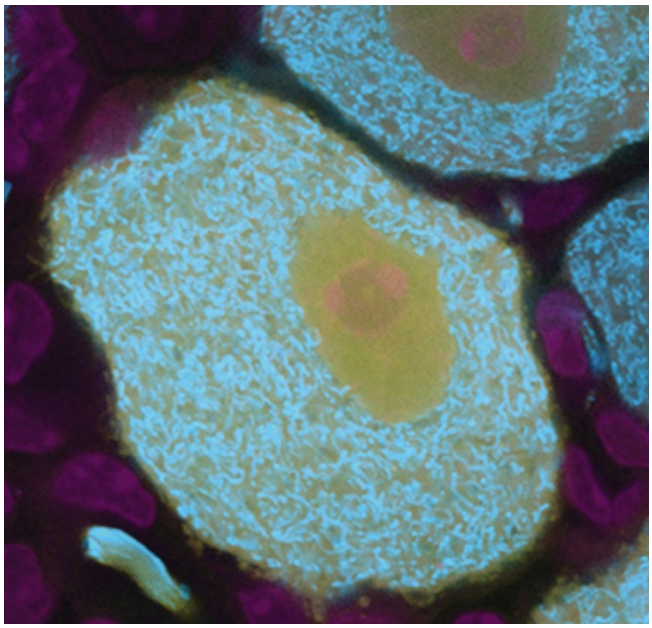
3D super-resolution image of microtubules color-coded according to depth.

The motors that work along these microtubules are on a similar scale, 20 to 30 nanometers. With tools like two-photon and confocal microscopy, we cannot visualize structures that are smaller than about 300 nanometers. That is the limit imposed by the wavelength of light. The tools that we're using and further developing break the limitation imposed by the wavelength of light and give us spatial resolution that is much higher. With this so-called super-resolution microscopy – for which the 2014 Nobel Prize in Chemistry was awarded – we can really visualize the complexity of the cellular cytoskeletons, the microtubule architecture, and where the roadblocks are at a great level of detail and try to understand how motors work in that complex environment.

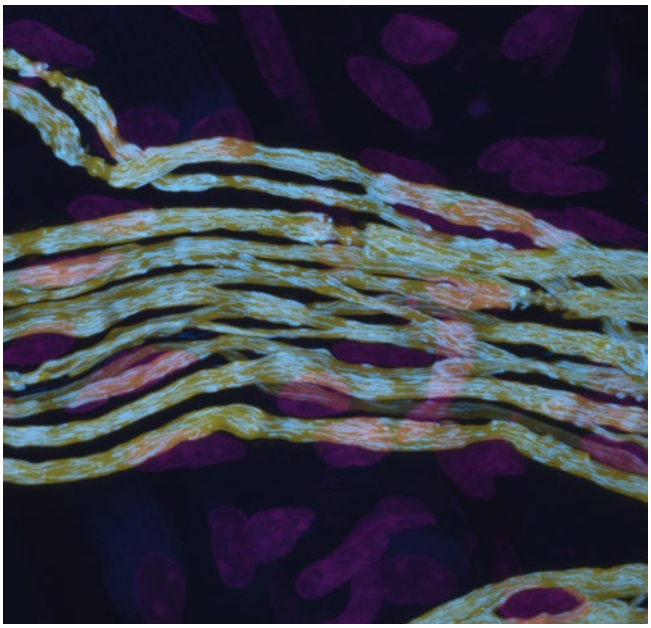
From the technical side, I think this ability to go below the diffraction limit, or the resolution limit of light microscopy, really was quite an exciting development. And we have been slowly pushing that limit to smaller and smaller scales. We're not quite at the molecular scale yet, but I think with new developments we will get to a level where we can look at individual molecules, individual complexes, inside a cell. That will be really exciting.

»I think with new developments we will get to a level where we can look at individual molecules, individual complexes, inside a cell.«

TM: I think it's important here to stress that in contrast to me and also Maya, Melike is a physicist. These super-resolution methods, either on the optical level or in the modeling that you have to use to actually extract information, are very sophisticated and well beyond my capabilities. I think one thing that is challenging – and very easily underestimated because we're so used to snapping a picture with a camera – is to be quantitative about those things on that scale. That's where the real power of this lies, because when you are now looking at small molecular assemblies, suddenly counting things becomes really important but far, far from trivial. People like Melike are really pushing that, and that's something people with my background will never be able to do.



Mitochondria (cyan) in sensory neurons (yellow) of a mouse - nuclei are labeled magenta.



Neuronal mitochondria in nerve cell processes (yellow) that innervate muscles of a mouse - nuclei of surrounding support cells and muscle are labeled magenta with a DNA dye.

ML: We've really been trying to go beyond, as Thomas says, snapping a pretty picture. To do that we are trying to understand, on a quantitative level, what the picture is telling us, and that is really challenging with these techniques. We've been developing methods to try to overcome those challenges as well.

Q: Are there more examples that show how the different lines of research are already reinforcing each other or coming together to achieve something new?

ML: We are normally looking mainly at epithelial cells, which are much simpler than neurons, but otherwise there is quite a lot of overlap. Lately we have been trying to understand the interplay between the motors and the cytoskeleton in the context of a biological process called autophagy, which means self-eating. It degrades cellular proteins to create amino acids to make new proteins, and it's also a process to help clear unwanted protein aggregates and damaged organelles like mitochondria.

For autophagy to happen, two compartments have to find each other inside the cell: what we call a lysosome, which contains all the enzymes that do the degradation, and an autophagosome that contains the unwanted proteins that damage organelles.

They have to meet each other, and they have to fuse, and these proteins are compartmentalized so that chemical reactions happen in a spatially and temporally controlled way. We have been wondering how these two compartments – in this really complex environment, where you have microtubules everywhere connecting every part of the cell and these organelles, if you look at them in a microscope, that seem to be just shuttling back and forth in the cell – find each other efficiently when they need to and fuse with each other. And we have been studying something called post-translational modifications of microtubules. Not every microtubule track is the same, and it is thought that chemical modifications to the microtubules may carry a code that the motors interpret.

Part of what we showed in our latest work is that yes, indeed, one type of modification is very important for enabling the encounter of these two compartments. There's a modification that is found in a very small population of microtubules – only about 30 percent of microtubules in the cell have this modification – and these two compartments that need to fuse with each other are enriched on these microtubules. And because there are only a few of these tracks, and these compartments travel largely on these few tracks, they can meet each other much more efficiently and fuse

with each other to initiate authophagy. Together with Thomas, we are looking at a specific form of autophagy, mitophagy, which is clearance of damaged mitochondria in the cell. We have looked at this in our lab in non-polarized cells, and now with Thomas we are looking at it in polarized cells like neurons, which are structurally very compartmentalized.

Q: Have you seen anything yet that surprised you?

ML: Yes!

TM: What came out of that study is that even within a subcompartment of a neuron, specifically the synapse – we're talking about neurons that have very large synapses, on muscles – there seems to be a geometric organization of this formation of the autophagosome and the lysosome. The lysosome seems to sit in a very specific position at the entry of the synapse. We don't know exactly at which step of autophagy yet, but at some point when mitochondria are fated to be removed, they move to this entry point. And rather than entering the axon and going all the way back to the soma – which is one of the assumptions about what they might be doing, and they might in fact be doing that in *in vitro* settings – here they seem to fuse locally and be degraded, meaning that there probably is a localized system of degradation.

Q: Would you call this a recycling center?

ML: More like a filter.

TM: Yes, a filter. But it also means that there is a local degradation. For the longest time, we have been puzzling why more mitochondria are shuttling into synapses than are coming out. There was always a mass discrepancy. And now using various higher-resolution approaches combined with electron microscopy, we have been able to do a mass balancing. Because of course you could say, well, you're shipping in more but what's coming back is bigger. So you have to measure very precisely the size of these cargoes in these different places to do a mass accounting. And that's something we have actually been able to do together, also using photoactivation to label individual organelles – where you have fluorescent proteins and you can change the colors. That allows us to label

Hoping for a breakthrough: Thomas Misgeld and Maya Schuldiner near the Danube Gorge ("Donaudurchbruch") with the Weltenburg Abbey in the background, 2018.

individual organelles, and we can now fix them and go to Melike's lab and measure them very precisely. It turns out mitochondria are long enough to measure them well with our microscopes, but the thickness is just at the level of the light wavelength, and so to decide how fat the mitochondrion is, we have to go to Pennsylvania. From that point of view it actually fits very nicely together.

It's conceivable – though we haven't looked at it, we haven't proven it – that there are actually very specialized microtubule modifications in the synapse itself, with some forms being relatively sparse over others, and we're very interested in the cytoskeleton as well. It's possible and could even be that the lysosome sits at the convergence point of these tracks. We haven't explored that, and perhaps we should.

ML: We need to look at that. I think this idea that compartmentalized autophagy can happen within the compartments of a neuron is really exciting. And it could be that different types of cargoes get degraded via autophagy that happens in these different compartments. And then, we know that mutations in a lot of neurodegenerative diseases impact proteins associated with autophagy. It would be interesting to probe whether they impact autophagy in general or they impact autophagy that happens within a specific subcompartment of a neuron. So these are some of the questions for future study.

TM: You could argue that this Focus Group has the same topic as the TUM-IAS overall: long-distance transport to create lasting contact sites. That's what we're doing in the Focus Group.

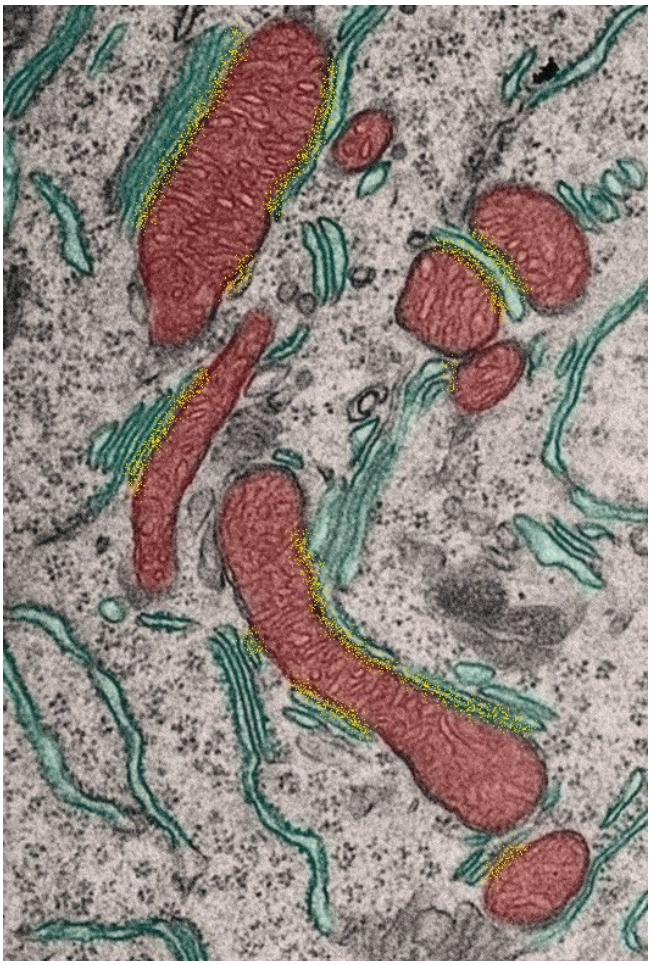
Q: How has the special framework of TUM-IAS Fellowships supported and shaped your collaboration?

TM: Fortunately for us, the TUM-IAS framework has shown a lot of flexibility, particularly with respect to Melike's Fellowship. TUM-IAS Fellows are expected to spend a significant amount of time here in Munich, for many good reasons. At the time we were arranging this, Melike was living in Spain, and her husband was free to go on sabbatical. But first Melike found out that she was expecting a child, and then she was offered a professorship at the University of Pennsylvania. So now she moved to America with a newborn, had to start up her lab in a new place, and was now in a situation where her husband would not be able to take a sabbatical in Munich. We proposed, and the TUM-IAS agreed, that Melike would come here for a few short visits instead of an extended stay. She has been here a couple of times for a week or ten days, and my people go there, to the University of Pennsylvania. This is great in terms of how the collaboration works, even though it is not optimal for the TUM-IAS. We are working very closely together on a project that is approaching publication.

Maya, on the other hand, was able to spend a full year here in Munich, with her whole family. Her husband Oren Schuldiner, who also is a highly distinguished scientist, was awarded the prestigious Bessel Research Award of the Alexander von Humboldt Foundation, which enabled him to come to Munich. And their three kids were able to attend the Bavarian International School.

Q: How did that work out for you and your family, Maya?

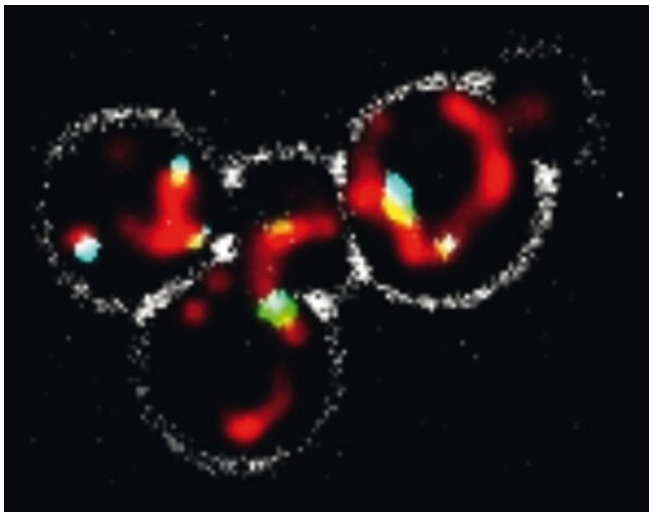
MS: This was really one of the most amazing experiences in my scientific career. I was able to work in Thomas's lab and join group meetings and take part in some TUM-IAS meetings, and really experience, first of all, how it is to work in a lab that has a very different expertise from mine. Also, this was a great opportunity to work in a city and a country that are very different from Israel, and to experience the cell biology in Germany, which is outstanding. It's really the best in the world in my eyes.



Close contacts between mitochondria (red) and the endoplasmic reticulum (cyan) are artificially rendered in yellow. The image shows an electron micrograph from Purkinje cells in the mouse cerebellum.

»You could argue that this Focus Group has the same topic as the TUM-IAS overall: long-distance transport to create lasting contact sites.«

I spent a year mostly in Thomas's lab, but I also took time to visit many other labs and many other cell biology departments all around Germany. I probably visited 20 different universities during this time. It was an amazing scientific experience.



Microscope image of a yeast cell showing how close mitochondria (red) are to peroxisomes (blue) and the contact sites that hold them together (green).

One of the things that people might not appreciate: In Israel, we have five universities, and if we want to go to any other university, we have to get on a plane and fly for a minimum of three and a half hours until we get to Europe. We're surrounded by countries that are either hostile, and we can't go there, or by countries where science is less advanced. When I was sitting in Munich, I would hop on the train at 7 a.m. and by 10 I could be anywhere – in Austria, Switzerland, Germany, France, Holland, the Czech Republic. Suddenly there are tens of universities that are just a couple of hours away by train. I felt like a kid in a candy store. Where do you go to first, when you can just hop on the train and get there?

The intellectual opportunities are amazing. And besides that, we loved living in Munich, and we were almost neighbors of Thomas's, just one street over. Our children were fifteen, twelve, and five at the time we arrived in August 2017. We stayed until August 2018. All the kids fell in love with Munich. My eldest son already told us that he's coming back to Germany to do his college studies.

TM: For us it was quite difficult and emotional to have them leave. That was one of the best things the people in my lab have experienced. We had training sessions with Maya for people who went for ERC interviews, and I think all of my people had one-on-one meetings with Maya and Oren for career advice. On their own campus, they are very engaged in outreach, and with gender and diversity issues. She's a very inspiring role model, a successful scientist who is a mother of three, with a husband who has been there for the children as much as she has. Scientifically, Maya and Oren had strong links to Germany before, but I think their year in Munich has really fortified them. They used the time to really get to know the science environment here.

Q: How is the Focus Group collaboration working for its earlier-career members, the doctoral candidates and postdoctoral researcher supported by the TUM-IAS?

TM: Our postdoc, Shabab bin Hannan, has moved on. He took a job at Tübingen. We have two doctoral candidates. Natalia Marahori, who is working on the project with Melike, is actually a medical doctor. She came to me in a specific program that we have in the TUM School of Medicine, called Translational Medicine, targeted at medical students who want to do a bit more science. They can do this for a year. And then, inspired I hope by interactions she had through that, she's now full-time. She's finished her medical degree and is here with us for a period of three years. She left the Translational Medicine program to upgrade to a full PhD. She's been in Philadelphia a couple of times already, imaging there. She's an absolutely outstanding person, has been with us for the whole length of the Fellowship, and will be the lead author of the study we are wrapping up.

Antoneta Gavoci, the doctoral candidate I am sharing with Maya, came to us from Italy. She's trained in molecular medicine and biological disciplines. She's been here for a year working on two tracks. One is to do what we originally proposed, trying to see whether these methods from yeast can be moved into our system. That proves to be a little more tricky. We may have underestimated the long-term effects of these modified tethers that we use as imaging tools. So what Antoneta is working on in parallel is to create an inventory of the cells at the molecular level, so that you can simply look at what, of the things that Maya finds in yeast, we also have in the specific motor neuron cells that we study.

And the projects are now also intersecting, because we decided to look at a mutation in a specific protein called spastin. That is mutated in patients with a disease called hereditary spastic paraplegia, essentially a motor neuron disease. The interesting thing about that protein is that its job is to cut microtubules. So it regulates transport, and we're now back to the idea that there are specific tracks inside of neurons that cargoes use. It turns out that spastin doesn't indiscriminately cut microtubules; it does it specifically in response to the modifications that Melike spoke about. It might be one of the proteins that read the code. So we decided that if Antoneta is doing an inventory, she might as well do an inventory not only of the normal situation, but also of the situation where that protein is missing, in order to understand how the cell responds to the challenge of having this code reader disrupted.

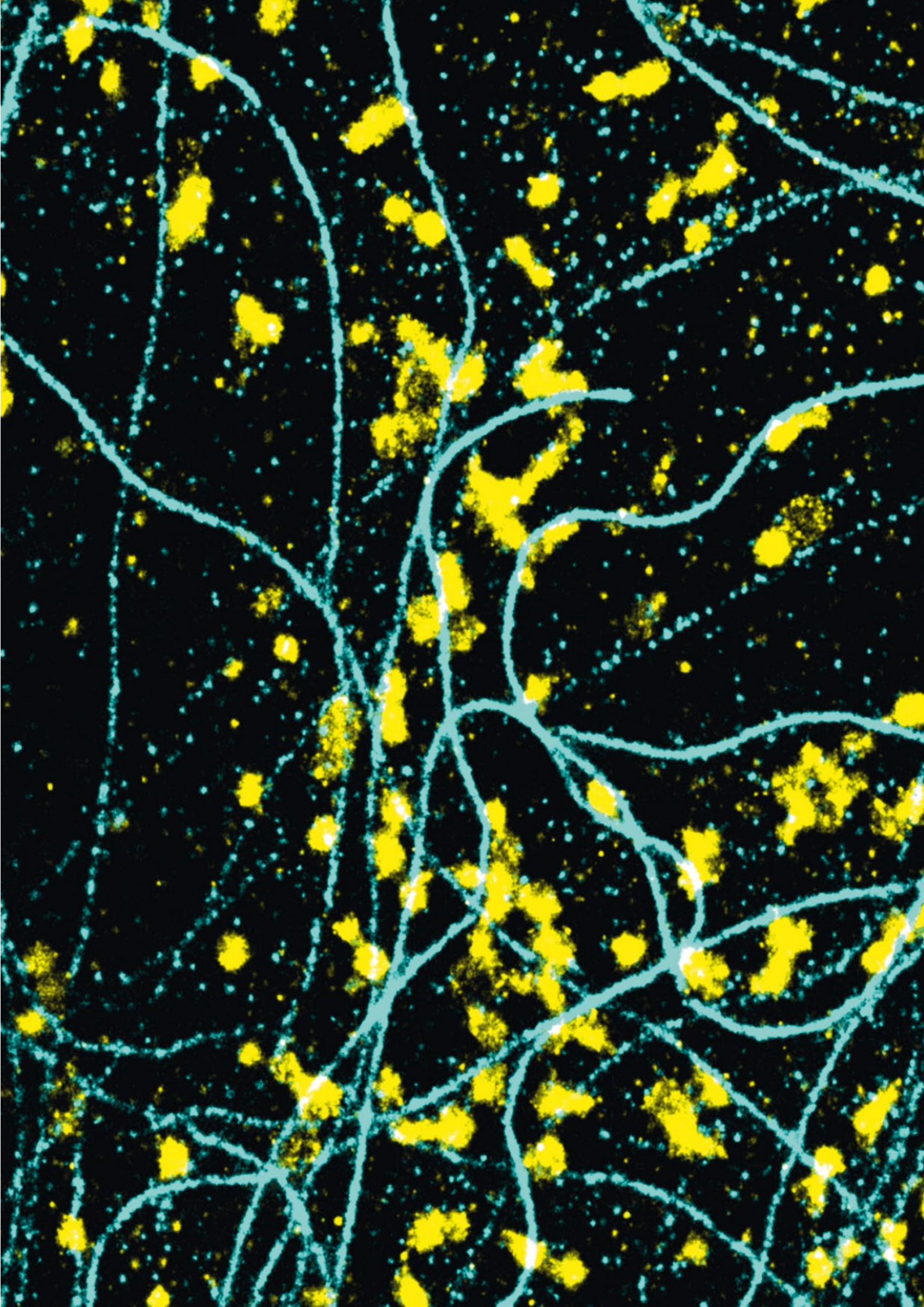
Q: When you're investigating something that can cause or at least influence a disease when it goes wrong, aren't you also learning more about how biology works when things go right? To what extent are these studies aimed toward understanding and curing diseases, and to what extent are they aimed toward better fundamental understanding of nature?

MS: I don't think you can differentiate between the two. Say you want a mechanic to fix your car. He can't fix your car unless he learns how every piece is supposed to be working when the car is functional, and then where things can go wrong. You can't fix something unless you know how it's supposed to be, and what the opportunities are when it goes wrong. The cell is a machine. It's a very complicated machine. It has a couple of thousands of parts. But it's finite, just like a washing machine or a car, and those parts have to be in a specific place and play a specific role. And if they're not sitting in the right place and doing the right thing, then the machine goes wrong, and you might be able to fix it if you know enough about it.

I do think some people primarily study disease states to try and understand what goes wrong. I think that it's much more powerful to look at what happens in a native state, because when you understand what goes right, it immediately becomes clear what can go wrong. This is why I study cell biology and not cancer or another specific disease. When you understand the principles of how things work, you immediately understand how they don't work.

TM: I would go a step farther. *Ex officio*, I should be saying we do it for disease. But I would differentiate between cells and washing machines and cars in that if nothing ever went wrong with washing machines or cars, I don't think anyone would study them. We would just accept that they're there and they're fine. This would not be true for cells, or the universe. We would study them even if they didn't go wrong. It's bad that they go wrong, and it's great that we can potentially fix them. But I would be happy to study mitochondria and peroxisome interactions, or mitochondria alone, just because it's deeply fascinating – how a nerve or even a yeast cell can simply work, just that it is possible, that this exists in the universe. I agree that for disease we need to understand it, and that's a useful side-effect of fundamental discoveries. But the simple fact that there is a physical chemical mechanism that can create something like a cell, which manages to survive and does so in such a sophisticated way – it's just marvelous that that can even work.

Right: Multi-color super-resolution image of detyrosinated microtubules (cyan) and lysosomes (yellow).



Scientific Reports

Scientific Reports

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

Symmetry-broken states in networks of globally coupled oscillators

Oscillatory networks play a crucial role in the understanding of complex systems such as the brain or electric power grids. Such networks may exhibit a vast variety of different dynamical phenomena, the underlying mechanisms of which still raise many questions. These phenomena include cluster states, in which the ensemble splits up in two or more groups which are internally synchronized. Furthermore, there are so-called chimera states, extraordinary chaotic states in which some of the oscillators show synchronized motion, whereas some others behave incoherently. We investigate the bifurcations leading from synchronous motion, that is from a state in which all oscillators behave identically, to cluster states, and the different scenarios through which chimera states are born from such cluster states.

Our work addresses the fundamental question in synchronization research: how clustering in small networks links to larger ensembles. In particular, we have discovered novel organizing structures that we dub cluster singularities. These are universal for coupled oscillatory systems, and they connect the dynamics of small networks to the thermodynamic limit of infinitely many oscillators, one of the central problems in nonlinear statistical physics. In particular, we find there is a certain arrangement of cluster states around such a singularity, with the singular point serving as an organizing center. On the basis of this arrangement, one can then infer where cluster states in larger, or even indefinitely large, networks are located.

For chimera states, we find different routes leading from cluster states to chaotic dynamics. Such routes include the Feigenbaum scenario, which is a sequence of infinitely many period-doubling bifurcations, and the Rouelle-Takens-Newhouse scenario, that is the break up of an invariant torus. The resulting chimera states might occur in different variations on which we shed some light in our work. Starting from very small networks of just four oscillators, we show that one can distinguish such chimera states using symmetry arguments: Some chimeras behave in a way which leaves the dynamical structure unchanged when some of the oscillators are interchanged, whereas other chimera states do not have that particular invariance. This difference in the symmetry properties may also be used to distinguish between states in larger ensembles of coupled oscillators. Due to the general nature of our approach, our results have implications in disciplines as diverse as neuroscience, sociology, and condensed matter physics, and our results might help elucidate the dynamics of partial synchrony occurring in nature, for example during unihemispheric sleep in certain animals.

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

1 | Left: Attractor projection of an asymmetric chimera state. Note that it is not invariant under a reflection along the diagonal. Right: Projection of a symmetric chimera state. This state remains invariant when flipped along the diagonal. Background: The orbit diagram of the Feigenbaum scenario, leading from cluster states (discrete points in the orbit diagram) to chimera states (vertical bands in the orbit diagram).

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

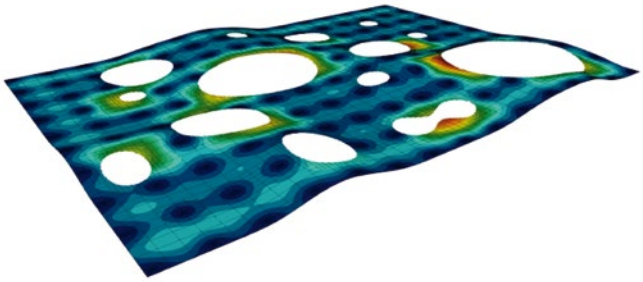
Host
Prof. Ernst Rank
Computation in Engineering, TUM

The main aim of this Focus Group is to take advantage of the unique approximation and geometric features of modern computational mechanics techniques, like isogeometric analysis and the finite cell method, as the best approach to create efficient analysis tools for effective simulation of complex problems including 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 that are 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 into very expensive simulations (in some cases even producing 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 third 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, the implementation strategy for local refinement in IGA proposed last year [1], a technique to locally increase the resolution of the simulation, was improved by leveraging the inherent local tensor structure. This concept served to integrate locally refined IGA in the software developed at the TUM Chair for Computation in Engineering. Currently this software is being used to simulate additive manufacturing processes.



1 | EPFL Rolex Learning Centre under self weight. Left: aerial view (commons.wikimedia.org/wiki/File:Rolex_Learning_Center_07-2009.jpg). Right: simulated displacement.

In addition, we investigated a way to compute the reactions for the FCM based on physical arguments. This approach extracts accurate values based on fundamental equilibrium properties of the FEA and the FCM. This can be used to estimate the thermal insulation of 3D-printed façade elements. This was done in collaboration with the TUM Department of Architecture. In this context, while the FCM allows for a direct simulation of such complicated 3D-printed geometries, the proposed approach allows us to accurately obtain the quantity of interest.

Finally, the use of a numerical integration technique suitable for high-order IGA was investigated in the context of explicit dynamics. This was done in collaboration with the faculty of mathematics of the University of Pavia, Italy. This promising approach can be combined with the above refinement strategy to improve efficiency.

Reference

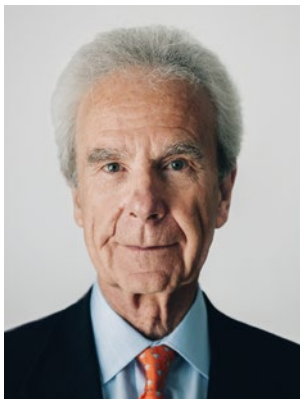
[1] D. D'Angella, S. Kollmannsberger, E. Rank, and A. Reali, "Multi-level Bézier extraction for hierarchical local refinement of Isogeometric Analysis," Comput. Methods Appl. Mech. Eng., vol. 328, pp. 147–174, 2018.

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

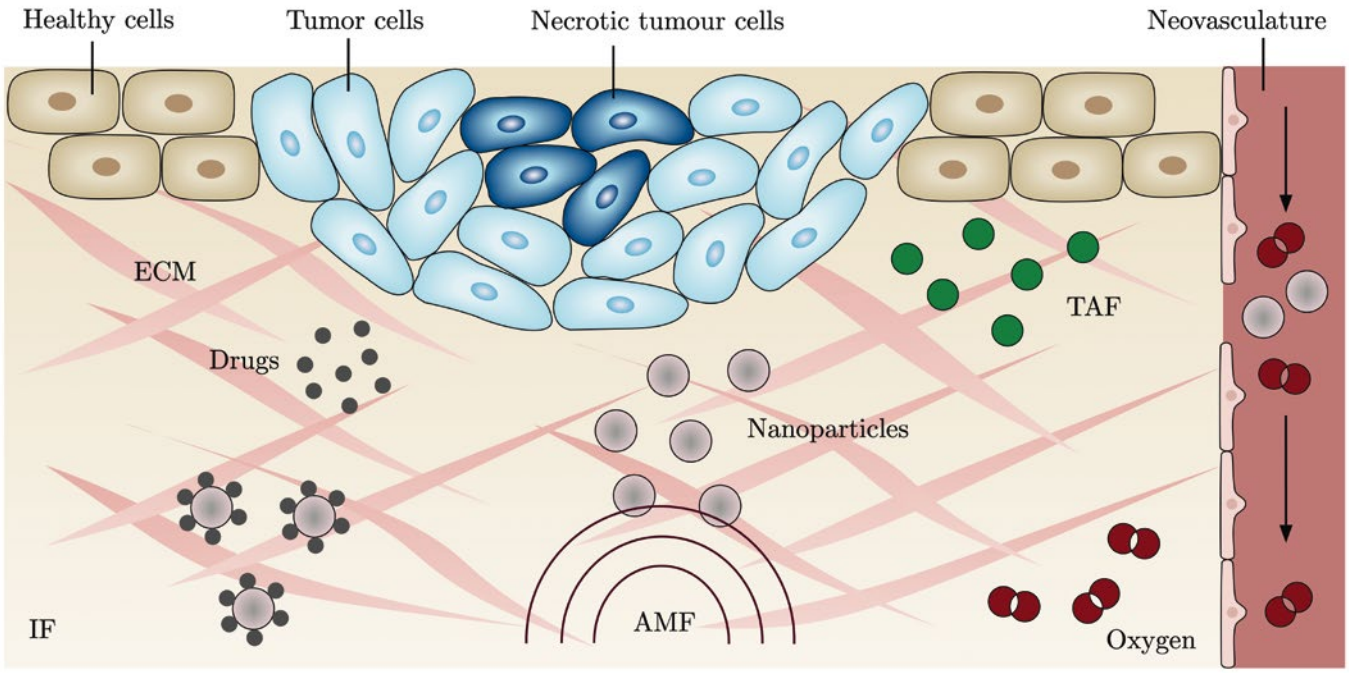
Host
Prof. Wolfgang Wall
Computational
Mechanics, TUM

A novel embedded multiscale approach to predict vascular tumor growth

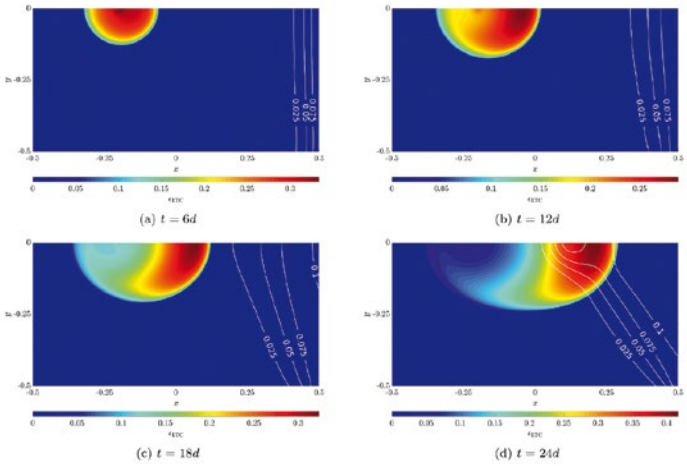
Numerous mathematical models have been proposed to study cancer progression. They aim at giving insight into biological and physical phenomena that play an essential role during tumor growth. An interdisciplinary collaboration bringing experts from chemistry, biology, and oncology together with mathematicians, physicists and computer scientists is the only option to develop computational models that constitute the first steps towards prediction of tumor growth *in silico*. However, the enormous complexity of cancer requires cutting-edge mathematical models and corresponding numerical algorithms. One of the most sophisticated tumor growth models has been developed by Prof. Bernhard Schrefler and his group [1]. While it has shown its applicability to reproduce experimental results [2]–[3], the previous realization lacked flexibility and efficiency. We have now established a model in a much more flexible and powerful computational environment, the in-house research code BACI of the Institute for Computational Mechanics, and besides gaining flexibility also achieved a considerable performance gain [4].

In order to enhance its applicability as a predictive tool, we have also included a novel approach to model angiogenesis, which is the formation of new blood vessels from the pre-existing vasculature [5]. During tumor growth the onset of angiogenesis is of fundamental importance. Tumors require a vast amount of nutrients, such as oxygen, to proliferate and grow. Therefore, the tumor microenvironment can easily become hypoxic, i.e., it lacks oxygen since pure diffusion mechanisms are not enough to sustain the large consumption. Under these conditions, tumors can trigger angiogenesis such that a new blood vessel network, the neovasculature, develops and the tumor has unlimited access to nutrients from the blood stream, enabling rapid cancer progression. Therefore, angiogenesis is crucial for a tumor to become malignant, which is why it has been identified as one of the six “hallmarks of cancer” [6]. The individual components of the new vascular model including angiogenesis are sketched in the Figure below, where five phases can be discerned: the extracellular matrix (ECM) as a deformable, porous solid phase; tumor cells, healthy cells and the interstitial fluid (IF), which flow in the pores of the ECM; and the neovasculature with blood flow. In addition, the IF and the neovasculature can transport different species, such as oxygen, nutrients, tumor angiogenic factors or nanoparticles loaded with drugs. The main advantage of our continuum-based approach is that we do not have to resolve every capillary in the neovasculature but can treat it as a distinct phase in a smeared or homogenized sense.

Recently, we have been working on a consistent coupling of the vascular multiphase tumor growth model with the pre-existing vasculature. For that, we developed a new embedded multiscale method, which allows for a mathematically elegant inclusion of arbitrarily complex vascular networks (a corresponding paper has been submitted for publication). Further research is currently being done aiming at the incorporation of drug delivery and hyperthermia treatment through nanoparticles. We have benefited greatly from the TUM-IAS Focal Period on Advanced Computational Modeling for Tumor Growth Prediction, enabling us to establish valuable contacts with clinicians and oncologists from TUM and experts in cancer modeling from all over the world. We hope to intensify these collaborations to further validate our model and enhance its predictive ability.



1 | Components of the multiphase model: The extracellular matrix (ECM) as the solid phase; the three fluid phases healthy cells (HC), tumor cells (TC), and interstitial fluid (IF); the neovasculature as an independent porous network; necrotic tumor cells (NTC), oxygen, TAF, nanoparticles, and drugs as species transported in the different phases.



2 | Exemplary results for the growth of a vascular tumor over 24 days: Tumor grows in half-moon shape toward a pre-existing blood vessel on the right, from which angiogenesis occurs (colors denote volume fractions of living tumor cells, contour lines the volume fraction of the neovasculature).

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

Focus Group **Computer Vision and Machine Learning**

Prof. Michael Bronstein (Imperial College London / Intel Perceptual Computing / Tel Aviv University / Università della Svizzera Italiana) | Rudolf Diesel Industry Fellow
Prof. Daniel Cremers (TUM) | Carl von Linde Senior Fellow

Scientific Reports

Michael Bronstein

Daniel Cremers

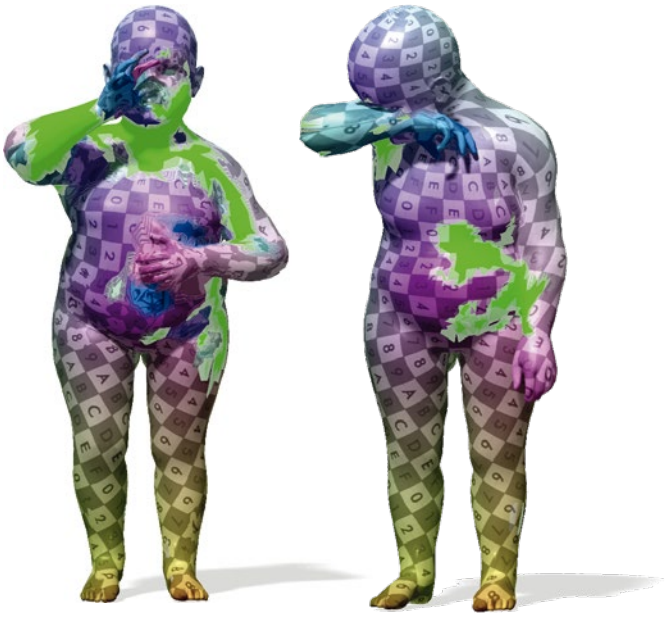
Host
Prof. Daniel Cremers
Computer Vision and Pattern Recognition, TUM

The activities of the Computer Vision and Machine Learning Focus Group is primarily centered on the interplay between geometry, machine learning, and computer vision. Analysis of geometric objects has been a topic of computer vision and pattern recognition since the inception of the field. Classical computer vision problems of "shape-from-X" aim at recovering the geometric structure of a 3D object from multiple images (shape from stereo) or different illumination conditions (photometric stereo). In recent years, interest in 3D data has increased dramatically, fueled in part by the commercial availability of affordable and compact 3D sensors. Such sensors are nowadays found in a broad range of applications from drones and augmented reality to self-driving cars. Members of the group have both academic and industrial experience in these applications (Michael Bronstein as Principal Engineer at Intel responsible for the development of RealSense range-sensing technology, and Daniel Cremers as the founder and Chief Scientist at the autonomous driving start-up Artisense).

Of particular interest to our Focus Group is the development of next-generation machine learning methods capable of dealing with geometric data. Deep learning, a particularly successful ML paradigm based on differentiable programming, has had a revolutionary impact on computer vision in the past decade. Deep learning technologies are estimated to have added billions in business value, created new markets, and transformed entire industrial segments. Most of today's successful deep learning methods, such as convolutional neural networks (CNNs), rely on classical signal-processing models that limit their applicability to data with underlying Euclidean grid-like structure, e.g., images or acoustic signals. Yet, many applications deal with non-Euclidean (graph- or manifold-structured) data such as social networks in computational sociology, molecular graphs in chemistry, interactomes in system biology, and 3D point clouds in computer vision and graphics. Until recently, the lack of deep learning models capable of correctly dealing with non-Euclidean data has been a major obstacle in these fields.

One of our research directions is trying to bridge the gap between geometric and deep learning by generalizing neural architectures and the underpinning mathematical models to non-Euclidean domains. The term "geometric deep learning" coined in [1] is now widely used as an umbrella term for graph- and manifold-based neural network architectures. So far, geometric deep learning methods have achieved spectacular results in some classical challenging problems in computer vision and shape analysis, such as finding dense deformable correspondence (Figure 1) or analysis of 3D point cloud data (Figure 2).

Geometric deep learning techniques also extend well beyond computer vision applications and can be applied to general abstract graphs in a broad range of applications. Such methods have gained acute interest in the machine learning community, since graphs can model very abstract systems of relations or interactions. For example, geometric deep learning has been applied to problems in particle physics, such as classifying astrophysical neutrino interaction events in the South Pole IceCube observatory [5] (best paper award at ICMLA 2018). Another promising direction is using graph-based methods to regularize deep neural networks used in image classification, making them more robust against adversarial attacks (Figure 3 [4]).



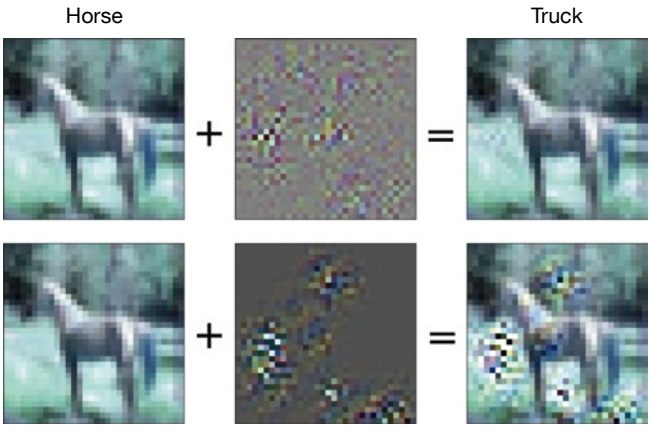
1 | Finding dense correspondence between deformable 3D shapes is a prototypical problem in computer vision arising in a plethora of applications. The correspondence is visualized by mapping texture from one shape to another, with almost no perceivable distortions (Figure from [3]).

2 | Semantic segmentation (left) of a point cloud obtained by scanning an indoor environment (right) using geometric deep learning. (Figure from [2])

Finally, Michael Bronstein and his research team have recently founded a start-up company Fabula AI exploiting such techniques for fake news detection on social media by learning the patterns in which such news spread.

Summer workshop

In July 2018, with TUM-IAS support, our Focus Group organized an interdisciplinary workshop on Machine Learning for 3D Understanding, bringing together world's leading experts in both fields coming from academic institutions such as Stanford, Harvard, UCL, and Imperial College, as well as industry (Google, Facebook, Intel). The workshop was a success and saw attendance by TUM students and faculty, including other TUM-IAS Fellows such as Prof. Matthias Nießner and Leonidas Guibas. A broad range of topics was covered, from large-scale point cloud analysis for autonomous driving cars and face modeling to protein design and structure prediction (please find a workshop summary in the section Activities and Events of this report).



3 | Adversarial attacks exploit a recently discovered vulnerability of deep neural networks to specially engineered input perturbations of the input. Adding such an adversarial noise significantly degrades the performance of a deep learning system, potentially leading to catastrophic results in some critical systems such as autonomous cars. In [4], we show how to regularize deep neural networks with graph convolutional layers resulting in a significantly better robustness to adversarial noise. Top row shows the almost imperceivable perturbation making a deep neural network recognize a horse as a truck; attacking our graph-regularized neural network requires a significantly stronger noise to achieve the same effect.

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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
Amir Akbarnejad, Marin Bilos, Aleksandar Bojchevski, Bertrand Charpentier, Maria Kaiser, Johannes Klicpera, Anna Kopetzki, Richard Kurle, Aleksei Kuvshinov, Richard Leibrandt, Armin Moin, Artur Mrowca, Oleksandr Shchur, Daniel Zügner (TUM) | Doctoral Candidates

Scientific Reports

Stephan Günnemann

Host
Data Mining and Analytics, TUM

Robust machine learning for non-independent data

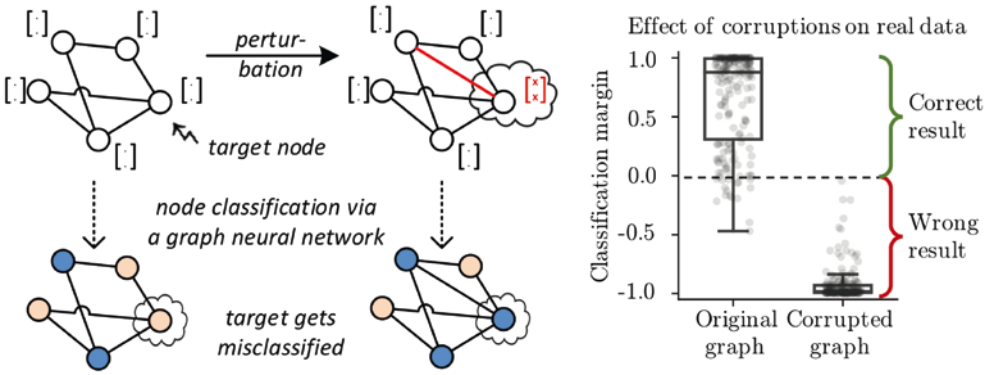
We conduct research in the area of machine learning and data analytics. Specifically, our group aims to develop machine learning methods able to handle erroneous and non-independent data.

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, and adversarial user inputs are only a few examples. Since applying standard learning methods on 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.

Adversarial attacks on graph neural networks

In this regard, our Focus Group is especially interested in analyzing and developing techniques for non-independent data such as graphs and networks: Sensors are interlinked with each other in networked cyber-physical systems, people exchange information in social networks, and molecules or proteins interact based on bio-chemical events. In all these domains effective machine learning techniques for graphs are required. Indeed, in this regard, graph neural networks have recently raised the bar with many success stories across various tasks.

In our work [1], we presented the first robustness analysis of such graph neural networks, specifically focusing on graph convolutional neural networks. As shown in our research, even only slight adversarial perturbations of the graph structure or the nodes' features can lead to dramatically wrong predictions (see Figure). The algorithm we developed enables efficient perturbations in a discrete, relational domain and ensures unnoticeable changes by preserving the graph's degree distribution and feature co-occurrences. In our work [2] we extended these studies to tackle training time attacks even more effectively by solving the underlying bilevel optimization problem via the principle of meta-learning. Our experiments show that small graph perturbations consistently lead to a strong decrease in performance for graph convolutional networks, and even transfer to unsupervised graph embeddings. Remarkably, the perturbations created by our algorithm misguide the graph neural networks such that they perform worse than a simple baseline that ignores all relational information, thus highlighting the need for more robust alternatives.



1 | A small deliberate change of the data (adding/removing edges, changing node features) leads to a different/wrong prediction. Almost any node in the graph is vulnerable to such small perturbations, as shown in the right diagram.

Deep generative models for graphs

In a second research direction, we studied the principle of generative models for graphs – that is, models that aim to automatically generate realistic graphs. Such models have a longstanding history, with applications including data augmentation, anomaly detection, and recommendation. *Explicit* probabilistic models such as Barabási-Albert or stochastic blockmodels are the de facto standard in this field. However, it has also been shown on multiple occasions that our intuitions about structure and behavior of graphs may be misleading.

In our research [3] we proposed the first *implicit* generative model for graphs able to mimic real-world networks. We pose the problem of graph generation as learning the distribution of biased random walks over the input graph. The proposed model is based on a stochastic neural network that generates discrete output samples and is trained using the Wasserstein GAN objective. Our model is able to produce graphs that exhibit well known network patterns, such as community structure and degree distribution, without the need to specify any of them manually. Our model can also be used for generating graphs with continuously varying characteristics using latent space interpolation. Overall, our research provides strong evidence that implicit generative models for graphs are well suited for capturing the complex nature of real-world networks.

References

[1] D. Zügner, A. Akbarnejad, and S. Günnemann, “Adversarial attacks on neural networks for graph data.,” Proceedings of the ACM SIGKDD Conference on Knowledge Discovery and Data Mining (KDD), pp. 2847–2856, 2018. (Best Research Paper Award)

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

Focus Group **Neuromorphic Computing**

Prof. Helen Li (Duke University) | Hans Fischer Fellow
Shuhang Zhang (TUM) | Doctoral Candidate

Scientific Reports

Helen Li

Host
Prof. Ulf Schlichtmann
Electronic Design Automation, TUM

Toward high performance and reliability in neuromorphic computing

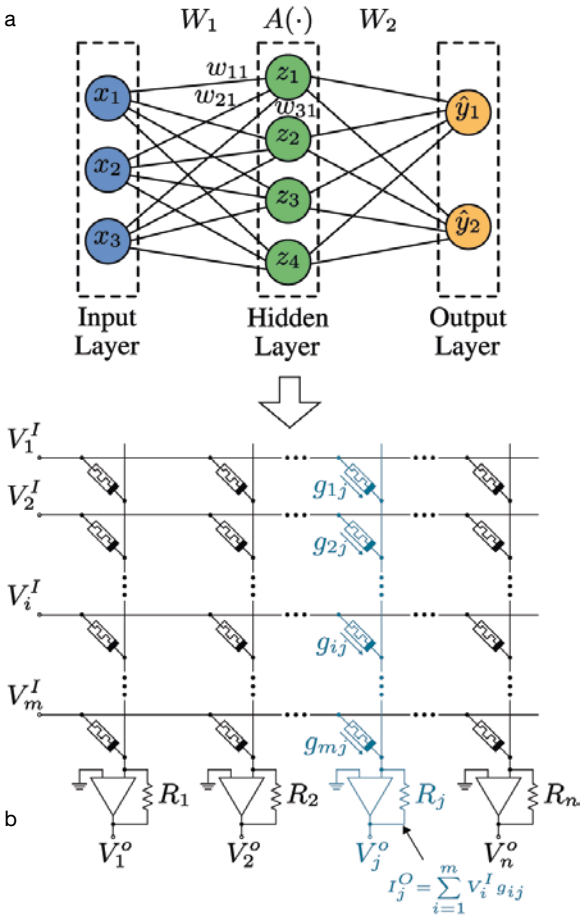
Neuromorphic computing, inspired by the human brain, aims to utilize very-large-scale-integration (VLSI) systems to mimic biological architectures and implement functionalities such as cognitive and self-learning abilities.

In the past decades, mimicking biological architectures was mainly achieved on the software level, especially with artificial neural networks. Figure 1a shows the basic structure of a neural network, which consists of an input layer, a hidden layer, and an output layer. The nodes represent neurons, and connections represent the relations between neurons in different layers. In a neural network, the output of a neuron is a function of the multiplication of the inputs and the weights of the connections. As the structure of neural networks is becoming more complex, a huge number of vector-matrix multiplications is required.

Previously the focus of research in this field has been mainly on optimization of neural networks on the software level. The huge number of vector-matrix computations are still executed on the traditional computing architecture, also known as the von Neumann architecture. Due to the separation of processor and memory, this architecture leads to a large latency since computing is much faster than data transfer. This phenomenon is also called the “memory wall” of the von Neumann architecture. This problem becomes more severe due to the explosive increase of generated data in neuromorphic computing.

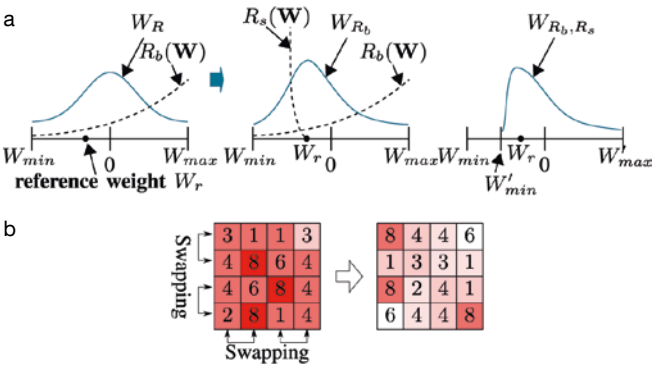
To tear down the memory wall, the traditional computing architecture can be reshaped by mimicking biological structures with memristor-based crossbars. Figure 1b shows such a crossbar, where memristors sit on the crosspoints of horizontal wordlines and vertical bitlines, representing the synapses between neurons. By programming these memristors (synapses) to different conductances to mimic different neuron connections in biological systems, this crossbar architecture can process input data similarly to the way biological systems work. In this crossbar, vector-matrix multiplications can be implemented efficiently. The vector can be represented by the input voltages onto the horizontal wordlines. The resulting current on a memristor is the multiplication of the voltage and its conductance, and the currents through memristors in a column are summed up naturally following Kirchoff’s Law. Consequently, the result of the vector-matrix multiplication is represented by the currents on the vertical bitlines.

Memristor-based neuromorphic computing has high scalability and power efficiency. As the memristor is a two-terminal thin-film structure, the dimension of memristors can be scaled down to the nanometer range, leading to a huge computing density in a single chip. In addition, memristors consume less power compared with the traditional computing components, and no power consumption at all if no voltage is applied on them. Therefore, they are also suitable for future high-efficiency mobile computing.



1 | a) Basic structure of neural networks;
b) memristor crossbar architecture

As a promising technology for next-generation computations, memristor-based neuromorphic computing faces reliability issues, e.g., aging and thermal effects. As a basic circuit element, memristors can only be programmed reliably a given number of times. Afterwards, the working ranges of the memristors deviate from the fresh state. This phenomenon is called aging. Consequently, the expected conductances of memristors corresponding to the weights after training may fall outside of the valid ranges, potentially leading to a significant accuracy degradation. In addition, an uneven temperature distribution due to different conductances across a crossbar further accelerates the aging effect. Moreover, uneven temperatures can cause accuracy discrepancy between the tuning process and inference, thus reducing the lifetime of these crossbars again.



2 | a) Regularizations in the modified weight training;
b) row-column swapping during hardware mapping

To deal with these issues, a software training and hardware swapping co-optimization framework [1] has been proposed in our group in 2018. During the software training phase, the trained weights are biased to smaller values based on a pre-selected reference weight, leading to a skewed weight distribution, as shown in Figure 2a. In this case, most of the weights are mapped to high resistances of memristors. Since higher resistances lead to smaller currents, thermal and aging effects can thus be reduced.

To deal with the unevenness of aging and thermal effects, the weights are also remapped according to the aging status and temperature of the memristors with row-column swapping, as shown in Figure 2b. In this method, large conductances of memristors are mapped onto less-aged memristors to balance aging stress. The temperature is also balanced with this technique, since memristors with large currents are moved away from each other. Consequently, the lifetime of crossbars can be improved significantly.

Reference

[1] S. Zhang, L. Zhang, B. Li, H. Li, and U. Schlichtmann, "Aging-aware Lifetime Enhancement for Memristor-based Neuromorphic Computing," in Proc. of the Conference on Design, Automation and Test in Europe (DATE), Florence, Italy, 2019.

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

Focus Group **Visual Computing**

Prof. Matthias Nießner (TUM) | Rudolf Mößbauer Tenure Track Professor
Prof. Leonidas Guibas (Stanford University) | Hans Fischer Senior Fellow
Dr. Angel X. Chang (Eloquent Labs / Simon Fraser University) | Hans Fischer Fellow
Armen Avetisyan, Manuel Dahnert, Ji Hou, Andreas Rößler, Dave Zhenyu Chen (TUM)
Doctoral Candidates

Scientific Reports

Matthias Nießner

Leonidas Guibas

Angel X. Chang

Host
Visual Computing, TUM

The Visual Computing Focus Group is a group of research enthusiasts pushing the state of the art at the intersection of computer vision, graphics, and machine learning. Our research mission is to obtain high-quality digital models of the real world, which include detailed geometry, surface texture, and material in both static and dynamic environments. In our research, we heavily exploit the capabilities of RGB-D and range sensing devices that are now widely available. However, we ultimately aim to achieve both 3D and 4D recordings from monocular sensors – essentially, we want to record holograms with a simple webcam or mobile phone. We further employ our reconstructed models for specific use cases, such as video editing, immersive AR/VR, semantic scene understanding, and many others. Aside from traditional convex and non-convex optimization techniques, we see great potential in modern artificial intelligence, mainly deep learning, in order to achieve these goals.

Relevance and impact

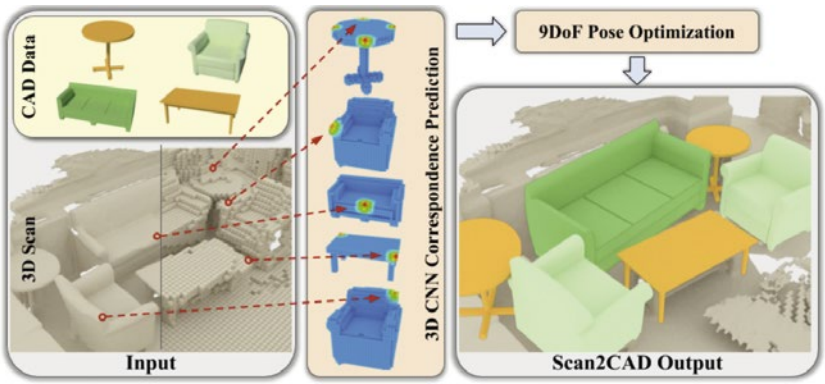
The relevance of the research applies to several areas that are impacted by 3D digitization and semantic scene understanding. These include applications ranging from entertainment and communication to medical and autonomous robotics applications. However, the primary goal is to replace videos and images with interactive but photo-realistic 3D content of the future – i.e., holograms, which we believe will impact the wide range of aforementioned industries.

The practical research impact of the group can be seen by massive media presence of the group, including several appearances in documentaries and news on German national TV (*Pro7 Galileo, ZDF Morgenmagazin, RTL Nachrichten*, etc.), and prominent news outlets (*Wall Street Journal, New York Times, Spiegel,* etc.).

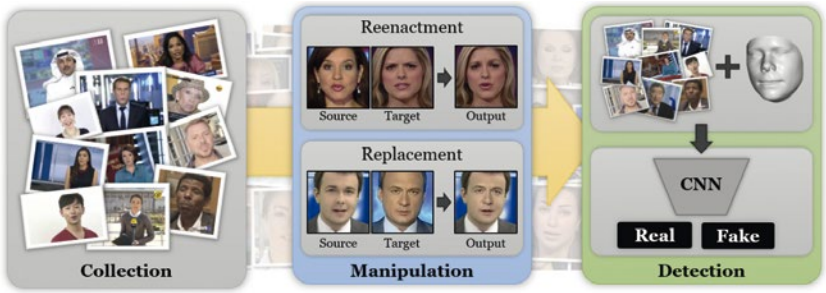
Future plans

Digitization and understanding of real-world, 3D environments is still a wide open research field. First of all, we will continue in the current developments on neural networks specifically tailored to the 3D case in order to process and analyze 3D geometry, associated RGB images, and alternative data input. Generative networks, which are required to generate clean 3D geometry for realistic 3D capture and photo-realistic re-rendering, are a critical component. While the community has seen a lot of progress in the last years along these lines, there are still significant challenges and exciting research opportunities in order to achieve 3D holographic capture.

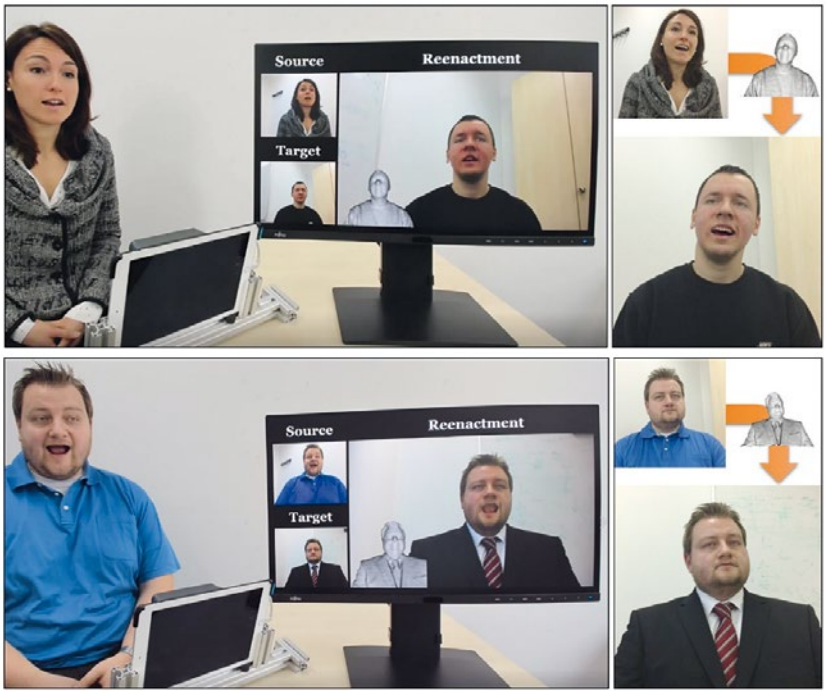
Additional material can be found on this website:
https://niessnerlab.org/publications.html



1 | Scan2CAD takes as input an RGB-D scan and a set of 3D CAD models (left). We then propose a novel 3D CNNapproach to predict heatmap correspondences between the scan and the CAD models (middle). From these predictions, we formulate an energy minimization to find optimal 9 DoF object poses for CAD model alignment to the scan (right).



2 | FaceForensicsis a database of facial forgeries that enables researchers to train deep-learning-based approaches in a supervised fashion. The database contains manipulations created with three state-of-the-art methods, namely, Face2Face, FaceSwap, and DeepFakes.



3 | Our novel HeadOn approach enables real-time reenactment of upper body motion, head pose, face expression, and eye gaze in human portrait videos. For synthesis of new photo-realistic video content, we employ a novel video-based rendering approach that builds on top of a fully controllable 3D actor model. The person-specific model is constructed from a short RGB-D calibration sequence and is driven by a real-time torso and face tracker.

Focus Group **Image-based Biomedical Modeling**

Prof. Bjoern Menze (TUM) | Rudolf Mößbauer Tenure Track Professor
Esther Alberts, Patrick Christ, Hongwei Li, Jana Lipková, Markus Rempfler, Judith Zimmermann (TUM) | Doctoral Candidates*

Scientific Reports

Bjoern Menze

Host
Image-based Biomedical Modeling, TUM

Image-based biomedical modeling

The 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.

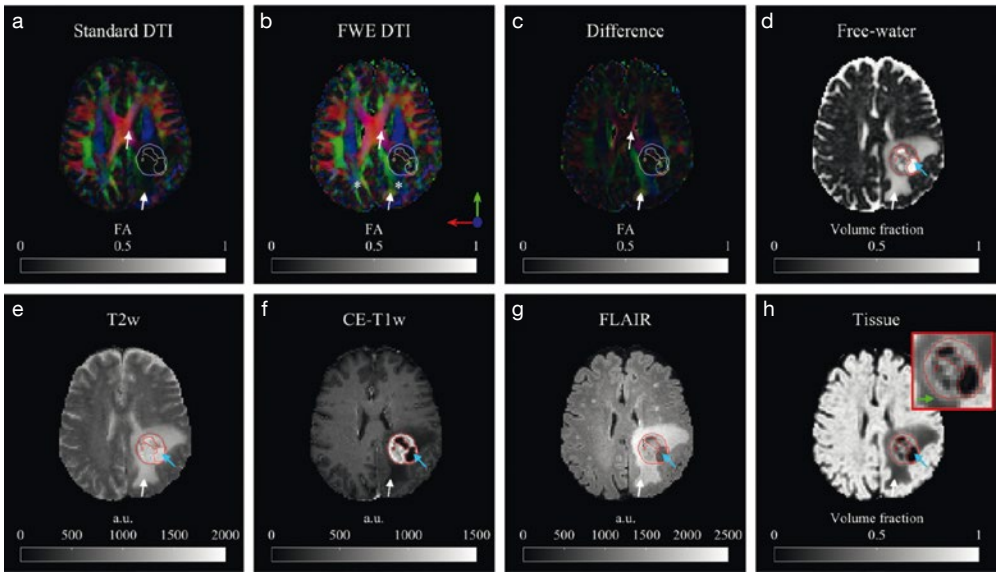
Clinical neuroimage analysis

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 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. In the past year, we proposed a new approach to segment brains also in images acquired in patients with large lesions [1] and presented a deep learning-based image segmentation algorithm that localizes white matter hyperintensities (WMH) and that had previously won the MICCAI WMH segmentation challenge [2].

Modeling physiological function in magnetic resonance images using machine learning

Another direction of research led to major publications in the past year. We demonstrated for several applications in magnetic resonance imaging (MRI) how to use machine learning approaches to estimate physiological parameters in perfusion and diffusion MRI. We developed algorithms for separating the signal of tissue water and tissue microstructure in diffusion MRI [3]–[4]. Here, tissue water is a common source of inaccuracies and errors, particularly in brain lesions, and the microstructure undergoing characteristic changes in various subtypes of brain tumors – as we had shown in a study in the previous year [5]. We also demonstrated how to infer parameters describing blood flow from perfusion image time series, and how to incorporate well known blood flow models from biophysics into the training of the convolutional neural network [6]–[7] and illustrated the application of these new techniques in blood flow images acquired in stroke patients [8]

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



1 | **Improving the imaging of brain tumors using machine learning.** We developed a machine learning-based correction of the tissue microstructure maps (a–c), which estimates the tissue water component (d). This adds to the information obtained from conventional magnetic resonance images (e–g), revealing additional tumor substructures in the tumor (h). (Figure from [3])

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

Focus Group **Microfluidic Design Automation (MDA)**

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Prof. Tsung-Yi Ho (National Tsing Hua University) | Alumnus Hans Fischer Fellow
Chunfeng Liu, Yasamin Moradi | Doctoral Candidates

Scientific Reports

Krishnendu Chakrabarty

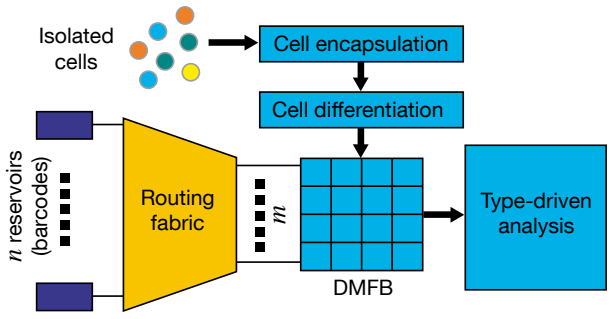
Tsung-Yi Ho

Host
Prof. Ulf Schlichtmann
Electronic Design Automation, TUM

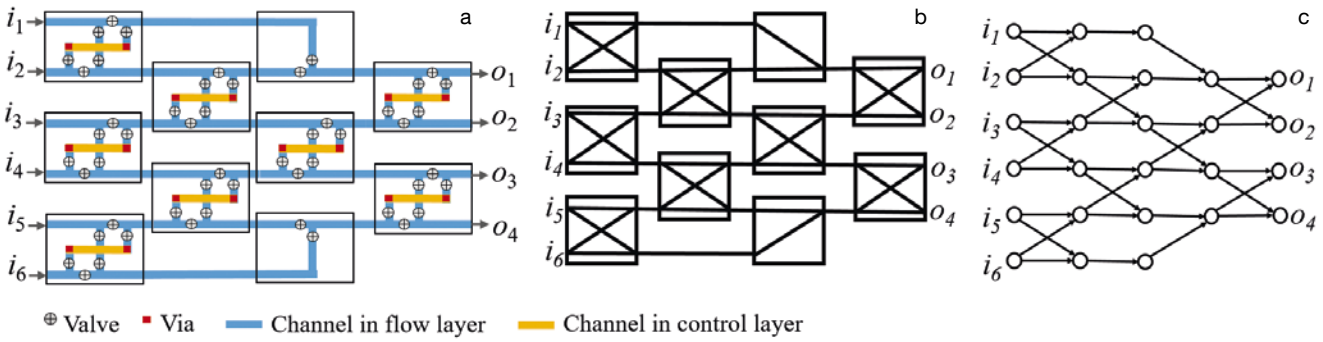
Fault-tolerant microfluidic routing fabric for droplet barcoding in single-cell analysis

Single-cell analysis is used to advance our understanding of diseases such as cancer [1]. In a single-cell analysis procedure, thousands of heterogeneous cells are analyzed individually in order to understand the cell population. Using recent advances in microfluidic technologies, single-cell analysis can now be performed in a high-throughput manner. Microfluidic platforms allow the precise control of samples and reagents for miniaturized bioassays. These platforms are typically based on two distinct technology domains. Flow-based microfluidic platforms consist of microvalves and channels that are used to guide liquid flow. On the other hand, in digital microfluidic biochips (DMFBs), an array of electrodes is used to manipulate discrete droplets of nano- and pico-liter volumes. The flow of a single-cell analysis experiment consists of several steps, each of which can only be carried out efficiently in a specific microfluidic technology domain. In the first step, input cells are isolated and encapsulated inside droplets. Next, heterogeneous cells are differentiated according to their type. After the type of a cell is identified, a barcoding droplet that represents the cell type must be mixed with the sample. Droplet barcoding is essential to keep track of the samples, because in the next step, each cell is manipulated through biochemical procedures and its type may no longer be identifiable. After droplet barcoding, a bioassay is carried out on each cell based on its type. The result of this analysis is associated with droplet barcodes to draw meaningful conclusions from the experiment.

To perform single-cell analysis efficiently, components that work in different microfluidic domains are required to be connected to each other by suitable interfaces. Recently, a hybrid platform for single-cell analysis was introduced [2]. Figure 1 illustrates a model of this platform. In this platform, a flow-based routing fabric is used to direct barcoding droplets from the barcode reservoirs to the DMFB. Samples are then mixed with barcoding droplets in the DMFB and single-cell bioassays are performed according to the cell type. The routing fabric consists of valves and channels, and it can be mapped to a directed graph. Figure 2 shows the layout of a 6-to-4 routing fabric and its corresponding graph model. This structure enables scalable and high-throughput droplet barcoding. However, recent studies show that channels and valves may be blocked due to physical defects [3]. Therefore, connections in the routing fabric are prone to failures. If an input and an output of the routing fabric get disconnected due to these failures, the barcoding droplet directed along the path between this input/output pair will not pass through and a sample in the downstream part will not receive any barcode. Therefore, no meaningful conclusion will be drawn from the analysis of the sample.

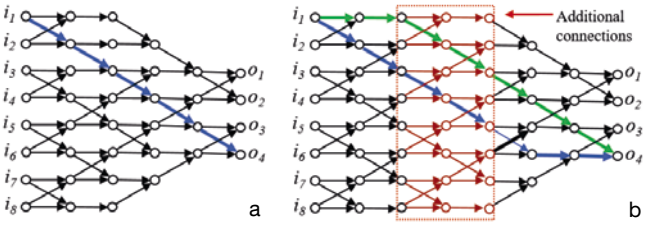


1 | The hybrid platform for single-cell analysis.



2 | (a) Layout of a 6-to-4 routing fabric; (b) model of a 6-to-4 routing fabric; (c) corresponding graph for a 6-to-4 routing fabric.

If an input/output pair of the routing fabric is connected through only one path, a partial failure on this path results in disconnection of the input/output pair. However, if multiple paths exist between each input/output pair, a faulty path can be avoided by using a dynamic routing algorithm and a barcoding droplet can be routed through an alternative path. We have focused on creating alternative paths to ensure tolerance of any single failure while maintaining efficiency and high performance of the design. The proposed method leads to a minimum increase in the size of the routing fabric. Figure 3 shows an input/output pair that is connected through only one path in the original design. The input/output pair is connected through two non-overlapping paths in the redesigned routing fabric. We have shown that the resulting design is also resilient to a high percentage of multiple failures. As part of future work, we will investigate the possibility of increasing the reliability of the platform. We will also look for efficient methods for testing the routing fabric. We will combine this with our ongoing research into testing of flow-based and programmable microfluidic biochips which we will report on in more detail next year. To avoid faulty parts of a path, we will apply fault detection and fault localization techniques. Finally, dynamic routing methods can be used for runtime adaptation.



3 | (a) The only path between i_1 and o_4 in the original design; (b) two non-overlapping paths between i_1 and o_4 in the redesigned routing fabric.

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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, Michael Tesch (TUM) | Doctoral Candidates

Scientific Reports

Dominique Sugny

Host
Prof. Steffen J. Glaser
Organic Chemistry, TUM

Our research is aimed at developing and applying 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. The main results are briefly summarized below.

Time-optimal selective pulses of two uncoupled spin 1/2 particles

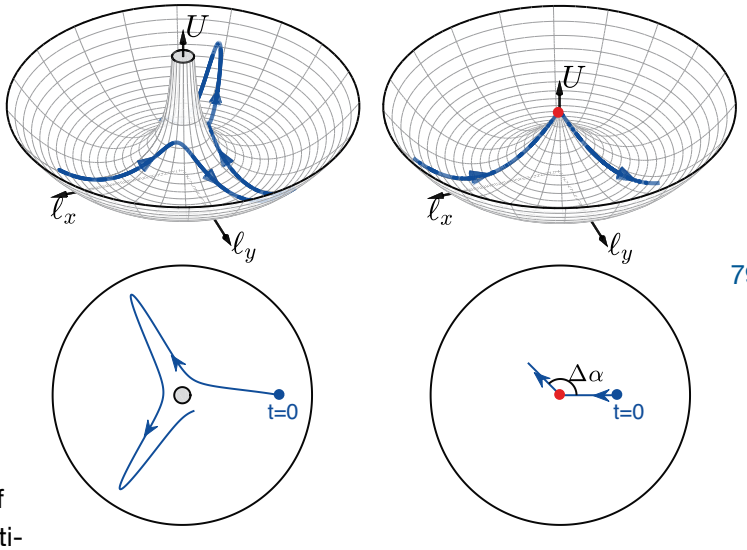
We have applied mathematical optimal control techniques to solve a standard control problem in spin systems. We investigate in [1] the time-optimal solution of the selective control of two uncoupled spin 1/2 particles. Using the Pontryagin maximum principle (PMP), we derive the global time-optimal selective pulses for two spins with different offsets. The PMP is a general mathematical procedure which consists in transforming an optimal control problem into a generalized Hamiltonian system subject to specific boundary conditions. In the case under study, we show that the Pontryagin Hamiltonian can be written as a one-dimensional effective Hamiltonian, i.e., it corresponds to a pseudo-particle moving in a given potential energy surface. An example of trajectories is given in Figure 1.

The optimal fields can be expressed analytically in terms of elliptic integrals using the trajectories of the pseudo-particle. The time-optimal control problem is solved for different selective processes. The two spins, which can move along a sphere, called the Bloch sphere, are assumed to be initially at the thermal equilibrium state, i.e., the north pole of the Bloch sphere. We consider in this work both the selective excitation and inversion processes for which the goal is to steer one of the two spins towards the equator or the south pole, while bringing the other back to the initial state.

Optimal control of an inhomogeneous spin ensemble coupled to a cavity

The detection of individual spins is a challenging issue in magnetic resonance. Different experimental strategies have been proposed to date to reach this single-spin limit. A promising option is to push to its physical limit the inductive detection method in electron spin resonance. Recent progress has shown that only 100 spins can by now be detected with a signal-to-noise ratio of 1. An example of the experimental setup used by our collaborators in Saclay (Paris) is displayed in Figure 2. In [2], we have numerically shown the extent to which optimal control fields that are robust against system uncertainties help to enhance the sensitivity of the detection process, thus reducing the number of detected spins.

Optimal control techniques for *in vivo* magnetic resonance imaging



1 | Trajectories of the pseudo-particle in the effective potential U in the regular (left) and singular (right) cases. The upper panels show the potential U as a function of the coordinates of the associated angular momentum. The red dot of the right panel depicts the singular point in which the particle holds during a finite time. While the particle is stuck on this point, the control fields are singular. The lower panels show a projection of this motion in the horizontal plane, providing a better view of the variation of the phase of the pulse.

We have developed new approaches in MRI based on optimal control theory. In [3], we propose a rigorous optimal control framework for the design of preparation schemes that optimize MRI contrast on the basis of differences in relaxation time. Compared to previous optimal contrast preparation schemes, a drastic reduction of the optimization parameter number is performed. The proposed approach reduces the computation time of robust preparation schemes to around a minute (whereas several hours were required with previous schemes), with negligible performance loss. Simulation, *in vitro*, and *in vivo* results validate this improvement, illustrate the straightforward applicability of the proposed approach, and point out its flexibility in terms of achievable contrasts.

Magnetic resonance elastography (MRE) is a standard technique to visualize biological tissue displacements induced by shear wave propagation. Mechanical properties of tissues can be derived from the wave characteristics (wavelength, attenuation). It was initially proposed to encode the tissue displacement in the magnetization phase image by applying appropriate time-varying gradients after the radio-frequency (RF) excitation. Instead of using standard motion-encoding gradients, we propose in [4] to design a tailored RF pulse to simultaneously perform selective excitation and motion encoding in presence of a constant gradient. This offers numerous advantages, such as reducing eddy current artifacts and relaxing the constraint on the maximum gradient switch rate. Simulations and *ex vivo* experiments were performed to show the efficiency of this new approach.

The different experiments were performed in CREATIS (Lyon, France). A patent on the control of the magnetization phase has also been published.

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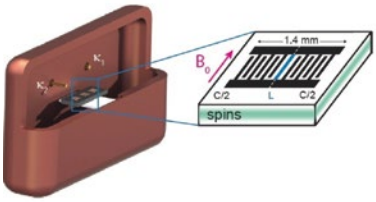

2 | Experimental setup used at the CEA Saclay (group of P. Bertet, Paris) for detecting individual spin in electron spin resonance.

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

Focus Group **Phase-Contrast Computed Tomography**

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Regine Gradl (TUM) | Doctoral Candidate

Scientific Reports

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Thomas Koehler

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Prof. Ernst Rummeny
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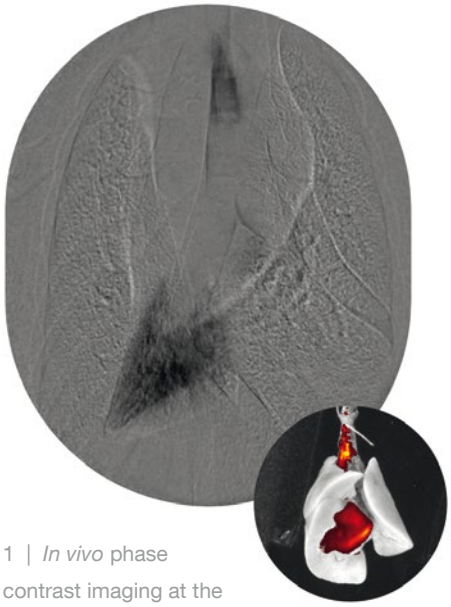
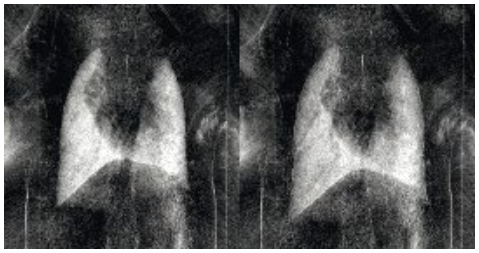
In conventional X-ray imaging, the image contrast is formed by X-ray attenuation, and reflects the physical interactions of photoelectric absorption and Compton scattering. Both of these interaction processes are modeled conveniently by interpreting X-rays as photonic particles. If, in contrary, X-rays are described as electromagnetic waves, other (wave-optical) interaction effects occur, and yield diffraction, refraction, phase-shift, and scattering. Our Focus Group aims to exploit these wave-optical interactions of X-rays with matter for biomedical research and clinical applications. Using the Munich Compact Light Source (MuCLS), the first table-top brilliant synchrotron X-ray source, we have obtained results in living mice that indicate that the scattering or "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).

In parallel with preclinical imaging studies, we have been developing fast phase-contrast X-ray imaging as a biomedical research tool. Until now, biomedical research was performed only at synchrotron research facilities, where a bright X-ray beam enables fast imaging and high resolution. However, synchrotron facilities are too large to fit within a normal research laboratory and are not widely available. 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. Having established phase-contrast and dark-field imaging techniques at this source during the last few years, this year we performed a range of biomedical research studies at the source [1].

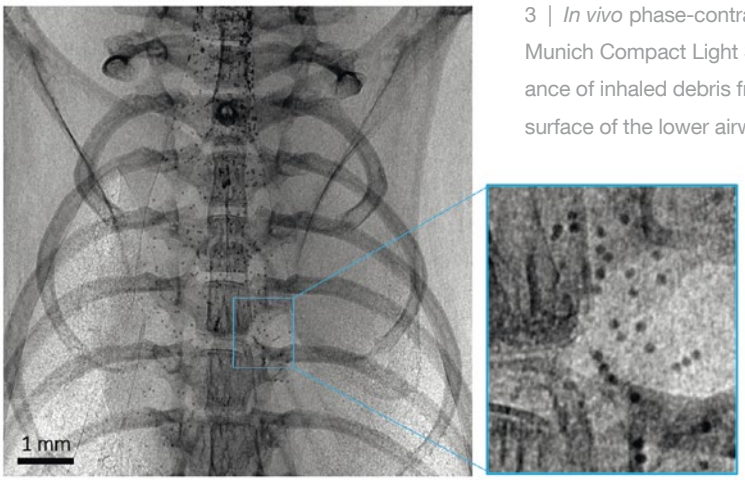


1 | *In vivo* phase contrast imaging at the Munich Compact Light Source captures the delivery of treatment to the lungs in a high speed movie (main), which corresponds well with the established fluorescence technique (lower panel, captured *ex vivo*).

In collaboration with Professor Otmar Schmid and colleagues from the Helmholtz Centre Munich, we looked at regional deposition of treatment in the lungs, shown in Figure 1 [2]. We also captured the first "dynamic" dark-field images, applied to monitor the lungs during the breath cycle, showing a change in signal as the lungs are expanded (compare panels in Figure 2), which relates to the expansion of the air sacs in the lung [3]. These results can inform the best point in the breath to capture a single diagnostic image, and a sequence like this can provide additional insight into the dynamic properties of a given lung. In addition, we captured the first sequences of the clearance of inhaled particulates from the lower airways, a key mechanism in maintaining healthy lungs, performed in collaboration with Professor Ernst Rummeny and his team from the University Hospital Klinikum rechts der Isar (Figure 3).



2 | *In vivo* dark field imaging at the Munich Compact Light Source captures changes in the lung during the breath cycle, observed here when the lungs are at minimum volume (left) and maximum volume (right).



3 | *In vivo* phase-contrast X-ray imaging at the Munich Compact Light Source captures the clearance of inhaled debris from the lungs along the surface of the lower airways and toward the mouth.

These imaging capabilities can provide a deeper understanding of respiratory physiology and help to accelerate new respiratory treatments and diagnostic imaging to the clinic.

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

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, Dr. Sven Puchinger (TUM) | Postdoctoral Researchers
Haider Alkim, Lukas Holzbaur, Andreas Lenz, Georg Maringer, Julian Renner (TUM)
Doctoral Candidates

Scientific Reports

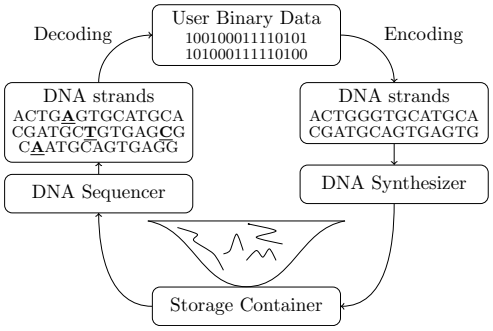
Antonia Wachter-Zeh

Camilla Hollanti

Host
Coding for Communications and Data Storage, TUM

The COD Focus Group studies coding for security, communications, and data storage.

Coding for DNA storage



1 | The principle of storing data in DNA sequences.

The existence of reliable and high-capacity archival storage is indispensable in a modern society, where large amounts of human data are stored in digital archives. This not only becomes evident with respect to the necessity of archived data for prosecuting criminals, but also has an essential ethical aspect concerning the preservation of historic events for future generations. DNA-based storage is a novel technology where digital information is stored in synthetic DNA molecules. The recent advances in DNA sequencing methods and decrease in sequencing costs have paved the way for storage methods based on DNA. The natural stability of DNA molecules – the genetic information from fossils is maintained over tens of thousands of years – motivates their use for long-term archival storage. Furthermore, because the information is stored on the molecular level, such storage systems would have extremely high data densities. Recent experiments report data densities of 2 PB/gram, which corresponds to the capacity of a thousand conventional hard disk drives in one gram of DNA.

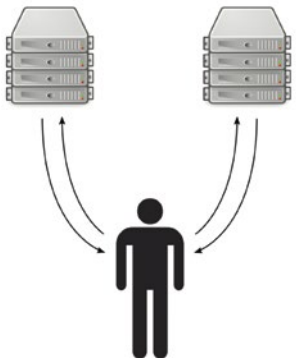
However, DNA storage is prone to errors, and therefore one must protect the embodied data with error-correcting schemes that can recover the stored data even in the presence of errors. There are three main types of errors that must be dealt with in DNA-based storage. Since the data is spread over many short DNA sequences, some DNA strands might be lost during the reading process. Then, during the data replication process, errors that result from mutations can corrupt the data. Error-correcting schemes for such errors, i.e., duplications, have been investigated in [1] and [2]. Further, current high-speed sequencing methods can be erroneous, and single symbols of the sequenced strands can be mistaken, inserted, or deleted from the sequence.

Our group also deals with the design of error-correcting schemes that can cope with these kinds of errors. One focus is on the design of efficient codes that require a small amount of redundancy but still provide sufficient reliability [3]. Further, we investigate the optimality of these schemes by finding the capacities of such DNA-based storage systems.

Private information retrieval

Data retrieval from a database shared by many users is a common occurrence in online services (e.g., Netflix, YouTube,...). Privacy protection regulations, such as the new EU data protection laws, pose new challenges for providers of such services, as not only privacy concerns against other users/attackers outside the system have to be addressed, but also the privacy of the user against the database provider.

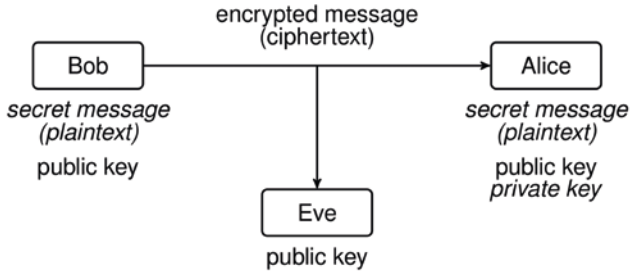
Classical approaches to this problem include anonymity, i.e., hiding the identity of the user, and data confidentiality, i.e., hiding the contents of the files from the database. However, none of these approaches is suitable, e.g., for a shared database that requires authentication of the user, such as, e.g., Netflix. This motivates the security goal referred to as Private Information Retrieval (PIR), in which the identity of the file desired by the user is hidden from the data base, either through cryptographic assumptions or solutions based on multiple servers and coding. In recent years several PIR systems have been introduced in an attempt to minimize the communication overhead and computational complexity. Most existing approaches focus on the retrieval of entire files without delay constraints, which is not well suited for, e.g., video streaming, which accounts for a large part of the downstream Internet traffic today. To address this issue we introduced a scheme that allows for the retrieval of large files (e.g., movies) in a streaming manner [3]. This decreases the decoding delay while keeping the storage and communication overhead low, thereby contributing to the continous efforts of making PIR practical. In future work we will consider the problem of privately searching a database, which is essential for any practical private information retrieval scheme, as these usually require the user to know the contents of the servers and the index of the desired file.



2 | Scheme of Private Information Retrieval: the user wants to download a file without revealing its identity to the server.

Code-based cryptography

Nowadays, cryptographic algorithms are essential for modern communication and authentification. For example, not only every mobile phone call and e-mail, but also each use of a debit card or a passport is protected by these techniques. Cryptographic algorithms that are used very frequently in practice are based either on the hardness of computing the discrete logarithm (e.g., ElGamal) or on the hardness of decomposing a large number into its prime factors (e.g., RSA). However, assuming an attack of a sufficiently large quantum computer, several classical public-key algorithms such as RSA and ElGamal become insecure, since computationally intensive mathematical problems like the factorization of numbers or the computation of discrete logarithms become easy-to-solve.



3 | Public key cryptography: Bob wants to send a secret message to Alice, but the eavesdropper (Eve) should not be able to decrypt it.

Thus, the realistic threat of a quantum supercomputer has motivated research on post-quantum cryptography. It is now necessary to design algorithms that are not only secure against an attack of a quantum computer, but also efficient such that they can be used in practical applications. Therefore, the National Institute of Standards and Technology (NIST) has initiated a process to solicit, evaluate, and standardize one or more quantum-resistant public-key cryptographic algorithms. One promising approach to achieve this security is code-based cryptography, where encryption and decryption are based on encoding and decoding an algebraic code. The main drawback of code-based cryptography is the large size of the public key. To overcome this issue, we repaired a recently broken code-based cryptosystem with small key sizes in [5], and we proposed a new system with relatively small key sizes in [6].

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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**

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Hela Jedda (TUM) | Doctoral Candidate

Scientific Reports

A. Lee Swindlehurst

Hosts
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Signal Processing
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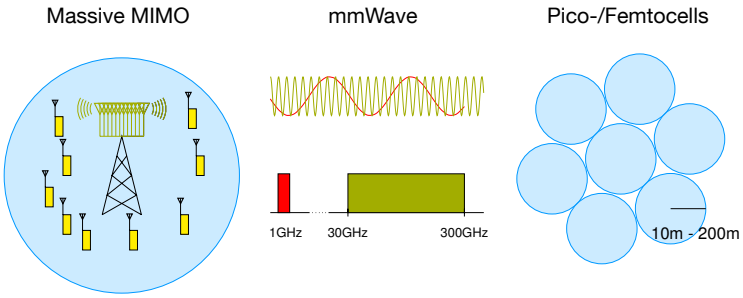
To meet the increasing demand for higher data rates, smaller latency, and high reliability, three technological trends are emerging as subjects of research:

- massive MIMO systems, where the base station is equipped with a large number of antennas and serves a smaller number of mobile stations,
- millimeter-wave (mmWave) communication, where carrier frequencies between 30 GHz and 300 GHz are deployed and thus much more spectrum is available, and
- pico- and femtocells, where the maximum range of the network cell is less than 200m.



1 | Three emerging technologies for future communication systems.

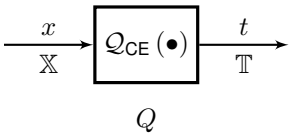
The combination of these three technologies leads to a much denser wireless network operating at higher frequencies. Consequently, the hardware power consumption per unit area increases alarmingly. Thus, power efficiency is one of the crucial challenges for future communication systems.

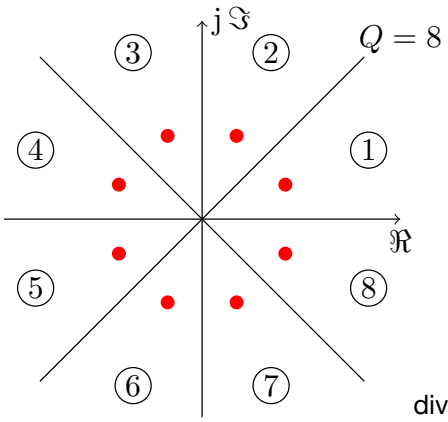
Quantized constant envelope signaling

In a massive MIMO wireless cellular network, the base station consumes the largest fraction of the power, since it is equipped with a large number of antennas. Behind each transmit antenna, there is a chain of hardware components for processing the signal and converting the digital data into an electromagnetic wave. The most critical components at the transmitter are:

- the power amplifier (PA), and
- the digital-to-analog converter (DAC).

The PA is a device that amplifies the signal before transmitting it in the air to reach the desired receiver. The amplification is applied linearly if the input signal lies within two thresholds values. Otherwise, the input signal gets clipped, and strong nonlinear distortions are produced. To make sure that the amplification is at the same time linear and power-efficient, the input signal should be of constant envelope (CE); that is, the input signal must have a constant magnitude but can have arbitrary phase values. In the context of CE signaling, a polar DAC is required. The information is then carried by the phase only, and the resolution of the DAC determines the number of discrete phase values that can be generated at the output. The lower the resolution, the less the power consumption. A power-efficient PA and DAC can be modeled in the baseband by the CE Quantizer (CEQ) that is illustrated in Figure 2.

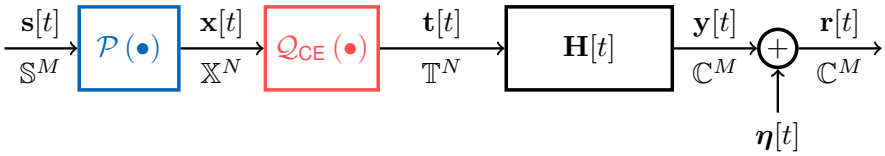




2 | Constant Envelope Quantizer (CEQ)

It is characterized by the number of discrete points that can be generated at the output, Q. The complex-valued plane is divided into Q rotationally symmetric angle sectors. Depending on which angle sector the quantizer input belongs to, the output gets a constant magnitude and one discrete phase value among Q values.

For the downlink of multi-user (MU) massive MIMO systems that are equipped with (CEQs) as modeled in Figure 3, the design of optimal transmit signal processing algorithms requires knowledge about the statistical properties of the CEQs.



3 | System model of downlink MU massive MIMO system with CEQs.

With the help of Price's theorem [1] and Pawula's theorem [2], we have been able to formulate a new theorem to derive the CEQ statistics. We used the derived expressions for the design of linear transmit signal processing techniques to mitigate the CEQ distortions in addition to the channel distortions and other sources of noise and interference. Linear transmit signal designs that consider the CEQ as an additional noise source show moderate improvement compared to the linear processing that ignores the presence of the CEQ in the design.

New one-bit sampling architectures

As mentioned above, to save power and chip area, low-resolution quantizers have recently been an area of active interest in the community. There has been extensive work on 1-bit ADCs for channel estimation in massive MIMO systems [2]–[6]. While it has been shown that 1-bit quantization causes only a minimal degradation at low signal-to-noise ratios (SNRs), at medium to high SNR the loss is substantial. To improve the performance of low-resolution sampling, one can of course increase the resolution of the quantizer. Simulations by a number of authors have shown that using ADCs with 3-5 bits of resolution in massive MIMO provides performance that is very close to that achievable with infinite precision and still provides higher energy efficiency [7]. As an alternative to increasing the ADC resolution, one can increase the sampling rate at which the 1-bit quantizers operate.

This approach has been studied in [8]–[10] and found also to be effective in reducing the medium-to-high-SNR performance loss for 1-bit quantization. A well known technique that combines 1-bit quantization and oversampling is the so-called ΣΔ ADC, which to date has primarily found application in ultrasound imaging. The ΣΔ converter scheme consists of an oversampled modulator,

which is responsible for digitization of the analog signal, and a negative feedback loop. This architecture provides noise shaping that alters the power spectral density of the quantization noise such that it is no longer uniform, as in regular quantization, but is shifted to higher frequencies. The quantization noise can then be filtered by a digital lowpass filter and decimation stage so that it has a reduced effect on the signal. The use of ΣΔ ADCs in parallel architectures for MIMO systems has been studied in [11]–[12].

A similar effect can be achieved by oversampling in space instead of time, i.e., using an antenna array whose elements are separated by less than half the wavelength. In spatial ΣΔ ADCs, the integration is performed by feeding the quantization error from one stage to the adjacent antenna input instead of feedback via a time delay. The spatial frequency is proportional to the sine of the angle of arrival measured from the array broadside. Low spatial frequency implies that signals are impinging from the broadside, and the ΣΔ modulator can be expected to exhibit lower quantization error than for signals from the endfire direction. The noise shaping characteristics of first- and second-order spatial and cascaded (space-time) ΣΔ architectures have been the focus of prior work in this area [13]–[17].

In our work, we have developed an optimal channel estimation method for massive MIMO systems with first-order spatial ΣΔ ADCs. The model for this system is derived and the Bussgang decomposition is applied in order to find an equivalent linear signal-plus-quantization-noise representation that is the basis for the LMMSE channel estimation [3]. Our approach explicitly takes into account the spatial correlation between the outputs of the ΣΔ ADC array. The feedback structure of the ΣΔ array complicates the calculation of the required covariance matrices needed for the Bussgang approach, rendering a closed-form solution impossible. However, the special structure of the data flow allows us to find a recursive solution for the covariance matrices, and hence the LMMSE estimator. The case with orthogonal pilots is considered since the block-diagonal nature of the correlation matrices can be leveraged.

Our numerical results indicate that, at low-to-medium SNRs, the LMMSE channel estimator for the ΣΔ array yields channel estimates that are very close to those provided with infinite resolution, and significantly better than standard 1-bit quantization, with a very small increase in hardware complexity.

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

Underground Reading during the Chinese Cultural Revolution

Prof. Lena Henningsen (TUM / University of Freiburg) | Amalie Baur Fellow

Scientific Reports

Lena Henningsen

This project investigates the literary and intellectual field during the Chinese Cultural Revolution through the lens of reading practices. The project investigates two subprojects: one focuses on actual reading practices as recorded in life-writing about the Cultural Revolution, while the other examines unofficial handwritten entertainment fiction from the era.

Tracking what actual people read during the era and how this mattered to their lives and to Chinese society at large, this project re-evaluates intellectual history through a more grassroots perspective. Other than what the propaganda of the Chinese Communist Party at the time may have wished for and contrary to what some literary histories still claim, the Cultural Revolution was not an era in which foreign texts did not matter. Quite the contrary, Chinese classics, Chinese modernism, and foreign literature such as Salinger's *Catcher in the Rye* or Kerouac's *On the Road* enjoyed immense popularity. These findings attest to a cosmopolitanism that was practiced by parts of the Chinese population during the Cultural Revolution, and they indicate that many of the literary and intellectual debates commonly associated with the post-Maoist reform era had their origin in grassroots practices of the Cultural Revolution, albeit often illegal and clandestine.

One type of reading was popular at the time, even though many of the autobiographical sources are silent about this genre: unofficial, handwritten entertainment fiction that was written by (mostly) anonymous writers and then circulated unofficially, being copied, rewritten, and modified by some of its readers. These texts narrate entertaining stories about crime, espionage, love, and (sometimes) sex. They thus fulfill their readers' (and authors') desires about entertainment and, at times, escapism, all of which were lacking from the official literature that propagated larger-than-life-heroes to be emulated by their readers. The characters in these manuscript stories, on the contrary, are ambivalent. In most cases, they are not outright dissidents. Rather, they are also portrayed as upright characters, often communists who go to great lengths for the well-being of the nation. But they are allowed instances of hesitation, and they are allowed to strive for a fulfilled partnership with the person they love. While, on the surface, most of these stories appear to be apolitical and "mere" entertainment, this project has established that the texts need to be taken as highly political: First, their mere existence is a political issue; the vast circulation and the entertaining nature of the majority of the texts make them outright counter-revolutionary within the historical context of the Cultural Revolution. Second, beyond the surface of entertainment, the texts invite interpretation along political lines and with reference to the realities suffered during the Cultural Revolution. Third, a number of texts are explicit in their criticism of the Cultural Revolution.

Both subprojects thus illustrate the value of grassroots perspectives and the plurality of intellectual and literary life during the Cultural Revolution.

A book manuscript has been finalized and was being submitted for review by an academic publisher as this report was written.

1 | Unofficial handwritten entertainment fiction from the Chinese Cultural Revolution.

Focus Group **Artificial Electronic Skin**

Prof. Takao Someya (University of Tokyo) | Hans Fischer Senior Fellow
Dr. Mohsen Kaboli (TUM) | Postdoctoral Researcher

Scientific Reports

Takao Someya

Host
Prof. Gordon Cheng
Cognitive Systems, TUM

Reaching for technology inspired by the human sense of touch

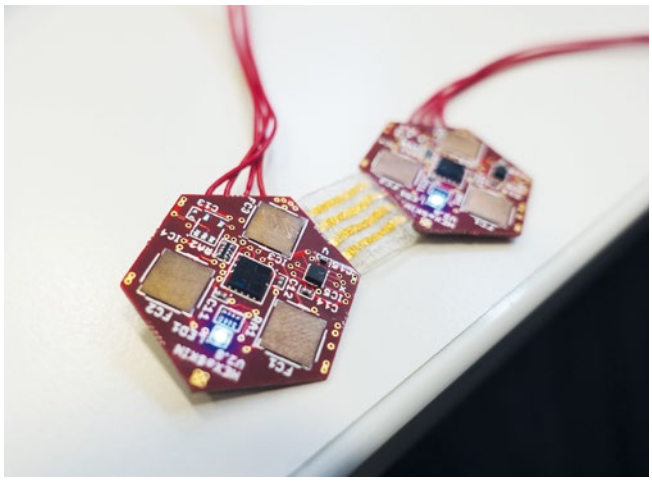
1 | Prof. Cheng and Prof. Someya after the keynote speech of Prof. Someya at IROS'18

The Focus Group aims at the realization of a novel paradigm that could lead to important advances in robotics and might even enhance human beings' quality of life. This research pursues the creation of an *artificial electronic skin* that imitates the properties of human skin using innovative fabrication techniques of printed electronics. The aim is to realize a network of fully printed unit-cells integrating printed sensors and specific integrated circuitry in order to mimic the human skin's sense of touch. A large number of sensor cells will be connected to a cell network that determines touch information across large areas and transmits it in a manner comparable to the human nervous system. One or more cells can be connected to a processing system to interpret the sensor information and support other perception channels of a humanoid. Printed electronics technology offers inherent advantages for the development of an artificial skin: Mechanically flexible and even stretchable materials of large size can be utilized as a substrate to recently developed inks of electronic materials. These possess interesting properties, such as high conductivity, high dielectric permittivity, and tunable work functions. One of the main challenges will be the integration of these sensors on large-scale areas while fulfilling mechanical requirements including stretchability and flexibility similar to that of human skin. A similar architecture may be applied on prostheses as well as for health and fitness monitoring.

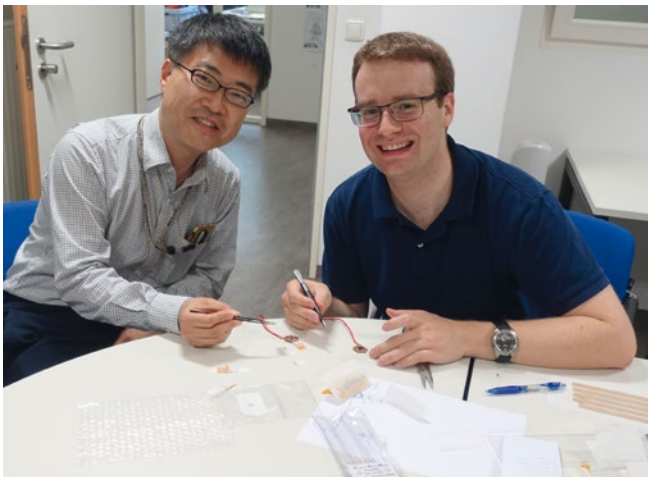
The potential impact of artificial electronic skin is enormous, as it could be applicable across multiple domains, from building safer robots to health-care monitoring, entertainment, and wearable technologies to enhance our lives.

During 2018, we investigated how best to optimize the bendability and stretchability of connections between skin cells, so that we can integrate stretch sensors into the connection to monitor the distance between skin cells. Measuring the distance between skin cells is essential to enable the automatic 3D surface reconstruction for skin patches (which provide the location of each skin cell).

The best solution would be to integrate the stretch sensor, the data communication links, and the power lines into the same substrate. In contrast to the material we currently use for the connection, that new substrate has to be not only bendable but also stretchable.



2 | A working prototype of a hybrid e-skin with stretchable connector.



3 | IAS-Fellow Prof. Someya with doctoral candidate Florian Bergner.

We investigated different substrates in combination with different conductor technologies to realize the power lines and the communication links on a stretchable substrate. The experiments revealed that current technology is not mature enough to realize these connections on stretchable substrates with the required properties.

Now we are pursuing a new concept, in which we would only implement the stretch sensor on stretchable material and then combine this sensor with the technology we currently use for connecting skin cells.

Due to multidisciplinary features of artificial electronic skin, it is important to enhance collaboration among researchers in different research fields, including electronics, mechanical engineering, computer science, materials science, chemistry, biology, medicine, dermatology, and more. To promote this new way of thinking, we hosted several workshops during the past year and presented our ideas to several research communities.

The First International Workshop on Smart Skins (SmartSkin2018) took place on November 19 and 20, 2018, hosted at the TUM-IAS in Garching with participants from around the world. Top scientists from the fields of robotics, materials science, biomedical engineering, and neuroscience joined in an intense scientific exchange (hosted by Prof. Someya and Prof. Cheng).

Dr. Mohsen Kaboli and Prof. Cheng hosted a workshop at IROS 2018 on Monday, October 1, 2018, titled RoboTac: New Progress in Tactile Perception and Learning in Robotics. IROS is a premier event for the robotics community with over 4000 attendees. Also at IROS, Prof. Someya gave a keynote on “Electronic skins for robotics and wearables” on October 2, 2018, chaired by Prof. G. Cheng. https://www.iros2018.org/plenaries-and-keynotes.

Prof. Someya also gave the keynote at the IEEE/RSJ International Conference on Intelligent Robots and Systems, which was held October 1–5, 2018, in Madrid, Spain. The keynote was introduced by Prof. Cheng, who emphasized the importance of a new paradigm bringing together different disciplines in attacking new challenges to advance a new generation of robots. Prof. Someya gave an impressive keynote to the robotic community.

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

Host
Embedded Systems and Internet of Things, TUM

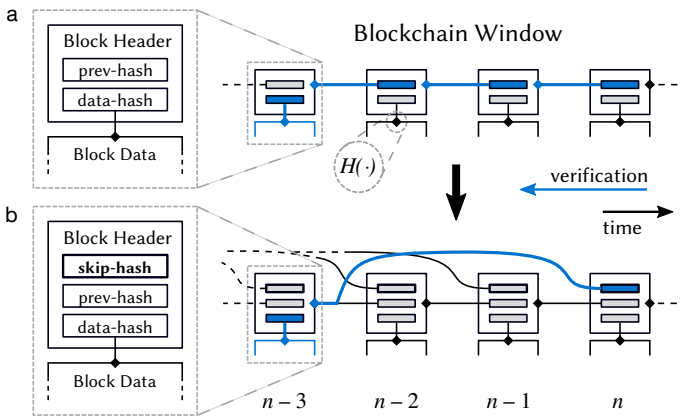
Making complex IoT system architectures manageable, interoperable and resilient

The Internet of Things (IoT) is driving technological advancements in almost all sectors of industry and society. At the same time, conventional IoT system architectures with a hierarchical and centralized organization can no longer keep up with the increasing requirements of scalability, manageability, efficiency, and security. Hence, decentralization of such architectures toward self-organizing systems is considered a core concept for meeting the requirements for future IoT systems. However, new methods and algorithms need to be developed for resource-constrained embedded IoT devices, as existing decentralization solutions significantly exceed the computational and communication capabilities of such devices. Embedded IoT systems often face the challenge to reach consensus about a global system state. Blockchain, the technology developed in the context of cryptocurrencies such as Bitcoin, makes it possible to reach consensus in a large, trustless, and open peer-to-peer network without any central authority. However, due to the constant growth of the blockchain, downloading and processing the entire chain requires more and more resources over time. Even light clients need to download and hash up to 40 MB of block headers for Bitcoin and up to 3 GB for Ethereum – too much for an embedded IoT device.

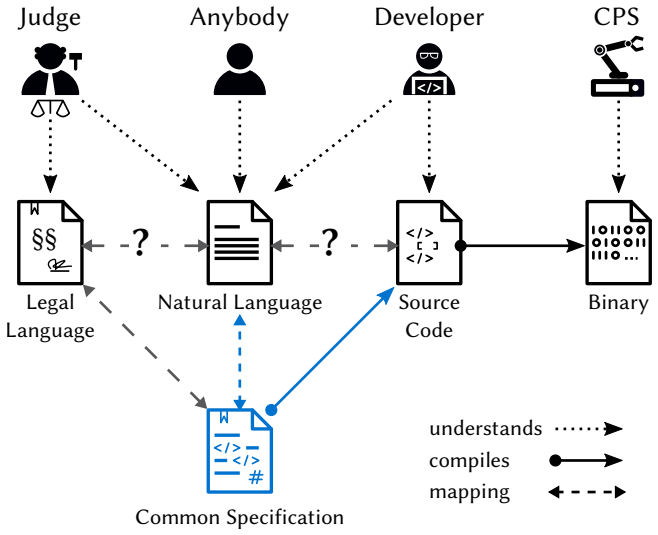
As a remedy, we have created LeapChain [1], a blockchain extension that makes it possible to verify the inclusion and integrity of any block using only a logarithmic amount of block headers. By inserting just one additional back-linking hash into each block header, as illustrated in Figure 1, the maximum processed header data is reduced to 7.3 kB in the worst case. The logarithmic scaling is achieved through a special repeating pattern of several backlink distances that are calculated as multiples of a common base value. Blockchain can be also used for secure automation in the context of IoT by using “smart contracts.” These are scripts that are stored in the blockchain and specify multi-step interactions between network nodes. Once a contract is deployed on the blockchain, its code is executed by all participants, enforcing the specified behavior. While this decentralized execution offers reliability and robustness, it also inherits a risk because the triggered interactions are non-revertible, even if they were not intended by the programmer.

We therefore have proposed SmaCoNat [2], a safe specification language for smart contracts that is based on natural language. As shown in Figure 2, the goal of SmaCoNat is to allow human reasoning on a higher abstraction layer, which is closer to real-world semantics but at the same time simple enough to be compiled to executable code.

At the same time, we are targeting the challenge of interoperability in decentralized industrial IoT architectures. For this purpose, while participating in the standardization efforts of the W3C Thing Description standard, we are developing approaches to extend the description of IoT devices in a semantically strong form.



1 | Our LeapChain approach: We extend the conventional block structure (a) such that each block header stores one additional backlinking leap-hash that "points" further back than just the direct predecessor (b). This leap-hash allows us to traverse the blockchain with a reduced amount of steps.



2 | SmaCoNat is used to create a common specification in natural language that can be compiled to smart contract source code and could be legally binding in the future. To achieve this goal we need an unambiguous mapping between natural language and smart contract instructions.

Our recent approach [3] demonstrates how IoT devices can coordinate themselves by exchanging their capabilities and hence collaborate to perform a system-level functionality in a sequential fashion.

Another relevant area to introduce decentralized system architectures is the automotive domain. As there will be no driver in autonomous systems who can act as a fallback, current fail-safe technologies are not sufficient. Instead, fail-operational behavior will be required in future systems. However, well established approaches from the avionics domain, such as triple modular redundancy, cannot be applied to the automotive domain as unit costs have a much higher impact on total costs.

Thus, intelligent approaches on the software level, such as graceful degradation will be a key technology for enabling autonomous driving at moderate costs. To promote solutions to such challenges, we co-organized a special session at CODES 2018 and published a paper on future automotive systems design [4].

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

Focus Group **Environmental Sensing and Modeling**

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Xiao Bi, Florian Dietrich, Lijuan Lan, Xinxu Zhao (TUM) | Doctoral Candidates

Scientific Reports

Jia Chen

Host
Environmental Sensing and Modeling, TUM

Measuring greenhouse gas (GHG) emission in cities

The majority of anthropogenic greenhouse gas (GHG) emissions originate from cities. Therefore, monitoring emissions in cities is essential to fight climate change. In Germany and many other countries worldwide the emission reduction goals are evaluated by using software that is based on a bottom-up calculation method instead of measuring the real emissions because of the difficulty to measure emissions of a big area source. That's why we have developed the so-called differential column measurement approach [1]. Thereby ground-based FTIR (Fourier-transform infrared) spectrometers are used to determine the column-averaged concentrations of CO_2, CO and CH_4 upwind and downwind of a city. The difference between those two concentrations is then proportional to the city emissions.

Munich city campaign

Our measurement concept is being tested with the help of measurement campaigns. The campaign in August 2018 was the first one worldwide that used the described differential column method in a fully automated sensor network. For that purpose automated enclosures (cf. Figure 1) for the spectrometer have been developed [2]–[3]. They are controlled by several sensors (rain, temperature, humidity, etc.) to protect the spectrometer inside from any harm caused by harsh environmental conditions. Five of them have been used in the campaign to reduce the need for operating personnel to a minimum and, therefore, to increase the amount of measurement data to a maximum. Thanks to those automated enclosures, it was possible to measure on each of the 25 sunny days in August from the very early morning to the late evening, independent of whether it was during the week, on a weekend, or on a public holiday. With the help of this measurement campaign we showed that we are capable of establishing a fully automated GHG measurement network using ground-based column measurements to determine GHG emission trends of a city over the course of years.

Measuring emissions of the Oktoberfest

A second measurement campaign was conducted in September and October to determine the emissions attributable to the Oktoberfest. This investigation had been already started in 2017. But this time the goal was to look more closely into the source attribution. For that reason we borrowed two portable Picarro GasScouters – installed in a backpack – for measuring methane and ethane from Utrecht University and the manufacturer Picarro Inc. to detect the methane sources. By using the ethane mode it is possible to determine whether the methane source is natural gas-based or not. The scientists walked and biked around the area of Oktoberfest many times, using the GasScouter as a backpack, as it was not permitted to go inside due to safety concerns. The measurements were carried out both during and after the time of the festival to compare the differences in emission strength and distribution.

1 | GHG measurement system on top of the roof of MPE Garching (© Andreas Forstmaier)

2 | Spatial distribution of methane concentrations during the Oktoberfest

The result of one of the measurement days can be seen in Figure 2. On that day there was a constant east wind, so that the gas molecules were transported to the western border of the Oktoberfest area. The highest concentrations were observed in the northwestern part. That's the area where all the big beer tents are located and, therefore, where most of the visitors are. There is a correlation between the concentrations, the wind direction, and the distance to the big tents.

CO_2 sensor development

We also focus on developing an *in situ* sensor of greenhouse gas emissions in urban areas. The compact sensor uses the vertical cavity surface-emitting laser (VCSEL) and is based on the technologies of tunable diode laser absorption spectroscopy (TDLAS) and wavelength modulation spectroscopy (WMS) [4]. The VCSEL has a narrow line width and is widely tunable so that multiple gas absorption lines can be measured simultaneously. Thus the sensor is uniquely well suited for trace gases detection given its properties of non-contact, high sensitivity, high precision, and rapid response, etc. WMS employs a high frequency sinusoidal modulation signal riding on a slowly varying diode laser injection current to produce harmonic signals using a lock-in amplifier. This technique is well known as means to increase signal-to-noise ratio (SNR) because the high frequency can reduce laser, 1/f, and other noises. Using multi-harmonic detection, the precision of the measurement system can reach to 0.02 ppm for CO_2 and 1 ppm for H_2O with 10 minutes averaged time.

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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 (TUM) | Postdoctoral Researchers
Nico Kühnel, Cat Silva, Qin Zhang (TUM) | Doctoral Candidates

Scientific Reports

Rolf Moeckel

Kelly J. Clifton

Host
Modeling Spatial
Mobility, TUM

Transport modeling and travel behavior research

The Focus Group Modeling Spatial Mobility (MSM) focuses on integrated land use/transport modeling and travel behavior research. This includes model development of land use, transport and related models, such as environmental impact models or health 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 particular interest.

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. The study area has been delineated based on commuter flows. The size of the study area was chosen because of long commute distances found in the area, driven in part by rather high costs of living in Munich. A zone system with gradually sized raster cells was developed using the quadtree algorithm (Figure 1) while respecting municipal boundaries.

The modeling suite consists of the land use model SILO, the travel demand model MITO, and the traffic assignment model MATSim. The former two were developed by this research group, and the latter was developed at ETH Zurich and TU Berlin. All three models are built as agent-based models that simulate individual households and persons.

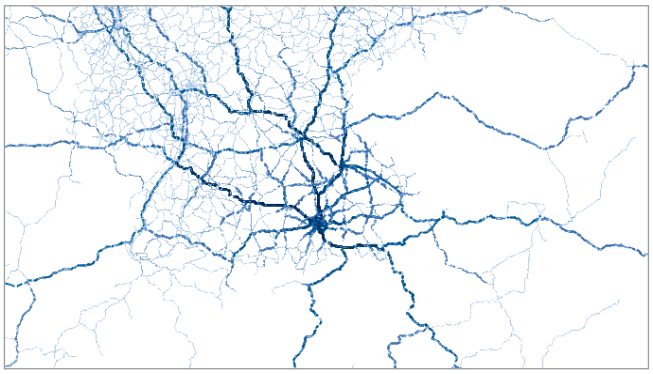
Over the course of 2018, the impacts of the spatial resolution of the network and the impact of scaling factors in the assignment were explored in detail. By optimizing the two, runtime of the model was reduced from days to under three hours for one model year.

The entire modeling suite was also implemented for Cape Town, South Africa, and the Kagawa region in Japan. By using various study areas in very different social and economic concepts, the transferability of these models is analyzed and the scenario sensitivities are being stress-tested.

In cooperation with Hans Fischer Senior Fellow Dr. Kelly Clifton from Portland State University, the existing modeling suite is further integrated with the pedestrian model MoPeD. Initial research was done to explore Google Timeline data to better understand habitual travel behavior. Traditional household travel surveys capture one (randomly chosen) day, which may or may not represent well the average travel behavior of the respondent. Using Google Timeline data, we plan to better capture habitual travel behavior, which will be related to socio-demographic attributes. This will allow us to predict habitual travel behavior, and the impact thereof on health conditions.

1 | The study area was subdivided into 4,700 zones, with smaller zones in urban areas and larger zones in rural area.

To complement person travel demand, we started, in cooperation with the chair of Logistics and Supply Chain Management of TUM's School of Management (Prof. Dr. Stefan Minner), a project funded by the German Ministry for Transport and Digital Infrastructure to simulate freight travel. A national database of freight flows is disaggregated to a finer spatial resolution using input-output coefficients. Flows traveling by truck are converted to vehicles and assigned to the network. Figure 2 shows the assignment of truck flows into and out of the Munich metropolitan area. The goal of this project is to explore the potential market for cargo bikes for last mile deliveries.



2 | Simulated truck flows into and out of the Munich metropolitan area

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 may be shared as well as long as no privacy considerations are affected.

Publications by this Focus Group can 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

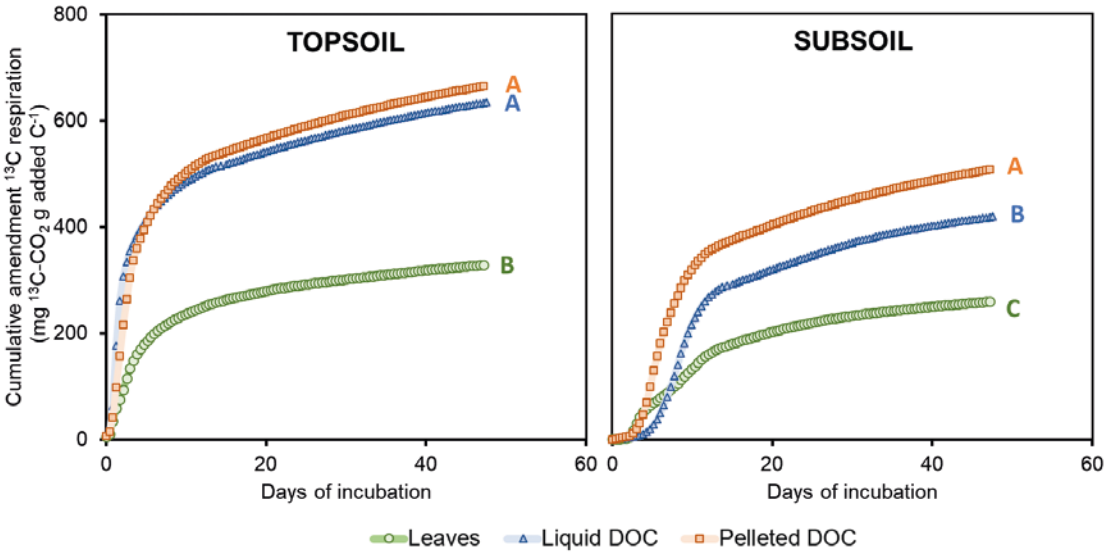
Host
Prof. Ingrid Kögel-Knabner
Soil Science, TUM

Soil organic matter (SOM) has an important role for food production, water quality, and climate. Its formation takes place mainly through the decomposition of plant inputs in the soil (i.e., litter and root exudates). These plant inputs can either be incorporated into the soil through different mechanisms (e.g., aggregation and mineral adsorption) [1] or mineralized and then released to the atmosphere as CO_2. Even small variations in these proportions can lead to significant changes in the emission of greenhouse gases. Therefore, as soils have a recognized capacity for carbon storage, the understanding of the mechanisms responsible for SOM stabilization are of extreme importance [2]. Yet, our knowledge about the factors and processes controlling the amounts of stabilized versus mineralized SOM is still remarkably limited.

Plant input stabilization in top- and subsoil: Investigating the mechanisms for soil organic matter protection

We examined the decomposition of different plant inputs in a top- (0–0.2 m) and subsoil (0.8–1.0 m) of an Andosol. This soil is characterized by an extraordinary capacity of SOM protection due to specific minerals that it contains (i.e., short-range order). We performed an incubation experiment using ^{13}C isotope-labeled plant leaves (*Salix spp.*) and dissolved organic carbon (DOC) extracted from them in different sizes (pelleted - 1 mm and liquid - < 0.7 µm). This experiment allowed us to observe very distinctive SOM stabilization and mineralization patterns in both soil layers depending on the added material. The DOC, whether pelleted or liquid, was significantly more respired than the leaves in both soil layers (Figure 1). In the subsoil but not the topsoil, we observed a significant difference between the respiration of the different DOC forms (pelleted and liquid). Since both DOC forms vary by location (distributed vs. point source) and size (pelleted vs. liquid), the mineralization results point toward several possible explanations: (i) smaller particles are more efficiently stabilized in subsoil layers by mineral interactions than larger structures due to their greater surface area, (ii) more dilute material is more efficiently adsorbed as concentrated organic matter exceeds sorption capacity (saturation concept), or (iii) more concentrated organic matter is more easily mineralized than more dilute because microorganisms are able to specialize on producing enzymes to metabolize the substrate.

These differences clearly illustrate distinct mechanisms for SOM protection depending on the evaluated soil layer and amendment added. Our next steps will be evaluating sectioned soil aggregates through nanoscale secondary ion mass spectrometry (NanoSIMS) to observe how the elements are co-localized in undisturbed soil samples. This will give us new insights about SOM stabilization mechanisms in the evaluated soils.



1 | Cumulative ^{13}C respiration of the amendments in top- (0–0.2 m) and subsoil (0.8–1.0 m) of an Andosol. Means followed by the same capital letter do not differ among amendments at $p < 0.05$ (LSD test).

Workshop Raitenhaslach: Re-Thinking Global Soil Carbon Modeling

Against the scenic backdrop of TUM's conference center at Raitenhaslach monastery, 12 participants from Austria, France, Germany, Sweden, and the US critically examined the state of global carbon modeling. The breadth of expertise from different fields provided an unusual opportunity for cross-disciplinary insights. The group developed exciting new avenues to re-imagine global prediction of soil carbon changes in response to climate change (please find a workshop summary in the section Activities and Events of this report).

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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: covalent stabilization, applications as biophysical tool

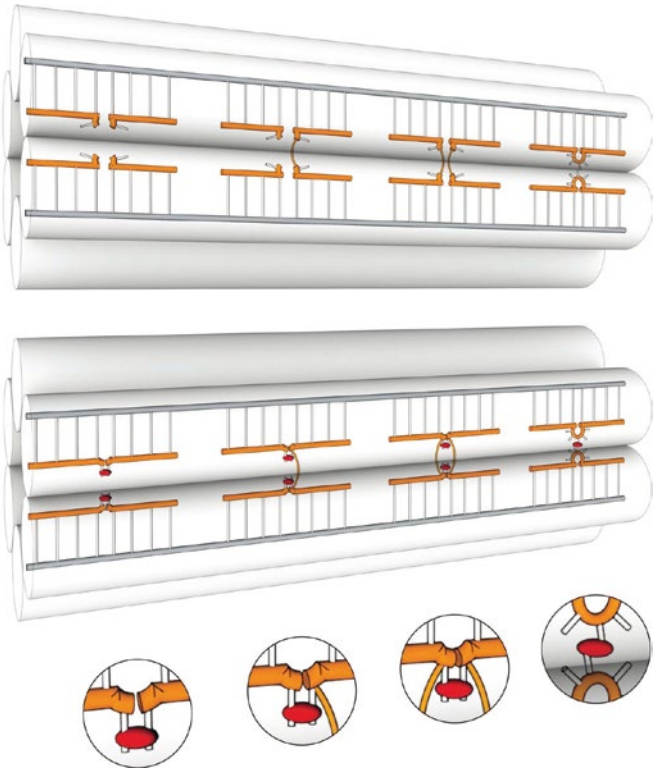
During 2018, the Focus Group made further advances toward harnessing so-called DNA origami for potential applications in science and technology and published a number of significant results, summarized below.

Sequence-programmable covalent bonding of designed DNA assemblies [1]

Bottom-up fabrication of custom nanostructures using the methods of DNA nanotechnology has great potential for applications in many areas of science and technology. One obstacle to applications concerns the constrained environmental conditions at which DNA objects retain their structure. We present a general, site-selective, and scalable method for creating additional covalent bonds that increase the structural stability of DNA nanostructures. Placement of thymidines in close proximity within DNA nanostructures allows the rational creation of sites for covalent cyclobutane pyrimidine dimer (CPD) bonds induced via ultraviolet irradiation. The additional covalent bonds may be used in a sequence-programmable fashion to link free strand termini, to bridge strand breaks at crossover sites, and to create additional interhelical connections. Thus designed multilayer DNA origami objects can remain stable at temperatures up to 90°C and in pure double-distilled water with no additional cations present. In addition, these objects show enhanced resistance against nuclease activity. Cryo-electron microscopy (cryo-EM) structural analysis of non-cross-linked and cross-linked objects indicated that the global shape and the internal network of crossovers are preserved after irradiation. A cryo-EM map of a CPD-stabilized multilayer DNA origami object determined at physiological ionic strength reveals a substantial swelling behavior, presumably caused by repulsive electrostatic forces that, without covalent stabilization, would cause disassembly at low ionic strength. Our method opens new avenues for applications of DNA nanostructures in a wider range of conditions.

Tethered multifluorophore motion reveals equilibrium transition kinetics of single DNA double helices [2]

Understanding cellular functions and dysfunctions often begins with quantifying the interactions between the binding partners involved in the processes. Learning about the kinetics of the interactions is of particular importance to understand the dynamics of cellular processes. We describe a tethered multifluorophore motion assay based on DNA origami for revealing bimolecular reaction kinetics on the single-molecule level. Molecular binding partners may be placed at user-defined positions and in user-defined stoichiometry; and binding states are read out by tracking the motion of quickly diffusing fluorescent reporter units. Multiple dyes per reporter unit enable singe-particle observation for more than one hour. We applied the system to study in equilibrium reversible hybridization and dissociation of complementary DNA single strands as a function of tether length, cation concentration, and sequence.

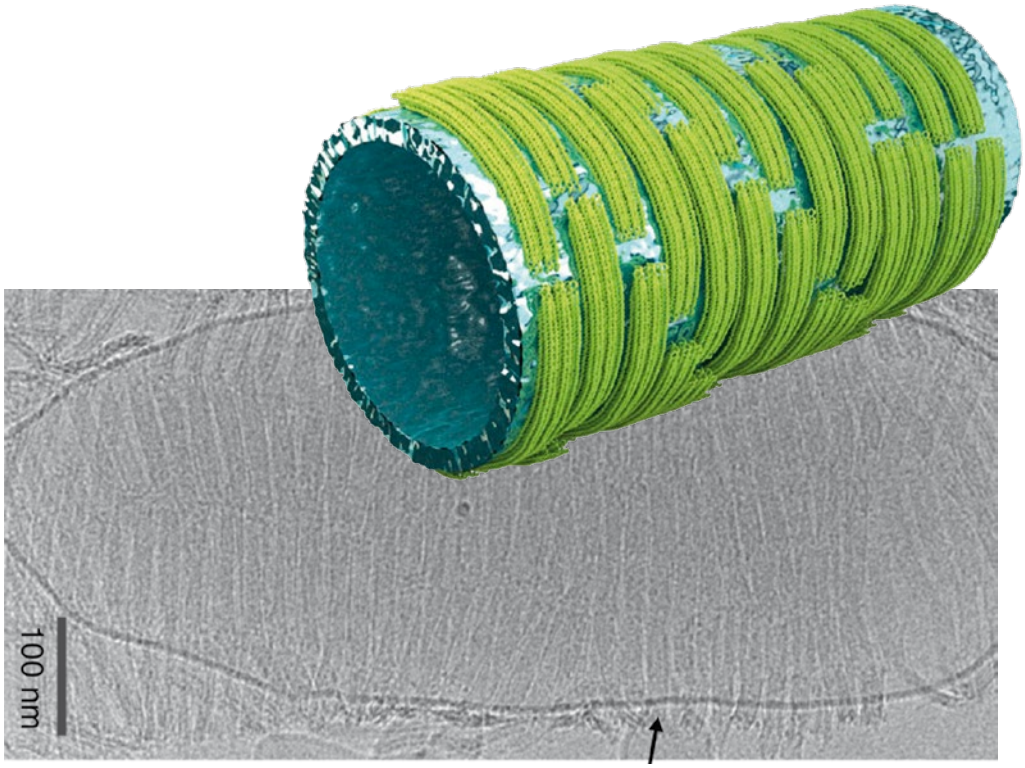


1 | Top: Schematic illustration of a six-helix bundle DNA nanostructure featuring single-stranded thymidines at strand termini (1), at half-crossovers (2), at full crossovers (3), and thymidine loops (4) before UV irradiation. Bottom: After exposure to light with 310-nm wavelength. Covalent cyclo butane pyramidine dimer bonds are indicated as red ellipsoids. With this treatment, DNA origami become substantially more durable.

We observed up to hundreds of hybridization and dissociation events per single reactant pair and could produce cumulative statistics with tens of thousands of binding and unbinding events. Because the binding partners per particle do not exchange, we could also detect subtle heterogeneity from molecule to molecule, which enabled the separation of data reflecting the actual target strand pair binding kinetics from falsifying influences stemming from chemically truncated oligonucleotides. Our data reflected that cation concentration affects mainly DNA strand hybridization, but not strand dissociation, in agreement with previous results from different assays. We studied 8-bp-long DNA duplexes with virtually identical thermodynamic stability, but different sequences, and observed strongly differing hybridization kinetics. Complementary full-atom molecular-dynamics simulations indicated two opposing sequence-dependent phenomena: helical templating in purine-rich single strands and secondary structures. These two effects can increase or decrease, respectively, the fraction of strand collisions leading to successful nucleation events for duplex formation. The experimental concept is simple and the data interpretation is very direct, making the system easy to use for a wide variety of researchers. Due to the modularity and addressability of the DNA origami-based assay, our system may be readily adapted to study various other molecular interactions.

DNA origami scaffold for studying intrinsically disordered proteins of the nuclear pore complex [3]

The nuclear pore complex (NPC) is the gatekeeper for nuclear transport in eukaryotic cells. A key component of the NPC is the central shaft lined with intrinsically disordered proteins (IDPs) known as FG-Nups, which control the selective molecular traffic. Here, we present an approach to realize artificial NPC mimics that makes it possible to control the type and copy number of FG-Nups. We constructed 34 nm-wide 3D DNA origami rings and attached different numbers of NSP1, a model yeast FG-Nup, or NSP1-S, a hydrophilic mutant. Using cryo-electron microscopy, we found that NSP1 forms denser cohesive networks inside the ring compared to NSP1-S.



2 | Top: Schematic illustration of a lipid membrane tubule decorated with curved DNA origami bundles. Bottom: cryo-EM micrograph of such assembly.

Consistent with this, the measured ionic conductance is lower for NSP1 than for NSP1-S. Molecular dynamics simulations reveal spatially varying protein densities and conductances in good agreement with the experiments. Our technique provides an experimental platform for deciphering the collective behavior of IDPs with full control of their type and position.

Membrane sculpting by curved DNA origami scaffolds [4]

Membrane sculpting and transformation are essential for many cellular functions, which thus are largely regulated by self-assembling and self-organizing protein coats. Their functionality is often encoded by particular spatial structures. Prominent examples are BAR domain proteins, the “banana-like” shapes of which are thought to aid scaffolding and membrane tubulation. To elucidate whether 3D structure can be uncoupled from other functional features of complex scaffolding proteins, we developed curved DNA origami with various shapes and stacking features, following the presumable design features of BAR proteins, and characterized their ability for membrane binding and transformation. We showed that dependent on curvature, membrane affinity and surface density, DNA origami coats can indeed reproduce the activity of membrane-sculpting proteins such as BAR, suggesting exciting perspectives for using them in bottom-up approaches toward minimal biomimetic cellular machineries.

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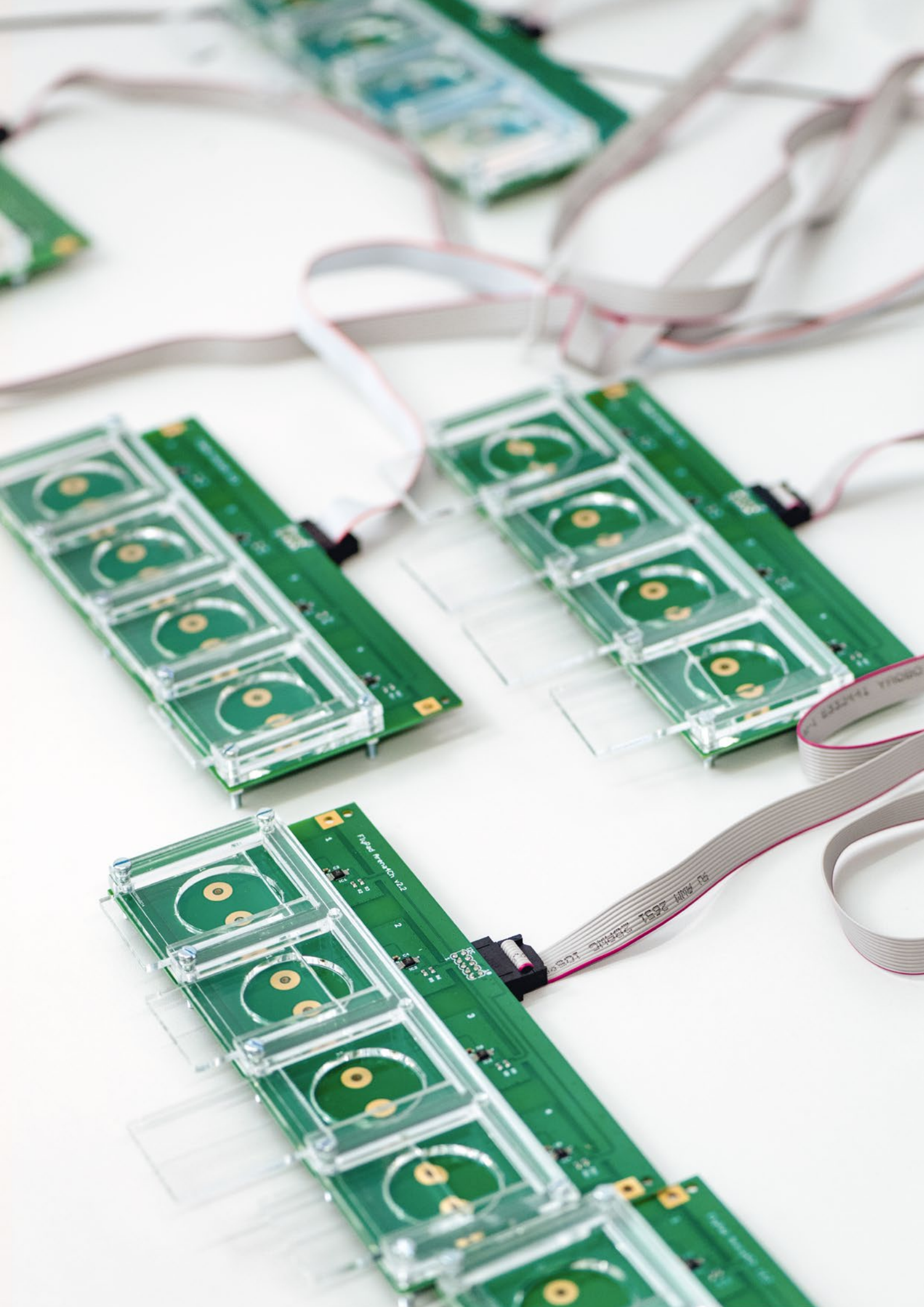
Publications by this Focus Group can also be found in the section Publications of this report.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Focus Group **Cellular Protein Biochemistry**

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

Matthias J. Feige

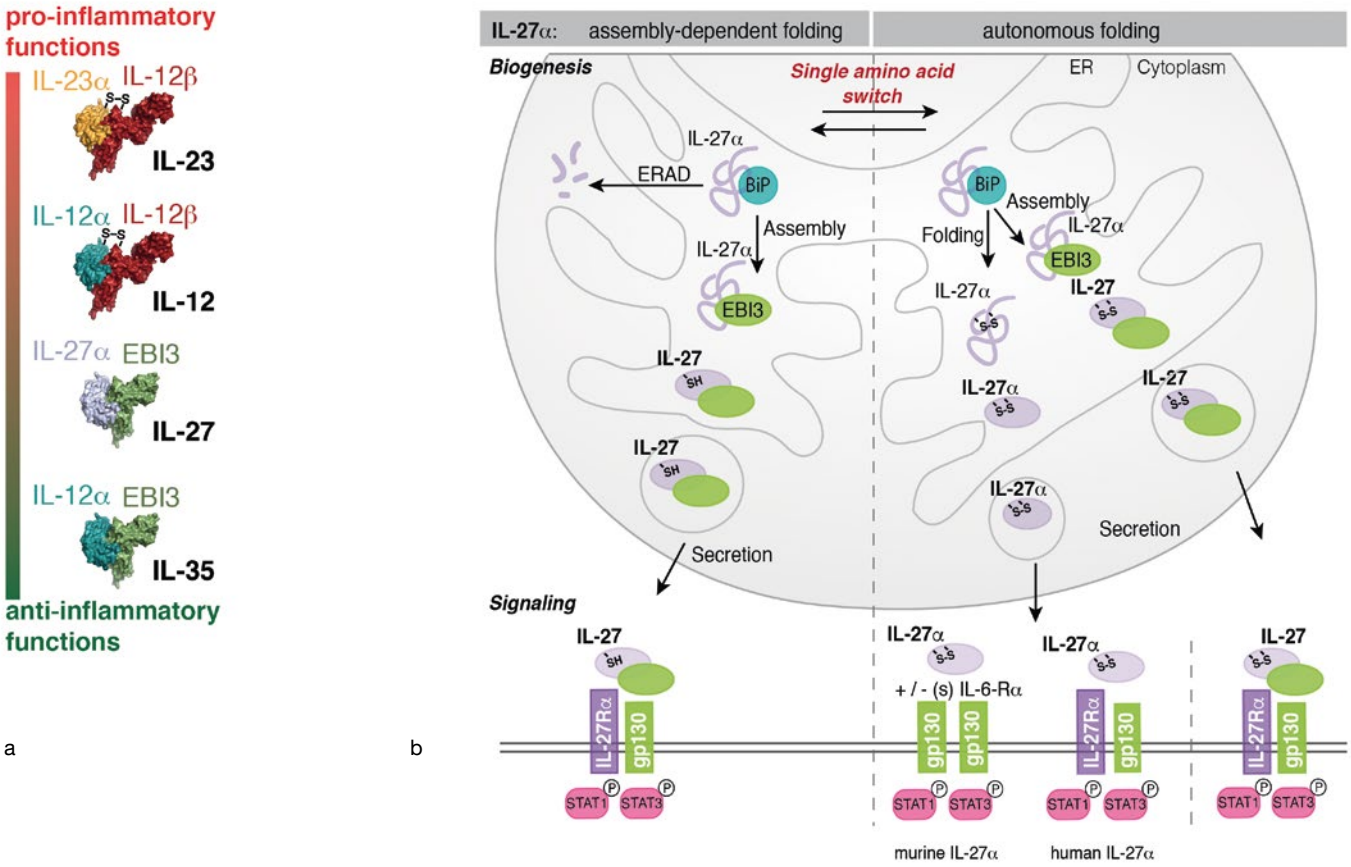
Host
Cellular Protein Biochemistry, TUM

Understanding and controlling vital cellular mechanisms

In complex organisms, cells need to communicate and interact with each other. This communication is the basis not only of growth, development, and motility, but also of immune defense. Key players in all cellular communication processes are proteins secreted from cells or displayed on the cell surface. Within a mammalian cell, a specialized sub-compartment exists that is responsible for the production of these proteins: the endoplasmic reticulum (ER), an extended net-like structure within the interior of the cell. Not only are proteins produced in the ER, they also are controlled there. Only proteins that have acquired their correct biologically active structure are allowed to leave the cell or to be displayed on the cell surface. Faulty proteins are recognized by a dedicated molecular quality control machinery and degraded. Insights into the formation and control of protein structure in the cell are of immediate medical relevance for human pathologies including Alzheimer's or Parkinson's disease – but may also inspire new approaches in biotechnology. In our laboratory for Cellular Protein Biochemistry (CPB lab) we use an interdisciplinary approach, from structural biochemistry to mammalian cell biology, to understand and ultimately engineer the underlying processes.

Current work in the CPB lab focuses on two major topics. The first is 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. Dependent on the individual IL, these mount, sustain, or suppress immune reactions in health and disease. Understanding interleukin biogenesis in the cell in more detail can thus provide an avenue toward rationally tuning immune responses. Our model system is the interleukin 12 (IL-12) family, which comprises four members (IL-12, IL-23, IL-27 and IL-35) that span a broad range of biological functions [1] – from activating immune responses to suppressing immunity (Figure 1A). As such, IL-12 family members are involved in a large number of human diseases including autoimmune disorders, cancer, and sepsis. A recent study from our lab has now revealed the molecular mechanisms of how cells produce IL-27, an IL-12 family member that is intimately involved in the development of inflammatory diseases. In close collaboration with TUM research groups in medicine and physics we were able to gain detailed insights into how IL-27 acquires its native structure and how cells monitor structure formation of this protein (Figure 1b) [2]. Using these insights, we engineered a new human interleukin that we are currently pursuing further as a potential new treatment option for sepsis (patent pending), one of the deadliest diseases in developed countries without any good causal treatment options.



1 | (a) Schematic of the IL-12 family. Each family member is an αβ heterodimer and performs distinct roles in regulating immune responses. IL-12 and IL-23 are covalent dimers, connected by a disulfide bond (S-S), whereas IL-27 and IL-35 are non-covalent dimers.
(b) A single amino acid protein folding switch underlies differences in biogenesis and signaling of the IL-27 system. The absence or presence of a disulfide bond-forming cysteine pair defines if IL-27α depends on EBI3-interaction for folding and secretion or if it can be secreted autonomously, inducing downstream signaling via different possible receptors. Signaling-competent IL-27 species are shown in bold. The Figure is adapted from [2].

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

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

Prof. Suljo Linic (University of Michigan) | Hans Fischer Fellow

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?

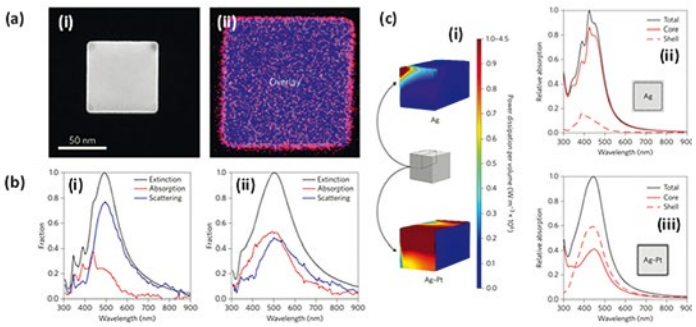
Dynamical processes at the gas-solid interface lie at the heart of many industrial applications of great technological value such as heterogeneous catalysis. Here, different forms of energy are constantly converted into each other, and the intricate ways in which this happens ultimately influence not only reaction rates but also the corresponding specificity and yield. This energy exchange is even more relevant for processes where external stimuli, such as light, are used to induce chemical transformations. In 2018 our Focus Group was able to advance the fundamental understanding of these processes. Specifically, we focused on developing a physical framework that allows us to explain the exchange of energy between optically excited plasmonic nanoparticles and various entities (adsorbates, semiconductors, or metal sites) that are in chemical contact (or in close proximity) to these nanoparticles.

How do excited plasmonic nanoparticles dissipate energy?

Plasmonic metal nanoparticles are promising platforms for manipulating the flow of electromagnetic energy at the nanometer length scale. Upon light illumination, incoming electromagnetic radiation interacts with the delocalized, free electrons of the metallic nanoparticles, resulting in excitation of the localized surface plasmon resonance (LSPR). LSPR acts to confine the energy of incoming radiation in the form of amplified electromagnetic fields at the surface of the nanostructure. In unreactive environments, the energy of these elevated fields is dissipated through either radiative scattering of photons or nonradiative excitation of energetic charge carriers (i.e., absorption) in the metal nanoparticle. In general, these energy dissipation pathways are not well understood on nano- and molecular scales, and therefore there are no established frameworks for controlling them [1].

Our aim was to develop a deeper understanding of the energy dissipation pathways in resonantly excited plasmonic nanoparticles with the ultimate aim of designing plasmonic nanostructures that offer a high degree of control over the LSPR decay process in terms of (1) the partitioning of energy between absorption and scattering and (2) the spatial distribution of the absorption process [1]. Manipulating the location of charge carrier excitation (photon absorption) in terms of surface versus bulk excitations is critical in a number of applications, including plasmonic photocatalysis, plasmon-enhanced photovoltaics, plasmonic heating, and photothermal cancer therapy [1]. Ideally, these high-energy charge carriers would be generated close to the particle surface to minimize their energy loss within the nanoparticle before their extraction [1].

In 2018, we studied the mechanisms of LSPR decay by designing hybrid bimetallic plasmonic nanostructures that contained a very thin shell (1 nm) of a nonplasmonic metal (Pt) coated onto a larger plasmonic nanoparticle core (75 nm Ag cube) [2]. We conclusively demonstrated that the energy concentrated via LSPR excitation in the core-shell nanoparticle was preferentially dissipated through the absorption process in the thin Pt shell (i.e., within ~1 nm of the bimetallic nanoparticle surface), increasing the extraction probability of the energetic charge carriers [2].



1 | Multicomponent plasmonic catalysts. (a) Dark-field scanning transmission electron microscopy (STEM) image and energy-dispersive X-ray spectroscopy (EDS) elemental map of an Ag-Pt core-shell nanocube showing distributions of Ag (blue) and Pt (red). (b) Extinction, absorption, and scattering spectra of (i) Ag and (ii) Ag-Pt nanocubes. The absorption-to-scattering ratio is drastically altered in favor of absorption when the Ag nanocube is coated with ~1 nm of Pt. (c) Simulated power dissipated through Ag and Ag-Pt nanocubes. (i) Contour map of power dissipated through an Ag (upper) or Ag-Pt (lower) nanocube. The thin coating of Pt strongly biases energy dissipation through the nanoparticle shell. (ii,iii) Simulated light absorption in the core vs. the outermost layers of (ii) an Ag nanocube and (iii) an Ag-Pt nanocube. In the pure Ag nanocube, nearly all the absorption takes place in the core of the nanoparticle. In contrast, the thin coating of Pt re-routes the flow of energy so that most of the absorption takes place in the thin ~1 nm shell of Pt. Figures taken with permission from Nature Publishing Group

We expanded on these studies by systematically investigating through experimental and modeling approaches, the LSPR decay mechanisms in Ag-Pt and Au-Pt core-shell nanoparticles of different shapes and sizes [3]–[5]. These studies showed that the nanoparticle size significantly impacts the plasmon decay pathways, where particle sizes supporting higher electric field intensities at the nanoparticle surface direct more energy to Pt.

We also showed that the choice of plasmonic metal (Ag vs. Au) strongly impacts the LSPR energy dissipation pathways. We demonstrate that, unlike for the Ag-Pt nanoparticles where the energy is dissipated through the Pt shell for all LSPR wavelengths, for the Au-Pt system a significant biasing of the particle absorption in Pt is only achieved at the LSPR wavelengths where the Au interband transitions are inaccessible.

Collectively, these studies have allowed us to develop a transparent physical mechanism for the LSPR decay in multimetallic plasmonic nanostructures [3]–[5]. By studying core-shell nanoparticles of varying size, shape, and composition, we demonstrated that the energy flow in multimetallic plasmonic nanostructures is dependent on two critical factors acting in concert: (i) the electric field intensity at the LSPR frequencies and (ii) the availability of direct transitions in the nonplasmonic metal relative to the plasmonic metal. We showed that nanoparticles displaying higher field intensities under LSPR conditions were more effective in dissipating energy through the nonplasmonic metal shell. Additionally, the extent of this energy transfer to the nonplasmonic shell depended on the ratio of ε_2 of the core and shell materials at the LSPR wavelength, where a higher shell-to-core ε_2 ratio resulted in more energy transfer to the shell. This framework allows for not only the design of hybrid nanostructures that localize charge carriers to desired parts of the nanostructure but also the generation and potential extraction of charge carriers that have energy distributions entirely different from those generated in plasmonic metals [3]–[5].

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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

Our focus has been on updating and improving our existing tools, **HFSP** [1] and ***fusion*DB** [2] as well as publishing the respective manuscripts.

We developed the **HFSP (Homology-driven functional similarity of proteins)** metric, an update on the HSSP metric published by Burkhard Rost over 25 years ago. HFSP is a method for accurate high-speed functional annotation of proteins via function transfer by homology. In both HFSP and HSSP, instead of relying on sequence similarity alone, the length of the alignment contributes to the calculation of functional similarity (Equation 1). HFSP improves on HSSP in two ways. First, we swapped the slow and well known PSI-BLAST alignments bottleneck for a much faster algorithm, MMSeqs2. Second, HFSP was reoptimized using an up-to-date set of proteins of experimentally determined enzymatic function (see Figure 1). HFSP is thus more than 40-fold faster than HSSP, while retaining high accuracy of protein function prediction, despite reference database growth and increasing complexity of enzyme classification.

$$HFSP = PIDE - \begin{cases} 101, & for\ L \leq 22 \\ 770 \cdot L^{-0.33 \cdot \left(1+e^{-\frac{L}{1000}}\right)}, & for\ 22 < L \leq 450 \\ 28.4, & for\ L > 450 \end{cases}$$

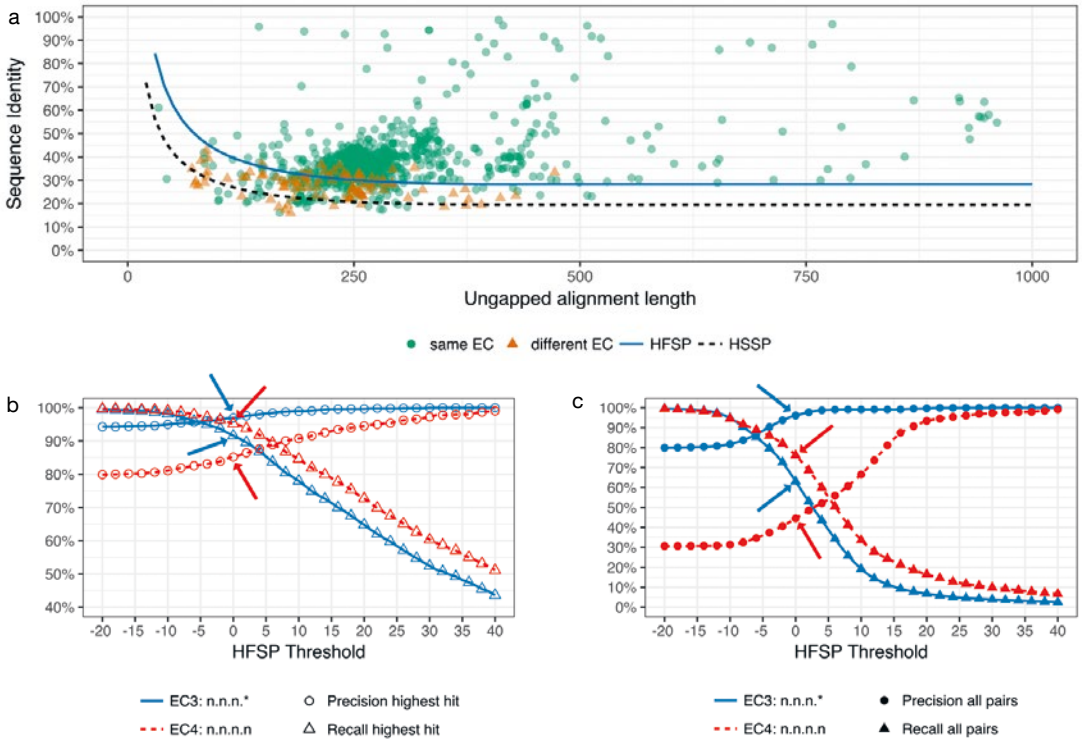
$$PIDE = Percent\ sequence\ identity\ of\ the\ alignment$$

$$L = ungapped\ alignment\ length$$

We are currently working on making HFSP available to a wider audience by building a web service around the foundation of clubber [3] a cluster load balancing tool developed earlier by our lab. This web service will enable users to assess the function of their proteins of interest by comparing them against a selection of curated protein databases. Consider an example, where we recently annotated the function of ~500,000 proteins using HFSP. This process took ~3 hours on a small 12-node cluster, as compared to the same process previously requiring ~5 days.

***fusion*DB**, our reference database for functional similarity of microbial organisms, received minor updates this year. Major updates are expected in 2019, as the creator of fusionDB, TUM-IAS doctoral candidate Yannick Mahlich, defends his dissertation. Updates are expected to include an improved function clustering method, functional profiles for an up-to-date list of available bacteria, and more robust ways for researchers to investigate and compare their organisms of interest. In 2018, *fusion*DB was updated to use the above-described HFSP methodology, vastly speeding up the mapping of new proteomes to *fusion*DB reference. This mapping algorithm aids users in assessing the functional similarity of new microbes to *fusion*DB reference organisms in near real time. While we've been working on major upcoming updates for *fusion*DB, the number of microbes available to analyze increased more than 6-fold. This, in conjunction with the updated mapping algorithm we are developing, will make *fusion*DB even more attractive to researchers around the world.

Additionally we continued to optimize **mi-faser** [4] over the course of the year, and participated successfully in this years CAMDA (Critical Assessment of Massive Data Analysis) Challenge at ISMB 2018, analyzing and differentiating microbial metagenomes extracted form metropolitan subways around the globe [5].



1 | HFSP precisely predicts functional identity. Available enzyme pairwise alignments were mapped into the sequence identity vs. ungapped alignment length space. In (A) protein pairs were differentiated according to identity of their EC level 3 (enzyme commission is a four level hierarchical classification scheme with increasing annotation detail though levels 1 to 4; same enzyme annotations are green circles; different annotations are red triangles). The HFSP curve (HFSP=0, light blue solid line) is shown relative to the HSSP curve (black dashed line). Protein pairs above the curve are predicted to be of same function, pairs below the curve of different function. In (B, C) precision (circles) and recall (triangles) in predicting functional identity, at 3rd (blue, solid curve) and 4th (red, dashed curve) EC level for available enzymes. Arrows indicate performance at default cutoff of HFSP = 0. In (B) prediction was done using the highest HFSP scoring alignment per protein. In (C) all alignments were used, resulting in significantly worse performance.

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[2] C. Zhu, Y. Mahlich, M. Miller and Y. Bromberg, "fusionDB: assessing microbial diversity and environmental preferences via functional similarity networks. ". Nucleic Acids Res., vol. 46, pp. D535-D541, 2018. 2018.

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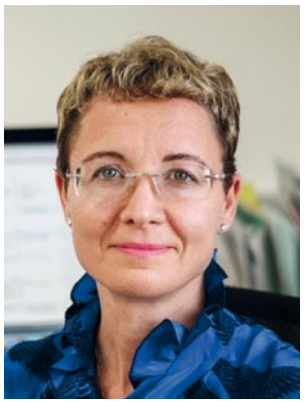
Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Medicinal and Bioinorganic Chemistry**

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

Scientific Reports



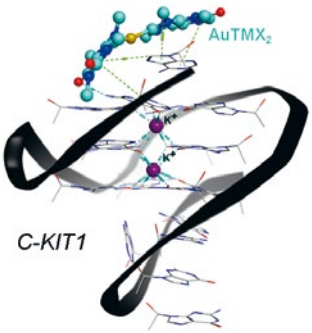
Angela Casini

Host
Prof. Fritz E. Kühn
Molecular Catalysis, TUM

Our main aim is to develop metal-based compounds for biological and biomedical applications. In detail, the research program focuses on the design of novel *organometallic gold compounds* as possible anticancer agents or as chemical probes to study the function of target biomolecules, including proteins and nucleic acids.

From coins and wedding rings to stained glass windows, by way of 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 certain pharmacological target, a feature that is not often ensured by other types of molecules. Thus, gold compounds can be designed to be active against specific biomolecules with a great degree of target selectivity and innovative mechanisms of action.

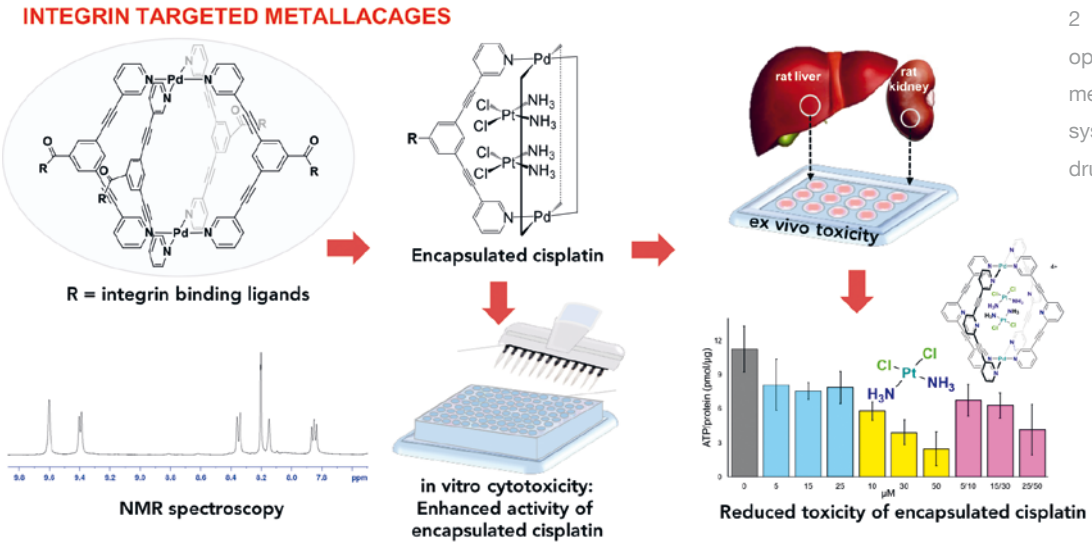
Within this framework, we studied the binding modes and free-energy landscape of two gold(I) N-heterocyclic carbene (NHC) complexes interacting with G-quadruplexes (Figure 1) for the first time by metadynamics. DNA can adopt different structures other than the canonical right-handed double helix (B-DNA), and numerous structural studies have revealed that guanine-rich DNA sequences can form secondary structures termed G-quadruplexes (G4s). These non-canonical DNA structures are present in telomeres and promoter regions of oncogenes and have been the subject of intense study over the past 10 years, being associated with a number of biological processes such as telomere maintenance, gene regulation, and replication. Thus, G4s emerge as promising targets for anticancer drug discovery. The theoretical results in our study are validated by FRET DNA melting assays and provide an accurate estimate of the absolute gold complex/DNA binding free energy. This advanced *in silico* approach is a valuable contribution to achieving rational drug design of selective G4s binders.



1 | Model of the interaction of a gold(I) NHC complex with a G-quadruplex DNA (C-KIT1) studied by metadynamics.

Discrete supramolecular constructs continue to attract important research interest because of their myriad of applications, including in biology. The biomedical application of supramolecular coordination complexes (SCCs) is still an emergent field of study, but the pioneering examples available so far exploiting their host-guest chemistry demonstrate their possible use as new generation of drug delivery systems for anticancer chemotherapeutics. In fact, the robustness of supramolecular metal-based complexes, particularly *metallacages*, allows incorporation of different functionalities in the same scaffold to enable imaging in cells, but also targeting and stimuli-responsiveness. Certainly, the myriad of possible metallacages and their almost limitless modularity and tunability, without significant synthetic penalty, suggest that the biomedical applications of such species will continue along this already promising path.

In this context, in collaboration with the group of Prof. Horst Kessler at TUM, we published new Pd_2L_4 cages (with L being *exo*-functionalized bipyridyl ligands, Figure 2) as drug delivery systems for the anticancer drug cisplatin.



2 | Scheme of the development of supramolecular metallacages as drug delivery systems for the anticancer drug cisplatin.

Cisplatin occupies a crucial role in the treatment of various malignant tumors. However, its efficacy and applicability are heavily restricted by severe systemic toxicities and drug resistance. Our study exploits the active targeting of supramolecular metallacages to integrin receptors to enhance the activity of cisplatin in cancer cells while reducing its toxicity.

Overall, the ambition of our Focus Group includes providing targeted gold-based *prodrugs* with unprecedented activity and control, but also an understanding of fundamental biological processes regulated by these compounds and their role in the development of diseases. Moreover, we aim at developing the promising field of supramolecular coordination chemistry for biomedical applications, particularly toward the design of novel targeted drug delivery systems.

Prof. Angela Casini was keynote speaker at the International 11th European Biological Inorganic Chemistry Conference (EuroBic), Birmingham, UK (August 2018), one of the main events in the bioinorganic chemistry area. In November 2018, she was also plenary speaker at the Symposium “New Trends in Organic Synthesis” organized by the University of Milan, Italy, as well as at the XXXII Regional Meeting of the Brazilian Chemical Society (Juiz de Fora, Minas Gerais State, Brazil). In 2019, she will be the plenary speaker of the Georgian Bay International conference on Bioinorganic Chemistry (CanBIC-7) in Parry Sound, Canada.

Since 2018, Angela Casini is also member of the international scientific committee of the international conference “Metallomics.”

The doctoral candidate funded by the HFSF, Jens Oberkofler, presented a poster on gold compounds as G-quadruplex binders at EuroBic in August 2018. In addition, Dr. Andreas Räder from the Kessler group received one of the JPS Excellent Poster Presentation Awards at the International Peptide Symposium held in Kyoto in December 2018. The poster concerned our joint work on integrin-targeted metallacages. 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.

As a highlight of this year, on October 27, 2018, Prof. Angela Casini received the prestigious Burghausen Diamond Chemistry Award during an official ceremony held at the TUM Akademiezentrum Raitenhaslach. The award is an acknowledgement of chemical and industrial innovation.

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

Focus Group **Multi-Messenger Astrophysics and the United Nations Open Universe Initiative**

Prof. Paolo Giommi (Italian Space Agency) | Hans Fischer Senior Fellow
Theo Glauch (TUM) | Doctoral Candidate

Scientific Reports

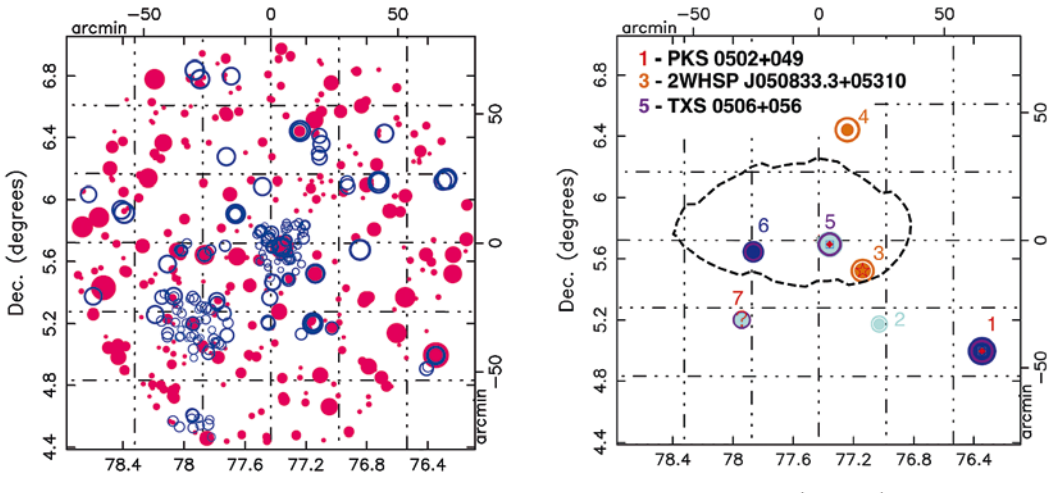
Paolo Giommi

Host
Prof. Elisa Resconi
Experimental Physics with Cosmic Particles, TUM

Multi-messenger Astrophysics and the United Nations Open Universe Initiative

For centuries humans have studied the sky in the only part of the electromagnetic spectrum that was accessible to them: the optical band, where our eyes are sensitive. About 100 years ago, however, Victor Hess discovered particles that penetrate the atmosphere from outer space with energies up to several quintillion (10^{18}) times higher than visible light. He called them *cosmic rays*, although they are not really *rays* in a strict sense, but rather charged particles like protons and heavier atomic nuclei. Despite all the research efforts carried out over the last century, the sources where these energetic particles are accelerated and the production mechanism remain largely unknown, making them one of the unsolved mysteries of modern astrophysics. More recently, the discovery of astrophysical neutrinos, as well as the detection of cosmic high-energy electromagnetic radiation (gamma rays), have greatly expanded our knowledge of the high-energy content of the Universe. For decades astronomers, including Hans Fischer Senior Fellow P. Giommi, have predicted that these particles could be produced in blazars – a peculiar subclass of active galaxies hosting a super-massive black hole in their nucleus and a narrow jet of material that moves away from the center at relativistic speed and happens to be pointing in the direction of the Earth – or in other astrophysical contexts, for example in supernova remnants or gamma ray bursts. Combining information from low-energy electromagnetic radiation (radio, microwave, infrared, etc.) up to the highest-energy cosmic rays is the foundation of *multi-messenger astrophysics*, a novel field that has recently gained large importance. While finding the astrophysical sources that produce these extremely energetic cosmic messengers is a major goal, their discovery would also open new windows for testing physical theories, such as the standard model of particle physics, up to energies that are far beyond the reach of Earth-based accelerators.

Neutrinos are very light particles that only extremely rarely interact with matter. While other cosmic messengers, like photons or charged particles, are deflected by magnetic fields or interact during their travel through the universe, neutrinos always point back to their source of origin. Hence they allow us to study objects to the far edge of the observable universe. On September 22, 2017, the IceCube Neutrino Observatory at the South Pole discovered a high-energy neutrino that is very likely of astrophysical origin. While this itself is not too special, it was found that the event points directly to an extremely bright and luminous blazar, *TXS 0506+056*, that was also found to be in a very active gamma ray state. As part of the IceCube team T. Glauch and other Fellows have evaluated the probability for a random coincidence of this to be less than 1/10,000. Moreover, a search through the IceCube observatory's archival data revealed that an even stronger neutrino outburst happened three years before, but in this case without any obvious associated gamma ray activity. At that stage our TUM-IAS Focus Group started analyzing all the available multi-messenger data to provide a maximum of information complementary to the other detections.



1 | The part of the sky where the IceCube neutrino mentioned in the text was detected on 22 September 2017. The left picture illustrates the complexity of the area, which includes dozens of radio and X-ray sources, represented by red filled circles and open blue symbols respectively. The right side plots the known and candidate blazars present in the region, based on the radio and X-ray data shown on the left. The dashed curve delimits the uncertainty in the neutrino arrival direction.

The starting point for the analysis was a software tool that Paolo Giommi and Fellows working at the Italian Space Agency developed in the framework of the United Nations Open Universe Initiative (see, e.g,. openuniverse.asi.it). Using open data from more than 30 observatories around the globe, we were able to identify several astrophysical objects with radio to X-ray flux ratio that hints to a strong acceleration of charged particles, i.e., protons or electrons, to very high energies. This is shown in Figure 1, reproduced from one of the papers that were published on that occasion. The left side of the picture illustrates the complexity of the part of the sky where the IceCube neutrino was observed, with hundreds of radio (red filled circles) and X-ray sources (blue open circles) present in the area, while the right side shows all the possible counterparts, as determined by the tool. The blazar TXS 0506+056 is the light blue symbol (or source nr.5), right in the middle of the area.

A *priori* all of them are possible counterparts to the IceCube neutrinos. Subsequently at the TUM-IAS we have also analyzed the gamma ray emission coming from these objects, as current theory requires that gamma rays must also be produced when neutrinos are generated. Digging deep into the available data, we found that indeed only the previous detected blazar TXS 0506+056 shows a gamma-ray behavior that is consistent with the observed neutrino measurements.

There is no doubt that the combination of all of these results is a big step toward explaining the origin of astrophysical neutrinos. Inspired by the success of the multi-messenger approach, our current work is focused on expanding the analysis methods to other regions in the sky that have associated high-energy neutrinos. The hope is to find and resolve a larger fraction of the astrophysical neutrino flux and finally take the next step – to learn about the sources themselves.

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

Puzzles surrounding the strong interactions

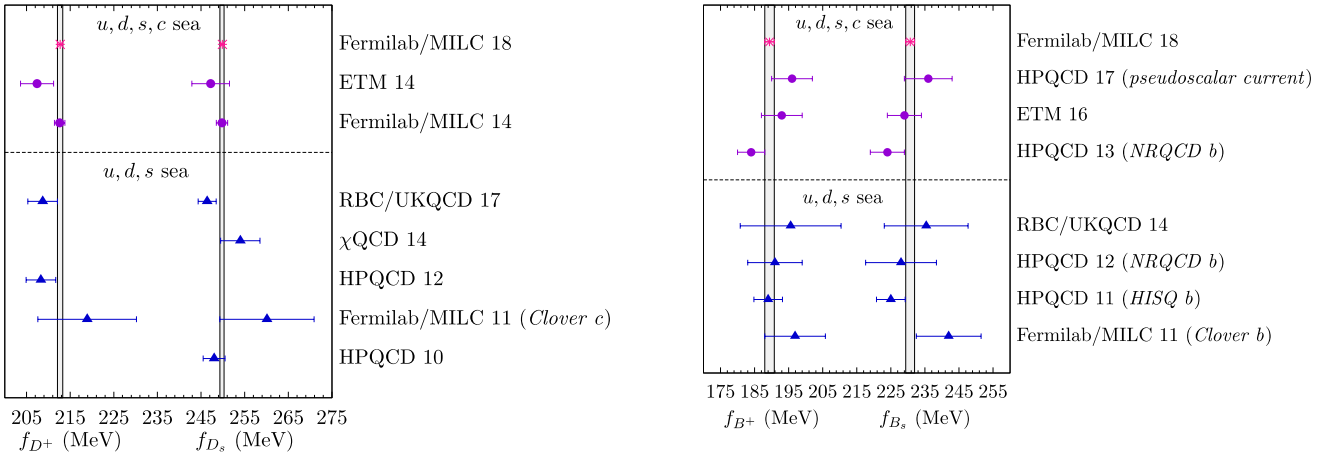
The main aim of elementary particle physics is to study fundamental interactions at the smallest distance scales, but the interpretation of experiments inevitably demands theoretical control over several length scales. A vital example lies in the search for new, as-yet unobserved interactions of quarks, 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 fourth year, our Focus Group achieved a spectacular synthesis of effective field theory and lattice QCD. Building on Komijani's 2017 work, we discovered a new definition of quark masses [1]; we expect this work to have wide application in quantum field theory. Using a simulation data set generated to study the decays of B and D mesons [2], we analyzed the masses of these mesons to obtain the most precise determinations of the masses of five of the six quarks found in nature [3]. (The sixth quark, known as "top," decays before it forms mesons, but the ideas in [1] will be helpful to determine its mass too.)

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 also 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 weakens steadily as the source and sink are separated farther and farther. Thus, 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.



1 | **Comparison plots of f_D [MeV] and f_B [MeV]**

Comparisons of the Fermilab/MILC results for charmed and bottom (*D* and *B*) de-cay constants with other work. The mesons contain a strange antiquark in addition to the charm and beauty quarks.

This is not so for QCD, because the chromoelectric field remains strong. Therefore, 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, a new approach based on asymptotic solution to a differential equation enabled a systematic calculation of the 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 [1].

When the Focus Group started, Komijani and Kronfeld had already started to analyze an enormous data set, generated with lattice QCD, with an aim to understand the simplest decays of *B* and *D* mesons. These decays are interesting because of the unusual quarks found in these mesons ("beauty" in *B* and "charm" in *D*; both have a much larger mass than the more common "up" and "down" quarks). The numerical results for these so-called "decay constants" will aid interpretation of the just-started Belle II experiment at the KEK laboratory in Japan. (Colleagues in the TUM Physics Department are part of Belle II.) The analysis [2] is arguably the most ambitious in lattice QCD to date. Figure 1 shows the improvement in precision for the *B* meson; here f_B is the symbol usually used for the decay constant.

At the same time, the Focus Group embarked on an equally ambitious analysis of the meson masses that were a by-product of the decay-constant simulation. Following a suggestion of Kronfeld in 2000, our aim was to apply a formula from an effective field theory relating the meson mass to the quark mass. A shortcoming of the formula consisted of ambiguities in the definitions of some of the ingredients. Precisely, this shortcoming was swept aside in [1] (after a long struggle with data and theory). With our new and unambiguous definitions, we produced the most precise determinations of the (short-distance) quark masses, as one can see in Figure 2. In particular, the masses of the up and down quarks, which are the constituents of protons and neutrons, are much better known than before, thanks to our work.

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.

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 led us to propose a four-week program at the Munich Institute for Astro- and Particle Physics (MIAPP). MIAPP received many fond testimonials from May 2016 participants, which helped lead to approval. The program was held from October 15 to November 9, 2018.

This work was conducted in cooperation with Prof. Antonio Vairo (Physics, TUM).

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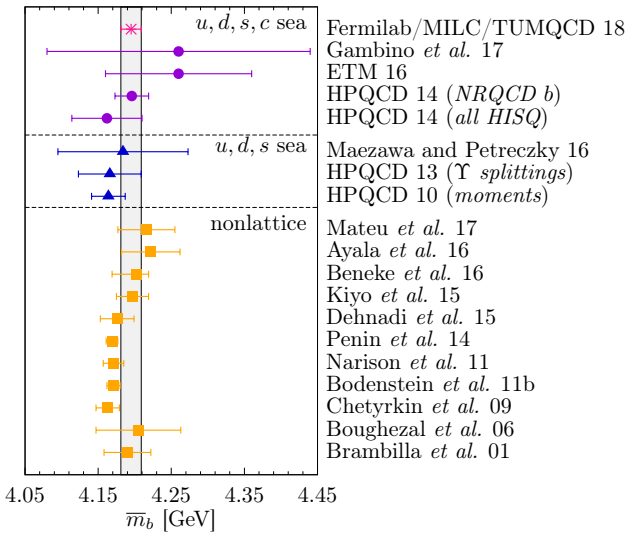
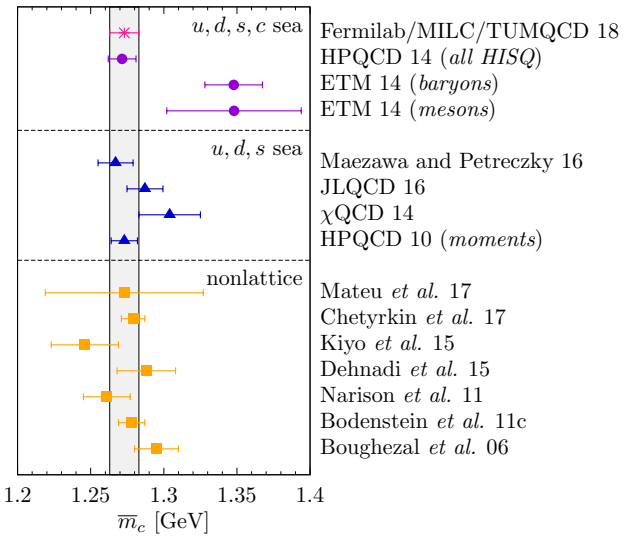
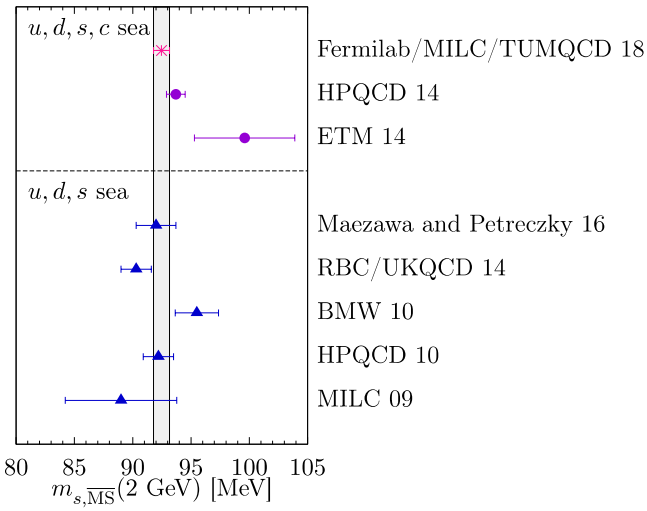
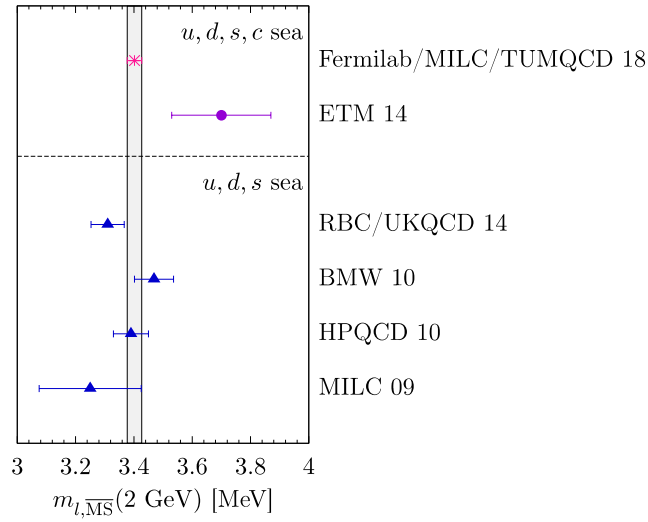
Publications by this Focus Group can also be found in the section Publications of this report.









2 | **Comparison plots of m_c [GeV], m_b [GeV], of m_s [MeV], m_l [MeV]**

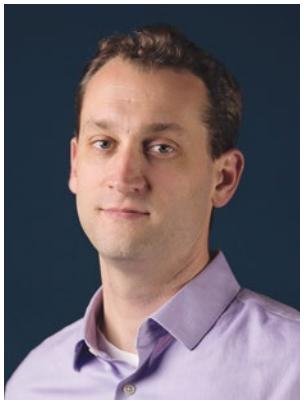
Comparisons of the Fermilab/MILC/TUMQCD results for charmed, beauty, strange, and the average up-down quark masses with other work.

Focus Group **Population Epigenetics and Epigenomics**

Prof. Frank Johannes (TUM) | Rudolf Mößbauer Tenure Track Professor
Prof. Robert J. Schmitz (University of Georgia) | Hans Fischer Fellow
Dr. Rashmi Hazarika (TUM) | Postdoctoral Researcher
Talha Mubeen (TUM) | Doctoral Candidate

Scientific Reports

Frank Johannes



Robert J. Schmitz

Host
Population Epigenetics and Epigenomics, TUM

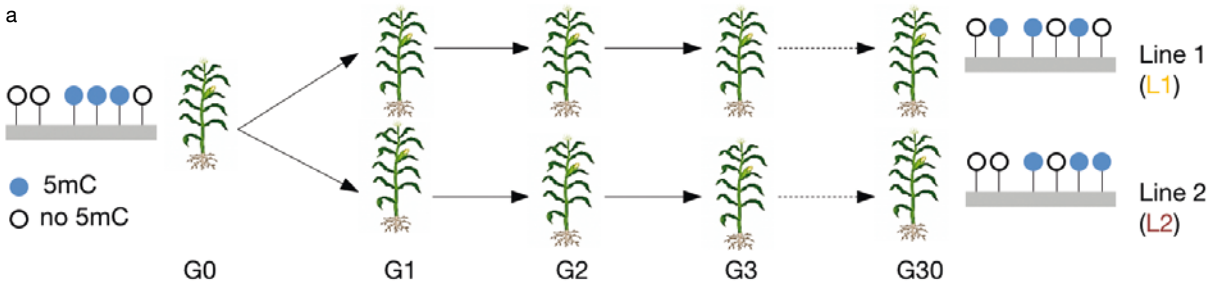
Overview

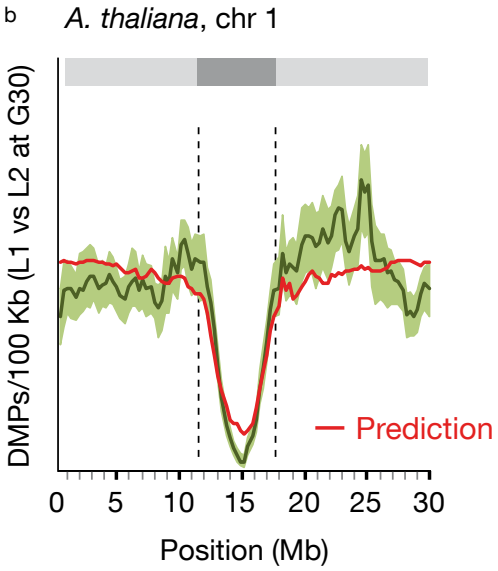
DNA stores heritable information in the form of a four-letter code; A, C, G, and T. Textbook genetics tells us that the code can be mutated (e.g., letter A turns into letter G), and that such mutations alter the functions of genes. In plants, it is becoming increasingly clear that heritable alterations 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 epimutations in plant genomes can be remarkably stable across generations [1]–[2] and can in some cases even 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.

Spontaneous epimutations in plants

One important question is how heritable epimutations arise in plant genomes in the first place. The group of Prof. Schmitz (newly appointed Hans Fischer Fellow) and ours have previously shown that cytosine methylation is sometimes gained or lost accidently during cell divisions [2], [5]. These rare stochastic changes, or so-called “spontaneous epimutations,” are not only confined to somatic tissues, but also occasionally pass through the gametes to subsequent generations, therefore giving rise to heritable epigenetic variation. Using mutation accumulation lines of the model plant A. thaliana (Figure A) in combination with multigenerational methylome measurements, we were able to estimate that the rate of spontaneous epimutations is about 10^{-4} per site (i.e., CG context) per haploid genome per generation ([2], [5]), which is five orders of magnitude higher than the genetic mutation rate in this species. Interestingly, the frequency of these stochastic events is not uniformly distributed across the genomes, but shows strong location-specific biases, which depend on local annotation density (Figure B). Evidence is emerging that these location-specific epimutations have a major role in shaping methylome diversity patterns in plant populations over evolutionary time-scales [3].

Yet a number of key question remain unanswered [6]: What are the molecular processes that give rise to spontaneous epimutations in plant genomes? What is the rate and spectrum of spontaneous epimutations in different plant species, genotypes, and environments? What are their precise functional and phenotypic consequences and their role in short- and long-term adaptive processes? Our Focus Group aims to tackle these questions in the context of Prof. Schmitz’s Hans Fischer Fellowship at the TUM-IAS.





1 | a. Mutation Accumulation (MA) lines are derived from a single inbred founder plant at generation G0 and propagated for many generations (only 30 generations and two lines L1 and L2 are shown here). Spontaneous epimutations arise at each generation leading to differentially methylated positions (DMPs) or differentially methylated regions (DMRs) between L1 and L2.
b. In *A. thaliana* MA-lines, the observed # of DMPs between L1 and L2 (green line with empirical confidence intervals) is not uniformly distributed across the genome. DMPs are more frequent in gene-rich chromosome arms (light-grey) and depleted in transposon-rich pericentromeric regions (dark-grey). Local DMP frequency (100 Kb resolution) can be predicted from annotation-specific CG epimutations rates along with local annotation density. Figures 1a and 1b taken from [6].

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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**

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Scientific Reports

Franz Hagn

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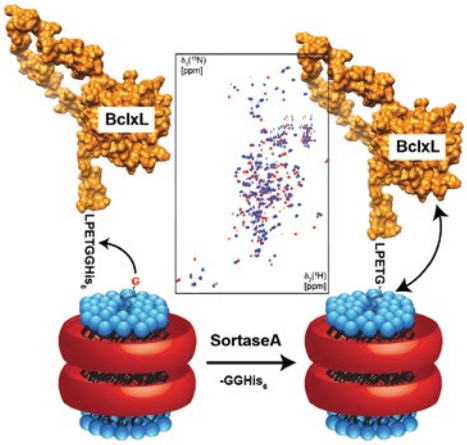
Structural Membrane Biochemistry, TUM

The TUM-IAS Focus Group Structural Membrane Biochemistry dedicates its efforts to the development of improved tools for the high-resolution structure determination of membrane proteins in a native environment. Our main method is nuclear magnetic resonance (NMR) spectroscopy [1], but we also employ other structural methods, including electron microscopy (EM). In order to study membrane proteins in a native environment, we develop and further optimize phospholipid nanodiscs, a novel membrane mimetic where a patch of a lipid bilayer membrane of defined size is encircled by two copies of a lipid-binding protein called membrane scaffold protein, or MSP.

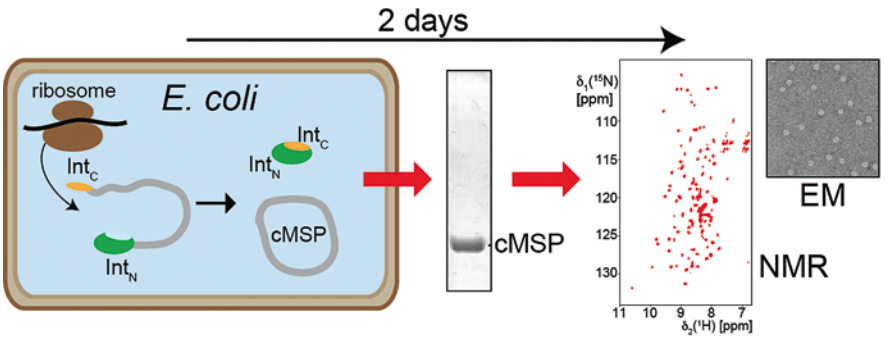
In 2018, among other projects, we were able to establish a novel method for the production of membrane-anchored proteins in phospholipid nanodiscs [2] and succeeded in developing a novel biochemical method to produce nanodiscs of markedly increased stability and size homogeneity [3] – features that are crucial for all structure determination methods.



1 | Production of membrane-anchored BclxL using SortaseA-mediated protein ligation. First, the transmembrane part of the protein (blue ribbons) is incorporated into phospholipid nanodiscs, then the soluble domain of BclxL is attached to the transmembrane helix to yield functional and correctly folded full-length protein. This prominent protein class is involved in many signaling processes, and thus it is essential to carry out structural and functional studies in a native membrane environment provided by a phospholipid bilayer membrane. Figure taken from [2].

Membrane-anchored proteins are key players in signal transduction. Prominent members are the T-cell receptor, integrins or members of the Bcl2 protein family involved in the regulation of mitochondrial apoptosis. A prototype member of the latter protein class is BclxL, an inhibitor of apoptosis and a verified target for anti-cancer therapy. All of these proteins contain one or more soluble, ligand-binding domains and a hydrophobic transmembrane (TM) helix that confers its membrane location. Due to the amphipathic nature of these proteins, production in milligram quantities that are required for structural studies is very difficult due to the accumulation of incorrectly folded protein or a complete lack of protein production in common protein production hosts. In addition, detergents that are required to solubilize the hydrophobic TM helix often lead to unfolding of the functional soluble domain. In the past, this issue was omitted by removing TM helices for structural studies, which abolishes the influence of a membrane surface on protein function.

Thus, we designed a versatile protocol for the production of this protein class attached to phospholipid nanodiscs [2]. By first inserting the isolated detergent-solubilized TM helix into nanodiscs and by subsequently attaching the correctly folded soluble domain to the TM helix using a protein ligase called SortaseA, membrane-anchored BclxL could be obtained in a folded conformation (Figure 1).



2 | Split-intein-based method to produce covalently circularized MSP proteins for nanodisc assembly *in vivo*. By this approach circular MSPs with improved biophysical properties can be obtained in high yields within 2 days and readily used for structural studies by nuclear magnetic resonance (NMR) and electron microscopy (EM). Figure taken from [3].

We were able to show that this strategy is suitable for high-resolution structure determination as well as for probing membrane location by NMR. As BclxL and other Bcl2 family members can insert into the membrane and eventually form pores, it is essential to probe possible membrane encounter complex states that initiate pore formation. With this method we now are able to probe the conformational change from the folded to a membrane incorporated state and finally to a fully assembled pore structure using NMR and EM.

Another feature that is essential for structural studies is the size homogeneity and stability of nanodiscs. In earlier studies, we realized that in particular smaller nanodiscs (6–7 nm diameter) do not show long-term stability due to the high strain within the MSP ring that wraps around the lipid bilayer patch [4]. An elegant solution to this problem is the use of covalently circularized MSP proteins, where the N- and C-termini are connected by a peptide bond. In an earlier paper, we introduced the use of SortaseA enzyme *in vitro* [5] to obtain circularized MSPs, with the drawback of low ligation yields and the requirement for the separation of circularized and linear MSP proteins after the ligation reaction. We have now provided a novel method for the production of circularized nanodiscs *in vivo*, i.e., in living *E. coli* cells, where circularized MSP proteins can be directly obtained from *E. coli* culture (Figure 2) [3]. We use Npu DnaE split-intein fusions with MSPs of various lengths and are able to consistently obtain circularized nanodiscs in high yields. Using this approach, we were able to produce a large variety of circularized nanodiscs ranging from 7 to 26 nm in diameter that are suitable for NMR as well as EM applications. These nanodiscs are superior to corresponding linear versions in terms of stability and size homogeneity, affecting the quality of NMR data as well as EM experiments. Due to their long-term stability and homogeneity, the small circular nanodiscs we presented are well suited for high-resolution NMR studies, as demonstrated with two membrane proteins of 17 or 32 kDa in size. The presented method will provide easy access to circularized nanodiscs for structural studies of membrane proteins as well as for applications where a defined and stable nanodisc size is required.

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

Focus Group **Supramolecular Chemistry**

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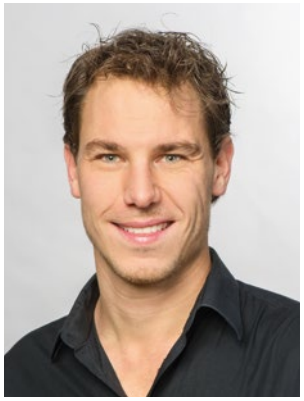
Scientific Reports



Job Boekhoven

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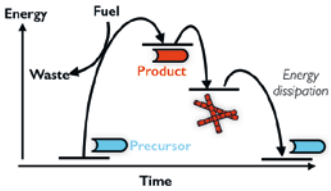
Dissipative supramolecular materials

Synthetic supramolecular materials can be found in a wide spectrum of applications ranging from electronics to health care. This type of material consists of molecular building blocks that are assembled via non-covalent interactions such as hydrogen bonding and solvophobic or ionic interactions. Most examples of such materials reside in equilibrium and are thus controlled by thermodynamics. This thermodynamic control endows the materials with a great feature: stability. However, living systems are not thermodynamically stable but intrinsically unstable and exhibit out-of-equilibrium processes driven by the constant consumption of energy (Figure 1a). In other words, biological materials are controlled by the kinetics of energy consumption and dissipation and therefore display unique properties unattainable when using supramolecular materials in equilibrium. These unique properties, including self-healing, adaptivity, and spatial or temporal control, can be of great interest when considering new strategies for the development of supramolecular materials [1]–[2].

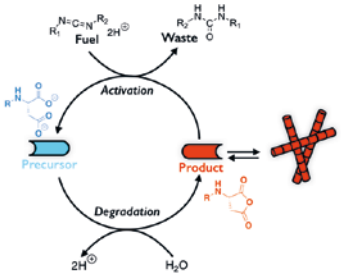
Inspired by biology, our Focus Group is interested in translating the attractive properties of biological materials into fully synthetic analogues. To do so, we have been working on a new strategy to develop out-of-equilibrium materials. We introduce the term dissipative supramolecular materials for these materials. We form them by coupling the self-assembly of molecules to irreversible chemical reaction cycles that are driven by energy.

Our chemical cycle (Figure 1b) uses carboxylic acids with different molecular structures as precursors and high-energy condensing agents as fuel. When the fuel is added, carboxylic acids are partially converted into metastable anhydrides, which rapidly hydrolyze back to carboxylic acids, restoring the equilibrium. During their limited lifetime, however, the anhydride self-assembles into a desired supramolecular material. This supramolecular material is, as a result of the continuous formation and degradation, dynamically formed and only present for as long as the fuel remains. In this way, we tuned the lifetime of our assemblies by changing components in the chemical reaction cycle, such as the amount of fuel added.

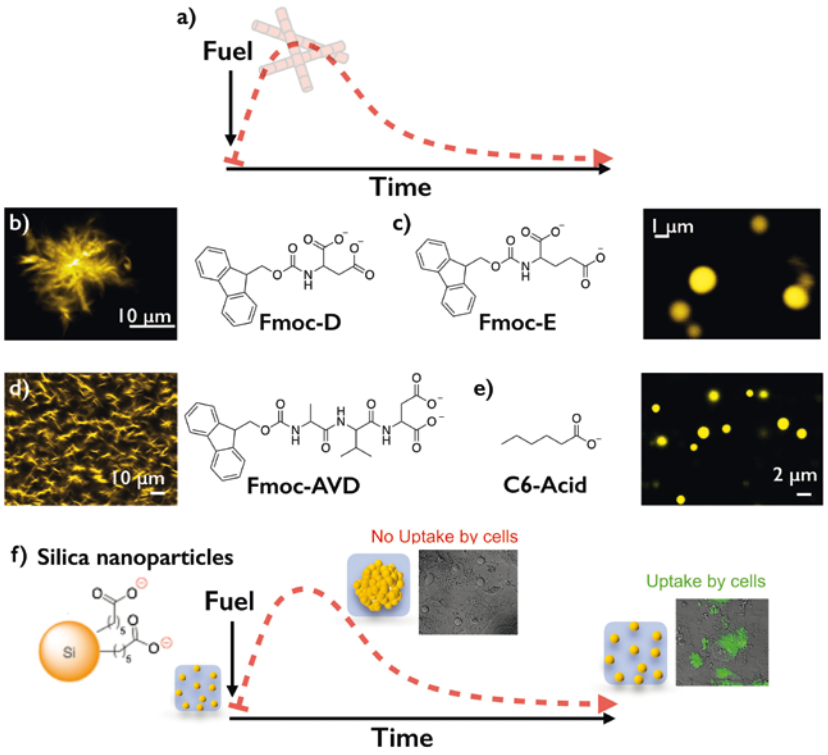
a Energy landscape



b Chemical reaction network



1 | (a) Energy landscape for assemblies out of equilibrium. Note that the assemblies formed due to fuel 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 cycle 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.



2 | Temporary control of dissipative supramolecular assemblies: (a) Schematic representation of the temporal control over material formation and degradation achieved by using the energy-dissipating approach previously described. (b, c, d, e) Molecular structures and confocal micrographs of the spherulites formed by Fmoc-D anhydride assemblies (b), colloids formed by Fmoc-E (c), fibers formed by FmocAVD (d) and oil droplets formed by C6-Acid (e). (f) Molecular structure of silica nanoparticles functionalized with carboxylic acids and schematic representation of their potential application as a platform to control the delayed uptake of the nanocrystals by mammalian cells.

We have investigated amino acid derivatives (Figure 2b–c), small peptides (Figure 2d), and aliphatic acids (Figure 2e) as precursors for the chemical reaction cycle [3]–[5]. All of them were able to form supramolecular materials upon fuel addition, and their lifetimes were tunable from minutes to hours. The different nature of the precursors translated into the diverse types of assemblies we explored as temporary supramolecular materials. For example, small peptides were used to develop temporary hydrogels. The spherulites formed upon addition of fuel to Fmoc-D were embedded in a gel matrix and used as a carrier for temporary messages. Sequential additions of fuel batches demonstrated the reusability of all the materials.

We adapted the reaction cycle to work with nanoparticles as precursors. Gold or silicon nanoparticles functionalized with carboxylic acids showed the formation of clusters when a batch of fuel was added (Figure 2f). In collaboration with the colleagues from Cellular Protein Biochemistry, we used dissipative silica nanoparticles to control the delayed uptake of nanocrystals by mammalian cells [6].

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

Focus Group **Synthetic Biochemistry**

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Scientific Reports

Kathrin Lang

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Synthetic Biochemistry
TUM

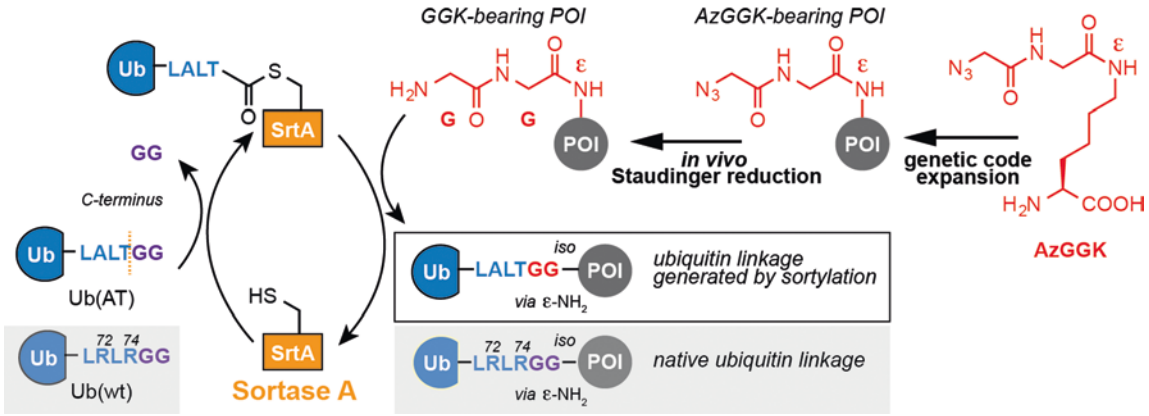
Expanding the genetic code to study and manipulate biological processes

The Focus Group Synthetic Biochemistry conducts research in the interdisciplinary area between chemistry and biology and combines organic chemical, biochemical, biophysical, structural, and cell biological techniques to develop new tools for studying and controlling biological systems.

We are especially active in enabling and advancing approaches to expand the genetic code and in developing new *in vivo* chemistries: a combination that is ideally suited to address unmet challenges in studying and manipulating biological processes with a new level of spatial, temporal, and molecular precision. We have developed approaches to site-specifically incorporate designer unnatural amino acids (UAAs) with tailored chemical and physical properties into proteins in bacteria and eukaryotes that allow the selective functionalization of proteins with biophysical probes and small molecules within their physiological context [1]–[4]. This enables diverse applications, including approaches for probing and imaging proteins *in vivo*, as well as controlling and manipulating their activity in living cells [5]–[6].

The genetic encoding of UAAs, combined with chemistries that are amenable to *in vivo* reactions, not only makes it possible to covalently decorate proteins with biophysical probes and small molecules, but can also be used to study and validate protein-protein interactions. With such applications in mind, we have developed approaches for the co-translational site-specific incorporation of UAAs bearing functional groups that are inert under physiological conditions but covalently link positions that are brought into proximity as a result of protein-protein interactions and protein complex formation. Such proximity-triggered crosslinking approaches (chemical crosslinking) allow covalent stabilization of low-affinity and transient protein complexes in living bacteria and mammalian cells. We have pioneered their use to aid structure elucidation of previously inaccessible transient, low-affinity protein complexes [7]–[8]. In future studies we want to expand this approach to map cytosolic protein-protein interactions and to decipher new enzyme targets in protein profiling studies.

Within the last year we have furthermore pioneered approaches in which site-specifically introduced UAAs serve as a platform for a chemoenzymatic reaction in order to install post-translational modifications such as ubiquitylation. Nearly all proteins in eukaryotic cells are at some point in their life-span tagged with the small protein ubiquitin. Ubiquitylation plays crucial roles in a variety of eukaryotic cellular processes, such as protein degradation, DNA repair, nuclear transport, endocytosis, and chromosomal organization. Hence it is not surprising that many different human diseases, including different types of cancer, are being linked to dysfunction of ubiquitylation pathways. Like many post-translational modifications, ubiquitylation is a reversible process and tightly regulated by a family of enzymes called deubiquitinases (DUBs). The human genome encodes around 100 DUBs, most of them being cysteine proteases. Since they antagonize cellular effects of protein ubiquitylation, DUBs have emerged in recent years as promising targets for drug development, notably against cancer. A full understanding of the cellular functions



1 | The unnatural amino acid AzGGK is incorporated site-specifically into a protein of interest (POI) via genetic code expansion. *In vivo* Staudinger reduction converts AzGGK proteins into GGK-bearing proteins, which in turn undergo sortase-mediated trans-peptidation with a modified ubiquitin Ub(AT) bearing a sortase recognition motif (LALTG). Figure taken from [9].

of ubiquitylation/deubiquitylation events is however crucial for the development of next-generation therapeutics. Our ability to study these effects is limited by the difficulty of preparing homogenously modified proteins *in vitro* and by the impossibility of selectively triggering specific ubiquitylation events in living cells. We have recently developed a novel chemoenzymatic approach, dubbed sortylation, to site-specifically ubiquitylate a protein of interest (POI) – both *in vitro* and *in cellulo* – in an inducible fashion using genetic code expansion and sortase-mediated transpeptidation (Figure 1).

The generated ubiquitin-conjugates display a native isopeptide-bond and bear two-point mutations in the ubiquitin C-terminus that confer resistance toward deubiquitinases. Nevertheless, the physiological integrity of sortase-generated diubiquitins in decoding cellular functions via recognition by ubiquitin-binding domains is retained. Sortylation allows the site-specific attachment of Ubls to non-refoldable, multi-domain proteins and enables inducible and ubiquitin-ligase-independent ubiquitylation of proteins in mammalian cells, providing a powerful tool to dissect biological functions of ubiquitylation with temporal control [9]. The study was accepted for publication in the Journal Nature Chemical Biology, and we have filed a patent concerning our sortylation approach.

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

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

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

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Maria Tensil, Dr. Michael Wenz | Research Assistants

Scientific Reports

Nicola Teresa Lautenschlager

Host
Prof. Janine Diehl-Schmid
Psychiatry and Psychotherapy, TUM

Modern technology to support cognitive and mental health

In 2018, we focused on completing our pilot study called RHAPSODY-plus. This pilot study builds on the Internet-based information and skill-building program RHAPSODY, which was specifically developed for family carers of care recipients with young onset dementia (YOD). YOD is defined as a dementia syndrome emerging in people younger than 65 years. The estimated prevalence of YOD is 100, and the annual incidence 5–20 per 100,000 in the population aged 45–64 in Europe, Japan and the United States. YOD is associated with specific and often severe problems, and therefore family carers are at increased risk of stress, depression, and sleep problems, and they often experience poor health outcomes. They have specific needs due to common difficulties diagnosing the cause of dementia accurately and promptly and the associated carer burden. RHAPSODY was well received, but feedback from carers included the wish to also be able to discuss their individual carer situation with an expert.

We therefore developed our pilot study RHAPSODY-plus, which invited 20 family carers to participate in two additional individual 60-minute support sessions provided by a social worker and a clinical psychologist via tele-video communication technology after they had used RHAPSODY for four weeks. The aims of this pilot study were to determine whether the intervention is considered useful by participating carers and to investigate the potential benefits and barriers of using communication technology in this context. The study was completed in late 2018; our Focus Group is currently analyzing the results, and a manuscript is in preparation. The 20 carers were recruited via Prof. Diehl-Schmid and the Center for Cognitive Disorders at the University Hospital Klinikum rechts der Isar after our study had received ethics approval. 75% of the carers were female, and their ages ranged between 40 and 77 years. 75% of carers were partners of the care recipients. 25% had a university degree, and 45% still worked full-time. 60% of the care recipients were diagnosed with Alzheimer's disease and 40% with fronto-temporal degeneration. 50% of participating carers lived in rural settings, and 80% already received some support services.

The vast majority of carers found the two additional individual support sessions useful, with 85% stating that they would recommend this program to other carers and 90% reporting that they would be prepared to pay something for such a service if it would be available outside a research setting. Many of the participants indicated that ongoing, continuous access to such support sessions, when needed, would be ideal. 50% of participants experienced some transient problems with the technology, but usually this could be resolved. Overall they did not mind having the conversations via the tele-video setup, and they preferred this compared to conversations over the phone as being able to see the professional was important to them. Several carers highlighted the benefits of tele-video communication technology compared to having to attend appointments in person, as this gives flexibility and saves travel time. Our two experts conducting the sessions also had positive feedback overall, preferring the tele-video approach over conversations via phone. In general they preferred face-to-face appointments with carers but acknowledged that having the flexibility of using tele-video communication technology would be very useful for carers who can't attend face-to-face appointments. While these reported results are only preliminary and detailed qualitative analysis is still pending, we conclude that tele-video communication technology in this context has potential, especially for diverse carer groups, which needs to be explored further.

Also in 2018 our Focus Group analyzed results from a small qualitative study with patients with mild cognitive impairment or Alzheimer's disease and their carers, exploring the potential benefits of an app for smartphones, which enabled simplified phone calls and messages to predefined contacts; a memory aid, allowing them to save speech and text notes as reminders; a one-click emergency call to a predefined carer; and a simplified pedestrian navigation system. We aim to submit this for publication soon.

Finally, on December 12, 2018, our Focus Group held the well attended 2018 Liesel Beckmann Symposium on the topic "Technology, Cognition and Dementia" involving diverse local, national, and international speakers exchanging their knowledge and ideas across multiple disciplines.

Focus Group **Engineering Immune Cells for Therapy**

Prof. Kathrin Schumann (TUM) | Rudolf Mößbauer Tenure Track Professor
Michael Lauber (TUM) | Doctoral Candidate

Scientific Reports

Kathrin Schumann

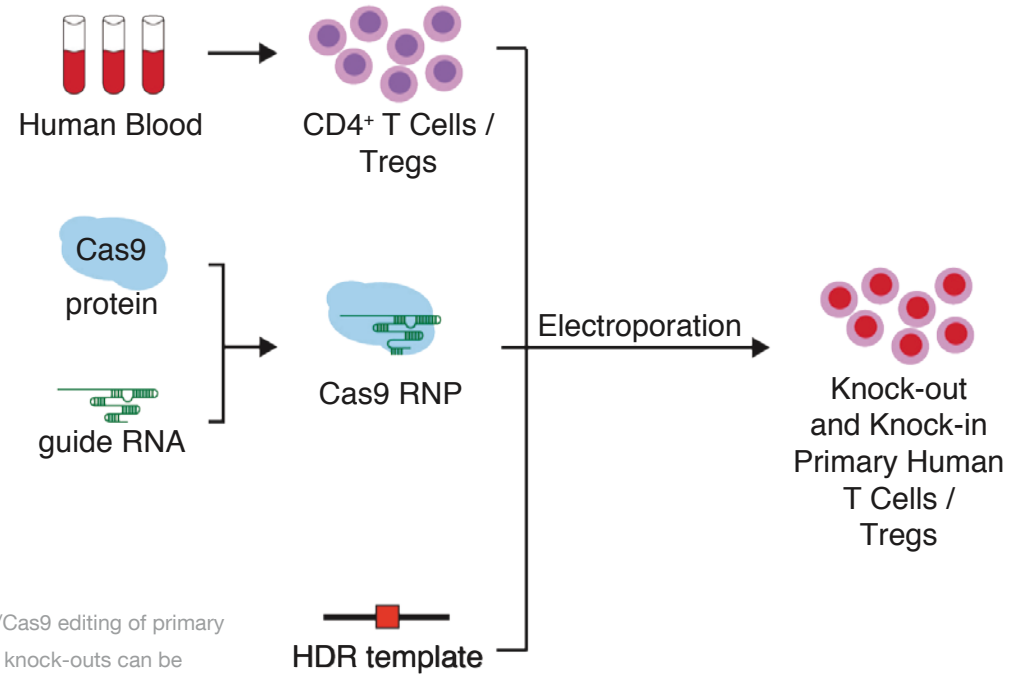
Host
Engineering Immune Cells for Therapy

Using CRISPR screens to understand human regulatory T cell identity

Our immune system protects us from a broad range of pathogens while preventing misguided or exaggerated immune responses that could harm the body. Regulatory T cells (Tregs) play a central role in these processes by sustaining immunological self-tolerance and homeostasis by suppressing autoreactive effector T cells. Absence or depletion of Tregs results in the development of immunodysregulation polyendocrinopathy enteropathy X-linked (IPEX) syndrome, which manifests in multi-organ autoimmunity. Multiple forms of Treg malfunction have been observed in common human autoimmune diseases including decreased Treg numbers, defective Tregs, and Tregs with destabilized cellular identity. In contrast to their protective role in autoimmune diseases, Tregs can contribute to tumor growth and metastasis by suppressing the cytotoxic CD8+ T cell anti-tumor response. In autoimmunity-stabilized Tregs and in tumors, “pro-inflammatory” Tregs with T effector functions would be beneficial. For these reasons Tregs are a promising target for cell therapies for both cancer and autoimmune diseases. However, our understanding of how human Tregs transcriptionally maintain their cellular identity is still scarce. So far Tregs have been mainly characterized in mouse models due to technical limitations. We developed Cas9 ribonucleoproteins (Cas9 RNPs), consisting of recombinant Cas9 protein loaded with chemically synthesized gRNAs, as a powerful tool to generate gene knock-outs and gene knock-ins, and to perform genetic screens in a pooled or arrayed format. We are now applying these technologies to dissect transcriptional circuits in human Tregs isolated out of the peripheral blood – cells that are a potential source for therapeutic approaches.

Transcriptional circuits are composed of transcription factors and cis-regulatory elements, non-coding DNA elements like enhancers and promoters that integrate transcription factor signals and adjust gene expression levels. Established in May 2018, the Focus Group EICT is now systematically analyzing which transcription factors are crucial for maintaining Treg cell identity and which are the key enhancers that integrate these transcription factor binding signals.

FOXP3 is the Treg master transcription factor and fundamental for functionality and stability of this special cell type. However, there are a multitude of transcription factors that work in concert or in parallel with FOXP3 to shape the Treg transcriptional signature. We perform Cas9 RNP screens to knock-out transcription factors that are predominantly expressed in Tregs compared to other T cell subsets and analyze how the deletion of transcription factors changes the pro- or anti-inflammatory features of this special cell type. We tested so far 40 different transcription factors including FOXP3 and Helios as positive controls. By integrating single-cell RNA-seq data we are starting to identify genetic modules controlled by individual transcription factors that regulate Treg survival, proliferation, metabolism, and suppressive function.



1 | Schematic workflow of CRISPR/Cas9 editing of primary human T cells including Tregs. Gene knock-outs can be generated by nucleofection of primary human Tregs with Cas9 ribonucleoproteins (Cas9 RNPs). For gene knock-ins, Cas9 RNPs are combined with an added DNA template for homology-directed repair (HDR).

Non-coding DNA elements like enhancers are notoriously difficult to characterize functionally. The best-characterized enhancers in (murine) Tregs are the so-called conserved non-coding sequences (CNS) of FOXP3, which control FOXP3 induction as well as maintenance. We are currently characterizing Treg FOXP3 CNS regions by deleting or introducing mutations via CRISPR editing into these elements to validate their function (positive controls). On the basis of these results, we will perform CRISPR screens for enhancers in primary human Tregs that effect key proteins of these cells.

Our goal is to identifiy genetic modules regulating Treg identity and to test how we can apply this knowledge to engineer Tregs with distinct features for advanced cellular therapies.

Publications by this Focus Group can 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

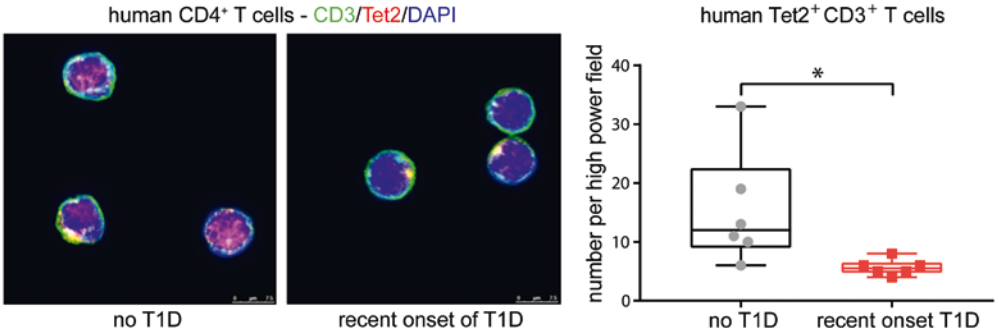
MiRNA-mediated control of immune activation in diabetes and obesity

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 of our group, have begun to reveal how multiple different 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.

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 both down- and upregulation of up to tenfold. 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*.



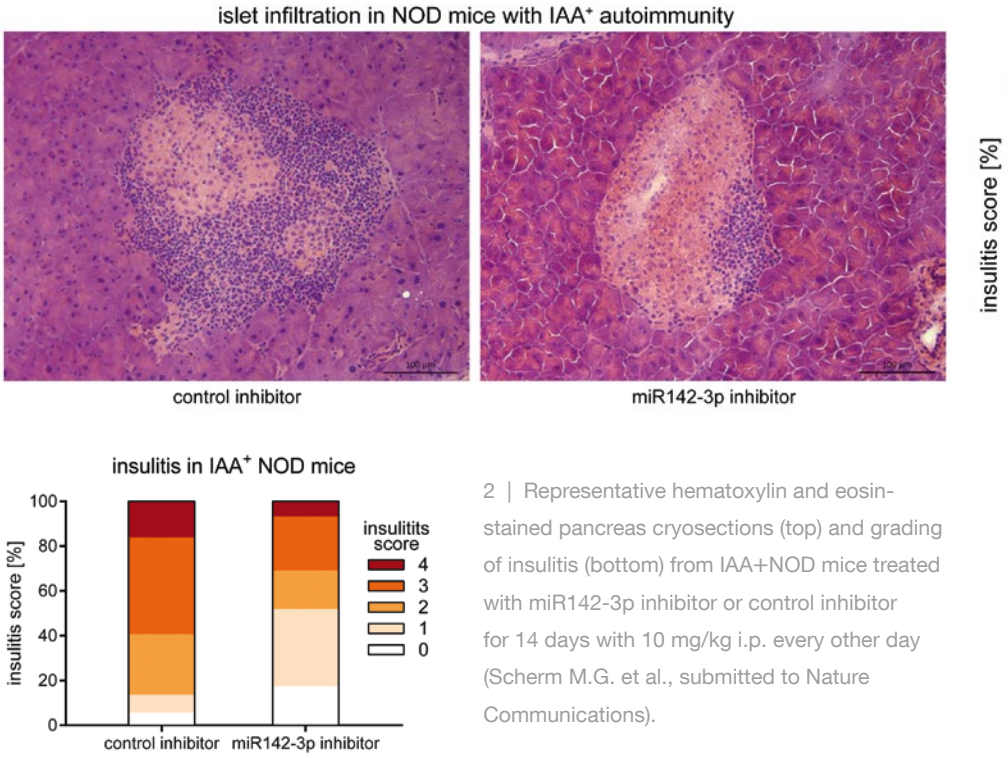
1 | Representative immunofluorescence staining (left) and quantification (right) of human CD4+ T cells from individuals with and without T1D. Staining for CD3 (green), Tet2 (red) and DAPI (blue). (Scherm M.G. et al., submitted to Nature Communications).

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 NOD mice [6].

In a second study, we showed that during early stages of islet autoimmunity a miRNA142-3p/Tet2 signaling axis in murine and human CD4+T cells interferes with efficient Treg induction, accompanied by impairments in Treg specific DNA demethylation and Treg stability. Specifically, we demonstrated that miR142-3p is induced in islet autoimmunity, while its inhibition enhances Treg induction and stability accompanied by an improved Treg specific DNA demethylation and a reduction of islet autoimmunity in non-obese diabetic (NOD) mice *in vivo*. Mechanistically, we used HITS-CLIP analyses [7] to show a high abundance of miR142-3p in the RISC complex of human CD4+ T cells and to identify the methylcytosine dioxygenase Tet2, an enzyme involved in DNA demethylation, as a direct target of miR142-3p. This miRNA-mRNA target relationship was confirmed using various experimental approaches, including miR142-3p inhibitor/mimic experiments and knockout models. Taking these together, we were able to link high miR142-3p levels during islet autoimmunity to epigenetic remodeling and impairments in Treg induction and stability. These findings offer a new mechanistic model where during islet autoimmunity miR142-3p/Tet2-mediated Treg instability can contribute to autoimmune activation and progression.

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, Group Immune Tolerance in Type 1 Dabetes, Helmholtz Zentrum München).



2 | Representative hematoxylin and eosin-stained pancreas cryosections (top) and grading of insulitis (bottom) from IAA+NOD mice treated with miR142-3p inhibitor or control inhibitor for 14 days with 10 mg/kg i.p. every other day (Scherm M.G. et al., submitted to Nature Communications).

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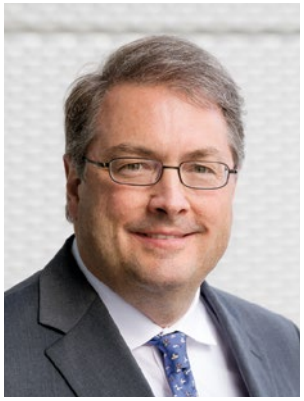
Publications by this Focus Group can also be found in the section Publications of this report.

Focus Group **Proteases in the Brain**

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

Scientific Reports



Carl P. Blobel

Host
Prof. Stefan Lichtenthaler
Neuroproteomics, TUM

The main goal of our Focus Group is to provide a better understanding of the role of specific molecular signaling scissors (proteases) in the normal brain and their contribution to brain pathologies such as Alzheimer's disease (AD) and traumatic brain injury (TBI).

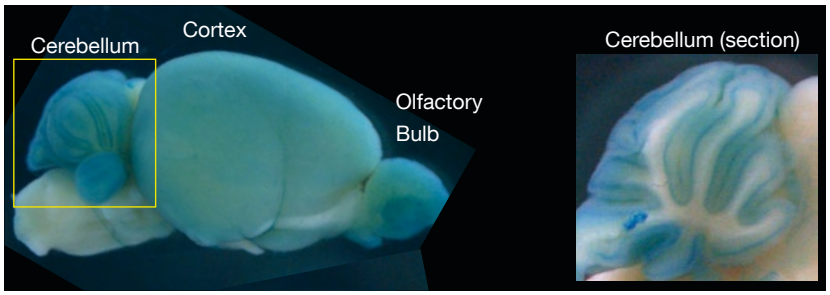
Our efforts are concentrated on molecular scissors termed ADAM17 (a disintegrin and metalloprotease 17, also referred to as TNFα converting enzyme or TACE), which are active in many different tissues in the body. Specifically, ADAM17 controls two major signaling pathways with important roles in development and disease: signaling by the pro-inflammatory cytokine TNFα (tumor necrosis factor α) and signaling through the epidermal growth factor receptor (EGFR). TNFα is also referred to as the "fire alarm of the body" because of its central role inflammation and autoimmunity. Usually, TNFα is responsible for orchestrating the response of the host to infection, for example by bacteria. However, when the production of TNFα becomes dysregulated, it can cause serious inflammatory and autoimmune diseases, such as rheumatoid arthritis, systemic lupus erythematosus (SLE), and most likely also neuroinflammation in AD and TBI. The EGFR pathway protects the skin and intestinal barrier but can also cause cancer when inappropriately activated. Because ADAM17 is a master regulator of these two pathways, it was considered an attractive target for treatment of diseases caused by dysregulated TNFα or EGFR signaling (e.g., autoimmune diseases, cancer, AD). However, since the ADAM17/EGFR pathway has a key role in protecting the skin and intestinal barrier, inhibitors of the EGFR pathway have strong side effects, including severe skin rash and intestinal inflammation, that limit their use, and the same side effects would be expected from inhibitors of ADAM17.

A few years ago, the Blobel lab discovered a potential solution to the side effects that would be caused by blocking ADAM17. They found that ADAM17 has two separate regulators, termed inactive rhomboids 1 and 2 (iRhom1/2), that can be thought of as two separate hands that control ADAM17. Interestingly, inactivation of iRhom2, which controls the pro-inflammatory functions of ADAM17, was well tolerated in mice because the related iRhom1 can protect the skin and intestinal barrier when iRhom2 is not present. Targeting iRhom2 should thus provide a novel approach toward blocking the pro-inflammatory functions of ADAM17 without affecting its protective roles in skin and intestinal barrier.

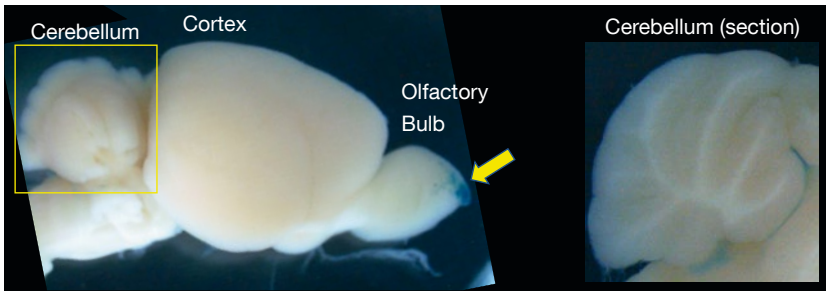
The premise for the Focus Group is that iRhom2 is responsible for controlling the function of ADAM17 in immune cells in the brain (microglia), whereas iRhom1 is important for the functions of ADAM17 in the rest of the brain. We hope to provide a better understanding of the role of iRhom2/ADAM17 in microglia in neuroinflammation, AD, and TBI, and of the function of iRhom1 in the brain, with an emphasis on AD.

The role of iRhom2/ADAM17 in AD has been the focus of Dr. Simone Scilabra's efforts. Previous studies had shown that changes in the methylation of the iRhom2 gene are linked to AD in patients (De Jager, PL et al., *Nat. Neurosci.* 2014), providing a strong incentive to understand the function of this gene in a mouse model of AD. Dr. Scilabra developed such a model by crossing mice that are prone to AD with mice that lack iRhom2 to study the development of AD in these animals.

iRhom1 expression in the brain



iRhom2 expression in the brain



1 | Expression of iRhom1 and iRhom2 in mouse brains. The Figure shows an expression analysis of iRhom1 and 2 in the brains from genetically modified mice (iRhom1, upper panel, iRhom2, lower panel, blue staining indicates gene expression). iRhom1 is relatively ubiquitously expressed in the brain, whereas hardly any iRhom2 expression can be detected, except in the olfactory bulb (yellow arrow). This is consistent with the expression of iRhom2 in microglia (immune cells), which presumably only express iRhom2 under neuroinflammatory conditions. The expression of iRhom2 in the olfactory bulb raises interesting questions about potential functions of iRhom2/ADAM17 in smell. The sections of the cerebellum on the right of both panels provides further insights into the expression of iRhom1 and iRhom2 in this part of the brain (outlined by yellow boxes on the left). These images were generated by Ms. Tüshaus as part of a comprehensive analysis of the functions of iRhom1 and 2 as regulators of ADAM17 in the brain.

His first results are encouraging, in that genetic inactivation of iRhom2 slowed neuroinflammation and resulted in improved cognitive abilities compared to controls. Together with Dr. Merav Shmueli in Dr. Lichtenthaler's lab, the Focus Group has been applying cutting-edge proteomic approaches and cell biological studies of neuroinflammation using microglia from mutant and wild type animals to investigate the contribution of iRhom2/ADAM17 to the neuroinflammatory process.

The second part of this project is focused on the role of iRhom1/ADAM17 in the brain, with an emphasis on AD. The medical relevance of ADAM17 in AD was recently underscored by the identification of mutations in ADAM17 that predispose to AD in patients (Hartl D. et al., *Mol Psychiatry* 2018). Studies of iRhom1/ADAM17 are spearheaded by Johanna Tüshaus, a TUM-IAS sponsored graduate student and recipient of a Boehringer Ingelheim PhD fellowship. Using the innovative "secretome protein enrichment with click sugars" (SPECS) method developed in the Lichtenthaler lab, Ms. Tüshaus has performed an in-depth secretome analysis of minor amounts of primary neurons in 2D and 3D cell culture models. In addition, she obtained minute droplets of cerebrospinal fluid (CSF) from mice and used these to identify differences in the CSF of iRhom1-deficient mice compared to controls, an exciting and promising new direction of our group. Ms. Tüshaus has identified several exciting new substrates for iRhom1/ADAM17 in the brain and has collaborated with the Blobel lab to analyze brains from mice lacking iRhom1 to understand the consequences of inactivation of iRhom1 and thus ADAM17 in the mouse brain. The Focus Group is also testing the hypothesis that iRhom1/ADAM17 protect against AD because they function as α-secretase in the brain, and thus compete with the pathogenic β-secretase (BACE).

We hope that the studies of our Focus Group on the iRhom/ADAM17 signaling scissors in the brain will ultimately help to uncover new targets for treatment of neuroinflammation in AD and TBI. We are most grateful to the TUM-IAS for supporting our Focus Group, and look forward to continuing our highly collaborative and interdisciplinary studies in Munich.

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

Focus Group **Collective Quantum Dynamics**

Prof. Michael Knap (TUM) | Rudolf Mößbauer Tenure Track Professor
Dr. Fabian Grusdt (TUM) | Postdoctoral Researcher
Annabelle Bohrdt, Johannes Feldmeier, Clemens Kuhlenkamp, Alexander Schuckert, Simon Weidinger, Elisabeth Wybo (TUM) | Doctoral Candidates

Scientific Reports

Michael Knap

Host
Collective Quantum Dynamics, TUM

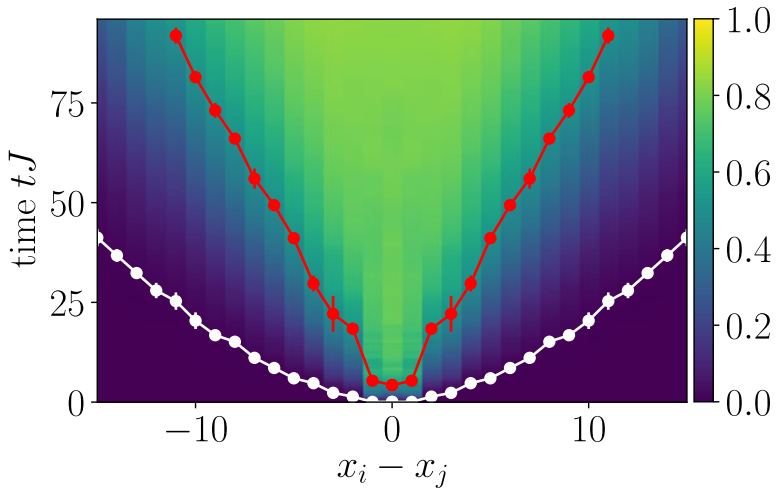
Collective quantum dynamics: Teamwork of quantum particles

The research in our Focus Group aims at a broad range of questions from condensed matter theory such as exotic quantum material, 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. An important factor of our research is also its immediate relevance for experiments, which leads to a close collaboration with experimental groups all over the world.

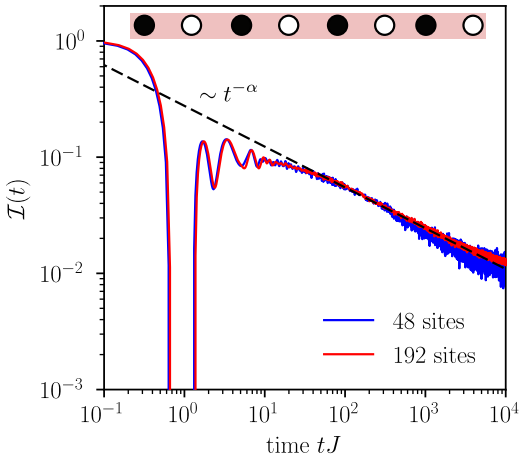
Correlated quantum systems out of equilibrium

Recent conceptual and technical progress makes it possible to prepare and explore strongly correlated non-equilibrium quantum states of matter. The tremendous level of control and favorable time scales achieved in experiments with synthetic quantum matter, such as ultracold atoms, polar molecules, or trapped ions, renders these systems ideal candidates to explore non-equilibrium quantum dynamics.

In a recent work [1], we study theoretically the entanglement and operator growth in a quantum spin system used to describe magnets coupled to an environment, which is modeled with classical dephasing noise. Using high-performance exact numerical simulations, we showed that the entanglement growth and its fluctuations are described by the celebrated Kardar-Parisi-Zhang equation, which was originally introduced to describe stochastic surface growth. Our results provide fundamental insights into the basic processes that occur in the far-from-equilibrium time evolution of strongly correlated quantum matter.



1 | The growth of a quantum operator in space-time follows a biased diffusion equation.



2 | Relaxation dynamics of a many-body localized quantum system [S2]

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. However, even beyond the vanishing transport, 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. In a recent work [2] we have developed a simple theoretical framework to describe the transition between the thermalizing phase and the localizing phase dynamically, using a low-order perturbation theory. We find that this simplified approach captures a lot of the many-body localization phenomenology, such as the logarithmic growth of the entanglement following a quantum quench initialized with a product state in the many-body localized phase and the slow subdiffusive dynamics at weak disorder.

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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

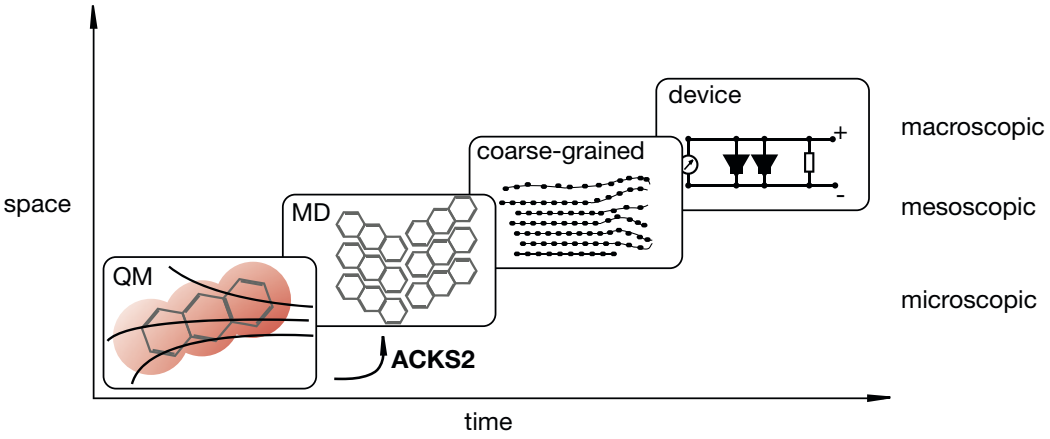
Hosts
Prof. Peter Müller-Buschbaum
Functional Materials, TUM
Prof. Karsten Reuter
Theoretical Chemistry, TUM

Ab *initio* based polarization correction in force field methods: The Acks2 method

In a world rich in technology, organic semiconductors (OSs) are one of the most thrilling materials discovered in the past decades. Light-weight, flexible, and relatively easy to produce from renewable fabrication resources, OSs 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 (OLEDS), or light-harvesting materials like organic photovoltaic devices.

Unfortunately, the loss of electric conductivity poses a serious downside for these newly found OS materials compared to default inorganic compounds, and addressing this is crucial for modern electronic devices. The quest to identify promising new OS compositions and systematically improve their electric conduction properties requires 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 electrons and electron holes, typical charge carriers, 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 and molecular level, OSs 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 OSs, 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 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 orbitals basis.



1 | Illustration of multi-scale approach in material modeling. The ACKS2 model provides efficient quantum-mechanic level derived electronic polarization for force field simulations.

In the last two years we systematically developed a new Gaussian-type basis set representation of the ACKS2 response. For the first time we implemented a solely ACKS2-based calculation of the electronic polarization energy, a fundamental property in dynamical processes and simulations. The linear response properties were finally validated for a representative set of electrostatic field perturbations and hydrocarbon molecules akin to organic semiconductor materials, yielding very good reproduction of the density functional reference. This marks a crucial first step in making ACKS2 applicable as a polarizable force field for accurate simulation of 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. Filippo Maglia (BMW Group) | Rudolf Diesel Industry Fellow
Dr. Peter Lamp (BMW Group) | Alumnus Rudolf Diesel Industry Fellow
Lennart Reuter (TUM) | Doctoral Candidate

Scientific Reports

Filippo Maglia

Peter Lamp

Host
Prof. Hubert A. Gasteiger
Technical
Electrochemistry, TUM

The development of renewable energy systems for efficient energy conversion and storage is strongly dependent on the fundamental understanding of interfaces in electrochemical environments. The efficiency of energy conversion and energy storage processes is almost entirely determined by the richness of interfacial processes that control the rate of electron and ion transfer.

Over the last three decades, the power of analytical techniques has increased to the extent that we can now “see” and measure these manifestations. This information has been instrumental in establishing the structure-function relationships, i.e., correlations between the morphology, the composition of the electrode/electrolyte, and the physicochemical properties of the interface such as activity, stability and selectivity in aqueous systems [1]. However, the picture of solid-organic interfaces is still quite hazy due to a lack of complementary information about structure-function relationships in organic solvents [2]. As a result, the development of electrolytes for lithium-ion batteries remains a somewhat empirical process, with the most common electrolytes consisting of a combination of lithium hexafluorophosphate ($LiPF_6$) salt with a binary solvent mixture of cyclic and linear alkyl carbonates. The selection of these electrolytes is based on their high salt solubility, high ionic conductivity, and the formation of a stable solid electrolyte interphase (SEI) that simultaneously minimizes electrolyte decomposition while still providing high Li^+ diffusivity [3].

The morphological and compositional picture of the SEI formed in such environments is complex, involving numerous proposed reaction products [4]. Despite playing a pivotal role in lithium-ion battery (LIB) performance and durability [5], a detailed mechanistic understanding of the nature of SEI formation and its resulting structure remains elusive. It is therefore imperative that the development of more efficient energy conversion and storage technology strongly relies on a rational description of the complex electrode processes that will allow us to control the transport, transformation, and redistribution of atoms, molecules, and electrons across the electrochemical interfaces in non-aqueous environments. Over the past few years, we developed a surface science-based strategy that allowed us to translate the knowledge obtained from well defined single-crystal surfaces to systematically more complex graphite-electrolyte interfaces in non-aqueous electrolytes. As one outcome of our previous activities [6], we presented experimental and theoretical investigations that elucidated the formation mechanism for LiF (one of the main SEI components). Our finding is of general importance and may open new opportunities for the improvement of existing Li-ion technologies and the design of new ones.

The activity of the Focus Group Electrochemical Interfaces in Batteries represents an ideal extension of the activity described above and will involve again, besides the BMW Battery Cell Technology Group and the Chair of Prof. Gasteiger, the contributions from ANL (Dr. Marković) and Copenhagen University (Prof. Rossmeisl).

The final goal of the overall cooperation is the understanding of the influence of the SEI on the performance/durability of real Li-ion batteries. While the SEI's composition and structure is a widely explored topic, there are perhaps as many different results as there are studies in terms of SEI composition/morphology and its role in controlling the performance of a real LIB cell. Although such complex phenomena can be "tested" in real systems, it is our opinion that the only way to resolve, understand, and therefore control the underlying fundamental processes, is to take a unique experimental-computational approach, capable of connecting fundamental knowledge with real cell performance.

The approach we propose incorporates three critical steps: (i) to employ well defined model systems and use such conditions to assess fundamental descriptors for the formation of the SEI; (ii) to probe more realistic carbon structures (e.g., graphene) with different morphologies; and (iii) to explore the properties of graphitic structures that are currently used in real lithium-ion batteries. In the initial phase of the project, we have selected and validated a variety of *ex situ* and *in situ* experimental methods (Argonne National Laboratory and TUM) as well as computational and theoretical tools (University of Copenhagen). In particular, the activity performed at TUM in the framework of the doctoral work of Lennart Reuter is dedicated to investigating gaseous products evolved during SEI formation as well as quantifying the performance/durability and impedance of electrodes with a tailored SEI, using battery cells with reference electrodes to conduct electrochemical impedance analysis and cell charge/discharge cyling.

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

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 pulses of light that are identical in terms of the spatial and temporal shape of the wavepacket 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 upscale 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.

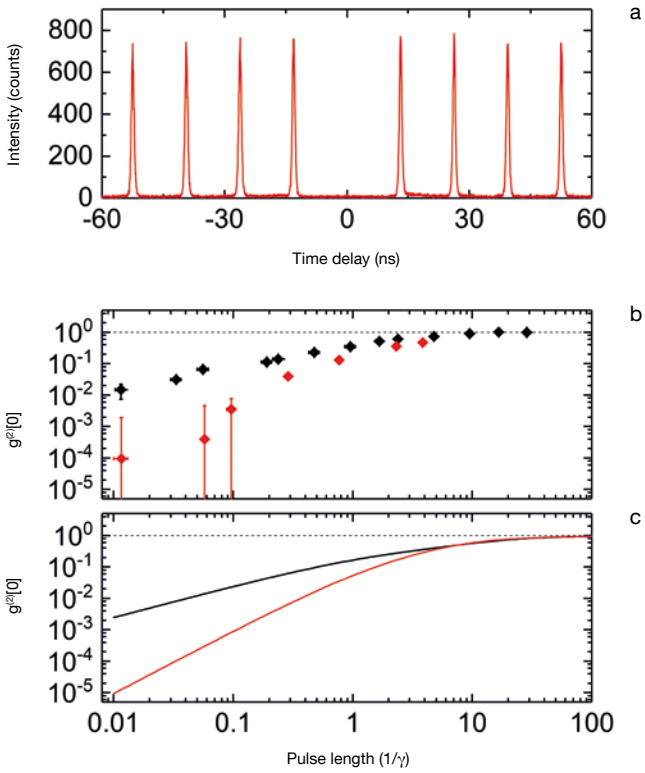
Semiconductor quantum dots (QDs) are "artificial atoms" in the solid state that can be controllably embedded within nanophotonic devices for various applications in quantum technologies. When individual QDs are resonantly optically excited with a picosecond (1 ps = 10^{-12} s) duration laser pulse, they can generate single photons on demand. Repeated optical excitation enables the generation of a stream of single photons, each having a wavepacket 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 exciting 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. Gaining a detailed understanding of the underlying processes is essential for developing novel sources of non-classical light, such as high-quality sources of single photons. To these ends, we have recently demonstrated that exciting a QD at an energy corresponding to a two-photon optical transition can dramatically improve the purity of single-photon generation and lead to unprecedented metrics [1].

With semiconductor QDs many different schemes for the generation of single photons, such as non-resonant excitation, quasi-resonant excitation and resonant excitation, have been developed over the past decade. Thereby, it was found that resonant schemes have the advantage that no free charge carriers are created in the environment of the QD that can cause spectral diffusion of the emitted photons, which is detrimental for many quantum-optical applications. On the other hand, while with resonant excitation the achieved single-photon purities were good, they were still limited since in this scheme emission during the presence of the excitation laser pulse may lead to a re-excitation of the QD and emission of a second photon, thus compromising the obtainable single-photon purity.

In our recent work [1] we demonstrated that this re-excitation of the system can be strongly suppressed by exciting a QD at an energy corresponding to a two-photon optical transition. After exciting the system at the two-photon optical transition, a radiative cascade occurs where two photons are emitted at two different frequencies due to few-Fermion interactions of the involved charge carriers. Since the system can only be re-excited after it has returned to the ground state, re-excitation is strongly suppressed. The single-photon purity can be quantified by the measured degree of second-order coherence $g^{(2)}(0)$ where a value of 1 corresponds to coherent light (laser) and a value of 0 corresponds to a perfect single-photon source.

Figure 1a shows a measurement of $g^{(2)}(\tau)$ 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 1 show the measured (Figure 1b) and calculated (Figure 1c) 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 two orders of magnitude better compared to resonant excitation.



1 | (a) High quality g^2 (τ) 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).

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).

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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 (Paul Scherrer Institut) | Hans Fischer Fellow
Franz Haslbeck (TUM) | Doctoral Candidate

Scientific Reports

Marc Janoschek

Host
Prof. Christian Pfleiderer
Topology of Correlated Systems, TUM

The properties of condensed matter emerge from the underlying atomic-scale interactions. For example, the thermal conductivity in an insulator is governed by the bonding forces between atoms, which determine how atoms may vibrate in the crystal and, hence, transfer heat or energy. Similarly, “quantum matter” is any novel phase characterized by interactions that are inherently “quantum” in nature. Such quantum materials are broadly considered to have vast potential for future applications, ranging from power management and transmission to quantum computation and novel versatile sensors, and even for applications that go beyond what we can currently imagine [1].

Our Focus Group investigates quantum matter that emerges in the vicinity of magnetic instabilities – that is, phase transitions between magnetically ordered and nonmagnetic states. Such magnetic instabilities are typically characterized by violent magnetic fluctuations. When the instability occurs at a temperature near absolute zero, those fluctuations are inherently quantum in nature because there is no thermal energy available to excite thermal fluctuations. In turn, these zero-temperature instabilities – so called magnetic quantum phase transitions (QPT) – are ideal model systems to study quantum matter. Indeed, a potpourri of novel quantum matter phases is observed near QPTs, and it is widely accepted that the underlying quantum magnetic fluctuations are at their origin.

Here it is surprising that although quantum fluctuations only become important 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 issue in solid-state physics. Simultaneously this highlights the relevance of quantum matter for future applications despite its low-temperature roots.

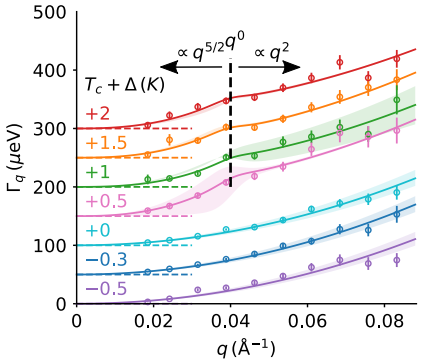
Our Focus Group has now exploited a new neutron spectroscopy method that makes it possible to study magnetic fluctuations with unheard-of levels of energy resolution to reveal that signatures of the underlying quantum fluctuations are also present at non-zero temperatures. Because neutrons carry a magnetic moment that can couple to magnetic fluctuations similar to a small compass needle, neutron spectroscopy is ideally suited to investigate magnetic instabilities. Here we additionally used the trick that ultra-low energies also correspond to ultra-low temperatures. The neutron resonant spin-echo (NRSE) technique, which we used here, encodes energy resolution in the neutron’s polarization to achieve ultra-high energy resolution of about one 1 μeV. This corresponds to a temperature of about 10 mK, or in other words temperatures of only one ten-thousandth of a degree above absolute zero. This discovery is particularly relevant because to date generally very little quantitative information is available on magnetic quantum fluctuations despite the fact that their importance for the understanding of quantum matter is widely appreciated. The material we have studied for this effort is UGe_2, which exhibits coexistence of ferromagnetism and superconductivity near a magnetic quantum phase transition [2]. The coexistence of ferromagnetism and superconductivity is an odd combination because strong magnetic fields typically lead to the destruction

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

of superconductivity. Thus, the internal magnetic field generated by a ferromagnet is expected to suppress superconductivity. This makes UGe_2 a candidate for a new form of superconductivity, so-called spin-triplet superconductivity, in which the Cooper pairs are formed in a distinctively different way compared to other superconductors [3]. However, experimentally this mechanism is hard to differentiate from the standard Cooper pairs.

Our experiments were carried out at the NRSE spectrometer RESEDA at the research reactor of the Heinz Maier-Leibnitz Zentrum (MLZ) at TUM (Figure 1a) [4]. Figure 1b shows the energy Γ_q of the magnetic fluctuations as a function of momentum *q*. *1/q* describes the length scale over which the fluctuations occur. We observe that below $1/q^0$ the fluctuations take on a different character. Interestingly, $1/q^0$ corresponds to a length scale of 16 nm, which is close to the superconducting coherence length $\xi_{SC} = 20$ nm over which the superconductivity in UGe_2 arises. Moreover, the character of the magnetic fluctuations below q^0 is consistent with current theoretical expectations for spin-triplet superconductivity. This suggests that our measurements observe a precursor to the magnetic fluctuations that drive spin-triplet superconductivity near a quantum phase transition.

In conclusion, we have demonstrated that the new method NRSE is able to quantitatively determine the magnetic fluctuations that are at the heart of many quantum matter phases. This will enable us to establish a much more detailed understanding of quantum matter in the future.



(b) Energy Γ_q of the magnetic fluctuations in the putative spin-triplet superconductor UGe_2 as a function of momentum q. *1/q* describes the length scale over which the fluctuations occur (see text for details) [4].

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

Focus Group **Quantum Technologies**

Prof. Menno Poot (TUM) | Rudolf Mößbauer Tenure Track Professor
David Hoch (TUM) | Doctoral Candidate

Scientific Reports

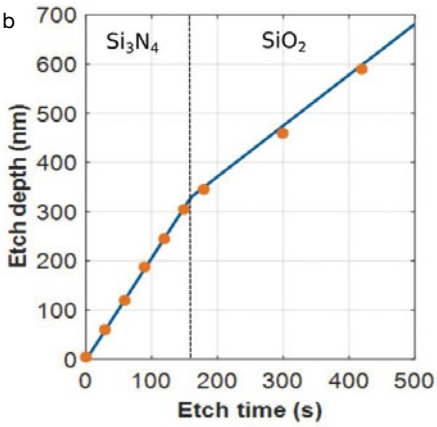
Menno Poot

Host
Quantum Technologies, TUM

Reactive ion etcher and measurement setups

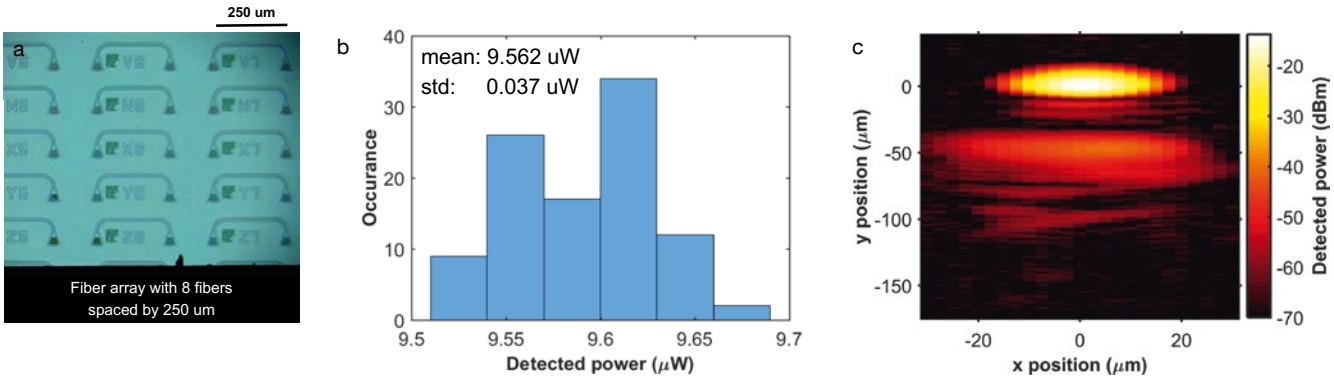
The Focus Group on Quantum Technologies is currently working on integrated photonic quantum circuits and opto-mechanical devices. The first will be used to generate, manipulate, and detect single photons. The integration of micromechanical phase-shifters and quantum gates shows promise to allow universal quantum computation. Opto-mechanical resonators allow coupling of photons and vibrational modes by using photonic and phononic crystal cavities. This can for example be used for the transfer of quantum information between different quantum mechanical systems. In 2018, we expanded our nanofabrication capabilities and developed several new setups to measure a wide range of photonic chips.

We purchased a plasma etcher to expand the nanofabrication capabilities on campus. The Oxford 80 NGP is a state-of-the-art system that can be operated in reactive-ion-etching (RIE) mode as well as in inductively-coupled-plasma (ICP) mode. Its eight gas lines enable etching using both fluorine (more chemical etching) and chlorine (more physical) chemistries. The etching system has already been used to make low-loss waveguides in silicon nitride using a mixture of SF_6 and CHF_3. Si_3N_4 is the material of choice for our integrated photonic quantum circuits, as well as for high-quality opto-mechanical resonators. Besides this important material platform, recipes for etching silicon (anisotropic and isotropic), silicon oxide, and gold have been tested. In collaboration with the Finley and Mueller groups at the Walter Schottky Institute, we have worked on process development for high-selectivity etching of III–V materials. The plasma etching system has been funded by the Nanosystems Initiative Munich (NIM) and the TUM-IAS and is located in the Center for Nanotechnology and Nanomaterials (ZNN).



1 | **Etcher**
a) The Oxford 80 NGP located in the ZNN. It can be operated in both reactive-ion-etching and inductively-coupled-plasma modes. Inset: Viewport of the plasma chamber during an etch process.
b) Reactive-ion etching of silicon nitride. After about 170 seconds the Si_3N_4 is etched completely as indicated by the different slope.

Furthermore, the setup to measure photonic chips in ambient conditions is now fully operational. It is designed around a two-axis motorized stage with 25 mm of travel and a step size of 1.25 micrometer. The stage specifications are verified through image processing. Photonic chips can be positioned using a home-built stepper motor driver, and our LabVIEW-based computer control allows for automated device location and subsequent optimization. This results in very reproducible positioning, as seen in Figure 2c. All measurement devices, such as lasers, optical detectors, multimeters, voltage sources, and oscilloscopes, are integrated into a comprehensive measurement program that allows for the most complex measurements that we currently envision.



2 | **Transmission**

a) Microscope image of optical devices with varying parameters on a chip. The devices consist of two grating couplers and a waveguide. By measuring their transmission spectra, the parameters of the grating couplers are optimized.

b) Histogram of the transmitted power for 100 fully automated position optimizations of a single device. The small spread (< 0.4%) indicates the excellent reproducibility.

c) Measured optical transmission map of an individual device. A shift in y-direction shows side lobes resulting from higher-order diffractions of the grating coupler.

With the combination of the newly built measurement setup and nanofabrication techniques, the first photonic chips have been made and measured. In particular, the amount of light that is transmitted through the devices can be measured. By using a tunable laser in the telecom range (i.e., a wavelength around 1550 nm), a measurement of the transmission spectrum can be made. This allows an optimization of the design parameters of the grating couplers, which form an optical interface between optical fibers and the on-chip waveguides. This optimization is essential for experiments with nanomechanical resonators, as well as for the measurements with quantum light on a chip.

A unique feature of the new setup is that it allows for reproducible scanning of the devices on the chip underneath the optical fibers (which are placed in a linear array of eight fibers). This way, not only the wavelength dependence but also the spatial profile of the transmission can be determined. The insights obtained from such measurements will lead to even higher coupling efficiencies.

Finally, besides the setup for measurements in ambient conditions, two more setups for measurements in a vacuum are currently being assembled. This is essential for the measurements on nanomechanical devices, where air damping can play a detrimental role.

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

Focus Group **Theory of Complex Quantum Systems**

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Daniel Stilck França, Martina Gschwendtner, Margret Heinze,
Stefan Huber (TUM) | Doctoral Candidates

Scientific Reports

Robert König

Host
Theory of Complex
Quantum Systems, TUM

Quantum information processing: Benefits and limitations

The Focus Group Complex Quantum Systems studies the potential of quantum systems for enhancing information processing. We combine information-theoretic, physical, and algorithmic considerations to identify and characterize novel uses for quantum systems and devices. We seek to develop mathematical and information-theoretic tools to quantify the usefulness of quantum systems for computation and communication. With a view to lowering technological requirements for the realization of robust quantum information processing, we study a range of operational questions and physical settings. This includes the following areas:

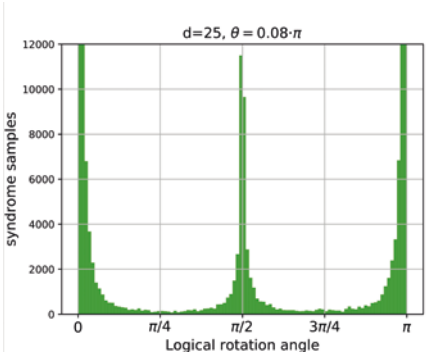
Quantum computation: Provable advantage over classical computation

A foundational question concerning quantum information processing is whether quantum devices are computationally more powerful than classical ones. Most currently known arguments for the existence of such a quantum advantage are conditional: They rely either on certain idealizations or on complexity-theoretic assumptions. Grover's celebrated quantum search algorithm belongs to the former category. Here one considers the so-called oracle model, where one assumes that the quantum computer can ask queries in superposition. This is an idealization that may not translate into a real-world advantage. Shor's famous quantum factoring algorithm is a result of the second type. It shows that a problem – that of finding prime factors of large integers – is efficiently solvable by a quantum computer. It is believed that this provides a quantum speedup: More precisely, it is a complexity-theoretic conjecture that this problem is hard for (i.e., cannot be efficiently solved by) classical computers.

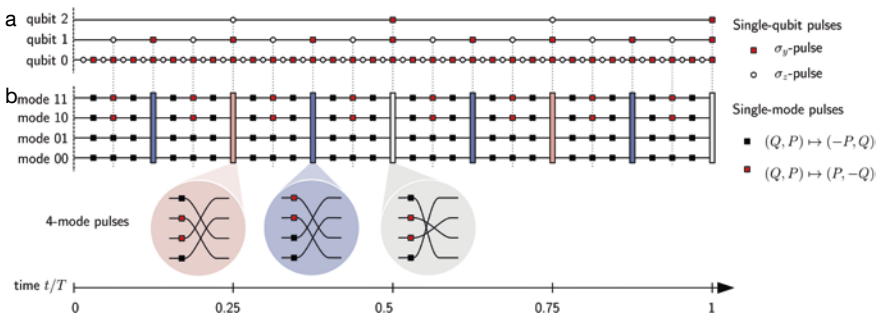
In our work [1], we have established the first unconditional separation between analogously defined classical and quantum complexity classes. More precisely, we consider quantum and classical circuits and show that there is a computational problem with the following properties:

- the problem can be solved with certainty by a constant-depth quantum circuit
- solving the problem with high probability using a classical circuit requires at least logarithmic depth.

Our proof is information-theoretic and does not require any complexity-theoretic hardness assumption.



1 | Storage of quantum information in surface codes: The storage process involving coherent errors, simulated for a surface code with distance d=25 (corresponding to 625 qubits): This shows the histogram of logical error angles, conditioned on the measured syndrome. The peaks, which become more pronounced as a function of the code distance d, indicate that the errors at the logical level essentially amount to probabilistic Pauli noise.



2 | Bosonic dynamical decoupling schemes: (a) The nested Uhrig dynamical decoupling sequence for three qubits suppresses arbitrary system-environment interactions (decoherence) to first order; (b) the deduced bosonic homogenization sequence for four modes "homogenizes" any evolution under a quadratic Hamiltonian (decoherence) up to first order resulting in non-interacting harmonic oscillators rotating at the same averaged frequency. In both cases (a) and (b), the evolution describing decoherence (horizontal straight lines) is interleaved with instantaneous control pulses.

Robust storage and transmission of quantum information

A key ingredient for fault-tolerant quantum information processing is the design and application of quantum error-correcting codes. Our group pursues several approaches: On the one hand, we seek to characterize the exact physical limits of information transmission over noisy quantum channels. In this context, we have found coding strategies that are provably close to optimal for a range of non-Gaussian bosonic channels: The use of simple coherent states can achieve rates that are at most a constant away from the capacity of such channels, independently of the available signal strength.

Robust storage of quantum information is achieved by encoding the information into specific subspaces and performing active error correction by measuring syndromes and applying correction operations. We have developed efficient classical simulation algorithms to investigate to what extent information encoded in so-called surface codes degrades under noise. Our algorithms are the first polynomial-time algorithms that permit simulation of the dynamics of the associated quantum many-body system under general coherent noise. Using these algorithms, we have performed large-scale simulations of systems with several thousand qubits. Our findings indicate that coherent noise is not significantly more detrimental than the probabilistic Pauli noise that is typically studied.

Other natural strategies for stabilizing quantum systems rely on application of unitary control pulse sequences, a technique pioneered in the context of NMR and known as dynamical decoupling: This suppresses unwanted system-environment interactions. We have recently generalized these schemes to the bosonic context, giving the first efficient pulse sequences achieving arbitrary decoupling order.

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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, Building Technology

Fundamental Natural and Life Sciences

Medical Natural Sciences

Surface, Interface, Nano- and Quantum Science

Advanced Computation and Modeling

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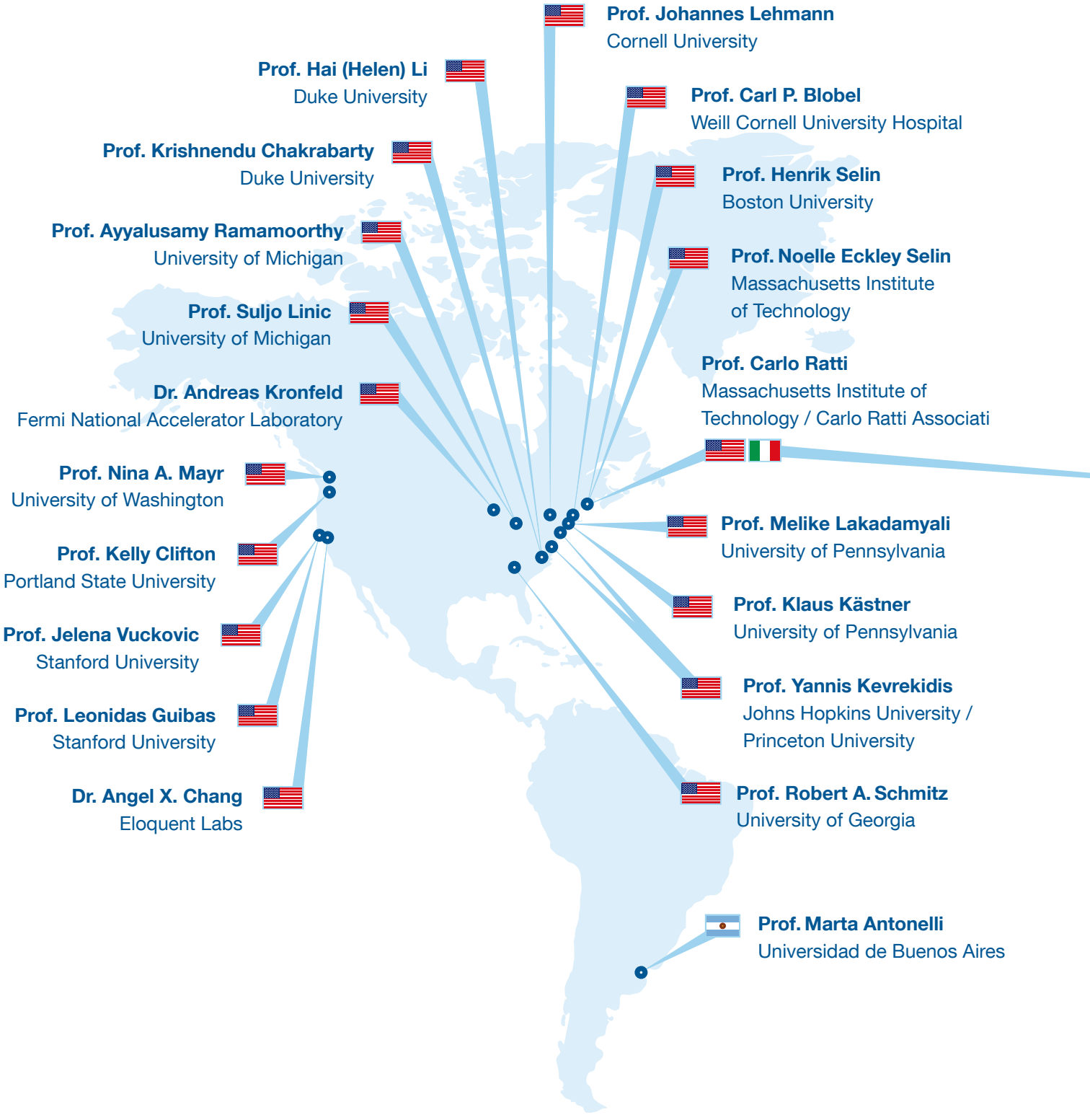
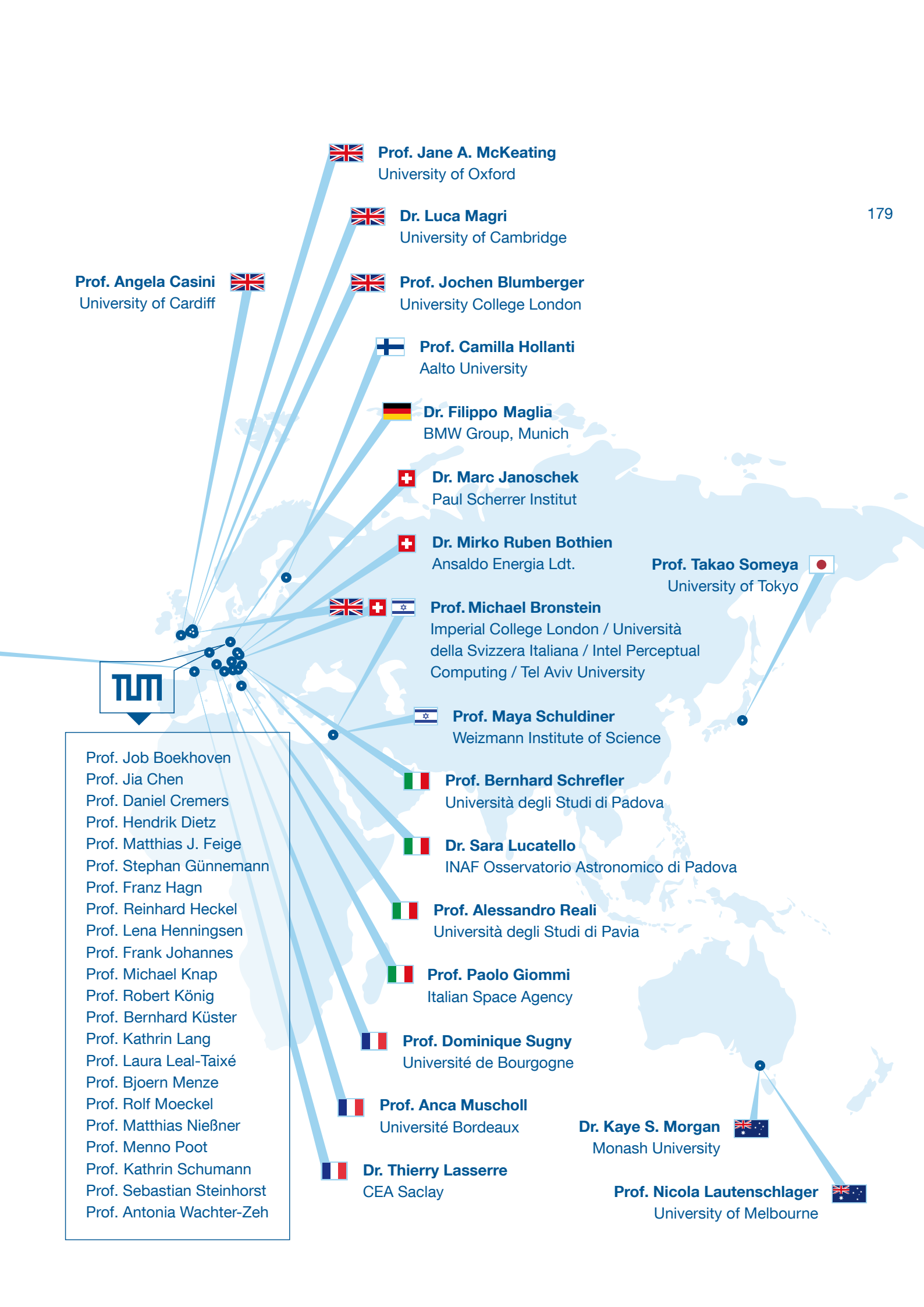
Facts and Figures

Where do the TUM-IAS Fellows come from?

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University of Cambridge
Prof. Angela Casini
University of Cardiff
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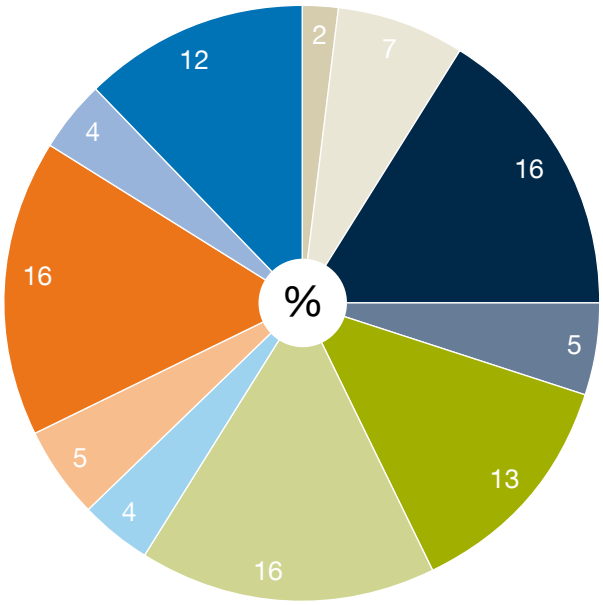
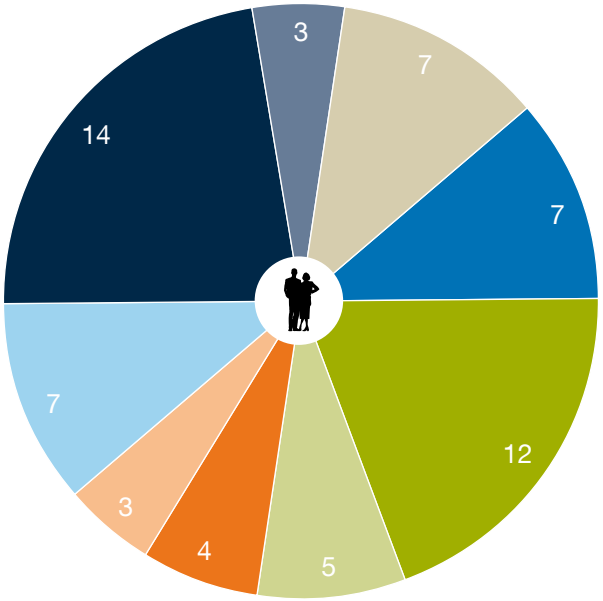
Fellow Distribution

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
- TUM School of Governance
- 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

Excellence Initiative

TUM-IAS was established as a flagship of TUM's institutional strategy to promote top-level research in the Excellence Initiative of the German federal and state governments. TUM was successful in both rounds (2006 and 2012) of this nationwide competition, and was thus officially named one of Germany's few "elite" universities.

Marie Curie COFUND Program

For 2012–2018, TUM-IAS was one of the projects co-funded by the European Union's Marie Curie COFUND program, which aims at nurturing excellence through cross-border and cross-sector mobility.

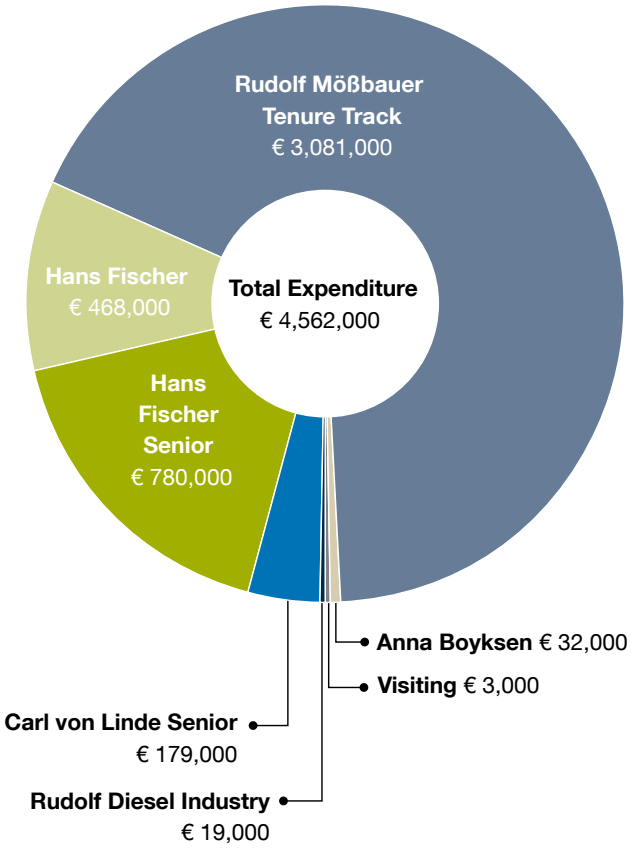
TÜV Süd Foundation

In 2015, the TÜV Süd Foundation and TUM agreed on introducing a "Hans Fischer Senior Fellowship awarded by the TÜV Süd Foundation." By funding this Fellowship the TÜV Süd Foundation aims to support the exchange of internationally renowned scientists as well as sustainable projects in groundbreaking research fields.

Siemens AG

Siemens AG provides funding for six Hans Fischer (Senior) Fellowships with over two million euros. The research focus is on the fields of "Simulation and Digital Twin" and "Future of Autonomous Systems/Robotics." The first two Fellows will start their Fellowship in 2019.

Expenditure per Fellowship Category in 2018



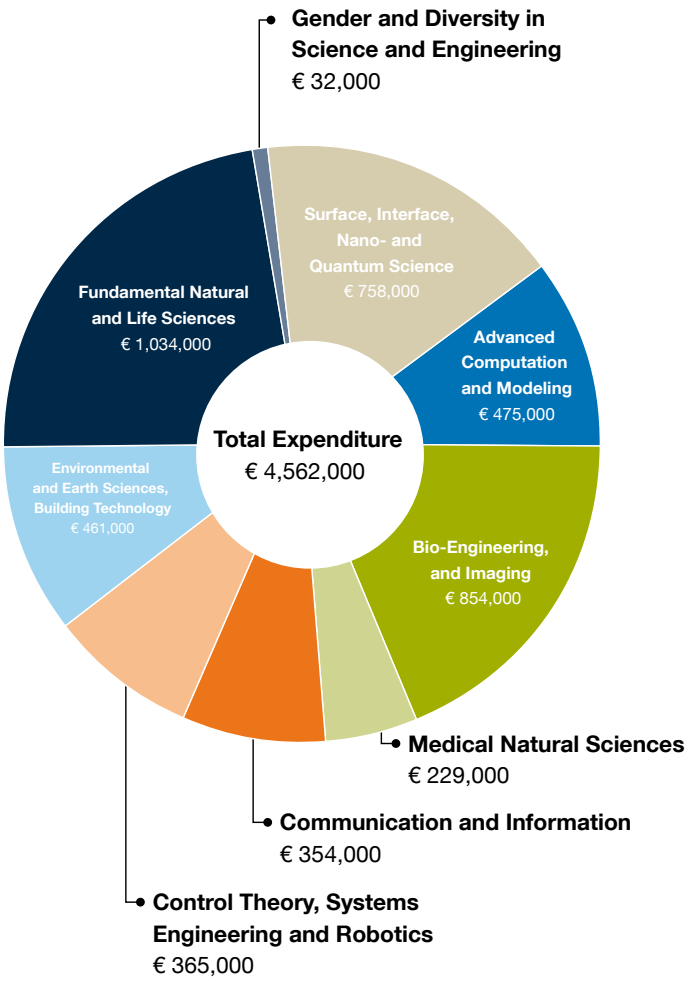
The chart on this page illustrates the expenditure in 2018 for each Fellowship category. Most dominant in terms of costs (as has been the case since 2015) – with 68 percent of the total Fellowship expenditures – are the Rudolf Mößbauer Tenure Track Assistant Professorships.

This program is devoted to the funding of outstanding, high-potential early career scientists who have already achieved a major scientific or technological breakthrough. The program was only established in 2013 (six calls have been published between 2013–2018), 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.

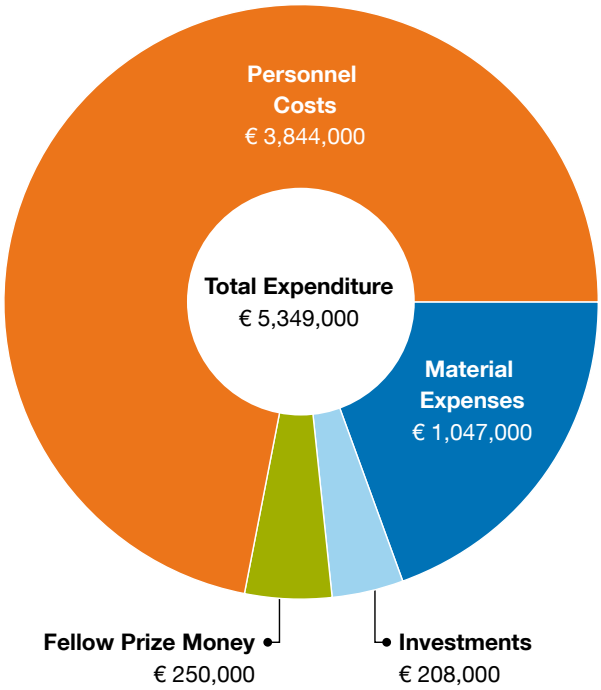
The Hans Fischer Senior Fellowship comes in second in terms of costs and comprises 17 percent of the total expenditure for our Fellowship programs, whereas the Hans Fischer Fellowship represents the third largest category. These Fellowships represent an integral part of the TUM internationalization strategy and are immensely valuable in terms of the exchange of complementary expertise and the grooming of emerging fields.

The Rudolf Diesel Industry Fellowship expenditures stayed almost on the same level as in 2017. The expenditures in the Anna Boyksen Fellowship category, however, decreased since 2017.

Expenditure per Research Area in 2018



Total Expenditure in 2018



A number of Hans Fischer, Hans Fischer Senior and Anna Boyksen Fellows reached the end of their tenure in fall 2017, which was originally the ending date of the second phase of the Excellence Initiative. Therefore, the number of active Fellows dropped in 2018. This is also shown in the decrease of expenses in these Fellowship categories compared to 2017.

Expenditure per Research Area in 2018

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 2018

On this chart, total TUM-IAS expenditure is displayed, including Fellowships, Start-up funding, Visiting Fellowships, events, and management. The total expenditure decreased in comparison to 2017 (€ 6,001,000) reflecting mainly the decrease in the number of Hans Fischer, Hans Fischer Senior and Anna Boyksen Fellows. The difference between the total expenditures per Fellowship category / Research Area and the total expenditure in 2018 is due to management and event expenses: € 722,000 for management and € 65,000 for event-related expenses.

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4, 6, 13 (Rank, Steinberger, Kohout, Wahler, Adler, Schnekenburger), 23, 25, 39, 58, 82 (Wachter-Zeh, Hollanti), 96 (Clifton), 103, 112, 118, 133, 134, 138, 175: Astrid Eckert.

13 (Santos Kühn), 66 (Cremers), 100 (Dietz): Astrid Eckert/Andreas Heddergott.

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10, 13 (Sturm), 58, 74, 80 (Koehler, Pfeiffer), 84, 92 (Steinhorst), 94 (Chen), 96 (Moeckel), 108, 120 (Hagn), 122 (Boekhoven), 128, 136, 140 (Lamp), 146 (Poot), 148: Andreas Heddergott.

27: Institute for Cognitive Systems, TUM.

31 (upper): Kate Maher/Stanford University.

31 (bottom): Will Wieder/National Center for Atmospheric Research, Boulder.

32 (poster), 34: Julie Rousset.

35 (upper): Institute of Flight System Dynamics, TUM.

35 (bottom left): Landslide Research, TUM.

35 (bottom right): 3D RealityMaps GmbH Baierbrunn Deutschland.

40, 41 (second from above): KW NEUN.

44, 50: Thomas Misgeld/TUM.

46: Dominik Paquet, Misgeld lab, TUM.

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52: Nicolas Snaidero/Caroline Fecher, Misgeld lab, TUM.

53: Maya Schuldiner/Weizmann Institute of Science.

61: Felix Kemeth, Chemical Physics Beyond Equilibrium, TUM.

63 (left): commons.wikimedia.org/wiki/File:Rolex_Learning_Center_07-2009.jpg

63 (right): Simulation by Chair for Computation in Engineering, TUM.

64: Dirk Bruniecki.

65 (upper): Courtesy of B. Wirthl, Institute for Computational Mechanics.

65 (bottom): J. Kremheller, A.-T. Vuong, L. Yoshihara, W. A. Wall, and B. A. Schrefler, “A monolithic multiphase porous medium framework for (a-)vascular tumor growth,” Comput. Methods Appl. Mech. Eng., vol. 340, pp. 657–683, 2018; reprinted with permission from Elsevier.

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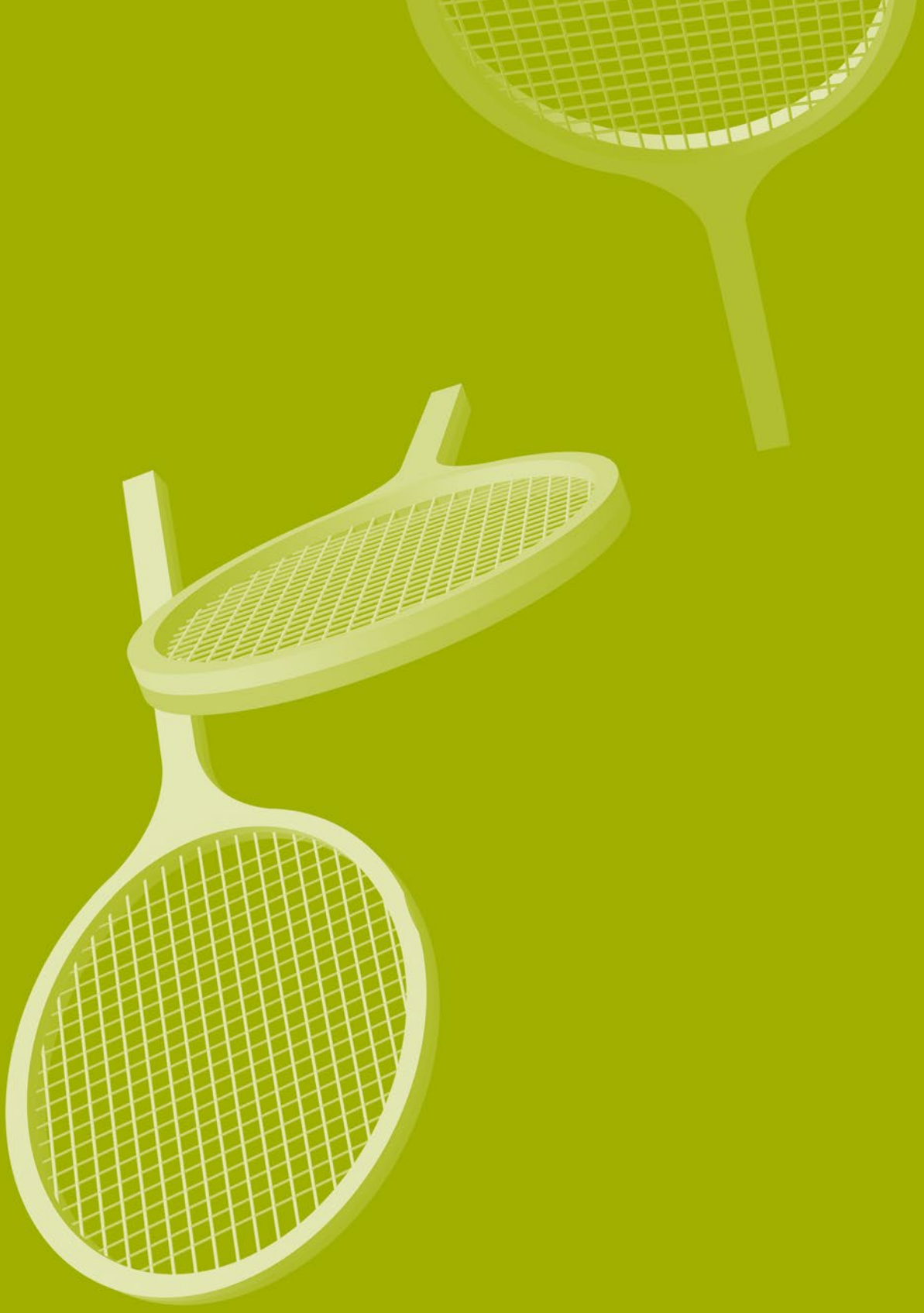
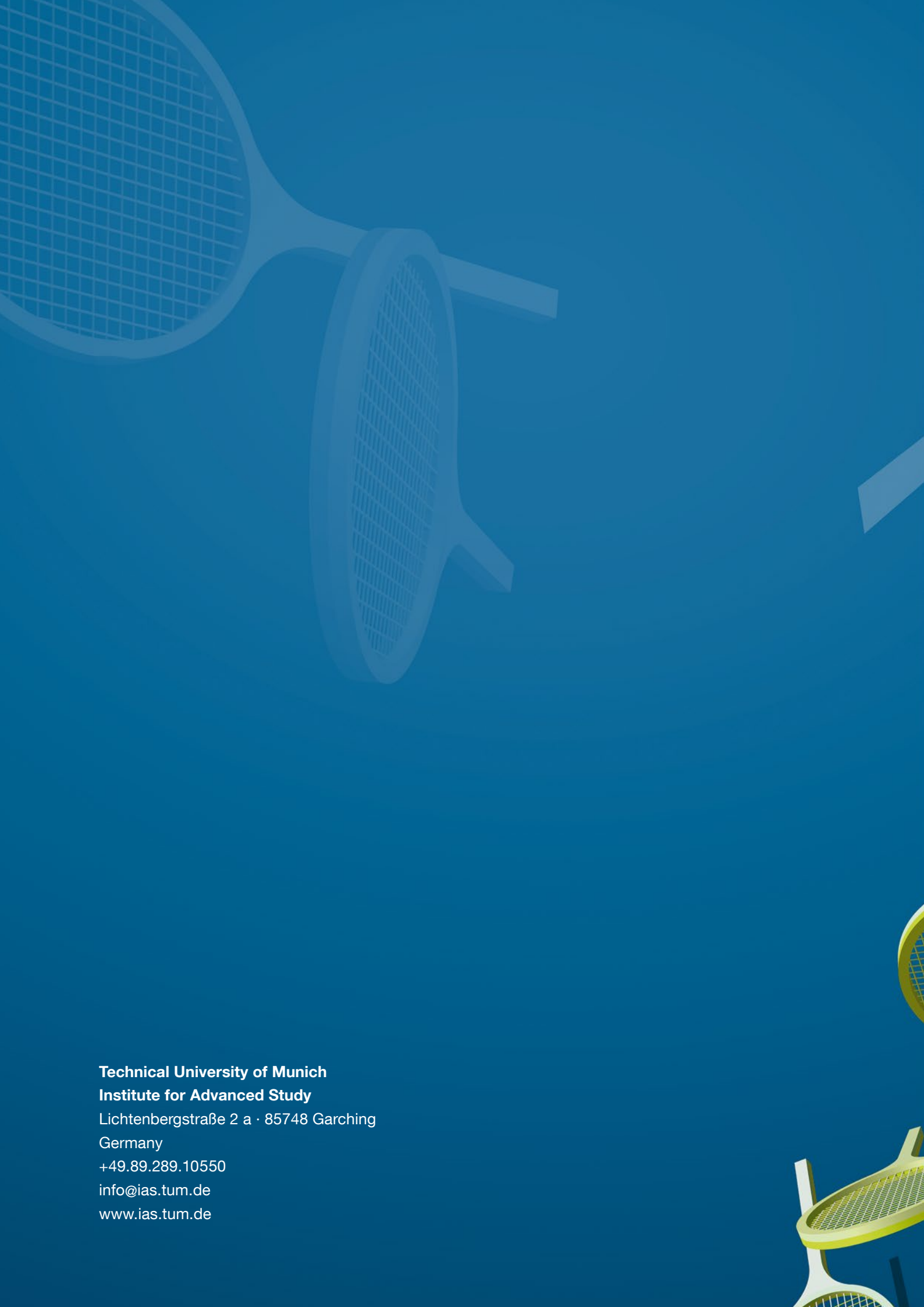


Cover and inside cover:
Snapshots of the simulated motion of a rotating tennis racket that has been thrown up in the air. When the thrower intends the racket to complete a full rotation around the horizontal axis, an unexpected additional half rotation occurs around the axis of the handle. Members of the TUM-IAS Focus Group Optimal Control and Medical Imaging have shown how a quantum analogue of this well known effect of classical mechanics can be used to improve the experimental control of, e.g., nuclear spins.

Reference:
L. Van Damme, D. Leiner, P. Mardešić, S. J. Glaser, and D. Sugny, “Linking the rotation of a rigid body to the Schrödinger equation: The quantum tennis racket effect and beyond,” Sci. Rep., vol. 7, art. 3998, pp. 1–8, 2017.



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