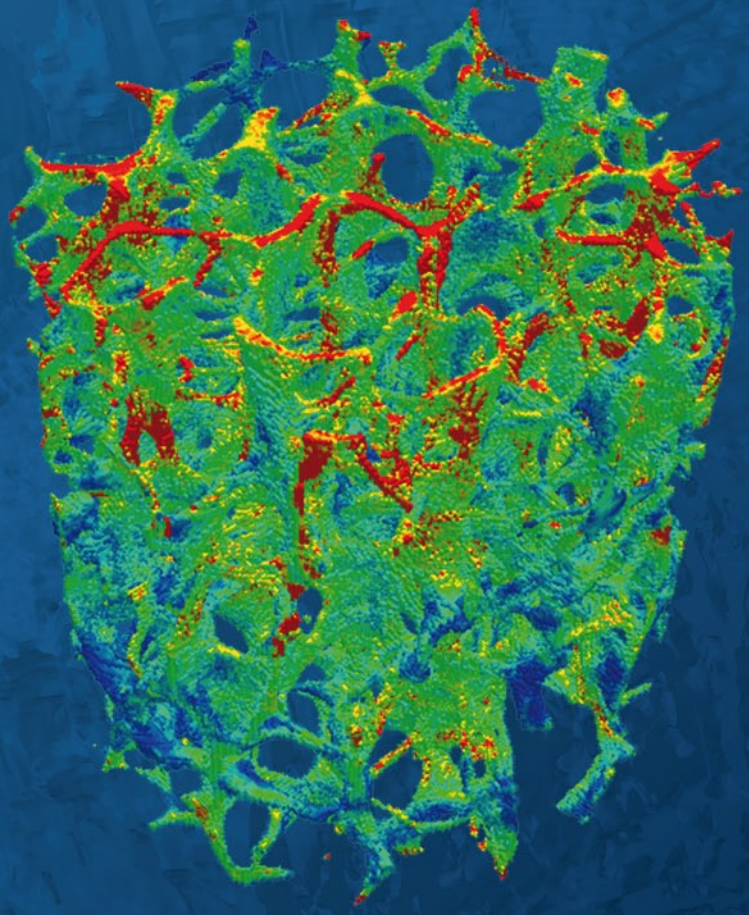
Annual Report

Technische Universität München

Institute for Advanced Study

2015



Annual Report

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TUM President's Foreword

It almost goes without saying that 2015 was a dynamic year in the life of our university, because that has become the norm, and the alternative is unthinkable for an entrepreneurial university.

Yet we still should mark and celebrate such a year, punctuated by cornerstone and topping-out ceremonies (Bavarian NMR Center, Center for Energy and Information, TranslaTUM) and the opening of unique facilities such as the TUM Entrepreneurship Center, the Munich Compact Light Source, and the Algae-to-Aviation Fuel Center on the Ludwig Bölkow Campus, as well as announcements of more to come – such as a €25M commitment from the Klaus Tschira Foundation enabling us to reinforce our multiple sclerosis research and bring it under one (new) roof. These were of course accompanied by the launch of other initiatives, spin-offs, and partnerships, not to mention the steady drumbeat of discovery and innovation across our research portfolio.

Like a magnet, this dynamism attracts both top-notch talent and excellent students: The pool of young faculty members and early-career researchers continues to become more diverse and international, and in 2015 our total student population topped 39,000, roughly double what it was as recently as 2005. TUM thus has to shoulder an enormous growth in size and, at the same time, keep its quality nimbus on a high level – a two-fold challenge.

In the midst of all this, we passed another kind of milestone: the ten-year anniversary of the founding of the TUM Institute for Advanced Study. Formally established in 2005 as part of an internal restructuring called innovaTUM, the TUM-IAS became the centerpiece of our institutional strategy in the Excellence Initiative and welcomed its first Fellows in 2007. Now you'll find it at the center of the action.

As this report documents, the TUM-IAS has proven as adventurous and productive as we hoped it would be. In addition, it serves TUM as an engine for research innovation, a focal point for talent, and a hub for interdisciplinary collaboration.
I want to congratulate and thank the TUM-IAS Fellows and their TUM Hosts, Directors Ernst Rank and Gerhard Abstreiter (who managed a smooth handoff in April 2015), founding Director Patrick Dewilde, their always capable staff, and everyone else who has contributed to the success of this remarkable institution.

Prof. Wolfgang A. Herrmann
President

TUM-IAS Director's Message

When President Wolfgang Herrmann asked me around Christmas, 2014, if I could imagine following Gerhard Abstreiter as Director of the TUM Institute for Advanced Study I was skeptical and enthusiastic at the same time. Skeptical, because I could hardly imagine how to continue building up a few exciting new research areas that we just had initiated at my Chair for Computation in Engineering. Enthusiastic, as leading the TUM-IAS would not only be a great challenge, but also a "coming home" to the core elements of TUM's institutional strategy in the Excellence Initiative, which I was privileged enough to help shape ten years ago. Many discussions with our President and with Gerhard made the decision easy. Wolfgang Herrmann supported the double affiliation at the Chair and at the Institute, and Gerhard Abstreiter promised to continue to help a lot, in particular during the transition phase. He as well as the excellent staff of our Institute guaranteed a "flying start" without significant difficulties or major disruptions. I am more than thankful to all of them!

Under the leadership of Patrick Dewilde and Gerhard Abstreiter, the TUM-IAS has matured to a flourishing hub for excellent research at TUM, and it is therefore only natural that we will continue on the way they set and build on what has been achieved in the past years. In 2015, the Hans Fischer Fellowship programs have again brought brilliant scholars to Munich, and the Rudolf Mößbauer Tenure Track Professorships have evolved into a strategic instrument of our university to attract excellent young scientists from all around the world. Currently we have a record number of more than 60 active Fellows, covering a wide range of research fields. Together with our Fellows, we were able to organize more than 30 high-impact workshops and symposia. Our Wednesday Coffee Talks, the Fellows' Lunches, and the General Assembly have contributed to community-building across disciplines and institutions.

Interconnecting Focus Groups and integrating the growing community of alumni into ongoing and new activities of TUM-IAS is *the* major goal of Focal Periods, a new format that we announced in autumn 2015. Under the titles "Clinical Cell and Tissue Engineering" and "Predicting Macroscopic Behavior from Microscopic Simulators," symposia, lecture series, and special workshops will take place in our headquarters in Garching as well as in the completely renovated TUM Study and Residence Center in the former Cistercian Monastery Raitenhaslach. In 2015 we also were able to strengthen our collaborations with partner institutes around the world. A major highlight was a double workshop on water research, with the first part taking place in Munich and the second in Hong Kong, jointly organized with the HKUST Jockey Club Institute for Advanced Study.

Finally, the TUM-IAS is happy to announce the first Hans Fischer Senior Fellowship awarded by the TÜV SÜD Foundation, as a new format for partnership with a private institution that is fully integrated into our core program and which extends our opportunities to support world-class research in science and technology.

Prof. Ernst Rank
Director

People

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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.

Members

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Technische Universität München, President

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Toyota Technological Institute President
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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, Nuclear Medical Clinic and Policlinic, Director
Prof. Henry Tye The Hong Kong University of Science and Technology, HKUST Jockey Club Institute for Advanced Study, 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 about four times a year.

Members

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Chair of Scientific Computing, Graduate Dean of the TUM Graduate School
Prof. Dirk Busch
Institute for Medical Microbiology, Immunology and Hygiene
Prof. Ulrich Heiz
Chair of Physical Chemistry
Prof. Horst Kessler
Department of Chemistry, TUM Emeritus of Excellence
Prof. Ingrid Kögel-Knabner
Chair of Soil Science
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Max Planck Institute of Quantum Optics - Quantum Dynamics Group
Prof. Daniel Straub
Engineering Risk Analysis Group
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Institute for Computational Mechanics
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TUM School of Management - Chair for Strategy and Organization
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Chair of Numerical Mathematics

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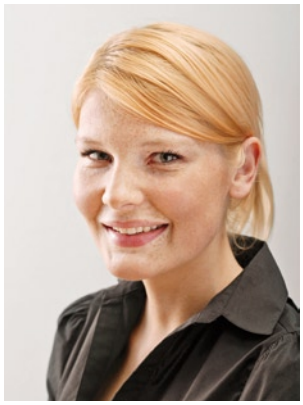
Director

Dr. Ana Santos Kühn
Managing Director

Anna Fischer
Program Manager

Eva Pettinato
Program Manager

Annette Sturm
Event Manager /
Web Coordinator



Sigrid Wagner
Event Manager /
Web Coordinator

Erika Höchtl
Secretary / Building
Coordination

Christina Schmid
Secretary / Guesthouse
Coordination

Farewells

Prof. Gerhard Abstreiter
Director (until 03/2015)

Stefanie Merz
Managing Director
(until 02/2015)

Kristina Schwarzer
Project Manager IESP
(until 10/2015)

Tatjana Steinberger
Program Manager
(on maternity leave)

Fellows

Carl von Linde Senior Fellows

2008 Prof. Horst Kessler
2013 Prof. Annette Menzel
2014 Prof. Martin Buss
2015 Prof. Franz Pfeiffer

Carl von Linde Junior Fellows

2011 Prof. Dongheui Lee
2013 Dr. Peer-Hendrik Kuhn

Hans Fischer Senior Fellows

2009 Prof. Stanley Riddell
2011 Prof. Silvio Aime, Prof. Polly L. Arnold, Prof. Daniel Gianola,
2012 Prof. Stephen M. Goodnick, Prof. Dietmar W. Hutmacher
2013 Prof. Harald Brune, Prof. Zvonimir Dogic, Prof. Josef P. Rauschecker, Prof. Jelena Vuckovic
2014 Prof. John S. Baras, Prof. Dirk Bergemann, Prof. Gregory D. Hager, Prof. Tamas Horvath, Dr. Andreas Kronfeld, Prof. A. Lee Swindlehurst, Prof. Nicholas Zabaras
2015 Prof. Carl P. Blobel, Prof. Klaus Kästner, Prof. Yannis Kevrekidis, Dr. Thierry Lasserre, Prof. Jane A. McKeating, Prof. Anca Muscholl, Prof. Ayyalusamy Ramamoorthy

Hans Fischer Fellows

2012 Prof. George Biros
2013 Prof. Matthias Batzill, Dr. Christian Hirt
2014 Prof. Yana Bromberg, Prof. Tsung-Yi Ho, Prof. Stuart Khan, Prof. Suljo Linic
2015 Dr. Kaye S. Morgan, Prof. Alessandro Reali, Prof. Dominique Sugny

Rudolf Diesel Industry Fellows

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
2015 Prof. Carlo Ratti

Rudolf Mößbauer Tenure Track Professors

2013 Prof. Kathrin Lang, Prof. Bjoern Menze, Prof. Alessio Zaccone
2014 Prof. Jia Chen, Prof. Matthias J. Feige, Prof. Franz Hagn, Prof. Michael Knap, Prof. Robert König
2015 Prof. Job Boekhoven, Prof. Carlo Camilloni, Prof. Frank Johannes, Prof. Rolf Moeckel

Anna Boyksen Fellows

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

Alumni Fellows

Carl von Linde Senior Fellows

2007 Prof. Andrzej Buras, Prof. Arthur Konnerth, Prof. Reiner Rummel
2008 Prof. Claudia Klüppelberg
2009 Prof. Axel Haase
2010 Prof. Ulrich Stimming, Prof. Gerhard Abstreiter
2011 Prof. Ingrid Kögel-Knabner

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, Dr. 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

Hans Fischer Senior Fellows

2007 Prof. Gerhard Beutler, Prof. Walter Kucharczyk, Prof. Bert Sakmann
2008 Prof. Anuradha M. Annaswamy, Prof. Yasuhiko Arakawa, Prof. Douglas Bonn, Prof. Mandayam A. Srinivasan, Prof. David A. Weitz
2009 Prof. Matthew Campbell, Prof. Richard Davis, Prof. Gino Isidori, Prof. Shuit Tong Lee, Prof. Wolfgang Porod, Prof. Peter Schröder, Prof. Zohar Yosibash
2010 Prof. Robijn Bruinsma, Prof. Markus Hegland, Prof. Michael Ortiz, Prof. Stefan Pokorski, Prof. Tim Sparks, Prof. Raman I. Sujith
2011 Prof. Frank R. Kschischang, Prof. Christian Werthmann

Hans Fischer Fellows

2012 Prof. Franz Hagn

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, Dr. Matthias Heller, Dr. Chin Man W. Mok

Visiting Fellows 2015

Prof. Natalia de Leon
Department of Agronomy
University of Wisconsin-Madison
Host: Prof. Chris-Carolin Schön

Dr. Filip Lankaš
Institute of Organic Chemistry and Biochemistry ASCR v.v.i., Prague
Hosts: Prof. Hendrik Dietz / Prof. Martin Zacharias

Prof. David Pan
Department of Electrical and Computer Engineering
The University of Texas at Austin
Host: Prof. Ulf Schlichtmann

Prof. Guilherme J. M. Rosa
Department of Animal Sciences
University of Wisconsin-Madison
Host: Prof. Chris-Carolin Schön

Dr. Ari Paavo Seitsonen
Departement de Chémie
Ecole Normale Supérieure
Host: Prof. Johannes Barth

Prof. William H. Starbuck
Lundquist College of Business
University of Oregon
Host: Prof. Isabell M. Welpe

Dr. Igor Walukiewicz
Laboratoire Bordelais de Recherche en Informatique
(Directeur de Recherche - CNRS)
Université de Bordeaux
Host: Prof. Javier Esparza

Honorary Fellows 2015

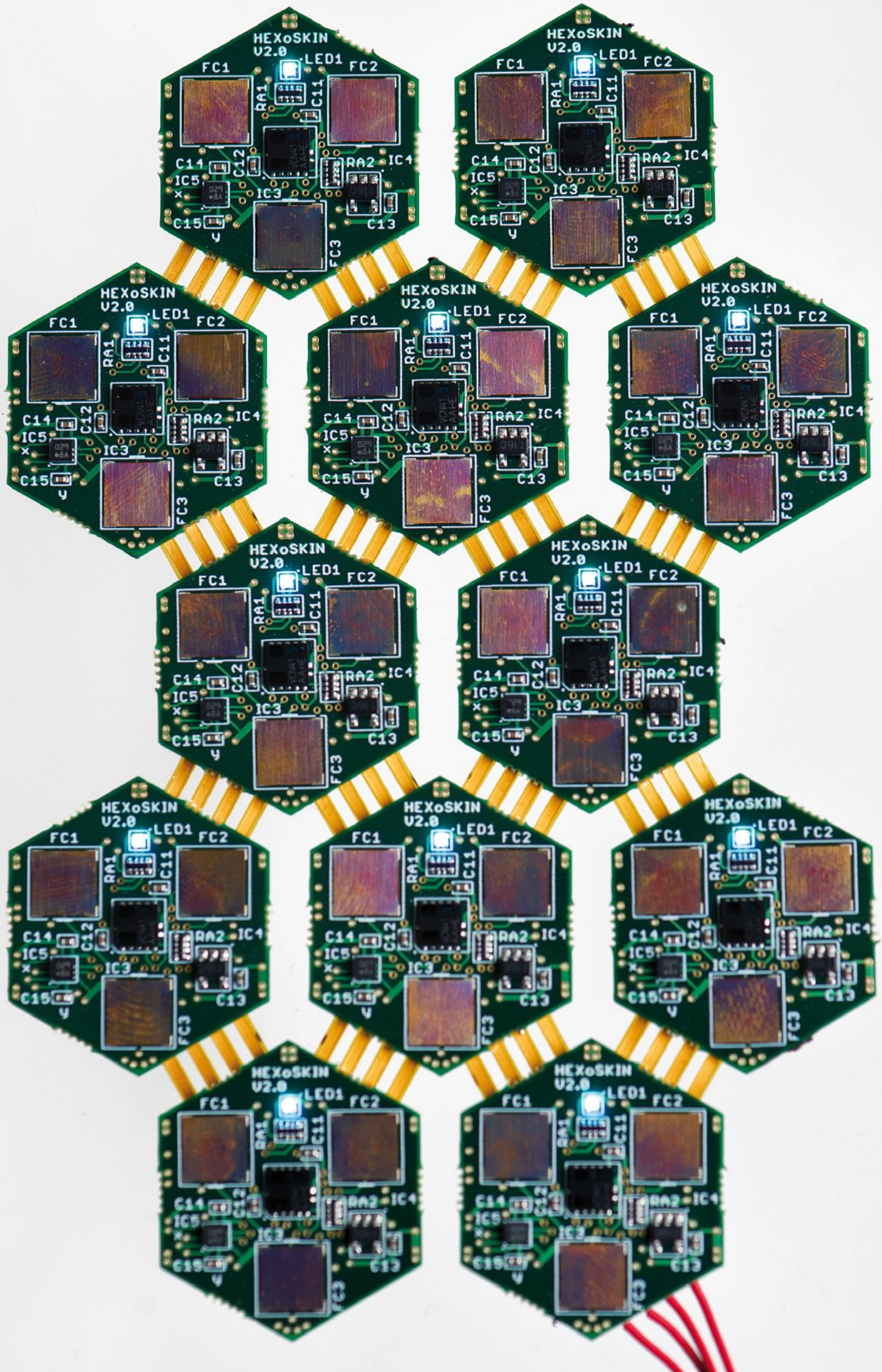
Alexander von Humboldt Research Awardees *Honorary Hans Fischer Senior Fellows*	Prof. Eugene Demler | Harvard University Dr. Stefano Fabris | CNR Italy Prof. Martin Reisslein | Arizona State University Prof. Tehshik Peter Yoon | University of Wisconsin-Madison
ERC Grantees	Prof. Nikolaus Adams | Aerodynamics and Fluid Dynamics, TUM Prof. Thorsten Bach | Organic Chemistry I, TUM Prof. Daniel Cremers | Computer Vision, TUM Dr. Pascal Falter-Braun | Plant Systems Biology, TUM Prof. Shigeyoshi Inoue | Silicon Chemistry, TUM Prof. Wolfgang Kellerer | Communication Networks, TUM Prof. Reinhard Kienberger | Laser and X-Ray Physics, TUM Dr. Jan Kirschke | Diagnostic and Interventional Radiology, TUM Prof. Thomas Korn | Experimental Neuroimmunology, TUM Prof. Dieter Saur | Gastroenterology, TUM Prof. Nils Thürey | Games Engineering, TUM
Gottfried Wilhelm Leibniz Prizewinner	Prof. Hendrik Dietz | Biomolecular Nanotechnology, TUM
Liesel Beckmann Distinguished Professor	Prof. Juliane Winkelmann | Neurogenetics, TUM
August-Wilhelm Scheer Visiting Professors	Prof. Walter Baratta | University of Udine Prof. Ghada Bassioni | Ain Shams University Prof. Olivier A. Bauchau | Hong Kong University of Science and Technology Prof. György Csaba | University of Notre Dame Prof. Julián Rafael Dib | Universidad Nacional de Tucumán Prof. Sonja Duempelmann | Harvard University Prof. N. Louise Glass | University of California, Berkeley Prof. Tiauw Go | Florida Institute of Technology Prof Hamid Reza Karimi | University of Agder Prof. Guangzhao Luo | Northwestern Polytechnical University Prof. Paul Martin Mai | King Abdullah University of Science and Technology Prof. Mike Manefield | University of New South Wales Prof. George A. Mashour | University of Michigan Medical School Prof. Thomas L. McKenzie | San Diego State University Prof. Pierre Mertiny | University of Alberta Prof. Annalisa Pastore | King's College London Prof. Michael Pennington | Jefferson Laboratory Dr. Matt Probert | University of York Prof. George D. Sergiadis | University of Thessaloniki Prof. Enrique Solano | University of the Basque Country Prof. Katherine Strandburg | New York University Prof. Arun K. Tangirala | IIT Madras Prof. Koen van Leemput | Technical University of Denmark Prof. David Zanatta | Central Michigan University

TÜV Süd Stiftung Visiting Professors 2015

Prof. Alexey Bulgakov
Department of Automation and Robotics
South West State University Kursk
Host: Prof. Thomas Bock

Prof. Marco Caccamo
Department of Computer Science
University of Illinois at Urbana-Champain
Hosts: Prof. Matthias Althoff, Prof. Samarjit Chakraborty

Dr. Bénédicte Cuenot
CFD/Combustion
Centre Européen de Recherche et de Formation Avancée en Calcul Scientifique
Host: Prof. Oskar J. Haidn


HEXoSKIN
V2.0
LED1
FC1
FC2
FC3
RA1
RA2
C11
C12
C13
C14
C15
IC3
IC4
IC5

Activities and Events

TUM-IAS General Assembly

April 23 – 24

With so many Fellows and members scattered all over the world, it is with very special pleasure that we invite everyone home once a year: to the General Assembly at the TUM-IAS in Garching. For two days, the building is always brimming with talks on exciting topics, lively discussions of posters, and the exchange of unusual ideas. This year, topics ranged from graphene interfaces to microRNAs in diabetes and obesity, from information theory and optical fiber to sustainable water cycles, and from molecular quality control in the cell to phase-contrast X-ray tomography, thus covering all research areas of the TUM-IAS. As always, the General Assembly was a great opportunity for our Fellows, postdoctoral researchers, doctoral students, and honorary members alike to find out not only who works in a similar field – while possibly approaching it from a wholly different angle – but also to learn more about developments and results in other areas of research.

The General Assembly's festive dinner gave us an opportunity to honor our parting director Prof. Gerhard Abstreiter, taking retirement after having shaped both TUM and the TUM-IAS for years: first as a Fellow, Advisory Council member and Host, then as a director during two particularly busy and challenging years.

Prof. Abstreiter is an invaluable member of our community, and we are very glad to be able to still seek his advice as well as to still see him regularly at the popular Wednesday Coffee Talks that were established during his directorship.

Fellows' Lunches

Typically once a month (but not every month), the TUM-IAS invites its Fellows, Honorary Fellows, Host professors and other community members to lunch. This tradition is a favorite of ours for two reasons: First, it is always fascinating to find out more about what our members currently work on – this year, talks covered topics as diverse as water recycling, genomics, robotic building construction, and complex data systems modeling. The discussion afterwards, inspired by questions from scientists who often have a very different background from the speaker's, is usually just as interesting. Secondly, and just as important, the Fellows' Lunches' main purpose is to get our community together. Whenever we see the scientists of the TUM-IAS getting to know each other, and more often than not establishing common research interests with colleagues from wholly different disciplines, we realize once more that in a way, the Fellows' Lunches represent what the TUM-IAS is all about.

February 2

Connecting Genotypes and Phenotypes in a Complex Genome, the Example of Maize
Prof. Natalia de Leon (University of Wisconsin-Madison) | Visiting Fellow
Utilizing Genomic Information for Prediction and for Causal Inference in Livestock Genetic Studies
Prof. Guilherme J. M. Rosa (University of Wisconsin-Madison) | Visiting Fellow

March 12

Drinking Recycled Water in a Land of Droughts and Flooding Rains
Prof. Stuart Khan | Hans Fischer Fellow

July 13

Atmospheric Column Measurements for Emission Estimates of Greenhouse Gase
Prof. Jia Chen | Rudolf Mößbauer Tenure Track Professor

September 21

Intelligent Robots - Human Interaction in Outdoor Environments
Prof. Martin Buss | Carl von Linde Senior Fellow

October 19

No Equations, No Variables - Data, and the Modeling of Complex Systems
Prof. Yannis Kevrekidis | Hans Fischer Senior Fellow

November 19

Energy/Resource Efficiency and Safe Work Procedures Based on Robotic Building Construction
Prof. Alexey Bulgakov (South West State University Kursk) | TÜV Süd Foundation Visiting Professor

Impact of Multicore on Cyber-Physical Systems: Challenges and Solutions
Prof. Marco Caccamo (University of Illinois at Urbana-Champain) | TÜV Süd Foundation Visiting Professor

Scientists Meet Scientists – Wednesday Coffee Talk

The Wednesday Coffee Talks seem to have become one of the best known and most popular activities of the TUM-IAS: Established in 2013 by former director Gerhard Abstreiter, Coffee Talks are held weekly after lunch at the TUM-IAS' atrium on the 1st floor of the building. All TUM scientists and their guests are invited to learn more about a recent TUM publication that was deemed important or interesting enough to be highlighted with a press release. Fondly calling it their "weekly free tutorial," retired scientists, busy heads of department, and doctoral candidates alike regularly make sure to find the time to chat over a cup of coffee and a piece of cake (often home-made, thanks to various generous donors) and to find out more about what is going on in other TUM departments. 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. The Wednesday Coffee Talks are therefore certainly serving their purpose to reinforce the TUM-IAS as a center for intellectual exchange and discourse at TUM.

January 7	Prof. Harald Luksch on how birds get by without external ears
January 14	Prof. Reinhard Kienberger on ultra-short x-ray pulses that explore the nano world
January 21	Prof. Thomas Brück on a novel LED technology that enables detailed investigation of algae productivity
January 28	Prof. Alexander W. Holleitner on a possible read head for quantum computers
February 11	Prof. Michael Sattler on having revealed a new mechanism in gene regulation
February 18	Prof. Roland Pail on the first harvest of research based on the final GOCE gravity model
February 25	Dr. Christoph Hugenschmidt on gummy bears under antiparticle fire
March 4	Prof. Florian Bassermann on how mutations prevent the programmed cell death
March 11	Prof. Fabian Theis on how mathematics can improve single-cell analysis
March 18	Dr. Andrea Schafferhans on a virtual journey to the innards of proteins
March 25	Prof. Konrad Tiefenbacher on how to generate cough medicine out of geranium scent

April 1	Prof. Stephan Paul on precision measurement for the strong interaction
April 8	Michael Huith and Prof. Franz Hagn on living in and with an energy-storage plus house
April 15	Prof. Peter Müller-Buschbaum on magnetic nanoparticles enhancing the performance of solar cells
April 29	Dr. Carlos-Andres Palma on moving molecules writing letters
May 6	Prof. Hendrik Dietz on a designer's toolkit for dynamic DNA nanomachines
May 13	Prof. Nils Thürey on the perfectly animated cloud of smoke
May 20	Prof. Christian Grosse on self-healing concrete
May 27	Prof. Markus Ploner on the brain processing ongoing pain more emotionally
June 3	Prof. Christian Pfleiderer on the taming of magnetic vortices
June 10	Prof. Siegfried Scherer on a new detection method for bacterial toxin that is a cause of food poisoning
June 17	Prof. Dietmar W. Hutmacher on soft-tissue 3D-printing for hard-working cartilage
June 24	Prof. Tilo Biedermann on marshaling the body's own weapons against psoriasis
July 1	Prof. Franz Pfeiffer on a compact synchrotron making tumors visible
July 8	Prof. Peter Fierlinger on the weakest magnetic field in the solar system
July 15	Prof. Steffen J. Glaser on an app providing insight into the quantum world of coupled nuclear spins
July 29	Prof. Wolfgang Eisenreich on making rubber from dandelions
October 7	Prof. Sevil Weinkauf on having deciphered the regulation of an embryonic small heat shock protein
October 14	Prof. Oliver Lieleg on mucins serving as lubricants and diffusion barriers
October 21	Dr. Caspar Ohnmacht on the role of symbiotic bacteria (microbiotica) in preventing allergies

October 28	PD Dr. Sandro Krieg on mapping the language or motor areas in the brain by magnetic stimulation	25
November 4	Prof. Fabian Theis on the pluripotency of embryonic stem cells and the role of mathematical modelling	
November 11	Prof. Michael Krautblatter on permafrost and climate change in the Alps	
November 18	Prof. Dominique Sugny on the physical limits of magnetic resonance imaging explored by optimal control techniques	
November 25	Prof. Massimo Fornasier on Big Data and the role of social dynamics	
December 2	Prof. Aliaksandr Bandarenka on designing better electrocalatysts for energy provision	
December 9	Prof. Burkhard Rost on the first large-scale cell-to-cell communication map	
December 16	Prof. Klaus Bengler on networked traffic systems and the role of pedestrian simulators	

International Symposium Big Data and Predictive Computational Modeling

May 18–21, 2015

Advances in networking, sensor technologies, and computer science have enabled the collection of gigantic amounts of data at ever accelerating rates. At the same time, developments in machine learning, computational statistics, and data mining have led to powerful tools for extracting patterns and trends from data. Most of this output is mapped to phenomenological but predictive models of increasing complexity and involving huge numbers of parameters.

In parallel, computational scientists in physics, chemistry, biology, and engineering have been experiencing their own Big Data revolution. Thanks to the sophistication of the mathematical models and the availability of high-performance computing platforms, we can simulate physical processes at unparalleled levels of spatiotemporal resolution. With almost every simulation we see exuberant growth of output data.

Despite their sophistication, our models are not always predictive. This can be attributed to various parametric and model uncertainties, as well as to vast differences between the scales at which we want to make predictions and the scales at which accurate simulation tools are available.

Can we extract meaningful information from huge amounts of simulation data? Can we use the data to make predictions at scales that are currently inaccessible? How can we couple tools from the data sciences—tools that are capable of dealing with high dimensions and uncertainty—with physical principles?

With a shared mindset grounded in computational discovery, but a wide spectrum of viewpoints, leading scientists from physics and chemistry, biology, engineering, applied mathematics, scientific computing, neuroscience, statistics, computer science, and machine learning met at the symposium “Big Data and Predictive Computational Modeling.” They engaged in discussions and exchanged ideas for four days.

Some conclusions:

1 Big data can mean different things in different communities.

Whereas data in machine learning applications comes at a low price and in abundance, in the physical sciences data is obtained from expensive and computationally demanding simulations. In the latter case what is produced might be better described as “tall data”: It is high-dimensional and structured, although we can expect neither to have a large number of instantiations nor that this data will uniformly populate the configuration space of the problem.

2 Physical scientists trust their models more than data scientists do.

To a large extent, physical models are anchored in venerated physical principles (e.g., conservation of mass, energy). Nevertheless, parts of these models (e.g., constitutive laws) are as phenomenological as the regression/classification models used in data mining. It has been said that you do not need to know the true cause as long as you can minimize the prediction error. This approach has been applied with great success in several machine learning tasks, but physical scientists would also like the discovery of patterns and trends to lead to comprehensible and interpretable physical principles as the underlying drivers of the complexity observed.

3 Quantifying model uncertainties is recognized as an important step.
Model-selection issues arise prominently in obtaining reduced or coarse-grained descriptions of physical models (e.g., in molecular dynamics), and along these lines the expertise and arsenal of tools from machine learning/computational statistics can be extremely powerful. Information-theoretic tools and pertinent concepts can be extremely useful in that respect and can be used even in non-equilibrium settings.

4 Models employed in both machine learning and the physical sciences are multi-level and high-dimensional, with thousands of parameters to be inferred or learned.
The feasibility of these tasks is often limited to distributed computational environments in which each node is aware of only a portion of the (experimental or simulation) data. Novel methods are needed that reduce communication costs but can nevertheless lead to accurate estimates.

5 A little bias in estimates can be a good thing if it also leads to reduced variance.
Advocating approximate inference and learning tools to the applied mathematics and engineering community is preaching to the choir—these groups have become comfortable with the idea of approximate solutions to difficult mathematical problems. Such algorithms, which have seen explosive growth in the machine learning community in the last few years as part of efforts to address big-data challenges, would be ideal for the computationally demanding tasks of fusing models with data in the physical sciences and in the context of Bayesian model calibration and validation. Deterministic tools from numerical analysis (e.g., adjoint formulations) can frequently complement and enhance probabilistic methods.

6 Many of the events of interest are rare.
Whether in seeking transition paths to overcome large free energy barriers in molecular simulations or in assessing the extremely small probabilities of failure in engineering systems, we need new tools that are capable of directing our simulations or data-acquisition mechanisms to the most informative regimes.

7 Symposium participants knew a priori that dimension reduction is a key aspect of the analysis, ...

... whether the task is to make sense of atomistic trajectories, to look at huge databases of features or networks, or simply to visualize high-dimensional data. Several nonlinear dimension-reduction tools and low-rank matrix factorization techniques were presented and discussed. It became apparent that for predictive purposes,

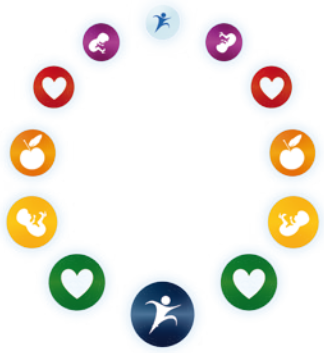
dimension reduction is necessary but not always sufficient. In addition to a lower-dimensional set of collective variables, we must simultaneously infer a model for their interaction and evolution in time. This would not only enable extrapolation into regions for which data is not available, but also could lead to efficient tools that exhibit sub-linear complexity with respect to the fine-scale degrees of freedom.

8 Relationships between different communities can be bidirectional.

For a long time, methods and tools developed by the computational physics community (e.g., Markov Chain Monte Carlo) have stimulated developments in statistics and machine learning, where the methods were formalized and their domain of application was expanded. Similarly, tools and techniques from machine learning have inspired developments and advanced our capabilities in the analysis of physical systems (e.g., ISOMAP for dimension reduction, graphical models for UQ).

Liesel Beckmann Symposium 2015

November 27



At the 8th Liesel Beckmann Symposium, the organizers brought together experts from the field of fetal programming based on adverse exposures during the earliest phases of life. The focus was on the development and early prevention of the global epidemic of cardiometabolic diseases including obesity, diabetes type 2, atherosclerosis, and its consequences, myocardial infarction and stroke. Nearly 100 participants responded to the joint invitation from the TUM Institute for Advanced Study, Prof. Renate Oberhoffer of the Institute for Preventive Pediatrics at TUM, and 2015 Anna Boyksen Fellow Regina Ensenauer, professor of Experimental Pediatrics and Metabolism at the University of Düsseldorf.

The origin of cardiometabolic diseases may occur very early in fetal life. However, the underlying mechanisms, referred to as “fetal programming,” resulting in increased risks of later-life health problems, are still poorly defined. Effective prevention programs have to integrate very early aspects, such as efforts to change life style during pregnancy.

This symposium provided insights into an emerging field with one introductory and four keynote lectures. After the welcome by Prof. Renate Oberhoffer and Prof. Regina Ensenauer, the introductory lecture was given by Prof. Sjurdur Olsen, head of the Danish Centre for Fetal Programming in Copenhagen, Denmark. He gave a general overview on fetal programming of cardiometabolic diseases.

The first keynote lecture by Prof. Andreu Palou, professor of Biochemistry and Molecular Biology at the University of the Balearic Islands, Spain, focused on animal models in the field of fetal programming research.

Thereafter, Prof. Thomas Haaf, head of the Institute of Human Genetics at the University of Würzburg, provided an overview on the epigenetics of gestational diabetes in the second keynote lecture. In the third keynote lecture, Prof. Helena Gardiner, a fetal cardiologist from the University of Texas, USA, focused on the prenatal environment and later human cardiovascular disease. The fourth keynote lecture by Prof. Wolfgang Koenig from the German Heart Center in Munich discussed epidemiological aspects of cardiometabolic diseases and highlighted the importance of prevention strategies.

During a “poster walk” at the lunch break, young investigators presented their scientific findings and had the opportunity to discuss them in detail with experts from the field. A poster prize was awarded. Two parallel afternoon sessions dealt with 1.) nutritional programming and aspects of prevention and 2.) cardiovascular programming and aspects of physical activity in early prevention. Experts provided overviews on state-of-the-art topics in these areas and discussed potential strategies for further research.

International Workshop: Central gating in tinnitus and chronic pain – the role of cortico-limbic networks

September 7–8, 2015
Organization: Hans Fischer Senior Fellow Josef P. Rauschecker,
Focus Group Neuroimaging

Central gating in tinnitus and chronic pain: The role of cortico-limbic networks

The International Workshop on Frontostriatal Gating of Tinnitus and Chronic Pain, organized by Prof. Josef Rauschecker, Hans Fischer Senior Fellow, and Prof. Markus Ploner, Heisenberg Professor at the Department of Neurology, was held September 7–8, 2015 at the Klinikum rechts der Isar. Nineteen speakers from the U.S., Canada, the UK, Portugal, and Germany discussed the commonalities and differences in the neural mechanisms leading to these pervasive disorders.

Clinical and basic neuroscience relevance

Tinnitus and chronic pain are frequently occurring medical conditions that impair quality of life for millions of people all around the world. About 25% of the adult population has experienced one or more acute tinnitus episodes, and about 10% report having permanent disabling tinnitus. Pain affects more people in the Western Hemisphere than diabetes, heart disease, and cancer combined. Both disorders are among the most common causes of long-term disability. Recent research using multimodal neuroimaging in humans has revealed an astonishing convergence of brain systems involved in tinnitus and chronic pain.

Continuously, our brain evaluates the salience of incoming sensory information, selects the important signals, and suppresses those that are not relevant for a given task. Top-down projections from the prefrontal cortex (the cognitive control center of the brain) to the striatum (a subcortical switchboard with cognitive and motor functions) provide the essential neural substrates for such gating functions. Recent evidence, mostly from neuroimaging studies in humans, suggests that impairment of these gating mechanisms may ultimately be responsible for common “sensory” disorders including tinnitus and chronic pain.

Dysregulation of cortico-limbic networks, including the medial prefrontal cortex and the nucleus accumbens (a part of the ventral striatum), seems to be at the heart of both disorders, which are common comorbidities of post-traumatic stress disorder (PTSD) and depression. Irrelevant hyperactivity is internally generated in sensory regions as a result of lesion-induced plasticity, but is no longer suppressed due to the faulty gating mechanisms. Understanding these gating mechanisms and the origin of their malfunction could be a big step toward treatment and cure.

The TUM-IAS workshop reported, reviewed, and discussed findings about brain regions and circuits that are involved in the impaired gating process that causes both tinnitus and chronic pain and how this dysfunction leads to these (often chronic and highly disabling) sensory phantom perceptions. The workshop reflected the

rethinking process that is going on in our understanding of tinnitus and chronic pain. Both fields originally focused on anomalies in the peripheral system and then on the primary sensory cortex, before looking at brain regions outside their specific senses. The last few years witnessed an increasing number of studies focusing on gating mechanisms responsible for the perception of these abnormal sensations, involving highly integrated global network activities instead of localized activity.

Besides its obvious clinical importance, the symposium attracted faculty and students from basic neuroscience because it discussed mechanisms of fundamental relevance for sensation, perception, and higher cognitive function. It illustrated central aspects of plasticity in the auditory and somatosensory systems and provided a direct comparison of their most prominent disorders. As was noted at the workshop by several participants, one of the most astonishing aspects is the convergence of mechanisms in the two fields, which emerged from research done completely independently.

Publications

[1] A full review discussing some of the fundamental ideas and concepts debated at the workshop was published by Trends in Cognitive Sciences in October 2015 (Rauschecker et al., TICS, 2015).

[2] J. P. Rauschecker, E.S. May, A. Maudoux, and M. Ploner, “Frontostriatal gating of tinnitus and chronic pain,” Trends in Cognitive Science, vol.19, no 10, pp. 567–578, 2015.

Events 2015

January 12
Talk **Controlling Electron- and Phonon-driven Chemical Transformations on Metals**
Speaker: Prof. Suljo Linic | Hans Fischer Fellow

January 22–23
Collaborative Workshop Series on Water Research for Sustainable Water Infrastructure and Climate Change
Remediating the Human Water Footprint
Organization: The Hong Kong University of Science and Technology (HKUST), TUM-IAS, IGSSE
Location: TUM-IAS

February 3
Speakers Series on New Frontiers in Battery Science and Technology **Fundamental Aspects for the Reliability and Safety of Batteries: Stresses in Battery Materials and Growth of Lithium Whiskers and Dendrites.**
Speaker: Dr. Dominik Kramer (Helmholtz Institute Ulm, Karlsruhe Institute of Technology).
Organization: Dr. Peter Lamp | Rudolf Diesel Industry Fellow

February 4
Kick-off Symposium TUM-IAS / IBM Fellowship Programs
III–V Nanowires – From Materials to Nanoscale Devices
Speakers: Dr. Heike Riel | Rudolf Diesel Industry Fellow, Bernhard Loitsch (IBM and Walter Schottky Institut, TUM), et al.

February 11
Talk **Reaction Pathways to MTG/MTO on ZSM-5: Recent Developments**
Speaker: Prof. Gary Haller (Yale University) | Visiting Fellow

March 4–6
Synbreed Colloquium **Understanding and predicting complex traits through genome discovery**
Speakers: Prof. Natalia de Leon, Prof. Guilherme Rosa (University of Wisconsin-Madison) | Visiting Fellows, et al.
Organization: Chair of Plant Breeding, TUM

March 1
Was machen eigentlich unsere Nachbarn, die Forscher, in Garching?
Lecture Series “Was machen eigentlich unsere Nachbarn, die Forscher, in Garching?” **Kernfusion – die Energiequelle der Sterne auf der Erde nutzen**
Speaker: Prof. Sibylle Günter (Max Planck Institute of Plasma Physics)

March 16–17
Munich Battery Discussions **Novel Approaches for High Energy Lithium Batteries**
Organization: Dr. Peter Lamp | Rudolf Diesel Industry Fellow
Prof. Hubert A. Gasteiger (Technical Electrochemistry, TUM)

March 22–25 — 582nd Wilhelm and Else Heraeus Seminar **III–V Nanowire Photonics**
Organization: Dr. Heike Riel | Rudolf Diesel Industry Fellow,
Dr. Gregor Koblmüller (Semiconductor Nanostructures and Quantum Systems, TUM)
Location: Bad Honnef, Germany

March 30–31 — Short Course **Gas Turbine Thermoacoustics**
Speaker: Dr. Bruno Schuermans | Rudolf Diesel Industry Fellow

April 13 — Kick-off Workshop **Open Problems in Quantum Information**
Organization: Prof. Robert König | Rudolf Mößbauer Tenure Track Professor

April 23–24 — **TUM-IAS General Assembly**

April 29 — Launch Event **C2C Registry Website**
Organization: Cradle to Cradle | TUM-IAS Start-Up Project

May 13 — ERIC CATALYSIS COLLOQUIUM **Glycerol Conversion to Acrolein, Olefins and Gasoline Precursors**
Speaker: Prof. Gary Haller (Yale University) | Visiting Fellow

May 18–22 — Symposium **Big Data and Predictive Computational Modeling**
Organization: Prof. Nicholas Zabaras | Hans Fischer Senior Fellow, Prof. Phaedon-Stelios Koutsourelakis (Continuum Mechanics, TUM), Prof. Mark Girolami (The University of Warwick)

May 28 — Speakers Series on New Frontiers in Battery Science and Technology **What is Special about Solid Ionic Conductors?**
Speaker: Prof. Werner J. F. Weppner (Christian-Albrechts-University Kiel)
Organization: Dr. Peter Lamp | Rudolf Diesel Industry Fellow

June 4–5 Collaborative Workshop Series on Water Research for Sustainable Water Infrastructure and Climate Change **Blue Water Green Environment For Smart Cities**
Organization: The Hong Kong University of Science and Technology (HKUST), TUM-IAS
Speakers: Prof. Jürgen Geist (TUM), Prof. Brigitte Helmreich (TUM), Prof. Annette Menzel Carl von Linde Senior Fellow, Prof. Reinhard Niessner (TUM), et al.
Location: Hong Kong

June 14 Lecture Series “Was machen eigentlich unsere Nachbarn, die Forscher, in Garching?” **Ornamente, Symmetrien und Computer**
Speaker: Prof. Jürgen Richter-Gebert (Chair for Geometry and Visualization, TUM)

June 16 Talk **Toward Exascale Algorithms for N-body Methods**
Speaker: Prof. George Biros | Hans Fischer Fellow

June 17 **TUM-IAS Summer Faculty Day**

June 27 **Long Night of Science on the Garching Research Campus**

July 29 Sino-German Symposium on **Biomimetics: From Animal Sensory Systems to Locomotion**
Organization: Prof. J. Leo van Hemmen (TUM), Prof. Zhendong Dai (Nanjing University)

July 9 Talk **Studying Thermoacoustics Using Complex Networks**
Speaker: Prof. Raman I. Sujith | Alumnus Hans Fischer Senior Fellow

July 14 Inaugural Lecture **Exploring Structure and Dynamics of Membrane Proteins by Solution NMR**
Speaker: Prof. Franz Hagn | Rudolf Mößbauer Tenure Track Professor

July 16
Talk **Testing of Flow-Based Microfluidic Biochips: Fault Modeling, Design-for-Testability, Fault Diagnosis, and Experimental Demonstration**
Speaker: Prof. Krishnendu Chakrabarty (Duke University)
Organization: Prof. Tsung-Yi Ho | Hans Fischer Fellow and Prof. Ulf Schlichtmann (Institute for Electronic Design Automation, TUM)

July 21–22
Workshop **Sensor Technologies & the Human Experience**
Speakers: Prof. Stephen M. Goodnick | Hans Fischer Senior Fellow, Prof. Paolo Lugli (Nanoelectronics, TUM), Prof. Wolfgang Porod Alumnus Hans Fischer Senior Fellow, et. al.
Organization: Prof. Klaus Mainzer (Philosophy and Philosophy of Science, TUM)

July 27–31
Course **Introduction to Bayesian Methods for Quantitative Geneticists**
Speaker: Prof. Daniel Gianola | Hans Fischer Senior Fellow
Organization: Synbreed, TUM-IAS

September 7–8
Symposium **Central Gating of Tinnitus and Chronic Pain – The Role of Cortico-Limbic Networks**
Organization: Prof. Josef P. Rauschecker | Hans Fischer Senior Fellow

September 20


Lecture Series “Was machen eigentlich unsere Nachbarn, die Forscher, in Garching?” **Mit Neutronen die Welt erforschen: Auf der Suche nach dem Wissen von morgen**
Speaker: Prof. Winfried Petry (Functional Materials, TUM)

September 24
Kick-off Symposium **Optimal Control Theory and Medical Imaging Applications**
Organization: Prof. Dominique Sugny | Hans Fischer Fellow, Prof. Steffen J. Glaser (Organic Chemistry, TUM)

October 21
8th International Workshop on **Human-Friendly Robotics**
Organization: Prof. Dongheui Lee | Alumnus Carl von Linde Junior Fellow

October 28
TUM Water Cluster Lecture Series **Panel Discussion: Resilient Water Systems under Dynamic Stress**
Organization: TUM Water Cluster, IGSSE, TUM-IAS

October 29
Inaugural Lecture **Isogeometric Analysis: An Innovative Paradigm for Advanced Simulation**
Speaker: Prof. Alessandro Reali | Hans Fischer Fellow

November 5
Inaugural Lectures **Yale Meets TUM: Information Design and Hunger Drives Life**
Speakers: Prof. Dirk Bergemann | Hans Fischer Senior Fellow
Prof. Tamas Horvath | Hans Fischer Senior Fellow

November 6
Speakers Series on New Frontiers in Battery Science and Technology **Ordered Structures and Microscopic Aspects in Energy Storage – Who Cares?**
Speaker: Prof. Dr. Harry E. Hoster (Lancaster University)
Organization: Dr. Peter Lamp | Rudolf Diesel Industry Fellow, TUM-IAS

November 10
MPP Colloquium **Experimental Searches for Sterile Neutrinos at the eV and keV Scales**
Speaker: Dr. Thierry Lasserre | Hans Fischer Senior Fellow

November 12
Talk **Consciousness and the Dying Brain**
Speaker: Prof. George Mashour (University of Michigan) | August-Wilhelm Scheer Visiting Professor

November 19
Kick-off Workshop **Proteases in the Brain**
Organization: Prof. Carl P. Blobel | Carl von Linde Senior Fellow,
Prof. Stefan Lichtenthaler (Neuroproteomics, TUM)

November 22
Was machen eigentlich unsere Nachbarn, die Forscher, in Garching?
Lecture Series “Was machen eigentlich unsere Nachbarn, die Forscher, in Garching?” **Fahrzeuge der Zukunft: Brennstoffzelle oder Batterie?**
Speaker: Prof. Hubert A. Gasteiger (Elektrochemistry, TUM)

November 24
Kick-off Workshop **Automated Controller Synthesis**
Organization: Focus Group Automated Controller Synthesis

November 27
LIESEL BECKMANN SYMPOSIUM 2015
Liesel Beckmann Symposium **Early Programming and Prevention of Cardiometabolic Disease**
Organization: Prof. Regina Ensenauer | Anna Boyksen Fellow,
Prof. Renate Oberhoffer (Preventive Pediatrics, TUM), TUM Department of Sport and Health Sciences

December 2
TUM-IAS Winter Faculty Day

December 7–9
Workshop ***ν*-Dark 2015**
Organization: Dr. Thierry Lasserre | Hans Fischer Senior Fellow,
Prof. Stefan Schönert (Experimental Astroparticle Physics, TUM)

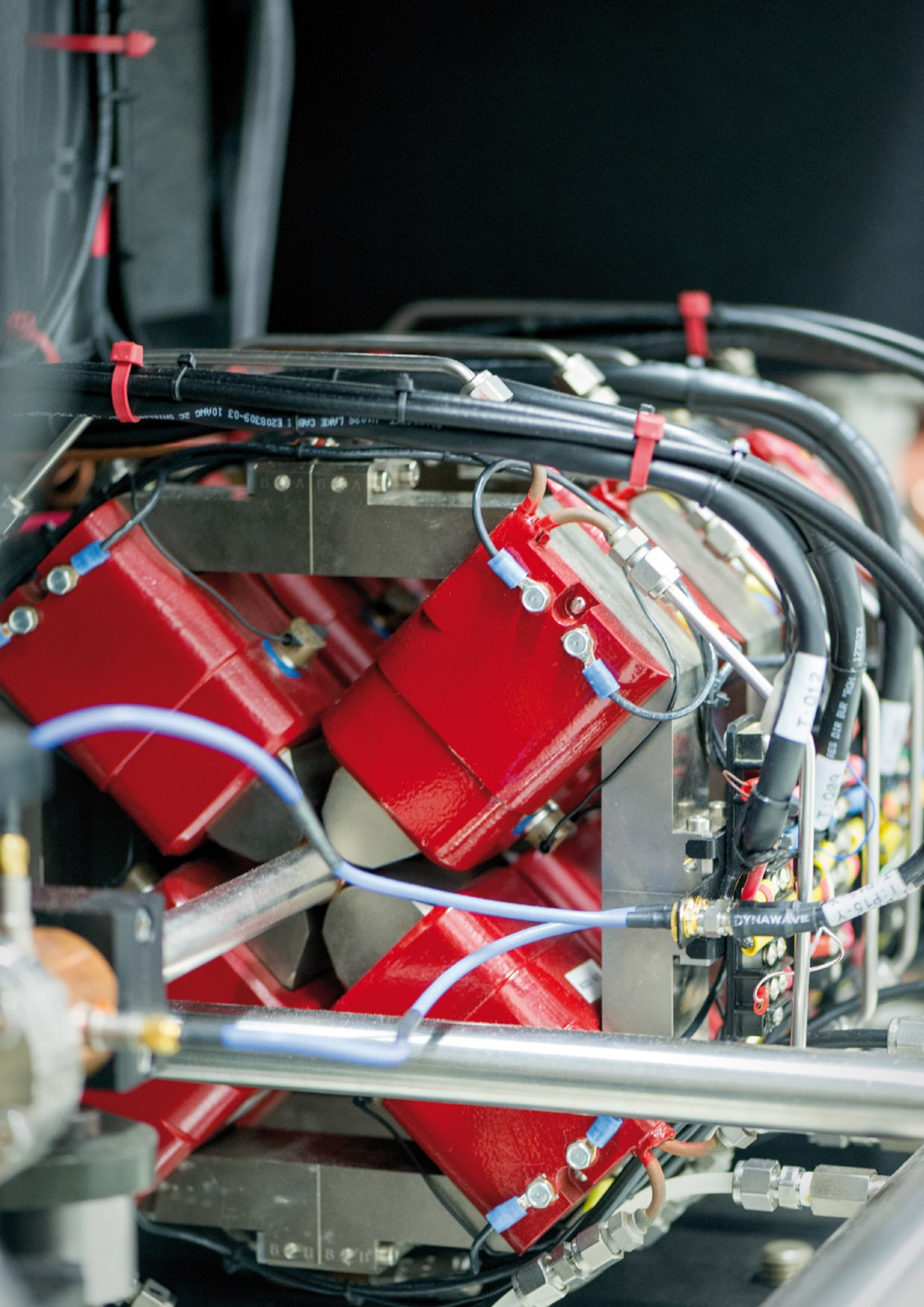
December 7–8 — Munich Workshop on **Information Theory of Optical Fiber (MIO 2015**)
Organization: Focus Group on Fiber-Optic Communication and Information Theory

December 11 — Kick-off Workshop **Respiratory X-Ray Phase-Contrast and Dark-Field Imaging for Biomedical Research**
Organization: Focus Group Phase Contrast Computed Tomography

December 15 — Inaugural Lecture **Protein Folding in the Cell: Structural Mechanisms, Cellular Pathways and Biomedical Applications**
Speaker: Prof. Matthias J. Feige | Rudolf Mößbauer Tenure Track Professor

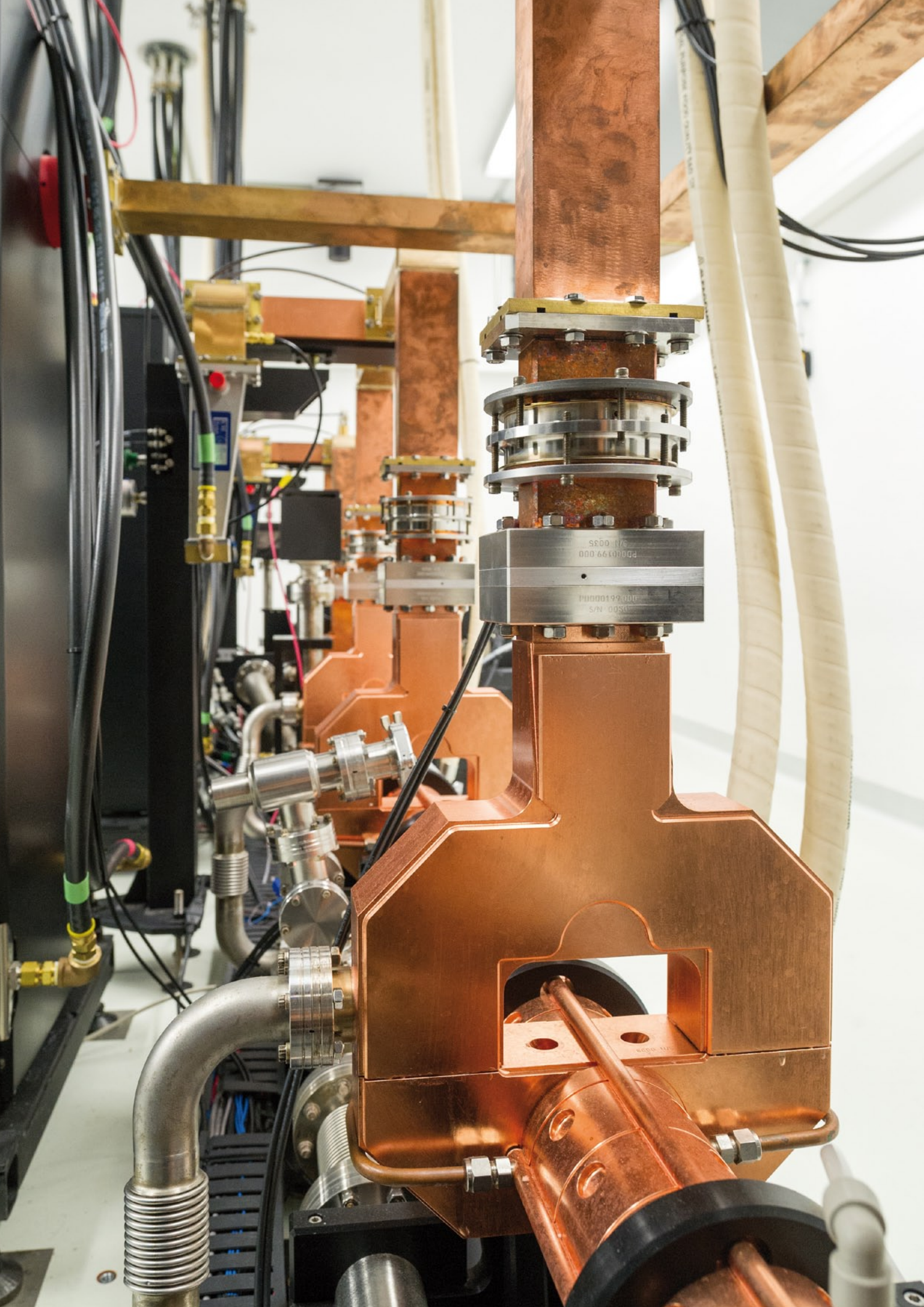
December 16–17 — International Symposium **Additive Biomanufacturing and Regenerative Medicine**
Speakers: Prof. Dirk Busch (Medical Microbiology, Immunology and Hygiene, TUM), Prof. Michael Friebe | Rudolf Diesel Industry Fellow, Prof. Arndt F. Schilling (Plastic Surgery and Hand Surgery, TUM) et al.
Organization: Prof. Dietmar W. Hutmacher | Hans Fischer Senior Fellow

December 21–22 — Mini-Symposium on **Metabolic Principles of Physiology and Disease**
Organization: Prof. Tamas Horvath | Hans Fischer Senior Fellow


DYNAWAVE

In Focus

Phase-Contrast Computed Tomography



Phase-Contrast Computed Tomography

Excerpts from an interview on Jan. 21, 2016
Patrick S. Regan

Jointly hosted by members of the TUM School of Medicine and the Physics Department, the Phase-Contrast Computed Tomography Focus Group provides a compact illustration of traits that, in combination, set the TUM Institute for Advanced Study apart. The TUM-IAS promotes international networking and

facilitates all sorts of connections: between disciplines, between established scientists and the next generation, between basic and applied research, and between academic and industrial expertise. Furthermore, these are not joined serially like links in a chain, but rather like compounds and catalysts in a crucible. And while it is like comparable institutes around the world in insisting on scientific excellence and frontier topics, the TUM-IAS is more open than others to the pursuit of practical outcomes.

In this case, the research frontier and the eventual aim coincide in new methods and instrumentation for X-ray computed tomography – with an eye toward clinical applications, in service of patients and their doctors, as well as enabling basic biological research.

On their way to Garmisch-Partenkirchen for IMXP 2016 – the International Symposium on BioMedical Applications of X-Ray Phase-Contrast Imaging – seven members of this collaboration met in Garching to discuss their work with interviewer Patrick S. Regan (PSR): Professor of Biomedical Physics Franz Pfeiffer (FP) is a Carl von Linde Senior Fellow of the TUM-IAS and Host of the Focus Group. His Co-host is Professor of Radiology Ernst Rummeny (ER), based at the university hospital Klinikum rechts der Isar. PD Dr. Peter B. Noël (PBN) is affiliated with both the Chair for Biomedical Physics and the university hospital. The home institution of Dr. Kaye S. Morgan (KSM), a Hans Fischer Fellow of the TUM-IAS, is the School of Physics at Monash University in Australia. Dr. Thomas Koehler (TK), of the Philips Research Laboratories in Hamburg, is a Rudolf Diesel Industry Fellow. Both Regine Gradl (RG) and Wolfgang Noichl (WN) hold MSc degrees and are doctoral candidates in Biomedical Physics. (Gradl is completing her PhD with TUM-IAS support).

Franz Pfeiffer

PSR: You're a diverse group with a lot of irons in the fire. To give an overview, what are the basic outlines of the group's common research program?

FP: We're focusing on several technology areas as well as a few specific clinical indications and applications. When we talk about X-ray imaging from a technology point of view, we are basically looking at three innovations, technological improvements that in themselves are research topics in our lab.

First is phase-contrast imaging, where the basic idea is that we exploit the wave nature of X-ray light instead of just using the absorption. Where we used to have only one information channel, now we have three. In addition to absorption we have a phase-imaging channel and a scattering or "dark-field" channel. These are still X-ray images, but they show slightly different interactions. The question then is: In which channel do you see what, in the best way? Second, we actually work with novel instrumentation, such as more brilliant X-ray sources, the highlight being the Munich Compact Light Source. Part of a joint TUM-LMU project called the Center for Advanced Laser Applications, this powerful new research tool is located right in this building, at IMETUM.

Finally, the C in computed tomography or CT has become increasingly important in the last ten years, with all the computational power that is available now. The third major technology focus for our group is novel algorithms to process the images we get.

TK: Ever since CT was introduced, we've been working on algorithms. After thirty years, there are really mature algorithms for attenuation images, well optimized. You learn over the years how imperfections in the system can be modeled, and how they can be treated in algorithms to produce very nice images.

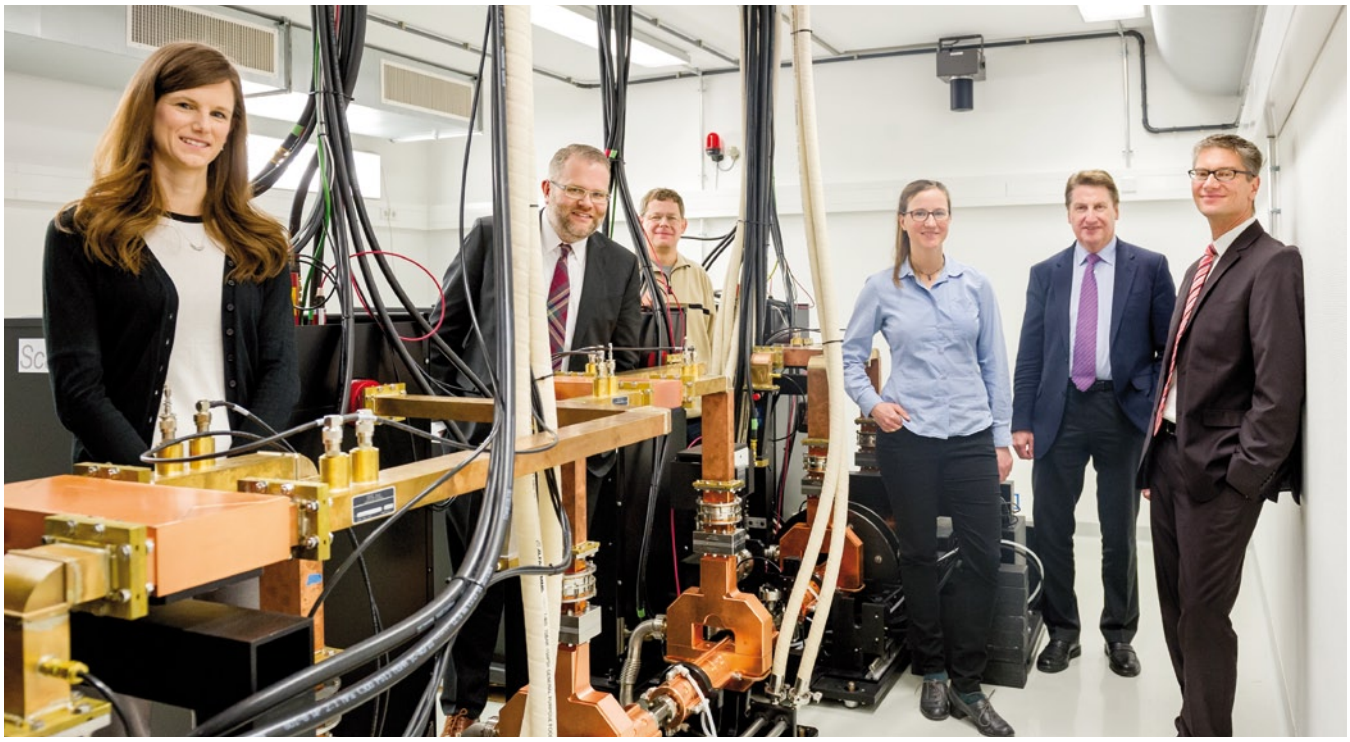
We'll have to do the same thing again with phase-contrast imaging. We're back on the learning curve. It may be clear from the physics point of view, but there are things you might want to neglect in order to make the algorithms faster. There are new imperfections in the system, which you might treat differently. Any time you modify your CT system, you have to model that in order to get good images.

PBN: As Thomas says, quite a lot of developments have already been done for absorption imaging. We try also to make the algorithms a lot more quick, a lot more efficient. Since phase-contrast has resulted in two other channels, you might also need different algorithms.

For instance, some algorithms you used before might only need a slight adjustment, but in other cases you need to think them through again from the very beginning. This is not only to make them quick, but maybe also to profit from the fact that those three channels are imaging the same thing and have something in common, something not in common – to take the quality in one of the images to remove artifacts from another imaging channel.

TK: The algorithmic research will be crucial to get to MRI-like images in the end, in the clinic, which is one of our aims. Here phase-contrast CT is competing with a very mature technology in terms of image quality, and this will be a challenge.

PSR: Ernst, how do you view the potential advantages from the medical point of view?



Kaye S. Morgan, Peter B. Noël, Thomas Koehler, Regine Gradl, Ernst Rummeny, Franz Pfeiffer

ER: With conventional CT, you see dense structures like the bone very nicely, and with MRI you see the soft tissue. Now with phase-contrast, we have the potential to get both with one system. I think of this as the MRI-zation of CT. Maybe when we have the technology in our hands, we will be able to do soft tissue diagnosis, finding small soft tissue tumors as well as bone diseases. In a small animal, we have shown that it works. Does it also work in humans? We'll see.

That's one potential advantage. We may also find we can reduce patients' exposure to X-rays. The technological goal in CT was first to make it faster and faster. It is now 200, 300, even 600 slices with one rotation, depending on the vendor. The other concern is how you keep the radiation dose down. We already have different technologies to keep the doses low, but this could be another.

I'm a clinical radiologist, and my goal is precisely this, to see what we can take from the technical part to the clinical part, to the translational part. That means when the machine comes to the hospital and a little bit before. I say little bit before because we are a technical university and thus have the opportunity to work closely together, even though our hospital is downtown. There is a lot of exchange back and forth between doctors and Franz's group, and we hope at some point to put a phase-contrast X-ray system into the hospital and do the first clinical trials, here in Munich.

Before that, we need a company. Franz cannot be the company to build the machine and distribute it all over the world. But if we find a company to build the system, then we may have two, three, or four prototypes, and even do research internationally.

PSR: Clearly it must help to have someone from industry on the team from the start. Thomas, how would you describe your role?

TK: I'm a physicist with a background of working on algorithms for computed tomography. In the Focus Group, my role is supporting or pushing this from the industrial side, into the clinic. There's some really cool stuff already in the fundamental physics, in developing the technology, in showing that there is some benefit to be expected, and even setting up a small animal scanner. But once you come to a clinical environment, it's an order of magnitude bigger effort to set up a machine.

Kaye S. Morgan

And that's a point where it's good to have a company on board, to support the development, to point to certain boundary conditions that you have to comply with.

FP: A good reality check.

PBN: It brings us back from our dreams to the real world sometimes.

PSR: And Kaye, what brings you here from down under?

KSM: Besides the group itself, one of the attractions is the Munich Compact Light Source. The physics group I was working with in Australia was also doing phase-contrast X-ray imaging. I'm particularly looking at applying the technique as a medical research tool. In parallel to clinical imaging, you can use this kind of imaging to better understand the body, how treatments work, and that kind of thing. But most of my research to date has been done using synchrotron X-ray sources. There's some limit to how much time you can access there, so we're now looking at doing the same kind of research using the Munich Compact Light Source, which is much more accessible.

RG: It's really useful that we have this instrument. It's similar to a synchrotron, which is normally a building with a circumference of five to eight hundred meters, shared by many scientists. And now we have something that can produce similar radiation yet fits nicely inside a lab. That is really amazing. We don't have to write proposals to get access for a couple of days in the year – we can use it every day. It's also very interesting because it's a prototype, and you want to improve it.

PSR: So the instrument becomes part of the research?

RG: Exactly.

PSR: What's the difference between the big systems and the small ones? Can you do the same things with the Munich Compact Light Source that you could do with a synchrotron?

KSM: The MuCLS is filling in a big gap in that it is far more capable than an off-the-shelf lab source but on the other hand far less expensive than a billion-euro synchrotron facility. The synchrotron produces really bright light, so you can take a high-speed X-ray movie. Until now, most of the sources that could fit in labs

weren't bright enough to do that, since you had to have quite a long exposure. But the CLS is much brighter than, say, a spinning anode X-ray source, and also it's very coherent – that is, much closer to a single wavelength and uniform phase. That's one of the qualities that make for very good phase-contrast X-ray imaging.

It's the only one in the world, so we're lucky to have it here. There are two different end stations where you can take images, and there are many different setups available. There are quite a few people working on different potential applications.

PSR: And what are you doing with it?

KSM: Some of the work we've been doing is imaging the airway surface. A lot of previous work that's looked at this on the micron scale has been using either a tissue culture or a piece of tissue in a dish, which is not quite as realistic as when the tissue is inside the body. Using this X-ray phase-contrast imaging, we can look at the airway surface *in vivo*. We can see how the liquid layer on the surface changes in response to treatments, and we can see how particles move along that liquid layer as they're inhaled.

PSR: What other kinds of biological questions become accessible with phase-contrast imaging?

FP: There are questions that go along with the clinical applications, such as how a certain state in the body changes as a disease progresses. If you take for example the liver, it's probably interesting to look at the chemical composition and how different diseases change that. This is information you would not always have from a clinical radiology picture but would still be worth investigating to know more about the reasons for disease – chemical, biological, or structural reasons – on a scale that is usually not accessible in the clinic.

Another example would be bone research. In the clinic you can look at bones from a certain length scale, or you have a resolution on the order of half a millimeter. But in the research lab, we can complement that by looking at small pieces of bone with a

Regine Gradl

micron resolution, so we get more information about why and how the structure changes on a different level. And maybe that leads back eventually to clinically relevant information that will add to our understanding of why a disease progresses this way or that way.

ER: Think about osteoporosis, a disease of the bone structure that affects everyone at a certain age. Why is this happening? Why is the structure changing? When is the bone breaking? All these things have to be evaluated for prevention, to protect people from that. Then there are new strategies in treating osteoporosis with drugs. Are they helping? Are they changing the bone structure?

Now you can take pieces of bone and examine them with high resolution. With the Munich Compact Light Source you can even go into molecular structures. You can see the molecules. What that means is that clinical questions inspire experiments that then feed back into medicine. That's the interface where these various disciplines meet, the basis of the whole collaboration.

PSR: This seems like a very special environment for you doctoral candidates, Wolfgang and Regine. Is that the way you see it?

Thomas Koehler

Wolfgang Noichl

WN: I did my master's degree in condensed matter physics. What I find really interesting about this applied research in physics for medical imaging is that it's so close to applications. So there is some chance that you will see how your work is used by someone. And I like the challenge of developing algorithms for computed tomography. Nowadays computers are so fast, and for most purposes you can just write a quick script and it will happen instantly. Here the data is still big, and the algorithms can be very complicated, and it's still interesting to leverage the most recent technology. The algorithms are in a way somewhat slow, and you have to push the limits. I find that really tempting.

RG: My research focuses mainly on the physics, working with the Munich Compact Light Source and trying to improve the imaging. We would like to do some lung imaging, and also investigate some new treatments for lung diseases, and here we get together with the medical part. I feel we're doing something important. You want to improve medicine, and you want to help people.

TK: I think that goes for all of us. Of course my motivation also has something to do with the fact that my employer earns money selling medical equipment. It's good to have innovations that could position us to create great products. But there's also the level of personal motivation, and as Wolfgang and Regine said, it's really cool to work in an environment where the outcome of your work could do something good for people. Having that in combination with great science is wonderful.

PSR: Taking stock of where the Focus Group has come so far and looking ahead, are there findings or milestones you would want to highlight?

FP: There were three nice demonstration papers showing proof of principle and the first imaging applications for the Munich Compact Light Source. There are by-products of these experiments that may have biologically or clinically interesting implications. For example, we looked at mice and found that we can tell the difference between brown and white fat. In terms of algorithms, there was also a paper on iterative CT for phase-contrast imaging. We worked a long time on that, with several students. Also, a small-animal CT proof-of-principle system has now been installed at Klinikum rechts der Isar. Planning is under way for the first biomedical studies in close connection to the clinics –

Ernst Rummeny and Patrick S. Regan

to look at various disease models in mice. I'm very excited about having such a direct connection to the clinics.

ER: We already learned a lot last year about the three channels. With phase contrast you see the bone and you see the soft tissue. Now with the dark field, we see certain structures in the bone better than with phase contrast alone. In fact, all air-containing tissues will have different contrast in the dark field, so we have the feeling we could do lung imaging.

FP: That brings up the most basic clinical questions: Where exactly would this technology be most beneficial? Which disease could you diagnose or treat better if you had this technology in the clinic? We can't yet answer these questions in a clinical setting because the machine is not there yet. But a big effort of this collaboration is to do pre-clinical experiments with what we have here – to look at small samples of bone or liver or brain to help determine where this technology would eventually be most helpful, and where it would be better than what's already available.

PSR: It may be a long way to commercialization of this technology, but you seem to be moving pretty quickly. How do you straddle the line between university-based research and the prospect of influencing the whole medical imaging industry?

TK: There's a master research agreement that was negotiated between the university, the hospital, and Philips. The intellectual property is split among the parties. The whole idea with patents is that you can disclose what you've invented while protecting the initial investment. But this is by no means proprietary research or product development.

PBN: The business case, for Philips or any other company, will come from what Franz and Ernst were discussing earlier – whether there is a business case based on osteoporosis, or some other applications.

FP: The main point is that the product cannot be envisioned tomorrow. There is still a big jump to take before anyone is going to embark on a multimillion-euro product development. What we're doing is the preparatory work for clinical indications, technology development, and algorithmics – all of this is research and will be published.

ER: All the companies are looking at us, and at the literature. TUM and Philips are not the only ones doing phase-contrast imaging. There are different concepts. At MIT they do it differently. We think we are better. We have a feeling we are in the lead, but it's always good to have competition in science.

PSR: How does the TUM-IAS Focus Group relate to your separate, larger research environments?

PBN: Only this framework makes it possible to set up such groups, with excellent people from different fields.

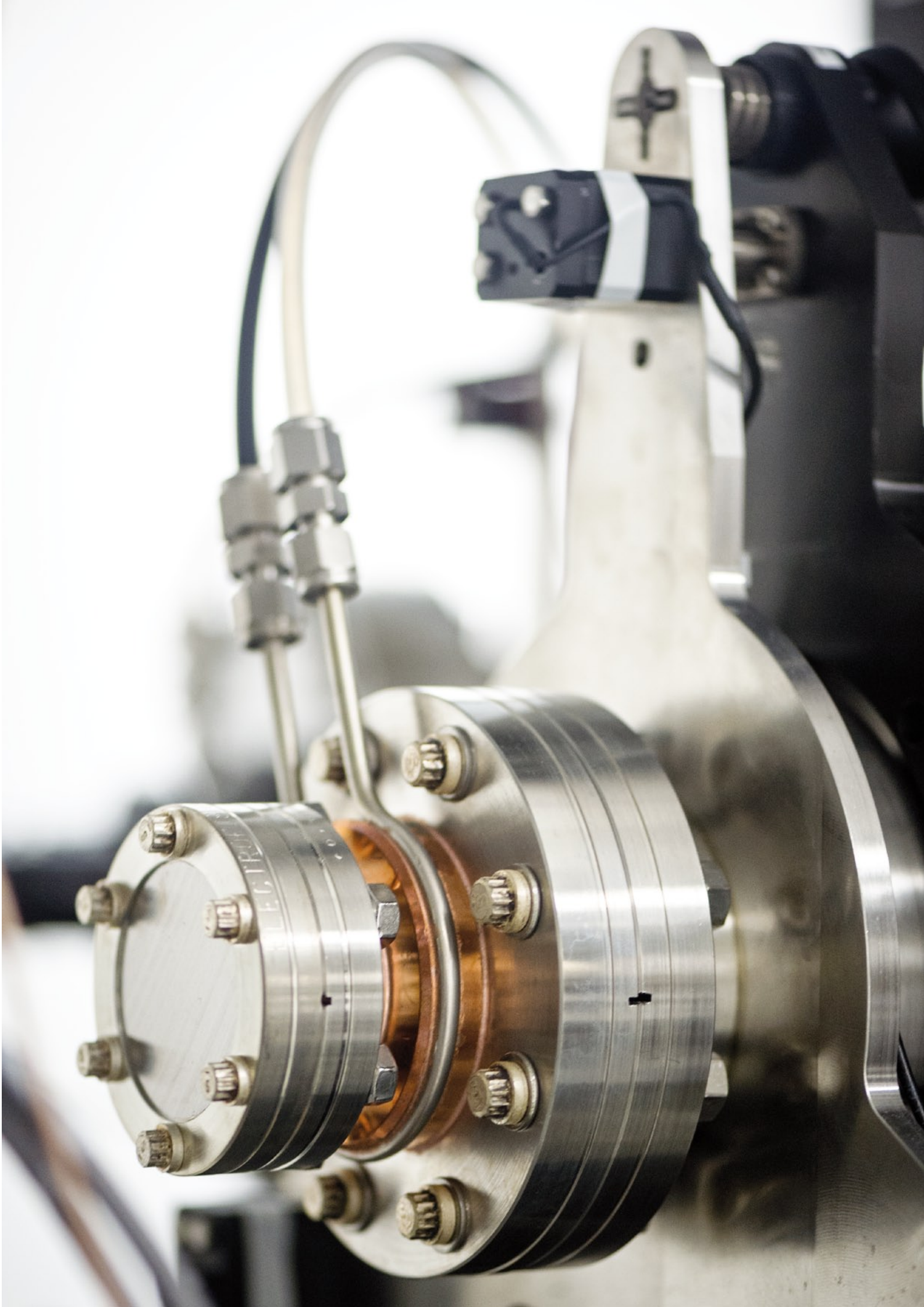
FP: This interdisciplinary effect is absolutely unique.

TK: Personal contact is a very important thing, if you want to get creativity in a room and create new ideas. I'm here on a regular basis, and I'm of course connected to colleagues back in Hamburg. They are also part of the team in a sense, even though they are not so often here. It's really good that we have the framework but can also connect other people.

PSR: So behind each of you, there may be ten, twenty, or fifty more people involved in some way?

FP: That's the point. With all our individual networks, we are able to bring in, or drag in, or tap into resources as needed. But I would say it's more a one-way street. We are not, with this Focus Group, answering questions for other researchers – because it really is focused!

Peter B. Noël



Scientific Reports

Scientific Reports

Focus Group **Advanced Stability Analysis**

Dr. Bruno Schuermans (GE Power) | Rudolf Diesel Industry Fellow
Tobias Hummel | Doctoral Candidate
Prof. Thomas Sattelmayer, Thermodynamics, TUM

Scientific Reports

Bruno Schuermans

Background

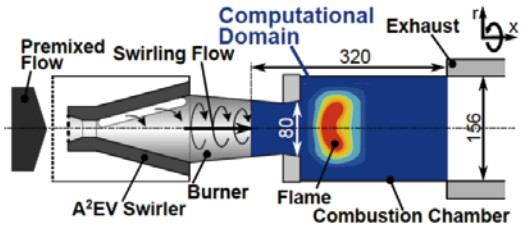
The transformation of our power generation landscape from dominantly conventional to renewable technologies depends on the successful implementation of operationally flexible and clean gas turbines. The associated implementation of novel – i.e., turbulent lean premixed – combustion technologies is confronted with the combustion chamber exhibiting a sensitive susceptibility to thermoacoustic instabilities. Physically, these instabilities evolve from constructive, self-sustaining feedback couplings between the combustor's acoustic oscillations and the flame's heat release rate fluctuations, which manifest as pressure pulsations through the chamber. The pulsations need to be avoided, as they can be detrimental to the engines' hardware, and also hamper operational flexibility and low-emissivity.

In particular, high-frequency pulsations occurring within the kilohertz frequency regime have been increasingly threatening smooth gas turbine operation, and have thus become a focus of attention for engineers and researchers in the field. These pulsations unfold in a multidimensional manner throughout the combustor, which suggests a significant increase in complexity regarding the understanding and modeling of the underlying physics compared to one-dimensional, low-frequency counterparts.

In the context of a TUM-IAS Rudolf Diesel Industry Fellowship, Bruno Schuermans is taking on the challenge of unraveling high-frequency combustion instabilities in gas turbine combustors together with Thomas Sattelmayer of TUM's Chair for Thermodynamics. For this purpose, an extensive network ranging from academic (TUM-IAS), industrial (ALSTOM & AG TURBO) and government (BMWi) research frameworks has been established. Within this framework, four doctoral candidates are collaboratively conducting high-frequency thermoacoustic research at TUM with experimental, numerical, and theoretical emphases.

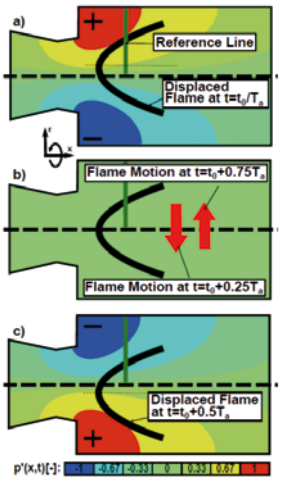
Recent activities

The year 2015 was particularly successful, as considerable advances were made toward understanding the physical mechanisms leading to the thermoacoustic generation of sound at high-frequencies. A lab-scale premixed combustor exhibiting high-frequency thermoacoustic instabilities served as subject of investigation. A schematic of this combustor is shown in figure 1.

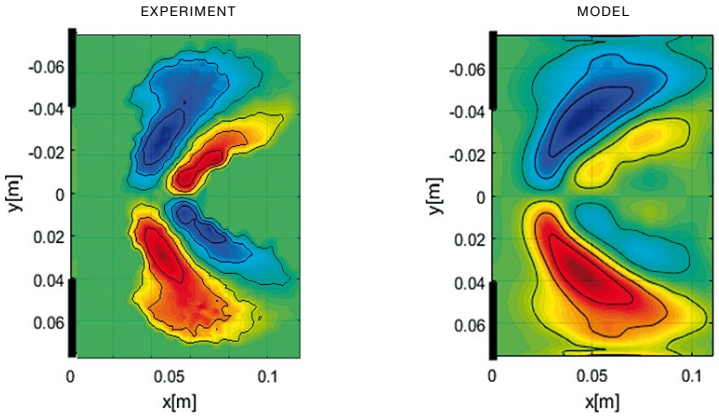


1 | Schematic of experimental combustor

Specifically, the group established a theoretical model with which the distribution and even the severity of high-frequency thermoacoustic source terms in flame tubes can be calculated on the basis of steady combustor parameters and the geometrical acoustic eigenmodes.



2 | Illustration of periodically displacing flame



3 | Comparison between experimental and model thermoacoustic source term distribution

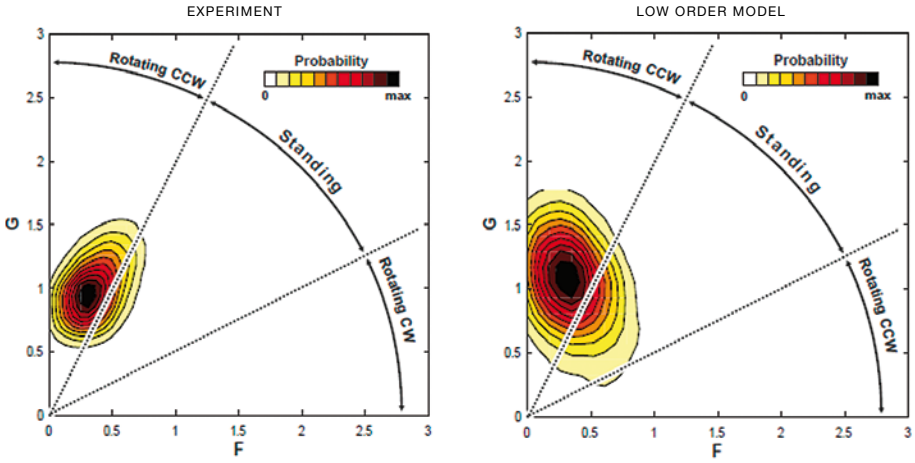
This model is built on the sheer experimental observation of a moving flame, which periodically displaces from its mean position in accordance with the acoustic pressure field at the instability frequency as illustrated on figure 2.

This displacement alone represents a thermoacoustic driving mechanism, and additionally it induces a deformation of the flame shape, which generates further sound. Dynamic high-speed camera diagnostics were utilized to visually capture the flame behavior during the instability. Employing tomographic reconstruction techniques yielded thermoacoustic source term distributions, which served as the validation benchmarks for the postulated models.

Figure 3 compares the experimental and calculate source terms, revealing excellent quantitative and qualitative agreement, which implies the correctness of the postulated theoretical model. This validation was carried out for several operation points, all of which consistently revealed matching (experiment vs. model) outcomes. Consequently, the postulated models can be confidently considered eligible to be used for predictive thermoacoustic analysis (e.g., for novel gas turbine combustors or refurbishment activities of existing engines). Respective scientific papers have been submitted for publication in 2016.

Furthermore, the low-order analysis tool for high-frequency thermoacoustic systems that we presented within last year's report, was applied to calculate the temporal performance of the model combustor in figure 1. Methodologically, these models are low-order state space systems, which are capable of modeling nonlinear and stochastic thermoacoustic processes in a straightforward and computationally efficient manner. Experimentally observed high-frequency mode dynamics – i.e., whether the pressure mode (cf. figure 2) rotates, stands, or exhibits a mix of both with respect to the azimuthal coordinate – was effectively reproduced as shown in figure 4.

These results gave physical insight into the dynamics of high-frequency thermoacoustic systems and underlined the importance of stochastic effects as these proved crucial for reproduction of the experimental observations. A corresponding paper was submitted for publication.



4 | Probability density distribution comparison between experimental and simulated mode dynamics

Workshops and events

Apart from the research advances, a short course on thermoacoustic instabilities was given by Bruno Schuermans in the TUM-IAS auditorium in March 2015.

This event offered a two-day lecture series covering theoretical fundamentals, modeling approaches, mitigation strategies, and control aspects of thermoacoustic oscillations in industrial gas turbine engines. It attracted around 30 scientists and engineers from industry and academia. Planning began for a symposium on thermoacoustic oscillations.

The theme of this symposium focuses on both gas turbine and rocket engine thermoacoustics, and additionally on the unification of industrial and academic perspectives. Thereby, our Focus Group and the TUM-IAS are proposing a novel form of scientific meeting, which aims to capture the attention of two internationally established research communities and seeks to bring them together at the TUM-IAS on the Garching campus in May 2016.

Selected Publications

[1] T. Hummel, C. Temmler, B. Schuermans, and T. Sattelmayer, “Reduced-Order Modeling of Aeroacoustic Systems for Stability Analyses of Thermoacoustically Noncompact Gas Turbine Combustors,” J. Eng. Gas Turbines Power, vol. 138, no. 5, p. 051502, 2016, accepted in 2015.

[2] T. Hummel, M. Schulze, B. Schuermans, and T. Sattelmayer, “Reduced Order Modeling of Transversal and Non-Compact Combustion Dynamics,” in 22nd International Congress on Sound and Vibration, Florence, Italy, 2015.

Publications by this Focus Group can also be found on page 162.

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

Prof. Alessandro Reali (Università degli Studi di Pavia) | Hans Fischer Fellow
Davide d'Angella | Doctoral Candidate
Prof. Ernst Rank, Computation in Engineering, TUM

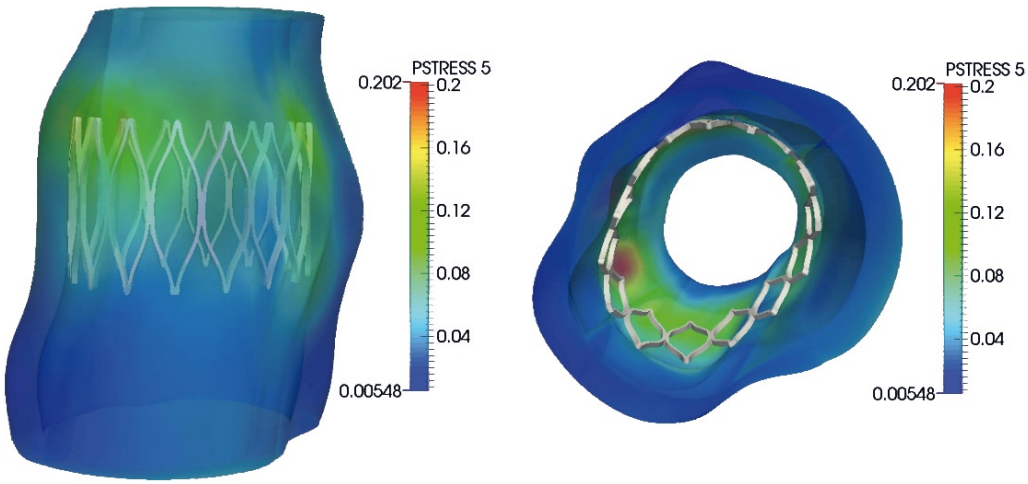
Scientific Reports

Alessandro Reali

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 way to go for creating efficient analysis tools for the effective simulation of complex problems such as those related to additive manufacturing.

Over the last decade, increasing numbers of researchers have come to accept the statement "geometry is the foundation of analysis" as a basic principle of modern computational mechanics. However, from the practical point of view, geometry has had a limited impact on the field so far. The main reason for this is that finite element analysis (FEA; i.e., the main numerical analysis tool for engineering) was developed in the 1950s and '60s, well before the advent and widespread use of computer-aided geometric design (CAGD; i.e., the main geometric design tool), which occurred only in the 1970s and '80s; also, the connection between the two worlds relies on interfaces often far from efficient. As a result, building analysis-suitable geometries is estimated to take up to 80% of the overall analysis time for complex CAGD-based engineering designs. Moreover, since low-order FEA methods are typically used, most meshes are made of simple geometrical objects like tetrahedra or hexahedra, which may not be able to represent highly sophisticated geometries with sufficient accuracy. Similar problems are present when the objects to be analyzed are obtained via imaging tools (in particular, in the medical field), and are further amplified when dealing with geometries evolving over time and involving the creation of new material, as in the case of additive manufacturing.

The above-mentioned low accuracy of classical FEA typically translates to very expensive simulations and, in some cases, even to modeling errors and misleading results, and such a gap definitely has to be dealt with. Isogeometric analysis (IGA), introduced in 2005, specifically aims at bridging the gap between analysis and geometric design. The idea is to construct isoparametric methods based on splines (which are the basic ingredient of CAGD geometries) in order to make the construction of analysis-suitable geometries that are much simpler and more efficient. In addition, the higher continuity properties of splines often lead to increased efficiency in terms of approximation power and open the door to the development of new formulations based on higher-order partial differential equations. Results to date have been much more than promising, and IGA is now regarded as one of the most powerful computational mechanics tools, able to attract also industrial interests.



1 | Isogeometric simulation of stent implantation

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 an incredibly simple and effective way (via the “immersed” concept). FCM can be easily combined with the IGA idea (and with spline functions), giving rise to very powerful and geometrically flexible computational tools. Given these premises, and also considering the fact that some of the pioneers of the above-mentioned methodologies are members of the Focus Group, it seems natural to consider the combination of IGA and FCM as the way to go for creating efficient analysis tools for additive manufacturing problems, which constitute one of the most interesting modern challenges of computational mechanics.

Selected Publications

[1] J. Kiendl, M.-C. Hsu, M. C. Wu, and A. Reali, “Isogeometric Kirchhoff–Love shell formulations for general hyperelastic materials,” Comput. Methods Appl. Mech. Eng., vol. 291, pp. 280–303, 2015.

[2] F. Auricchio, M. Conti, M. Ferraro, S. Morganti, A. Reali, and R. L. Taylor, “Innovative and e_cient stent flexibility simulations based on isogeometric analysis,” Comp. Meth. Appl. Mech. Eng., vol. 295, pp. 347–361, 2015.

Publications by this Focus Group can also be found on page 162.

Focus Group **High-Performance Computing (HPC)**

Prof. George Biros (University of Texas at Austin) | Hans Fischer Fellow
Arash Bakhtiari, Benjamin Uekermann | Doctoral Candidates
Prof. Hans-Joachim Bungartz, Scientific Computing, TUM

Scientific Reports

The multi-challenge at the dawn of exa-scale

George Biros

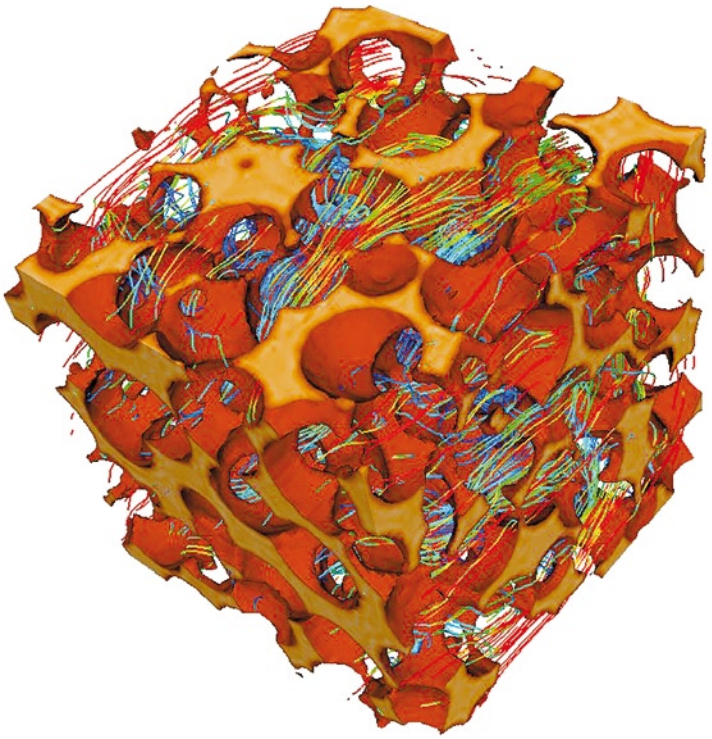
The upcoming exa-scale era promises the implementation of a new range of simulations, allowing ground-breaking insights into applications such as modeling climate change or the human body. This, however, will only be possible if all parts of the multi-challenge are tackled successfully and in close collaboration. The HPC Focus Group gathers, therefore, experts in multi-physics, multi-core systems, and multi-dimensional problems.

Miriam Mehl, Benjamin Uekermann and further collaborators from the University of Stuttgart work on black-box coupling approaches for multi-physics simulations. Such approaches make it possible to couple existing single-physics codes in a minimally invasive way. This can speed up the development of complex multi-physics simulations tremendously. The coupling library preCICE [1] enables such black-box coupling by providing methods for, first, interpolation between non-matching discretizations, second, data communication between separate executables and, third, fixed-point acceleration. A main part of our work in 2015 dealt with the efficient realization of those three building blocks on distributed computing systems. A closer focus was also set on the numerical stability of fixed-point acceleration techniques, which we were able to improve through filtering and preconditioning. To this end, Benjamin Uekermann visited Carol Woodward and colleagues at the Lawrence Livermore National Laboratory throughout September and October.

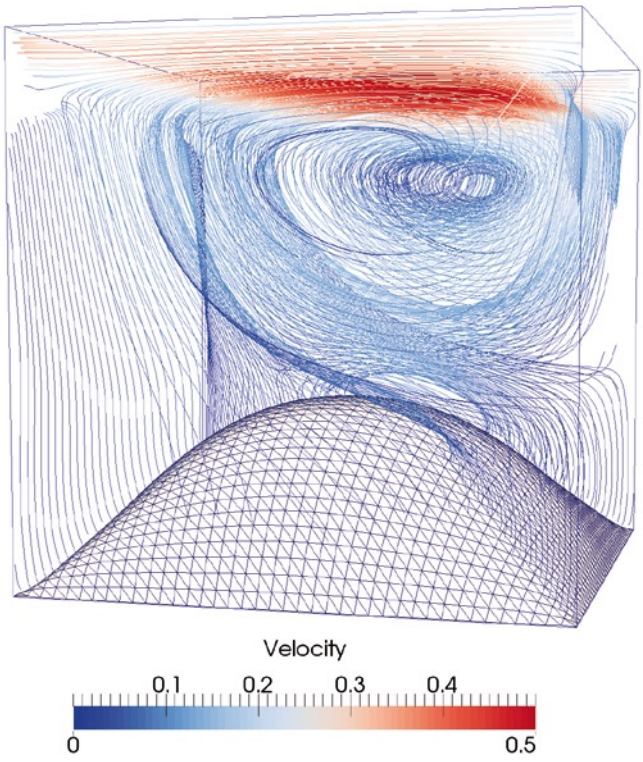
Markus Hegland, Christoph Kowitz, and Valeriy Khakhutskyy work on multi-dimensional problems. Christoph Kowitz won a Best Poster award at the SIAM CSE 2015 conference in Salt Lake City. He presented his research on the application of the sparse grid combination technique to gyrokinetic simulations of hot magnetized plasmas, which leads to a significant reduction of the computational effort for this important tool in fusion energy research. Markus Hegland hosted the research stay of Alfredo Parra Hinojosa, another TUM doctoral candidate, and Valeriy Khakhutskyy, to work on the application of sparse grids methods in high-performance computing. Valeriy Khakhutskyy and Markus Hegland continued their ongoing work on sparse models for supervised machine learning problems. They established a new link between the regression with adaptive sparse grid models and the submodular optimization techniques. This link advanced both the theoretical understanding and the algorithmic performance of the adaptive sparse grid regression. The work with Alfredo Parra Hinojosa was dedicated to the algorithmic identification of soft faults for scientific computing applications [2]. Soft faults constitute the corruption of floating point data; one of the known causes is cosmic rays hitting the computer hardware. For a desktop computer such faults are unlikely. But for exa-scale systems with myriads of computational and storage units, the probability becomes significant and, if not prevented, faults accumulate and render the program results useless. The sparse grids combination technique offers the possibility of a very elegant and rather unique algorithmic approach to treat these faults.

In June, George Biros visited the TUM-IAS and continued the collaboration with Arash Bakhtiari. During this visit, the group worked on parallelization of their advection-diffusion solver and developed a novel load-balancing technique for Lagrangian schemes.

Alumni Members
Prof. Miriam Mehl (University of Stuttgart) | Carl von Linde Junior Fellow
Prof. Markus Hegland (Australian National University) | Hans Fischer Senior Fellow
Christoph Kowitz, Valeriy Khakhutskyy (TUM) | Doctoral Candidate



1 | Stokes flow through a porous medium. The velocity field, visualized by streamlines, is computed by PVFMM, a volume integral solver developed in George Biros's group [3].



2 | Driven cavity with flexible bottom, simulated by the incompressible Navier-Stokes solver Alya (Barcelona Supercomputing Center) and the membrane solver Carat (STATIK, Technical University of Munich), coupled at runtime via preCICE.

In addition, George Biros gave two lectures at the regular courses of the Informatics Department: "Scientific Computing" and "Modelbildung und Simulation." He also delivered a presentation at the Leibniz Supercomputing Center regarding exa-scale algorithms for n-body problems. To continue the collaboration, Arash Bakhtiari visited George Biros in Austin from October to December 2015. During this stay, Arash Bakhtiari developed a new algorithm to reduce the communication overhead of the distributed-memory tree evaluation in their advection-diffusion solver.

Beyond the individual projects in each of the three parts of the multi-challenge, the close cooperation among all Fellows of the Focus Group led to a strong reciprocal synergy, which fostered each individual's work significantly. We eagerly await the first exa-scale systems.

References

[1] H.-J. Bungartz, F. Lindner, B. Gatzhammer, M. Mehl, K. Scheufele, A. Shukaev and B. Uekermann, "preCICE - A Fully Parallel Library for Multi-Physics Surface Coupling," Comp. Fluids, submitted in 2015.

[2] D. Malhotra, A. Gholami, and G. Biros, "A volume integral equation stokes solver for problems with variable coefficients," in International Conference for High Performance Computing, Networking, Storage and Analysis, New Orleans, USA, 2014.

Selected Publication

[3] A.P. Hinojosa, B. Harding, M. Hegland, and H.-J. Bungartz, "SDC-Resilient Algorithms Using the Sparse Grid Combination Technique," SPPEXA Workshop 2016, Munich, Germany, accepted in 2015.

Publications by this Focus Group can also be found on page 163.

Focus Group **Uncertainty Quantification and Predictive Modeling**

Prof. Nicholas Zabaras (University of Warwick) | Hans Fischer Senior Fellow
Markus Schöberl | Doctoral Candidate
Prof. Phaedon-Stelios Koutsourelakis, Continuum Mechanics, TUM

Scientific Reports

Nicholas Zabaras

How confident are we in the predictions of computational models?

With the increased computational capabilities afforded by the utilization of peta-scale computing resources throughout engineering and the physical sciences, the issue of confidence in simulation results has come to the center of current research. The objective of obtaining an average computational representation of a physical process is being replaced by the new paradigm of predictive simulations, where the analysis delivers quantitative confidence metrics due to aleatoric and epistemic uncertainties.

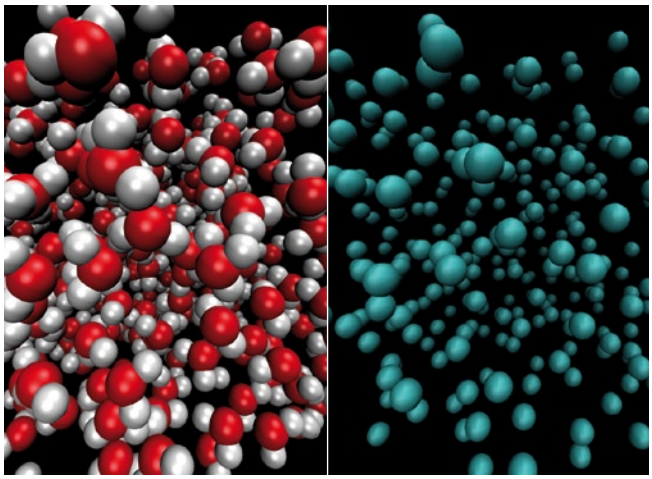
Our goal is to develop novel modeling frameworks and computational tools that advance predictive modeling in a broad range of applications. To this end we explore synergistic activities between physical and mathematical sciences, machine learning and computation. Particular fundamental problems of interest include methods for addressing the curse of stochastic dimensionality, stochastic coarse-graining in multiscale/multiphysics simulations, data-driven model calibration and validation, modeling of rare events, and solution of multiscale inverse problems.

In the past year we focused on coarse-grained (CG) models in the context of molecular simulation (figure 1). A reduced or coarse-grained description improves computational efficiency and enables the simulation of large molecular ensembles over spatial and temporal scales of interest. Existing coarse-graining approaches rely on mapping degrees of freedom from the micro- to the macro-scale and finding various ways to project the full-order description to the reduced, generalized coordinates. Such methodologies do not account for the information loss that unavoidably takes place during coarse-graining. Furthermore, the predicted macroscopic properties are based on single-point estimates, which do not account for model uncertainties and the use of finite-size training data.

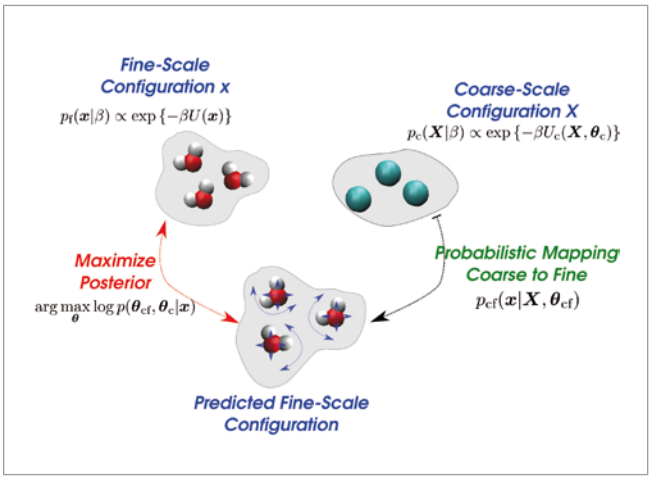
To address these limitations we developed a novel, data-driven approach based on probabilistic generative models. It builds upon a flexible coarse macroscopic description and a probabilistic lifting operator, for reconstructing microscopic configurations given the macroscopic state (figure 2).

- The coarse description should allow sufficient flexibility and reflect physical insight of the problem. Flexibility raises the dimensionality in the parameter space and thus increases the computational cost. We explore sparse Bayesian learning techniques that reveal salient features of the CG description.
- The probabilistic lifting operator accounts for the non-uniqueness of the coarse-to-fine mapping.

We learn simultaneously the probabilistic description of coarse variables and the mapping in order to best predict available microscale data. Dependencies on control variables (e.g., strength of external field) can be readily accounted for and extrapolative predictions can be carried out. More important, all predictions include uncertainty bands that reflect the aforementioned sources of uncertainty.



1 | Coarse-graining water: Atomistic fine-scale description (left), coarse description (right)



2 | Predictive coarse-graining scheme

Being able to quantify information loss during coarse-graining is fundamental to all multiscale problems, and thus the development of the presented model will have an impact on diverse applications from predictive materials modeling to predictive models in biology and life sciences.

Further effort is needed to develop a hierarchical coarse-graining approach connecting different scales and propagating the induced mapping uncertainty. This allows for a highly efficient description at high resolution in reactive system regions while describing others with less detail. Another important aspect is to address an efficient reduction of predictive uncertainty by adding data at system states promising a large information gain. For predicting properties that depend on the system's evolution in time, a non-equilibrium coarse-grained description including uncertainty propagation needs to be developed.

A highlight of the year was the international symposium on "Big Data and Predictive Computational Modeling" that took place at the TUM-IAS during May 18–21, 2015. The symposium was sponsored by the European Office of U.S. Aerospace Research & Development (EOARD), the TUM-IAS, and the Department of Mechanical Engineering. It included plenary and keynote talks from preeminent scientists in applied mathematics, computational physics/chemistry, computer science, and engineering.

The event received considerable interest from various communities, and an article on it appeared in SIAM News [2]. Videos and slides from the symposium are available on the TUM-IAS homepage [1].

Reference

[1] International Symposium: Big Data and Predictive Computational Modeling, TUM Institute for Advanced Study, May 2015. www.tum-ias.de/bigdata2015/

Selected Publications

[2] P.S. Koutsourelakis, N. Zabaras and M. Girolami, "Symposium Yields Insights on Big Data and Predictive Computational Modeling," SIAM News, July 2015.

[3] M. Schöberl, N. Zabaras, and P. S. Koutsourelakis, "Predictive Coarse Graining", in Predictive Multiscale Materials Modelling, Turing Gateway to Mathematics, Cambridge, UK, 2015.

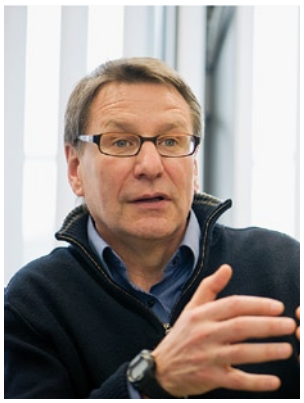
[4] M. Schöberl, N. Zabaras, and P. S. Koutsourelakis, "A Bayesian Approach to Coarse Graining," Poster in Predictive Multiscale Materials Modelling, Turing Gateway to Mathematics, Cambridge, UK, 2015.

Publications by this Focus Group can also be found on page 164.

Focus Group **Clinical Cell Processing and Purification**

Prof. Stanley Riddell (University of Washington) | Hans Fischer Senior Fellow
Prof. Dirk Busch, Medical Microbiology, Immunology and Hygiene, TUM

Scientific Reports

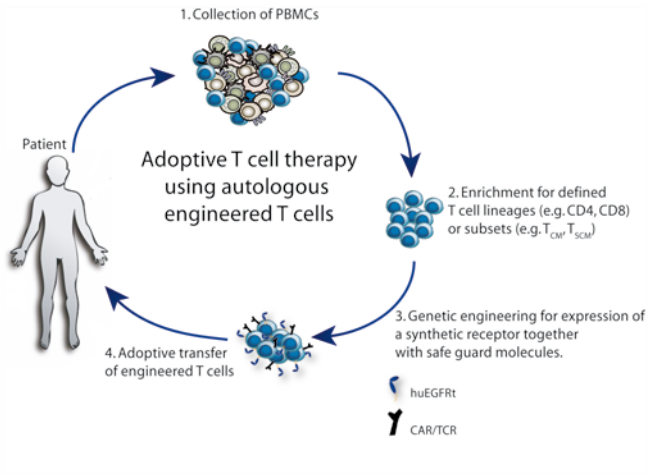


Stanley Riddell

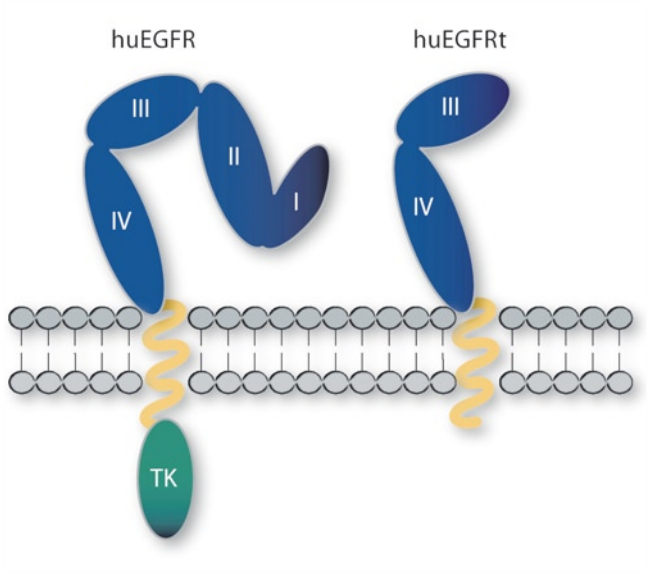
Our Focus Group Clinical Cell Processing and Purification aims at the development of unique, user-friendly, integrated cell-processing platforms to facilitate the preparation of effective and minimally manipulated therapeutic cells for highly individualized medical care. Recent studies performed by Focus Group members have elucidated fundamental properties of T cells that provide superior functionality and persistence. Furthermore, the group implemented and tested a novel safety switch that serves dual functions: in cell selection and elimination. In collaboration with Stanley Riddell, first in-human clinical trials of novel cell therapies using Focus Group innovations have been started in Seattle to evaluate safety and efficacy. With the merger of our industrial partners STAGE Cell Therapeutics and Juno Therapeutics and in collaboration with TUMCells, these novel clinical applications should soon also be made available in Munich, Germany, and Europe.

Research highlight: Development of a safeguard for adoptive immunotherapy using genetically engineered T cells

Over the past years attempts to utilize a patient's adaptive immune system to combat chronic infections and certain types of cancer have gained tremendous attention. One approach to immunotherapy is called adoptive cell transfer (ACT), which can for example be achieved by genetic modification ("engineering") of patient-derived T lymphocytes to selectively recognize and attack defined target cells. Within our TUM-IAS Focus Group, we have explored methods to rapidly select defined T cell subsets for clinical applications. Thereby, so-called central memory T cells (TCMs) were identified to be of special relevance for ACT, as they can engraft, expand, and persist long-term, even at very low numbers of transferred T cells. TCMs can be genetically engineered to express novel antigen-targeting receptors, such as natural T cell receptors (TCRs) or chimeric antigen receptors (CARs) without affecting their *in vivo* behavior. The modular structure of CARs allows the combination of antibody-like specificities with the signaling characteristics of a TCR. First clinical trials using engineered T cells expressing CARs recognizing an antigen on B cell leukemia (anti-CD19-CARs) have provided outstanding clinical results, including cases of complete remission of end-stage, blood-borne malignancies. However, key issues still need to be addressed to improve the quality and safety of gene-modified T cells for therapy. For example, safeguard mechanisms have to be developed that allow selective elimination of transferred cells in the event of side-effects. Such a safeguard has to be stably co-expressed with the recombinant receptor and should be non-immunogenic to allow long-term survival of transferred cells. Our strategy was to co-express a truncated Epidermal Growth Factor Receptor (EGFRt) that is functionally inert. For *in vivo* depletion, the EGFRt marker can be specifically targeted by the clinically approved αEGFR mAb (Cetuximab), which mediates antibody-dependent cellular cytotoxicity (ADCC). Our *in vitro* and *in vivo* studies in pre-clinical mouse models demonstrate proof-of-concept that this approach makes it possible to selectively eliminate mouse antiCD19-CAR engineered T cells by Cetuximab treatment, thereby abrogating CD19-CAR T cell-mediated long-term toxicities like B cell aplasia. Since EGFRt can be incorporated into many clinical applications to regulate the survival of gene-engineered cells, this approach represents a promising concept to improve the safety of cell-based therapies.



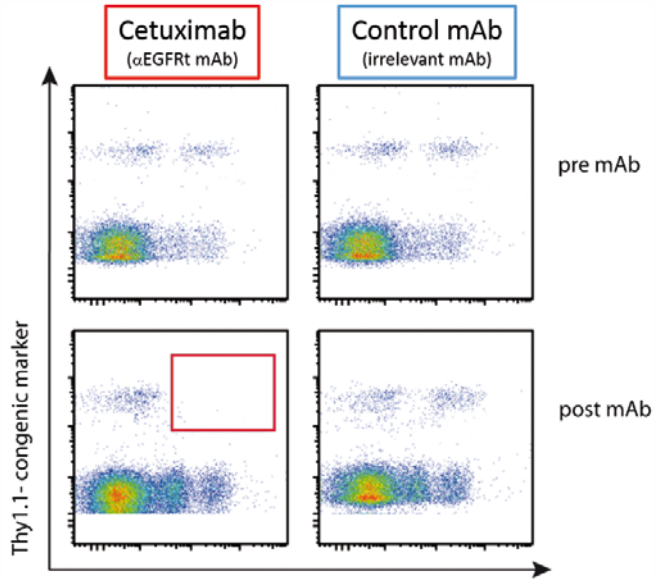
1 | Workflow of adoptive cell therapy using engineered autologous T cells. After isolation of patient-derived peripheral blood leukocytes (PBMCs, 1) , defined T cell lineages or subsets (like central memory T cells (T_{CM}) or memory T stem cells (T_{SCM}) might be further selected (2) from the cell mixture before subsequent genetic engineering (3). Engineered T cells express chimeric antigen receptors (CARs) or T cell receptors (TCRs) together with safeguard molecules like truncated human epidermal growth factor receptor (huEGFRt). Finally, engineered T cells are transferred back into the patient (4).



2 | Schematic of the design of an immunologically inert safeguard molecule (huEGFRt). To the left, structural components (including extracellular domains (I–IV) and intracellular tyrosine kinase domain (TK) of normal human Epidermal Growth Factor Receptor (huEGFR) are illustrated. To the right, a functionally inert truncated form of the EGFR (huEGFRt) is shown that lacks domain I and II and most of the cytoplasmic region of the full-length EGFR. This molecule can still be recognized by Cetuximab, a EGFR-specific antibody which is already in clinical use.

With the first spectacular clinical results, clinical cell processing combined with genetic cell engineering is becoming a rapidly emerging field in biomedical research. This has also been recognized by pharmaceutical industry, a partner that will be essential in bringing cell-based therapies into first clinical trials. Juno Therapeutics GmbH (Munich) is supporting our Focus Group by financing two doctoral candidate positions.

This work was conducted in cooperation with doctoral candidates Simon Fräßle and Manuel Effenberger.



3 | *In vivo* depletion of engineered (CD19 CAR and EGFRt expressing) by treatment with depleting EGFR-specific antibodies (Cetuximab). Mice received adoptively transferred engineered EGFR-positive cells, and were subsequently treated with either Cetuximab (left panel) or control antibody (right panel). Cetuximab depleted the engineered T cells completely from the blood (indicated by the loss of cell within the area indicated by the red box).

Selected Publications

[1] D. Sommermeyer, M. Hudecek, P. L. Kosasih, T. Gogishvili, D. G. Maloney, C. J. Turtle, and S. R. Riddell, “Chimeric antigen receptor-modified T cells derived from defined CD8(+) and CD4(+) subsets confer superior antitumor reactivity *in vivo*,” (eng), Leukemia, vol. 30, no. 2, pp. 492–500, 2016, accepted in 2015.

[2] M. Flossdorf, J. Rössler, V. R. Buchholz, D. H. Busch, and T. Höfer, “CD8(+) T cell diversification by asymmetric cell division,” Nat. Immunol., vol. 16, no. 9, pp. 891–893, 2015.

Publications by this Focus Group can also be found on page 164.

Focus Group **Human-Machine Collaborative Systems**

Prof. Gregory D. Hager (Johns Hopkins University) | Hans Fischer Senior Fellow
Christian Rupprecht | Doctoral Candidate
Prof. Nassir Navab, Computer-Aided Medical Procedures & Augmented Reality, TUM

Scientific Reports

Gregory D. Hager

Our world will be transformed by the growth of smart devices that connect people with the physical world through sensing and computation. The “internet of things” foresees a world in which nearly any item we touch is connected through the cloud. Advanced manufacturing anticipates a day when humans and robots work in collaboration and leverage each other’s strengths. Transportation foresees a day when cars are highly automated and communicate with one another as we drive. The mediation of human activity through devices means that it is possible to gather data and develop human activity models with a scale and complexity that was heretofore not possible. For example, there are now nearly 500,000 robotic surgeries performed per year with the da Vinci surgical robot.

The Focus Group Human-Machine Collaborative Systems is interested in developing methods to model human task performance and in using those models to teach computation systems to achieve similar performance. In the case of robotic surgery, for example, our modeling activities have the goal of creating ways to answer very fundamental questions such as: “What are the basic components of surgery?” “How can we model and automatically recognize those components?” and “How can we assess the quality or skill of execution?” In manufacturing or home settings, we include also “How can we quickly teach a robot to collaborate on a new task, or a new instantiation of a previously learned task?”

In the first year of our activities with the TUM-IAS, we have focused on developing methods that are able to extract models of task performance from video and movement data in a variety of domains, and on developing methods to create dialoguess to infer the intent of the user.

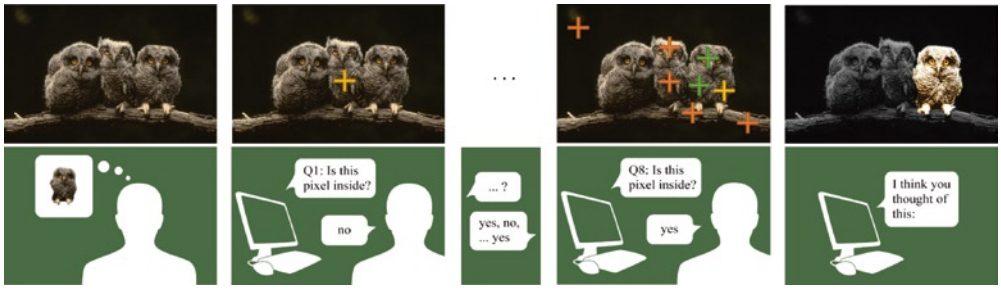
One line of research has been focused on developing general methods that are able to detect component activities from a continuous video and/or movement stream. In [3], we demonstrate methods that are able to detect and cluster similar activity components, while in [5], we demonstrate methods to learn models for component activities and to recognize those activities in new instances of similar task performances. Methods that are the most effective to date at recognizing objects to be used in task instances are described in [4].

In [2] the focus was directed toward interaction. For many tasks it is important to understand the body pose of the user from simple digital photos as depicted in figure 1.

1 | Results of our human pose estimation in single, monocular images. The task is to infer the human’s body pose just from the picture.

In this work we were not only able to improve the state of the art in human pose estimation but could also contribute a novel, theoretical insight to “deep learning,” a machine learning method that has become popular in the last three years.

In [1] we explored how to use interactive dialogue to perform image segmentation. As detailed in figure 2, we try to infer the segmentation the user has in mind by just asking simple yes/no questions.



2 | The user thinks about a segmentation in the given image, and the algorithm tries to guess it within 20 questions by just asking yes/no questions.

We can show that even with only 20 binary answers the algorithm can guess what the human was thinking about accurately in most cases.

In summary, we have achieved first results in understanding the key components of human-machine collaboration: automated development and recognition of task models, the use of goal-directed interactions between humans and machines to accomplish complex tasks, and fundamental results related to task-relevant perception.

Selected Publications

[1] C. Rupprecht, L. Peter, and N. Navab, “Image segmentation in twenty questions,” in Proceedings of the IEEE Conference on Computer Vision and Pattern Recognition (CVPR), Boston, USA, 2015, pp. 3314–3322.

[2] V. Belagiannis, C. Rupprecht, G. Carneiro, and N. Navab, “Robust optimization for deep regression,” in Proceedings of the International Conference on Computer Vision (ICCV), Santiago, Chile, 2015.

[3] S. Krishnan, A. Garg, S. Patil, C. Lea, G. Hager, P. Abbeel, and K. Goldberg, “Transition state clustering: Unsupervised surgical trajectory segmentation for robot learning,” in 2015 International Symposium of Robotics Research (ISRR), Sestri Levante, Italy.

[4] C. Li, J. Bohren, E. Carlson, and G. Hager, “Hierarchical semantic parsing for object pose estimation in densely cluttered scenes,” in 2016 IEEE International Conference on Robotics and Automation (ICRA), Stockholm, Sweden, accepted in 2015.

[5] C. Lea, G. Hager, and R. Vidal, “Learning convolutional action primitives from multimodal time-series data,” in 2016 IEEE International Conference on Robotics and Automation (ICRA), Stockholm, Sweden, accepted in 2015.

Publications by this Focus Group can also be found on page 165.

Focus Group **Image-based Biomedical Modeling**

Prof. Bjoern Menze (TUM) | Rudolf Mößbauer Tenure Track Professor
Dr. Vasileios Zografos | Postdoctoral Researcher
Esther Alberts, Jana Lipkova, Markus Rempfler | Doctoral Candidates
Image-based Biomedical Modeling, TUM

Bjoern Menze

Image-based biomedical modeling

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

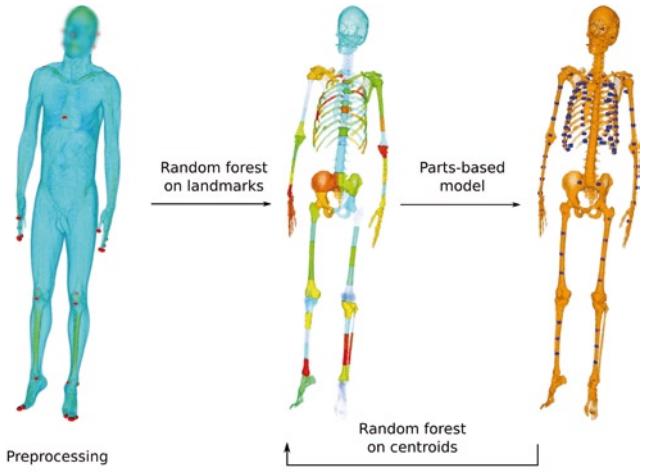
Clinical neuroimage analysis

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, as well as new computational techniques for extracting vascular networks from angiographic images (figure 1) [1]. The main sources of information are multimodal and multiparametric clinical image data featuring magnetic resonance, position-emission-tomography, and computer tomography scans. To quantify patterns visible in images from brain tumor or stroke patients, we developed a new algorithm that automatically segments lesions using machine learning techniques [2].

Disease progression models

The second direction deals with the task of optimal oncological staging. It includes the anatomical annotation of images with a large field of view, such as abdominal scans or whole body images, the detection of lesion across modalities and in repeated scans, and the analysis of individual lesions using pathophysiological models. Emphasis is put on clinical applicability, and algorithms are supposed to scale well to large data sets enabling the development of population-wide disease progression models. As a first step, we developed algorithms that automatically parse whole body CT images of bone tumor patients in order to segment and annotate structures and substructures of the skeleton (figure 2) [3] and of different organs visible in CT images [4].

1 | **Segmenting vascular structures of the brain.** We developed an algorithm that automatically extracts the three-dimensional vascular network in angiographic images of the brain (above). The algorithm employs machine learning techniques and makes use of physiological prior knowledge



2 | **Automatic annotation of the skeleton.** Shown is the algorithmic workflow for the annotation of skeletal substructures. The CT image is first preprocessed, and landmarks are generated by Hough regression (left). A first labeling (middle) is obtained using a random forest classifier. Centroids of each segment (right) are assigned anatomical labels by the parts-based model. Centroids serve as new landmarks for another random forest classifier. The last two steps can be iterated, and output is a dense annotation of the skeleton that can be used to describe the localization of the bone lesions observed in the patients.

Selected Publications

[1] M. Rempfler, M. Schneider, G. D. Ielacqua, X. Xiao, S. R. Stock, J. Klohs, G. Székely, B. Andres, and B. H. Menze, “Reconstructing cerebrovascular networks under local physiological constraints by integer programming,” Med. Image Anal., vol. 25, no. 1, pp. 86–94, 2015.

[2] B. H. Menze, K. van Leemput, D. Lashkari, T. Riklin-Raviv, E. Geremia, E. Alberts, P. Gruber, S. Wegener, M.-A. Weber, G. Szekely, N. Ayache, and P. Golland, “A generative probabilistic model and discriminative extensions for brain lesion segmentation – with application to tumor and stroke,” IEEE T. Med. Imaging, accepted in 2015.

[3] M. Bieth, R. Donner, G. Langs, M. Schwaiger, and B. H. Menze, “Anatomical triangulation: from sparse landmarks to dense annotation of the skeleton in CT images,” in Proc. BMVC 2015, accepted in 2015.

[4] V. Zografos, A. Valentinitsch, M. Rempfler, F. Tombari, and B. H. Menze, “Hierarchical multi-organ segmentation without registration in 3D abdominal CT images,” in MICCAI Medical Computer Vision Workshop, Munich, Germany, 2015.

Publications by this Focus Group can also be found on page 165.

Focus Group **Intra-Operative Therapy**

Prof. Michael Friebe (IDTM GmbH & Univ. of Magdeburg) | Rudolf Diesel Industry Fellow
Philipp Matthies | Doctoral Candidate
Prof. Nassir Navab, Computer Aided Medical Procedures & Augmented Reality, TUM

Michael Friebe

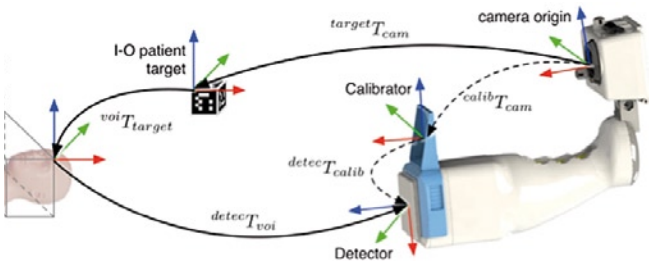
Oncology therapies benefit greatly from diagnostic imaging that is available for the actual procedure monitoring. However the images are mainly acquired prior to a surgery, and live updates are done with systems different from the ones used for the high-resolution and high-contrast images.

Intraoperative and minimally invasive procedures require another imaging functionality, which registers and follows instruments to the images to allow guidance of the tool exclusively with the real-time imaging or with pre-operative imaging data that is used at the surgical table (“tracking”).

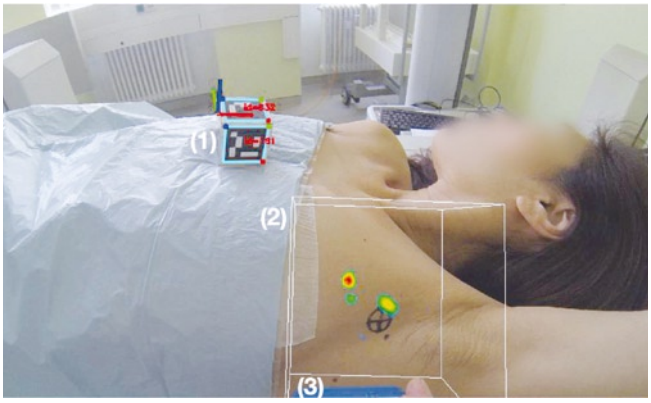
Our goal in the last three years was to develop new intraoperative therapy devices that allow minimally invasive tumor removal under imaging guidance and a subsequent tumor bed radiation to ensure that all cancer cells are killed while at the same time reducing the total tissue volume that is removed. Needed are diagnostic systems, ideally combining molecular information with high-resolution anatomical imaging data (e.g., SPECT with ultrasound or X-ray); tracking systems that follow and register the tools and imaging systems to each other; and finally the actual therapy devices, which also need to be tracked and image-registered. We came up with several new approaches in 2015.

Tracking systems are used in many medical scenarios for the localization of devices or the patient, for example in intra-operative nuclear imaging. Commonly used outside-in tracking systems often suffer from line of sight issues (e.g. human body is blocking the path between object and camera). To overcome that problem we developed a combination of an inside-out tracking technique with a hand-held mini gamma camera and an image reconstruction pipeline to provide 3D SPECT-like (single photon emission computed tomography) images in a compact flexible setup suitable for interventions. The system setup involves the marker cube and the mobile gamma detector with attached video camera. Black arrows mark the coordinate system transformations between the video camera, calibrator, gamma detector, volume of interest, and patient target ([1] and figure 1). This approach eases the interventional procedure in terms of hardware used and line of sight requirements and provides the desired molecular/anatomical imaging in combination of handheld SPECT with Ultrasound imaging [2]. We believe that this new tracking approach can be used for many other applications that require tool to image or image to image registration.

On the therapy tool side we continued our work using small X-ray tubes based on carbo-nanotube technology for intraoperative radiation delivery and subsequent tumor bed radiation. We also developed a new catheter that employs two ballons that are expanded using the cavitary access path to the site where the tumor was removed. Rather than using a gamma emitting X-ray tube a beta emitting liquid based on 188 Rhenium was filled into the outer of two ballons, while the inner one filled with water or air presses the outer balloon to the tumor bed tissue ([3] and figure 2). This technique can be combined with a newly developed tumor removal catheter for solid tumors in the size up to 2cm diameter or even for larger volumes like the prostate [4].

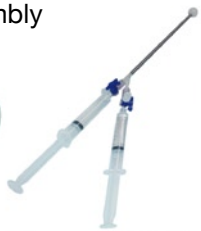


1 | Visualization of freehand SPECT reconstruction in augmented reality view. The patient target (1) is tracked and the volume of interest is rendered (2) in front of the gamma camera (3).

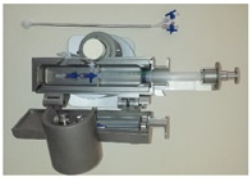


Prototype assembly

Stainless steel tube with inner plastic tube, inner balloon, outer balloon



Prototype of the new brachytherapy balloon catheter

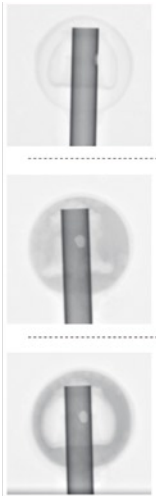


ITM Rhenium applicator

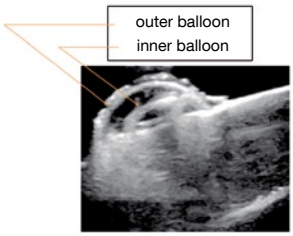
Possible handheld applicator

Results

X-Ray Images of the filling of the brachytherapy balloon catheter



This first prototype and setup shows that an approach using Rhenium-188 for intracavitary or interstitial radiation therapy delivery that could be feasible (mainly for small tumors) for delivering a radiation boost of around 20 Gy in 3mm from the balloon surface in an acceptable time (around 30 minutes).



Ultrasound catheter image

2 | Double-balloon catheter that accesses the intracavitary path of the minimally invasive tumor removal. The inner balloon is filled with water or air and presses against the tumor bed. The outer balloon is subsequently filled with a beta(-) radiation liquid (188 Rhenium) and will deliver a tumor bed dose of around 30Gy in 20 minutes. The catheter can be tracked and imaged via ultrasound and X-ray.

The Focus Group activities will continue in close collaboration between the chair of Nassir Navab at TUM-CAMP and the chair of catheter technologies and image guided surgeries of Michael Friebe at the Otto-von-Guericke-University in Magdeburg, Germany. Joint lectures for Master students of both universities have been initiated two semesters ago and will continue even though 2015 was the final year of the Focus Group Intra-Operative Therapy. Many thanks to TUM-IAS for allowing this exciting form of collaborative research.

Selected Publications:

[1] P. Matthies, B. Frisch, J. Vogel, T. Lasser, M. Friebe, and N. Navab, “Inside-out tracking for flexible hand-held nuclear tomographic imaging,” in 2015 IEEE Nuclear Science Symposium and Medical Imaging Conference, San Diego, USA.

[2] M. Horn, S. Paepke, E. Klein, T. Wendler, and M. Friebe, “Hybrid interventional imaging for non-surgical sentinel lymph node staging,” Int. J. Comput. Assist. Radiol. Surg., vol. 10, no. 1, p. 36, 2015.

[3] M. Friebe and A. Boese, “Image guided double-balloon brachytherapy concept,” Int. J. Comput. Assist. Radiol. Surg., vol. 10, no. 1, pp. 183–184, 2015.

[4] A. van Oepen, A. Boese, and M. Friebe, “Minimally invasive tumor extraction combined with subsequent intraoperative radiation,” in Image-Guided Interventions Conference (IGIC), Mannheim, Germany, 2015.

Publications by this Focus Group can also be found on page 166.

Focus Group **Microfluidic Design Automation**

Prof. Tsung-Yi Ho (National Tsing Hua University) | Hans Fischer Fellow
Chunfeng Liu | Doctoral Candidate
Prof. Ulf Schlichtmann, Electronic Design Automation, TUM

Scientific Reports

Tsung-Yi Ho

The coming of age of microfluidics: Design automation solutions enabling biochemistry on a chip

Miniaturized and low-cost microfluidic biochips are revolutionizing a wide range of applications, including air quality studies, point-of-care clinical diagnostics, drug discovery, and DNA sequencing. Yole Development recently predicted a 28% compound annual growth rate for the microfluidic biochip ("lab-on-chip") market during 2013–2018, and the market size for lab-on-chip alone (not including microarrays, biosensors, and microreactors) is projected to grow swiftly from $1.4B in 2012 to $5.7B by 2018.

However, continued growth (and larger revenues resulting from technology adoption by pharmaceutical and health care companies) depends on advances in chip integration and design-automation tools. In particular, design-automation tools are needed to ensure that biochips are as versatile as the macro-labs that they are intended to replace. Furthermore, as more bioassays are executed concurrently on a biochip, system integration and design complexity are expected to increase dramatically. There is now a need to deliver the same level of computer-aided design (CAD) support to the biochip designer that the semiconductor industry today takes for granted. These CAD tools will allow designers and chip users to harness the new technology that is rapidly emerging for integrated biofluidics. This Focus Group will develop CAD tools for hardware/software co-design and cyberphysical system integration of microfluidic biochips. In addition, it will offer researchers at TUM a bridge between the electronic chip/system design industries, on the one hand, and the biomedical and pharmaceutical industries on the other.

In 2015, Tsung-Yi Ho won the IEEE Transactions on Computer-Aided Design Donald O. Pederson Best Paper Award for the first-ever approach for automated testing of flow-based microfluidic biochips [1]. In the past, there was no systematic testing solution, and only visual inspection under microscopes had been adopted. This work has substantially reduced the time and cost of testing and, more important, the fault coverage is significantly improved.

The group has developed a concept to cache fluid samples in transportation channels and synthesize storage cells, addressing fluid conflict for flow-based microfluidic biochips. By minimizing channel conflicts and recognizing maximum independent sets, storage requirements are handled by channels, i.e., distributed and dedicated storage cells. This synthesis algorithm can reduce the assay's overall execution time and the chip area at the same time. To promote research in microfluidic design automation, the group also co-organized and contributed to a Dagstuhl seminar at Schloss Dagstuhl - Leibniz-Zentrum für Informatik during August 23–26 in 2015. The participants, shown in the group photo, came from eight countries.

1 | Dagstuhl Seminar: Design of Microfluidic Biochips - Connecting Algorithms and Foundations of Chip Design to Biochemistry and the Life Sciences

Reference

[1] K. Hu, F. Yu, T.-Y. Ho, and K. Chakrabarty, “Testing of flow-based microfluidic biochips: Fault modeling, test generation, and experimental demonstration,” IEEE Transactions on Computer-Aided Design of Integrated Circuits and Systems (IEEE TCAD), vol. 33, no. 10, pp. 1463–1475, 2014.

Selected Publications

[2] T.-M. Tseng, B. Li, U. Schlichtmann, and T.-Y. Ho, “Storage and caching: Synthesis of flow-based microfluidic biochips,” IEEE Des. Test, vol. 32, no. 6, pp. 69–75, 2015.

[3] T.-M. Tseng, B. Li, T.-Y. Ho, and U. Schlichtmann, “Reliability-aware synthesis for flow-based microfluidic biochips by dynamic-device mapping,” in 2015 ACM/IEEE Design Automation Conference (DAC), San Francisco, USA, pp. 1–6.

Publications by this Focus Group can also be found on page 166.

Focus Group **Neuroimaging**

Prof. Josef P. Rauschecker (Georgetown University) | Hans Fischer Senior Fellow
Lukas Utz | Doctoral Candidate
Prof. Bernhard Hemmer, Neurological Clinic and Policlinic, TUM

Scientific Reports

Josef P. Rauschecker

Frontostriatal gating of tinnitus and chronic pain

One of the year's highlights was the International Workshop on Frontostriatal Gating of Tinnitus and Chronic Pain, which was held September 7–8 at the Klinikum rechts der Isar (see page 31–32).

A publication reviewing some of the fundamental ideas behind our concepts appeared shortly thereafter in October 2015 [7].

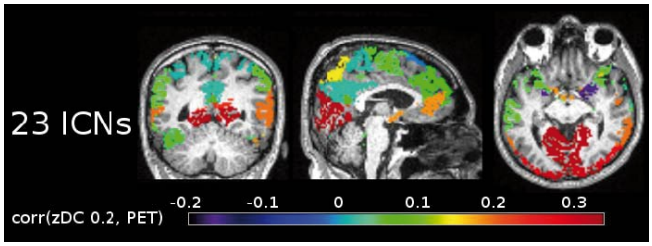
Energetic Costs and Directionality of Global Functional Connectivity in the Human Brain

The human brain, with its $>10^{10}$ neurons and $>10^{14}$ synapses, is known to consume a high amount of energy. The demand for metabolized glucose in the human brain is high in proportion to its size: It accounts for about 25% of total body glucose consumption at rest [5]. However, only a small amount of energy is utilized for basic metabolism, leaving a significant fraction for the implementation of neuronal communication [2].

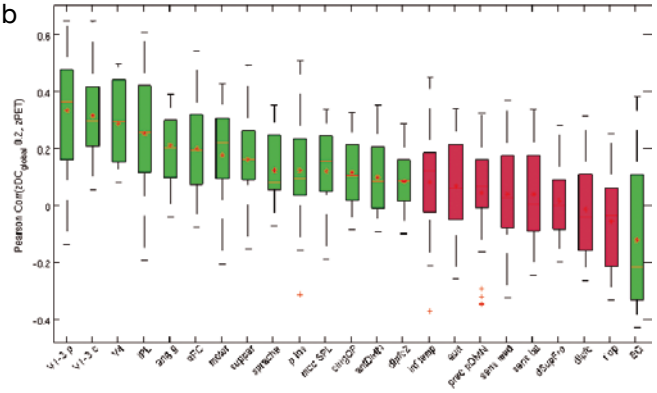
We investigated whether a linear relationship between local energy consumption and global connectivity exists in the brain. A linear relationship would imply that each connection, maybe depending on its distance or location, would cost a constant amount of energy. In contrast, a logarithmic or exponential relationship would indicate an increase or decrease in efficiency, respectively, for highly connected regions in the human brain. Therefore, we used data of 22 healthy human subjects who were simultaneously scanned with [18F]fluorodeoxyglucose-PET (FDG) and fMRI in the new integrated PET/MRI-scanner (positron emission tomography/magnetic resonance imaging) at the Klinikum rechts der Isar. The simultaneous acquisition allows a reliable correlation of the glucose consumption (local energy usage) in the neurons through PET and measures of global functional connectivity – gFC, i.e., degree centrality (DC - REST V1.8) and the eigenvector centrality (EC - [4]) – between different brain regions using fMRI. The global measures of DC and EC capture the entire functional connectome, as they calculate the connectivity between all pairs of voxels in the human brain.

First, we performed these analyses across the entire cortex and found a significant correlation between DC/FDG and EC/FDG of around r=0.22 across all subjects. Furthermore, we limited the analysis of spatial correlation to previously defined large-scale networks (through independent component analysis), which revealed a clear distinction between networks with strong FDG/gFC relationship (figure 1b, green bars) and those with no significant relationship. Most significant relationships, independent of network size, exist in occipito-parietal cortices and along midline structures rather than in frontal cortices (figure 1a). The same picture holds true when restricting the analysis to even further specialized subunits or functional regions of interest (ROIs). In a third approach, we used the parcellation atlas by Shen, Tokoglu, Papademetris, and Constable [1] and analyzed all 93 regions independently. We found the strongest correlation between energy consumption and

a



b



1 | Spatial correlation of mean DC- and FDG-values in a single subject (a) and across subjects (b). Individual FDG-gFC correlations across all 22 subjects have been masked by independent component networks (ICNs) separately, and their spatial correlation is reported, revealing a decreasing correlation from parietal (especially visual) to frontal regions ($p < 0.05$ shown in green, others red).

global connectivity in ROIs of the occipito-parietal cortex and along the midline, again independent of ROI size.

These results highlight the complexity and heterogeneity of the signaling-dependent glucose utilization in the human brain and show that linear correlation is highest in early sensory and motor regions as well as in regions associated with the regulation of emotions.

Metabolic connectivity mapping reveals effective connectivity in the resting human brain

We used the multimodal data from Section 2 to introduce a new method of metabolic connectivity mapping (MCM) to infer the effective connectivity, i.e., the directionality of functional connectivity [6]. Assuming the biological model that around 80% of glucose is consumed post-synaptically, one can infer a measure of directionality by correlating the reciprocal connectivity between pairs of brain regions with their glucose consumption. This means that across the group, if the spatial correlation of functional connectivity from a region Y to X with the FDG-uptake in region X is higher than from X to Y, the direction of signaling would be Y to X. We applied MCM to data sets including both healthy subjects and patients diagnosed with mild cognitive impairment (MCI) and Alzheimer's disease (AD). In healthy subjects, we identified bidirectional communication between early and higher visual regions but top-down signaling from parietal regions. We performed a detailed analysis of differences of effective connectivity between healthy subjects and AD/MCI patients within the default mode network (DMN), a network that is often found to be active in a state of non-focusing or rest. This revealed a significant loss of long-range connections from medial prefrontal cortex to both medial and lateral parietal cortex, together with a loss of short-range crosstalk connections between the lateral parietal cortices.

All these results are either already published or in preparation to be published (not listed). Furthermore, the novel approach of MCM is near completion as a Matlab Toolbox and will serve as a beneficial extension to the research community.

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[3] M. P. van den Heuvel, and O. Sporns, "Network hubs in the human brain," Trends Cogn. Sci., vol. 17, no. 12, pp. 683–696, 2013.

[4] A. M. Wink, J. C. de Munck, Y. D. van der Werf, O. A. van den Heuvel, and F. Barkhof, "Fast eigenvector centrality mapping of voxel-wise connectivity in functional magnetic resonance imaging: implementation, validation, and interpretation," Brain Connect., vol. 2, no. 5, pp. 265–274, 2012.

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Selected Publications

[6] V. Riedl, L. Utz, G. Castrillón, T. Grimmer, J. P. Rauschecker, M. Ploner, K. J. Friston, A. Drzezga, and C. Sorg, "Metabolic connectivity mapping reveals effective connectivity in the resting human brain," Proc. Natl. Acad. Sci. USA, vol. 113, no. 2, pp. 428–433, 2016, accepted in 2015.

[7] J. P. Rauschecker, E. S. May, A. Maudoux, and M. Ploner, "Frontostriatal gating of tinnitus and chronic pain," Trends Cogn. Sci., vol. 19, no. 10, pp. 567–578, 2015.

Publications by this Focus Group can also be found on page 166.

Focus Group **Optimal Control and Medical Imaging**

Prof. Dominique Sugny (University of Bourgogne) | Hans Fischer Fellow
Dr. Thomas Schulte-Herbrüggen | Postdoctoral Researcher
Quentin Ansel, Bálint Koczor | Doctoral Candidates
Prof. Steffen J. Glaser, Organic Chemistry, TUM

Dominique Sugny

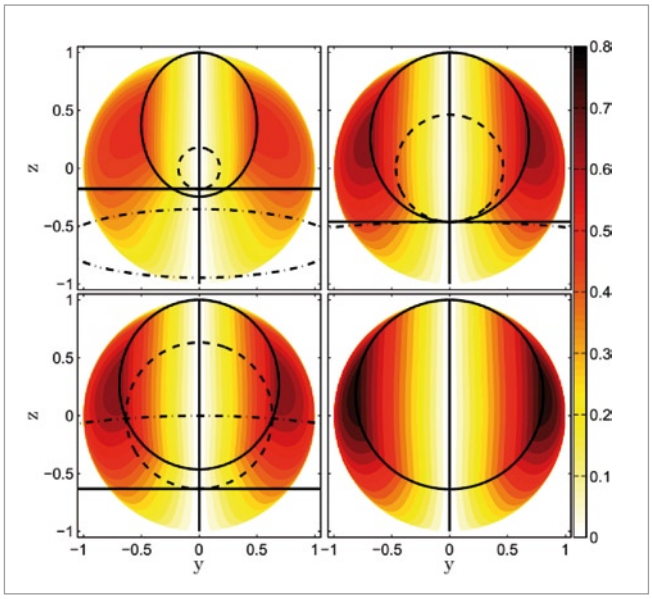
The goal of our Focus Group is to develop and apply innovative mathematical tools coming from optimal control theory (OCT) to improve theoretical and experimental techniques in magnetic resonance imaging (MRI) and nuclear magnetic resonance (NMR) spectroscopy. This approach allows us to explore and to experimentally reach the physical limits of the corresponding spin dynamics in the presence of typical experimental imperfections and limitations. We anticipate that the proposed techniques will find practical applications in medical imaging in the near future to aid in medical diagnosis. D. Sugny spent a sabbatical year at TUM, beginning on August 1, 2015. This long stay has given the Focus Group the opportunity to start ambitious research projects extending from optimization of the signal-to-noise ratio (SNR) per unit time in spin systems to the implementation of OCT in electron paramagnetic resonance (EPR). These different projects are briefly summarized below. Other promising preliminary results (not discussed in this report) have also been obtained in different directions, from the geometric design of robust control fields to the experimental implementation of new pulse sequences maximizing the contrast in MRI. Finally, D. Sugny and S. J. Glaser contributed to a strategic report on the future of quantum optimal control within a European consortium gathering ten experts in this domain [1].

Optimization of the signal-to-noise ratio per unit time of spin systems

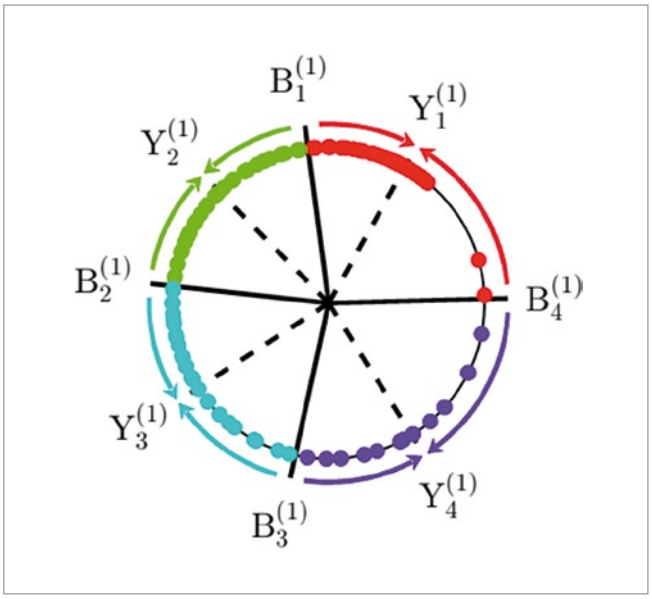
Using techniques of geometric optimal control theory, we have shown how to maximize the SNR of a spin. This problem finds direct applications in MRI, where the SNR is one of the crucial features of fast imaging techniques. In particular, for the idealized case of unbounded pulse amplitudes, our general analysis shows the optimality of the Ernst angle solution, which is well established and widely used in spectroscopic and medical imaging applications. In addition to its emphasis on spin dynamics, our approach paves the way to systematic use of optimal control techniques in other domains beyond NMR or EPR, where it is also desirable to maximize the SNR for a given measurement time. Figure 1 illustrates the geometric techniques used to maximize the SNR associated with a particular steady state. We are currently investigating the effect of bounded fields and magnetic field inhomogeneities on the optimal control field.

Discrete-valued-pulse optimal control algorithms

The design of control sequences accounting for experimental constraints is a central task in spin dynamics. Optimal control theory provides highly efficient and versatile tools to address the different issues raised by the experimental setups. To date, most studies have assumed that the amplitude and phase of the control field can vary continuously. However, in many cases the available hardware only allows one to switch between a discrete set of pulse phases. Hence the control is quantized and restricted to a fixed finite number of values, which can nevertheless be optimized. We have recently shown in [2] how to extend the optimal control techniques to this singular experimental situation. Figure 2 gives a schematic representation of the Lloyd algorithm used to account for these experimental constraints. Experiments are currently in progress with the group of G. Smith (University of Saint-Andrews, UK).



1 | Figure of merit surface Q associated with the steady-state syntheses. The solid, dashed, and dot-dashed lines represent boundaries between the different regions of the Bloch ball where the control law is not the same.



2 | Schematic representation of one step of Lloyd's algorithm in the case of 4 discrete values of the field.

Strategic report on current status, visions, and goals for quantum control

D. Sugny and S. J. Glaser are members of a European consortium, QUAINT (2012–2015 FP7 program), which unites expertise in OCT and applications to quantum systems, both in existing and widely used areas such as spectroscopy and imaging and in emerging quantum technologies. One of the main achievements of this consortium has been the publication of a document [1] aimed at reviewing state-of-the-art quantum optimal control techniques. Key challenges are also addressed and put into perspective in order to highlight anticipated future developments of this field of research. More precisely, challenges to quantum control have been gathered by a broad poll of leading researchers. One hundred forty-four experts have provided feedback and specific input on the state of the art, as well as midterm and long-term goals. These have been summarized in [1], which can be viewed as a perspectives paper, providing a roadmap for the future development of quantum control.

In addition, this roadmap is designed as a living document, where additional aspects as well as new developments and ideas will be included each year.

This work was conducted in cooperation with doctoral candidate Michael Tesch.

Selected Publications

[1] S. J. Glaser, U. Boscain, T. Calarco, C. P. Koch, W. Köckenberger, R. Kosloff, I. Kuprov, B. Luy, S. Schirmer, T. Schulte-Herbrüggen, D. Sugny, and F. K. Wilhelm, "Training Schrödinger's cat: Quantum optimal control," Eur. Phys. J. D, vol. 69, no. 12, pp. 1–24, 2015.

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Publications by this Focus Group can also be found on page 167.

Focus Group **Phase-Contrast Computed Tomography**

Dr. Kaye S. Morgan (Monash University) | Hans Fischer Fellow
Dr. Thomas Koehler (Philips Research Laboratories) | Rudolf Diesel Industry Fellow
Prof. Franz Pfeiffer (TUM) | Carl von Linde Senior Fellow

Scientific Reports

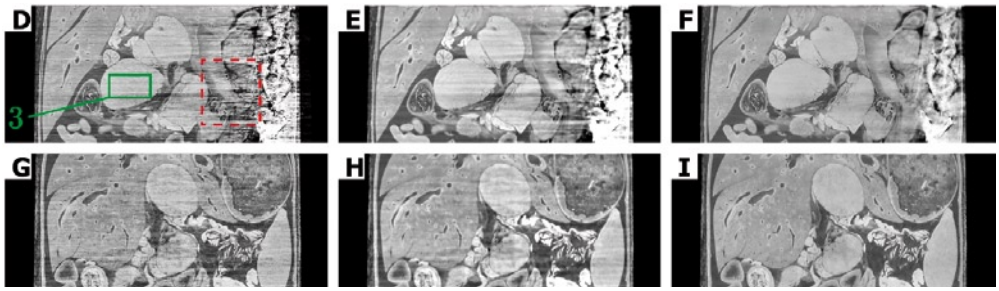
Kaye S. Morgan

Thomas Koehler

Franz Pfeiffer

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 to diffraction, refraction, phase-shift, and scattering. Several methods to exploit the latter mentioned wave-optical interactions of X-rays with matter have been investigated in recent years. Although some of them yield excellent results at highly brilliant synchrotron sources, none of them has so far found its way to routine medical CT applications, which require a large field of view of many centimeters, the efficient use of polychromatic and strongly diverging radiation, and a reasonably compact setup.

To make the advantages of phase- and/or dark-field contrast X-ray imaging available for routine X-ray medical diagnostics applications, we have started developing a grating-based approach to wave-optical X-ray imaging. One focus in 2015 was to develop new processing and reconstruction algorithms, which are able to handle special problems that will routinely show up in a clinical application. The first problem is the presence of bones, which creates severe streak artifacts in state-of-the-art reconstruction. Example images of a mouse abdomen reconstructed with state-of-the-art methods and a newly developed method are shown in figure 1. The second problem that has been addressed is the challenge of data acquisition and a corresponding processing scheme using a continuous rotation. Previous approaches to solve this problem suffered from a reduction of spatial resolution. Introducing a new, so-called intensity-based iterative reconstruction [4], we have been able to demonstrate that it is possible to reconstruct data acquired using a continuously rotating system without compromising image quality.



1 | Results of reconstructions from *ex vivo* mouse X-ray phase contrast CT measurements using a state-of-the-art analytical method (left), a state-of-the-art iterative method (middle), and a newly developed iterative method [3].

Regine Gradl | Doctoral Candidate
Prof. Franz Pfeiffer, Biomedical Physics, TUM,
Prof. Ernst Rummeny, Radiology, TUM

2 | A sharworkshop on "Respiratory x-ray phase-contrast and dark-field imaging for biomedical research" was held in December 2015, bringing together almost 50 physicists, mathematicians, engineers, physiologists, doctors, and neonatologists who are all working on projects that involve respiratory imaging.

In addition to the clinical applications, phase and/or dark-field contrast X-ray imaging can be used as a tool in biomedical research, revealing soft tissue structure and function. Much of the existing biomedical research using these imaging modalities has been at bright, highly coherent synchrotron X-ray sources. These facilities enable high speed imaging to capture, for example, the motion of the lungs breathing, the clearance of inhaled debris along the airway surface, and changes in the liquid lining of the airways in response to a treatment. However, the limited availability of the synchrotron makes longitudinal studies difficult.

Another project in this Focus Group is the translation of these types of biomedical research to the new Munich Compact Light Source (MuCLS), a laser-driven high-flux X-ray source that produces highly coherent radiation and is around 200 times smaller in size than a synchrotron. This is the first instrument of its kind in the world and was installed at TUM in 2015. We have captured the first phase contrast X-ray images using this facility and are currently planning high-speed imaging studies to capture respiratory function.

Additional members of this Focus Group are PD Dr. Peter B. Noël, and doctoral candidates Andreas Fehringer, Wolfgang Noichl and Maximilian von Teuffenbach (all Biomedical Physics, TUM).

Selected Publications

[1] B. Brendel, M. von Teuffenbach, P. B. Noël, F. Pfeiffer, and Th. Koehler, “Intensity based iterative reconstruction for differential phase contrast imaging with reconstruction parameter estimation,” in International Meeting on Fully Three-Dimensional Image Reconstruction in Radiology and Nuclear Medicine (Fully3D), Newport, USA, 2015.

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Publications by this Focus Group can also be found on page 167.

Focus Group **Regenerative Medicine**

Prof. Dietmar W. Hutmacher (QUT) | Hans Fischer Senior Fellow
Dr. Elizabeth Rosado Balmayor | Postdoctoral Researcher
Prof. Arndt F. Schilling, Clinic for Plastic Surgery and Hand Surgery, TUM

Scientific Reports

Dietmar W. Hutmacher

Innovation is synonymous with risk-taking, and research that creates revolutionary innovations is often disruptive and leads to new paradigms. We are confident that the research program of the Focus Group Regenerative Medicine will be disruptive, because it will change the paradigm for the bioprinting field by changing the question: from “what can we do with this fabrication method?” to “how can we change this fabrication process to achieve what we need?”

The innovation is rooted in developing, from an engineering point of view, a ground-breaking additive manufacturing technology platform that makes it possible to address, from a scientific point of view, the two new proposed paradigms “manufacture for design” and “certify-as-you-build.”

Mimicking the biological and functional organizational complexity of native tissues is now regarded as the next challenge in bioengineering and biotechnology, and across the wider life sciences community. To address this challenge, bioprinting has been employed to generate bioengineered 3-D structures – not to replicate one-to-one the complex nature of tissues, but to design biomimetic architectures capable of guiding tissue formation and maturation.

Bioprinted hydrogels typically have a lower stiffness than their target tissue, especially for application in tissues such as cartilage and breast tissue. A stiff and coherent hydrogel construct will be required to withstand challenging biomechanical environments in the human body. Pre-culturing cells in these constructs cannot significantly increase stiffness. Disregarding the influence of incorporated cells, improving the stiffness of the hydrogel itself could be achieved by increasing crosslink density. Unfortunately, this compromises *in vitro* formation of tissue through impaired diffusion through the hydrogel system. An innovative solution is to combine favorable biological and chemo-physical hydrogel properties with fiber reinforcement of hydrogels. In these approaches the crosslink density of the hydrogel could remain relatively low, allowing for *in vitro* tissue formation.

To this end, we propose developing a revolutionary additive manufacturing technology platform with multiple-tool biofabrication heads, combined with melt electrospinning and stereolithography, in which hydrogel constructs are reinforced via melt electrospinning co-deposited thermoplastic polymer fibers. This will allow hydrogels to be processed at low polymer concentrations while the thermoplastic polymer network secures the shape and strength of the overall construct. Moreover, it can be used to fabricate complex shaped tissue constructs. Critically, we can tailor the Young’s modulus of the target construct by adjusting the thermoplastic polymer scaffold.

1+2 | Additive biomanufactured breast scaffolds

Electrospinning produces a higher resolution of fibers compared to other 3-D printing methods, and results in a network that more closely approximates the structure of natural extracellular matrix. However, state-of-the-art solution electrospinning techniques are not able to control fiber deposition, and the small pore size of the resulting random 2-D meshes ultimately limits 3-D cell migration.

Recently the Hutmacher laboratory has developed melt electrospinning-writing techniques to overcome both of these limitations, resulting in fibers that can be deposited with high spatial resolution and orientation. Further, we were able to show that hydrogel deposition approaches will allow for the generation of enforced hydrogel constructs with high control over the intricate spatial organization and cell deposition. This novel strategy addresses scientific gaps discussed in the biomedical community.

In collaboration with PD Dr. Jan-Thorsten Schantz and postdoctoral researcher Dr. Mohit Chhaya.

Selected Publications

[1] M. P. Chhaya, P. S. Poh, E. R. Balmayor, M. van Griensven, J. T. Schantz, and D. W. Hutmacher, “Additive manufacturing in biomedical sciences and the need for definitions and norms,” Expert Rev. Med. Devices, vol. 12, no. 5, pp. 537–543, 2015.

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Publications by this Focus Group can also be found on page 168.

Focus Group **Biochemistry**

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

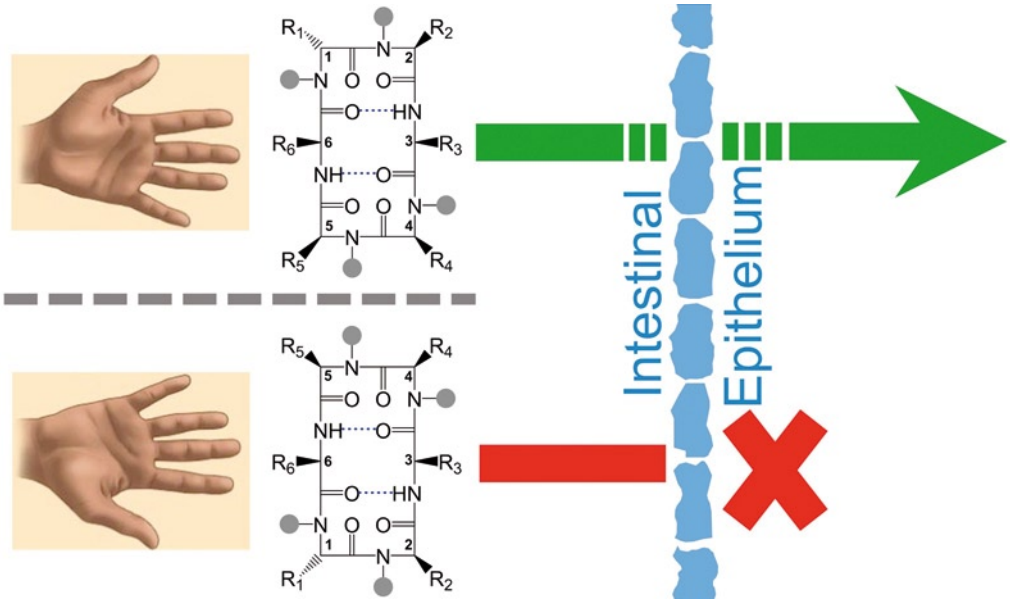
Scientific Reports

In 2015 we published 16 manuscripts with a total impact factor of 121.6. Two highlights are outlined briefly below.

Horst Kessler

Toward the design of orally available peptides

Peptides are among the most important compounds in life. One of their functions is in cellular communication (e.g., hormones) and as subunits in recognition of the surroundings of cells (e.g., as ligands for integrins – see previous reports of our group). Many peptides have interesting biological functions that would make them ideal drugs. However, peptides usually are unstable against enzymatic degradation. We and others have found that this disadvantage can be overcome by conformational control, such as by cyclization, by incorporation of unnatural D-amino acids, and by N-methylation of peptide bonds. Even with these modifications, the lack of oral availability remains a problem. To achieve this, we investigated small cyclic model peptides and discovered for some compounds unexpectedly high permeability through CaCo-2 cell layers, which is the common test model for oral availability. But this desired effect is present only in some distinct compounds and by far not in all cyclic peptides. It turned out that structural elements could be identified as prerequisite for permeability. The question is if these model peptides (which will later be used for biological tests) are entering the blood from the gut via passive transport or if they need a transporter. To answer this question we investigated cyclic N-methylated peptides with high CaCo-2 permeability and compared them to their mirror images (the enantiomers). We observed that both the inside-out transport and the outside-in transport are different not only within each compound, but also show a strong difference in permeability between enantiomers. This proves that there are chiral molecules involved in the transport mechanism, which is a clear proof of a receptor-mediated event (transporter).

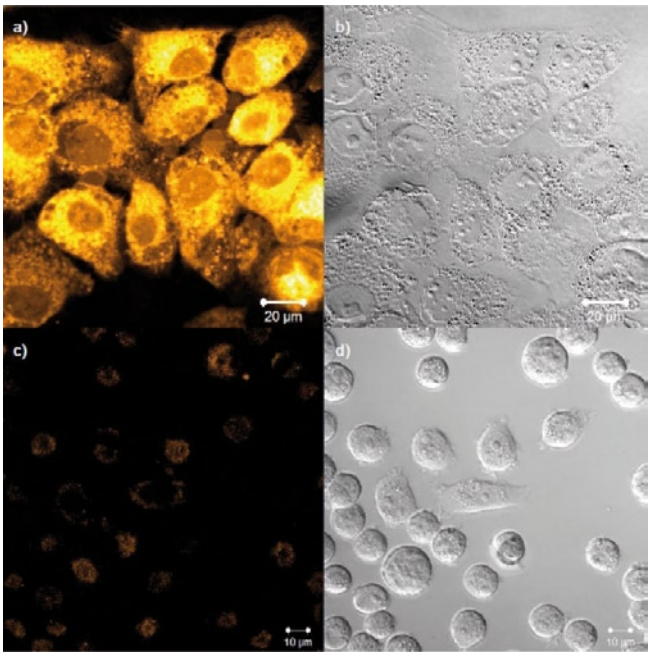


1 | Enantiomers exhibit different permeability (uptake for compounds from gut into the blood stream).

A new technique to develop subtype selective integrin ligands – key compounds for medical and biophysical applications

Integrins are cell surface receptors that enable the cell, among other things, to adhere to the extracellular matrix and to communicate with neighboring cells. A big subfamily among these integrins is the eight RGD-binding integrins; they recognize the tripeptide sequence Arg-Gly-Asp in their ligands. Although they share a common binding motif, they fulfill fundamentally different tasks in their biological environment. Subtype-selective compounds that can only bind to one distinct subtype are therefore a highly important tool for biophysical and medical investigations. We have been able to develop a general methodology that allows us to tune the binding properties of formerly unselective compounds to selective binders. This easy-to-apply method involves the modification of the guanidine group in the side chain of arginine. The proof-of-principle was demonstrated on the example of the αvβ3/α5β1-biselective integrin antagonist Cilengitide. The guanidine group was methylated on the terminal Nω- and the Nδ-position, leading to two fully selective compounds for the αvβ3 and α5β1-integrin subtype, respectively. The concept was then transferred to two αvβ6 / α5β1-biselective integrin ligands; we found that their subtype selectivity could also be enhanced. In another investigation, we were able to develop αvβ6-selective cyclic nonapeptides. αvβ6 plays a huge role in many cancer types as well as in the development of fibrosis. We used the already known helical binding motif RGDLXXL and developed compounds that interact with the receptor in the same way (mimics) but exhibit highly improved stability in blood serum, a key property for applications *in vivo*. Furthermore, the molecule possesses a group (lysine side chain) where further lables (e.g., a fluorescent label for making αvβ6-expressing cells visible *in vitro*) can be attached. Our ligand has big potential to be used in the diagnosis of αvβ6-expressing tumors by molecular imaging (PET, positron emission tomography) and is currently being investigated in this regard.

This work was conducted in cooperation with Doctoral Candidate Tobias Kapp as well as with postdoctoral researchers Dr. Udaya Kiran Marelli, Dr. Oleg V. Maltsev and Dr. Stefanie Neubauer.



2 | a) Fluorescence bioimaging with Cy5.5-labelled selective avb6-ligand of the human oral squamous cell carcinoma (OSCC) cell line HN with high level of αvβ6-integrin expression. b) Illustration of HN cells as shown in a) by transmitted light microscopy. c) Fluorescence bioimaging with Cy5.5-labelled ligand of the human ovarian cancer cell line OVMZ6, with low integrin αvβ6 and high integrin αvβ3 expression. d) Illustration of OVMZ6 cells as shown in c) by transmitted light microscopy

Selected Publications

[1] U. Kiran Marelli, J. Bezençon, E. Puig, B. Ernst, and H. Kessler, "Enantiomeric cyclic peptides with different caco-2 permeability suggest carrier-mediated transport," Chem. Eur. J., vol. 21, no. 22, pp. 8023–8027, 2015.

[2] U. Kiran Marelli, O. Ovadia, A. O. Frank, J. Chatterjee, C. Gilon, A. Hoffman, and H. Kessler, "Cis-peptide bonds: A key for intestinal permeability of peptides?," Chem. Eur. J., vol. 21, no. 43, pp. 15148–15152, 2015.

[3] O. V. Maltsev, U. Kiran Marelli, T. G. Kapp, Di Leva, Francesco Saverio, S. Di Maro, M. Nieberler, U. Reuning, M. Schwaiger, E. Novellino, L. Marinelli, and H. Kessler, "Stable peptides instead of stapled peptides: Highly potent αvβ6-selective integrin ligands," Angew. Chem., Int. Ed., vol. 55, no. 4, pp. 1535–1539, 2016, accepted in 2015.

[4] T. G. Kapp, M. Fottner, O. V. Maltsev, and H. Kessler, "Small cause, great impact: Modification of the guanidine group in the RGD motif controls integrin subtype selectivity," Angew. Chem., Int. Ed., vol. 55, no. 4, pp. 1540–1543, 2016, accepted in 2015.

Publications by this Focus Group can also be found on page 169.

Focus Group **Biologically Inspired Material Science**

Prof. Zvonimir Dogic (Brandeis University) | Hans Fischer Senior Fellow
Felix Keber | Doctoral Candidate
Prof. Andreas Bausch, Molecular and Cellular Biophysics, TUM

Zvonimir Dogic

Biologically inspired soft materials

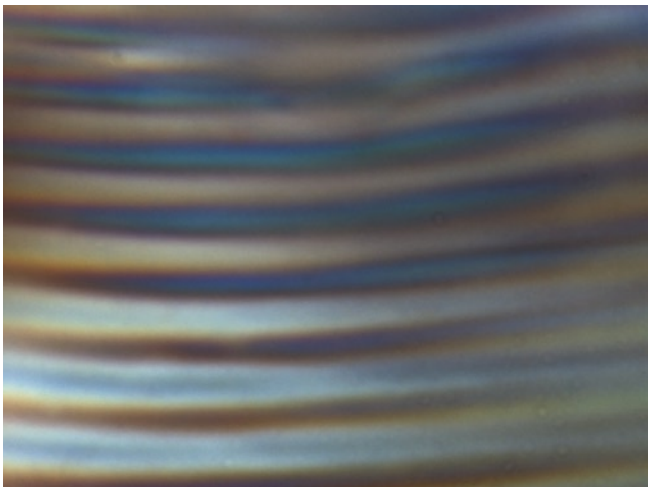
During the past year the Focus Group has made substantial progress in two complementary research areas. In one area, the groups of Bausch and Dogic have collaborated to develop a new model system of active matter that is based on composite microtubule actin materials. In another direction, the groups of Dogic and Dietz have combined their expertise to develop a new class of liquid crystalline materials and elucidate new pathways for assembly of origami-like particles into macroscopic materials.

Composite actin-microtubule active materials: Our understanding of how complex materials assemble from simple inanimate molecules is remarkably advanced. Given the interaction between a pair of molecules, laws of fundamental physics predict with high accuracy the collective emergent behavior, such as a temperature at which a freely flowing liquid freezes into a solid crystal. Compared to these remarkable advances, our ability to describe and predict collective behavior of animate energy-consuming ensembles of objects is still in its infancy. A particularly striking example of this is seen in the murmurations of a flock of starlings as they settle at dusk for a night's sleep. Within such a flock, hundreds of thousands of birds form a seemingly continuous collective that exhibits rich dynamics consisting of endless turns, twists, and shape changes. It remains an open question if there any fundamental laws that are able to predict the dynamics of such a social and inherently far-from-equilibrium collective. The long-term goal of the collaboration between the group of Andreas Bausch at TUM and Hans Fischer Senior Fellow Zvonimir Dogic is to experimentally establish fundamental principles that are able to predict the collective behavior of such far-from-equilibrium systems.

A flock of birds or a school of fish is a traditional example of an active system that undergoes an inherently non-equilibrium flocking transition. However, obtaining quantitative information required to test the theoretical predictions from a collective of living organisms is a highly challenging proposition. In an important early advance that has furthered the field of active matter, the group of Andreas Bausch has developed a highly controllable experimental system to study flocking transitions from isolated biochemical building blocks. Specifically, they have formed a dense layer of actin filaments on a layer of myosin molecular motors that are permanently attached to a solid support. As myosin motors hydrolyse ATP, they move along the backbone of actin filaments, continuously powering their motility. The Bausch group demonstrated that at high enough actin concentrations, the filaments undergo a discontinuous transition into a dense flock in which thousands of filaments collectively move accross the surface. Despite the important role it has played in developing the field of active matter, the motility assay geometry of the original experiments is inherently limited to a solid 2-D surface. Consequently, there are no detailed experimental studies of the flocking transition in three dimensions.

In order to overcome these limitations and lay the foundation for studying 3-D flocking transitions, the Dogic and Bausch groups have developed composite actin-microtubule active gels. Specifically, they have assembled 3-D actin networks with covalently attached kinesin motors. Subsequently microtubule filaments have been introduced into porous 3-D gels. Important preliminary findings demonstrate that the kinesin motors affixed onto a rigid actin network attach to microtubule filaments and propel them through a relatively open structure of the actin gel. In many ways this setup is a 3-D analogue of classical 2-D motility assay geometry. In the next step, this collaboration will focus on systematically increasing the density of the gliding microtubules in order to identify the possible regime in which the gliding filaments undergo a collective far-from-equilibrium transition in order to form 3-D flocks. If successful, these efforts would represent another important class of active systems that would spur further advances of the rapidly developing field of active matter.

Assembly of origami filaments into bulk materials: The remarkable progress over the past few years has led to the development of DNA origami technology that robustly produces 3-D particles of almost arbitrary geometrical complexity. However, despite these advances, assembling origami particles into 3-D bulk materials still remains a challenge. In an important advance the groups of Dogic and Dietz have demonstrated that origami filaments behave as colloidal particles. Subsequently, they have used rules of colloidal assembly to organize rod-like origami filaments into novel bulk liquid crystals, 2-D colloidal membranes and 1-D twisted ribbons. These findings outline a general strategy for rational engineering of macroscopic materials that couples DNA origami technology with methods developed for assembly of conventional colloids.



1 | A characteristic fingerprint textures observed with polarizing microscopy demonstrates that DNA origami filaments robustly assemble into bulk liquid crystals.

Reference

[1] F. C. Keber, E. Loiseau, T. Sanchez, S. J. DeCamp, L. Giomi, M.J. Bowick, M. C. Marchetti, Z. Dogic, and A. R. Bausch, "Topology and dynamics of active nematic vesicles," Science, vol. 345, no. 6201, pp. 1135–1139, 2014.

Publications by this Focus Group can also be found on page 170.

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

Prof. Tamas Horvath (Yale University) | Hans Fischer Senior Fellow
Tim Gruber | Doctoral Candidate
Prof. Matthias Tschöp, Metabolic Diseases, TUM

Scientific Reports

Tamas Horvath

Insulin signaling in astrocytes control glucose uptake by the brain

The overarching aim of our Focus Group is to understand the role of brain temperature in control of systemic metabolism and its disorders. Temperature generation by the brain hinges on fuel availability of brain cells. In the past year, we have explored cellular mechanisms that enable uptake of glucose by hypothalamic regions of the brain, a crucial site in the control of systemic metabolism.

Balanced glucose and energy metabolism are achieved through the coordinated regulation of neuronal circuits that respond to nutrients and hormones whose availability in the blood fluctuates according to energy needs. Cerebral blood glucose flow is regulated by the blood brain barrier (BBB), which is formed by endothelial cells from microvessels that interact with pericytes and astrocytes that also control blood supply to and within the brain. Astrocytes respond to nutrients via metabolic receptors and transporters extending throughout their membrane surface and are located in the interface between vessels and neurons, placing these glial cells in a privileged position to control glucose fluxes between the periphery and the central nervous system (CNS). Insulin as the master regulator of cellular glucose metabolism has been shown to act in the CNS to control systemic metabolic homeostasis. However, the question of whether or not insulin signaling in astrocytes plays a functional role for systemic metabolism has never been studied. We used a series of glia-specific loss-of-function models to uncover the function of astrocytic insulin signaling in the brain, and more specifically for hypothalamic glucose uptake and related circuit functions.

We discovered that postnatal genetic ablation of insulin receptors (InsRs) in glial fibrillary acidic protein (GFAP)-expressing cells affected hypothalamic mitochondrial function and circuit connectivity, and impaired physiological and neuronal responses to metabolic challenges. Postnatal genetic ablation of InsRs in astrocytes by targeting glutamate aspartate transporter (GLAST)-expressing cells replicated this phenotype, indicating functional contribution of insulin signaling in astrocyte subpopulations beyond GFAP-expressing glia. Hypothalamus-specific knockout of astrocytic InsRs was sufficient to replicate the phenomenon, but the physiological response to brain glucose changes originating in the CNS remained normal. Glucose monitoring in cerebral spinal fluid and positron emission tomography in GFAP-InsR KO mice confirmed that brain glucose uptake is regulated by glial InsRs. We conclude that insulin signaling in hypothalamic astrocytes co-controls CNS glucose sensing and systemic glucose metabolism via regulation of glucose uptake across the blood brain barrier. These novel observations will aid the better understanding of physiological and pathological metabolic conditions, including obesity and type 2 diabetes.

Selected Publication

[1] The manuscript containing the aforementioned study is currently under review by the journal Cell.

Focus Group **Cellular Protein Biochemistry**

Prof. Matthias J. Feige (TUM) | Rudolf Mößbauer Tenure Track Professor
Stephanie Müller, Susanne Reitberger | Doctoral Candidates
Cellular Protein Biochemistry, TUM

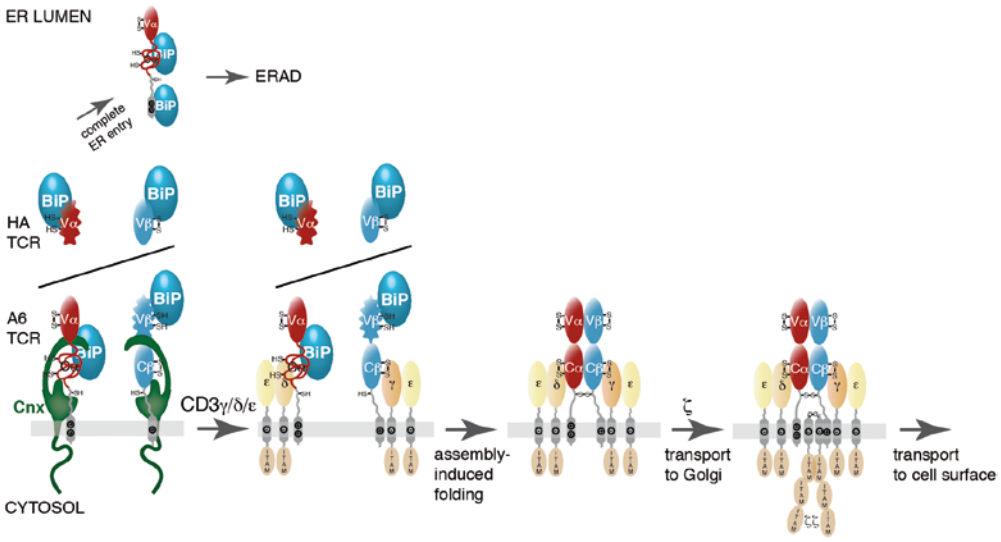
Scientific Reports

Matthias J. Feige

In spring 2015 we established our laboratory for Cellular Protein Biochemistry at the TUM Department of Chemistry and the TUM-IAS. In our laboratory we combine biochemical and biophysical approaches with mammalian cell biology to understand how proteins acquire their native structure in a cellular context. The function of proteins underlies all biological processes that cells and organisms depend on – from immune defense to memory formation. In order to fulfill this broad array of functions, proteins have to adopt a defined three-dimensional structure. This structure is encoded in the specific sequence of amino acids that make up a protein. In the cell, protein folding is aided by a class of dedicated protein folding helpers, the chaperones, and proteins that fail to mature properly are targeted for degradation. We aim at developing a molecular understanding of the mechanisms and the machinery of protein folding in the cell. A particular focus of our work is on secreted proteins and membrane proteins, which allow cells to interact with their environment and are of particular biomedical and biotechnological relevance. Failures in protein folding are the molecular basis of multiple human pathologies, from cystic fibrosis to Alzheimer's disease.

One of our model systems is the αβT cell receptor (αβTCR). This receptor allows our immune system to discriminate the body's own structures from foreign structures, e.g., to detect virus-infected cells or mount an immune response against bacteria. The αβTCR is among the most complex cell surface receptors, and thus its biogenesis poses a formidable challenge to the cell but is absolutely essential for the functioning of our immune defense. In recent work we were able to dissect two critical steps in the assembly process of the αβTCR. Our work revealed that membrane integration of this receptor is coupled to its correct assembly, thus providing the cell with an opportunity to distinguish correctly assembled from incorrectly assembled receptors by their localization within the cell – in the membrane or not [1]. Building on these findings, we more recently showed that another critical step of the αβTCR, the assembly of the so-called clonotypic chains, which are directly involved in pathogen recognition, is mediated by assembly-induced folding processes. This means that until assembly these chains are incompletely folded and can thus be recognized by molecular chaperones and retained in the cell. Only complete assembly induces folding, relieves them from retention in the cell, and allows this immune receptor to be transported to the cell surface to perform its biological functions [3]. Taken together, our work has provided a detailed explanation of how assembly of immune receptors can be coordinated and monitored in the cell (figure 1).

On the basis of these findings, we now continue to investigate the mechanisms of membrane protein biogenesis in the cell. Another focus of our work is the biosynthesis of interleukins, key signaling molecules in the immune system. For both projects we continue to use an interdisciplinary approach from protein biochemistry to cell biology to provide a comprehensive understanding of protein biosynthesis in mammalian cells. This work will have an immediate impact on our understanding of protein folding and misfolding and might open a path for a future targeting of specific steps in protein biogenesis in the cell for therapeutic purposes. At the same time, these insights can provide the basis for rational engineering of better biopharmaceuticals [2].



1 | A model for αβTCR assembly control in the cell. Unassembled clonotypic α- and β-chains are both substrates of the chaperone calnexin (Cnx). The α-chain comprises either one (Cα) or two (Cα and Vα) incompletely folded domains. The β-chain Cβ domain is well folded, whereas Vβ, in at least some αβTCRs, is not. All incompletely folded domains provide interaction sites for the Hsp70 chaperone BiP, with particularly strong binding to incompletely folded variable domains. Over time, due to their hydrophilic TM region, unpaired α-chains completely enter the ER lumen and are degraded by ER-associated degradation (ERAD). Correctly assembled α-CD3δε and β-CD3γε pairs en route to the native receptor, whose interaction with Cnx might be reduced or abolished, still provide BiP binding sites in Vβ and likely Cα, even though the temporal relationship of Cnx and BiP binding is not entirely clear. Upon αβ-heterodimerization the incompletely folded domains in the clonotypic chains become structured and are thus released from chaperones. Finally, assembly with ζ-dimers in the Golgi allows transport to the cell surface to occur. Figure taken from [3].

References

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Selected Publication

[3] M. J. Feige, J. Behnke, T. Mittag, and L. M. Hendershot, “Dimerization-dependent Folding Underlies Assembly Control of the Clonotypic αβT Cell Receptor Chains,” J. Biol. Chem., vol. 290, no. 44, pp. 26821–26831, 2015.

Publications by this Focus Group can also be found on page 170.

Focus Group **Functional Metagenomics**

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

Scientific Reports

Yana Bromberg

Functional studies of the microbial world

The research in the Metagenomics Focus Group is focused on developing a data-driven approach for elucidating molecular functional properties of microbial organisms and microbiomes.

Microorganisms carry out many molecular functions relevant to a range of human interests, including health, industrial production, and bioremediation. Experimental study of these functions is expensive and time-consuming; e.g., as many as three hundred biochemical/physiological tests only reflect 5–20% of the bacterial functional potential. Evolutionary relatedness, used as a proxy for functional relationships, can be inferred from phylogenetic markers but does not guarantee functional identity between members of the same taxon (particularly in different environments) or lack of similarity between different taxa (e.g., in the same environment). The recent drastic increase in the number of sequenced microbial genomes has facilitated access to microbial molecular functionality from the gene/protein *sequence* side.

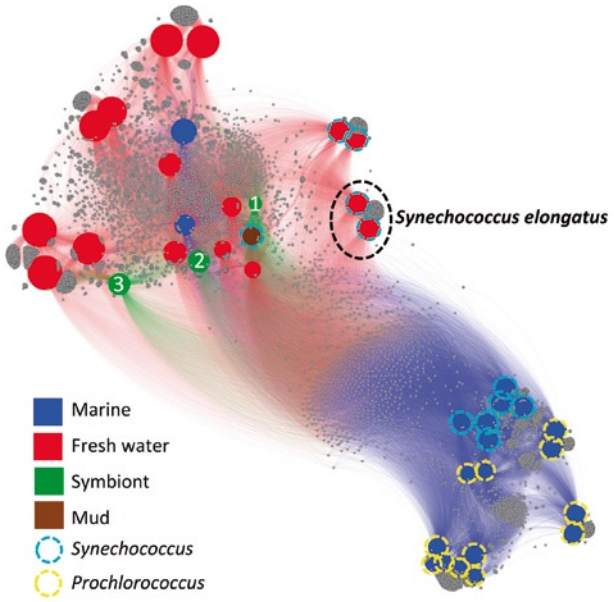
We recently mapped bacterial proteins to molecular functions, built a network-based microorganism classification scheme – where similarity between organisms is defined in terms of functional potentials (*fusion*, functional-repertoire similarity-based organism network, *PLoS Comp Biol 2015*) – and studied the functional relationships between bacteria in the light of their chosen habitats. We apply clustering techniques to identify natural groupings of organisms, as opposed to the currently accepted taxonomic classifications. Our methods create a framework for explicitly annotating functions of genes that differentiate closely related organisms living in diverse environments. For example, we found that water salinity seems to drive the functional diversification in Cyanobacteria – a finding that we are following up experimentally (figure 1).

Our scheme is phenetic, based on a network of quantitatively defined organism relationships across the known prokaryotic space. It correlates with the current taxonomy, but the observed discrepancies reveal both (1) the inconsistency of functional diversity levels among different taxa and (2) an (unsurprising) bias toward prioritizing, for classification purposes, relatively minor traits of particular interest to humans. Our dynamic network-based organism classification is independent of the arbitrary pairwise organism similarity cut-offs traditionally applied to establish taxonomic identity. Instead, it reveals natural, functionally defined organism groupings and is thus robust in handling organism diversity. Additionally, *fusion* can use organism metadata to highlight the specific environmental factors that drive microbial diversification. Our approach provides a complementary view to cladistic assignments and holds important clues for further exploration of microbial lifestyles.

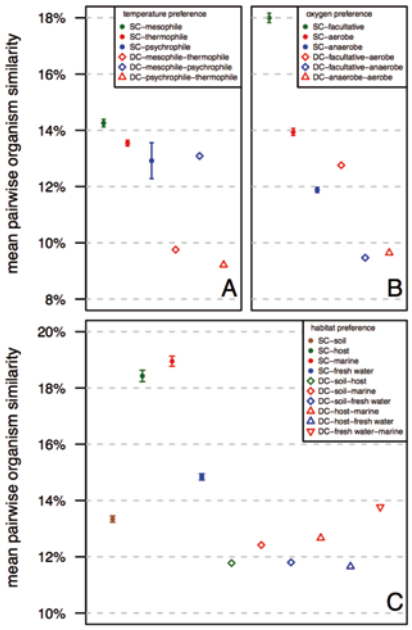
To facilitate further research of this kind, we developed *fusion*DB (bromberglab.org/databases/fusiondb) – a database containing bacterial functional repertoires, similarities, and applicable environmental metadata (manuscript submitted). Our web interface allows querying for combinations of organism names and environments to produce a *fusion* network of selected organisms. Our analyses of the data reveal environmental factors driving microbial functional diversification (figure 2) and illustrate the detection of traces of environmentally driven horizontal gene transfer.

By mapping organism-specific genes to globally-defined molecular functions we are working to (1) identify and annotate molecular pathway components, i.e., sets of proteins that consistently co-occur, (2) trace evolution of such pathways by considering relationships among organisms that carry pathway components, and (3) establish environment- or host-specific pathways, i.e., those sets of genes that never co-occur in organisms occupying different environmental niches. Our methodology also allows for a novel way of assessing organismal and functional diversity of microbiomes – directly from reads and with no need for assembly.

We are developing a means of mapping metagenome reads to functions of their "parent" genes (manuscript in preparation) – a method that will improve precision of functional annotation by bypassing the issues of genome assembly from metagenomic data. This approach will facilitate both the environmentally focused research, e.g., changes of microbiomes in response to environmental stresses, such as oil spills and heavy metal contamination, and the study of the increasingly obvious microbiome involvement in human health. As a whole, our *fusion*-related research is a practical fit for biomedical, industrial, and ecological applications that rely on understanding the functional capabilities of the microbes in their environment.



1 | **Fusion+ of 40 Cyanobacteria reveals environment impact on functions.**
The *Cyanobacteria* form one mostly fresh water cluster and one marine cluster. The members of *Synechococcus* exist in both clusters. The functions that are shared between marine *Synechococcus* and *Prochlorococcus*, yet not found in fresh water *Cyanobacteria*, are likely important in the marine environment. Symbiont1-cyanobacterium UCYN-A; Symbiont2- *Acaryochloris marina* MBIC11017; Symbiont3-Nostoc *azollae* 0708.



2 | **Pairwise organism similarity is higher among organisms living in the same (SC) environmental conditions than those living in different conditions (DC)**. The mean pairwise similarity for same (SC) and different (DC) condition organisms according to their (A) temperature preference, (B) oxygen requirement, and (C) habitat. Note that for all points without error bars the standard errors are vanishingly small.

Selected Publication

[1] C. Zhu, T. O. Delmont, T. M. Vogel, and Y. Bromberg, „Functional Basis of Microorganism Classification," PLoS Comput. Biol., vol. 11, no. 8, pp. e1004472, 2015.

Publications by this Focus Group can also be found on page 170.

Focus Group **Proteases in the Brain**

Prof. Carl P. Blobel (Hospital of Special Surgery, Weill Cornell Medicine) | Hans Fischer Senior Fellow
Johanna Tüshaus | Doctoral Candidate
Prof. Stefan Lichtenthaler (Neuroproteomics, TUM)

Carl P. Blobel

Our Focus Group is dedicated to improving the understanding of how inflammation causes diseases of the brain. We hope that our efforts will ultimately allow us to contribute to the development of better treatments for devastating human diseases such as Alzheimer's dementia and traumatic brain injury. Toward this end, we are studying molecular scissors in immune cells in the brain that most likely are important for generating an inflammatory milieu, and we hypothesize that this contributes to the development of neurodegenerative diseases.

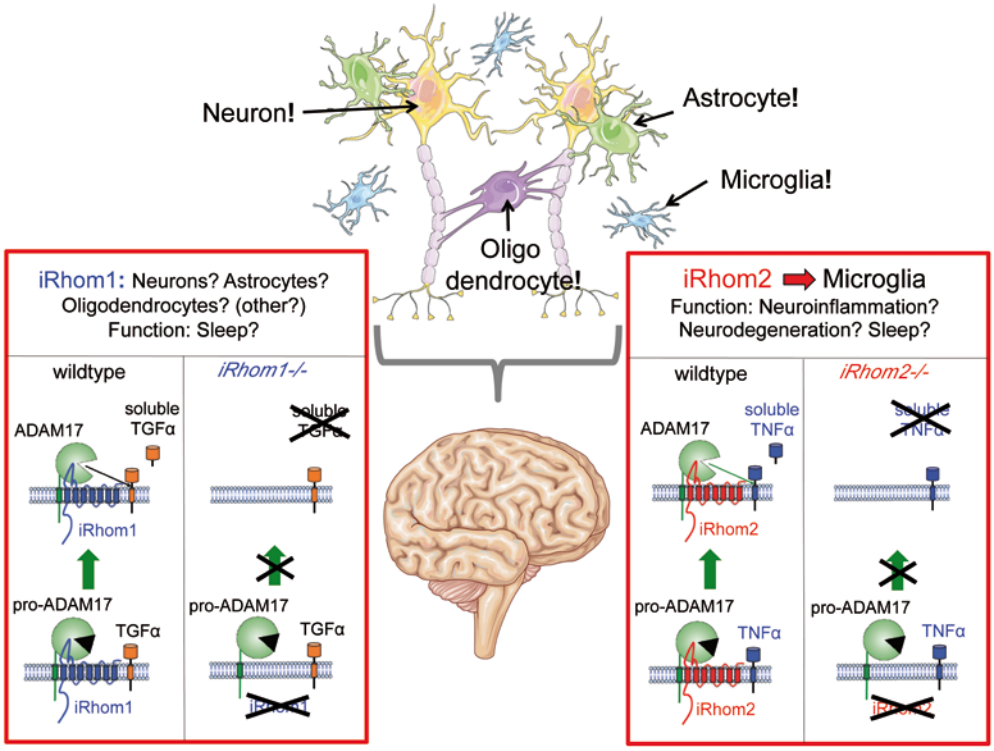
In pursuing these goals, our Focus Group will benefit tremendously from ongoing collaborations with outstanding labs at TUM and in the larger Munich area that have synergistic expertise in the areas of inflammation of the brain and molecular scissors. This includes a research consortium (Forschergruppe 2290) newly funded by the DFG, with TUM professor Dieter Langosch as the speaker. The Hans Fischer Senior Fellowship award to Carl Blobel has enabled several important collaborations: with his Host, Stefan Lichtenthaler, their joint doctoral candidate, Johanna Tüshaus, and Rudolf Mößbauer Tenure Track Professor Franz Hagn. Moreover, the kick-off symposium in November highlighted several additional opportunities for collaborations with experts in diseases of the brain and in the studies of molecular scissors.

With respect to neuroinflammation, Stefan Lichtenthaler and Carl Blobel co-authored an editorial entitled "iRhoms in the brain – a new frontier?" in the journal *Cell Cycle*, outlining the scientific background and rationale for ongoing studies of their Focus Group: A recent PNAS paper from Carl Blobel's lab demonstrated that iRhoms (inactive Rhomboid-like proteins) differentially regulate a pair of molecular scissors termed ADAM17 (a disintegrin and metalloprotease) in different cell types in the brain. iRhom2 most likely regulates pro-inflammatory functions of ADAM17 in microglia (immune cells of the brain), whereas iRhom1 controls the function of ADAM17 in other cell types in the brain, but not in microglia. During the kick-off symposium in November, the Focus Group explored the best approaches to test the hypothesis that iRhoms and ADAM17 have a role in neuroinflammation. Moreover, Stefan Lichtenthaler's group has already identified several novel substrates for iRhom2/ADAM17 in immune cells, using an innovative and powerful technique that previously allowed his group to identify substrates and functions of a different set of molecular scissors in the brain (see for example [3]).

The second major interest of the Focus Group is to figure out the molecular details of how exactly the scissors ADAM17 interact with their regulators, the iRhoms. Franz Hagn has developed exciting new approaches to probe the interaction of iRhoms and ADAM17 at the level of individual atoms, and information from his work is guiding complementary studies of these interactions in cell culture in the Blobel and Lichtenthaler labs.

Finally, in February Carl Blobel was elected to the Association of American Physicians in recognition of his dedication to the advancement of scientific and practical medicine. We are grateful to the TUM-IAS for supporting our Focus Group, and look forward to continuing our collaborative studies in Munich over the next two years.

In cooperation with Dr. Simone Scilabra (DZNE, TUM)



1 | **iRhoms in the brain – a new frontier?**

Different cell types in the brain are indicated above. The red boxes show diagrams of the molecular scissors ADAM17 (a disintegrin and metalloprotease 17) together with their newly discovered regulators, termed iRhom1 or iRhom2 (inactive Rhomboid-like protein 1 and 2). In normal (wild type) cells, ADAM17 can cut other molecules and release them from the cell: a growth factor called transforming growth factor α (TGFα, left panel), and a pro-inflammatory molecule called tumor necrosis factor α (TNFα, right panel). The Focus Group will mainly work on the role of iRhom2 in microglia, which are the immune cells of the brain. We hypothesize that iRhom2, together with ADAM17, is responsible for releasing TNFα in the brain, which could conceivably contribute to inflammation in the context of Alzheimer's disease and traumatic brain injury. The Focus Group will rely on several different synergistic collaborations to test this hypothesis.

Selected Publications

[1] S.F. Lichtenthaler, B.F. O'Hara, and C.P. Blobel, "iRhoms in the brain - a new frontier?" Cell Cycle, vol. 14, no. 19, pp. 3003–3004, Oct. 2015.

[2] C. Blobel, C. Haxaire, G. Kalliolias, E. DiCarlo, J. Salmon, and A. Srivastava, "Blood-Induced Arthropathy in Hemophilia: Mechanisms and Heterogeneity," Semin. Thromb. Hemost., vol. 41, no. 08, pp. 832–837, 2015.

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Publications by this Focus Group can also be found on page 170.

Focus Group **Protein Misfolding and Amyloid Diseases**

Prof. Ayyalusamy Ramamoorthy (University of Michigan) | Hans Fischer Senior Fellow
Dr. Diana Rodriguez | Postdoctoral Researcher
Prof. Bernd Reif, Solid-State NMR, TUM

Scientific Reports

Ayyalusamy Ramamoorthy

More than 20 diseases are related to protein deposition in various tissues...

Alzheimer's disease, type II diabetes (T2D), Parkinson's disease, and prion diseases are the most prominent among them. Primarily, T2D is characterized by impaired insulin secretion. Concomitant abundant production of the hormone hIAPP (human islet amyloid poly-peptide, also known as amylin) induces disruption and apoptosis of pancreatic beta-cells.

Our main focus is to investigate the structure, dynamics, and aggregation of hIAPP in the presence of lipid membranes using "magic angle spinning" (MAS) solid-state NMR experiments. In addition, conformational changes of IAPP aggregates induced by small molecule amyloid-inhibitors will be studied. These studies are likely to facilitate the design of small molecules with improved binding properties and β-cell protective properties.

In the past, we have reported protocols for a high-yield expression of isotopically labeled human-IAPP [10]; we have investigated IAPP aggregation, IAPP-induced membrane disruption [3], IAPP intermediate state structures in solution [7], and the role of zinc [1] and insulin [2] on IAPP aggregation. We have further worked on NMR spectroscopic investigations of Alzheimer's disease Abeta aggregates [4], [11], and their interference with small molecules [5], [8]–[9]. In addition, amyloid chaperone interactions have been studied [6].

References

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[2] J. R. Brender, E. L. Lee, K. Hartman, P. T. Wong, A. Ramamoorthy, D. G. Steel, and A. Gafni, "Biphasic effects of insulin on islet amyloid polypeptide membrane disruption," Biophys. J., vol. 100, no. 3, pp. 685–692, 2011.

[3] J. R. Brender, S. Salamekh, and A. Ramamoorthy, "Membrane disruption and early events in the aggregation of the diabetes related peptide IAPP from a molecular perspective," Acc. Chem. Res., vol. 45, no. 3, pp. 454–462, 2012.

[4] J. M. Lopez del Amo, M. Schmidt, U. Fink, M. Dasari, M. Fändrich, and B. Reif, "An asymmetric dimer can be the basic subunit in Alzheimer's disease β-amyloid fibrils", Angew. Chem., Int. Ed., vol. 51, no. 25, pp. 6136–6139, 2012.

[5] J. M. Lopez del Amo, M. Dasari, U. Fink, G. Grelle, E. E. Wanker, J. Bieschke, and B. Reif, "Structural Properties of EGCG-induced, nontoxic Alzheimer's disease Aβ oligomers," J. Mol. Biol., vol. 421, no. 4-5, pp. 517–524, 2012.

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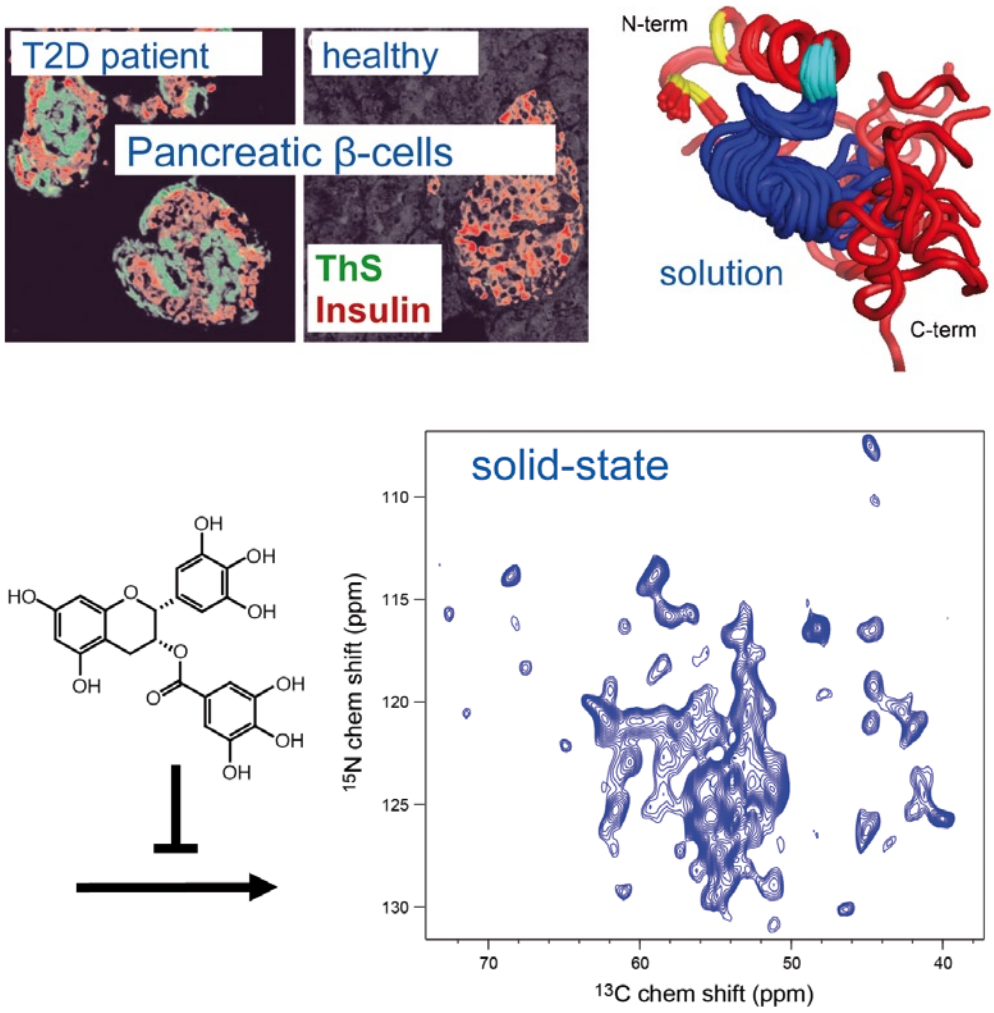
[7] H. R. Patel, A. S. Pithadia, J. R. Brender, C. A. Fierke, and A. Ramamoorthy, "In search of aggregation pathways of IAPP and other amyloidogenic proteins: Finding answers through NMR spectroscopy," J. Phys. Chem. Lett., vol. 5, no. 11, pp. 1864–1870, 2014.



1 | In Diabetes type 2, overexpression of the hormone hIAPP (human islet amyloid poly-peptide) results in loss of beta cells in the pancreas. We will study the structure of hIAPP aggregates using MAS solid-state NMR in the presence and absence of small molecules. Furthermore, we will probe interactions of hIAPP with liposomes which potentially induce conformational changes in the aggregate.

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Focus Group **Proteomics**

Dr. Peer-Hendrik Kuhn (TUM) | Carl von Linde Junior Fellow
Alperen Serdaroğlu | Doctoral Candidate
Prof. Stefan Lichtenthaler, Neuroproteomics, TUM,
Prof. Wilko Weichert, Pathology, TUM

Scientific Reports

Peer-Hendrik Kuhn

The common denominator of our research is the analysis of cellular secretomes, which contain the entirety of all released factors of a given cell type, including proteins released upon proteolysis. To this aim we developed the SPECS technology, which enables the systematic analysis of secretomes with mass spectrometry. Our first field of research deals with the deorphanization of extracellular proteases, molecular scissors that are able to release membrane tethered proteins from the membrane by cleavage.

In 2015, our Focus Group finished studies on the proteases SPPL3 and ADAM10. Our proteomic data published in *Molecular & Cellular Proteomics* early in 2015 revealed that SPPL3 cleaves numerous glycosylation modifying enzymes such as MAN2A1, B4GAT1 and B4GALT1 besides the initially identified MGAT5 enzyme, which speaks in favor for a general regulatory function of SPPL3 in glycosylation.

Recently, we published a proteomic study on ADAM10 substrates in neurons in the journal *Elife*. ADAM10 is another protease that has been considered as a pharmacological target in Alzheimer's disease, as it reduces the production of neurotoxic amyloid β (Aβ), the major culprit in Alzheimer's disease. Our study revealed that besides reducing Aβ production, ADAM10 cleaves more than 80 membrane-tethered proteins in neurons that are especially involved in synapse function and axon targeting. Indeed, we found deficits in synapse morphology and mistargeted axons in the hippocampus and the olfactory bulb, supporting the results of our initial proteomic analysis. This study reveals that ADAM10 is a major sheddase in the brain whose proteolytic activity is indispensable for regulation of many physiological processes such as synapse function and axon targeting. Hence, pharmacological stimulation of ADAM10 in Alzheimer's disease might cause major side effects.

Our second field of research is the study of secretomes in acute myeloid leukemia, a cancer in the bone marrow that causes white blood cell expansion at the expense of other blood elements, causing anemia and thrombocytopenia. In doing so, we aim to identify soluble biomarkers that might make diagnostic bone marrow punctures obsolete in the future. Doctoral candidate Alperen Serdaroğlu finished the quantitative secretome and surface analysis of acute myeloid leukemia cell lines. The next step will be the validation of identified biomarkers in patient samples such as serum and bone marrow biopsies. Therefore, we plan to collaborate closely with the oncology department of Klinikum rechts der Isar. The second part of Alperen's project deals with studying the impact of receptor tyrosine kinase signaling on the secretome of AML cell lines. Therefore, he established the CrispR/Cas9 technology in the lab to specifically knockout the receptor tyrosine kinases FLT3 and c-kit in AML cell lines.

Selected Publications

[1] P.-H. Kuhn, A. V. Colombo, B. Schusser, D. Dreymueller, S. Wetzel, U. Schepers, J. Herber, A. Ludwig, E. Kremmer, D. Montag, U. Müller, M. Schweizer, P. Saftig, S. Bräse, and S. F. Lichtenthaler, "Systematic substrate identification indicates a central role for the metalloprotease ADAM10 in axon targeting and synapse function," eLife, vol. 5, 2016, accepted in 2015.

[2] P.-H. Kuhn, M. Voss, M. Haug-Kröper, B. Schröder, U. Schepers, S. Bräse, C. Haass, S. F. Lichtenthaler, and R. Fluhrer, "Secretome analysis identifies novel signal peptide peptidase-like 3 (SPPL3) substrates and reveals a role of SPPL3 in multiple golgi glycosylation pathways," Mol. Cell. Proteomics, vol. 14, no. 6, pp. 1584–1598, 2015.

Publications by this Focus Group can also be found on page 171.

Focus Group **Statistical and Quantitative Genomics**

Prof. Daniel Gianola (University of Wisconsin-Madison) | Hans Fischer Senior Fellow
Prof. Natalia de Leon, Prof. Guilherme Rosa
(University of Wisconsin-Madison) | Visiting Fellows

Scientific Reports

Daniel Gianola

Investigating genomic relationships among phenotypic traits

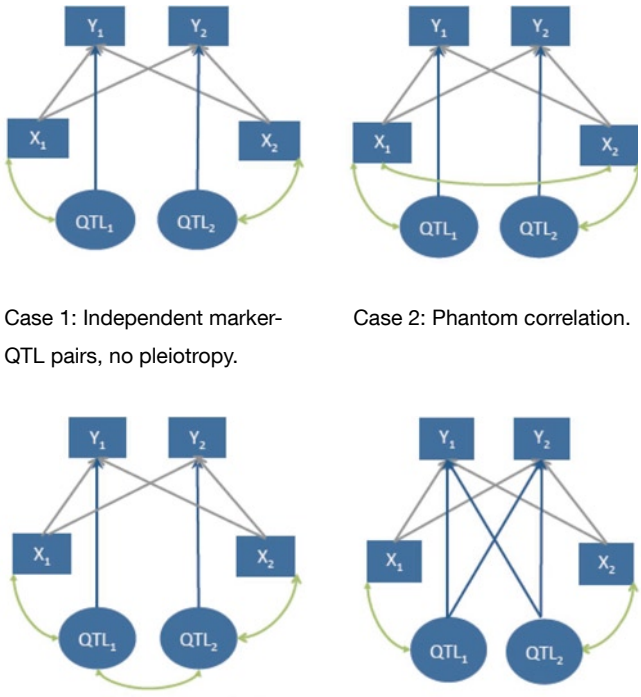
Massive genome information helps to unravel the structure of complex quantitative traits in human, animal, and plant genetics and has become a main tool for making pharmaceutical, medical and, with respect to animals and plants, breeding decisions. As the genotypic information consists of large numbers of molecular markers, there are many more predictors than individuals with phenotypic records in the sample. Thus, marker effects are usually statistically unidentified and spurious, a problem known as “$p > n$” in the respective disciplines.

Until recently, observed traits were analyzed individually, not taking advantage of novel statistical developments for modeling several traits jointly. Combining information of genome markers and multiple traits may result in more accurate and precise predictions of complex phenotypes. It is also the expectation that such an approach may offer insights into mechanisms affecting more than one trait simultaneously, leading for example to genomic correlations via pleiotropy, environmental associations via nutrition, or phenotypic correlations induced by developmental processes. Our Focus Group addresses these issues with current state-of-the-art methodology for multi-trait analysis.

We investigated theoretically and with the help of toy examples (figure 1) the interpretation of correlation parameters inferred using markers, such as genomic correlations between traits. We were able to show that these correlations are at best conjectural and can frequently be misleading [1]. This is all the more true in the absence of knowledge about linkage disequilibrium (LD) patterns between quantitative trait loci (QTL) and markers, which in real data sets remain largely unknown. Investigation of these toy examples indicated that all or a fraction of the real genetic correlation based on LD among QTL is likely to be missed by an analysis based on markers that are in imperfect LD with QTL. We elucidated the factors that lead to missing genetic correlations due to pleiotropy, and we demonstrated cases where an illusion of genetic correlation is created. We discussed implications of the study and further issues arising when sequence data are used instead of molecular marker data.

We also studied how to extract a more parsimonious, multi-variable representation of relationships among complex traits than one stemming from pairwise inferred correlation parameters. Pairwise parameter correlations can be spurious and reflect confounding, because of connections among other traits that induce a high correlation between them; in such a case, the connection cannot be statistically confirmed when testing conditionally on the other traits (figure 2). Another source for such induced trait connections can be an unidentified discrimination between genomic, phenotypic, or environmental trait relationships in the multi-trait model. We developed a framework based on multi-trait analysis, Bayesian network analysis, and structural equation models with the help of a multi-environment maize data set to depict trait connections as networks.

Katrin Töpner | Doctoral Candidate
Prof. Chris-Carolin Schön, Plant Breeding, TUM



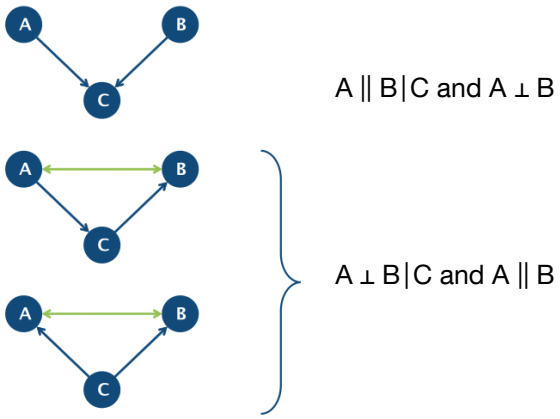
Case 1: Independent marker-QTL pairs, no pleiotropy.

Case 2: Phantom correlation.

Case 3: Missing correlation.

Case 4: Pleiotropy.

1 | The figure shows four cases of a two-trait system with the interplay between QTL, markers, and phenotypes. The systems consist of two traits (Y_1 and Y_2) involving two QTL (QTL_1 and QTL_2) and two markers (X_1 and X_2). Single-pointed blue arrows denote causal effects, green double-pointed arrows denote LD, and single-pointed gray arrows represent regression coefficients.



2 | Stochastic dependence (denoted by ||) and independence (denoted by ⊥) for the three fundamental connections in a Bayesian network (from top to bottom): converging connection, serial connection, and diverging connection. Single-pointed blue arrows denote stochastic dependence and green double-pointed arrows denote the associations induced by them.

We investigated various algorithms combined with several independence tests and two scores for their usefulness in discovering genomic and phenotypic trait networks. Inferred networks were assessed for their fit and predictive ability in genome-enabled prediction of maize phenotypes by using structural equation models that can incorporate connections among traits by a structure matrix instead of co-variances. Some genomic trait correlations could be identified as induced by other connections, and the usefulness of the approach in genome-assisted prediction was shown.

In addition to research, the Focus Group was also active in teaching. In July 2015, Daniel Gianola held the course “Introduction to Bayesian Methods for Quantitative Geneticists,” for 22 doctoral candidates and postdoctoral researchers from animal, plant, and biometrical sciences. The lecture and practicals sessions covered the theoretical background and application of many Bayesian prediction models and their implementation.

The Focus Group was also happy to welcome Guilherme J.M. Rosa and Natalia de Leon from the University of Wisconsin–Madison as visiting scientists during the first half of 2015. Guilherme Rosa mainly contributed to the Bayesian network analyses, and with Natalia de Leon a study was initiated on the genetic analysis of complex traits relevant for mitigating the effects of climate change. International and interdisciplinary exchange was intensified by shared supervision of two doctoral candidates between TUM Plant Breeding and the Departments of Animal Science and Agronomy at the University of Wisconsin–Madison.

Selected Publication

[1] D. Gianola, G. de los Campos, M. A. Toro, H. Naya, C.-C. Schön, and D. Sorensen, “Do molecular markers inform about pleiotropy?,” Genetics, vol. 201, no. 1, pp. 23–29, 2015.

Publications by this Focus Group can also be found on page 171.

Focus Group **Structural Membrane Biochemistry**

Prof. Franz Hagn (TUM) | Rudolf Mößbauer Tenure Track Professor
Dr. Kai Fredriksson | Postdoctoral Researcher
David Goricanec | Doctoral Candidate
Structural Membrane Biochemistry, TUM

Scientific Reports

Franz Hagn

Structural biology and functional studies of membrane proteins

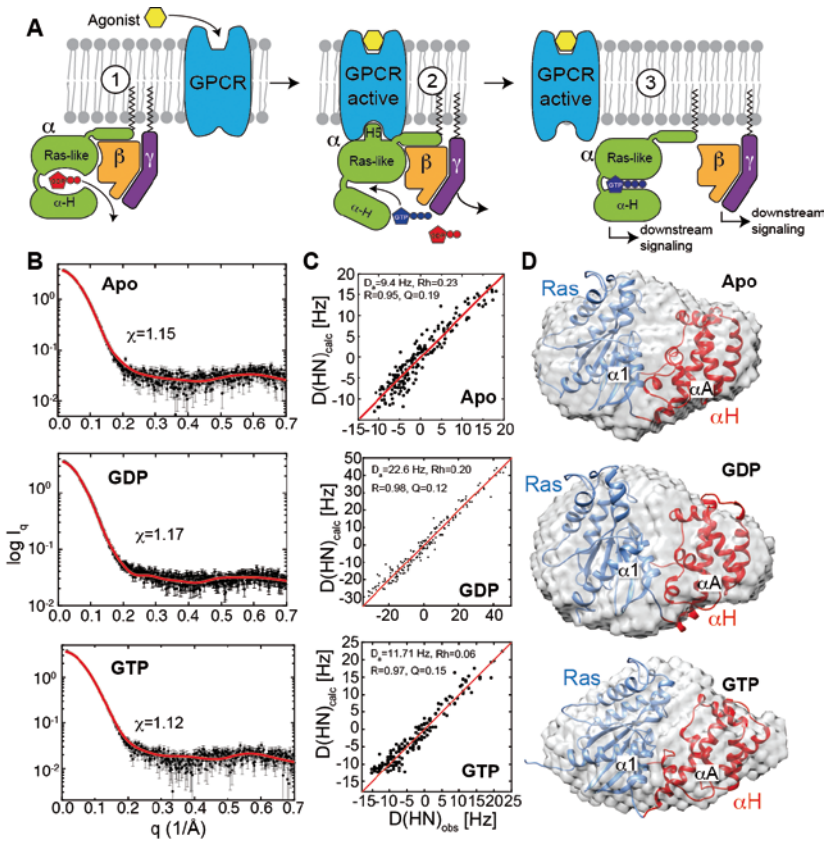
The research of the Focus Group Structural Membrane Biochemistry is concentrated on the structure and function of membrane proteins and their partner proteins using mainly NMR spectroscopy, but also a variety of other biophysical and biochemical methods. We are interested in the mechanism and the mode of action of membrane protein systems connected to cancer, neurological disorders, and metabolic diseases. For these pharmaceutically relevant membrane protein systems, molecular and structural details are sparse or absent.

In order to obtain high-quality structural data, we are employing cutting-edge biochemical methods for membrane protein sample preparation, using various membrane mimetics, like detergent micelles, detergent-lipid bicelles, and phospholipid nanodisks, a novel detergent-free and native-like membrane system. This system has recently been optimized in the lab to enable structure determination by NMR and electron microscopy [1]. More recently, we have established a protocol for high-resolution structure determination of membrane proteins in nanodisks. A combination of specific isotope labeling and suitable NMR methods yielded the first protein side chain-based structure of a membrane protein in nanodisks [2].

To produce otherwise elusive eukaryotic membrane proteins, we are employing cell-free protein expression and have adapted this method for the production of selectively labeled membrane proteins that could not be obtained in living cells. We were able to record high-resolution NMR data [4].

A major project in 2015 was the investigation of structural changes and conformational dynamics of a G-protein alpha subunit upon binding to nucleotides [3]. We were able to characterize this important signaling molecule with NMR spectroscopy and small angle X-ray scattering (SAXS). Nucleotide exchange of G-proteins is stimulated by activated G-protein coupled receptors (GPCRs), leading to the propagation and amplification of cellular signals across the biological membrane. The conformational state of a G-protein is crucial for its ability to interact with partner proteins such as other G-protein subunits, GPCRs and downstream effector proteins. We showed that G-alpha conformation in the inactive guanosine nucleotide di-phosphate (GDP)-bound state is highly dynamic where the relative orientation of its structural subunits is fairly ill defined. In its active guanosine nucleotide triphosphate (GTP)-bound state the protein adopts a markedly rigid conformation that induced dissociation of the heterotrimeric G-protein complex and subsequent binding to downstream partner proteins. Our future goal is to study the interaction between a GPCR and the G-protein on the surface of a phospholipid bilayer nanodisk, using NMR and other structural methods, and to investigate changes in dynamics and structure of G-alpha induced by an activated GPCR.

Alumni member
Joka Pipercevic | Doctoral Candidate



1 | Structural changes upon nucleotide binding to a G-protein alpha subunit. (A) Activation mechanism of a G-protein by a G-proteincoupled receptor (GPCR). The agonist-bound activated receptor interacts with the GDP-bound G-protein and induces exchange from GDP to GTP at the alpha subunit. After binding to GTP, the heterotrimeric G-protein dissociates into the alpha and the beta-gamma subunits leading to activation of downstream signaling molecules. (B-D) Structural characterization of the conformational states of a G-protein alpha subunit in the Apo (no nucleotide), GDP- or GTP-bound states by a hybrid approach using small angle X-ray scattering (SAXS) (panel B) and NMR residual dipolar couplings (RDCs) (panel C) to define the relative orientation of the two subdomains in the various states. (D) Structural models of the different states fitted into a bead model obtained by de novo modeling based on SAXS data. In the Apo and GDP-bound forms the two domains adopt a more open conformation permitting nucleotide exchange, whereas the GTP-bound state represents the closed conformation that is locked in a defined domain orientation.

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[3] D. Goricancec, R. Stehle, P. Egloff, S. Grigoriu, A.Plückthun, G. Wagner, and F. Hagn, "Conformational dynamics of a G-protein alpha subunit is tightly regulated by nucleotide binding,” Proc. Natl. Acad. Sci. U.S.A., 2016, in press.

Selected Publication

[4] F. Hagn and G. Wagner, “Structure refinement and membrane positioning of selectively labeled OmpX in phospholipid nanodiscs,” J. Biomol. NMR, vol. 61, no. 3, pp. 249–260, 2015.

Publications by this Focus Group can also be found on page 171.

Focus Group **Synthetic Biochemistry**

Prof. Kathrin Lang (TUM) | Rudolf Mößbauer Tenure Track Professor
Marko Cigler, Susanne Mayer | Doctoral Candidates
Synthetic Biochemistry, TUM

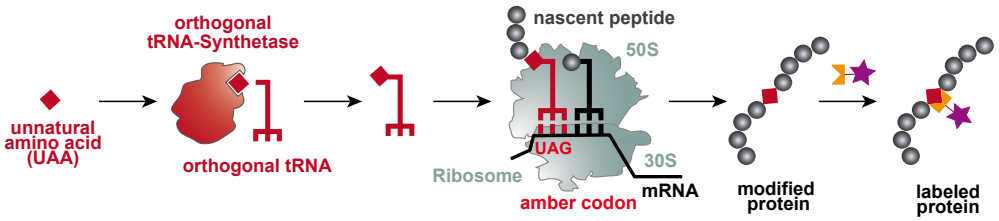
Scientific Reports

Kathrin Lang

Introducing new chemistries into proteins

The Focus Group Synthetic Biochemistry conducts research in the interdisciplinary area of chemical biology, applying concepts from organic chemistry to develop new tools for studying and manipulating complex biological systems.

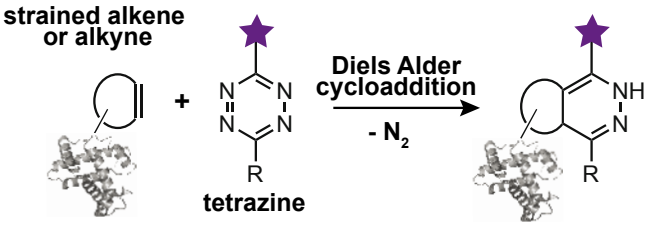
In particular, we develop and apply approaches that allow the site-specific incorporation of unnatural amino acids (UAAs) with tailored physical and chemical properties into proteins in diverse cells and organisms by genetic code expansion. This can be achieved by using an expanded machinery of translation, consisting of an "orthogonal" aminoacyl-tRNA synthetase (aaRS) /tRNA pair that directs the incorporation of an unnatural amino acid in response to an amber stop codon (UAG) placed at a user-defined site in a gene of interest (amber suppression, figure 1). By incorporating new UAAs bearing different functional moieties, it has been possible to leverage genetic code expansion approaches to address unmet challenges in studying and controlling biological processes with a new level of spatial, temporal, and molecular precision [1].



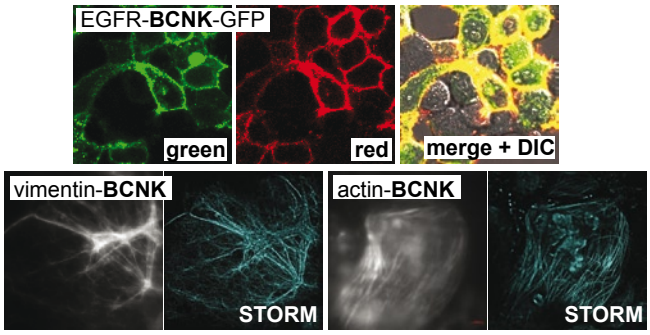
1 | Site-specific incorporation of unnatural amino acids with bioorthogonal handles via amber suppression into proteins and selective labeling of these proteins via bioorthogonal chemistries.

An emerging area with enormous potential is the site-specific incorporation of UAAs that contain functional groups, which allow subsequent chemoselective and rapid labeling with biophysical probes at defined sites within the protein of interest. In the first step, a UAA bearing a bioorthogonal group is co-translationally inserted into the protein, and in a second step the probe is site-specifically attached to the protein (figure 1). We have developed aaRS variants for the efficient site-specific incorporation of several UAAs, bearing strained alkene or alkyne moieties into proteins expressed in *E. coli* and mammalian cells. These amino acids react chemoselectively with tetrazine conjugates via the inverse electron demand Diels Alder cycloaddition (figure 2a). Such cycloadditions are exceptionally fast, highly specific, and thus compatible with living cells; they may also be fluorogenic if the tetrazine is linked to a suitable fluorophore. We have demonstrated the site-specific and selective labeling of proteins *in vitro*, and *in vivo* in *E. coli* and live mammalian cells (both on the surface and intracellularly) with tetrazine-fluorophore conjugates [2]–[3].

Very recently we have used our approach for imaging of cell-surface and intracellular proteins in living mammalian cells via super-resolution techniques such as STORM, STED, and SIM (figure 2b) [4]. The invention of these techniques was awarded the Nobel Prize in Chemistry in 2014, and we envision that our labeling approach will have a further impact on the development of super-resolution techniques and on addressing important biological questions, since it allows the non-invasive, site-specific, efficient and rapid labeling of target proteins using chemical probes with tailored physical and biological properties.



2a | Site-specific labeling of proteins via inverse demand Diels Alder cycloadditions



2b | Fluorescent labeling of cell membrane and intracellular proteins in living mammalian cells.

We have used our bioorthogonal chemistry also to selectively inhibit a target protein (a kinase) within living cells that contain closely related protein family members. By installing photoswitchable linkers on an inhibitor, we have shown that we can selectively and reversibly control the activity of a specific enzyme within living mammalian cells [5].

Future aims of our research include gaining insights into mechanisms of complex biological processes through the application of synthetic molecules with tailored functions and properties. Research will focus on the targeted chemical synthesis of new artificial biomolecules (amino acids, proteins, nucleotides, oligonucleotides), designed to investigate and manipulate complex cellular processes *in vitro* and *in vivo* in biological systems. In particular, we plan to extend and apply approaches to site-specifically modify and engineer proteins, thereby endowing them with new function, by using and developing extended, engineered, orthogonal translation machineries *in vivo*. Chemical focus will lie on the synthetic development of new, genetically encodable bioorthogonal reactions, including photo-inducible reactions that enable the *in vivo* site-specific modification of target proteins with modified ligands, oligonucleotides and biophysical probes. This will be interesting not only for the study of important protein interactions and imaging of proteins *in vivo*, but also with regard to drug design and new biomaterials. Furthermore, genetically encodable bioorthogonal reactions will be implemented for the reversible photo-control of enzyme activity *in vivo* to dissect and study biological pathways, thereby enabling the control of biological processes in a reversible fashion by light. Another focus is on development of new proximity-enhanced chemistries to enable structural elucidation of low-affinity protein complexes.

In general, our Focus Group pursues efforts to develop and extend toolkits and approaches with the rational approach of a synthetic organic chemist to contribute to the exploration of questions that arise on the fascinating interdisciplinary boundary of chemistry and biology. The ability to precisely design novel protein functions with new chemistries will open up many possibilities for synthetic biology, drug design, and gene therapy.

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Selected Publications

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Publications by this Focus Group can also be found on page 172.

Focus Group **Theory of Soft Matter**

Prof. Alessio Zaccone (TUM) | Rudolf Mößbauer Tenure Track Professor
Johannes Kraußer, Rico Milkus | Doctoral Candidates
Theory of Soft Matter, TUM

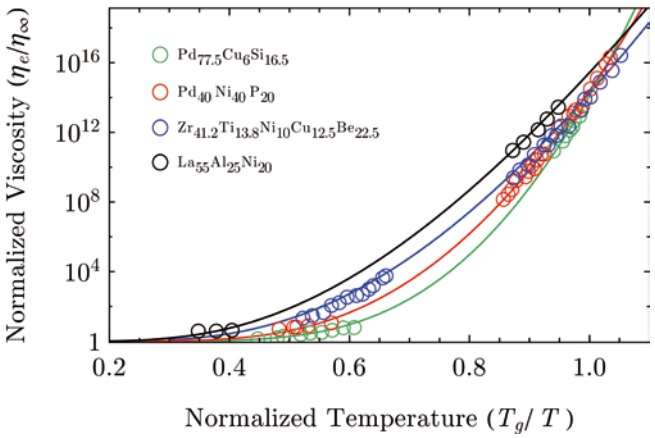
Scientific Reports

Alessio Zaccone

The activity of the Soft Matter Theory Focus Group...

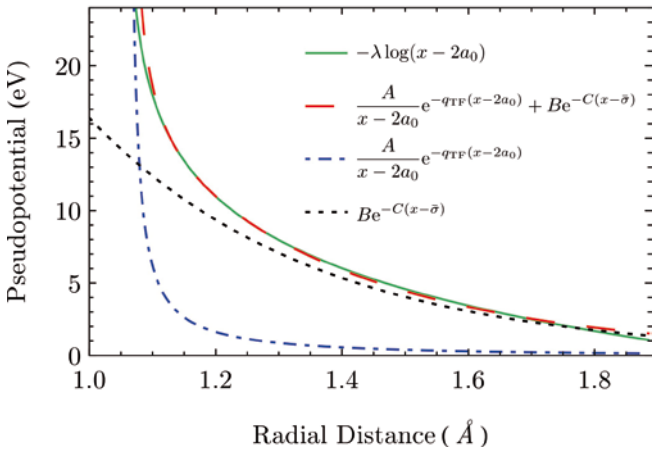
...was very diversified in 2015. An important part of this activity has been directed toward further developing our framework of nonaffine lattice dynamics. This framework is based on our proposed extension of standard lattice dynamics of solids to include the effect of local atomic-level disorder.

One line of research has focused on applying these concepts to metallic glasses, to understand the glass transition and emergence of rigidity in metallic systems when they are cooled down very rapidly from the high-T melt. In this context, we developed a new theory that connects the features of atomic-level structure as embodied in the radial distribution function (the standard tool to describe the atomic structure of liquids) to the macroscopic response in terms of viscosity and high-frequency shear modulus upon varying the temperature in the vicinity of the glass transition. Upon mixing different metallic elements together at high temperatures, new materials called metallic glasses can be formed by rapidly quenching the liquid to room temperatures. This technology enables the formation of solid materials with a disordered atomic-level structure (thus similar to glasses) with outstanding mechanical properties. For example, metallic glasses are as stiff as steel but can sustain much larger loads prior to yielding. This key property could revolutionize several fields of engineering where materials that can sustain large loads under extreme conditions are required. The viscosity of these metallic alloys in the liquid state is the crucial parameter to control the solidification process (glass transition) to form the new materials. At the glass transition, the viscosity increases by many orders of magnitude within a narrow range of temperature. This phenomenon has puzzled scientists for decades, and no first-principle theory is able to capture this dramatic viscosity increase. Our new theory predicts a double-exponential dependence of the viscosity on temperature, in perfect agreement with experimental data obtained at the University of Goettingen, in Germany. These results were published in the *Proceedings of the National Academy of Sciences of the USA* in October 2015.



1 | Viscosity as a function of temperature for various metallic alloys; symbols are experimental data, continuous line are theoretical fits [3].

Along a different line, my group has developed numerical simulations of the vibrational density of states of glasses and defective crystals. In these systems, an anomalously large density of low-frequency of vibrational modes (atomic vibrations about the stable positions) is typically observed; this is referred to as the boson peak of glasses.



2 | Interatomic effective potential estimated from the theoretical fits of viscosity as a function of temperature. The total potential (continuous line) is the sum of a Thomas-Fermi component (dashed-dotted line) representing the ion-ion Coulomb repulsion screened by the electron gas, and of a Born-Mayer component (dashed line) stemming from the Pauli repulsion of overlapping electron shells [3].

Our numerical results show that in model systems where the interatomic interaction is harmonic, the boson peak is exactly the same for both random glasses and defective FCC crystals where interatomic bonds are removed at random. This result is surprising, because the two structures are very different. Using theoretical considerations, we were able to resolve this paradox by showing the role of local inversion-symmetry, which is an important internal symmetry of the lattice. This symmetry is broken in both the glass and the defective crystal, allowing us to identify this symmetry-breaking as the ultimate cause of the boson peak in disordered solids, in a unifying framework. These important results are reported in an article which has been accepted and is in press in *Physical Review B*.

Another theoretical effort has been finalizing a microscopic theory of the effect of local excluded volume correlations on the values of the shear and bulk elastic moduli of amorphous solid. We demonstrated that local packing correlations are responsible for larger values of bulk modulus with respect to shear modulus because these correlations reduce the nonaffine displacements responsible for the lowering of the elastic moduli in disordered materials. The results have been published by the journal *Scientific Reports (Nature)*.

We also collaborated with the group of Prof. Peter Schall at the University of Amsterdam on the interpretation of experimental X-ray scattering data on colloidal glasses that are simultaneously being deformed with oscillatory shear. Upon increasing the oscillation amplitude, the glass undergoes a mechanical failure transition, i.e., a sharp transition to a liquid-like state across a critical strain amplitude. Our theoretical model allows us to elucidate the symmetry induced by the strain in the solid glass, which is due to the existence of affine components of the response, which vanish altogether at the transition. These results have been published in the journal *Scientific Reports (Nature)*.

Our disordered elasticity model has also been applied to quantitatively describe and understand the effect of nanoparticle filler to reinforce the mechanical response of nano-composite rubber materials. Results were published in the journal *Polymer*.

Other projects were finalized in 2015 in the field of nanoparticles in solution. In a paper in collaboration with the Helmholtz Zentrum Berlin, the catalytic activity of gold nanoparticles for organic reactions was demonstrated using both experiments and theoretical analysis. Results were reported in the journal *Catalysis Letters*. In another contribution, our model for gelation kinetics of nanoparticles was used to elucidate the role of molecular-level structuring of water molecules in the gelation kinetics of colloidal silica in the presence of different ions. In terms of different water structuring, we were able to explain why monovalent salts, in the same concentration in water, induce very different gelation times of silica particles. This work was published in *Journal of Physical Chemistry Letters*.

We also applied this kinetic model to quantitatively analyze and model the kinetics of aggregation of thermoresponsive polymers in solution. Our model was used to interpret neutron scattering data in collaboration with the group of Prof. Christine Papadakis and Prof. Peter Müller-Buschbaum in the TUM Physics Department. The results have been published in the journal *Macromolecular Rapid Communications*. Finally, also in the area of polymer and bio-polymers, we developed numerical simulations to study the thermal breakup of non-covalently bonded polymers, including bio-polymers. Our simulations show that the distribution of fragments is bell-shaped for flexible filaments but becomes U-shaped for stiff filaments. These results are reported in the *Journal of Chemical Physics*.

Selected Publications

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Publications by this Focus Group can also be found on page 172.


Prozeß-
Kühlwasser VL
Prozeß-
Kühlwasser VL
Prozeß-
Kühlwasser RL
Betriebs-
Wasser
WNC
Kühlwasser
WCF
WCR

Focus Group **Viral Hepatitis**

Prof. Jane McKeating (University of Birmingham) | Hans Fischer Senior Fellow
Anindita Chakraborty, Lisa Wolff | Doctoral Candidates
Prof. Ulrike Protzer, Virology, TUM

Scientific Reports

Jane McKeating

Research focus: Chronic infection of the liver is a major global health problem, with an estimated 400 million individuals infected with hepatitis B, C or Delta viruses (HBV, HCV, HDV) at risk of progressive liver disease, liver cirrhosis, and hepatocellular carcinoma. Viral hepatitis is the major cause of hepatocellular carcinoma, for which we have very limited therapeutic options, rendering it the second most frequent cause of cancer-related death. This highlights the need to increase our understanding of host pathways playing a role in virus control and in viral-associated carcinogenesis.

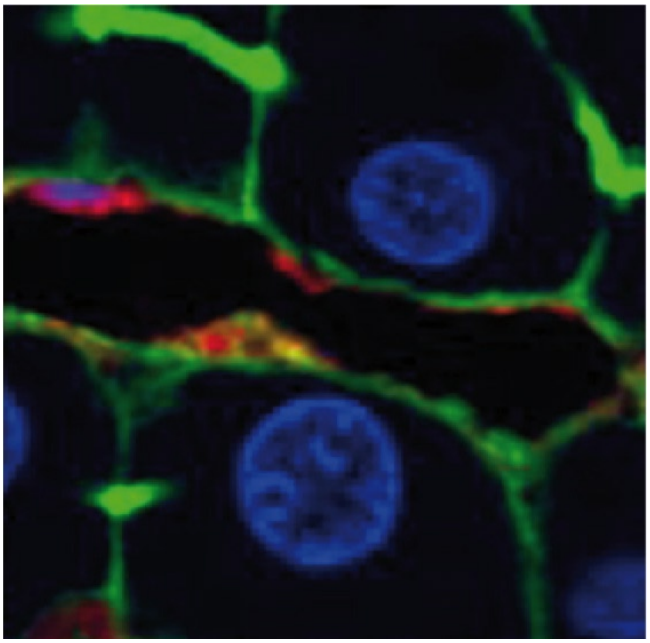
Hepatitis B is one of the world's unconquered diseases, with approximately 4% of the world's population suffering with chronic HBV infection (WHO March 2015). While a prophylactic vaccine exists, current antivirals control HBV but don't eliminate the virus. Only interferon does so in 15% of treated subjects, but at a high cost in terms of high side-effects. In contrast, recently available antiviral agents for HCV can eliminate the virus in about 90% of patients, but a vaccine is missing. For the hepatitis Delta virus, no specific treatment exists at all. Thus, new treatments are urgently needed. The high treatment costs for hepatitis C, along with the risk of re-infection, highlight the need for continued research to develop new antiviral drugs for hepatitis B and Delta and a hepatitis C vaccine.

Our goals are to gain an improved understanding of the molecular pathways that allow virus persistence and are involved in disease pathogenesis, and to translate this molecular understanding into novel therapies.

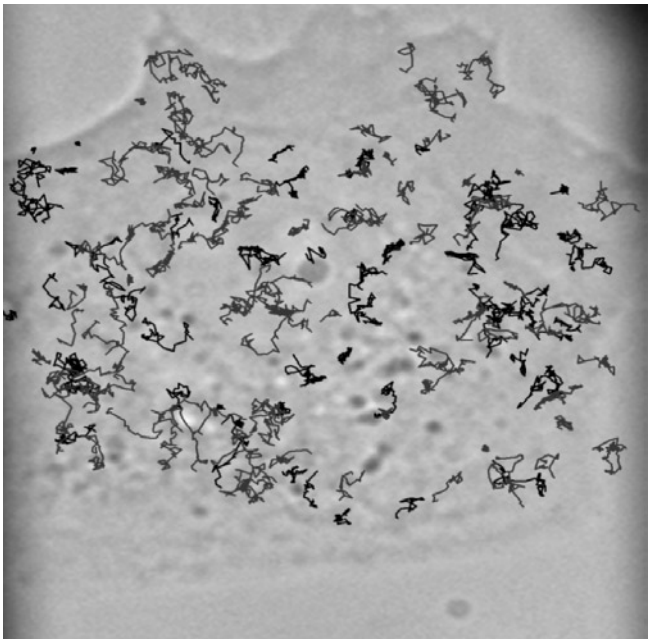
New methodology to quantify hepatitis B virus entry.

Our limited knowledge of the host pathways regulating hepatitis B virus (HBV) entry and dissemination hinders the development of model systems that recapitulate the dynamics of HBV infection and antigen expression in the liver. Lentiviral-based pseudoparticles are frequently used to study the entry pathways of a range of viruses, including human immunodeficiency virus (HIV), hepatitis C virus (HCV), influenza and Ebola, providing a functional and quantitative measurement of viral glycoprotein-receptor interactions. We optimized the genesis of infectious lentiviral pseudoparticles (HBVpp) and demonstrated that HBVpp preferentially infect hepatoma cells expressing the recently discovered bile salt transporter NTCP. However, non-liver cells engineered to express NTCP failed to support HBVpp infection, suggesting that additional hepatocyte-specific factors are required for HBVpp entry and fusion. These results highlight the value of the HBVpp system to dissect the pathways of HBV entry and dissemination (Meredith 2015).

New recruits: Lisa Wolff and Anindita Chakraborty registered for their PhDs in autumn 2015 at the TUM School of Medicine doctoral program in Experimental Medicine and will be mentored by PIs within the TUM-IAS Focus Group. Lisa will generate antibodies to redirect CD8 T cells to cure HBV infected cells, and Anidita will study HBV entry pathways.



1 | Imaging hepatitis C virus particles (red) 1h after perfusion into a human liver sample, where the virus localizes at the surface of hepatocytes (green).



2 | Single particle tracking of hepatitis C virus particles at the basolateral surface of polarized HepG2 cells.

Grant funding news: Continued funding for The German Center for Infection Research (DZIF) 2016–2020 was granted. Within DZIF, the TUM-IAS Focus Group Viral Hepatitis contributes to the "HDV cure" and "HBV cure" projects with Ulrike Protzer directing this research. A Wellcome Trust clinical doctoral training fellowship to study the cross talk between hypoxia and autophagy in hepatitis B virus infection was awarded to Donall Forde to commence autumn 2016 and will be mentored by Jane McKeating and Ulrike Protzer. Our Horizon 2020 EU consortium *Hep-CAR* application to study 'Mechanisms underlying Hepatocellular carcinoma Pathogenesis and Impact of co-morbidities' was funded. Jane McKeating will be the Scientific Director and Ulrike Protzer serves as a PI. The goal of *Hep-CAR* is to further our understanding of common mechanisms underlying hepatocellular carcinoma development and to assess the impact of co-morbidities on disease pathogenesis and response to treatments. On the basis of our success in securing these EU funds we are preparing a Marie Curie PhD training network *LIGHT* 'Liver immunology in health and disease' including UoB and TUM scientists for the January 2016 deadline. This application will provide opportunities for young scientists to train within our TUM-IAS Focus Group.

Prof. Michael Roggendorf and Dr. Sabrina Schreiner (both Institute of Virology, TUM) also work with this Focus Group.

Selected Publications

[1] T. F. Baumert, P. Balfe, L. W. Meredith, K. Hu, U. Protzer, van de Graaf, K. F, X. Cheng, J. A. McKeating, and C. R. Howard, "Lentiviral hepatitis B pseudotype entry requires sodium taurocholate co-transporting polypeptide and additional hepatocyte-specific factors," J. Gen. Virol., vol. 97, no. 1, pp. 121–127, 2016, accepted in 2015.

Publications by this Focus Group can also be found on page 172.

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

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

Scientific Reports

A. Lee Swindlehurst

Coarsely quantized massive MIMO communication systems

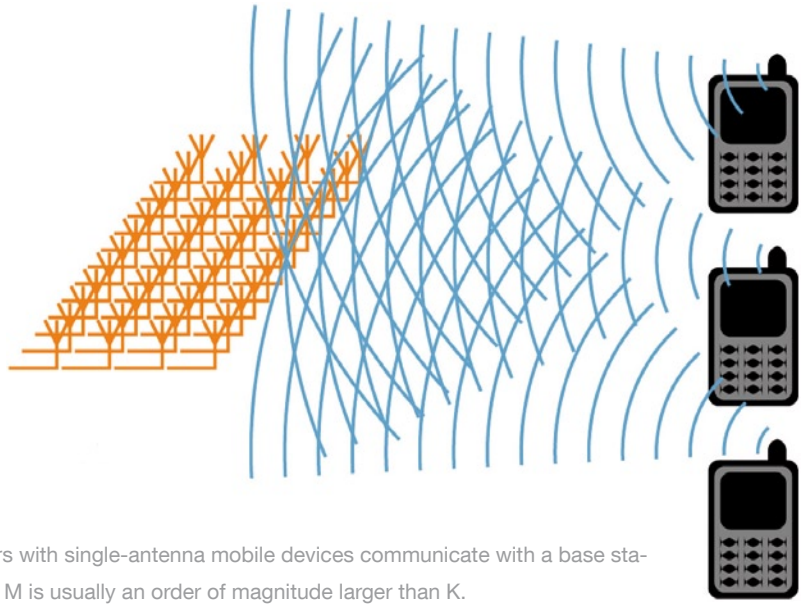
Today's world is characterized by an ever increasing demand for information and data exchange around the entire globe. It is estimated that there are more wireless devices in use today than people on the planet. This explosive growth has created a capacity crisis for mobile operators, with an impact well beyond the inconveniences experienced by casual users. Wireless communication is now a commodity, like roads, water, and electricity, on which the world's economic development and government services rely. Emergency services, medical information systems, environmental monitoring, smart-grid energy distribution, smart transportation systems – all of these technologies depend on reliable access to high-speed broadband wireless. Terms like "big data," "cloud computing," "internet of things," and "5G" provide a glimpse at what this trend might actually mean: All of our electronic devices will be connected, exchange data in an intelligent way, and revolutionize the way public services, logistics, and our daily lives are conducted. It is clear that dramatic improvements in spectral access and capacity will be needed soon to accommodate the multitude of users who need broadband services anytime, anywhere – current industry white papers foresee a mandatory 1000-fold increase in data rate to cope with future demands.

To address this explosively growing demand, we are investigating two new trends in wireless communications, trends that potentially offer enormous gains in wireless capacity: (1) the use of base stations equipped with a very large number (100 or more) antennas that can simultaneously accommodate many co-channel users (referred to as massive MIMO, see figure 1) [1]–[2] and (2) the use of frequencies in the millimeter wave (mmwave) bands, where tremendous amounts of bandwidth are available [3]–[5]. Due to the smaller wavelength at mmwave frequencies, more antennas can be packed in the same volume compared with current communication systems, which makes the massive MIMO idea attractive. Furthermore, although mmwave propagation is not "multipath rich" and thus not ideal for providing spatial degrees of freedom, the large massive MIMO array gain can compensate for this effect. Additionally, the large number of antennas provide additional means to mitigate interference [6].

However, there is still skepticism about the practicality of such systems; increasing both the number of antennas and the bandwidth by an order of magnitude would appear to require an enormous investment in hardware, particularly if a separate RF chain is used for each antenna, considering that the analog-to-digital converters (ADCs) and digital-to-analog converters (DACs) must be extremely high-speed to handle the large mmwave bandwidths. High-precision ADCs/DACs operating at gigasample-per-second rates have extremely high fabrication costs and energy consumption; operating more than 100 of these in parallel is prohibitively expensive.

One particular idea on which we are focusing is the use of very low-resolution ADCs, even down to a single bit of resolution, in which only the sign of the signal at any given sampling instant is retained.

Prof. Josef A. Nossek, Institute of Circuit Theory and Signal Processing, TUM
Prof. Wolfgang Utschick, Signal Processing Methods, TUM



1 | Typical massive MIMO scenario: A number of K users with single-antenna mobile devices communicate with a base station that possesses a large antenna array of M antennas. M is usually an order of magnitude larger than K.

Our research is currently concentrated on one-bit ADCs, and in particular on detection algorithms that exploit the availability of a large number of antennas to compensate for the loss of resolution.

A special class of algorithms known as “message passing procedures” has been shown to yield promising results, as they inherently assume a large system setting [6]. Prior to their application here, they have been successfully used for decoding of low-density parity check codes and for general statistical inference problems.

Closing the ultimate gap to Shannon capacity

“Shannon capacity” refers to the theoretical limit to the rate at which data can be communicated [7]. There is a considerable gap between the rate of today’s communication systems and the Shannon limit because they employ uniform signaling, which violates Shannon’s blueprint of transmitting signal points that follow a Gaussian distribution.

The theory behind this has been known since Shannon’s seminal work in 1948, and many researchers have been studying the idea of probabilistic shaping to transform uniform input bits into shaped symbols that can be transmitted. However, these approaches have rarely been implemented in practical systems, as their complexity was too high and/or needed complicated receiver designs to resolve ambiguities. A key to solving this problem has come from Dr. Georg Böcherer (TUM Institute for Communications Engineering), whose notion of reversing the order of forward error correction (FEC) and shaping circumvents the need for complicated receiver architectures and allows the use of standard, pragmatic schemes [10]. Combining this idea with Patrick Schulte’s (TUM Institute for Communications Engineering) distribution matcher [9], which performs the actual shaping of the uniform input bits, one can obtain a transceiver that is able to close the gap due to shaping.

The only gap that remains is caused by the FEC itself. Even if state-of-the art techniques such as low-density parity-check (LDPC), Turbo, or Polar codes are used, this gap still persists for practical applications, since complexity and latency issues dictate that the code words must have a finite length.

Our work on protograph-based LDPC codes for shaped bit-metric decoding takes the specific channel and shaping conditions into account in order to come up with a flexible and reliable code design approach. These codes can now be combined with the optimized modulation scheme to yield a system that can operate very close to the Shannon limit with high flexibility and for different communication systems, including not only MIMO wireless systems but also wired, optical, and satellite systems.

The TUM team consisting of Georg Böcherer, Patrick Schulte, and Fabian Steiner submitted their proposal for participation in the 2015 Bell Labs Prize competition, which awards ideas that "have the potential to change the way we live, work, and communicate with each other." Initially, 250 ideas were submitted in April, and the field was narrowed to seven finalists in December after an intense period of collaboration and field trials to prove practical applicability. Eventually, one first prize was awarded; the TUM team tied for third place and received an award of $25,000.

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[7] A. Mezghani and J. A. Nossek, "Belief propagation based MIMO detection operating on quantized channel output," in 2010 IEEE International Symposium on Information Theory - ISIT, pp. 2113–2117.

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[9] P. Schulte and G. Böcherer, "Constant composition distribution matching," IEEE Trans. Inform. Theory, vol. 62, no. 1, pp. 430–434, 2016, accepted in 2015.

Selected Publications

[10] G. Böcherer, F. Steiner, and P. Schulte, "Bandwidth efficient and rate-matched low-density parity-check coded modulation," IEEE Trans. Commun., vol. 63, no. 12, pp. 4651–4665, 2015.

[11] F. Buchali, G. Böcherer, W. Idler, L. Schmalen, P. Schulte, and F. Steiner, "Experimental demonstration of capacity increase and rate-adaptation by probabilistically shaped 64-QAM," in European Conference on Optical Communication (ECOC), Valencia, Spain, 2015.

[12] F. Buchali, F. Steiner, G. Böcherer, L. Schmalen, P. Schulte, and W. Idler, "Rate Adaptation and Reach Increase by Probabilistically Shaped 64-QAM: An Experimental Demonstration," J. Lightwave Technol., vo. 34, no. 7, pp. 1599–1609, 2016, accepted in 2015.

[13] F. Steiner, G. Böcherer, and G. Liva, "Protograph-based LDPC code design for shaped bit-metric decoding," IEEE J. Select. Areas Commun., vol. 34, no. 2, pp. 397–407, 2016, accepted in 2015.

[14] L. You, X. Gao, A. L. Swindlehurst, and W. Zhong, "Adjustable phase shift pilots for sparse massive MIMO-OFDM channels," in IEEE 16th International Workshop on Signal Processing Advances in Wireless Communications (SPAWC), 2015, pp. 206–210.

Publications by this Focus Group can also be found on page 174.

2 | Fabian Steiner, Georg Böcherer, and Patrick Schulte in front of the statue of Claude E. Shannon (the father of information theory) after receiving second place in the 2015 Bell Labs Prize.

Focus Group **Fiber-Optic Communication and Information Theory**

Dr. René-Jean Essiambre (Bell Labs, Alcatel-Lucent) | Rudolf Diesel Industry Fellow
Dr. Luca Barletta, Dr. Mansoor Yousefi | Postdoctoral Researchers
Prof. Gerhard Kramer, Communications Engineering, TUM

Scientific Reports

René-Jean Essiambre

Information theory for optical fiber channels

Optical fiber forms the backbone of the world's communication networks, carrying much of the Internet traffic. A large bandwidth, on the order of THz, is available in silica fiber, allowing reliable transmission of information over distances as long as 6000 km with only 0.2 dB/km loss. Pulse propagation is well modeled by the stochastic nonlinear Schrödinger (NLS) equation.

Three factors interact in this equation: chromatic dispersion, Kerr nonlinearity, and amplified spontaneous emission (ASE) noise. Several studies suggest that global fiber-optic networks face a looming "capacity crunch" due to the impact of the Kerr nonlinearity. This alarming observation has called for more research into understanding the challenges presented by the fiber nonlinearity.

The objective of the Focus Group in 2015 was to further develop results on the fundamental limits on fiber capacity. We made progress in several directions.

1. The first upper bound on the capacity of optical fiber was established in [1]–[2]. The bound uses the split-step Fourier method as the basic tool. The main insight was that the nonlinearity of optical fiber does not change the energy and entropy of a signal.

2. Experiments showed the viability of nonlinear frequency division multiplexing (NFDM) via the nonlinear Fourier transform (NFT) [3]. This work was in collaboration with the Hong Kong Polytechnic University.

3. An efficient inverse NFT was developed in the defocusing regime, e.g., in fibers with negative dispersion. The algorithm avoids complex numerical methods, some of which are based on complicated integral equations [8]. The main insight was to consider the inverse NFT as the dual of the forward NFT, thereby using the same algorithms for both transforms.

4. Using the new algorithms, NFDM simulations were generalized from single-user to multi-user channels for the first time. Initial results are promising, indicating the potential of interference-free communication over multi-user optical fiber. Error-free transmission was demonstrated at 3 bits/symbol in the defocusing regime and in the presence of distributed noise [8].

5. New bounds on channels with phase noise were established [4]–[5]. Phase noise arises due to the instability of oscillators, including lasers, and limits the capacity of optical links.

6. New tracking algorithms for compensating phase noise were developed [6]–[7], in collaboration with a doctoral student from the Technical University of Denmark (DTU).

7. A new simplified model for waveform propagation in fiber was developed, called the Kolmogorov-Zakharov model.

Alumni Member
Prof. Frank R. Kschischang (University of Toronto) | Hans Fischer Senior Fellow

1 | Group photo of MIO 2015 participants with St. Nicholas.

Workshops

The Focus Group organized two workshops, named the Munich Workshop on Information Theory of Optical Fiber (MIO 2014 and MIO 2015). The workshops focused on information theory, especially how fiber nonlinearities affect channel capacity, and on experimental work that leads to new insights on capacity.

MIO 2015 took place on December 7–8 and was attended by over 90 leading researchers from the fields of information theory, optical fiber, and photonics. This was approximately three times the number of participants as the year before (MIO 2014). MIO 2015 featured 13 invited talks and 13 poster presentations, as well as in-depth discussions. Participants were scientists and engineers from universities and industry.

More information on the workshops, such as the participating institutions, slides, posters, and pictures, can be found on the following TUM LNT web pages:

MIO 2014: http://www.lnt.ei.tum.de/en/events/munich-workshop-on-information-theory-of-optical-fiber-2014/

MIO 2015: http://www.lnt.ei.tum.de/en/events/munich-workshop-on-information-theory-of-optical-fiber-2015/

Selected Publications

[1] G. Kramer, M. I. Yousefi, and F. R. Kschischang, “Upper bound on the capacity of a cascade of nonlinear and noisy channels,” in 2015 IEEE Information Theory Workshop, Jerusalem, Israel.

[2] M. I. Yousefi, G. Kramer, and F. R. Kschischang, “Upper bound on the capacity of the nonlinear Schrödinger channel,” in IEEE 14th Canadian Workshop on Information Theory (CWIT), St. John’s, Canada, 2015, pp. 22–26.

[3] Z. Dong, S. Hari, T. Gui, K. Zhong, M. I. Yousefi, C. Lu, P.-K. A. Wai, F. R. Kschischang, and A. P. T. Lau, “Nonlinear frequency division multiplexed transmissions based on NFT,” IEEE Photon. Technol. Lett, vol. 27, no. 15, pp. 1621–1623, 2015.

[4] L. Barletta and G. Kramer, “Upper bound on the capacity of discrete-time Wiener phase noise channels,” in 2015 IEEE Information Theory Workshop (ITW), Jerusalem, Israel, pp. 1–5.

[5] L. Barletta and G. Kramer, “Lower bound on the capacity of continuous-time Wiener phase noise channels,” in 2015 IEEE International Symposium on Information Theory (ISIT), Hong Kong, China, pp. 2326–2330.

[6] T. Fehenberger, M. P. Yankov, L. Barletta, and N. Hanik, “Compensation of XPM interference by blind tracking of the nonlinear phase in WDM systems with QAM input,” in European Conference on Optical Communication (ECOC) 2015, Valencia, Spain, pp. 1–3.

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[8] X. Yangzhang and M. I. Yousefi, “Implementation of the inverse nonlinear Fourier transform,” poster presentation at the Munich Workshop on Information Theory of Optical Fiber, Germany, 2015 (available on the MIO 2015 webpage).

Publications by this Focus Group can also be found on page 174.

Focus Group **Automated Controller Synthesis**

Prof. Anca Muscholl (LaBRI, University of Bordeaux) | Hans Fischer Senior Fellow
Dr. habil. Igor Walukiewicz (CNRS, LaBRI) | Visiting Fellow
Dr. Denis Kuperberg | Postdoctoral Researcher

Scientific Reports

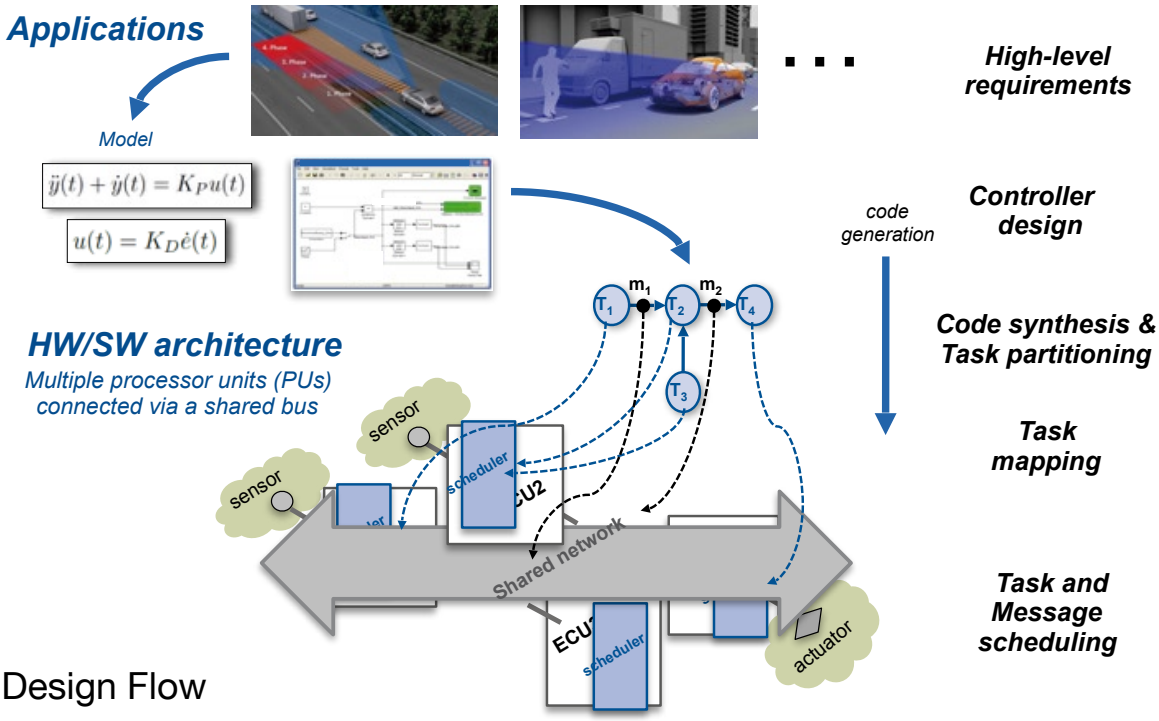
Anca Muscholl

The research of the newly established Focus Group Automated Controller Synthesis concentrates on algorithmic techniques for the design and validation of complex controlled systems. Cars, planes, power grids, manufacturing plants, robots, and many other systems are increasingly controlled by software and require formal certification. Controller synthesis techniques produce correct-by-construction solutions that do not need post factum testing or verification. They are a very promising approach to address today's growing complexity and time-to-market pressures.

A distinguishing feature of complex controlled systems is that they often involve communication over a network connecting spatially distributed devices (networked control systems). For example, contemporary automotive in-vehicle architectures consist of up to 100 electronic control units, sensors, controllers, and actuators connected via shared buses. The current state of the art for the design of these networks is based on a number of abstractions or idealistic assumptions about the implementation platform for the controllers. These include the availability of infinite arithmetic precision, zero computation and communication delays, and no loss of control signals, to name a few. As a result, control performance that is obtained at the controller design phase significantly deviates after the mathematical models of the designed controllers are implemented on a hardware architecture. This so-called semantic gap between controller models and their implementations gives rise to the need for intensive post factum testing and debugging, which currently dominate the design cost in many application domains. Further, since the testing, debugging and iterative design processes are often ad hoc in nature, this makes certification very time-consuming. One of our objectives is to develop techniques for joint automated design and verification of controllers and their implementation infrastructure — which includes both software requirements and quantitative characteristics of the computation/communication architecture.

Distributed control synthesis is also a major challenge for the development of high-performance software such as concurrent programs. Such programs are particularly fault-prone, because faults may happen under very specific thread schedules. Since the likelihood of exploring such "corner case" schedules during regular testing is very low, fault tolerance is a major concern of developers. The vision here is to let the programmer design the system so that it behaves correctly in the "happy case," and let automatically synthesized controllers deal with the multiple corner cases arising from the interplay of exceptional events, taking suitable steps towards error recovery. The mathematical theory and algorithmic solutions for controller synthesis are well developed for monolithic, centralized software. But these techniques cannot be transferred easily into a distributed environment because of additional constraints imposed by communication and synchronization.

Prof. Samarjit Chakraborty, Institute of Real-Time Computer Systems, TUM
Prof. Javier Esparza, Foundations of Software Reliability and Theoretical Computer Science, TUM



Design Flow

Our first objective here is to develop scalable algorithms for building distributed monitors, a prerequisite for distributed control. Identifying settings where solving distributed games for controller synthesis is tractable is a leading theme that will help in setting up a generic algorithmic approach for the certification of complex distributed software.

Further members of the Focus Group are Prof. Matthias Althoff (Cyber-Physical Systems, TUM), and Prof. Majid Zamani (Hybrid Control Systems, TUM).

Selected Publications

[1] P. Mundhenk, S. Steinhorst, M. Lukasiewycz, S. A. Fahmy, and S. Chakraborty, “Security analysis of automotive architectures using probabilistic model checking,” in 52nd Annual Design Automation Conference, 2015, pp. 1–6.

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Publications by this Focus Group can also be found on page 175.

Focus Group **Cognitive Technology**

Prof. Angelika Peer (University of the West of England) | Carl von Linde Junior Fellow
Prof. Martin Buss, Automatic Control Engineering, TUM

Scientific Reports

Angelika Peer

Haptic interaction and collaboration in human-human and human-robot dyads

Touch is an indispensable component of interaction in real and virtual collaborative environments. Compared to other fields of interaction research, such as communication via speech and gestures, haptic interaction is still largely underrepresented. Doubtlessly, however, haptic interaction is an essential component for future robotic systems that are expected to collaborate closely with humans in performing physical tasks, as required when assisting elderly persons in standing up, walking, and sitting down or when enhancing motor training and rehabilitation.

In such situations, people are not only expected to interact, but also to collaborate, which means that both partners try to accomplish a common goal and therefore share intentions and action plans. Thus, haptic collaboration not only implies the physical coupling of two bodies either directly or via an intermediate object, but also involves higher-level cognitive processes. The underlying principles of these processes, however, are largely unknown, which makes their implementation on a robotic platform challenging.

To gain better insight in processes involved in intention recognition and decision-making, a series of recordings of human-human dyads was made over the last years. This involved the recording of pairs of healthy subjects in typical decision-making situations, as well as the recording of more complicated situations capturing the interaction of a caregiver and an elderly person in situations of standing up, walking, and sitting down. We also undertook first attempts to model decision-making processes by investigating the win-stay-lose switch rule and the drift-diffusion model first introduced in cognitive science. Both models were analyzed for their capability to model haptic interaction in human-human dyads and were finally also implemented on a robotic platform to mimic human-like haptic assistance behavior [1].

While these early models were able to capture basic human intention-recognition and decision-making rules, we decided to move on to a more complex cognitive decision-making framework formulated as a dynamical model that enforces concepts of “embodied embedded cognition,” where intelligent behavior is a product of interaction between the agent’s body, cognitive abilities, and the environment he is situated in to realize human action, plan and intention recognition, and which is based on the dynamic field theory. First implementations considered the learning of human individual action templates from observation. More recent versions include also the possibility to interface with human motor control models for internal simulation of human movements. Ongoing work focuses on extending the developed framework toward different collaboration policies, as well as the integration of motor control models involving physical interaction.

Reference

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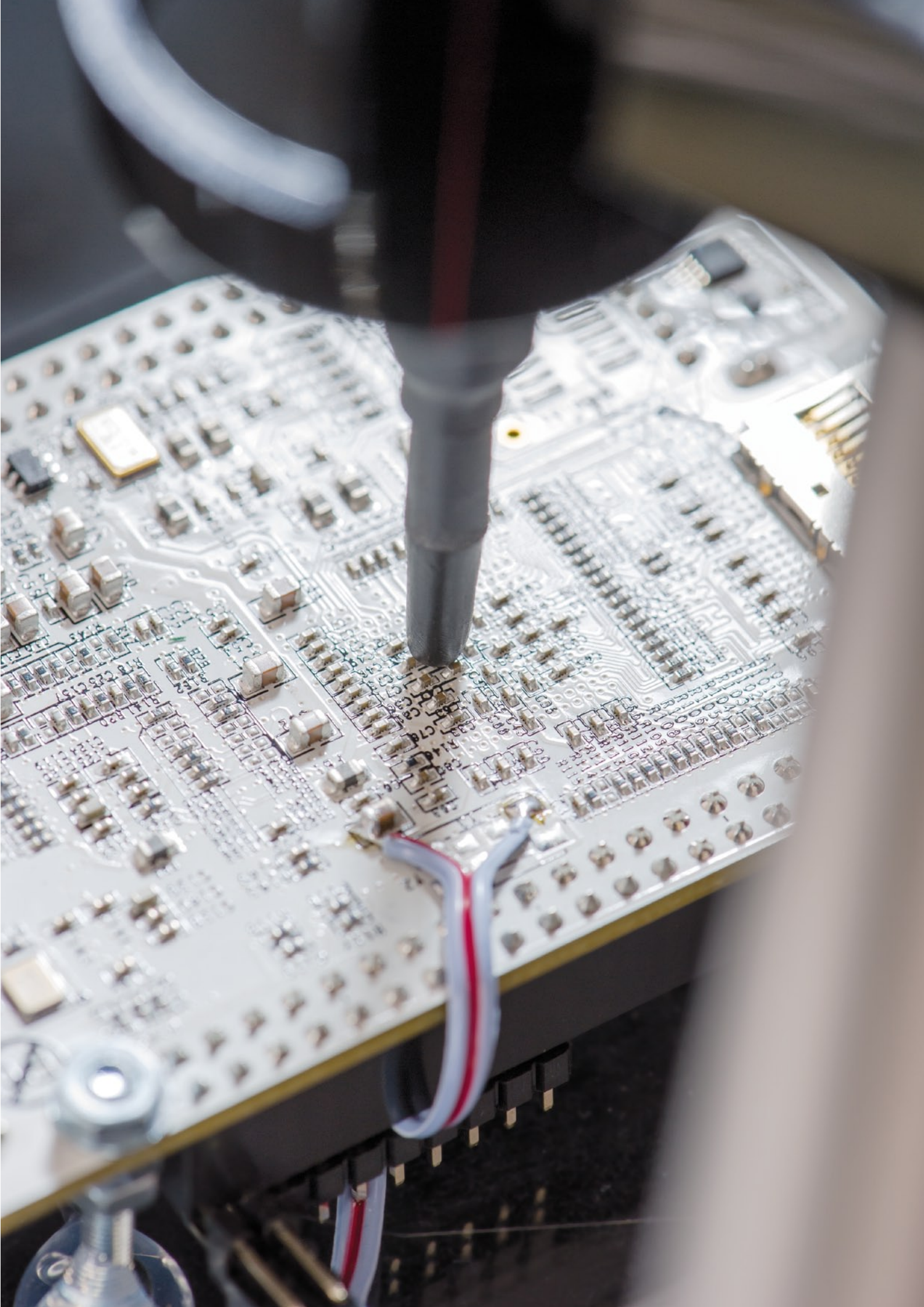
Publications by this Focus Group can also be found on page 175.

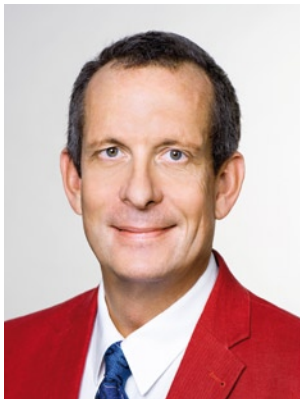


Focus Group **Control and Robotics**

Prof. Martin Buss (TUM) | Carl von Linde Senior Fellow
Prof. Dongheui Lee (TUM) | Carl von Linde Junior Fellow
Sang-Ik An | Doctoral Candidate
Automatic Control Engineering, TUM

Scientific Reports

Toward robots beyond human dexterity

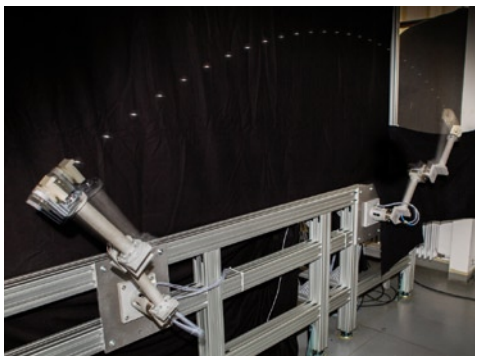


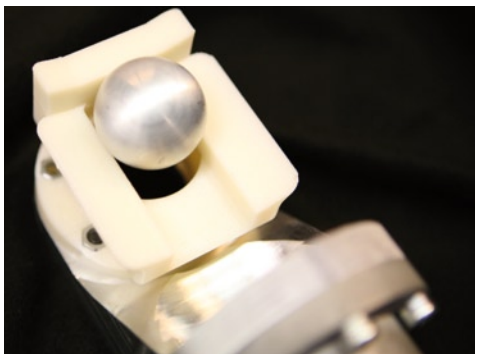
Martin Buss

The recent history of robotics has shown that the applicability of new robotic systems scales significantly with their ability to match and exceed human capabilities. Today, robots provide capabilities like fast and precise manipulation at the cost of being oversized and highly specialized. However, to conquer new fields of application, robots must become capable of handling a large variety of objects and tasks in real-world scenarios.

Still, the most common way to execute a robotic manipulation task is to grasp an object with a specialized gripper and then to relocate or reorient it before release. The advantage of such a “pick and place” strategy is clearly the fixed object state with respect to the robot coordinate frame during the operation. But a grasp also limits the state of the object to the kinematic and dynamic capabilities of the robot in use. Consider, for example, the transport of an object from a point A to a point B. If this task should be done by a robot manipulator, the workspace size of the robot must scale with the distance the object is supposed to travel. Alternatively, additional systems such as conveyor belts or autonomously driving robots are used.

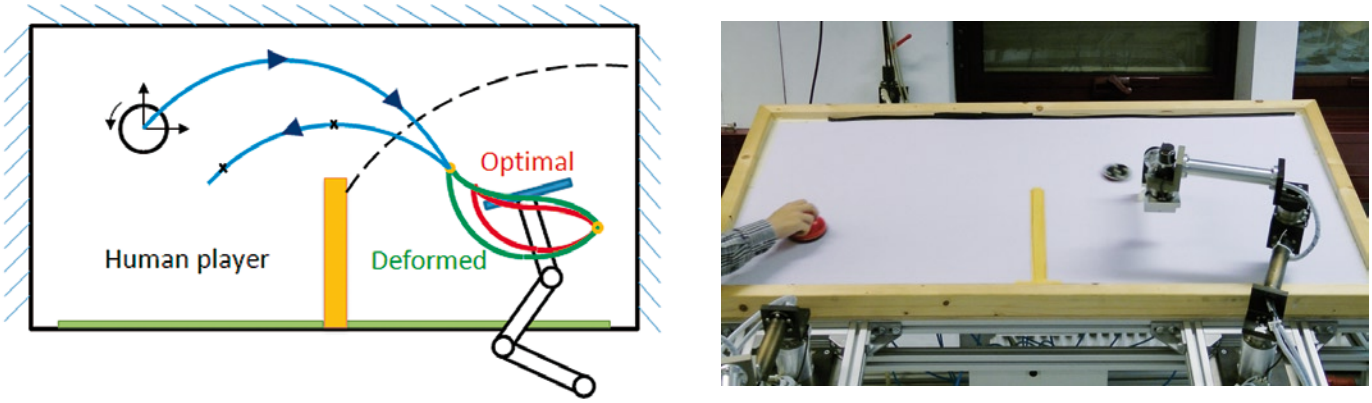
We consider solutions based on dynamic manipulation, which actively exploit the dynamics of a manipulated object instead of merely tolerating them. Throwing an object to a desired target and catching it on the other side is just one example where two generic simple manipulators could replace a large and expensive handover transit system. As a result, the throughput capability is significantly increased.





1 | Stroboscopic image of throwing and catching of a steel ball (left). Precision and repeatability of the task is achieved by using a nonprehensile end-effector (right) [1].

Moreover, future multi-purpose robots will be better able to perform a large variety of tasks with various object shapes and size without grasping. The term “non-prehensile” describes such manipulation that is performed without grasping. The non-static contacts between robots and objects bring up new challenges, such as on-line replanning of motions, reduction of impact forces to prevent damage, and task execution with success guarantees.



2 | Several experiments are implemented to investigate optimality and robustness of dynamic manipulation on an inclined air-table, which provides decreased gravity. The findings on trajectory deformation are tested in a planar volleyball scenario [2].

Our recent investigations take into consideration previous results of off-line optimal trajectory generation with a direct collocation method and extend them with the approach of online trajectory deformation to fit real-world feasibility requirements. We gain the ability to modify trajectories to fit new boundary conditions and preserve the acceleration profile of precalculated optimal trajectories.

This new method is based on spline decomposition of Laplacian trajectory editing (LTE), which minimizes the acceleration deviation between optimal and deformed trajectories and guarantees non-colliding trajectory generation.

This minimization results in preservation of the optimal acceleration profile for the deformed trajectory. The problem has a reduced dimensionality, as we split our trajectory into a set of piecewise polynomials for which we can guarantee boundedness of the trajectory and the resulting torques [3]. This spline decomposition drastically decreases computational time for trajectory generation by deformations and provides real-time capability. Moreover, hierarchical re-segmentation of equitemporally spaced sampling points in the robot task space provides the capability of on-line obstacle avoidance.

All in all, such a deformation framework is a tool to reactively generate new trajectories on line, do safety checks, and guarantee feasibility for the overall motion. With these tools at hand, we now plan to use formal methods from control theory to directly address the reliability of manipulation tasks and thus to be able to guarantee task success.

Selected Publications

[1] M. M. Schill, F. Gruber, and M. Buss, “Quasi-direct nonprehensile catching with uncertain object states,” in 2015 IEEE International Conference on Robotics and Automation (ICRA), pp. 2468–2474.

[2] A. Pekarovskiy, T. Nierhoff, J. Schenek, Y. Nakamura, S. Hirche, and M. Buss, “Online deformation of optimal trajectories for constrained nonprehensile manipulation,” in 2015 IEEE International Conference on Robotics and Automation (ICRA), pp. 2481–2487.

[3] A. Pekarovskiy, T. Nierhoff, S. Hirche, and M. Buss, “Online deformation of locally optimal trajectories: feasibility and upper bound on control inputs,” in IEEE Conference on Decision and Control, Osaka, Japan, 2015.

Publications by this Focus Group can also be found on page 175.

Focus Group **Control and Robotics**

Prof. Martin Buss (TUM) | Carl von Linde Senior Fellow
Prof. Dongheui Lee (TUM) | Carl von Linde Junior Fellow
Sang-Ik An | Doctoral Candidate
Automatic Control Engineering, TUM

Scientific Reports

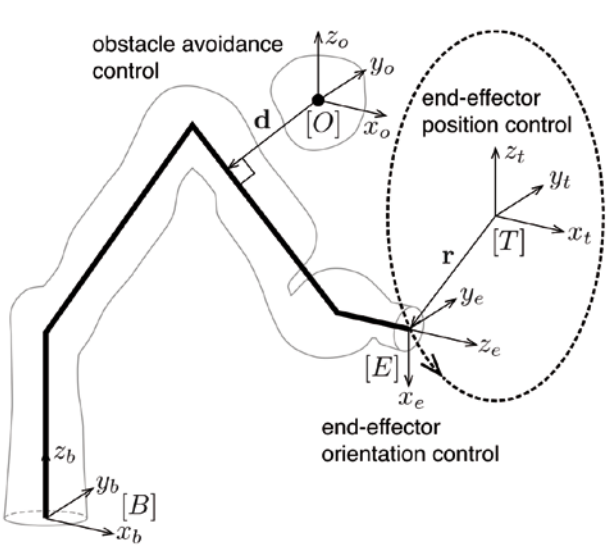
Dongheui Lee

Control strategies with multiple tasks and multiple task definition

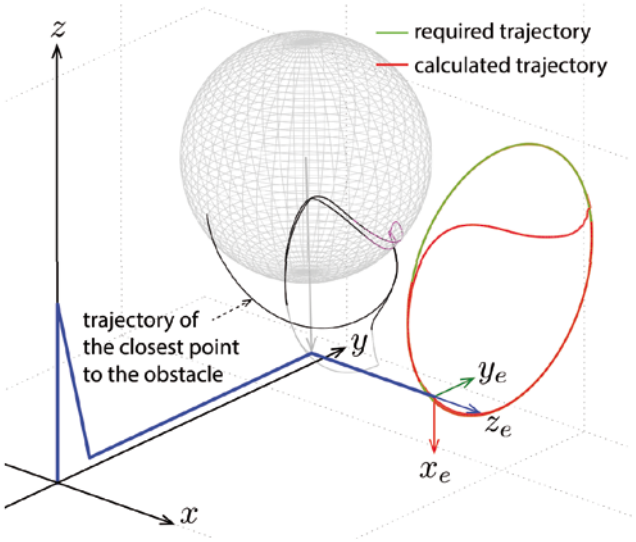
In the natural world, variability is one of the most important strategies for living creatures to survive in the unstructured and unpredictable environment. As seen from the control point of view, they can easily modify the currently executing motions to respond to the unpredicted events, e.g., escaping from predators while feeding. Also, from the mechanical point of view, redundant body structures enable them to consider multiple goals at the same time to adapt to complicated environments, e.g., catching an object while avoiding obstacles. For a roboticist, it is a reasonable approach to construct control strategies that capture such features to make robots available in more practical cases, e.g., a human-friendly environment. We have developed robot control methods that can handle multiple tasks and multiple task definitions.

In robot kinematic control, a task is defined with a task variable, which is a mathematical description of motions of specific body parts, and a desired value. The control problem is to find a smooth joint motion to move the robot that realizes the desired task motion. If there are multiple tasks, then we find a joint motion that realizes multiple tasks at the same time. A difficulty arises when the tasks are not compatible with each other, so that no solution exists that realizes all tasks. A well known strategy for this problem, which is called prioritized inverse kinematics (PIK), is to assign different priorities to the individual tasks and to find a solution that realizes tasks with higher priorities when there is a conflict. However, this sophisticated approach suffers from discontinuity of the solution, making it impossible to execute the calculated motion. Therefore, in this regularization technique priority always comes at the expense of task errors caused by imperfect orthogonalization and inversion. We have proposed a PIK method that can eliminate the problem of the imperfect orthogonalization [1]. The basic idea is to separate the orthogonalization process from the inversion process by using the QR decomposition, which is a matrix decomposition technique that finds an orthonormal basis. Also, the numerical reconditioning technique that uses both QR and Cholesky decompositions further improves the performance of the proposed method.

The environment in our daily life is unpredictable, so the robot in that situation should be adaptable to the unexpected events, e.g., human movement near the robot. In other words, the robot should be able to replace currently executing tasks with the tasks required by the new events. If we consider multiple tasks with priority, then the problem becomes more complicated; a smooth joint motion needs to be calculated from the discontinuous change of the prioritized tasks. To tackle this problem, we have proposed a method called task transition control (TTC), which interpolates joint motions by using barycentric coordinates and linear dynamical systems [2]–[3].



task definitions



simulation results

1 | The end-effector of the robot is supposed to follow the circular path while avoiding the obstacle. If the robot is close to the obstacle, then there is a conflict between the end-effector task and the obstacle avoidance task. The task transition control allows the robot to smoothly switch priority between tasks, so that obstacle avoidance has priority over other tasks only in the vicinity of the obstacle. The simulation results show that there is a modification of the end-effector trajectory to avoid the obstacle.

To begin with, we have built a mathematical description of multiple task definitions that provides an efficient way of handling complicated task definitions, so an event can be easily correlated to a definition of the prioritized tasks. Then, the barycentric coordinates are introduced to represent smooth and bounded transitions among multiple task definitions. Finally, the linear dynamical system is combined with the barycentric coordinates to achieve arbitrary and consecutive task transitions. Our comparative study showed that the proposed method, which interpolates joint motions, generalizes conventional methods that interpolate task motions. The effectiveness of the method was simulated with the 7-DOF manipulator as shown in figure 1.

Reference

[1] S. An and D. Lee, “Prioritized inverse kinematics using QR and Cholesky decompositions,” IEEE International Conference on Robotics and Automation, 2014, pp. 5062–5068.

Selected Publications

[2] S. An and D. Lee, “Prioritized inverse kinematics with multiple task definitions,” IEEE International Conference on Robotics and Automation, 2015, pp. 1423–1430.

[3] M. Saveriano, S. An, and D. Lee, “Incremental kinesthetic teaching of end effector and null space motion primitives,” IEEE International Conference on Robotics and Automation, 2015, pp. 3570–3575.

[4] S. An and D. Lee, “Inverse kinematics with multiple tasks and multiple tasks definitions,” International Workshop on Human-Friendly Robotics, 2015.

Publications by this Focus Group can also be found on page 175.

Focus Group **Networked Cyber-Physical Systems**

Prof. John S. Baras (University of Maryland) | Hans Fischer Senior Fellow
Touraj Soleymani | Doctoral Candidate
Prof. Sandra Hirche, Information-Oriented Control, TUM

Scientific Reports

John S. Baras

The Focus Group on Networked Cyber-Physical Systems (Net-CPS)...

... was established in October 2014 by Hans Fischer Senior Fellow John S. Baras and Sandra Hirche. The purpose of the research undertaken by the group is the development of fundamental principles for the design, manufacturing, and operation of cyber-physical systems (CPS) that can collaborate under various networking arrangements and constraints. CPS are technological systems where physical components and cyber components are tightly integrated. Examples abound, ranging from smart phones, smart sensors, smart homes, and smart cars to smart power grids, smart manufacturing, integrated transportation systems, and human robotic teams, Most modern CPS are actually networked, typically via the Internet or the cloud, or via special logical or physical networks. Examples include modern factories, modern enterprises, heterogeneous wireless networks, heterogeneous wireless sensor networks, social networks over the Internet, the Industrial Internet Consortium (IIC), and the Internet of Things (IoT). When networks are under consideration, new fundamental challenges emerge as the network semantics and characteristics must be modeled and taken into account.

The Focus Group's research is addressing fundamental challenges on two fronts: (a) joint design and performance evaluation at the interface between the cyber and physical components their; (b) the implications of the networked interfaces and the systems' collaborative aspects for their design and performance evaluation.
An additional challenge that has emerged in the last few years, also addressed by the Net-CPS Focus Group, is the incorporation of humans – who must be considered as ubiquitous elements of such networked CPS – as system components from the start of the analysis and performance evaluation.

With doctoral candidate Touraj Soleymani, John S. Baras and Sandra Hirche initiated research on the important topic of "value of information" in order to understand the interrelationship between the communications and data exchanged by the various components and systems in Net-CPS and the task-oriented performance of such systems. The focus of this research thrust is to develop quantitative methodologies that describe instances when actions or decisions must be taken by the various components and systems and explain why. These ideas are central to the event-driven characteristics of Net-CPS and promise to lead to better and more efficient and adaptive operation and performance.

The first such problem considered by the group in 2015 is distributed estimation and inference when various constraints forbid continuous transfer of observed data between the collaborative agents, leading to event-driven operations. These inference and estimation problems are central for wireless sensor networks such as the ones shown in the picture. In contrast to previous studies, the group emphasizes event triggering mechanisms based on a new concept of "value of information."

1 | Application domains of networked cyberphysical systems

Consider an observer (reporter) who desires to optimally inform a distant agent regarding a physical stochastic process in the environment. If the observer is not constrained in terms of energy, medium, security, etc., then observations should be transmitted continually with the highest rate and quality. In practice, however, such an observer has various limitations, for instance a constraint on the energy resource for direct communication to the agent. An example is an observer that relies on a capacity-limited cell yet wishes to have an extended duration of operation. In practice, transmission of each measurement by the observer consumes a specific amount of energy. As a result, only a fixed amount of data can be transmitted. Therefore, the observer should transmit only data that is of more valuable information to the agent. Applications of this study include surveillance and reconnaissance, planetary exploration, wireless wearables, teleoperation, and many examples of networked CPS.

A metric, from a task-oriented perspective, has been developed, for the information transferred from the observer to the agent over a time interval, based on the change in the agent's knowledge regarding the state of the process given the transmitted measurements. The task of minimizing estimation error for the stochastic process of interest has been considered in [1]. A framework for maximization of this information has been developed subject to a bound on the amount of data transmitted through a binary channel over a finite horizon by using two controls: sampling period (temporal resolution), which is non-uniform, and quantization step-size (amplitude resolution), which is time-varying. The optimal sampling and quantization policies were obtained [1] through solving a mixed-integer nonlinear programming problem.

Extensions of the theory were obtained in [2], employing an augmented utility function, which is the summation of the transferred information and the communication cost. The optimal sampling schedule was obtained in [2], and it was shown that the resulting sampling schedule corresponds to an event-triggered sampling policy based on the value of information at each time instant.

John S. Baras gave an invited plenary lecture [3] on these new ideas in the first International Conference on Event-Based Control, Communication, and Signal Processing. He discussed distributed collaborative decision making and control from the perspectives of "value of information" and "actionable information." He showed that having more communications and more data exchanged is not always beneficial in such multi-agent problems. Examples were provided from collaborative sensor fusion and tracking, and from collaborative control, where these novel concepts coupled with a need for efficiency result in event-based strategies being "best." The reasons such strategies are superior to continuous or uniformly sampled exchanges of data or signaling were examined. Several emerging foundational problems were also presented.

A new DFG priority program on "Cyber-physical Networking (SPP1914)" was approved in 2015 with Sandra Hirche serving as coordinator (together with Prof. Klaus Wehrle, RWTH Aachen). The program starts in 2016.

Selected Publications

[1] T. Soleymani, S. Hirche, and J. S. Baras, "Maximization of information in energy-limited directed communication," in 2016 European Control Conference (ECC), Aalborg, Denmark, accepted in 2015.

[2] T. Soleymani, S. Hirche, and J. S. Baras, "Event-triggered optimal sampling based on value of information in estimation," in 2016 International Workshop on Discrete Event Systems (WODES), Xi'an, China, accepted in 2015.

[3] J. S. Baras, "Event based distributed collaborative control and the value of information," invited plenary address, in 1st IEEE International Conference on Event-Based Control, Communication and Signal Processing (EBCCSP), Krakow, Poland, 2015.

Publications by this Focus Group can also be found on page 176.

Focus Group **Cradle to Cradle**

Prof. Michael Braungart | EPEA Internationale Umweltforschung GmbH
Michiel Kulik | Doctoral Candidate
Prof. Werner Lang, Energy Efficient and Sustainable Design and Building, TUM

Michael Braungart

In the past academic year,...

...the work of C2C@TUM focused mainly on the launch of an online platform for buildings and building elements with a positive ecological footprint, corresponding to the Cradle to Cradle® (C2C) design principles. This platform, called *The Registry for Cradle to Cradle inspired Elements for Building Developments*, was designed and launched. Furthermore, criteria for the admission of buildings and products were developed and potential candidates for admission were located.

Overview

The Registry for Cradle to Cradle® inspired Elements for Building Developments is an online platform that collects buildings and building elements that were designed after the Cradle to Cradle design principles. Its purpose is to inspire builders, architects and other stakeholders in the built environment and to serve as a reference for best-practice buildings. Furthermore, the Registry shows in an easily accessible way how Cradle to Cradle® can be transferred to the built environment. Not only Cradle to Cradle® certified products and buildings are being shown on the Registry. It is also possible to upload non-certified elements if they correspond to the Cradle to Cradle® design principles. This will be verified with the help of criteria developed by the work group. This is expected to promote the implementation of Cradle to Cradle® in the built environment and enable highly innovative ideas to be shared more easily. The Registry is intended to celebrate and validate C2C-inspired elements in buildings in a convenient, quality-assured way and to create value beyond mere sustainability.

Project examples

Several excellent Cradle to Cradle® certified projects and products have been gathered already and demonstrate how Cradle to Cradle® can be implemented into practice. The Netherlands Institute of Ecology (NIOO), for example, created a showcase building that benefits its environment more than it harms it. And still, all necessary functions can be performed to the user's full content. NIOO's new headquaters, the NIOO-KNAW, was inspired by biological cycles and processes. All materials used for construction are made from renewable sources, were produced in an environmentally friendly way, and do not emit any noxious substances. Waste water is being treated locally until it attains drinking water quality. The whole complex builds on the principle "waste is food"; vacuum toilets transfer the biomass to a fermenter, where part of it is being converted to biogas. Not only does the green roof of the building filter rainwater and climatize the rooms, but a company also uses the space to experiment with a new technology that gains energy from living plants. Furthermore, the vegetation helps to preserve the region's biodiversity and endemic animals and plants. Outside of the building, biodiversity is a goal as well. The surroundings serve as an ideal environment for native endangered animals, such as bees and bats. To promote this even further, many endemic plants have been grown on the site.

1 | NIOO-KNAW building, The Netherlands

2 | Troldtekt acoustic panels, Denmark

Because of its holistic approach and the self-imposed standard to continuously improve the design, the NIOO-KNAW has become an outstanding example for the implementation of the Cradle to Cradle® principles and serves as a best-practice example for builders who want to do the same.

Notable examples for Cradle to Cradle® certified products on the Registry are the acoustic panels of Troldtekt (Denmark). The panels are part of the biological cycle in the Cradle to Cradle® concept. This means that they consist of biological nutrients or minerals, so they can be part of a biological material cycle without harming its integrity. None of the materials used contain harmful chemicals from the “Banned List” of the Cradle to Cradle® certification and 100% of their content is declared. The wood for the panels is either FSC® or PEFC™ certified. The company is about to establish a take-back system for all of their products. Used products are being collected at municipal recycling points and directly at the construction site. Then the waste is reprocessed appropriately. One-hundred percent of the energy used in production of the acoustic panels originates from renewable sources. The company implemented a Cradle to Cradle® Roadmap making sustainability the focus of Troldtekts’ business strategy. Thus, the example of the acoustic panels can be an inspiration for manufacturers and developers who want their buildings to have a positive influence on the environment.

The Registry has a big added value for the whole construction industry, which is the cause of a major part of global waste and of enormous environmental pollution. The examples shown demonstrate how buildings with qualitative and ecological value can be built.

In collaboration with Jenny Pfau.

The Registry

Cradle to Cradle inspired elements for building developments

3 | Introduction Event of the Registry, April 29, 2015

Focus Group **Environmental Sensing and Modeling**

Prof. Jia Chen (TUM) | Rudolf Mößbauer Tenure Track Professor
Andreas Meichelböck | Doctoral Candidate
Environmental Sensing and Modeling, TUM

Scientific Reports

Jia Chen

Urban greenhouse gas emission assessment using differential column measurements

The group's current research focus is on quantifying greenhouse gas emissions and understanding the metabolism of pollutants in urban environments. For achieving this scientific goal, wide ranges of research topics need to be covered, such as optical sensing using the sun or novel semiconductor lasers as the light source, spectroscopic methods (such as tunable diode laser spectroscopy and Fourier transform spectroscopy), ground-based and satellite-based remote sensing, and atmospheric transport modeling.

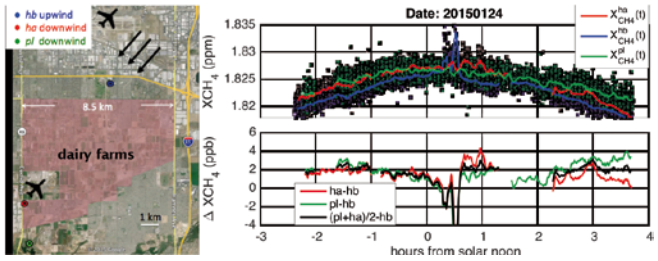
It is challenging to use *in situ* surface measurements of CO_2 and CH_4 to derive emission fluxes in urban regions. Surface concentrations typically have high variance due to the influence of nearby sources, and they are strongly modulated by mesoscale transport phenomena that are difficult to simulate in atmospheric models.

The mass loading of the atmosphere can be directly determined by measuring the column-integrated amount of a tracer through the whole atmosphere. Column measurements are insensitive to vertical redistribution of tracer mass, e.g., due to growth of the planetary boundary layer, and are also less influenced by nearby point sources, whose emissions are concentrated in a thin layer near the surface. Column observations are more compatible with the scale of atmospheric models and hence provide stronger constraints for inverse modeling.

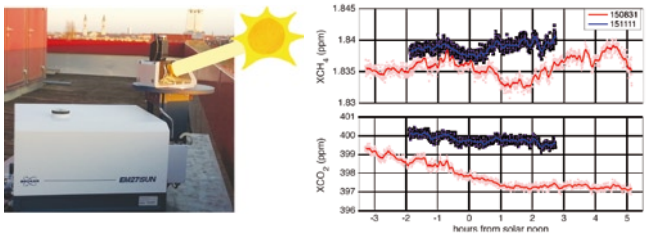
Therefore, we are aiming at establishing a regional sensor network with novel differential column measurements, i.e., column measurements inside and outside of the city. Using these measurements, combined with models of atmospheric transport, the group wants to demonstrate a new experimental strategy to determine greenhouse gas and pollutant emissions in urban areas.

To test the differential column measurements methodology, we carried out field measurements in California and Boston. We report tests of the differential column measurement, and its sensitivity to emission sources, by measuring the column gradient ΔXCH_4 between downwind and upwind locations across dairy farms in the Chino California area, and using these data to quantify emissions (figure 1). The determined methane emissions of 25 Gg/year agree well with the literature numbers. Spatial column gradient ratios $\Delta XCH_4/\Delta XCO_2$ were observed across Pasadena within the Los Angeles (LA) basin, indicating values consistent with regional emission ratios from the literature. The results for differential column measurements and the emission study are presented in [1].

We are starting to build up the differential column measurements in Munich, with an inner-city station located on the roof of TUM building N5. Exemplary measurements in winter and summer are shown in figure 2. In summer, the measured column concentration XCO_2 decays during the course of the day, due to photosynthesis activities. On 11th Nov. the concentration is 3 ppm higher than 31st Aug., traceable to more fossil fuel emissions and less photosynthesis in the wintertime.



1 | [Chen et al. 2016]: Left: locations of the solar-tracking Fourier Transform spectrometers (ha, hb, pl) and mean wind directions. The airplanes symbolize the nearby airports, which provide the wind measurements. Right: column-averaged dry-air mole fraction measurements at three stations (XCH_4) and downwind-upwind differences shown on the second panel. ΔXCH_4 was steady at 2 ppb most of the day, 10 times larger than our measurement precision, and provides a methane emission estimate of 25 Gg/year for the dairy farms in Chino, California.



2 | Left: solar-tracking spectrometer in central Munich, on the roof of the N5 building of TUM (48.15N, 11.57E, 516 m above sea level). Right: measured column-averaged dry-air mole fraction of CO_2 and CH_4. Exemplary winter and summer measurements are shown: the higher winter concentrations are attributable to less photosynthesis/photolysis activities and more fossil fuel emissions in the wintertime.

The same is true for XCH_4 measurements: the winter concentration is higher mainly given by less oxidation by atmospheric OH radicals.

A prerequisite for deploying the compact spectrometers for stationary monitoring of urban emissions is to devise an automatic protection and control system – a challenging task. This must allow solar measurements whenever the sun is out and reliable protection of the instrument when it starts to rain. We are working on a simplified and reliable solution; our novel concept has been accepted as an invention disclosure [3] and is to be published in 2016.

We are also working on the development of a novel sun-tracking Fourier Transform spectrometer system, to further improve the concept initiated at Harvard University [2]. Furthermore, we are validating satellite-based OCO2 measurements with our ground-based measurements and combining the two for a better emission estimate. In 2016 we plan to establish an upwind station outside the city for differential column measurements and to deploy the methodology for quantifying and attributing CO_2 and CH_4 emissions in Munich.

Reference

[1] J. Chen, C, Viatte, J. K. Hedelius, T. Jones, J. E. Franklin, H. Parker, E. W. Gottlieb, P. O. Wennberg, M. K. Dubey and S. C. Wofsly, "Differential Column Measurements Using Compact Solar-Tracking Spectrometers," Atmos. Chem. Phys., accepted in 2016.

Selected Publications

[2] J. Chen, J. Samra, J. Budney, and S. C. Wofsy, “Diffuser-Based Solar-Tracking with Camera for Atmospheric Measurements,” U.S. patent application 62/164,179, filed May 20t, 2015.

[3] L. Heinle, J. Chen, G. Wunsch, and A. Meichelboeck, “Automatisches, kompaktes Wetterschutzgehäuse für atmosphärische Messgeräte,” Erfindungsmeldung 2015-12E16.

Publications by this Focus Group can also be found on page 177.

Focus Group **Global Change**

Prof. Annette Menzel (TUM) | Carl von Linde Senior Fellow
Dr. Ricardo Acevedo-Cabra | Postdoctoral Researcher
Ecoclimatology, TUM

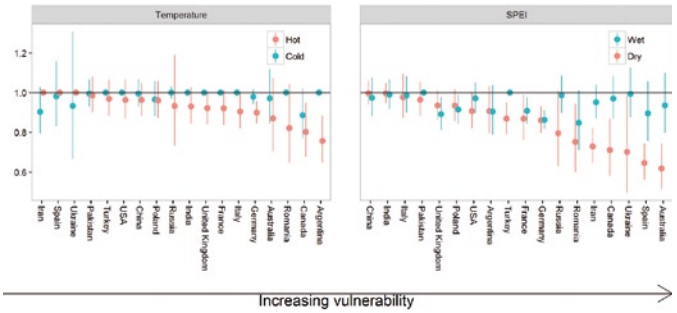
Scientific Reports

Annette Menzel

Goodbye winter? Sensitivity of plants and human health in a record-warming world

Our last annual report noted that “the year 2014 is heading toward the highest temperature on record.” Now, the year 2015 has broken all previous records, with temperatures being ~1°C above the pre-industrial area [WMO Press release N°2, 2016]. In line with this, the central questions of our Focus Group are whether the inherent adaptability and plasticity of biological systems are still adequate to cope with these fast changes and which of the anticipated impacts are crucial for ecosystems and humans.

Food security under changing climate is studied in an ongoing cooperation with TUM Biostatistics and Agricultural Production & Resource Economics within an ERC Grant (Michael Matiu). Temperature and drought are major drivers for crop yields and prices; thus climate variability is leading to nonlinear decreases in yield. Figure 1 displays the country-specific sensitivities of wheat yield to extreme temperature and drought conditions (SPEI) based on FAO data as one example.



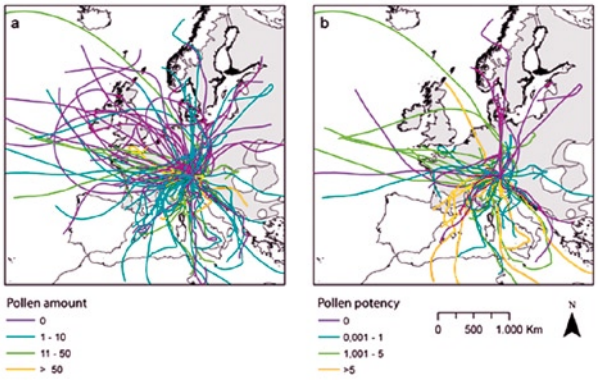
1 | Sensitivity of wheat yield as ratio compared to optimal conditions under hot and cold growing season temperatures and wet and dry conditions given by the Standardized Precipitation Evaporation Index (SPEI).

Warmer springs, higher atmospheric CO_2 concentrations, and invasive species render the pollen season earlier, longer, and more intense, with pollen captured now all year round. We tested if and to what extent landscape management, e.g., prescribed burning in Texas, or human behavior (indoor or holiday stays) allow spatially or temporally mitigating high allergenic pollen loads. Besides urban studies, a special focus was set on the alpine area likely providing more suitable conditions for allergy sufferers. However, a key risk assessment [1] in collaboration with the TUM School of Medicine revealed that there are still medically relevant pollen loads at high-altitude sites and that pollen allergenicity is linked to specific wind directions and most likely short- / long-range transport. Susanne Jochner, who was most involved in these papers, started a W2 professorship on April 1, 2015 at KU Eichstätt.

Several of our studies besides the pollen topic mentioned above can be seen as “lost winter season” obituary. The TUM climate station Felsenkanzel near Garmisch was affected by a forest fire after Christmas, a season that has been unknown for this specific danger but more and more events have been recorded in dry late autumn and warm winter / earliest spring in the alpine region.

In July 2015, Julia Laube successfully completed her doctoral thesis, “Performance of native and invasive plant species under climate change - phenology, competitive ability and stress tolerance,” with highest distinction (*summa cum laude*). Her research used different experimental settings – from climate chamber experiments up to field studies – and resulted in several international publications [e.g., 2 in 2015]. The thesis was co-supervised by Annette Menzel and Tim H. Sparks.

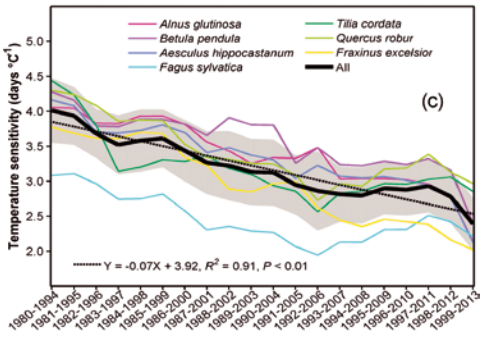
Alumni Members
Prof. Tim H. Sparks (Coventry University) | Hans Fischer Senior Fellow
Dr. Nicole Estrella (TUM), Prof. Susanne Jochner (Catholic University of Eichstätt-Ingolstadt), Dr. Christian Zang (TUM) | Postdoctoral Researchers
Dr. Julia Laube (TUM) | Doctoral Candidate



2 | Pollen amount and pollen potency / allergenicity of Birch (Betula ssp.) captured in April and May 2009 and 2010 at the UFS Schneefernerhaus and corresponding 72-h back-trajectories by HYSPLIT using meteorological model data of GDAS (NOAA). Grey shading indicates the distribution of silver birch (Betula pendula Roth). Figure modified from [1].

Her findings, which suggest that temperature-related air humidity as the main trigger of the spring development of trees [3], are being implemented in a model framework by Ricardo Acevedo-Cabra in collaboration with TUM Biostatistics. Since the work of Réaumur in 1735, the onset of phenological phases (annually recurring events such as leaf unfolding or flowering) has been linked to temperature. Now, a model based on air humidity has been developed to optimize the critical humidity sum of six different temperate tree species and to forecast the timing of leaf unfolding. Preliminary results show that this approach produces better forecasts than benchmark models including temperature.

Tim H. Sparks was co-author of an important paper on the 1980s regime shift in temperature, caused by anthropogenic warming and the recovery from the El Chichón volcanic eruption, and associated biophysical systems leading to abrupt environmental changes [4] such as much earlier onset dates in plant phenology. Photoperiod and winter dormancy could prevent too early leaf unfolding, which is associated with higher risk from late spring frost events. Whether a potential lack of winter chilling in the course of recent climate change has already altered the sensitivity of spring phenology to warming is heavily debated in the scientific community. An international team with Annette Menzel as co-author used long-term leaf unfolding dates of seven tree species at more than 1200 sites in Europe and showed for the first time, as published in



3 | Decreasing temperature sensitivity for seven European tree species. Figure modified from [5].

Nature [5], that the apparent temperature sensitivity (expressed in days advance per °C spring warming) has significantly decreased by 40% in the last three decades. This weaker sensitivity is likely to be attributed to the reduced chilling, thus the "lost winter season," and might slow down advancing spring phenology with further warming.

Reference

[1] J. Laube, T. H. Sparks, N. Estrella, and A. Menzel, "Does humidity trigger tree phenology? Proposal for an air humidity based framework for bud development in spring," New Phytol., vol. 202, no. 2, pp. 350–355, 2014

Selected Publications

[2] S. Jochner, M. Lüpke, J. Laube, I. Weichenmeier, G. Pusch, C. Traidl-Hoffmann, C. Schmidt-Weber, J. T. Buters, and A. Menzel, "Seasonal variation of birch and grass pollen loads and allergen release at two sites in the German Alps," Atmos. Environ., vol. 122, pp. 83–93, 2015.

[3] J. Laube, T. H. Sparks, C. Bässler, and A. Menzel, "Small differences in seasonal and thermal niches influence elevational limits of native and invasive Balsams," Biol. Conserv., vol. 191, pp. 682–691, 2015.

[4] P. C. Reid, R. E. Hari, G. Beaugrand, D. M. Livingstone, C. Marty, D. Straile, J. Barichivich, E. Goberville, R. Adrian, Y. Aono, R. Brown, J. Foster, P. Groisman, P. Hélaouët, H.-H. Hsu, R. Kirby, J. Knight, A. Kraberg, J. Li, T.-T. Lo, R. B. Myneni, R. P. North, J. A. Pounds, T. Sparks, R. Stübi, Y. Tian, K. H. Wiltshire, D. Xiao, and Z. Zhu, "Global impacts of the 1980s regime shift," Glob. Chang. Biol, vol. 22, no. 2, pp. 682–703, 2016, accepted in 2015.

[5] Y. H. Fu, H. Zhao, S. Piao, M. Peaucelle, S. Peng, G. Zhou, P. Ciais, M. Huang, A. Menzel, J. Peñuelas, Y. Song, Y. Vitasse, Z. Zeng, and I. A. Janssens, "Declining global warming effects on the phenology of spring leaf unfolding," Nature, vol. 526, no. 7571, pp. 104–107, 2015.

Publications by this Focus Group can also be found on page 177.

Focus Group **High-Resolution Gravity Modeling**

Dr. Christian Hirt (Curtin University) | Hans Fischer Fellow
Moritz Rexer | Doctoral Candidate
Prof. Roland Pail, Chair for Astronomical and Physical Geodesy, TUM

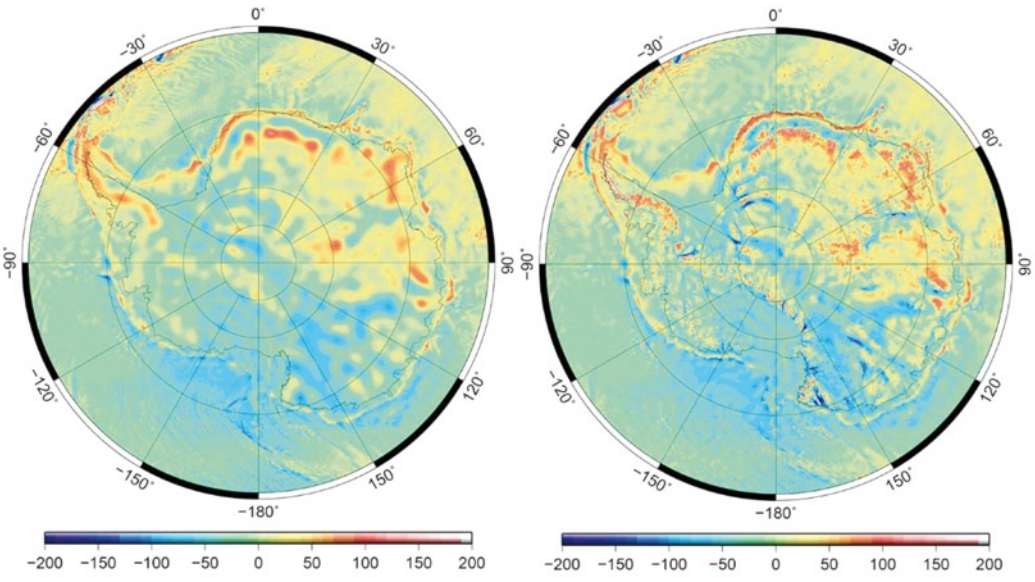
Scientific Reports

Christian Hirt

The research goal of the Focus Group High-Resolution Gravity Modeling is the development of a gravity field model with highest resolution of about 100 to 200 m over land and coastal areas of our planet. Such a gravity field model is important for several geoscience and engineering applications. For instance, gravity is a fundamental quantity for precision heighting and topographic mapping with satellite systems. In geophysics, gravity is crucial for making inferences on the location and size of mass-density anomalies, e.g., salt domes or iron-ore bodies. In metrology, gravity is required for the calibration of precision scales. In these and other applications, the higher the spatial resolution of the gravity model, the better the representation of field structures, and, hence, the overall applicability of the model.

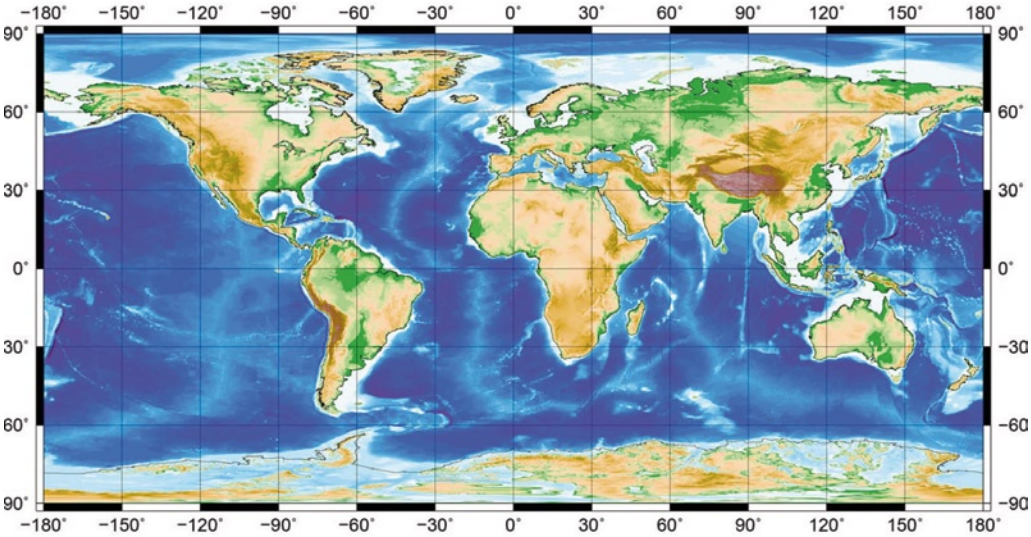
To achieve the goals, the group's research focus is on (a) assessment and improvement of modeling methods, (b) assessment and combination of data sets (observations of the gravity field and auxiliary data such as topography models carrying information on the gravity field), and (c) application of methods and data to create products describing the gravity field to ultra-high resolution.

In 2015, the group's research focused on high-resolution modeling of the gravity field over Antarctica. Exploiting the much improved data situation over Antarctica – initial results were noted in the group's 2014 report, and the new Bedmap2 model of Antarctica's bedrock and ice geometry recently became available – we calculated the gravity field generated by the Bedmap2 ice, water, and rock masses. The result was combined with contemporary satellite gravimetry from the GOCE and GRACE missions, yielding a high-resolution model of the Antarctic gravity field [1]. Our new model improved the resolution of gravity field features from about 80 km to 10 km detail; see also figure 1.



1 | Left: Satellite-only gravity field from the GRACE and GOCE missions over Antarctica (80 km resolution); right: combination of satellite data with short-scale gravity from the Bedmap2 product, offering increased resolution to 10 km scales [1].

The group placed considerable attention on ultrahigh-resolution gravity field modeling and representation with spectral techniques. In spectral gravity modeling, field structures are represented through series of weighted sine- and cosine terms



1 arc-min Earth2014 bedrock map

2 | Earth2014 bedrock topography (i.e., Earth surface in the absence of water and ice) at 1 arc-min resolution [3].

(i.e., Fourier series on the sphere), with the number of terms determining the spatial resolution of the model. In 2015, thanks to major contributions of our doctoral candidate Moritz Rexer, the group's capabilities were extended such that gravity field features of up to ~400 m spatial resolution (around the globe) can now be represented spectrally. At this level of resolution, up to 3 billion terms are taken into account in the evaluation of the series expansions. The new capabilities were initially used to analyze the topographies of Earth and other planets for the first time to ultrahigh resolution [2], as well as in light of future gravity modeling based on topography data and spectral methods.

Further group research concentrated on the compilation and release of a new global map of Earth's topography, bedrock, water, and ice masses (~1.8 km or 1 arc-min resolution), cf. figure 2 and [3]. This work is important to achieve the group's research goal, because this compilation can act as a reference surface for residual modeling of the gravity field down to 100–200 m resolution. Another notable activity, the investigation of signal power laws for the Earth's gravity field to few 100 m resolution, succeeded in providing improved statistical knowledge of short-scale gravity field characteristics at very fine spatial scales [4].

Selected Publications

[1] C. Hirt, M. Rexer, M. Scheinert, R. Pail, S. Claessens, and S. Holmes, "A new degree-2190 (10 km resolution) gravity field model for Antarctica developed from GRACE, GOCE and Bedmap2 data," J. Geod., vol. 90, no. 2, pp. 105–127, 2016, accepted in 2015.

[2] M. Rexer, and C. Hirt, "Ultra-high degree surface spherical harmonic analysis using the Gauss-Legendre and the Driscoll/Healy quadrature theorem and application to planetary topography models of Earth, Moon and Mars," Surv. Geophys., vol. 36, no. 6, pp. 803–830, 2015.

[3] C. Hirt, and M. Rexer, "Earth2014: 1 arc-min shape, topography, bedrock and ice-sheet models - available as gridded data and degree-10,800 spherical harmonics," Int. J. Appl. Earth Obs. Geoinf., vol 39, pp. 103–112, 2015.

[4] M. Rexer, and C. Hirt "Spectral analysis of the Earth's topographic potential via 2D-DFT - a new data-based degree variance model to degree 90,000," J. Geod., vol 89, no. 9, pp 887–909, 2015.

Publications by this Focus Group can also be found on page 179.

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

Prof. Stuart Khan (University of New South Wales) | Hans Fischer Fellow
Philipp Michel | Doctoral Candidate
Prof. Jörg Drewes, Urban Water Systems Engineering, TUM

Scientific Reports

Stuart Khan

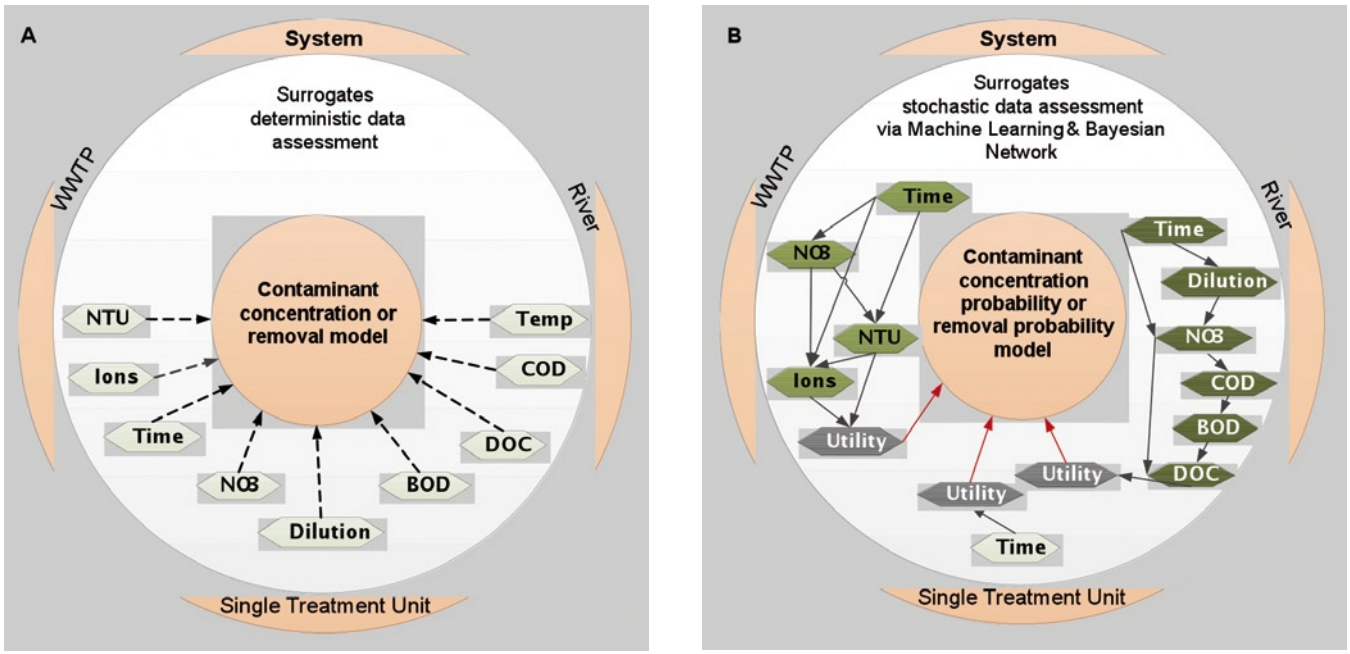
The EU Water Framework Directive (WFD) was adopted by the European Commission and went into force in 2000. The principal objective of the WFD is to protect water quality and ecological attributes of Europe's rivers, lakes, groundwater, and coastal beaches. It sets out strategies against pollution of water, outlining the steps to be taken. An important focus of the WFD is the control of chemical substances that may, when released into bodies of water, lead to detrimental ecological impacts. Priority chemical substances have been identified according to approaches outlined in the WFD.

As a direct consequence of the WFD, EU member states are gearing up to minimize point sources such as wastewater treatment plant discharges by upgrading treatment processes. Most notably, in 2014 the Swiss Parliament set in place requirements for the nation's 100 largest plants to be upgraded by the incorporation of ozonation and powdered activated carbon as final polishing treatment stages. However, the control of these trace substances by ozonation/activated carbon treatment comes with significant economic and energy costs. Current monitoring programs, coupled with contaminant modeling techniques for urban water cycles, are indicating that some German waterways may be unacceptably contaminated with chemical contaminants, as well as with nutrients and pathogens.

Advanced wastewater treatment technologies (e.g., ozonation, UV/hydrogen peroxide, activated carbon adsorption, and membrane technologies) have been proposed to reduce contaminant loads from these point sources. However, these advanced treatment technologies are energy-intensive, operationally complex, and expensive. Therefore, investment in implementing advanced treatment should be balanced against the environmental benefits versus environmental impacts and financial costs. The relationships between these benefits and costs will vary between locations and also over time, for instance as a function of seasonal variations.

In balancing the benefits and costs of advanced water treatment, there are potential opportunities to establish more flexible modes of operation, for instance by incorporating a dynamic load-dependent dosing regime (e.g., for ozonation) or a dynamic hydraulic flux adjustment (e.g., for membrane systems). However, the ability to apply these flexible and potentially more ideal operational modes will depend on our ability to dynamically assess and respond to a range of diverse factors affecting the performance and desired outcome of the treatment process. Considerations may include variable concentrations of contaminants in raw wastewater, the inherent treatment process performance, environmental dilution, natural attenuation capability, and variable exposure factors as well as energy costs and energy sources.

This research is based on the hypothesis that understanding and modeling cause-effect relationships could enable dynamic and more outcome-focused decision-making for the selection and flexible operation of advanced water treatment processes. This approach could lead to significant savings in overall energy consumption and thus lower costs and greenhouse gas emissions. While using state-of-the-art modeling approaches, this research will advance the predictive power



1 | Surrogate models

for diverse contaminant concentrations in wastewater treatment and receiving environmental systems. The focus is on the removal of trace organic chemicals and surrogate parameters that correlate with their removal. Issues relating to data, model structures, incorporations of variability and uncertainty, calibration, potential surrogate parameters, and model validation are being investigated. The contributions of existing systems and parameters determining environmental contaminant concentrations (e.g., source variability, existing treatment, discharge dilution, environmental processing) will be accounted for. The proposed paradigm change is outlined in figure 1.

Figure 1A illustrates the common, more linear system for assessing water quality. In this concept, surrogates directly feed into a fate model. In the context of trace organic chemical removal (TOrC), this is very limited because individual possible surrogates appear to be too weak for a direct correlation. In the new, proposed approach (figure 1B), the surrogates pass through a clustering process. Furthermore, they are not single values, but incorporate distribution functions that are triggered by incoming conditions of other surrogates. This approach will employ and evaluate clustering machine learning and probabilistic modeling, including deterministic and continuous "Bayesian belief networks" (BBN), Monte-Carlo simulation, and multi-criteria decision analysis (MCDA).

This new concept even allows real-time monitoring of surrogates to be considered as a model input. Furthermore, the combination of static surrogate or contaminant data sets and continuous monitoring data can lead to a comprehensive dynamic monitoring approach.

During 2015, our main focus was to prepare a review discussing the regulatory tools and controls for a dynamic water quality risk profile that could meet upcoming needs in water quality management. In addition, we established the foundation for subsequent statistical work with Bayesian belief network modeling. Also, a long-term sampling campaign along the river Isar was performed to establish an initial large data set for statistical evaluation, and to generate data to assess the relative contributions of photolytic degradation processes of selected TOrCs in receiving streams.

Doctoral candidate Sofia Veloutsou (Urban Water Systems Engineering, TUM) also works with this Focus Group.

Selected Publication

[1] S. J. Khan, T. Walker, B. D. Stanford, and J. E. Drewes JE, "Advanced treatment for potable water reuse," in Advanced Oxidation Processes for Water Treatment: Fundamentals and Applications, M. I. Stefan (Ed.), London: IWA Publishing, 2016, accepted in 2015.

Publications by this Focus Group can also be found on page 179.

Focus Group **Physics with Effective Field Theories**

Dr. Andreas S. Kronfeld (Fermilab) | Hans Fischer Senior Fellow
Dr. Javad Komijani | Postdoctoral Researcher
Prof. Nora Brambilla, Theoretical Particle and Nuclear Physics, TUM

Scientific Reports

Andreas S. Kronfeld

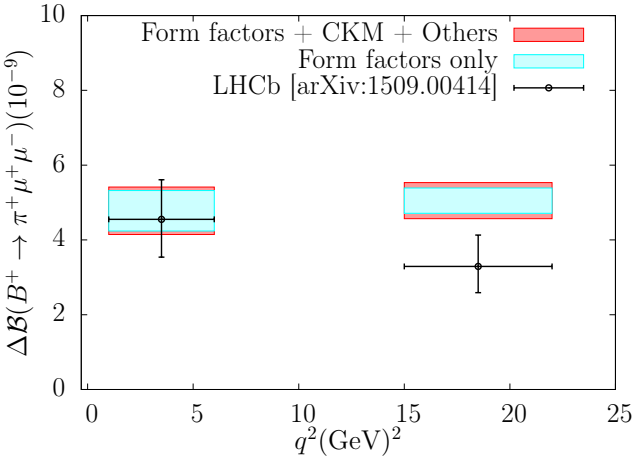
The flavor of the most microscopic

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, 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.

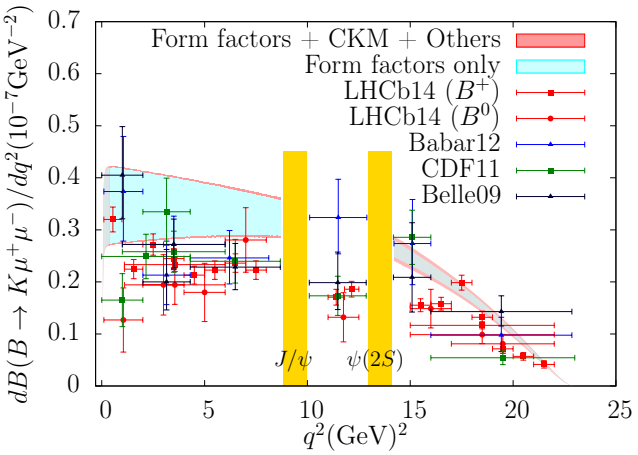
The other central element in our research is *lattice gauge theory*, which sets up quantum fields on a space-time lattice. Especially pertinent is the lattice gauge theory of the strong force, quantum chromodynamics (QCD). Lattice QCD allows large-scale computations of QCD dynamics, which are needed to connect the intriguing world of quarks with the detectable world of hadrons. During the first year of this Focus Group, we published several papers combining the techniques of effective field theory and lattice QCD. Two of the most interesting studies incorporate everything in the Standard Model of elementary particles to predict the reaction rate for certain rare decay processes. If measured decay rates deviate from the predictions significantly, then a new physical phenomenon will have been observed.

The plots show results for two such processes, $B \to \pi l^+ l^-$ [2] and $B \to K l^+ l^-$ [3]. The B, K, and π mesons are hadrons made from a quark and an antiquark, but with different *flavors* of quarks. The π contains the same quarks as protons and neutrons, the K contains a so-called strange quark, and the B a so-called bottom quark. The Standard Model rates for these processes are suppressed by several dynamical mechanisms, making it plausible that a non-Standard interaction could contribute in a noticeable way. The curves in the plots represent the theoretical predictions, and the data points show measurements from the LHCb experiment, which runs at CERN's Large Hadron Collider (LHC). The variable q^2 on the horizontal axis is the total mass (squared) of the $l^+ l^-$ system. Our calculation with π in the final state preceded the measurement. Tantalizingly, the measurements with K in the final state are discrepant with the theoretical prediction at nearly two standard deviations.

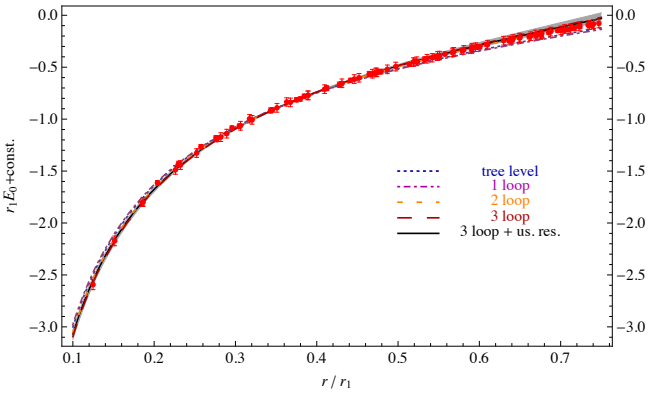
It will be exciting to repeat these comparisons with new data being taken at LHCb over the next year or so. Another example of the marriage of effective field theory and lattice QCD is work completed soon after the founding of the Focus Group. Here we use lattice QCD to calculate the static energy stored in the chromoelectric field between a heavy quark and a heavy antiquark [1]. These numerical data are analyzed with an effective field theory. Comparing the two – as shown in the figure – yields the basic measure of the strong force, denoted αs, in analogy with the fine-structure



1 | Branching fraction for the rare decay $B \to \pi l^+ l^-$ [1] integrated over two bins of the invariant mass of the l^+l^- system, q^2. The theoretical predictions (cyan and pink bands) agree well with measurements from the LHCb experiment at CERN in Geneva, Switzerland.



2 | Branching fraction for the rare decay $B \to Kl^+l^-$ [3] as a function of the invariant mass of the l^+l^- system, q^2. The theoretical predictions (cyan and pink bands) lie higher than the most precise measurements from the LHCb experiment (red data points). If this "tension" is confirmed by new data and better calculations, the discrepancy would be evidence for new physical phenomena at the smallest distance scales ever probed by humankind.



3 | The chromoelectric energy between a heavy quark and a heavy antiquark, comparing lattice-QCD calculations (red data points) with formulas derived with an effective field theory for this system (curves) [1]. A fit of the lattice-QCD data to the most sophisticated effective theory—labelled "3 loop + ultrasoft resummation (us. res.)"—yields an accurate determination of the fundamental gauge coupling of QCD.

constant α of atoms. Despite the theoretical sophistication applied here, the central idea is just like in atomic physics, where α is determined from the energy stored in the electric field. We are furthering this work, aiming for a determination of αs that is competitive with the world's best. Because of the fundamental nature of αs, such improvements will influence hadron experiments from the PANDA facility being built in Darmstadt to the LHC at CERN.

Our Focus Group hosted two notable activities. One was a kickoff symposium for the Focus Group and associated Hans Fischer Senior Fellowship, "Lattice Gauge Theory and Effective Field Theories," which covered several areas of particle physics. We plan to expand the reach of these tools not only via the Focus Group but also our initiative European Bridges with Effective Theories (EUBET). We hosted the symposium "EUBET 2014: Applications of Effective Field Theories to Particle Physics, Condensed Matter and Quantum Optics" to explore similarities in physical phenomena in particle, nuclear, atomic, and condensed-matter physics. In addition, EUBET will provide a forum in which condensed-matter and particle physicists can exchange ideas about field-theoretic computer simulations. In particular, we have begun discussions with researchers at the Max Planck Institute for Quantum Optics, who are pioneers in the interplay of lattice gauge theory and ultracold atoms.

For its project, this Focus Group collaborates with postdoctoral researcher Dr. Johannes Weber and senior researcher Dr. PD Antonio Vairo.

Reference

[1] A. Bazavov, N. Brambilla, X. Garcia i Tormo, P. Petreczky, J. Soto, and A. Vairo, "Determination of αs from the QCD static energy: An update," Phys. Rev. D, vol. 90, no. 7, p. 074038, 2014.

Selected Publications

[2] Jon A. Bailey, J. Komijani, A. S. Kronfeld, et al. (Fermilab Lattice and MILC Collaborations), "B → πl+l– form factors for new-physics searches from lattice QCD," Phys. Rev. Lett., vol. 115, no. 15, p. 152002, 2015.

[3] D. Du, A. X. El-Khadra, S. Gottlieb, A. S. Kronfeld, J. Laiho, E. Lunghi, R. S. Van de Water, and R. Zhou, "Phenomenology of semileptonic B-meson decays with form factors from lattice QCD," Phys. Rev. D, vol. 93, no. 3, p. 034005, 2016, accepted in 2015.

Publications by this Focus Group can also be found on page 180.

Focus Group **Sterile Neutrino and Dark Matter**

Dr. Thierry Lasserre (CEA, Saclay / APC, Paris) | Hans Fischer Senior Fellow
Konrad Altenmüller, Julia Sawatzki | Doctoral Candidates
Prof. Stefan Schönert, Experimental Physics and Astroparticle Physics, TUM

Thierry Lasserre

Sterile neutrinos

Neutrinos are neutral leptons at the cutting edge of particle physics. In 2015 the Nobel Prize for Physics was given to A. McDonald and T. Kajita for the discovery of neutrino oscillations, which shows that the three known neutrinos have mass. In the Standard Model of particle physics, the neutrino mass is zero. Non-zero masses allow the neutrinos to oscillate – to change type – as they travel in space and time. Beyond the Standard Model, other types of neutrinos could exist. They are usually called sterile neutrinos, since they don't interact with matter, or only extremely weakly. They could oscillate, however. The Sterile Neutrino and Dark Matter TUM-IAS Focus Group investigates phenomenology and experimental perspectives for detecting sterile neutrinos.

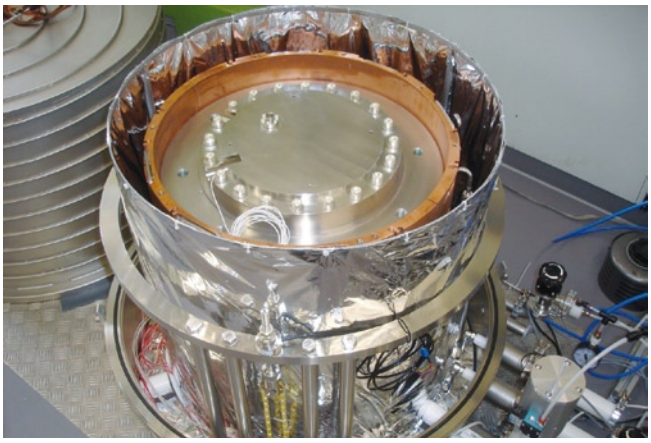
keV sterile neutrinos

Nowadays the unidentified nature of the dark matter is one of the major open issues in physics. Massive relic sterile neutrinos at the keV mass scale are well suited candidates to explain the dark matter in our universe.

In 2015 our Sterile Neutrino and Dark Matter Focus Group addressed the possibility of searching for keV sterile neutrinos with the KATRIN experiment (KIT, Karlsruhe), primarily designed to measure neutrino mass by studying precisely the beta-decay of tritium. KATRIN currently provides the highest tritium-source luminosity usable for physics experiments. A sterile neutrino would manifest itself as a specific spectral distortion in the tritium beta-decay energy spectrum. Our group performed substantial studies of experimental systematic uncertainties and of the accurate modeling of the tritium beta-decay spectrum. Moreover, we are contributing to the realization and testing of new silicon pixel detector prototypes, in collaboration with KIT (Karlsruhe), LBL (Berkeley), and HLL/MPI (Munich). Our group contributed to designing a new readout system, in close collaboration with CEA (Saclay). Detectors will be commissioned and characterized in 2016.

In addition, our group is leading a worldwide effort to meticulously assess the physics case for sterile neutrinos and dark matter. A white paper is in preparation, gathering more than 125 authors from almost 90 institutions. The ν-Dark 2015 international workshop took place at the TUM Institute for Advanced Study in December 2015. This workshop was devoted to reviewing the evidence – for and against – keV neutrinos as a possible dark matter candidate. At the crossroads of particle physics, astrophysics, and cosmology, the observational constraints, the production mechanisms in the early universe, and the experimental perspectives were fruitfully discussed.

1 | ν-Dark 2015 Workshop group picture in December 2015.



2 | TUM-Genova thermal calorimeter to measure the heat generated by the ^{144}Ce source.

eV sterile neutrinos

In the last two decades several short-baseline neutrino experiments reported results that could be interpreted as a hint for a sterile neutrino in the eV mass range. Such a new particle could mix with the active neutrino flavor, but it would be insensitive to the standard weak interaction.

Our Focus Group is contributing to the CeSOX experiment that consists of an intense ^{144}Ce antineutrino source deployed next to the large liquid scintillator detector Borexino at the Laboratory Nazionali del Gran Sasso.

In 2015 the R&D for realization of the intense ^{144}Ce antineutrino source was completed. At TUM a calorimeter was built and tested, in order to measure the source activity within 1% uncertainty. Measurements of the ^{144}Ce and ^{144}Pr beta-spectra have been started in order to assess the expected signal in Borexino. The smoking-gun signal of eV sterile neutrinos would be an oscillatory pattern in space and energy inside the Borexino detector volume. A study reviewing all systematics and background was published in *Physical Review D* [1]. The experiment will start taking data at the end of 2016.

Selected Publication

[1] J. Gaffiot, T. Lasserre, G. Mention, M. Vivier, M. Cribier, M. Durero, V. Fischer, A. Letourneau, E. Dumonteil, I. S. Saldikov, and G. V. Tikhomirov, “Experimental parameters for a Cerium 144 based intense electron antineutrino generator experiment at very short baselines,” Phys. Rev. D, vol. 91, no. 7, p. 072005, 2015.

Publications by this Focus Group can also be found on page 180.

Focus Group **C-H Activation Chemistry**

Prof. Polly L. Arnold (University of Edinburgh) | Hans Fischer Senior Fellow
Julia Rieb, Max McMullon | Doctoral Candidates
Prof. Fritz E. Kühn, Molecular Catalysis, TUM

Polly L. Arnold

The vision of this Focus Group is to develop world-leading research in the form of the first useful catalytic conversion of the C-H bonds in hydrocarbons such as petrol or biomass to more interesting functional groups, by the application of our hydrocarbon-soluble, reactive molecular complexes.

Burning petrol and other hydrocarbons from fossil fuels is damaging to the environment and wasteful of resources that could otherwise be used to make substances that improve the quality of life. However, the strength of the carbon-hydrogen bond, coupled with the difficulties associated with selectively accessing a specific site on a particular molecule, means that highly reactive metal compounds are needed to catalyze such processes.

A single C-H bond in methane, the simplest and most abundant hydrocarbon, is potentially the most financially important target for selective functionalization, but the activation of C-H bonds in more complex hydrocarbons is also a highly desirable “toolbox” component for scientists working in all areas of chemical synthesis. This selectivity will become increasingly important as our palette of platform chemicals changes from fossil fuel-derived to biomass-derived in the coming years.

Hydrocarbon-soluble compounds of the lanthanides and actinides first gave a tantalizing glimpse of their potential with the selective cleavage of one C-H bond in methane some 25 years ago, but the limitations of the supporting molecular structures precluded any further functionalization step. Since then, a variety of C-H bond activation chemistry has been demonstrated using molecules that harness these metal cations. This has increased our fundamental understanding of this reaction but has not yet provided profitable applications.

The published manuscripts outline our progress to date on the selective activation and functionalization of a variety of small, inert molecules, including a range of hydrocarbon C-H bonds.

During the lifetime of the Focus Group, students, postdoctoral researchers, staff, ideas, and catalyst samples have begun to move freely between Edinburgh and Munich, and the collaborations between associated academics are still growing in number. Preliminary results have been published and presented at international conferences as talks and posters, and we are preparing further publications for high-quality international journals. Members of the team have also been awarded a variety of prizes.

Highlights of this year's work include:

1. Synthesis and characterization of bis(N-heterocyclic carbene) complexes of rare-earth elements

Despite an anionic anchor, most of the rare-earth metal complexes reported so far are extremely air- and moisture-sensitive; however preliminary *in situ* transmetallation experiments with $CeCp_3$ show promising results. Experiments in this direction are ongoing.

2. bimetallic Au(I)-rare-earth complexes

A series of Ag(I) and corresponding Au(I) complexes of a different chelating ligand (see Kühn et al., *Organometallics* 2015, 34, 2573) have been synthesized and characterized, including by neutron diffraction (example crystal structure in figure 2). The **Au-IPr** complex shown in figure 2 forms a *cis*-hydroxyl-bridged isomer to make new metalla-ligands for rare earths.

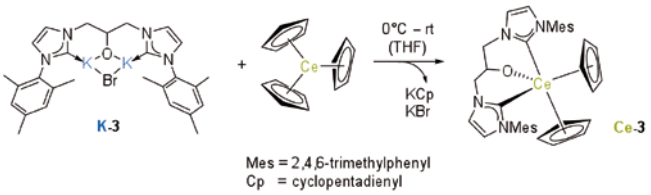
3. Tin, iron, zinc, cobalt, cerium and europium complexes of aryloxide-tethered-NHCs

The use anionic aryloxide tethers for the synthesis of p/d/f-block complexes has been very successful leading to number of novel complexes. The europium complex is shown in figure 3. A change in substituents for the tin complexes (not shown) results in an unusual ligand binding mode; a so-called abnormal carbene is formed where binding is from one of the backbone carbons. The isomers show surprisingly different reactivity for carbon dioxide activation. Work is in progress to combine the CO_2 activation with the substrate C-H bond activation chemistry that we have already reported for these reactive metal carbene complexes.

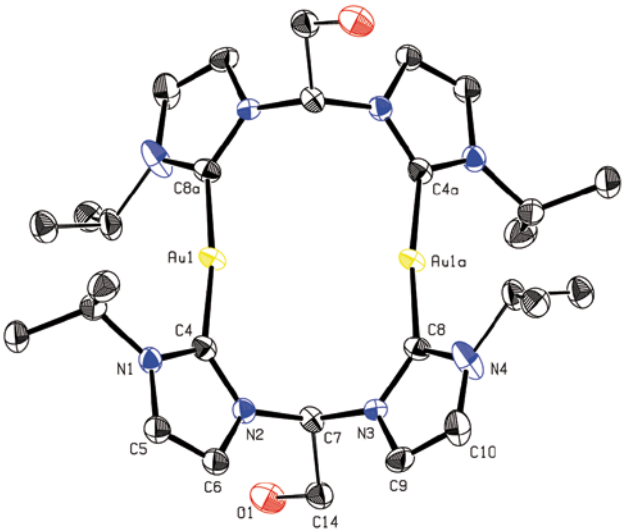
Selected Publications

[1] P. L. Arnold, M. W. McMullon, J. Rieb, and F. E. Kühn, "CH bond activation by f-block complexes," Angew. Chem., Int. Ed., vol. 54, no. 1, pp. 82–100, 2015.

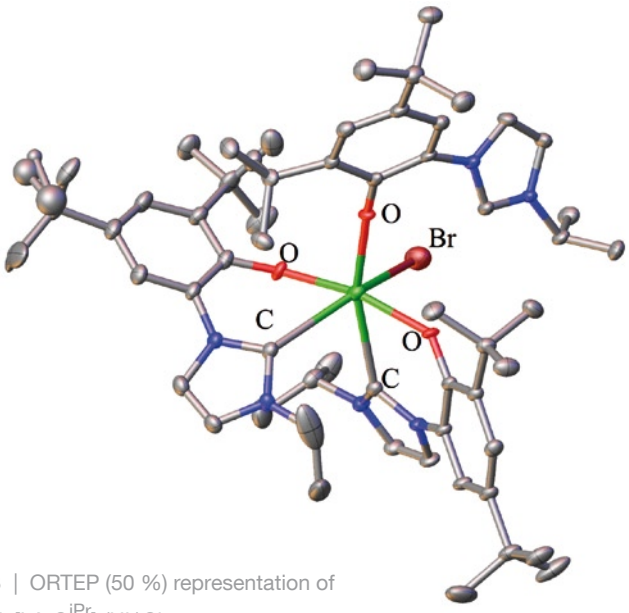
[2] P. L. Arnold, A. Prescimone, J. H. Farnaby, S. M. Mansell, S. Parsons, and N. Kaltsoyannis, "Characterizing pressure-induced uranium C-H agostic bonds," Angew. Chem., Int. Ed., vol. 54, no. 23, pp. 6735–6739, 2015.



1 | Transmetallation of potassium carbene adduct and possible **Ce-3** product.



2 | ORTEP (50 %) representation of the **Au-IPr** complex



3 | ORTEP (50 %) representation of $Eu[LArO^{iPr}]_2(HL)Cl$

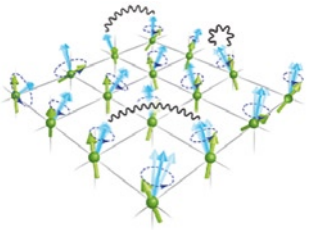
Publications by this Focus Group can also be found on page 181.

Focus Group **Collective Quantum Dynamics**

Prof. Michael Knap (TUM) | Rudolf Mößbauer Tenure Track Professor
Dr. Johannes Oberreuter | Postdoctoral Researcher
Collective Quantum Dynamics, TUM

Scientific Reports

Michael Knap



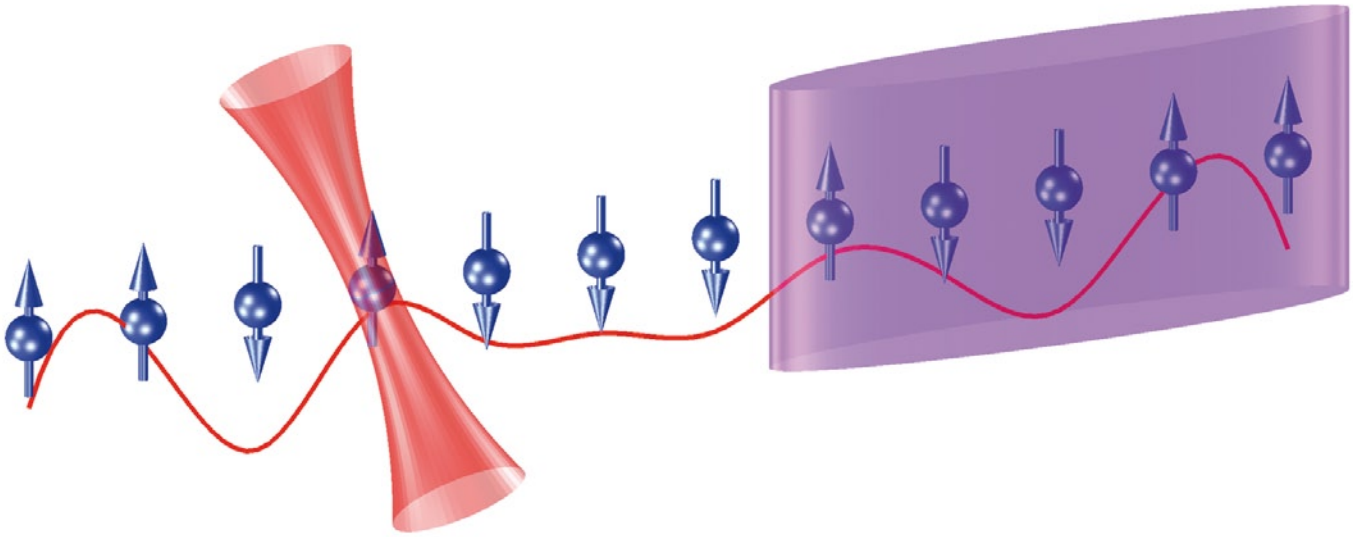
1 | A quantum magnet out of equilibrium

Collective quantum dynamics: A teamwork of quantum particles

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

Correlated quantum systems out of equilibrium
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. Furthermore, very powerful experimental techniques have been developed to study dynamic processes in condensed matter systems as well. These techniques are based on pump-probe spectroscopy on time scales reaching down to sub-femtoseconds. Such technology therefore makes it possible to manipulate and control material properties.

We develop both analytical and numerical techniques to explore the far-from-equilibrium quantum dynamics of these systems. The techniques range from non-equilibrium field theories to exact numerical calculations based on matrix product states. We study fundamental questions including thermalization in closed quantum systems, dynamic phase transitions, intertwined order far from equilibrium, and the competition between coherence and dissipation.



1 | Probing the exotic properties of disordered quantum matter

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 – a phenomenon 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. We study how these particular properties can be characterized by interferometric techniques, explore distinct experimental signatures of disordered systems, and analyze the transition from the localized to the delocalized phase.

Doctoral candidate Simon Weidinger also works in this Focus Group.

Selected Publications

[1] M. Babadi, E. Demler, and M. Knap, “Far-from-equilibrium field theory of many-body quantum spin systems: Prethermalization and relaxation of spin spiral states in three dimensions,” Phys. Rev. X, vol. 5, no. 4, p. 041005, 2015.

[2] M. Bukov, S. Gopalakrishnan, M. Knap, and E. Demler, “Prethermal floquet steady states and instabilities in the periodically driven, weakly interacting Bose-Hubbard model,” Phys. Rev. Lett., vol. 115, no. 20, p. 205301, 2015.

Publications by this Focus Group can also be found on page 181.

Focus Group **Electrochemical Interfaces in Batteries**

Dr. Peter Lamp (BMW Group) | Rudolf Diesel Industry Fellow
Roland Jung | Doctoral Candidate
Prof. Hubert A. Gasteiger, Technical Electrochemistry, TUM

Scientific Reports

Peter Lamp

The development of novel and innovative battery systems is crucial for the large-scale commercialization of electric and hybrid electric vehicles. In order to penetrate the mass market, significant improvements are required with respect to energy and power density as well as safety, lifetime, and costs. In order to optimize future battery systems, a detailed knowledge of the root causes of battery aging is essential. As most of the degradation processes occur at the interface between the solid electrodes and the liquid electrolyte, this interface is of special interest to understand today's batteries and improve those of the future.

This Focus Group concentrates on a fundamental understanding of the aging mechanisms that cause a loss of capacity and therefore reduce battery life. In particular, one of the most critical degradation mechanisms, namely the dissolution of transition metals from the positive electrode (typically a transition metal oxide or transition metal phosphate) into the electrolyte (typically a solution of a lithium-containing salt, such as $LiPF_6$, in an organic carbonate solvent) is being investigated. Even though the exact origin of the transition metal dissolution is not yet fully understood, it is common knowledge that it depends on several causes such as phase transitions in the positive electrode material or corrosion from electrolyte contaminants. The subsequent deposition of the dissolved transition metals on the negative electrode, which has severe negative impact on the surface protective layer, is also within the scope of our TUM-IAS research. Additionally, the gassing behavior during electrochemical cycling of the battery will be investigated, as it not only plays an important role with respect to the stability of the battery cell, but also is crucial for the safety of Li-ion batteries.

Munich Battery Discussions

As in the years 2013 and 2014, Peter Lamp co-organized, together with his group at BMW and the TUM-IAS, the 3rd annual Munich Battery Discussions, which took place March 16–17, 2015. This international conference is dedicated to the most recent topics in battery research and brings together many of the leading scientists in the development of future battery materials and systems. The topic of the 2015 Munich Battery Discussions was "Novel Approaches for High-Energy Lithium Batteries." Eighteen invited speakers from all over the world presented their latest results on novel and innovative materials for high-energy and high-power battery systems for a viable large-scale automotive market. Additionally, very fruitful discussions among students, scientists, and engineers made the Munich Battery Discussions a great success.

The speakers series "New Frontiers in Battery Science and Technology", established in 2014, continued in 2015. The purpose of these invited seminars is to offer the BMW and TUM-IAS communities a continuous update on the most exciting new findings in the field of battery research and to create a platform for frequent exchange of ideas between academic and industrial researchers.

Participants of the Munich Battery Discussions 2015: “Novel Approaches for High Energy Lithium Batteries”

Focus Group **Functional Interfaces**

Prof. Matthias Batzill (University of South Florida) | Hans Fischer Fellow
Yuanqin He | Doctoral Candidate
Prof. Johannes Barth, Molecular Nanoscience and Chemical Physics of Interfaces, TUM

Scientific Reports

Matthias Batzill

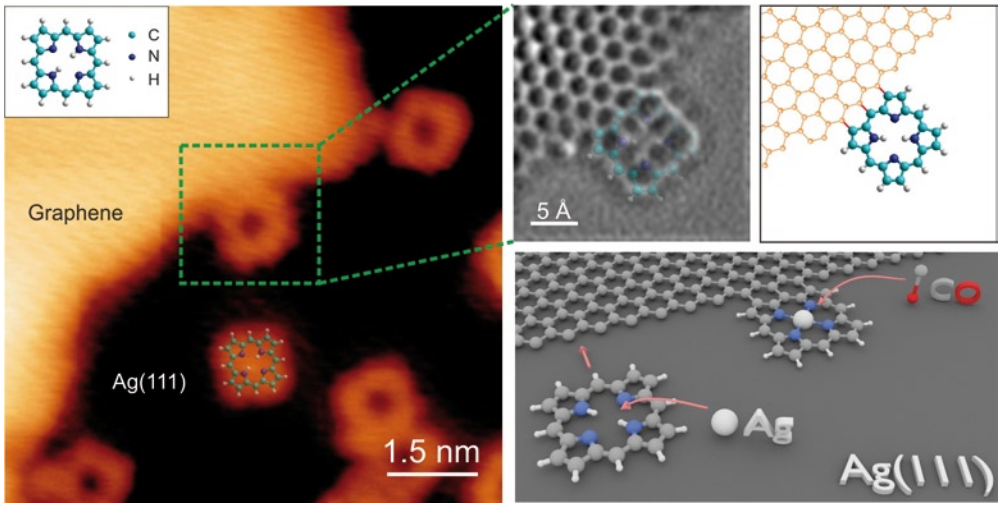
Achieving and visualizing edge functionalization of graphene

Porphyrins are a versatile group of molecules that can be adapted for various technological applications, such as molecular electronics, gas sensing, and light harvesting. Combining the properties of porphyrins with the high physical strength and charge mobility of graphene, a single atomic layer of carbon in a sp^2 honeycomb structure, can enable complex hierarchical architectures and the design of novel functional materials. The goal of this project is to investigate processes and molecular structures for the coupling of porphyrins to undercoordinated graphene edge sites. These coupling reactions are investigated on planar metal surfaces. The metal surface catalyzes the activation of the porphyrins and thus facilitates the covalent linking to graphene edges. The resulting bonding structures of the functionalized graphene edges are directly visualized in our measurements by non-contact force microscopy using a special probe functionalized with a single carbon monoxide (CO) molecule.

Based on observations that porphyrins can be linked at metal surfaces to dimers and oligomeric chains [1], we proposed the concept of a general procedure of on-surface covalent linking of porphyrins to heteromaterials and in particular to sp^2 carbon sites at graphene edges [2]. In this process, first graphene nano-flakes are grown on metal surfaces, e.g. silver, by physical vapor deposition of atomic carbon in vacuum. Subsequently, porphyrins are deposited and covalently fused to the graphene edges. The scanning tunneling microscopy (STM) image (left) shows a base porphyrin module (porphine) coupled to graphene edges, but the atomic and bonding structure could not be clearly resolved. Therefore non-contact atomic force microscopy (nc-AFM) with a CO-functionalized probe is utilized. This advanced imaging technique enables to resolve chemical bonds in carbon materials (right top) in exquisite detail. These coupled porphyrin molecules could further accommodate metal atoms and have gas ligands adsorbed to these metal centers (right bottom).

This study [3] is a proof of principle for the synthesis of complex molecular heterostructures by on surface covalent linking of diverse carbon materials. This process may lead to precise linking of, for example, electric leads (graphene) to single molecules for molecular electronics or attachment of light harvesting dye-molecules for solar energy harvesting.

In close collaboration with Prof. Willi Auwärter (Molecular Engineering at Functional Interfaces, TUM).



1 | Left: STM image showing porphine molecule coupled to the graphene edges (marked with green square). Right top: Laplace-filtered nc-AFM image of a porphine forming three C-C bonds with a graphene zigzag edge (left) and the corresponding structural model (right). Right bottom: Schematic model illustrating the main processes on the Ag(111) surface.

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[1] A. Wiengarten, K. Seufert, W. Auwärter, D. Ecija, K. Diller, F. Allegretti, F. Bischoff, S. Fischer, D. A. Duncan, A. C. Papageorgiou, F. Klappenberger, R. G. Acres, T. H. Ngo, and J. V. Barth, "Surface-assisted dehydrogenative homocoupling of porphine molecules," J. Am. Chem. Soc., vol. 136, no. 26, pp. 9346–9354, 2014.

[2] M. Batzill, "The surface science of graphene: Metal interfaces, CVD synthesis, nanoribbons, chemical modifications, and defects," Surf. Sci. Rep., vol. 67, no. 3–4, pp. 83–115, 2012.

[3] Y. He, W. Auwärter, F. Bischoff, J. Ducke, M. Garnica, M. Batzill, and J. V. Barth, "Fusing tetrapyrroles to graphene edges by surface-assisted covalent coupling", currently under review.

Selected Publication

[4] H. C. Diaz, J. Avila, C. Y. Chen, R. Addou, M. C. Asensio, and M. Batzill, "Direct observation of interlayer hybridization and Dirac relativistic carriers in graphene/MoS2 van der Waals heterostructures" Nano Lett., vol. 15, no. 2, pp. 1135–1140, 2015.

Publications by this Focus Group can also be found on page 181.

Focus Group **Metal-Organic Superlattices of Quantum Magnets**

Prof. Harald Brune (EPFL) | Hans Fischer Senior Fellow
Raphael Hellwig, Georg Michelitsch | Doctoral Candidates

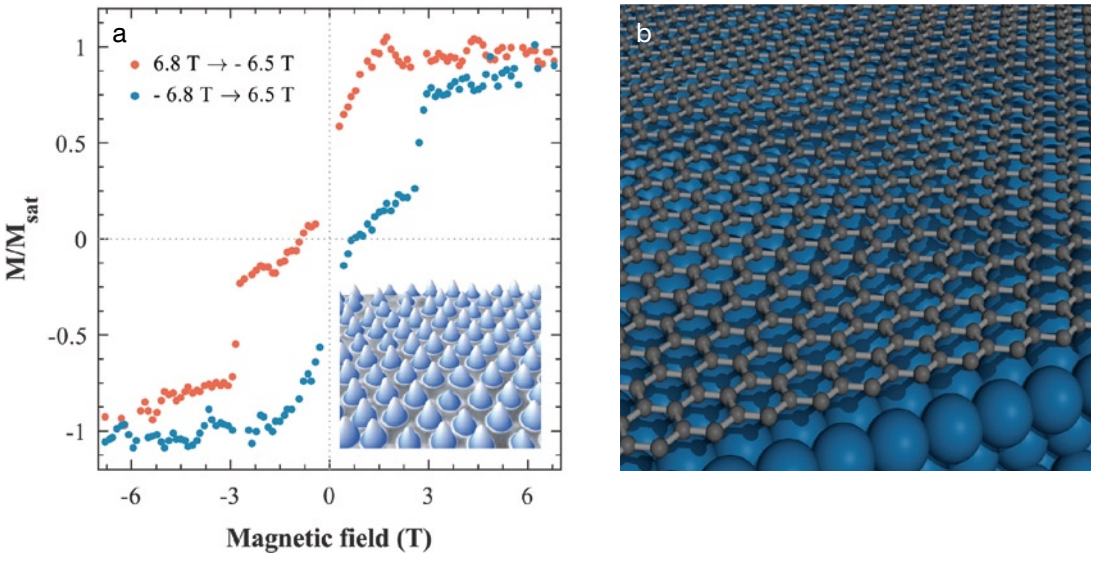
Scientific Reports

Harald Brune

Our project aims at the creation of equally spaced quantum magnets. Quantum magnets explore the ultimate size limits of magnetic information storage. Since their magnetic properties are governed by quantum mechanics, they also are ideal candidates for quantum bits (qubits). Very recently, we discovered that single surface adsorbed atoms can exhibit magnetic relaxation times in the range of hours [1]. Arranging these single-atom magnets in regular lattices is the next step to realize ultra-dense memories or qubit lattices. The synergy between the three collaborating research groups is in magnetism of surface adsorbed atoms and molecules [3], the self-assembly of well ordered metal-organic networks at surfaces [4], and density functional theory calculations of absorption spectra [2] and of magnetic properties. In light of the most recent discoveries in the Lausanne group, we enlarged the project focused on metal-organic networks by adding superlattices of single adatoms.

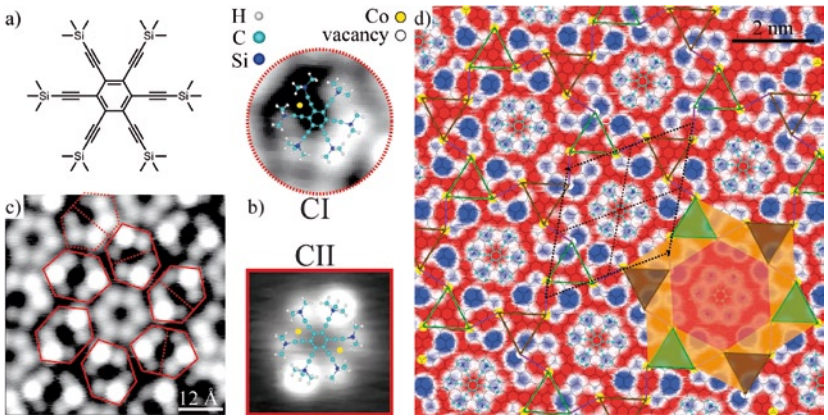
Single atoms

Figure 1(a) shows the out-of-plane magnetization of an ensemble of Dy atoms adsorbed onto a graphene layer on an Ir(111) surface. It is clearly seen that these atoms exhibit magnetic remanence on the time-scale of these X-ray magnetic circular dichroism (XMCD) measurements. In that sense they are classical magnets that remember their magnetic state for a certain time. Their quantum nature becomes apparent in the steps of the magnetization at given fields where quantum tunneling of the magnetization becomes possible. The inset shows a scanning tunneling microscope (STM) image of the superlattice with one Dy atom per (9 x 9)-moiré pattern formed by graphene on Ir(111). Figure 1(b) shows this moiré pattern calculated by dispersion-corrected density functional theory. The mean graphene surface distance is exactly the experimental value. Ongoing calculations focus on the Dy adsorption site, the nature of the Dy–graphene bonding, and on the magnetic ground state.



1 | a) Magnetic hysteresis for single Dy atoms on graphene/Ir(111) acquired with XMCD in the out-of-plane direction (Θ = 0.004 ML, *T* = 3 K, ϕ = 5.1 × 10–3 photons nm–2s–1). Inset: STM image showing that the Dy atoms are equally spaced with the period of the moir´e lattice formed by graphene on Ir(111) (Θ = 0.010 ML, *T*dep = 50 K, *T*STM = 5 K).
b) Calculated moiré pattern with (10 × 10) graphene unit cells on (9 × 9) Ir(111) unit cells.

Prof. Johannes Barth, Molecular Nanoscience and Chemical Physics on Interfaces, TUM
Prof. Karsten Reuter, Theoretical Chemistry, TUM



2 | a) Structure of Hexa-trimethylsilyl-ethynyl-benzene (Hex-TMSEB). b) Co decoration leads to two complexes: CI (one Co atom) and CII (two Co atoms). c) Windmill pattern (red outline) resulting from 6 CII around an undecorated molecule. d) Extended Co-Hex-TMSEB island. Co atoms are marked in yellow and those sites where one Co atom is missing to form a CII complex in white.

Metal-organic

The on-surface synthesis of metal-organic networks can be accomplished either by co-deposition of organic molecules and metal atoms or by the self-assembly of purely organic patterns that are subsequently decorated with metal atoms or clusters. Figure 2 shows an example of the second method. Hexa-trimethylsilyl-ethynyl-benzene (Hex-TMSEB) molecules have six alkynes, see figure 2(a), by which they interact to form a regular lattice on Ag(111). This lattice was decorated by Co atoms that were predicted to preferentially bind between two alkyne groups. As can be seen from the STM images in figure 2(b), we observe two Hex-TMSEB species. The first species (CI) is more abundant at lower Co coverage. It has a single protrusion that appears opposite to the location of the single Co atom between two alkynes, since the inclusion of Co atoms pulls two triple bonds down and pushes noninteracting terminal groups up. The second (CII) is more abundant at higher Co coverage; it has two opposite protrusions coinciding with the terminal groups of two alkynes and originating from two Co atoms adsorbed between the respective other two alkynes. At suited Co coverage, deposition and annealing temperature, this system forms highly ordered patterns with six CII units surrounding one undecorated molecule, see figure 2(c). The two Co atoms per molecule are located along highlighted axes. Figure 2(d) shows a larger area of this network. The Co atoms are marked in yellow. Connecting always three of them leads to alternating up and down pointing triangles (green and brown) forming a 3.4.6.4-tiling pattern that can be divided into regular polygons, i.e., hexagon, rhomboid, and triangle as highlighted in the image.

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[2] K. Diller, F. Klappenberger, F. Allegretti, A. C. Papageorgiou, S. Fischer, D. A.Duncan, R. J. Maurer, J. A. Lloyd, S. C. Oh, K. Reuter, and J. V. Barth, “Temperature-dependent templated growth of porphine thin films on the (111) facets of copper and silver,” J. Chem. Phys., vol. 141, no. 14, p. 144703, 2014.

Selected Publications

[3] S. Baumann, F. Donati, S. Stepanow, S. Rusponi, W. Paul, S. Gangopadhyay, I. G. Rau, G. E. Pacchioni, L. Gragnaniello, M. Pivetta, J. Dreiser, C. Piamonteze, C. P. Lutz, R. M. Macfarlane, B. A. Jones, P. Gambardella, A. J. Heinrich, and H. Brune, “Origin of perpendicular magnetic anisotropy and large orbital moment in Fe atoms on MgO,” Phys. Rev. Lett., vol. 115, no. 23, p. 237202, 2015.

[4] W. Auwärter, D. Écija, F. Klappenberger, and J. V. Barth, “Porphyrins at interfaces,” Nat. Chem., vol. 7, no. 2, pp. 105–120, 2015.

Publications by this Focus Group can also be found on page 181.

Focus Group **Nanoscience for Renewable Energy Sources**

Prof. Stephen M. Goodnick (Arizona State University) | Hans Fischer Senior Fellow
Pietro Luppina | Doctoral Candidate
Prof. Paolo Lugli, Nanoelectronics, TUM

Scientific Reports

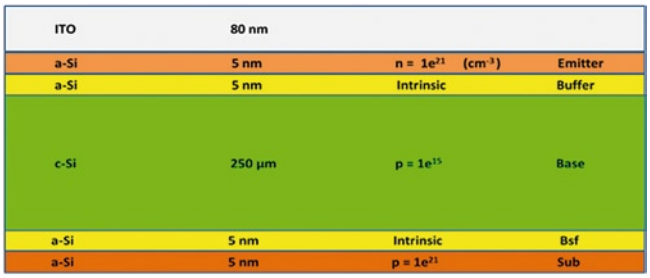
Modeling of silicon-based heterojunction solar cells

Stephen M. Goodnick

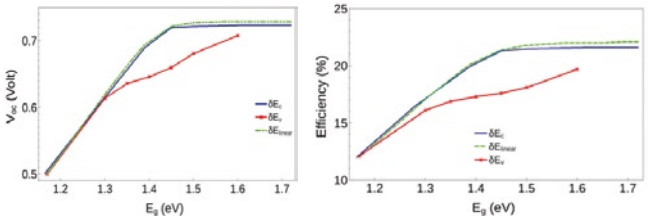
As part of the TUM-IAS Focus Group, we have analyzed and shown results on crystalline Si (c-Si)/amorphous Si (a-Si) heterojunction solar cells using a physical simulation that includes various models for the defect states in the a-Si barriers, as well as explicit models for the ITO (indium tin oxide) emitter contact. We first investigated the impact of band offsets and barrier heights of the a-Si/c-Si interface, particularly in terms of the open circuit voltage. We also found that the solar cell performance is sensitively dependent on the quality of the a-Si in terms of defect states and their distribution, particularly on the emitter side. Finally, we analyzed the role of tunneling and thermionic emission across the heterointerface in terms of transport from the Si to the ITO contact layer.

We have studied HIT solar cells (silicon-based heterojunction with intrinsic layer) using numerical simulations based on the Synopsys Sentaurus device simulator. The results include various models for defect states in the a-Si barriers, as well as explicit models for the band structure of the ITO emitter contact. We investigated the impact of the band offsets and barrier heights of the a-Si/c-Si interface, and we demonstrated that the band alignment of a-Si layers is critical to device performance, particularly in terms of the open circuit voltage. We showed that the solar cell output is particularly sensitive to the quality of amorphous silicon, and especially to defect states in the emitter layer. Finally, we investigated the role of tunneling and thermionic emission across the heterointerface in terms of the carrier transport from Si into the ITO contact layer. The open circuit voltage in HIT cell structures appears to be maximized with respect to the choice of barrier materials, in which increasing band tailing eventually reduces the open circuit voltage and degrades performance.

The standard HIT cell layer structure simulated here, shown schematically in figure 1, consists of a highly n-doped indium tin oxide (ITO) window layer, n-doped a-Si, intrinsic a-Si, p-doped c-Si, p-doped a-Si, and intrinsic a-Si. The metal contacts are not explicitly simulated, and an ideal ohmic contact is assumed. The contact on the rear is made of heavily doped a-Si, and the combination of intrinsic a-Si and doped a-Si layers acts as back surface field, providing excellent rear surface passivation. The intrinsic layer in the front is a buffer layer that improves the open circuit voltage by providing a layer of substantially reduced defect density at the heterointerface between a-Si and c-Si. An Air Mass 1.5 global (AM 1.5G) spectrum was used as the incident solar irradiation. Carrier photogeneration was modeled using a ray-tracing model, and the drift-diffusion model was used for carrier transport. Physical parameters – such as a material's bandgap, charges' carrier mobility, surface recombination velocity, trap capture cross section, distribution of tail states in the a-Si, and dangling bond of the a-Si – were taken from literature, while other material parameters were default values. The defects in amorphous silicon can be divided into two types: band tail states (two exponential) and dangling bond states (two Gaussian acceptor and donor type at mid-gap states).



1 | Layers stack of the HIT solar cell; the light is incident from the top.

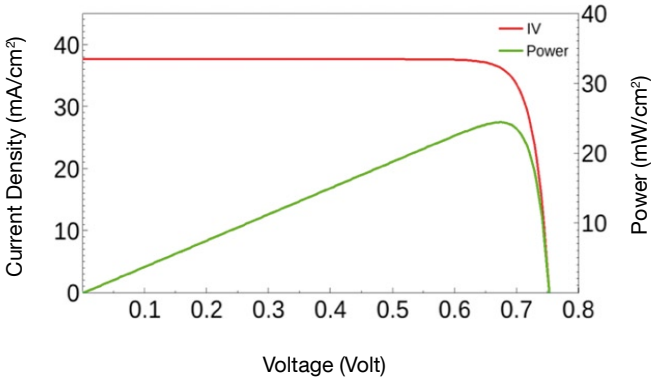


2 | Dependence of the power conversion efficiency and the open circuit voltage varying on the band offsets.

Defect recombination was modeled in the bulk and at the surface with Shockley-Read-Hall (SRH) Auger recombination was taken into account for c-Si using the default model in Sentaurus. Intrinsic and doped a-Si have the same material properties, the only difference being the defect concentration, which is two orders of magnitude higher in doped versus intrinsic a-Si:H.

Previous studies have focused only on the carrier transport mechanism and the optimization of structure, while we have also analyzed the influence of the concentration of defect states of a-Si and studied the role of their strong impact on the performance of the device. Figure 2 presents the results showing that band bending and band offsets affect the transport of minority carriers and hence influence the performance of a-Si/c-Si heterojunction solar cell. Further improvements in cell performance require increasing the built potential and the band bending, especially in the emitter layer. The open circuit voltage in HIT cell structures appears to be maximized with respect to the choice of barrier materials, where increasing band tailing eventually reduces the open circuit voltage and degrades performance.

Our results have implications for the device design of a-Si/c-Si heterostructure solar cells, suggesting a better quality of a-Si (or the materials that can replace it) as key parameter to further improve performance for heterojunction solar cells. Figure 3 shows the best current-voltage characteristic after device optimization, corresponding to Jsc = 37.7 mA/cm^2, Voc = 0.75 V, FF = 87.3 % and η= 24.8 %.



3 | Best I-V characteristic after device optimization.

Selected Publications

[1] P. Luppina, P. Lugli, and S. M. Goodnick, “Modeling of silicon heterojunction solar cells,” in 2015 IEEE 42nd Photovoltaic Specialists, New Orleans, USA, pp. 1–6.

[2] B. Popescu, D. Popescu, P. Luppina, T. Julian, G. Koblmuller, P. Lugli, S. M. Goodnick, “Modeling and simulation of In1-xGaxAs nanowire solar cells,” in Proceedings of the 2015 IEEE 15th International Conference on Nanotechnology (IEEE-NANO), Rome, Italy, pp. 728–731.

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Publications by this Focus Group can also be found on page 181.

Focus Group **Nanophotonics and Quantum Optics**

Prof. Jelena Vuckovic (Stanford University) | Hans Fischer Senior Fellow
Armin Regler | Doctoral Candidate
Prof. Jonathan Finley, Semiconductor Quantum Nanosystems, TUM

Scientific Reports

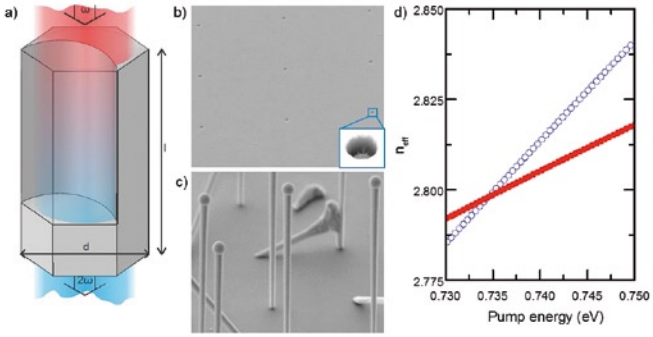
Jelena Vuckovic

Splicing, splitting and detecting quantum light using nanowires

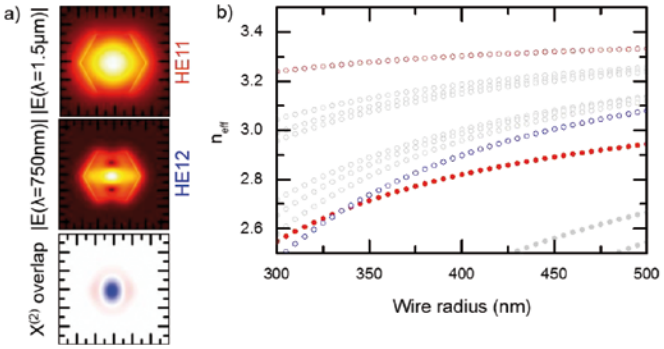
For many applications ranging from medicine and environmental sensing to imaging and emergent quantum technologies, it is necessary to develop novel optical sources at well defined frequencies. This is particularly true in the green and mid-infrared regions of the electromagnetic (EM) spectrum where efficient light-emitting materials simply do not exist. An attractive alternative involves using *nonlinear* optical phenomena, whereby an efficient optical source is built at a practically accessible frequency but then the output is *frequency-converted*. Here, green laser pointers are the most commonly encountered devices, in which pairs of infrared photons are *spliced together* to form green light.

The III-V semiconductors are highly nonlinear optical materials; they can be used, e.g., for sum-frequency generation, where two input fields with frequencies ω_1 and ω_2 are mixed to produce a third output wave at a frequency $\omega_{SFG} = \omega_1 + \omega_2$, or difference frequency generation, where infrared photons are combined to produce an output wave at $\omega_{DFG} = \omega_1 - \omega_2$. Unfortunately, in a macroscopic optical medium the three EM waves having different frequencies (ω_1, ω_2 and $\omega_{D/SFG}$) continually run into and out of phase with each other, limiting the overall efficiency of the nonlinear conversion process. As a result, several tricks have to be applied, including the use of wavelength scale nano-resonators to recirculate light many times through the medium and precisely match the phase of the input and output fields.

This TUM-IAS Focus Group is exploring the use of III–V semiconductor nanowires (NWs) grown directly on silicon substrates to generate quantum light produced by nonlinear optical processes (see figure 1b). The semiconductor NWs are grown by molecular beam epitaxy at predetermined positions on the silicon substrate, defined by <100nm-diameter holes made using electron beam lithography in the few-nm-thick SiO2 oxide (figure 1b). After growth of an AlGaAs NW-core, having a typical diameter of ~100nm and length >10µm, an AlGaAs shell is formed around the core to carefully tailor the refractive index of modes at ω_1, ω_2 and $\omega_{D/SFG}$ and, thereby, enhance the efficiency of the nonlinear optical process. Figure 1 shows scanning electron microscopy images of the pre-patterned substrate before the growth of the NWs (figure 1b) and a post-growth image of GaAs NWs (figure 1c). The thickness of the NWs can be precisely controlled to facilitate guiding of an optical beam in a manner similar to the way light is guided through an optical fiber.



1 | (a) Core-shell NW geometry used for 2nd harmonic generation, consisting of $Al_xGa_{1-x}As$ with accurate Al content and a well-defined thickness. (b) SEM image of the nano apertures in the SiO_2 layer acting as nucleation sites for NWs. (c) GaAs NWs grown site selectively on such a Si/SiO_2 substrate. (d) Dispersion of the NW waveguide modes. The dispersion of the HE_{11} fundamental mode (red) is matched to the corresponding HE_{12} 2nd harmonic mode (blue) at ≈0.735 eV.



2 | a) Profiles of the fundamental HE_{11} mode at a wavelength of 1.5 μm, the 2nd harmonic mode HE_{12} at 750nm, and the spatially resolved overlap for 2nd harmonic generation of the two modes in the lower panel. By integrating over the entire NW profile, a finite second harmonic signal can be obtained. b) Calculated effective refractive indices for the lowest-order modes at pump and 2nd harmonic frequencies for different NW diameters at a uniform NW aluminum content of 40%. For diameters of ~670nm they effective reproduce a nonlinear output.

Figure 1a shows a typical nanowire structure design for a waveguide supporting second harmonic generation at 750nm, i.e. $2 \times \omega$ photons → $1 \times 2\omega$ photon. In this case, the diameter of the NW should be large enough to facilitate refractive index matching of the participating modes, as is shown in figure 1d for the HE_{11} fundamental (red) to the HE_{12} 2nd harmonic (blue) mode. Figure 2a shows finite element simulations of the fundamental waveguide mode (HE_{11}) at 1.5 μm and the desired 2nd harmonic mode (HE_{12}) at 750 nm. A sufficiently small refractive index difference can be achieved by using a tuned NW profile as shown in figure 1a, where a NW was modeled with varying layer thickness and Al content. Figure 2a shows the mode profile of the fundamental mode (HE_{11}) at 1500nm (top panel), the 2nd harmonic mode (HE_{12}) at 750nm (middle panel) and the calculated mode overlap of both modes (bottom panel). The integral of this overlap over the whole waveguide region yields a finite value, indicating that 2nd harmonic conversion will occur. According to the simulated values for the effective refractive indices, geometrically optimized nanowire structures have been designed and are currently being fabricated and tested.

In related work, the Focus Group is exploring the use of superconducting NWs to detect photons propagating in silicon waveguides. Here, absorption of a single photon in the NW locally destroys the superconductivity and leads to a measurable signal in the attached readout circuit. Such superconducting NW detectors promise near unity detection quantum efficiencies, low dark count rates (<10 Hz), and ultrafast (<80ps) timing resolution. By integrating *superconducting* NW single photon detectors and *semiconductor* nonlinear frequency conversion elements onto a single silicon ridge waveguide, the Focus Group aims to frequency-convert, distribute and detect single photons on a silicon chip.

Focus Group **Semiconductor Nanowires**

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Heike Riel

Advanced hetero-nanowires for opto/electrical circuits

Semiconductor nanowires (NW) attract great interest due to their high potential for advancing fundamental and applied research toward inherently one-dimensional (1-D) nanostructures. In particular, bottom-up NWs represent a unique architecture allowing *both* electronic and optical confinement in all directions, while circumventing detrimental issues in integrating heteroepitaxial systems on diverse platforms. This versatility enables the development of various novel 1-D device technologies, including nanoscale transistors, advanced nanosensors, thermo-electric energy conversion and optoelectronic and nanophotonic elements.

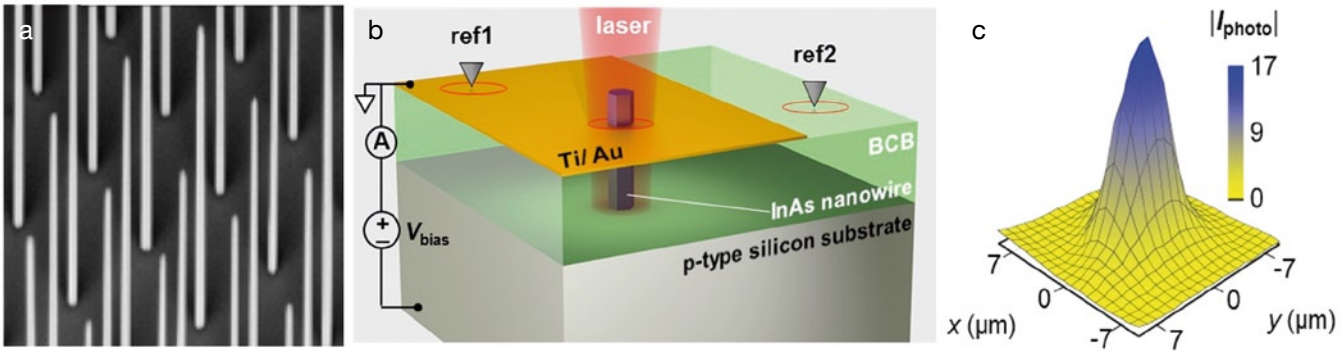
The role of the Focus Group on Semiconductor Nanowires is to advance the fundamental understanding and performance of NW-based electronic and optical devices and circuits toward new, unprecedented functionalities. These goals are realized in a joint research program between TUM and the IBM Research Laboratory, which allows us to develop an innovative platform for novel, highly scaled III–V semiconductor NWs.

The IBM Zurich Research Labs bring in strong R&D efforts in advanced device concepts and architectures for future NW-electronic applications, such as post-CMOS III–V semiconductor-nanowire field-effect and tunneling transistors (NW-FETs, TFETs) as well as thermoelectric platforms for energy harvesting. In excellent synergy, the host institution at the Walter Schottky Institute (TUM WSI) offers strong expertise in the growth of high-performance III–V nanowire materials on silicon, highly spatially and time-resolved methods for advanced physical characterization of charge carrier and photocurrent dynamics (ultra-fast pump-probe spectroscopy), and novel optical device concepts (lasers and ultrafast photodetectors) employing semiconductor NWs.

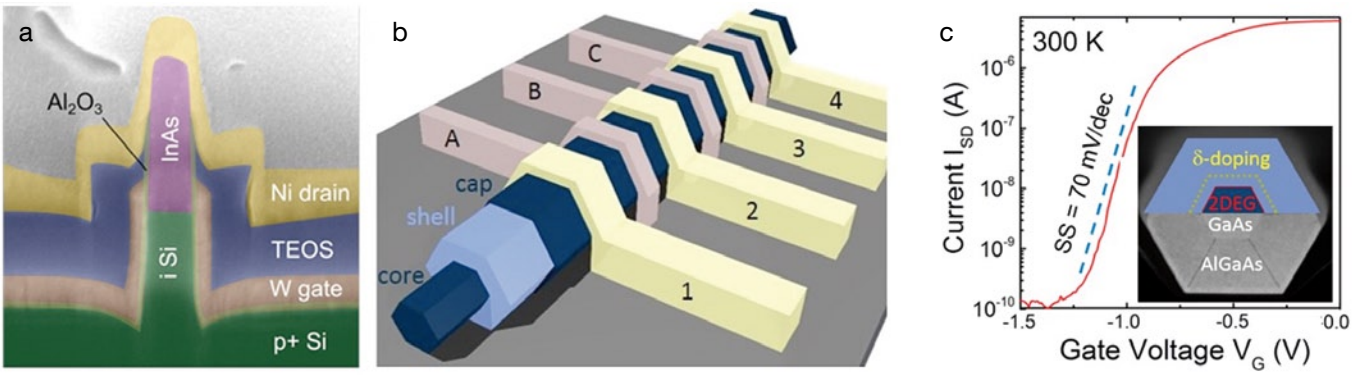
In April of 2015, the Focus Group held the kick-off symposium for Rudolf Diesel Industry Fellow Dr. Heike Riel (IBM). The topic of this stimulating event was “Growth and characterization of III-V semiconductor NWs and their devices.” The audience comprised TUM researchers from the Departments of Physics and Electrical and Computer Engineering, including members of the Walter Schottky Institute and the Center for Nanotechnology and Nanomaterials (ZNN). Besides an impressive talk by Dr. Heike Riel on “III–V nanowire: from materials to nanoscale devices,” four WSI-ZNN student researchers presented their PhD thesis work, including Bernhard Loitsch, recent recipient of the renowned IBM International PhD Fellowship.

In 2015, the Focus Group made significant progress in all aspects of growth, advanced characterization, device fabrication, and testing for III–V semiconductor NWs. In terms of growth, monolithic integration of site-selective In(Ga)As-based nanowires on Si has been realized [1], and their III–V/Si heterointerface functionalities has been examined with respect to TFET device [2] and photoresponse characteristics [1] (figure 1).

In addition, we pioneered the development of ultrathin epitaxial III–V NWs on Si to allow access to truly 1-D electronic properties and exploit strong confinement effects of charge carriers. Here, for the first time, we realized sub-10 nm diameter GaAs NWs using novel growth techniques, and we demonstrated incorporation of a new type of nanoscale emitter, i.e., a crystal phase quantum dot.



1 | (a) Site-selective In(Ga)As nanowires on Si; the optoelectronic properties of the n-InAs/p-Si heterojunction diode are probed by scanning photocurrent microscopy (b) with a typical result in (c) [1].



2 | (a) Vertical gate-all-around InAs-on-Si NW-TFET device [2]; (b) Multi-gated modulation-doped GaAs-AlGaAs core-shell NW-FET (b) with excellent transfer characteristics shown in (c) [4].

The properties of such low-dimensional systems embedded in GaAs-based NWs, including radial GaAs quantum-well core-shell NWs, have been further explored with respect to their ultrafast optoelectronic properties [3].

On the device-oriented side, we have demonstrated unique concepts for advanced InAs/Si NW-based TFETs [2] and high-electron mobility transistors (NW-HEMTs) using modulation-doped core-shell GaAs-AlGaAs NWs [4] (see figure 2). Employing sophisticated multi-gate electrodes along a single NW, as in the latter case, we were able to realize steep-slope turn-on characteristics (~70 mV/dec) and excellent dc output characteristics, as well as to spatially probe the transport properties along the NW for defect spectroscopy. Employing the same material system of GaAs-AlGaAs core-shell NWs, we also realized monolithically integrated NW lasers on Si for the first time.
These free-standing nanoscale lasers exhibit surprisingly large spontaneous emission coupling factors ($\beta > 0.2$) and hence provide a promising platform for future on-chip optical data communication on Si (Si photonics). Such advanced core-shell hetero-NWs are being investigated in ongoing work with respect to their thermoelectric device properties, combining unique platforms developed at IBM with novel 1-D-like core-shell NW and advanced charge carrier dynamic characterization available at WSI-ZNN.

Doctoral candidate Bernhard Loitsch (Semiconductor Nanostructures and Quantum Systems) works also in this Focus Group.

Selected Publications

[1] A. Brenneis, J. Overbeck, J. Treu, S. Hertenberger, S. Morkötter, M. Döblinger, J. J. Finley, G. Abstreiter, G. Koblmüller, and A. W. Holleitner, “Photocurrents in a single InAs nanowire/silicon heterojunction,” ACS Nano, vol. 9, no. 10, pp. 9849–9858, 2015.

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[4] S. Morkötter, N. Jeon, D. Rudolph, B. Loitsch, D. Spirkoska, E. Hoffmann, M. Döblinger, S. Matich, J. J. Finley, L. J. Lauhon, G. Abstreiter, and G. Koblmüller, “Demonstration of confined electron gas and steep-slope behavior in delta-doped GaAs-AlGaAs core–shell nanowire transistors,” Nano Lett., vol. 15, no. 5, pp. 3295–3302, 2015.

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Focus Group **Theory of Complex Quantum Systems**

Prof. Robert König (TUM) | Rudolf Mößbauer Tenure Track Professor
Dr. Milán Mosonyi | Postdoctoral Researcher
Stefan Huber | Doctoral Candidate
Theory of Complex Quantum Systems, TUM

Scientific Reports

Robert König

Physical limits to information processing: quantum communication and computation

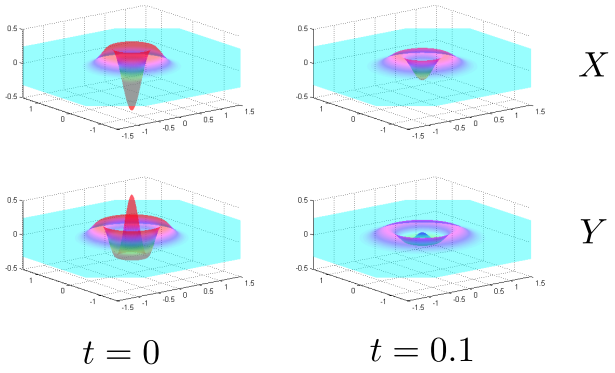
The Focus Group Complex Quantum Systems was established in 2015. We are conducting research in quantum information theory, an interdisciplinary area at the intersection of physics, mathematics, and computer science. Our objective is to develop quantitative tools for assessing the potential of quantum systems when used as an information-processing resource, and to find new and improved techniques for this purpose.

Quantum effects can significantly enhance information processing. Shor's algorithm for factoring (a problem believed to be hard classically) is arguably the most well-known theoretical proposal taking advantage of quantum mechanics. Since it requires a working quantum computer, its realization is beyond the current state of the art. In contrast, certain information-processing primitives in communication and cryptography also rely on quantum effects but are technologically less demanding. We aim to identify scenarios where quantum mechanics can enhance information-processing capabilities and characterize the exact technological requirements for doing so. To advance our understanding of information-theoretic applications, our primary focus is on the following areas:

Quantum communication

A key problem is to characterize when quantum correlations provide an operational advantage. It is known that the use of entanglement can boost communication capacities beyond what is achievable by means of classical correlations only. Unfortunately, though, a general understanding of when this happens is missing. In fact, there are currently no explicit examples illustrating this effect. It is thus natural to wonder whether such a quantum advantage really exists for natural channels, that is, typical processes occurring in nature.

In this context, we are studying bosonic communication channels, which describe typical fiber-optic communication systems. Here our work [2] shows that, if an advantage in using entanglement exists at all, it must be negligibly small and of no operational interest. More recently, we have obtained general results for scenarios involving free auxiliary entanglement (that is, so-called entanglement-assisted capacities) [3]. The derivation is based on an analysis of the behavior of entropic quantities under the action of the channel. It yields powerful generalizations of an inequality discovered by Shannon in classical information theory. Such inequalities are of interest since they can provide quantitative information about processes involving non-Gaussian noise. This is also subject of ongoing work by Stefan Huber, who joined our group in the fall of 2015. Other activities of our group in this area center on more basic questions related to the "distinguishability" of quantum states, a prerequisite for communication: Milán Mosonyi considered hypothesis testing (and related error exponents) when trying to distinguish quantum states and developed techniques for computing these quantities.



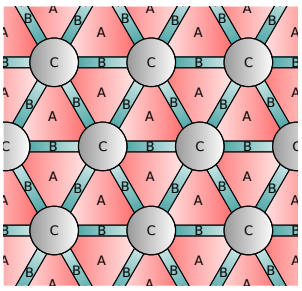
1 | Physically motivated processes – in this case a quantum diffusion process – can be used as a mathematical tool to "Gaussify" states, yielding results for possibly non-Gaussian codes and channels. The figure illustrates the evolution of the Wigner function of certain initial states under such a process.

Quantum error correction and fault tolerance

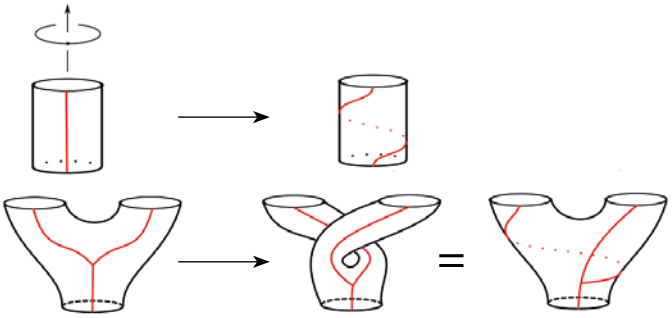
Robust information processing cannot be achieved without mechanisms providing resilience to noise. This is particularly challenging for quantum information due to its fragile nature: any undesired interaction with the environment leads to decoherence. Our work tries to develop such mechanisms, effectively isolating logical information by means of error-correction methods.

Balancing the need to protect against noise with the ability to operate on encoded information (to execute a computation) presents significant theoretical and experimental obstacles. In this context, we are examining the use of topologically ordered quantum many-body systems, which provide intrinsic stability against noise. Motivated by earlier work [1] on particular codes, we have characterized gates implementable in a robust fashion in such systems [4].

We are currently studying related methods for the use of such systems, especially for state preparation and readout.



2 | Ground spaces of certain spin lattices embedded in 2D surfaces are excellent quantum error-correcting codes. These topologically ordered systems provide intrinsic mechanisms for computation by time-dependent deformations of the surface.



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Selected Publications

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Advanced Computation and Modeling

Advanced Stability Analysis

- F. Berger, T. Hummel, M. Hertweck, B. Schuermans, and T. Sattelmayer, “High-frequency thermoacoustic modulation mechanisms in swirl-stabilized gas turbine combustors, Part I: Measurement of non-compact flame transfer functions,” in ASME Turbo Expo 2016 GT2016-57913, Seoul, South Korea, 2016, accepted in 2015.
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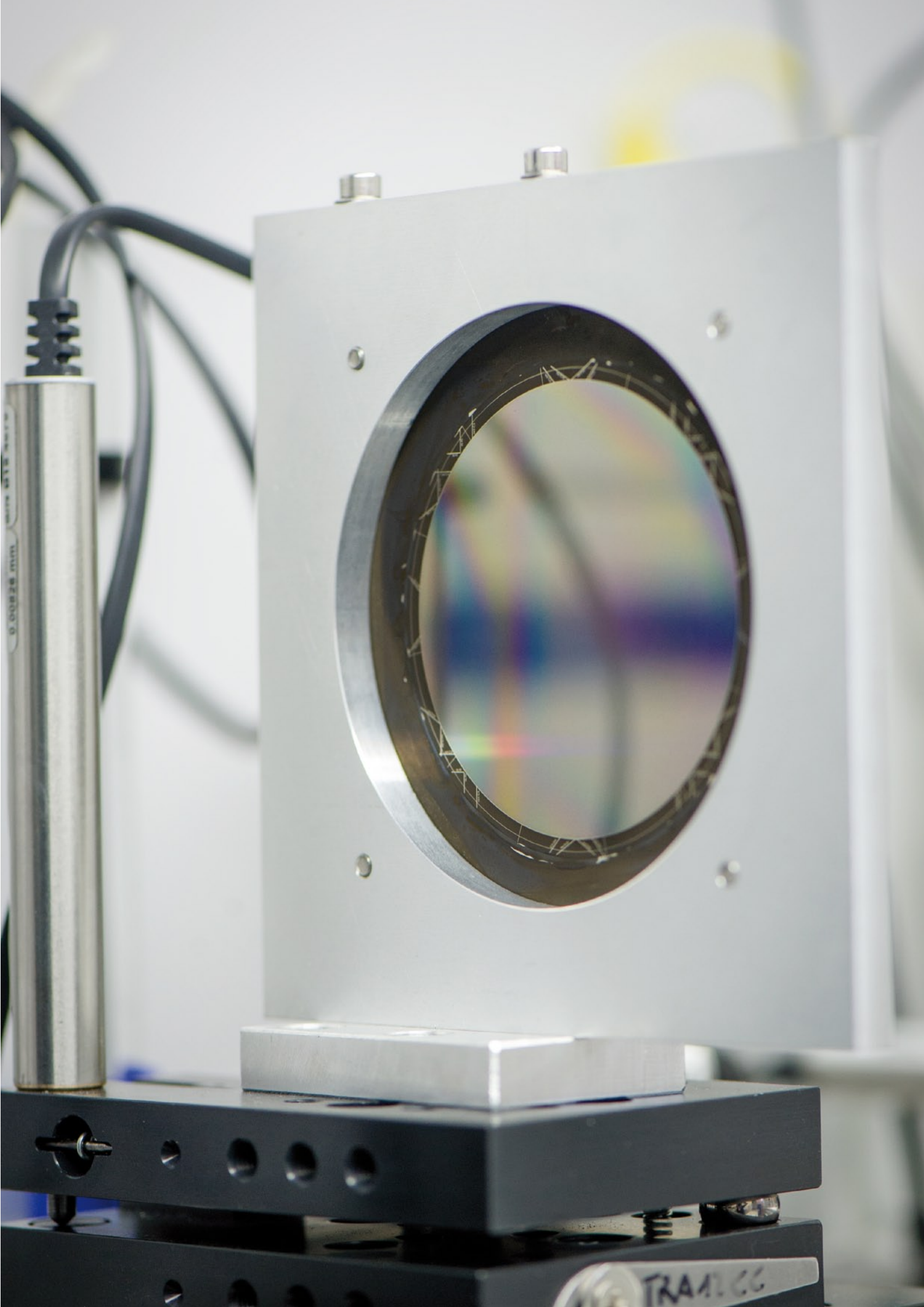
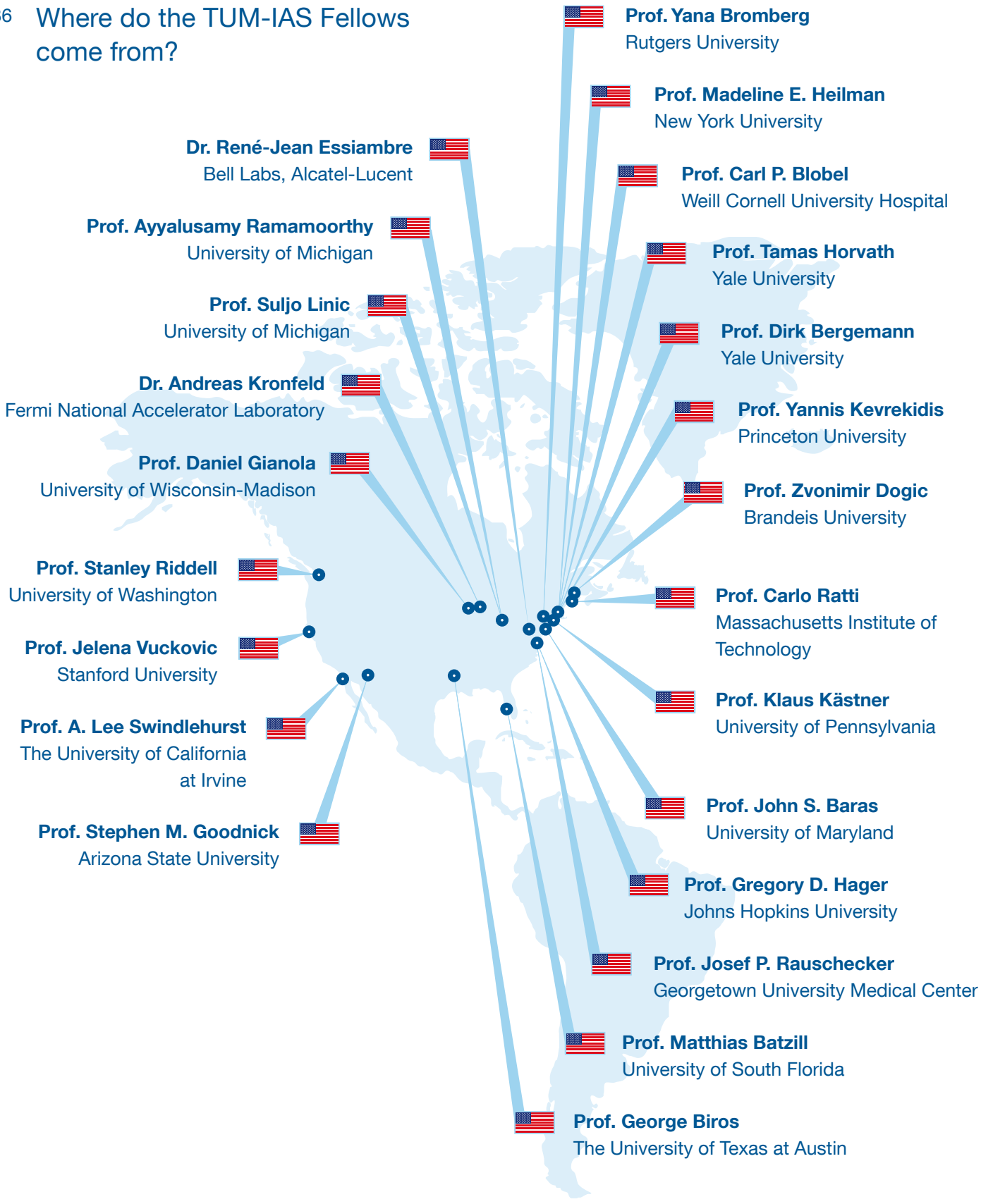


Facts and Figures

Where do the TUM-IAS Fellows come from?

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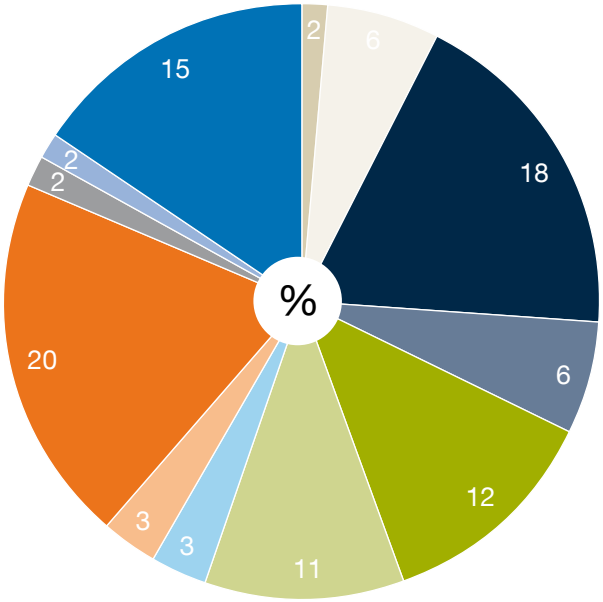
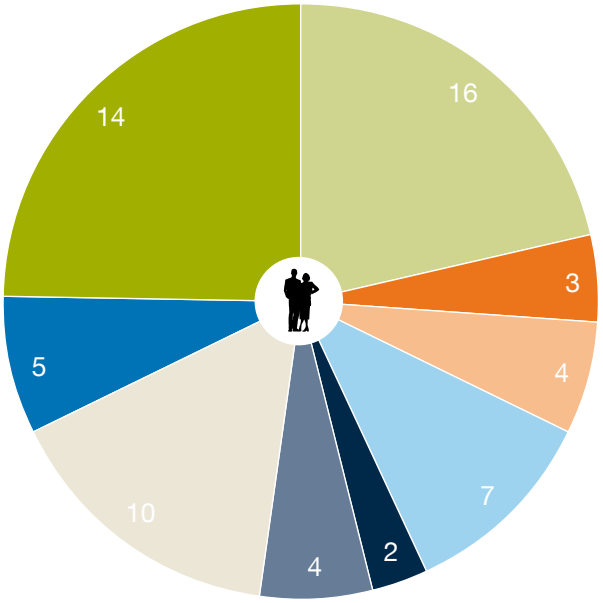
Fellow Distribution

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
- Mechanical Engineering
- Mathematics
- Physics
- Sports and Health Sciences
- TUM School of Management
- TUM School of Medicine (ME)

Distribution According to Research Areas

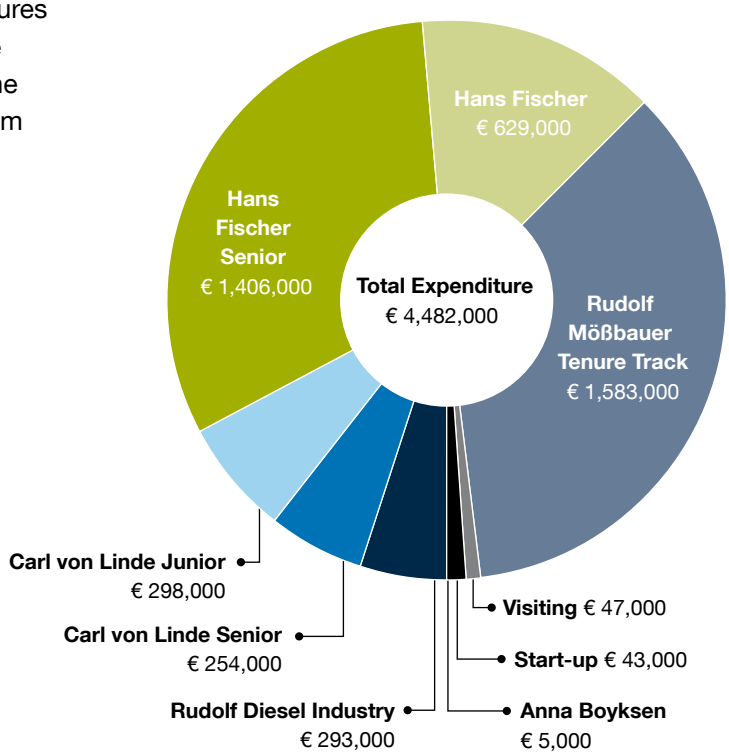


- Advanced Computation and Modeling
- Biomedical Engineering, Bio-Imaging, Neuroscience
- Bio-related Natural Sciences
- Communication and Information
- Control Theory, Systems Engineering and Robotics
- Environmental and Earth Sciences, Building Technology
- Fundamental Physics
- Gender and Diversity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

Finances

In this section we present a brief survey of the financial data of the TUM-IAS. The expenditures are covered by the “third funding line” of the German Excellence Initiative as well as by the European Union Seventh Framework Program (Marie Curie COFUND).

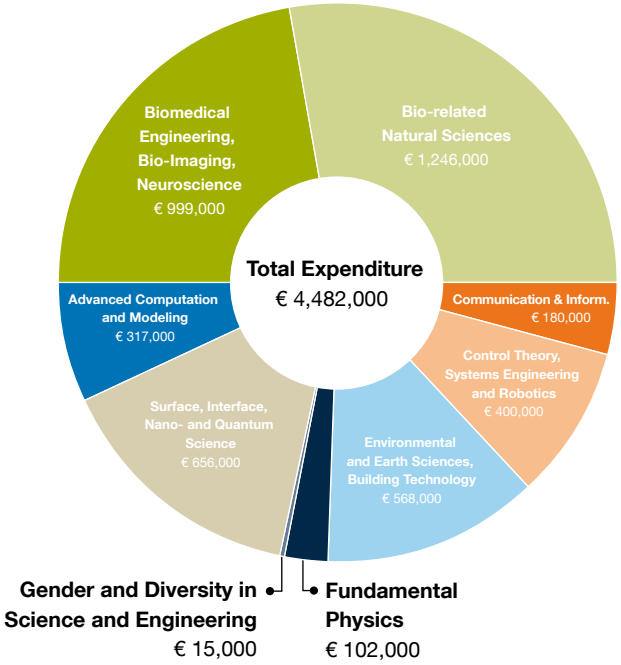
Expenditure per Fellowship Category in 2015



This chart illustrates the expenditure in 2015 for each Fellowship category. Most dominant in terms of costs – with 35% of the total expenditure – are, for the first time in the history of the Fellowship program at the TUM-IAS, not the Hans Fischer Senior Fellowships, but the Rudolf Mößbauer Tenure Track Professorships. This program is devoted to the funding of outstanding, high-potential early career scientists who have already achieved a major scientific or technological breakthrough and who have the ambition of developing a new field of endeavor when joining TUM (as a Tenure Track Assistant Professor). The Hans Fischer Senior Fellowship comes second with 31% of the total expenditure; these Fellowships are 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. Even if this year this was not the most expensive Fellowship category, the expenditures increased about 50% in comparison with 2014.

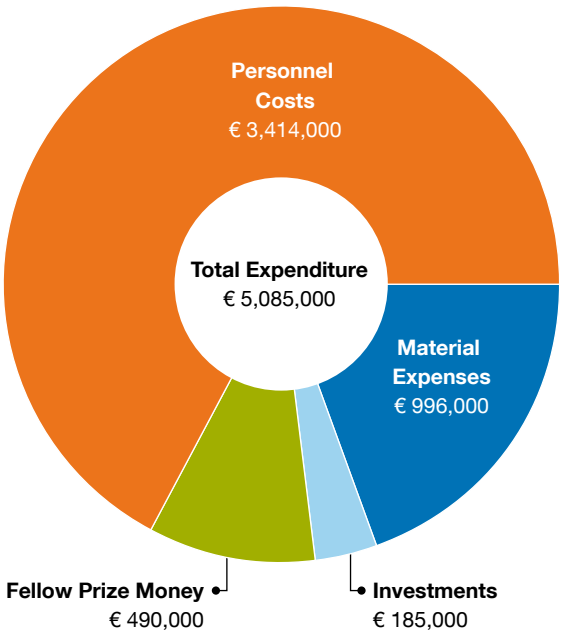
Expenditure for the Carl von Linde Senior Fellowship category decreased in comparison to 2014, due to the fact that the appointed Fellows in 2010 have finished their tenure, 2012 no Fellow was appointed in this category and afterwards only one Fellowship per year. Furthermore from 2014 onwards, doctoral candidates have no longer been financed in this category. The Rudolf Diesel Industry Fellowship expenditures were slightly lower than in 2014, still reflecting the fact that doctoral candidates are no longer financed in this category. Expenditure for the Hans Fischer Fellowship category increased – reflecting the high number of Fellows appointed in 2014 and 2015. The Anna Boyksen Fellowship category was newly established in 2014. Although the expenditures more than doubled in comparison to 2014, this is still the Fellowship category with the lowest expenditure level in the TUM-IAS program.

Expenditure per Research Area in 2015



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, also according to Research Areas. Interdisciplinary projects were classified according to their most dominant field. Again, engineering was the most strongly represented field in terms of costs, accounting for about 55% of the total expenditure. The remaining 45% are divided among life sciences, medicine, and natural sciences. Expenditure per main scientific field reflects the distribution of Fellows according to the same divisions (see page 189 “Fellow Distribution”). The Research Area with the highest expenditures was Bio-related Natural Sciences, reflecting a high number of Rudolf Mößbauer Tenure Track Professors and Hans Fischer Senior Fellows working on this topic.

Total Expenditure in 2015



On this chart, the total TUM-IAS expenditure is displayed, including Fellowships, Start-up funding, Visiting Fellowships, events, and management. The total expenditure increased significantly in comparison to 2014 (3.550.000 Euro) reflecting the high number of Fellows appointed in 2014 and 2015 in both the Hans Fischer and Hans Fischer Senior Fellowship categories and the full capacity operation of the Rudolf Mößbauer Tenure Track program. The difference between the total expenditures per Fellowship category/Research Area and the total expenditure in 2015 amounts to the expenses with the management, 415.300,00 Euro for Personnel and 187.400,00 Euro for Material and Event expenses.

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4, 5, 8, 11 (Rank, Santos Kühn, Fischer, Höchtl, Abstreiter, Merz, Schwarzer, Steinberger), 17, 21, 35 (photographs), 35 (bottom center and right), 39, 42–51, 54, 66, 72, 94, 116, 118, 132 (Menzel), 134 (Hirt), 142, 183: Astrid Eckert.

11 (Sturm, Schmid), 31, 32, 56 (Schuermans), 59, 70, 76, 80 (Koehler, Pfeiffer), 86, 88, 89, 98, 100, 102, 106 (Zaccone), 109, 112, 120, 121, 122 (Buss), 124, 130, 144 (Knap), 146, 148, 158: Andreas Heddergott.

11 (Santos Kühn): Astrid Eckert/Andreas Heddergott.

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43, 44, 45, 46, 47, 48, 49, 50 Interview

56–58 (figure 1– 4): Chair for Thermodynamics, TUM.

61: Mauro Ferraro, Alessandro Reali, et al.

79: American Physical Society (APS).

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84 (Kessler): facesbyfrank; (figure 1): U. Kiran Marelli, J. Bezençon, E. Puig, B. Ernst, and H. Kessler, “Enantiomeric cyclic peptides with different caco-2 permeability suggest carrier-mediated transport,” Chem. Eur. J., vol. 21, no. 22, pp. 8023–8027, 2015 (license no. 3831330005575).

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115: Denise Panyik-Dale/Alcatel Lucent.

119: Samarjit Chakraborty/RCS, TUM.

122 (figure 1): M. M. Schill, F. Gruber, and M. Buss, “Quasi-direct nonprehensile catching with uncertain object states,” in 2015 IEEE International Conference on Robotics and Automation (ICRA), pp. 2468–2474.

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131 (map): Google Earth; (illustrations): Landsat, Data SIO, NOAA, U.S. Navy, NGA, and GEBCO.

133 (figure 1): modified from J. Laube, T. H. Sparks, N. Estrella, and A. Menzel, “Does humidity trigger tree phenology? Proposal for an air humidity based framework for bud development in spring,” New Phytol., vol. 202, no. 2, pp. 350–355, 2014; (figure 2): modified from Y. H. Fu, H. Zhao, S. Piao, M. Peaucelle, S. Peng, G. Zhou, P. Ciais, M. Huang, A. Menzel, J. Peñuelas, Y. Song, Y. Vitasse, Z. Zeng, and I. A. Janssens, “Declining global warming effects on the phenology of spring leaf unfolding,” Nature, vol. 526, no. 7571, pp. 104–107, 2015.

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144 (figure 1): M. Knap / Phys. Rev. Lett. 113, 147204 (2014).

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154: Craig Lee/Stanford University.

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157 (figure 1): A. Brenneis, J. Overbeck, J. Treu, S. Hertenberger, S. Morkötter, M. Döblinger, J. J. Finley, G. Abstreiter, G. Koblmüller, and A. W. Holleitner, “Photocurrents in a single InAs nanowire/silicon heterojunction,” ACS Nano, vol. 9, no. 10, pp. 9849–9858, 2015.; (figure 2): S. Morkötter, N. Jeon, D. Rudolph, B. Loitsch, D. Spirkoska, E. Hoffmann, M. Döblinger, S. Matich, J. J. Finley, L. J. Lauhon, G. Abstreiter, and G. Koblmüller, “Demonstration of confined electron gas and steep-slope behavior in delta-doped GaAs-AlGaAs core–shell nanowire transistors,” Nano Lett., vol. 15, no. 5, pp. 3295–3302, 2015.

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