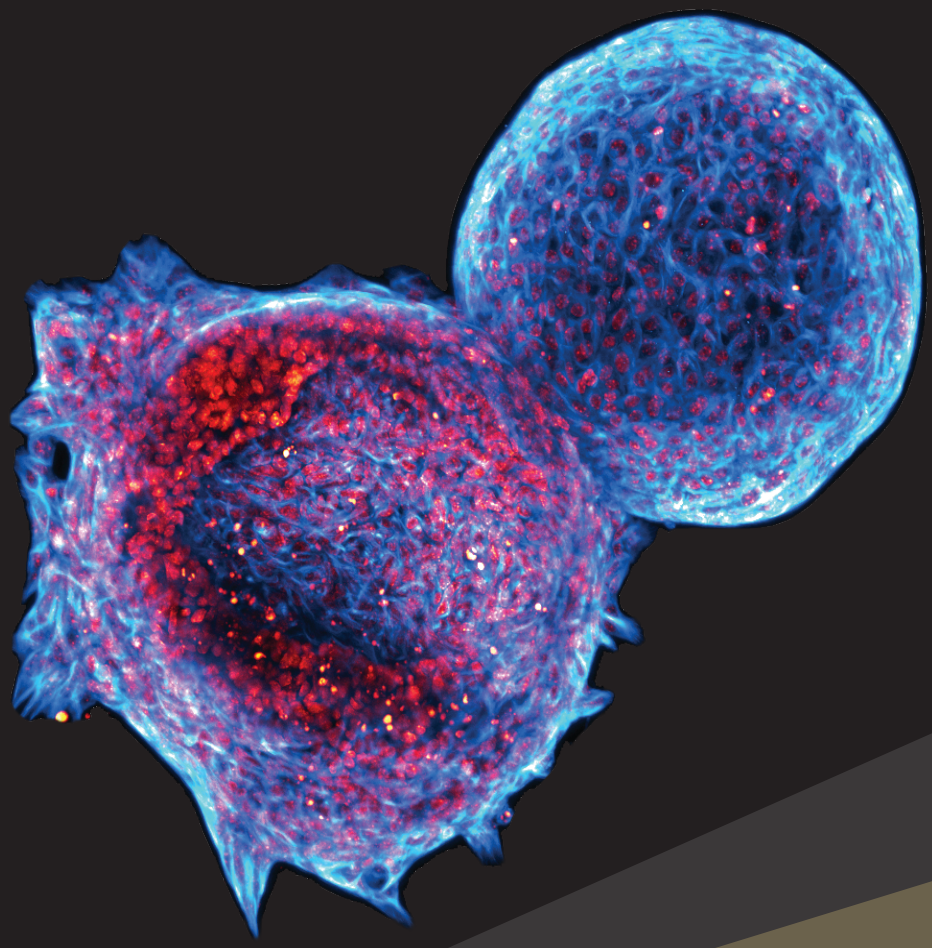
Giersch - Summer School & International Conference

Online hosted by Frankfurt Institute for Advanced Studies

Theoretical and Experimental Quantitative Cell Biology



February 22 to March 04, 2021

For further information, please visit: https://fias.institute/en/events/gsic2020

For registration, please visit: https://www.set-digital.com/qM7729

This event is funded by Stiftung Giersch.

STIFTUNG GIERSCH

FIAS Frankfurt Institute for Advanced Studies

GOETHE UNIVERSITÄT FRANKFURT AM MAIN

CMMS

DynaMem

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Max-Planck-Institut für Polymerforschung / Max Planck Institute for Polymer Research

JG|U

Rhein-Main Universitäten Eine strategische Allianz

mpibp max-planck-institut für biophysik

西安科大 Xidian University

International Joint Research Center

FIAS 法兰克福高研院

The Conference and Summer School is funded by the Giersch-Foundation

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Organisation Committee

Enrico Schleiff

Volker Lindenstruth

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Day 6	**AI in … Biology**
Day 7	**Theoretical and digital Medicine**
Day 8	**Experimental and theoretical Neurosciences**

Day 1 - Monday, 22nd of February

08:30 - 08:45	Welcome by Enrico Schleiff / President of the Goethe University
08:45 - 09:00	Welcome by Volker Lindenstruth / head of FIAS
New Frontiers in: *Chair: Mike Heilemann*	**Quantitative Imaging in Life Sciences**
09:00 - 09:30	**Niklas Klusch** **Plant and alga mitochondrial complex I** Max Planck Institute of Biophysics, Frankfurt Germany
09:30 - 10:00	**Achilleas Frangakis** **Sticky spots: Adhesion mechanisms for cell-cell communication and infection** Goethe University Frankfurt am Main, Germany
10:00 - 10:30	**Ernst Stelzer** **Dynamic three-dimensional imaging with light sheet microscopy** Goethe University Frankfurt am Main, Germany
10:30 - 11:00	Break
11:00 - 11:30	**Valentin Nägerl** **Super-resolution imaging of dynamic nano-structures and spaces in the brain** University of Bordeaux, France
11:30 - 13:00	Break
13:00 - 15:00	**Demonstration videos** *Electron Microscopy* - Lab Werner Kühlbrandt, Max Planck Institute of Biophysics, Frankfurt am Main, Germany - Lab Achilleas Frangakis, Goethe Universität Frankfurt am Main, Germany *Light Microscopy* - Lab Stelzer, Goethe Universität Frankfurt am Main, Germany - Lab Heilemann, Goethe Universität Frankfurt am Main, Germany
15:00 - 15:30	Break
Chair: Ute Hellmich	Next Generation talk of students organized by DynaMem Students
15:30 - 15:45	**Mark Schröder** **The FGFR network studied with DNA-assisted single-molecule super-resolution microscopy**

Goethe University Frankfurt am Main, Germany

16:00 - 17:30 Break

17:30-19:00 **Public lecture by Chris Boos**
The AI world
arago GmbH, Frankfurt, Germany

Day 2 - Tuesday, 23rd of February

New Frontiers in: **Quantitative Cell Biology**
Chair: Achilleas Frangakis

Next Generation talks of students organized by DynaMem Students

09:30 - 09:45 **Aljoscha Joppe**
Manipulation of mitochondrial membrane dynamics: Impact on aging
Goethe University Frankfurt, Germany

09:45 - 10:00 **Marc Pereyra Mari**
Particle image velocimetry to quantify 3D collective cell migration
Frankfurt Institute for Advanced Studies, Germany

10:00 - 12:30 Break

12:30 - 13:00 Information about Germany and funding options for international fellows

13:00 - 14:00 **Open Keynote Lecture by Werner Kühlbrandt**
High-resolution cryoEM of membrane protein complexes
Max Planck Institute of Biophysics Frankfurt, Germany

14.00 - 14:30 Break

Chair: Thomas Sokolowski

14:30 - 15:00 **Anna Kreshuk**
Machine learning for microscopy
EMBL Heidelberg, Germany

15:00 - 15:30 **Andreas Reichert**
Continuous cycles of MICOS-dependent cristae membrane remodelling revealed by STED nanoscopy
University Hospital Düsseldorf, Germany

15:30 - 16:00 **Neal Devaraj**
Reconstituting phospholipid membrane synthesis
University of California, San Diego, USA

16:00 - 16:30 Break

16:30 - 17:00 **Mike Heilemann**
TNFR1 oligomerization in the plasma membrane studied with quantitative super-resolution microscopy
Goethe University Frankfurt, Germany

17:00 - 17:30 **Ivan Dikic**
Dynamics of endoplasmic reticulum remodelling
Goethe University Hospital Frankfurt, Germany

17:30 - 18:00 **Paul Macklin**
tba
Indiana University, Bloomington, USA

18:00 - 18:30 **Ute Hellmich**
An integrated structural biology approach for a molecular understanding of TRP ion channels
Friedrich-Schiller-University Jena, Germany

Day 3 - Wednesday, 24th of February

New Frontiers in: BIG DATA in Life Sciences
Chair: Franziska Matthäus

09:00 - 09:30 **Kathi Zarnack**
Decoding a cancer-relevant splicing decision in the RON proto-oncogene using high-throughput mutagenesis
Goethe Universität Frankfurt am Main, Germany

09:30 - 10:00 **Ingo Ebersberger**
What comparative genomics tell us about the emergence of human pathogens
Goethe University Frankfurt am Main, Germany

10:00 - 10:30 **Stefanie Kellner**
Mass spectrometry of the epitranscriptome
Goethe University Frankfurt am Main, Germany

10:30 - 11:00 **Maria Barbarossa**
A mathematical view on the complex dynamics of infectious diseases
Frankfurt Institute for Advanced Studies, Germany

11:00 - 13:00 Break

13:00 - 14:00 **Open Lecture by Martin Meier-Schellersheim**
Aim for mechanistic models!
National Institute of Allergy and Infectious Diseases (NIAID), Bethesda, USA

14:00 - 14:30 Break

Chair: Roberto Covino

14:30 - 16:00 **Demonstrations**

Mass spectrometry
- Lab Marschall (FIERCE)
- Lab Bode (Metabolomics)
- Lab Kellner (Mass spectrometry)

Day 4 - Thursday, 25th of February

New Frontiers in: **Structural Analysis and Modelling in Life Sciences**
Chair: Gerhard Hummer

Next Generation talks of students organized by CMMS Students

09:00 - 09:15 **Julian Heidecke**
Modeling and evaluating test-trace-and-isolate strategies for the control of infectious diseases
Frankfurt Institute for Advanced Studies, Germany

09:15 - 09:30 **Josephine Tetteh**
COVID-19 network model to evaluate vaccine strategies towards herd immunity
Frankfurt Institute for Advanced Studies, Germany

09:30 - 09:45 **Gianmarco Lazzeri**
Atomically detailed characterization of RNA folding by means of biased computer simulations
Frankfurt Institute for Advanced Studies, Germany

09:45 - 10:00 **Tien Duy Vo**
Microbial cationic peptides as a natural defense mechanism against insect antimicrobial peptides
Goethe University Frankfurt am Main, Germany

10:00 - 11:00 Break

11:00 - 11:30 **Demonstration**
- Structural Genomics Consortium SGC Knapp Lab, Frankfurt am Main, Germany

11:30 - 13:00 Break

13:00 - 13:30 **Sebastian Thallmair**
Fine-tuned PI(4,5)P_2 sensitivity of the Tubby domain unravels local PI(4,5)P_2 pool dynamics at ER-PM contact sites
Frankfurt Institute for Advanced Studies, Germany

13:30 - 14:00 **Gerhard Hummer**
Molecular simulations in times of COVID-19
Max Planck Institute of Biophysics Frankfurt, Germany

14:00 - 14:30 **Harald Schwalbe**
Integrated structural biology to understand disulfide bond formation in the ribosomal exit tunnel
Goethe University Frankfurt am Main, Germany

Chair: Friederike Schmid Gerhard Hummer

14:30 - 15:00 Break

15:00 - 15:30 **Roberto Covino**
Deep reinforcement learning discovers simple molecular mechanisms from complex physical models
Frankfurt Institute for Advanced Studies, Germany

15:30 - 16:00 **Thomas Dandekar**
Live is complicated, but models have to be simple: Boolean semi-quantitative Models
University Würzburg, Germany

16:00 - 17:00 Break

17:00 - 18:00 **Open Lecture by Thomas Südhof**
Molecular codes enabling brain function
Stanford University, USA

Day 5 - Monday, 1st of March

New Frontiers in: **Theory on cellular Dynamics**
Chair: Maria Barbarossa

09:00 - 09:30 **Franziska Matthäus**
Mathematical Modeling of collective cell motility in development and disease
Goethe University Frankfurt am Main, Germany

09:30 - 10:00 **Nadine Flinner**
Image segmentation and classification to uncover characteristics in different types of cancer
Goethe University Frankfurt am Main, Germany

10:00 - 10:30 **Friederike Schmid**
Coarse-grained modelling of lipids and membranes
Johannes Gutenberg-University Mainz, Germany

10:30 - 11:00 Break

11:00 - 11:30 **Katrin Heinze**
Lessons from the glassy bone: Spatiotemporal insights into the bone marrow *in vivo*, *in situ* **and** *in silico*
University of Würzburg, Germany

11:30 - 12:00 **Arthur Korte**
Understanding genotype-phenotype relationships using the model plant *Arabidopsis thaliana*
University of Würzburg, Germany

12:00 - 12:30 **Sabine Fischer**
Image-based systems biology of cell differentiation in mouse blastocysts
University of Würzburg, Germany

12:30 - 13:00 Break

Chair: Sebastian Thallmair

13:00 - 14:00 **Open Lecture by Hanieh Saeedi**
Marine biodiversity advances in a digital era
Senckenberg Research Institute and Natural History Museum, Department of Marine Zoology, Biodiversity Information, Fellow of the JQ Young Academy, Frankfurt am Main, Germany

14:00 - 14:30 Break

Next Generation talks of students organized by FIGGS Students

14:30 - 14:45 **Camile Fraga Delfino Kunz**
Chemotaxis impact on a Turing reaction-diffusion system
Frankfurt Institute for Advanced Studies, Germany

14:45 - 15:00 **Simon Schardt**
The range of cell-cell communication influences the pattern in cell differentiation
University of Würzburg, Germany

15:00 - 15:15 **Tim Liebisch**
Cell fate clusters in ICM organoids arise from cell fate heredity & division – a modelling approach
Frankfurt Institute for Advanced Studies, Germany

15:15 - 15:30 **Silas Boye Nissen**
Theoretical tool bridging cell polarities with development of robust morphologies
Stanford University, USA

15:30 - 16:00 Break

Next Generation talks of students organized by XFIJRC Students

16:00 - 16:15 **Franziska Krämer**
Investigating Mechanical Force Dynamics of Extra-Embryonic Membranes in *Tribolium castaneum Part I*
Goethe University Frankfurt am Main, Germany

16:15 - 16:30 **Zoë Lange**
Investigating Mechanical Force Dynamics of Extra-Embryonic Membranes in *Tribolium castaneum Part II*
Goethe University Frankfurt am Main, Germany

16:30 - 16:45 **Fabian Reinisch**
Observing cell fate decisions and clustering live in a 3D model for pre-implantation embryos
Goethe University Frankfurt am Main, Germany

Day 6, Tuesday, 2nd of March

New Frontiers in: **AI in Biology**
Chair: Ernst Stelzer

09:00 - 09:30 **Xiyang Liu**
tba
Xidian University, Xi'an, China

09:30 - 10:00 **Su-In Lee**
tba
Paul G. Allen School of Computer Science & Engineering, University of Washington, Seattle, USA

10:00 - 10:30 **Peng Liu**
tba
Xidian University, Xi'an, China

10:30 - 11:00 Break

11:00 - 11:30 **Chuipeng Gou**
tba
Xidian University, Xi'an, China

11:30 - 12:00 **Bing Han**
tba
Xidian University, Xi'an, China

12:00 - 13:00 Break

Chair: Daniel Merk

13:00 - 13:30 **Cecilia Clementi**
Designing molecular models by machine learning and experimental data
Freie Universität Berlin, Germany

13:30 - 14:00	**Philip Kollmannsberger** **AI for quantitative high-resolution microscopy** University of Würzburg, Germany
14:00 - 14:30	**Thomas Sokolowski** **The many ends of a never-ending story: Deriving the *Drosophila* gap gene system by ab-initio optimization** Frankfurt Institute for Advanced Studies, Germany
14:30 - 15:00	Break Next Generation talks of students organized by FIGGS Students
15:00 - 15:15	**You Zhou** **Deep and accurate detection of m6A RNA modifications using miCLIP2 and m6Aboost machine learning** Goethe University Frankfurt am Main, Germany
15:15 - 15:30	**Neetika Nath** **Discovering association patterns of individual serum Thyrotropin concentrations using machine learning: An example from the study of health in Pomerania (SHIP)** University Greifswald, Germany
15:30 - 17:00	Break
17:00 - 18:30	**Open Lecture by Andreas Widl** **"AI in industry"** SAMSON AG

Day 7, Wedesday, 3rd of March

New Frontiers in: *Chair: Kathi Zarnack*	**Theoretical and digital Medicine**
10:00 - 11:30	**Demonstration, how to model and simulate in Medicine** Xiyang Liu - tba Marcel Schulz – Bioinformatics in cardio-circulatory research Maria Barbarossa - tba
11:30 - 12:00	Internal Meeting CMMS PhDs
12:00 - 12:30	iQBio Meeting
12:30 - 13:00	Break

13:00 - 14:00 **Open Lecture by Peter Wild**
Challenges in medicine
Senckenberg Institute of Pathology, Germany

Chair: Jochen Triesch

14:00 - 14:30 Break

14:30 - 15:00 **François Nédélec**
Cytoskeleton scaling laws in blood platelets
EMBL Heidelberg, Germany

15:00 - 15:30 **Creating a catalogue of human regulatory elements to find novel disease genes**
Marcel Schulz
Goethe University Hospital Frankfurt, Germany

15:30 - 16:00 **Daniel Merk**
Prospective application of artificial Intelligence in the de novo design of bioactive NCEs
Goethe University Frankfurt, Germany

16:00 - 16:30 **Christian Wachinger**
Intelligent algorithms in neuroimaging: toward generalizable and transparent prediction of brain disease
University Hospital München, LMU München, Germany

Day 8, Thursday, 4th of March

New Frontiers in: **Experimental and theoretical Neurosciences**
Chair: Achilleas Frangakis

09:00 - 9:30 **Christian Fiebach**
Decoding the mind using brain imaging
Goethe University Frankfurt am Min, Germany

9:30 - 10:00 **Tatjana Tchumatchenko**
Neuronal network models
Max Planck Institute for Brain Research, Frankfurt am Main, Germany

10:00 - 10:30 **Matthias Kaschube**
The dynamics of internally generated brain activity
Frankfurt Institute for Advanced Studies, Germany

10:30 - 11:00 Break

11:00 - 11:30	**Jochen Triesch** **Staging epileptogenesis with deep neural networks** Frankfurt Institute for Advanced Studies, Germany
11:30 - 12:00	**Yee Lee Shing** **The roles of memory for predictive processing** Goethe University Frankfurt am Main, Germany
13:00 - 14:00	**Open lecture by Moritz Helmstädter** **Cerebral Cortex Connectomics / the interactions between natural and artificial intelligence** Max Planck Institute for Brain Research, Frankfurt am Main, Germany

Titles & Abstracts

Day 1 - Monday, 22nd of February

Quantiative Imaging in Life Sciences

Niklas Klusch

Max Planck Institute of Biophysics, Department of Structural Biology, Frankfurt am Main, Germany

Plant and alga mitochondrial complex I

Mitochondrial complex I is the main site for electron transfer to the respiratory chain and generates much of the proton gradient across the inner mitochondrial membrane. It is composed of two arms, which form a conserved L-shape. We report the structures of the intact, 47-subunit mitochondrial complex I from Arabidopsis thaliana and 51-subunit complex I from the green alga Polytomella sp. at 3.4 and 3.1 Å resolution. In both, a heterotrimeric γ-carbonic anhydrase domain is attached to the membrane arm on the matrix side. Two states are resolved in A. thaliana complex I, with different angles between the two arms and different conformations of the ND1 loop near the quinol binding site. The angle appears to depend on a bridge domain, which links the peripheral arm to the membrane arm and includes an unusual ferredoxin. We suggest that the bridge domain is relevant for complex I activity.

Achilleas Frangakis

Electron Microscopy, Buchmann Institute for Molecular Life Sciences (BMLS), Goethe University Frankfurt am Main, Frankfurt am Main, Germany

Sticky spots: Adhesion mechanisms for cell-cell communication and infection

Desmosomes are cell-cell junctions that link tissue cells experiencing intense mechanical stress. Although the structure of the desmosomal cadherins is known, the desmosome architecture-which is essential for mediating numerous functions-remains elusive. Here, we recorded cryo-electron tomograms (cryo-ET) in which individual cadherins can be discerned; they appear variable in shape, spacing, and tilt with respect to the membrane. The resulting sub-tomogram average reaches a resolution of ?26 Å, limited by the inherent flexibility of desmosomes. To address this challenge typical of dynamic biological assemblies, we combine sub-tomogram averaging with atomistic molecular dynamics (MD) simulations. We generate models of possible cadherin arrangements and perform an in silico screening according to biophysical and structural properties extracted from MD simulation trajectories. We find a truss-like arrangement of cadherins that resembles the characteristic footprint seen in the electron micrograph. The resulting model of the desmosomal architecture explains their unique biophysical properties and strength.

Ernst Stelzer

Physical Biology, Buchmann Institute for Molecular Life Sciences (BMLS). Goethe University Frankfurt am Main, Frankfurt am Main, Germany

Dynamic three-dimensional imaging with light sheet microscopy

A major objective of the modern life sciences is to perform experiments under near natural conditions (NNC) and to rely on morphologically intact three-dimensional biological specimens such as cysts, organoids, spheroids, embryonic bodies, tissue sections and small model organisms. Hence, scientific projects relate to developmental biology, including embryogenesis and tissue formation, as well as to cell biology, e.g. investigating specific pathways in three dimensions rather than in inadequate cell culture systems that rely on hard and flat surfaces.

In general, fluorescence microscopy provides a high contrast, since only specifically labelled cellular components are observed

while all other structures remain “dark”. Fundamental issues of fluorescence microscopy that must be addressed are: 1) Excitation light degrades endogenous organic compounds and bleaches fluorophores. 2) Specimens provide only a finite number of fluorophores, which limits the number of collectable emitted photons. 3) Organisms are adapted to a solar flux of 1.4 kW/m2. Thus, irradiance should not exceed a few mW/mm2 or nW/µm2 in live imaging assays. LSFM can be operated in HC as well as HT modes.

The optical sectioning capability is fundamental for dynamic three-dimensional imaging. One of the very few instruments, with this property is light sheet-based fluorescence microscopy. LSFM makes the sincerest effort to address the NNC-related issues by decoupling the excitation and emission light pathways. The significance of LSFM’s illumination-based optical sectioning property is that the viability and the fluorescence signal of a living specimen are retained even though millions of images are recorded for days or even weeks.

Particular benefits of LSFM are: (i) good axial resolution, (ii) imaging along multiple directions, (iii) deep tissue penetration due to the low numerical aperture of the illumination objective lens, (iv) high signal-to-noise ratio, (v) unrestricted compatibility with fluorescent dyes and proteins, (vi) reduced fluorophore bleaching and (vii) reduced photo-toxicity at almost any scale, (viii) millions of pixels recorded in parallel, (ix) excellent specimen viability and (x) compatibility with many functional imaging technologies (FCS, FLIM, FRET etc.).

Mark Schröder

Single Molecule Biophysics, Institute of Physical and Theoretical Chemistry, Goethe University Frankfurt am Main, Frankfurt am Main, Germany

The FGFR network studied with DNA-assisted single-molecule super-resolution microscopy

Fibroblast growth factor receptors (FGFRs) belong to the family of receptor tyrosine kinases and play central roles in health and disease. Upon ligand binding, FGFRs form homo- and heteromeric complexes which trigger cellular responses. To study interactions within the FGFR subfamily with respect of their heterogeneity in the plasma membrane of human cancer cells, an observation technique which resolves individual protein complexes on an endogenous protein level was needed. We established a multiplexing single-molecule localization microscopy pipeline to image and analyze the FGFR network. By using DNA-labeled primary antibodies and the super-resolution microscopy method DNA-PAINT, all four FGF receptors were visualized with near-molecular spatial resolution in the same cell. Based on these data, information on FGFR density, spatial distribution, and inner-subfamily colocalization were extracted.

Valentin Nägerl

Interdisciplinary Institute for NeuroScience, French National Centre for Scientific Research, University of Bordeaux, France

Super-resolution imaging of dynamic nano-structures and spaces in the brain

The extracellular space (ECS) forms an important but understudied frontier in neuroscience. It consists of the narrow gaps that surround all brain cells, which are filled with interstitial fluid and extracellular matrix molecules, occupying around one fifth of the volume of the brain. It likely provides the molecular cues and physical rails that incite and guide morphogenic processes and the migration of immune cells like microglia. However, mapping the dynamic landscape of the ECS with enough spatial resolution has been impossible to accomplish until now for lack of appropriate tools. In my presentation, I will review our technical progress in labeling and imaging the ECS vis-à-vis fluorescently labeled neurons, astrocytes and microglia cells in living brain slices using a of STED microscopy and lattice light sheet Ca2+ imaging.

Recent papers:

1. *Henneberger et al. LTP induction boosts glutamate spillover by driving withdrawal of perisynaptic astroglia. Neuron (2020)*
2. *Arizono et al. Structural basis of astrocytic Ca2+ signals at tripartite synapses. Nat. Communications (2020).* *Inavalli et al. A super-resolution platform for correlative live single-molecule imaging and STED microscopy. Nature Methods (2019)*
4. *Tønnesen et al. Super-resolution imaging of the extracellular space in living brain tissue. Cell (2018)*
5. *Pfeiffer et al. Chronic STED imaging reveals high turnover of dendritic spines in the hippocampus in vivo. eLife (2018)*
6. *Chéreau et al. Super-resolution imaging reveals activity-dependent plasticity of axon morphology linked to changes in action potential conduction velocity. PNAS (2017)*

Public Lecture

Chris Boos

arago GmbH, Frankfurt, Germany

The AI World

Chris Boos has a mission: empowering human potential, freeing up time for creativity and innovative thinking through artificial intelligence (AI). To that end, Chris founded arago in Germany in 1995, pushing existing boundaries in AI technology to build a general AI. Since then, Chris has led arago to become a key partner and driver for the established economy, positioning arago's AI HIRO™ as a platform for companies to reinvent their business models in the digital age.

Day 2 - Tuesday, 23rd of February

Quantitative Cell Biology

Aljoscha Joppe

Molecular Developmental Biology, Institute for Molecular Biosciences, Goethe University Frankfurt am Main, Frankfurt am Main, Germany

Manipulation of mitochondrial membrane dynamics: Impact on aging

Aging is an inescapable, progressive biological process, which is associated with physiological impairments that end inevitable with death. We examined the fungus Podospora anserina, a well- established model organism for aging and especially for the mitochondrial etiology of aging. We focused on the inner mitochondrial membrane phospholipid cardiolipin. This phospholipid is exclusively synthesized in the inner mitochondrial membrane, where it plays an essential role for mitochondrial fission and fusion and is very important for stabilizing respiratory chain super complexes. We investigate synthetic molecules, which specifically affect cardiolipin in this fungus. Unfortunately, hitherto no substances are known which only have an influence on cardiolipin and not on other phospholipids like phosphatidylglycerol. Therefore, control experiments are very important. In these experiments a strain is used in which the gene encoding the cardiolipin synthase (PaCRD1), that catalyzes the last step of cardiolipin biosynthesis, is deleted. This mutant thus cannot synthesize cardiolipin and in consequence should not be affected by synthetic molecules, which specifically interfere with cardiolipin. In cooperation with Prof. Bereau (University of Amsterdam), who bioinformatically identified suitable cardiolipin-binding molecules and Prof. Schneider (University of Mainz), who measured the cardiolipin binding specificity in liposomes, we analyzed the mitochondrial respiration and the impact of the best suited molecules on the wild type and the ΔPaCrd1 mutant. So far, three molecules were investigated, of which two molecules (1-[2-oxo-2-(4-pentylphenyl)ethyl]quinolin-1-ium bromide and 10-propylacridin-10-ium iodide) seem to be not cardiolipin-specific. However, the third molecule (2-[(E)-2-[4-(dimethylamino)phenyl]ethenyl]-3-ethyl-1,3-benzothiazol-3-ium iodide) affects wild-type respiration without impairing the respiration rate of the mutant and thus seems to display cardiolipin-specificity. Currently, the impact of this substance on lifespan is investigated.

Marc Pereyra Mari

Life Sciences, Frankfurt Institute for Advanced Studies, Frankfurt am Main, Germany

Particle Image Velocimetry to quantify 3D Collective Cell Migration

Three-dimensional recordings in developmental biology allow us to extract valuable quantitative descriptions of biological processes. To quantify collective cell migration, we have implemented a three-dimensional particle image velocimetry (PIV) package using the Julia programming language, PIV3D. The application of PIV3D is illustrasted on a three-dimensional dataset of the embryonic development of Tribolium Castaneum. Since PIV performs pattern matching to extract cell displacements, it can be applied to non-segmentable datasets (non-labelled or labelled for any persistent intracellular marker).

Public Lecture

Werner Kühlbrandt

Max Planck Institute of Biophysics, Department of Structural Biology, Max-von-Laue Str. 3, 60438 Frankfurt am Main, Germany.

High-resolution cryoEM of membrane protein complexes

Structural biology and molecular cell biology is currently undergoing a revolution, brought about by technical developments in electron cryo-microscopy (cryoEM). The "resolution revolution" in cryoEM is primarily due to a new generation of direct electron detectors and image processing programs. With these developments it is now possible to determine the detailed structures and molecular mechanisms of large and dynamic protein assemblies, in particular membrane proteins, that have been intractable for decades. Single-particle cryoEM of membrane protein complexes now routinely achieves 2-3 Å resolution, where all side¬chains, cofactors and (in the case of membrane proteins) lipids, bound ions and even water molecules in a protein complex are visible. As an added bonus, cryoEM simultaneously records images of co-existing conformational states of a protein complex; the different confor¬mations can be separated by image processing and put into a functional sequence. Using the same instruments, electron cryo-tomography (cryoET) can image macromolecular assemblies in their cellular or orga¬nellar environment at increasingly high resolution.

We combine both approaches to investigate the structure and molecular mechanisms of energy-converting membrane protein complexes. CryoET of Mgm1 on lipid membranes indicates how this mechano-chemical GTPase may shape the mitochondrial cristae. CryoET of mitochondrial mem-branes indicates that the respiratory chain supercomplex is essentially conserved from plants to mammals. Single-particle cryoEM of complex I from Yarrowia lipolytica reveals bound substrates and lipids at 3.2 Å resolution. While the chloroplast ATP synthase is monomeric, all mitochon¬drial ATP synthases form dimers that assemble into long rows that induce local membrane curvature. Single-particle cryoEM of the chloroplast ATP synthase shows how the complex is turned off at night to prevent unpro¬ductive ATP hydrolysis. The 2.7 Å map of a mitochondrial ATP synthase dimer resolves 13 different rotary substates, providing unexpected new insights into the universal mechanism of ATP synthesis by rotary catalysis that drives most cellular processes.

Anna Kreshuk

Cell Biology and Biophysics Unit, European Molecular Biology Laboratory, Heidelberg, Germany

Machine learning for microscopy

Machine learning has revolutionized computer vision over the recent years, continuously pushing the boundaries of what's possible in image reconstruction and analysis. I will briefly discuss the underlying principles and then show some examples from the work of my lab where we develop new algorithms and tools for reconstruction, segmentation and downstream analysis tasks.

Mike Heilemann

Single Molecule Biophysics, Institute of Physical and Theoretical Chemistry, Goethe University Frankfurt am Main, Frankfurt am Main, Germany

TNFR1 oligomerization in the plasme membrane studied with quantitative super-resolution microscopy

Ligand-induced tumor necrosis factor receptor 1 (TNFR1) activation controls nuclear factor κ-light-chain-enhancer of activated B cells (NF-κB) signaling, cell proliferation, programmed cell death, and survival and is crucially involved in inflammation, autoimmune disorders, and cancer progression. Despite the relevance of TNFR1 clustering for signaling, oligomerization of ligand-free and ligand-activated TNFR1 remains controversial. At present, models range from ligand-independent receptor predimerization to ligand-induced oligomerization. Here, we used quantitative, single-molecule superresolution microscopy to study TNFR1 assembly directly in native cellular settings and at physiological cell surface abundance. In the absence of its ligand TNFα, TNFR1 assembled into monomeric and dimeric receptor units. Upon binding of TNFα, TNFR1 clustered predominantly not only into trimers but also into higher-order oligomers. A functional mutation in the preligand assembly domain of TNFR1 resulted in only monomeric TNFR1, which exhibited impaired ligand binding. In contrast, a form of TNFR1 with a mutation in the ligand-binding CRD2 subdomain retained the monomer-to-dimer ratio of the unliganded wild-type TNFR1 but exhibited no ligand binding. These results underscore the importance of ligand-independent TNFR1 dimerization in NF-κB signaling.

Neal K. Devaraj

Departments of Chemistry & Biochemistry and Bioengineering, University of California, San Diego, La Jolla, CA 92093, USA

Reconstituting Phospholipid Membrane Synthesis

In cells, all lipid membranes are generated from pre-existing membranes. In Eukarya and Bacteria, phospholipids are generated enzymatically by the reaction of a polar head group with long-chain acyl derivatives. These key steps rely on integral membrane proteins, such as acyltransferases, which require lipid membranes for proper folding and function. This mechanism implies that all biological membranes must arise from pre-existing membranes and it is therefore unsurprising that there are no examples of de novo membrane synthesis in cells. The principle of membrane continuity raises questions about how the first biochemical membrane synthesis machinery arose and has hampered efforts to develop simplified pathways for membrane generation in artificial cells. We are exploring methods to reconstitute lipid membrane synthesis using chemoenzymatic approaches. This relies on coupling enzymatic reactions that form lipid precursors, with spontaneous chemical reactions that form membrane assembling amphiphiles. The result leads to de novo formation of phospholipid membranes. We are exploring mechanisms to generate membranes from single-chain and small molecule precursors and have been able to achieve membrane formation in the minimal transcription/translation systems. An outstanding challenging is to form lipid membranes while simultaneously inserting integral membrane proteins, leading to the *in situ* generation of proteoliposomes.

Andreas Reichert

Institute for Biochemistry and Molecular Biologie I, University Hospital Düsseldorf, Düsseldorf, Germany

Continuous cycles of MICOS-dependent cristae membrane remodelling revealed by STED nanoscopy

Mitochondrial membranes are highly dynamic. This is also true for the mitochondrial inner membrane which is known to reshape under different physiological conditions. Here we will show using e.g. state-of-the-art live-cell stimulated emission depletion (STED) super-resolution nanoscopy that neighbouring crista junctions (CJs) move within the inner membrane in a reversible and balanced manner in human cells. Moreover, we report that cristae membranes (CM) undergo continuous cycles of membrane remodelling in a MICOS-dependent manner. By employing advanced imaging techniques including FRAP (Fluorescence-Recovery-After-Photobleaching), SPT (Single-Particle-Tracking), live-cell STED, and high resolution Airyscan microscopy and various approaches, we propose a model of CJ-dynamics being mechanistically linked to CM remodelling likely involving bona fide cristae fission and fusion events. The impact of cristae membrane remodelling on metabolic and other mitochondrial functions will be discussed.

Ivan Dikic

Institute of Biochemistry II, Goethe University Hospital, Frankfurt am Main, Germany

Dynamics of endoplasmic reticulum remodelling

The endoplasmic reticulum (ER) is the largest intracellular endomembrane system enabling synthesis and transport of cellular components. Constant ER turnover is needed to meet different cellular requirements and autophagy plays an important role in this process. In mammalian cells the ER is degraded via a selective autophagy pathway (called ER-phagy) and mediated by specific ER-resident proteins that interacts with LC3, via conserved LC3-interacting region (LIR). Reticulon-type protein FAM134B is responsible for the turnover of ER sheets as its overexpression stimulates ER fragmentation and delivery to lysosomes via the autophagy pathway. Conversely, blockade of autophagy or depletion of FAM134B triggers a marked increase in the ER volume. Mutations of FAM134B in humans are unable to act as ER-phagy receptors and cause sensory neurodegeneration. We have recently identified full length reticulon 3 (RTN3) as a specific receptor for the degradation of ER tubules. The major questions we are exploring at the moment deal with the action of reticulon domains in banding the membranes and the regulatory mechanisms of a family of co-receptors that assist FAM134B or RTN3 proteins in selecting the appropriate cargoes during the ER-phagy process. In addition, genetic and proteomic screens have revealed a subset of proteins that are required for diverse ER-phagy pathways. Given the physical and functional connection of ER to other organelles inside the cell – ER-phagy might also impact the function of other organelles as well.

Paul Macklin

Melvin and Bren Simon Cancer Center, Indiana University, Bloomington, IN 47408, USA

tba

tba

Ute A. Hellmich

Institute of Organic Chemistry & Macromolecular Chemistry (IOMC), Friedrich-Schiller-University Jena, and Centre for Biomolecular Magnetic Resonance (BMRZ), Goethe University Frankfurt, Germany

An integrated structural biology approach for a molecular understanding of TRP ion channels

Transient receptor potential (TRP) channels are a large eukaryotic ion channel family with remarkable functional diversity. They consist of six mammalian subfamilies. TRPV1, a member of the vanilloid channel subfamily in particular has gained wide recognition as the first TRP channel member to be characterized by cryo electron microscopy and for heralding the "resolution revolution". TRP channels play important roles in e.g. temperature and pain sensation or organ development and thus mutations can lead to devastating diseases. Intriguingly, regulatory partners such as cytosolic proteins or lipids often interact with the proximal TRP channel termini, which despite the recent technological advances in structural biology, often remain functionally and structurally orphaned, presumably because they are unstructured and/or very dynamic. We use a combination of biophysical approaches to characterize the interaction of TRP channel termini with their protein and lipid partners for a more detailed understanding of the molecular details of TRP channel regulation. A particular focus lies on members of the TRP vanilloid (TRPV) and TRP mucolipin (TRPML) families due to their complex lipid-based regulation patterns and involvement in neurodegenerative diseases.

Day 3 - Wednesday, 24th of February

BIG DATA in Life Sciences

Kathi Zarnack

Computational RNA Biology, Buchmann Institute for Molecular Life Sciences (BMLS), Goethe Universität Frankfurt am Main, Frankfurt am Main, Germany

Decoding a cancer-relevant splicing decision in the RON proto-oncogene using high-throughput mutagenesis

Mutations causing aberrant splicing are frequently implicated in human diseases including cancer. Splicing requires tight control of trans-acting factors that recognise cis-regulatory elements in the RNA sequence. However, the position and function of most cis-regulatory elements remain unknown, hindering the interpretation of disease-associated mutations and resulting splicing changes. We recently established a high-throughput screen of randomly mutated minigenes to decode the cis-regulatory landscape of selected splicing decisions. As a prototype example, we tested the cancer-relevant alternative exon 11 in the proto-oncogene MST1R (RON). Skipping of RON exon 11 results in the pathological isoform RONΔ165 results that promotes tumour invasiveness and is frequently upregulated in solid tumours. Mathematical modelling of splicing kinetics enables us to identify more than 1,000 mutations affecting RON exon 11 skipping. Importantly, the effects correlate with RON alternative splicing in cancer patients bearing the same mutations. Moreover, we highlight heterogeneous nuclear ribonucleoprotein H (HNRNPH) as a key regulator of RON splicing in healthy tissues and cancer. Using iCLIP and synergy analysis, we pinpoint the functionally most relevant HNRNPH binding sites and demonstrate how cooperative HNRNPH binding facilitates a splicing switch of RON exon 11. Our results thereby offer insights into splicing regulation and the impact of mutations on alternative splicing in cancer.

Ingo Ebersberger

Applied Bioinformatics Group, Inst. of Cell Biology and Neuroscience Goethe University Frankfurt am Main, Senckenberg Biodiversity and Climate Research Centre (S-BIK-F), Frankfurt, LOEWE Centre for Translational Biodiversity Genomics, Frankfurt am Main, Germany

What comparative genomics tell us about the emergence of human pathogens

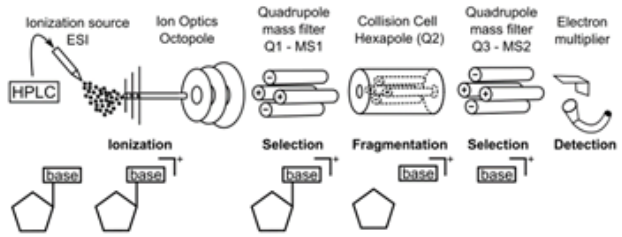
Bacterial and viral pathogens have a substantial impact on human health and economy. A conceptual understanding of how these organisms interact with their host is essential for the development of novel antimicrobial treatments with the aim to cure or—in the better case—to prevent the infection. Here I will present how placing a pathogen into its evolutionary context aids in this process. On the example of two human pathogens, Acinetobacter baumannii and SARS-CoV-2, I will outline how the wealth of available genomic data and of the proteins encoded therein can be mined for delineating genetic innovations that likely form the molecular scaffold underlying pathogenicity. In particular I will discuss the application of phylogenetic profiles, the presence/absence pattern of characters across related species comprising both pathogens and their benign relatives. In this context, I will

outline how gradually increasing the character resolution from proteins to their domain architectures to linear epitopes on the protein surface successively carves out the relevant evolutionary signal. On this basis, models of host-pathogen interaction can be established or refined, which should help to find novel and more informed routes to contain the pathogen.

Stefanie Kellner

Institute for Pharmaceutical Chemistry, Goethe University Frankfurt am Main, Frankfurt am Main, Germany

Mass spectrometry of the epitranscriptome



RNA is a dominant macromolecule in all organisms. Its monomeric units are the canonical nucleosides cytidine, uridine, guanosine and adenosine which are interconnected by a 3'-5'-phosphate backbone. After transcription, enzymes target the RNA and introduce a variety of modifications onto nucleobases or the ribose 2'-OH. This epitranscriptome consists of more than 150 unique RNA modifications in many RNA types and throughout all domains of life.

The detection, localization and quantification of the epitranscriptome is crucial for understanding the elusive function of RNA modifications. Mass spectrometry is ideally suited to unambiguously identify the chemical nature of the modified nucleoside even with minute amounts of sample material. Unfortunately, nucleoside MS depends on the complete enzymatic digestion of the RNA and thus all sequence information and the location of the modified nucleoside remains unknown.

Here, I will present advantages and disadvantages of mass spectrometry-based techniques for epitranscriptome analysis in the context of bacterial stress response, human RNA maturation and neurological diseases.

Sabine Fischer

Center for Computational and Theoretical Biology (CCTB), Julius-Maximilians-Universität Würzburg, Germany

Image-based systems biology of cell differentiation in mouse blastocysts

Tissue development and maintenance rely on coordinated interactions of individual cells. The correct composition of the three-dimensional cell neighbourhood is essential. However, often the details of the spatial arrangement of the cells are unknown and the processes underlying its establishment and maintenance are understudied.
We focus on the development of the mouse blastocyst. Just before implantation, the cells of the inner cell mass differentiate into embryonic or extraembryonic precursor cells. Hallmarks of the cell fate decision are the expression levels of the two transcription factors NANOG and GATA6 in the cells. We quantitatively analysed the three-dimensional spatio-temporal arrangement of cells with different expression levels in ICM organoids and mouse embryos. We describe a so far unknown local clustering of cells with comparable expression levels that is already present at the early blastocyst stage. Our results highlight the importance of analysing the three-dimensional cell neighbourhood while investigating cell fate decisions during early mouse embryonic development.

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Fischer, S.C. et al. (2020) The transition from local to global patterns governs the differentiation of mouse blastocysts. Plos One 15, 1-29.
Mathew, B. et al. (2019). Mouse ICM Organoids Reveal Three-Dimensional Cell Fate Clustering. Biophys. J. 116, 127–141

Maria Barbarossa

Mathematical Immuno-Epidemiology, Frankfurt Institute for Advanced Studies, Frankfurt am Main, Germany

A mathematical view on the complex dynamics of infectious diseases

In this talk we present mechanistic models for the dynamics of infectious diseases, in particular focusing on the interplay between the pathogen circulation in a community and the immune status of single infected or immune hosts.

Open Lecture

Martin Meier-Schellersheim

Computational Biology Section, National Institutes of Health, National Institute of Allergy and Infectious, Bethesda,

USA

Aim for mechanistic models!

Theoretical modeling in cell biology has to strike a balance between finding parsimonious, manageable models with not too many parameters or assumptions that are not directly accessible to experimentation on one hand and, on the other hand, not suggesting models that are regarded as too simplistic and biologically unrealistic. During the search for such balance, it is frequently overlooked that concise models implicitly make many assumptions without actually exposing them to scrutiny. In my talk, I will illustrate this issue using computational models of simple signaling pathways and show how detailed mechanistic models of intracellular reaction networks can be explored efficiently.

This research was funded by the intramural program of the NIAID, NIH.

Day 4 - Thursday, 25th of February

Structural Analysis and Modelling in Life Sciences

Julian Heidecke

Mathematical Immuno-Epidemiology, Frankfurt Institute for Advanced Studies, Frankfurt am Main, Germany

Modeling and evaluating test-trace-and-isolate strategies for the control of infectious diseases

Test-trace-and-isolate-strategies (TTIs) can be implemented by health organizations to contain the spread of infectious diseases in a country. Classical mathematical models of infectious disease dynamics can be extended to include TTIs. The closer the model goes towards the “real-world process”, the larger and more complex the underlying system of differential equations becomes. Such models can be simplified assuming constant tracing and testing rates, which leads to predictions of unrealistically high isolation and detection ratios when a large proportion of the population is infected at a certain point in time. Here, we propose a model which considers a limited daily capacity for tracing and testing activity and couple these dynamics to the spread of the infectious disease in the population. This leads to a system of nonlinear differential equations operating on different time scales, which is computationally efficient and allows the simulation of different TTIs. The model is flexible and can be applied to the dynamics of various infectious diseases. Here we present the example of TTIs in the context of the ongoing CoVid19 outbreak.

Josephine Tetteh

Life Sciences, Frankfurt Institute for Advanced Studies, Frankfurt am Main, Germany

COVID-19 network model to evaluate vaccine strategies towards herd immunity

COVID-19 has been the major cause of morbidity and mortality worldwide in the past couple of months. It has paralysed our societies, leading to self isolation and quarantine for several months. A COVID-19 vaccine remains a critical element in the eventual solution to this public health crisis. From 52 candidate COVID-19 vaccines in clinical trials, some vaccines are already being mass produced and available to the general public. Here, we develop an epidemiological network model able to represent COVID-19 epidemic dynamics. Stochastic computational simulations identify the necessary number of vaccines and vaccine efficacy thresholds capable of preventing an epidemic whilst adhering to lockdown guidelines. Simulation results suggest that achieving low levels of infection would require that a high percentage of the population is vaccinated.

Gianmarco Lazzeri

Life Sciences, Frankfurt Institute for Advanced Studies, Frankfurt am Main, Germany

Atomically detailed characterization of RNA folding by means of biased computer simulations

Despite its key role in many biological processes of our cells, we know little about the ribonucleic acid (RNA) dynamics at the atomic resolution. Most of the recent studies focused their attention on proteins. With its gene-coding, gene-regulating, enzymatic, and even signalling functions, RNA is possibly a more versatile, yet still enigmatic macromolecule.

Computer molecular dynamics (MD) is the “brute force” solution to the problem. As simple as it could seem, simulating a polynucleotide chain on a high-end supercomputer presents some serious challenges. First, the most validated force fields which describe the interatomic interactions are limited, mostly because they lack an explicit term for the polarization energy.

Second, the amount of computational resources needed for the task is overwhelming, as even the most advanced instruments struggle to produce a trajectory which exceeds the millisecond —and interesting processes occur at much longer time scales. With technological advancement, things are likely to change. To tackle the issue now, one must resort to ad hoc techniques.

Biased molecular dynamics (BMD) introduces an unphysical force to speed up a process of interest. Although it allows to substantially increase the number of observed events, this comes at the cost of losing their time-dependent information. Moreover, there is no guarantee that the so-obtained trajectories still relate to their unbiased counterparts. A solid theoretical framework is required to extract physical knowledge out of BMD simulations. The Bias Functional Approach (BFA) provides such a framework. Along with the ratchet-and-pawl bias, it has been successfully employed to study the folding of various proteins. To date, it has never been applied to RNA. In this work, I adopt this combination to characterize the folding mechanics of two small molecules: a hairpin, and a pseudoknot. The analysis takes its first steps from the protein benchmark, and includes the classification of the folded and misfolded trajectories, the individuation of the main folding strategies, the heatmaps of the transition path densities, and the computation of the trajectories' order matrices and path-similarity.

The results are encouraging, especially for a frontier topic. We observe significant departures from the behaviour of proteins of comparable size, with emerging features confirmed by the literature. This suggests that large-scale simulations on more complex systems and with further sophisticated analysis may lead to original findings, as we gain more insight on the ribonucleic acid's folding mechanisms.

Tien Duy Vo

Molecular Biotechnology, Institute for Molecular Biosciences, Goethe University Frankfurt am Main, Frankfurt am Main, Germany

Microbial cationic peptides as a natural defense mechanism against insect antimicrobial peptides

Bacteria produce a plethora of specialized metabolites (SM), with the ecological function of most of them not known. A major group of SM are peptides derived from non-ribosomal peptide synthetases (NRPS). In entomopathogenic bacteria of the genus *Xenorhabdus* PAX (Peptide antimicrobial *Xenorhabdus*) were described as NRPS-derived lipopeptides, which show antimicrobial activities against bacteria and fungi. We analyzed the production of PAX in *Xenorhabdus doucetiae* and found the major amount bound to the cells. We derivatized PAX with fluorophores and show binding to cells when added externally using super-resolution microscopy. Externally added PAX in *X. doucetiae* and *E. coli*, as well as inducible PAX production in *X. doucetiae*, showed a protective effect against various antimicrobial peptides (AMPs) from insects where they are used as a defense mechanism against pathogens. Since AMPs are often positively charged, our results suggest a PAX-induced repulsive force due to positive charge at the bacterial cell wall.

Sebastian Thallmair

Development of Pharmacological Probes, Frankfurt Institute for Advanced Studies, Frankfurt am Main, Germany

Fine-tuned PI(4,5)P_2 sensitivity of the Tubby domain unravels local PI(4,5)P_2 pool dynamics at ER-PM contact sites

V. Thallmair[1], L. Schultz[1], S. Evers[1], C. Goecke[1], W. Zhao[1], M. G. Leitner[2], S. J. Marrink[3], D. Oliver[1], S. Thallmair[4]

Phosphoinositides (PIs) are important signaling lipids multitasking in diverse cellular signaling pathways. They operate by recruiting proteins to the membrane surface by means of PI recognition domains. One of the recognition domains for PI(4,5)P2 lipids, which is the major PI species in the plasma membrane (PM), is the tubby domain. It is conserved in the tubby-like protein (TULP) family and plays an important role in targeting proteins into cilia.1

We used coarse-grained (CG) molecular dynamics (MD) simulations with the Martini force field to explore the PI(4,5)P2 affinity of the C-terminal tubby domain (tubbyCT). While the previously described canonical binding site2 showed a comparatively low affinity, our MD simulations revealed a second binding site. It consists of a conserved cationic cluster at the protein-membrane interface. The CG MD simulations together with mutation experiments in living cells showed that the second binding site substantially contributes to the fine-tuned PI(4,5)P2 affinity of tubbyCT.3

Besides its important role in ciliary trafficking,1 we showed that the tubby protein preferentially localizes to endoplasmic reticulum (ER)-PM contact sites where it binds to both PI(4,5)P2 and the ER-PM tether E-Syt3.4 After depletion of PI(4,5)P2 by means of PLCβ, recruitment of tubby to ER-PM contact sites unravels an increase of the local PI(4,5)P2 concentration due to local synthesis by PI kinases.

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Gerhard Hummer

Theoretical Biophysics, Max Planck-Institute of Biophysics, 60438 Frankfurt am Main, Germany

Molecular simulations in times of COVID-19

Mateusz Sikora (1,2), Laura Schulz (1), Florian Blanc (1), Sören von Bülow (1), Michael Gecht (1), Roberto Covino (1,3), Ahmad Reza Mehdipour (1), Gerhard Hummer (1,3,4,5)

We use molecular dynamics (MD) simulations to study key molecular processes of the SARS-CoV-2 virus. We concentrate on the structure of the spike (S) protein at the viral surface, its interactions with the host cell, and on viral modulation of the host immune response. In molecular dynamics (MD) simulations of full-length S with a palmitoylated transmembrane domain and a fully glycosylated ectodomain, we identified three hinges in the stalk connecting the S head to the viral membrane. Hinge flexibility and glycosylation have been confirmed by high-resolution cry-electron tomography (Turonova, Sikora, Schürmann et al., Science 2020). We are now using the detailed structural and dynamic models for a computational antibody epitope scan (Sikora et al., biorxiv). In addition, we study the interactions of S with the host-cell receptor ACE2 (Mehdipour, Hummer, biorxiv). In MD simulations of the SARS-CoV-2 papain-like protease PLpro, MD simulations provided detailed insight in its function as immunomodulator by suppressing the host interferon (IFN) and NF-κB pathways through preferential cleavage of ISG15 (Shin et al., Nature 2020). Overall, MD simulations help us to uncover some remarkable biology associated with viral infection and, as we hope, guide our fight against COVID-19.

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Acknowledgments. Our special thanks go to Martin Beck and Beata Turonova plus team (MPIBP and EMBL) for the electron tomography, to Jacomine Krijnse Locker, Michael Mühlebach and Christoph Schürmann plus team (Paul Ehrlich Institute) for the virus preparation and purification, and to Donghyuk Shin and Ivan Dikic plus team (Goethe University and MPIBP) for the structural and mechanistic studies of PLpro.

Harald Schwalbe

Structural Chemistry and Biology / NMR-Spectroscopy, Goethe University Frankfurt am Main, Germany

Integrated structural biology to understand disulfide bond formation in the ribosomal exit tunnel

Understanding the conformational sampling of translation-arrested ribosome nascent chain complexes is key to understand co-translational folding. Up to now, coupling of cysteine oxidation, disulfide bond formation and structure formation in nascent chains has remained elusive. Here, we present our collaborative work on the eye-lens protein γB-crystallin in the ribosomal exit tunnel. Using mass spectrometry, theoretical simulations, dynamic nuclear polarization-enhanced solid-state nuclear magnetic resonance and cryo-electron microscopy, we show that thiol groups of cysteine residues undergo S-glutathionylation and S-nitrosylation and form non-native disulfide bonds. Thus, covalent modification chemistry occurs already prior to nascent chain release as the ribosome exit tunnel provides sufficient space even for disulfide bond formation which can guide protein folding.

The talk will present collaborative work of the laboratories of C. Glaubitz, M. Blackledge, A. Frangakis, and H. Schwalbe Nat. Comm. (2020) 11: 559 doi: 10.1038/s41467-020-19372-x.

Roberto Covino

Life Sciences, Frankfurt Institute for Advanced Studies, Frankfurt am Main, Germany

Deep reinforcement learning discovers simple molecular mechanisms from complex physical models

Collective self-organization of molecular systems plays a central role in the physical and life sciences. These events emerge from the many-body interactions between the system's fundamental constituents, be it atoms or molecules, and give rise to self-

assembly phenomena that explain the organization of complex materials and living matter. Understanding these phenomena in terms of physical mechanisms is a formidable challenge. One powerful strategy is to reproduce all atoms and molecules' dynamics as described by accurate physical models and observe collective phenomena emerge from the underlying physics and chemistry. Numerical solutions of these models require sophisticated molecular dynamics (MD) computer simulations. Outstanding limitations restrain this strategy's potential: focusing the computational power to sample trajectories containing the mechanism and extracting quantitative models from these high-dimensional trajectories. We present a deep reinforcement learning artificial intelligence (AI) that learns the mechanism of collective molecular phenomena from computer simulations. The AI simulates complex molecular reorganizations and learns how to predict their outcome, building simple quantitative mechanistic models. We discuss applications ranging from material science to biophysics.

Thomas Dandekar

Bioinformatics, University Würzburg, Germany

Live is complicated, but models have to be simple: Boolean semi-quantitative models

Boolean Networks find out the logical connectivity in signaling networks. They are next turned into semi-quantitative dynamic Models to show the time-dynamics of signaling cascades. For normalizing these models data from cell culture experiments are used. The validated *in silico* models can then be used to explore now all responses and all individual nodes and their time-trajectories, saving hence efficiently many experiments. A reliable model of human cells and their signaling dynamics is thus established.

We introduce and discuss a number of such models from our current work on cancer, cardiac disease plant signaling, bacterial and infection biology with the aim to better understand how such models are set-up, validated and implemented and discuss current and advantages and limitations.

Open Lecture

Thomas Sudhof

Molecular and Cellular Physiology, Stanford University, Stanford, CA 94305-5453, USA

Molecular codes enabling brain function

For a person to think, act, or feel, the neurons in a person's brain must communicate continuously, rapidly, and repeatedly. This communication occurs at synapses, specialized junctions between neurons that transfer and compute information on a millisecond timescale. By forming synapses with each other, neurons are organized into vast overlapping neural circuits.

As intercellular junctions, synapses are asymmetric with a presynaptic terminal that emits a transmitter signal and a postsynaptic cell that receives this signal. Synapses differ in properties and exhibit distinct types of plasticity, enabling fast information processing as well as learning and memory. Synapses are the most vulnerable component of the brain whose dysfunction initiates multifarious brain disorders. Despite their importance, however, synapses are poorly understood beyond basic principles.

Thomas Südhof's laboratory studies how synapses form in the brain and how their properties are specified, which together organize neural circuits. Moreover, the Südhof laboratory examines how synapses become dysfunctional in neurodegenerative and neuropsychiatric disorders to pave the way for better therapies.

Day 5 - Monday, 1st of March

Theory on cellular Dynamics

Franziska Matthäus

Frankfurt Institute for Advanced Studies, Frankfurt am Main, Germany

Mathematical modeling of collective cell motility in development and disease

Cell motility plays an important role in immune and developmental processes, wound healing and regeneration, but also in diseases such as cancer. In epithelial systems, cells often migrate collectively, because they adhere to each other to form connected tissues. Collective migration is characterized by a strong coordination of neighboring cells and spatial velocity correlations. To gain understanding on the characteristics and the regulatory processes guiding collective cell motility we combine exhaustive data analysis with mathematical modeling.

We use particle image velocimetry (PIV) to obtain quantitative data from time-lapse microscopy. From the resulting velocity fields we derive spatio-temporal velocity distributions, divergence, vorticity, streamlines or pathlines. Based on these data we develop agent-based or hybrid mathematical models accounting for mechanical cell-cell interaction (adhesion, repulsion), mechanotransduction, chemotaxis, as well as the interaction with a dynamically changing chemical environment. We present results for two systems – collective migration of lung cancer cell lines, and skin patterning in embryonal development.

Our models demonstrate that many observed phenomena can be explained by the mechanical interplay between the cells, or the interplay of cell mechanics and cell response to chemical cues. Altered migration phenotypes in lung cancer cell lines following growth factor treatment can be attributed to changes in cell elasticity, cell adhesion or mechanotransduction. Pattern formation in embryonal skin development involves the interplay of cell mechanics, a chemical Turing system and chemotaxis. We also outline a possible approach for the inference of model parameters, enabling the estimation of single-cell mechanical properties from time-lapse data.

Nadine Flinner

Computer Sciences, Frankfurt Institute for Advanced Studies, Frankfurt am Main, Germany

Image segmentation and classification to uncover characteristics in different types of cancer

The first part of the talk will deal with the migration of lymphoma cells and shows a classical image segmentation pipeline to detect the cells and to quantify the occurrence of filapodia-like structures. These structures can be used during cell communication or cell migration, which is one of the fundamental properties in the formation of metastasis.

The second part of the talk shows how cNN's (convolutional neuronal networks) can be used to predict molecular properties of cancer for the example of gastric cancer based on image data, routinely generated for every patient. To uncover these molecular properties normally many time and cost intensive techniques are necessary and in future machine learning could help to guide testing.

Friederike Schmied

Institute of Physics, Johannes Gutenberg-Universität Mainz, Germany

Coarse-grained Mmodelling of lipids and membranes

As membranes are central components of cells, membrane modelling has a long history, and a huge variety of lipid models to describe processes on different scales have been proposed over the years. In the lecture I will first give an overview over different modelling approaches and then discuss two examples: The physics of Tube and branch formation on large scales, and the role of lipids in drug delivery on small scales.

Katrin Heinze

Rudolf-Virchow-Center for Experimental Biomedicine, University Würzburg, Germany

Lessons from the glassy bone: Spatiotemporal insights into the bone marrow *in vivo*, *in situ* and *in silico*

Fluorescence imaging has tremendously contributed to our understanding of platelet biogenesis during the last decade. Light microscopy of whole murine bones with subcellular resolution, however, is still challenging as the compact bone is hard and opaque whereas the soft, vessel-rich bone marrow inside shows high autofluorescence. Recently, we developed different image processing pipelines for precise 3D identification and tracking of different cell types and vessels of uncut bones. In mammals, circulating platelets are essential players in hemostasis and thrombosis. Platelets are produced by large cells, called megakaryocytes, that are predominantly residing in the bone marrow. Megakaryocytes originate from hematopoietic stem cells and were commonly thought to migrate from an endosteal niche towards the vascular sinusoids during their maturation. By combining *in vivo* two-photon microscopy and *in situ* LSFM with computational simulations, we reveal

surprisingly slow megakaryocyte migration, limited intervascular space, and a vessel-biased megakaryocyte pool; All of these results would have been hidden or still unclear if only queried based on tissue sections. Beyond image analysis, segmented objects of cellular distributions or the microvasculature in the bone structures can serve as biological templates, and thus support advanced and realistic computational simulations. Typically, cell-vessel simulation studies use artificial spheres and meshes as templates to minimize the computational effort or due to the lack of experimental data. Using segmented objects derived from 3D fluorescence images can dramatically improve simulations as those maximally mimic the physiological situation. Such reliable whole-bone analysis *in silico* identify megakaryocytes as biomechanical restraints for bone marrow cell mobilization and extravasation influencing for example neutrophil and hematopoietic stem cell migration. Thus, quantitative imaging and simulations go hand in hand; fortunately, simulations can even help to understand scenarios that cannot be assessed by fluorescence approaches due to the lack of specific markers or due to ethical reasons in animal experiments.

Arthur Korte

Center for Computational and Theoretical Biology, University Würzburg, Germany

Understanding genotype-phenotype relationships using the model plant *Arabidopsis thaliana*

Understanding the causal relationship between genotype and phenotype (G2P) is a major objective in biology. The goal is to better understand trait architecture and the evolution of different traits, as well as to identify variants that are related to disease or targets for trait improvement A default tool to illuminate these relationships are genome-wide association studies (GWAS) that can identify genetic loci that associate with the trait of interest. Genomic prediction (GP), on the other hand, aims to predict the phenotype from the genome. This is of uttermost importance in plant and animal breeding as well as in predicting disease onset in humans. Both methods have been successfully used in many different species to elucidate trait architecture or prognoses trait values. However, most studies concentrate on marginal marker effects and ignore multi-scale interactions. These interactions are problematic to account for, but are likely to make major contributions to many phenotypes that are not regulated by independent genetic effects but by more sophisticated gene-regulatory networks. I will use data from the model plant species *Arabidopsis thaliana* to highlight recent progress and present data on different statistical approaches and machine learning methods to tackle these challenges.

Hanieh Saeedi

Senckenberg Research Institute and Natural History Museum, Department of Marine Zoology, Biodiversity Information, Fellow of the JQ Young Academy, Frankfurt am Main, Germany

Marine biodiversity advances in a digital era

After a general introduction on how to define normativity, we survey different accounts on the relationship between normative and non-normative properties and the use of our language. In the second part of our talk, we focus on the concept of biodiversity as a case study involving conservation biology techniques and social sciences.

Camile Fraga Delfino Kunz

Life Sciences, Frankfurt Institute for Advanced Studies, Goethe University Frankfurt am Main, Frankfurt am Main, Germany

Chemotaxis impact on a Turing reaction-diffusion system

During embryo development there is a rapid growth in cell numbers that forms complex structures. Skin pattern formation is an early process during the embryogenesis and happens before the cells fully differentiate. In the present project we consider skin patterning in mouse embryos, where cell aggregates form based on a hierarchical process, involving interactions between the epidermal cell populations. The reaction-diffusion pre-pattern is driven by fibroblast growth factor (FGF20), bone morphogenic protein (BMP) and WNT. Considering mathematical models, there are two main processes involved in the pattern formation: Turing reaction-diffusion systems and chemotaxis. The Turing system models the concentration of two interacting chemicals, and the patterns arises from an instability driven by a difference between their diffusion coefficients. Some previous studies show that this behavior is essential for self-organization in the mouse hair follicle and chicken feather pre-pattern formation. Another key mechanism is chemotaxis, where the cells move in the direction of a chemical attractant, where patterns can also be observed. Experimental data indicates a hierarchical system, where cell chemotaxis is guided by a Turing system. We aim at developing mathematical models to describe the underlying biological processes leading to skin patterning, especially the interaction of chemotaxis with reaction-diffusion (Turing) systems. A mathematical model using partial differential equations is solved numerically, and some results are presented and compared to the experimental data. We study the parameter-dependence

of the model and different model structures, and their impact on the pattern forming process. According to the experimental data the Turing system and the chemotaxis seems to be intrinsically related on the mouse skin patterning. Using a numerical approach for the PDE system, we develop a framework to study quantitatively how chemotaxis and Turing systems are related and their impact on the patterning process.

Simon Schardt

Supramolecular and Cellular Simulations, Center for Computational and Theoretical Biology, University of Würzburg, Germany

The range of cell-cell communication influences the pattern in cell differentiation

Three-dimensional recordings in developmental biology allow us to extract valuable quantitative descriptions of biological processes. To quantify collective cell migration, we have implemented a three-dimensional particle image velocimetry (PIV) package using the Julia programming language, PIV3D. The application of PIV3D is illustrasted on a three-dimensional dataset of the embryonic development of *Tribolium Castaneum*. Since PIV performs pattern matching to extract cell displacements, it can be applied to non-segmentable datasets (non-labelled or labelled for any persistent intracellular marker).

Tim Liebisch

Life Sciences, Frankfurt Institute for Advanced Studies, Goethe University Frankfurt am Main, Frankfurt am Main, Germany

Cell fate clusters in ICM organoids arise from cell fate heredity & division – a modelling approach

Background: During the mammalian preimplantation phase, cells undergo two subsequent cell fate decisions. During the first cell fate decision, cells become either part of an outer trophectoderm or part of the inner cell mass. Subsequently, the inner cell mass (ICM) segregates into the epiblast and the primitive endoderm, giving rise to the embryo and the placenta respectively. Recently, ICM organoids have been published as an in vitro model system towards preimplantational development. ICM organoids mimic the second cell fate decision taking place in the *in vivo* mouse embryos. In a previous study, the spatial pattern of the different cell lineage types was investigated. The study revealed that cells of the same fate tend to cluster stronger than expected for the currently hypothesised purely random cell fate distribution. Three major processes are hypothesised to contribute to the final cell fate arrangements at the mid and late blastocysts or 24 h old and 48 h old ICM organoids, respectively: 1) intra- and intercellular chemical signalling; 2) a cell sorting process; 3) cell proliferation.

Methods & Results: In order to quantify the influence of cell proliferation on the emergence of the observed cell lineage type clustering behaviour, an agent-based model was developed. The model accounts for mechanical cell-cell interactions, cell growth and cell division and was applied to compare several current assumptions of how ICM neighbourhood structures are generated. The model supports the hypothesis that initial cell fate acquisition is a stochastically driven process, taking place in the early development of inner cell mass organoids. The model further shows that the observed neighbourhood structures can emerge due to cell fate heredity during cell division and allows the inference of a time point for the cell fate decision.

Discussion: Simulations based on the model show that cell divisions involving cell fate heredity seem sufficient to lead to the local clustering observed in 24 h old ICM organoids, and that the initial cell differentiation process takes place only during a small time window, during or prior to ICM organoid composition. Our results leave little room for extracellular signaling believed to be important in cell fate decision, therefore we are discussing an alternative role of chemical signaling in this process.

Silas Boye Nissen

Department of Pathology, Stanford University School of Medicine, Germany

Cell fate clusters in ICM organoids arise from cell fate heredity & division – a modelling approach

Despite continual renewal and damages, a multicellular organism is able to maintain its complex morphology. How is this stability compatible with the complexity and diversity of living forms? Looking for answers at protein level may be limiting as diverging protein sequences can result in similar morphologies. Inspired by the progressive role of apical-basal and planar cell polarity in development, we propose that stability, complexity, and diversity are emergent properties in populations of proliferating polarized cells. We support our hypothesis by a theoretical approach, developed to effectively capture both types of polar cell adhesions. When applied to specific cases of development – gastrulation and the origins of folds and tubes – our theoretical tool suggests experimentally testable predictions pointing to the strength of polar adhesion, restricted directions of cell polarities, and the rate of cell proliferation to be major determinants of morphological diversity and stability.

Franziska Krämer

Physical Biology, Buchmann Institute for Molecular Life Sciences (BMLS), Goethe University Frankfurt am Main, Frankfurt am Main, Germany

Investigating Mechanical Force Dynamics of Extra-Embryonic Membranes in *Tribolium castaneum, Part I*

Efficient energy use and storage is crucial in living organisms. In the context of evolution, energy management is continuously optimized to ensure an individual's ability to successfully compete. This is especially true for embryonic development of oviparous species, as all required energy has to be provided at the moment of oviposition, and, has to be sufficient to give rise to a fully functional organism. Therefore, it is particularly interesting to investigate extra-embryonic tissues, as these are transient structures that do not become part of the fully developed organism. The red flour beetle Tribolium castaneum, an emerging insect model organism, is a representative species for investigating the complex formation and degradation principles of extra-embryonic membranes in insects. In contrast to the best-studied insect model organism *Drosophila melanogaster*, *Tribolium* develops two extra-embryonic membranes during gastrulation, the amnion and the serosa. The amnion covers the embryo only on its ventral side, while the serosa starts on the dorsal side, extends during gastrulation over the embryonic rudiment and closes on the ventral side of the embryo, covering the embryo completely in a process called serosa window closure. Hereby, apical surface area of the serosa cells increases significantly. The serosa plays an important coordinative role during dorsal closure, a later developmental stage. During dorsal closure, the serosa re-opens at the same location where it closed and migrates, together with the amnion, over the poles, inverts on the dorsal side of the embryo and is eventually internalized and degraded. Based on our preliminary imaging data, we formulate the hypothesis that serosa cells utilize shape change during gastrulation to allocate and store energy that is later on required for their extensive movement during dorsal closure.

To investigate this possible functional connection, we want to gain further insights into the multi-scale effects of force propagation from cellular to tissue level. Long-term live imaging assays were performed using light sheet-based fluorescence microscopy to record three-dimensional dynamic imaging data of nuclei-labeled *Tribolium* embryos. The data shows the developing embryo at subcellular levels along multiple directions over periods of up to one week. To generate isotropic and evenly illuminated three-dimensional images, the directional data were subsequently fused and deconvolved. Multiple software solutions for cell segmentation and tracking are currently evaluated to obtain a priori data for a cell-based three-dimensional structural representation of the serosa.

Further, the data will be used to estimate serosa cell membrane position via Voronoi reconstruction as a first step, both during gastrulation and dorsal closure. In a second step, based on the cell-shape estimate of the serosa membrane, spatial and temporal dynamics of forces are calculated using a computational approach, termed Force Inference (FI). FI utilizes a biomechanical model, a mathematical inverse method and a Bayesian framework to estimate cell membrane tensions, cell pressures and both cell and tissue stress from three-dimensional image data. Advantages of FI are: (1) investigation is non-invasive, as no mechanical probing of the tissue is needed, (2) estimates are obtained for the entire embryo simultaneously, and (3) analysis of both static and time-lapse images is possible. With this framework comprising both *in vivo* and *in silico* efforts, we aim to investigate the mechanisms of mechanical energy storage and reallocation between gastrulation and dorsal closure.

Zoë Lange

Life Sciences, Frankfurt Institute for Advanced Studies, Frankfurt am Main, Germany

Investigating Mechanical Force Dynamics of Extra-Embryonic Membranes in *Tribolium castaneum, Part II*

see abstract Franziska Krämer

Fabian Reinisch

Physical Biology, Institute for Cell Biology and Neuroscience, Buchmann Institute for Molecular Life Sciences, Goethe University Frankfurt am Main, Frankfurt am Main, Germany

Observing cell fate decisions and clustering live in a 3D model for pre-implantation embryos

In the earliest phase of vertebrate development, the pre-implantation phase, three distinct cell populations arise from the dividing cells of the fertilized oocyte. The differentiation into trophectoderm and inner cell mass is the first cell fate decision. Subsequently, the epiblast and primitive endoderm populations form.

Previous work of Schröter et al., Mathews et al., Fischer et al., and Liebisch et al. established a three-dimensional model system of

inner cell mass stem cells from mice to investigate the second cell fate differentiation. One major observation was the clustering of cells with the same cell fate, exceeding the assumed random distribution of cell fates. Subsequently, a mathematical model has been developed to investigate the influence of cell division, cell-cell-interaction, and cell fate heredity on the measured cell fate clustering.

Unfortunately, the highly dynamic events were not observed with live microscopy in the 3D model yet. In this project, we aim to get a better understanding of the events and test the published mathematical model, by utilization of live microscopy. In a dual approach, light sheet-based fluorescence microscopy (LSFM) and confocal laser scanning microscopy are combined with new sample holder and imaging plate designs to observe the formation of ICM organoids and the cell fate decisions live. Subsequently, cell tracking and population affiliation by immunohistochemical labeling as well as fluorescent expression reporters will be utilized to shed more light on the cell fate decisions and clustering in the pre-implantation embryo.

Day 6, Tuesday, 2nd of March

AI … in Biology

Xiyang Liu

Xidian University, Xi'an, China

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Su-In Lee

Paul G. Allen School of Computer Science & Engineering, University of Washington, Seattle, USA

tba

t b a

Peng Liu

Xidian University, Xi'an, China

tba

t b a

Chuipeng Gou

Xidian University, Xi'an, China

tba

t b a

Bing Han

Xidian University, Xi'an, China

tba

t b a

Cecilia Clementi

Einstein Professorship, Freie Universität Berlin, Department of Physics, Germany

Designing molecular models by machine learning and experimental data

The last years have seen an immense increase in high-throughput and high-resolution technologies for experimental observation as well as high-performance techniques to simulate molecular systems at a microscopic level, resulting in vast and ever-increasing amounts of high-dimensional data.

However, experiments provide only a partial view of macromolecular processes and are limited in their temporal and spatial resolution. On the other hand, atomistic simulations are still not able to sample the conformation space of large complexes, thus leaving significant gaps in our ability to study molecular processes at a biologically relevant scale. We present our efforts to bridge these gaps, by exploiting the available data and using state-of-the-art machine-learning methods to design optimal coarse models for complex macromolecular systems. We show that it is possible to define simplified molecular models to reproduce the essential information contained both in microscopic simulation and experimental measurements.

Philip Kollmannsberger

Philip Kollmannsberger, University of Würzburg, Germany

AI for quantitative high-resolution microscopy

AI-inspired methods such as deep learning offer exciting opportunities for the automated quantitative interpretation of subcellular details from high-resolution microscopy, but also introduce new challenges. This talk will show examples where deep learning helps to interpret protein structure and synaptic organization in electron microscopy, improves resolution and image acquisition in single-molecule localization microscopy, and automatically correlates light- and electron microscopic images. Limitations and challenges of AI-based methods in microscopy as well as strategies to overcome them will be discussed.

You Zhou

Computational RNA Biology, Buchmann Institute for Molecular Life Sciences, Goethe University Frankfurt, Germany

Deep and accurate detection of m6A RNA modifications using miCLIP2 and m6Aboost machine learning

N6-methyladenosine (m6A) is the most abundant internal RNA modification in eukaryotic mRNAs and influences many aspects of RNA processing, such as RNA stability and translation. miCLIP (m6A individual-nucleotide resolution UV crosslinking and immunoprecipitation) is an antibody-based approach to map m6A sites in the transcriptome with single-nucleotide resolution. However, due to broad antibody reactivity, reliable identification of m6A sites from miCLIP data remains challenging. Here, we present several experimental and computational innovations, that significantly improve transcriptome-wide detection of m6A sites. We established a robust computational pipeline to identify true m6A sites from our miCLIP2 data. The analyses are calibrated with data from Mettl3 knockout cells to learn the characteristics of m6A deposition, including a significant number of m6A sites outside of DRACH motifs. In order to make these results universally applicable, we trained a machine learning model, m6Aboost, based on the experimental and RNA sequence features. Importantly, m6Aboost allows prediction of genuine m6A sites in miCLIP data without filtering for DRACH motifs or the need for Mettl3 depletion. Using m6Aboost, we identify thousands of high-confidence m6A sites in different murine and human cell lines, which provide a rich resource for future analysis. Collectively, our combined experimental and computational methodology greatly improves m6A identification.

Neetika Nath

Systems Biology and Bioinformatics, University Greifswald, Leibniz Institute for Natural Product Research and Infection Biology, Germany

Discovering association patterns of individual serum Thyrotropin concentrations using machine learning: An example from the Study of Health in Pomerania (SHIP)

Background: During the mammalian preimplantation phase, cells undergo two subsequent cell fate decisions. During the first cell fate decision, cells become either part of an outer trophectoderm or part of the inner cell mass. Subsequently, the inner cell mass (ICM) segregates into the epiblast and the primitive endoderm, giving rise to the embryo and the placenta respectively. Recently, ICM organoids have been published as an in vitro model system towards preimplantational development. ICM organoids mimic the second cell fate decision taking place in the *in vivo* mouse embryos. In a previous study, the spatial pattern of the different cell lineage types was investigated. The study revealed that cells of the same fate tend to cluster stronger than expected for the currently hypothesised purely random cell fate distribution. Three major processes are hypothesised to contribute to the final cell fate arrangements at the mid and late blastocysts or 24 h old and 48 h old ICM organoids, respectively: 1) intra- and intercellular chemical signalling; 2) a cell sorting process; 3) cell proliferation.

Methods & Results: In order to quantify the influence of cell proliferation on the emergence of the observed cell lineage type clustering behaviour, an agent-based model was developed. The model accounts for mechanical cell-cell interactions, cell growth and cell division and was applied to compare several current assumptions of how ICM neighbourhood structures are generated. The model supports the hypothesis that initial cell fate acquisition is a stochastically driven process, taking place in the early development of inner cell mass organoids. The model further shows that the observed neighbourhood structures can emerge due to cell fate heredity during cell division and allows the inference of a time point for the cell fate decision.

Discussion: Simulations based on the model show that cell divisions involving cell fate heredity seem sufficient to lead to the local clustering observed in 24 h old ICM organoids, and that the initial cell differentiation process takes place only during a small time window, during or prior to ICM organoid composition. Our results leave little room for extracellular signaling believed to be important in cell fate decision, therefore we are discussing an alternative role of chemical signaling in this process.

Thomas Sokolowski

Biophysics and Neuroscience, Institute of Science and Technology Austria, 3400 Klosterneuburg, Austria

The many ends of a never-ending story: Deriving the *Drosophila* gap gene system by ab-initio optimization

Early embryogenesis is driven by complex spatio-temporal patterns that specify distinct cell identities according to their locations in the embryo. This process is remarkably reproducible, even though it results from regulatory interactions that are individually noisy. Despite intense study, we still lack a comprehensive, biophysically realistic model for at least one biological system that could simultaneously reproduce quantitative data and rigorously explain the emergence of developmental precision. Moreover, traditional approaches fail to provide any insight as to why certain patterning mechanisms (and not others) evolved, and why they favor particular sets of parameter values. We address both questions during early fly embryo development. Previous work has shown that the gap gene expression patterns in Drosophila optimally encode positional information. We therefore asked whether one can mathematically derive the gap gene network—without any fitting to data—by maximizing the encoded positional information. To this end we constructed a generic, biophysically accurate spatial-stochastic model of gene expression dynamics, where genes respond to morphogen input signals and mutually interact in an arbitrary fashion, and optimized its parameters for positional information. Firstly, our results show how the experimentally observed precision can be achieved with basic biochemical processes and within known resource and time constraints. Secondly, we show that multiple optimal solutions exist and systematically explore their characteristics. Finally, we show that some of the optimal solutions closely correspond to the real Drosophila gap gene expression pattern. To our knowledge this is the first successful ab-initio derivation of any biological network in a biophysically realistic setting. Our results suggest that even though real biological networks are hard to intuit, they may represent optimal solutions to optimization problems which evolution can find.

Open Lecture

Thomas Widl

SAMSON AG, Frankfurt am Main, Germany

"AI in industry"

SAMSON operates wherever there is controlled flow of oils, gases, vapors or chemical substances. Valves are our core business. With our valves, we are active in a market that has enormous potential for future innovations. We are further expanding the valves' decentralized intelligence. By developing new, smart systems, we are transforming process automation to the benefit of our customers and to achieve greater flexibility, safety and reliability in industrial processes.

Day 7, Wedesday, 3rd of March

Theoretical and digital Medicine

Open Lecture

Peter Wild

Senckenberg Institute of Pathology, Frankfurt am Main, Germany

Challenges in medicine

Structured pathological findings, digital histological and radiology images, and molecular data are the basis for personalized medicine, where individual predictions can be made for each individual patient. The Dr. Senckenberg Institute of Pathology is an important and central component for the implementation of the concept of precision medicine.

François Nédélec

Cell Biology and Biophysics, EMBL Heidelberg, 69117 Heidelberg, Germany

Cytoskeleton scaling laws of blood platelets

Aastha Mathur, Sandra Correia, Serge Dmitrieff, Romain Gibeaux, Iana Kalinina, Tooba Quidwai, Jonas Ries and Francois Nedelec

Platelets are cell fragments essential to maintaining hemostasis. While traveling in the blood, they adopt a flat discoid shape that is sustained by a ring of microtubules. Platelets are naturally made in various sizes ranging from 1.6 µm to 5 µm. In resting human and mouse platelets, we found a quadratic law between the size of platelets and the amount of microtubule polymer they contain. We further estimate the length and number of microtubules in the ring using Electron and Super-resolution microscopy. In platelets activated with ADP, the microtubule ring bends as a consequence of cortical contraction driven by actin. However, this elastic buckling response is followed by reorganization and subsequent elongation of the ring. To explain these observations, we build a quantitative model with stochastic microtubules and associated factors. This model illustrates a novel mechanism by which a circular network can produce outward forces. The model also exhibits the measured scaling relationship between cell size and pushing forces.

Marcel Schulz

Computational Biology, Institute for Cardiovascular Regeneration, Goethe University Hospital, Frankfurt am Main, Germany

Creating a catalogue of human regulatory elements to find novel disease genes

A current challenge in disease genomics is to interpret non-coding regions and their role in transcriptional regulation of possibly distant target genes. Genome-wide association studies show that a large part of genomic variants in disease are found in those non-coding regions, but their mechanisms of gene regulation are often unknown. An additional challenge is to reliably identify the target genes of the regulatory regions, which is an essential step in understanding their impact on gene expression. This talk will illustrate

how machine learning can be used to mine large datasets of epigenome and transcriptome data for the creation of a catalogue of human regulatory elements. Applications to cardiovascular disease mutations illustrate the potential for novel disease gene discovery.

Daniel Merk

Institute of Pharmaceutical Chemistry, Goethe University Frankfurt, Germany

Prospective application of artificial intelligence in the *de novo* design of bioactive NCEs

Instances of artificial intelligence (AI) coupled with the availability of large chemical and biological datasets enable data-driven drug discovery1. We have applied a generative machine learning strategy based on a deep recurrent neural network (RNN) for de novo molecular design2. The computational model was first trained to capture the grammar of SMILES representations of bioactive small molecules, and then used to automatically generate SMILES strings of new chemical entities (NCEs). Transfer learning on small collections of bioactive templates enables fine-tuning of the model to generate application-tailored sets of molecules with a target focus. In a pioneering prospective study3, the generative RNN was trained on drug-like molecules (540'000) from a public compound database (ChEMBL22) and fine-tuned on a set of 25 fatty acid mimetics with known activity on two nuclear receptors (RXR, PPAR). The computationally designed samples from this model resembled drug-like molecules and comprised favourable synthetic accessibility. Five top-ranked examples were selected for synthesis and biological characterization. Four designs were active on the studied nuclear receptors in specific hybrid reporter gene assays with up to nanomolar potencies (EC50 0.13 - 14 µM), resembling the activities of the fine-tuning set (EC50 0.024 - 31 µM). These results confirm the potential of AI-driven de novo design for the discovery of synthetically accessible and bioactive NCEs as lead compounds for medicinal chemistry.

After this successful proof-of-concept application3, we further refined utilization4 of generative AI models for de novo molecular design and studied its potential in various prospective application studies. For example, the AI-algorithm was fine-tuned on small collections of RXR activating natural products5 to generate synthetically accessible NCEs populating an unexplored chemical space at the interface between drug-like molecules (used for training) and natural products (used for fine-tuning). Top-ranked examples of these innovative designs inherited the bioactivity profile of the natural product template collection. Again, the computational designs were synthesized and confirmed active in vitro with similar potencies (EC50 16 - 27 µM) as the fine-tuning set (EC50 2.1 - 43 µM)6.

In further examples, we applied AI-driven de novo molecular design to develop novel nuclear receptor modulators with various innovative scaffolds. Our results highlight generative AI as valuable data-driven tool for medicinal chemistry to obtain synthetically accessible and innovative NCEs7 that inherit properties and bioactivity of a template collection without the need of explicitly including molecule design rules. Current studies focus on improved synthesizability, autonomous prioritization of designs, intensified automation, and application in low data regimes with the aim of refining the AI-driven de novo design technique for future medicinal chemistry.

1. Gawehn, E. et al.: Mol. Inf. 2016, 35, 3–14, 2. Gupta, A. et al.: Mol. Inf. 2018, 37, 1700111., 3. Merk, D. et al.: Mol. Inf. 2018, 37, 1700153., 4. Merk, D. et al.: J. Med. Chem. 2018, 61, 5442–5447., 5. Merk, D. et al.: Commun. Chem. 2018, 1, 68., 6. Schneider, G.: Nat. Rev. Drug Discov. 2018, 17, 97–113.

Christian Wachinger

University München Hospital, LMU München, Germany

Intelligent algorithms in neuroimaging: toward generalizable and transparent prediction of brain disease

Neuroimaging provides detailed *in vivo* information of the human brain, which can be used by machine learning algorithms for the automated prediction of brain diseases to support diagnosis and prognosis. In particular, convolutional neural networks have recently achieved remarkable performances by learning hierarchical representations from images. However, there are still challenges that impede the translation of intelligent algorithms to the clinic on a larger scale. One is the lacking generalization of trained models across datasets, which is a prerequisite for the deployment on clinical data. A further challenge is the black box nature of complex prediction models, which can hinder clinical acceptance. In my talk, I will present our ongoing work on addressing these challenges by designing transparent models for for image analysis that generalize well.

Day 8, Thursday, 4th of March

Experimental and theoretical Neurosciences

Christian Fiebach

Cognitive Neuroscience, Department of Psychology, Goethe University Frankfurt am Main, Germany

Decoding the Mind using Brain Imaging

In the last decades, the introduction of functional brain imaging methods has revolutionized research in human neuropsychology and human cognitive neuroscience. However, a strong focus on massive univariate statistics has often limited functional brain imaging to localizing cognitive functions in the brain. Recent applications of multivariate pattern analysis have made it possible to more directly link functional brain imaging to cognitive psychology, by ‚decoding' mental states from brain activation patterns. In this talk I will give a brief overview of this approach and demonstrate some key and forward-looking findings.

Tatjana Tchumatchenko

Theory of Neural Dynamics, Max Planck Institute for Brain Research, 60438 Frankfurt am Main, Germany

Neuronal network models

Despite recent experimental advances, understanding how connectivity and single neuron properties interact in neural circuits remains a mayor challenge in neurobiology. Neural firing rates and their dependence on external inputs can be measured in individual neurons or neural populations. However, how exactly neural firing rates are determined by recurrent interactions with local surrounding neurons and feed-forward inputs from distant upstream cortical areas is difficult to investigate with the state-of-the-art experimental methods. The inhibition stabilized network model put forward by previous studies offers an attractive alternative to balanced networks and describes networks in which neurons have low to medium firing rates that are consistent with experimental measurements. In such networks the firing rates of excitatory and inhibitory neurons are described by two coupled nonlinear differential equations and include a power law activation function for individual neurons. Here, we present the first complete solution showing that such the single-neuron non-linearity in such networks can lead to oscillations, persistent states and bistability as well as other forms of nonlinear computation.

Matthias Kaschube

Neurosciences, Frankfurt Institute for Advanced Studies, Frankfurt am Main, Germany

The dynamics of internally generated brain activity

Neural activity in the neocortex of primates and carnivores exhibits two fundamental characteristics: it is modular, comprising domains of coactive neurons with an approximately regular spacing on the order of 1mm, and spatially distributed, linking functional units that are spread across cortical space. In visual cortex, these two fundamental characteristics of cortical activity arise early in development, as evident from patterns of endogenous (spontaneous) activity, and remain present even after eliminating the feed-forward drive, suggesting a cortical origin. Here I discuss theoretical models that have been proposed to explain how these two properties of neural activity in the neocortex can emerge from network interactions in its neural circuits. I will highlight important unresolved issues with the suggested mechanisms and propose potential solutions to overcome these limitations, pointing towards a Turing mechanism and the importance of self-inhibition and network heterogeneities. Moreover, given that rigorous experimental tests of such models are still lacking, I will derive several critical predictions for the effects of manipulations of inhibitory network components and local circuit heterogeneities on modular and distributed cortical activity. I will discuss concrete possibilities to perform these manipulations in the visual cortex to test the validity of the proposed mechanisms. This work highlights the importance of an improved physical description for understanding the mechanisms underlying two of the most prominent features of cortical activity in the neocortex.

Jochen Triesch

Neurosciences, Frankfurt Institute for Advanced Studies, Frankfurt am Main, Germany

Staging epileptogenesis with deep neural networks

Epilepsy is a common neurological disorder characterized by recurrent seizures accompanied by excessive synchronous brain activity. The process of structural and functional brain alterations leading to increased seizure susceptibility and eventually spontaneous seizures is called epileptogenesis (EPG) and can span months or even years. Detecting and monitoring the progression of EPG could allow for targeted early interventions that could slow down disease progression or even halt its development.

Here, we propose an approach for staging EPG using deep neural networks and identify potential electroencephalography (EEG) biomarkers to distinguish different phases of EPG. Specifically, continuous intracranial EEG recordings were collected from a rodent model where epilepsy is induced by electrical perforant pathway stimulation (PPS). A deep neural network (DNN) is trained to distinguish EEG signals from before stimulation (baseline), shortly after the PPS and long after the PPS but before the first spontaneous seizure (FSS). Experimental results show that our proposed method can classify EEG signals from the three phases with good accuracy. To the best of our knowledge, this represents the first successful attempt to stage EPG prior to the FSS using DNNs.

Yee Lee Shing

Developmental Psychology, Goethe University Frankfurt am Main, Germany

The roles of memory for predictive processing

The study of the human brain within a predictive processing framework has become prominent in the last decade. One core (often implicit) assumption that underlies this view is that some form of stored information is available for the brain to generate predictions; in other words, predictions should derive from memory. However, the interactions between predictions and the memory from which they are derived have not been the focus of research until recently. In my talk, I will present recent work from my lab that aims at advancing our understanding of memory as a driving force behind prediction generation in the brain.

Open Lecture

Moritz Helmstädter

Max Planck Institute for Brain Research, Frankfurt am Main, Germany

Cerebral Cortex Connectomics / the interactions between natural and artificial intelligence

The mapping of neuronal connectivity is one of the main challenges in neuroscience. Only with the knowledge of wiring diagrams is it possible to understand the computational capacities of neuronal networks, both in the sensory periphery, and especially in the mammalian cerebral cortex. Our methods for dense circuit mapping are based on 3-dimensional electron microscopy (EM) imaging of tissue, which allows imaging nerve tissue at nanometer-scale resolution across substantial volumes, extending to more than one millimeter on the side. The most time-consuming aspect of circuit mapping, however, is image analysis; human contributions to analysis time far exceeds the time needed to acquire the data. Therefore, we are developing methods to make circuit reconstruction feasible by increasing analysis speed and accuracy, using a combination of human-machine interaction and artificial intelligence. We are applying these methods to neuronal circuits in the mammalian cerebral cortex in order to extract algorithmic properties of cortical circuits, quantify connectomic traces of experience, and study the alterations of cortical circuits over development, evolution, and in models of psychiatric disease.