From Multiscale Models to Digital Twins

Report of Contributions

https://indico.global/e/6654

Contribution ID: **1** Type: **not specified**

Atomistic simulations of concentrated, multi-component liquids and biomolecular systems

Wednesday 25 September 2024 11:45 (45 minutes)

Molecular dynamics simulations with atomistic resolution are a standard tool to study liquids and biomolecular systems. Most often, force field (FF) limitations mean that simulations must be performed at low concentrations. I will discuss recent advances in FFs of ions and the insight they enabled into the molecular scale mechanisms leading to protein halophilicity, as well as the non-monotonic nature of solvation in multicomponent organic liquids revealed from simulations with high-quality FFs.

Presenter: VILA VERDE, Ana (University of Duisburg-Essen)

Session Classification: Multiscale Models in Cell Biology I (Chair: Thomas Sokolowski)

Contribution ID: **2** Type: **not specified**

A Less Artificial Intelligence

Friday 27 September 2024 09:00 (45 minutes)

"You, your joys and sorrows, your memories and ambitions, your sense of personal identity and free will, are in fact no more than the behavior of a vast assembly of nerve cells and their associated molecules."Francis Crick's words encapsulate a core challenge in neuroscience: cracking the neural code. This challenge has been hindered by two major limitations: (1) our ability to record activity from large neuronal populations at single-cell resolution under the complex, variable conditions in which brains evolve to survive and thrive, and 2) our capacity to model the relationships between stimuli, behaviors, neural activity, and internal brain states, given the complexity of the natural world.

Recent technological advances have begun to overcome these obstacles. High-throughput recording technologies, such as multi-photon imaging and multi-electrode arrays, now enable large-scale recordings, sometimes approaching one million neurons. Simultaneously, cutting-edge machine learning (ML), artificial intelligence (AI), and the availability of large-scale GPU clusters now provide the power to analyze this complex, high-dimensional data and build multi-modal foundation models that relate stimuli, neural activity, behavior, and internal brain states. These models can serve as digital twins of the brain, enabling limitless in silico experiments to test theories and generate hypotheses that are impossible to achieve in biological brains due to technical limitations.

I will discuss our progress in designing large-scale physiology experiments, leveraging these technologies and brain data to build foundation models and digital twins, which allow us to run in silico experiments to test theories and generate hypotheses. Applying mechanistic interpretability tools developed for artificial neural networks—techniques designed to make AI neural network systems more interpretable and transparent—we can uncover mechanisms and principles of neural representation in the digital twin. We then use our "Inception Loop"approach to validate these principles in real brains through closed-loop experiments—bridging the gap between computational models and biological reality to uncover new insights into brain function. Finally, I will describe our efforts to answer the long-standing question of the relationship between function and structure using the MICrONS functional-connectomics dataset (https://www.microns-explorer.org). This dataset of paired functional and connectonomic data from around 70,000 neurons can provide unprecedented insight into the elegant inner workings of biological neural networks.

Presenter: TOLIAS, Andreas (Stanford University)

Session Classification: Multiscale Models in Neuroscience (Chair: Hermann Cuntz)

Contribution ID: **3** Type: **not specified**

True Medical Digital Twins and Multiscale Virtual Tissue Models of Health and Disease: Challenges and Opportunities

Wednesday 25 September 2024 14:30 (45 minutes)

Unlike personalized predictive models, which operate independently of the real world and are sometimes incorrectly labeled as digital twins, Medical Digital Twins require a tightly integrated workflow. This workflow includes sensors to monitor the health state, predictive models (propagators) to forecast changes in that state over time, comparators to assess the agreement between forecast and observation, and actuators to respond to any discrepancies. Depending on the application (e.g., diagnosis, prognosis, or therapy design and delivery), the actuators may notify a human to intervene, adjust the real-world system by administering a treatment, or update the digital twin model itself. At the core of modeling lies the propagator, which forecasts the future state based on the current one. In medical contexts, this involves understanding how molecular states translate into physiological outcomes at the tissue and organ levels. Forecasting these outcomes is complex due to feedback mechanisms across cellular, multicellular, organ, and organismal scales. These feedback interactions make classical data-driven AI/ML approaches less accurate, as they often struggle to account for dynamic, interdependent biological processes. In such cases, mechanistic models—which explicitly incorporate these interactions—are often necessary for reliable forecasting. Virtual Tissue simulations, which use an agent-based, middle-out approach, model cell behaviors and interactions, scaling up and down to different biological levels. These simulations have improved our understanding of development, homeostasis, disease mechanisms, and toxicology, and their integration into clinical applications holds promise for therapy discovery and personalized medical digital twins. However, both Virtual Tissues and Medical Digital Twins face significant technical challenges. One major challenge is the incomplete and noisy nature of real-world clinical data, which can degrade model accuracy and make validation more difficult. Noisy data feeds from sensors or diagnostics may lead to poor agreement between predicted and observed outcomes, requiring advanced data-cleaning and preprocessing techniques. Additionally, parameterization, model updating, and optimal control inference remain technical bottlenecks, especially for complex stochastic spatial models where validation data is patient-specific and not easily reproducible. These challenges are further exacerbated by the time-consuming nature of individualized simulations. Socially, the field lacks a culture of shared model development, reuse, and standardization, which undermines credibility in medical and regulatory settings. To fully realize the potential of Virtual Tissue modeling in medical discovery and personalized therapy, solutions to these technical challenges are required, along with a shift towards community-based model development and validation. There are also promising opportunities, particularly in integrating mechanistic modeling with AI/ML approaches for forecasting, parameter optimization, anomaly detection, and therapy design. I will briefly review key issues in implementing digital twins, the achievements and limitations of Virtual Tissues so far, and potential paths forward for delivering effective Medical Digital Twins. Insights from more mature disciplines like weather forecasting may offer valuable lessons in advancing Medical Digital Twins, despite significant differences between fields.

Presenter: GLAZIER, James A. (Indiana University Bloomington)

Session Classification: Multiscale Models in Tissue Biology (Chair: Matthias Kaschube)

Contribution ID: **4** Type: **not specified**

The Minimal Cell under a Computational Microscope

Thursday 26 September 2024 09:45 (45 minutes)

Molecular dynamics (MD) is a well-established simulation method that has successfully been applied to study a wide range of biomolecular processes. As a result of continuous improvements in both modeling methods and computational infrastructures, the study of mesoscopic, multicomponent systems has become more attainable. However, the intricacies involved in setting up MD simulations for these systems remain daunting, requiring the integration of diverse data from both experimental and in silico sources.

Here we present how the coarse-grained Martini force field and its associated tools, form an ideal ecosystem for facilitating a integrative modeling pipeline. Employing a CG resolution, typically representing four heavy atoms by one CG bead, significantly reduces the computational cost inherent in simulating large-scale MD models. Furthermore, a key feature of the force field is its universality, which allows us to create CG models of all major biological components and construct complete cellular environments.

The Martini force field's capabilities are showcased in an ongoing effort to simulate a genetically minimal cell: JCVI-syn3A. We constructed the first near-atomistic MD model of a cell based on data from kinetic models, Cryo-Electron Tomograms, and omics experiments. Studying entire cells under the computational microscope will allow us to look into a wide range of problems, ranging from drug design to understanding the internal organization of cellular environments.

Presenter: STEVENS, Jan (University of Groningen)

Session Classification: Multiscale Models in Cell Biology II (Chair: Sebastian Thallmair)

Contribution ID: **5** Type: **not specified**

Topics on biochemical simulations: multiscale methods, thermodynamics, and field theory representations for open systems

Wednesday 25 September 2024 11:00 (45 minutes)

This presentation explores advanced topics in the simulation of biochemical systems, with a particular emphasis on multiscale approaches for modeling open systems characterized by varying particle/molecule numbers. We will discuss key methods, including hybrid and coarse-grained simulation schemes, as well as the integration of thermodynamic principles and field theory representations to develop and enhance multiscale methodologies. These approaches provide a robust framework for understanding complex biochemical interactions and can be extended to model a wide range of other complex systems beyond biochemistry, demonstrating their versatility and broad applicability.

Presenter: DEL RAZO SARMINA, Mauricio (Free University of Berlin)

Session Classification: Multiscale Models in Cell Biology I (Chair: Thomas Sokolowski)

Contribution ID: **6** Type: **not specified**

The Virtual Brain: Linking Theory and Data Towards Understanding Pathophysiological Processes

Wednesday 25 September 2024 17:15 (45 minutes)

The effectiveness of therapies and preventive strategies for nervous system disorders relies on our ability to customize treatments to the unique needs of each individual. Digital twins of the nervous system have the potential to revolutionize precision medicine. As a result, one of the key research and innovation areas for advancing brain health is the development of digital twins for both healthy and diseased individuals. While recent progress has underscored the potential of this approach and addressed some technical challenges in building digital twins to support decision-making in neurology and psychiatry—ranging from prevention and diagnosis to personalized care and therapy—many questions remain before these systems can be fully translated into the clinical practice. Among the remaining challenges there are: 1) the acquisition of new data types and the integration large datasets 2) the definition of relevant biomarkers, 3) the inclusion of physiologically meaningful details into synthetic models, 4) the effective personalization of custom models. These obstacles are being addressed by combining mechanistic models, artificial intelligence, and multimodal data. We will explore two examples, namely Parkinson's disease and Multiple Sclerosis, where these tools have started to be integrated to create personalized models.

Presenter: SORRENTINO, Pierpaolo (Aix-Marseille University)

Session Classification: Multiscale Models in Neuroscience (Chair: Hermann Cuntz)

Contribution ID: **7** Type: **not specified**

Nuclear and Globular Star Clusters on the path to Exascale

Friday 27 September 2024 14:45 (45 minutes)

Nuclear and globular star clusters (NSC and GC) are spectacular self-gravitating stellar systems in our Galaxy and across the Universe - in many respects. They populate disks and spheroids of galaxies as well as almost every galactic center. In massive elliptical galaxies NSCs harbor supermassive black holes, which influence the evolution of their host galaxies as a whole. The evolution of star clusters is not only governed by the aging of their stellar populations and simple Newtonian dynamics. For increasing particle number, gravitational effects of collisional many-body systems, described by methods borrowed from plasma physics, determine the cluster evolution. Direct N-body simulations are the most computationally expensive but also the most astrophysically advanced method to simulate GC and NSC evolution, using massively parallel supercomputers with GPU acceleration. The current legacy code Nbody6++GPU has seen many algorithmic and astrophysical improvements in recent years. A timing model shown and confirmed by benchmarks with up to 16 million bodies is presented (a record number in this domain), which approach the Exaflop regime. Current and projected astrophysical results will be shown, for example on intermediate mass black hole formation in star clusters, on clusters as gravitational wave sources, and on powerful tools to predict and analyze properties of TDEs (tidal disruption events in nuclear star clusters, where stars are disrupted by tidal forces of a supermassive black hole). Such events will be observable by large numbers through next generation astrophysical instruments. Compared to molecular and biological computer modelling we are still not able to produce digital twins of astrophysical systems, it is currently more like multi-scale modelling. Future perspectives will be discussed - a fruitful exchange with other fields on the computational methods may be possible and useful.

Presenter: SPURZEM, Rainer (Heidelberg University)

Session Classification: Multiscale Models beyond Biology & Outlook (Chair: Eckhard Elsen)

Contribution ID: **8** Type: **not specified**

Multi-resolution simulations of intracellular processes

Thursday 26 September 2024 14:30 (45 minutes)

All-atom and coarse-grained molecular dynamics (MD), Langevin dynamics (LD) and Brownian dynamics (BD) are computational methodologies, which have been applied to spatio-temporal modelling of a number of intracellular processes. I will discuss connections between MD, LD and BD, with a focus on the development, analysis and applications of multi-resolution methods, which use (detailed) MD simulations in localized regions of particular interest (in which accuracy and microscopic details are important) and a (less-detailed) coarser stochastic model in other regions in which accuracy may be traded for simulation efficiency. I will discuss applications of multi-resolution methodologies to modelling of intracellular calcium dynamics, actin dynamics and DNA dynamics.

Presenter: ERBAN, Radek (University of Oxford)

Session Classification: Multiscale Models in Cell Biology III (Chair: Franziska Matthäus)

Contribution ID: **9** Type: **not specified**

The role of promiscuous molecular recognition in the evolution of self-incompatibility in plants

Wednesday 25 September 2024 09:00 (45 minutes)

Bisexual flowering plants are at high risk of self-fertilization, which would produce less fit offspring (known as 'inbreeding depression'). Hence, more than 100 flowering plant families have developed various mechanisms to avoid self-fertilization, generally called 'self-incompatibility'(SI). Under these mechanisms, the species is subdivided into multiple 'types' or 'classes', such that a pollen grain cannot fertilize a maternal plant of its own type. The type is encoded by a single highly polymorphic locus that encodes for both male and female type-specifying proteins. Self-incompatibility relies on specific molecular recognition between these highly diverse proteins, such that the combination of genes an individual possesses determines its mating partners. Although a few dozen mating specificities are known from population surveys, previous models struggled to pinpoint the evolutionary trajectories by which new specificities evolved. In this talk, I will discuss a novel theoretical framework we recently proposed to study the evolution of the collaborative non-self-recognition self-incompatibility, found in the Solanaceae and Rosacea plant families. This framework uniquely incorporates the molecular recognition between male and female-determinant proteins into the evolutionary model. Our modeling framework crucially relies on interaction promiscuity and facilitates many-to-many interactions between the female and male-determinant proteins, in agreement with empirical evidence. Using this framework, we found that most members of the population spontaneously self-organize into 'compatibility classes', such that members of each class are incompatible with each other but compatible with all members of all other classes, in agreement with empirical findings. The model exhibits a dynamic balance between class birth and death and shows a stable equilibrium in their number. These behaviors prevail under a broad range of parameters. Lastly, I will discuss the selection pressures driving the evolution of the self-incompatibility genes and how they reconcile the possibly conflicting requirements to simultaneously attract some partners but repel others. Our work highlights the importance of molecular recognition promiscuity to the evolution of multi-component biological systems. Promiscuity was found in additional systems suggesting that our framework could be more broadly applicable.

Presenter: FRIEDLANDER, Tamar (Hebrew University)

Session Classification: Multiscale Models in Cell Biology I (Chair: Thomas Sokolowski)

Contribution ID: **10** Type: **not specified**

Multiscale Simulation of Biomembranes: bridging the gap between simple models and complex reality

Thursday 26 September 2024 09:00 (45 minutes)

Biomembranes are integral part of the cell, the basic building block of all life. They are a two-dimensional fluid, composed of myriad proteins and lipid species, which provide identity to the cell and to many internal organelles. An intriguing aspect of membranes is their ability to assume a variety of shapes, which is crucial for many cellular processes such as food update, waste disposal, energy generation and cell division. Uncovering the mechanisms that control biomembrane shapes are essential for understanding their function in cells, dysfunction in disease and for many biotechnological purposes such as the rational design of drug delivers vehicles and vaccine development.

In this talk, I will first present our recent advances in building multiscale computer simulations to explore biomembrane spatial organizations. I will discuss how simulations can provide detailed insight into these processes and provide predictions for experimental validation. Then I will show why emerging forces at the mesoscale (10-100 nm) such as membrane-mediated interactions and curvature instability are essential for controlling biomembrane shapes. Finally, I will discuss how close we are to simulating realistic cellular membranes and sketch a possible way ahead.

Presenter: PEZESHKIAN, Weria (University of Copenhagen)

Session Classification: Multiscale Models in Cell Biology II (Chair: Sebastian Thallmair)

Contribution ID: **11** Type: **not specified**

Multiscale modeling of cell regulation and dynamics

Thursday 26 September 2024 15:15 (45 minutes)

My research is focused on the mathematical and computational modeling of cell regulatory processes. We and others have developed an approach to modeling the reaction kinetics of biochemical systems that allows detailed knowledge about protein-protein interactions to be encoded as rules that generalize the standard reaction network formulation and enables the building, simulation, and analysis of models in a scalable and precise manner. Using this rule-based approach, we developed foundational models of early events in immunoreceptor and growth factor signaling that allowed us to investigate the mechanistic roles of specific interaction domains and phosphorylation sites. My group currently leads the development of widely-used software tools that enable rule-based modeling, and we develop models employing these methods across a wide range of biological processes including immune signaling, viral replication dynamics, and signaling pathways in cancer. In each of these applications a significant focus of our work is on the development of novel drug combinations and other intervention strategies to treat human disease.

Presenter: FAEDER, James R. (University of Pittsburgh)

Session Classification: Multiscale Models in Cell Biology III (Chair: Franziska Matthäus)

Contribution ID: **12** Type: **not specified**

Properties of Long-Chain Lipid Enriched Regions in Biological Membranes: Insights from MD Simulations

Thursday 26 September 2024 11:00 (20 minutes)

In the yeast plasma membrane, domains rich in long-chain sphingolipids are observed. Our study employs MD simulations to explore the influence of these lipids on membrane properties. We utilize both coarse-grained and all-atom models, employing a simplified lipid composition with varying concentrations of long-chain lipids. We assess the impact on diverse parameters such as order parameter, and degree of nonaffineness to unravel the relationship between long-chain lipids and membrane properties.

Presenter: QUAS, Annemarie (University of Münster)

Session Classification: Multiscale Models in Cell Biology II (Chair: Sebastian Thallmair)

Contribution ID: **13** Type: **not specified**

Functional digital twins in visual neuroscience

Friday 27 September 2024 09:45 (45 minutes)

For years, neurons in visual cortex have been characterized in terms of simple feature dimensions such as orientation and spatial frequency. However, in recent years deep learning methods have set new standards in predicting the activity of neurons in visual cortex to arbitrary stimuli. Because of this property, these models are sometimes referred to as digital twins (DTs). Here we show how DTs can be used to efficiently and flexibly explore the space of tuning and invariance properties of neurons –beyond the manifold of parametric stimuli such as Gabor gratings. We find that while DTs reproduce classical experimental characterizations of neurons in primary visual cortex (V1), optimizing novel stimuli beyond the classical parametrizations and verifying them experimentally, can lead to novel and surprising results, that challenges classical interpretations of the computational role of neurons in V1. We will provide two examples for that: Center-surround contextual modulation and color tuning with behavioral context.

Presenter: SINZ, Fabian (University of Göttingen)

Session Classification: Multiscale Models in Neuroscience (Chair: Hermann Cuntz)

Contribution ID: **14** Type: **not specified**

Multi-scale and multi-physics modeling in Astrophyiscs

Friday 27 September 2024 14:00 (45 minutes)

Astrophysical research often relies on sophisticated software tools to model, simulate, and analyze complex astronomical phenomena. The dynamic range in astrophysics simulations often covers more than 20 orders of magnitude in temporal and spatial scales. Further complications are introduced by the interaction among various physicals process, such as gravity, hydrodynamics, nuclear fusion processes and radiative transfer. The Astrophysical Multipurpose Software Environment (AMUSE) stands as a pivotal platform in this domain, offering a versatile and comprehensive suite of tools tailored to address the multifaceted challenges of modern astrophysics.

Author: PORTEGIES ZWART, Simon (Leiden University)

Presenter: PORTEGIES ZWART, Simon (Leiden University)

Session Classification: Multiscale Models beyond Biology & Outlook (Chair: Eckhard Elsen)

Contribution ID: **15** Type: **not specified**

Opening Remarks

Wednesday 25 September 2024 08:45 (15 minutes)

Session Classification: Multiscale Models in Cell Biology I (Chair: Thomas Sokolowski)

Contribution ID: **16** Type: **not specified**

The Human Lymph Nodes and Digital Twins

Wednesday 25 September 2024 09:45 (20 minutes)

The human immune system consists of lymphoid tissue in different localisations, including about 600 lymph nodes. The latter can be divided in different compartments, concentrating specialised immune cells in a highly effective manner. We investigated and defined human lymph nodes applying confocal laser technologies to generate 3-D pictures and 4Dmovies. Many parameters as cell speeds tracks and interactions, such as contact numbers and times could be investigated. The data organisation open new possibilities to build mathematical models. These can be used to get new insights in the biology of cellular processes, diagnostics and to simulate drug responses. The values of different levels of abstraction as well as methods of artificial intelligence are important for analysis of real and artificial immune systems.

Presenter: HANSMANN, Martin-Leo (Frankfurt Institute for Advanced Studies)

Session Classification: Multiscale Models in Cell Biology I (Chair: Thomas Sokolowski)

Contribution ID: **17** Type: **not specified**

Development of a multiscale model of limb morphogenesis

Wednesday 25 September 2024 16:50 (20 minutes)

The limb bud development exemplifies the complexity of organogenesis, whereby the organ's macroscopic state feeds back on cellular decisions. Digital twins are an exciting approach towards understanding such systems. Regarding limb bud elongation, diverse hypotheses have been proposed. Involving ectodermal constraints, proliferation, motility, migration, as well as PCP induced intercalation. We develop a computational approach, allowing to systematically simulate the individual hypotheses, examining which cellular behaviours are consistent with morphogenesis.

Presenter: LIEBISCH, Tim (EMBL Barcelona)

Session Classification: Multiscale Models in Tissue Biology (Chair: Matthias Kaschube)

Contribution ID: **18** Type: **not specified**

Physical aspects of Drosophila gastrulation

Wednesday 25 September 2024 15:15 (45 minutes)

Drosophila gastrulation is a popular model used to study morphogenesis. Despite a long-standing effort to determine the physical nature of cell shape changes in this key model system, there is no consensus on the underlying biophysical mechanism. Any predictive model of a morphogenetic event requires the knowledge of material properties of the tissue undergoing morphogenesis. Using our previously developed methods to apply pulling force to a single cell of an early embryo, we were able to quantify the profile of tissue deformation and the dynamics of tissue recoil after the force is released. Comprehensive computational modeling suggest that these data can only be explained assuming that apical domains are much softer than both the lateral and the basal domains. Motivated by this prediction, we developed a novel protocol to probe individual cellular domains using iron microspheres. Strikingly, applying concentrated pulling force to apical and lateral cellular domains resulted in formation of remarkably long membrane tethers. Tether formation required orders of magnitude smaller force than our typical global tissue deformations when the force probe contacts the basal side. Our measurements thus suggest that cells are extremely rigid on their basal side, whereas lateral and basal domains are orders of magnitude softer, likely lacking stable membrane-associated cytoskeleton. Furthermore, using the newly developed AID-2 degron, we show that (nearly) complete depletion of myosin II has no effect on the mechanical measurements, indicating that the measured responses are passive. A novel 3D computational model integrating our experimental findings suggests that (1) cell elongation during the early phase of gastrulation is a passive process driven primarily by viscous shear forces, and (2) tissue invagination must require active tension in the lateral membranes as well as forces transmitted through the cytoplasm.

Presenter: DOUBROVINSKI, Konstantin (University of Texas Southwestern Medical Center)

Session Classification: Multiscale Models in Tissue Biology (Chair: Matthias Kaschube)

Contribution ID: **19** Type: **not specified**

Invited Talk (TBC) or Contributed Talks

Session Classification: Multiscale Models in Tissue Biology (Chair: Matthias Kaschube)

Contribution ID: **20** Type: **not specified**

Predicting interactions of polymers with cellular matter

Thursday 26 September 2024 11:45 (45 minutes)

Combining synthetic polymers with biological matter such as proteins or DNA is a cornerstone technique in nanomedicine and biotechnology. For example, antibody formulations can be stabilized through the addition of low molecular weight polymers or nucleic acid delivered by combining them with ionic polymers to form polyplexes. Exploiting the vast chemical composition space spanned by synthetic polymers holds great promise for designing application-specific sequences to overcome problems such as cell-type targeting in nucleic acid-based gene therapy. However, the interactions of these polymers with biological matter are little understood, sequence dependent data scarce, and the system complexity high. In this talk, I will present our recent advances in creating a multiscale simulation framework to simulate, analyze, and ultimately predict the interactions of polymers with cellular matter. Using chemically specific coarse-grained simulation in combination with machine learning and atomistic simulations we aim to create digital twins of near to realistic resolution, which can be used to understand and optimize these systems.

Presenter: GRÜNEWALD, Fabian (HITS - Heidelberg Institute for Theoretical Studies)

Session Classification: Multiscale Models in Cell Biology II (Chair: Sebastian Thallmair)

Contribution ID: **21** Type: **not specified**

Molecular dynamics simulations shed light on critical events in the early stages of human IRE1 activation

Thursday 26 September 2024 16:30 (20 minutes)

The inositol-requiring enzyme 1 (IRE1) serves as a highly conserved stress sensor within the endoplasmic reticulum (ER), crucial for mitigating the cytotoxic effects resulting from the accumulation of unfolded proteins. Dysregulation of the unfolded protein response (UPR), a network of signaling pathways aimed at alleviating ER stress, is implicated in various human pathologies including diabetes, and cancer. IRE1, a transmembrane protein, relies on its core luminal domain (cLD) to sense misfolded protein accumulation and initiate downstream signaling events. While the involvement of IRE1 in recognizing unfolded proteins is well-established, the precise mechanism underlying this process in human cells remains contentious. To address this, we conducted extensive molecular dynamics (MD) simulations to explore how the dimeric cLD of human IRE1 (hIRE1) directly interacts with unfolded polypeptides at the atomic level. Our investigations revealed that hIRE1 cLD dimers are stable under non-stress conditions, with peptide binding occurring predominantly on the surface of the dimer rather than within its central MHC-like groove, as observed in the yeast homolog. These novel findings support a model wherein the direct interaction between IRE1 and unfolded proteins represents a crucial early event in the assembly of supramolecular complexes associated with activated IRE1. Insights from this study into the molecular mechanisms governing IRE1 activation hold potential implications for the development of therapeutic strategies targeting the UPR pathway.

Presenter: SPINETTI, Elena (Frankfurt Institute for Advanced Studies)

Session Classification: Multiscale Models in Cell Biology III (Chair: Franziska Matthäus)

Contribution ID: **22** Type: **not specified**

Contributed Talk (TBC)

Session Classification: Multiscale Models beyond Biology & Outlook (Chair: Eckhard Elsen)

Contribution ID: **23** Type: **not specified**

The developmental emergence of reliable cortical representations

Friday 27 September 2024 11:00 (20 minutes)

The fundamental structure of cortical networks arises early in development prior to the onset of sensory experience. However, how endogenously generated networks respond to the onset of sensory experience, and how they form mature sensory representations with experience remains unclear. Here we examine this 'nature-nurture transform'at the single trial level using chronic in vivo calcium imaging in ferret visual cortex. At eye opening, visual stimulation evokes robust patterns of modular cortical network activity that are highly variable within and across trials, severely limiting stimulus discriminability. These initial stimulus-evoked modular patterns are distinct from spontaneous network activity patterns present prior to and at the time of eye opening. Within a week of normal visual experience, cortical networks develop low-dimensional, highly-reliable stimulus representations that correspond with reorganized patterns of spontaneous activity. Using a computational model, we propose that reliable visual representations derive from the alignment of feedforward and recurrent cortical networks shaped by novel patterns of visually-driven activity.

Presenter: TRÄGENAP, Sigrid (Frankfurt Institute for Advanced Studies)

Session Classification: Multiscale Models in Neuroscience (Chair: Hermann Cuntz)

Contribution ID: **24** Type: **not specified**

Towards a Digital Twin of Human Cognitive Development

Friday 27 September 2024 11:45 (30 minutes)

Human intelligence and human consciousness emerge gradually during the process of cognitive development. Understanding this development is an essential aspect of understanding the human mind and may facilitate the construction of artificial minds with similar abilities. In this talk I will describe our lab's recent efforts to develop a digital twin of the developing human mind and body. To this end, we have created MIMo, the Multimodal Infant Model, an open-source simulation platform for studying early cognitive development through computer simulations. MIMo allows to investigate how cognitive abilities arise from embodied interactions with the physical and social environment. I will describe MIMo's modular design and how it can be used to study the developmental origins of human cognition.

Presenter: TRIESCH, Jochen (Frankfurt Institute for Advanced Studies)

Session Classification: Multiscale Models in Neuroscience (Chair: Hermann Cuntz)

Contribution ID: **25** Type: **not specified**

Mechanical Forces and Geometric Properties in Tissue Phase Transitions: Insights from Active Vertex Model

Wednesday 25 September 2024 16:30 (20 minutes)

During the embryonic stage, mechanical forces such as contraction, stretching, and bending play a crucial role in forming structured cell groups and patterns. However, it is still unclear how these different forces affect pattern formation in developing tissues. In order to understand how these different factors affect tissue dynamics and cellular rearrangements we used the active vertex model. By including passive forces representing competition between cellular adhesion and contractility, as well as active forces, included as vertex motility in randomly selected directions we obtained phase diagram of the tissue. The phase diagram indicated that increasing active forces alone or in combination with increasing passive forces resulted in fluidization of the tissue. Next, we investigated geometric properties of the tissue, such as the cell shape index, number of cell vertices, average cell area, and more, to derive observables that could distinguish fluid-like from solid-like tissue behavior. The results show that in the fluid state, cells are elongated with a higher number of vertices, while in the solid state, they are more compact, suggesting that tissue state can be determined through geometric properties. In the next step, we considered a group of cells with varying geometric properties, specifically compact cells with higher contractility. Our simulation showed that this group can form an elongated pattern, which may be related to processes like cell sorting or branching.

Presenter: GHASEMI NASAB, Mohammad Salar (Jagiellonian University Cracow)

Session Classification: Multiscale Models in Tissue Biology (Chair: Matthias Kaschube)

Contribution ID: **26** Type: **not specified**

GPCR Surface Facilitates Membrane Crossing of Drug Molecules and Lipids: A Martini 3 Study

Thursday 26 September 2024 11:20 (20 minutes)

G protein-coupled receptors (GPCRs) play a crucial role in modulating physiological responses by transmitting extracellular signals into the cell. Moreover, they are the main target of drugs like salmeterol and salbutamol, which act against pulmonary diseases by activating the GPCR, β2-adrenergic receptor (β2AR). In this study, we employ coarse-grained molecular dynamics simulations with the Martini 3 force field to investigate the behavior of these drugs and phospholipids in the presence of β2AR. Our results reveal that both drugs and lipids exploit the protein surface to traverse the membrane and change leaflets (flip-flop). During unbiased trajectories, 50% to 70% of the drug flip-flops occur on the β2AR surface, while lipids exclusively flip-flop on β2AR. We analyzed the primary drug flip-flop path on the β2AR surface and conducted umbrella sampling calculations along spontaneous flip-flop pathways. The resulting energy barriers for the permeation of both drugs drop by more than 15 kJ/mol, and the flip-flop rate constant increases by three orders of magnitude on β2AR. Our findings provide valuable insights into the membrane permeation mechanisms and interactions of drugs and lipid flip-flops. They contribute to comprehending GPCR dynamics, the most abundant class of transmembrane proteins in the human body. Beyond this, these results could benefit strategies for designing drugs necessitating efficient cell permeation as we validated with two different kinase inhibitors.

Presenter: GIL HERRERO, Cristina (Frankfurt Institute for Advanced Studies)

Session Classification: Multiscale Models in Cell Biology II (Chair: Sebastian Thallmair)

Contribution ID: **27** Type: **not specified**

Multiscale Computational Modelling in the field of 3R Animal Protection

Friday 27 September 2024 11:20 (20 minutes)

Qualitative, cartoon-based understanding of physiological processes is not sufficient and needs to be taken to a deeper, quantitative (computational) level. Two types of computational models, namely statistical & mechanistic models, can be used to predict subcellular, cellular and supracellular phenomena in silico. This talk will mainly focus on mechanistic models. A simulation of a large number of parameter combinations may lead to a reduction in the number of necessary experiments. However, experimental data from in vitro and in vivo experiments are necessary to adjust the parameters of computer models. Relatively recently established, so called population-based compartmental modeling will be presented as a promising tool to predict and partially replace pharmacological/genetical perturbations. Examples from cardiac and neuronal physiology will be described to show how population-based computational modeling enables studies of the functional impact of intercellular ion channel variability. In addition, morphological modeling will be mentioned as a useful complementary approach to traditional compartmental modeling of electrophysiological data in neurobiology. In combination, morphological and compartmental modeling facilitates generalization of computational predictions to any morphology and supports the search for universal principles valid across different species and cell types. Multi-objective Pareto optimality will be discussed as a helpful guiding principle to address the degeneracy of model parameters. Pareto optimality might help identify the subpopulations of models that strike the best balance between their economy and functionality. This approach could potentially reduce the high-dimensional parameter space of models to geometrically simple low-dimensional manifolds.

Presenter: JEDLIČKA, Peter (Justus-Liebig-University Gießen)

Session Classification: Multiscale Models in Neuroscience (Chair: Hermann Cuntz)

Contribution ID: **28** Type: **not specified**

Modelling for Efficient Scientific Data Storage Using Simple Graphs in DNA

Wednesday 25 September 2024 10:05 (20 minutes)

Data analytics requires large data archives beyond current world storage media, causing researchers to seek alternative storage media. Scientists in fields like biology, ecology, life sciences, and medicine are using data archiving to aid their research. During the last decade, DNA (Deoxyribonucleic Acid) storage has been significantly investigated as a method for archiving data at massive scales. Digital information can be encoded at high density with synthetic DNA that is durable and long-lasting. However, expensive synthesis and sequencing processes hinder DNA data storage at a large scale and lead us to compress the data beforehand. Network science applications are eager to store graph data archives efficiently using DNA storage, even though it has been demonstrated with raw data storage. Graph-aware data archiving has a significant advantage over raw data, reducing the related data size for DNA storage in terms of nucleotides and resulting in lower database operational costs. This paper presents a theoretical model for storing scientific data efficiently in DNA using simple graphs. The Re-Pair compression algorithm is utilized to investigate individual and composite graph storage strategies, and simple graph-based datasets, particularly from the biological domain, are used for experimental analysis. Composite graphs, however, yield a higher compression ratio than aggregated standalone graphs. Noticeably, the compression ratios range from 1.18 to 1.53, saving a substantial amount of money in a DNA storage system's synthesis and sequencing processes. Consequently, data analytics could be performed cost-effectively using DNA as an emerging storage medium.

Presenter: USMANI, Asad (Goethe University Frankfurt)

Session Classification: Multiscale Models in Cell Biology I (Chair: Thomas Sokolowski)

Contribution ID: **29** Type: **not specified**

AI-powered simulation-based inference of a genuinely spatial-stochastic model of early mouse embryogenesis

Thursday 26 September 2024 17:10 (20 minutes)

Understanding how multicellular organisms reliably orchestrate cell-fate decisions is a central challenge in developmental biology. This is particularly intriguing in early mammalian development, where early cell-lineage differentiation arises from processes that initially appear cell-autonomous but later materialize reliably at the tissue level. In this study, we develop a multi-scale, spatial-stochastic simulator of mouse embryogenesis, focusing on inner-cell mass (ICM) differentiation in the blastocyst stage. Our model features biophysically realistic regulatory interactions and accounts for the innate stochasticity of the biological processes driving cell-fate decisions at the cellular scale. We advance event-driven simulation techniques to incorporate relevant tissue-scale phenomena and integrate them with Simulation-Based Inference (SBI), building on a recent AI-based parameter learning method: the Sequential Neural Posterior Estimation (SNPE) algorithm. Using this framework, we carry out a large-scale Bayesian inferential analysis and determine parameter sets that reproduce the experimentally observed system behavior. We elucidate how autocrine and paracrine feedbacks via the signaling protein FGF4 orchestrate the inherently stochastic expression of fate-specifying genes at the cellular level into reproducible ICM patterning at the tissue scale. This mechanism is remarkably independent of the system size. FGF4 not only ensures correct cell lineage ratios in the ICM, but also enhances its resilience to perturbations. Intriguingly, we find that high variability in intracellular initial conditions does not compromise, but rather can enhance the accuracy and precision of tissue-level dynamics. Our work provides a genuinely spatial-stochastic description of the biochemical processes driving ICM differentiation and the necessary conditions under which it can proceed robustly.

Presenter: RAMÍREZ SIERRA, Michael Alexander (Frankfurt Institute for Advanced Studies)

Session Classification: Multiscale Models in Cell Biology III (Chair: Franziska Matthäus)

Contribution ID: **30** Type: **not specified**

Bivariate change detection in absolute movement direction and speed on multiple scales

Thursday 26 September 2024 16:50 (20 minutes)

Biological movement patterns are sometimes quasi linear with abrupt changes in direction and speed, as in movements of plastids in root cells of plants. We discuss random walk (RW) models suggesting that modelling absolute movement direction can be advantageous as compared to relative direction as assumed in the widely used correlated RWs. A new stochastic model called linear walk is proposed that describes movement along linear structures with piecewise constant movement direction and speed. We provide maximum likelihood estimators and propose a moving kernel estimator in order to estimate change points on multiple time scales. Finally, we also propose a graphical technique to distinguish between change points in movement direction and speed.

Presenter: PLOMER, Solveig (Goethe University Frankfurt)

Session Classification: Multiscale Models in Cell Biology III (Chair: Franziska Matthäus)

Contribution ID: **31** Type: **not specified**

Local distributed cellular information processing and cell autonomous feedback control facilitates global tissue-scale properties during development

Thursday 26 September 2024 17:30 (20 minutes)

Precise spatial patterning of cell fate during morphogenesis requires accurate inference of cellular position. In making such inferences from morphogen profiles, cells must contend with inherent stochasticity in morphogen production, transport, sensing and signalling. Motivated by the multitude of signalling mechanisms in various developmental contexts, we show how cells may utilise multiple tiers of processing (compartmentalisation) and parallel branches (multiple receptor types), together with feedback control, to bring about fidelity in morphogenetic decoding of their positions within a developing tissue. By simultaneously deploying specific and nonspecific receptors, cells achieve a more accurate and robust inference. We explore these ideas in the patterning of Drosophila melanogaster wing imaginal disc by Wingless morphogen signalling, where multiple endocytic pathways participate in decoding the morphogen gradient. The geometry of the inference landscape in the high dimensional space of parameters provides a measure for robustness and delineates stiff and sloppy directions. This distributed information processing at the scale of the cell highlights how local cell autonomous control facilitates global tissue scale design.

Presenter: IYER, Krishnan (Institute of Science and Technology Austria (ISTA))

Session Classification: Multiscale Models in Cell Biology III (Chair: Franziska Matthäus)