BP 31: Computational Biophysics (joint session BP/CPP)

Time: Thursday 9:30–13:00 Location: SCH A251

BP 31.1 Thu 9:30 SCH A251

Effectiveness of Ca^{2+} clearance by PMCA pumps — •Barbara Schmidt[1], Cristina Constantin[2], Bernd Fakler[2], and Heiko Rieger[1] — [1]Center for Biophysics and Department of Theoretical Physics, Saarland University, 66123 Saarbrücken, Germany — [2]Institute of Physiology, University of Freiburg, 79104 Freiburg, Germany

Ca^{2+} influx through voltage-gated (Cav) channels leads to an increase in the intracellular Ca^{2+}-concentration ($[Ca^{2+}]_i$) that can be monitored by BK-type Ca^{2+}-activated K^+ channels. Due to their gating kinetics they may be used as sensors for $[Ca^{2+}]_i$ underneath the plasma membrane. Here, K^+ currents through BK channels were used to determine the Ca^{2+} transport activity of Ca^{2+}-ATPases of the plasma membrane (PMCA), the classical Ca^{2+} pumps. Experimentally we monitored PMCA-mediated Ca^{2+} clearance by the decay of BK-currents following their activation by a short (0.8 ms) period of Ca^{2+}-influx through Cav2.2 channels. Our theoretical model describes the Ca^{2+} diffusion within a spherical cell. Time- and Ca^{2+} concentration-dependent boundary conditions model the initial Ca^{2+} influx and the following outflow via the PMCA pumps. The time scale of this diffusion process is used to predict the strength of the PMCA pumps. Based on the experimentally determined density of Cav channels and PMCA pumps within the membrane we predict a PMCA pump strength that is at least 1.5 orders of magnitude larger than what has been assumed so far.

BP 31.2 Thu 9:45 SCH A251

Talin impacts force-induced vinculin activation by 'loosening' the vinculin inactive state — Florian Franz[1,2] and •Frauke Gräter[1,2] — [1]HITS gGmbH, Schloß-Wolfsbrunnenweg 35, 69118 Heidelberg, Germany — [2]IWR - Interdisciplinary Center for Scientific Computing, Im Neuenheimer Feld 368, 69120, Heidelberg, Germany

Focal Adhesions (FA) are large, multi-protein complexes connecting the cytoskeleton to the extracellular matrix. Their adhesive functionality is tightly regulated by mechanical stress. A key component of FA-associated mechanosensing is vinculin, which can assume either a closed ("inactive") or open ("active") conformation. The underlying activation mechanism, however, remains yet to be fully understood.

Here, we employ molecular dynamics (MD) simulation to demonstrate that vinculin activation is greatly facilitated by the binding of vinculin on talin's vinculin binding site. Steered MD simulations reveal that the force required for activation is drastically reduced upon formation of the vinculin-talin complex. Using correlated motions and force distribution analysis, we illuminate how the force propagation through vinculin changes upon complex formation. Interestingly, after talin dissociation, vinculin returns to its native conformation on a submicrosecond time scale, with 60% of its native contacts restored.

Our results suggest a rapid dynamic equilibrium between 'tight' and 'loosened' inactive vinculin, which depends on talin and determines the level of mechanical stress required for activation. Our study has important implications for our understanding of mechano-sensing mechanisms at FAs.

BP 31.3 Thu 10:00 SCH A251

Protein-ligand dynamics on multisecond timescales from submicrosecond atomistic simulations — •Steffen Wolf, Benjamin Lickert, Simon Bray, and Gerhard Stock — Biomolecular Dynamics, Institute of Physics, Albert Ludwigs University, 79104 Freiburg, Germany

Coarse-graining of fully atomistic molecular dynamics simulations is a long-standing goal to allow the prediction of processes occurring on biologically relevant timescales. To achieve the necessary enhanced sampling, we first perform dissipation-corrected targeted molecular dynamics simulations which yield free energy and friction profiles of the molecular process of interest. In a second step, we use these fields to perform Langevin equation simulations which account for the desired molecular kinetics. By introducing the concept of "temperature rescaling" of the Langevin equation, this combination of methods allows for the simulation of biomolecular processes occurring on multisecond timescales and beyond. Adopting the dissociation of solvated sodium chloride and several protein-ligand complexes as test problems, we are able to reproduce rates from atomistic MD simulation and experiments within a factor of 1.5-4 for rates up to the range of milliseconds and 2-10 in the range of seconds.

BP 31.4 Thu 10:15 SCH A251

Active processes in cellular networks and comparison with viscoelastic models — •Joris Paijmans[1], Mandar Inamdar[2], and Frank Jülicher[1,3] — [1]Max Planck Institute for the Physics of Complex Systems, Dresden, Germany — [2]Department of Civil Engineering, Indian Institute of Technology Bombay, Mumbai, India — [3]Center for Systems Biology Dresden, Dresden, Germany

During morphogenesis, the collective behavior of many cells determines the emergence of tissue shape. How the mechanical properties and behavior of individual cells lead to a desired morphology is not well understood. Here we use a vertex model, modeling the cellular network, and a hydrodynamic theory, describing the tissue as a continuous viscoelastic material, to study this problem in epithelial tissues.

First, we consider different scenarios for how cells drive local stresses in cellular networks such as orientation dependent edge tensions and oriented cell divisions. Coarse-graining over the cellular dynamics, we find the large scale deformation of the tissue and how cells contributed to this deformation such as cell shape changes and rearrangements in the cell network. This allows us to compare the dynamics of the cellular network to a hydrodynamic model of a viscoelastic material with active and passive contributions to the stress and cell rearrangements in the tissue. We find that the large scale viscoelastic properties of the cellular network depend strongly on the details of how cells locally generate stress. We compare results with the developing wing blade in Drosophila, where phases of active and passive cell rearrangements are observed.

BP 31.5 Thu 10:30 SCH A251

Morphology of spherical epithelial monolayers — •Aboutaleb Amiri[1], Carl Modes[2,3], and Frank Jülicher[1,3] — [1]Max Planck Institute for the Physics of Complex Systems, 01187 Dresden, Germany — [2]Max Plack Institute for Molecular Cell Biology and Genetics, 01037 Dresden, Germany — [3]Center for Systems Biology Dresden, 01307 Dresden, Germany

We develop a generalised vertex model off the mechanics of epithelial cell monolayers to study morphogenesis in three dimensions. In this approach, a cell is represented by a polyhedron which is characterised by the location of its vertices in 3D space. We take into account apical, basal, and lateral cell surface tension, as well as pressure differences between outside and inside the cells. We consider an epithelium with spherical topology enclosing a lumen and investigate mechanisms that can generate different morphologies. In particular, we are interested in the roles of mechanical feedback on cell behaviours for the morphogenesis of closed epithelial monolayers.

BP 31.6 Thu 10:45 SCH A251

The role of thickness inhomogeneities in brain folding — •Lucas da Costa Campos[1,2], Svenja Caspers[2,3,4], Gerhard Gompper[1], and Jens Elgeti[1] — [1]Theoretical Soft Matter and Biophysics (ICS-2 / IAS-2), Research Centre Jülich, Jülich, Germany — [2]Institute of Neuroscience and Medicine (INM-1), Research Centre Jülich, Germany — [3]JARA-Brain, Jülich-Aachen Research Alliance, Jülich, Germany — [4]Institute for Anatomy I, Medical Faculty, Heinrich-Heine University, Düsseldorf, Germany

The morphology of the mammalian brain cortex is highly folded. Misfolds of the brain correlate with a long list of cognitive disabilities, such as schizophrenia and epilepsy. Having realistic models of gyrogenesis is the first step in the understanding of these issues. It has been hypothesized that mechanical instabilities play an essential role in gyrogenesis. However, the emergence of higher order folding, one of the main characteristics of the human brain, has not been fully tackled. We perform finite element simulations of rectangular slabs divided into two distinct regions. Differential growth is introduced by growing the top layer (gray matter) tangentially, while keeping the underlying layer (white matter) unchanged. The material is modelled as a Neohookean hyperelastic. Simulations are performed with system with either homogeneous or inhomogeneous cortical thickness. In early stages of development, we obtain structures reminiscent of the deep sulci in the brain, which can be mapped into the primary sulci.

As the cortex continues to develop, we obtain secondary undulations whose characteristics are consistent with those of higher order folding.

30 min. coffee break

Invited Talk BP 31.7 Thu 11:30 SCH A251

Predicting Protein and RNA Structures via data inference: from Potts models to machine learning — •Alexander Schug — John von Neumann Institute for Computing, Jülich Supercomputer Centre, Forschungszentrum Jülich — Faculty of Biology, University of Duisburg-Essen

On the molecular level, life is orchestrated through an interplay of many biomolecules. To gain any detailed understanding of biomolecular function, one needs to know their structure. Yet the structural characterization of many important biomolecules and their complexes - typically preceding any detailed mechanistic exploration of their function- remains experimentally challenging. Tools rooted in statistical physics such as Direct Coupling Analysis (DCA) but also increasingly Machine Learning driven approaches take advantage of the explosive growth of sequence databases and infer residue co-evolution to guide structure prediction methods via spatial constraints. Going beyond anecdotal cases of a few protein families, systematic large-scale studies of >1000 protein families are now possible and other information, such as low-resolution experimental information (e.g. SAXS or FRET) can be used as further constraints in simulations.

BP 31.8 Thu 12:00 SCH A251

A machine learning assessment of the two states model for lipid bilayer phase transitions — •Vivien Walter[1], Céline Ruscher[2], Olivier Benzerara[2], Carlos Marques[2], and Fabrice Thalmann[2] — [1]Department of Chemistry King's College London, London, UK — [2]Institut Charles Sadron, Strasbourg, France

We have adapted a set of classification algorithms, also known as Machine Learning, to the identification of fluid and gel domains close to the main transition of dipalmitoyl-phosphatidylcholine (DPPC) bilayers. Using atomistic molecular dynamics conformations in the low and high temperature phases as learning sets, the algorithm was trained to categorize individual lipid configurations as fluid or gel, in relation with the usual two-states phenomenological description of the lipid melting transition. We demonstrate that our machine can learn and sort lipids according to their most likely state without prior assumption regarding the nature of the order parameter of the transition. Results from our machine learning approach provides strong support in favor of a two-states model approach of membrane fluidity.

BP 31.9 Thu 12:15 SCH A251

Rational optimization of drug-membrane selectivity by computational screening — •Bernadette Mohr and Tristan Bereau — Max Planck Institute for Polymer Research, Mainz, Germany

Success rates of drug discovery are non-satisfactory considering the high cost in time and resources. This leads to an increased demand for development of improved screening methods. In our work, we explore the capabilities of using a coarse-grained (CG) model to efficiently find candidate structures with desired properties. The Martini CG force field is a physics-based model that incorporates both the essential chemical features with a robust treatment of statistical mechanics. Martini simplifies the molecular representation through a small set of bead types that encode a variety of functional groups present in organic chemistry. This offers two advantages: (i) many molecules map to the same CG representation and (ii) screening boils down to systematically varying among the set of CG bead types available. The combination of these two aspects makes Martini a remarkably efficient candidate for high-throughput screening. We apply this approach to the selective binding of drugs between Cardiolipin and phosphoglycerols in mitochondrial membranes. A systematic screening starting from an already-reported compound will be presented. We identify clear design rules for improved selectivity, and rationalize them on a physical basis. As an outlook, we explore prospects of further boosting screening at higher throughput by means of connecting the CG simulations within a deep-learning framework.

BP 31.10 Thu 12:30 SCH A251

Quantifying membrane curvature sensing — •Kai Steffen Stroh[1] and Herre Jelger Risselada[1,2] — [1]Institute for Theoretical Physics, Göttingen, Germany — [2]Leiden Institute of Chemistry, Leiden, The Netherlands

When considering the interplay of lipid membranes and proteins, membrane curvature is an important factor, as it can act as a control mechanism for protein function. Several proteins feature subunits that serve as membrane curvature sensors. This sensing ability together with the spatial information provided by membrane curvature allows for site specific binding, and thus regulation of, e.g., transport processes.

Naturally, the curvature-dependent binding free energy provides valuable quantitative information about a protein's curvature sensing abilities. Therefore, we present a novel molecular dynamics simulations protocol to obtain such free energy profiles.

BP 31.11 Thu 12:45 SCH A251

Load distribution among the main structures of a passively flexed lumbar spine — •Julia M. Riede[1], Falk Mörl[2], Michael Günther[1], Maria Hammer[1], and Syn Schmitt[1] — [1]Computational Biophysics&Biorobotics, IMSB/Simtech, University of Stuttgart, Germany — [2]Biomechanics&Ergonomics, FSA mbH Erfurt, Germany

Mechanical loads may induce degeneration of spinal structures. It is still unknown how the load during spine motion is distributed among the spine's main structures: muscles, vertebrae and facet joints, ligaments, and intervertebral discs. Currently, there are no measurements that capture the load on all spinal structures at once. Therefore, computer simulations are the method of choice to overcome the lack of knowledge about the biophysical properties and processes determining spinal in vivo dynamics.

For predicting the load distribution of spinal structures, we combined experimental and simulation methods. In experiments, we determined the overall stiffness for forward-flexing rotations between the lumbar vertebrae L5 and L4 of subjects lying in sideways position and being bent by a machine, without active muscle resistance. Forward dynamics simulations of this experiment using our detailed musculoskeletal multibody model of the human allowed for a structural resolution of the loads in the L4|5 region. The results indicated that stiffness values of particularly ligaments and passive muscle tissue put in from literature resources were too high. With now corrected values, our model has gained validity for future investigations on human movement dynamics and modelling applications like e.g. exoskeletons.