Wednesday - November 7, 2012

9:15 – 9:20 **Welcome**

Session I *Chairperson:* Gerhard Gompper

9:20 – 9:55 **M. Rief, *TU München, Germany***
Single Molecule Mechanics of Protein Folding and Interaction

9:55 – 10:30 **M. Wilmanns, *EMBL Hamburg, Germany***
The architecture of the muscle filament myomesin by hybrid structural biology

10:30 – 11:00 **Break**

Session II *Chairperson:* Gerhard Gompper

11:00 – 11:35 **H. Gohlke, *University of Düsseldorf, Germany***
Analyzing biomacromolecular flexibility: from fuzzy constraint networks to entropically dominated allostery

11:35 – 12:10 **F. Nedelec, *EMBL Heidelberg, Germany***
Design principles of yeast spindles

12:10 – 12:30 **S. Xiao, *Heidelberg Institute for Theoretical Studies, Germany***
Bottom-up multiscale modeling of silk fiber mechanics

12:30 – 14:15 **Lunch at Seecasino**

Session III *Chairperson:* Dieter Willbold

14:15 – 14:50 **S. Grill,** ***MPI Molecular Cell Biology and Genetics, Germany***
Mechanochemical pattern formation

14:50 – 15:25 **J. Song,** ***National University of Singapore, Singapore***
At the lowest and smallest: diverse salt effects on protein dynamics

15:25 – 16:00 **D. van der Spoel,** ***Uppsala University, Sweden***
Virus Swelling and Prediction of Genome Location in Virus Capsids

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16:00 – 16:30 **Break**

Session IV *Chairperson:* Dieter Willbold

16:30 – 17:05 **D. Hoffmann,** ***University Duisburg-Essen, Germany***
Tracking retroviral evolution in patients with a molecular model

17:05 – 17:25 **A. Steinmetz,** ***SANOFI R&D , Vitry-sur-Seine, France***
Protein engineering of hybrid proteins

17:25 – 18:00 **M. Sippl,** ***University of Salzburg, Austria***
Structural transitions in the evolution of protein complexes

18:30 – 21:00 **Poster Session and Dinner at Seecasino**

Thursday - November 8, 2012

Session V *Chairperson:* Gunnar Schröder

9:00 – 9:35 **S. Auer, *University of Leeds, UK***
Phase diagram and nucleation kinetics of proteins.

9:35 – 10:10 **S. Mohanty, *Forschungszentrum Jülich, Germany***
More than the sum of its parts: MC Simulations of 3 proteins, 60-100 residues and their fragments

10:10 – 10:30 **H. Müller, *Forschungszentrum Jülich, Germany***
Structural diversity of full-length prion protein, PrP – fibrils: Insight from solid-state NMR spectroscopy

10:30 – 11:00 **Break**

Session VI *Chairperson:* Gunnar Schröder

11:00 – 11:35 **K. Kruse, *Saarland University, Germany***
Homeostasis of the actin cortex

11:35 – 12:10 **C. Peter, *MPI Polymer Research, Germany***
Multiscale simulations of virus capsids

12:10 – 12:30 **B. Barz, *Forschungszentrum Jülich, Germany***
All-atom molecular dynamics study of Amyloid β – protein (1-40) and (1-42) oligomers relevant to Alzheimer's disease

12:30 – 14:15 **Lunch at Seecasino**

Session VII *Chairperson:* Birgit Strodel

14:15 – 14:50 **D. Fange, *Uppsala University, Sweden***
From micro to macro using spatially discrete stochastic reaction-diffusion models

14:50 – 15:25 **D. Head, *University of Leeds, UK***
Self-organisation in active gels: The role of confinement

15:25 – 16:00 **C. Sachse, *EMBL Heidelberg, Germany***
Cryo-EM structure determination of large macromolecular assemblies from proteinaceous aggregates and their cellular disposal machinery

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16:00 – 16:30 **Break**

Session VIII *Chairperson:* Birgit Strodel

16:30 – 17:05 **M. Bachmann, *University of Georgia, USA***
Microcanonical Statistical Analysis of Conformational Transitions in Molecular Systems

17:05 – 17:40 **P. Derreumaux, *Institut de Biologie Physico-Chimique, France***
Exploring non-amyloid monomers and amyloid aggregates with the OPEP coarse grained protein force field

17:40 – 18:15 **B. Meier, *ETH Zürich, Switzerland***
Amyloids by Solid-State NMR: Atomic-resolution Structure, Dynamics, and Characterization of the Pharmacophore

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18:30 – 21:00 **Dinner at Seecasino**

Friday - November 9, 2012

Session IX *Chairperson:* Gunnar Schröder

9:00 – 9:35 **O. Ernst, *University of Toronto, Canada***
Activation of the G protein coupled receptor Rhodopsin: From femtoseconds to seconds

9:35 – 10:10 **R. Böckmann, *University Erlangen-Nuernberg, Germany***
Membrane Processes Studied by Molecular Dynamics Simulations

10:10 – 10:45 **S. Khalid, *University of Southampton, UK***
Molecular Dynamics Simulations of the E.coli Cell Envelope: capturing the complexity

10:45 – 11:15 **Break**

Session X *Chairperson:* Gerhard Gompper

11:15 – 11:35 **J. Hub, *Georg-August University, Germany***
Unexpected effects of cholesterol on membrane permeability

11:35 – 12:10 **H. Wille, *University of Alberta, Canada***
The structure of the infectious prion protein: Challenges and experimental lines of attack

12:10 – 12:30 **J. Dreyer, *German Research School for Simulation Sciences, Germany***
Physical basis for efficient proton conduction in the Gramicidin A ion channel

12:30 – 13:05 **M. Tarek, *Henri Poincare University Nancy, France***
On the function and modulation of voltage gated cation channels. Insights from molecular dynamics simulations

13:05 – 13:15 **Good bye**

13:15 – 14:00 **Lunch**

TALKS

Single Molecule Mechanics of Protein Folding and Interaction

Matthias Rief

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The development of nano-mechanical tools like Atomic Force Microscopy and optical traps has made it possible to address individual biomolecules and study their response to mechanical forces. In my talk, I will show how single molecule mechanical methods can be used to study the folding and interaction of proteins. Examples include the folding of calmodulin as well as the interaction of the cytoskeletal protein filamin with transmembrane proteins.

The architecture of the muscle filament myomesin by hybrid structural biology

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Some of the largest proteins identified to date are found in muscle sarcomeres. Their principle function is to form a stable overall architecture to support contraction/relaxation by the actomyosin system under substantial mechanical forces. We are investigating two important filament systems in terms of structural/functional relationships: the first one is titin, a protein of almost 4 MDa in molecular weight and composed of about 300 single protein domains. The second one is myomesin, a protein of about 150 kDa, which elastically links titin and the thick filaments (myosin) in the central M-band of sarcomeres. At the molecular level, myomesin has a domain structure related to the one of titin and, hence, has been described as “mini titin”. Recently, we have unraveled the filament architecture of the complete C-terminal part of myomesin, involving domains My9-My10-My11-My12-My13. We have chosen a “divide-and-conquer” approach by combining electron microscopy (in collaboration with E. Morris, ICR, London), small angle X-ray scattering (in collaboration with D. Svergun, EMBL Hamburg) and high-resolution X-ray crystallography. Our data revealed a dimeric tail-to-tail filament structure that is folded into an irregular superhelical coil of almost identical domain modules, separated by highly exposed α-helical linkers [1]. Unfolding of these linkers, when tension is applied (in collaboration with M. Rief, Munich), can stretch this myomesin segment to about 2.5 times, returning to its original state when the tension is removed. To gain further insight into the myomesin molecular architecture and identify the borders of its elasticity we have solved an additional crystal structure of the myomesin domains My8-My11, in which My8 is folded as a fibronectin type III domain. In contrast to the helical linkers connecting the My9-My13 [1], the My8-My9 interface is tight and unrelated to the following ones, indicating that the established mechanism of myomesin filament elasticity is strictly confined to the C-terminal domain array My9-My13. We have generated an extended myomesin model My8-My13 with an overall length of about 38 nm, thus approaching the measured M4-M4’ distance of 44 nm, which characterizes the distance of the distal myomesin anchoring sites in the central M-band of muscle sarcomeres [2]. Our new data present an important step to dissect different functions of myomesin along its highly repetitive domain structure.

References

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Analyzing biomacromolecular flexibility: from fuzzy constraint networks to entropically dominated allostery

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Protein flexibility is important for a wide range of biological phenomena, such as enzymatic reaction and control, complex formation, macromolecular stability, and information flow. Equally important as flexibility per se are changes in the flexibility upon complex formation. Thus, analyzing flexibility of macromolecules without having to do expensive calculations is of great importance. Here, flexibility concepts grounded in rigidity theory are further developed by introducing fuzzy constraint networks and novel global and local indices to characterize biomolecular flexibility. The constraint counting is then applied to link protein thermostability and rigidity, to efficiently estimate changes in receptor vibrational entropy upon complex formation, and to investigate entropically dominated allostery.

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Design Principles of Yeast Spindles

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Bundled cytoskeletal arrays are a universal feature of eukaryotic cells. The anaphase B spindle from fission yeast serves as an excellent model system for studying cytoskeletal arrays under compressive forces as it can be perturbed genetically, is easily visualized using electron or light microscopy and has an organization that is highly stereotyped between different cells. We have used calculations based on electron tomographic reconstructions of the spindle to show that the length, number and axial organization of microtubules within the fission yeast spindle is optimized to achieve maximal compressive strength. A combination of simulations and live cell imaging are used to show that changes in the dynamics of microtubule cross-linkers leads to a transition in the axial organization of the spindle from a disordered phase to highly ordered crystalline state that underlies the structural integrity of the spindle. We further show that both antagonism and cooperativity between microtubule cross-linkers is used to provide positional information that directs microtubule growth over extremely short length scales, and that this mechanism is likely to be responsible for the precise regulation of spindle morphology in fission yeast.

Bottom-up multiscale modeling of silk fiber mechanics

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Silk is an intriguing protein-based material that combines elasticity and strength to an extent not yet reached by any synthetic material today. Silk consists of highly-ordered beta-sheet crystals and unstructured amorphous peptides that both contribute to the outstanding fiber mechanical properties. However, how the organization of these two components affects silk fiber mechanics has remained to be understood. Here, we combine large scale molecular dynamics simulations and finite element methods to quantify the relationship between a silk fiber's structural components and its mechanics properties in a bottom-up approach. Namely, elastic and rupture parameters of silk composite units as extracted from all-atom molecular simulations serve as element properties in finite element analysis [1,2]. By doing so, we can derive macroscopic fiber mechanics from the nano-structure, in quantitative agreement with experimental results. One of our most striking predictions is that a serial arrangement of silk crystalline units in the fiber, as commonly observed in form of lamellae for other block copolymers, outperforms a random distribution of crystals, in sharp contrast to the current view of silk fiber organization [3]. We also show why the typical beta-strand length of eight residues in silk crystals is mechanically optimal [2]. Finally, a smaller cross-sectional area of silk crystals (~ 1nm2) in fibers provides a better reinforcement of the amorphous phase than larger ones. [4] We expect our straightforward multiscale approach to serve as a guideline for the design of silk-like synthetic materials.[5]

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Mechanochemical pattern formation

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I will present recent advances in our understanding of the generic forms of coupling between mechanics and biochemistry in morphogenesis, and I will discuss the physical mechanisms by which the actomyosin cortex drives large-scale morphogenetic events. I will focus on two emergent physical activities of the actomyosin cytoskeleton, an active contractile tension and an active torque, both of which can serve to drive flows and large-scale chiral rotations of the actomyosin cytoskeleton. Discussing two biological examples, polarization of the C. elegans zygote and epiboly during zebrafish gastrulation, I will illustrate how active tension drive flows, how molecular constituents of the cortex affect flows, and how morphogenetic patterns can be formed by coupling regulatory biochemistry to active cortical mechanics. A particular focus will be the investigation of how active chiral torques drive chiral flow, and the resulting functions of such chiral activities of the actomyosin cytoskeleton for left-right symmetry breaking in C. elegans development.

At the lowest and smallest: diverse salt effects on protein dynamics

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We discovered that "insoluble proteins" could in fact be solubilized in pure water, thus allowing insights into structures and dynamics of insoluble proteins [1-3]. Very unexpectedly, we recently demonstrated that the transmembrane peptide of influenza A M2 channel, one of the most hydrophobic sequences in nature, was also soluble in unsalted water without lipid molecules to form a highly-helical conformation. These findings strongly imply that salt ions may have previously-unrecognized effects on proteins.

Indeed, by use of NMR spectroscopy, we revealed that in contrast to the common belief, 8 anions did have saturable bindings to an intrinsically-unstructured [4] and a well-fold proteins, with variable binding affinity and specificity. Analysis of the results deciphers that the properties of both anions and proteins mediate the binding. Currently, we initiated a systematic mapping of the effects of different salts on protein dynamics. Very surprisingly, salts have extremely-diverse effects on protein dynamics: some have only minor effects, some are able to enhance while other to suppress protein dynamics. Their implication in evolution and role in mediating protein functions will be explored.

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Virus Swelling and Prediction of Genome Location in Virus Capsids

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Dissolution of many plant viruses is thought to start with swelling of the capsid caused by calcium removal following infection, but no high-resolution structures of swollen capsids exist. Here we have used microsecond all-atom molecular simulations to describe the dynamics of the capsid of satellite tobacco necrosis virus with and without the 92 structural calcium ions [1]. The capsid expanded 2.5% upon removal of the calcium, in good agreement with experimental estimates. The water permeability of the native capsid was similar to that of a phospholipid membrane, but the permeability increased 10-fold after removing the calcium, predominantly between the 2-fold and 3-fold related subunits. These findings suggest that the dissociation of the capsid is initiated at the 3-fold axis.

The complete structure of the genomic material inside a virus capsid remains elusive. Knowledge of the principles of genome packaging might be exploited for both anti-viral therapy and technological applications, therefore we have performed an investigation of the electrostatic properties of the inside of the capsids of two small plant viruses, tobacco mosaic satellite virus (TMSV) and tobacco necrosis satellite virus (TNSV) [2]. For both TNSV and TMSV a hot-spot for RNA encapsulation is predicted close to the five-fold symmetry axis. The Chloride Screening procedure is compared to calculations of ionic distributions using the non-linear Poisson-Boltzmann equation calculations that predict a somewhat smaller volume of ions close to the capsid, than the MD simulations, which include protein motions and an atomistic description of solvent and ions. We conclude that the Chloride Screening method allows for detailed predictions of regions inside the three-dimensional capsid that are suitable for RNA binding from an energetic point of view.

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2. Daniel S.D. Larsson and David van der Spoel: *Screening for the Location of RNA using the Chloride Ion Distribution in Simulations of Virus Capsids* J. Chem. Theor. Comput. **8** pp. 2474-2483 (**2012**)

Protein design elucidates the relationship between structure, function and stability of a metabolic enzyme

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The anthranilate phosphoribosyl transferase from the hyperthermophilic archaeon *Sulfolobus solfataricus* (sAnPRT), which catalyzes the third step in tryptophan biosynthesis, is a thermostable homodimer with low enzymatic activity at room temperature. We have generated a monomerized version of sAnPRT by replacing two apolar residues at the dimer interface with negatively charged ones (I36E, M47D) [1]. Moreover, we have increased the catalytic activity of sAnPRT by a combination of random mutagenesis and library selection in *Escherichia coli* at 37°C. The two identified beneficial mutations D83G and F149S eliminate the Mg2+-inhibition of the wild-type enzyme and increase its turnover number by the acceleration of product release [2]. We have then combined the two mutations leading to the monomerisation with the two mutations leading the activation of sAnPRT. The resulting "activated monomer" sAnPRT-I36E-M47D+D83G-F149S, is much more labile than wild-type sAnPRT. It was stabilized by a combination of random mutagenesis and metabolic library selection at 79°C using the extremely thermophilic bacterium *Thermus thermophilus* as host. This approach led to the identification of 5 mutatiosns which increased the thermal stability of sAnPRT-I36E-M47D+D83G-F149S individually by 1 °C to 8 °C, and in combination by 13 °C. The beneficial exchanges were located in different parts of the protein structure, but none of them led to the "re-dimerization" of the enzyme. We observed a negative correlation between thermal stability and catalytic activity of the mutants, which suggests that conformational flexibility is required for catalysis by sAnPRT [3].

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Protein engineering of hybrid proteins

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Protein engineering presents a particular challenge when multimeric proteins are to be hybridized such that precise conservation of domain interfaces is ascertained in order to maintain independently the function and activity of the parent proteins in the hybrid protein. The generation of such a generic multifunctional hybrid protein format by rational design will be presented.

A protein dimer was used to create insertions domains into another dimeric protein which were no simple N- or C-terminal extensions. The hybrid proteins retained the functional properties of the original proteins that were fused. The design of the hybrid proteins by molecular modelling as well as experimental data on activity, yield, and stability will be presented.

A patent application covering the generation, characterization, and use of these hybrid proteins will be published by end of September 2012. Thus, on 1st of October we can provide a more detailed abstract.

Tracking retroviral evolution in patients with a molecular model

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Human Immunodeficiency Virus-1 (HIV-1) enters host cells by transiently binding to two membrane proteins on the cell surface, namely CD4 as receptor, and a G-protein coupled receptor as co-receptor. In the early stages of a retroviral infection, the co-receptor is usually CCR5 ("R5"), while in the late stages the virus often switches to CXCR4 ("X4"). It is known that a variable protein loop (V3) of the retroviral envelope protein gp120 is the main determinant of co-receptor tropism. Importantly, only R5 can be blocked by drugs such as Maraviroc that in this way prevent viral entry. A fast test that, based on the V3 sequence, accurately predicts the co-receptor tropism would help clinicians to decide whether a patient should be treated with these entry inhibitors or not. We have developed a computational method ("T-CUP") that does exactly this, based on a physico-chemical description of V3 [1]. The model takes into account the electrostatic potential around molecular models of V3 and the physico-chemical sequence composition of V3. Given a set of pairs of V3-sequences and experimentally determined co-receptor tropism, we derive a rather accurate statistical model that predicts co-receptor tropism from V3 sequence. We use this model to study retroviral evolution in four patients failing therapy with Maraviroc [2]. The input data comprises V3 sequences of the retroviral quasi-species obtained from deep sequencing of patient samples at several time points, and also experimentally determined co-receptor tropisms for the same patients [3]. We find that T-CUP predictions are in good agreement with experiment and allow a tracking of retroviral evolution between R5 and X4 tropic virus at the molecular level.

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Structural transitions in the evolution of protein complexes

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With the massive increase in the number of solved protein structures we begin to see more clearly how new protein folds arise from old templates. In general the native state of an operative protein is a molecular complex of strongly interacting polypeptide chains. The complex acts and evolves as an entity. We briefly review the specific techniques required for the investigation of the structural evolution of protein complexes. Then we focus on recurring transitions in the structures of various oligomeric enzymes that drive the creation of new protein folds while conserving fundamental functional traits. The common principles observed include conservation of symmetry by asymmetric sequences, truncation of molecular complexes by gene elongation, and irreversible structural changes that define the direction of evolution from progenitors to descendant proteins.

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Phase diagram and nucleation kinetics of proteins.

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In the first part of my talk will present our recent work on the calculation of a peptide phase diagram and its importance in the kinetics of peptide aggregation [1,2,3]. In the second half I will present our recent work on the application of nucleation theory to describe amyloid fibril formation [4,5,6]

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More than the sum of its parts:
MC Simulations of 3 proteins (60-100 residues) and their fragments

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Using parallel tempering Monte Carlo simulations, I will compare the folding behaviour of 3 small proteins (60--100 residues) with sub-chains corresponding to their secondary structure elements. Each of the 3 proteins fold to their native states in unbiased simulations starting from random initial conformations. When simulated separately as excised peptides, the above mentioned sub-chains often behave differently compared to their roles in the whole protein. The simulations are performed using an all-atom model with an implicit solvent force field. The force field is known to describe the folding behaviour of at least 25 small peptides and proteins with α-helical as well as β-sheet secondary structures, using the same set of parameters.

Structural diversity of full-length prion protein (PrP) – fibrils: Insight from solid-state NMR spectroscopy

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In contrast to other neurodegenerative diseases, transmissible spongiform encephalopathies may be acquired by transmission of *pro*teinaceous *in*fectious particles (prions) which are formed by β-sheet-rich amyloid fibrils. Due to the failure of biophysical structure analysis on insoluble, non-crystalline, and heterogeneous protein fibrils, not amenable to X-ray crystallography and liquid-state NMR, the detailed structural architecture of prions is unknown. Because all model concepts available to date are based on low resolution data, it is a current matter of intense debate in which prion protein (PrP) sequence segment the β-sheet core is situated, whether prions are β-helices1 or β-sandwiches2, and how the presence of infectious as well as non-infectious PrP fibrils can be explained structurally. As demonstrated recently3, solid-state NMR proved to be valuable for structural characterisation of PrP fibrils.

In our contribution, we will report on our experimental progress in using high resolution solid-state NMR to structurally characterize amyloid fibrils of full-length ovine recombinant (rec) PrP comprising residues 25-233. Our first focus will be on explaining the generation of amyloid fibrils formed spontaneously as well as by seeding with pre-formed recPrP fibrils or infectious sheep brain-derived prions in NMR-sufficient yields. Based on biophysical characterization we will demonstrate that our *in vitro*-derived recPrP fibrils closely emulate prions in living organisms. Thereafter, we would like to present our solid-state NMR data about resonance assignment and secondary structure of recPrP fibrils as well as comparing fingerprint spectra of recPrP fibrils formed spontaneously or by seeding. We will demonstrate that our recPrP fibril preparations are characterized by enough homogeneity to draw first structural conclusions such as where the β-sheet core as well as a remaining a-helical region appears to be situated and which influence seeding with highly infectious prions seems to exert.

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Homeostasis of the actin cortex

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Underneath the plasma membrane of animal cells, there is a dense network of actin filaments and associated proteins. In spite of permanent filament turnover, the cortex has a well-defined thickness of a few hundred nano-meters. The molecular processes underlying cortical actin turnover are largely unknown and it is poorly understood, how a well-defined cortex is maintained in presence of highly dynamic filaments. We will first discuss the length dynamic of actin filaments. In steady state, the corresponding distribution might be exponential or unimodal. We then present results of FRAP (Fluorescence Recovery After Photobleaching) experiments on the actin cortex of living cells that suggest the existence of two populations of actin filaments with vastly different turnover times. Stochastic simulations of the dynamics of cortical actin filaments in presence of actin nucleating proteins support our interpretation of the FRAP data. If time permits, we will also present a mechanism that leads to a well-defined cortex with a roughly constant actin density extending from the membrane up to a point, where it sharply drops to zero.

Multiscale simulations of virus capsids

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Large multiprotein complexes such as the capsids of most viruses are one of the challenges for modern computer simulation methods. While chemically accurate atomistic models are unfortunately still too limited in terms of the accessible time- and length scales, lower resolution (coarse grained, CG) models often lack local chemical specificity that has been lost upon coarse graining. Here, combined, multiresolution approaches can help to overcome the limitations of the individiual simulation scales.

I will show two examples for dual scale approaches to study different aspects regarding the protein capsid of CCMV (Cowpea Chlorotic Mottle Virus).

In the first example, a suitable CG model is used in combination with clustering algorithms and free energy reweighting methods to explore the conformational equilibrium of unstructured regions of the CCMV capsid proteins for which experimental data is lacking or limited. In particular, we have focused on the folding process of converging strands at the protein-protein interfaces, more precisely at the 3-fold (hexamer) and 5-fold (pentamer) symmetry points of the capsid. The CG simulations reproduce the experimentally observed beta-barrel structure for the hexamer while the pentamer geometry is unable to stabilize a beta-barrel conformation. Here, a large variety of states are sampled instead, again in accordance with the experimental results which do not indicate a well defined structure for the pentameric interface. From this CG ensemble of various folded structures, atomistic coordinates can be generated via backmapping. The latter remain relatively stable which is indicative of plausible CG conformations and slow kinetics on the atomistic level.

In the second example, a method is introduced to refine the parameters of the supportive elastic network which is typically used in the framework of the MARTINI CG forcefield from detailed atomistic simulations of CCMV capsid protein dimers in aqueous solution. The resulting bottom-up model correctly predicts structural and elastic properties of bigger aggregates (intermediates in the assembly process) and mechanical properties of an entire virus capsid such as the force response of the capsid under external stress – which is in excellent agreement with data from Atomic Force Microscopy – not just for the linear regime of small stresses, but all the way to structural failure, where hysteresis sets in.

All-atom molecular dynamics study of Amyloid β - protein (1-40) and (1-42) oligomers relevant to Alzheimer's disease

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Alzheimer disease (AD) is the leading cause of dementia among elderly. Amyloid β - protein (Aβ) plays a central role in the pathology of the disease. Small differences (~5%) in the primary structure between two Aβ alloforms, Aβ(1-40) and Aβ(1-42), were shown to lead to their distinct assembly and toxicity properties. The structure of low molecular weight soluble Aβ(1-40) and Aβ(1-42) oligomers, which are believed to be the proximate neurotoxins in AD, was previously examined by discrete molecular dynamics (DMD) combined with a coarse-grained peptide model in implicit solvent [1]. However, the effect of explicit solvent or the detailed representation of amino acids was not taken into account. Here we examine key differences between Aβ(1-40) and Aβ(1-42) monomers and dimers derived from coarse grained DMD conformations, using all-atom molecular dynamics simulations, with implications for the different cellular toxicities of the two alloforms. Differences in free energy profiles and salt bridge propensities between the two allorforms, observed in the context of monomer to dimer transition, indicate Aβ(1-42) as more structurally disordered than Aβ(1-40) [2]. Future directions regarding the interaction of Aβ oligomers with coarse-grained DMD lipid bilayers are also discussed.

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From micro to macro using spatially discrete stochastic reaction-diffusion models

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Both the spatial and stochastic aspects of chemical reactions may be important when making models of intracellular processes. A commonly used method for stochastic reaction-diffusion modelling is the spatially discrete description based on the reaction-diffusion master equation (RDME). The RDME has, however, been shown to give diverging results with increasing spatial resolution. The underlying reason is that RDME commonly uses macroscopic rate constants, which include time for diffusional transport between reactions. However, for bi-molecular reactions, in a high spatial resolution RDME, the diffusional transport is modelled explicitly and should therefore not be included in the rate constant.

Recently we have sought to resolve this issue by deriving rate constants based on a microscopic hard-sphere model. Here the amount of diffusional mixing within each lattice point depends on the spatial resolution of the simulations, and thus the reaction rate constants become scale dependent in a microscopic consistent manner. By implementing these scale dependent reaction rate constants into the simulation software MesoRD, we have now made it easy to perform physically consistent, spatially discrete, stochastic reaction diffusion simulations down to a spatial resolution of the size of molecules.

Using simple examples we have also shown how strikingly important it is to choose a correct modelling-framework for the problem at hand. For example, spatial correlations between reactive substrates can change the overall properties of the system, especially for molecules in two dimensional geometries such as cell membranes; an effect that can only be captured in a stochastic reaction diffusion model.

Self-organisation in active gels: The role of confinement

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Non-equilibrium systems can spontaneously produce complex patterns in the absence of detailed control. Such self-organisation represents a powerful tool to be exploited by natural selection, as evident in the division of fission yeast cells, where the spindle of protein fibres necessary for cell division forms even without organising centres [1]. This raises fundamental questions as to what self-organised structures can arise in fibre-motor protein mixtures or '*active gels'*, and what factors select between them. Mathematical modelling complements experiments by providing bottom-up representations of systems of reduced complexity, aiding the identification of the minimal mechanisms required for the observed phenomena. Here I present results of numerical simulations of a model for active gels, with the goal of identifying and quantifying the self-organised structures that emerge. The effect of confinement proves to be crucial. With confining walls, static structures spontaneously form that are similar to those observed in physical systems, including asters [2] and spindles [3]. The exotic dynamic structure with coherent fibre rotation known as a *vortex* was also observed, but found to be transient, with a lifespan that anti-correlates with the degree of confinement. Replacing the confining walls with periodic boundaries presents a very different picture, with no ordered pattern formation at the densities of interest [4], but with quantitative characteristics similar to hydrodynamic equations for active media, including anomalous (super-)diffusion and large amplitude long-wavelength density fluctuations. Relaxing the excluded volume interaction by allowing limited fibre overlap admits polarised layers of laterally-bound fibres in one region of parameter space, but does not alter the general picture. This study highlights the power of mathematical modelling in elucidating naturally-occurring phenomena.

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Cryo-EM structure determination of large macromolecular assemblies from proteinaceous aggregates and their cellular disposal machinery

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Electron cryo-microscopy (cryo-EM) has become a versatile tool to visualize large macromolecular structures and multi-protein complexes. In this lecture, I will give an overview of the cryo-EM technique and on illustrate the potential for studying the structure of large ordered assemblies. Small amounts of material are sufficient to obtain snapshots of 'single particles' in the electron cryo-microscope and subsequent computer-aided image processing enables three-dimensional (3D) image reconstruction. Recently, numerous well-ordered high-molecular-weight structures have been elucidated at near-atomic resolution from cryo-EM images. For example, we worked on improving image processing methods to increase the resolution of structures with helical symmetry. The procedures were tested with images of Tobacco Mosaic Virus (TMV), and we were able to obtain a structure of the helical virus at better than 5 Å resolution (Sachse et al., 2007). Other examples of large helical assemblies are amyloid fibrils that can be formed in vitro and under pathological conditions, such as Creutzfeld-Jakob, Parkinson's and Alzheimer's disease. We analyzed the 3D structure of a mature amyloid-β (Aβ) fibril at subnanometer resolution using single-particle electron cryo-EM optimized for helical specimens (Sachse et al., 2008). The cell disposes of extracellular amyloid fibrils by internalization via endocytosis that trafficks these otherwise harmful protein deposits to their degradation site in the lysosome. Dynamin, a GTPase, is an essential component of vesicle formation in receptor-mediated endocytosis acting at the plasma membrane. Using single-particle based helical reconstruction we determined the 3D structure of a bacterial dynamin assembled on lipid tubes at 12 Å resolution (Low et al., 2009). The structure allowed the building of a reliable quasi-atomic model and provides a mechanism for assembly and membrane curving. In both cases, the structure determination process was greatly helped by expanding existing image processing algorithms. Thus, they are examples of an overall effort to enhance the cryo-EM method to make it a routine tool for structure elucidation of macromolecular assemblies.

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Microcanonical Statistical Analysis of Conformational Transitions in Molecular Systems

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Folding and aggregation of molecules, as well as the adsorption of soft organic matter to solid inorganic substrates belong to the most interesting challenges in studies of structure formation and function of complex macromolecules. The substantially grown interest in the understanding of basic physical mechanisms underlying these processes is caused by their impact in a broad field that ranges from the molecular origin of the loss of biological functionality as, for example, in Alzheimer's disease, to the development of nanotechnological applications such as biosensors. Most of these systems are necessarily of finite size, but molecular structure formation exhibits cooperative effects that resemble similar processes in thermodynamic phase transitions. Inspired by the fact that the density of states, and with it the microcanonical entropy, is the natural result of any generalized-ensemble Monte Carlo simulation, we have introduced a method that allows for a systematic and unique identification and Ehrenfest-like classification of structural transitions in small systems by means of microcanonical analysis [1]. This computational approach to phase transitions, which is hardly accessible in theoretical studies, is particularly useful for the analysis of cooperative behavior in folding [2], aggregation [3], and adsorption processes [4] of polymers and proteins. In this talk, I am going to discuss background and application of this method.

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Exploring non-amyloid monomers and amyloid aggregates with the OPEP coarse grained protein force field

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Biological systems are complex, yet elegant, machines fine-tuned by evolution to properly fulfill a variety of tasks in the crowded cellular environment. They are very challenging numerically due to their dimension and number of degrees of freedom. With aging, some proteins misfold and form harmful amyloid aggregates associated with multiple neurodegenerative diseases, and in particular Alzheimer's, which challenge our society today. Here, I present the coarse-grained OPEP force field [1] and what we can learn from OPEP simulations to get insights into the structures of monomeric peptides [2,3] and the self-assembly of amyloid peptides [4,5].

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Amyloids by Solid-State NMR: Atomic-resolution Structure, Dynamics, and Characterization of the Pharmacophore

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Amyloids are β-sheet-rich proteinaceous aggregates that are a pathological hallmark of a number of important human diseases. However, atomic-resolution structures are still very rare. Solid-state NMR is starting to fill in this gap. For the amyloid prion form of the fungal HET-s prion an atomic resolution structure has been obtained, while of other amyloids, including the a-synuclein (linked to Parkinson's disease) and a-beta (linked to Alzheimer's) there are still problems to be solved. We will review the state of the field and give special emphasis to the phenomenon of polymorphism and to the interaction with dyes, markers and drugs in an attempt to characterize the pharmacophore of HET-s(218-289) and other amyloid structures.

Full-length prions and other proteins of biological interest are often of large size (in terms of solid-state NMR). Spectroscopic issues and sample preparation techniques for such systems will be discussed.

Activation of the G protein coupled receptor Rhodopsin: From femtoseconds to seconds

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Rhodopsin is a highly specialized G protein-coupled receptor (GPCR) employed in the visual process [1]. Located in the outer segment of photoreceptor cells, rhodopsin comprises the GPCR apoprotein opsin and the photoreactive chromophoric ligand 11-*cis*-retinal. Rhodopsin is the only GPCR which contains its ligand covalently bound. In the rhodopsin ground state, the inverse agonist 11-*cis*-retinal is tethered in a central ligand binding pocket by a Schiff base to Lys-296, rendering the GPCR virtually inactive. A single photon is sufficient to trigger ultrafast *cis* to *trans* isomerization of retinal yielding the photoproduct photorhodopsin within hundreds of femtoseconds. Subsequently and orders of magnitude slower, the protein adjusts to the new retinal configuration and conformational changes in the receptor lead within milliseconds to the active metarhodopsin II state. The light-induced gain in activity towards the G protein is the largest known for the huge GPCR family. The crystal structures of inactive and active rhodopsin conformations as well as early photointermediates give an idea about the switch-like behavior of rhodopsin and global protein changes associated with activation of GPCRs [1]. Further insight comes from the structure of active metarhodopsin II solved by soaking crystals of the active GPCR conformation with the all-*trans*-retinal agonist [2]. I will discuss the activation mechanism of rhodopsin starting with the primary retinal isomerization event and discuss studies on uptake and release of retinal from its binding site yielding an active receptor [3].

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Membrane Processes Studied by Molecular Dynamics Simulations

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Interactions at biological membranes such as binding to, transport through and along, or aggregation at membrane surfaces are intimately coupled to the (phase) structure and the dynamics of the membrane. While knowledge on the composition of different organelle membranes is increasing, the interplay between (membrane) proteins and and their environment is largely elusive. This is contrasted by growing evidence for a crucial role of the membrane architecture e.g. for the function of ion channels, the aggregation of proteins on or in membranes, or the action of antibiotic peptides. Also, phospholipid membranes not only adapt a passive function deliminating the cell or organelle interior from the exterior maintaining ion concentration or nutrient gradients, but may act themselves as lipid ion channels close to their phase transition temperature.

Here, we'll discuss different membrane processes studied in atomistic molecular dynamics simulations, ranging from the interaction of drugs with lipid bilayers and the role of membranes in anesthesia, to the function of tryptophanes in peptides involved in membrane fusion, and membrane phase transitions in external fields.

Molecular Dynamics Simulations of the E.coli Cell Envelope: capturing the complexity

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Gram-negative bacteria such as *E.coli* are typically regarded as "simple" model organisms, yet their cell envelopes are surprisingly complex. Recent experimental and theoretical studies have revealed that contrary to the traditional view of the cell membrane as a passive bystander in membrane protein function, it plays a key role in protein folding, assembly, and function. To study the influence of the bacterial membrane on the dynamics of embedded outer membrane proteins (OMPs), we have created a virtual *E.coli* outer membrane. Our atomistic-level model incorporates the heterogeneity of the inner leaflet lipids, the biochemical complexity of the lipopolysaccharide outer leaflet and also includes the peptidoglycan matrix within the periplasmic space. We have performed a series of simulations exploring how these various membrane components influence the structure and dynamics, and therefore function of the proteins that reside within them.

Coarse-grain models that enable simulation of larger systems on longer timescale are also being used to explore the lateral mobility and aggregation of membrane proteins within the *E.coli* outer membrane.

Our approach of running extended simulations of complex systems i.e. incorporating the molecular complexities at both atomistic and coarse-grained levels of details, and performing simulations at of hundreds of nanoseconds to microseconds, is enabling us to gain new insights into the specific interactions with the outer membrane that play a key role in the correct functioning of OMPs.

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Unexpected effects of cholesterol on membrane permeability

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Understanding and predicting the permeability of lipid membranes, based on the membrane composition and the properties of the permeating solute, is one of the central goals in membrane biology. One important component of lipid membranes is cholesterol, that is abundant in animal cells in concentrations ranging from 20 to 50 mol %. Here we apply systematic molecular dynamics simulations to study the partitioning of solutes between water and cholesterol-containing membranes. We derive potentials of mean force for six different solutes permeating across 20 different lipid membranes containing one out of four types of phospholipids plus a cholesterol content varying from 0 to 50 mol %.

Surprisingly, cholesterol decreases solute partitioning into the lipid tail region of the membranes much more strongly than expected from experiments on macroscopic membranes, suggesting that a laterally inhomogeneous cholesterol concentration and permeability may be required to explain experimental findings. The simulations indicate that the cost of breaking van der Waals interactions between the lipid tails of cholesterol-containing membranes account for the reduced partitioning.

In addition, we find that the lipid head groups constitute the main barrier against permeation of bulky apolar solutes, and that cholesterol is able to reduce this barrier and thereby increase the permeability. We present new experimental data, confirming these computational predictions.

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The structure of the infectious prion protein: Challenges and experimental lines of attack

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To date, only limited information is available about the structure of the infectious prion protein, PrPSc, and its proteolytically truncated homolog, PrP 27-30. In absence of an experimental structure, molecular modeling has been used extensively to predict the structure of PrPSc, but different modeling approaches have produced a large number of alternative models. Moreover, little consensus exists on the interpretation of the available experimental data regarding the structure of PrPSc [1].

X-ray fiber diffraction on samples from eight natural prion isolates, six synthetic prion strains, and one inherited human prion disease model indicated the presence of a compact, four-stranded ß-sheet core, possibly in a ß-solenoid or ß-helical configuration. The diffraction patterns from all prion strains exhibited the same repeating unit of 19.2 Å per molecule, represented by a series of characteristic, meridional diffraction signals at 4.8, 6.4, and 9.6 Å. The underlying structure was previously identified as a four-stranded ß-sheet core in a cross-ß arrangement [2]. Interestingly, these prion strains vary substantially in their biological properties, e.g. incubation times (from ~75 to ~600 days) and proteinase K resistance levels (resistant, intermediate, and fully sensitive), but still share a common core structure. Negative-stain electron microscopy was used to determine the diameters of individual amyloid fibrils from several of these prion strains. The average diameters fell into a narrow range of 48 to 60 Å. The relatively homogeneous fibril diameters confirm the compact nature of the ß-sheet structure and exclude more extended ß-sheet folds.

In summary, combining data obtained by X-ray fiber diffraction and electron microscopy on natural, synthetic, and mutant prion protein strains allowed us to determine a feature that may be common to most, if not all, mammalian prion strains: a compact, four-stranded ß-sheet core in a cross-ß configuration.

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Physical basis for efficient proton conduction in the Gramicidin A ion channel

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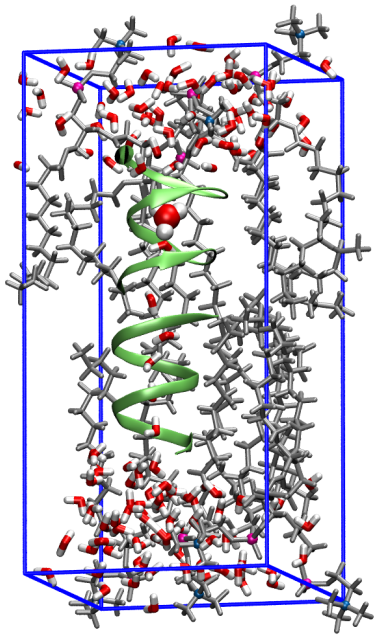

Biological ion channels are pore-forming transmembrane proteins which selectively regulate transport of ions in and out of every living cell. Dysfunction of ion channels are at the basis of several diseases called channelopathies, including, for instance, cystic fibrosis, epileptic seizure, diabetes and migraine [1]. The strikingly efficient proton conduction in the gramicidin A (gA) ion channel [2] – the measured rate is up to 2×10^9 H^+ s^{-1} [3] – has significant implication for its antibiotic function. Here we investigate proton permeation through gA embedded in a solvated membrane environment by *ab initio* metadynamics simulations [4, 5]. The system comprises almost 2,000 atoms. Our calculations, which are consistent with the available experimental data, indicate a dominant role for the membrane dipole potential and electronic polarization underlying the free energy barrier, which is located at the channel entrance. This explains why the rate of proton conduction increases dramatically under a membrane voltage, as observed experimentally. This project of simulating a fundamental biological system in laboratory-feasible conditions fully from first-principles is made possible by access to supercomputing facilities and support through the PRACE (Partnership for Advanced Computing in Europe) 1st regular call.

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On the function and modulation of voltage gated cation channels. Insights from molecular dynamics simulations

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Voltage-gated cation channels (VGCCs) are transmembrane (TM) proteins ubiquitous to excitable cells of superior organisms. Their role is to transport ions across the cell membrane in a manner that depends on its polarization state. Being implicated in a wide variety of biological functions such as the transmission of the nervous impulse, mutations in genes encoding them may give rise to inherited genetic diseases such as long and short QT syndrome of the heart, epilepsies, periodic paralyses, deafness, diabetes, etc.

The physiological role of VGCCs has made them objects of interest since their discovery in the 1950s and understanding their function at a molecular level has benefited greatly from results from a large number of experimental techniques, especially structural biology, electrophysiology, and pharmacology, as well as spectroscopies of various kinds. The resolution in 2005 of the X-ray crystal structure of a mammalian member of this family had in particular a remarkable impact: It enabled one to start envisioning the molecular level operation mechanism of these channels. In particular, it allowed computational approaches such as Molecular Dynamics simulations to step in and contribute to answering questions concerning their functional mechanism.

In this contribution we will present our perspective and a summary of the exquisite results obtained so far using an MD approach during the last few years. We address in particular key questions that pertain to (1) the function and (2) the modulation of the VGCC's arising from mutations involved in certain genetic diseases or from the membrane lipid alteration.

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POSTERS

History-feedback Molecular Dynamics Simulations

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With a known three dimensional structure, experimental vibrational spectra of proteins can be interpreted with the help of Normal Mode Analysis (NMA). In general normal modes are computed at the energy minimum using harmonic approximation and compared to a spectrum in which the molecule is neither in the energy minimum nor in the limit of harmonic approximation. As a result NMA is not able to explain the coupling between the modes due to the anharmonicity of the potential. As an alternative to NMA we propose to use periodicity restraints during a molecular dynamics simulation which reinforce motions that occur with a specific period. These restraints couple the trajectory of a molecule to its own history. This allows to identify all (also non-linear) periodic motions that are in agreement with a given period and yields generalized vibrational modes. We implemented this type of feedback in GROMACS(4.5) and tested our method with a single amino-acid glycine and two small proteins Trp-cage (1L2Y) and chicken-villin (1QQV). If the given feedback matches the time scale of a generalized vibrational mode, the amplitude of the motion as well as the energy of the system increases and the analysis of such motions often clearly shows the presence of more than one normal mode in it. This knowledge about the time scales and the corresponding composition of normal modes would be helpful to design a composite pulse to excite a specific generalized vibrational mode.

Scoring multipole electrostatics in atomistic protein-ligand binding simulations

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The incorporation of fluorine in pharmaceutical products has enjoyed growing interests due to its ability to improve protein-ligand binding, metabolic stability, and modulate physicochemical properties, e.g., lipophilicity, basicity. While the effects of fluorine are relatively well understood [1], an accurate determination of the energetics of specific protein-ligand interactions still call for quantitative studies. In this regard, a computational approach provides both atomistic resolution and a decomposition of the interactions at hand.

In this work, we study the effects of degrees and patterns of fluorination on the binding affinity of various inhibitors with carbonic anhydrase II. The method is validated by comparing free-energy calculations with experimentally determined binding affinities—similar to a previous study of non-fluorinated ligands [2].

While the computational power at hand limits these simulations to a point-charge (PC) representation of the electrostatics, we evaluate the effects of multipole (MTP) interactions on the ligand by scoring PC-sampled conformations with a MTP energy function. The protein-ligand free energies are re-evaluated with the more detailed force field to assess the increased accuracy with respect to the experimental values. A careful and consistent parametrization of the two force fields yields encouraging results. Gaining insight from a MTP representation holds many promises to provide a detailed decomposition of the multipolar interactions that drive protein-ligand binding.

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Domain structure and dynamics of proteins observed by neutron scattering methods

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The biological function of enzymes is often related to large-scale domain motions, which are sometimes induced by the binding of a substrate. These configurational changes are observed by methods like x-ray crystallography giving a static image of the protein structure and suppressing large-scale domain motions. Configurational changes can be related to the substrate binding or the crystal packing, which favors specific configurations. The structure of a protein in solution can deviate from the crystal structure, but also allows fluctuations between different configurations. Are these fluctuations important for protein function?

We present here examples of large-scale structure determination by SANS and SAX combined with Neutron Spinecho Spectroscopy to determine the dynamics of the proteins on nanometer length scale and a timescale up to several hundred nanoseconds.

Wrapping of ellipsoidal particles by membranes

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Membrane budding initiates intracellular vesicle transport and has been studied for a variety of soft matter systems. Despite the importance of membrane budding and wrapping of particles (e. g. viruses, nano particles), several aspects of this process are not yet well understood. In general, the energy cost for membrane deformation competes with the adhesion energy that is gained where the particle touches the membrane. Bud formation can be induced by a spontaneous membrane curvature and by line tension at a domain boundary[1,2], as well as by conical inclusions[3,4] such as partially attached viruses. We investigate wrapping of nano particles using the Helfrich model for lipid-bilayer membranes. With our theoretical calculations for a mathematical surface with appropriate curvature-elastic constants, we calculate deformation and adhesion energies to predict membrane budding. We investigate the role of particle shape and size and of different surface energies in the wrapping process.

By using simple analytical models, one can investigate the role of adhesion, surface tension and preferred curvature for the membranes to obtain wrapping diagrams to find parameter regimes for unbound, partially-wrapped, and fully-wrapped particles. The partially-wrapped state can be a metastable or a stable minimum. For cylindrically-symmetric particles one may use such approximate models or may even solve the shape equations to obtain exact solutions for the membrane deformation profiles. For non-axisymmetric particles such as ellipsoids, an exact analytical solution is not possible, therefore we have tried to calculate deformation profiles for uptake of ellipsoidal particles numerically. The membrane is modelled as a network of triangles forming a mesh and relevant energies such as mean squared curvature and adhesion energies are calculated over this discretized surface. For ellipsoidal particles, stable partially wrapped states exist for a model involving bending and adhesion energies only. We have obtained numerically a wrapping phase diagram for different aspect ratios of ellipsoids where critical adhesion strengths demarcate unbound, partially-wrapped, and fully-wrapped regimes.

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Exploring the relative orientation of the free and B3-bound fibronectin module pair ^{1}F1^{2}F1 using molecular dynamics simulations

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Fibronectin is a large extracellular glycoprotein that is involved in a number of physiological processes such as cellular adhesion, differentiation and wound healing. It is composed of three types of modules, F1, F2, and F3, which are separated by short sequences of amino acids. Structures of the human ^{1}F1^{2}F1 module pair free in solution and in complex with a streptococcal peptide B3 have been determined using solution NMR spectroscopy.[1,2] While the family of NMR models structures calculated for the unbound ^{1}F1^{2}F1 module pair shows that significant variations in the orientation of the ^{1}F1 and ^{2}F1 modules are possible, the bundle of structures of the ^{1}F1^{2}F1−B3 complex deposited in the PDB data bank is rather rigid, consisting of 14 elongated and one bend conformation. This suggest that binding of the peptide restricts the relative flexibility of ^{1}F1^{2}F1 module pair. Yet due to the lack of intermodule nuclear Overhauser enhancements (NOEs) the spatial arrangement of the two fibronectin modules cannot be determined unequivocally from the available NOE data set. This prompted us to perform a series of unrestrained and restrained molecular dynamics simulations of ^{1}F1^{2}F1 free in solution and in complex with B3 to explore the differences in the interdomain dynamics of this module pair in its bound and unbound form. The results of our simulations indicate that significant variations in the orientation of the ^{1}F1 and ^{2}F1 modules are possible also for the ^{1}F1^{2}F1−B3 complex, providing important insights into the ^{1}F1^{2}F1−B3 complex flexibility and highlighting the problem posed by the limited number of long range NOEs typically used in the determination of the structure of large multimodular proteins.[3]

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Tissue Simulations

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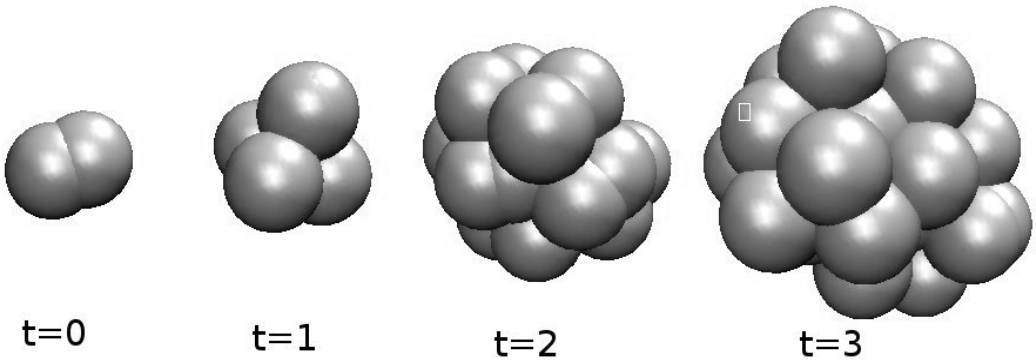

The elementary building block of all living organisms is the cell. Cell division and apoptosis, adhesion and migration, differentiation and mutation are all determining factors of life. Tissues are collections of cells, ordered or chaotic, dynamic or static that form functional parts of the organism. Over the past decades, the notion that physics, and especially mechanics plays an essential role in growth and development has evolved from hypothesis to fact. Even though an increasing number of experiments and theoretical works have focused on this puzzle, and many pieces have been found, we are still far from seeing the whole picture.

In this work, tissue simulation techniques are used to connect some of the dots
towards a coherent picture. The description of tissues is based on a mesoscopic particle based approach. Similar to mesoscopic hydrodynamic techniques, capturing the individual cell dynamics correctly is of lesser importance. Instead, the goal is to atain the right meso- to macroscopic dynamics of the tissue.

Here we present the basics of the simulation method and some applications. Growth of tumor spheroids was studied experimentally and corresponding simulations help to identify mechanic effects. Fluidization due to cell turnover is shown analytically and with simulations. Competition by homeostatic pressure is demonstrated.

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Soft domains on a spherical crystal

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We study the pattern formation of the groundstate of two-component crystalline shells, with one component considerably softer than the other with respect to stretching. Using approximate solutions of this nonlinear elasticity problem, we envisage the picture of invasion of vesicle surface by the soft material. The energy minimum demands that the soft material occupies the regions of the surface with a maximal density of the elastic energy and stress. These are located around the crystalline defects that are needed on geometrical grounds, in the simplest case 12 defects arranged like the vertices of an icosahedron. A difference in bending rigidity is needed before the soft material can spread to other parts of the crystal

Our theoretical results can be applicable to the description of shape morphologies monitored for two-component shells with different elastic moduli. From a biological perspective, the analysis can be relevant for the formation of viral capsids from different protein capsomer subunits, in particular for large viruses like the mimi virus.

Effects of the potential width on the folding behavior of flexible polymers

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We systematically investigate how the range of interaction between non-bonded monomers influences the formation of structural phases of elastic, flexible polymers. Massively parallel replica-exchange simulations of a generic coarse-grained model, performed partly on graphics processing units and in multiple-Gaussian modified ensembles, pave the way for the construction of a structural phase diagram, parametrized by potential width and temperature. Conformational transitions between (pseudo)phases are identified by microcanonical statistical inflection point analysis. We find evidence for finite-size effects that cause the crossover of "collapse" and "freezing" transitions for very short interaction ranges. Finally, we analyze low-temperature structures for different potential widths.

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Protein structure prediction using Basin-Hopping with NMR shift restraints

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We work on the combination of the basin-hopping approach with NMR chemical shift restraints obtained from a modified version of CAMSHIFT. The basin-hopping approach is based on Monte Carlo with minimization and has already been employed to find the global minimum of peptides. However, for larger peptides and proteins the effective sampling of the high-dimensional conformational space has remained a challenge, thus necessitating the development of a guided basin-hopping approach. One such approach is to use NMR chemical shifts as structural restraints as they facilitate to determine near-native structures with very high accuracy. CAMSHIFT calculates chemical shifts using differentiable functions of the atomic coordinates, which allows its implementation into the basin-hopping approach. Our results for small test peptides show that the final structures are very near to the target structures, which could be faster identified than with unrestrained basin-hopping runs.

Dual effect of PIP2 on Shaker potassium channels

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Voltage-gated potassium channels (VGKCs) are transmembrane proteins that enable rapid and coordinated conduction of potassium ions across the membrane upon depolarization. They consist of four identical subunits, each spanning the membrane six times. The bundles of S1 to S4 helices constitute the peripheral voltage-sensor domains, in which S4 sense the transmembrane voltage and trigger the channel conformational changes responsible for the gating. The central pore, formed by S5 and S6, allows ions to flow.

Phosphatidylinositol-(4,5)-bisphosphate (PIP2), a negatively-charged phospholipid found in the inner membrane leaflet, was shown to modulate VGKCs channels from the Shaker family. Thus, the application of PIP2 to these channels leads to a gain-of-function, namely an increase of the ionic current, and at the same time a loss-of-function manifested by the right shift of G/V and I/V curves.

Using atomistic molecular dynamics simulations we show that PIP2 interacts with the channel in a state-dependent manner. In particular, PIP2 is in interaction with the bottom residues of S4 in the closed state and with the terminal residues of S6 in the open state. The proposed model seems to rationalize the experimental data and provides an insight into the molecular mechanisms involved in the modulation of VGKCs by PIP2.

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Modelling platelet margination in blood flow

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As a response to an injury of a vessel wall platelets bind to the damaged site and build clots to close the opening, and thus stop the bleeding (hemostasis). The platelets must be located near the vessel wall to start the process promptly. For instance, a decrease of hematocrit (volume density of red blood cells) leads to a reduced concentration of platelets near the wall, which may considerably increase the bleeding times [1]. Numerical simulations of blood flow help us to understand this complex process.

Blood flow simulations are performed in two and three dimensions in idealised geometries using the dissipative particle dynamics method. The blood is modelled as a fluid with suspended red blood cells (rbcs) and platelets. The cells are represented by a viscoelastic spring network model [2]. The platelet distribution in flow is investigated depending on the hematocrit, shear rate, shape and deformability of the platelets in order to identify the conditions for their efficient margination as well as wall contact. Furthermore, different mechanisms which are mainly responsible for the platelet margination are characterised.

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Structure of an Intermediate State in Protein Folding and Aggregation

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Protein folding intermediates have been implicated in amyloid fibril formation involved in neurodegenerative disorders. However, the structural mechanisms by which intermediates initiate fibrillar aggregation have remained largely elusive. To gain insight, we used CPMG relaxation dispersion NMR spectroscopy to determine the atomic-resolution three-dimensional solution structure of a 2% populated, on-pathway folding intermediate of the A39V/N53P/V55L Fyn SH3 domain. To this end, we used the backbone chemical shifts and RDCs/RCSAs of the "invisible" intermediate reconstructed from CPMG experiments as experimental input for structure calculations based on chemical shift restrained replica exchange molecular dynamics simulations via the CamShift approach [1]. The COOH-terminus remains disordered in this intermediate [2], thereby exposing the aggregation-prone NH_2-terminal ° -strand. Accordingly, mutants lacking the COOH-terminus and thus mimicking the intermediate fail to safeguard the folding route and spontaneously form ° -sheet-rich fibrillar aggregates with a diameter of several nanometers and an affinity for the dye Congo red. The structure provides a detailed characterization of the non-native interactions stabilizing an aggregation-prone intermediate under native conditions and insight into how such an intermediate can derail folding and initiate fibrillation.

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Alzheimers disease: modelling the inhibition of β-amyloid aggregation using D-peptides

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Abstract

We have employed a number of computational approaches to examine the nature of interactions between D3 and different Alzheimer's disease amyloid-β species (monomer and oligomer). Using an implementation of the global- optimization approach employing Monte Carlo sampling with energy minimization, 6000 D3-Aβ monomer and 4000 D3-Aβ pentamer complexes were independently generated, and scored according to calculated binding energies. The best 100 complexes in each category were then subjected to molecular dynamics simulation in explicit water and the Aβ-D3 interactions monitored . The interaction energies were decomposed into residue-residue contributions showing that the association is driven by electrostatic attraction involving D3's arginines and the negatively charged residues populating the Aβ N-terminal segment, GLU22 and ASP23 in particular. Our findings are in agreement with dot blot experiments which showed fluorescein isothiocyanate- labeled D3 as mainly binding to Aβ's N-terminal portion. The effect of D3 on Aβ's structure was investigated and shown to destroy the β-sheet in the Aβ pentamer.

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Adsorption of 3H-BLIP on a gold surface

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Protein-surface interactions have great significance in many applications ranging from nanotechnology to medicine. To understand the basis of the selective interactions and to accurately predict the binding necessitates a reliable computational atomistic model. In this study, we apply the recently developed ProMetCS [1] model to simulation of protein adsorption on gold. ProMetCS is a protein-metal continuum solvent force field that has been parameterized using quantum mechanical and molecular dynamics techniques for organic molecules and peptides. We performed rigid-body Brownian Dynamics simulations to identify docking orientations of 3H-BLIP on an Au(111) surface. Further, to investigate the binding in more detail, we performed explicit solvent molecular dynamics simulations of the 3H-BLIP protein on a gold surface. In these simulations, the image charge effects are included in the description of the gold surface and are represented by a rod model to account for polarization [2,3].

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Computer Simulations of Erythrocyte Sedimentation

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Sedimentation of erythrocytes (red blood cells, RBCs) under gravitation is an often used generic diagnostic tool [1]. As such it suffers from lack of specificity; high sedimentation rates typically indicate problematic blood composition, whereas low rates are associated with samples from healthy individuals. Microscopic origins and mechanisms of a given sedimentation rate cannot be pointed, however.

We consider the gravitationally driven sedimentation of RBCs by three-dimensional computer simulations. The blood plasma is simulated as a particle-based solvent using the multiparticle collision dynamics (MPC) technique [2]. The RBC membrane is modeled as a triangulated surface [3] consisting of point particles. The membranes have bending rigidity, linear elasticity, and constant surface area and enclosed volume [4]. The driving gravitation is volumetric, ie. coupled to the mass density difference between the fluid inside and outside the RBC. The strenght of the effective gravitational field is varied, since values outside the standard range are achieved by centrifugation [5] and are therefore of interest.

We show that individual sedimenting erythrocytes assume different shapes depending on the strength of the driving field and the elastic parameters. These include parachutes, asymmetric discocytes, and shapes with extrusions in the direction of the flow. For high sedimentation rates, the results can be compared to experiments [5] of centrifugation. Collective effects of sedimenting discocytes are discussed.

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Mesoscale Simulations of Multi-Domain Protein Dynamics

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The dynamics of the subdomains of a protein can play a fundamental role in its functionality. Such motions can be studied by techniques like neutron spin-echo spectroscopy, which has been shown to be able to resolve the time and length scales in the study of proteins like alcohol dehydrogenase (ADH) and phosphoglycerate kinase (PGK) [1,2]. On the other hand, computer simulations can provide a deeper insight of the protein dynamics, and be of great help for the interpretation of the experimental results.

Our system of interest is the merA protein. This enzyme, present in certain bacteria, is a fundamental part of the operon responsible for their resistance to toxic mercury compounds[3]. Since previous works have shown[4] that the different subdomains of this protein can have a specific role in the reduction of mercury, the study of their dynamics is demanding.

In this context, we have developed a highly coarse-grained model at a mesoscopic scale based on the basic geometry of the merA protein. The model resembles its basic geometry: two end groups attached to the protein core by short polymer chains. The simulations were performed using Multiparticle Collision Dynamics[5,6], a particle-based simulation approach able to capture the hydrodynamic interactions between the domains of our model.

We analyze some basic dynamic features of the protein domains, like diffusion coefficient and velocity autocorrelation functions. The effect of the terminal motion is studied by contrasting two models with flexible and rigid linkers respectively. The effective diffusion coefficient, obtained from the intermediate scattering function, can be directly compared to experimental data.

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Aggregation of amyloids at biomembranes and its implications in Alzheimer's disease and type II diabetes

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The aggregation of the amyloid-β peptide (Aβ) into neurotoxic oligomers on the neuronal membrane surface and its insertion into the membrane is considered to be a crucial event in the development of Alzheimer's disease (AD). However, the mechanism of insertion, pore formation and membrane disruption still needs to be uncovered. We used atomistic molecular dynamics (MD) simulations to investigate the behavior of Aβ in zwitterionic and anionic lipid bilayers. We studied the effect of Aβ secondary structure, oligomerization and mutation on its transmembrane stability and membrane maintenance. Our main finding is that β sheet-oligomerization is required for A*β* to *be* stable in the membrane and to induce membrane permeabilization [1].

Aggregation of human islet amyloid polypeptide (hIAPP) at beta-cell membranes is associated with the onset of type II diabetes. It is proposed that hIAPP aggregates induce cytotoxicity to the pancreatic islets of langerhans cells by membrane disruption. Chiral surface-specific vibrational sum frequency generation (SFG) spectroscopy in conjunction with *ab initio* simulations revealed a tilted orientation of hIAPP β sheet-aggregates at lipid/aqueous interfaces [2]. We used this orientation for the starting structure of a hIAPP trimer inserted into a lipid bilayer and followed its effects on membrane maintenance using MD simulations. We observe β barrel-formation, which allows massive water and even ion flow across the membrane.

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Hydrodynamic Simulation of Bacteria Swimming

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Bacteria such as *Rhizobium meliloti* can modulate the rotation speed of an individual motor, which they exploit to change their swimming direction [1]. Starting from a bundled state, where all flagella are synchronized, the decelerated flagellum gets out-of-phase and unbundles. To understand the fundamental mechanisms in this bacteria locomotion, we perform mesoscale hydrodynamic simulations using the multiparticle collision dynamics (MPC) method [2,3], which adequately captures the hydrodynamic interactions between the flagella and bridges the length- and time-scale gap between the fluid and bacteria. A flagellum is constructed by a sequence of mass points interacting by bond, bending, and torsional potentials. Such a model can efficiently be coupled to the MPC fluid. Results are presented for synchronization and bundle formation of flagella. The synchronization and bundling times are analysed in terms of the applied torque, the flagella separation, and the number of flagella [4]. Unbundling is studied in terms of the motor-torque difference between various flagella, and the resulting phase mismatch and tumbling-torque are determined.

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Deprotonation mechanism and the free energy landscape of a single-stranded DNA i-motif

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We present the results of atomistic Molecular Dynamics simulations of a single-stranded protonated and deprotonated DNA i-motif [1]. We are able to determine the full unfolding and deprotonation mechanism by using a variant of a Metadynamics approach [2].
The free energy landscape indicates the protonated native configuration as the global energetic minimum which validates the significant stability of the i-motif in acidic solution.
The release of protons which form the stabilizing hemiprotonated cytidine pairs can be identified as a two-step process which is obligatory for a partial unfolding of the i-motif into a hairpin structure. Our results indicate that the hairpin structures are stable deprotonated equilibrium conformations at 300 K [3]. The entropic preference of these configurations compared to a fully unfolded state can be explained by strong water ordering effects due to the present number of hydrogen bonds.
We observe a full unfolding at higher temperatures in good agreement to experimental results [3,4].

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Including electronic polarizability effects in molecular dynamics simulations of liquid phase *n*-alkanes

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Explicit treatment of polarizability effects is important for obtaining accurate results of properties of (bio)molecular systems in computer simulation [1]. In molecular dynamics (MD) simulations, the polarizability effects are usually taken into account implicitly, e.g. by using effective charges, continuum electric methods or dielectric permittivities. In our study, we use a one-site charge-on-spring (COS) polarizable model [2] to account for the polarizability effects in simulations of liquid phase *n*-alkanes. In the COS methods an inducible dipole is modeled by attaching a virtual site with charge qi^{v} at a distance r_i^{v} from the atom of interest with a parabolic restrained potential. The separation is calculated in response to instantaneous electric field. The total force acting on the charge must be zero at any time: $f_i^{ho} + f_i^{el} = 0$.
Assuming linear polarization response: $\mu_i = \alpha_i E(r_i)$ and a harmonic oscillator spring constant the displacement of the virtual site and the induced dipole on the atom of interest are, respectively:
$\Delta r_i^{v} = q_i^{v} E_i / k_{ho}$, and $\mu = (q_i^{v})^2 E_i / k_{ho}$
A virtual site charge was assigned to each united atom representing the CH_2- and CH_3-functional groups of *n*-alkanes of different length. We used the applied electric field method [3] to generate the induced dipole moments in a non-polar system, and to determine the dielectric constants of the various liquids. This allowed for the parametrization of the model together with calibrating the model for various thermodynamic properties.

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Protein Structure Refinement Augmented to Sequence Space

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Access to structural information of proteins is limited, time consuming and sometimes impossible, though needed to understand and finally potentially simulate the nature we live in. On the other hand, access to protein sequence information is in comparison quite ubiquitous. Due to that fact, the sequence space available right now is several magnitudes higher compared to the known structures deposited in databases. In addition to the tremendous amount of available data, those sequences also carry a huge amount of precious information, usually not accessible to molecular refinement simulations.
Protein sequences are exposed to an everlasting evolutionary pressure. Sequences can change over time by natural trail and error selection processes. Code that worked persisted in time, also carrying the differences arising from the selection mechanisms.
With our approach we are able to use the huge amount of sequence information in our refinement simulations, exploiting the differences of homolog sequences with identities of not less than 50%, hence combining the energy landscapes of several evolutionary filtered data sets. As a result we expect a smoothening of the former rugged energy landscape, allowing the simulation to overcome barriers previously insuperable. The simulations use the deformable network (DEN) inspired adaptive deformable position restraint (ADPt) approach to combine the sequence information with the structural data.

Prestress in Protein Disulfide Bonds Tunes Their Stabilities

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Disulfide bonds are ubiquitous covalent links in proteins. By providing a protein fold with additional structural constraints they can tune protein stability and function. We find disulfide bonds to exhibit a varying degree of pre-stress [2]. Using a new Force Distribution Analysis of forces obtained from Molecular Dynamics simulations [1], we identified particularly tensed disulfides, with inter-cysteine forces of 143.34 pN for Cys130-Cys159 in CD4 and 165.472 pN for Cys27-Cys37 in the von Willebrand factor C1 (vWFC1) domain. Remarkably, the order of magnitude of these internal forces is coinciding with those required to unfold or activate proteins, and thus likely to play an important role in the protein's integrity. The pre-stressed disulfide bonds link adjacent strands in the same antiparallel β-sheet, and have been previously classified as 'allosteric disulfide bonds' due to their unusual and unfavourable dihedral configuration [3]. We calculate reduction rates of the two disulfide bonds to increase due to the intrinsic tension by a factor of two to three as compared to the other comparably relaxed disulfide bonds in CD4 and vWFC1. This trend is preserved in a survey over all disulfide bonds in protein structures currently deposited in the Protein Data Bank, with disulfide bonds linking two adjacent strands in a β-sheet featuring a significantly larger sulphur-sulphur bond length on average. The decreased thermodynamic and kinetic stability of pre-stressed disulfide bonds as identified in our proteome-wide survey is likely to have functional implications, in particular in the light of mechano-chemical disulfide bond shuffling of von Willebrand factor an other highly disulfide-linked proteins.

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Focal adhesion kinase as a cellular force sensor

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Focal adhesion kinase (FAK) is a crucial component of focal adhesion sites, which exerts its activity by transducing signals between the cytosol and the extracellular matrix. The translocation of FAK to focal adhesion sites and its functional activation by tyrosine phosphorylation leads to the formation of large enormous multi-molecular complexes. Theses complexes can trigger different signaling pathways, including the MAPK pathway.

The three-dimensional structure of FAK consists of a tyrosine kinase domain and two large non-catalytic regions. The N-terminal FERM domain is involved in auto-inhibition of the kinase by blocking a phosphorylation site (Tyr576/577)[1]. The exposure of this phosphorylation site induces the maximum activity of FAK. We tested if mechanical forces as they are present at focal adhesion sites can induce an allosteric switch to an active state of FAK with an exposed phosphorylation site, using Molecular Dynamics simulations.

We indeed find mechanical forces propagated onto FAK when tethered between the membrane and the cytoskeleton can remove the auto-inhibitory FERM domain from the kinase domain of FAK. This functional activation of FAK can then trigger a sequence of downstream signaling events. The mechano-transduction mechanism of FAK can explain how FAK acts as a force sensor, translating mechanical forces at the focal adhesion site into a biochemical signal.

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