Title: Aging processes in the cytoskeleton

Nasrin Afzal

Motivated by a series of experiments that study the response of the cytoskeleton in living cells to time dependent mechanical forces, we investigate, through Monte Carlo simulations, a three-dimensional network subjected to perturbations. After having prepared the system in a relaxed state, shear is applied and the relaxation processes are monitored. We measure two-time functions of various quantities of the system. We discuss possible implications of our results for relaxation processes taking place in the cytoskeleton.

Title: Interfacial Microrheology of Protein Layers During Formation at the Air-Water Interface

Daniel Allan

Proteins can adsorb to the air-water interface to form viscoelastic layers. Characterizing the rheology of such layers is challenging, due to the confined geometry, the fragility of the layers, and the possibility of mesoscale spatial heterogeneity. Passive microrheology --- using the thermal motion of colloidal probes to interrogate the mechanical response of the surrounding medium --- is a suitable technique for addressing these difficulties. In particular, this approach sheds light on the properties of incipient protein layers that are characterized by modest interfacial viscosities. We describe microrheology studies of protein layers at the air-water interface, in which we determine the evolving interfacial shear response through the viscoelastic transition that signifies layer formation. Spatial heterogeneity in the interfacial rheology is identified and discussed within the framework of layer formation as a gel transition. Layers formed by adsorption of protein from the aqueous subphase and by spreading protein directly onto the interface are compared and studied across a range of concentrations, demonstrating the sensitivity of layer properties to the rate and manner of protein accretion.

Colloidal Interactions in Protein Assembly Processes

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Colloidal interactions between proteins determine the behavior and stability of globular proteins such as monoclonal antibodies (mAbs) against their propensity to cluster formation in solution. We study interactions between these proteins through their dilute solution behavior. Experiments to quantify intermolecular interactions were done using Dynamic and Static Light Scattering (DLS and SLS) in parallel with zeta potential measurements with Laser Doppler Electrophoresis method (M3-PALS) and Atomic Force Microscopy (AFM) measurements. This approach offers a rapid indirect determination of colloidal interactions through their second virial coefficient. Electrostatic part of the DLVO interaction was quantified via the corresponding surface charge and/or surface potential, while the van der Waals interactions were quantified via their Hamaker coefficient, both as functions of ionic strength and pH of the bathing solution. In addition, a steric barrier in the form of a "hydration layer" is sometimes assumed to surround the molecules and effectively represents an additional excluded volume term; the thickness of the hydration layer may then serve as an adjustable parameter [1,2]. When the soluble polymer is present in the solution as another component, the phenomena and the theoretical treatment resemble those for electrostatics and its role could be as stabilizer, bridging element between particles, increasing their attraction. The study of protein interactions then should be extended to non-DLVO predictions and some new insights into the limits of the validity of classical DLVO models considered with the ion specificity, solvation/hydration near protein interfaces and effects of soluble polymers added to the solution. Parametrization of protein-protein interactions improves our understanding of mAb assembly and provides a means for its control by variation of the solution pH, ionic strength, ionic type and the nature of the soluble polymer.

[1] B.L. Neal, D. Asthagiri, and A.M. Lenhoff. Molecular origins of osmotic second virial coefficients of proteins. Biophys. J., 101(75):2469–77, 1998.

[2] Dan Ben-Yaakov, David Andelman, Rudi Podgornik, and Daniel Harries. Ion-specific hydration effects: Extending the poisson-boltzmann theory. Current Opinion in Colloid & Interface Science, 16:542–550, 2011.

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Salvatore Assenza

Twisting Structure of Amyloid Fibrils Emerges as a Compromise between Competing Forces

Under abnormal circumstances, normally soluble proteins may aggregate and form highly stable filamentous structures, known as amyloid fibrils. Such structures play a central role in neurodegenerative disorders such as Alzheimer's, Parkinson's and Huntington's diseases, to cite but a few examples. Because of the heterogeneity in sequence of the several proteins able to undergo a disorder-leading fibrillation process, it has been proposed that such ability is a general property of polypeptides, and systematic in vitro experiments have shown that even disease-unrelated proteins form fibrils and probed their structure features. Some recent experiments focusing on β-lactoglobuline fibrils showed that they are made of several inter-twisting filaments organized in ribbon-like structures, thus showing a *pitch*, i.e. a period in length, which depends on the width of the ribbon and on the concentration of salt added in the solution. Here, we propose a simple model where the filaments are considered as chains made of springs and charged beads, whose interaction is implemented by means of the Poisson-Boltzmann equation. In spite of its simplicity, the model turns out not only to capture the physics of the system, but also to quantitatively describe the experimental data.

Title: Defects in crystalline packings of twisted ﬁlament bundles, Dislocations and grain boundaries.

Amir Azadi

Abstract:

Twisted and ropelike assemblies of ﬁlamentous molecules are common and vital structural elements in cells and tissues of living organisms. We study the intrinsic frustration occurring in these materials between the two-dimensional organization of ﬁlaments in cross section and out-of-plane interﬁlament twist in bundles. Using nonlinear continuum elasticity theory of columnar materials, we study the favorable coupling of twist-induced stresses to the presence of edge dislocations in the lattice packing of bundles, which leads to a restructuring of the ground-state order of these materials at intermediate twist. The stability of dislocations increases as both the degree of twist and lateral bundle size grow. We show that in ground states of large bundles, multiple dislocations pile up into linear arrays, radial grain boundaries, whose number and length grows with bundle twist, giving rise to a rich class of “polycrystalline” packings.

Title: Antiviral activity of squalamine: Role of electrostatic membrane binding

Bernard Beckerman

Abstract

M. Zasloff et al., Proc. Nat. Acad. Sci. (USA) 108, 15978 (2011). has demonstrated that squalamine, a molecule found in the liver of sharks, exhibits broad-spectrum antiviral properties. It has been proposed that this activity results from the charge-density matching of squalamine and phospholipid membranes, causing squalamine to bind to membranes and displace proteins such as Rac1 that are crucial for the viral replication cycle. Here we investigate this hypothesis by numerical simulation of a coarse-grained model for the competition between Rac1 and squalamine in binding affinity to a flat lipid bilayer. We perform free-energy calculations to test the ability of squalamine to condense stacked bilayer systems and thereby displace bulkier Rac1 molecules. We directly compare our findings to small-angle x-ray scattering results for the same setup.

Phase Diagram of Star-Shaped DNA Structures

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By exploiting the selectivity of Watson-Crick pairing, we built star-shaped DNA nano-structures with mutual tip-to-tip attractive interactions. We conceived these structures to mimic molecules with limited valence and short-range interactions. We studied the phase diagram of solutions 3-arms and 4-arms constructs, determining at each temperature the homogeneity of the solution and measuring the concentration of the coexisting phases when phase separation was found. Samples were investigated by UV absorbance and fluorescence, while macroscopic phase separation was speeded up by centrifuging. We found that both systems display a liquid-vapor-like phase behavior, with a coexistence region terminating, at higher temperature, in a critical point. Our results show that by reducing the valence of the structures, the coexistence region is greatly shrunk both in temperature and in concentration, in a way that agrees with recent theoretical predictions [1].
Static light scattering measurements show a critical divergence of the scattering intensity as the critical temperature is approached along the critical isochore, while dynamic light scattering reveals that the system is characterized by two dynamics processes. The slower dynamics follows an Arrhenius behavior and becomes dominant as the temperature is lowered. Such a behavior can be coherently interpreted as the dynamic evolution of a percolating network of DNA stars.

References:

1. E. Bianchi, J. Largo, P. Tartaglia, E. Zaccarelli, F. Sciortino *Physical Review Letters* **97**, 168301 (2006)

EVALUATING A METHOD FOR PRODUCING ASYMMETRIC GIANT UNILAMELLAR VESICLES

Matt Blosser

Giant unilamellar vesicles (GUVs) are important model systems for investigating physical properties of lipid bilayers. Recently, a method was developed called continuous droplet interface crossing encapsulation (cDICE)[1], which creates GUVs by passing a stream of droplets through an oil water interface. Several methods, such as electroformation and gentle hydration, exist to produce GUVs. In comparison, cDICE is better suited to incorporating large fractions of charged lipids in membranes, to creating vesicles in a high-salt environment, and to encapsulating large objects within vesicles. All of these features are important for achieving larger goals of understanding both the underlying physics and the biological role of lipid bilayers. Here, we investigate an extension of the cDICE method for producing asymmetric GUVs, which are GUVs with inner and outer leaflets of different compositions. We tested asymmetry by fluorescence quenching experiments. Our goal is to create a model system mimicking the asymmetry found in biological membranes.

1. Abkarian, M, Louiseau, E, and Massiera, G. ***Soft Matter***, 2011, **7**, 4610-4614

Title:
The Self-Assembly of Twisted Filament Bundles

By:
Isaac R. Bruss

Abstract:
Densely packed and twisted assemblies of filaments are crucial structural motifs in macroscopic materials (cables, ropes and textiles) as well as synthetic and biological nanomaterials (fibrous proteins). We explore the ground state structure of twisted filament assemblies formed under the influence of adhesive interactions by a computational model. Here, we find that the underlying non-Euclidean geometry of twisted fiber packing disrupts the regular lattice packing of fibers above a critical radius, proportional to the helical pitch. Above this critical radius, the ground state packing is geometrically frustrated, and includes the presence of between one and six excess 5-fold disclinations in the cross-sectional order.

Airway Surface Brush Keeps the Lung Healthy

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Abstract

Clearance of mucus is the primary defense mechanism that protects airways from inhaled infectious and toxic agents. The current two-layer Gel-on-Liquid model, in which a gel-like mucus layer is propelled on top of a "watery" periciliary layer (PCL) surrounding the cilia, does not adequately describe the maintenance of mucociliary clearance in health nor quantitatively predict failure of mucus clearance in disease. We propose and provide evidence for a qualitatively different Gel-on-Brush model with a gel-like mucus layer, dominated by secreted mucins, in contact with a "brush-like" periciliary layer, composed of membrane-spanning mucins and mucopolysaccharides tethered to the airway surface. The physicochemical properties of the mucus layer in apposition to the "brush-like" PCL layer, e.g., their relative osmotic moduli, explain both the stability of mucus clearance in health and its failure in airway disease. This Gel-on-Brush model of airway surface layer opens important new directions for treatments of airway diseases.

Magnetic tweezers measurements of the DNA nanomechanical stability at different environmental conditions of pH and ionic strength.

V. Cassina

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Abstract

The fundamental processes of the DNA transcription and duplication begin with the formation of local denaturation bubbles or DNA breathing whose characteristics are not yet entirely clear. In the present work, by using single molecule Magnetic Tweezers (MT) techniques, we study the temporal fluctuations of DNA molecule extension approaching the denaturated state, in presence of external mechanical constraints. Indeed the Magnetic Tweezers technique allows to apply in a controlled manner a force and a twist to a single DNA molecule, with the possibility to denature the double helix when negative turns are applied. We observe a specific range of torsion and force where the DNA length variations are particularly relevant. These DNA length oscillations indicate that the DNA structure is fluctuating between two states: a plectonemic state, and a second state characterized by denaturation bubbles.

The DNA extension fluctuations are analyzed at different conditions of pH and ionic strength by performing a statistical analysis of the temporal behavior of the DNA length measurements. The measured values of the forces where the fluctuations takes place are theoretically confirmed by the predictions provided by an original simplified model based on the standard theories of DNA temperature melting.

Overall the whole body of these single molecule data present new, innovative, and fundamental aspects of DNA biophysics description, namely its stability against the denaturation in presence of various environmental conditions.

Scientific activity

My scientific activity is devoted to the study of DNA and Abeta amyloid fibrils with single molecule techniques such as Magnetic and Optical Tweezers and Atomic Force Microscopy.

My recent publications about the subject are:

Single molecule study of the DNA denaturation phase transition in the force-torsion space.
arXiv (2012) arXiv:1203.6251v1

Magnetic tweezers measurements of the nanomechanical properties of DNA in the presence of drugs.
Nucleic Acids Research, 38, 7089-7099, (2010)

Stability of A (1-42) peptide fibrils as consequence of environmental modifications.
European Biophysics Journal, **39**, 1613-1623, (2010)

Atomic force microscopy study of DNA conformation in the presence of drugs
European Biophysics Journal, **40**, 59-68, (2011)

"Diffusing diffusivity": A model of anomalous and "anomalous Brownian" diffusion

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A particle diffusing in a simple liquid carries out a random walk with the mean square displacement (MSD) linear in time and the displacement distribution (DD) Gaussian at all times (normal diffusion). In complex, "crowded" systems, anomalous diffusion with sublinear MSD (subdiffusion) and generally non-Gaussian DD is often observed. Recently, Granick's group has found [1] that in several systems, the linear time dependence of MSD of diffusing colloidal particles, as in normal diffusion, is accompanied by a non-Gaussian DD, with roughly exponential tails at short times, a situation termed "anomalous yet Brownian" diffusion. The diversity of systems in which the phenomenon is observed (the surface of lipid tubes, entangled actin networks, mixtures of colloids of different sizes) calls for a generic model. We point out that lack of "direction memory" in the particle trajectory (a jump in a particular direction does not change the probability of subsequent jumps in that direction) is sufficient for a strictly linear MSD (assuming that the system is pre-equilibrated), but if at the same time there is "diffusivity memory" (a particle diffusing faster than average is likely to keep diffusing faster for some time), the DD will be non-Gaussian at short times. A gradual change in diffusivity can be due to the environment of the particle changing slowly on its own, the particle moving between different environments, or both. In our model, this is represented by the particle diffusivity itself undergoing a (perhaps biased) random walk ("diffusing diffusivity"). The DD is exactly exponential at short times, if the distribution of diffusivities is itself exponential, but an exponential remains a good fit to the DD for a variety of diffusivity distributions. The model can also be modified to produce subdiffusion.

[1] Wang *et al.*, PNAS 106 (2009) 15160.

Title:

Helmut Schiessel, Maria D. Correa-Rodriguez, Sergii Rudiuk, Damien Baigl, and Kenichi Yoshikawa.

Abstract:

We present a theory of spherical micelle formation from cationic amphiphiles in the absence and in the presence of DNA. Micelle formation is favored by the hydrophobic tails but disfavored by the entropic cost associated with counterion condensation. Counterion release drives the complexation between DNA and amphiphiles and causes micellation at a much smaller concentration than in the absence of DNA. The stiffness of double-stranded DNA favors the formation of large micelles leading to a bimodal distribution of micelle sizes. The resulting complexes are of interest as non-virial vectors to deliver genes into cells. These complexes might, however, also be useful as model systems to study DNA-wrapped complexes with a lipid core that can adjust its size over a wide range of values.

Title: Development of Interfacial Strength and Entanglements During Welding of Polymers

Ting Ge

Abstract:

Thermal welding is a common means of joining polymer parts. Interfacial strength increases with welding time $t_w $ as polymer chains diffuse across the interface. The microscopic origin of this interfacial strength enhancement was investigated with large scale molecular simulations employing a coarse-grained bead-spring model. Polymer surfaces were held together at a temperature well above the glass transition temperature T_g. States at $t_w $ up to 10^{9} time steps were then quenched to a temperature below $T_g $ for mechanical tests. We test the interfacial strength by shearing the weld along a direction parallel to the interface. The maximum shear stress $\sigma _{\max} $before failure is used to characterize the interfacial strength. We find that $\sigma _{\max} $ increases as $t_w ^{1/4}$ before saturating to its bulk value. This agrees with previous experiments by a lap-joint shear method. In addition, our analysis shows that the dominant shear failure mode changes from chain pull-out at the interface for small $t_w $, to chain scission for large $t_w $. Formation of sufficient amount of entanglement across the interface is required to prevent the catastrophic chain pull-out. We track the evolution of entanglements using the Primitive Path Analysis(PPA) algorithm. Our results show that the bulk response is not fully recovered until the density of entanglements reaches its bulk value at the interface. Furthermore, the total number of interfacial entanglements is directly related to interfacial strength . It also increases as $t_w ^{1/4}$, in consistence with the prediction based on reptation dynamics.

Path Sampling for Optimal Assembly Protocols

Todd Gingrich
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The tendency of chemical and biological systems to form ordered structures depends sensitively on a balance of thermodynamic and kinetic factors. In equilibrium systems, statistical mechanics allows one to compute expected chemical conformations by minimization of a free energy. Many nanoscale systems, however, rely upon fundamentally out-of-equilibrium procedures where simple governing principles do not exist. Because control parameters are modulated on a time scale faster than the system can equilibrate, nontrivial structures can be obtained, which would not be expected in equilibrium experiments. I address the inverse problem - idenfitication of the (potentially nonequilibrium) protocol which is most likely to yield a target structure. A mixture of Monte Carlo and dynamical sampling strategies can be combined with rare event sampling algorithms to elucidate how nonequilibrium protocols can amplify the probability of forming particular structures of interest. These strategies are illustrated in a one-dimensional model system as significant sampling challenges remain in the extension to higher dimensional systems.

Title: Implications of polymer brush theory for the budding yeast nucleus.

Anton Goloborodko, Geoffrey Fudenberg, Leonid Mirny.

Abstract:

The budding yeast nucleus is a model system for studies of chromosomal organization. The current biological understanding of yeast chromosomal organization is that chromosomes are tethered at their centromeres to a relatively small patch on the inner surface of the almost spherical nuclear envelope in a “Rabl conformation”. However the implications of this organization have not been analysed.

Understanding the implications of Rabl conformation is increasingly important in light of recent genome-wide characterization of chromosomal contacts via the 3C-based methods. These methods (i.e. Hi-C) experimentally measure contact probabilities between each pair of genomic loci.

In this work, we analyze the obtained contact map from the point of view of the SCF polymer brush theory. We also obtain numerical estimates with the DiMarzio & Rubin lattice model.

The main results of our work are the following: 1) chromosomes in the yeast nucleus are stretched by excluded volume interactions; 2) in an ensemble of nuclei, grafting points for centromere-tethered chromosomes are random; 3) under nonlinear stretching, the contact probability between two genomic loci on the same chromosomal arm depends both on the distance and the position of the mid-point; 4) analytical results agree with brownian dynamics simulations which explicitly account for the proposed geometry of the nucleus.

Based on our results, extending one-parameter scaling analyses to account for tethering is an important step towards characterizing the polymer organization of chromosomes in the yeast nucleus. Moreover, this might have implications for higher eukaryotes, and the applicability of various scaling arguments, if multiple chromosomal regions are tethered to nuclear substructures.

Forces between polymers and repulsive surfaces

Yosi Hammer

Recent advances in atomic force microscope, optical and magnetic tweezers allow detailed study of the forces acting on long polymers. The shape of the probe to which the polymer is attached may influence the results of the measurement. Some features of the polymer-probe interaction are independent of the microscopic details, but depend on the geometry of the probe.

I consider a long polymer with one of its ends held close to the tip of a repulsive cone or wedge. The entropic pressure on the surface is found analytically for an ideal polymer and is shown to exhibit singular behavior near the tip, similar to the behavior of the electric field near a conducting needle. The total force between the polymer and the cone can be also found for a cone with an elliptical cross section. The dependence of the force on the axial ratio of the conic section will be discussed. For self avoiding polymers I will discuss results obtained from numerical simulations.