The Role of Binding Specificity in Limiting the Number of Realizable Self-Assembled Structures: Towards the Stabilization of a Shell

Arkus, Natalie
Harvard University

Perhaps the primary difficulty with using colloidal self-assembly as a nanofabrication method is the large number of mechanically stable conformations available to a system of N identical, spherical colloidal particles. We present improved lower bounds on the number of stable conformations in a system of N particles and demonstrate that, for identical colloidal spheres with short-ranged attractions, the number of conformations in the lowest energy state grows exponentially with N. By uniformly coating the particles with homophilic neuroreceptors called Dscam (of which there are over 38,000 different isoforms), a virtually limitless degree of spherically symmetric binding specificity can be added to the system. Such binding specificity can break the degeneracy, stabilizing a given packing; we discuss the possibility of stabilizing a shell of N particles.

Non-equilibrium Statistical Mechanics of self-propelled hard rods

Baskaran, Aparna
Syracuse University

Motivated by recent simulations and by experiments on aggregation of gliding bacteria, a physical model of the collective dynamics of self-propelled hard particles on a substrate in two dimensions is studied. The particles have finite size, interact via excluded volume and are frictionally damped by the interaction with the substrate. Starting from a microscopic model of dynamics that includes non-thermal noise sources, a continuum description of the system is derived. The hydrodynamic equations are then used to characterize the possible steady states as a function of the particles packing fraction and examine their stability with respect to the self-propulsion velocities. This analysis is used to shed light on the mechanism underlying various phenomena predicted by other authors based on more macroscopic analysis.

Making an Analogy between Forming a Josephson Junction and the Use of Wave Functionals to Form Soliton- Anti Soliton Pairs in Both Biological and Condensed Matter Physics

Beckwith, Andrew
American Physical Society

Our paper generalizes techniques initially explicitly developed for CDW applications only with respect to what is needed for multi dimensional instantons forming in complex condensed matter/ biophysics applications. This involves necessary conditions for formulation of a soliton- anti soliton pair, assuming a minimum distance between charge centers, and discusses the prior density wave physics example as to why a Pierels gap term is added to the tilted washboard potential for insuring the formation of scalar potential fields with an arctan value ranging in value between zero to two pi. We state that much the same methodology is needed for higher dimensional condensed matter systems/ bio physics, with strict conditions stated as to necessary potential terms needed to form a Josephon junction interpretation as to how to form wave functionals with necessary Gaussian character which can model instanton physics via a process analogous to Pierels gap and Brillouin zone boundary physics.

Alignment of rods and Partition of Integers

Ben-Naim, Eli
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Abstract unavailable

Plasticity and Polymorphism within the Amyloid Cross-Beta Motif

Berryman, Josh
Leeds University (UK)

Amyloid fibrils are dissimilar to native-folded proteins in that a variety of stably folded forms will commonly exist for the same protein sequence. Numerical techniques are used to investigate the forces which select between these conformations (polymorphs) and to analyse the responsivity of the different polymorphs (plasticity) in the amyloidogenic protein fragment GNNQQNY. Protofibrils of two and four parallel beta-sheets, derived from the crystal structure are examined as well as invented systems composed of antiparallel beta-sheet. The antiparallel systems are found to have approximately equivalent free-energies to the parallel systems under a range of conditions and the network of adaptive, mutually balancing, interactions which permits this to occur is illustrated using simple geometric and statistical techniques.

DNA repair triggered by sensors of helical dynamics

Krastan B. Blagoev
Los Alamos National Laboratory

Nucleotide excision repair is a ubiquitous cut and patch mechanism that eliminates DNA lesions induced by multiple genotoxic agents. Unlike the recombinatorial approach of the immune system, which generates billions of immunoglobulins and T-cell receptors, the nucleotide excision repair complex uses only few generic factors to recognize an infinite range of base modifications. New data favor an unexpected strategy predicted by theoretical calculations, whereby damage recognition is initiated by the detection of abnormal oscillations in the undamaged strand opposite to DNA lesions. Another core subunit recognizes the increased susceptibility of DNA to be kinked at injured sites. Thus, early nucleotide excision repair factors avoid direct contacts with modified bases and, instead, achieve their broad molecular versatility by exploiting the altered dynamics of damaged DNA.

Genetic catalysis of metabolic containers in a minimal protocell

DeClue, Michael
Los Alamos National Laboratory

The goal of the project is to transform simple inanimate molecules into an organized system resembling living units through a bottom-up approach. In particular, the coupling of two man-made chemical processes, one mimicking metabolism and the other heredity, inside of a dividing chemical compartment is needed. Our initial strategy attempts to genetically regulate the conversion of synthetic precursors into fatty acid based lipids inducing the formation, growth and division of chemical containers or vesicles. Precursor molecules are designed to undergo photolytic conversion into protocellular building blocks via a metabolic mediated process using a nucleic acid coupled with a transition metal complex as a cofactor. Photolysis kinetics may ultimately show a rate dependency on nucleic acid sequence, providing the system a mechanism for evolutionary control. Towards this goal, we have successfully used a derivative of a nucleotide (8-oxo-guanine) that acts as an electron donor in a photoinduced electron transfer cleavage reaction providing carboxylic acid from ester precursor. The system uses a ruthenium containing photocatalyst to harvest visible light energy and shuttle an electron to ester molecules releasing decanoic acid. While the initial reaction mixture is a homogeneous aqueous solution, as the photolysis proceeds the solution becomes opalescent over time suggesting that inhomogeneous structures are forming. Indeed, after 24 h of exposure the reaction was significantly complete (>95%) and the solution contained bilayer vesicles and tubular structures as confirmed through fluorescence microscopy. Control experiments under matching conditions using a guanine-based catalyst showed only very low background reaction (<5%) after 24 h with the solution remaining homogenous without structures. Since guanine has the lowest oxidation potential of the natural bases its the most likely nucleotide to participate in an electron transfer process with [Ru(bpy)3]2+. The inability of guanine to catalyze the reaction demonstrates that the process is dependent upon the presence of a specific information molecule having the correct redox potential and is therefore base specific. This implies that certain nucleic acid sequences embedded with at least one oxoG may lead to systems with enhanced catalytic efficiencies having inheritable advantages. The design criterion for our protocell uses an operational definition of a living system in which a container, a metabolic process and an information material interact to transform resources into building blocks which assemble into a container that can grow, divide, and undergo evolution. While we still have many experimental hurdles to overcome before realizing our protocell the above results are a significant advancement towards our design.

Molecular theory of lipid bilayers: Effects of alcohols and pore-forming peptides

Frischknecht, Amalie
Sandia National Laboratories

Lipid bilayers are important inhomogeneous fluid systems that mediate the interaction of cells with their environment. We have applied a classical density functional theory (DFT) to a coarse-grained model of lipid and solvent, designed to self-assemble into a bilayer. I will present two recent results: the effects of alcohols on the mechanical properties of lipid bilayers, and the structure and free energy of pores formed in the bilayer by assemblies of model peptides.

Ab initio study of exciton transfer dynamics from a core–shell semiconductor quantum dot to a porphyrin-sensitizer

Kilin, Dmitri
Los Alamos National Laboratory

The observed resonance energy transfer in nanoassemblies of CdSe/ZnS quantum dots and pyridyl-substituted free-base porphyrin molecules [Zenkevich et al., J. Phys. Chem. B 109 (2005) 8679] is studied computationally by ab initio electronic structure and quantum dynamics approaches. The system harvests light in a broad energy range and can transfer the excitation from the dot through the porphyrin to oxygen, generating singlet oxygen for medical applications. The geometric structure, electronic energies, and transition dipole moments are derived by density functional theory and are utilized for calculating the Förster coupling between the excitons residing on the quantum dot and the porphyrin. The direction and rate of the irreversible exciton transfer is determined by the initial photoexcitation of the dot, the dot–porphyrin coupling and the interaction to the electronic subsystem with the vibrational environment. The simulated electronic structure and dynamics are in good agreement with the experimental data and provide real-time atomistic details of the energy transfer mechanism.

Electronic Properties of DNA Base Molecules Adsorbed on a Metallic Surface

Kilina, Svetlana
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The internal electronic structure of single deoxyribonucleic acid (DNA) base molecules, i.e. guanine, adenine, cytosine, and thymine, adsorbed on a metallic surface of Cu(111), is determined in detail using density functional theory (DFT) computations. In contrast to the intuitive belief that a molecule weakly interacts with a substrate and its electronic structure is only slightly perturbed, our simulations reveal strong hybridizations and interactions between molecular and metallic states. Stipulated by the symmetries of a base molecule and the Cu(111) surface, oxygen atoms of a base approach close to the substrate, breaking the parallel orientation of the π-system with respect to the surface. Such a behavior is the most pronounced for one oxygen containing bases, leading to the chemisorption of cytosine and guanine and stronger hybridization of their electronic states with metallic ones. Oxygen free adenine, on the other hand, lies nearly flat on a Cu substrate and interacts weakly with the surface through physisorption. The calculated local electron density of states spectra demonstrate the absence of pure localized molecular states for all four DNA bases, yet, show the smallest delocalization for adenine and thymine and the largest for guanine and cytosine. The observed diversity of the geometrical and electronic structures of the nucleobases on the Cu substrate provides guidelines for interpreting DNA tunneling spectra in the scanning tunneling microscopy (STM) measurements. Our results open a new prospective for understanding bio-molecule adsorbates and have an important implication for a possible differentiation of nucleotide sequences in DNA through STM.

Simulation of water in nanoconfinement between self-assembled monolayers

Lane, J. Matthew D.
Sandia National Laboratories

Abstract unavailable

3D tracking of individual quantum dots

Lessard, Guillaume
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We describe an instrument that extends the state of the art in single-molecule tracking technology, allowing extended observations of single fluorophores and fluorescently-labeled proteins as they undergo directed and diffusive transport in three dimensions. Our instrument is based on a modified confocal microscope geometry with multiple single-photon detectors. We demonstrate 3D tracking of single quantum dots diffusing at rates comparable to those of intracellular signaling processes.

Dynamics, Rectification, and Fractionalization for Colloids on Flashing Substrates

Libal, Andras
University of Notre Dame

We show that a rich variety of dynamic phases can be realized for mono- and bidisperse mixtures of interacting colloids under the influence of a symmetric flashing periodic substrate. With the addition of dc or ac drives, phase locking, jamming, and new types of ratchet effects occur. In some regimes we find that the addition of a non-ratcheting species increases the velocity of the ratcheting particles. We show that these effects occur due to the collective interactions of the colloids.

Structural Model for Estane Based on Self-Consistent Field Theory

Maniadis, Panagiotis
Los Alamos National Laboratory

We are investigating the equilibrium properties of multi-block copolymer melts using self consistent field theory (SCF). Our model block copolymer is Estane 5703, which is a multi-block with 28 repeats of alternating soft and hard segments. About one-fourth of the hard segments are present as oligomers with the remainder being monomers separated by soft segments. The SCF model has been extended to include this level of structural complexity. The mechanical properties of this material arise from the phase separation of the components and the creation of hard and soft domains. The oligomeric and monomeric hard segments have different temperature dependent separation properties which accounts for the gradual softening of the material as the temperature is raised. We use the SCF theory to study the phase separation processes and determine the contribution of the detailed structure to the elastic properties. SCF theory is also now extended to explicitly include the elastic fields (stress and strain), allowing further inspection of the structural contributions to the mechanical properties. LA-UR-06-2665, LA-UR-07-0466

Modeling aggregation of multivalent biomolecules in cellular systems.

Monine, Michael
Los Alamos National Laboratory

Aggregation of receptors on cell surface by extracellular multivalent ligand initiates a variety of biochemical reactions at early stages of signal transduction in cells. It is a dynamic process; alterations in kinetics of receptor aggregation can result in different levels of receptor activity. This, in turn, modifies intracellular regulatory pathways that include reactions between cytoplasmic signaling molecules. For example, receptor aggregate formation is vital for proper functioning in many antigen, hormone and cytokine receptor systems that control immunological reactions [1-3]. Recent studies of signal transduction in T cells have shown that receptor aggregation can also be mediated by intracellular molecules, such as adaptor and effector proteins, which act cooperatively [2]. In last two decades, the phenomenon of receptor aggregation has been studied by many groups, both experimentally and mathematically. In experimental systems, however, an exact statistics on receptor aggregates cannot be obtained yet. Therefore, the simulations, in which dynamics of aggregates is quantified explicitly, are of great benefit to understanding the kinetics of aggregation. Aggregation phenomenon is associated with the exponential increase in the number of chemical species and distinct cross-linking interactions, therefore, dynamic simulations of such complex biomolecular systems with the help of conventional methods (such as ODEs, etc.) become intractable. To resolve the complexity of this problem, we propose a stochastic algorithm based on Gillespie method [4]. Our kinetic model is originally designed for well-mixed systems, however, in case of diffusion-limited interactions, diffusion effects can be included as corrections to the reaction rates. To validate the simulation results, we use a thermodynamic equilibrium theory that quantifies all possible configurations on the surface [5]. We apply the

developed model to simulate recent experimental data obtained for various systems of multivalent interactions [2,3,6]. Using reasonable values of kinetic parameters in the developed model, we are able to reproduce quantitatively the experimental observations. We are currently working on generalization of the algorithm and incorporating it in to a rule-based software [7].

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Collective Behavior in Epithelial Sheets

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The movement of epithelial sheets plays fundamental roles in the development and renewal of complex tissues, from the separation of early embryonic tissue to homeostasis in the adult intestine. Yet, considering its broad importance as an essential biological process, it has eluded a clear and quantitative interpretation in physical terms, prohibited by the lack of understanding of the basic relationship between motility, cell-cell contact, and their mediation by the physical environment. In particular, the factors that influence how physical interactions that originate at the cellular level, i.e. the balance between cell-cell and cell-matrix stability evolve to bring about stable multi-cellular behavior are completely unknown, complicated by seemingly contradictory observations. Most glaringly, the presumed translation of cells on soft media (basal lamina), and the physical role of cell division (as a motive force) in this process constitute two physical paradoxes in the movement of epithelial sheets. Thus, in this study, we use statistical methods to quantify the precise cell-cell interaction as mediated by adhesion to surfaces that are constant in adhesivity, but vary in rigidity. We further use this uncovered relationship to prove that sheet motion is not an individual effort, but collective - whose degree is mediated by modes of adhesion to a substrate.

How does a straight polymer relax?

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Although the relaxation dynamics of semiflexible polymers from an initially straight conformation has been discussed extensively in the literature, this seemingly simple problem involves nontrivial physics that is not yet completely understood. This is partly due to the ambiguous meaning of ``initially straight'', for which various realizations are conceivable. The filament could be stretched (by optical tweezers, electric fields, elongational flows, ...), but it could also be quenched, i.e., prepared in an initial low-temperature environment. In all cases, the longitudinal contraction is driven by the same purely stochastic forces, yet the resulting deterministic growth laws for pertinent observables reflect for short times fundamental differences in the underlying relaxation processes. We present a comprehensive explanation how these differences emanate from the various realizations and how they give rise to universal long-time relaxation. Further, we compare my theoretical results to recent experiments and simulations, give suggestions on how to test our predictions, and comment on the choice of proper observables.

Quantum dynamics of isomerization - Making a Bio-molecule qubit for a quantum computer

Santamore, Deborah
Los Alamos National Laboratory

Abstract unavailable

A unified geometric theory of mesoscopic stochastic pumps and reversible ratchets.

Sinitsyn, Nikolai
Los Alamos National Laboratory

I will present a unifying theory of geometric effects in mesoscopic stochastic kinetics, such as the adiabatic pump and the reversible ratchet effects, as well as similar phenomena in other domains. I will show that all they follow from geometric phase contributions to the effective action in the stochastic path integral representation of the moment generating function of particle fluxes. The theory provides a universal technique for identification, prediction and calculation of pump-like phenomena in an arbitrary mesoscopic stochastic framework. The applications to a simple Michaelis-Menten reaction as well as to complicated biochemical reaction networks will be reviewed.

Studies of myoglobin dynamics by dielectric relaxation spectroscopy

Stroe, Izabela
Los Alamos National Laboratory

Proteins are dynamic molecules and their motions are intimately linked to the fluctuations of their solvent environment. In this work we studied the protein-solvent interactions by measuring the dielectric response of horse myoglobin (Mb) in glycerol/H2O mixtures over a frequency range of 40Hz-110MHz. Two relaxation processes were observed at temperatures above 220K. The high frequency process corresponds to the fluctuations of the glycerol/H2O solvent and its rates were found to increase slightly at the presence of the Mb protein. The low frequency process, slower by roughly four orders of magnitude, is relevant to Mb motions and absent for the samples without Mb. The temperature dependence of the two processes can be approximated with the same Vogel-Tammann-Fulcher temperature dependence. Preliminary analyses suggest that the Mb-related process is associated with the conformational fluctuations of the whole Mb protein. Such fluctuations require the coordinated motions of surrounding solvent molecules and are thus an example of protein slaving to the solvent fluctuations

Simulation of suspensions of hydrodynamically interacting self-propelled particles

Underhill, Patrick
University of Wisconsin, Madison

Recently large collections of swimming microorganisms have been observed producing collective motions on a scale much larger than the scale of a single organism. To better understand the cause of these motions, simulations of large populations of hydrodynamically interacting swimming particles have been performed at low Reynolds number in periodic and confined geometries. Each swimmer is modeled as a rod containing beads with a propulsion force exerted on one bead (with an equal and opposite force exerted on the fluid) and excluded volume potentials at the beads. At small concentrations, the swimmers behave analogously to a dilute gas in which the hydrodynamic interactions perturb the ballistic trajectories into diffusive motion. Simple scaling arguments can explain the swimmer behavior as well as the behavior of passive tracer particles. As the concentration increases, the multi-body hydrodynamic interactions lead to large-scale collective motion.

Nanofluidic Diode

Vlassiouk, Ivan
UC Irvine

We present a nanofluidic diode that at voltage range (-5 V, +5V) rectifies ion current with degrees of rectification reaching several hundreds. The diode is based on a single asymmetric nanopore whose surface was patterned so that a sharp boundary between positively and negatively charged regions is created. This boundary defines a zone that is enriched with positive and negative ions or creates a depletion zone. The principle of operation of the nanofluidic diode is analogous to that of a bipolar semiconductor diode.

Hidden Structure in Protein Energy Landscapes

Wall, Michael
Los Alamos National Laboratory

We have used inherent structure (IS) theory to study the vibrations about local minima in the energy landscapes of three proteins using a coarse-grained Go model. The vibrational free energy Fv, estimated in a harmonic approximation, decreases with the potential energy ea of IS a, and drops faster after a critical value ec, where breaking native contacts tends to create residues without any native contacts. The density of inherent structures with ec initially rises exponentially; however, due to the structure of Fv vs. ea, it exhibits a shallow maximum at the highest potential energies, like a structural glass. The results indicate that vibrations are a nontrivial consideration in protein dynamics, including the kinetics of protein folding.

An Iterative Matrix-Free Method in Implicit Immersed Boundary/Continuum Methods

Wang, X. Sheldon
New Jersey Institute of Technology

The objective is to present an iterative solution strategy for implicit immersed boundary/continuum methods. Mixed finite element formulations are introduced for compressible immersed solids and compressible surrounding viscous fluid. As a key ingredient of the fully implicit time integration, a matrix-free combination of Newton-Raphson iteration and GMRES iterative linear solver is proposed. This iterative implicit finite element approach marks the beginning of a general computation framework for various continua immersed in another continuum, which is essential for biological system modeling.

Dendrimers as Synthetic Gene Delivery Agents

Welch, Paul
Los Alamos National Laboratory

Several recent medical advances require the delivery of nucleic acid strands into living cells, a nontrivial task necessitating a protective vehicle for the genetic material. The precise molecular-level picture of how the therapeutic strands are loaded into the carrier, how the complexes enter the cell, and how the genetic material is transported into the nucleus is missing. This is a major roadblock to the development of new treatments for a host of genetic diseases and viral infections, as well as to the creation of safer, more robust immunization methods to protect against potential bioterror assaults. We will present a first step toward removing this barrier in this poster. In particular, we will report the results from computer simulations of coarse-grained models of host/polyelectrolyte complexes and the dynamics of their attachment to charged planar surfaces.

Application of molecular dynamics simulations in the design of a minimal self-replicating molecular machine

Weronski, Pawel
Los Alamos National Laboratory

When is a molecular aggregate alive? Although the definition of life is still controversial, there is general agreement that a chemical assembly of molecules can be considered alive if it can ingest resources and convert them into building blocks; has the ability to grow and self-reproduce; and can evolve. In the design recently proposed by Rasmussen and Chen [Science 303 (2004) 963–965] the assembly or protocell could be as simple as a small micellar surfactant aggregate acting as a container by anchoring an informational molecule to its exterior and incorporating a metabolism within the oily interior. The physics of such a system can be modeled using Molecular Dynamics (MD) simulations. Based on MD investigations we present the process of the protocellular grow and division. Second we demonstrate the potential applications of the MD approach for calculating the affinity of a peptide nucleic acid (PNA) informational molecule to the protocell/water interface. Finally we use the MD method to calculate the conformation dynamics of a PNA dimer molecule in water, as the conformation influences the molecule's redox potential, which turns out to be an important parameter in designing the protocellular metabolism. The work is supported by the Los Alamos LDRD-DR project Protocell Assembly for the Department of Energy under the contract W-7405-ENG-36.

Fluctuating Polymer Rings

Winkler, Karen
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Geometric constraints have been proven to induce interesting behavior on polymers. We consider polymers confined to a ring-like structure as observed for DNA and cytoskeletal biopolymers. To account for the internal structure of polymers and polymer bundles, a coarse-grained elastic ribbon model with anisotropic bending stiffness and twist stiffness is investigated analytically for small fluctuations. The model predicts the mean square diameter of a ribbonlike ring, thus giving a novel parameter to determine bending and twist stiffness of polymers in experiment. Comparison with Monte Carlo simulations show agreement up to tremendously high flexibility. The reason for this finding is an effective stiffening of the polymer's conformations due to the ring geometry which can be quantified. A further phenomenon caused by the geometric constraint is the coupling of bending and twisting modes. Polymer rings occur in biology on different scales of flexibility. The change of their behavior on increasing the flexibility is studied by observing the shape of polymer rings with symmetric cross sections. We identify two distinct shape regimes. In the stiff regime planar, elliptical conformations dominate, while in the flexible regime three-dimensional, crumpled structures prevail. In the stiff limit a scaling regime explains the observed behavior. In the flexible regime a power law is extracted. In-between the two regimes both structures are almost equally probable. We suppose that these findings have implications for a variety of biological processes such as the polymer's flow behavior, the mobility in heterogeneous media such as the cytoplasm and the search process of enzymes to their specific binding site on DNA.
[1] Karen Alim and Erwin Frey (2007) The shape of semiflexible polymers, q-bio/0703049 [2] Karen Alim and Erwin Frey (2007) Fluctuating semiflexible polymer ribbon constrained to a ring, in preparation

Excited State Electronic Structure in Branched conjugated Molecules and Complexes: Exciton Scattering Approach

Wu, Chao
Los Alamos National Laboratory & Washington State University

pi - conjugated dendrimers are molecular examples of quasi-one-dimensional tree-like structures known in physics as Bethe lattices. Electronic excitations in these systems can be spatially delocalized or localized depending on the branching topology. Without a priori knowledge of the localization pattern, rationalization and understanding photoexcitation dynamics refected in experimental optical spectra is difficult and 'supramolecular'-like quantum-chemical calculations quickly become intractable as the molecular size grows. Here we develop reduced exciton scattering (ES) model, which attributes excited states to standing waves in quasi-one-dimensional structures, assuming quasi-particle picture of optical excitations. Direct quantum-chemical calculations of branched conjugated phenylacetylene chromophores are used to verify our model and to derive relevant parameters. Complex and non-trivial delocalization patterns of photoexcitations throughout the entire molecular tree can then be universally characterized and understood using the proposed ES method, completely bypassing 'supramolecular' calculations. Frenkel-exciton models appear as limiting cases of our approach. This opens a new and accurate way to model excited state dynamics and energy transfer in arbitrary branched structures.

Reversal Facilitates the Collective Motion of Gliding Bacteria

Wu, Yilin
University of Notre Dame

Different from flagella driven bacteria, some types of bacteria use gliding motility to move, like myxobacteria. Myxobacteria are rod-shape and commonly found in cultivated soil. They glide along their long-axis direction with small deviations, and reverse gliding directions regularly with almost fixed periods. By means of computational modeling, we try to understand how reversal facilitates the collective motion of myxobacteria. We also investigate how cell size and cell density affect the relation between reversal period and collective motion efficiency. The study may help to understand the genetic origin of reversal in rod-shape gliding bacteria.

Optical investigations of the liquid crystal phases of nano-scale duplex DNA and RNA

Zhu, Chenhui
University of Colorado

Polymeric DNA duplexes are known to exhibit a chiral Nematic (N*) and a hexagonal columnar LC phase. We found that even very short douplex DNA oligomers (6- to 20- bp (base pairs)) form Lyotropic LC phases depending on the concentration of DNA in water, even though the length-to-diameter ratio of the shortest oligomer is hardly bigger than 1. Based on texture observations by polarized light microscopy, we identified the N* phase, two distinct columnar phases (C1 and C2), and a non-LC X phase. The N* phase appears in the lowest concentration of DNA, forming the “cholesteric focal conic” (Fig. a) or “planar” texture. As the DNA concentration is increased, the C1 phase appears, forming circular or leaf-shaped domains of uniform birefringence color [Fig. b]. The next higher concentration phase is the C2 phase, which forms dendrites or tree-branch shaped domains [Fig. c]. The highest density X phase is optically isotropic [Fig. d] but solid, and therefore might either be crystal or an amorphous glassy phase. Temperature induced transitions among N*, C1 and C2 were not observed as is expected in lyotropic systems. We used optical interferometry to measure DNA concentration. We have found that the structure of C1 is hexatic by x-ray microbeam diffraction using synchrotron radiation source. To understand the existence of the LC phases of such short oligomers, we propose that short DNA duplex stack end-to-end, forming long rods. Unpaired bases at the ends of oligomers (or the presence of salts) suppress the LC phases, although mixing with long DNA (500-900bp) does not. In parallel, we are also working on short RNA and PNA (peptide nucleic acid) systems. RNA/RNA duplexes (8bp, 10bp) have shown some LC phases, such as C1 and X phase. PNA is an analogue of DNA and it has no charge unlike DNA (negatively charged). The binding of PNA/PNA, PNA/DNA and DNA/DNA decreases. We have seen that PNA/PNA duplex form big crystals easily, which could be due to its lack of the electric repulsion between neighbor duplexes. Work supported by NSF MRSEC Grant DMR 0213918 and NSF Grant 0072989.

Physical theory of the transport through the nuclear pore complex

Zilman, Anton
Los Alamos National Laboratory

Proper functioning of all eukaryotic cells depends critically on the transport of macromolecules between the cell nucleus and the cytoplasm, which proceeds through the nuclear pore complexes (NPC). Several characteristics of the NPC transport make it distinct from other common forms of biological transport. In addition to being central biological question, the transport through the NPC poses challenging physical problems. We develop a physical theory of transport through the NPC that explains its functional properties in terms of its structure. In particular, we propose a novel mechanism of selectivity enhancement that does not require input of metabolic energy. The theory can be extended to other signaling mechanisms, and suggests strategies for creation of artificial nano-molecular sorting devices.

I. BACKGROUND

Proper functioning of all eukaryotic cells depends critically on the transport of macromolecules between the cell nucleus and the cytoplasm, which proceeds through the nuclear pore complexes (NPC). This transport is mediated by transport proteins that bind their cargo in the nucleus (or the cytoplasm), and transport it through the NPC [1,2]. In milliseconds time [1], the NPCs are able to selectively transmit - over the background of vast amount of non-specifically interacting macromolecules - only the cargoes that are bound to the transport proteins.

Remarkably, this fast and highly selective filtering does not require an active input of metabolic energy, and occurs purely by diffusion. Moreover, unlike common ‘lock and key’ transport gating mechanisms, the NPC is always in the ‘open’ state, known as ‘virtual gating’ [2].

Internal space of the pore and large parts of its nuclear and cytoplasmic surfaces, are filled by unfolded, flexible polypeptide chains that create the permeability barrier [2]. A crucial component of the selective NPC transport is the transient binding of the transport proteins to this unfolded filaments [1]. Strikingly, the NPCs have been shown to function even when a large fraction of the material comprising the pore is deleted [1].

We have developed a physical theory of transport through the nuclear pore complex, which rigorously models the diffusion of the transport proteins through the meshwork of fluctuating filaments, controlled by the transient binding to the filaments [3].

II. RESULTS OF THE MODEL

Using analytical theory, and computer simulations, we have modeled the transport through the NPC as diffusion in an effective potential, determined by the interactions of the transport factors with the meshwork of fluctuating filaments inside the pore.

The first question we address is how binding to the pore can enhance the transport efficiency. The theory shows that the macromolecules that do not interact with the pore have a very low probability of traversing it. By contrast, binding of

the transport proteins to the pore increases the time they spend inside the pore, but also increases the probability to traverse it [3].

Limitations of space inside the pore lead to the competition between translocating cargoes, and at too high binding affinities, the pore becomes jammed. This leads to a preferential binding affinity that optimizes the transport, and provides the mechanism for the selectivity [3].

However, the predicted and measured optimal binding affinity is relatively low- of the order of 10-20 kT. The NPC, however, has to filter out non-specifically binding macromolecules whose binding affinity sometimes lies in the range of several kT from the optimal one. We have proposed a novel selectivity mechanism, and shown that in the case of direct competition between the cognate transport proteins, and non-specific cargoes, the selectivity increases far beyond the differences in the equilibrium binding affinities, and the non-specific cargoes are essentially filtered out [3].

Finally, we have shown how the flexibility of the filaments makes the transport relatively insensitive to their total number. Due to the thermal fluctuations of flexible filaments, the transport proteins can diffuse while still attached to a filament, and transfer to the next one. This makes the transport insensitive to the total number of filaments as long as the regions of their fluctuations overlap [3].

The proposed mechanisms of selectivity apply to other modes of biological signaling, e.g. transport through narrow channels, and cascades of enzymatic reactions, and suggest strategies for creation of artificial molecular sorting devices.

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