Abstracts

Phase-Field Model of Self-Polarization and Cell Movement

Igor S. Aranson

Modeling the movement of living motile cells on substrates is a formidable challenge; regulatory pathways are intertwined and forces that influence cell motion on adhesive substrates are not fully quantified. Additional challenges arise from the need to describe a moving deformable cell boundary and contact line dynamics. Here, we present a simple mathematical model coupling cell shape dynamics, treated in the framework of the Ginzburg-Landau-type equation for auxiliary mass density (phase field), to a partial differential equation describing the mean orientation (polarization of actin filaments) of the cell’s cytoskeletal network. In order to maintain the total area of the cell, the phase field equation is subject to a global conservation constraint. Correspondingly, the equation for mean polarization incorporates key elements of cell mechanics: directed polymerization of actin network at the cell membrane, decay of polarization in the bulk of the cell, and formation of actin bundles (stress fibers) in the rear. The model successfully reproduces the primary phenomenology of cell motility: discontinuous onset of motion, diversity of cell shapes and shape oscillations, as well as distribution of traction on the surface. The results are in qualitative agreement with recent experiments on the motility of keratocyte cells and cell fragments. The asymmetry of the shapes is captured to a large extent in this simple model, which may prove useful for the interpretation of recent experiments and predictions of cell dynamics under various conditions.

Microscopic reversibility: the Organizing Principle for Design, Operation, and Characterization of Molecular Machines

Dean Astumian

Molecular machines are often viewed as miniaturized versions of macroscopic machines – nano-cars, molecular elevators, microscopic scissors, etc. The goal in designing such devices is to achieve controlled mechanical motion on the molecular scale, where just as in the macroscopic world the device is operated by application of a force that causes a well-defined local movement that initiates a more or less deterministic sequence of motions that define the function of the machine - cause and effect. The problem with this perspective is that the ineluctable presence of thermal noise is ignored. While this is a reasonable approximation on the macroscopic scale, this picture breaks down at the molecular level, where energy differences between states are generally less than 50 times the thermal energy $k_B T$, and where the power input by an external energy source is typically very much less than the thermal noise power that continually washes over any molecular system in contact with a thermal environment. The bottom line is that attempts to apply external forces to cause well defined motion of molecules are unlikely to be successful in practice.
The presence of thermal noise does however open up approaches for controlling motion at the nanometer scale that are not viable at the macroscopic scale. Since by equipartition thermal noise excites all motions of a molecule, the use of external energy to prevent undesired motion leaves behind the motion the motion by which a molecule can carry out a specific mechanical function. This principle of operation has come to be known as a Brownian motor mechanism.

In my presentation I will discuss how microscopic reversibility is the organizing principle of molecular machines just as “cause and effect” is the organizing principle for macroscopic machines.

Stabilized microtubules displaced by a high-density carpet of dyneins are well described as aligning self-propelled particles

Hugues Chaté

Motility assays provide an ideal playground for controlled experiments on active matter/collective motion. Here I report on experiments in which stabilized microtubules are displaced by a carpet of dynein c motors grafted to a substrate. At large densities of motors and filaments, a lattice of large-scale vortices spontaneously emerges. Each vortex is formed by moving microtubules turning both clockwise and anticlockwise.

A Vicsek-style model where microtubules are represented by aligning self-propelled particles, whose features are determined by further experimental data on single filament motion and binary collisions, accounts well for the observed collective dynamics. If time allows I will discuss the general properties of such models, and in particular their "active crystal" phases.

Modeling of the Janus particle via mesoscopic simulations

Pierre de Buyl

I will present recent results on the self-propulsion of the Janus particle, studied via computer simulations. The modeling method will be presented, including hydrodynamical, chemical and geometrical aspects.

The model is based on an assembly of spheres, held together by holonomic constraints and immersed into a solvent described by the Multiparticle Collision Dynamics algorithm. The fluid is chemically active: solvent particles may be converted from a species to another species.

The chemical assymetry of a compound makes it possible to generate a chemical gradient around the compound that drives its motion, hence the term "self-propulsion".

Results of microscopical simulations will be presented, clarifying the nature of the gradient. The propulsion mechanism, in combination with the orientational motion, leads to ballistic motion (on a first timescale) then, for larger times, to diffusive motion. Those results are
presented for two kinds of chemical reactions: a unimolecular and a dissociation-
recombination reaction.

Organization of the microtubule cytoskeleton by molecular motors

Marileen Dogterom

Models of synthetic molecular motors

Holger Flechsig

Molecular motors are nanoscale engines that carry out a variety of functions in the cells
related to force generation and intracellular transport. Underlying their organized activity are
cyclic ordered conformational changes induced by the hydrolysis of ATP molecules. Since
these internal motions are slow, they cannot be reproduced in molecular dynamics
simulations and, therefore, approximate descriptions of reduced complexity are needed.
Recently, coarse-grained network models, with a protein pictured as a deformable elastic
object have been employed to study biologically relevant motions in various molecular
motors [1-3].

To understand general aspects of the operation of molecular motors, it can be beneficial to
consider artificially constructed analogs of protein motors. We have proposed and
investigated an elastic-network model of a device that can be viewed as a prototype of an
artificial molecular motor. Similar to real motors, the model is able to perform cyclic ordered
conformational motions powered by ligands. Comparable to myosin responsible for force
generation in the muscles, the designed motor device is able to convert, through a ratchet
mechanism, its active cyclic internal motions into a steady net force applied to a filament. In
computer experiments, effects of thermal fluctuations and of external forcing were
investigated.


Active motion and information processing at the molecular scale

Pierre Gaspard

Energy transduction processes powering molecular motors and information transmission are
described in the perspective of recent results in nonequilibrium statistical mechanics.

In the first part, the chemomechanical coupling between the hydrolysis of ATP (adenosine
triphosphate) and the rotation of the F1-ATPase molecular motor is modeled with stochastic
processes fitted to experimental results [1,2,3].
The modeling reveals the importance of the nonlinearities in the chemomechanical coupling at the nanoscale, as well as the regimes where the thermodynamic efficiencies reach their maximal values allowed by the second law.

In the second part, copolymerization processes are studied from the viewpoint of thermodynamics and information [4,5]. In biological systems, examples of copolymerization are given by DNA replication, the transcription of DNA into mRNA, and the translation of mRNA into proteins. These nonequilibrium processes can be considered as active motion in the heterogenous landscape formed by the random sequence of units composing the copolymer.

At the single-molecule level, these systems are described in terms of stochastic processes.

In free copolymerization, the thermodynamic entropy production turns out to be related to the Shannon disorder of the grown sequence.

In the case of copolymerization with a template as in the biological examples, the thermodynamic entropy production is also related to the mutual information between the sequence of the template and its copy.

The consequences of these results are discussed.

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Self-phoresis, anomalous dynamics, and collective behavior of active colloids

Ramin Golestanian

The force-free nature of phoretic transport mechanisms allow us to design self-propelled particles by equipping them with a mechanism that could create the appropriate gradient that could lead to directed motion, e.g. by using asymmetric particles with built-in sources.

This idea was verified experimentally using polystyrene Janus particles half-coated with platinum in a solution of hydrogen peroxide.

In my talk, the following two aspects of the dynamics of such active colloids will be examined. It will be shown that the stochastic motion of self-diffusiophoretic colloids is anomalous due the memory effect of the concentration profile of the solute molecules and density fluctuations. The collective behavior of a dilute solution of thermally active particles
will be probed, and shown to lead to interesting effects including depletion and instabilities depending on the parameters.

Enzymes as Molecular Machines
Raymond Kapral

Biological systems make frequent use of molecular motors to perform tasks such as active transport of material in the cell, cell locomotion and replication. Even simpler examples of molecular machines are proteins performing enzymatic catalysis which undergo cyclic internal conformational motions that are coupled to ligand binding and dissociation events. Like molecular motors, these enzymes must carry out their functions in highly fluctuating, often-complex environments. The talk will describe recent work on the meso-scale dynamics of protein machines and motors.

Active diffusion and fluctuations in cells
Fred MacKintosh

Modeling collective behavior of motile eukaryotic cells, and coordination of cell motility via the extracellular matrix
Roeland Merks

Brownian search-and-catch mechanism in motor protein and the quantification for the energy conversion
Mitsuhiro Iwaki

It is believed that biological linear molecular motors (myosin, kinesin, dynein, etc.) generate force by dominantly structural changes in their composition. Myosin’s swinging lever-arm model is a typical hypothesis, where the tilting of the lever-arm domain is strongly coupled to the force generation. On the other hand, random diffusion and forward catch of myosin head to actin is also directly visualized during the directional motion. Myosin-V and -VI are appropriate target in that both (1) Lever-arm swing and (2) Brownian search-and-forward catch can be directly visualized during the directional motion. Remaining mystery is which process is critical for the force generation? And how is the mechanism for rectifying random Brownian motion? Here, we answered the questions by improving single molecule measurement techniques (Iwaki et al., Nat. Chem. Biol., 2009; Fujita and Iwaki et al., Nat. Commun., 2012). We report the strain-sensor mechanism to realize the rectification of random Brownian motion and the quantification for the force generation. Also, we’ll discuss the physiological meaning of the dual function (lever-arm swing the Brownian search-and-catch) in myosin transporters.
Elastic-Network Modeling of Protein Machines

Alexander S. Mikhailov

Protein machines, operating as motors, enzymes or ion pumps and processing other molecules, such as DNA, play a fundamental role in biological cells. Full molecular-dynamics (MD) simulations of such active molecules on the scales covering their complete cycles are still far beyond the reach of modern computers. Over the past decade, efficient coarse-grain descriptions for proteins, picturing them as elastic networks (EN), have however been developed and explored. In this talk, I will show how the EN models can be applied for studies of protein machines and give examples of their application for several important proteins, including two molecular motors, myosin and HCV helicase, and actin.

Open issues in averaging pedestrian flows and collagen structures

Adrian Muntean

We study the evolution of a class of self-propelled systems of particles or of density of particles driven by nonlocal velocities, incorporating clearly defined and strong drift terms as well as additional perturbative (social) effects like anisotropies, two-scale local pressures, eventual visco-elasticity etc. The main question triggering our research refers especially to which extent effects visible at the microscopic discrete or stochastic scale (i.e. at the particle/individual level) can lead to significant macroscopic effects (at the population level). In other words, we wish to prepare the proper terrain for the passage to the many particle limit $N\to\infty$, where $N$ denotes the number of particles.

Chromatin organizing molecular motors

John van Noort

Chromosome structure, cell type specificity and DNA metabolic processes are all affected by the positions of nucleosomes along DNA. Here I will discuss the apparent paradox between the high abundance of ATP-dependent DNA based molecular motors, dedicated to shift nucleosomes around, and the recent success of DNA sequence-based predictions of nucleosome positions in vivo. We have used single-molecule techniques to characterize two very different types of remodeler complexes, i.e. yRSC and dMi2. Both reposition the histone octamer with the same 10 bp intervals, which appears to be intrinsic to the DNA sequence that was used for reconstitution of the nucleosome substrates. The data are consistent with a diffusive model composed of successive remodeler binding, nucleosome translocation and remodeler release steps. On top of this generic behavior we observed a directional preference for repositioning and increased translocation processivity outside of the nucleosome positioning sequences. We adapted a nucleosome position prediction algorithm to reproduce nucleosome positioning with single base-pair accuracy, as demonstrated for some well-known nucleosome positioning sequences. From this model we extracted the
energy landscape for nucleosome positioning which is key to the detailed understanding of nucleosome repositioning DNA-based molecular motors.

Collective Motion of Self-Propelled Soft Particles

Takao Ohta

We investigate dynamics of deformable self-propelled particles based on the model equations for a single soft particle which has a coupling between migration and shape deformation [1]. The dynamics is governed by the time-evolution equations of the center of mass and the deformation tensor. Two models are introduced to study the collective motions of interacting particles. The first one (model I) has a repulsive interacting potential whose magnitude depends on the relative direction of elongation of a pair of particles [2, 3]. The force from other particles as well as a noise term are added to the equation for the center of mass. The other model (model II) has also a repulsive pair-wise potential but without an explicit alignment mechanism. This force enters both in the equation of the center of mass and in the equation for the deformation tensor so that existence of other particles causes directly shape deformation [4].

Numerical simulations are carried out in two dimensions by changing the noise intensity, the interaction strength and the particle density to obtain the phase diagram of the ordered and the disordered states. We take a Gaussian form of the interaction potential as a function of the distance between a pair of particles. In model I, the ordered state is a collective motion of the elongated particles which form a translational hexagonal lattice. By increasing the particle density and/or noise intensity, the collective motion is broken via a discontinuous transition. We show by a mean field analysis that deformability is a favorable origin for the transition [2, 3]. In model II, we show a variety of dynamics, not only the collapse of ordered state at high density, but also “cluster lattices” and “laning” depending on the density and the interaction strength [4]. It is noted that the instability of the ordered state at high density exhibited in both models might be related to the so-called reentrant fluids predicted in colloids with a Gaussian core potential [5, 6].


Geometries of phosphatidylinositol waves and large-scale membrane deformation during spreading and random movement of Dictyostelium.

Satoshi Sawai
By employing phase map analysis, we show that geometry of phosphatidylinositol (3,4,5)-trisphosphate (PIP3) and F-actin waves at the basal membrane in randomly moving growth-stage Dictyostelium cells can be characterized by the number, charge and position of spatial phase singularities; i.e. points which represent organizing centers of rotating waves. A single isolated singularity near the cellular edge induced a rotational protrusion, whereas a pair of singularities supported translational extension. These singularities appeared by strong phase resetting due to de-novo nucleation at the back of pre-existing waves. Analysis of a theoretical model indicates excitability of the system that is governed by a positive feedback from PIP3 to PI3K activation, and we show experimentally that this requires polymerization of actin. By comparing experimental data with the model, we demonstrate that outwardly propagating spiral and concentric waves that those that are reflected back from the boundary compete for dominance and dictate the complex patterns of temporal and spatial changes in the global cell morphology.

Breathing, sliding, proof reading: On how to access packed DNA

Helmut Schiessel

DNA in plants and animals are densely packed inside DNA-protein complexes called chromatin. In this talk I focus on the first level of compaction, the nucleosome. Nucleosomes are DNA-spools with a protein-core and engage about three quarter of DNA at any time. How DNA can nevertheless be accessed by the various proteins that have to bind to specific DNA target sequences will be the subject of my talk. I show how all the DNA is temporarily exposed through thermal fluctuations and why, nevertheless, nucleosomes are very stable against those fluctuations. I then discuss chromatin remodeller, active molecular machines, that can pull or push nucleosomes along DNA. Rather than discussing molecular details of those machines that yet have to be uncovered, I propose a possible kinetic proofreading scheme that might be at work inside chromatin.

Active Brownian Motion - Effects of Noise on Self-Propelled Particles

Lutz Schimansky-Geier

I consider self-propelled particles under the influence of noise, a concept which was called "active Brownian motion". First, I discuss the influence of active fluctuations, as independent stochastic processes in the direction of motion and velocity. Such description leads to an accumulation of probability at vanishing speed values. Secondly, effects of correlations in the noise and of scattering boundaries on the motion of the active particles are investigated. I present transport properties as the mean flux and the diffusion coefficient in different situations, e.g., overdamped, or with inertia, or with constant speed, and affected by additional torques etc. Furthermore, we consider interacting active Brownian agents. I focus on the problem how the onset of collective motion depends on the choice of the specific noise. Special attention is paid for the occurring large scaled spatial structures of chemotactically interacting Brownian agents.
**Motion Analysis of Self-Propelled Pt-Silica Particles in Hydrogen Peroxide Solutions**

**Ken Showalter**

Silica microspheres that are half coated with platinum metal undergo self-propulsion in solutions of H$_2$O$_2$, with the average speed increasing with increasing H$_2$O$_2$ concentration. Microscopic observation of the particle motion, with segmentation of the image data, demonstrates that the particles move, on average, with the platinum coated region oriented opposite to the direction of motion. Velocity autocorrelation and motion direction analyses show that the direction of motion is highly correlated with the particle orientation. The effect of the observation time interval on the measured translational diffusion coefficient and the apparent particle motion is analyzed.

**Emergent Collective Behavior of Self-Powered Catalytic Single Molecules and Nanoparticles**

**Ayusman Sen**

One of the more interesting recent discoveries has been the ability to design species which catalytically harness the chemical energy in their environment to move autonomously. These "bots" can be directed by chemical and light gradients. Further, our group has developed systems in which translating bots initiate long-range, collective interactions among themselves. We will discuss recent experimental results, as well as approaches to the modeling of the complex emergent behavior of these species.

**Active Protein Dynamics on DNA: Molecular assembly and fuelled collapse**

**Gijs Wuite**

Homologous recombination is essential for the preservation of genome stability. The core protein in this process, RAD51, drives homology search and DNA strand exchange, processes that requires the nucleation, assembly and disassembly (collapse) of a RAD51 filament on single-stranded (ss) and double-stranded (ds)DNA, coupled to ATP binding and hydrolysis. Here we show that we can characterize all these RAD51 DNA transactions on long individual DNA molecules, in real-time, at the single-protein level using a combination of single-molecule fluorescence microscopy and optical tweezers. These experiments show that the sizes of RAD51 nuclei on ssDNA vary and display a broad Poissonian distribution with an average size of 4 monomers. Filament extension tracked in time with single-protein resolution reveals that nuclei extend by one RAD51 monomer at a time with a rate independent of tension on the ssDNA. This is in contrast to force-dependent monomeric extension on dsDNA. Counting and timing individual RAD51 monomers disassembling from nucleoprotein filament on ssDNA also yields contrasting results compared with dsDNA, reflecting the difference in the underlying mechanical properties ssDNA and dsDNA based nucleoprotein filaments. Together, these results yield unprecedented quantitative insight in the mechanical rearrangement during formation and collapse of RAD51 nucleoprotein filaments.