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Structure and Function of G Protein-coupled Membrane Receptors – A Topic for Soft Matter Research

G protein-coupled membrane receptors (GPCR) are located in the plasma membrane of cells where they transmit extracellular signals elicited by compounds like neural transmitters, hormones, odorants, or light to the cell interior where they activate GTP-binding proteins (G proteins). This large superfamily of heptahelical molecules comprises receptors for dopamine, serotonin, epinephrine, opioids, and cannabinoids, just to mention a few. The proper function of GPCR is critical for all higher forms of life. GPCR are the known target of over 25% of all pharmaceuticals on the market and of an estimated 60% of all drugs that are currently under development. It has been shown that GPCR require a fluid lipid matrix of proper composition for their function.

My lab conducts structural and functional studies on two reconstituted GPCR of class A, bovine rhodopsin and recombinantly expressed cannabinoid receptor CB2. We investigate GPCR at close to functional conditions, in a fluid lipid matrix with a biologically relevant composition of lipids, with particular emphasis on polyunsaturated lipids as found in brain. There is evidence that neuronal GPCR may require high concentrations of lipids with polyunsaturated hydrocarbon chains for full activation. Lipids with polyunsaturated hydrocarbon chains are distinctly different from saturated and monounsaturated chains in their structure and motional properties, a topic to which studies by neutron scattering have made a major contribution.

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Glass transitions and Solid-solid Transitions in Colloidal Thin Films

Colloids are excellent model systems for the study of phase transitions.

Significant insights about glass transitions have been obtained from experiments on colloidal glasses composed of isotropic particles, but much less effort has been expended to study glasses composed of anisotropic particles. We measured the dynamics of a monolayer of colloidal ellipsoids by video microscopy and revealed that the rotational and translational motions become glassy at different densities; thus an intermediate "orientational glass" with glassy-rotational dynamics and liquid-like translational dynamics has been found. This intermediate phase was predicted to exist in 3D, but has never been observed. Interestingly, the fastest translating and rotating particles are anticorrelated in space. A crossover to a nematic phase for large aspect ratio particles and a crossover to a "rotator" phase for small aspect ratio particles are expected. In the second set of experiment, we studied the nucleation of a solid-solid transition between triangular and square lattices in microgel colloidal thin films. When the mother phase is a crystal, its nonzero strain energy and precursor defects can induce new behaviors in the nucleation process. We observed a surprising two-step nucleation: a liquid nucleus was first generated from a square lattice and then became a solid nucleus with triangular lattice. These results provide new challenges in theory and simulation.

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Theory of Slow-equilibration and Aging of Glass-forming Liquids

The self-consistent generalized Langevin equation (SCGLE) theory of colloid dynamics and dynamic arrest [1,2] has been recently been extended [3] to describe the irreversible evolution of the static structure factor and of the intermediate scattering function of a liquid in response to changes in the external macroscopic control parameters. This non-equilibrium theory has been applied to the description of the aging processes occurring in a suddenly quenched model colloidal liquid with hardsphere plus short-ranged attractive interactions, whose structure and dynamics evolve irreversibly from the initial conditions before the quench to a final, dynamically arrested state [4]. Here we also apply the same theory to the description of the slow dynamics of incompletely equilibrated glass-forming liquids. For this, we consider the equilibration process of a hard-sphere fluid prepared in a non-equilibrium state with the desired final volume fraction ϕ but with a prescribed non-equilibrium static structure factor $S_0(k; \phi)$ different from the equilibrium structure factor $S_{eq}(k; \phi)$. The evolution of the α -relaxation time $\tau_{\alpha}(k)$ and of the long-time self-diffusion coefficient D_L as a function of the evolution time t_w is then monitored for an array of volume fractions. For a given waiting time the plot of $\tau_{\alpha}(k;t_w,\phi)$ as a function of ϕ exhibits two regimes corresponding to samples that have fully equilibrated within this waiting time $(\phi < \phi^{(c)}(t_w))$ and to samples for which equilibration is not yet complete $(\phi > \phi^{(c)}(t_w))$. This two-regime scenario is observed in molecular dynamics simulations of incompletely equilibrated hard-sphere. In soft-sphere systems a similar scenario is also found to occur as a function of the pressure-totemperature ratio.

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Using Interfacial Manipulations to Generate Functional Materials from Nanostructured Polymers

As future technological progress necessitates the design and control of nanoscale devices, new methods for the facile creation of smaller features must be discovered. One sub-class of soft material, block copolymers, provides the opportunity to design materials with attractive chemical and mechanical properties based on the ability to assemble into periodic structures with nanoscale domain spacings. To employ block copolymers in many applications, it is essential to understand how interfacial energetics influence copolymer morphologies. Two areas of recent research in the group involve: (1) probing the effects of interfacial composition on block copolymer self-assembly using tapered block copolymers, and (2) generating gradient substrate and "free" surfaces for thin films block copolymer studies. In the first area, we are manipulating the interfacial region between blocks to control ordering transitions in tapered diblock copolymers and triblock copolymers. As an example of recent work, our normal and inverse tapered diblock copolymers show measurable decreases in the order-disorder transition temperature (T_{ODT}) relative to the corresponding non-tapered diblock copolymers; with the inverse tapered materials showing the greatest deviation in T_{ODT}. In the second area, we are manipulating polymer thin film interfacial interactions using discrete gradient methods to control the free surface interactions, and gradient arrays of assembled monolayers to influence the substrate surface interactions. In particular, our chlorosilane monolayer gradients and solvent vapor gradients permit rapid screening of the surface/polymer interactions necessary to induce the desired nanostructure orientations in many block copolymer systems.

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Effects of Neuronal Membrane Geometry on Ion Channel Distribution, Mobility and Activity

Neuronal activity depends upon the precise localization and concentration of a multitude of ion channel and receptor types, yet the individual molecules are surprisingly mobile. How do neurons modulate receptor diffusion to control synaptic strength? Could the high curvature of synaptic and dendritic membranes influence channel distribution or activity? To isolate the role of neuronal membrane geometry, we developed a biomimetic system based on cell-sized Giant Uni-lamellar Vesicles (GUVs) containing voltage-gated ion channels. With the GUV body acting as the neuronal "soma", an "axon" was formed by extracting a membrane tube from the GUV. Single particle tracking was then used to measure the diffusion of individual ion channels in the tubular membrane. Channels moved more slowly in membrane tubes with smaller radii (up to a 5-fold slowdown) and this reduced mobility was consistent with a hydrodynamic theory that extends the Saffman & Delbrück model to cylindrical geometries. Work is ongoing to understand how membrane curvature, composition and tension influence ion channel distribution and activity.