Welcome to the 9th Annual

Clorox-Amgen Graduate Student Symposium

Friday, September 30, 2016

Department of Chemical Engineering

University of California, Santa Barbara

Program and Abstracts

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9th Annual Clorox-Amgen Graduate Student Symposium

Friday, September 30, 2016

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Oral Presentation Abstracts

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Douglas Vogus	Engineering polymer drug conjugates to schedule synergistic chemotherapeutics

Session I: *Transport and Theory*

Enhancing the Accuracy and Applicability of Mechanistic Crystal Growth Models for Rapid Morphology Predictions

Carl Tilbury and Michael Doherty

Department of Chemical Engineering, University of California, Santa Barbara, CA, USA

The ability to make rapid *in-silico* predictions of crystal growth habit (shape) can provide a valuable screening step in the selection of crystallization conditions that confer optimum product functionality. In both industry and academia, simple non-mechanistic models are often applied towards this goal due to ease of use. Mechanistic models of crystal growth, however, offer far greater fidelity, but come at the expense of a higher barrier to entry. A proof-of-concept framework has recently been developed [1] that automates such mechanistic models for systems of industrial complexity, paving the way for future adoption. As a result, the systematic development of these techniques to extend their predictive capability is valuable. To this end, we have made various advancements. First, we introduced a framework to determine the dominant surface-integration-limited crystal growth mechanism operating on each face. This enables prediction of supersaturation-dependent habits, where faces may disappear from the morphology or the crystal aspect ratio may change; our model is able to reproduce experimentally observed examples of such effects. Second, we developed the interfacial model used to modify surface energetics according to the solvent used; by comparing sublimation and solution growth predictions and experiments over a variety of systems we confirmed its utility [2]. Third, we have augmented the expression for step velocity (a critical quantity in mechanistic models) of non-centrosymmetric growth units with a generalized model for kink density and a strategy to account for stable/unstable step edge layers. This strategy is supported by kinetic Monte Carlo simulations for the simple non-centrosymmetric example of a 2-layer step. These improvements act to increase the accuracy of habit predictions and enable application across a wider array of systems and growth conditions. Furthermore, such techniques can enable rational crystal engineering by offering physical, mechanistic insight into how habit modifications may be realized by tailoring growth conditions.

References:

[1] Li, J.; Tilbury, C. J.; Kim, S. H.; Doherty, M. F. *Prog. Mater. Sci.* **2016**, *82*, 1-38.
[2] Tilbury, C. J.; Green, D. A.; Marshall, W. J.; Doherty, M. F. *Cryst. Growth Des.* **2016**, *16* (5), 2590-2604.

Size-Dependent Surface Free Energy of Water Nanodroplets: Energetic and Entropic Components and Implications for Nucleation

Mark N. Joswiak,[1] Michael F. Doherty,[1] Baron Peters[1,2]

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Curved interfaces are present in emulsions, near protein surfaces, at membranes, and in atmospheric aerosols. They can differ greatly from planer interfaces; for example, surface curvature can influence coordination numbers and mobility of molecules at the vapor-liquid interface. Moreover, several experiments, theories, and simulations [1] point to a curvature-dependent surface free energy, where for droplets, $\gamma(R) = \gamma(\infty)\ (1 - 2\delta/R)$, where R is the droplet radius and δ is the Tolman length [2]. Reasonable estimates for the Tolman length can dramatically alter predicted nucleation kinetics, and can therefore be a route to improved predictions.

We compute $\gamma(R)$ by reversibly splitting droplets into equal-sized subclusters (Figure 1) for the TIP4P/2005 (all-atom) and mW (coarse-grained) water models [3,4]. While the two models differ significantly, they yield equivalent $\gamma(R)$, with a Tolman length of $\delta = -0.56$ Å at 300 K. Our computed Tolman length agrees well with independently measured kinetics [5,6]. To understand why TIP4P/2005 and mW water yield the same δ, we decompose the surface free energy into energetic and entropic components. We find that the surface energy dominates the change in γ for TIP4P/2005, whereas the surface energy and entropy are nearly equal contributors for mW water. We explain our findings in terms of surface broken bonds and correlations within the droplet (Figure 2). Our findings have potential implications in atmospheric science and in hydrophobic drying transitions.

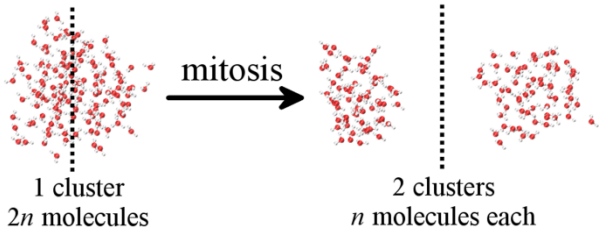

Figure 1: Snapshots from simulations of TIP4P/2005 for a single droplet (left) that is reversibly split into two equal-sized subclusters (right).

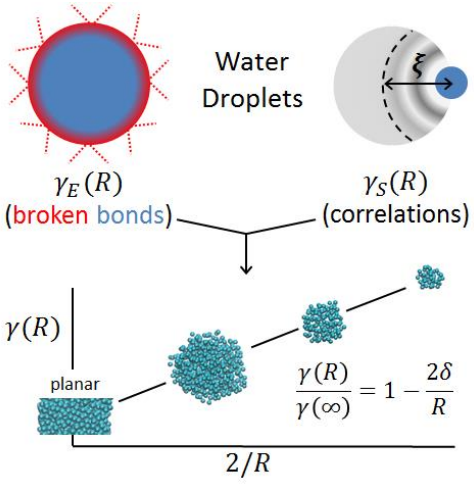

Figure 2: Schematic summary of our hypothesis for the energetic and entropic contributions to γ(R). Snapshots are from simulations of mW water droplets.

References:

[1] Malijevský, A.; Jackson, G. *J. Phys-Condens. Mat.* **2012**, *24*, 464121.
[2] Tolman, R.C. *J. Chem. Phys.* **1949**, *17*, 333-337.
[3] Joswiak, M. N.; Duff, N.; Doherty, M. F.; Peters, B. *J. Phys. Chem. Lett.* **2013**, *4*, 4267-4272.
[4] Joswiak, M. N.; Doherty, M. F.; Peters, B. *in review*
[5] Azouzi, M. El M.; Ramboz, C.; Lenain, J.-F.; Caupin, F. *Nat. Phys.* **2013**, *9*, 38-41.
[6] Brus, D.; Ždímal, V.; Smolík, J. *J. Chem. Phys.* **2008**, *129*, 174501.

Accelerating nucleation with trace additives

Geoffrey G. Poon, Stefan Seritan, and Baron Peters

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Additives are used to control nucleation in many natural and industrial processes. However, the mechanisms by which additives inhibit or accelerate solute precipitate nucleation are not well understood. We developed a theoretical design equation that predicts changes in the nucleation rate based on the adsorption properties and concentration of dilute additives. The equation shows that the most efficient additives at promoting nucleation have a large adsorption equilibrium constant, suggesting that assays of the equilibrium constant might facilitate additive design. We show that the design equation applies to a lattice model with surfactant-like additives.

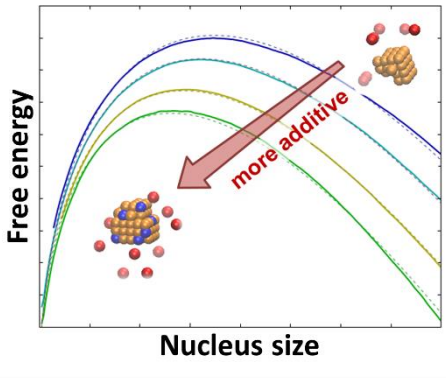

Figure 1: Increasing additive concentration reduces the free energy barrier and accelerates nucleation.

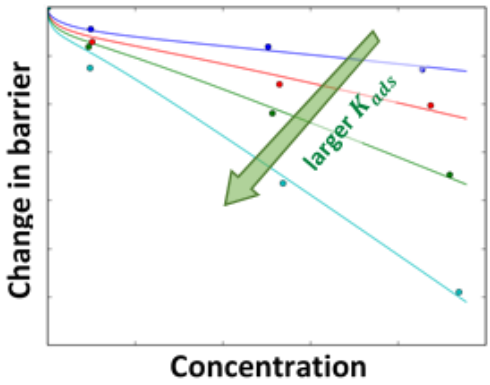

Figure 2: Increasing the adsorption equilibrium constant reduces the free energy barrier and accelerates nucleation.

Interfacial Polymerization Kinetics for Reverse Osmosis Membranes

Arash Nowbahar,[1] Vincent Mansard,[1] Mou Paul,[2] Jodi M. Mecca,[3] Todd M. Squires[1]

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Reaction kinetics for interfacially polymerized reverse osmosis (RO) membranes are difficult to obtain and seldom reported due to the rapid (~seconds) formation of a thin film. In this work, film formation is studied using an interferometric based technique (Figure 1). Light is passed through a semireflective microfluidic device, to obtain fringes of equal chromatic order (FECO fringes). The wavelengths of FECO fringes are tracked as a function of time to obtain changes of refractive index, which correspond to changes in solute concentrations. Hence, monomer depletion in each phase is tracked throughout the reaction, with data acquisition at rates up to tenths of a second. Directly visualizing the depletion zone near the interface allows for measuring the reagent flux and ultimately properties of the reaction itself. We report the first measurement of concentration profiles as the reaction proceeds, as well as reaction rate and total mass formed (Figure 2).

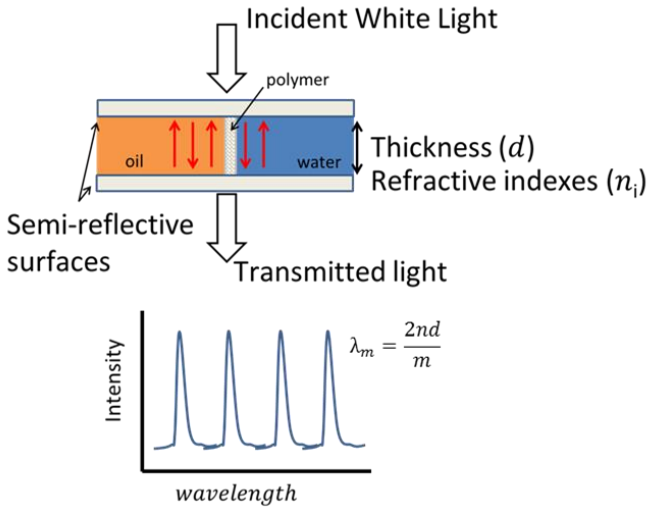

Figure 1: Interferomety setup for studying interfacial polymerization. Transmitted light shows interference pattern whose peaks are determined by the refractive index.

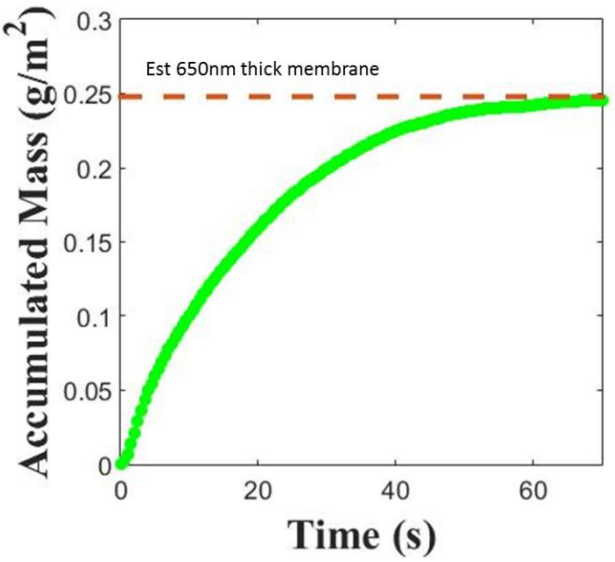

Figure 2: Example of total mass of monomer reacted to form membrane. Dashed line shows estimate for the mass of a 650nm thick membrane

Session II: *Materials*

Photo-responsive membrane proteins in nanostructured silica as new materials for light-activated ion transport

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Membrane proteins are versatile biomolecules with diverse functionalities that fulfill sensing, signaling, transport, or catalytic roles to support the viabilities of biological cells. Such proteins typically span the hydrophobic lipid bilayers of cellular membranes and allow the highly selective transport of molecules or signals between the hydrophilic extracellular and cytoplasmic environments. One interesting example is the membrane protein proteorhodopsin that, in response to light, selectively transports H^+-ions across the soft lipid bilayers of bacterial cells in support of cellular metabolic processes. To exploit membrane proteins for technological purposes often requires their incorporation into mechanically robust synthetic materials that enable the proteins to function stably and be integrated into macroscopic devices. However, this has been exceedingly challenging, because the highly hydrophobic membrane proteins are notoriously difficult to process in stable and functionally active forms. We have developed a synthetic protocol that allows high concentrations (up to 20 wt%) of active proteorhodopsin molecules to be incorporated within nanostructured silica-surfactant membrane hosts. Synthesis conditions and compositions were selected to stabilize proteorhodopsin molecules in the presence of the structure-directing surfactants and aqueous-soluble network-forming silica species that co-assemble to form nanostructured silica host matrices, as established by small-angle X-ray diffraction analyses. By using state-of-the-art multidimensional solid-state NMR techniques, the molecular structures of proteorhodopsin guests in the synthetic host materials are shown to be native-like, though with several interesting differences. In addition, the transient photo-responses of the proteorhodopsin molecules in nanostructured silica are very similar to those in native-like environments, which establishes that the proteorhodopsin guests undergo a native-like photochemical reaction cycle. This materials platform is general and has been adapted to incorporate other functionally active membrane proteins in nanostructured silica host membranes. The versatile nanostructured silica-surfactant host materials are expected to open opportunities to integrate other membrane proteins and their diverse functionalities into synthetic semi-permeable membranes for applications such as chemical or biological sensing, separations, bioanalytics and energy conversion.

Correlating atomic-scale compositions, structures, & properties of heterogeneous zeolite catalysts

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The macroscopic reactivities and selectivities of heterogeneous zeolite catalysts depend strongly on atomic-scale order and disorder that develop during their initial synthesis/crystallization or subsequent exposure to reactor conditions. For example, nanoporous aluminosilicate zeolites, such as zeolite H^+-Y, ZSM-5, and chabazite (SSZ-13), are of considerable interest for conversion of hydrocarbons or removal of nitric oxides from automotive exhaust streams. These technological applications are enabled by the adsorption and catalytic reaction properties of zeolites, which are strongly influenced by the distributions and local environments of non-stoichiometric framework aluminum atoms and their associated exchangeable cations. Measuring the atomic-scale aluminum environments has been challenging, due to the complicated distributions of the framework aluminum atoms to which scattering techniques are insensitive. Here, complementary analyses by X-ray diffraction, solid-state nuclear magnetic resonance (NMR) spectroscopy, and electron microscopy provide detailed information on both the long-range structural order and distributions of atomic environments in aluminosilicate zeolites. Notably, new dynamic-nuclear-polarization (DNP)-enhanced NMR techniques provide significantly enhanced signal sensitivity (ca. ×100) that allows the detection and correlation of distinct ^{29}Si and ^{27}Al framework species in materials at natural isotopic abundance (4.7%) of ^{29}Si, which until now have been infeasible to characterize. Our analyses establish the types, distributions, and relative proximities of different silicon and aluminum environments, the latter of which influence the cation-exchange sites that account for the macroscopic catalytic properties of the materials. The results yield new insights on zeolite catalysts and their complicated atomic-scale structures, which we correlate with technologically important (e.g., methanol-to-olefin and deNO_x) reaction properties. We are using similar techniques and analyses to understand the types and distributions of atomic environments that govern the macroscopic properties of other non-stoichiometric engineering materials, including compound semiconductors, solid-state oxide phosphors, and cementitious structural materials with diverse technological applications.

New non-precious-metal mesoporous carbon electrocatalysts and their properties

Niels P. Zussblatt, Todd Squires, and Brad F. Chmelka

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Fuel cell technologies, while promising for their high efficiencies, have tended to be used for specialized applications, often because of the high costs of platinum-based electrocatalysts required for their operation. Although Pt-based materials are used for both anode and cathode catalysts, the slow kinetics of the cathodic oxygen reduction reaction (ORR) have required much higher Pt cathode catalyst loadings, and thus there is a strong cost incentive to replace the cathode catalyst with a non-precious-metal alternative. Pt-based electrocatalysts are also susceptible to deactivation by many liquid fuels, including methanol or ethanol [1]. In addition, commercial catalyst supports are often based on activated carbon, which generally have small mean pore sizes (<2 nm) that often result in severe diffusion limitations that reduce the rates of O_2 reaction. One way of overcoming these challenges is to use nitrogen- and transition-metal-functionalized mesoporous carbon materials as electrocatalysts. Such mesoporous carbon materials are attractive, because they exhibit high electrical conductivities, large surface areas (>800 m^2/g), and uniform, adjustable, and larger mean pore dimensions (3-5 nm), with improved mass transport and reaction properties. We have developed a series of high-nitrogen-content mesoporous carbon materials and the means to alter their compositions, structures and stabilities by the inclusion of transition metal species (e.g., Fe) to increase the extents of graphitization of the materials [2,3]. Our Fe,N-containing mesoporous carbon catalysts exhibit oxygen reduction activities that are comparable to commercial electrocatalysts that rely on platinum supported on activated carbon (Pt/C). Compared to the commercial catalysts, the Fe,N-functionalized mesoporous carbon materials also exhibit much higher robustness to deactivation by residual alcohol, carbon monoxide, or other deactivating species. Through close feedback of synthesis, characterization, and electrocatalytic activity testing, we have acquired detailed atomic-level understanding of the origins that underlie the optimal catalyst properties. The new non-precious-metal electrocatalysts are promising alternatives to Pt/C and are expected to be less expensive and exhibit fuel cell performances, particularly in alcohol-fueled devices. On-going efforts aim to operate fuel cells using ethanol produced in an integrated microbial fermentation chamber, to demonstrate their suitability for unconventional, biomass-based fuels. Similar nitrogen-functionalized mesoporous carbon materials are expected to be adaptable to other applications, including for water treatment, battery electrodes, and supercapacitors.

References:

[1] Gewirth, A.; Thorum, M. *Inorg. Chem.* **2010**, 49, 3557-3566.

[2] Fechler, N.; Zussblatt, N. P.; Rothe, R.; Schlögl, R.; Willinger, M.-G.; Chmelka, B. F.; Antonietti, M. *Adv. Mater.* **2016**, *28*, 1287-1294.

[3] Kim, D.; Chung, H. T.; Zussblatt, N. P.; Zelenay, P.; Chmelka, B. F. submitted to *ACS Appl. Mater. Interfaces*.

Session III: *Polymers and Interfacial Phenomena*

Directed self-assembly of diblock copolymers in multi-VIA configurations: using chemically patterned substrates to reduce defectivity and placement errors

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Directed self-assembly (DSA) of block copolymers is a promising low-cost, high throughput patterning tool to supplement existing techniques in microelectronic manufacture. One highly attractive application is the patterning of vertical interconnect accesses (VIA) for fabricating conducting channels between circuit layers. In order to accommodate the continued push towards more densely-patterned systems, it is advisable to move to multi-VIA configurations in which two or more features are assembled within a single template. Unfortunately, these larger systems contain more plentiful and complicated defect modes than those found in single-hole shrink systems. In the case of 1D linear arrays of multiple VIAs in a single prepattern, there exists the additional complication of thermal fluctuations. Previous work has demonstrated that thermal fluctuations in larger arrays cause cylinder placement to vary widely around the equilibrium positions in a manner analogous to the collective excitations in a simple 1D coupled oscillator model. In order to suppress these thermal placement errors and plentiful defect modes, we introduce chemically selective patterns on the substrate of the system. In the present work, we identify chemopatterning schemes that maximize defect energies and assess their efficacy in suppressing the thermal placement errors in these linear arrays using self-consistent field theory (SCFT) simulations.

Self-Assembly and Crystallization of P3EHT Containing Block Copolymers

Emily Davidson, Victor Ho, Bryan Beckingham, and Rachel Segalman

Department of Chemical Engineering, University of California, Santa Barbara, CA, USA

Conjugated polymers are of considerable interest for organic electronic devices, and the crystallization of conjugated polymers is highly coupled to their charge transport properties. Here, block copolymers are leveraged as a controlled platform to study the impact of confinement on conjugated polymer crystallization. In particular, the polymer poly(3-(2'-ethyl)hexylthiophene) (P3EHT) is leveraged as a model system in these diblock architectures because the depressed melting transition relative to the widely-studied P3HT enables both robust microphase separation of the resulting diblocks and detailed control over the crystallization processes. A series of block copolymers with rubbery (poly(methyl acrylate), PMA) and glassy (polystyrene, PS) second blocks were synthesized to investigate the impact of chain tethering on the resulting crystallization. All diblocks robustly self-assemble in the melt, forming both lamellar and (minority P3EHT) cylindrical morphologies. The resulting crystalline P3EHT successfully confined within P3EHT-*b*-PMA microdomains illustrates the importance of careful design strategy to balance the driving force for crystallization (which can result in crystallization dominated self-assembly) with large segregation strengths (which can impede block copolymer ordering kinetics). While P3EHT successfully crystallizes with a rubbery poly(methyl acrylate) block, crystallization is inhibited when confined by a glassy PS block. X-ray scattering of shear-aligned crystallized P3EHT-*b*-PMA reveals that microdomains induce an orientation of chains perpendicular to the domain interfaces. Furthermore, P3EHT-*b*-PMA samples exhibit considerable expansion of domains upon crystallization, emphasizing that P3EHT prefers to form extended-chain crystals in confinement. The inhibited crystallization in P3EHT-*b*-PS is attributed to the inability of glassy PS domains to accommodate either the extended chain P3EHT crystals or local densification of chains at the interface [1]. This work emphasizes the unique constraints that the drive for extended-chain crystallization places on self-assembly, and the importance of considering these interactions when designing such hierarchical architectures.

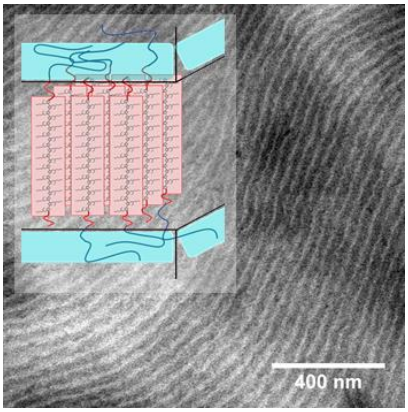

Figure 1: Block copolymers containing the conjugated polymer P3EHT self-assemble into microphase separated domains in the melt; microdomains morphology and block identity distinctly template and control crystallization.

References:

[1] Davidson, E.C.; Beckingham, B.S.; Ho, V.H.; Segalman, R.A. *J. of Polymer Science Part B: Polymer Physics* **2015**, *54*, 205-215.

Characterizing the Surface Interactions between Gecko-Inspired Adhesives and Diversified Substrates

Nicholas Cadirov, Jacob Israelachvili

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Geckos have developed foot pads that allow them to maintain their supreme climbing ability despite vast differences in environment, from dry desert to humid rainforest. The discovery and understanding of the gecko's footpad structure and frictional-adhesion climbing mechanism has allowed researchers to mimic and create gecko-inspired adhesives. Successful gecko-inspired mimics should exhibit necessary adhesive and frictional performance across a similarly diverse range of terrain and climate. As of yet, there have been limited studies on the combined effects of preload, shearing speed, surface roughness (topographical or chemical), or humidity on adhesion and friction properties of the biomimetic adhesives. In this study, a Surface Forces Apparatus (SFA) was used to measure adhesion and friction forces of an array of anisotropic (tilted) half-cylinder-shaped polydimethylsiloxane (PDMS) microfibers against smooth and rough silica surfaces, as well as in varied humidity. The SFA provides a controllable experimental setup to create such environments and allow for the measurement of adhesion and friction forces down to the μN (10^{-6} N) level. A fundamental understanding of the adhesion and friction mechanisms taking place between the gecko mimetic adhesives and diverse surfaces, including capillary forces and stick-slip friction, can be obtained by studying these systems in real time at the microscale. The anisotropy of the fibers is shown to play an important role in creating gripping and releasing states in the adhesives, just as geckos do. With the results from these studies, it will be possible to determine the best way to design a biomimetic adhesive and create an actuating mechanism for a climbing robot that requires a low energy input and enables high speed and versatile climbing and movement in any environment.

Characterizing surface hydration through parallel measurements of water diffusivity and surface forces

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The fundamental molecular origins of solvent-structural forces, such as hydration and hydrophobic interactions, remain a mystery. Surface forces measurements, while accurate, are complicated by the need to distinguish between simultaneous electrostatic, steric, and solvent-structural forces, a task that is particularly challenging for silica and lipid bilayer surfaces. Here, I will discuss our efforts to use two complementary nanoscale measurements of surface water diffusivity, using Overhauser Dynamic Nuclear Polarization (ODNP), and surface forces measurements, using the surface forces apparatus (SFA), to elucidate the mechanisms of surface hydration at silica and lipid bilayer surfaces. Bilayer surfaces were studied in the presence of varying bulk concentrations of dimethyl sulfoxide (DMSO), a commonly used cellular cryoprotectant. The surface water diffusivity increases with DMSO concentration, as does the adhesion force between bilayers. Both trends appear to be caused by a shrinking of the hydrated volume of lipid head groups by DMSO, which allows for extraction of quantitative surface hydration length scales. Similar insight was gained for silica surfaces by adjusting surface, rather than solution, properties. Silica (SiO_2) surfaces are composed of silanol (Si-OH) groups, which impart hydrophilic character, and siloxane (Si-O-Si) groups, which give rise to modest hydrophobicity. Over a range of silica surface compositions, water diffusivity near the surface increases with decreasing silanol density (increasing hydrophobicity), and the surfaces exhibit a corresponding decrease in the range of the hydration repulsion. None of the silica surfaces adhere in water due to a short-range (1-4 nm) repulsion, likely arising from the hydration of uncharged (deprotonated) silanols. Overall, our work suggests two contrasting paradigms for surface hydration: hydrated excluded volume of individual surface groups, and a collective hydrogen bond network.

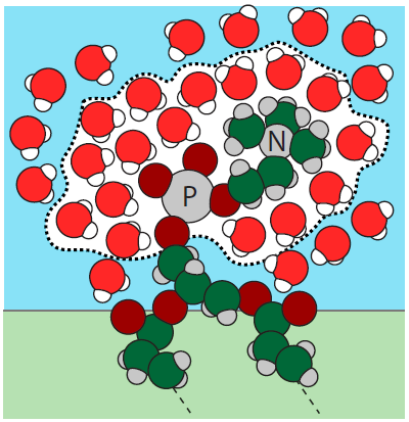

Figure 1: Schematic view of a lipid head group in water. A white background indicates solvation/hydration/bound water, and a blue background indicates bulk water.

Session IV: *Biomolecules and Biomaterials*

Estimating ribozyme kinetics from analysis of in vitro evolution

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Ribozymes and other biological reagents generated through *in vitro* selection have become important tools in medicine and the life sciences; but as selection methodology advances, our understanding of the evolutionary dynamics involved lags far behind. Selections often fail, require additional rounds to converge on a candidate sequence, or simply behave erratically. Existing theory does little to predict such difficulties or offer solutions, relying on distribution parameters and assumptions never tested in a selection environment. By combining selection theory with observations of real-world evolving molecular populations, it should be possible a mathematical description of the actual dynamics involved in a ribozyme selection. Here, we demonstrate several statistical techniques and that show promise in analyzing the ideality, scope of evolution, and fitness landscape present in a selection for a triphosphorylation ribozyme. Using new methodology, we find evidence for novel models of stochastic effects during *in vitro* selection, as well as of an initial distribution of chemical activity in random molecular space. The magnitude of such distributions is consistent with existing difficulties in selection design, suggesting that stochastic effects play a significant role in complicating selections, and suggesting selection parameters for optimizing future similar selection. Our results also show some correlation between estimated fitness and measured ribozyme activity, suggesting a viable alternative to the heuristic methods typically used to interpret high-throughput selection data, with further significance to many types of *in vivo* selection.

Engineering Regulation in Anaerobic Gut Fungi during Lignocellulose Breakdown

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To strengthen existing renewable technologies, it is critical to engineer efficient methods to extract sugars from crude biomass (lignocellulose). Recent efforts have focused on consolidated bioprocessing to address this challenge, which combines breakdown and product fermentation steps in one microbial platform. However, it is extremely difficult to engineer industrial platform microbes to hydrolyze lignocellulose. An exciting alternative to this approach would combine multiple microbes in consortia that compartmentalize the difficult processes of lignocellulose breakdown and product conversion within separate platforms. For this application, anaerobic gut fungi possess a wide array of biomass degrading enzymes required to efficiently break plant material into its constituent sugars. Here, we look to characterize the substrate uptake, metabolism, and enzyme networks within a diverse panel of anaerobic fungi isolated from large herbivores. To apply this technology, we have also constructed a two microbe co-culture system consisting of anaerobic fungi and the yeast *S. cerevisiae*, where fungi function to hydrolyze biomass and yeast act to ferment sugar-rich hydrolysate into target chemicals.

We have used RNA sequencing technologies to elucidate the regulation patterns of biomass degrading enzymes in response to growth on a variety of carbon sources ranging in complexity from simple sugars to complex biomass. These results pinpoint the environmental conditions that maximize production of biomass degrading enzymes. Two novel strains of gut fungi demonstrated unique regulation patterns that could be harnessed for biotechnology. *Anaeromyces robustus* utilizes a global mechanism for regulation in response to cellobiose to increase expression of all types of biomass degrading enzymes. In contrast, *Neocallimastix californiae* demonstrates a more dynamic regulation with separate mechanisms governing expression of cellulases and hemicellulases. These diverse mechanisms in two genera of gut fungi underscore the importance of developing a deeper understanding of regulation for individual gut fungal strains.

We further identified that the activity of anaerobic gut fungal enzymes was sufficient to release excess fermentable sugars during growth on cellulose and lignocellulose. During growth on crystalline cellulose as much as 50% of the cellulose is converted into excess glucose that can be fed to a model microbe for production. During growth on crude reed canary grass, only 10% of the cellulose present in the plant material was released as excess glucose, but a reducing sugar analysis revealed that glucose represented only a small portion of the sugars present overall. Metabolic reconstruction identified gaps in sugar metabolism pathways within anaerobic fungi such as galactose, arabinose, and mannose metabolism. While the fungi are capable of releasing these sugars from biomass, our models show that the fungi will not metabolize them, presenting opportunities to link the growth of another organism through nutrient dependency. These gaps in sugar metabolism as well as the excess activity of biomass degrading enzymes demonstrate the potential of anaerobic gut fungi for consortia-based consolidated bioprocessing. While they still lack genetic tools, they may be applied in co-culture with organisms commonly used for production, particularly organisms that can take advantage of the gaps in fungal sugar metabolism.

Engineering polymer drug conjugates to schedule synergistic chemotherapeutics

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While combination chemotherapy is commonly used to treat metastatic breast cancer, the success is typically limited by systemic toxicity. To improve therapeutic efficacy, polymer drug conjugates carrying synergistic ratios of chemotherapy drugs can be used to selectively target cancer cells. While the importance of drug ratio on synergy has been previously investigated, the effect of temporal scheduling is not well understood. Here, we systematically evaluated the effect of temporal scheduling of doxorubicin (DOX) and gemcitabine (GEM) to determine both synergistic drug ratios and drug schedules. To engineer the temporal scheduling of DOX and GEM, hyaluronic acid drug conjugates with distinct linkers conjugating both DOX and GEM were optimized to control: (i) their individual release kinetics so as to match the optimized schedule and (ii) their molar ratios so as to optimize the synergistic dose. We show that polymer conjugates that expose breast cancer cells to GEM at least hours prior to DOX at GEM:DOX ratios > 1 are more effective at killing breast cancer cells compared to healthy epithelial cells. These results emphasize the importance in understanding the effect release rates have on the efficacy of synergistic drugs and provide the groundwork for the design of novel delivery systems capable of delivering exact molar ratios of synergistic drugs with temporal control.

Poster Presentation Abstracts

1	**Anirudha Banerjee**	Soluto Inertial Phenomena: Designing Long-Range, Long-Lasting, Surface Specific Interactions in Suspensions
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3	**Chih-Cheng Chang**	Aging oil-water interfaces with asphaltene adsorption: interface rheology and heterogeneity
4	**Scott P. O. Danielsen**	Hierarchical Structure and Structural Transitions of a Conjugated Polyelectrolyte in Aqueous Solution
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7	**Jeffrey A. Frumkin**	A Target Upper Bound on Reaction Selectivity via Feinberg's CFSTR Equivalence Principle
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18	**Nicole Schonenbach**	Elucidating the role of the adenosine A2a receptor's C-terminus on oligomerization and function
19	**David J. Smith**	A Molecular Thermodynamic Model for Nanoparticle-Membrane Interactions
20	**Justin I. Yoo**	Development of tools and strategies to engineer G Protein-Coupled Receptors

Soluto Inertial Phenomena: Designing Long-Range, Long-Lasting, Surface Specific Interactions in Suspensions

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Equilibrium interactions between particles in aqueous suspensions are limited to distances less than 1 μm. Here, we describe a versatile concept to design and engineer non-equilibrium interactions whose magnitude and direction depends on the surface chemistry of the suspended particles, and whose range may extend over hundreds of microns and last thousands of seconds. The mechanism described here relies on diffusiophoresis, in which suspended particles migrate in response to gradients in solution. Three ingredients are involved (Fig. 1): i) a soluto-inertial (SI) "beacon" designed to emit a steady flux of solute over long time scales; ii) suspended particles that migrate in response to the solute flux; and iii) the solute itself, which mediates the interaction. We demonstrate soluto-inertial interactions that extend for nearly half a millimeter and last for tens of minutes, and which are attractive or repulsive, depending on the surface chemistry of the suspended particles. Experiments agree quantitatively with scaling arguments and numerical computations, confirming the basic phenomenon, revealing design strategies, and suggesting a broad set of new possibilities for the manipulation and control of suspended particles [1].

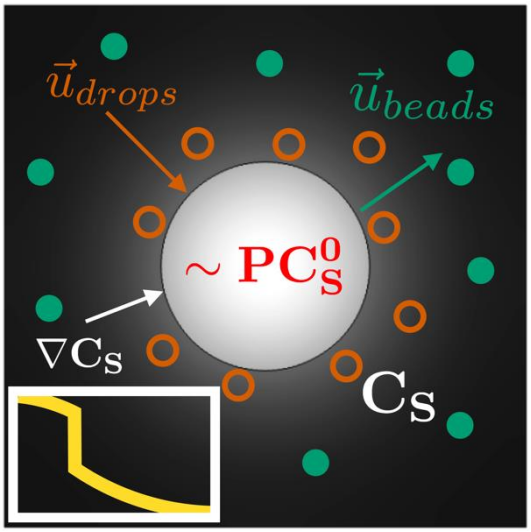

Figure 1: Long-range SI interactions. An SI beacon (gray), initially loaded with a high solute concentration, is placed in a solute-free suspension. A solute out-flux is established during equilibration, driving nearby suspended particles into diffusiophoretic migration. The magnitude and direction of migration depends on interactions between the particle surface and the solute, depicted here by particles of different surface chemistries (orange and green) that migrate either up or down the solute gradient. (Inset) Schematic radial profile of solute concentration inside and outside of the beacon.

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Analyzing the antibody specificity repertoire in age-related macular degeneration

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Age-related macular degeneration (AMD) is a leading cause of blindness in aged individuals due to deterioration of the macula, a small region of the retina responsible for sharp, central vision. Immune system activation plays a significant role in the development and progression of AMD but the exact origins and targets of the immune system are not well understood. A common product of immune activation in inflammatory diseases is the production of antibodies, and identification of these antibodies can indicate disease risk, onset, or progression. Here, we used random peptide libraries to analyze the collection of peptides that bind to serum antibodies, or the antibody specificity repertoire, from AMD patients and matched controls. Computational analysis of the bound peptide sequences enabled the identification of antibody specificities present in AMD patients and absent in controls. Identifying antibody specificities unique to patients with AMD could lead to the development of biomarkers for improved diagnostics and early detection, providing opportunities for treatment before vision loss. Furthermore, the peptide sequences determined responsible for antibody binding in AMD patients could reveal novel antigens involved in disease onset and progression.

Aging oil-water interfaces with asphaltene adsorption: interface rheology and heterogeneity

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Water is often used in the production and processing of oil, but the water and oil must ultimately be separated. Such separations can be very challenging, because various surface-active materials naturally exist in crude oil that stabilize water-oil interfaces. Polycyclic aromatic hydrocarbons called asphaltenes are a broad class of surface-active compounds that adsorb at water-oil interfaces and stabilize such emulsions.

We use ferromagnetic microbuttons as interfacial rheological probes to probe the evolution of oil/water interfaces as asphaltenes adsorb, and the effect of chemical additives like ethylcellulose (EC) on the evolution of the mechanical properties of the interface. Oil/water interfaces progressively stiffen as asphaltenes adsorb; this process, however, can be prevented or reversed with the addition of EC.

To probe the mechanism behind these observations, we visualize the deformation (strain) field of the oil/water interface in response to the stresses imposed by the microbutton. Asphaltene-adsorbed oil/water interfaces show significant mechanical heterogeneity, with pronounced stiff and weak regions. EC affects these heterogeneous regions differently, suggesting various hypotheses for its action on asphaltene-stabilized interfaces.

Our study reveals the rich properties of water/asphaltene/oil interfaces, and highlights new tools to probe mechanically heterogeneous interfaces as they evolve in response to their local chemical environments.

Hierarchical Structure and Structural Transitions of a Conjugated Polyelectrolyte in Aqueous Solution

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The microscopic network structure and structural transitions of a conjugated polyelectrolyte (Poly[2,6-(4,4-bis-potassium butanylsulfonate-4H-cyclopenta-[2,1-b;3,4-b']-dithiophene)-alt-4,7-(2,1,3-benzothiadiazole)], CPE-K) were explored with X-ray and neutron scattering to highlight a novel, hierarchical structure formed upon gelation of CPE-K in water in the semi-dilute regime. CPE-K forms an entangled polymer mesh, where polymer chains are tied together by ionic crosslinks, comprising microgel clusters that percolate to form a macroscopic network. Melting of the gel structure with increasing temperature occurs through the dissolution of ionic crosslinks where ions gain mobility to move towards the exterior of microgel clusters inhibiting network percolation through electrostatic repulsion. Further, CPE-K lacks π-π stacking interactions, yielding conductive matrices that rely exclusively on intra-chain charge transfer.

Characterizing the electrochemically enhanced dissolution of silica and alumina in alkaline environments

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Alumina (Al_2O_3) and silica (SiO_2) materials are prevalent in geological environments and complex materials used for device fabrication, structural materials, and catalysts. In each of these systems, the solid-liquid-solid interface plays a crucial role in determining material properties and interactions in aqueous environments, especially with regards to dissolution. In particular, both pressure solution and chemical-mechanical polishing demonstrate that the dissolution of alumina and silica materials can be drastically enhanced in aqueous environments however the cause of enhancement is highly debated. Dissolution enhancement in both of these systems share the same setup: asymmetric, or distinct, materials in close proximity in a saline, aqueous environment. In this work, we study the enhanced dissolution of alumina and silica in alkaline environments due to the presence of asymmetric surfaces. Using the surface forces apparatus (SFA) to characterize the enhanced dissolution of alumina and silica in proximity to muscovite mica surfaces, we found that the dissolution is enhanced to varying degrees depending on the relative surface potentials of the asymmetric surfaces. The impact of key parameters of the electrostatic double layer, such as the decay length and surface potential, were explored to provide insight into the electrochemical enhancement. Our findings highlight the importance of the asymmetric solid-liquid-solid interface and have implications in a variety of technological applications, such as structural materials development and chemical mechanical polishing.

Polymorph Selection by Continuous Crystallization

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Polymorphic solids are ubiquitous in both nature and industry and generally exhibit unique mechanical, electrical, and physicochemical properties, as well as unique solubility curves in solution. Polymorph selective processing is necessary in many systems due to the typical material and pharmacokinetic property variation among polymorphs of the same chemical composition. The study of polymorphism in batch systems has a long history that has led to deep understanding of the concepts of solvent-mediated phase transformations and Ostwald's rule of stages. These fundamental ideas are applied in many papers and processes to steer batch processes towards a desired polymorph. Here, we present the implications of continuous processing on polymorphism, and outline a methodology that enables polymorph selection and simplifies the necessary process control strategies in applicable systems.

It is well known in batch crystallizer design that the polymorph distribution is governed by the induction time of the most stable form, and that in the limit of very long batch times the most stable polymorph is obtained. Continuous devices do not operate under a similar constraint. After an initial start-up phase, a continuous device can operate at a dynamically stable operating point indefinitely, regardless of the thermodynamic stability of the effluent crystals. Interestingly, essentially pure, thermodynamically metastable steady-states exist in systems in which the thermodynamically stable solid cannot nucleate and grow on the time scale of the crystallizer residence time. These conditions depend on design choices (such as solvent choice, temperature, residence time, feed supersaturation, etc.), and are therefore accessible in many systems. This concept has been formalized with the use of a bi-polymorph population balance model, the method of moments, and a linear stability analysis. The analysis gives simple functions of parameters (dimensionless groups) for which one can continuously produce thermodynamically metastable products based only on the relative polymorph dynamics.

This work was motivated by the experiments recently reported by Lai, Trout, and Myerson et al [1] on continuous crystallization in the L-glutamic acid system. We demonstrate agreement with their L-glutamic acid results as well as another set of data describing the continuous crystallization of p-aminobenzoic acid [2]. For many polymorphic compounds, engineering a process to produce a desired polymorph is as simple as finding a reasonable operating point for the continuous mixed-suspension mixed-product removal crystallization process (temperature, residence time, initial supersaturation, etc.).

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A Target Upper Bound on Reaction Selectivity via Feinberg's CFSTR Equivalence Principle

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Mole balances are widely used in the design of chemical plants and processing equipment as well as in conducting techno-economic and environmental analyses of potential chemical business ventures [1]. They allow us to calculate unknown flowrates into and out of a system once an appropriate number of specifications are made. On a broader level, mole balances also serve to bound the attainable region of a reaction system. That is, they tell us the maximum production rates of a desired product and the minimum waste generation rates of undesired products. We should not, however, expect that the entire attainable region be accessible for a process on which capacity constraints are imposed. For example, certain areas of the attainable region may be accessible only by permitting extremely low single-pass reactor conversions to achieve high selectivities resulting in impractically large recycle flowrates. It is the underlying kinetics of a chemistry that determine the size and location of these inaccessible regions.

Feinberg and coworkers developed the Continuous Flow Stirred Tank Reaction (CFSTR) Equivalence Principal which allows one to decompose any arbitrary steady-state reactor separator system with total reaction volume "V" into a new system comprising "R+1" CFSTRs (where R is the number of linearly independent reactions) with the same total reaction volume and a perfect separations system [2,3]. Using this methodology in conjunction with the kinetics of a system of interest, the attainable region given by the mole balances can be refined. Our work aims to further refine the attainable region by introducing flowrate capacity constraints on the CFSTR Equivalence Principle. The constraints on molar flowrates between the "R+1" CFSTRs and the separations system prevent large recycle streams and small reactor conversions. By optimizing this constrained system of CFSTRs, we can determine the maximum possible selectivity of several chemistries completely independent of reactor design given capacity constraints. We have investigated serial reaction networks and more complex reaction networks involving serial and parallel reactions. With the added constraints, the maximum possible selectivity for both types of reaction networks is less than 100%.

We have used this methodology to analyze the maximum possible selectivity of a selection of realistic chemistries and have compared the results to archetypal reactors (e.g., CFSTR, PFR). The results all support the hypothesis that this CFSTR reactor decomposition can be constrained and optimized to obtain a target upper bound on selectivity for chemistries completely independent of reactor-separator design.

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Engineering synthetic systems inspired by anaerobic fungi

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Anaerobic fungi in the hindgut of large herbivores are among the most robust organisms at degrading crude lignocellulose. Their remarkable cellulolytic capabilities have great potential for use in biomass breakdown and biofuel processing. Anaerobic fungi achieve cellulolytic efficiency through the production of large, multi-enzyme complexes called fungal cellulosomes. In isolation, anaerobic fungi metabolize some of the released sugars and convert them into fermentation products. In nature, however, they exist in a community with archaea, bacteria, and protozoa, which drastically alter the behavior of the fungi. By elucidating the "parts" responsible for efficient biomass degradation at both the protein and cellular level, we seek to replicate this efficiency in synthetic systems.

Previously, anaerobic fungi have been shown to interact closely with methane producing archaea (methanogens). Methanogens reduce CO_2 with H_2 for growth and methanogenesis, which maintains a low partial pressure of H_2 in their environments, allowing the fungi to more efficiently metabolize sugars. To further investigate this mechanism, minimal fungal/methanogen consortia were isolated from herbivore fecal materials. ITS profiling and genomic sequencing revealed the presence of one fungus, two methanogens, and one bacterium in one native consortium, which was stable under continuous passage for over 20 months. The consortium demonstrated faster and more complete degradation of cellulosic substrates, as well as a wider range of utilized substrates compared to the monocultured fungus. By introducing the methanogens into cultures of other well-characterized anaerobic fungi, stable synthetic co-cultures were established. These synthetic consortia demonstrated similar efficiency, and suggest a promising option for conversion of crude biomass into sustainable chemicals.

Anaerobic fungi create large enzyme complexes called fungal cellulosomes, which they utilize for biomass degradation. Fungal cellulosomes are similar to bacterial cellulosomes in that the protein-protein interactions are mediated through parts termed the dockerin and cohesin, however the exact sequence for the cohesin module has yet to be established. Through a combination of –OMICs approaches and traditional biochemical assays, a large putative scaffoldin molecule was identified in fungal cellulosomes. The scaffoldin was heterologously expressed and screened for interaction with recombinant dockerin through an Enzyme Linked Immunosorbent Assay (ELISA). The $K_{D,app}$ was determined using Equilibrium Surface Plasmon Resonance (SPR). A transcriptomic survey of dockerin domain-containing proteins revealed some degree of conservation in dockerin location on classes of CAZymes. Furthermore, many cellulases were phylogenetically more similar to bacterial cellulases than fungal cellulases, suggesting horizontal gene transfer and the ability of the fungal cellulosomes to accept fungal and non-fungal cellulases. Using these observations, the dockerin domains were adapted to thermostable cellulases, demonstrating its applicability as a novel protein scaffolding systems and provide a path forward for constructing synthetic cellulosomes for biomass degradation.

Mapping conformational epitopes via random peptide display and high-throughput sequencing

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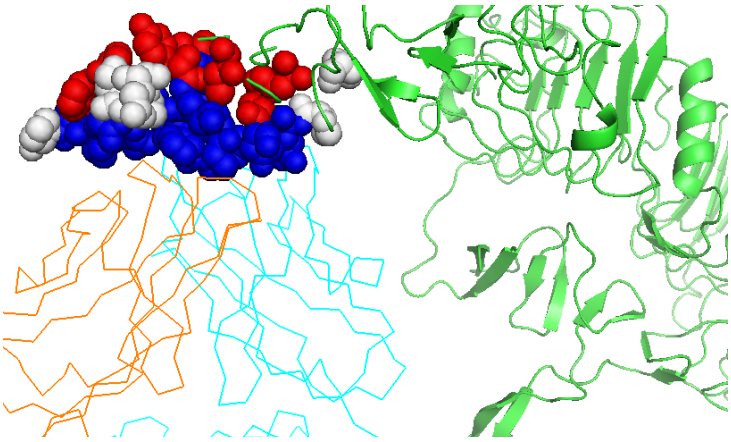
A large class of antibodies bind to regions of molecules, or epitopes, that are conformational. The amino acid sequences in these epitopes are discontinuous (i.e. not fully contiguous) and require intact secondary and higher structures to localize into a functional binding site. Development of efficient vaccines, therapeutics and diagnostic assays requires detailed knowledge of binding interactions. Specifically, in antibody engineering, high affinity and fine specificity is achieved from intimate knowledge of the epitope region as well as the effects of mutations around the epitope. While X-ray crystallography and NMR elegantly elucidate antibody-antigen interfaces, they do not identify the key residues necessary for binding.

In epitope mapping, binding residues are identified by comparing the antigen to peptides that bind to the antibody of interest. The functional epitope is confirmed via directed mutagenesis combined with binding affinity measurements. Epitope mapping requires 1) a display library, 2) cell sorting methods, and 3) DNA sequencing to recover the peptide sequence. The current state of the art uses primarily linear antigen fragment libraries that are inherently unsuited to mimic discontinuous epitopes. Several rounds of fluorescence-activated cell sorting (FACS) are typically performed to reduce the starting library to a small set of high-binding consensus peptides suitable for Sanger sequencing, but repeated selection can introduce cell growth and protein expression biases. Inspection for sequence homology is sufficient to identify linear epitopes; for discontinuous epitopes, algorithms that match the mimotopes with residue paths on the antigen structure are required.

We developed a mapping protocol to specifically target discontinuous epitopes using random peptide libraries sorted magnetically and sequenced with next generation (high-throughput) sequencing. Random peptide libraries can mimic discontinuous epitope sequences, and magnetic-activated cell sorting (MACS) is less expensive and requires less training than FACS. Next generation sequencing can reduce the number of sorting rounds. Using a motif-discovery program, we identified motifs in the NGS data, which were input to an epitope prediction algorithm to map them to the antigen. Using this protocol, the top motif from NGS data correctly identified residues in the true epitopes of two well-characterized antibody/antigen complexes. For Herceptin/HER2, NGS motifs predicted the true epitope residues with higher accuracy (50%) than published Sanger consensus sequences (36%). Combining NGS motifs improved the prediction accuracy to 73% (figure right), suggesting NGS data can be a valuable tool in mapping discontinuous epitopes.



NGS motifs predicted true epitope residues for HER2 antigen (green) binding with the Herceptin antibody light chain (orange) and heavy chain (blue). Blue spheres (16 residues) are correctly identified true epitope residues, white spheres are true epitope residues not identified (6), and red spheres were incorrectly identified as epitope residues (8).

Rate Limiting Steps in Crystal Growth: Desolvation Barriers and 1D Nucleation

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Our ability to engineer crystals requires a fundamental understanding of how crystals grow and the impact of process variables. When mass transfer is not rate-limiting, crystals grow via a layer-by-layer mechanism, wherein crystal steps spread across the surface through attachment at kink sites [1]. This mechanism forms the basis for a model that yields accurate steady-state crystal shape predictions for organic crystals [2]. The extension of the model to organic salts, biominerals, etc. and the transformation of the model into making growth rate predictions require accurate models for the rate limiting steps that govern crystal growth.

The step velocity depends on the rate of kink attachment and the density of kink sites along the edge. We investigate these two factors with atomistic simulations, rare-event techniques, mechanistic hypothesis testing, and model development [3]. We compute the desolvation barriers for attachment/detachment of ions to/from a NaCl crystal in water (Figure 1) and find that our computed detachment rates agree with an independent study [4]. We highlight the different desolvation behavior for Na and Cl ions and discuss the applicability of our results to other crystals, such as calcium carbonate.

Kink sites can be created by the nucleation of new rows along a step edge and/or thermal rearrangements. We examine the scenario of stable/unstable edges of non-centrosymmetric crystals, such as paracetamol. We develop a nucleation model to determine the non-equilibrium kink density that connects the limit of stability to that of instability, and can therefore improve crystal growth models. Our model yields predictions in agreement with simulations (Figure 2).

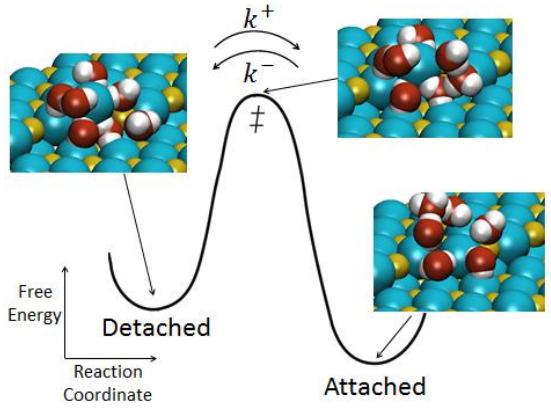

Figure 1: Schematic free energy barrier for Cl^- attachment/detachment at a kink site. Cl^- is blue, Na^+ is yellow, oxygen is red, and hydrogen is white (not all waters shown for clarity).

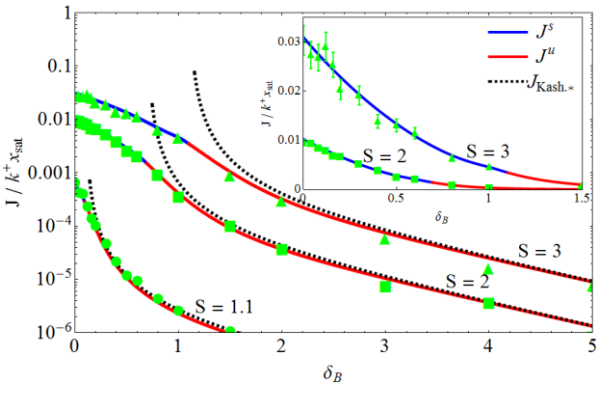

Figure 2: Comparison of computed (green symbols) and predicted (red and blue lines) nucleation rates (J) of stable/unstable rows at various supersaturations and stabilities (i.e., the parameter δ_B)

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Phase field mapping for fast and accurate polymer simulations

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Block copolymer self-assembly is a powerful tool for nanoscale patterning. Pattern design using this technique benefits from simulations to predict defect formation and stability. Two classes of simulations are self-consistent field theory (SCFT), which is accurate but computationally expensive, and phase field models, which are faster but historically less accurate.

We refine a mapping procedure that uses results from SCFT to optimize parameters in a phase field model for diblock copolymers. We validate the performance of this optimized model with regards to accuracy and computational speed in perfect and defective configurations. The optimized phase field model is faster than SCFT and more accurate than previous phase field models, making it a viable design tool for industrial processes.

Figure 1: A defective lamellar pattern formed by a diblock copolymer melt (400nm x 400nm), calculated using SCFT (left); the closest metastable pattern predicted by an unoptimized phase field model (center); and the closest metastable pattern predicted by our optimized phase field model (right). Because the unoptimized model has the wrong natural domain spacing, it makes poor predictions of features. The optimized model has the correct domain spacing and better captures features obtained in SCFT.

Free Energy Approach to Nanobubble Stability

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Surface nanobubbles are nanoscopic gaseous domains with heights of ~10 nm and widths of ~100 nm that are found along hydrophobic surfaces. They pose a fundamental problem in our understanding of hydrophobicity at the nanoscale, due to a number of unusual properties that are not explained by classical theories. Perhaps the most surprising feature of nanobubbles is their extended lifetimes, which experiments show are on the order of hours or even days. This discrepancy in several orders of magnitude has driven researchers for over two decades to try and understand the phenomenon of nanobubble stability. In addition to the perplexing longevity, nanobubbles have unusually small gas-side contact angles that appear to be independent of the substrate chemistry, in violation of Young's law. In our work, we seek to understand where a breakdown in macroscopic thermodynamic analyses might occur for these systems, through a combination of molecular dynamics simulation and thermodynamic theory. Although gas enrichment near hydrophobic surfaces is a phenomenon that has been studied in the literature, it has only recently been considered in the context of nanobubbles, prompting more detailed simulations. Therefore, we investigate the surface energies of atomically-resolved hydrophobic surfaces with realistic water models in the presence of dissolved gas, using molecular simulations. We find that the overall free energy landscape of the system depends on the surface energies of all the interfaces in the problem, importantly including the magnitude of the difference between the solid-liquid surface tension and the solid-vapor surface tension.

Scaling of single-molecule hydrophobic interactions from experiment and simulation

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Hydrophobic interactions (HIs) drive structural transitions and self-assembly processes in many natural and synthetic systems. Past experimental investigations into the HI have probed macroscopic interfaces or indirectly investigated molecular-level details. In contrast, simulations have historically focused on HIs for microscopic, idealized systems. Here, we use both atomic force microscopy experiments and molecular dynamics simulations to directly probe the HI between peptides of controlled hydrophobic content and an extended hydrophobic self-assembled monolayer (SAM) surface. Specifically, a hydrophilic glycine-serine repeat scaffold is systematically modified to contain one to four leucine residues, which are allowed to interact with the SAM surface. Simulated systems closely mirror the experimental set-up, even employing the same non-equilibrium technique, specifically Jarzynski's equality, to evaluate free energy differences. This constitutes a unique convergence of simulation and experiment in directly probing the HI on a molecular level for a realistic, soft-matter system. Experimental results indicate that the HI scales as 3.4 k_BT per added hydrophobic leucine residue, while simulations predict a scaling of 1.7 k_BT/leucine. In addition to qualitatively agreeing with experiment, our simulations also identify key molecular structural factors driving the increase in the strength of the observed HI. While all peptides are relatively disordered in both solution and absorbed to surfaces, we observe differences in the tetrahedral structure of nearby water, as well as in changes in the solvent accessible surface area of hydrophobic residues. Based on these same metrics, we find signatures of both small- and large-scale hydrophobic solvation theories. Additionally, non-equilibrium simulations provide a detailed dynamical view of how peptides detach from the surface. In accord with the idea that the free energy, and thus the work to remove the peptides, is dominated by hydrophobic association, the greatest contribution to the non-equilibirum work is found to come from the process of detaching leucine residues from the surface.

Probing Quench-Dependent Gelation in Thermoresponsive Attractive Colloids

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We investigate the effects of thermal quench on gelation in thermoresponsive, phase separating colloids. As a model system, we employ recently established oil-in-water nanoemulsions which contain thermosensitive telechelic polymers in the continuous phase and undergo temperature-induced colloidal gelation via polymer-mediated interdroplet attractions [1]. Modeling the effective interactions with a detailed statistical mechanical model for polymer bridging, we establish the equilibrium colloidal phase behavior of the system. Under appropriate conditions, the system forms colloidal gels in regions of fluid-fluid phase instability, where gelation and spinodal decomposition compete to direct the arrested gel structure [2]. Here, time-dependent quenches of various depths and rates are performed along isochores of volume fraction from 0.1 to 0.4, and linear viscoelasticity and optical microscopy are used to track the evolution of rheology and structure in the system. We find that gelation depends significantly on both the depth and rate of quenching into the gelled state. For example, the kinetics of gelation vary by several orders of magnitude with relatively minor changes in the quench rate, even for relatively shallow quenches into the spinodal region. Furthermore, we find that the onset of solid-like viscoelastic behavior for sufficiently slow quenches is consistently deeper than the predicted equilibrium coexistence line, suggesting the presence of an attractive glass transition line within the spinodal region. These results offer a starting point for more rationally controlling colloidal gelation and phase separation, and underscore the active interplay between viscoelastic phase separation and glassy dynamics in the formation of dense colloidal gels.

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Breaching the Blood-Brain Barrier at the Nanoscale: Understanding the Influence of Physical Characteristics

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The Blood-Brain Barrier (BBB) is one of nature's most exclusive biological barriers. Despite our wealth of knowledge about it in general, however, our understanding of the factors that modulate how nanoparticles cross the BBB is limited. As various nanotechnologies become more impactful in the clinic for indications such as prostate or breast cancer, the question of how to translate these successes to diseases across the BBB becomes more salient.

Manipulating physical particle properties (i.e. size, shape, and flexibility) is an excellent place to begin these investigations; the design space is less diverse than the chemical property design space and is therefore more tractable for identifying optimal approaches. Here we discuss our progress towards understanding this problem using simpler models like Transwell® assays and a microfluidic BBB. Our microfluidic platform recapitulates the flow and architecture present in vivo while retaining enough simplicity to ensure a well-controlled environment. We demonstrate not only our ability to create and characterize these models, but also show how we can quantitatively analyze particle transport, even in real time. Using these data, we then propose some preliminary design criteria for optimal BBB crossing.

High-throughput epitope mapping of common antigens

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Knowledge of where antibodies bind on an antigen, the epitope, is important information used in vaccine development, infection diagnosis, and therapeutic development. Current epitope mapping methods are slow and laborious, focusing on a single antigen of interest. High-throughput epitope mapping of the numerous antibodies in blood could enable the identification of relevant antigens and pathogens without biasing the results towards a particular antigen. A library of random peptides displayed on bacteria was used to determine a large set of peptides bound by serum antibodies. To computationally determine epitopes, putative antigen sequences were first decomposed into short patterns. The patterns which were found more often than expected in the patients' peptide sets ('enriched patterns') were aligned back to the original protein sequence. Subsequences of the protein sequence that mapped to multiple overlapping enriched patterns were deemed putative epitopes. The application of this method to antibodies with linear epitopes successfully identified the known epitopes. By analyzing the sequences of common protein antigens from viruses and bacteria, we found expected epitopes and antigens. We have demonstrated that specific targets of antibody responses can be identified from the set of all antibody targets present in serum. Future application of this method could be to groups of samples with different phenotypes to determine a difference in antibody response. For diseases in which antibody responses are involved in progression, it may be possible to isolate the aberrant immune targets.

Aptamer-Peptide Conjugates: Delivering Synergistic Drug Combinations With Precision

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Combination chemotherapy, a widely used treatment method for metastatic cancer, has superior therapeutic efficacies compared to single drug regimens. More recently, molar ratios were found to play a role in multi-drug interactions and remarkable improvements in the anti-cancerous potencies of drug combinations were reported when they were delivered in certain molar ratios. Ratiometric drug delivery can thus be used to significantly decrease the current clinically administered doses, thereby minimizing the drug resistance rates and toxic side effects of chemotherapy and enhancing their remedial potential. Different pharmacokinetics, biodistributions, transport properties and inability of small molecules to distinguish between healthy and cancer cells pose a drastic challenge in delivering the precise drug ratio to the target tissue. In order to unify the pharmacokinetics of the drugs and deliver the chemotherapeutic combination in a precise and specific fashion to cancer cells we have developed a novel Aptamer-Peptide Drug conjugate (APDC) platform. The aptamer targets overexpressed cancer specific cell surface receptors promoting exclusive uptake of construct in target tissue. To enable drug loading, a peptide scaffold is attached to the aptamer to which drug combinations in the precise molar ratio can be covalently attached via a variety of chemistries. These covalent linkages have been engineered to release the drugs preferentially upon cellular uptake thereby eliminating cytotoxic effects to healthy tissues during systemic circulation.

In preliminary work, we successfully made and characterized several different APDCs carrying chemotherapeutic drugs doxorubicin (DOX) and camptothecin (CPT). The aptamer in our APDC targets overexpressed cell surface nucleolin receptors on MDA-MB-231 cells, an aggressive metastatic triple negative breast cancer cell line. Our APDCs were highly selective to these nucleolin overexpressing breast cancer cells as compared to a control healthy epithelial cell line, MCF 10A. Next, we systematically combined DOX and CPT in several molar ratios and evaluated the *invitro* cytotoxic effect in order to identify the most synergistic combination. Drug ratios, $0.25 \leq R \leq 1$ (R: DOX/CPT) were found to be significantly synergistic over others. Similar *invitro* cytotoxicity studies were performed by systematically combining APDCs to account for release kinetics and cellular uptake effects on the optimal ratio. Here, a ratio of 1:1 (DOX:CPT) was identified to be the most synergistic. Furthermore, this molar ratio was also found to be more effective at killing breast cancer cells as compared to the control cell line, MCF 10A thereby enhancing the selectivity of the combination to cancer cells. Finally, a 20-fold improvement in toxicity was observed when MDA-MB-231 cells were subjected to a nucleolin APDC treatment versus a non-targeting drug conjugate treatment. These results demonstrate the importance of delivering drug combinations in a precise yet specific fashion to cancer cells in order to exploit the full potential of synergistic interactions of a particular drug ratio.

Our novel APDC system for the first time provides a strategy to (i) deliver an exact synergistic molar ratio of (ii) various chemotherapy combinations in a (iii) highly specific fashion to cancer cells using aptamers.

Elucidating the role of the adenosine A2a receptor's C-terminus on oligomerization and function

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The human genome contains approximately 800 G protein-coupled receptors (GPCRs) that play a critical role in cell signaling to mediate intracellular responses to changes in the extracellular environment. Located within the plasma membrane, these proteins are ideal targets for small molecule therapeutics, and they are targeted by 40-60% of all commercially available pharmaceuticals. The adenosine A2a receptor (A2aR) is involved in cardioprotection, neuroprotection, and regulation of the central nervous system through its ability to modulate blood flow as well as influence the signaling of other G protein-coupled receptors (GPCRs) through oligomerization. Its unusually long C-terminus (120 a.a.) has been identified as an interaction partner to several proteins including USP4, calmodulin and the dopamine D2 receptor, suggesting that it plays a role in mediating protein-protein interactions. However, due to its flexible and disordered nature, structural characterization of A2aR thus far has largely relied upon truncations of the C-terminus. Such truncations of the receptor C-terminus have resulted in reduced constitutive activity, yet do not significantly alter ligand binding or G protein-coupling. While a truncated receptor is able to form homodimers *in vivo*, very little structural information exists for the A2aR homodimer or the C-terminus.

We have developed a system to express, purify and characterize the full length human adenosine A2a receptor, as well as a mutant receptor, to investigate the structural role of the A2aR C-terminus in function and oligomer formation. Utilizing a previously optimized mixed micelle system consisting of DDM, CHAPS, and CHS, we found that upon SEC separation, full length A2aR solubilized in this system exists as a distribution of oligomers including a monomer, dimer, and a higher order oligomer that corresponds to the molecular weight of a 7-mer[1]. Upon mutation of a C-terminal cysteine (C394S), the propensity for solubilized A2aR to form stable dimers *in vitro* is dramatically decreased. Spin label electron paramagnetic resonance (EPR) measurements on both the wild type A2aR and C394S A2aR revealed a significant reduction in EPR signal and change in EPR lineshape upon the mutation of C394 to serine, indicating that most of the EPR signal in wild type spin labeled A2aR is due to the labeling of residue C394, as opposed to other cysteines located within the transmembrane regions. In order to investigate conformational shifts of C-terminus upon ligand binding, wild type A2aR was incubated with inverse agonists XAC and ZM241385 during the spin label reaction. Under these conditions, we observed what appear to be a reduced labeling efficiency and subtle changes in EPR lineshape, suggesting a conformational shift that changes the local environment around C394. New evidence suggests that at least part of these observed differences arise from varied distributions of the oligomer populations. These results lend new insight into the role of the A2aR C-terminus plays in stabilizing receptor conformation and oligomer states. The future of this work aims to further explore this role by investigating whether these observations are a result of a "rigid body" movement of the C-terminus, or a distinct conformational change within the C-terminus upon ligand binding.

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A Molecular Thermodynamic Model for Nanoparticle-Membrane Interactions

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The thermodynamics of nanoparticle (NP) interactions with cellular membranes has momentous consequences for nanotechnology with biological, toxicological, and pharmacological applications. The pervasiveness of NPs in therapeutics, foods and beverages, cooking products, packaging, cosmetics and sunscreens, and agriculture, amongst many other areas, coupled with the lack of fundamental understanding of the interplay of NP design effects like size, chemistry, shape, and elasticity on product performance, underscores the importance of a biophysical approach to NP-membrane interactions. Here, we use molecular dynamics simulations to characterize the behavior of homogeneous, spherical, rigid NPs with model lipid bilayers. We delineate unique mechanistic modes of NP-membrane interaction in the space of NP size and chemistry (hydrophobic, hydrophilic, interfacially active). We uncover a diverse array of stable and long-lived metastable configurations that vary sensitively with the effective NP attractions to lipid head and tail groups, and with size as particles move from the molecular (<0.5 nm) to lower "colloidal" (>10 nm) regime.

Continuum theory provides a starting point for understanding some of these behaviors, particularly at the extremes of small molecules (solubility theory) and large colloidal particles (membrane elastic theory). The intermediate nanoscale regime, however, is complex because the membrane thickness (~5 nm) is comparable to the particle size, individual lipid fluctuations become relevant, and significant geometric asymmetries of inserted configurations emerge. We implement the molecular simulations to direct the development of new theory in this regime. We use calculated lipid leaflet distributions and field-based descriptors of membranes with inserted NPs to extend existing theoretical models with free energetic contributions from deformations in lipid molecular tilt, twist, and splay [1]. We then investigate improvements in these continuum predictions through comparison with detailed umbrella sampling free energy calculations. While focused on model systems, this NP study has interesting implications for a wide range of organic and inorganic NPs, and also for biomacromolecules like membrane proteins.

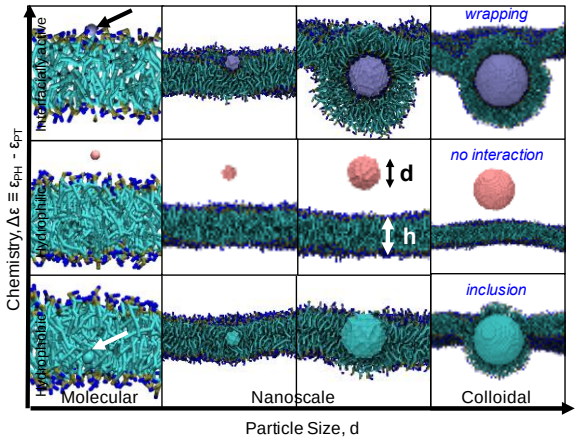

Figure 1: Size-Chemistry Subspace of Homogeneous, Spherical, Rigid NP-Membrane Interactions.

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Development of tools and strategies to engineer G Protein-Coupled Receptors

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G-protein coupled receptors (GPCRs) comprise a family of integral membrane proteins that mediate eukaryotic cells' responses to a wide array of extracellular signals. By coupling extracellular ligand binding with intracellular signaling pathways, GPCRs modulate cellular responses to environmental stimuli and act as a key intermediary between organisms and their surrounding environments. As a result of their ligand specificity and sensitivity and capacity for signal transduction, GPCRs are thought to have great potential as biosensors for toxic chemical and biological reagents. Despite their inherent advantages as biosensors, many GPCRs are difficult to express functionally and in high numbers within heterologous hosts such as yeast that are amenable platforms for cell-based biosensors. Thus, there is a need to engineer functionally expressed GPCRs to bind ligands of interest with high affinities and specificities. Towards that end, progress has been made towards the engineering of the human adenosine A_{2A} receptor ($hA_{2A}AR$) to modulate its binding properties towards a target ligand. Protein design strategies were guided by high-resolution crystal structures of $hA_{2A}AR$ bound to various agonists and antagonists. Fluorescent ligand-binding and an agonist-induced fluorescent reporter system were used to leverage fluorescence-activated cell sorting as a high-throughput screening platform to isolate yeast cells expressing desirable $hA_{2A}AR$ mutants. The use of this platform to further evolve and isolate desirable $hA_{2A}AR$ mutants is expected to generate mutants with even greater binding affinity and specificity towards ligands of interest.

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