UCSB ChE's 3rd Clorox-Amgen Grad Student Symposium

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Self-Assembled, Multifunctional Micelles Containing Therapeutic Peptide Amphiphiles

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Peptides have enormous potential as therapeutic agents due to their ease of rational design and target specificity, but they are limited by low stability and their ability to reach their desired target. Peptide amphiphiles consist of a biofunctional peptide as the hydrophilic head group and either a single-chain fatty acid or a double-chain lipid as the hydrophobic group, often separated by a polyethylene glycol (PEG) or other spacer to drive self-assembly in aqueous solutions. In aqueous solution, these molecules self assemble into micelles that display a high density of functional peptides. Mixing different monomers leads to multifunctional mixed micelles with precise control over number and ratio of functionalities without the need for orthogonal chemical reactions. Therefore, multiple therapeutic, targeting, or internalizing peptides can be easily incorporated into the same structure. We have demonstrated that self-assembled peptide-displaying micelles can be used to combine targeting and therapeutic peptides and are useful for *in vivo* tumor targeting. We have shown that pro-apoptotic peptides can be incorporated into these micelles and be used to kill multiple types of cancer cells *in vitro.* Our current work aims at taking advantage of the multifunctional nature of these micelles to increase the efficacy of therapeutic peptides by incorporating synergistic anticancer agents.

A Quantitative Study of Bulk Stresses in Nonlinear Microrheology

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We investigate the nonlinear microrheology of a simple model system - a spherical probe translating through a dilute suspension of rigid rods - to elucidate a variety of issues inherent in the interpretation of nonlinear microrheology. We have developed a computational system to quantitatively examine the issues present in interpretation of nonlinear microrheology, as originally discussed by Squires [1]. Following recent work emphasizing the importance of the microstructural behavior in the bulk [2], we focus our attention on the bulk microstructural deformation, and examine the significance of its (Lagrangian) transient nature, as well as the consequences of the mixed and inhomogeneous flows inherent to nonlinear microrheology. From this quantitative study, we pose solutions for the current theoretical issues facing nonlinear microrheology in interpretation and comparison of the microviscosity with the shear viscosity from traditional bulk rheometry.

References:
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Understanding Polyelectrolyte Brush Behavior in Mixed Valence Ionic Environments

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The overall goal of this work is to strengthen the understanding of polyelectrolyte brush behavior in the presence of both mono and multi-valent counterions. While polyelectrolyte brush behavior in a purely mono-valent salt environment has been well investigated [1-3], the presence of multi-valent counterions drastically changes both the physical properties and the behavior of these highly charged brushes leaving much to be studied [4,5]. The motivation behind this work stems from the many uses and applications of polyelectrolyte brushes, all of which exist in mixed ionic environments, both from nature (e.g., surfaces of cartilage and mammalian lung interiors) and commercially (e.g., skin care products, shampoo, and surfaces of medical devices).

The polyelectrolyte brushes used (PtBS – PSSNa) consist of a short hydrophobic block of poly-t-butyl styrene (N~20) and a long polyelectrolyte block of poly-styrene sulfonate (N~420). The hydrophobic block is used to tether the polyelectrolyte chains to a hydrophobic surface in the presence of water which in turn allows the strong polyelectrolyte chains to form a brush structure. The work in this presentation will consist of results from primarily two experiments; electrochemical data obtained through cyclic voltammetry and force interaction data measured using the Surface Forces Apparatus (SFA). Using the electroactive multi-valent counterion ruthenium hexaammine, one can measure the amount of multi-valent ions which are confined inside the polyelectrolyte brush as the bulk concentration of these multi-valent ions is varied. Separately, SFA experiments show the structural and physical changes of the brushes at the same conditions. The combination of electrochemical data and SFA data at identical conditions allows new insight of how and when multi-valent ions affect the properties of polyelectrolyte brushes.

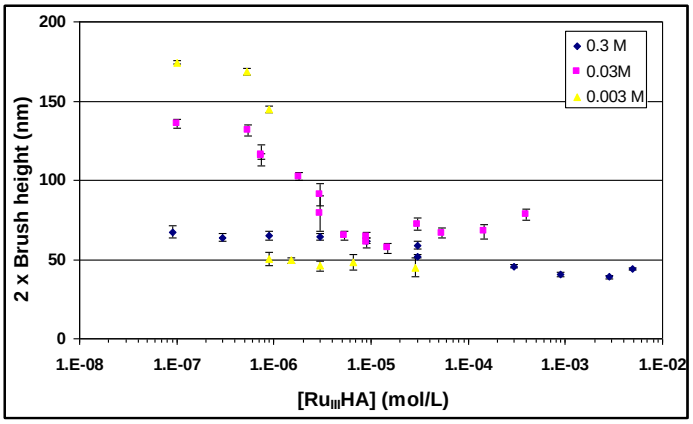

Figure 1: The attached graph was obtained via SFA experiments and shows the height of these polyelectrolyte brushes as a function of the ruthenium hexaammine (RuHA) bulk concentration in its 3+ valence state. The three different data sets are based on the fixed ionic strength of the solutions (0.3M, 0.03M and 0.003M respectively), which were held constant using NaNO3. As two surfaces are brought together in the SFA, repulsive forces will eventually begin as the two brushes approach one another. This point is the equivalent of two times the brush height and corresponds to the y-axis values in the graph. As the concentration of RuHA is increased, the brushes concurrently collapse and form adhesion between one another after contact (the latter not seen in this graph).

References:

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Role of Symmetric Grafting Copolymer on Suppression of Drop Coalescence

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In this study, we analyze the rheological properties of "symmetric" blends of Polybutadiene (PBd) and Polydimethylsiloxane (PDMS) with a symmetric grafting PBd-$COO^{-}NH^{3+}$-PDMS copolymer as compatibilizer. The zero shear viscosity of the PBd and PDMS were exactly matched. The blends were prepared by varying the volume fraction of PBd and PDMS between 20:80 and 80:20. The experiments were conducted on blends containing 0.1 and 1 wt. % of grating copolymer. In blends with 1 wt. % of grating copolymer and PBd as the continuous phase, the coalescence is totally inhibited. In blends with PDMS as continuous phase, the rheological properties are less strongly affected. These results are similar to the previously published results using PIB/PDMS[1]. In the present work, we further explore the role of the symmetric compatibilizer by studying the effects on coalescence.

Flow induced coalescence of a pair of these drops with compatibilizer was also studied at the level of individual drops using 4-roll mill. With PBd as the continuous phase, we found that there are two critical interface concentrations of copolymer, Γ_{c1} and Γ_{c2}. For interface concentrations $\Gamma<\Gamma_{c1}$, coalescence can happen, while there's a transition behavior. At low Capillary number (Ca) the droplet coalescence is slowed down by compatibilizer while not at high Ca. For interface concentrations between these two values, $\Gamma_{c1}<\Gamma<\Gamma_{c2}$, coalescence can happen, but are much slower than drop coalescence without compatibilizer present. For $\Gamma>\Gamma_{c2}$, however, in the system with PBd as the continuous phase, coalescence is suppressed, at least on the time scales that are accessible in the 4-roll mill. We suggest Marangoni effects as the main mechanism for suppression of coalescence in the former case ($\Gamma_{c1}<\Gamma<\Gamma_{c2}$), while steric effects as the main mechanism for the latter case ($\Gamma>\Gamma_{c2}$). When PDMS forms the continuous phase, we did not find a level of copolymer coverage that can totally suppress the coalescence. The adsorption isotherm for PBd drops in PDMS matrix and PDMS drops in PBd matrix are very similar. We suggest that the Marangoni effects on both cases are expected to be the same. The brush conformation and thickness are the main effect that causes the asymmetric effect. The asymmetric terminal viscosity found in rheology experiment can be explained by different effective volume fraction of drop phase due to different brush thickness. The PBd-COOH with 26K molecular weight (in 8K bulk phase) forms wet brush and has a larger effective volume fraction than the PDMS-NH_2 with 27K molecular weight (in 80K bulk phase) which forms dry brush and has smaller effective volume fraction. Different molecular weight of PBd-COOH on drop coalescence was also investigated and confirms that the molecular weight ratio of the copolymer with matrix is the key factor to determine brush conformation and thickness, therefore influence both the drop size and the stability of the blends.

References:

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Peptides for Use in Transdermal Delivery

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The delivery of macromolecules across skin is still a major obstacle in the field of transdermal delivery. In particular, the delivery of siRNA has proved challenging. siRNA has the potential to treat various skin diseases of great importance including psoriasis, atopic dermatitis, and cancer. Although many methods have been proposed for the delivery of siRNA (i.e. chemicals, microneedles, ultrasound, and iontophoresis) few have found success in delivering siRNA. In addition to penetration across the skin barrier, delivery of siRNA requires penetration into epidermal and dermal cells to achieve therapeutic effect. Peptides, a relatively new method in transdermal delivery, have the potential to address this challenge.

Through *in vitro* phage display, we have discovered a skin penetrating and cell entering peptide (SPACE). SPACE was found to penetrate human, porcine, and mouse skin in significant quantities compared to a control peptide (containing same sequence but with amino acids scrambled). When conjugated to SPACE, molecules ranging in size from a fluorescent dye (~500 Daltons) to quantum dots (~ 20nm diameter) were found to penetrate into skin. SPACE was also shown to penetrate cell lines such as human keratinocytes, fibroblasts, and endothelial cells. *In vitro* delivery of GFP siRNA conjugated to SPACE resulted in significant knockdown of GFP in a GFP expressing endothelial cell line. *In vivo* delivery of IL-10 siRNA conjugated to SPACE, when topically administered in Balb/C mice, resulted in significant knockdown of IL-10.

SPACE has shown the ability to carry macromolecules across the skin and into skin cells. This ability opens up many possibilities for the topical delivery of molecules and the potential to treat skin diseases effectively with improved patient compliance.

Field-Base Simulations for Directed Self-Assembly of Polymeric Systems

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The self-assembly of block copolymer thin films has attracted considerable attention as a promising high resolution lithographic tool due to both the scale of microdomain ordering and the facility for modulation of size and pattern. However, for block copolymer lithography to be a viable solution for nano-lithographic technology, several critical requirements need to be satisfied. Our research has focused on developing block copolymer lithography techniques that satisfy the required criteria by using self-consistent field theory (SCFT) simulations. Specifically, we concentrated on the graphoepitaxy-type technique, in which lateral confinement is used to control the self-assembly.

First, we expanded the scope of graphoepitaxy technique to fabricate various desirable nanoscale structures, which do not occur naturally in the bulk. In particular, we looked at the tetragonal (square) packing of cylinders since they are of interest in the semi-conductor industry. We demonstrate that defect-free tetragonal arrays can be obtained by subjecting a simple AB block copolymer system along with A homopolymer to graphoepitaxial confinement in a square well. We also constructed a phase diagram indicating the region of defect-free tetragonal arrays as well as possible defective structures. We also investigated the robustness of tetragonal ordering to line edge roughness.

Our second study is inspired by the experimental work at IBM Almaden Research Center (ARC). Recently, Cheng et al. at ARC have succeeded in obtaining an isolated cylindrical hole having a critical dimension of ~40-50 nm from PS-b-PMMA block copolymer thin films that were laterally confined in a larger cylindrical hole of diameter ~60-110 nm. Using SCFT simulations, we investigated the detailed shape of the phase-separated morphologies. We were able to explain why the PMMA domain in the center has a larger critical dimension than a cylinder in the bulk phase and why it has smaller size variation as compared to the pre-patterned confinement.

Lastly, we also explored the possibility of using mixed polymer brushes, in which dissimilar A and B chains phase separate at nano-scales due to the grafted chain ends, for the lithographic applications in collaboration with Sandia National Lab. In block copolymer lithography, it is difficult to generate features with multiple sizes and pitches in the same layer in different regions of a substrate, since the size of the features and their spacing is dictated primarily by the molecular weight of the each block of the chains. Due to the strong correlation between morphology and grafting density in mixed brush systems, our SCFT results demonstrate the possibility of forming multiple sizes and pitches on a single layer by modulating the grafting density. We also showed that long-ranged ordering can be obtained by laterally confining the mixed A/B brush region with a pure polymer brush region of either A or B homopolymer (chemical confinement) instead of topological confinement of the patterned substrate.

Molecular Insights on Meso- and Macroscale Properties of Self-Assembled Organic-Inorganic Solids

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Organic-inorganic materials exhibit unique combinations of properties due to mixing of and interfaces between their highly dissimilar components. Typically, the organic species are soft, processable, and may self-assemble, while the inorganic species are mechanically robust, thermally stable, and exhibit catalytic, optoelectronic, or other diverse properties. A great deal of recent progress has been achieved by using organic structure-directing surfactants or block copolymers to form liquid crystal phases, together with soluble network-forming inorganic or hybrid precursors, to obtain materials with uniform and adjustable pore sizes and large interfacial areas between the organic and inorganic components. Such materials combine properties of both the organic and inorganic species that allow their pore structures and dimensions to be adjusted to modify their mass transport properties, accompanied by high functionalizable surface areas and processabilities into diverse macroscopic morphologies. These attributes result in hybrid materials with versatile transport, adsorption, catalytic reaction, mechanical, and/or optoelectronic properties, according to their compositions and structures.

Recently, the use of multiple types of structure-directing species and framework precursors has enabled compositional and structural control of inorganic-organic materials over several discrete length scales. This approach has resulted in materials with amorphous or crystalline frameworks and multimodal distributions of pore sizes over molecular, meso-, and/or micron-scale dimensions. However, controlling the compositions, structures, and processes by which hierarchically-structured organic-inorganic materials form remains challenging, because much remains unknown about the interactions that govern their syntheses across multiple length scales. This is exacerbated by the absence of long-range molecular order, starkly different dynamics of the organic and inorganic moieties, and their heterogeneous, multi-component characters. New results and insights will be presented on progress in understanding how molecular compositions and material structures are correlated with their meso- and macroscale properties. For example, we establish for nano/mesoporous zeolites the interactions between distinct structure-directing species and framework moieties that account for the development of crystalline and mesoscopic order and which correlate with bulk catalytic reaction measurements. Similarly, for nano/mesostructured organosilicas, different network-forming precursors, structure-directing agents, and thermal treatments yield differences in molecular compositions, structures, and dynamics that are directly correlated with mesostructural ordering, pore diameters, framework wall thicknesses, porosity, specific surface areas, and adsorption properties. Understanding the molecular level interactions among highly dissimilar organic and inorganic moieties allows the selection of materials compositions and synthesis/processing conditions to produce new multiscale heterogeneous materials with novel and technologically promising properties.

Coarse-Graining of Polymer Field Theories

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Field theoretic models are widely used to investigate self-assembly and phase behavior of heterogeneous polymeric materials, particularly block copolymers. Numerical methods commonly employed to study these models often increase computational speed by neglecting fluctuation physics, an approximation that is very accurate for long-chain polymer melts but which breaks down for some systems of engineering interest, including polyelectrolytes and dilute polymer solutions. Methods that accurately handle these fluctuating systems, such as the complex Langevin method, are computationally demanding; to improve the efficiency of these methods and permit study of larger systems, we propose the use of systematically coarse-grained field theories that can be simulated on coarsely-spaced simulation lattices without truncation of important short-wavelength physics. We present a flexible and rigorously founded variational framework for parameterizing such coarse-grained models from fine-grained simulation data, and results from the application of this formalism to some model systems.

Protease-Resistant Peptide Ligands from a Stable Knottin Scaffold

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Peptides within the knottin family have been shown to possess inherent stability, making them attractive scaffolds for the development of therapeutic and diagnostic agents. Given its remarkable stability to enzymatic degradation, the cyclic peptide kalata B1 was employed as a scaffold to create a large knottin library displayed on the surface of bacteria. A library exceeding 10^9 variants was constructed by randomizing seven amino acids within a loop of the kalata B1 scaffold and screened using fluorescence-activated cell sorting to identify peptide ligands specific for human thrombin. Refolded thrombin binders exhibited high nanomolar affinities in solution, slow dissociation rates, and were able to inhibit thrombin's enzymatic activity. Importantly, a knottin-based thrombin inhibitor exhibited at least 100-fold increased resistance to the digestive enzyme trypsin, when compared to the same seven residue binding peptide constrained by a single covalent disulfide bond, demonstrating that modifying the kalata B1 sequence did not compromise its stability properties. Our results indicate that peptide libraries derived from the kalata B1 scaffold can yield high affinity protein ligands that retain the protease resistance associated with the parent peptide. More generally, this strategy may prove useful in the development of stable peptide ligands suitable for *in vivo* diagnostic and therapeutic applications.

Visualizing Periodic Bond Chain Networks to Predict and Categorize Structural Motifs that Form Needle Shaped Crystals

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Needle shaped crystals, as typified by aspect ratios in the range of ~100-1,000, are frequently formed as the final product in the crystallization of active pharmaceutical ingredients (APIs) from solution. This shape presents several difficulties for the subsequent processing (e.g., filtering, drying, tabletting) and formulation steps required for the formation of a final product. Therefore, the ability to design crystallization processes in a manner such that this shape can be avoided is of great interest within the pharmaceuticals industry.

Molecules with specific structures in the solid state (i.e., polymorphs), that obtain such a shape upon crystallization, can be categorized as "absolute" or "conditional" needles, based on whether they form needles in all solvents (absolute) or only in a specific set of solvents (conditional) [1]. The classification of a molecule and corresponding structure as "likely to form" an absolute or conditional needle can be used to guide subsequent process and experimental design steps; as for absolute needles, shape should not be considered when determining an ideal solvent (or solvent mixture), where by contrast for conditional needles, the ability to avoid this shape on the basis of solvent selection should be evaluated.

To enable this classification, a program was developed to visualize the network of repeating intermolecular interactions, and subsequently the periodic bond chains (PBCs, defined in [2]), found within a molecular crystal composed of small organic molecules. On the basis of this program, molecules (packed in a specific structure) classified as "likely to form" needles, were determined to contain a single strongest PBC direction with interaction strengths ~5 k_bT greater than the remaining PBCs in the crystal. The further classification as either absolute or conditional, was determined on the basis of the nature of the interactions within that PBC; for instances where these interactions were mostly dispersive (as in lovastatin, Figure 1), the formation of an absolute needle was predicted, by contrast when this interaction was mostly coulumbic (d-mannitol, Figure 2) a conditional needle was predicted. On this basis for a conditional needle, growth within a non-polar solvent will result in the formation a needle shaped crystal, while growth within a polar solvent will result in the formation of a more equantly shaped crystal.

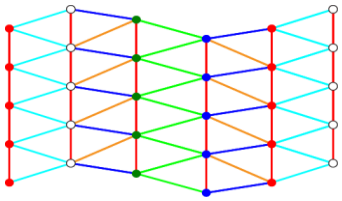

Figure 1: Intermolecular interactions within the (20-1) face of paracetamol. The red interactions are ~2 × as strong as the remaining interactions and 93% dispersive in nature. Interactions strengths were determined using the generalized amber force field.

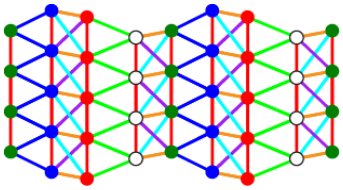

Figure 2: Intermolecular interactions within the (20-1) face of d-mannitol. The red interactions are ~1.5 × as strong as the remaining interactions and are ~100% coulumbic in nature.

References:
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Two Distinct Mechanisms of Enhanced Lung Surfactant Adsorption

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Lung surfactant is a mixture of lipids and proteins that lines the air-liquid interface of the alveolar walls. It modulates the surface tension in the lungs which greatly reduces the mechanical work of breathing and also prevents alveolar collapse upon expiration. Blood serum leaking into the alveoli during lung trauma can lead to lung surfactant inhibition, which is one characteristic of acute respiratory distress syndrome. The competitive adsorption of albumin, a blood serum protein, to the alveolar air-liquid interface blocks lung surfactant from forming a functional monolayer. As a result, normal surface tension modulation in the lungs is significantly reduced and respiratory distress ensues.

The addition of hydrophilic polymers to the liquid subphase has been shown to reverse albumin's inhibition of lung surfactant *in vitro*. We hypothesize that two polymers of interest, polyethylene glycol (PEG) and chitosan, function through two distinct mechanisms. PEG is believed to induce a depletion-attraction force whereas chitosan acts through electrostatic interactions. Here, we used confocal microscopy to provide visual evidence of these two differing mechanisms. Confocal microscopy allowed us to simultaneously track multiple components and determine their relative lateral and axial concentrations. As a result of these capabilities, we have shown that PEG did not associate with interfacial layers of albumin or lung surfactant, which was consistent with the depletion-attraction mechanism. In contrast, the positively charged chitosan strongly associated with the negatively charged albumin and lung surfactant films, which suggested a charge neutralization or bridging mechanism. Confocal microscopy has proven to be a useful technique for examining the distinct mechanisms by which PEG and chitosan enhance lung surfactant adsorption under inhibitory conditions representing those in the alveoli during acute respiratory distress syndrome.