Biomaterial Interfaces
Room 317 - Session BI-WeM

Bionanoscale Analysis: Theory to Experiment

Moderator: R.A. Latour, Clemson University

8:20am **BI-WeM1 Calculation of Free Energy of Peptide-Surface Adsorption Using Molecular Dynamics Simulations**, ***V. Raut***, *S.J. Stuart, R.A. Latour,* Clemson University

Proteins, which are bioactive molecules, adsorb on implants placed in the body and directly influence biocompatibility. Molecular dynamics (MD) modeling provides one of the most direct methods of analyzing individual molecular-level interactions and can be used to simulate protein adsorption behavior using empirical force fields. In order to correctly simulate protein adsorption behavior, a force field must correctly represent the thermodynamic driving forces governing peptide residue-surface interactions (i.e., adsorption enthalpy, entropy & free energy). However, since existing force fields were developed without consideration of protein adsorption, they may not accurately represent this type of molecular behavior. Therefore the objective of our research is to develop computational chemistry methods to calculate thermodynamic parameters of peptide-surface adsorption and compare them with experimental results for the assessment of force field accuracy. Various MD simulations demonstrating individual residue-surface reactions are being studied. These models represent the behavior of small peptides over functionalized SAM surfaces in a water box with periodic boundary conditions. Statistical mechanics methods are being developed based on positionional probability distributions obtained from MD simulations to enable us to calculate the change in enthalpy, entropy & free energy as a function of distance between the peptide & surface. Comparison of these results with experimental results will enable us to determine the accuracy of available force fields. If necessary, the developed methods will then also serve as a basis for the development of a new force field that is specifically parameterized to accurately simulate protein adsorption behavior.

8:40am **BI-WeM2 Molecular Simulation Studies of Protein and DNA Interactions with Surfaces**, *J. Zheng, J. Zhou, J.P. Sullivan, L. Zhang,* ***S. Jiang***, University of Washington

Molecular-level understanding of protein behavior on surfaces will facilitate the development of biomaterials with superior biocompatibility and biosensors with high sensitivity and specificity. In this work, we report various molecular simulation studies of non-fouling mechanism, protein orientation/conformation on surfaces, molecular recognition, and DNA chips. First of all, molecular dynamics (MD) simulations are performed to study lysozyme interactions with SAMs presenting oligo (ethylene glycol) (OEG) groups in the presence of explicit water molecules and ions. The behavior of water at protein/SAM interfaces is characterized by self-diffusion coefficient, order parameter, hydrogen bonding, and radial distribution. The effects of surface (charge, hydrophobicity, and defect), solvent, pH, and ion strength will be taken into account. Results from this work will shed light on non-fouling mechanism at the atomic-scale level and guide the design of better biocompatible materials and biosensors. Second, Monte Carlo simulations are performed to study IgG orientation on positively charged NH2 and negatively charged COOH terminated self-assembled monolayers (SAMs) on Au(111). Simulations are confirmed by experimental results from surface plasmon resonance (SPR) biosensor and time-of-flight secondary ion mass spectrometry (ToF-SIMS). Third, MD simulations are performed to study molecular conformation of cytochrome c on charged SAMs in the presence of explicit water molecules and ions. The ability to predict protein orientation and conformation will enable one to control and manipulate protein behavior on surfaces, important for biomaterials and biosensors. Fourth, hybrid molecular simulations are performed to study the unbinding pathway of biotin/avidin interactions at the atomic force microscopy time scale. Finally, MD simulations are performed to study the molecular packing of thiolated ssDNA and dsDNA on Au(111) and then mixed DNA and OEG SAMs.

9:00am **BI-WeM3 Macromolecular Dynamics: Insights from Simulation**, ***B.R. Brooks***, National Institutes of Health **INVITED**

Examples of recent macromolecular simulations will be presented which explore the relationship between modeled systems and real systems probed by experiment. In particular, data from neutron scattering, NMR, and crystallography can be compared and contrasted with corresponding results from molecular dynamics simulation. Also presented will be examples where simulation can provide insights that are difficult to obtain with experiment. There will be some discussion of recently developed methods that enhance our ability to accurately model interfacial systems and interactions between macromolecules. Also, protein conformational change and enzyme catalysis can be examined with a variety of methods. We present several methods, such as the Replica/Path method and extensions of the Nudged Elastic Band method, for examining such events and their application to interesting biological systems.

9:40am **BI-WeM5 Molecular Modeling of Adsorption-Induced Exposure of Integrin Binding Sites in Fibrinogen**, ***M.A. Agashe***, *S.J. Stuart,* Clemson University; *L. Tang,* The University of Texas at Arlington; *R.A. Latour,* Clemson University

Implants invoke inflammatory responses from the body even if they are chemically inert and non-toxic. It has been shown that a crucial precedent event in the inflammatory process is the spontaneous adsorption of fibrinogen on implant surfaces, which is typically followed by the presence of phagocytic cells. It has been found that interactions between the phagocyte integrin Mac-1 and one short sequence within the fibrinogen D domain (@gamma@190 to 202) partially explain phagocyte accumulation at implant surfaces. However, it is still unknown what makes adsorbed fibrinogen proinflammatory when soluble fibrinogen is not. One premise is that adsorption exposes the normally occult P1(@gamma@190 to 202) and P2 (@gamma@377 to 395) epitopes that reside in the D domains of fibrinogen; these epitopes are also involved in thrombin-mediated conversion of fibrinogen to fibrin. The objective of our research is to use molecular modeling to investigate how surface chemistry influences the adsorption behavior of the D fragment of fibrinogen with a particular focus on characterizing adsorption-induced conformational changes in the P1 and P2 region of this fibrinogen fragment that may lead to epitope exposure for integrin binding. Modeling is being conducted using Insight II software (Accelrys) with the CHARMM force field. The adsorption of the @gamma@ chain of fibrinogen is being simulated on 4 types of SAM surfaces (hydrophobic, hydrophilic, + - charged). An implicit solvent model (generalized Born) is being used to represent the solvent and solvent-mediated interactions during the molecular dynamics simulations. The study of these changes in conformation will help us to understand the likely molecular mechanisms that are responsible for the exposure of the P1 and P2 domains, and how this may be able to be controlled by surface chemistry. This understanding may help in the design of biomaterial surfaces with improved biocompatibility.

10:00am **BI-WeM6 Scaled Interfacial Activity of Proteins at the Liquid-Vapor Interface**, ***A. Krishnan***, *J. Sturgeon, C.A. Siedlecki, E.A. Vogler,* The Pennsylvania State University

A principal conclusion drawn from observations of time- and concentration-dependent liquid-vapor (LV) interfacial tension @gamma@@sub lv@ of a diverse selection of proteins ranging from albumin to ubiquitin is that concentration scaling substantially alters perception of protein interfacial activity, as measured by the amount adsorbed to the hydrophobic LV surface. Proteins appear more similar than dissimilar on a weight/volume basis whereas molarity scaling reveals a "Traube-rule" ordering by molecular weight, suggesting that adsorption is substantially driven by solution concentration rather than diversity in protein amphilicity. Scaling as a ratio-to-physiological-concentration demonstrates that certain proteins exhibit the full possible range of interfacial activity at-and-well-below physiological concentration whereas others are only weakly surface active within this range, requiring substantially higher solution concentration to achieve maximum adsorption to the LV interface. Important among this latter category of proteins are the blood factors XII and XIIa, assumed by the classical biochemical mechanism of plasma coagulation to be highly surface active, even in the presence of overwhelming concentrations of other blood constituents such as albumin and immunoglobulin that are shown by this work to be among the class of highly-surface-active proteins, at physiologic concentration. A comparison of pendant-drop and Wilhelmy-balance tensiometry as tools for assessing protein interfacial activity shows that measurement conditions employed in the typical Wilhelmy plate approach fails to achieve the steady-state adsorption state that is accessible to pendant-drop tensiometry. A comparison of bovine and human proteins reveals substantial differences in adsorption to the LV interface, apparently arising from as-yet unresolved speciation effects.

10:20am **BI-WeM7 Nanodevices Integrating Biomolecular Motors: Design Strategies and Applications**, ***H. Hess***, *J. Clemmens,* University of Washington*; C. Matzke, G.D. Bachand, B.C. Bunker,* Sandia National Laboratories*; V. Vogel,* University of Washington

Biomolecular motors are at present the engines of choice for nanodevices.@footnote 1,2@ Their small size, high efficiency, and functional integration allow the construction of hybrid devices, which demonstrate the promise of engineering at the nanoscale. We will discuss the tools employed in designing these devices, which include surface patterning, microfabrication, and genetic engineering. Our recent results@footnote 3@ show that these tools have to be employed in concert, in order to achieve outstanding results. For example, controlled placement of motor proteins on a surface requires non-fouling regions of high quality, as well as fine-tuning of the adsorption properties of the motors by genetic engineering. The design process in general requires an in-depth understanding of the motor properties as well as the properties of the filaments the motor proteins bind to (e.g. microtubules). New measurements aim at determining these properties. We will also present an overview of the applications studied by us, ranging from molecular shuttles@footnote 4,5@ to surface imaging @footnote 6@ and force measurements.@footnote 7@ @FootnoteText@@footnote 1@ H. Hess and V. Vogel, Reviews in Molecular Biotechnology, 82, 67-85 (2001)@footnote 2@ H. Hess, G. Bachand, and V. Vogel in: Encyclopedia of Nanoscience and Nanotechnology. Edited by James A. Schwarz, Cristian Contescu, and Karol Putyera (Marcel Dekker, New York, in print)@footnote 3@ J. Clemmens, H. Hess, J. Howard, V. Vogel, Langmuir, 19, 1738-1744 (2003)@footnote 4@ H. Hess, J. Clemmens, D. Qin, J. Howard, and V. Vogel, Nano Letters, 1 (5), 235-239 (2001)@footnote 5@ H. Hess, J. Clemmens, C. M. Matzke, G. D. Bachand, B. C. Bunker, and V. Vogel, Appl. Phys. A, A 75, 309-313 (2002)@footnote 6@ H. Hess, J. Clemmens, J. Howard, and V. Vogel, Nano Letters, 2 (2), 113-116 (2002)@footnote 7@ H. Hess, J. Howard, and V. Vogel, Nano Letters, 2(10), 1113-5 (2002).

10:40am **BI-WeM8 Nanoparticle Transport Using Microtubules and Motor Proteins**, ***B.C. Bunker***, *G.D. Bachand, A.K. Boal, S.B. Rivera, T.J. Headley, J.M. Gaudioso, J.M. Bauer, R.P. Manginell,* Sandia National Laboratories*; H. Hess, V. Vogel,* University of Washington

Active transport systems consisting of motor proteins and microtubules can potentially provide a dynamic mechanism for assembling and reconfiguring materials at nanometer length scales. We are interested in using motor protein-microtubule systems to manipulate gold nanoparticles and quantum dots to create programmable or responsive conductive or optical arrays within microfluidic systems. The primary active transport strategy we have investigated involves the use of patterns of tethered motor proteins to transport short functionalized microtubules attached to nanoparticles. This talk will focus on two central issues associated with developing a viable transport system: 1) the development of surface functionalization schemes that optimize the guiding of microtubule shuttles through lithographically-defined networks, and 2) the development of functionalized microtubule configurations that allow nanoparticles to be carried without affecting critical motor protein-microtubule interactions. For guiding, we have obtained the best results using lithographic patterns containing both gold and silica surfaces. The gold surfaces are coated with self-assembled monolayers (oligoethylene glycol and amine terminations are most effective) that are antifouling with regard to proteins, confining the adsorption of motor proteins and their support structures onto exposed silica at the channel bottoms. In terms of microtubule functionalization, we have demonstrated that both gold nanoparticles and CdSe quantum dots can be attached to microtubules using standard biotin-streptavadin linkages. The structures of the nanoparticle-microtubule constructs have been characterized using both transmission electron and atomic force microscopies. Flourescence microscopy results show that the number and spatial distributions of particles must be controlled to achieve active transport. Several successful strategies for controlling such distributions will be described.

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