**2002-Pos**

**A New, Fundamental Multiscale Modeling Framework Based on the Relative Entropy**

**M. Scott Shell**, Aviel Chaimovich.
University of California Santa Barbara, Santa Barbara, CA, USA.

Our understanding of biology stems from models at many resolutions, as we seek from detailed atomic-scale interactions simpler emergent physical principles to support our understanding and to produce useful theoretical reductions and tractable simulations. In particular, multiscale methods coupling coarse-grained and atomic models are essential to modeling, predicting, and understanding the basic driving forces that operate across many biomolecular length and time scales. Yet, though coarse-graining strategies exist, it has been challenging to identify universal approaches to the multiscale problem that build systematic, quantitative connections between atomic interactions and reduced models.

We have created a powerful, rigorous theoretical framework that addresses this problem. Its focus is the relative entropy, an information-theoretic and statistical-thermodynamic quantity that measures the information lost when moving from a detailed to coarse-grained description of a system. We postulate that the most descriptive physical principles and simple models are those that minimize this quantity, hence minimizing the physical information lost when atomic detail is removed. Importantly, we show that this concept unifies and broadens a number of established statistical-mechanical principles. For the first time, the relative entropy provides a general, systematic framework for multiscale modeling.

A practical benefit is that the relative entropy suggests how to transform atomistic models into reduced ones that capture the same physics, enabling seamless integration of models spanning scales. We describe a family of algorithms that optimize coarse-grained molecular models by minimizing the relative entropy numerically. These coarse-graining algorithms are general to arbitrary models and the first to offer a universal metric for model quality. We describe the application of these algorithms to the development of simple models of water for modeling large-scale association processes driven by hydrophobic interactions, and to models of peptides for interrogating early steps in aggregation.

**2003-Pos**

**Using Statistically Significant Correlated Motions of Residues in a MD Based Approach to Investigate Allostery in Ubiquitin Conjugating Protein**

**Salma B. Rafi**, Christopher L. McClendon, Matthew P. Jacobson.
University of California at San Francisco, San Francisco, CA, USA.

Ubiquitin conjugating proteins (E2s) are an important component of the ubiquitin proteasome pathway. E2s interact with ubiquitin activating enzyme (E1) and ubiquitin ligases (E3s) to transfer ubiquitin to target proteins to mark them for degradation. In some E3s, RING domains act as scaffolds to bind E2s and target proteins so that the ubiquitin can be directly transferred from the E2 to the target protein. This ubiquitin transfer has been shown to be allosterically regulated: E3 RING domain binding to E2 at one site promotes ubiquitin release from the active site cysteine (~15Å distance) without substantial conformational change in E2. Previous studies used statistical coupling analysis (SCA) to identify clusters of residues that might transmit information. Here, we use a novel information-theory approach to identify residues with statistically significant correlated conformations in a set of equilibrium molecular dynamics simulations. From the matrix of correlations between residues, we observed substantial coupling between an E2's active site and its E3 RING domain binding site. However, in the I88A mutant, the pattern of correlations is disrupted, consistent with the experimental observation that this I88A mutation abrogates the allostery in the E2s. Thus, our approach is sensitive enough to identify effects of single point mutations in the protein. Unlike SCA, which infers couplings from many protein sequences, our approach identifies couplings between residues in individual proteins, some of which coincide with residues identified by SCA. As our approach is general and sensitive to small physical-chemical differences in sequence, structure, and dynamics, we can apply our approach to study similarities and differences in the allosteric networks of different E2s in order to better understand how protein degradation is regulated, also providing a mechanistic insight of the process.

**2004-Pos**

**Toward Accurate Simulations of Cu+ - Protein Binding: Computational Studies of Model Systems with a Polarizable Force Field**

**George Kaminski**.
Worcester Polytechnic Institute, Worcester, MA, USA.

Cu+ binding and transport plays an important role in biological processes. It would be advantageous to have the ability to accurately determine their binding affinities via computational means. At the same time, simulation of ions presents a number of fundamental and practical difficulties. We have compared energetic and structural properties of the Cu+ ion complexes with small model molecules. While these simulations without explicit treatment of electrostatic polarization have in some cases lead to more than three-fold errors in the magnitudes of the binding energies, similar calculating with a polarizable force field produced results in good agreement with the available experimental and high-level quantum mechanical data. We believe that this work (a) demonstrates the importance of explicit treatment of the electrostatic polarization in ion-transport and binding simulations and (b) opens a road to accurate *in silico* determination of Cu+ and other ions binding affinities with proteins.

**2005-Pos**

**Simulation Studies of a TRI-PEDAL, Protein-Based Artificial Molecular Motor**

**Nathan J. Kuwada**[1], Gerhard A. Blab[2], Martin J. Zuckermann[2], Paul M.G. Curmi[3], Elizabeth H.C. Bromley[4], Roberta Davies[3], Derek N. Woolfson[4], Nancy R. Forde[2], Heiner Linke[5].
[1]University of Oregon, Eugene, OR, USA, [2]Simon Fraser University, Burnaby, BC, Canada, [3]University of New South Wales, Sydney, Australia, [4]University of Bristol, Bristol, United Kingdom, [5]Lund University, Lund, Sweden.

Though the biological function of many natural molecular motors is fairly well established, many structure-function details responsible for motor performance remain vague or unknown completely. Recently, we have undertaken a new bottom-up approach to understanding biological molecular motors by designing and building an artificial, protein-based molecular motor dubbed the Tumbleweed (TW). The TW is a purely diffusive motor construct consisting of three DNA-binding proteins attached to a designed, protein-based central hub, where directional stepping along a DNA track is maintained by a temporally periodic external chemical supply. To better understand important design and performance characteristics of the TW, coarse-grained Langevin Dynamics (LD) simulations and numerical solutions to the Master Equation (ME) were carried out. The LD approach, which is a single motor simulation, is particularly suitable for exploring the diffusional behavior of the system, where the ME approach, which models an ensemble of motor states, is best suited for statistically exploring the parameter space of the system and the interaction of processes at different time scales. We present results from these two theoretical approaches that illuminate not only important design and experimental considerations, such as motor geometry and track spacing, but also produce unexpected diffusional behavior. Of particular interest is that the addition of certain internal symmetric potentials can increase motor performance. For example, the addition of a non-specific binding potential, symmetric about the DNA track, can double motor speed by replacing some of the 3D diffusional search by a relatively fast 1D diffusional slide along the DNA. This, and other symmetric potential inputs that increase motor performance by subtly amplifying asymmetries in the system, are not only fundamentally interesting but also may be applicable to any molecular motor that incorporates a diffusional search in its stepping cycle.

**2006-Pos**

**Thermodynamic Efficiency Out of Equilibrium**

**David A. Sivak**, Gavin E. Crooks.
Lawrence Berkeley National Laboratory, Berkeley, CA, USA.

Equilibrium thermodynamics satisfactorily explains the efficiency of macroscopic machines, whose operation is posited as a quasi-static, infinite time, zero power process exemplified by the Carnot heat engine. Microscopic biomolecular motors differ markedly from their macroscopic counterparts, as they are subject to large fluctuations, operate far from equilibrium, and by necessity accomplish their tasks in finite time with non-zero power. They thus demand novel non-equilibrium frameworks. We explore thermodynamic length as an analytic framework for understanding the physical limits on biomolecular motors. Thermodynamic length defines the length of a non-equilibrium transformation as the root-mean squared fluctuations of the variables conjugate to the control parameters. It is a natural measure of distance between equilibrium thermodynamic states, but unlike the free energy change explicitly depends on the path taken through thermodynamic state space. Thermodynamic length equips thermodynamic state space with a Riemannian metric and thus facilitates the discovery of minimum thermodynamic length paths, which minimize the dissipation for slow, but finite time, transformations. We derive analytic expressions for Fisher information (related to the derivative of thermodynamic length) in simple bistable energy landscapes, finding that it can vary by several orders of magnitude across a given energy landscape. Our novel dynamic programming approach allows more detailed analysis of these model landscapes, establishing that thermodynamic length analysis accurately predicts the instantaneous dissipation of

far-from-equilibrium processes across the entire energy landscape. We also derive thermodynamic length as a special case of linear response theory, a standard non-equilibrium framework. Thermodynamic length analysis should prove useful in the further analysis of molecular motors, as it gives access to non-equilibrium properties (dissipation) through equilibrium properties (Fisher information and relaxation time).

**2007-Pos**

**A Webserver for Generating Stereochemically-Acceptable Protein Pathways and Movies**

**Daniel W. Farrell**, Kirill Speranskiy, Michael F. Thorpe.
Arizona State University, Tempe, AZ, USA.

We introduce a new, quick method for generating stereochemically-acceptable pathways in proteins, The method, called geometric targeting, is an alternative to the computationally-intensive targeted molecular dynamics approach. Geometric targeting takes as input two distinct protein conformations and produces an all atom pathway between the two states, guided by geometric considerations that will be described. We also present our new webserver for protein pathways. The user submits two protein structures to the webserver, and the geometric targeting method is run automatically to generate a pathway. The webserver also includes tools for visualization of the pathway and downloading of pathway movie files for use in presentations. The strategy behind the geometric targeting method is to take random steps while gradually decreasing the RMSD to the target, and while imposing various geometric constraints to make sure that each snapshot has good stereochemistry. The pathways maintain good covalent bond distances and angles, keep backbone dihedral angles in allowed Ramachandran regions, avoid eclipsed side-chain torsion angles, avoid non-bonded overlap, and maintain a set of hydrogen bonds and hydrophobic contacts. The method does not necessarily produce the optimal pathway, but rather a stereochemically-acceptable pathway. By running multiple times, a collection of random pathways between the two states can be generated. These pathways will be useful for further quantitative analysis, such as to study free energy changes or search for transition states.

**2008-Pos**

**B Cell Affinity Discrimination Requires Kinetic Proofreading**

**Philippos Tsourkas**, Subhadip Raychaudhuri.
UC Davis, Davis, CA, USA.

B cells signaling in response to antigen is proportional to antigen affinity, a process known as affinity discrimination. Recent research suggests that B cells can acquire antigen in membrane-bound form on the surface of antigen-presenting cells (APCs), with signaling being initiated within a few seconds of B cell/APC contact. During the earliest stages of B cell/APC contact, B cell receptors (BCRs) on protrusions of the B cell surface bind to antigen on the APC surface and form micro-clusters of 10-100 BCR/Antigen complexes. In this study, we use computational modeling to show that B cell affinity discrimination at the level of BCR-antigen micro-clusters requires a threshold antigen binding time, in a manner similar to kinetic proofreading. We find that if BCR molecules become signaling-capable immediately upon binding antigen, the loss in serial engagement due to the increase in bond lifetime as affinity increases results in a considerable decrease in signaling with increasing affinity. Adding a threshold antigen binding time for BCR to become signaling-capable favors high affinity BCR-antigen bonds, as these long-lived bonds can better fulfill the threshold time requirement than low-affinity bonds. A threshold antigen binding time of ~10 seconds for BCR to become signaling-capable results in monotonically increasing signaling with affinity, replicating the affinity discrimination pattern observed in B cell activation experiments. This time matches well (within order of magnitude) with the experimentally observed time (~ 20 seconds) required for the BCR signaling domains to undergo antigen and lipid raft-mediated conformational changes that lead to association with Syk.

**2009-Pos**

**Study of the Role of Factor VII in Venous Thrombus Formation Using Combination of a Multiscale Model and Experiment**

**Mark Alber**[1], Zhiliang Xu[1], Joshua Lioi[1], Malgorzata Kamocka[2], Xiaomin Liu[1], Jian Mu[1], Danny Chen[1], Elliot Rosen[2].
[1]University of Notre Dame, Notre Dame, IN, USA, [2]Indiana University School of Medicine, Indianapolis, IN, USA.

To prevent the loss of blood following a break in blood vessels, components in blood and the vessel wall interact rapidly to form a venous thrombus to limit hemorrhage. Combination of extended multiscale model, new image processing algorithms and biological experiments is used for studying the role of Factor VII (FVII) in venous thrombus formation. A detailed sub-model of the tissue factor (TF) pathway of blood coagulation is introduced within the framework of the multiscale model to provide detailed description of coagulation cascade. Macro scale dynamics of the blood flow is described by the continuum Navier-Stokes equations. Micro scale interactions between activated platelets, platelets and fibrin(ogen) and platelets and vessel wall are modeled using an extended stochastic discrete model. The novelty of the approach is in representing each platelet as an extended object with a boundary and modeling in detail the production of thrombin by each individual platelet. Also, clot is treated as a porous medium. Surface reactions of the extrinsic coagulation pathway on membranes of platelets are studied under different flow conditions. It is shown that low levels of FVII in blood result in a significant delay in thrombin production leading to changes in the surface composition of developing thrombi. The changes likely alter the mechanism and dynamics of thrombus stabilization which we are now studying in computational and experimental models.

Xu, Z., Chen, N., Shadden, S., Marsden, J.E., Kamocka, M.M., Rosen, E.D., and M.S. Alber [2009], Study of Blood Flow Impact on Growth of Thrombi Using a Multiscale Model, Soft Matter 5, 769-779.
Xu, Z., Chen, N., , Kamocka, M.M., Rosen, E.D., and M.S. Alber [2008], Multiscale Model of Thrombus Development, Journal of the Royal Society Interface 5 705-722.

**2010-Pos**

**Multiscale Modelling of Membrane Systems**

**Jonathan W. Essex**[1], Mario Orsi[1], George Chellapa[1], Wendy E. Sanderson[2], Massimo G. Noro[3].
[1]University of Southampton, Southampton, United Kingdom, [2]Johnson & Johnson PRD, Beerse, Belgium, [3]Unilever R&D, Port Sunlight, United Kingdom.

We have developed both 10- and 2-site molecular dynamics simulation models of biological membranes, tested their ability to model various lipid phases, and to reproduce important membrane physical properties, particularly the lateral pressure profile which is critical in determining the phases adopted in lipid systems [1]. The novelty in these models lies predominantly in the way they capture shape anisotropy, and the realistic way in which electrostatic interactions are incorporated. Furthermore, through careful design, the 10-site model in particular is compatible with atomistic models, allowing multiscale simulations of membrane systems [2].

In this presentation, the design philosophy and parameterisation procedures for these models will be described, together with their validation, with a particular focus on their lateral pressure profiles and phase behaviour. The application of these models in the context of multiscale simulations will then be considered. First, their use to calculate the permeability coefficients of small molecules through phospholipid bilayers, by combining molecular dynamics simulations with constraints, will be outlined [3]. Second, the effect of small molecules on membrane properties will be discussed, focusing particularly on antibacterials, which, it is postulated, may work through modifying the underlying physics of the membrane.

[1] M. Orsi, D. Y. Haubertin, W. E. Sanderson and J. W. Essex, J. Phys. Chem. B, 2008, 112, 802-815.
[2] J. Michel, M. Orsi and J. W. Essex, J. Phys. Chem. B, 2008, 112, 657-660.
[3] M. Orsi, W.E. Sanderson and J.W. Essex, J. Phys. Chem. B, 2009, 113, 12019-12029.

**2011-Pos**

**Techniques for Modeling the Electrostatic Field of Large Biomolecules**

**Apostol Gramada**, Philip E. Bourne.
University of California San Diego, La Jolla, CA, USA.

Electrostatic interactions play an essential role in many molecular processes within living organisms. However, for the large biological macromolecules typically involved in such processes, the accurate representation of the electrostatic potential is difficult to achieve in simple and, at the same time, computationally efficient ways: coarse-graining the electrostatic interactions becomes therefore necessary for any meaningful computational simulation of these processes. Multipole expansions offer a natural approach to coarse-graining due to their ability to capture directional variation of the interacting fields. Yet, the dependence of the multipole moments on the center of expansion and their limitations in accuracy near the molecular surface makes their application to large molecules unreliable. We present strategies in which we combine our Rankwise Distributed Multipole Analysis (RWDMA) method with partitioning schemes to overcome these limitations and develop relatively simple electrostatic models for large molecules. We illustrate the method with models of the electrostatic potentials of the histone core of a nucleosome complex and of the Arc repressor protein.