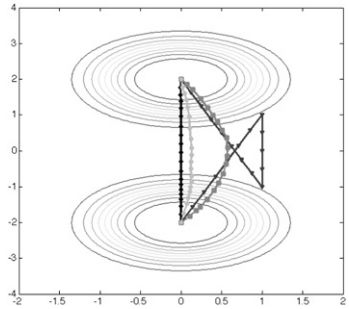
Platform BH: Computational Methods

2946-Plat
Prediction of Allosteric Linkages in Proteins
David W. Dreisigmeyer, **Michael E. Wall**.
Los Alamos National Laboratory, Los Alamos, NM, USA.
Cells often control protein activity using allostery, in which a functional site is controlled by interactions at a remote allosteric site. Although much is known about functional sites in proteins, less is known about the allosteric sites that control them. We are developing a method for high-throughput prediction of linkages between functional sites and allosteric sites. Our approach is distinct from previous computational methods to study allosteric linkages [1,2,3]: it works by seeking relatively strong thermodynamic linkages between interactions at a functional site and interactions at all possible allosteric sites on the protein surface. To implement the method, we use a coarse-grained model that enables fast predictions using a highly scalable algorithm: this approach enables predictions to be made in a few minutes per processor for a typical protein. We illustrate the method and characterize its performance using results from several test cases. The results are consistent with known allosteric linkages in proteins, and yield new insights into allosteric mechanisms.
1. D. Ming and M.E. Wall. Allostery in a coarse-grained model of protein dynamics. 2005. Phys Rev Lett 95:198301.
2. C. Chennubhotla, I. Bahar. Markov propagation of allosteric effects in biomolecular systems: application to GroEL-GroES. 2006. Mol Syst Biol 2:36.
3. V.J. Hilser, E.B. Thompson. Intrinsic disorder as a mechanism to optimize allosteric coupling in proteins. 2007. Proc Natl Acad Sci U S A 104:8311-8315.

2947-Plat
Artificial Reaction Coordinate "Tunneling" In Free Energy Calculations: Nucleic Acid Cleavage By Ribonuclease-H
Edina Rosta[1], H. Lee Woodcock[2], Bernard R. Brooks[2], Gerhard Hummer[1].
[1]Laboratory of Chemical Physics, NIDDK, NIH, Bethesda, MD, USA,
[2]Laboratory of Computational Biology, NHLBI, NIH, Bethesda, MD, USA.
Phosphate esters are essential components of living systems, with phosphate groups being key participants in signaling, energy transduction and storage, protein synthesis, and replication processes. In a large number of enzymes and ribozymes, catalysis of phosphate ester synthesis and hydrolysis is aided by two bound divalent metal ions. However, the mechanistic details of two-metal ion catalysis remain unclear. We used QM/MM simulations to construct the potential of mean force for the catalytic reaction of the Bacillus halodurans ribonuclease-H enzyme complexed with an RNA/DNA hybrid substrate. Reaction free energies are calculated from umbrella sampling simulations with and without Hamiltonian replica exchange. The calculations provide a detailed and quantitative picture of ribonuclease-H catalyzed cleavage of the nucleic acid backbone, producing barrier heights consistent with experimental kinetics. However, by comparing the results obtained for two reaction coordinates probing the same reaction mechanism, we show that the use of typical one-dimensional coordinates may result in an artificially lowered apparent reaction barrier. We describe a method that constructs an improved one-dimensional reaction coordinate to take into account the missing degrees of freedom.

2948-Plat
Transition Pathway Calculation Using Interpolated Parameters From Swarms Of Trajectories
Dmitry A. Kondrashov, Albert C. Pan, Benoit Roux.
University of Chicago, Chicago, IL, USA.
Understanding the mechanism of conformational changes in macromolecules requires the knowledge of the intermediate states. A version of the string method, which uses multiple short dynamics trajectories to propagate the pathway, was recently developed by Pan et al. Here we use data from swarms of trajectories calculated at discrete points in phase space to interpolate the average displacement and variance at arbitrary points. This is tested on model potentials using statistics from actual swarms of trajectories. We use the interpolated parameters to compute the Markovian propagators from one point on the transition path to the next. We use them to obtain a time-dependent action of a path, which can be optimized to produce the highest probability pathway. We describe the optimization protocol and demonstrate that in artificial flat potentials the existing string method cannot correct problems such as loops in the initial path, while the new method produces the correct pathway (Figure shows pathway in 2D potential). We further illustrate the utility of our method by applying it to protein conformational transitions, such as the KcsA potassium channel, and comparing its performance to existing transition pathway methods.



2949-Plat
Thermal Motions of the E. Coli Glucose-Galactose Binding Protein Studied Using Well-Sampled "Semi-Atomistic" Simulations
Derek J. Cashman, Artem B. Mamonov, Divesh Bhatt, Daniel M. Zuckerman.
University of Pittsburgh, Pittsburgh, PA, USA.
The E. coli D-galactose chemosensory receptor is a 309 residue, 32 kDa protein consisting of two distinct structural domains, organized into alpha/beta folding motifs. In this computational study, we analyze the protein's thermal fluctuations, including large scale interdomain movements that contribute to the receptor's mechanism of action. We employ extremely fast ''semi-atomistic'' Monte Carlo simulations, which produce several statistically-independent configurations per day on a single processor. Our results are consistent with previous disulfide trapping experiments performed by Careaga & Falke (JMB, 1992; Biophys. J., 1992), which indicate that distant residues in the crystal structure (i.e. beta carbons separated by 10 to 20 angstroms) form spontaneous transient contacts in solution. The simulations illustrate possible ''mechanisms'' (configurational pathways) for these fluctuations. Furthermore, we observe large hinge movements between the two domains, which open and close the binding site. The possibility to simulate such fluctuations stems from our pre-calculation of fully atomistic peptide plane configurations, leading to a semi-atomistic model with alpha- and beta-carbon interaction sites. Energetically, our method employs G[[Unable to Display Character: ō]]-like interactions, which may include specific enhancements, such as Ramachandran propensities, backbone hydrogen-bonding, and Miyazawa-Jernigan contact interactions.

2950-Plat
PRIMO: A Transferable Coarse-Grained Model for Proteins
Srinivasa M. Gopal, Michael Feig.
Department of Biochemistry and Molecular Biology, Michigan State University, East Lansing, MI, USA.
Coarse-grained (CG) models for biological systems promise a considerable advantage over all atom models with respect to conformational sampling of large systems over long timescales. A major bottleneck in most existing CG modeling approaches has been a lack of transferability to a wide array of systems and physical conditions.
A new, fully transferable model PRIMO (PRotein Intermediate Model) is introduced. This model is comparable to all-atom models in terms of accuracy and transferability. The PRIMO model consists of interaction sites each combining 1-3 heavy atoms. The interaction potential is similar to standard molecular dynamics (MD) forcefield terms plus additional empirical hydrogen bonding and solvation terms. PRIMO is parameterized primarily based on atomistic simulations. PRIMO has been tested by comparing energies to the CHARMM27 all-atom forcefield for $(AAXAA)_N$ peptides and protein decoy sets. We demonstrate the application of PRIMO model by comparing stability of MD simulations of proteins to results from atomistic simulations and by comparing folding studies of $(AAXAA)_N$ peptides.