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.