1997-Pos

Life Cycle of an Electropore: A Molecular Dynamics Investigation of the Electroporation of Heterogeneous Lipid Bilayers (PC:PS) In the Presence of Calcium Ions

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To aid in understanding the mechanism of electric field-driven pore formation in lipid bilayers, we propose a scheme for characterizing the life cycle of a transient membrane electropore, from the formation of the initial defect to the restoration of the intact bilayer. We apply this analysis to heterogeneous phospholipid bilayers (phosphatidylcholine:phosphatidylserine, PC:PS) in the presence of calcium ions. Previous reports of molecular dynamics (MD) simulations of similar PC:PS systems containing Ca2+ [1,2] are consistent with experimental observations [3]. In this study we assembled systems containing varying amount of PC, PS, and Ca2+ and observed how long it took each bilayer to porate after the application of an electric field. We also measured the effect of Ca2+ on pore lifetime (the time it takes to restore the porated bilayer after removal of the electric field). We find that systems containing Ca2+ are more difficult to electroporate, and that this effect is magnified in systems containing PS. We also observe that Ca2+ has little effect on pore lifetime, but that PC:PS systems have shorter lifetimes than pure PC systems. Finally, we report binding isotherms for Ca2+ and PC:PS bilayers, an additional metric for the validity of phospholipid bilayer simulations containing calcium.

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1998-Pos

Molecular Dynamics Study of the Interaction of HHC-10 with the Mixed POPG/POPE Membrane

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The documented selectivity [A.Cherkasov et al, ACS Chem. Biol., 4, 65, (2009)] for disrupting bacterial membranes as opposed to mammalian membranes exhibited by many cationic antimicrobial peptides (CAPs) is poorly understood. Molecular dynamics simulations are a useful tool for exploring the underlying molecular mechanisms for this selectivity [I. Tolokh et al, 80, 031911, (2009).]. The interaction of the cationic peptide HHC-10, a novel antimicrobial peptide recently designed through a neural network investigations of large families of antimicrobial peptides, is studied when in the vicinity of a pure POPC (mammalian model) membrane and mixed POPG/POPE (bacterial model) membrane. Non-equilibrium methods are used for performing the molecular dynamics simulations and for obtaining the PMF of the interaction along the reaction coordinate of interest, namely the distance from the center of the mass of HHC-10 peptide with the outer leaflet of the membrane.

Computational Methods I

1999-Pos

Multiscale Modeling of PCNA - Ubiquitin Interactions

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Covalent attachment of ubiquitin (Ub) to proliferating cell nuclear antigen (PCNA) plays a crucial role in translesion synthesis (TLS). However, structural knowledge of the complex between Ub and PCNA is currently lacking. The problem is important from a biological perspective since ubiquitinated PCNA is involved in the recruitment of specialized lesion bypass polymerases. A loss of regulation of TLS and other damage-avoidance pathways can lead to a variety of cell fates including apoptosis and uncontrolled cell growth. We have modeled the Ub-PCNA complex using a combination of tethered Brownian dynamics (TBD), protein-protein docking with RosettaDock, flexible loop modeling with ModLoop, and molecular dynamics(MD). The TBD simulations were used to generate a large ensemble of electrostatically and geometrically favorable configurations, subsequently used as a starting point for local docking searches. The final models were refined with all-atom explicit solvent MD simulations. Ubiquitin was found to bind in a groove on the PCNA surface directly above the PCNA subunit interface. A mutation originally identified in genetics screens (pol30-113) and known to interfere with TLS, is positioned directly beneath the bound ubiquitin in our models. Thus, the results provide unexpected insight into previously unexplained biological observations.
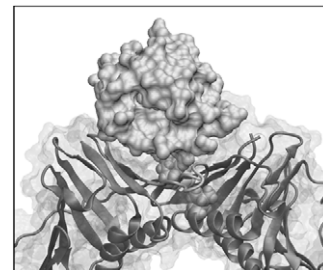
2000-Pos

Adaptive Anisotropic Kernels for Nonparametric Estimation of Absolute Configurational Entropies in High-Dimensional Configuration Spaces

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The quasiharmonic approximation is the most widely used estimate for the configurational entropy of macromolecules from configurational ensembles generated from atomistic simulations. This method, however, rests on two assumptions that severely limit its applicability (i) that a principal component analysis yields sufficiently uncorrelated modes an (ii) that configurational densities can be well approximated by Gaussian functions. In this paper we introduce a nonparametric density estimation method which rests on adaptive anisotropic kernels. It is shown that this method provides accurate configurational entropies for up to 45 dimensions thus improving on the quasiharmonic approximation. When embedded in the minimally coupled subspace framework, large macromolecules of biological interest become accessible, as demonstrated for the 67-residue coldshock protein.

2001-Pos

Construction of Energy Based Protein Structure Networks: Application in the Comparative Analysis of Thermophiles and Mesophiles

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Thermophilic proteins sustain themselves and function at higher temperatures. Despite their structural and functional similarities with their mesophilic homologues, they show enhanced stability. Various comparative studies at genomic, protein sequence and structure levels, and experimental works highlight the different factors and dominant interacting forces contributing to this increased stability. In this comparative structure based study, we have used interaction energies between amino acids, to generate structure networks called as Protein Energy Networks (PENs). The interaction energy is the averaged sum of the Lennard-Jones and the Coulombic energies, over an equilibrium ensemble of conformations. The PENs are used to compute network parameters like largest connected component, clusters, cliques, communities and hubs. These parameters are then compared between the thermophile-mesophile homologues. The results show an increased number of clusters and low energy cliques in thermophiles as the main contributing factors for their enhanced stability. Further more, we see an increase in the number of hubs in thermophiles. We also observe no community of electrostatic cliques forming in PENs of both thermophiles and mesophiles. In summary, we have developed protein structure networks based on non-covalent interaction energies between amino acids. These networks are then exploited to identify the factors responsible for enhanced stability of thermophilic proteins, by comparative analysis. We were able to point out that the sub-graph parameters are the prominent contributing factors and also that the thermophilic proteins have a better packed hydrophobic core. We have also discussed how thermophilic proteins, although increasing stability through higher connectivity, retain conformational flexibility, from a cliques and communities perspective.