dynamical properties. Furthermore, DPC micelles have been used to examine the influence of the micellar environment on the structure and localization of transmembrane peptides of a large MP, hMRP1.

2011-Pos Board B781

Probing the Role of Lipid Substitution on Polyethylenimine Mediated DNA Aggregation: An All-Atom Molecular Dynamics Study

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Understanding the dynamics of DNA condensation is important because of the biological significance of DNA packaging in cell nuclei, as well as its applications in gene delivery therapy. Synthetic polycations such as polyethylenimine (PEI) can condense DNA into nanoparticles, and have attracted much research efforts for their applications as nonviral gene carriers. Specifically, it has been found that hydrophobically modifying the polycations through lipid substitution can greatly improve some polycations' efficacy as gene carriers, however, the role of the hydrophobic modification remains to be probed. In this work, we performed a series of all-atom molecular dynamics (MD) simulations to study the complexation of lipid modified PEI (lmPEI) with DNA, and lmPEI mediated DNA aggregation. We found that i) a significant fraction of the lipid tails on the lmPEI stay outside of the formed lmPEI/DNA complex, which potentially leads to the formation of hydrophobic nanoparticles and benefits their translocation across the cell membrane; ii) the lipid tails from different lmPEIs tend to associate with one another and form a lipid aggregate in the core of the formed lmPEI-DNA aggregate, which can contribute to the formation of stable nanoparticles. We have also calculated the DNA-DNA spacing in the formed lmPEI/DNA aggregate. The simulations shed light on the dynamics of lmPEI mediated DNA aggregation and serve as a model to test proposed polycation modification schemes through computations.

2012-Pos Board B782

Accelerating the Rate of Convergence of Umbrella Sampling Simulations in Lipid Bilayers

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All molecular dynamics simulations are susceptible to sampling errors, which degrade the accuracy and precision of observed values. Systems containing atomistic lipid bilayers are particularly susceptible to sampling errors because bilayer conformational autocorrelation times can exceed hundreds of nanoseconds. To identify optimal methods for enhancing sampling efficiency, we quantitatively evaluate convergence rates using generalized ensemble sampling algorithms in calculations of the potential of mean force for the insertion of a side chain analog of arginine in a lipid bilayer. Umbrella sampling (US) is used to restrain solute insertion depth along the bilayer normal, the order parameter commonly used in simulations of molecular solutes in lipid bilayers. The rate of statistical convergence of the standard free energy of binding of the solute to the lipid bilayer is increased three-fold when US simulations are modified to conduct random walks along the bilayer normal using Hamiltonian exchange algorithms. We introduce a new metric, computed from simulations conducting random walks along the bilayer normal, to detect sampling barriers in degrees of freedom orthogonal to the US order parameter, which often result in systematic sampling errors but usually remain hidden. This new metric is used to evaluate the height of hidden free energy barriers in order to identify solute insertion depths which are prone to systematic sampling errors. Accordingly, we demonstrate that applying random walks in temperature at these selected insertion depths leads to further increases in the rate of convergence of the binding free energy. Finally, we apply an enhanced US protocol combining random walks in insertion depth and in temperature to quantify the influence of embedded arginine on lipid flip-flop and on the formation of transient water pores, effects that are likely to contribute to the activity of arginine-rich antimicrobial peptides.

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A Nano-Scavenger in Action: The Molecular Mechanism of Membrane Cholesterol Extraction by Cyclodextrins

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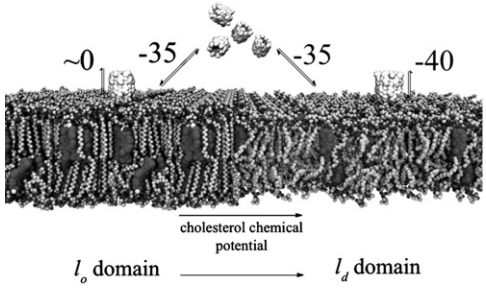
Cholesterol concentration balance in biological membranes is of vital importance for the regulation of several critical processes (e.g. domain formation, membrane protein activity, signaling etc.) and tightly regulated during cell development. Abnormal cholesterol levels may eventually lead to clinical disorders like Niemann-Pick type C disease, with minimal chances of survival for the patient.

It is well known that cyclodextrins (CDs), and especially beta-cyclodextrin, are able to modify the cholesterol concentration in membranes; either *in situ* (e.g. model membranes) or *in vivo* (cells). However, the molecular mechanism of this process is still unknown. Using molecular dynamics simulations, we have been able to study the CD-mediated cholesterol extraction from lipid membrane models.

CD dimers strongly bind to membranes (free energy of adsorption ~ −35 kJ mol^{-1}); however, only the extraction of cholesterol by a dimer from the cholesterol-poor Liquid disordered (l_d) region is a favorable process (−40 kJ mol^{-1}). We suggest that the continued extraction of cholesterol from the l_d region eventually destabilizes the domain separation.



With a clearer understanding of the basic molecular mechanism, we can begin to rationalize the design of more efficient CDs in numerous applications.

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PMF Analysis for Interaction of Two Different Three Fingered Proteins and Lipid Bilayer: Molecular Dynamics Study

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One of interesting phenomena in the world of proteins and alive cell's lipid membrane interactions is interaction of a group of small three fingered proteins from cobra venom, called cytotoxins, and lipid bilayers. In this work two different cytotoxins are selected to be studied: cytotoxin a3 and cytotoxin a4. System including one protein, water, lipid bilayer and ions has been simulated with coarse grained molecular dynamics simulation. Ions are added to make whole system neutral. Computation of potential of mean filed (PMF) has been performed to find the most probable final position of cytotoxins in this interaction. GROMACS 405 package is used to simulate the systems and MARTINI force fields are chosen to define the forces between different particles. There are two different coarse grained modeled to simulate water molecules: the standard model and the polarizable model. Each coarse grained water molecule in the standard MARTINI water has only one neutral particle but polarizable water molecule includes three particles involving electrical charges.

The results of PMF analysis report that in both cases of MARTINI water and polarizable water center of mass (COM) of cytotoxin a3 will be closer to center of mass of lipid bilayer in comparison with that of cytotoxin a4. Also for each of cytotoxins use of polarizable water model leads to less distance between COMs of cytotoxin and lipid bilayer.

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Computer Simulations of the Interactions Between Cationic and Anionic Lipids in Lipid Nano Particles for Drug Delivery

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We used molecular dynamics simulation to investigate the structure and properties of lipid nanoparticles (LNP), with as long-term goal improving the efficiency of delivery of nucleic acids in gene therapy. LNPs are synthetic vectors with cationic nature. They are composed of a mixture of cationic lipids, fusogenic lipids, cholesterol and polymer-grafted lipids, and encapsulate siRNA. The presence of ionizable cationic lipids increases the charge density of LNPs at low pH, Cationic lipids were hypothesized to form ionic pairs with anionic lipids in the acidic environment of the endosome [1]. Due to interactions between the charges the ion pair becomes cone shaped and prone to form nonlamellar phase [1]. This contributes to the membrane disruption and release of nucleic acids from endosome.

In this work we focus on the details of lipid-lipid interactions in the LNP and perform atomistic simulations of bilayers containing the cationic lipid (DLin-KC2-DMA), anionic lipids (DSPS) and zwitterionic lipids (DSPC). The cationic lipid DLin-KC2-DMA has been shown experimentally to improve the delivery capacity [1]. Force field parameters for DLin-KC2-DMA lipids were developed to reproduce thermodynamic properties, and tested to ensure compatibility with existing lipid parameters. The study is also important for understanding the mechanism of membrane breakdown upon change of pH/charge density.

[1] Semple, S.C., et al., Rational design of cationic lipids for siRNA delivery. Nat Biotechnol, 2010. 28(2): p. 172-6.