Molecular dynamics simulations of liposomes: From formation to fusion and fission

COMP 91

Improved methods for predicting the structure and function of G protein-coupled receptors

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G protein-coupled receptors (GPCRs) are intrinsic membrane proteins with 7 transmembrane helices, and modulated by diverse bioactive molecules (biogenic amines, peptides, lipids) to regulate essential physiological processes (neurotransmission, metabolism, secretion, growth, immunity). Thus, GPCRs have been implicated in all major disease areas. Development of drugs with reduced side effects has been hampered by the availability of 3D structure for only one GPCR. Our research group has been developing computational methods based on first principles to predict the structure and function of GPCRs. The methods have been validated for many systems against experimental mutagenesis data. We will present some of the recent method developments aimed at more accurate and faster predictions of GPCR structure and function. These include the use of implicit membrane (multi-dielectric) solvation for scoring monte carlo generated helical packings, accurate placement of protein side chains, use of thermodynamic hydrophobicities, and generation of ligand rotamer libraries for flexible docking.

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Molecular dynamics simulations of liposomes: From formation to fusion and fission

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Lipid bilayer membranes are known to form various structures, such as large sheets and vesicles. Using coarse grained molecular dynamics, we first studied the processes of spontaneous bilayer and vesicle formation, showing the bilayer-vesicle transition to be entropy-driven. Next, the same lipid model allowed us to elucidate fusion mechanisms of such vesicles in detail. Furthermore, we found that a difference in composition between the two bilayer leaflets may result in curved bilayers and a wide variety of vesicle shapes, such as ellipsoids, discoids,

pear-shaped, cup-shaped and budded vesicles. Lately, we also have been able to investigate the fission process using the same lipid model. Two distinct routes, being phase separation of lipids within the monolayers and a different composition of the monolayers, for vesicle fission are observed. The difference between the fusion and fission pathway is shown, indicating that one pathway is not simply the reverse of the other.

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Molecular dynamics simulations of surfactant protein C mimic in phospholipid bilayers

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Surfactant protein C (SP-C) is an extremely hydrophobic lipopeptide found in mammalian lung surfactant. Important SP-C functions include lipid bilayer interactions with the lung surface monolayer and modulation of the surfactant lipid viscosity. Previous solution NMR studies in organic solvents indicate that the secondary structure of SP-C and the (34 residue) synthetic SP-C derivative SP-Cff is largely helical in this environment and is localized to the poly-valine sequence. Our infrared measurements of SP-Cff in palmitoyloleoylphosphatidylcholine (POPC) bilayers confirm the helical nature of the peptide, with the helical axis oriented parallel to the long axis of the phospholipid acyl chains. Moreover, our molecular dynamics simulations of SP-Cff in hydrated POPC bilayers validate the helical structure of the poly-valine sequence, with the helical axis oriented perpendicular to the bilayer surface.

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Molecular-scale understanding and design of low friction and biocompatible surfaces

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