Degeneracy in Molecular Scale Organization of Biological membranes

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Abstract

From lipidomics research, it is now known that there are more that 40,000 lipid structures in Eukaryotic cells and the plasma membrane itself has more than 800 different types of lipids. Differential molecular interactions among these extremely diverse constituents give rise to spatiotemporal heterogeneities in the membrane structure. These sub-100 nm transient sub-structures, which are generally stabilized far away from equilibrium in cells, are believed to be functionally important in various physiological processes. One of the fundamental questions in the field is "Why are there so many lipids?"
In this work, we explore the molecular origin of the variety in membrane organization using tools from simple statistical mechanics theories. We use a lattice model for the lipid mixtures, where the lattice Hamiltonian is trained from long microseconds all-atom (AA) simulations [1,2] on lipid bilayer systems that exhibit ordered and disordered fluid phase co-existence. Using stochastic optimization process of Monte Carlo simulated annealing, we evolve the Hamiltonian for lateral organization and show that model membrane with "realistic" lipid constituents show the ability to form a large range of membrane sub-structure space (higher degeneracy and complexity) as compared to "in-vitro" lipids, which form only one kind of substructure even with changing composition. We show that the disconnectivity graph [3] of the potential energy landscape for "in-vitro" systems have distinct funnel energy landscape, while physiologically relevant systems have a more frustrated glass-like energy landscape, which are capable of higher functional diversity due to their ability to form multiple degenerate membrane sub-structures.

Experimental results on membrane dynamics from super resolution techniques and single particle tracking diffusion measurements [4,5] have indicated that smaller domains with highly complex morphologies, resulting from non-ideal mixing of membrane constituents, are observed in both lipids only systems and lipids-proteins bilayer systems. The new non-affine displacement-based framework to characterize lipid order and disorder at nanoscale (with surface diffusion data) could be useful in interpreting data from super high resolution tracking experiments that exhibit highly complex dynamical behavior of lipids in the crowded in-vivo membrane environments.

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