Computational Models of Heterogeneous Lipid Assemblies

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Introduction: Computational models of lipid assemblies provide flexible tools for investigating the principles and processes that lead to early membrane formation, the stabilization of protocells, growth, division, and selection. Several ventures have aimed to establish a modeling framework for protocells [1,2,3]; these simplify the chemistry of the real world while preserving key functional properties, allowing us to observe how protocells might emerge. Thousands of experiments can run systematically in-silico, and provide access to information on every component of the system. This enables us to explore a vast landscape of initial conditions and behaviors, posing predictions that directly complement in-vitro experimentation.

Model: The work presented uses coarse-grained molecular dynamics [4] to model heterogeneous lipid assemblies. At present, the model consists of about 100 different lipids, including simple fatty acids that can be saturated or unsaturated, and more complex lipids such as phospholipids, cardiolipins, sterols. These are combined in different compositions, and then simulations reveal how these compositions self-assemble into bilayer structures, vesicles, micelle, and more potentially more complex structures such as multilamellar and multivesicular vesicles. They can be brought in contact with different environments, which consist of varying temperatures, pHs, obstacles, and different molecules.

Results: Each resulting lipid assembly and environment pairing is then analyzed according to functional properties such as permeation of neutral molecules and ions, robustness to fluctuations, fluidity, and order. Membranes can demonstrate the formation of microdomains with different functional properties. The model is currently applied to study the effects of regulated cell death, in which lipid oxidation increases following the inhibition of a lipid repair enzyme. Future work will look at interactions of different lipid assemblies with simple polypeptides to determine whether they can assist with folding.

Goals: The long-term goal of this project is to observe a minimal form of Darwinian selection, in which protocells change and adapt over a few generation of growth and division. The work has begun with simple bilayers and vesicles, but will extend to vesicles with internal metabolisms, and ultimately vesicles with metabolisms that synthesize lipids. Developing and analyzing models will force us to confront many theoretical challenges related to the transition to Darwinian selection, and will deepen our understanding of this fundamental step in life's origins. In tackling these challenges, we can develop novel concepts and techniques that can directly complement and inform in-vitro work that aims to synthesize protocells in a lab setting.

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