Computational and Experimental Advances in Biomembranes

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Special Issue Preface

Computational and Experimental Advances in Biomembranes: Resolving Their Complexity

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As integral components of cellular architecture and signaling, cell membranes are central to cell physiology. Comprising a vastly complex mixture of proteins and lipids, cell membranes are constantly adapting their structural organization to regulate cellular processes. Malfunctions of lipid composition and lipid−protein interactions are implicated in numerous diseases,[1] and hence, understanding cell membrane organization at the molecular level is of critical importance.

Currently, the field is at a truly exciting tipping point, with research on cellular membranes positioned at the forefront of cellular biology and biophysical chemistry. With computational modeling, we are rapidly transitioning toward simulations of more and more realistic cell membranes, catching events at ever larger spatiotemporal scales.[2] These advances are converging with experimental approaches probing membrane structure and dynamics at ever increasing resolution and extending these insights into the context of a living cell.[3] Combined, the powers of experiment and simulation are synergizing to yield an unprecedented understanding of the functional complexity of living membranes. With this Virtual Special Issue, we collected a series of state-of-the-art examples of the recent progress in this rapidly changing field.

The power of combining experimental and computational assays is exemplified by contributions from various groups on the structural characterization of membranes, e.g., revealing the effect of Ca^{2+} on PS-containing membranes,[4] characterizing the order of SM bilayers,[5] and revealing the special roles of plasmalogen lipids[6] and a particular class of glycolipids found in bacterial membranes.[7] In addition, a number of studies address protein−lipid interplay, revealing novel binding sites from *in silico* predictions, often corroborated or validated with experimental assays.[8−11] Computational studies furthermore show how specific lipids can effect protein dimerization[12] and modulate protein induced membrane curvature.[13,14] These are supported by experimental investigations of diffusion constraints and peptide-binding in models of mammalian[15] and bacterial[16] membranes.

Understanding the mechanism of translocation and binding of a variety of drugs, transfection reagents, and antifungal/antimicrobial compounds also remains a hot topic,[17,18] with additional complexity arising from the presence of certain lipids,[19] synergetic effects,[20] and modulation of pH.[21,22]

Apart from these more applied studies, this Virtual Special Issue includes exciting contributions aimed at increasing our understanding of fundamental physical mechanisms that govern membrane behavior. Examples include studies on the production of heat during membrane depolarization,[23] the extent to which protein rotational diffusion is hindered under crowding conditions,[24] and the dependency of membrane bending modulus on either the membrane composition[25], or on the presence of constraints posed by a nanodisk environment.[26] Also in this category are simulations showing how bilayer pressure profiles depend on force field details,[27] and how many lipid types are actually required to capture the complexity of real cell membranes.[28]

As usual, liquid-ordered/liquid-disordered phase separation is a topic of interest, with studies investigating the influence of pairwise lipid interactions on line tension,[29] the partitioning of multipass transmembrane proteins between phases,[30] and the structural modifications related to raft affinity and membrane curvature of mammalian and viral transmembrane proteins.[31]

Finally, we find a number of methodological advances that are aimed at increasing the efficiency of molecular dynamics simulations of lipid-based systems, such as the use of multiscale hybrid force fields,[32] smart ways to perform free energy calculations making use of density fields,[33] and a new method to compute membrane capacitance,[34] as well as new tools for clustering analysis applied to characterize PIP and water networks.[35,36]

We hope that the collection of articles in this Virtual Special Issue provides a survey of the advances in both computational and experimental characterization of the complex processes underlying the behavior of cellular membranes. We thank all the authors and reviewers for their efforts in making this Virtual Special Issue possible.

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