Title
Preface to Emergence of Complex Behavior in Biomembranes

Journal
Biochimica et Biophysica Acta (BBA) - Biomembranes, 1860(10)

ISSN
0005-2736

Author
Longo, Marjorie L

Publication Date
2018-10-01

DOI
10.1016/j.bbamem.2018.08.015

Peer reviewed

Preface to Emergence of Complex Behavior in Biomembranes

Many observations and theories have been put forward to try to explain how complex behavior emerges in living systems from the ubiquitous lipid bilayer structure and its integrated molecules such as proteins and carbohydrates. Some of the most prominent of these are now being tested and questioned, including the membrane (or lipid) raft hypothesis and mechanisms for generation of membrane curvature and anesthetic effects. The Special BBA issue "Emergence of Complex Behavior in Biomembranes" shares recent results and techniques to inspire new ideas regarding emergence of complex behavior in living cell membranes and non-living model biomembrane systems. The articles are arranged to progress somewhat in scale and complexity. The issue starts with a comprehensive group of research and review articles in the area of membrane rafts and phase behavior. These are followed by research and review articles in the areas of membrane curvature and mechanics, helical membrane protein folding, ligand receptor interactions in membranes, and finishes with membranes of bodily systems.

The lipids that comprise biological membranes are diverse in molecular structure and, it is becoming increasingly recognized, mix non-randomly - form domains - possibly to facilitate protein function. The area of model membranes has made important contributions towards gaining an understanding of mixing and phase separation in membranes. Phase transitions and domain formation, dynamics and stability in raft-like mixtures are probably some of the most intensively investigated.

Model membranes with complex phase behavior are an important tool for revealing fundamental biophysics, and a clear parameterization and comparison of varying fabrication methods is critical. An increasing number of studies highlight the potential of giant unilamellar vesicles (GUVs) when addressing questions in membrane biophysics and cell-biology. GUVs are a convenient tool to study membrane phase behavior using optical microscopy. The research paper by Knorr, Steinkühler and Dimova reports domain formation above the main phase transition temperature of a commonly used lipid, DPPC. The authors propose that these domains are likely caused by impurities in glucose, which is widely used in GUV studies. Supported lipid bilayers (SLB) on glass offer another popular model system to study membrane phase behavior by fluorescence microscopy. In the research paper by Honerkamp-Smith and Gunderson the miscibility transition temperature for coexisting liquid ordered-liquid disordered domains in SLBs prepared from lipid raft-like mixtures is shown to be different compared with giant unilamellar vesicles (GUV).

Model membranes can offer increasing levels of complexity through varying lipid composition, temperature, pressure and the introduction of patterning and reactions. Fanani and Wilke, in a review, provide an interesting overview of this area. The inclusion of hybrid lipids containing one saturated and one unsaturated acyl chain (such as the multi-unsaturated omega-3 fatty acid chain) into model membranes helps to approximate mammalian cell membranes and such studies may have important health implications. The paper by Wassal and co-workers describes a multi-faceted study of how a particular omega-3 fatty acid (docosahexaenoic acid (DHA))-modified PC lipid alters the miscibility properties of lipid mixtures. The authors use a combination of solid state proton NMR, small angle neutron scattering, fluorescence microscopy, and monolayer compression experiments, complemented

by molecular dynamics simulations. They show that the multi-unsaturated lipid promotes lipid demixing to a greater degree than a monounsaturated lipid. In the review by Zeno, Ogunyankin and Longo a set of scaling relationships for diffusion constants of membrane domains and clusters from the literature is reviewed. The focus is on the validity of these relationships and their approximate ranges of usefulness in understanding dynamic processes in model membrane caused by steric pressure, temperature, and patterning. The work discussed in this review, represents a step toward more complete models and analysis of rate processes that involve membrane diffusion, such as sorting and signaling, in biomembranes.

Cholesterol-enriched liquid-ordered domains have been considered to be a good model of lipid rafts in cellular membranes. However, there are scarce methods that can interrogate the cholesterol-content of raft-like structures in cell membranes because of their small size and lifetimes. The research article of Yeager, Weber and Kraft uses high-resolution secondary ion mass spectrometry (SIMS) to study the distribution of 15N-sphingolipids and 18O-cholesterol in non-polarized canine kidney cells. This work supports their previous findings of sphingolipid-rich cholesterol-free domains and furthermore suggest release of sphingolipid/cholesterol-enriched particles. Rafts are thought to provide spatial organization of proteins in the membrane, with some proteins partitioning into rafts while others do not. Morigaki and Tanimoto review membrane protein distributions in model membranes with raft-mimicking coexisting liquid-ordered and liquid-disordered domains, including the added complexity of patterned membranes. The comprehensive review by Raghunathan and Kenworty focuses on the latest technical developments for the study of lipid rafts in cell membranes, summarizes the current state of understanding of these structures and provides an outlook toward future research needs.

Complex membrane behavior sometimes emerges out of changes in membrane curvature or changes in membrane mechanical properties in model systems. Interesting, cell-like dynamics sometimes appear with equally interesting theoretical explanations. In the research article by Chabanon and Rangamani a biophysical model that explains the pulsatory membrane pore dynamics of lipid vesicles exposed to the detergent Triton X-100 is put forward. The model highlights the role of membrane tension and pore line tension during the solubilization process and predicts a sharp transition between short-lived pores and long-lived pores. The paper of Angelova and coworkers provides a detailed literature review on the influence of pH changes on membrane curvature and migration, both experimental and theoretical. Furthermore, it provides evidence on how the theories can be applied to biological relevant situations such as mitochondrial christae morphology.

Solid supports that impose precise mechanical constraints on membranes, membrane proteins, and cells have been used to make important contributions in understanding membrane and cell behavior. Building on this work, Woodward, Stimpson and Kelly, in a research article, use a supported nanoparticle substrate to study how curvature affects the diffusion of head-labeled vs. tail-labeled lipids in a bilayer membrane. Single particle tracking and Monte Carlo simulations capture phenomenon that influences diffusion such as curvature-induced lipid sorting, slowing and aggregation. The review by Naumann and Shilts describes supported lipid bilayers for studying cell-surface mechano-sensing, transduction and influencing of cell functions. A broad range of research on the interactions between solid supported lipid bilayers and cells are included with special emphasis devoted to polymer-tethered lipid bilayers.

Protein sequence interacting with geometric and thermodynamic constraints of the membrane drives membrane protein folding. In this important area of research, Pourmousa and Pastor present new results and a review of simulations of lipoproteins in a lipid nanodisc environment. This work represents an important contribution to the understanding of lipoproteins and summarizes the status of this emerging field. McKay, Afrose, Koeppe and Greathouse present a review on the formation of transmembrane helices in the context of membrane protein folding. The review covers most of the structure and related functions associated with this class of alpha helical proteins that have been studied to date using mostly solid state NMR.

The factors that determine the interaction between membrane proteins and between proteins and membranes is an active area of study, required to understand complex membrane behavior. In this direction, King, Wirth, Workman, and Hristova continue their pioneering use of quantitative fluorescence resonance energy transfer to study membrane protein oligomerization in the plasma membrane of mammalian cells. They focus on the competition between dominant populations of homodimer or hetero-oligomer membrane protein clusters of NRP1 and VEGFR2 controlled by the binding of a key ligand. Lee and coworkers review a family of peripheral membrane binding proteins known as the TIM proteins. The review touches on methods used to study how peripheral membrane proteins interact with membranes, what roles the negatively charged lipid, phosphatidylserine plays in bringing proteins to membranes, and biophysical/ biological implications.

Finally, we move up in scale to the emergence of complex behavior in the membranes of bodily systems, with research articles that focus on the visual and nervous systems. Adam, Wang, Zhuang and Klauda employ molecular dynamics simulations to show that cholesterol-enrichment in simulated human and bovine ocular lens membranes plays a major structural role. Important differences between human and bovine lenses are described which may lead to a better understanding of the evolution of the lens membranes in relation to disease such as cataract onset. Wang, Muzic, Jackson and Heimburg present semi-quantitative predictions from a thermodynamic perspective for the effect of general anesthesia on nerves from different species, with comparisons to in-vivo measurements. A fundamental new aspect of this work is the prediction and observation that anesthesia does not completely block the excitability of nerves and rather changes the threshold.

We thank the authors who have contributed key work and comprehensive reviews and acknowledge the many expert reviewers of this special issue.

Marjorie L. Longo

Department of Chemical Engineering, University of California Davis, Davis, California, 95616, United States