
2069-Pos Board B206
Simulation Study of Composition Fluctuations in Lipid Bilayers
Svetlana Baoukina, Dmitri Rozmannov, D. Peter Tieleman.
University of Calgary, Calgary, AB, Canada.
Lipid bilayers constitute the basis of biological membranes. Understanding lipid mixing and phase behavior can provide important insights into membrane lateral organization (the raft hypothesis). Here we investigate model lipid bilayers below and above the miscibility transition temperatures. Molecular dynamics simulations with the MARTINI coarse-grained force field are employed to model bilayers on a length scale approaching 100 nm laterally and a time scale of tens of microseconds. We simulate lipid mixtures containing saturated and unsaturated lipids, and cholesterol at different concentrations and temperatures between 270 and 340 K. The coexistence of liquid-crystalline and gel, as well as liquid-ordered and liquid-disordered phases is reproduced. We induce a gradual transition from phase separation to mixing by raising the temperature and adding hybrid lipids (with a saturated and an unsaturated chains). The evolution of bilayer properties along this transition is analyzed. Domain size and phase boundary length, the length and time scales of composition fluctuations, and inter-leaflet coupling are quantified. The results allow characterizing partitioning of hybrid lipids between the coexisting phases, their role in composition fluctuations, and also the effect of spontaneous curvature on composition fluctuations. Curved domains are observed in both symmetric and asymmetric bilayers (with different composition of the two leaflets).

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Fatty Acid Interactions with RNA Building Blocks: Origin of Life Implications
Parisa Akhsi, Peter Tieleman.
Centre for Molecular Simulation and Department of Biological Sciences, University of Calgary, Calgary, AB, Canada.
Several experimental and computational methods have been used to address important questions regarding fatty acid interactions with RNA building blocks that have implications in the origins of life1,2,3. A recent study by Keller et al.2 showed that nucleobases can bind to and stabilize the aggregation of prebiotic amphiphiles, which could support a possible mechanism for the emergence of protocols. Some nucleobases were found to bind stronger to the aggregates of putative prebiotic amphiphiles. Among carbohydrates, ribose has shown a greater potential to permeate through bilayers compared to its diastereomers. This is fundamentally interesting; as ribose/deoxyribose are sugars found in RNA and DNA. The mechanisms, however, are not fully understood. We use molecular dynamics simulation to systematically study the permeation of furanose and pyranose carbohydrates as well as RNA nucleobases through different fatty acid bilayers as model of primitive conditions. The membrane fluidity and hydrogen bonding interactions have found to play significant roles in selective permeability.

References:
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Open Collaboration that uses NMR Data to Judge the Correctness of Phospholipid Glycerol and Head Group Structures in Molecular Dynamics Simulations
Patrick F.J. Fuchs1,2, Matti Juvanainen1, Aarti Lamberg1, Markus S. Mistten2, Luca Monticelli1, Jukka Määttä1, O.H. Samuli Ollila3, Marius Retegan1, Hubert Santuz2,9.
1 Institut Jacques Monod, CNRS, Paris, France, 2 Université Paris Diderot, Sorbonne Paris Cité, Paris, France, 3 Tampere University of Technology, Tampere, Finland, 4 Department of Chemical Engineering, Kyoto University, Kyoto, Japan, 5 Fachbereich Physik, Freie Universität Berlin, Berlin, Germany, 6 IBCP, CNRS UMR 5086, Lyon, France, 7 Arizona State University, Espoo, Finland, 8 Max Planck Institute for Chemical Energy Conversion, Mülheim an der Ruhr, Germany, 9 INSERM, U1134, D5SMB; Institut National de la Transfusion Sanguine (INTS); Laboratoire d’Excellence GR-Ex, Paris, France.
We compare the C-H order parameters measured by Nuclear Magnetic Resonance (NMR) experiments to those predicted by 12 different molecular dynamics (MD) simulations (most focus on the order parameters of the lipid headgroups and glycerol backbones in phospholipid bilayers. Only two of the models (CHARMM36 [1] and Maciejewski-Rog [2]) give a reasonable agreement with experiments for a fully hydrated lipid bilayer. We then compare (for the two best-performing models at full hydration and for the Berger model [3], the most used lipid model in the literature) to NMR experiments the changes in the order parameters as a function of hydration level, NaCl and CaCl2 concentrations, and cholesterol content. The results clearly show that the glycerol and headgroup structures in the Berger model are not realistic, the Na ion partitioning is significantly too strong and cholesterol-induced structural changes are overestimated. The CHARMM36 and Maciejewski-Rog perform better, but the Na partitioning is too strong at least in the latter. This is an open science project that is progressed at nmrlipids.blogspot.fi. All the results and discussions are available at; address. [1] J. B. Klauda, … W. R. Pastor. J. Phys. Chem. B 114 7830 (2010) [2] A. Maciejewski, M. Pasenkiewicz-Gierula, O. Cramariuc, I. Vattulainen, T. Rog. J. Phys. Chem. B 118 4571 (2014) [3] O. Berger, O. Edholm, F. Jähnig. Biophys. J. 72 2002 (1997)
Phosphatidylcholine (PDPC) is indicated. Our observations confirm what distinguishes PUFAs from more common monounsaturated and saturated fatty acids. The aversion to cholesterol is exemplified by a solubility of only ~15 mol% in di-polyunsaturated 1,2-diarachidonylphosphatidylcholine (DAPC), as opposed to most phospholipid bilayers that can solubilize >50 mol%. According to our earlier neutron scattering experiments using deuterated analogs of cholesterol, the head group and tail of the sterol reside within the DAPC bilayer at the center. An orientation parallel to the plane of the bilayer and between leaflets is implied that, remarkably, differs from the generally accepted one in which the head group sits near the aqueous interface while the sterol tails point toward the middle of the bilayer. Here we present solid state $^2$H NMR spectra acquired with aligned multilayers that establish the bilayer normal constitutes the axis of motional averaging for a deuterated analog of cholesterol incorporated into DAPC. The dilemma that this result creates is being evaluated, including with the aid of molecular dynamics simulations.

Dietary omega-3 polyunsaturated fatty acids (n-3 PUFAs), such as docosahexaenoic acid (DHA, 22:6), have a wide variety of health benefits. However, the origin of the benefits at the molecular level is yet to be elucidated. A membrane-mediated mechanism in which n-3 PUFAs are incorporated into phospholipids and modulate molecular organization is one possibility. Cellular membranes are inhomogeneous where structurally diverse lipids can exist in separate domains. Regions rich in sphingomyelin (SM) and cholesterol, commonly called lipid rafts, contain important signaling proteins. In a recent solid-state $^2$H nuclear magnetic resonance ($^2$H NMR) study of a model membrane composed of 1-$^2$H$_{31}$ palmitoyl-2-docosahexaenoylphosphatidylcholine (PDPC-$d_{31}$), a deuterated analog of a DHA-containing phospholipid, in mixtures with SM and cholesterol, we discovered that DHA could significantly enter raft-like domains. How DHA affects the molecular organization within the raft-like domains is addressed by observing PSM-$d_{31}$, an analog of SM with a perdeuterated N-palmitoyl chain. The $^2$H NMR spectra for PSM-$d_{31}$ in mixtures with PDPC and cholesterol exhibit two spectral components, a larger more ordered component that we attribute to raft-like domains and a smaller less ordered component that we attribute to non-raft-like domains. On average, the order of PSM-$d_{31}$ is reduced and, thus, disordering of PSM-$d_{31}$ by PDPC is indicated. Our observations confirm that DHA can infiltrate rafts and affect molecular organization, which has implications for the signaling of raft and non-raft proteins. Furthermore, these results are consistent with in vivo studies showing that DHA infiltrates rafts.