When anomalous becomes the norm: Compositional complexity and (sub)diffusion in lipid bilayers and cell membranes

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New experimental data are challenging long held models of membrane organization and dynamics. Interferometric scattering (iSCAT) based single particle tracking reveals subdiffusion in cholesterol rich liquid phases, on timescales out to a millisecond.[1] In live cell membranes, super resolution methods such as STED-FCS report very complex, hierarchical structure and dynamics, with important roles for both membrane composition and cortical cytoskeleton structure.[2] Lipidomics of cell membranes obtains a dizzying variety of lipid species — some 800 different combinations of headgroup, hydrocarbon chain, and backbone chemistry.[3] I will report a series of results obtained with different types of computational modeling, each designed to grapple with a different aspect of membrane complexity. First, I describe long timescale all-atom simulations of lipid mixtures, which explain the subdiffusion mechanism observed in the iSCAT experiments, and seek to determine the usefulness of model membranes for understanding lipidomic complexity. Next, a fast method for solvent hydrodynamics is coupled to the Dry MARTINI lipid model, to test the limits of quasi 2D hydrodynamic theory for complex membranes. Lastly, a stochastic modeling approach will be presented, that aims to rationalize the observed subdiffusive dynamics in the context of STED-FCS data. Taken together, these approaches aim to eventually connect spatiotemporal dynamics on micron lengthscales to the underlying molecular interactions.

[1] Wu et al, *Sci. Rep*. **6**:20542(2016)
[2] Honigmann et al, *Nature Comm*. **5**:5412(2014)
[3] Gerl et al, *J. Cell Biology* **196**:213(2013)