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Membrane protein interactions with lipids: GPCRs and Ion Channels

Abstract:
Interactions with specific lipids are important in the function and stability of membrane proteins. Multi-scale molecular dynamics simulations allow us to explore structural, energetic, and dynamic aspects of these interactions. We employ an approach based on coarse-grained (CG) simulations in mixed lipid bilayers to identify potential lipid interaction sites. These interactions are then probed further by: estimation of CG free energy landscapes of protein/lipid interactions to explore lipid specificity; and atomistic MD simulations to refine models of the structure and dynamics of lipid binding. This approach has been applied to a number of GPCRs and ion channels. Analysis of lipid interactions with Class A GPCRs (e.g. the A2a receptor) has revealed binding sites for GM3, cholesterol, and PIP_2 [1]. Interactions with PIP_2 have been shown to be dependent on the activation state of the receptor, suggesting a functional role for the lipid via allosteric modulation. PIP_2 also plays a role in strengthening GPCR/G protein interactions [2]. Interactions of lipids with other classes of GPCRs have been explored, including the interactions of cholesterol and PIP_2 with the Class F GPCR Smoothened [3]. Analysis of the interactions of lipids with ion channels has focussed on PIP_2, a known allosteric modulator of a number of ion channel families. PIP_2 interactions have been characterised for Kir channels, and more recently for members of the TRP channel family. Simulations of large membrane systems containing multiple copies of Kir channels suggest that the lipid composition of the bilayer may modulate channel-channel interactions within crowded membranes [4].

References: [1] Song *et al.* (2018) *Structure* 27: 392; [2] Yen *et al.* (2018) *Nature* 559: 423.; [3] Hedger *et al.* (2018) *Structure* 27: 549.; [4] Duncan *et al.* (2017) *Sci. Reports* 7: 16647.

Friday, April 5, 4pm

Keck Seminar at RICE UNIVERSITY
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