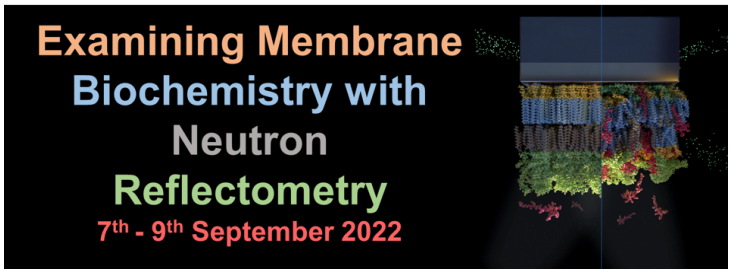

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The structure of membrane-bound KRas from neutron reflectometry and molecular simulation.

Thursday, 8 September 2022 13:30 (40 minutes)

KRas4B is a membrane-anchored signaling protein and a primary target in cancer research. Predictions from molecular dynamics simulations have shaped our mechanistic understanding of KRas signaling but disagree with recent experimental results from neutron reflectometry [1]. Therefore, we implemented restrained and bias-free molecular simulations for a quantitative comparison with NR and complementary nuclear magnetic resonance and thermodynamic binding data. Our results show that KRas4B approximates an entropic ensemble of configurations at model membranes, which is not significantly affected by interactions between the globular G-domain of KRas4B and the lipid membrane [2]. These findings promote a model of KRas, in which the G-domain explores the entire accessible conformational space while being available to bind to effector proteins. Our results deemphasize a mechanism in which KRas4B purposefully assumes discrete configurations at the membrane that modulate signaling activity.

[1] Van, Q. N. et al. Uncovering a membrane-distal conformation of KRAS available to recruit RAF to the plasma membrane. PNAS 117:24258 (2020)
[2] Heinrich F., et al., Membrane-Bound KRAS Approximates an Entropic Ensemble of Configurations. Biophysical Journal 120:4055 (2021)

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