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Solution NMR relaxation and µs molecular dynamics simulations of dynamic protein-protein and protein-membrane complexes

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It is now recognized that protein-protein interactions in solution are often dynamic, especially if the binding affinities are only moderately strong. Dynamics originate in part from the interconversion between structures of the protein complex, e.g. one bound state that is in equilibrium with one or several alternate configurations. We determined the structure of such a complex using NMR restraints and saw the transitions between different configurations in microsecond length all-atom molecular dynamics simulations. Recently, we also studied the dissociation process of mutant complexes which had a weakened primary interaction interface. Those simulations suggested that there is no single dissociation pathway, but that the separation first involves transitions to binding interfaces with fewer/weaker contacts. Comparison is made between experimental NMR relaxation measurements on the ps-ns as well as µs-ms timescale with the microsecond all atom simulations, also in the context of new simulations of the protein association process. The functional significance of the protein complex alternate states and their dynamics are discussed. In a second part of the presentation, we consider a second system involving transient interactions; this time between K-Ras and the lipid bilayer of the plasma membrane. Our recent simulations the full length GTPase at different membranes reveal the underlying rules of the interactions, emphasizing electrostatic contacts but also protein topology. Again, simulations are compared with NMR experiments, carried out at model systems for the membrane.

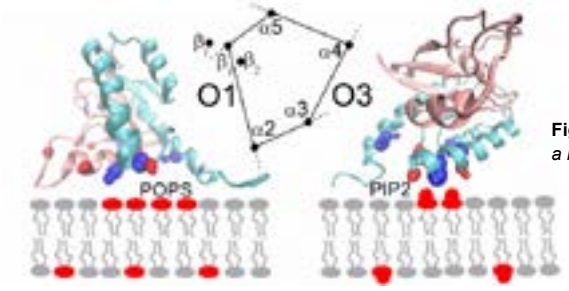

Figure1: *K-Ras4A in two preferred orientations at a membrane containing anionic lipids.*

Biography

Matthias Buck has completed his BA, MA from the University of Cambridge and pursued his DPhil from the University of Oxford. He was a Group Leader since 2002 and Professor since 2014. The Buck laboratory studies two receptor families responsible for cell guidance and positional maintenance (Plexins and Ephrins), both with key involvement in cardiovascular and neuronal development and disease, esp. cancer. They use a wide range of structural biology (solution NMR / x-ray crystallography) and protein biophysical tools (CD, fluorescence spectroscopy, ITC and SPR) in a problem oriented approach. Part of the laboratory also pursues computational modeling and molecular dynamics to provide additional perspective on the problems, provide new insights into the experimental data and to suggest further studies. Small GTPases and their interaction with the plexin receptor cytoplasmic domains has been a major focus of the laboratory and recently they have become very interested in protein-membrane interactions; both the transmembrane regions of the receptors as well as the transient interactions of receptor and GTPase domains with membranes.

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