Exploring Multiple Timescale Motions in Folded and Intrinsically Disordered Proteins using NMR

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Proteins are inherently flexible, displaying a broad range of dynamics over a hierarchy of time-scales from pico-seconds to seconds. This plasticity enables conformational changes that are essential for biomolecular function. NMR is sensitive to all conformational fluctuations occurring up to the millisecond and we have recently developed robust methods to quantitatively describe these molecular motions from NMR data. We combine analytical and numerical approaches to develop a self-consistent representation of all motions occurring in proteins on timescales from the picosecond to the millisecond. [1,2] The next step involves the determination of the structural, dynamic and kinetic behaviour of proteins in their physiological complexes, and we introduce novel techniques for the study of these properties in weakly interacting complexes.[3]

Intrinsically disordered proteins (IDPs) represent extreme examples where protein flexibility plays a determining role in biological function. The development of meaningful descriptions of the behaviour of IDPs is a key challenge for contemporary structural biology, due to their inherent conformational disorder. Explicit molecular ensembles representing a dynamic equilibrium of rapidly interconverting conformers are gradually becoming established as appropriate descriptors to determine protein conformational disorder. [4] Due to the increase in available degrees of freedom compared to a static picture, the identification of accurate protein conformational ensembles requires the development of robust approaches to determine the significance and uniqueness of any proposed equilibrium.[5] We present novel approaches to determine local and long-range structural behaviour in IDPs from NMR and small angle scattering data. We develop new techniques to determine the level of intrinsic structure in IDPs and apply this to describe the pre-recognition state of active sites of viral proteins.[6,7]

References:

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