MONDAY

COLLOQUIUM

Solution NMR experiments to Study Protein Conformational Dynamics and 'Challenging' Spin-Systems

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24 Mar 2025 (Monday) | 16:00 Hrs (Tea / Coffee 15:45 Hrs) | Venue: TIFRH Auditorium

Despite the tremendous accomplishments of AlphaFold in predicting protein structure, the protein folding problem remains unsolved in the sense that the accurate atomistic mechanism by which protein molecules fold into their native conformation from the unfolded ensemble remains elusive. Recently we realised that the CEST NMR experiment can be used to detect very sparsely populated states (~0.1%) with lifetimes over the ~0.1 to 100 millisecond range. Using CEST experiments we discovered that the FF domain from human HYPA/FBP11 folds via two intermediates I1 & I2 with lifetimes of ~0.1 & ~1 ms and populations of ~0.4 & ~0.1% respectively. The structures of I1 & I2 provide a detailed picture of the folding landscape of the protein. It is anticipated that the strategy for elucidation of sparsely populated and transiently formed structures of intermediates along kinetic pathways described here will be of use in other studies of protein dynamics.

Although NMR experiments can be used to record high-resolution spectra from most sites in protein molecules, characterisation of aromatic residues in proteins still poses a challenge. To overcome this problem, we recently developed a deep neural network (DNN) that transforms NMR spectra recorded on uniformly ^{13}C labelled samples to yield high-resolution ^{1}H-^{13}C correlation maps of aromatic sidechains even in large ~40 kDa proteins. Key to the success of the DNN is the design of NMR experiments that produce data with unique features to 'aid' the DNN produced high-resolution spectra. This synergistic development of new NMR experiments and customised DNNs represents an advance that will have several applications in the study of molecules using NMR.

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