Capturing the dynamics of intrinsically disordered proteins using NMR relaxation and molecular dynamics simulations

N. Salvi, A. Abyzov, M. Ringkjøbing Jensen, M. Blackledge

Institut de Biologie Structurale (IBS), CEA, CNRS, University Grenoble Alpes, Grenoble 38044, France,
nicola.salvi@ibs.fr

Intrinsically Disordered Proteins (IDPs) lack a stable three-dimensional structure and their function is encoded both in their conformational heterogeneity and dynamics. NMR relaxation rates report on the timescales and amplitudes of ps-ns motions. However, traditional analytical tools (e.g. the conventional model-free analysis) are not sufficiently insightful in the case of IDPs because measured relaxation rates are averaged over the entire ensemble of conformations accessed by the protein.

We measure an extensive range of both auto- and cross-correlated ^{15}N relaxation rates at different magnetic fields over a large range of temperatures (268-298K) on three constructs of different length of the N_{tail} domain of the nucleoprotein of Sendai virus. By introducing a robust procedure based on an Arrhenius-type relationship to analyse up to 61 relaxation rates per residue, we are able to assign the physical origin of different dynamic modes in this archetypal IDP [1].

Molecular Dynamics (MD) simulations have the potential to complement NMR relaxation data. However, MD studies of IDPs require efficient *sampling* schemes to characterize the vast phase space of disordered peptides and suitable *force fields* to reproduce accurately the rugosity of the free-energy landscape and, consequently, the motions probed by NMR relaxation. To overcome these challenges, we develop an original approach termed ABSURD (Average Block Selection Using Relaxation Data, [2]) in which an adequate sampling of the conformational space is achieved combining short (~100 ns) trajectories initiated from conformers that are distant in the energy landscape. In doing so, we select only the subset of trajectories in agreement with the experimental relaxation data. In particular, we show that selection using rates reporting on the spectral density function evaluated at zero frequency (e.g., R_2 values) are a very sensitive probe of systematic errors in the force field. ABSURD eliminates most of the limitations of available force fields when reproducing the dynamics of IDPs without affecting the conformational properties of the parent trajectories and allows us to simultaneously reproduce with good accuracy a set of 16 NMR relaxation rates measured at 4 different magnetic fields, from 600 to 950 MHz.

Finally, combining molecular dynamics simulation and NMR, we introduce a framework in which distinct motions are attributed to local librations, backbone dihedral angle dynamics and longer-range tumbling of one or more peptide planes [3]. This model provides unique insight into segmental organization of dynamics in IDPs and allows us to investigate the presence and extent of the correlated motions that are essential for function.

References

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