Atomistic simulations of intrinsically disordered proteins

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Intrinsically disordered proteins are recognized to play many important roles within the cell. Due to the broad structural ensembles which they populate, it is much harder to characterize them by experiment than is the case for folded proteins. Molecular simulations could clearly play an important role in bridging the gap between experiment and structure. For the most part, coarse-grained models are most appropriate for treating the time- and length-scales relevant to intrinsically disordered proteins. Nonetheless, in some circumstances, the detail of all-atom simulations with explicit solvent is necessary. I present here an example of how atomistic simulations can be used to address some of the challenges in interpretation of typical experimental data used to characterize intrinsically disordered, or unfolded, proteins. In particular, I will address a long-standing controversy in the interpretation of small-angle X-ray scattering (SAXS) and single-molecule Förster resonance energy transfer (smFRET) experiments relating to the collapse of unfolded proteins with denaturant. Using carefully parameterized atomistic simulations, we have been able to rule out some potential artifacts that had been envisaged; at the same time we are able to reproduce the raw experimental data from both experiments, revealing that there is no fundamental contradiction between them. We have been able to show that most of the apparent discrepancy between the experiments comes from the way the experimental data are interpreted. Using explicit ensemble fitting of the experiments is one possible solution to the challenging inverse problem of obtaining molecular information from ensemble-averaged experimental data.