UNRAVELING THE SECRETS OF PROTEIN (UN)FOLDING: DYNAMICS AND FREE ENERGY LANDSCAPE

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Protein folding is one of the most fundamental and fascinating biological processes. However, it remains a long-standing problem to understand the detailed mechanisms of protein folding from primary sequence to the three-dimensional structures. A number of small proteins with ~10-100 amino acid residues fold on the microsecond to sub-millisecond timescales, known as "fast-folding" proteins. Here, folding of four fast-folding proteins, including chignolin, Trp-cage, villin headpiece and WW domain, is simulated via accelerated molecular dynamics (aMD). Free energy profiles calculated through improved reweighting of the aMD simulations using cumulant expansion to the 2nd order are in good agreement with those obtained from conventional MD simulations. This allows us to identify distinct conformational states (e.g. unfolded and intermediate) other than the native structure and the protein folding energy barriers.

In addition, the potential of aMD as a tool to efficiently explore the free energy landscape of (metallo)proteins and its applications to the study of molecular recognition in both proteins and supramolecular complexes will be highlighted.

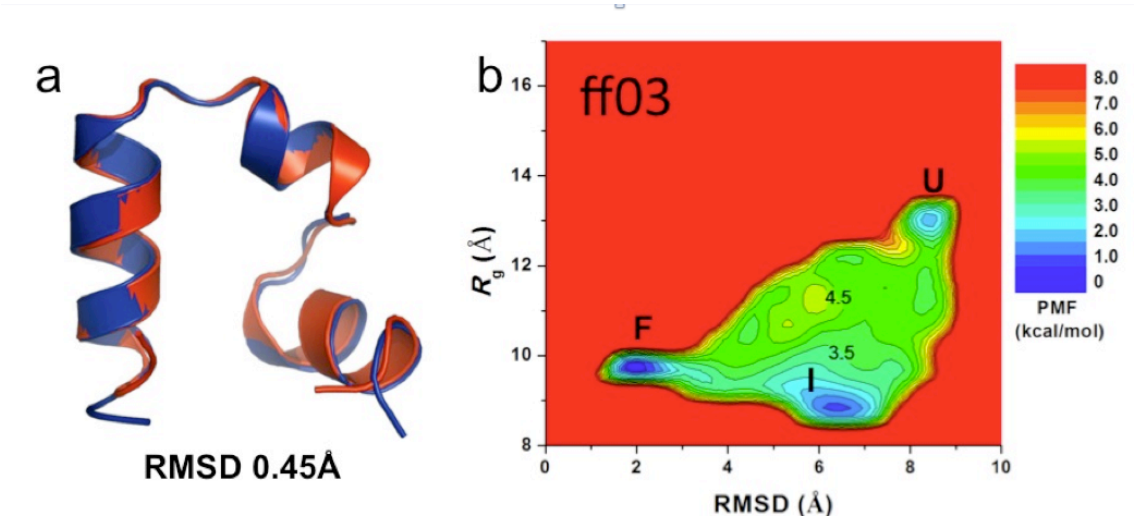

Figure 1. Folding of wild-type villin simulated via aMD: (a) comparison of simulation-folded villin (blue) with the PDB (1YRF) native structure (red) (b) two-dimensional (RMSD, Rg) free energy profiles calculated by reweighting the aMD simulations.