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(U*) Finding Order in Disorder: Modelling the Disordered Protein 4E-BP2

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The 120-residue 4E-BP2 (BP2) protein undergoes a transition from disordered to partially folded upon multi-site phosphorylation, reducing its binding affinity with eIF4E (4E) and thus regulating the initiation of translation in neuronal cells. Although BP2 is an attractive target of anticancer drugs, its disordered nature makes it challenging to model. An initial ensemble of BP2 conformers were generated using FastFloppyTail (FFT), a Rosetta-based program. The non-phosphorylated (NP) conformers were generated by applying the FFT algorithm to the entire 120-residue chain, while the 5-phosphorylated (5P) structures were produced by fixing the 18-62 folded domain and applying FFT sampling to the N- and C-terminal tails only.

To obtain a compromise between uncertainties in the biophysical experiments and in the initial conformational ensemble, a Bayesian method of structural refinement was applied through the Bayesian-Maximum-Entropy (BME) method. The degree of reweighting is determined by optimizing agreement with various restraints on both local and nonlocal scales: Small-Angle X-ray Scattering (SAXS), Chemical Shifts (CS) and single molecule Forster Resonance Energy Transfer (smFRET). Paramagnetic Relaxation Enhancement (PRE) data were withheld and used as validation criteria, external to the refinement process. By implementing differential weighting of restraints and mitigating overfitting, the resulting NP and 5P BP2 ensembles were found to be in good agreement with all available experimental data. Secondary structure analysis reveals local structure of biological relevance for both BP2 phosphoforms and the replication of the canonical 4E-binding helix in NP BP2. Applying clustering algorithms to partition the conformational landscape leads to distinct and significantly populated structural states that provide new insights into the extended dynamic interaction interface between 4E-BP2 and eIF4E.

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