

Integrating Molecular Dynamics Simulations with Small-angle X-ray Scattering to Characterize Multidomain Proteins and Their Assemblies



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Abstract

Many proteins consist of multiple folded domains connected by intrinsically disordered regions and display a high level of structural heterogeneity. Determining the conformational states that such proteins adopt, along with the associated thermodynamic weights, often requires a combination of computational modeling and biophysical experiments. Here, we use a Bayesian/Maximum entropy reweighting approach to combine coarse-grained molecular dynamics simulations with small-angle X-ray scattering data to characterize the structure and dynamics of two multidomain protein systems. (1) We investigate the interplay between folded and disordered domains in mediating phase separation of the RNA-binding protein hnRNPA1. Our conformational ensemble model reveals that folded domains can modulate the phase behavior of disordered regions through solubilization effects and interdomain interactions. (2) We characterize the structure and dynamics of higher-order oligomers of the ubiquitin ligase adaptor protein SPOP. Our conformational ensemble model reveals that SPOP oligomers adopt rigid, helical structures, with flexible linkers enabling substrate-binding domains to extend outward. Our results also show that a cancer-associated mutation destabilizes oligomers.



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