Macromolecular structure and dynamics based on SAXS profiles

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Proteins generally populate multiple structural states in solution. Transitions between these states are important for function, such as allosteric signaling and enzyme catalysis. Structures solved by X-ray crystallography provide valuable, but static, atomic resolution structural information. In contrast, Small angle X-ray scattering (SAXS) profiles, while limited in resolution, contain information about conformational and compositional states of the system in solution. Moreover, SAXS profiles can be rapidly collected for a variety of experimental conditions, such as ligand-bound and unbound protein samples, different temperatures, or pH values. The challenge lies in the data interpretation since the profiles provide rotationally, conformationally, and compositionally averaged information about protein shape in solution.

We have developed a novel computational method, MultiFoXS[1] that simultaneously uncovers the set of structural states and their population weights for multiple input SAXS profiles. The input is a single atomic structure, a list of flexible residues, and one or more SAXS profile(s) for the protein. The method proceeds in two steps. In the first step, it samples the input structure by exploring the space of the φ and ψ main chain dihedral angles of the user-defined flexible residues with a Rapidly exploring Random Trees (RRTs) algorithm. In the second step a SAXS profile is calculated for each sampled conformation with FoXS, followed by a branch-and-bound enumeration of the multi-state models that are consistent with the SAXS profile. The method was benchmarked on over 30 cases with experimental SAXS profiles, including large multi-domain proteins and proteins with long disordered fragments. Moreover, comparison of conformations and their weights between the ligand-bound and unbound SAXS profiles can help in determining the allosteric mechanism. The applicability of the method extends beyond SAXS and it has been applied to datasets from cross-linking mass spectrometry, Electron Microscopy, and residual dipolar couplings.

In protein-protein docking with SAXS profile of the complex, in addition to conformational heterogeneity (multiple conformations of the same protein or complex), we also observe a compositional heterogeneity (complex and separate protein components in solution). I will present a protein-protein docking method that can account for both types of heterogeneity in SAXS data. The method relies on docking algorithms to sample possible interaction complexes[2, 3], and on the SAXS scoring function[4] from MultiFoXS[1] to account for heterogeneity. The method was applied to antibody-antigen and addtional complexes[5].

References:

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