

# Multimodal Modeling of Flexible and Conformationally Heterogeneous Molecules

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Many macromolecules have multimodal conformational diversity. Proteins can have different folded domains connected by flexible linkers; predominantly folded proteins can have intrinsically disordered domains; and many biologically important complexes form between folded protein chaperones and their unfolded clients. Determination of the sizes and shapes of these macromolecules is challenging using traditional structural methods and requires a combination of experimental and simulation techniques. Validation of structural ensembles by comparison to experimental properties requires methods to rapidly calculate the relevant ensemble-average hydrodynamic properties. We will present a method to generate ensembles of unfolded proteins targeted to an experimental sedimentation coefficient.

Preliminary data suggests this method produces ensembles consistent with X-ray scattering data as well. An essential tool is the use of a program we developed, termed HullRad, that facilitates the fast calculation of hydrodynamic and structural parameters enabling quick ensemble evaluation.

HullRad also provides insight on a second important aspect of using modeling for multiple experimental techniques, which is the appropriate inclusion of macromolecular hydration. Calculation of sedimentation and diffusion parameters requires the inclusion of two types of hydration, first shell and entrained. HullRad calculates and distinguishes these two hydration modes.

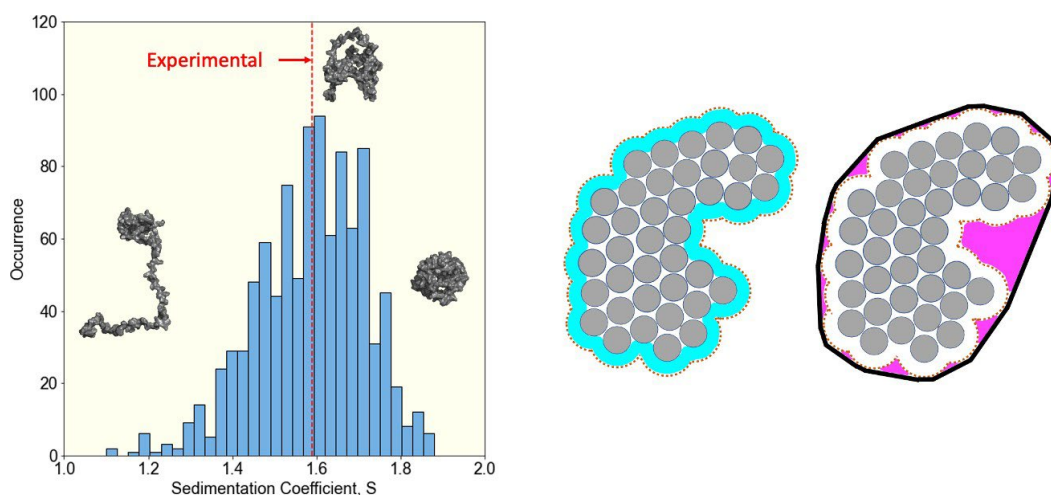


Figure 1