SAXS for Integrative Structure Determination of Macromolecular Assemblies

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Our broad goal is to contribute to a comprehensive structural characterization of large macromolecular assemblies. Detailed structural characterization of assemblies is generally impossible by any single existing experimental or computational method. We suggest that this barrier can be overcome by hybrid approaches that integrate data from diverse biochemical and biophysical experiments (*e.g.*, X-ray crystallography, NMR spectroscopy, electron microscopy, immuno-electron microscopy, footprinting, chemical cross-linking, FRET spectroscopy, small angle X-ray scattering, immunoprecipitation, and genetic interactions). Even a coarse characterization of the configuration of macromolecular components in a complex (*i.e.*, the molecular architecture) helps to elucidate the principles that underlie cellular processes, in addition to providing a necessary starting point for a higher resolution description.

We formulate the hybrid approach to structure determination as an optimization problem, the solution of which requires three main components: the representation of the assembly, the scoring function, and the optimization method. The ensemble of solutions to the optimization problem embodies the most accurate structural characterization given the available information. The key challenges remain translating experimental data into restraints on the structure of the assembly, combining these spatial restraints into a single scoring function, optimizing the scoring function, and analyzing the resulting ensemble of solutions.

To address these challenges, we are developing the Integrated Modeling Platform (IMP) (http://salilab.org/imp). IMP is designed to allow mixing and matching of existing modeling components as well as easy adding of new functionality. It supports a wide variety of assembly representations and input data. We also provide infrastructure that encourages and supports contributions from other laboratories.

The presentation will focus on the design and applications of the SAXS module in IMP.