SOFTWARE APPLICATIONS TO SMALL-ANGLE X-RAY AND NEUTRON SCATTERING

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While crystallography has been providing atomic-resolution structures of biomolecules for over half a century, the real challenge of today's biophysicists is to correlate molecules' structure and dynamics in solution with their function. Small-angle scattering (SAS) is the fundamental techniques for structural studies of biological systems in solution. Thanks to advances in instrumentation and data analysis software, small-angle X-ray scattering (SAXS), complemented by other methods, is becoming very popular in structural biology. Over the years, a number of computational tools have been developed for the analysis of SAXS curves, calculation of theoretical profiles and low-resolution reconstruction of model shapes. Many efforts have been spent to reduce the running time of these tools without degrading the quality of their approximations. The number of Bio-SAXS publications exploded as a result of this effort. Comparatively, the lack of user-friendly analysis tools has hindered the development of Small Angle Neutron Scattering (SANS), more complex but providing more information.

Recently, we developed SAXS and SANS packages called Pepsi-SAXS [1,2], and Pepsi-SANS [3], correspondingly. Pepsi-SAXS is a very efficient method that calculates small angle X-ray scattering profiles from atomistic models. It is based on the multipole expansion scheme and is significantly faster with the same level of precision compared other methods. We have later extended it for neutron scattering applications [3].

One of the challenges of structural biology is flexible fitting of atomistic models into small-angle scattering profiles. Very recently, we designed a computational scheme that uses the nonlinear normal modes [4,5] as a low-dimensional representation of the protein motion subspace and optimizes protein structures guided by the SAXS and SANS profiles. For example, in the CASP12 and CASP13 exercises, this scheme obtained best models for some (3 out of 9 in CASP12) SAXS-assisted targets [6]. Overall, this flexible fitting scheme typically allows a significant improvement of the goodness of fit to experimental profiles in a very reasonable computational time.

Another challenge in the field is (data-assisted) protein docking. We have designed a scheme for SAXS-assisted rescoring of docking predictions. This was made possible due to the polynomial representation of partial scattering amplitudes for each of the docking partners. The scheme is very computationally efficient, it allows explicit representation of the hydration shell, and computes around 100,000 of Chi2 values per minute on a standard laptop for a mid-size protein complex.

Overall, I will present

- a method for an efficient Normal mode Analysis (NOLB),
- a method for the generation of structural ensembles,
- a method for the computation of scattering profiles (Pepsi-SAXS and Pepsi-SANS)
- a method for flexible fitting of structures into scattering profiles (Pepsi-SAXS --opt)
- a method for rescoring rigid-body predictions with respect to the scattering data

References

[1] S. Grudinin, *et al*, Acta Cryst D, (2017), D3, 449.
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