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Structure modeling from small angle X-ray scattering data with elastic network normal mode analysis

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ABSTRACT

Computational algorithms to construct structural models from SAXS experimental data are reviewed. SAXS data provides a wealth of information to study the structure and dynamics of biological molecules, however it does not provide atomic details of structures. Thus combining the low-resolution data with already known X-ray structure is a common approach to study conformational transitions of biological molecules. This review provides a survey of SAXS modeling approaches. In addition, we will discuss theoretical backgrounds and performance of our approach, in which elastic network normal mode analysis is used to predict reasonable conformational transitions from known X-ray structures, and find alternative conformations that are consistent with SAXS data.

1. Introduction

Macromolecular complexes, such as ribosome and polymerases, are of great interest in the area of molecular biology. They are involved in replication, transcription, protein synthesis, regulation of cellular transport and other core biological functions. Dynamics is essential as these complex machines go through several conformational transition processes to achieve their function. Even for small enzymes, conformational transitions are important to facilitate substrate-binding processes by preparing the optimal environment for biochemical reactions. Therefore characterization of structure and dynamics of these macromolecular complexes is crucial to understand their functional mechanisms, and play an important role in lead discovery and optimization of new drugs to treat human disease.

X-ray crystallography and NMR have been the primary tool to study protein conformations, providing high-resolution structures. However, for those macromolecules, X-ray structure determination is an extremely difficult task due to the difficulty of crystallization process (Price et al., 2009) and NMR is limited to the size of the protein. The number of solved structures is still small compared to the number of possible complexes indicated from genomics studies. In addition, the solution condition needs to be adjusted to achieve crystallization, which is often unphysiological and extreme. Thus it is difficult to trap proteins in a certain functional state of biological interest. In addition, crystal environment may also affect the conformations (Anselmi et al., 2008; Vorontsov and Miyashita, 2009).

Therefore, alternative low-resolution experimental techniques, such as cryo-Electron Microscopy (cryo-EM), Small Angle X-ray Scattering (SAXS) and Fluorescence Resonance Energy Transfer (FRET), are often used to obtain additional information on the structure and dynamics (Saibil, 2000; Heller et al., 2004; Priddy et al., 2005; Vestergaard et al., 2005; Ermolenko et al., 2007; Hickerson et al., 2005; Hammel et al., 2005; Aramayo et al., 2005). Each of these experimental approaches offers different advantages and all meet with different pitfalls, artifacts and limitations. For example, some techniques reveal the overall shape of the structure, and others extract the distances between specific sites. Therefore more accurate descriptions of the dynamics could be obtained if all pieces of experimental data were taken together to annotate conformational states (Alber et al., 2008; Russel et al., 2009). Several articles in this issue tackle such problems.

In this review, we focus on computational tools for analyzing SAXS experiments. More specifically, our review is centered on its applications to proteins or protein assemblies, however we should note that SAXS method is also being extensively used to study RNA molecules in solution and determine their structures (Lipfert and Doniach, 2007; Lipfert et al., 2007, 2009; Doniach and Lipfert, 2009; Rambo and Tainer, 2010a,b; Yang et al., 2010). Additionally, we focus on computational methods that enable the characterization of protein or protein assembly conformational changes at the atomic level, and computational methods that have been developed for protein structure prediction will not be reviewed (Petoukhov et al., 2002; Zheng and Doniach, 2002, 2005; Wu et al., 2005).

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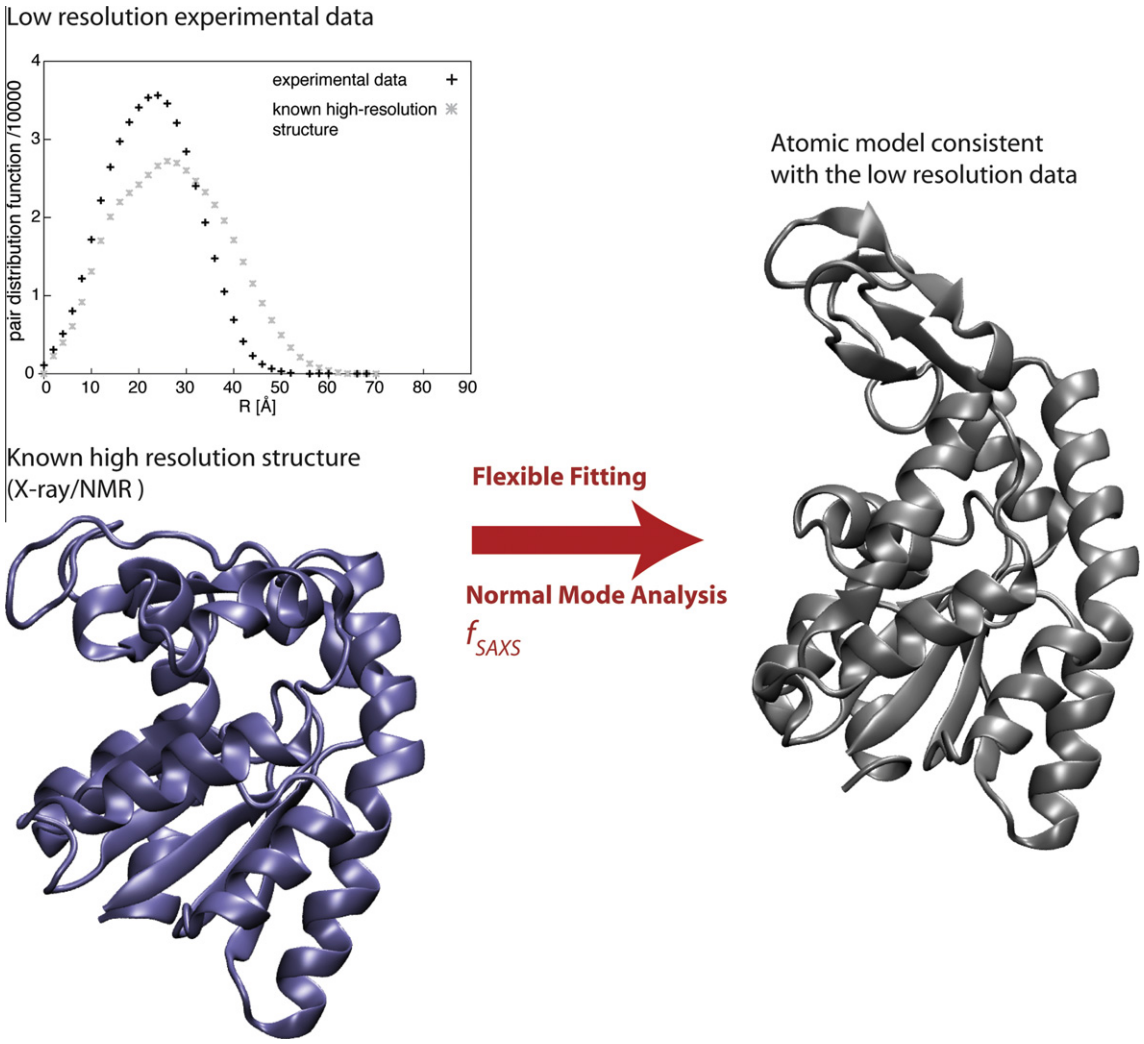

Fig. 1. Given a SAXS experimental profile and a known high-resolution structure methods are being developed to build an atomic model consistent with the low-resolution data. Such approaches needs algorithms to deform the known high-resolution structure as well as tools to measure the fitness of the modeled structure with the data.

SAXS experiment is an old but interesting tool to study structure of biological molecules in solution (Koch et al., 2003; Putnam et al., 2007; Lipfert and Doniach, 2007; Tsuruta and Irving, 2008; Jacques and Trewhella, 2010). Its strength arises from its simpleness, i.e., it does not require special sample preparation. SAXS can supply a rich perspective on the structure and dynamics of proteins and macromolecular assemblies under physiological conditions that are not accessible to other structural methods. However, only the overall shape and size of the molecule can be derived from SAXS data. It does not distinguish individual atom, and thus reconstruction of 3D structure is inherently degenerate.

Substantial amount of work has been performed to reconstruct shape of biological molecule from SAXS data using beads models (Svergun, 1999; Svergun et al., 2001; Chacon et al., 2000; Walther et al., 2000; Svergun and Koch, 2002; Mertens and Svergun, 2010). In those tools biological molecules are represented by beads and different arrangements of beads are explored to find the shape that is in agreement with the SAXS experimental data. Thus they are *ab inito* method, i.e., the model is constructed solely from the data. While it only provides the overall shape of the molecule and no information of the internal arrangement, it brings useful insights with the aide of additional information such as the structure of compositing molecules. Since SAXS data cannot provide atomic detail information, it is tempting to interpret such low-resolution data using available X-ray structures (Putnam et al., 2007). When SAXS experiments are used to study the structure of the complex of multiple proteins, often the high-resolution structures of individual component protein are known. Thus a common approach is to find the suitable arrangement of those structural pieces that reproduce the experimental data (Petoukhov and Svergun, 2005; Leggio et al., 2008; Förster et al., 2008; Mertens and Svergun, 2010). In addition, considerable amount of work has also been performed to predict 3D structure of multidomain proteins by combining SAXS experiments with restraints derived from high-resolution NMR spectroscopy (Mattinen et al., 2002; Choy et al., 2002; Yuzawa et al., 2003; Bernadó et al., 2005; Grishaev et al., 2005; Gabel et al., 2006, 2008; Bernado et al., 2007; Mareuil et al., 2007; Wang et al., 2009).

SAXS has been also used to study the dynamical conformational transitions of the proteins. While X-ray data provides detailed structural information, it is a snapshot of one conformational state. In contrast, SAXS data can be used to monitor how protein changes conformations in response to the solution condition or binding of substrate molecules (Canady et al., 2001; Aramayo et al., 2005; Nishimura et al., 2009). For a more explicit interpretation of these conformational transitions observed by SAXS, integration with already known X-ray structures is often used (Arai et al., 2004; Vestergaard et al., 2005).