Pepsi-SAXS/SANS - small-angle scattering-guided tools for integrative structural bioinformatics

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I will present some recent developments of our Pepsi package for integrative modeling of macromolecules guided by small-angle scattering profiles. These include very fast tools for the all-atom computations of X-ray and neutron small-angle scattering profiles, called Pepsi-SAXS and Pepsi-SANS, respectively [1,2]. These tools implement algorithms specifically designed to handle two notable properties of large macromolecules and their complexes, such as for instance viral capsids, namely their high flexibility and high degree of symmetry. Flexibility of macromolecules is not spontaneous but linked with their structure and function. Computationally, it can be often approximated with just a few collective coordinates, which can be computed e.g. using the Normal Mode Analysis (NMA). NMA determines low-frequency motions at a very low computational cost and these are particularly interesting to the structural biology community because they give insight into protein function and dynamics. On our side, we have proposed a computationally efficient nonlinear NMA method that can be applied to largest complexes from the Protein Data Bank (PDB), and which also very well preserves local stereochemistry [3-5].

Flexibility of macromolecules is often linked with their structure and function. Computationally, it can be approximated with just a few collective coordinates computed using the Normal Mode Analysis (NMA). NMA determines low-frequency motions at a very low computational cost. This technique is particularly interesting for the structural biology community as it allows extrapolating biologically relevant motions starting from high-resolution structures. Recently, we have shown that it can be extended to model local deformations and to better preserve the stereochemistry of the protein. We have developed a computationally efficient nonlinear NMA method that can be applied to the largest complexes from the Protein Data Bank (PDB) [3-5].

Large symmetrical protein structures have seemingly evolved in many organisms because they carry specific morphological and functional advantages compared to small individual protein molecules. Recently we have proposed a novel free-docking method for protein complexes with arbitrary point-group symmetry [6]. It assembles complexes with cyclic symmetry, dihedral symmetry, and also those of high order (tetrahedral, octahedral, and icosahedral). We also proposed an efficient analytical solution to the inverse problem, that is the identification of symmetry group with the corresponding axes and their continuous symmetry measures in a protein assembly [7-8].

With Pepsi-SAXS and Pepsi-SANS, one can leverage the above-mentioned developments, by optimizing structures along low-frequency « normal modes », performing automatic and adaptive coarse-graining of molecular models, rescoring free-docking predictions, including those of symmetric assemblies, and also optimizing structural transitions. Structural models produced by Pepsi-SAXS/SANS were ranked top in the recent data-assisted protein structure prediction sub-challenge in CASP13 [9].

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