Understanding intermolecular structure and forces in concentrated protein solutions through multi-protein simulations and structure factor measurements

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Small angle X-ray solution scattering, as most widely conducted by structural biologists, is performed under dilute conditions where information about the structures of the isolated molecules can be deduced. In contrast, living cells are remarkably dense, crowded environments at the molecular level. Growing interest in molecular crowding, liquid-liquid phase separation (LLPS), rheological properties of biopharmaceuticals, and desiccation tolerance of extremophiles requires information about the way that molecules distribute themselves around one another. Radial distribution functions and one-dimensional intermolecular interaction potentials for concentrated solutions can be obtained from experimental structure factors, but it requires the decoupling approximation (Kotlarchyk and Chen) and the Ornstein Zernike equation in a complicated line of mathematics. To better understand the connection between structure factors, anisotropy in protein-protein interaction potentials, and large-scale solution structure, we have implemented an efficient B-spline based rigid-body simulation that preserves full atomistic detail. Such detail is necessary in highly concentrated solutions where proteins are in very close proximity separated by only thin layers of water. Because cubic B-spines are C2 continuous, full force and torque on bodies are available, enabling molecular dynamics simulations. The method is capable of reproducing known protein-protein complexes in isolation and can perform both multi-protein Monte Carlo and molecular dynamics simulations with periodic boundary conditions using implicit solvation. We examine the simple model system of lysozyme under highly-concentrated conditions (> 100 mg/ml) to gain insight into how forcefield anisotropy and large-scale structure contribute to the structure factor. We will also discuss experimental structure factor measurements under ambient and high-pressure conditions at the CHEXS HP-Bio beamline.

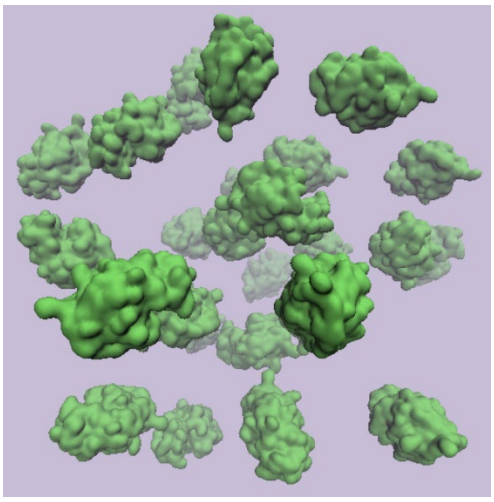

Figure 1