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Applications of density reconstruction from solution scattering to drug discovery

Protein-ligand interactions play a pivotal role in drug discovery and understanding biological processes. Structural biology techniques, such as X-ray crystallography, offer atomic-level insights into these interactions in a static environment. However, in solution, ligand binding can cause proteins to adopt multiple conformations that differ from those observed in crystals, making it challenging to obtain accurate structures. X-ray solution scattering (XSS) is a valuable tool for studying proteins in solution due to its ability to provide complementary information to high-resolution techniques, and it can be performed in high throughput at modern X-ray sources. In this presentation, we describe our algorithm called DENSS, which reconstructs *ab initio* density maps directly from XSS data. We discuss our latest developments in DENSS, which enable us to probe the structure and dynamics of protein-ligand complexes in solution with substantially improved resolution. Our developments, coupled with the ability to perform XSS at room temperature and in high throughput, represent a significant advancement in the field of structural biology and drug discovery. Overall, our algorithm offers a valuable tool for studying protein-ligand interactions in solution, where biological processes take place. Our approach enables researchers to probe the structure and dynamics of proteins and their ligands at higher resolution, facilitating the design of more effective drugs.

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