Complementing high resolution structure methods with small angle X-ray scattering data.

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The last decades were accompanied by impressive advancements for many of the structural biology techniques. Classical approaches such as NMR and macromolecular X-ray crystallography have profited from the developments in high-field magnets and synchrotron radiation, the latter allowing to study microcrystals – even in vivo. Paired with advances in automation, high throughput screening of drug candidates from many therapeutic areas have become possible. The free electron lasers may further pave the way for the analysis of even smaller samples such as nanocrystals, nanoclusters and single molecules. Impressively, the "resolution revolution" in cryoEM has resulted in many intriguing new structures, now even with the possibility to detect single hydrogens. However, the bottleneck of these experiments remains the preparation of high quality samples. Protein crystallographers still have to spend a respectful amount of time performing trial-and-error approaches to obtain diffracting crystals. Even in the era of the "resolution revolution", electron microscopists need to master the process of preparing high-quality grids on which the homogenous macromolecules are evenly distributed in random orientations and embedded in vitreous thin films. And even after successful data collection and interpretation of the data, the question remains of the relevance of the obtained high resolution models for natural environments such as native-like solutions. Here, we will discuss the unique niche that small-angle X-ray scattering (SAXS) occupies and usefully complements such high resolution studies. One of SAXS main advantages is the ability to quantitatively characterize complicated systems and mixtures in native environments and their responses to changing physical and chemical conditions. SAXS can provide low resolution structures ab initio, validate available high resolution structures in solution environment and aid in constructing hybrid models utilizing partial models of domains or subunits. Furthermore, the degree of flexibility can be assessed providing, among others, also hints to why a probe is not crystallizing. Importantly, the sophisticated ensemble approaches and mixture analysis can be used to address the question of sample polydispersity. The presented examples will include current investigations on disease-related antibodies and biomedical relevant molecules such as the oligomerization states of Insulin formulations and Sars-CoV-2 Spike S1 protein.