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Small-angle X-ray scattering as a quantitative screening tool: initial benchmarks across synchrotron beamlines

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The process of ligand recognition can significantly alter the physical morphology of macromolecules, as a part of their in-vivo function. These changes can be quantified via solution small-angle X-ray scattering (SAXS), a technique that provides structural information as a distribution of distances between all solute atoms. Measurements can be sufficiently precise to detect small yet global conformational changes. In the context of drug discovery, this not only enables differentiation between agonists and antagonists, but also to derive effective binding affinities by extracting the population of bound and unbound receptors from the mixed scattering intensities. However, the current lack of extensive screening benchmarks render it difficult to predict how informative this technique will be for an arbitrary system.

To help push things forward, we selected the 26 kDa bacterial periplasmic protein HisBP as an initial benchmark, and titrated its interactions with four ligands with *KD* values spanning 40 nM ~ 200 μM at multiple synchrotron beam-lines. These small-scale screening trials are found to be reproducible and transferable across the 96-well plate automated setups available on-site. Our current titration protocols allow structural differentiation between the native histidine-bound versus decoy arginine-bound HisBP, and quantitative *KD* predictions at receptor concentrations as low as 0.5 mg/ml (20 μM). The practical *KD* sensitivity range is bounded by receptor concentration and total measurement time, which translates into effective limits on expected throughput within available beamtime. We hope to encourage broader testing so as to eventually establish a general protocol for SAXS-based screening.

Speakers Gender

Male

Travel Funding

No

Level of Expertise

Experienced Researcher

Do yo wish to take part in the poster slam

No

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