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Watching protein-ligand interaction dynamics using X-ray free electron lasers

The molecular structure of protein-ligand complexes provides much insight into the biochemical processes in living cells. However, to understand protein activation, we also need to resolve how proteins interact with their many small molecule ligands over time. In this presentation, I will outline the opportunities and challenges of using X-ray free electron lasers to follow protein-ligand interaction dynamics at near-atomic spatial and temporal resolution in the femtosecond range.
Our first target to establish the technology was bacteriorhodopsin, a project where we resolved the mechanism of light-driven proton pumping from the photochemical isomerization of retinal in the femtoseconds, up to the proton uptake reaction in the millisecond range. In piloting experiments at the Swiss X-ray free electron laser, we have studied how nature adapted related rhodopsins to pump sodium or chloride ions across membranes or act as the principal photoreceptor in vision.
To demonstrate how relevant reactions can be triggered in non-photoactive proteins, we have followed the cis-trans isomerization of the photochemical affinity switch azo-combretastatin A4 and the resulting conformational changes in the anti-cancer target tubulin. Similar azobenzene-based photoswitches to control kinases, channels, or G protein-coupled receptors, will be important tools to study a range of other pharmacologically relevant targets.

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