How does protein-drug binding happen inside cells?

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Protein-ligand binding is the first step in any cell signaling pathway, leading to short or long range physiological effects. Proteins can also interact with exogenous ligands, not produced by the body, which can lead to protein activation or inactivation. Because of this, protein-ligand binding has been explored in the pharmaceutical industry to fight infections and diseases. Ligands able to interact with a target protein can be further modified to become drugs. Furthermore, ligands can be designed or improved based on mechanistic knowledge about the protein-ligand binding process.

Experiments to characterize protein-drug binding and other biological phenomena are usually done in vitro. For protein-drug binding, this means a low concentration of protein. However, biological phenomena happen inside cells, which is an environment with a huge concentration of macromolecules, up to 300 g/L. The effects of this crowded environment can be due to volume exclusion, which reduces the space available for diffusion, or due to soft or quinary interactions, which are weak interactions of crowders with proteins and ligands. While experiments and simulations to characterize protein-drug binding in in vitro conditions are well-established (1), few experiments and simulations so far have been done to understand the effects of macromolecular crowding over the protein-drug binding process and the associated time scales.

In this talk, I will highlight past work that provided some mechanistic insights of how macromolecular crowding affects protein-drug binding and the diffusion of drug molecules. I will also highlight challenges and current efforts in the modeling and simulation of cells with atomistic detail. Knowledge about how protein-drug binding happens inside cells can lead to new concepts and ideas to optimize drugs and enzyme substrates for higher mobility inside cells, impacting fields such as biotechnology and drug design.

References