Physical Chemistry Seminar

It's Aliiive!: Generative Modeling of Chemical Matter in Living Proteins

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A common first step in drug design is virtual high throughput screening (VHTS), where a large number of potential drug molecules are computationally modeled in a protein binding pocket and filtered down to a smaller set of hits. Traditional strategies for VHTS do not account for ligand-induced conformational changes in proteins, as they typically rely on a single static structure to represent the protein. This neglects the role of binding entropy and the fact that different ligand molecules can induce slightly different conformations in the protein binding site that significantly affect the assessment of a given molecule's fit. To address this challenge, we have developed a method called "Flexible Topology", where a subset of atoms – typically representing a small molecule ligand – can continuously change their atomic identities, which are encoded by a set of attributes that parametrize the non-bonded interactions. These attributes are all implemented as dynamic variables that have masses and evolve in time using gradients of the energy function. In other words, the attributes feel forces from their surrounding environment and respond accordingly. In this way, by observing a set of flexible topology particles move and change in a ligand binding site, we can learn the preferences of a binding pocket. In this talk I will present how flexible topology simulations can be used to explore ligand binding sites and reveal desirable properties of potential ligands.

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