How Does a Drug Molecule Find Its Target Binding Site?

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Although the thermodynamic principles that control the binding of drug molecules to their protein targets are well understood, detailed experimental characterization of the process by which such binding occurs has proven challenging. We conducted relatively long, unguided molecular dynamics simulations in which a ligand (the cancer drug dasatinib or the kinase inhibitor PP1) was initially placed at a random location within a box that also contained a protein (Src kinase) to which that ligand was known to bind. In several of these simulations, the ligand correctly identified its target binding site, forming a complex virtually identical to the crystallographically determined bound structure. The simulated trajectories provide a continuous, atomic-level view of the entire binding process, revealing persistent and noteworthy intermediate conformations and shedding light on the role of water molecules. The technique we employed, which does not assume any prior knowledge of the binding site's location, may prove particularly useful in the development of allosteric inhibitors that target previously undiscovered binding sites.