Tackling receptor flexibility in computer-aided drug design: how to hit a moving target

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The computational identification of drug leads out of large compound libraries through receptor-based virtual screening (VS) is a well-established method to predict putative inhibitors for target receptors. Although advances in the general practice and technical details of VS experiments have incrementally improved the field's ability to predict binding events, a number of obstacles remain. A major outstanding challenge in the practice of VS is the treatment of larger-scale receptor flexibility, which is especially difficult owing to the many degrees of conformational freedom in target receptors. Today, more rigorous physics-based methods for exploring the druggable conformational space of receptors are emerging as a new paradigm in VS. In this lecture, we will review different methods to take protein flexibility into account in computer-aided drug design, including how these methods can help us: (1) better understand the structural dynamics of receptors, (2) improve our quantitative assessments of ligand-receptor interactions, (3) discover novel modes of ligand binding, and (4) develop new therapeutics that are able to outsmart resistant strains by utilizing novel modes of binding and inhibition. Highlights using these methods on targets involved in AIDS and influenza will be presented.