An efficient opioid (medicinally perfect) would be a potent pain reliever without side effects such as harmful respiratory effects or constipation, would show sustained efficacy in chronic treatments, and would not be addictive. The grand challenge questions are "How to design a perfect opioid?" and "How can we use the Blue Waters supercomputer to do that?"

Following the solution of the first structure, crystallography of GPCRs has both illuminated the structural biology and empowered medicinal chemistry of this class of receptors [2,3]. Recently, crystal structures of µOR itself were solved in its "inactive" and "active" conformations [4,5]. However, other biophysical and pharmacological experiments have definitively demonstrated that µOR traverses multiple functionally important conformational states [6]. These states are important in designing the "perfect opioid" but are not tractable by the experiments and crystallography. Using Blue Waters, we attempted to discover states of µOR that have different conformation compared to crystallography but are physiologically significant. In addition, we also tried to unravel how opioid of different scaffold classes tune the receptor toward distinct conformational energy landscapes.

METHODS & CODES

We performed multiple rounds of MD simulations on Blue Waters starting from the active with ligand, active APO, and inactive crystal structures. We used MDTraj (the package developed in the Pande lab) to convert and assemble the trajectories. Then, we used the Conformation software package written for and applied to the crystal structures. We used

\[ \text{equation} \]

optimization, etc.) that we could not do on other platforms such as adaptive sampling, Markov State Model construction, force field restrained equilibrations.

WHY BLUE WATERS

Blue Waters is an extremely powerful and versatile computational resource. In addition to powerful CPU and GPU hardware, the fast interconnect allows us to do types of calculations (rapid adaptive sampling, Markov State Model construction, force field optimization, etc.) that we could not do on other platforms such as distributed resources (e.g., Folding@home). Also, the availability of the NAMD (nanoscale molecular dynamics) simulation package on Blue Waters has particular advantages for adaptive sampling and restrained equilibrations.

PUBLICATIONS AND DATA SETS