

MAR14-2013-020174

Abstract for an Invited Paper  
for the MAR14 Meeting of  
the American Physical Society

**Computing Rates of Small Molecule Diffusion Through Protein Channels Using Markovian Milestoning<sup>1</sup>**  
CAMERON ABRAMS, Drexel University

Measuring diffusion rates of ligands plays a key role in understanding the kinetic processes inside proteins. For example, although many molecular simulation studies have reported free energy barriers to infer rates for CO diffusion in myoglobin (Mb), they typically do not include direct calculation of diffusion rates because of the long simulation times needed to infer these rates with statistical accuracy. We show in this talk how to apply Markovian milestoning along minimum free-energy pathways to calculate diffusion rates of CO inside Mb. In Markovian milestoning, one partitions a suitable reaction coordinate space into regions and performs restrained molecular dynamics in each region to accumulate kinetic statistics that, when assembled across regions, provides an estimate of the mean first-passage time between states. The mean escape time for CO directly from the so-called distal pocket (DP) through the histidine gate (HG) is estimated at about 24 ns, confirming the importance of this portal for CO. But Mb is known to contain several internal cavities, and cavity-to-cavity diffusion rates are also computed and used to build a complete kinetic network as a Markov state model. Within this framework, the effective mean time of escape to the solvent through HG increases to 30 ns. Our results suggest that carrier protein structure may have evolved under pressure to modulate dissolved gas release rates using a network of ligand-accessible cavities.

<sup>1</sup>Support: NIH R01GM100472