The role of conformational dynamics on the ligand binding coupled to conformational change: The case of a periplasmic binding protein for basic aminoacids

Alejandro Sosa-Peinado, Jesús Agustín Banda Vázquez, Daniel-Adriano Silva. [1]Department of Biochemistry, School of Medicine, UNAM, México D.F. 04510, México.

Using unrestrained molecular dynamic simulations we studied the ligand binding mechanism for a periplasmic binding protein that present a conformational change upon ligand binding. Our analysis have an excellent correlation with each of the two main movements described by principal component analysis (PCA). We propose from the analysis of hydrogen bonds along the trajectory a model in which the hydrogen bond interactions place the ligand in the correct orientation to induce a cation-π interaction with Tyr-14 and Phe-52, thereby stabilizing the closed state.

Our results shown that this protein adopts slightly different closed conformations "to *make available specific hydrogen bond interactions for each ligand, allowing a single mechanism to attain multiple specificity"*. Furthermore, we use Markov State Models (MSMs) built from atomistic simulations for a deeper study of protein binds to its substrate. We show that our model can predict the bound state, binding free energy, and association rate of this system with reasonable accuracy and then use the model to dissect the mechanism of LAO binding. *We have found that both the conformational selection and induced fit mechanisms play important roles in LAO binding mechanism.*