MAR09-2009-020403

Abstract for an Invited Paper
for the MAR09 Meeting of
the American Physical Society

Modeling Conformational Transitions and Energetics of Ligand Binding with the Glutamate Receptor Ligand Binding Domain

MARIA KURNIKOVA, Chemistry Department, Carnegie Mellon University, Pittsburgh, PA 15213

Understanding of protein motion and energetics of conformational transitions is crucial to understanding protein function. The glutamate receptor ligand binding domain (GluR2 S1S2) is a two lobe protein, which binds ligand at the interface of two lobes and undergoes conformational transition. The cleft closure conformational transition of S1S2 has been implicated in gating of the ion channel formed by the transmembrane domain of the receptor. In this study we present a composite multifaceted theoretical analysis of the detailed mechanism of this conformational transition based on rigid cluster decomposition of the protein structure [1] and identifying hydrogen bonds that are responsible for stabilizing the closed conformation [2]. Free energy of the protein reorganization upon ligand binding was calculated using combined Thermodynamic Integration (TI) and Umbrella Sampling (US) simulations [3]. Ligand – protein interactions in the binding cleft were analyzed using Molecular Dynamics, continuum electrostatics and QM/MM models [4]. All model calculations compare well with corresponding experimental measurements.

[1] Protein Flexibility using Constraints from Molecular Dynamics Simulations *T. Mamonova, B. Hespenheide, R. Straub, M. F. Thorpe, M. G. Kurnikova* , Phys. Biol., 2, S137 (2005)

[2] Theoretical Study of the Glutamate Receptor Ligand Binding Domain Flexibility and Conformational Reorganization *T. Mamonova, K. Speranskiy, and M. Kurnikova* , Prot.: Struct., Func., Bioinf., 73,656 (2008)

[3] Energetics of the cleft closing transition and glutamate binding in the Glutamate Receptor ligand Binding Domain *T. Mamonova, M. Yonkunas, and M. Kurnikova* Biochemistry 47, 11077 (2008)

[4] On the Binding Determinants of the Glutamate Agonist with the Glutamate Receptor Ligand Binding Domain *K. Speranskiy and M. Kurnikova* Biochemistry 44, 11208 (2005)