Modulation of Catalytic Function by Differential Plasticity of the Active Site: A Study on *Trypanosoma cruzi* trans-Sialidase and *Trypanosoma rangeli* Sialidase

Özlem Demir,[1,2] Adrian E. Roitberg[1,2]

[1]Department of Chemistry, University of Florida, Gainesville, Florida 32611-8435, USA
[2]Quantum Theory Project, University of Florida, Gainesville, Florida 32611-8435, USA

Trans-sialidase is a vital enzyme for *Trypanosoma cruzi*, the causative agent of Chagas' disease, to escape from the host immune system and to invade the host cells. Therefore, *Trypanosoma cruzi* trans-sialidase (TcTS) presents a potential and appealing therapeutic target for this lethal disease. Availability of a structurally very similar enzyme with strict hydrolase activity (*Trypanosoma rangeli* sialidase, TrSA) provides us a unique opportunity to understand the determinants of their structure and catalytic mechanism. In this study, we compare the catalytic cleft plasticity of free (apo) and ligand-bound (holo) forms of the two enzymes using molecular dynamics simulations. We focus on the mouth of the catalytic cleft that is defined by two residues—W312 and Y119 in TcTS, and W312 and S119 in TrSA. Our results indicate that TcTS has a very flexible, widely open catalytic cleft, mostly due to W312 loop motion, in apo form. However, when the catalytic cleft is occupied by a ligand, the flexibility and solvent exposure of TcTS is significantly reduced. On the other hand, TrSA maintains a more open catalytic cleft compared to its crystal structures in both apo and holo forms (and compared to holo forms of TcTS). The reduced solvent exposure of TcTS catalytic cleft, might be partially or fully responsible for TcTS to be a less efficient hydrolase than TrSA.