# Structure, Function, and Dynamics of Monoamine Transporters

Jeffry D. Madura
Center for Computational Sciences, Department of Chemistry & Biochemistry,
Duquesne University, Pittsburgh, PA 15282.

There are a variety of computational methods, e.g. continuum electrostatics, molecular dynamics, Brownian dynamics, free energy perturbation, principal component analysis, comparative modeling, docking and anisotropic network model that are available to model biomolecular structures. We have used several of these methods as well as combinations of these methods to study the structure, function and dynamics of monoamine transporters. Monoamine transporters, a class of Neurotransmitter Sodium Symporters (NSS) involved in the re-uptake of substrates such as dopamine, serotonin and norepinephrine that regulate neuronal functions, are highly homologous in structure and function with the bacterial leucine transporter (LeuT). These symporters cotransport sodium along its gradient to facilitate the reuptake of monoamine substrates. Different conformations of LeuT can give insight into transport and binding mechanisms of the NSS transporters. To identify various conformations, seven 250ns accelerated molecular dynamics simulations were performed with LeuT in a solvate bilayer. The simulation trajectories were analyzed using Principal Component Analysis (PCA). The PCA of TMs 1b and 6a of LeuT revealed that greater than ten different conformations were observed, including occluded opening-to-in, while all currently published X-ray structures only fall into four conformational categories. Other simulations, e.g. random acceleration molecular dynamics and multiconfiguration thermodynamic integration, were used to study the transport of substrate through the transporter. Virtual screening methods are being used to identify new scaffolds as potential drug leads in the search for new antidepressants. Finally free energy perturbation methods are used to calculate binding free energy of various substrates and inhibitors to the transporters.