

EASTERN MICHIGAN UNIVERSITY

Chemistry Department Seminar

Wednesday December 3, 2014

2:00 p.m.

Room 300 Strong Hall

Fourth Biochemistry Faculty Candidate

Structure, Dynamics, and Mechanism in the Neurotransmitter Sodium Symporter Family

Neurotransmitter sodium symporters (NSS) including human dopamine, serotonin, and norepinephrine transporters harness sodium and chloride gradients to facilitate reuptake of neurotransmitters from the synapse into presynaptic neurons. This function is vital for terminating neurochemical signals, maintaining intracellular neurotransmitter concentrations, and priming the cell for subsequent signaling events. Our understanding of structure in this family is informed by only two crystallographically-determined members, LeuT, the bacterial amino acid transporter from *Aquifex aeolicus* and DAT, a heavily-modified eukaryotic dopamine transporter from *Drosophila melanogaster*. Previously, my work described the intermediate structures, equilibrium dynamics, and ligand-dependent transport mechanism of LeuT using pulsed electron paramagnetic resonance spectroscopy. We proposed a novel model of transport that described previously unidentified inward-facing and substrate-occluded conformations. Also, this work revealed specific shifts in conformational equilibria associated with Na^+ and substrate binding, which form the basis of the transport cycle. As a natural progression of the work conducted with LeuT, investigations in my laboratory will focus on a structurally uncharacterized archaeal member of the NSS family referred to in this proposal as LmaT from *Methanosarcina acetivorans*. Using computational and experimental methods, we will investigate structure, dynamics, and mechanism in LmaT to broaden our understanding of NSS transport across all three domains of life and develop an understanding of evolutionary mechanistic conservation to apply to human NSS members.