Neurotransmitter transporters are proteins located in the cellular membrane of neurons that re-uptake the neurotransmitter released during synapses after each event. Many proteins of this class are pharmacological targets for modulating neurotransmission [1]. In particular, X-ray structures of homologous bacterial transporters LeuT and Mhp1 are available and have been characterized using FRET, NMR and computational modelling [2] [3]. It was shown that the mechanism of transport of these proteins involves large domain motions between an inward-facing state and an outward-facing state, being a good example of the general alternating access model. However the complete set of structural elements on these conformational changes remains unknown, as well as their role on the physiological transport rates.

Here we will focus on the inward and outward-facing structures of LeuT and Mhp1 as well as the occluded structure of the latter. The inward-facing structure of LeuT is especially interesting because it has some intriguing information has been published recently, although it contains three major mutations that have been proven to inhibit transport [4].Our specific aim is to find an energetically feasible complete path between the outward and inward facing structures of these transporters. For that we will compare these simulations with PathRover found structures simulations. PathRover is a framework for the generation of pathways between two known protein conformations that uses probabilistic motion-planning techniques, allows the efficient generation of collision-free motion pathways, while considering a wide range of degrees of freedom involved in the motion [5]. With this information we will be able to define a pathway of conformational changes between the structures in both extremes of the transport process. This aspect is a very important factor towards the understanding of the overall neurotransmitter transport mechanism in both LeuT and Mhp1. The proposed project will require MD simulations at the atomistic level of the proteins (451 and 515 amino acids respectively). The proteins in each simulation would be immersed in a lipid bilayer patch and water, for a total of approximately 220,000 atoms. Previous experience in the lab suggests that they should be ran in parallel on a large number of CPU cores (typically 256 or 512) with optimized software such as NAMD. We will run preliminary calculations and benchmark efficiency, including the NAMD version that takes advantage of the Intel Phi coprocessor of the Stampede nodes.

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