The aim of Mr. Jaime Medina’s project in the lab is to explore the feasibility of a rigid body alternating access model of NSS transporters using new structural information and new computational algorithms.

The proposed project is new in the lab, and will allow Mr. Medina to start his thesis research in the field of computational biophysics of Neurotransmitter Transporters. These ,, are of great physiological importance as theyperform theof to the synapsesignaling to enable the formation of an information carrying signaling cycleDue to their key physiological role in neurotransmission, manyinly and medically importantwhich corresponds to the established isidetermining

The practical importance of the evaluation project assigned to Mr. Medina is high because modulation of the transition from outward-open to inward-open states of the transporters can affect greatly their efficacy in a number of key processes of great consequence for the cell. Because rigid body models for the conformational transitions essential to function have been proposed on the basis of structural symmetry observable in the crystal structures of particular states, it is now necessary to evaluate the feasibility of such transitions at the molecular level based on dynamics and energetics of the transition. The requested startup allocation will allow him to set up these studies by examining the transition between the known inward and outward-facing structures of LeuT and Mhp1 (as well as the occluded structure of the latter). In particular, X-ray structures of homologous bacterial transporters LeuT and Mhp1 are available and have been characterized using FRET, NMR and computational modeling [2] [3].

Based on these considerations, Mr. Medina has elaborated the following research plan:

The inward-facing structure of LeuT is a somewhat complicated target for evaluating the transition, because it is not clear to what extent the intriguing structural information it provides, relates to the three major mutations it contains, each of which has been shown to have significant functional consequences, including the inhibition of transport [4]. The specific aim is to find an energetically feasible complete path between the outward facing structures of the two transporters, towards a functionally relevant inward facing structure which, in the case of LeuT will still have to be confirmed.

A transition path between the end point structures of the two transporters has already been mapped out with the computationally efficient, but highly approximate PathRover algorithm. 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]. In this work we will use this preliminary result to obtain MD simulation results for structures along the PathRover-determined path, and evaluating the feasibility of the transitions when the structure is allowed to evolve dynamically. This is a very important factor towards 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 run in parallel on a large number of CPU cores (typically 256 or 512) with optimized software such as NAMD. We will begin by performing preliminary calculations and benchmark efficiency for my studies using the NAMD version that takes advantage of the Intel Phi coprocessor of the Stampede nodes. This will be essential to evaluate and establish the feasibility and direction of the long range components of his thesis research project, for which he must utilize the type of computational performance offered by access to the Stampede resources.

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