Modeling Molecular Motor Procession

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***Short Abstract* — Kinesins are molecular motors that transport cargo along cellular microtubules by transducing chemical energy into forward motion. However, the mechanism by which this is accomplished is not fully understood. The purpose of this study is to explore the kinesin stepping mechanism using a robotics-inspired, physics-based model. In this work, we model a kinesin head and a microtubule surface. We use a motion planning technique to generate kinesin conformations and calculate their respective energies. A transition graph is constructed and used to simulate kinesin dynamics, and identify low energy paths in the graph from a starting point to the native state.**

***Keywords* — Molecular walkers; kinesin; motion planning; OBPRM; energy landscape; protein-protein interaction; motor protein**

I. Introduction

Kinesins are molecular motor proteins that transport cargo while performing a hand-over-hand procession on the surface of microtubules. Each 8-nm step uses the energy of 1 ATP hydrolysis. Much work has been done to understand the mechanism by which these motor proteins convert chemical energy from ATP hydrolysis to mechanical energy. However, the process underlying kinesin's navigation to the plus end of microtubules during cargo transport has not yet fully elucidated. In our work [1], we explore how a kinesin motor domain traverses the molecular interaction energy landscape to find the low energy binding sites to anchor itself on the microtubule surface.

II. Methods

A. Models and generating samples with OBPRM

Kinesins are protein dimers consisting of two motor domains (heads) that bind to the microtubule during stepping, a stalk, and a cargo domain. Microtubules are biopolymers constituted of protofilaments of tubulin heterodimers. We created a model of the kinesin-microtubule system based on the PDB structure 4LNU that includes a single kinesin head interacting with a tubulin heterodimer. A small patch of the microtubule surface with 9 heterodimers and 3 protofilaments was created by aligning the PDB structure with an EM map of a microtubule. Samples were generated using Obstacle Based Probabilistic Roadmaps (OBPRM) [2], in which the microtubule is treated as an obstacle. We produced samples at 5 Å intervals along vectors generated at random directions from the microtubule surface. The benefit of this method is that samples can follow the contours of the microtubule patch more closely.

B. Energy calculations

For each sample, we calculated the non-bonded interaction energy between the kinesin head and the microtubule patch surface based on the Amber94 force field. Both the kinesin and microtubule are treated as rigid bodies, so only inter-molecular interactions are considered in the energy evaluation.

C. Roadmap construction and searching for a path

We constructed a graph from the set of samples, where each sample corresponds to a vertex. For each pair of samples that are within 5 Å of each other, we added an edge connecting those two vertices. We used a graph-based approach to search for a path from a given start state to a goal state, the native state in the PDB structure. Beginning with the start state, we chose the best vertex for a transition, defined as the one that maximally decreases the energy. This is repeated after each transition until the goal is reached.

III. Conclusions and Future Work

Our energy calculations show the presence of low energy regions at the positions on the microtubule surface where kinesin is known to bind. However, we also find low energy regions in between binding sites, which could indicate the existence of metastable states. We also find that there exists a low energy path from a start state to the native state along a single protofilament with no sidestepping. Future work will include random walks on the roadmap and will investigate how adding obstacles to the model can affect the kinesin stepping mechanism.

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