IMPACT OF STRUCTURAL AND DYNAMICAL COMPLEXITY ON KINESIN KINETICS

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1. Abstract

One hypothesis for the onset of Alzheimer's disease associates the aggregation of excess tau-protein on microtubules with the hindrance of cargo transport by molecular motors. This hypothesis has motivated experimental and modeling studies of kinesin procession in the presence of such obstacles. Very recently, it has been shown that kinesin?s neck linker length is closely related to its ability to bypass obstacles and avoid early detachment from the microtubule, by sidestepping to adjacent microtubule tracks. Here we present results from kinetic models that explicitly account for such sidestepping by analyzing published experimental single-molecule data on the processivity of kinesin-1 and kinesin-2, both with and without obstacles. The mechanochemistry is investigated via the construction of a Markov chain including all states assumed by the coupled kinesin-microtubule system, and mechanical rate constants optimized to fit experimental data. Further analysis with kinetic Monte Carlo yields sidestepping probabilities for each kinesin species. We also report preliminary results on the use of motion planning methods for simulating the geometry and dynamics of the protein/tubulin/obstacle system, using coarse-graining of PDB protein structures. The results of these simulations are compared to the Markov chain results, and used to reconcile and refine both methods.

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