

## IDENTIFYING THE POWER STROKE STEP OF MYOSIN V USING A NOVEL DWELL-TIME DISTRIBUTION ANALYSIS

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Molecular motors convert chemical energy into mechanical work and provide the engine for all motion in the body, from beating of the heart to division of cells. The myosin family of motor proteins is involved in a wide variety of cell movements and changes in cell shape. We are aiming to link the structural information and the experimental data together by suitable computational models to understand this mechanochemical energy transduction. One open question for myosin is what the sequence of the mechanochemical steps is involving the power stroke and the Pi release. It is difficult to resolve this issue because the power stroke step and the Pi release step occur so rapidly that it is difficult to determine if they are separate steps, and if so, which one occurs first.

Dwell-time distributions, waiting-time distributions, and distributions of pause durations are widely reported for molecular motors based on single molecule biophysical experiments. These distributions provide important information for understanding the functional mechanism of an enzyme and its underlying kinetic and mechanical processes. We have developed a novel computational method specifically for the cyclic characteristics of molecular motors to simulate dwell-time distributions of complex kinetic schemes including branching and reverse transitions. This method allows global fitting of dwell-time distributions under different experimental conditions. We numerically solved ensemble average based kinetic equations with absorbing boundary states, so that the computational result equals dwell-time distribution statistics of an infinitely long trajectory.

Using this new method, we simulated the possible mechanochemical mechanism of single-headed myosin V. By fitting the data of dwell-time distributions under different nucleotide concentrations and different directions of optical trap forces, we conclude that the power stroke is neither coupled to the Pi release step nor the ADP release step. Our analysis suggests that the power stroke is coupled to the conformational changes in the ADP-bound state.

Our computational method is widely applicable to single molecule dwell-time distributions for other molecular motors such as kinesin, RNA polymerase, helicase, and F<sub>1</sub> ATPase. The software for simulating the dwell-time distributions will be downloadable from [simtk.org](http://simtk.org).

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