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# The walk of myosin V: a kinetic model

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Molecular motors are proteins or protein complexes that transform chemical energy into mechanical work on a molecular level, generating forces and leading to motion. Myosin V is a processive molecular motor involved in intracellular transport that is found in many animal cell types and is particularly plentiful in neurones. It has two heads that attach to an actin track, and a long neck region that attaches to its cargo, such as vesicles and organelles. The coordinated binding and release of the myosin heads to actin result in a walking motion along the track, fuelled by the hydrolysis of ATP.

The precise details of how the biochemical reactions and mechanical motions of the two head elements engineer effective processive molecular motion along actin filaments remain unresolved. In our model [1] (and others) the walk is broken down into substeps and ODEs are given for the time-dependent probability of a myosin molecule being in each of the corresponding substates. We consider five basic states augmented by two others that allow for futile hydrolysis and detachments. We compare the outcomes with experimental results for run lengths, velocities, and dwell times and their dependence on ATP and ADP concentrations and external loads (from attached cargo) in both directions. The model reveals how myosin-V can use the internal strain in the molecule to synchronise the motion of the head elements.

A powerful new feature of our approach is that estimates for the rate constants in the reaction cycle and the internal strain energy are obtained by a computational comparison scheme involving an extensive exploration of a large parameter space. We use simulated annealing to minimise a cost function based on the deviation of our results from experimental data, exploiting the fact that we have obtained analytic results for our reaction network, e.g. for the velocity but also the run length, diffusion constant and fraction of backward steps. The agreement with experiment is often reasonable but some open problems are highlighted, in particular the inability of such a general model to reproduce the reported dependence of run length on ADP concentration. The novel way that we explore parameter space means that any confirmed discrepancies should give new insights into the reaction network model.

Our approach could be used in future to differentiate between competing theoretical models of the myosin-V stepping cycle and indeed between those of other translatory molecular motors, such as kinesins, dyneins and other members of the myosin family.

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[1] K.I. Skau, R.B. Hoyle and M.S. Turner, *Biophys. J.*, to appear (2006). doi:10.1529/biophysj.105.070888