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# On the kinetics that moves Myosin V

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## HIGHLIGHTS

- We emphasize the kinetic aspect or stochastic transport in terms of dynamical activity.
- The motion of molecular motors such as Myosin V is due to an asymmetry in dynamical activity.
- We predict a fluctuation symmetry.

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## ABSTRACT

Molecular motor proteins such as Myosin V, Dynein or Kinesin are no ratchets, at least not with a flashing asymmetric potential; the crucial asymmetry is in the dynamical activity. We make that explicit in terms of a simple Markov model, emphasizing the kinetic (and non-thermodynamic) aspects of stochastic transport. The analysis shows the presence of a fluctuation symmetry in that part of the dynamical activity which is antisymmetric under reversal of trailing and leading head of the motor. The direction of the motor motion is determined by it.



## 1. Introduction

Molecular motors are chemical engines essential to many aspects of life. Myosin V is a well-known example and typically move forward on actin tracks by the consumption of adenosine triphosphate (ATP). What follows applies more generally and is very relevant to two-headed motors moving in a head-over-head fashion, but the theory of Myosin V is interesting because it has also been largely explored experimentally, in particular thanks to its long (24 nm) lever arms and big displacement (36 nm per step) [1,2]. Rather detailed mechanochemical aspects of the motor have been verified and visualized [1,3]. The cycles of subsequent detachment and attachment with hydrolysis of ATP allow here some simplification and make it possible to concentrate the discussion on essential aspects of molecular motor motion. In the present paper we do not propose new chemical or structural aspects to the main cycle of Myosin V motion except for focusing on the question *why* it is selected from the various thermodynamic possibilities. For major inspiration we refer here in particular to the papers by Dean Astumian [4,5]. There are many more Markov models and more complex and realistic schemes but for our purposes many details do not matter so much. We are interested in the essential features that make Myosin V move in the *right* direction. Astumian discusses the motor's kinetics with emphasis on the microscopic reversibility. We will formalize some of those ideas here using simple Markov models and, while fully agreeing with the main points, we want to emphasize instead the frenetic aspects in the motor's working [6]. The point is that the leading and trailing heads of the molecular motor are thermodynamically and for the ATP binding and hydrolysis indistinguishable. It also leads to the prediction of a fluctuation symmetry in these kind of motors which does not involve the entropy flux (in contrast with the standard fluctuation theorem

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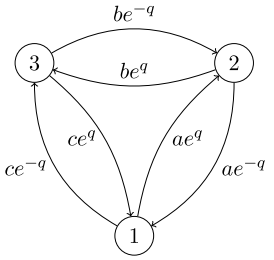


**Fig. 1.** Graph-theoretical representation of a 3-state Markov process.

for Markov jump processes [7,8]) but involves the dynamical activity [10,9]. In that way Myosin V offers a nice illustration of the role of time-symmetric aspects and how they can play a role in constructing nonequilibrium statistical mechanics.

Before we start however with the more detailed analysis of the stepping of Myosin V, we present in the next section more elementary Markov toy models to illustrate key points that will be applied further on. We first relate the Myosin V stepping with a Markov model in Section 3. We then have to present the broader theoretical framework of dynamical ensembles, in Section 4, to arrive at our main findings for Myosin V in Section 5.

## 2. Preliminary abstraction

To start with the simplest nonequilibrium model, suppose a three-state Markov process with state space $\{1, 2, 3\}$ and transition rates $k(x, y) \equiv k(x \to y)$

$$k(1,2) = a\mathrm{e}^{q}, \qquad k(2,3) = b\mathrm{e}^{q}, \qquad k(3,1) = c\mathrm{e}^{q},$$
$$k(1,3) = c\mathrm{e}^{-q}, \qquad k(3,2) = b\mathrm{e}^{-q}, \qquad k(2,1) = a\mathrm{e}^{-q}$$

parameterized by external field $q \geq 0$ and numbers $a > b > c > 0$ (see Fig. 1).

If $q = 0$, there is detailed balance with the equilibrium distribution being uniform on $\{1, 2, 3\}$, whatever the $a, b, c$. From the moment $q > 0$, the asymptotic behavior is that of steady nonequilibrium where the driving $q$ does not as such distinguish between the three states. However, the prefactors $a, b, c$, while time-symmetric over the jumps $1 \leftrightarrow 2 \leftrightarrow 3$, now determine the stationary condition. As is easily seen, for large $q$ the stationary distribution concentrates on state 3. The reason is that the escape rate from state 3 is the least; the system will spend most of its time in 3; see Refs. [12,11] for a more precise and general version of the statement. That concerns a static property, but there is a dynamical analogue, which is next.

Suppose next a more general Markov jump process with states $x, y, \ldots \in K$ modeling an open physical system in contact with one or more sufficiently separated thermal equilibrium reservoirs. For all transitions $x \to y$ we assume known the corresponding calorimetric entropy flux $S(x, y) = -S(y, x)$ into the environment. Physical modeling (the microscopic reversibility as emphasized in Ref. [5]) then requires that the Markov process satisfies local detailed balance in the sense that $k(x, y) > 0$ not only implies $k(y, x) > 0$ but also that

$$\frac{k(x,y)}{k(y,x)} = \exp S(x,y)/k_B \tag{1}$$

for all transition rates [14,13]. (We come back to that condition in Section 4.) It allows to compute the entropy flux over a path or trajectory in state space by multiplying the factors in (1) according to the jumps that have taken place.

Suppose then that for a certain state $D$ there are cycles $\omega^{(1)} : D \to x_2^{(1)} \to \ldots x_n^{(1)} \to D$ and $\omega^{(2)} : D \to x_2^{(2)} \to \ldots x_m^{(2)} \to D$ on $K$ having the same entropy flux,

$$S(\omega^{(1)}) = S(D, x_2^{(1)}) + \cdots S(x_n^{(1)}, D) = S(D, x_2^{(2)}) + \cdots S(x_m^{(2)}, D) = S(\omega^{(2)}). \tag{2}$$

(Residence or dwelling times in each state of the cycle do not matter for the entropy flux.) Similar to our previous example, (2) implies that the dissipative driving aspect does not distinguish between the two cycles; whence we ask which one will be taken more often? What decides whether $\omega^{(2)}$ or rather $\omega^{(1)}$ will be preferred by the system? The answer is a version of Landauer's principle *motion out of noise* [16,15,11] to be recalled in Section 4, which is, so we claim, the heuristics behind much of the kinetics of at least some class of molecular motors. The following sections will make that precise. Let us however already make that more specific by realizing the above on six states $K = \{D, x, v, T, w, y\}$ in precisely the set-up that we need for Myosin V, see Fig. 2.

Here are the rates, first for the transitions $D \to v \to T \to y \to D$,

$$k(D,v) = a, \qquad k(v,T) = \psi_1, \qquad k(T,y) = \psi_2\, \mathrm{e}^{s_2}, \qquad k(y,D) = d\, \mathrm{e}^{s_3}$$

and with the rates for the inverse transitions decided by local detailed balance:

$$k(v,D) = a\, \mathrm{e}^{s_0}, \qquad k(T,v) = \psi_1\, \mathrm{e}^{-s_1}, \qquad k(y,T) = \psi_2, \qquad k(D,y) = d.$$