Chemomechanical Coupling of Molecular Motors

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Living cells contain a large number of molecular motors: membrane pumps, stepping motors, growing filaments, and molecular assemblers such as polymerases and ribosomes. In many cases, these nanomachines are driven by the energy released from fuel molecules such as adenosine triphosphate (ATP). The coupling of the motor to these non-equilibrium reactions provides energy which is converted into conformational transformations of the motor and enables it to perform useful work.

Linear Stepping Motors with Two Motor Heads

The conversion of chemical energy into mechanical work is particularly striking for linear stepping motors such as kinesin, see **Fig. 1**, whose movements cover many length and time scales **[1]**. These motors have two heads, by which they bind to and walk along actin filaments and microtubules. In their bound states, they undergo cyclic sequences of conformational transitions, so-called motor cycles, that enable them to transform the chemical energy of single ATP molecules into discrete steps along the filament. Two-headed motors walk in a "hand-over-hand" fashion, i.e., by alternating steps in which one head moves forward while the other one remains bound to the filament.

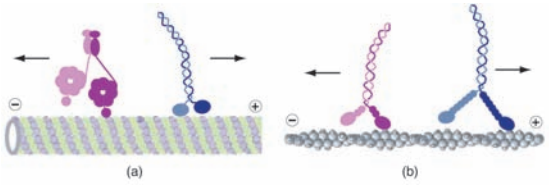

Fig. 1: Molecular motors that bind to and walk along cytoskeletal filaments, which are polar and have two different ends, a "plus" and a "minus" end: (a) Kinesin and dynein that move to the plus and minus end, respectively, of a microtubule; and (b) Myosin V and myosin VI that move to the plus (barbed) and minus (pointed) end, respectively, of an actin filament. The diameter of the microtubule and the actin filament are 25 nm and 8 nm, respectively. For simplicity, the cargo binding domains of the motors have been omitted. All four types of molecular motors are dimers consisting of two identical protein chains and use ATP hydrolysis in order to move in a directed manner. Kinesin and the two myosin motors walk in a "hand-over-hand" fashion.

Each step corresponds to a motor displacement of the order of 10 nanometers, comparable to the size of the motor heads. If there is no shortage of ATP, the motor kinesin, e.g., makes about 100 steps in one second which leads to a velocity of about one micrometer per second. The absolute value of this velocity is not very impressive, but relative to its size, the motor molecule moves very fast: On the macroscopic scale, its movement would correspond to an athlete who runs 200 meters in one second! This is even more surprising if one realizes that the motor moves in a very viscous and noisy environment since it steadily undergoes thermally excited collisions with a large number of water molecules.

Chemical States of Two-Headed Motors

In order to obtain a useful description of such a motor, we can first focus on the different chemical states of the two-headed motor. Each head has a catalytic domain, which is able to hydrolyze ATP into ADP plus P. The corresponding catalytic cycle consists of four subsequent transitions: binding of ATP, hydrolysis of ATP into ADP-P, release of P, and release of ADP. It is convenient to combine ATP hydrolysis and P release into a single transition and to distinguish 3 different states of a single motor head: state (T) with bound ATP, state (D) with bound ADP, or no bound molecule, i.e., empty (E), see **Fig. 2**. The two-headed motor can then attain 3 x 3 = 9 different chemical states and undergo transitions between these states as shown in **Fig.2**. In this figure, each motor state *i* corresponds to the vertex of a network graph. Every pair, *i* and *j*, of states is connected by two directed edges or di-edges corresponding to the forward transition I *ij* > from *i* to *j* and the backward transition I *ji* > from *j* to *i*. In **Fig. 2**, these two di-edges are combined into a single, undirected edge.

In general, the motor may undergo a chemical transition in which one of the catalytic motor domains changes its chemical composition or a mechanical transition corresponding to a mechanical step or substep. For the cytoskeletal motor kinesin, recent experiments indicate that this motor does not exhibit mechanical substeps on the timescale of microseconds **[2]**. In **Fig. 2**, chemical and mechanical transitions are indicated by solid and broken lines, respectively.

The chemical kinetics of the two heads is coordinated: binding of ATP to one head leads to the release of ADP from the other head. The tight coupling of ATP hydrolysis and stepping as well as the hand-over-hand movement indicate that such an out-of-phase behavior of the two heads also governs the catalytic action of stepping kinesin. In order to describe this behavior, we may omit all states in **Fig. 2(a)** for which both heads have the same chemical composition. In this way, we arrive at the reduced state space shown in **Fig. 2(b)** which consists of only six states.

Nonequilibrium Processes and Motor Cycles

Nonequilibrium processes are intimately related to cycles in state space and nonzero fluxes along these cycles. Each cycle, C, consists of two directed cycles or dicycles, C+ and C-, that differ in their orientiation. The network graph in Fig. 2(a) contains a huge number of cycles (more than 200) whereas the one in **Fig. 2(b)** contains only three cycles. Two of these latter cycles, namely <25612> and <52345>, contain both a hydrolysis transition, during which the motor consumes chemical energy, and a mechanical stepping transition, during which the motor can perform mechanical work.

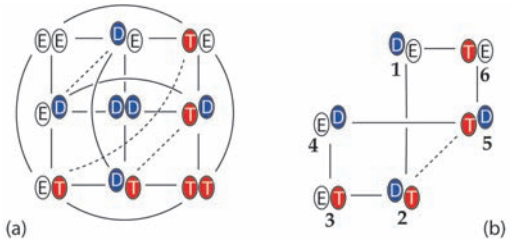

Fig. 2: Network graph with 9 states for a molecular motor with two catalytic domains, each of which can be empty (E), or bind an ATP (T) or ADP (D) molecule. This network contains 21 edges representing 18 chemical forward and backward transitions (solid lines) as well as 3 mechanical forward and backward steps (broken lines); and (b) Reduced state space with 6 states obtained from the 9-state network in (a) by omitting the three states E-E, T-T, and D-D. This network contains 7 edges corresponding to 6 chemical transitions (full lines) plus 1 mechanical transition (broken line).

Steady State Balance Conditions

In our theory, the dynamics of the motor is described by a continuous-time Markov process with transition rates ω_{ij} from state *i* to state *j*. Each dicycle can be characterized, in the steady state of the motor, by a statistical entropy that is produced during the completion of this dicycle **[3]**. Identifying this statistical entropy with the heat released by the motor and using the first law of thermodynamics, we have derived rather general steady state balance conditions of the form

$$k_B T \sum_{ij} \ln(\omega_{ij} / \omega_{ji}) = E_{ch}(C+) - W_{me}(C+)$$

that relate the transition rates ω_{ij} to the chemical energy, $E_{ch}(C+)$, consumed and the mechanical work, $W_{me}(C+)$, performed during the cycle C+. The basic energy scale is provided by the thermal energy $k_B T$, the summation runs over all di-edges $I\ ij >$ of the dicycle C+.

The mechanical work is determined by external load forces experienced by the motor and vanishes in the absence of such forces. This implies that one can decompose the steady state balance conditions into a zero-force and a force-dependent part. In addition, it is straightforward to include other energetic processes into the steady state balance conditions. Two examples are (i) energy input arising from the adsorption of photons and (ii) work against an electrochemical potential. **[3]**

Kinesin's Network of Motor Cycles

In principle, both the transition rates ω_{ij} and the energetic terms on the right hand side of the steady state balance conditions can be measured. If such a complete set of experiments were available for a certain motor, one could use the balance conditions to estimate the experimental accuracy. In practise, some of the transition rates will be difficult to measure, and the balance conditions can then be used to estimate the values of the unknown rates.

We have recently applied this latter strategy to the cytoskeletal motor kinesin **[4]**. One important consequence of our analysis is that the stall force of the motor is determined by the flux balance of two different cycles that govern the forward and backward mechanical step and both involve the hydrolysis of one ATP molecule. This differs from previous unicycle models in which the stall force was determined by the flux balance between the two dicycles of the same cycle. The latter flux balance is, however, not possible for small ADP concentrations as typically considered in motility assays. A detailed comparison between our theory and the experimental data of Ref. **[2]** is shown in **Fig. 3**. In fact, our theory provides a quantitative description for all motor properties as observed in single molecule experiments **[4]**.

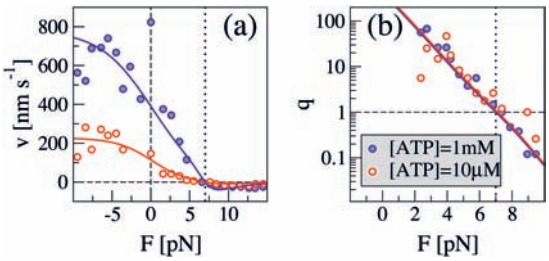

Fig. 3: (a) The motor velocity v and (b) the ratio q of the number of forward to the number of backward mechanical steps as a function of external load force F. The data are for drosophila kinesin and taken from Ref. [2]. The solid lines are calculated using the 6-state network in Fig.2(b). The vertical dotted line corresponds to the stall force at which the velocity vanishes.

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References:

[1] Lipowsky, R., Chai, Y., Klumpp, S., Liepelt, S., and Müller, M.J.I., Molecular Motor Traffic: From Biological Nanomachines to Macroscopic Transport, Physica A **372**, 34 (2006).

[2] Carter, N.J. and Cross, R.A.: Mechanics of the kinesin step, Nature **435**, 308 (2005).

[3] Liepelt, S., and Lipowsky, R.: Steady state balance conditions for molecular motor cycles and stochastic nonequilibrium processes, EPL **77**, 50002 (2007).

[4] Liepelt, S., and Lipowsky, R.: Kinesin's network of chemomechanical motor cycles, Phys. Rev. lett. (in press, 2007).