Motor Cycles and Operation Modes of Kinesin

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Kinesin is a motor protein that moves directly along rigid cytoskeletal filaments (microtubules) to transport intracellular cargo. The energy for this transport is supplied by the hydrolysis of adenosine-triphosphate (ATP) to adenosine-diphosphate (ADP) and an inorganic phosphate group (P). For small load forces, each individual motor step of kinesin is coupled to the hydrolysis of exactly one ATP molecule and displaces the center of mass by 8 nm towards the microtubule plus-end. The different chemical reactions and conformational transformations of a motor molecule constitute its specific chemomechanical network. The cycles of this network govern the dynamics of the molecular motor.

Catalytic Action and Processive Walk

Kinesin consists of two identical amino acid chains dimerized in a coiled coil. One end of the protein dimer binds to cargo particles, while at the other end, each of the two chains forms a globular head-domain, which is able to bind to microtubules. The motor heads do not only mediate the binding of kinesin to the microtubule track, but also contain a catalytic site for ATP hydrolysis, see **Fig. 1**.

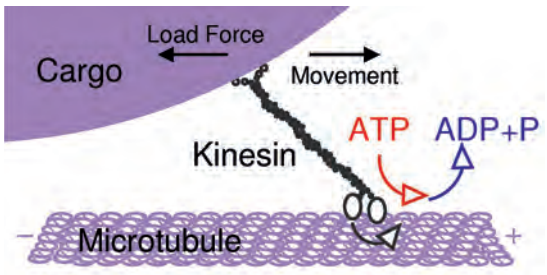

Fig. 1: The kinesin motor actively transports intracellular cargo towards the plus-end of microtubules. The motor stepping against a load force is driven by the hydrolysis of ATP to ADP and P.

The energy μ_T gained from binding an ATP molecule is partly released as $\mu_D+\mu_P$ by the unbinding of the hydrolysis products (ADP+P). The difference $\Delta\mu=\mu_T-(\mu_D+\mu_P)$ defines the chemical energy supply that can be used to perform mechanical work $W=L\,F$ via a translation of the motor by a step length L against a load force F, see **Fig. 2**.

Conservation of energy leads to the released heat $Q=\Delta\mu-W$. We have established the thermodynamics for the cycles of chemomechanical networks for molecular motors, **[1, 2]**. As a result, we obtained balance conditions for directed cycles that serve as constraints and ensure thermodynamic consistency. The obtained relations quantitatively connect thermodynamic control parameters of the motor environment with variables of the motor kinetics.

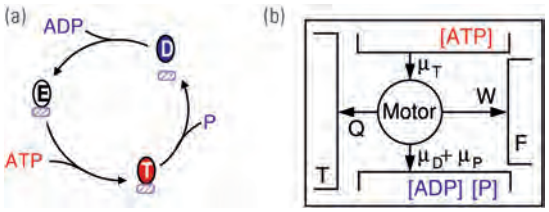

Fig. 2: (a) ATP hydrolysis cycle for an individual kinesin motor head. Each motor head may be occupied by ATP (T) or ADP (D), or be empty (E). In contrast to the E and T heads, the D heads are only weakly bound to the microtubule. (b) Energy flux diagram for a molecular motor, which is coupled to particle reservoirs with densities [ATP], [ADP], and [P], to an external load F and to a heat bath of temperature T.

Enzymatic Network Representations

The conformational state space for the dimeric kinesin molecule includes nine states as shown in **Fig. 3 (a)**. These states are connected by two types of transitions. Chemical transitions correspond to ligand binding or release events, as introduced in **Fig. 2 (a)**. Mechanical transitions correspond to the movement of the trailing motor head to the leading position, which translates the whole motor molecule by a step length L. In a systematic analysis we showed **[3, 4]**, that the main motor properties as observed in single molecule experiments by several groups as well as biochemical experiments concerning the processive walk of kinesin are described by a relatively simple model that is based on a seven state sub-network. This part of the general nine state network is composed of the three fundamental directed cycles $F1^+=|12561>$, $F2^+=|12571>$, and $B^+=|45234>$. As one can see from **Fig. 3 (b)**, the seven state network contains two additional cycles apart from the fundamental forward and backward stepping cycles, $F1^+$, $F2^+$, and B^+, namely $D1^+=|1234561>$ and $D2^+=|1234571>$. On these latter pathways the kinesin motor consumes ATP without stepping in any direction.

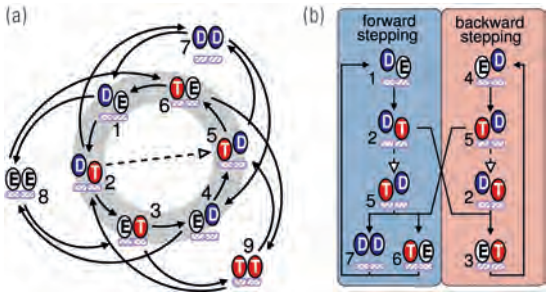

Fig. 3: (a) Network representation of the dimeric kinesin motor. While solid lines represent chemical transitions (with arrows indicating the ATP hydrolysis direction), the dashed line represents a mechanical transition (where a forward step corresponds to traveling of the weakly bound trailing head to the leading position). (b) The relevant seven state sub-network for the processive walk of kinesin.

Motor Velocity and ATP Hydrolysis Rate

The dynamics of the motor molecule is determined by excess fluxes $\Delta J(C^+)$ for each directed cycle C^+ of its chemomechanical network. In the seven state network, the motor velocity is given by $v=L(\Delta J(F1^+)+\Delta J(F2^+)-\Delta J(B^+))$, whereas the ATP hydrolysis rate is obtained from $h=\Delta J(F1^+)+\Delta J(F2^+)+\Delta J(B^+)+2(\Delta J(D1^+)+\Delta J(D2^+))$. The dicycle excess fluxes are functions of the rates that characterize each transition of the motor network. Because the transition rates by themselves depend on the three concentrations [ATP], [ADP], and [P] as well as on the load force F, the excess fluxes and consequently the motor velocity and the ATP hydrolysis rate become functions of these four thermodynamic control parameters. For fixed product concentrations [ADP] and [P], the motor velocity and hydrolysis rate can be expressed as functions of the load force and the chemical potential difference $\Delta\mu=\ln(K^{eq}[ATP]/([ADP][P]))$, where K^{eq} is the equilibrium constant for ATP hydrolysis, see **Fig. 4**. While the zeros of the motor velocity $v(F_s, \Delta\mu)=0$, for a given chemomechanical potential difference $\Delta\mu$, define the stall force F_s, the zeros of the ATP hydrolysis rate $h(F, \Delta\mu_b)=0$, for a given load force F, define the balancing chemical potential difference $\Delta\mu_b$.

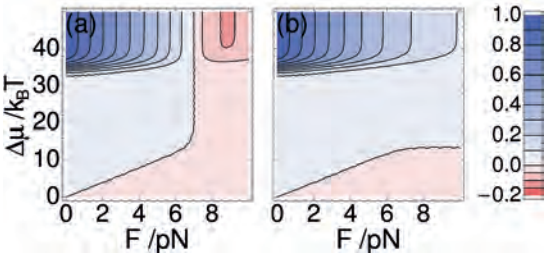

Fig. 4: (a) Motor velocity v and (b) ATP hydrolysis rate h as functions of load force F and chemical potential difference $\Delta\mu$ for fixed product concentrations [ADP]=[P]=0.5μM. Shown are the relative values with respect to $v(F=0, \Delta\mu\to\infty)$ and $h(F=0, \Delta\mu\to\infty)$.

Operation Mode Diagram for Kinesin

In **[5]** we derived explicit results for the stall force $F_s(\Delta\mu)$ and the balancing potential $\Delta\mu_b(F)$. It turned out that the dependence of the latter two quantities on the hydrolysis product concentrations [ADP] and [P] is rather weak for the relevant scales. While the stall force separates forward and backward stepping modes, the balancing potential separates ATP hydrolyzing and ATP synthesizing modes of the motor. In this way the (F, $\Delta\mu$) plane is divided up into four operation mode regions, see **Fig. 5**.

The operation mode diagram displayed in **Fig. 5** predicts for example, that the stall force F_s increases linearly with the chemical potential difference for $\Delta\mu<\Delta\mu_b(F\to\infty)=14\,k_BT$, but remains constant for larger $\Delta\mu$. Moreover, ATP synthesis against a positive chemical potential difference $\Delta\mu$ by pulling the kinesin motor into the backward direction can only be induced in the small $\Delta\mu$ regime. Thus, the operation mode diagram of the seven state network for kinesin provides explicit predictions that can be tested by future experimental studies.

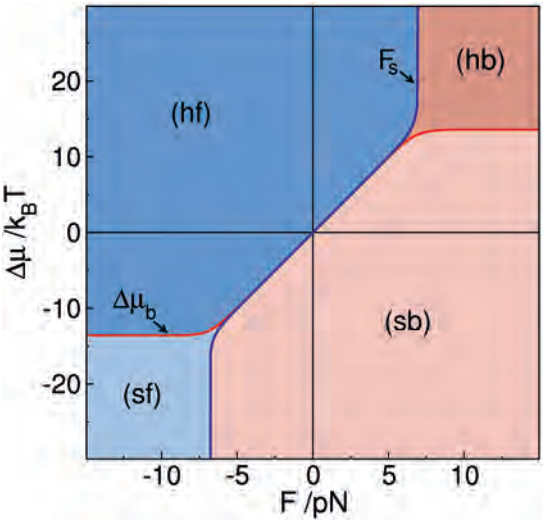

Fig. 5: Operation modes of the kinesin motor in the (F, $\Delta\mu$)-plane. The stall force F_s (blue line) separates forward and backward stepping modes. The balancing potential $\Delta\mu_b$ (red line) on the other hand, separates ATP hydrolyzing and synthesizing modes.

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