
A mechanochemical theory for the ATP-fuelled biomolecular motors

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Abstract: Biomolecular motors are normally single or complex biomolecules exerting mechanical forces over molecular and cellular scales. The ATP-fuelled biomolecular motors can transduce the chemical energy from ATP hydrolysis into forces and motions in cells. In biomolecular motors, transport reactions are both stoichiometric and enzymatic. We outline a mechanochemical theoretical framework for biomolecular motors to understand their enzymatic kinetics and continuous dynamics. The theory is validated by describing the operating mechanism and dynamics of several ATP-fuelled molecular motors driving various loads.

Keywords: biomolecular motors; mechanochemistry; ATPase; enzymatics; Langevin dynamics; operating dynamics.

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1 Introduction

Biomolecular motors are natural proteins or hybrid molecular systems that exert forces and motions at both molecular and cellular scales while fulfilling unique cellular functions [1,2]. Biomolecular motors are normally powered by the hydrolysis or synthesis of nucleotides, such as adenosine triphosphate (ATP), and/or by photon or proton-motivated forces. For ATP-fuelled biomolecular motors, the mechanochemistry involves the conversion of ATP catalysis energy into mechanical forces and motions with exceptional thermodynamic efficiency. Experiments down to the level of single molecules have revealed the operating dynamics of some biomolecular motors, such as the linear kinesin and myosin motors and the rotary F_1 -ATPase motor [1–9]. The dynamics are found to be dependent on the physiological and external loading conditions. For biomolecular motors, the time scale of ATP reactions and conformational changes is at sub nano-second or shorter, whereas the directional motions with loading occur over micro-seconds or longer. Currently for the ATP-fuelled molecular motors, our understanding of the molecular structures and pathways vs. the operational forces and driving capabilities is incomplete. Developing a valid mechanochemical concept is of fundamental importance for a complete understanding of biomolecular motors and their manipulation.

We have proposed a mechanochemical theory for the rotary F_1 -ATPase motor [3]. The theory was based on enzyme kinetics and Langevin dynamics. The introduction of an effective ‘ratchet’ drag coefficient and a chemomechanical coefficient has correlated the molecular catalysis and micro operating dynamics. The theory can successfully reproduce the results from motor experiments [2]. In this work, we extend it to the general cases of steady operations of both rotary and linear ATP-fuelled molecular motors.

2 Mechanochemistry in the ATP-fuelled biomolecular motors

2.1 Energy transduction in the ATP-fuelled biomolecular motors

The ATP-fuelled molecular motors are intrinsically ATP synthase (ATPase) proteins. Their power source comes from the ATP hydrolysis (or synthesis) reaction,



A fundamental issue is how these biomolecular motors harness the free energy from this simple reaction to generate forces and drive the entire motor in directional motions [1,2]. The tight coupling between ATP hydrolysis and the mechanical steps is the foundation of the mechanochemical mechanisms. This is also important because of the essential roles biomolecular motors have in energy transduction, regulation of metabolism and many other cellular functions.

2.2 Mechanochemical mechanism of biomolecular motors

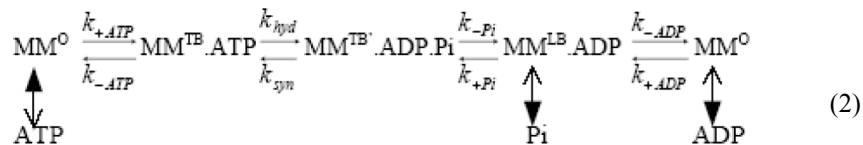
In the ATP-fuelled molecular motors, a conformational change of the structural elements caused by ATP hydrolysis at the ATP-binding site is communicated to either the next corresponding track-binding site (for kinesin and myosin) or to the alternative binding site (for F₁-ATPase). It is then relayed at much larger spatial scales via homotropic structural elements to a mechanical amplifier of the active subunits [1–6]. The mechanochemical coupling ratio – defined as the number of ATP molecules hydrolysed per mechanical step – remains 1 : 1 over a wide range of loads [3,5–9]. The main aspects of the mechanochemistry can be divided into the hydrolysis of nucleotides (mainly ATP and its analogues), inducing the conformational changes, and tightly coupled transfer of conformational changes into forces and other mechanics of the active subunits [2,3].

3 Master equations for the mechanochemistry

To solve the mechanochemical processes from ATP reactions to the micro stepping/rotating motions, we establish the following theory based on enzyme kinetics and modified Langevin dynamics.

3.1 Pathway of conformational changes

Under cellular physiological conditions (either in vivo or in vitro), the pathway of conformational changes [3–6] of the active subunits of the ATP-fuelled molecular motors are found to be,



where MM refers to the enzymatic molecular motor. The binding conformational states of the multiple catalysis subunits are identified as tight binding (TB, bound with ATP), loose binding (LB, bound with ADP and/or P_i), and Open (O), respectively. The open (O) site has a very low affinity for substrates and is catalytically inactive. k_{+ATP} , k_{-ATP} (or, k_{+ADP} , k_{-ADP} and k_{+P_i} , k_{-P_i}) refer to the rate constants of association and dissociation of ATP (or, ADP and P_i) molecules to the motor, i.e., they are the rate of ATP (or, ADP and P_i) binding to or unbinding from active subunits. The terms k_{hyd} , k_{syn} are the hydrolysis and synthesis rate constants of ATP. In this catalysis pathway, the direction of hydrolysis resulting in binding/unbinding to the motor of ATP, ADP and P_i is given by

the solid arrow heads. In each hydrolysis cycle, the different subunits interact in a cooperative way as the motion domains sequentially contact and interact with each other. The binding and conformational changes are highly coupled to the ATP hydrolysis cycle at different catalysis sites. In steady cycles of ATP hydrolysis reactions, the hydrolysis reactions at the active sites could be regarded as an equilibrium process with the same reaction sequence and dynamics.

3.2 Enzymetic kinetics

To interpret equation (2) in terms of kinetics under a steady equilibrium, where the steps of forces and motions are coupled with the chemical reaction cycles, we derived the kinetics equation [3],

$$\begin{cases} P_o + P_{ATP} + P_{ADP \cdot Pi} + P_{ADP} = 1 \\ k_{ATP} \cdot [ATP] \cdot P_o + k_{syn} \cdot P_{ADP \cdot Pi} - (k_{hyd} + k_{-ATP}) \cdot P_{ATP} = 0 \\ k_{hyd} \cdot P_{ATP} + k_{Pi} \cdot [Pi] \cdot P_{ADP} - (k_{syn} + k_{-Pi}) \cdot P_{ADP \cdot Pi} = 0 \\ k_{-Pi} \cdot P_{ADP \cdot Pi} + k_{ADP} \cdot [ADP] \cdot P_{open} - (k_{Pi} \cdot [Pi] + k_{-ADP}) \cdot P_{ADP} = 0 \\ k_{-ATP} \cdot P_{ATP} + k_{-ADP} \cdot P_{ADP} - (k_{ATP} \cdot [ATP] + k_{ADP} \cdot [ADP]) \cdot P_o = 0. \end{cases} \quad (3)$$

where [ATP], [ADP] and [Pi] are the concentrations of ATP, ADP and Pi respectively. P_o , P_{ATP} , $P_{ADP \cdot Pi}$ and P_{ADP} are the probability of states when different active subunits of the motor are either empty or occupied by ATP, ADP·Pi or ADP molecules, respectively. From equation (3), the overall kinetic rate of catalytic hydrolysis, R , can be determined by $R = k_{hyd}P_{ATP} - k_{syn}P_{ATP \cdot Pi}$.

3.3 Langevin dynamics with a 'ratchet' mechanism

Langevin dynamics can be used to implicitly simulate the effect of a solvent on biomolecules, which in our case are the motor proteins. In setting up the Langevin equations for biomolecular motors, the solvent molecules are excluded and their effect on the dynamics of the solute macromolecule is incorporated by an electrostatic potential-of-mean-force term added to the potential $U(x)$, by random collisions (the random force vector below), and by a frictional drag on its motion through the solvent (the friction term $\zeta \mathbf{v}$ or $\zeta \boldsymbol{\omega}$ below).

We define the master equations of Langevin dynamics for

- a linear or
- b rotating molecular motors respectively as [3,10],
- for a linear molecular motor

$$\begin{cases} \mathbf{v} = \frac{dx}{dt} \hat{\mathbf{x}} \\ \frac{d\mathbf{p}}{dt} = \mathbf{f}_{mm} + \mathbf{f}_{ext} - \zeta \mathbf{v} + \mathbf{f}_B(t) \end{cases} \quad (4a)$$

- for a rotating molecular motor

$$\begin{cases} \boldsymbol{\omega} = \frac{d\theta}{dt} \hat{\boldsymbol{\theta}} \\ \frac{d\mathbf{L}}{dt} = \boldsymbol{\tau}_{\text{mm}} + \boldsymbol{\tau}_{\text{ext}} - \zeta \boldsymbol{\omega} + \boldsymbol{\tau}_B(t) \end{cases} \quad (4b)$$

where

- \mathbf{v} (or $\boldsymbol{\omega}$): Velocity (or angular velocity) of molecular motor and $\hat{\mathbf{x}}(\hat{\boldsymbol{\theta}})$ is the unit vector.
- $\mathbf{p}(\mathbf{L})$: Momentum (angular momentum) of the motor system. It is conserved for the steady operation of molecular motors.
- $\mathbf{f}_{\text{mm}}(\boldsymbol{\tau}_{\text{mm}})$: Force (torque) generated directly from the hydrolysis reactions at corresponding functional subunits of the motor. $\mathbf{f}_{\text{mm}} = -(\partial U(\mathbf{x})/\partial \mathbf{x})$ ($\boldsymbol{\tau}_{\text{mm}} = -(\partial U(\boldsymbol{\theta})/\partial \boldsymbol{\theta})$) and U is the corresponding potential energy at position \mathbf{x} (or $\boldsymbol{\theta}$) of the molecular motor. It is expected that the molecular motor will switch between a series of U when it steps or rotates and undergoes continuous conformational changes.
- $\mathbf{f}_{\text{ext}}(\boldsymbol{\tau}_{\text{ext}})$: Force (torque) on a load applied by an external force (if any).
- $\zeta \mathbf{v}(\zeta \boldsymbol{\omega})$: Frictional drag term in a viscous medium, with ζ the frictional factor of the load against the media.
- $\mathbf{f}_B(\boldsymbol{\tau}_B)$: Brownian motion term due to thermal fluctuation-dissipation of the acting subunits of the motor and it's loading.

Given the very fast Langevin relaxation time, e.g., approximately 2×10^{-12} s for the case of driving an actin filament, a steady state approximation implies that the moment of inertia is constant and the momentum (or angular momentum) should be conserved. On the other hand, we have to take into account the ‘ratchet’ mechanism in the ATP-fuelled biomolecular motors. The ‘ratchet’ mechanism is a critical feature of biomolecular motors. It is either a structural or thermodynamic mechanism that is capable of utilising random thermal fluctuations to generate a unidirectional drive to the motor [3]. We define a conserved Langevin with the ‘ratchet’ restrictions for equations (4a) and (4b), as following,

- for a linear molecular motor

$$\begin{cases} \left\langle \frac{d\mathbf{p}}{dt} \right\rangle_t \equiv 0, \left\langle \frac{d\mathbf{p}}{dt} \right\rangle_x \equiv \zeta_r \bar{v} \\ \langle \mathbf{f}_B(t) \rangle \equiv 0, \langle \mathbf{f}_B(t) \mathbf{f}_B(t') \rangle \equiv 2k_B T \zeta \delta(t-t') \end{cases} \quad (5a)$$

- for a rotating molecular motor [3,11]

$$\begin{cases} \left\langle \frac{d\mathbf{L}}{dt} \right\rangle_t \equiv 0, \left\langle \frac{d\mathbf{L}}{dt} \right\rangle_\theta \equiv \zeta_r \bar{\omega} \\ \langle \boldsymbol{\tau}_B(t) \rangle \equiv 0, \langle \boldsymbol{\tau}_B(t) \boldsymbol{\tau}_B(t') \rangle \equiv 2k_B T \zeta \delta(t-t') \end{cases} \quad (5b)$$

Note that $\delta(t-t')$ is the Dirac δ -function and the Brownian fluctuation is represented by Gaussian white noise. To account for the ‘ratchet’ mechanism occurring in biomolecular motors, we assume that the average momentum at any given time is in effect a constant drag (torque), $\zeta_r \bar{v}(\zeta_r \bar{\omega})$. Here a fitting constant, ζ_r , is introduced as the effective ‘ratchet’ drag coefficient. This will ensure the motor stepping or spinning unidirectionally. Physically in the distribution space, the value of ‘ratchet’ can be converted (via the Smoluchowski equation) to the diffusion constant of the motors’ active subunits.

3.4 When molecular motors drive a load

When a molecular motor works steadily, e.g., when it drives an external load under the saturation [ATP] conditions, it was demonstrated that a stepwise stepping/rotation is accomplished with the hydrolysis of one ATP molecule per step [1,4,5–7,9]. Therefore we have, on average, $\Delta U(\mathbf{x}) = R\Delta G_{\text{hyd}}\Delta t$ or $\Delta U(\boldsymbol{\theta}) = R\Delta G_{\text{hyd}}\Delta t$, which leads to,

- for a linear molecular motor

$$\left\langle \frac{\partial U(\mathbf{x})}{\partial x} \right\rangle = \frac{\eta R \Delta G_{\text{hyd}}}{\bar{v}} \quad (6a)$$

- for a rotating molecular motor [3,11]

$$\left\langle \frac{\partial U(\boldsymbol{\theta})}{\partial \theta} \right\rangle = \frac{\eta R \Delta G_{\text{hyd}}}{\bar{\omega}} \quad (6b)$$

here we define η as the chemomechanical coefficient, which indicates the efficiency of biomolecular motor in converting ATP hydrolysis energy into forces or torques. The perfect motor would possess η of 1.0. For a practical biomolecular motor, η is between 0–1.0 due to the fact that the motor is not a steady mechanochemical equilibrium system and it will have some energy dissipation, such as heat dissipation. As discussed previously, R is the overall ATP hydrolysis rate of the motor. In equation (6), the chemical energy released from ATP hydrolysis reactions is given by [12],

$$\Delta G_{\text{hyd}} = G_o + k_B T \ln \frac{[\text{ADP}][\text{Pi}]}{[\text{ATP}]} \quad (7)$$

with $G_o \approx -50.74$ pN.nm for the free energy released from the hydrolysis of a single ATP molecule at pH = 7 at 25°C.

In the single molecular and nano motor applications [1,6–9], biomolecular motors normally drive two kinds of loads,

- spherical beads or
- polymeric filaments.

We determine the drag frictional factor, ζ , of these loads in viscous media as,

- for linear-drag spherical beads [10],

$$\zeta = 6\pi r \zeta_o \quad (8a)$$

where ζ_o ($\sim 1 \times 10^{-3} \text{ N m}^{-2} \text{ s}$ for a physiological media) is the viscosity of the media, and r is the radius of the bead;

- for rotary-drag polymeric filaments [13],

$$\zeta = \frac{4\pi}{3} \zeta_o l^3 \left/ \left[\ln \frac{l}{2r} - 0.447 \right] \right. \quad (8b)$$

where l and r are the length and the radius of the filament.

Substituting equations (3) and (5)–(8) into equation (4) allows us to determine the mechanochemical properties of biomolecular motors driving loads of beads or actin filaments. For example, the stepping speed of a motor, as a function of nucleotide concentration and the load strength or the actin length, can be determined.

4 Linear kinesin and rotary F₁-ATPase

We now demonstrate the application of our mechanochemical theory to the ATP-fuelled motors of kinesin and F₁-ATPase. In both cases, the Brownian term is treated as two parts: one is the effective drag force at the active subunits where the ‘ratchet’ mechanism takes place, and the remaining contribution is a disturbing term at the load. In equations (4) and (5), the parameter ζ_r accounts for the former component and $\bar{\mathbf{f}}_B$ (or $\bar{\tau}_B$) refers to the Brownian term from the loading and external perturbation. This treatment is justified as we attribute the internal Brownian fluctuation into the fitting parameter of ζ_r without knowing the exact potential landscape (i.e., $U(\theta)$) in motors [3]. This process averages the stochastic nature of internal fluctuations and accumulates the overall force from Brownian motions at the motor proteins.

4.1 Linear kinesin driving a bead

Kinesin is a motor walking hand-over-hand along microtubules, as shown in the inset of Figure 1 [1,5,6,9]. It was found that kinesin walks at the processive step of 8 nm/step while dragging different loads of beads [9]. The maximum velocity of stepping was estimated up to 800 nm/s.

Figure 1 Kinesin drags a bead of different load with an effective ‘ratchet’ drag coefficient of $0.03 \pm 0.02 \text{ pN nm s}$. (with $k_{\text{ATP}} = 1.1 \times 10^6 \text{ M}^{-1} \text{ s}^{-1}$, $k_{\text{ADP}} = \text{n.d.}$, $k_{\text{Pi}} = \text{n.d.}$, $k_{-\text{ATP}} = 1.5 \times 10^2 \text{ s}^{-1}$, $k_{-\text{ADP}} = 2.0 \times 10^2 \text{ s}^{-1}$, $k_{-\text{Pi}} = 40 \text{ s}^{-1}$, and $k_{\text{hyd}} = 1.0 \times 10^2 \text{ s}^{-1}$, $k_{\text{syn}} = \text{n.d.}$ The symbols are from experimental measurements [9] and the solid lines are the simulation results. n.d. = not determined, the values were taken as zero to account for the kinetic pathways in the kinesin motor) (see online version for colours)

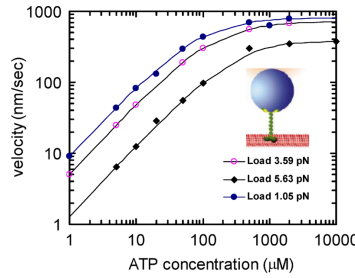
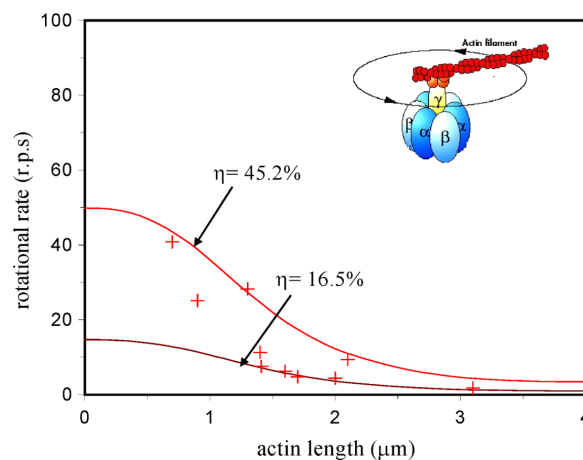


Figure 1 shows how the kinesin motor drives a bead load of different pN forces under varying [ATP] concentrations. The theoretical simulation ([ADP] and [Pi] are set at cellular physiological conditions of 10 μM and 1.0 mM) gives good agreement with the experimental data. For this kinesin motor, a chemomechanical coefficient of 0.6 ± 0.2 and an effective ‘ratchet’ drag coefficient of 0.03 ± 0.02 pN.nm.s respectively are determined by best fitting to the experimental data. Compared with the rotary motor, such as F_1 -ATPase (see below), linear kinesin motor walks with weaker ‘ratchet’ drag but higher chemomechanical efficiency.

4.2 Rotary F_1 -ATPase driving an actin filament

F_1 -ATPase is a rotary motor while transducing energy from hydrolysis/synthesis of ATP molecules (as shown in the inset of Figure 2) [1–4,7,8]. Using the above mechanochemical theory, we could also determine the mechanochemical properties of the F_1 -ATPase molecular motor when it steadily drives an actin filament.

Figure 2 F_1 -ATPase drives an actin filament. The theoretical solid lines indicate that the chemomechanical coefficients of F_1 -ATPase fall between 0.165–0.452 with an effective ‘ratchet’ drag coefficient of 1.07 pN nm s [3] (with $k_{\text{ATP}} = 2.08 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, $k_{\text{ADP}} = 8.90 \times 10^6 \text{ M}^{-1}\text{s}^{-1}$, $k_{\text{Pi}} = 8.10 \times 10^5 \text{ M}^{-1}\text{s}^{-1}$, $k_{-\text{ATP}} = 2.70 \times 10^2 \text{ s}^{-1}$, $k_{-\text{ADP}} = 4.90 \times 10^2 \text{ s}^{-1}$, $k_{-\text{Pi}} = 2.03 \times 10^3 \text{ s}^{-1}$ and $k_{\text{hyd}} = 4.5 \times 10^5 \text{ s}^{-1}$, $k_{\text{syn}} = 1.15 \times 10^{-3} \text{ s}^{-1}$). The crosses are from experimental measurements [7]. [ADP] and [Pi] are set at cellular physiological condition of 10 μM and 1.0 mM, respectively. The rotation rate is in units of radians per second, $\text{rad}\cdot\text{s}^{-1}$) (see online version for colours)



The dependence of rotation rate upon the length of loading actin is plotted in Figure 2 (solid lines). To compare our results with experiments, we used [ATP], [ADP] and [Pi] of 2 mM, 10 μM and 10 mM, respectively. The crosses in Figure 2 are from experimental measurements [7], and the two solid lines indicate that the F_1 -ATPase motor works at mechanochemical coefficients within the range $0.165 \leq \eta \leq 0.452$. The effective ‘ratchet’ drag coefficient, which is 1.07 pN.nm.s in this case, is calculated to ensure the rotational rates’ convergence at zero length and to comprise the top and bottom range of the scattered experimental data. This value is found to be close to the drag coefficient of driving a 1 μm actin filament at one end. It was claimed [7,8] that the F_1 -ATPase-actin

motor system would have a thermodynamic coefficient of about 1.0, or may at least have a coefficient of ~ 0.8 . However, our theoretical investigation indicates that this may not be the case. The theoretical rotational rates show that the motor system works at different chemomechanical coefficients falling in the range of $\eta = 0.165\text{--}0.452$.

5 Conclusion

We established a mechanochemical theory to link the molecular-scale chemical hydrolysis reactions to micro-scale mechanical motions of biomolecular motors. It can adequately account for the operating dynamics of the ATP-fuelled biomolecular motors, particularly the coupling of ATP hydrolysis reactions to the motions and activities in the presence of spherical or polymeric loads. Complex functions and cooperativity of the ATP-fuelled biomotors can also be determined with the extension of the theory [11,14]. This work is promising as a theoretical framework for the control and manipulation of biomolecular motors [15].

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References

- 1 Schliwa, M. and Woehlke, G. (2003) 'Molecular motors', *Nature*, Vol. 422, pp.759–765.
- 2 Karplus, M. and Gao, Y.Q. (2004) 'Biomolecular motors: the F₁-ATPase paradigm', *Curr. Opin. Struct. Biol.*, Vol. 14, pp.250–259.
- 3 Liu, M.S., Todd, B.D. and Sadoski, R.J. (2003) 'Kinetics and chemomechanical properties of the F₁-ATPase molecular motor', *J. Chem. Phys.*, Vol. 118, pp.9890–9898.
- 4 Boyer, P.D. (1997) 'The ATP synthase – a splendid molecular machine', *Annu. Rev. Biochem.*, Vol. 66, pp.717–749.
- 5 Farrell, C.M., Mackey, A.T., Klumpp, L.M. and Gilbert, S.P. (2002) 'The role of ATP hydrolysis for kinesins processivity', *J. Biol. Chem.*, Vol. 277, pp.17079–17087.
- 6 Vale, R.D. and Milligan, R.A. (2000) 'The way things move: looking under the hood of molecular motor proteins', *Science*, Vol. 288, pp.88–95.
- 7 Yasuda, R., Noji, H., Yoshida, M., Kinosita, K. and Itoh, H. (2001) 'Resolution of distinct rotational substeps by submillisecond kinetic analysis of F₁-ATPase', *Nature*, Vol. 410, pp.898–904.
- 8 Soong, R.K., Bachand, G.D., Neves, H.P., Olkhovets, A.G., Craighead, H.G. and Montemagno, C.D. (2000) 'Powering an inorganic nanodevice with a biomolecular motor', *Science*, Vol. 290, pp.1555–1558.
- 9 Schnitzer, M.J., Visscher, K. and Block, S.M. (2000) 'Force production by single kinesin motors', *Nat. Cell. Biol.*, Vol. 2, pp.718–723.
- 10 Doi, M. and Edwards, S.F. (1986) *The Theory of Polymer Dynamics*, Oxford University Press, Oxford, UK.

- 11 Liu, M.S., Todd, B.D. and Sados, R.J. (2004) 'Complex cooperativity of ATP hydrolysis in the F₁-ATPase molecular motor', *Biochim. Biophys. Acta*, Vol. 1698, pp.197–202.
- 12 Fersht, A. (1999) *Structure and Mechanism in Protein Science: A Guide to Enzyme Catalysis and Protein Folding*, Ch. 3, Freeman Press, New York.
- 13 Hunt, A.J., Gittes, F. and Howard, J. (1994) 'The force exerted by a single kinesin molecule against a viscous load', *Biophys. J.*, Vol. 67, pp.766–781.
- 14 Liu, M.S., Todd, B.D. and Sados, R.J. (2005) 'Cooperativity in the motor activities of the ATP-fuelled molecular motors', *Biochim. Biophys. Acta*, Vol. 1752, pp.111–123.
- 15 Liu, M.S., Todd, B.D. and Sados, R.J. (2005) 'Mechanochemical theory for the ATP-fuelled biomolecular motors', *Proc. IEEE on ROBIO 2005*, Hong Kong and Macau, China, pp.348–351.