STATISTICAL PHYSICS OF BIOLOGICAL MOLECULAR MACHINES*

Michał Kurzyński

Institute of Physics, A. Mickiewicz University
Umultowska 85, 61-614 Poznań, Poland
e-mail: kurzphys@main.amu.edu.pl

(Received January 31, 2005)

Dedicated to Professor Andrzej Fuliński on the occasion of his 70th birthday

Each biological molecular machine can be effectively considered a common chemochemical enzymatic machine occurring, however, in multitude rather than a few conformational substates distinguished by the conventional kinetics. The cases of the proton pump cytochrome bc_1 and the actomyosin motor are considered in some detail. In the steady state, a slow character of conformational transition dynamics causes the necessity of replacing conventional reaction rate constants by more sophisticated quantities, the mean first-passage times between some distinguished conformational substates of the machine. The most important results obtained for the flux-force dependence of the actomyosin motor are noted.

PACS numbers: 05.70.Ln, 87.15.He, 87.15.Rn, 87.16.Nn

1. Introduction

There is no denying the fact that the great recent progress in molecular biology would not have been possible without powerful tools of the contemporary experimental physics. However, the conceptual apparatus offered to biology by the present-day theoretical physics is unaccountably poor. The basis of molecular biology of the beginning of 21st century is still physical chemistry of the first half of 20th century. A great challenge for the contemporary statistical physics is to create a formalism capable of describing adequately a frozen hierarchical structure and the lack of a clear time scale separation characteristic for animate systems [1]. There are many impressive problems to be elucidated. One such a problem is the mechanisms of action of biological molecular machines.

* Presented at the XVII Marian Smoluchowski Symposium on Statistical Physics, Zakopane, Poland, September 4–9, 2004.

We understand the word *machine* quite generally as denoting any physical system that enables two other physical systems to perform work one on each other. Under isothermal conditions, performance of work is equivalent to a transfer of free energy. Thus machines that operate under such conditions are referred to as free energy transducers [2]. An approach we present here is based on a reasonable assumption that any biological molecular machine can be considered a common chemochemical machine but a stochastic internal dynamics of a protein macromolecule composing the machine is very complex.

2. Chemochemical machines

Each biochemical reaction must be catalyzed by a protein enzyme. Separately, each reaction proceeds in the direction determined by the second law of thermodynamics such that the amount of chemical energy dissipated is positive. However, when two reactions occur simultaneously using the same enzyme, one reaction proceeding according to the second law of thermodynamics can force the second reaction to proceed against the second law. In this case, the first reaction transfers a part of its free energy recovered from dissipation performing work on the second reaction. The mechanism of energy transfer is very simple: if both reactions occur in a common cycle, they must proceed in the same direction [2].

As an example, let us consider the action of kinases, the enzymes that catalyze the phosphate group transfer from ATP (adenosine triphosphate) to some substrate. Kinases play important role both in the metabolism and in the processes of biological signal transduction. The phosphate transfer reactions can be considered as coupling two reactions: the exoergic ATP hydrolysis to ADP (adenosine diphosphate) and P_i (the inorganic phosphate), and the endoergic substrate, Sub, phosphorylation by the P_i group. In addition to the transfer of the phosphate group P_i from ATP to Sub, it is also possible to detach this group from the enzyme unproductively (Fig. 1(a)). The direct detachment of the phosphate from the enzyme partly decouples the free energy donating reaction from the free energy accepting one and causes a slippage of the two corresponding cycles.

Kinase is a molecular chemochemical machine, *i.e.*, a machine that conveys the chemical free energy from one reaction to other. The chemical variables are concentrations of the reaction products and the conjugate forces are differences between the product and the reactant chemical potentials. The main difference between molecular and macroscopic machines is in their organization. The macroscopic machines are devices characterized by macroscopic spatial organization while the enzymes are microscopic or at best mesoscopic entities. Macroscopically, the chemochemical machine is a more

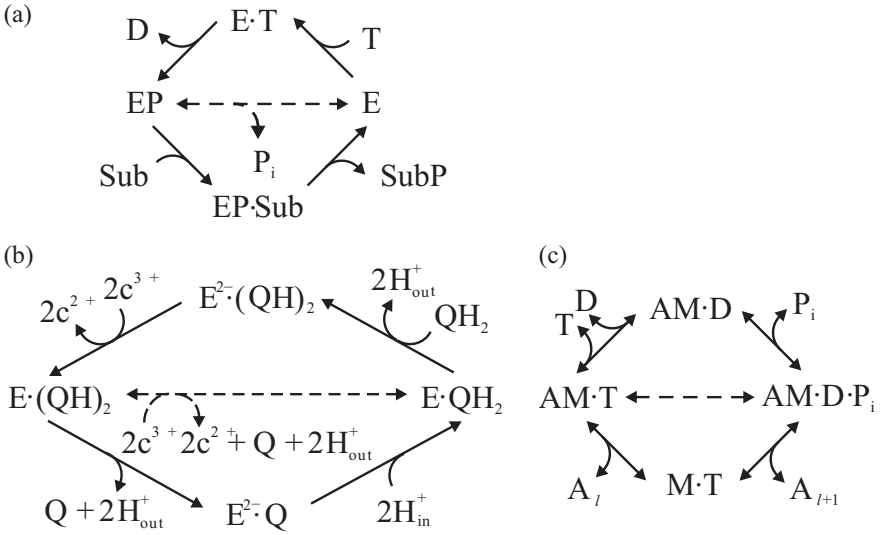

Fig. 1. Simplified chemical cycles of three exemplary biological molecular machines. (a) A chemochemical machine, the kinase. E denotes the enzyme and Sub the substrate. T, D and P_i stand for ATP, ADP and the inorganic phosphate, respectively. (b) A chemoelectrical machine, cytochrome bc_1. c^{3+} and c^{2+} denote the cytochrome c in two different oxidation states. QH_2, QH, and Q stand for quinol, semiquinone and quinone, respectively. Protons from internal and external sides of the membrane are denoted as H^+_{in} and H^+_{out}, respectively. (c) A chemomechanical machine, the actomyosin motor. M denotes the myosin head and A the actin filament. AM·D is the strongly attached and AM·T/AM·D·P_i the weakly attached state of the myosin head to the filament. Positions of bounding actin molecules along the filament are labeled when detached from the myosin head. In all three schemes the broken lines represent an unproductive (without performing work) closure of the free energy donating reaction that causes a possible slippage of the two component cycles.

or less spatially homogeneous solution of enzymes (Fig. 2(a)) with a typical concentration of 10^{-6} M, *i.e.*, close to 10^{15} molecules per cubic centimeter or 10^3 molecules per cubic micrometer (the typical size of a bacterial cell or an organelle of a eukaryotic cell).

Besides simple phosphorylation reactions, the reaction of ATP hydrolysis is coupled to many other biological processes. It can force the transport of ions across membranes in the direction of increasing ion concentration, not directly allowed by the second law of thermodynamics. The chemoosmotic or chemoelectric molecular machines performing such a function are called molecular pumps. Here the machine output variable is a concentration or a

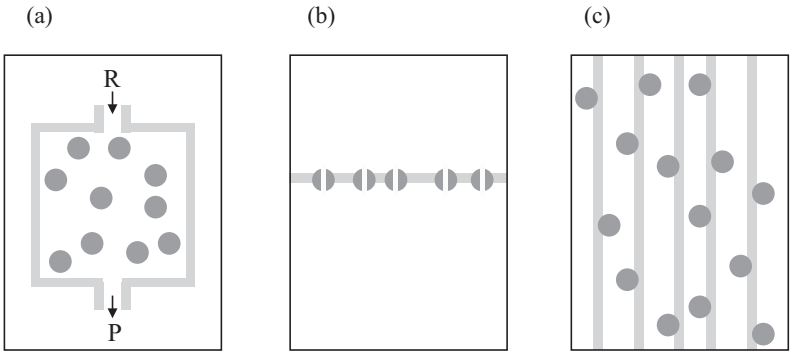

Fig. 2. Functioning of biological molecular machines at a thermodynamic (macroscopic) scale is possible due to appropriate organization of the system. Molecular chemochemical machines operate within a reactor formed by a cellular organelle (a). Molecular pumps are embedded into the two-dimensional structure of the membrane (b). Molecular motors move along an organized system of one-dimensional tracks, microfilaments or microtubules (c).

charge of ions on one membrane side and the conjugate force is a transmembrane difference in the electrochemical potential. The ATP hydrolysis can also result in a mechanical motion along molecular tracks (microfilaments, microtubules or nucleic acid chains). The corresponding chemomechanical machines are called molecular motors.

From a theoretical point of view, it would be convenient to treat all molecular biological machines as chemochemical machines. Treating molecular pumps as chemochemical machines is not a great problem. The molecules present on different sides of a biological membrane can be considered to occupy different chemical states while the transport process across the membrane can be regarded as an ordinary chemical reaction. Fig. 1(b) shows a simplified chemical cycle of cytochrome bc_1, a proton pumps taking part in membrane phosphorylation [3]. Cytochromes are proteins that contain heme, an iron ion in a planar square coordination of porphyrin ring. Cytochrome bc_1 functions as quinol : cytochrome c-oxidoreductase, an enzyme that oxidizes the membrane-soluble electron carrier quinol and reduces the water-soluble carrier cytochrome c. From among four electrons, two are transferred from quinol to cytochrome c through an opposite side of the membrane from where they take two protons. A possible slippage is realized if more electrons omit the latter way [3].

Molecular motors present a more complicated case. Fig. 1(c) shows a simplified version of the Lymn–Taylor–Eisenberg kinetic scheme of the chemomechanical cycle of the actomyosin motor [4]. A head of the myosin molecule is ATPase, an enzyme that hydrolyzes ATP to ADP and the inorganic phos-

phate P_i. The scheme indicates how the ATPase cycle of the myosin head is related to a detached, weakly attached and strongly attached states to the actin filament. Both the substrate and products of the catalyzed reaction bind to and rebind from the myosin in its strongly attached state, whereas the reaction takes place either in the weakly attached or detached state. Only completion of the whole cycle with the ATP hydrolysis achieved in the detached state results in the directed motion of the myosin head along the actin track. ATP hydrolysis in the weakly bound state alone (the broken line) is ineffective and corresponds to slippage.

The question is how to represent a load acting on a motor in chemical terms. Because the force exerted by individual motor molecules is a strictly molecular property, not dependent on macroscopic external constraints such as the external load [2], the latter, being simply subtracted from the mean force exerted by the statistical ensemble of all motor molecules, can be only a property of the organization of the ensemble, in particular the number of myosin heads bound to the actin filaments composing the myofibril. In other words external load attached to the myofibril influences the energy of binding of the myosin head to actin filament and not the energy of particular conformational states of the myosin. The changes in the binding free energy owing to the external load can be expressed as the changes in the effective rather than actual concentrations of the actin filament, which allows the motor to be really treated as a usual chemochemical machine.

At a macroscopic level, the action of molecular pumps and motors manifests as a directed transport of a substance. The possible functioning of mesoscopic machines on a macroscopic scale is due to appropriate organization of the statistical ensemble. Molecular pumps are embedded in the two-dimensional structure of the membrane (Fig. 2(b)), while molecular motors move along a structurally organized system of one-dimensional tracks, microfilaments or microtubules (Fig. 2(c)).

3. Intramolecular stochastic dynamics of proteins

Fig. 3 presents the structure of the mitochondrial cytochrome bc_1. It is a protein dimer, each monomer consisting some 2150 amino acids [3, 5, 6]. Functionally, four subunits can be distinguished in the monomer (Fig. 3(b)). The largest, intra-matrix subunit (900 amino acids) is not involved in redox process. The cytochrome b complex (570 amino acids, *i.e.*, about 8.5 thousand atoms) transfers one electron from a quinol binding site q_o through two b-type heme groups b_L and b_H to a semiquinone binding site q_i. The iron-sulfur protein complex (270 amino acids, about 4.0 thousand atoms) transfers the second electron from the quinol binding site q_o to a c_1-type

heme. The latter is a component of the cytochrome c_1 complex (440 amino acids, about 6.5 thousand atoms) that transfers this electron further to cytochrome c molecule, soluble in intra-membrane mitochondrial medium.

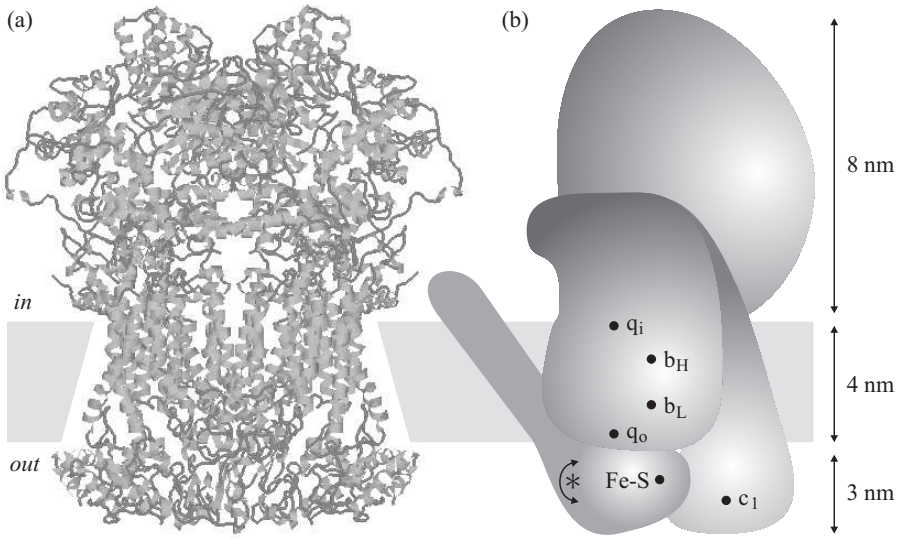

Fig. 3. Structure of the quinol:cytochrome c-oxidoreductase. Drawing (a), made using the program Rasmol on the basis of Protein Data Bank (pdb) entry 2BCC, shows the particular secondary structure elements, α-helices and β-strands, composing the supramolecular dimer. Drawing (b) presents schematically the component subunits of the monomer. See text for details. An asterisk denotes the position of a rotation axis of the moving domain of iron-sulfur complex.

The cycle of quinol to quinone reduction shown in Fig. 1(b) appears to be actually composed of two cycles: that of quinol to semiquinone reduction proceeding on one monomer and that of semiquinone to quinone reduction proceeding on the other. There is a cave in between the both monomers that facilitates diffusion of all forms of the quinone molecules between the appropriate binding sites [6]. The transfer of two electrons perpendicularly to the membrane combined with the transfer of two hydrogens on a quinol molecule diffusing in the cave in the opposite direction is equivalent to the transfer of two protons. The large scale domain movement in the iron-sulfur complex (Fig. 3(b)) makes possible a transfer of only one electron per cycle. This is the main mechanism minimizing the slippage [3].

Fig. 4 presents the structure of the myosin head, a protein composed of some 1200 amino acids, *i.e.*, about 18 thousand atoms [7]. Functionally, one can distinguish in it a catalytic subunit (630 amino acids) joined by a swivel with a regulatory subunit, a "lever arm" (570 amino acids). Only after strong

attachment to the actin filament the myosin head becomes able to bind and rebind substrates and products of the catalyzed ATP hydrolysis reaction. The binding site is a cleft between the upper and the lower domains of the catalytic subunit. This cleft can be in the open or closed state. Through a long α-helix, referred to as the relay, the state of the cleft is transmitted onto the orientation of the lever-arm domain, unless another α-helix, called the SH1-SH2 helix, is melted [8].

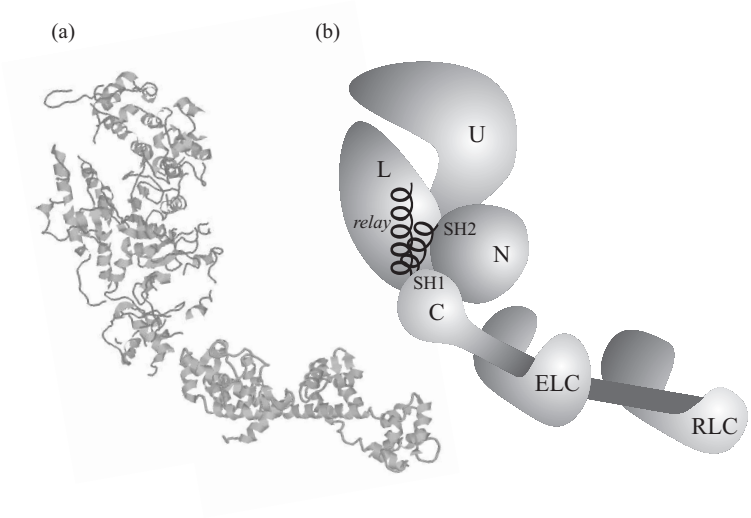

Fig. 4. Structure of the myosin head. Drawing (a), made using the program Rasmol on the basis of Protein Data Bank (pdb) entry 2MYS for the catalytic subunit and 1SCM for the regulatory subunit, shows the particular secondary structure elements, α-helices and β-strands. Drawing (b) presents schematically the component domains of the catalytic subunit: the upper (U), the lower (L) and the amino end (N) one, as well as those of the regulatory subunit: the globular converter (C) becoming a single α-helix stabilized by the essential light chain (ELC) and the regulatory light chain (RLC). The relay and the SH1-SH2 helices are shown. The swivel is close to the hydrosulfide group SH2.

The protein macromolecules shown in Figs. 3 and 4 do not resemble small molecules of conventional physical chemistry with rapidly equilibrating intramolecular dynamics. Rather, they look like highly organized assemblies of mechanical elements: levers, hinges, springs (or pistons) and triggers. Also some electrical elements: conductors, semiconductors and insulators can be distinguished. It seems it might be possible to describe them in the same terms as the common macroscopic machines. However, the molecular machines are not macroscopic but mesoscopic systems. They act due to thermal fluctuations. Energy is borrowed from and returned to the surroundings.

The ATP hydrolysis only makes this process directed. In consequence, the action of the molecular machines have to be described in the same way as common chemical reactions, but a multitude of conformational states have to be taken into account.

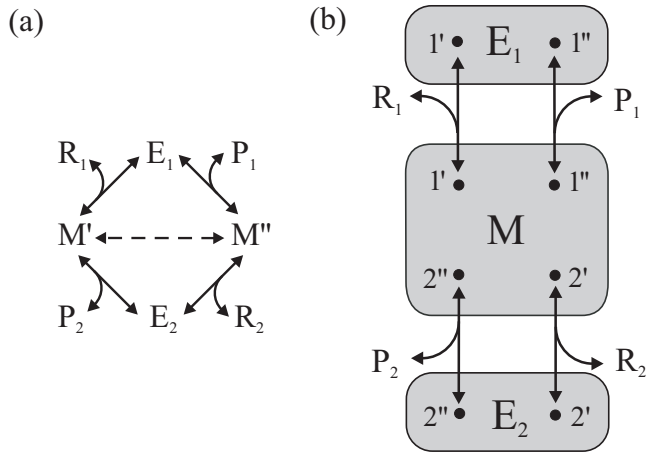

Fig. 5. Lymn–Taylor–Eisenberg kinetic model of mechanochemical cycle of the actomyosin motor. (a) The simplified version from Fig. 1(c) in new notation. R_1 = ATP, $P_1 = P_i$ whereas R_2 and P_2 stand for the actin filament before and after translation by a unit step, respectively. E_1 denotes the myosin-ADP complex strongly attached to the actin filament, M′ or M″ the myosin-ATP or ADP·P_i complex weakly attached, and E_2 the same complex detached from the actin filament. (b) The version considered in the present paper. The multitudes of conformational transitions within E_1, M and E_2 are represented by shaded boxes. All bimolecular reactions are assumed to be gated, *i.e.*, they take place only in certain conformational substates of the myosin head. The distinguished conformational substates composing the gates are labeled as 1′, 1″, 2′ and 2″.

Many studies performed in recent years indicate a rich stochastic dynamics of transitions between a multitude of conformational substates in native proteins [9, 10]. A slow character of this dynamics is the reason why the steady-state kinetics of biochemical processes involving protein enzymes cannot in general be described in terms of the conventional chemical kinetics, *i.e.* reaction rate constants. A more sophisticated language of mean first-passage times has to be used [10]. A technique was developed, enabling a calculation of the steady-state fluxes for systems of enzymatic reactions controlled and gated by an arbitrary type stochastic dynamics of the enzymatic complex [11]. Here we present the most important results of application of this technique to the actomyosin motor [11, 12].

On assuming a low fixed value of the ADP concentration, we can consider the ATP hydrolysis reaction as an irreversible unimolecular reaction ATP $\rightarrow$ P_i and replace the scheme shown in Fig. 1(c) by the one presented in Fig. 5(a) with R_1 = ATP, R_2 = P_i R_2 and P_2 denoting the actin filament before and after translation by a unit step, respectively. Fig. 5(b) shows an extended version of the model we consider. Shaded boxes represent the multitudes of conformational substates and transitions within the three main states of the motor: E_1 (the myosin-ADP complex strongly attached to the actin filament), M (the myosin-ATP or ADP·P_i complex weakly attached) and E_2 (the latter complex detached from the actin filament). All binding–rebinding reactions are assumed to be gated, *i.e.*, they take place only in certain distinguished conformational substates Notation used is the same as in the paper [12] and differs slightly from that in the paper [11].

4. Flux-force dependence

As said above, the motor is formally considered a chemochemical machine that enzymatically couples the two unimolecular reactions: the free energy-donating reaction 1 and the free energy-accepting reaction 2. The input and output fluxes J_i ($i = 1$ and 2, respectively) and the conjugate thermodynamic forces A_i are defined as

$$J_i = \frac{d[\mathrm{P}_i]/dt}{[\mathrm{E}]_0}, \qquad [\mathrm{E}]_0 \equiv [\mathrm{E}_1] + [\mathrm{M}] + [\mathrm{E}_2] \tag{1}$$

and (2)

$$\beta A_i = \ln K_i \frac{[\mathrm{R}_i]}{[\mathrm{P}_i]}, \qquad K_i \equiv \frac{[\mathrm{P}_i]^{\mathrm{eq}}}{[\mathrm{R}_i]^{\mathrm{eq}}}. \tag{3}$$

Here, symbols of the chemical compounds in square brackets denote the molar concentrations in the steady state (no superscript) or in the equilibrium (the superscript eq), and β is proportional to the reciprocal temperature, $\beta \equiv (k_{\mathrm{B}}T)^{-1}$, where k_{B} is the Boltzmann constant. Thermodynamic forces measure the distance from the equilibrium at which they vanish. The free energy transduction is realized if the product J_2A_2, representing the output power, is negative.

The flux-force dependence for the two coupled reactions has a general functional form [1]:

$$J_i = \frac{1 - e^{-\beta(A_i - A_i^{\mathrm{st}})}}{J_{+i}^{-1} + J_{-i}^{-1} e^{-\beta(A_i - A_i^{\mathrm{st}})}} [\mathrm{E}]_0 \tag{4}$$

($i = 1,\ 2$). The parameters J_{+i}, J_{-i} and A_i^{st} depend on another force and are determined by a particular kinetic scheme. A_i^{st} have a meaning of the

stalling forces, for which the fluxes J_i vanish: $J_i(A_i^{\rm st}) = 0$. The dependence $J_i(A_i)$ is strictly increasing with an inflection point and two asymptotes (Fig. 6). As noted earlier, free energy transduction takes place if one of the fluxes is of the opposite sign to its conjugate force. From Eq. (4) it follows that this condition holds when the corresponding stalling force $A_i^{\rm s}$ is negative. The dependence $J_i(A_i)$ in the range $A_i^{\rm st} \leq A_i \leq 0$ can be convex, concave or involving an inflection point as well. Fig. 6 clearly shows that the Onsager linear approximation of nonequilibrium thermodynamics cannot describe properly the action of biological molecular machines.

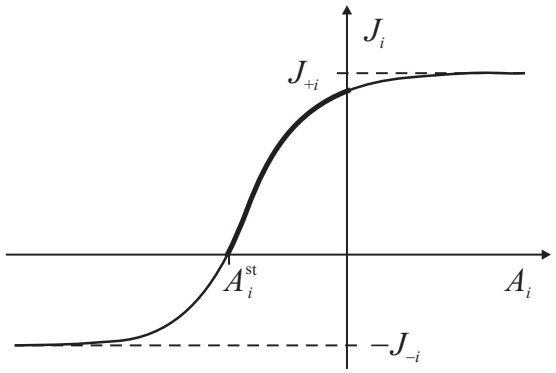

Fig. 6. Character of the functional dependence of the output flux J_i *versus* force A_i. Only when the stalling force $A_i^{\rm st}$ is negative, does free energy transduction take place. The $J_i(A_i)$ dependence in this range is marked with the bold line

For the actomyosin motor, it is reaction 2 that accepts the free energy. The $J_2(A_2)$ dependence is concave [7] which means that $J_{-2} \ll J_{+2}$. In such a case, Eq. (4) for J_2 can be simplified to a form [12]

$$J_2 = J_{-2}\, e^{-\beta A_2^{\rm st}} \left(e^{\beta A_2} - e^{\beta A_2^{\rm st}} \right) . \tag{5}$$

The efficiency of the machine is the ratio $-J_2A_2/J_1A_1$ of the output power to the input power. In general, the flux J_2 can differ from the flux J_1. Using the technique described in Ref. [11], we calculated in a reasonable approximation the ratio of both fluxes to be

$$\frac{J_2}{J_1} = \frac{\tau_{\rm M}(1'' \leftrightarrow \{1', 2''\})}{\tau_{\rm M}(2' \leftrightarrow \{1'', 2''\})} \left(e^{\beta A_2} - e^{\beta A_2^{\rm st}} \right) . \tag{6}$$

Above, $\tau_{\rm M}(1'' \leftrightarrow \{1', 2''\})$ denotes the mean first-passage time in the state M from the substate $1''$ to $1'$ or $2''$ and back and $\tau_{\rm M}(2' \leftrightarrow \{1'', 2''\})$ denotes the mean first-passage time from the substate $2'$ to $1''$ or $2''$ and back.

The difference of two exponentials in the brackets defines a slippage of both reaction cycles whereas the ratio of the two mean first-passage times, independent of the external force, can be accounted a transmission coefficient. It represents the number of steps the myosin head can travel without slippage per one ATP molecule hydrolyzed. Until recently, almost commonly accepted supposition was that only one movement can be made per each ATP molecule consumed [7]. It seemed to be well grounded on the single myosin molecule motility assays [13]. However, a new instrumentation of higher resolution convincingly indicates that each movement consists of several shorter regular steps. The step size depends on a geometry of the experiment and can equal either 5.5 nm (the actin molecule diameter) [14] or 2.7 nm (the monomeric repeat along the actin filament) [15]. As a mean distance of a single movement in the motility assays equals about 10 nm [13,14], some 2 to 4 steps are made on average per each ATP molecule consumed.

Probably, sliding in several steps per one ATP molecule hydrolyzed takes also place in an assembly of the actomyosin motors organized in the myofibril. To evaluate the step size in this case let us realize that the flux J_2 multiplied by the step size d equals the shortening velocity v of the myofibril. The motion of myofibrillar actin filaments is overdamped thus, under zero external load, $v = F/\zeta$ where F is the force the myosin heads exert on the actin filaments and ζ is a friction coefficient. F is proportional to the number of the myosin heads strongly attached to the actin filaments whereas ζ is proportional to the number of the myosin heads weakly attached [16]. Like F, also the ATPase flux J_1 is proportional to the number of the myosin heads strongly attached. A consequence of the ratio J_2/J_1 constancy and the reasoning described above is that the step size d should be inversely proportional to the number of the myosin heads weakly attached to the actin filaments. This number varies during the unloaded myofibrillar shortening and is smaller at the beginning and larger at the end of contraction, what results from increasing overlap between the myosin and actin filaments. It explains experimental ascertainments that the total ATP consumed during unloaded myofibril contraction is independent of the initial sarcomere length and that the total myofibrillar ATPase does not vary in time [17]. The shortest sliding distance per one ATP molecule consumed equals about 270 nm at 4°C [17] which is the sevenfold multiplicity of the actin filament period 36 nm that can be considered an elementary step distance for the myofibril. It should be noted that the sliding distance strongly depends on temperature [18].

To conclude, there is stronger and stronger experimental evidence that the actomyosin motor makes several steps per one ATP molecule hydrolyzed. Eq. (6) is able to describe this fact provided that the ratio of the two mean first-passage times included in it is several times larger than unity. The

long mean first-passage time $\tau_{\mathrm{M}}(1'' \leftrightarrow \{1', 2''\})$ can be explained by the necessity of melting and recrystallization of the SH1-SH2 helix [8] during a transition from the substate $1''$ and back in the state M, *cf.* Fig. 3(b). The relatively short mean first-passage time $\tau_{\mathrm{M}}(2'' \leftrightarrow \{1'', 2'\})$ is the reason why, before coming back to the strongly attached state E_1, the myosin head can stochastically undergo several mechanical cycles through the detached state E_2.

This result is very important. It can help to answer a still open question about the origin of the free energy for the directed motor motion [7]: one-step conformational changes or a thermal ratchet-type mechanism? The power stroke, being the source of the force the myosin head exerts on the actin filament, takes place in the strongly-attached state E_1. A diffusive motion of the myosin head with respect to the actin filament takes place in the detached state E_2. Eq. (6) implies that neither details of the dynamics in E_1 [2,19] nor in E_2 [20,21] are important for the action of the actomyosin motor. Essential is the dynamics in M. This result is a far reminiscent of Huxley's idea [22] of a thermal ratchet in the intramolecular dynamics.

5. Concluding remarks

The stochastic model of the actomyosin motor action presented in the last section is consistent with all presently available experimental data [11, 12]. However, it is only phenomenology. A challenge for theorists is to fill the interiors of the shaded boxes with simple but adequate models of conformational transition dynamics that afford possibilities for calculating appropriate mean first-passage times.

The dynamics both in E_1 and E_2 can be reasonably approximated by a biased one-dimensional diffusion [2,19–21] described, in the continuous limit, by a simple Langevin equation. However, the dynamics in M is certainly not a one-dimensional diffusion. Presumably, it should involve diffusion on fractal lattices [23] which has been demonstrated to be a reasonable model of the protein's intramolecular dynamics [24]. On such a dynamical background the melting of SH1-SH2 helix should be described. Here, an experience with the protein folding dynamics can be helpful. An open question remains importance of nonadiabatic energy transfer, a phenomenon analogous to nonadiabatic electron and proton transfer in cytochrome bc_1.

REFERENCES

[1] M. Kurzyński, *The Thermodynamic Machinery of Life*, Springer, Heidelberg 2005 (in press).

[2] T. L. Hill, *Free Energy Transduction and Biochemical Cycle Kinetics*, Springer, New York 1989.

[3] E. Darrouzet, C.C. Moser, P.L. Dutton, F. Daidal, *Trends Biochem. Sci.* **26**, 445 (2001).

[4] Y.Z. Ma, E.W. Taylor, *Biophys. J.* **66**, 1542 (1994).

[5] A.R. Crofts, E.A. Berry, *Curr. Opin. Cell Biol.* **8**, 501 (1998).

[6] Z. Zhang *et al.*, *Nature* **392**, 677 (1998).

[7] J. Howard, *Mechanics of Motor Proteins and the Cytoskeleton*, Sinauer Associates, Sunderland 2001.

[8] N. Volkmann, D. Hanein, *Curr. Opin. Cell Biol.* **12**, 26 (2000).

[9] H. Frauenfelder, P.G. Wolynes, R.H. Austin, *Rev. Mod. Phys.* **71**, S419 (1999).

[10] M. Kurzyński, *Prog. Biophys. Molec. Biol.* **69**, 23 (1998).

[11] M. Kurzyński, P. Chełminiak, *J. Stat. Phys.* **110**, 137 (2003).

[12] M. Kurzyński, P. Chełminiak, *Physica A* **336**, 123 (2004).

[13] J.T. Finer, R.M. Simmons, J.A. Spudich, *Nature* **368**, 113 (1994).

[14] K. Kitamura, M. Tokunaga, A.H. Iwane, T. Yanagida, *Nature* **397**, 129 (1999).

[15] X. Liu, G.H. Pollack, *Biophys. J.* **86**, 353 (2004).

[16] R. Stehle, B. Brenner, *Biophys. J.* **78**, 1458 (2000).

[17] C. Lionne, F. Travers, T. Barman, *Biophys. J.* **70**, 887 (1996).

[18] R. Candau, B. Iorga, F. Travers, T. Barman, C. Lionne, *Biophys. J.* **85**, 3132 (2003).

[19] T.A. Duke, *Proc. Natl. Acad. Sci. USA* **96**, 2770 (1999).

[20] R.D. Astumian, *Science* **276**, 917 (1997).

[21] F. Jülicher, A. Ajdari, J. Prost, *Rev. Mod. Phys.* **69**, 1269 (1997).

[22] A. F. Huxley, *Prog. Biophys. Molec. Biol.* **7**, 255 (1957).

[23] P. Chełminiak, M. Kurzyński, *Physica A* **342**, 507 (2004).

[24] M. Kurzyński, K. Palacz, P. Chełminiak, *Proc. Natl. Acad. Sci. USA* **95**, 11685 (1998).