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Eur. Phys. J. E **032**, 411–418 (2010) DOI: 10.1140/epje/i2010-10641-0

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L. Marcucci and L. Truskinovsky

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THE EUROPEAN PHYSICAL JOURNAL E

Regular Article

Muscle contraction: A mechanical perspective

L. Marcucci[a] and L. Truskinovsky

Laboratoire de Mechanique des Solides, CNRS-UMR 7649, Ecole Polytechnique, 91128, Palaiseau, France

Received 6 February 2010 and Received in final form 7 June 2010
Published online: 7 September 2010 –

Abstract. In this paper we present a purely mechanical analog of the conventional chemo-mechanical modeling of muscle contraction. We abandon the description of kinetics of the power stroke in terms of jump processes and instead resolve the continuous stochastic evolution on an appropriate energy landscape. In general physical terms, we replace *hard spin* chemical variables by *soft spin* variables representing mechanical snap-springs. This allows us to treat the case of small and even disappearing barriers and, more importantly, to incorporate the mechanical representation of the power stroke into the theory of Brownian ratchets. The model provides the simplest non-chemical description for the main stages of the biochemical Lymn-Taylor cycle and may be used as a basis for the artificial micro-mechanical reproduction of the muscle contraction mechanism.

1 Introduction

The sliding-filament hypothesis [1–3] assumes that during contraction actin filaments move past myosin filaments while actively interacting with them through myosin heads known also as cross-bridges. The interaction is powered by the hydrolysis of ATP and the motor part of the myosin head acts as an enzyme which, simultaneously, increases the hydrolysis reaction rate and converts the released chemical energy into useful work. The whole system remains in permanent disequilibrium because the chemical potentials of the reactant (ATP) and the products of the hydrolysis reaction (ADP and P) are kept out of balance by a steadily operating exterior mechanism (*e.g.* [4–6]). From an engineering point of view, it is of interest to understand how the energy input due to a non-equilibrium chemical reaction and a random thermal noise are incorporated in this ingenious design to produce a highly efficient force-producing machinery. A purely mechanical model of an attached cross-bridge has been recently introduced in [7]. Here we develop this model further by including also the description of attachment-detachment process.

A simplified four-state biochemical scheme of the cross-bridge cycle, known as Lymn-Taylor model [3], contains the description of the most important chemical states involved in muscle contraction. These states, commonly known by their chemical compositions as M-ATP, A-M-ADP-P, AM-ADP and AM, can be associated with particular *mechanical* configurations of the globular region. The Lymn-Taylor model assumes that when attached to actin, each myosin head uses stored potential energy to stretch (or move) the actin filament through a rotation of the lever arm representing the terminal part of the myosin head (power stroke). The underlying conformational change, advancing the system from the pre-power-stroke state to the post-power-stroke state, is assumed to be related to a chemical transition A-M-ADP-P → AM. To return in its original pre-power-stroke configuration the head needs to split an ATP molecule. In the process, it first detaches from the actin filament (chemical transition AM → M-ATP) and then uses the energy of hydrolysis to recharge (reprime) the power stroke mechanism and to bind a new active site on the actin filament (chemical transition M-ATP → A-M-ADP-P). Subsequently, the whole process repeats itself (*e.g.*, [5, 8–10]).

The chemo-mechanical approaches to muscle contraction were developed to complement purely biochemical schemes. They mostly follow the ideas first proposed in the classical papers [11, 12] that can be seen as complementary since the first paper describes the attachment-detachment process and the events related to the slow time scale (hundreds of milliseconds), while the second paper deals with the power stroke and the events related to the fast time scale (milliseconds). There have been a considerable number of attempts to extend (*e.g.* [8, 13–16]) and to unify these two types of models (*e.g.* [6, 15, 17–24]). In the chemo-mechanical framework, muscle contraction is modeled as a set of reactions among discrete chemical states of a motor molecule. These states form a network describing, on one side, various chemical compositions of the catalytic domain and, on the other side, different mechanical configurations of the myosin head. A variety of crystallographically identified configurations (attached

[a] *Present address:* Graduate School of Frontier Biosciences, Osaka University, 1-3 Yamadaoka, Suita, Osaka 565-0871 Japan; e-mail: lorenzo.marcucci@gmail.com

and detached [11], strongly and weakly attached [25], pre and post power stroke [12], associated with the first or second myosin head [26], etc.) are then identified with particular sites of the chemical network.

The mechanics enters the chemical models through phenomenological assumptions regarding the dependence of the chemical rate constants on a single continuous variable characterizing the state of the force-generating spring. It is implied that the discrete chemical states are replaced by one-parametric configurational spaces. The functional freedom remaining in these models after the local conditions of detailed balance are fulfilled originates from the lack of information about the energy barriers separating different states. In the chemo-mechanical models this freedom is used to fit the experimental curves and therefore the best of these models reproduce available data quite well. However, such approach gives only limited insight regarding the actual micro-mechanical functioning of the force-generating mechanism (*e.g.* [24] and references therein).

The development of the theory of Brownian motors which are fundamentally involved in muscle contraction, has followed a more mechanically explicit path (*e.g.* [27–34]). In this class of models the motion of the myosin II is typically represented as a biased diffusion of a particle on a periodic asymmetric potential subjected to a colored noise. The white component of the noise reflects the presence of a heat reservoir while the correlated component mimics the non-equilibrium chemical environment. A direct application of these models to muscle can be found in the papers [21, 35, 36] that are focussed on the attachment-detachment process at the expense of the analysis of the short time scales, requiring a detailed description of the power stroke. Such reduced models collapse the four-state Lymn-Taylor cycle onto a two-state cycle by absorbing the configurational changes associated with the transitions M-ATP $\rightarrow$ A-M-ADP-P and AM $\rightarrow$ M-ATP into more general transitions M-ATP $\rightarrow$ AM-ADP and AM-ADP $\rightarrow$ M-ATP. On the mechanical level the complexity of the structure of the myosin head is once again reduced to a single degree of freedom representing a stretch of a series elastic spring.

Despite the unquestionable heuristic value of such minimal models, the crystallographic reconstructions suggest that the myosin head is formed by at least two irreducible domains which act in synchrony to generate force. Thus, in the classical lever arm theory, the myosin is divided into a motor or catalytic domain (CD), which contains the actin binding site together with the ATP binding pocket. This domain is attached to the actin filament during the power stroke. The power stroke is generated by the combined action of the converter region, which ensures rotation (in the range of 70 degrees), and the long terminal part of the myosin head, which amplifies the rotation acting as a lever arm and causing the relative motion of the two filaments. Since the lever is formed of a heavy chain helix which carries two light chains, it is sometimes called light chain domain [5, 37, 38]. Mechanically, the converter and the lever arm can be seen as one bi-stable molecular complex and in what follows we refer to it as the "snap-spring" (SS) [7]. Notice that most of the converter related activity (associated with a millisecond time scales) is lost in the Brownian ratchet theories where the SS domain and the CD domain are usually combined into one collective variable which represents the motor location on the actin filament.

In this paper we argue, following [17, 39], that in order to deal simultaneously with the *fast* time scale response, which implies an almost mechanical discharge of a power stroke mechanism [12], and the *slow* time scale isometric contractions, necessarily implying the attachment-detachment cycle [40], the minimal theory must operate with at least *two* non-trivial mechanical degrees of freedom describing separately the state of the CD and the state of the SS. The CD related internal variable, responsible for the attachment-detachment process, should be exposed to a periodic asymmetric potential generated by the actin filament. On the contrary, the SS related variable, responsible for the power stroke, is expected to see a bi-stable energy landscape. In addition to these two degrees of freedom one also needs a trivial mechanical variable describing a series elastic spring. This spring creates micro-metastability (see [7]) and allows one to bridge the cases of isotonic (soft device) and isometric (hard device) contractions.

Following these heuristic ideas, we develop in the present paper a minimal purely mechanical analog of the conventional chemo-mechanical approach. To achieve uniformity of the mathematical language we abandon the Huxley-Simmons–type description of kinetics of the power stroke in terms of a jump process and instead attempt to resolve the continuous stochastic evolution on an appropriate energy landscape. In general physical terms, we replace a conventional description of the active-force–generating system in terms of *hard* spin variables (indicating different mechanical states in the chemical approach) by a fully mechanical description in terms of *soft* spin variables imitating bi-stable snap-springs. This allows us to treat the cases of small and even disappearing barriers which are not amenable to classical Kramers theory [41] and, more importantly, to incorporate seamlessly the mechanical representation of the power stroke into the theory of Brownian ratchets (see other advances in the same direction in [6, 21–23, 42]).

To represent all three main collective variables characterizing skeletal Myosin II —position of the motor domain, configuration of the lever domain and the stretch state of the series elastic element— we use three continuous coordinates and project a more general MD picture into the stochastic Langevin dynamics on a three-dimensional phase space. For determinacy and mechanical transparency we utilize a particular representation of the Brownian ratchet proposed by Magnasco [29, 43–45]. Although this ratchet has low efficiency due to considerable diffusion which accompanies the drift, it has unambiguous mechanical meaning. We expect that other ratchet models could also be used as the building blocks of similar mechanical models (*e.g.* [33–35]).

The paper is organized as follows. In sect. 2 we introduce the system of stochastic ordinary differential

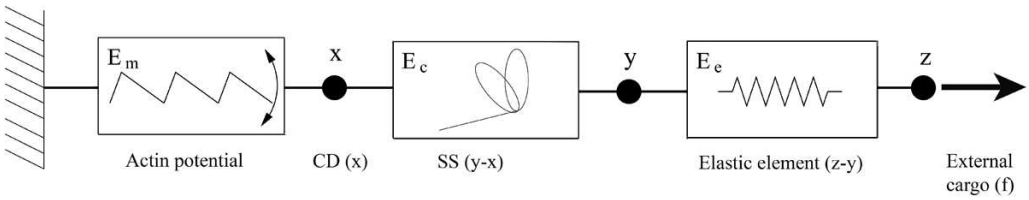

Fig. 1. The mechanical representation of a cross-bridge as a series connection of a linear elastic element E_e, a bi-stable snap-spring E_c and a Brownian ratchet E_m.

equations describing the behavior of N cross-bridges posed in parallel. The parameter selection and scaling are discussed in sect. 3. In sect. 4 we simulate the behavior of an effective sarcomere and show that the model can successfully reproduce the observed mechanical response of the muscle fiber to sudden length and force increments and produces a realistic force-velocity curve. In sect. 5 we focus on the detailed description of the sequence of mechanical processes behind isotonic contractions. The final sect. 6 contains our conclusions.

2 The model

We view a half-sarcomere as a parallel connection of N cross-bridges. Each cross-bridge is represented as a chain containing a linear elastic spring, which generates the force, a bi-stable contractile element, responsible for the power stroke (SS), and a molecular motor representing the ATP regulated attachment-detachment process (CD) (see fig. 1). As in [35], each cross-bridge is attached to a common rigid backbone (thick filament), however, we substitute the rigid links adopted in [35] with the bi-stable snap-springs. The system is loaded either by a given force f representing a cargo or is constrained by the fixed displacement of the backbone.

The elastic energy of the linear spring can be written as

$$E_e(\epsilon_e) = \frac{1}{2}K(\epsilon_e - l)^2, \tag{1}$$

where ϵ_e is the deformed length, K is the elastic modulus and l is the reference length characterizing the pre-strain. The energy of the bi-stable lever arm mechanism (light chain domain or SS) is assumed to be piece-wise quadratic

$$E_c(\epsilon_c) = \begin{cases} \frac{1}{2}k_1(\epsilon_c)^2, & \epsilon_c \geq b_1, \\ -\frac{1}{2}k_3(\epsilon_c - b)^2 + c, & b_2 \leq \epsilon_c < b_1, \\ \frac{1}{2}k_2(\epsilon_c - a)^2 + d, & \epsilon_c < b_2, \end{cases} \tag{2}$$

where ϵ_c is the elongation, k_i, $i = 1, 2$ are the curvatures of the distinct energy wells representing pre-power-stroke and post-power-stroke configurations, respectively; $a < 0$ is the characteristic size of the power stroke. The driving force d sets the bias towards the post-power-stroke state and is somewhat arbitrarily chosen to ensure that the two wells have the same energy in the isometric contraction. The energy barrier is characterized by the position b, the height c and the curvature k_3 of the maximum. The values of parameters b_1 and b_2 are chosen from the condition of continuity of the energy function.

We model the catalytic domain (CD) as the Brownian ratchet of Magnasco type [29]. It can be viewed as a particle moving in an asymmetric periodic potential and subjected to a correlated noise. The periodic potential is assumed to be piece-wise linear in each period n

$$E_m(\epsilon_m) = \begin{cases} \frac{Q}{\lambda_1 L}(\epsilon_m - nL), & 0 < \epsilon_m - nL < \lambda_1 L, \\ \frac{Q}{\lambda_2} - \frac{Q}{\lambda_2 L}(\epsilon_m - nL), & \lambda_1 L < \epsilon_m - nL < L, \end{cases} \tag{3}$$

where Q is the amplitude, L is the period, $\lambda_1 - \lambda_2$ is the measure of the asymmetry of the potential and $\lambda_1 + \lambda_2 = 1$. The variable ϵ_m indicates the location of a particle in the periodic energy landscape: by our convention it is *attached* if it is close to one of the minima and is *detached* if it is close to one of the maxima.

It is convenient to identify the coordinates of the nod points on fig. 1 as x, y and z, implying that $\epsilon_m = x$, $\epsilon_c = y - x$ and $\epsilon_e = z - y$. Using these notations the system of N cross-bridges connected in parallel can be described by the set of Langevin equations

$$\begin{cases} \eta_x \dot{x}_i = -E_m'(x_i) + E_c'(y_i - x_i) + F(t + t_i) + \sqrt{\eta_x k_B \theta}\Gamma(t), \\ \eta_y \dot{y}_i = -E_c'(y_i - x_i) - K(y_i - z - l_i) + \sqrt{\eta_y k_B \theta}\Gamma(t), \\ \eta_z \dot{z} = \sum_{i=1}^{N} K(y_i - z - l_i) + f + \sqrt{\eta_z k_B \theta}\Gamma(t). \end{cases} \tag{4}$$

Here the random term $\Gamma(t)$, representing thermal fluctuations, has the standard properties

$$\langle \Gamma(t_1) \rangle = 0, \qquad \langle \Gamma(t_1)\Gamma(t_2) \rangle = 2\delta(t_1 - t_2),$$

where θ is the temperature and k_B is the Boltzmann constant. All elements experience viscous resistance characterized by the corresponding drag coefficients η_x, η_y, η_z. The correlated component of the noise $F(t)$, imitating the activity of the ATP, is assumed to be periodic and piecewise constant

$$F(t) = \begin{cases} +A, & 0 < t - mT < T, \\ -A, & T < t - mT < 2T. \end{cases} \tag{5}$$

$m = 0, 2, 4, \ldots$, where A is the amplitude and $2T$ is the period.

Since the ATP activity at different sites is expected to occur independently, we introduced temporal de-synchronization in (4) through the phase shift parameters t_i. We assume t_i as independent random variables uniformly distributed in the interval $[0, 2T]$. Following [18] we also assume that the pre-strains l_i are different for different i which introduces spatial de-synchronization. Again, we assume that l_i are independent random variables that are now uniformly distributed in the intervals $[iL - a/2,\ iL + a/2]$. Such temporal and spatial desynchronization eliminates spontaneous oscillations that were observed in muscles under some special conditions (*e.g.* [46]) and later explained in the collective Brownian ratchet framework by introducing chemo-mechanical feedback effects [47].

3 Normalization and parameter selection

To obtain quantitative predictions, we need first to non-dimensionalize the system of equations (4). For normalization we choose the (power-stroke–related) length scale a and the (viscosity related) time scale $\tau = a^2\eta_y/(k_B\theta)$. It is also natural to choose the energy scale $k_B\theta$ and the force scale $k_B\theta/a$. The dimensionless system depends on several non-dimensional parameters which fully define its qualitative behavior.

Knowing that $K \sim 2\,\mathrm{pN/nm}$, $a \sim 8\,\mathrm{nm}$ and $k_B\theta \sim 4\,\mathrm{pN/nm}$ (*e.g.* [5]), we put for the main measure of elasticity the value $Ka^2/k_B\theta = 32$; the values of relative elasticities of the two conformations $k_1/K = 5$, $k_2/K = 2$ then guarantee that we can reproduce the linear regimes in the T_1 and T_2 data. The last elastic parameter $k_3/K = 2.45$, defining the energy barrier for the power stroke, was chosen to ensure the appropriate rate of fast force recovery relatively to the rate of slower movement of the CD controlled by parameter Q (see below). The assumptions $b/a = -0.247$ and $c/a = 1.61$ make the barrier between the two energy wells sufficiently localized to exclude its interference with the equilibrium behavior associated with the two energy minima. We have chosen the value $\eta_x/\eta_y = 10$ to make the process of detachment and reattachment of the myosin head sufficiently slower than the power stroke. The parameter $\eta_z/\eta_y = 100$ describes even slower movement of the backbone.

The period of the actin potential L was taken to be twice as large as the characteristic amplitude of the power stroke $L/a = 2$. It implies a much longer distance traversed by the CD in the attachment-detachment process comparing to the characteristic amplitude of the power stroke. This assumption is crucial for the possibility of a purely mechanical recharge of the power stroke mechanism and at this stage of the schematization, we did not attempt to link it with the actual geometry of the actin and myosin molecules.

The normalized period of the external force imitating the ATP hydrolysis $T/\tau = 2\ 10^4$ was chosen to ensure sufficient number of tilting oscillations in the ratchet between two attachment-detachment events. We fixed the asymmetry parameter at $\lambda_1 = 0.3$. To speed up numerical experiments we artificially increased the rate of the processes reducing the energy barrier and choosing $Q/(k_B\theta) = 60$. For the ATP-related force amplitude we assumed the value $A = 1.4\ Q/(1 - \lambda_1)L$ between the minimal and the maximal values of the force generated by the asymmetric potential. Given the size of the energy barrier in the power stroke mechanism, the above "accelerating" assumptions do not affect the normalized curves $T(\delta)$ and $V(t)$.

We studied the system (4) numerically by using the simplest Euler discretization of the Langevin equations. We assumed that $N = 2000$ implying that experimental data are obtained for many sarcomeres working in unison. The dimensionless time scale of discretization $5\ 10^{-5}$ was chosen to be below the smallest physical time scale in the model.

4 Length clamp and force clamp experiments

The mechanical behavior of the contracting muscle in the short time scale (milliseconds) revealing the quasi-mechanical nature of the power stroke mechanism was first studied in [12] and our model allows one to reproduce numerically these classical length clamp experiments. In the simulations we applied to the backbone z a sudden increment of length δ at time t. The increments varied in the interval $[-1.4a,\ 0.1a]$ and the force generated by the system was evaluated from

$$T(t) = \sum_{i=1}^{N} K(y_i(t) - z(t) - l_i). \tag{6}$$

The normalized response curves $T(t)$ (see fig. 2), closely resemble the experimentally observed behavior (*e.g.*, [12]). Thus, in the first few microseconds after the application of the displacement increment one observes an elastic response usually denoted by $T_1(\delta)$, which is followed by a recovery of the initial value of the isometric force (T_0). Between $T_1(\delta)$ and T_0 one can distinguish a plateau, known as $T_2(\delta)$. The simulated functions $T_1(\delta)$ and $T_2(\delta)$, shown in fig. 3, quantitatively agree with experimental observations (experimental points from [48] normalized for $a = 8\,\mathrm{nm}$), including the prediction of a pronounced softening region around $\delta = 0$.

A particularly important prediction concerns the difference in slopes of the linear segments of the curves $T_1(\delta)$ and $T_2(\delta)$ at large values of the applied shortening. Such divergence of the two curves agrees well with recent precise measurements [48] and indicates the sensitivity of the amplitude of the power stroke to the value of the applied force. We stress that this effect, which is due to the different curvatures of the two wells in the power stroke potential E_c, cannot be obtained in the hard spin model with only two chemical states.

In another typical experiment, illustrating the mechanical response of skeletal muscles, one records the velocity of contraction at different external loads (*e.g.* [40]). It is known that a myofibril contracting against a constant load lower than T_0, assumes, after a transient related to the

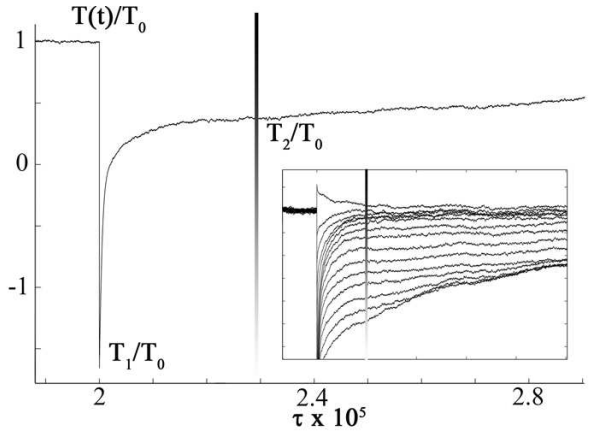

Fig. 2. Force *versus* time response curve for $\delta = -1.1a$. The value of T_2 is obtained by averaging in the dashed column. The insert shows the functions $T(\tau)$ at different values of δ (see also fig. 3).

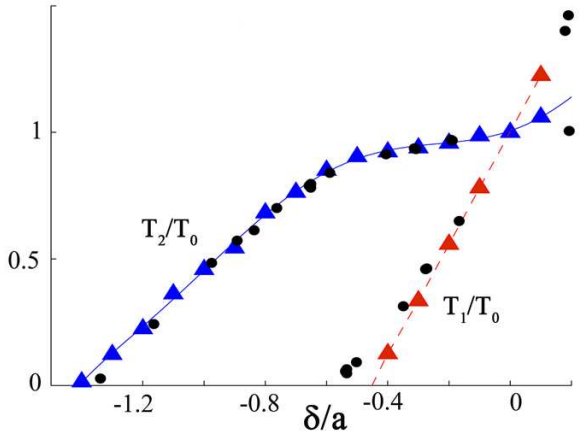

Fig. 3. Triangles: the values of T_1 and T_2 generated from the force trajectories shown in fig. 2. Dots: experimental data from [48] scaled with $a = 8\,\mathrm{nm}$.

synchronization of the power strokes [48], a constant velocity. To analyze the force-velocity behavior in our model we impose an external force f and study the behavior of the backbone coordinate. The typical $z(t)$ curves are shown in the insert in fig. 4, for the values of f ranging from $0.8\,T_0$ to zero. The general structure of the normalized force-velocity curve, shown in fig. 4, agrees reasonably well with the experimental data reported in the figure from [48].

5 Mechanical phenomena behind isotonic contractions

In this section we study the details of the mechanical functioning of the model at different time scales by looking more closely at the case of isotonic contraction against a fixed load.

To interpret correctly the behavior of the individual mechanical units we first fix the parameter $z = 0$ and write the total energy of an attached cross-bridge as a

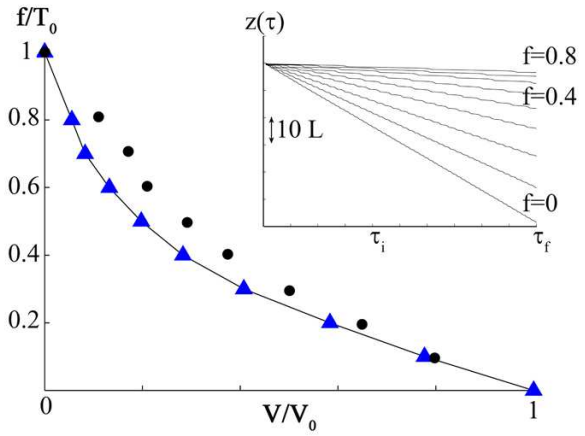

Fig. 4. Force-velocity curve generated by the model (triangles) compared to the experimental points (dots). The triangles are obtained from the trajectories $z(t)$ corresponding to different values of f (see the insert). The velocity of shortening is computed as $(z(t_f) - z(t_i))/(t_f - t_i)$ and normalized to V_0. The experimental points are obtained from [48].

function of two remaining mechanical variables y and x:

$$E_t(x, y) = E_m(x) + E_c(y - x) + E_e(-y). \qquad (7)$$

The corresponding energy landscape is shown in fig. 5. Here the upper two local minima A and B indicate the pre-power-stroke and the post-power-stroke configurations of an attached motor, respectively. The two lower local minima A' and B' correspond to the pre-power-stroke and the post-power-stroke configurations of a motor that has shifted to a new attached position on actin potential. We associate the detached state with an unstable position around the maximum separating the minima (A, B) and (A', B'). One can see that the system cannot remain in a detached position without an appropriate stimulation.

Using fig. 5 we can visualize the combined working of the power stroke and the attachment-detachment mechanism. Suppose that the upper right minimum A corresponds to the initial pre-power-stroke configuration with the attached portion of the head fixed in the first preferred site on the actin filament. In this state the system can lower the energy by rotating the lever arm and reaching the post-power-stroke configuration B. This process does not require the energy supply from outside and can be viewed as a purely mechanical relaxation.

Suppose next that external stimulation, representing the ATP activity, can shift variable x towards smaller values (transition $B \to B'$). If the corresponding ratchet is sufficiently strong it can simultaneously advance the representative point on fig. 5 further into the pre-power-stroke position corresponding to the point A'. The new transition $B \to A'$ would then mean mechanical recharging of the power stroke mechanism in the course of transition to the next preferred actin site. If in the meanwhile the muscle shortens, making the power stroke again energetically preferable, the process can be potentially repeated again starting with a mechanical relaxation $A' \to B'$. In fig. 6 we

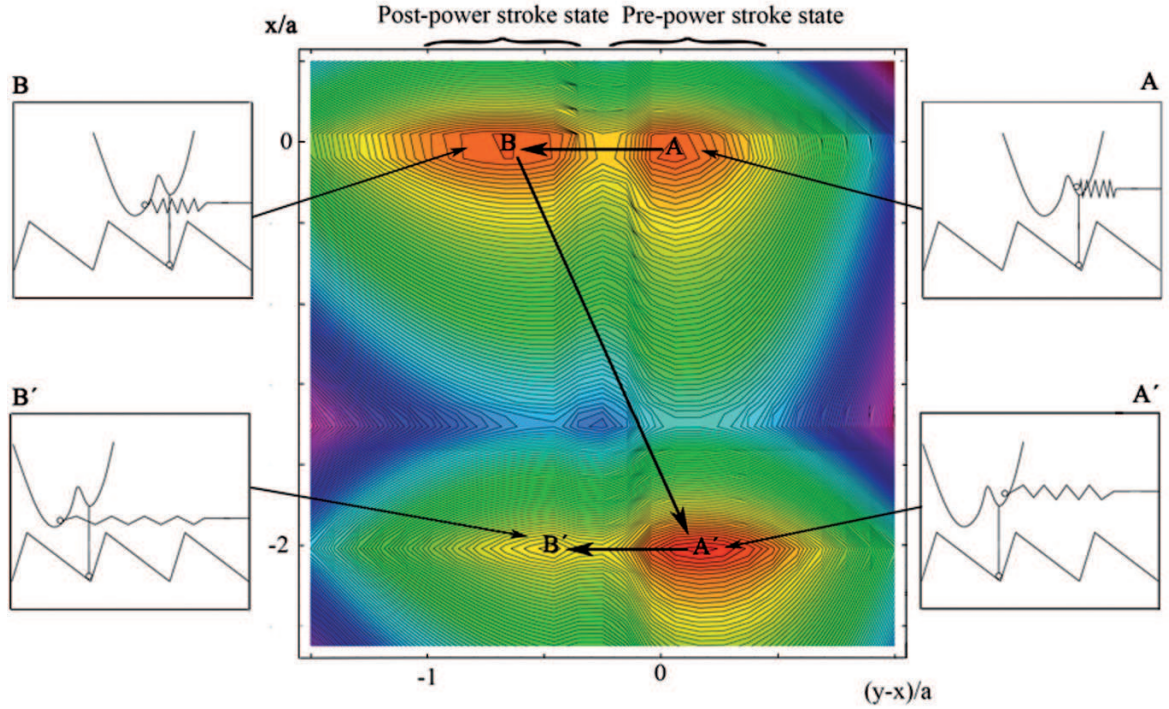

Fig. 5. Contour plot of the effective energy $E_t(x, y; z_0)$ at $z_0 = 0$. Inserts illustrate the states of various mechanical subunits.

show that this scenario indeed takes place in our numerical simulations when we reproduce load clamp experiment at $f = 0.5\ T_0$.

From fig. 6 one can see that the CD of an individual head, x, goes through three different attachment positions (see fig. 6a). In fig. 6b we show the time history of the variable $x - y$ characterizing the internal configuration of a given head (SS) during the cycle. The first vertical line shows the moment in which the power stroke $A \to B$ takes place. The second vertical line shows the motion of the attached portion from the active site i on the actin filament to the next site $i' = i+1$ corresponding to the transition $B \to A'$. This motion induces a change of state in the bi-stable element which brings the lever arm into the pre-power-stroke position. Due to the evolution of the variable z (isotonic contraction, see fig. 6d) the elastic element whose configuration can be read in fig. 6c, relaxes and the post-power-stroke minimum B' becomes preferable. The third vertical line shows the moment in which the new power stroke $A' \to B'$ takes place. Then the cross-bridge cycle starts again.

Observe that the position of the backbone can be considered constant during the recharging of the power stroke. In this situation, the key factor for the possibility of recharging (after the variable x has overcome the barrier in the periodic potential) is that the total energy $E_t(x, y)$ has a minimum when SS is in the pre-power-stroke state. This is true providing $(Q/(k_B\theta))/(\lambda L) > d/a$ which places an important constraint on the choice of parameters.

One can see that the model is able to qualitatively reproduce some of the elementary steps of the basic cross-bridge cycle. Thus, the fast power stroke of the head stretches the elastic element which in turn pulls the myosin backbone and causes contraction. In the meantime a slower process allows the myosin head to come back to the pre-power-stroke state (recharge), leaving the tension in elastic element almost constant. Finally, due to the motion of the myosin backbone, the head becomes capable of producing another power stroke and the cycle repeats itself. We observe that the power stroke recharges at exactly the same times when the main force producing motor is detached. This suggests that the important role of the power stroke in this cycle is to *smoothen* the functioning of the force-generating mechanism.

A direct comparison of the simulated mechanical cycle with the conventional Lymn-Taylor cycle shows that while the two attached configurations are represented by the model rather faithfully, the detached configurations appear only as transients. In fact, one can see that our (slow) transition $B \to A'$ represents a combined description of the detachment, of the power stroke recharge and then of another attachment. In the biochemical cycle such a transition would be described by at least two distinct chemical states. To achieve such splitting in the framework of our model one would need to have a more adequate representation for the detached state. More specifically, an assumed simple passing through a single energy barrier may be in reality a complex series of events which include different stages along the way towards the final change in the attachment position and the recovery of the power stroke. This suggests the necessity of an additional fine structure of the areas near maxima of the actin potential.

The reasons for the observed discrepancies between mechanical and chemical cycles may also lay deeper.

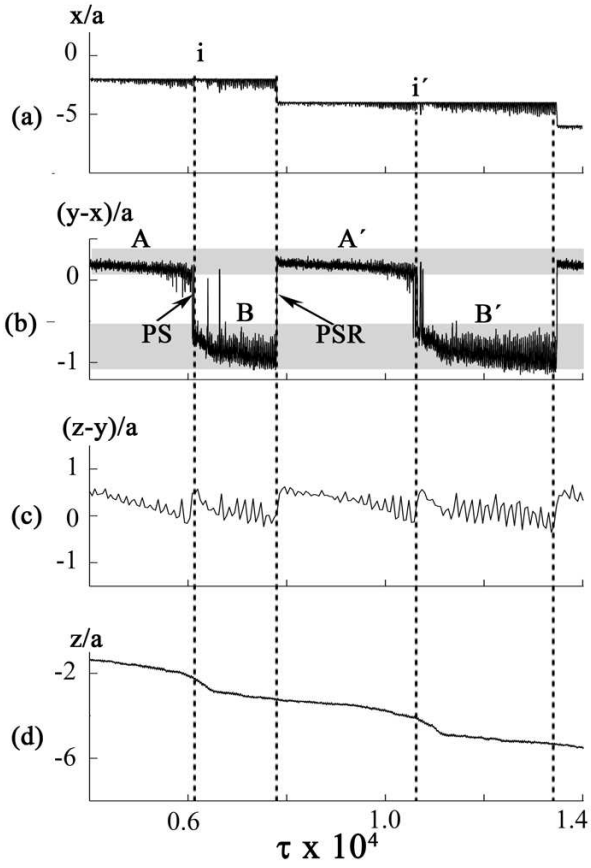

Fig. 6. The numerical simulation of the time histories for different mechanical units in a load clamp simulation at zero external force: (a) the behavior of the CD; (b) the behavior of the SS; (c) the behavior of the elastic element; (d) the total displacement of the thick backbone.

Recall, for instance, the implicit assumption in all chemo-mechanical models that the ATP energy can be decomposed into two parts. One part drives the attachment-detachment process by sustaining the out-of-equilibrium transition rates (*e.g.* [32]). The remaining part ensures the recovery of the power stroke and our model provides a simple mechanism of how it may be working: the power stroke is mechanically recharged in the course of the change of the attached position of the CD. It is clear, however, that the effect of the ATP hydrolysis may not be fully reducible to the periodic rocking of the actin potential. For instance, the ATP-induced mechanical signal may also affect the bi-stable potential and this will considerably change the structure of the effective cycle.

6 Concluding remarks

In this paper we argue that a mechanical approach to muscle contraction, initiated by the theory of Brownian ratchets, offers certain important advantages comparing to the purely biochemical approach. First, it allows one to deal in a consistent manner with distributed chemical states, each characterized by several continuous degrees of freedom. Second, it lets one insert the essential information about the energy barriers in an explicit and coherent way. Third, it offers the possibility to include into the study the states that are only minimally stable in the sense that they are surrounded by arbitrarily small barriers.

Despite its rather elaborate mechanical nature, our model remains mostly schematic and can be considered only as prototypical. A particularly serious simplification consists in the decoupling of the chemical and mechanical pictures in relation to the power stroke. In this way we neglect the fact that ADP has to be released during the discharge and that ATP has to be hydrolyzed during the recharge of the power stroke mechanism. Instead, the power stroke is recharged and discharged due to the mechanical stretch assisted by thermal fluctuations. Another simplification is that we associate the detachment with the state of the weakest interaction between the cross-bridge and the actin filament without trying to distinguish the sub-states (M-ATP, A-M-ADP-P) and match the observed duty ratio [5]. Finally, the non-equilibrium chemical reservoir enters the picture only through the correlated external noise imitating simultaneously both binding and hydrolysis.

The reported numerical experiments raise important questions regarding mechanical interdependency between different biochemical states involved in muscle contraction. Thus, in the framework of chemo-mechanical models the force generation is usually linked exclusively to the power stroke. The power stroke, indeed, plays a major role in the fast recovery of tension, however, at slower time scales the attachment-detachment mechanism also contributes to force generation by effectively recharging the power stroke mechanism. Since the ATP activity is required for such recharging, one can say that the hydrolysis of ATP plays an essential role in the working of the power stroke despite its apparently "mechanical nature". This idea is supported by the fact that even the fast tension recovery in rigor is much smaller than in tetanus [49]. Here it is appropriate to mention that already Eisenberg and Hill [39] associated the difference in the level of the minima in the energy of the bi-stable element with the free energy liberated by the ATP hydrolysis.

The recharging mechanism proposed in the present paper could be made compatible with other choices of Brownian ratchets provided that certain conditions on $E_t(x, y)$ detailed in the previous section are satisfied. For instance, rocking ratchet used in this paper could be replaced by the flashing ratchet (*e.g.* [21,35]) generating correct duty ratio and producing interesting cooperative effects [50]. Flashing ratchet models, however, introduce a jump switching process which is not easy to interpret in purely mechanical terms.

Due to the minimal nature of the present model many other important features of the phenomenon of muscle contraction, including the possibility of additional conformational states [12], the double-head structure of the myosin head [26], the elasticity of the filaments [51], the elastic interaction among many sarcomeres in series [20], the contractional instabilities and waves [52] and the

strong temperature dependence of the entropic elasticity of the elements [53], have been left outside the scope of the analysis. Despite these limitations our mechanical model offers a consistent description of the ATP-driven motor undergoing periodic attachment detachment which is concurrent with a mechanically driven configurational change. The use of the mechanical framework allows one to resolve the long standing controversy regarding the load dependence of the magnitude of the power stroke and provides the first non-chemical description for the main stages of the biochemical Lymn-Taylor cycle. Most importantly, the mechanical perspective opens the way to recreate the intricate machinery behind muscle contraction *artificially* and to potentially build larger devices exhibiting active elasticity.

The authors thank J.M. Allain, J.F. Joanny, F. Jülicher, V. Lombardi and G. Piazzesi for helpful discussions. The work was supported by the EU contract MRTN-CT-2004-505226.

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