Mechanics of the power stroke in myosin II

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Power stroke in skeletal muscles is a result of a conformational change in the globular portion of the molecular motor myosin II. In this paper we show that the fast tension recovery data reflecting the inner working of the power stroke mechanism can be quantitatively reproduced by a Langevin dynamics of a simple mechanical system with only two structural states. The proposed model is a generalization of the two state model of Huxley and Simmons. The main idea is to replace the rigid bistable device of Huxley and Simmons with an elastic bistable snap spring. In this setting the attached configuration of a cross bridge is represented not only by the discrete energy minima but also by a continuum of intermediate states where the fluctuation induced dynamics of the system takes place. We show that such *soft-spin* approach explains the load dependence of the power stroke amplitude and removes the well-known contradiction inside the conventional two state model regarding the time scale of the power stroke.

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I. INTRODUCTION

A broadly accepted molecular mechanism of force generation in skeletal muscles is embodied in the swinging lever-arm model (e.g., [1–3]). In this model each myosin head, attached to the actin filament, stretches a series elastic element by undergoing one or more conformational transitions generally referred to as a power stroke [4,5]. The systematic experimental and theoretical study of the myosin stroke was initiated in the pioneering work of Huxley and Simmons (HS) [6] who applied to an isometrically contracting muscle fiber a length drop δ and showed that the tension almost instantaneously (tens of nanoseconds) diminishes to a value $T_1(\delta)$ but then partially recovers in a milliseconds time scale reaching a plateau $T_2(\delta)$. The system returns to the original value of the isometric tension T_0 during a much longer time (fraction of a second) via an attachment-detachment process involving ATP splitting. Since the rapid recovery of the force value $T_2(\delta)$ does not appear to be rate limited by the chemical stages, the release of the power stroke is widely believed to be a largely mechanical phenomenon (e.g., [7]). In this paper we stay with this point of view although alternative hypotheses implying certain role of the attachment detachment in the fast transients of tension have also been discussed in the literature [2,8].

The mechanics enters the conventional chemomechanical models of the power stroke (e.g., [9]) through phenomenological assumptions regarding the dependence of the chemical rate constants on a single continuous variable which represents a state of the force generating spring. In this paper we take a more mechanically consistent point of view and represent the power stroke as a continuous stochastic dynamics of a set of elastic *snap springs*. In view of its simplicity the model is surprisingly successful in reproducing the fine structure of the fast tension recovery data.

We begin by recalling that despite years of intense studies, there still exists considerable uncertainty regarding the nature of the conformational change responsible for the power stroke and the exact magnitude of the corresponding lever arm rotation (e.g., [10,11]). Crystallographic and structural data suggest that the power stroke must be around 11 nm [12–15]. This value is comparable to what has been observed in the length step experiments at the fiber level [6], however, it is at least two times larger than the value obtained in single molecule measurements [16,17]. Besides, recent single fiber experiments [18,19] revealed that the power stroke amplitude may vary from 6 to 12 nm depending on the force acting at the motor level. The question whether this variability is due to a large number of configurational states or to the range of amplitudes available to just a few states, remains open.

In the classical HS model of the power stroke [6] the myosin head is viewed as a linear elastic spring in series with a bistable contractile unit. The energy of the bistable element is represented by a double-well potential with infinitely narrow wells separated by a fixed distance in the configurational space. The switching between the wells is modeled as a random jump process which can stretch or relax the elastic element if the motor remains attached. The HS model interprets the $T_1(\delta)$ response as purely elastic deformation and views the configurations corresponding to $T_2(\delta)$ as the state of thermal equilibrium. This interpretation is preserved in the present model, however we go further by fully characterizing the corresponding free-energy landscape and giving to the equilibrium an explicit dynamical meaning.

On a quantitative side, it is well known that the classical HS model can fit the experimental curves $T_1(\delta)$ and $T_2(\delta)$ under the assumption that the stiffness of the elastic element is low $K \simeq 0.2$ pN/nm. A large number of experimental studies have unambiguously shown that cross-bridge stiffness must be at least an order of magnitude larger [20–28]. It has been also realized that such an increase in the value of the crucial parameter K would affect considerably the predictions of the HS model [29]. For instance, the HS model with sufficiently high stiffness of the elastic element predicts that all cross bridges are in the high tension state after already a small shortening step. This makes the function $T_2(\delta)$ almost linear after a small threshold value of δ. Under the HS as-

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sumptions the slope of this linear function must be identical to the slope of the linear function $T_1(\delta)$, which however, contradicts observations showing a pronounced load dependence of the power stroke amplitude [6,19,30]. The second incongruence is that the higher value of K obliges the curve $T_2(\delta)$ to have a negative slope around $\delta=0$ which was not observed experimentally [31]. Finally, in a model with stiffer elastic spring the rate of fast tension recovery becomes much larger than in experiments [29,31].

There have been several attempts to improve the quantitative predictions of the HS theory (e.g., [9,31–37]). A standard way to match this theory with observations is to adopt for the myosin motor the existence of three or more stable attached chemical states. Mechanochemical models based on this idea and maintaining the discrete jump structure of the HS model are all based on the phenomenological assumptions regarding the dependencies of the reaction-rate constants on δ (meaning essentially infinite number of parameters). Since kinetics in these models remains disconnected from the detailed structure of the energy landscape, the link between the macroscopic response and the microscopic dynamics remains rather weak. More precisely, the freedom left by the conditions of detailed balance is used to interpolate the existing experimental curves, which limits the predictive power of the model.

Here we report a simple alteration of the HS model which allows one to fit the experimental data on fast tension recovery while preserving the assumption of the two configurational states and remaining in the fully transparent mechanical framework. Most importantly, we operate with just a few parameters whose values are extracted from independent measurements.

In our theoretical development we follow the insights of Hill and Eisenberg [29,32,38,39]. We relax the HS hypothesis regarding the infinite narrowness of the energy wells and allow each conformational state to have its own elasticity. Although this idea is implicit in several models (e.g., [9,34]), the elasticities of the chemical states are usually combined with the elasticity of the spring in series. This removes the configurational degree of freedom and enforces the jump structure on dynamics. Ultimately this brings one back to the necessity of handling the dependence of the chemical rate constants on the stretch of the elastic element phenomenologically. Instead, by retaining the configurational variable in the model we recreate a detailed link between the energy landscape and the kinetic constants. The importance of the continuous reaction energy landscape has been recently emphasized in [40,41]. Here we extend these ideas by presenting a systematic study of the effect of mechanical loading on the detailed shape of the effective energy landscape. Most importantly, we show that the idea of a continuous landscape leads to a natural explanation of the mysterious force dependence of the size of the power stroke (e.g., [4]) already in the simplest two state framework.

It is noteworthy that in our attempt to make the mechanical nature of the power stroke explicit we follow the corresponding development in the studies of attachment-detachment dynamics (e.g., [42–45]). The emerging common ground provided by the theory of continuous stochastic processes allows one to represent both the attachment detachment and the power stroke inside a single framework of Brownian ratchets (see also [46–49]). This opens a way to reproduce the machinery behind muscle contraction artificially.

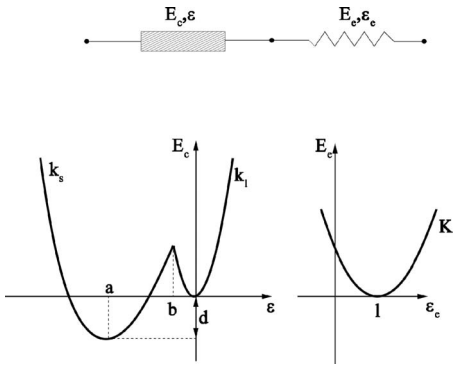

FIG. 1. Schematic representation of a single cross bridge as a series connection of a bistable snap spring with the energy $E_c(\varepsilon)$ and a linear elastic spring with the energy $E_e(\varepsilon_e)$.

II. MODEL

Following HS [6] we represent a cross bridge as a linear spring in series with a bistable contractile element (see Fig. 1). The total energy of this mechanical system is the sum of the energy of a double-well snap spring and the energy of a linear spring

$$E(\varepsilon,\varepsilon_e)=E_c(\varepsilon)+E_e(\varepsilon_e),$$

where ε_e is the elongation of the elastic element and ε is the elongation of the contractile element.

We assume that detachment is suppressed and use the total elongation

$$\delta=\varepsilon_e+\varepsilon$$

as the control parameter (length clamp device). In the model of HS, and in most of its recent mechanochemical extensions parameter δ is used as the only mechanical variable while the configurational variables such as ε are treated as discrete chemical degrees of freedom. For instance, our snap spring is replaced by a discrete spin-type variable. Instead, below we follow [29] and treat ε as a continuous variable akin to δ. This amounts to a transition from *hard*- to *soft*-spin model.

The quadratic elastic energy of the series spring with stiffness K and prestrain l is given by

$$E_e(\varepsilon_e)=\frac{1}{2}K(\varepsilon_e-l)^2. \quad (1)$$

For the energy of the bistable element (known also as switch II, relay or converter) we use the simplest piecewise quadratic approximation,

$$E_c(\varepsilon) = \begin{cases} \frac{1}{2}k_s(\varepsilon - a)^2 + d, & \varepsilon \le b \\ \frac{1}{2}k_l(\varepsilon)^2, & \varepsilon > b, \end{cases} \tag{2}$$

where following Hill [38] we assume that the curvatures of the wells corresponding to "long" (prepower stroke) and "short" (postpower stroke) conformations, k_l and k_s, are different; in the HS model $k_s = k_l = \infty$. The chemical ground-state parameter d describes a bias toward the short conformation which drives the power stroke. This energy may or may not be associated with the ATP activity (see Fig. 1) and we specify it, as in HS model, by the assumption that at $\delta = 0$ the energies in the bottoms of the wells are equal. We assume that $a < 0$ meaning that the overall shortening $\delta < 0$ shifts the global minimum toward the short phase. The parameter b can be found from the condition of energy continuity at the point of switching between the two parabolas.

The total energy of the system can be written as

$$E(\varepsilon, \delta) = E_c(\varepsilon) + E_e(\delta - \varepsilon) = \begin{cases} E_s(\varepsilon, \delta), & \varepsilon \le b \\ E_l(\varepsilon, \delta), & \varepsilon > b, \end{cases} \tag{3}$$

where

$$E_{l,s}(\varepsilon, \delta) = 1/2(K + k_{l,s})[\varepsilon - a_{l,s}(\delta)]^2 + h_{l,s}(\delta). \tag{4}$$

At the fixed δ the minima of the energy are given by

$$a_l(\delta) = \frac{K(l+\delta)}{k_l + K}, \quad a_s(\delta) = \frac{K(l+\delta) + k_s a}{k_s + K}. \tag{5}$$

while the corresponding energy levels have the values

$$h_l(\delta) = \frac{1}{2}\frac{k_l K}{k_l + K}(l+\delta)^2, \quad h_s(\delta) = \frac{1}{2}\frac{k_s K}{k_s + K}(l + \delta - a)^2 + d. \tag{6}$$

Notice that in our model, in contrast to [6], not only the "chemical" driving force but also the geometrical distance between the bottoms of the energy wells (power stroke size) depends on δ.

In equilibrium we must have

$$\partial E(\varepsilon, \delta)/\partial \varepsilon = 0,$$

which gives $\varepsilon = \hat{\varepsilon}(\delta)$ and

$$\hat{E}(\delta) = E_c[\hat{\varepsilon}(\delta)] + E_e[\delta - \hat{\varepsilon}(\delta)]. \tag{7}$$

Observe that the function $\hat{\varepsilon}(\delta)$ is multivalued in the interval $[\delta_l, \delta_s]$ where δ_l and δ_s are implicitly given by $a_s(\delta_s) = b$ and $a_l(\delta_l) = b$. Along the metastable branches, representing local minima of the energy, we have

$$\hat{T}(\delta) = \frac{d\hat{E}(\delta)}{d\delta} = \begin{cases} \hat{T}_l(\delta), & \delta > \delta_l \\ \hat{T}_s(\delta), & \delta < \delta_s, \end{cases} \tag{8}$$

where

$$\hat{T}_l(\delta) = K[\delta + l - a_l(\delta)],$$

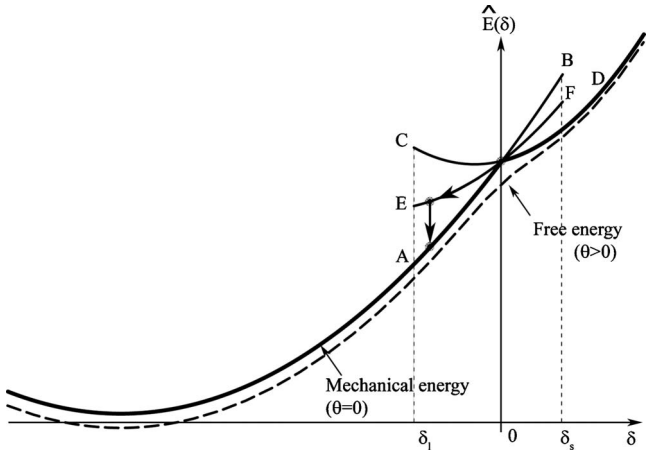

FIG. 2. Mechanical energy and free energy presented as functions of δ: $\theta = 0$ (local and global minima, solid lines), $\theta > 0$ (free energy, dashed line). Arrows show the behavior of the system in a typical HS experiment. Here we consider the case $k_s < k_l$. Other symbols are explained in the text.

$$\hat{T}_s(\delta) = K[\delta + l - a_s(\delta)].$$

One can see that in the interval $[\delta_l, \delta_s]$ the equilibrium tension has two values (thin lines in Fig. 2) corresponding to two local minima of the energy. The global minimum of the energy is defined by the conditions $\varepsilon_{\rm gl} = a_l(\delta)$, for $\delta > 0$, and $\varepsilon_{\rm gl} = a_s(\delta)$, for $\delta < 0$ (thick lines in Fig. 2). In the global minimum

$$\hat{T}_{\rm gl}(\delta) = \begin{cases} \hat{T}_l(\delta), & \delta \ge 0 \\ \hat{T}_s(\delta), & \delta \le 0. \end{cases} \tag{9}$$

Notice that the definition of tension $\hat{T}_{\rm gl}$ remains ambiguous at $\delta = 0$ where the two metastable states have the same energies.

We can summarize the mechanical response of our soft-spin mechanical system as follows. Due to the presence of the series linear spring, the double-well snap spring is loaded in a mixed device even if the whole cross bridge is loaded isometrically (hard device). This allows for micrometastability and the multivaluedness of the load-elongation relation which in turn gives rise to a temporal pinning and linear elastic behavior at short-time scales.

Exponentially more metastable states are available to the system of N identical cross bridges arranged in *parallel*. Let N_l be the numbers of elements in the long phase. Then, any equilibrium configuration with a given fraction of long elements $c = N_l/N$ corresponds to a local minimum of the energy. With such metastable configuration we can associate the equilibrium tension

$$T_{\rm loc}(\delta, c)N^{-1} = c\hat{T}_l(\delta) + (1-c)\hat{T}_s(\delta) = K(\delta + l - \langle\varepsilon\rangle), \tag{10}$$

where

$$\langle\varepsilon\rangle(\delta) = ca_l(\delta) + (1-c)a_s(\delta). \tag{11}$$

In Fig. 2 we show three of these metastable branches with $c = 0$ (line AB), $c = 1$ (line CD) and $c = c^*$ (line EF) where c^*

is the value of c at the moment of the elastic unloading (to be specified below).

To account for finite temperature θ we can follow [6,38,50] and use equilibrium statistical mechanics for defining $T_2(\delta)$. Observe that the motor degrees of freedom are always out of equilibrium due to ATP activity. However, while the motor remains attached, the conformational degrees of freedom, responsible for the fast force recovery, can be expected to equilibrate. At even shorter time scale of the elastic response generating $T_1(\delta)$ the power stroke will also be out of equilibrium.

In thermal equilibrium the system of N parallel cross bridges is distributed with the probability

$$p(\varepsilon_1, \ldots, \varepsilon_N, \delta, \beta) = \mathcal{Z}^{-1} \exp\left[-\beta \sum_i E(\varepsilon_i, \delta)\right], \quad (12)$$

where

$$\mathcal{Z}(\delta, \beta) = \left[\int_{-\infty}^{\infty} e^{-\beta E(\varepsilon, \delta)} d\varepsilon\right]^N, \quad (13)$$

where $\beta = 1/(k_B\theta)$ and k_B is the Boltzmann constant. The free energy can be obtained from

$$F(\delta, \beta) = -\frac{1}{\beta} \ln \mathcal{Z}(\delta, \beta)$$

and the corresponding equilibrium tension takes the form

$$T(\delta, \beta) = \partial F(\delta, \beta)/\partial \delta.$$

A direct substitution of Eqs. (1) and (2) into Eq. (12) shows that

$$T(\delta, \beta)/N = K(\delta - l - \langle \varepsilon \rangle), \quad (14)$$

where

$$\langle \varepsilon \rangle(\delta, \beta) = \int_{-\infty}^{\infty} \varepsilon p_s(\varepsilon; \delta, \beta) d\varepsilon \quad (15)$$

and

$$p_s(\varepsilon; \delta, \beta) = \frac{e^{-\beta E(\varepsilon, \delta)}}{\int_{-\infty}^{\infty} e^{-\beta E(\varepsilon, \delta)} d\varepsilon}. \quad (16)$$

It is natural to link $T(\delta)$ at fixed β to $T_2(\delta)$ in HS experiments; the tension generated during isometric contraction T_0 can then be identified with $T_2(0)$.

The integrals in the statistical sum and in Eq. (15) can be easily expressed through special functions. Moreover, we found that in the relevant range of parameters a simple Kramers' approximation [51] is already adequate. By assuming that the distribution in each well is close to equilibrium we write

$$\mathcal{Z}(\delta, \beta) \approx Z_l(\delta, \beta) + Z_s(\delta, \beta), \quad (17)$$

where

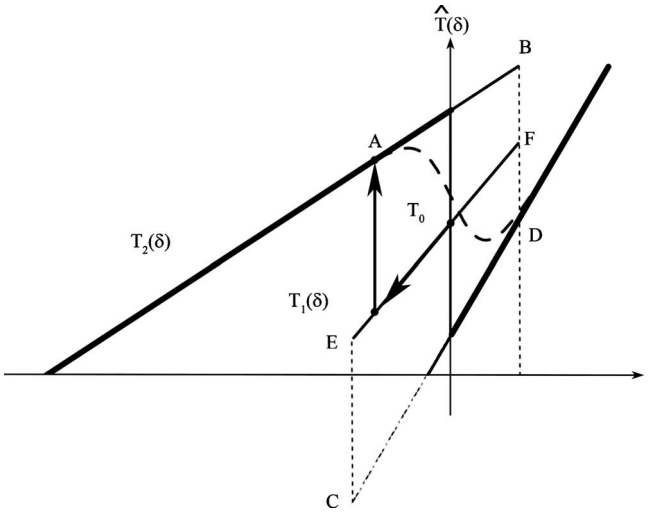

FIG. 3. Equilibrium tension as a function of δ: $\theta=0$ (mechanical model, solid lines), $\theta>0$ (thermal model, dashed lines). Here we again consider the case $k_s<k_l$, arrows and symbols correspond to Fig. 2.

$$Z_{l,s}(\delta, \beta) = \sqrt{\frac{2\pi}{\beta(K + k_{l,s})}} e^{-\beta h_{l,s}(\delta)}. \quad (18)$$

Then

$$\langle \varepsilon \rangle(\delta, \beta) \approx c(\delta, \beta) a_l(\delta) + [1 - c(\delta, \beta)] a_s(\delta), \quad (19)$$

where the fraction of the prepower stroke myosin heads is given by

$$c(\delta, \beta) = Z_l(\delta, \beta)[Z_s(\delta, \beta) + Z_l(\delta, \beta)]^{-1}. \quad (20)$$

We can then identify $T_1(\delta)$ describing instantaneous elastic response in HS type experiments with the value $T_{\mathrm{loc}}(\delta, c^*)$ where $c^* = c(0, \beta)$. The generic structure of the functions $T_1(\delta)$ and $T_2(\delta, \beta)$ is shown in Fig. 3.

We can now move from equilibrium to kinetics and use the obtained information about the structure of the energy landscape to estimate the rate of tension recovery. We assume that the N cross bridges connected in parallel are described by the following system of overdamped Langevin equations:

$$\eta_i \dot{\varepsilon}_i = -\sum_j A_{ij}\, \partial E/\partial \varepsilon_j + \sqrt{2\eta_i/\beta}\Gamma(t). \quad (21)$$

Here $E(\varepsilon_1, \ldots, \varepsilon_N, \delta) = \Sigma_i E(\varepsilon_i, \delta)$ and $\Gamma(t)$ represents thermal fluctuations with standard properties $\langle \Gamma(t_1) \rangle = 0, \langle \Gamma(t_1)\Gamma(t_2) \rangle = \delta(t_1 - t_2)$. We neglect correlations in the noise assuming strong time scale separation between the power stroke release and the ATP related energy input. We also neglect coupling between the elements assuming that A is the unit matrix and put for simplicity $\eta_i = \eta$ for $i = 1, \ldots, N$.

Since the individual cross bridges are independent, we can write the joint probability density as

$$p(\varepsilon_1, \ldots, \varepsilon_N, t; \delta, \beta) = \prod_i p_i(\varepsilon_i, t; \delta, \beta).$$

Moreover for all $i=1,\ldots,N$ we have $p_i(\varepsilon,t;\delta,\beta)=p(\varepsilon,t;\delta,\beta)$ where $p(\varepsilon,t;\delta,\beta)$ satisfies the Fokker-Plank equation

$$\eta \partial_t p = \partial_\varepsilon [E'(\varepsilon;\delta)p] + \beta^{-1}\partial_\varepsilon^2 p. \tag{22}$$

The stationary solution of this equation $p_s(\varepsilon;\delta,\beta)$ generates the equilibrium distribution in Eq. (16), in particular, one can rewrite Eq. (12) as $p(\varepsilon_1,\ldots,\varepsilon_N,\delta,\beta)=\Pi_i p_s(\varepsilon_i;\delta,\beta)$.

To study the nonstationary case we make an assumption that the relaxation within a well is fast comparing to the time required to overcome the energy barrier. This allows us to use the Kramers' ansatz (e.g., [52])

$$p(\varepsilon_i,t;\delta,\beta) = \begin{cases} p_s(\varepsilon_i;\delta,\beta)\left[\dfrac{1-c(t,\delta,\beta)}{1-c(\delta,\beta)}\right], & \varepsilon_i \le b \\ p_s(\varepsilon_i;\delta,\beta)\left[\dfrac{c(t,\delta,\beta)}{c(\delta,\beta)}\right], & \varepsilon_i > b, \end{cases}$$

where $c(t,\delta,\beta)=\int_b^\infty p(\varepsilon_i,t;\delta,\beta)d\varepsilon$. We recall that b denotes the location of the barrier represented by a common point of the two parabolic wells (see Fig. 1).

To find $c(t,\delta,\beta)$ we need to solve a first-order "kinetic" equation

$$\dot{c}(t,\delta,\beta) = r_l c(t,\delta,\beta) + r_s[1-c(t,\delta,\beta)],$$

where $r_l=[\beta\eta c\int_a^{a_l} p_s(\varepsilon_i;\delta,\beta)^{-1}d\varepsilon]^{-1}$, $r_s=[\beta\eta(1-c)\times\int_{a_s}^{a_l} p_s(\varepsilon_i;\delta,\beta)^{-1}d\varepsilon]^{-1}$, and $c(\delta,\beta)$ is given by Eq. (20). Observe that in contrast to most of the currently used chemomechanical models here we do not need to postulate the dependence of the chemical rate constants r_l and r_s on the mechanical variable δ. Instead, by performing numerical integration we can directly obtain the relaxation time $r(\delta,\beta)$

$$r(\delta,\beta) = r_l + r_s = \left[\beta\eta c(1-c)\int_{a_s}^{a_l} p_s(\varepsilon,\delta,\beta)^{-1}d\varepsilon\right]^{-1}. \tag{23}$$

The resulting model depends on only five dimensional parameters. Two of them, the modulus K and the prestrain l, characterize the series elastic element. The remaining three, the elastic moduli in two conformations k_l, k_s and the scale of the lever arm rotation $|a|$, describe the bistable element. The total number of myosin heads N does not affect the dimensionless tension T/T_0, which, if expressed through normalized elongation $\delta/|a|$, depends only on *four* nondimensional parameters: $l/|a|$, $k_{l,s}/K$, and $Kl^2/(k_B\theta)$.

III. RESULTS

To obtain the realistic values of the nondimensional parameters we use the following experimental data: (i) $T_2(\bar{\delta})=0$ at $\bar{\delta}=-10.8$ nm [34]; (ii) the curve $T_2(\delta)/T_0$ can be approximated near $\bar{\delta}$ by a straight line with the slope 0.138 nm^{-1} [34]; (iii) the slope of the (almost) straight line $T_1(\delta)/T_0$ is 0.258 nm^{-1} [34]; (iv) the experimentally measured value of the motor rigidity is in the range 2–4 pN/nm [28,30,53]. Notice that the account of elasticity in both the contractile element and the series spring makes the definition of the stiffness of a motor ambiguous. Also, the overall force changes recorded in experiments [34] necessarily incorporate the compliance of the filaments. In this paper, we neglect the latter and assume that the overall stiffness of a cross bridge is equal to $k_sK/(k_s+K)=1$ pN/nm. Our fitting procedure (see [54] for details) produced an additional constraint $k_s/K \le 0.3$ and we took the maximal admissible value for k_s. Finally, we obtained $|a|=10.4$ nm, $l=0.4$ nm, $k_l=11.4$ pN/nm, $k_s=1.3$ pN/nm, and $K=4.0$ pN/nm. For β^{-1} we used the value 3.82 pN nm, corresponding to $\theta=4$ °C.

The computations based on these data show that the curve $T_2(\delta)$ has an expected overall structure. In particular, it exhibits *different slopes* of the $T_1(\delta)$ and the $T_2(\delta)$ curves at large shortening steps δ which reflects the *load dependence* of the amplitude of the power stroke. We observe, however, that the $T_2(\delta)$ curve exhibits a negative slope around $\delta=0$ (as in Fig. 2, dotted line) which contradicts typical experiments. One way to moderate this effect is to consider the whole myofibril, interpreted as a large number of half-sarcomeres in series, and allow for locally inhomogeneous configurations [37,55]. Another approach, which we pursue here, is to take into consideration the dispersion in the attachment positions as suggested in [31,56].

More specifically, we assume that the prestrain l may vary for individual motors. Then

$$T(\delta,\beta) = K\sum_i^N (\delta + l_i - \langle\varepsilon\rangle_i), \tag{24}$$

where for each i the average value $\langle\varepsilon\rangle_i$ corresponds to the prestrain $l=l_i$. Following [31] we assume that parameters l_i are independent random variables distributed uniformly in the interval $[l-2.75\ \text{nm}, l+2.75\ \text{nm}]$. The overall relative tension $T(\delta,\beta)$ is then equal to the average of Eq. (14) over the interval $[\delta-2.75\ \text{nm}, \delta+2.75\ \text{nm}]$.

A comparison of the computational results for $T_1(\delta)/T_0$ and $T_2(\delta)/T_0$ with the experimental data from [34] is presented in Fig. 4. The agreement is rather good in the whole shortening range. Interestingly, with our choice of parameters we obtain that $\delta_l=3.5$ nm. This means that in the shortening range the long phase disappears exactly around the point where the experimental data for $T_1(\delta)/T_0$ start to deviate from a straight line. The remaining discrepancies in the stretching range may be at least partially related to the fact that in the corresponding experiments the recovery of $T_2(\delta)$ is too slow for the power stroke to be distinguished from the attachment-detachment process [57].

Turning now to kinetics we recall that in the HS model the assumption of infinitely narrow energy wells was essential for obtaining an exponential dependence of the tension recovery rate on δ. It has been observed, however, that with realistic K the model with sharp wells (hard spins) predicts a time scale for the power stroke which is three orders of magnitude larger than the characteristic time of ATP hydrolysis [2]. This follows from the fact that infinite stiffness in the

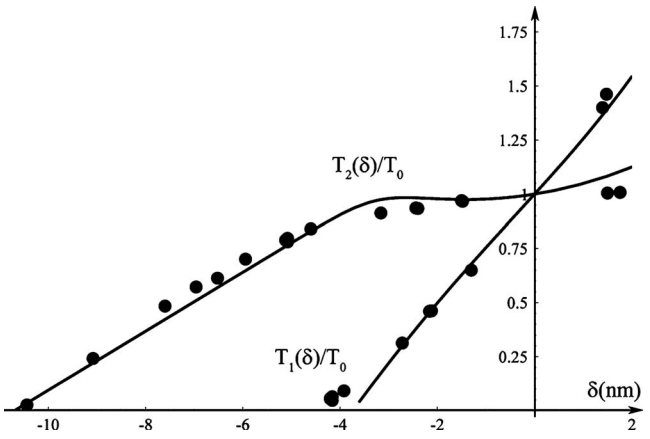

FIG. 4. Computed tension-length curves are plotted against the experimental data from [34].

short state obliges the elastic element to be stretched to the full power stroke length before the conformational transition takes place. Since this stretch must be achieved through thermal fluctuation, the transitions become unreasonably rare events.

To compute the rate of recovery in the soft-spin model we must use Eq. (23) but with one precaution. In the case of a nontrivial dispersion in the attachment positions l_i one obtains a multiexponential tension-time curve (as in real experiments). A single function $r(\delta,\beta)$ can be obtained from the sum of individual contributions $\frac{1}{n}\sum_{i=1}^{n} e^{-r_i(\delta,\beta)t}$ by one-exponential fitting of the resulting curve. To complete this task we need to supply the value of only one additional parameter, the drag coefficient η. If we take the value $\eta = 90$ pN ns/nm recommended by [2] we obtain from Eq. (23) a time scale which is much faster than what has been observed experimentally. To obtain the realistic time scale we must increase the value η by four orders of magnitude.

A way to deal with this unrealistically fast time scale while remaining in the framework of the model with realistic value of η is to introduce an additional energy barrier between the two states. This is also appropriate in view of another drawback of the oversimplified two parabolic approximation: disappearance of the barrier at $\delta_l = 3.5$ nm. The simplest way to deal with these problems is to use a three parabolic approximation which agrees with the two parabola model everywhere outside a narrow transition region and therefore preserves the equilibrium response $T_2(\delta)$. We can then write

$$E_c(\varepsilon) = \begin{cases} \frac{1}{2}k_s(\varepsilon - a)^2 + d, & \varepsilon \le b_s \\ -\frac{1}{2}k_m(\varepsilon - b)^2 + e, & b_s < \varepsilon \le b_l \\ \frac{1}{2}k_l(\varepsilon)^2, & \varepsilon > b_l. \end{cases} \quad (25)$$

If the values of the constants b_l and b_s are chosen to ensure the continuity of the function $E_c(\varepsilon)$ we are left with three new constants: the position of the energy barrier b, its height

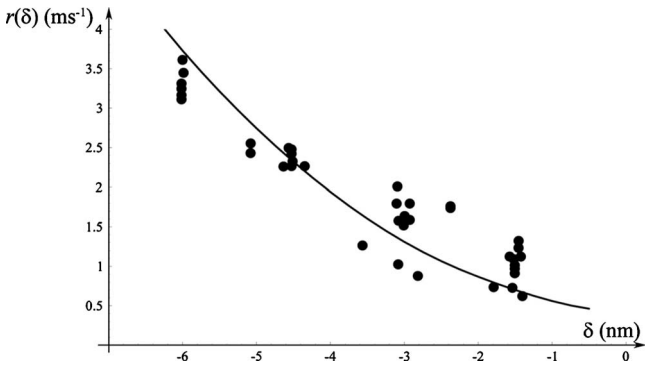

FIG. 5. Computed rate of recovery plotted against the experimental data from [4,6,20].

e and its curvature k_m. The best fit of the experimental data was achieved for $k_m = 1.05 \times 10^4$ pN/nm, $b = -0.4$ nm, and $e = 65$ pN nm (see Fig. 5).

Knowing that our augmentation of the model does not affect the equilibrium curves shown in Fig. 4, we can conclude that the three parabola model can reproduce both equilibrium and kinetics of shortening rather faithfully. We did not try to simulate the kinetics in the stretching region having again in mind that in this domain the effects of the second head [58] and the attachment detachment [57] may be of considerable importance.

In summary, our analysis shows that the main features of the fast response of skeletal muscles can be captured by a simple mechanical model with only two attached states if those states are interpreted not as discrete chemical components but as extended configurations of an elastic snap spring. A nonconventional aspect of the resulting model is in the use of two rather than one mechanical degrees of freedom. The main theoretical ingredient of our approach is the representation of the power stroke as a continuous stochastic process which allows one to couple it potentially with a Brownian ratchet.

In this paper we offer an interpretation of the load dependence of the amplitude of the power stroke. According to our model, the origin of the variability of the power stroke size lays in the sensitivity of the minima of the total energy, replacing the fixed chemical states of the HS model, to the stretch of the series elastic element. By taking this effect into consideration the model provides a natural explanation how the size of the power stroke, which may be loosely identified with the distance between the energy minima, can become a function of the imposed length shortening in length clamp device (or of the imposed external force in load clamp device). The experiments show that the amplitude of the power stroke is indeed changing continuously with tension [53]. Such observations can be explained inside chemomechanical framework only if one assumes the existence of three or more stable configurations for the attached cross bridge [31,34,59].

An interesting consequence of the above stretch sensitivity of the energy minima is the resolution of the long-standing claim [34] that in a two state model the elastic energy associated with the power stroke of 11 nm must be larger than the free energy of ATP hydrolysis. Instead, in our

model the amplitudes of this scale can be reached only if the series elastic element is completely relaxed.

Since the goal of this short communication was to capture only the principal effects, several features of the muscle system which may affect the interpretation of the power stroke phenomenology have been left outside. For instance, we did not try to address the peculiar temperature dependence of the functions $T_1(\delta)$ and $T_2(\delta)$ [53] which would require the replacement of mechanical springs by entropic ones (e.g., [2]). We also did not address the delicate asymmetry between shortening and stretching which may require the account of the second head leading to a substantial modification of the model. Finally, we left aside the analysis of the additional coupling due to filaments extensibility, the study of the inhomogeneity of the relative displacement between myosin and actin filaments, and we neglected the possibility of a nonaffine character of the displacements distribution in the system of many sarcomeres connected in series. The incorporation of the corresponding effects in the Langevin framework requires large scale numerical computations and the results of such simulations will be reported elsewhere.

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