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Microscopic model of the actin-myosin interaction in muscular contractions

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We define and study a detailed many body model for the muscular contraction taking into account the various myosin heads. The state of the system is defined by the position of the actin and by an internal coordinate of rotation for each myosin head. We write a system of Fokker-Planck equations and calculate the average for the position, the number of attached myosin heads, and the total force exerted on the actin. We also study the correlation between these quantities, in particular between the number of attached myosin heads and the force on the actin.

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I. INTRODUCTION

Muscular cells have the ability to convert chemical energy, stored in ATP bonds, into mechanical energy. The description of this mechanism has been known for a long time and is described in many text books (such as Refs. [1–4]). It involves a passive protein, called actin, which can contract the cell when it is dragged by other proteins, called myosin. Each myosin molecule is articulated into two parts: one part is fixed, the other part is a kind of head which can rotate around the fixed part. For a cell at rest (no neural excitation), the myosin head cannot reach and attach to the actin, due to the presence of another protein called troponine. When a neural excitation occurs, for example, if the muscle is loaded, this results in an inhibition of the troponine molecule, and the myosin heads, equipped with an ADP molecule, can attach to the actin, lose the ADP molecule, and relaxes towards a new equilibrium position (with respect to the fixed part of the myosin), thus dragging the actin molecule. This process is stopped by a random arrival of an ATP molecule on the attached myosin head, resulting in the detachment of the head, and the hydrolysis of ATP into ADP and phosphate (this hydrolysis is catalyzed by the myosin head). During the whole cycle, an ATP molecule is consumed ($\triangle G \simeq 30$ kJ/mol), and the actin molecule is dragged over around 10 nm. The first model was proposed by Hill (Refs. [5–7] for the original reference, and Ref. [8] for a general discussion of energy transduction in biology). The general idea of this model, which is the basis of all subsequent models, is that a given myosin head fluctuates between two free energy states with different potential energy curves, one corresponding to the attached state, the other one to the detached state. This idea was also used in more recent works (see Ref. [9] for a general review on molecular motors as well as Refs. [10–18]).

A rough estimation shows that the number of myosin heads which can attach to an actin filament is of the order of one thousand. In a way, the situation is similar to the one of an engine with many cylinders, the role of a cylinder being taken by the role of a myosin head, except that there are much more myosin heads than cylinders, and that the myosin heads can attach or detach independently, whereas usually engineers arrange the cylinders in an engine in such a way that they work cooperatively.

We think that this cooperative behavior is very important for natural molecular motors, and that it is one of the main differences with respect to man-made engines. However, this feature of molecular motors is not taken into account completely in many papers on the subject, when the muscular contraction is modeled by the motion of a single effective myosin head. In fact, usual models of muscular contractions only involve the motion of a single myosin head: this was the original model of Hill. Others models are derived as a mean field approximation from a many body theory (see, for example, Ref. [10]).

Our model takes into account explicitly the many body nature of the problem, namely, the fact that myosin heads can be attached or detached at random, which generates fluctuations and correlations which are not usually taken into account by other models.

Each myosin head involved in the muscular contraction is described by an internal coordinate, which takes continuous value. Moreover, the actin heads undergo chemical transitions between the attached and the detached configurations, at certain rates. We assume that the system is in the regime of high friction, and we write a Fokker-Planck system of equations for the evolution of the probability distribution of the configuration system actin + myosin heads (see Sec. II). We study the evolution of symmetric observables (Secs. III and IV), and specialize to the average value and correlations of the natural observables of the system, namely, the number of attached myosin heads, the center-of-mass coordinate of the system, and the total force acting on actin. We can solve the evolution of these quantities provided that a natural Markovian approximation is made (see Sec. V). Finally, we calculate the work (Sec. VI) for large time. An appendix provides the details of the calculations.

In another paper [19], we shall treat a self-consistent but less detailed model, representing the cycle by transition processes taking into account the chemical reactions.

II. A FOKKER-PLANCK SYSTEM FOR THE MYOSIN-ACTIN INTERACTION

We refer to Refs. [1,3] for the general biochemical description of the motion of the actin and myosin, as well as for

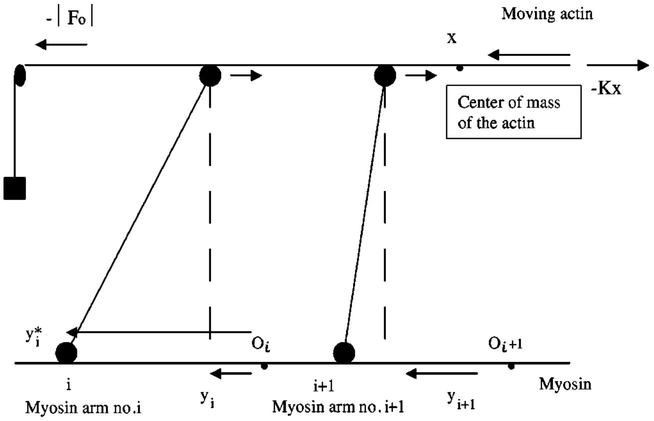

FIG. 1. Interaction between the myosin heads and the actin filament.

the terminology and notations.

We represent the actin filament by a moving massive line and we denote by x the abscissa of its center of mass referred to a fixed origin. The various myosin arms which can attach to the actin filament are numbered by $i=1,\ldots,n$. These arms spring out of a certain line, parallel to the actin. When the myosin head is attached to the actin, its equilibrium angle with the myosin filament is θ_0: recent observations show that $\theta_1 \simeq \pi/6$, corresponding to a point O_i on the myosin line [20]. The actual position of the myosin head is measured by an abscissa y_i with respect to O_i. When the myosin head is not attached, the equilibrium angle of the arm is about θ_0, with $\theta_0 \simeq \pi/2$ (Ref. [1]), corresponding to a value y^* of y_i (see Fig. 1). The myosin head is submitted to the potential $U_i^{(0)}(y_i)$ if it is not attached, and to the potential $U_i^{(1)}(y_i)$ if it is attached. Following Hill (see Refs. [5,8]), we assume that these potentials are approximately harmonic and write

$$U_i^{(1)}(y_i)=\frac{\chi_1}{2}y_i^2,$$

$$U_i^{(0)}(y_i)=\frac{\chi_0}{2}(y_i-y^*)^2+U_0. \tag{1}$$

These potentials are approximatively represented in Fig. 2, showing the various levels of energy.

The state of the entire system actin + myosin heads is specified by the following data.

(a) The abscissa x of the center of mass of the actin.

(b) The abscissa y_i of each myosin head.

(c) A Boolean variable $\epsilon_i=0$ or 1, which indicates if the myosin head no. i is unattached ($\epsilon_i=0$) or attached ($\epsilon_i=1$). In the usual Langevin description, the equations of motions are of the following type.

(1) If the myosin head no. i is not attached, we take a high friction limit and

$$dy_i=\frac{1}{\eta_M}f_i^{(0)}(y_i)dt+d\xi_i(t), \tag{2}$$

where

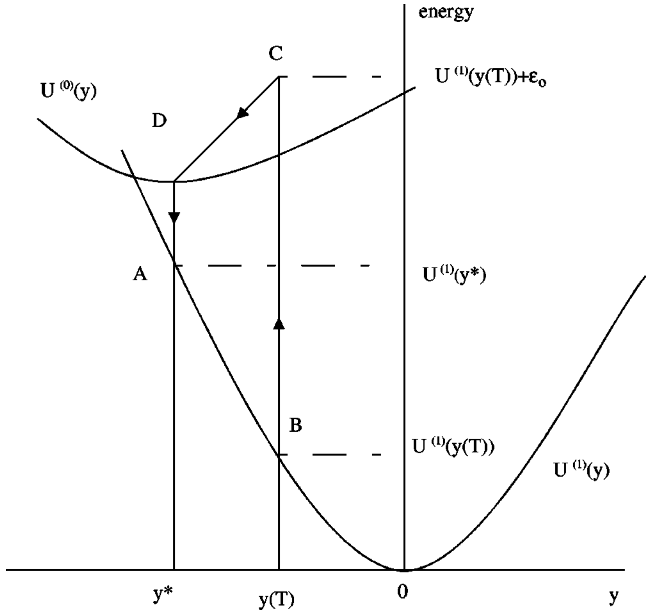

FIG. 2. The cycle for a single myosin head.

$$f_i^{(0)}=-\frac{\partial U_i^{(0)}(y_i)}{\partial y_i}=-\chi_0(y_i-y^*). \tag{3}$$

η_M is the viscosity of the motion of the free myosin head and $\xi_i(t)$ is a white noise force with

$$\langle d\xi_i(t)\rangle=0,\langle d\xi_i(t)d\xi_j(s)\rangle=2D_M\delta_{ij}\delta(t-s)dtds, \tag{4}$$

where D_M is a difusion coefficient related to η_M by the Einstein relation

$$\frac{1}{\eta_M}=\frac{D_M}{k_BT}.$$

[δ_{ij} is the Kronecker symbol and $\delta(t-s)$ is the Dirac function.]

(2) If the myosin head no. i is attached, then

$$\frac{dy_i}{dt}=\frac{dx}{dt}. \tag{5}$$

(3) Finally, x is submitted to the following.

(i) The force exerted by the attached myosin heads,

$$f_i^{(1)}(y_i)=-\frac{\partial U_i^{(1)}(y_i)}{\partial y_i}=-\chi_1 y_i \quad \text{if} \quad \epsilon_i=1.$$

(ii) The external force $F_e(x)$, which includes the external loading force $-|F_0|$ and a springlike force $-Kx$ exerted by the wall of the sarcomer,

$$F_e(x)=-|F_0|-Kx.$$

(iii) A white noise force $d\xi$,

$$dx=\frac{1}{\eta_A}\left(F_e+\sum_{i=1}^{M}\delta_{\epsilon_i 1}f_i^{(1)}(y_i)\right)dt+d\xi(t), \tag{6}$$

$$\langle d\xi(t)\rangle = 0,\ \langle d\xi(t)d\xi(s)\rangle = 2D_A\delta(t-s)dtds,$$

$$\frac{1}{\eta_A} = \frac{D_A}{k_BT}. \tag{7}$$

The probability distribution for the state of the system is $P(t,x,\{\epsilon_i\},\{y_i\})$ at time t. We shall also assume that the myosin head can attach to the actin filament with rate $k_{10}(y_i)$,

$$\epsilon_i = 0 \overset{k_{10}}{\rightarrow} \epsilon_i = 1, \tag{8}$$

or detach from the actin filament with rate $k_{01}(y_i)$,

$$\epsilon_i = 1 \overset{k_{01}}{\rightarrow} \epsilon_i = 0. \tag{9}$$

We denote by τ_i the transformation of the ϵ variables which changes the value of ϵ_i only.

$$\tau_i(\{\epsilon_k\}) = \{\epsilon_k'\},$$

$$\epsilon_k' = \epsilon_k \quad \text{for} \quad k \neq i,$$

$$\epsilon_i' = \overline{\epsilon_i}, \tag{10}$$

where $\overline{\epsilon_i} = 1 - \epsilon_i$.

So τ_i is the operation of attachment (or of detachment) of the myosin head no. i.

One can write a Fokker-Planck equation for the probability distribution $P(x,\{\epsilon_i\},\{y_i\},t)$ using the equations of motion, Eqs. (2), (5), and (6). One has

$$\begin{aligned}\frac{\partial P(x,\{\epsilon_i\},\{y_i\},t)}{\partial t} = {} & \sum_{i=1}^{M} \delta_{\epsilon_i,0}\{k_{01}(y_i)P(x,\tau_i\{\epsilon_k\},\{y_k\},t) - k_{10}(y_i)P(x,\{\epsilon_k\},\{y_k\},t)\} + \sum_{i=1}^{M} \delta_{\epsilon_i,1}\{k_{10}(y_i)P(x,\tau_i\{\epsilon_k\},\{y_k\},t) \\ & - k_{01}(y_i)P(x,\{\epsilon_k\},\{y_k\},t)\} + \sum_{i=1}^{M} \delta_{\epsilon_i,0}\frac{\partial}{\partial y_i}\left(-\frac{1}{\eta_M}f_i^{(0)}(y_i)P\right) + \left(\frac{\partial}{\partial x} + \sum_{i=1}^{M} \delta_{\epsilon_i,1}\frac{\partial}{\partial y_i}\right) \\ & \times\left[-\frac{1}{\eta_A}\left(F(x) + \sum_{i=1}^{M} \delta_{\epsilon_i,1}f_i^{(1)}(y_i)\right)P\right] + \sum_{i=1}^{M} \delta_{\epsilon_i,0}D_M\frac{\partial^2}{\partial y_i^2}P + D_A\left(\frac{\partial}{\partial x} + \sum_{i=1}^{M} \delta_{\epsilon_i,1}\frac{\partial}{\partial y_i}\right)^2 P.\end{aligned} \tag{11}$$

Let us comment briefly on the origin of each term in Eq. (11). In the right-hand side, the first sum is the contribution to $P(x,\{\epsilon_i\},\{y_i\},t)$ of the detachment process of a myosin head. Namely, the myosin head no. i is in an attached state $\epsilon_i = 1$, and gets detached with probability $k_{01}(y_i)dt$ during the time interval dt. The second sum is the corresponding term for the attachment process. The third sum is the contribution of the current of probability of the motion of unattached myosin heads. It comes from the term $(1/\eta_M)f_i^0(y_i)dt$ of the equation of motion, Eq. (2). The fourth term is the contribution to the current of probability of the motions of the center of mass (coordinate x) of the actin filament together with the motion of the myosin heads which are rigidly attached to the actin filament. It comes from the term $(1/\eta_A)[F_e + \Sigma_{i=1}^{M}\delta_{\epsilon_i 1}f_i^{(1)}(y_i)]dt$ of Eqs. (5) and (6). The last two sums are the diffusion currents coming from the white noise forces, either on the free myosin heads or on the center of mass of the actin filament, together with the rigidly attached myosin heads.

We shall assume that the constants $k_{01}(y_i)$ and $k_{10}(y)$ are independent of y. We can justify this hypothesis in the following manner. First the ratio k_{01}/k_{10} is $\exp(-(1/k_BT)[U^{(0)}(y) - U^{(1)}(y)])$. But $U^{(0)}(y) - U^{(1)}(y)$ is of the order ΔG of the bond energy of ATP, so that k_{01}/k_{10} is extremely small at normal temperature ($\Delta G \sim 30$ kJ/mole) and the variation of k_{01}/k_{10} with y is also extremely small. Thus we can assume that k_{01}/k_{10} is constant.

Moreover, there is almost no information on the magnitude of k_{10} and k_{01} in the literature for the obvious reason that the attachment and detachment processes are very complex chemical reactions *in vivo*. So we take them as constant parameters. In fact, we will introduce later a Markovian hypothesis which is a much stronger hypothesis.

We define the probability $P(\{\epsilon_l\},t)$ that the myosin heads are in states $\{\epsilon_l\}$ at time t. This probability is the integral over x and y_l of the full probability $P(x,\{\epsilon_i\},\{y_i\},t)$ and satisfies an equation obtained by integration of Eq. (11) over all the spatial variables,

$$\begin{aligned}\frac{\partial P(\{\epsilon_l\},t)}{\partial t} = {} & \sum_{i=1}^{M} \delta_{\epsilon_i,0}[k_{01}P(\tau_i(\{\epsilon_l\}),t) - k_{10}P(\{\epsilon_l\},t)] \\ & + \sum_{i=1}^{M} \delta_{\epsilon_i,1}[k_{10}P(\tau_i(\{\epsilon_l\}),t) - k_{01}P(\{\epsilon_l\},t)].\end{aligned} \tag{12}$$

Let us denote by N the total number of attached myosin heads, so that N is the random variable given by

$$N = \sum_{i=1}^{M} \epsilon_i. \tag{13}$$

We shall denote by F the total force exerted on the center-of-mass coordinate x of the actin filament,

$$F=-|F_0|-Kx-\chi_1\sum_{i=1}^{M}\delta_{\epsilon_i,1}y_i\,, \tag{14}$$

and we denote by Φ the force exerted by the attached myosin heads on the actin filament,

$$\Phi=-\chi_1\sum_{i=1}^{M}\delta_{\epsilon_i,i}y_i\,. \tag{15}$$

The quantities F and Φ are random variables.

III. SYMMETRY WITH RESPECT TO THE MYOSIN HEADS

We shall assume in the sequel that the probability distributions $P(x,\{\epsilon_l\},\{y_l\},0)$ at time $t=0$ is symmetric with respect to any permutation of the myosin heads, i.e., it is unchanged by any permutation operation,

$$\{\epsilon_l\,,y_l\}\to\{\epsilon_{\sigma(l)}\,,y_{\sigma(l)}\}, \qquad \text{(S)}$$

where σ is a permutation of $\{1,\ldots,M\}$.

It is clear that this property remains valid for all t because the operator in the second member of the evolution equations, Eq. (11), is also symmetric with respect to the permutation S.

Let $A(x,\{\epsilon_l\},\{y_l\})$ be an observable of the system which is symmetric with respect to the operations of permutation S. We denote by $\langle A\rangle(t)$ its average value with respect to the probability P, namely,

$$\langle A\rangle(t)=\sum_{\{\epsilon_l\}}\int\int A(x,\{\epsilon_l\},\{y_l\})P(x,\{\epsilon_l\},\{y_l\},t)dx\{dy_l\}, \tag{16}$$

where we integrate over all the space variables x,y_l. We also denote by $\langle A\rangle(n,y)$ the average value of A, restricted on the configuration $\{\epsilon_l\}$ such that

$$N\equiv\sum_{l=1}^{M}\epsilon_l=n$$

for a given n, namely,

$$\langle A\rangle(n,t)=\sum_{N=n}\int\int A(x,\{\epsilon_l\},\{y_l\})P(x,\{\epsilon_l\},\{y_l\},t)dx\{dy_l\}, \tag{17}$$

so that obviously

$$\langle A\rangle(t)=\sum_{n=1}^{M}\langle A\rangle(n,t). \tag{18}$$

Note that $\langle A\rangle(n,t)$ is not a conditional expectation. It is only a restricted average over configurations with $N=n$.

Now it is clear that under the symmetry assumptions for A and P, all the quantities in Eq. (17),

$$\int\int A(x,\{\epsilon_l\},\{y_l\})P(x,\{\epsilon_l\},\{y_l\},t)dx\{dy_l\},$$

are equal, so that the common value is

$$\int\int A(x,\{\epsilon_l\},\{y_l\})P(x,\{\epsilon_l\},\{y_l\},t)dx\{dy_l\}=\frac{n!(M-n)!}{M!}\langle A\rangle(n,t), \tag{19}$$

given that

$$\sum_{l=1}^{M}\epsilon_l=n.$$

As a particular case, let us consider the probability $P(n,t)$ that there are n myosin heads attached to the actin filament, so that we take for A the characteristic function $\chi_{\{N=n\}}$. We have, using notations of Sec. II,

$$P(n,t)=\sum_{N=n}P(\{\epsilon_l\},t), \tag{20}$$

and all the $P(\{\epsilon_l\},t)$ are equal when $N=n$, so that Eq. (19) becomes

$$P(\{\epsilon_l\},t)=\frac{n!(M-n)!}{M!}P(n,t). \tag{21}$$

From Eq. (12), we can obtain a differential equation for $P(n,t)$. We sum Eq. (12) for all configurations $\{\epsilon_l\}$ such that $\Sigma\epsilon_l=n$. Then, using Eq. (21),

$$\begin{aligned}\frac{\partial P(n,t)}{\partial t}&=k_{01}(n+1)P(n+1,t)+k_{10}(M-n+1)P(n-1,t)\\&\quad-[k_{10}(M-n)+k_{01}n]P(n,t).\end{aligned} \tag{22}$$

This equation can be obtained directly, thanks to the hypothesis that k_{01} and k_{10} are independent of $\{y_i\}$. It is well known that it can be solved exactly if we assume that at $t=0$, $P(n,0)$ is a binomial distribution. $P(n,t)$ remains binomial at all t with average $p(t)$,

$$P(n,t)=\frac{M!}{n!(M-n)!}[1-p(t)]^{M-n}p(t)^n, \tag{23}$$

with the average $p(t)$,

$$p(t)\equiv\frac{\langle N\rangle(t)}{M}=\frac{1}{M}\sum_{n=0}^{M}nP(n,t), \tag{24}$$

given explicitly by

$$p(t)=p(0)e^{-(k_{10}+k_{01})t}+\frac{k_{10}}{k_{10}+k_{01}}(1-e^{-(k_{10}+k_{01})t}). \tag{25}$$

IV. THE EVOLUTION OF AN OBSERVABLE

A. Decomposition of the variation

We rewrite Eq. (11) with slight rearrangements in the two summations,

$$\begin{aligned}\frac{\partial P(x,\{\epsilon_l\},\{y_l\},t)}{\partial t} ={}& k_{01}\left[\sum_{i=1}^{M} \delta_{\epsilon_i,0} P[x,\tau_i(\{\epsilon_l\}),\{y_l\},t] - \sum_{i=1}^{M} \delta_{\epsilon_i,1} P(x,\{\epsilon_l\},\{y_l\},t)\right] + k_{10}\left[\sum_{i=1}^{M} \delta_{\epsilon_i,1} P(x,\tau_i\{\epsilon_l\},\{y_l\},t)\right.\\ &\left. - \sum_{i=1}^{M} \delta_{\epsilon_i,0} P(x,\tau_i\{\epsilon_l\},\{y_l\},t)\right] + \frac{1}{\eta_A}\left(\frac{\partial}{\partial x} + \sum_{i=1}^{M} \delta_{\epsilon_i,1}\frac{\partial}{\partial y_i}\right)\left[\left(|F_0| + Kx + \sum_{i=1}^{M} \delta_{\epsilon_i,1}\chi_1 y_i\right)P\right]\\ &- \frac{1}{\eta_M}\left(\sum_{i=1}^{M} \delta_{\epsilon_i,0}\frac{\partial}{\partial y_i}[f_i^{(0)}(y_i)P]\right) + D_A\left(\frac{\partial}{\partial x} + \sum_{i=1}^{M} \delta_{\epsilon_i,1}\frac{\partial}{\partial y_i}\right)^2 P + D_M\left(\sum_{i=1}^{M} \delta_{\epsilon_i,0}\frac{\partial^2}{\partial y_i^2}\right)P. \end{aligned} \tag{26}$$

Let $A(x,\{\epsilon_l\},\{y_l\})$ be a quantity which is symmetric with respect to the permutation S of the myosin heads. We can obtain the derivative $(d\langle A\rangle/dt)(n,t)$ of $\langle A\rangle(n,t)$ using Eq. (26). We multiply Eq. (26) by $A(x,\{\epsilon_l\},\{y_l\},t)$, integrate over the spatial variables, and sum over configurations $\{\epsilon_l\}$ with $N=n$. We obtain four contributions,

$$\frac{d\langle A\rangle}{dt}(n,t) = \left(\frac{d\langle A\rangle}{dt}\right)_d + \left(\frac{d\langle A\rangle}{dt}\right)_a + \left(\frac{d\langle A\rangle}{dt}\right)_F + \left(\frac{d\langle A\rangle}{dt}\right)_D, \tag{27}$$

corresponding to the four types of contributions to the right-hand side of Eq. (26), namely, (i) the contributions of detachment processes (proportional to k_{01}), (ii) the contributions of attachment processes (proportional to k_{10}), (iii) the contributions of friction processes (proportional to $1/\eta_A$ and $1/\eta_M$), and (iv) the contributions of diffusion processes (proportional to D_A and D_M).

These different contributions are studied below.

B. Friction and diffusion processes

The contributions of these processes to $d\langle A\rangle/dt$ are obtained by multiplying the corresponding terms in the right-hand side of Eq. (26) by $A(x,\{\epsilon_l\},\{y_l\})$, integrating over the spatial variables, and summing over configurations $\{\epsilon_l\}$ with $\Sigma\epsilon_l=n$. After integration by parts, we obtain

$$\begin{aligned}\left(\frac{d\langle A\rangle}{dt}(n,t)\right)_F ={}& -\frac{1}{\eta_A}\sum_{N=n}\int\int\left(|F_0| + Kx + \chi_1\sum_{i=1}^{M}\delta_{\epsilon_i,1}y_i\right)\\ &\times P\left(\frac{\partial}{\partial x} + \sum_{i=1}^{M}\delta_{\epsilon_i,1}\frac{\partial}{\partial y_i}\right)A\,dx\{dy_l\}\\ &+ \frac{1}{\eta_M}\sum_{N=n}\int\int\sum_{i=1}^{M}\delta_{\epsilon_i,0}f_i^{(0)}(y_i)P\left(\frac{\partial}{\partial y_i}A\right)dx\{dy_l\}\end{aligned} \tag{28}$$

$$\begin{aligned}\left(\frac{d\langle A\rangle}{dt}(n,t)\right)_D ={}& D_A\sum_{N=n}\int\int P\left(\frac{\partial}{\partial x} + \sum_{i=1}^{M}\delta_{\epsilon_i,1}\frac{\partial}{\partial y_i}\right)^2 A\,dx\{dy_l\}\\ &+ D_M\sum_{N=n}\int\int P\left(\sum_{i=1}^{M}\delta_{\epsilon_i,0}\frac{\partial^2}{\partial y_i^2}\right)A\,dx\{dy_l\}.\end{aligned} \tag{29}$$

C. Attachment and detachment processes

At an instant of attachment or of detachment, the quantity A varies discontinuously. Let us consider the detachment process, given by the terms proportional to k_{01} in Eq. (26). We have

$$\begin{aligned}\left(\frac{d\langle A\rangle}{dt}(n,t)\right)_d ={}& k_{01}\sum_{N=n}\left[\sum_{i=1}^{M}\delta_{\epsilon_i,0}\int\int A(x,\{\epsilon_l\},\{y_l\})\right.\\ &\times P(x,\tau_i(\{\epsilon_l\}),\{y_l\},t)dx\{dy_l\}\\ &-\sum_{i=1}^{M}\delta_{\epsilon_i,1}\int\int A(x,\{\epsilon_l\},\{y_l\})\\ &\left.\times P(x,\{\epsilon_l\},\{y_l\},t)dx\{dy_l\}\right].\end{aligned} \tag{30}$$

Using Eq. (19), the last sum in the square bracket reduces to

$$\begin{aligned}&-\left(\sum_{i=1}^{M}\delta_{\epsilon_i,1}\right)\frac{n!(M-n)!}{M!}\langle A\rangle(n,t)\\ &= -n\frac{n!(M-n)!}{M!}\langle A\rangle(n,t),\end{aligned}$$

and the sum over the configurations with $\Sigma\epsilon_i=n$ gives a contribution

$$-k_{01}n\langle A\rangle(n,t). \tag{31}$$

We rewrite the square bracket in the first sum of Eq. (30) as

$$\begin{aligned}&\sum_{i=1}^{M}\delta_{\epsilon_i,0}\int\int A(x,\tau_i\{\epsilon_l\},\{y_l\})P(x,\tau_i(\{\epsilon_l\}),\{y_l\},t)dx\{dy_l\}\\&\quad+\sum_{i=1}^{M}\delta_{\epsilon_i,0}\int\int[A(x,\{\epsilon_l\},\{y_l\})-A(x,\tau_i\{\epsilon_l\},\{y_l\})]\\&\quad\times P(x,\tau_i(\{\epsilon_l\}),\{y_l\},t)dx\{dy_l\}.\end{aligned}\tag{32}$$

In Eq. (32), let us consider the first summation. It is

$$\left(\sum_{i=1}^{M}\delta_{\epsilon_i,0}\right)\frac{(n+1)!(M-n-1)!}{M!}\langle A\rangle(n+1,t),$$

with $\Sigma_{i=1}^{M}\delta_{\epsilon_i,0}=M-n$. We sum this quantity over all configurations with $\Sigma\epsilon_i=n$, so that this term gives a contribution to Eq. (30), which is

$$(n+1)k_{01}\langle A\rangle(n+1,t). \tag{33}$$

In Eq. (32), we can calculate the contribution to Eq. (30) of the second summation as follows. It is

$$\begin{aligned}&k_{01}\sum_{N=n+1}\sum_{i=1}^{M}\delta_{\epsilon_i,1}\int\int A(x,\tau_i\{\epsilon_l\},\{y_l\})\\&\quad-A(x,\{\epsilon_l\},\{y_l\})P(x,\{\epsilon_l\},\{y_l\},t)dx\{dy_l\}.\end{aligned}\tag{34}$$

Indeed, in the sum over configurations $\{\epsilon_l\}$, we can use $\{\epsilon_l\}$ in P, provided that $\Sigma\epsilon_i=n+1$.

Let us define

$$\begin{aligned}(\delta_i A)_d(x,\{\epsilon_l\},\{y_l\})=\delta_{\epsilon_i,1}[&A(x,\tau_i\{\epsilon_l\},\{y_l\})\\&-A(x,\{\epsilon_l\},\{y_l\})],\end{aligned}\tag{35}$$

which is the jump of A when the myosin head no. i gets detached, and

$$(\delta A)_d(x,\{\epsilon_l\},\{y_l\})=\sum_{i=1}^{M}(\delta_i A)_d(x,\{\epsilon_l\},\{y_l\}), \tag{36}$$

which is the a symmetric state function. Then, expression (34) is exactly

$$k_{01}\langle(\delta A)\rangle_d(n+1,t). \tag{37}$$

If we collect the contribution of Eqs. (31), (33), and (37), we obtain

$$\begin{aligned}\left(\frac{d\langle A\rangle}{dt}(n,t)\right)_d=&k_{01}[(n+1)\langle A\rangle(n+1,t)-n\langle A\rangle(n,t)\\&+\langle(\delta A)_d\rangle(n+1,t)].\end{aligned}\tag{38}$$

We proceed exactly in the same manner for the attachment processes of the myosin heads. We have instead of Eq. (30),

$$\begin{aligned}\left(\frac{d\langle A\rangle}{dt}(n,t)\right)_a=k_{10}\sum_{N=n}\Bigg[&\sum_{i=1}^{M}\delta_{\epsilon_i,1}\int\int A(x,\{\epsilon_l\},\{y_l\})\\&\times P(x,\tau_i(\{\epsilon_l\}),\{y_l\},t)dx\{dy_l\}\\&-\sum_{i=1}^{M}\delta_{\epsilon_i,0}\int\int A(x,\{\epsilon_l\},\{y_l\})\\&\times P(x,\{\epsilon_l\},\{y_l\},t)dx\{dy_l\}\Bigg].\end{aligned}\tag{39}$$

We define

$$\begin{aligned}(\delta_i A)_a(x,\{\epsilon_l\},\{y_l\})=\delta_{\epsilon_i,0}[&A(x,\tau_i(\{\epsilon_l\}),\{y_l\})\\&-A(x,\{\epsilon_l\},\{y_l\})],\end{aligned}\tag{40}$$

which is the jump of A when the myosin head no. i gets attached to the actin and we define

$$(\delta A)_a(x,\{\epsilon_l\},\{y_l\})=\sum_{i=1}^{M}(\delta_i A)_a(x,\{\epsilon_l\},\{y_l\}), \tag{41}$$

which is a symmetric quantity. Then, the analog of Eq. (40) for the attachment process is

$$\begin{aligned}\left(\frac{d\langle A\rangle}{dt}(n,t)\right)_a=&k_{01}[(M-n+1)\langle A\rangle(n-1,t)-(M-n)\langle A\rangle\\&\times(n,t)+\langle(\delta A)_a\rangle(n-1,t)].\end{aligned}\tag{42}$$

D. Generating functions

We define the generating function as usual,

$$\langle A\rangle(s,t)=\langle s^N A\rangle=\sum_{n=0}^{M}s^n\langle A\rangle(n,t).$$

Again $(d\langle A\rangle/dt)(s,t)$ is the sum of four contributions,

$$d\langle A\rangle dt(s,t)_p=\sum_{n=0}^{M}s^n\left(\frac{d\langle A\rangle}{dt}(n,t)\right)_p,$$

where the index p stands for $a,d,F,$ and D.

Using Eqs. (38) and (42), we obtain

$$\frac{d\langle A\rangle}{dt}(s,t)_d=k_{01}\left[(1-s)\frac{\partial\langle A\rangle}{\partial s}(s,t)+\frac{1}{s}\langle(\delta A)_d\rangle(s,t)\right],\tag{43}$$

$$\begin{aligned}\frac{d\langle A\rangle}{dt}(s,t)_a=k_{10}\Bigg[&s(1-s)\frac{\partial\langle A\rangle}{\partial s}(s,t)-M(1-s)\langle A\rangle(s,t)\\&+s\langle(\delta A)_a\rangle(s,t)\Bigg].\end{aligned}\tag{44}$$

We also denote

$$P(s,t)=\sum_{n=0}^{N} s^n P(n,t). \tag{45}$$

Using Eq. (23), one obtains

$$P(s,t)=[1-p(t)(1-s)]^M. \tag{46}$$

Remark. Notice that in Eq. (43), the term $(1/s)\langle(\delta A)_d\rangle(s,t)$ is nonsingular because $\langle(\delta A)_d\rangle|_{n=0}=0$ due to Eqs. (35) and (36), which shows that if $n=0$, then there is nothing to be detached.

E. Simplifying assumptions

We shall now make some reasonable approximations, which will permit to complete the calculations.

H1. We assume that the myosin head is instantaneously equilibrated when it is detached from the actin filament and moreover that its equilibrium distribution is $\delta(y-y^*)$ [recall that y^* is the mechanical equilibrium position for the force $f_i^0(y)$]. Thus, we neglect the transient equilibrium regime as well as the fluctuations around y^*, which is reasonable for the free evolution of a single myosin head since we should have $\eta_M \ll \eta_A$ and $D_M \gg D_A$.

H2. We assume that when a detached myosin head becomes attached to the actin filament, it is attached at the value $y=y^*$ of its coordinate y (which is coherent with the previous hypothesis).

As a consequence of hypothesis $H1$, we will drop the terms in $1/\eta_M$ and D_M in Eqs. (28) and (28), respectively, so that they reduce to

$$\left(\frac{d\langle A\rangle}{dt}(n,t)\right)_F = -\frac{1}{\eta_A}\sum_{N=n}\int\int\left(|F_0|+Kx+\chi_1\sum_{i=1}^{M}\delta_{\epsilon_i,1}y_i\right) \times P\left(\frac{\partial}{\partial x}+\sum_{i=1}^{M}\delta_{\epsilon_i,1}\frac{\partial}{\partial y_i}\right)A\,dx\{dy_l\}, \tag{47}$$

$$\left(\frac{d\langle A\rangle}{dt}(n,t)\right)_D = D_A\sum_{N=n}\int\int P\left(\frac{\partial}{\partial x}+\sum_{i=1}^{M}\delta_{\epsilon_i,1}\frac{\partial}{\partial y_i}\right)^2 \times A\,dx\{dy_l\}. \tag{48}$$

V. POSITION AND FORCE IN THE ACTIN FILAMENT

A. Equation for the position

At first, we take for the quantity A the position. The position does not vary when a myosin head is attached or detached and from Eqs. (47) and (47), we have

$$\left(\frac{d\langle x\rangle}{dt}(n,t)\right)_F = \frac{1}{\eta_A}\langle F\rangle(n,t),$$

$$\left(\frac{d\langle x\rangle}{dt}(n,t)\right)_D = 0,$$

so that

$$\left(\frac{\partial\langle x\rangle}{\partial t}(s,t)\right) = k_{01}(1-s)\frac{\partial\langle x\rangle}{\partial s} + k_{10}s(1-s)\frac{\partial\langle x\rangle}{\partial s} - k_{10}M(1-s)\langle x\rangle + \frac{1}{\eta_A}\langle F\rangle, \tag{49}$$

from which we deduce for $s=1$ the obvious relation

$$\frac{d\langle x\rangle}{dt}(t) = \frac{1}{\eta_A}\langle F\rangle(t) \tag{50}$$

and also by taking the s derivation of Eq. (49) at $s=1$,

$$\frac{d}{dt}\left.\frac{\partial\langle x\rangle}{\partial s}\right|_{s=1} = -(k_{01}+k_{10})\left.\frac{\partial\langle x\rangle}{\partial s}\right|_{s=1} + k_{10}M\langle x\rangle(t) + \frac{1}{\eta_A}\left.\frac{\partial}{\partial s}\langle F\rangle\right|_{s=1} \tag{51}$$

which will be needed later.

B. Equation for the force F

Now, we take for A, the force F given by Eq. (14). In Eq. (47), we have to calculate

$$\left(\frac{\partial}{\partial x}+\sum_{i=1}^{M}\delta_{\epsilon_i,1}\frac{\partial}{\partial y_i}\right)F = -\left(K+\chi_1\sum_{i=1}^{M}\delta_{\epsilon_i,1}\right).$$

In the restricted summation of Eq. (47), $\Sigma_{i=1}^{n}\delta_{\epsilon_i,1}=n$, so that Eqs. (47) and (47) give

$$\left(\frac{d\langle F\rangle}{dt}(n,t)\right)_F = -\frac{1}{\eta_A}(K+\chi_1 n)\langle F\rangle(n,t), \tag{52}$$

$$\left(\frac{d\langle F\rangle}{dt}(n,t)\right)_D = 0, \tag{53}$$

and thus

$$\left(\frac{d\langle F\rangle}{dt}(s,t)\right)_F = -\frac{1}{\eta_A}\left[K\langle F\rangle(s,t)+\chi_1 s\frac{\partial\langle F\rangle}{\partial s}(s,t)\right]. \tag{54}$$

From hypothesis $H2$, we deduce that the variation of the force F during the attachment of the myosin head no. i is

$$(\delta_i F)_a(x,\{\epsilon_l\},\{\epsilon_l\}) = -\chi_1 y^*\delta_{\epsilon_i,0}.$$

Then

$$(\delta F)_a(x,\{\epsilon_l\},\{\epsilon_l\}) = -\chi_1 y^*\sum_{i=1}^{M}\delta_{\epsilon_i,0} \tag{55}$$

and in Eq. (44)

$$\langle (\delta F)_a \rangle (s,t) = -\chi_1 y^* \sum_{n=0}^{M} s^n (M-n) P(n,t)$$

$$= -\chi_1 y^* \left[M P(s,t) - s \frac{\partial P}{\partial s} \right]. \qquad (56)$$

So, Eq. (44) can be rewritten as

$$\left(\frac{d\langle F\rangle}{dt}(s,t) \right)_a = k_{10} \left[(1-s) \left\{ s \, \frac{\partial \langle F\rangle}{\partial s}(s,t) - M\langle F\rangle(s,t) \right\} - \chi_1 y^* \left\{ sMP(s,t) - s^2 \frac{\partial P}{\partial s}(s,t) \right\} \right]. \qquad (57)$$

Finally, we calculate the contribution of the detachment processes given by Eq. (43) with $A=F$. During the detachment process of the myosin head no. *i*, the variation of the force is given by

$$(\delta_i F)_d (x, \{\epsilon_l\}, \{\epsilon_l\}) = \delta_{\epsilon_i,1} \chi_1 y_i$$

because when the myosin head no. *i*, which is attached and has an internal coordinate y_i, gets detached, there is a drop of the total force $-(-\chi_1 y_i)$. This formula leads to an exact, but untractable hierarchy of equations. Instead, we reason as follows.

When the myosin head no. *i* gets detached at a certain random time *T*, the variation of the force is $\chi_1 y_i(T)$, where $y_i(T)$ is the position of the internal coordinate y_i of the myosin head no. *i* at time *T*. But, we have

$$y_i(T) = y^* + \int_{T'}^{T} \frac{dy_i}{dt} dt,$$

where T' is the random time of the previous attachment of this myosin head no. *i*, so that

$$\mathrm{Prob}(T - T' > t) = e^{-k_{01} t}.$$

But during the time interval $[T, T']$, the myosin head no. *i* is always attached to the actin filament, so that

$$\frac{dy_i}{dt} = \frac{dx}{dt} = \frac{1}{\eta_A} F + \frac{d\xi}{dt}$$

and

$$y_i(T) = y^* + \frac{1}{\eta_A} \int_{T'}^{T} F dt + \xi(T) - \xi(T').$$

We make now a Markovian approximation, namely, we assume that k_{01} is large, so $\langle T - T' \rangle \simeq k_{01}^{-1}$ is small and we approximate *F* during the time interval $[T, T']$, for the myosin head no. *i* by the final value $F(T)$ so that

$$y_i(t) \sim y^* + \frac{\langle (T-T') \rangle}{\eta_A} F \sim y^* + \frac{F}{\eta_A k_{01}}, \qquad (58)$$

so that from Eqs. (35) and (36)

$$(\delta F)_d (x, \{\epsilon_l\}, \{y_l\}) = \chi_1 \left(y^* + \frac{F}{\eta_A k_{01}} \right) \left(\sum_{i=1}^{M} \delta_{\epsilon_i,1} \right), \qquad (59)$$

and we obtain

$$\langle (\delta F)_d (s,t) \rangle = \chi_1 y^* s \frac{\partial P}{\partial s} + \frac{\chi_1}{\eta_A k_{01}} s \frac{\partial \langle F \rangle}{\partial s}. \qquad (60)$$

Using Eq. (43), we obtain using Eq. (60),

$$\left(\frac{d\langle F\rangle}{dt}(s,t) \right)_d = (1-s) k_{01} \frac{\partial \langle F\rangle}{\partial s}(s,t) + \frac{\chi_1}{\eta_A} \frac{\partial \langle F\rangle}{\partial s} + k_{01} \chi_1^* \frac{\partial P}{\partial s}. \qquad (61)$$

Finally, the equation of evolution of the force is obtained using Eqs. (52), (54), (57), and (61).

$$\frac{\partial \langle F\rangle}{\partial t}(s,t) = (1-s) \left(k_{01} + k_{10} s + \frac{\chi_1}{\eta_A} \right) \frac{\partial \langle F\rangle}{\partial s} - \left(\frac{K}{\eta_A} + k_{10} M (1-s) \right) \langle F\rangle + \chi_1^* y^* \times \left[k_{01} \frac{\partial \langle P\rangle}{\partial s} + k_{10} s^2 \frac{\partial \langle P\rangle}{\partial s} - k_{10} M s P \right] \qquad (62)$$

which leads, for $s=1$, to the equation for $\langle F\rangle(t)$ [see Eq. (A5)].

By taking the derivative with respect to *s* for $s=1$, we obtain also an equation for $\partial\langle F\rangle/\partial s|_{s=1}$, namely,

$$\frac{d}{dt} \left(\left. \frac{\partial \langle F\rangle}{\partial s} \right|_{s=1} \right) = -\left(k_{01} + k_{10} + \frac{K+\chi_1}{\eta_A} \right) \left. \frac{\partial \langle F\rangle}{\partial s} \right|_{s=1} + k_{10} M \langle F\rangle|_{s=1} + \chi_1 y^* \left. \frac{\partial}{\partial s} \right|_{s=1} \times \left[(k_{01} + k_{10} s^2) \frac{\partial P}{\partial s} - k_{10} M s P \right]. \qquad (63)$$

C. Evolution of $\langle x \rangle$ and $\langle F \rangle$

Equation (62) easily leads [see Eq. (A5)] to

$$\langle F(t) \rangle = \frac{M k_{10} \chi_1 y^*}{k - \frac{K}{\eta_A}} [e^{-kt} - e^{-(K/\eta_A)t}] \qquad (64)$$

with

$$k = k_{10} + k_{01}, \qquad (65)$$

which shows that $\langle F\rangle$, starting from the initial value 0, is always positive because in our convention, y^* is negative. It quickly reaches a maximum value, and then decreases exponentially to 0,

$$\langle F(\infty)\rangle = 0,$$

as it could be anticipated. Then the average position $\langle x\rangle(t)$ of the actin can be studied by Eq. (50). The exact value of $\langle x(t)\rangle$ is given by Eq. (A9). It is proved in Appendix A that $\langle x(t)\rangle$ reaches a limit when $t\to\infty$,

$$\langle x(\infty)\rangle - x(0) = -\frac{Mk_{10}\chi_1 y^*}{kK} > 0, \tag{66}$$

where $x(0)$ satisfies $|F_0| + Kx(0) = 0$.

Moreover, if $t\to\infty$, the attached myosin heads create a total force which is in average

$$|F_0| + K\langle x(\infty)\rangle.$$

Because $|F_0| + Kx(0) = 0$, we see that the total force exerted by the myosin heads on the actin filament is

$$\langle \Phi(\infty)\rangle = -\frac{Mk_{10}\chi_1 y^*}{k}. \tag{67}$$

Equation (67) is rather natural, because Mk_{10}/k is the average number $\langle N(\infty)\rangle$ of attached myosin heads, $-\chi_1 y^*$ is the force exerted by an attached myosin head when it has just attached, and in our Markovian aproximation ($k_{01} \gg 0$), the force $-\chi_1 y^*$ is essentially the force exerted by an attached myosin head.

D. Correlations $\langle Nx\rangle$ and $\langle NF\rangle$

The stochastic theory developed previously is mainly useful for studying the correlations, which cannot be obtained from simple arguments.

In fact, these are the correlations between the position or the force and the number of attached myosin heads. They are given by

$$\langle Nx\rangle = \frac{\partial\langle x\rangle}{\partial s}(s,t)\bigg|_{s=1},$$

$$\langle NF\rangle = \frac{\partial\langle F\rangle}{\partial s}(s,t)\bigg|_{s=1}.$$

Their values are given by Eqs. (A16) and (A21) for $t=\infty$,

$$\langle NF\rangle(\infty) = -\frac{Mk_{10}^2 k_{01}\chi_1 y^*}{k^2\xi}, \tag{68}$$

$$\langle Nx\rangle(\infty) = -\frac{M^2k_{10}^2\chi_1 y^*}{k^2K} + M\frac{k_{10}}{k}\left(x(0) - \frac{k_{10}k_{01}\chi_1 y^*}{\eta_A k^2\xi}\right), \tag{69}$$

with

$$\xi = k + \frac{K+\chi_1}{\eta_A}. \tag{70}$$

Note that the correlation between N and x is given by

$$\langle Nx\rangle(\infty) - \langle N(\infty)\rangle\langle x(\infty)\rangle \sim -\frac{Mk_{10}^2k_{01}\chi_1 y^*}{\eta_A k^3\xi} > 0,$$

which is proportional to M and to $(\eta_A k_{01}^3)^{-1}$ because of the value of ξ in Eq. (70), for large η_A and k_{01}. Moreover, there is clearly a positive correlation between N and F given by the formula of Eq. (68) (recall that $\langle N(t)\rangle$ decreases exponentially rapidly for large t).

VI. SECOND MOMENTS, WORK, AND EFFICIENCY

A. Diffusion and friction coefficient

The diffusion coefficient D_A is related to the friction coefficient η_A by the usual Einstein formula

$$D_A = \frac{k_B T}{\eta_A}, \tag{71}$$

which is the condition of consistency to reach thermal equilibrium for the actin coordinate x, for a given configuration of the myosin heads, in the high friction limit. Moreover, η_A is proportional to the total surface of the actin filament, with the myosin heads which are attached to it. So it seems reasonable to write

$$\eta_A = \eta_A^0 + \sigma\sum_{i=1}^{M}\delta_{\epsilon_i,1},$$

where η_A^0 is the friction coefficient for the actin filament with no attached myosin. Because we are interested only in the large time limit, we replace this expression by

$$\eta_A = \eta_A^0 + \sigma M\frac{k_{10}}{k}. \tag{72}$$

B. Second moments $\langle F^2\rangle$ and $\langle xF\rangle$

Obtaining the time-dependent expressions of these moments needs lengthy and intricate calculations which will be published elsewhere. Their stationary values are given by

$$\frac{1}{\eta_A}\langle F^2\rangle(\infty) \simeq KD_A + (\chi_1 y^*)^2 k_{10}k_{01}M/(k^2\eta_A), \tag{73}$$

$$\frac{1}{\eta_A}\langle xF\rangle(\infty) = -D_A. \tag{74}$$

C. The cycle for a single myosin head

Figure 2 represents a full cycle, in terms of free energy, for a single myosin head. The cycle starts when a given myosin head is attached to the actin filament. According to our hypothesis $H2$ in Sec. IV E, this takes place at a point A, with $y=y^*$ at a certain time T'. The myosin coordinate y relaxes along the potential energy curve $U^{(1)}$, along the arc AB and gets detached at a certain time T, at a position $y(T)$. After that time, an ATP molecule is attached and the free energy increases by ϵ_0, to point C, above the potential energy $U^{(0)}$ of the detached myosin head. According to our hypothesis $H1$, the free myosin head releases instantaneously to is mechanical equilibrium position y^* at point D, and then, is attached again closing the cycle at point A, while the ATP molecule is hydrolyzed in ADP+P$_i$.

D. Work and efficiency

The work produced by the muscular fiber per unit time is the work of the mesoscopic force $|F_0|+Kx$, so this is

$$\frac{dW}{dt}=(|F_0|+Kx)\frac{dx}{dt}. \tag{75}$$

We obtain

$$\left\langle\frac{dW}{dt}\right\rangle=|F_0|\frac{1}{\eta_A}\langle F\rangle+\frac{K}{\eta_A}\langle xF\rangle.$$

If t is large, the first term in the right-hand side tends to 0, and the average power is given by Eq. (74),

$$\left\langle\frac{dW}{dt}\right\rangle=-KD. \tag{76}$$

This residual power is consumed by the fiber although its macroscopic motion has stopped. It is due to the diffusion effects.

Now, in the stationary state, the energy which is put in the system per unit time, is the energy ϵ_0 of an ATP bond multiplied by the number of ATP bonds which are destroyed per unit time, which is also the number of detachment processes per unit time, so the energy fueled in the system per unit time, due to the ATP molecules is

$$\left\langle\frac{dE}{dt}\right\rangle=\epsilon_0\langle N\rangle(t)k_{01}. \tag{77}$$

The efficiency is

$$R=\frac{\left\langle\frac{dW}{dt}\right\rangle}{\left\langle\frac{dE}{dt}\right\rangle}. \tag{78}$$

This efficiency is smaller than 1, as it should be, but this is not so obvious. To show this, we rewrite the expression for dW/dt in the following way. We start from Eq. (75) and use

$$|F_0|+Kx=-F-\sum_{i=1}^{M}\delta_{\epsilon_i,1}\chi_1 y_i.$$

But by Eq. (6),

$$dx=\frac{1}{\eta_A}F\,dt+d\xi, \tag{79}$$

where $d\xi$ is the white noise force, so that

$$(|F_0|+Kx)dx=-\frac{1}{\eta_A}F^2dt-F\,d\xi-\sum_{i=1}^{M}\delta_{\epsilon_i,1}\chi_1 y_i\,dx. \tag{80}$$

On the other hand, when the myosin head no. i is attached to the actin filament, $dy_i=dx$, so that

$$y_i dx=y_i dy_i=d\left(\frac{y_i^2}{2}\right)-\frac{1}{2}(dy_i)^2=d\left(\frac{y_i^2}{2}\right)-\frac{1}{2}(dx)^2.$$

Let us take the average of Eq. (80) and use the previous relation. We notice that because $d\xi(t)$ is independent of the past,

$$\langle F\,d\xi\rangle=0.$$

Moreover $(dx)^2$ is $(d\xi)^2$ independent of the number of myosin heads which are attached and so, because $\langle(d\xi)^2\rangle=2D_A dt$ [see Eq. (7)],

$$\langle(|F_0|+kx)dx\rangle=-\frac{1}{\eta_A}\langle F^2\rangle dt-\left\langle\sum_{i=1}^{M}\delta_{\epsilon_i,1}d(U^{(1)}(y_i))\right\rangle+\chi_1 D_A\langle N(t)\rangle dt. \tag{81}$$

Let us examine the behavior of this expression for large t. The last term $D_A\langle N(t)\rangle dt$ is of order $O(1)$ with respect to M and so it is negligible compared to the first term $-(1/\eta_A)\langle F^2\rangle dt$ which is of order $O(M)$ [see Eq. (73)]. Moreover, for a single attached myosin head, the variation $-dU^{(1)}(y)$ of the potential energy during a time interval $[T,T']$ between an instant T' of attachment and the following instant of detachment T, is surely less then the value ϵ_0 of an ATP bond energy. This is explained in Sec. VI C and shown in Fig. 2. As a consequence, one has

$$-\langle dU^{(1)}(y_i)\rangle\leqslant\epsilon_0 k_{01}dt$$

and

$$-\left\langle\sum_{i=1}^{M}\delta_{\epsilon_i,1}dU^{(1)}(y_0)\right\rangle\leqslant\epsilon_0\langle N(\infty)\rangle k_{01}dt,$$

so that from Eqs. (81) and (77),

$$\begin{aligned}\left\langle\frac{dW}{dt}\right\rangle&=\left\langle\frac{(|F_0|+kx)dx}{dt}\right\rangle\\&\leqslant\epsilon_0 M\frac{k_{10}k_{01}}{k}-\frac{1}{\eta_A}\langle F^2\rangle+O(1)\\&\leqslant\left\langle\frac{dE}{dt}\right\rangle.\end{aligned}$$

This proves that $R\leqslant1$.

VII. CONCLUSION

In this paper, we have defined a detailed microscopic model for the conversion of chemical energy into translational mechanical energy for the contraction of a muscle. We have taken into account the fact that the actin filament (which is set in motion) is coupled to a large number of independent myosin molecules, and we have treated each individual myosin molecule using its own internal degree of freedom. This led us to a system of Fokker-Planck equations for the evolution of the probability distributions of the configuration of the system actin-myosin molecules. Using a kind of Markovian approximation which was justified in Sec. V, we have been able to avoid an infinite hierarchy and to solve for the time evolution of the average and correlation of the three main physical quantities for the system, namely, the total number of attached myosin heads, the coordinate of the center of mass, and the total force on the actin filament. In fact, we have introduced a reduced ‘‘coarse grained’’ description of the system. In particular, we have considered the work and the efficiency in the transient regime as well as in the stationary state.

The expressions for the work and the efficiency can be considered as the main results of this microscopic model. In fact, their calculations need the second moments and correlations of the stochastic variables. These correlations cannot be obtained from a ‘‘mean field’’ model of muscular contraction when only one effective myosin head is considered (whereas the mean values of the variable can be estimated in this way). On the other hand, the efficiency of muscular contraction is an important quantity in practice, and our theoretical results should be compared to experimental observations. This necessary comparison should use the explicit expression of *R* obtained from Eq. (78) after lengthy calculations which will be given in a further publication. It includes many parameters with clear physicochemical meaning, but which may be difficult to measure individually. It can be expected that further progress in this direction will result from close collaboration with biologists.

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APPENDIX A: SOLUTIONS OF THE EQUATIONS FOR *F* AND *x*

1. Calculation of $\langle x\rangle$ and $\langle F\rangle$

Using Eq. (46), we obtain

$$\left.\frac{\partial P}{\partial s}\right|_{s=1}=Mp(t)=\langle N(t)\rangle. \tag{A1}$$

We assume that at time $t=0$, no myosin head is attached, so that $p(0)=0$ and by Eq. (25),

$$p(t)=\frac{k_{10}}{k}(1-e^{-kt}), \tag{A2}$$

with

$$k\equiv k_{10}+k_{01}. \tag{A3}$$

Then we need in Eq. (62)

$$(k_{01}+k_{10}s^2)\frac{\partial P}{\partial s}-k_{10}MsP=M[1-p(1-s)]^{M-1}\times[k_{01}p+k_{10}s(p-1)]. \tag{A4}$$

For $s=1$, this reduces to $-Mk_{10}e^{-kt}$, and Eq. (62) becomes for $s=1$,

$$\frac{d\langle F\rangle(t)}{dt}=-\frac{K}{\eta_A}\langle F\rangle(t)-Mk_{10}\chi_1 y^* e^{-kt}. \tag{A5}$$

This equation must be solved with the initial value $\langle F\rangle(0)=0$. Indeed at time $t=0$, when the muscle is stretched by the external force $-|F_0|$, it goes to an equilibrium position $x(0)$ such that

$$-|F_0|-Kx(0)=0 \tag{A6}$$

and no myosin is attached, so there is no force exerted by the myosin and $F(0)=0$. The solution of Eq. (A5) with $\langle F(0)\rangle=0$ is

$$\langle F(t)\rangle\equiv\frac{Mk_{10}\chi_1 y^*}{k-\dfrac{K}{\eta_A}}[e^{-kt}-e^{-(K/\eta_A)t}], \tag{A7}$$

which is always positive, since $y^*<0$.

Recall here that we are in the large friction limit, so the dominant term for large *t* is

$$\langle F(t)\rangle\sim-\frac{Mk_{10}\chi_1 y^*}{k-\dfrac{K}{\eta_A}}e^{-(K/\eta_A)t}. \tag{A8}$$

Then Eq. (50) for $\langle x(t)\rangle$ can be solved immediately using Eq. (A7) and the initial condition $x(0)$ is given by Eq. (A6),

$$\langle x(t)\rangle=x(0)+\frac{Mk_{10}\chi_1 y^*}{k\eta_A-K}\left[\frac{\eta_A}{K}(e^{-(K/\eta_A)t}-1)-\frac{1}{k}(e^{-kt}-1)\right] \tag{A9}$$

for $t\to+\infty$, so we see that

$$\langle x(\infty)\rangle=x(0)-\frac{Mk_{10}\chi_1 y^*}{kK}. \tag{A10}$$

We recall that y^* is negative according to our conventions, so clearly $\langle x(\infty)\rangle$ is larger than $x(0)$ as it should be.

2. A lemma

Before continuing the calculations, we need a simple lemma. Consider a differential equation

$$\frac{du}{dt} = -\alpha u + g,$$

$$u(0) = 0, \tag{A11}$$

where α is a positive constant and $g(t)$ is a function such that for large t

$$g(t) = g_\infty + O(e^{-\gamma t}) \quad (\gamma > 0). \tag{A12}$$

Then the solution $u(t)$ of Eq. (A11) satisfies

$$u(t) \equiv \frac{g_\infty}{\alpha} + O(e^{-\gamma' t}) \quad (\gamma' > 0). \tag{A13}$$

Indeed we define

$$u(t) = v(t) e^{-\alpha t},$$

so that v satisfies

$$\frac{dv}{dt} = g(t) e^{-\alpha t},$$

and

$$u(t) = e^{-\alpha t} \int_0^t g(s) e^{\alpha s} ds,$$

from which the result of Eq. (A13) follows.

3. Calculation of $\partial\langle F\rangle/\partial s|_{s=1}$ for large t

$\partial\langle F\rangle \partial s|_{s=1}$ satisfies Eq. (63) which is of the type (A11). At time $t=0$ it is obviously 0. We study the asymptotic behavior of the inhomogeneous terms in Eq. (63). First, we know that $\langle F\rangle|_{s=1}$ decreases exponentially [see Eq. (A8)]. Then, using Eq. (A4), we can compute

$$\begin{aligned}
\left.\frac{\partial}{\partial s}\right|_{s=1} &\left((k_{01} + k_{10} s^2) \frac{\partial P}{\partial s} - k_{10} M s P \right) \\
&= M(M-1) p [kp - k_{10}] + M k_{10} (p-1) \\
&= -M^2 p k_{10} e^{-kt} - M k_{01} p^2.
\end{aligned}$$

So for $t \to \infty$, this is $-M k_{10}^2 k_{01}/k^2$ and the asymptotic behavior of the inhomogeneous term of Eq. (63) is

$$g_\infty = -\frac{M k_{10}^2 k_{01}}{k^2} \chi_1 y^*. \tag{A14}$$

Define

$$\xi = k + \frac{K + \chi_1}{\eta_A}. \tag{A15}$$

Then using Eq. (A13), we obtain

$$\left.\frac{\partial\langle F\rangle}{\partial s}\right|_{s=1} \to -\frac{M k_{10}^2 k_{01} \chi_1 y^*}{k^2 \xi}. \tag{A16}$$

4. Calculation of $\partial^2\langle F\rangle/\partial s^2|_{s=1}$ for large t

For further use, we need to calculate this limit. First we derive an equation for this quantity by taking the second derivative in s for Eq. (62) and then take $s=1$,

$$\begin{aligned}
\frac{d}{dt}\left(\left.\frac{\partial^2\langle F\rangle}{\partial s^2}\right|_{s=1} \right) &= -2 \frac{\partial}{\partial s}\left[\left(k_{01} + k_{10} s + \frac{\chi_1}{\eta_A} \right) \frac{\partial\langle F\rangle}{\partial s} \right] \\
&\quad - \frac{K}{\eta_A} \left.\frac{\partial^2\langle F\rangle}{\partial s^2}\right|_{s=1} + 2 k_{10} M \frac{\partial\langle F\rangle}{\partial s} \\
&\quad + \chi_1 y^* \left.\frac{\partial^2}{\partial s^2}\right|_{s=1} \left(k_{01} \frac{\partial P}{\partial s} + k_{10} s^2 \frac{\partial P}{\partial s} \right. \\
&\quad \left. - k_{10} M s P \right)
\end{aligned}$$

or

$$\begin{aligned}
\frac{d}{dt}\left(\left.\frac{\partial^2\langle F\rangle}{\partial s^2}\right|_{s=1} \right) &= -\left(2k + \frac{2\chi_1 + K}{\eta_A} \right) \left.\frac{\partial^2\langle F\rangle}{\partial s^2}\right|_{s=1} \\
&\quad + 2 k_{10} (M-1) \left.\frac{\partial\langle F\rangle}{\partial s}\right|_{s=1} + \chi_1 y^* \left.\frac{\partial^2}{\partial s^2}\right|_{s=1} \\
&\quad \times \left(k_{01} \frac{\partial P}{\partial s} + k_{10} s^2 \frac{\partial P}{\partial s} - k_{10} M s P \right).
\end{aligned} \tag{A17}$$

This equation (A17) is of the same type as Eq. (A11), with

$$\alpha = 2\xi - \frac{K}{\eta_A}. \tag{A18}$$

We need the asymptotic behavior of the inhomogeneous term in Eq. (A17). Using Eq. (A4), we have

$$\begin{aligned}
\left.\frac{\partial^2}{\partial s^2}\right|_{s=1} &\left((k_{01} + k_{10} s^2) \frac{\partial P}{\partial s} - k_{10} M s P \right) \\
&= M \left(\left.\frac{\partial^2}{\partial s^2}\right|_{s=1} [1 - p(1-s)]^{M-1} \right) (kp - k_{10}) \\
&\quad + 2M \left(\left.\frac{\partial}{\partial s}\right|_{s=1} [1 - p(1-s)]^{M-1} \right) k_{10} (p-1).
\end{aligned}$$

But $kp - k_{10} = -k_{10} e^{-kt}$ is exponentially small so that the asymptotic behavior is

$$-2M(M-1)\frac{k_{10}^2k_{01}}{k^2}.$$

Thus, using this expression and Eq. (A16), the asymptotic behavior for large t of the inhomogeneous term of Eq. (A17) is

$$g_\infty = -2M(M-1)\frac{k_{10}^2k_{01}}{k^2}\chi_1 y^*\left(\frac{k_{10}}{\xi}+1\right), \qquad \text{(A19)}$$

and from Eq. (A13), we have

$$\left(\left.\frac{\partial^2\langle F\rangle}{\partial s^2}\right|_{s=1}\right) \to -2M(M-1)\frac{k_{10}^2k_{01}\chi_1 y^*}{k^2\left(2\xi-\dfrac{K}{\eta_A}\right)}\left(\frac{k_{10}}{\xi}+1\right). \qquad \text{(A20)}$$

5. Calculation of $\partial\langle x\rangle/\partial s|_{s=1}$ for large t

This quantity is given by Eq. (51). The inhomogeneous terms of this equation are

$$k_{10}M\langle x\rangle(t)+\frac{1}{\eta_A}\left.\frac{\partial\langle F\rangle}{\partial s}\right|_{s=1},$$

which has the asymptotic behavior [using Eqs. (A10) and (A16)],

$$g_\infty = k_{10}M\left(x(0)-\frac{Mk_{10}\chi_1 y^*}{kK}\right)-\frac{Mk_{10}^2k_{01}\chi_1 y^*}{\eta_A k^2\xi}$$

or

$$g_\infty = -\frac{M^2k_{10}^2\chi_1 y^*}{kK}+Mk_{10}\left(x(0)-\frac{k_{10}k_{01}\chi_1 y^*}{\eta_A k^2\xi}\right),$$

so that, using Eq. (A13) with $\alpha = k$,

$$\left.\frac{\partial\langle x\rangle}{\partial s}\right|_{s=1} \to -\frac{M^2k_{10}^2\chi_1 y^*}{k^2K}+M\frac{k_{10}}{k}\left(x(0)-\frac{k_{10}k_{01}\chi_1 y^*}{\eta_A k^2\xi}\right). \qquad \text{(A21)}$$

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