Power-stroke-driven actomyosin contractility

R. Sheshka^{1,2} and L. Truskinovsky^{1,*}

¹LMS, CNRS-UMR 7649, École Polytechnique, Route de Saclay, 91128 Palaiseau, France ²LITEN, CEA-Grenoble, 17 rue des Martyrs, 38054 Grenoble Cedex 9, France (Received 16 April 2013; revised manuscript received 18 November 2013; published 13 January 2014)

In ratchet-based models describing actomyosin contraction the activity is usually associated with actin binding potential while the power-stroke mechanism, residing inside myosin heads, is viewed as passive. To show that contraction can be propelled directly through a conformational change, we propose an alternative model where the power stroke is the only active mechanism. The asymmetry, ensuring directional motion, resides in steric interaction between the externally driven power-stroke element and the passive nonpolar actin filament. The proposed model can reproduce all four discrete states of the minimal actomyosin catalytic cycle even though it is formulated in terms of continuous Langevin dynamics. We build a conceptual bridge between processive and nonprocessive molecular motors by demonstrating that not only the former but also the latter can use structural transformation as the main driving force.

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I. INTRODUCTION

Active contractility in actomyosin networks results from stochastic interaction between individual myosin crossbridges and the adjacent actin filaments. It includes cyclic attachment of myosin heads to actin binding sites together with a concurrent conformational change in the core of the myosin catalytic domain (of folding-unfolding type). A lever arm amplifies this structural transformation producing the *power stroke*, which is believed to be the crucial part of a mechanism allowing the attached cross-bridges to generate macroscopic forces [1,2].

A prototypical biochemical model of the myosin ATPase reaction in solution, linking together the attachment-detachment, the power stroke, and the hydrolysis of adenosine triphosphate (ATP), is known as the Lymn-Taylor cycle [3]; see Fig. 1. While this minimal description of enzyme kinetics is common for most myosins motors [4], its association with microscopic structural details and its relation to micromechanical interactions remains a subject of debate [5–7].

In physiological literature it is usually implied that force generation is, to a large degree, *driven* by the power stroke, which is then perceived as an active mechanism [8]. This opinion is supported by observations that both the power stroke and the reverse power stroke can be induced by ATP even in the absence of actin filaments [6], that contractions can be significantly inhibited by antibodies which impair lever arm activity [9], that sliding velocity in mutational myosin forms depends on the lever arm length [10], and that the directionality can be reversed as a result of modifications in the lever arm domain [11,12].

A perspective that the power stroke is the driving force of active contraction was challenged by the suggestion that myosin catalytic domain could operate as a Brownian ratchet, which means that it can move and produce contraction without assistance from the power-stroke mechanism [13–15]. In this interpretation the contraction is driven directly by the attachment-detachment machinery which can rectify correlated noise and select directionality following, for instance, the polarity of actin filaments [16,17].

Although the simplest models of Brownian ratchets neglect the conformational change in the head domain, some phases of the attachment-detachment cycle can be interpreted as the power stroke if the actin potential undergoes additional externally driven horizontal shifts [18,19]. Ratchet models were also proposed where the periodic spatial landscape is supplemented by a reaction coordinate, representing the conformational change [20,21]. In all these models, however, the role of the power stroke was viewed as secondary and the contraction could be generated even if the power-stroke mechanism was disabled. The main functionality of the powerstroke mechanism is attributed in this approach to fast passive force recovery. The power stroke then plays the role of a passive folding-unfolding mechanism which can be activated by loading but is not directly ATP driven [22–24].

The conflicting viewpoint that the power-stroke mechanism consumes chemical energy is the underpinning of the broadly accepted phenomenological chemomechanical models that assign active roles to both the attachment-detachment and the power stroke [25,26]. These models pay great attention to structural details and in their most comprehensive versions faithfully reproduce the main experimental observations [27,28]. The chemomechanical models, however, are not transparent mechanistically because they deal with elastic interactions implicitly. In these models chemical states are interpreted as continuous manifolds (parameterized by the strain) and to characterize jump processes between the points on these manifolds the authors choose the transition rate functions phenomenologically. While this functional freedom compensates the lack of knowledge of the underlying multidimensional energy landscape, the inherent arbitrariness of some of these choices limits the ultimate predictive power of this approach.

In an attempt to reach a synthetic description, several hybrid models, allowing chemical states to coexist with springs and forces, have been also proposed [29–31]. The phenomenological side of these models is minimal; however, they still combine continuous dynamics with jump transitions which makes the precise identification of structural prototypes

^{*}trusk@lms.polytechnique.fr



FIG. 1. Schematic illustration of the four-step Lymn-Taylor cycle showing the power stroke $A \rightarrow B$, the detachment $B \rightarrow C$, the recocking of the power stroke $C \rightarrow D$, and the final reattachment $D \rightarrow A$, which brings the system back into the original state.

and the underlying micromechanical interactions challenging. In this class of models the power stroke in an individual cross-bridge was reproduced most faithfully by Geislinger and Kawai, who introduced a 2D energy landscape by coupling a bistable potential with a symmetric periodic potential [32]. In their model both the attachment-detachment mechanism and the power-stroke mechanism were effectively endowed with activity; however, the ATP hydrolysis was still represented by a flashing energy landscape.

In the present paper, drawing upon these earlier insights, we propose a model which shows that the power stroke can be, in principle, the main driving force behind muscle contraction. The model is fully mechanistic in the sense that all jump processes are replaced by continuous Langevin dynamics in a simple energy landscape. To emphasize the idea of an active power stroke, driven directly by the ATP hydrolysis, we intentionally simplify the real picture and model actin filaments as passive nonpolar tracks. The power-stroke mechanism is represented by a symmetric bistable potential associated with an internal degree of freedom and the ATP activity is modeled as a center-symmetric correlated force with zero average acting on the corresponding configurational variable. We show that the model renders a fully mechanical interpretation of all four chemical states in the minimal Lymn-Taylor cycle, which opens an interesting perspective of building artificial engineering devices mimicking enzymatic activity.

To justify the proposed coupling of the power-stroke machinery with the attachment-detachment mechanism, we argue that the conformational state of the power-stroke element provides *steric regulation* of the distance between the myosin head and the actin filament. More specifically, we assume that when the lever arm swings, the interaction of the head with the binding site weakens; see Fig. 2(a). This and other aspects of steric rotation-translation coupling in ratchet models have been previously discussed in Refs. [32–34].

A schematic representation of the proposed model is shown in Fig. 2(b), where x is the observable position of a myosin head, y is the internal variable characterizing the phase configuration of the power-stroke element, and z is another internal variable responsible for the coupling. The



FIG. 2. (a) An illustration of the steric effect associated with the power stroke; (b) sketch of the mechanical model.

"macroscopic" variable *x* sees a symmetric energy landscape and is not directly affected by the ATP hydrolysis. Both asymmetry and driving can then originate only from the coupling between the external and the internal degrees of freedom.

The idea that the symmetry breaking mechanism and the source of nonequilibrium may be resting exclusively in internal degrees of freedom [35,36] is borrowed from the theory of *processive* motors [37–40]. Thus, in the description of dimeric motors it is usually assumed that ATP hydrolysis induces a conformational transformation which then changes the relative position of the motor legs ensuring motility [41]. In our study, we use the same idea to describe a *nonprocessive* motor with a single leg that remains on track due to the presence of a thick filament.

The two-legged version of our motor, shown in Fig. 3, would then work similarly to the models of kinesin motors [37]; in particular, such a motor will be able to advance along the track without being guided by a thick filament. By placing emphasis on active role of the conformational change in nonprocessive motors, we bring closer the descriptions of porters and rowers as it has been envisaged in Ref. [42].

The proposed framework allows for three different modes of *power-stroke-driven* contractility which may operate simultaneously.

The first mode is activated only if correlations are present in the additive noise as in the conventional rocking ratchets [43]. The peculiarity of our rocking ratchet is that the periodic potential is symmetric and time independent. The correlated component of the noise affects the bistable potential and, since it is also symmetric, the directional motion is due exclusively to an asymmetry induced by the coupling between the internal degrees of freedom and the center of mass of the motor.

The second mode does not necessitate correlations in the noise but instead requires that the coupling between the powerstroke element and the actin filament is *hysteretic*. The motor can then extract energy directly from the delay mechanism which represents a nonequilibrium reservoir. We show that the



FIG. 3. A simplified representation of a processive, two-legged version of the nonprocessive motor shown in Fig. 2(b).

two active mechanisms, correlations induced and hysteresis induced, can favor motions in different directions and can play complimentary roles.

Finally, the third mode functions if the internal forces acting between the myosin head and the actin filament are *nonpotential* even without being hysteretic [15,20,44]. This assumption introduces another active mechanism which can drive the motor even if the thermostat is in equilibrium. The correlations-induced and non-potentiality-induced mechanisms can again impose opposite directionality; in particular, they can be used in combination to slow down and even to stop the motor.

The variety of the available regimes is particularly rich when the forces are nonpotential and the coupling between the power stroke and the actin filament is hysteretic. The resulting ratchet shows complex reversals of current depending on the amplitude of the external driving and temperature. The importance of the hysteretic coupling is revealed by the observation that only in this case can the model reproduce all four steps of the Lymn-Taylor cycle.

The paper is organized as follows. In Sec. II, we introduce the collective coordinates describing the motor position and the internal configuration of the myosin head. We proceed by studying the continuous Langevin dynamics in the corresponding energy landscape driven by the ac forcing of the power-stroke element (mode 1). In Sec. III, we consider hysteretic coupling (mode 2) and show that the ensuing motor can actively advance in both directions depending on the amplitude of the ac noise. We then demonstrate that the mechanical cycle of a hysteretic motor can be mapped on the biochemical cycle of the actomyosin enzyme and explain how the particular mechanical transients can be identified with the basic chemical states observed in solution. In Sec. IV, we study the nonpotential model (mode 3) and compare it with the hysteretic model by juxtaposing the force-velocity relations and the Péclet numbers. Finally, we present examples of the interplay between all three active mechanisms. The last section, Sec. V, summarizes our results and lists some open problems.

Throughout the paper we use dimensionless variables normalized by the scales of lengths l, time τ , and energy E which we specify in Sec. II.

II. ACTIVE POWER STROKE

The idea to treat an individual myosin head as a mechanical system with configurational degrees of freedom is rather old [22,25]. The challenge, however, is to find a minimal description capturing the most important mechanical interactions. Our attempt at such schematization is presented in Fig. 2(b).

We identify the external degree of freedom with the variable x representing the location of actin binding face on the actin filament. The most natural internal degree of freedom, describing the configurational state of the power-stroke element, is y - x, where the variable y was defined in the Introduction. By introducing the second internal variable, z, characterizing the separation of the myosin head and the actin filament, we attempt to capture the higher-dimensional effects of detachment in the simplest 1D setting.



FIG. 4. The coupling function $\Psi(y - x)$ linking the degree of attachment *z* with the state of the power-stroke element y - x.

The role of different variables is clear from the way we write the energy of the system,

$$\hat{G}(x,y,z) = z\Phi(x) + V(y-x), \tag{1}$$

where $\Phi(x)$ is a nonpolar periodic potential representing the binding strength of the actin filament and V(y - x) is a doublewell potential describing the power-stroke element. The twowell structure of the potential implies that the power-stroke mechanism can be either *folded* into the post-power-stroke state or *unfolded* into the pre-power-stroke state. For simplicity, we assume that the two wells of the potential V(y - x)are symmetric, which eliminates a redundant polarity.

The coupling between the state of the power-stroke element y - x and the spatial position of the motor x is implemented through the internal variable z. In the simplest version of the model z is assumed to be a function of the state of the power-stroke element,

$$z(x,y) = \Psi(y-x).$$
(2)

This function must have a particular structure in order to mimic the underlying steric interaction; see Fig. 4. We assume that when a myosin head executes the power stroke it moves away from the actin filament and therefore the control function $\Psi(y - x)$ should progressively switch *off* the actin potential. Similarly, when the power stroke is recharging, the myosin head moves closer to the actin filament and the function $\Psi(y - x)$ should bring the actin potential back into the *on* configuration.

We observe that since the double-well potential V(y - x) is fully symmetric, the assignment of the wells to pre- or post-power-stroke states is arbitrary. Had we decided to invert the choice presented in Fig. 4 by relabeling the energy wells, we would have to replace $\Psi(s)$ by $\Psi(-s)$. As we see later in the paper, such switch results in a simple reversal of the directionality of the motion.

By using the coupling (2) we can eliminate the variable z and introduce the redressed potential,

$$G(x,y) = \hat{G}(x,y,\Psi(y-x)).$$
(3)

As it tracks the state of the power-stroke element the potential G(x, y) effectively "flashes" between the periodic and flat (in x) configurations; see Fig. 5. However, in contrast to conventional flashing ratchets, the switch here is not imposed from outside but results from the coupling with a *fluctuating* internal variable.

The overdamped stochastic dynamics of the system with energy (3) is described by the following 2D system of



FIG. 5. The energy landscapes: $\hat{G}(x, y, 1)$, describing the attached state where $\Psi(y - x) = 1$, and $\hat{G}(x, y, 0)$, describing the detached state, where $\Psi(y - x) = 0$.

(dimensionless) Langevin equations:

$$\dot{x} = -\partial_x G(x, y) - f(t) + \sqrt{2D}\xi_x(t)$$

$$\dot{y} = -\partial_y G(x, y) + f(t) + \sqrt{2D}\xi_y(t).$$
(4)

Here $\xi(t)$ is a conventional white noise with $\langle \xi_i(t) \rangle = 0$ and $\langle \xi_i(t)\xi_j(s) \rangle = \delta_{ij}\delta(t-s)$. The parameter $D = k_B\theta/E$ is a dimensionless measure of temperature θ and k_B is the Boltzmann constant; for simplicity the viscosity coefficients are assumed to be the same for variables *x* and *y*. The *force couple* f(t) with zero average represents a correlated component of the noise and characterizes mechanistically the degree of nonequilibrium in the external reservoir (the abundance of ATP).

We can say that the system (4) describes the *power-strokedriven* ratchet because the correlated noise f(t) acts on the relative displacement y - x. It effectively "rocks" the bi-stable potential and the control function $\Psi(y - x)$ converts such "rocking" into the "flashing" of the periodic potential $\Phi(x)$. Various other types of rocked-pulsated ratchet models have been previously studied in Refs. [45,46].

The goal of any ratchet design is to generate a systematic drift,

$$v = \lim_{t \to \infty} \frac{\langle x(t) \rangle}{t},\tag{5}$$

without applying a biasing force. This is possible in the model governed by Eq. (4) because of an implicit symmetry breaking imposed by the control function (2).

To justify this claim, let us, for simplicity, set f(t) = 0and rewrite (4) in the variables representing the position of the center of mass q = (x + y)/2 and the power-stroke configuration r = y - x, which is a conventional step in such problems [47]. The new potential is

$$G(q,r) = \Psi(r)\Phi(q - r/2) + V(r),$$

and if we recall that the equilibration of the variable r takes place at much faster time scale than the overall drift, we can adiabatically eliminate it and obtain a one-dimensional stochastic system with an effective periodic potential,

$$G_{\text{eff}}(q) \sim \ln\left[\int_{-\infty}^{\infty} \exp\left(-G(q,r)/D\right)dr\right].$$



FIG. 6. The functions Φ , V, and f used in numerical experiments.

In the absence of the feedback $\Psi(s) = 0$ this potential is symmetric $G_{\text{eff}}(q) = G_{\text{eff}}(-q)$ because $\Phi(s) = \Phi(-s)$ and V(s) = V(-s). When $\Psi(s) \neq \Psi(-s)$, it loses symmetry because pre- and post-power-stroke configurations are no longer equivalent. It is also clear that by reverting the control function $\Psi(s) \rightarrow \Psi(-s)$, we change the directionality of the average motion; see Fig. 10.

To illustrate the dependence of the average velocity (5) on the parameters of the model, we studied the system (4) numerically. In our computational experiments we use a periodic extension of the symmetric triangular potential $\Phi(x)$ with amplitude Q and period L [see Fig. 6(a)],

$$\Phi(x) = \begin{cases} \frac{2Q}{L}x & \text{if } 0 \leq x < L/2, \\ \frac{2Q}{L}(L-x) & \text{if } L/2 \leq x < L \end{cases}$$

The symmetric potential V(y - x) is assumed to be biquadratic with the same stiffness k in both phases. The distance between the bottoms of the wells is denoted by a [see Fig. 6(b)], so

$$V(y-x) = \begin{cases} \frac{1}{2}k(y-x+a/2)^2 & \text{if } y-x < 0\\ \frac{1}{2}k(y-x-a/2)^2 & \text{if } y-x \ge 0. \end{cases}$$

The correlated component of the noise f(t) is interpreted as the simplest *ac driving* described by a periodic extension of a rectangular-shaped function with amplitude A and period T [shown in Fig. 6(c)],

$$f(t) = \begin{cases} +A & \text{if } 0 \leqslant t \leqslant T/2, \\ -A & \text{if } T/2 \leqslant t \leqslant T. \end{cases}$$

Finally, the steric control ensuring the gradual switch of the actin potential is described by a gradual step function,

$$\Psi(s) = (1/2) \left[1 - \tanh(s/\varepsilon) \right], \tag{6}$$

where ε is a small parameter; see Fig. 4.

To fix the parametrization, we need to specify the dimensional scales. It is natural to use the distance between the bottoms of the wells in the bistable potential as the length scale l so a = 1. We have also made a standard assumption that the separation between the binding cites along the actin filament is of the same order as the power-stroke size and therefore L = 1. The height of the barrier between the binding sites was chosen as the energy scale E, so we put Q = 1. The relaxation time scale was set by the viscosity coefficient η and therefore $\tau = \eta l^2 / E$. To ensure that the ac driving is slow at the scale of internal relaxation we took T = 10. The curvature of the energy wells in the bistable potential should be comparable with E/l^2 and therefore we took a generic value k = 1.5. In the computations we used the value of the small parameter $\varepsilon = 0.2$ which made the attachment and the detachment events sufficiently sharp.



FIG. 7. The dependence of the average velocity v on temperature D and the amplitude of the ac signal A in the model with coupling (6). The pre- and post-power-stroke states are labeled in such a way that the purely mechanical ratchet would move to the left.

To integrate the system (4) numerically, we used the simplest Euler-Maryama scheme [48] with a constant time step $\Delta t = 0.5 \times 10^{-3}$. The ensemble averaging was performed over $N = 10^4$ stochastic realizations.

Our numerical results are summarized in Fig. 7. First, we see that the drift is absent (v = 0) when the noise is uncorrelated and the external reservoir is in equilibrium (A = 0). This is an obvious consequence of the potential nature of this holonomic model. Indeed, the stationary probability flux satisfies $\nabla J = 0$ and $\mathbf{J} = f\mathbf{F} - D\nabla f$, where f(x,y) is the stationary probability distribution and \mathbf{F} is the internal force. Since $\mathbf{F} = -\nabla G$, one can use periodicity in x and growth in y - x (of the potential G) to show that $\mathbf{J} = 0$; see also Refs. [15,20,44].

It is then clear that the drift in this model is exclusively due to $A \neq 0$. When A is small, the drift velocity shows a maximum at finite temperatures which implies that the system exhibits stochastic resonance [49]. At high amplitudes of the ac driving, the motor works as a purely mechanical ratchet and the increase of temperature always worsens the performance [13,14,16].

As we have already seen, the direction of motion in this model is decided by the choice of steric biasing of the otherwise symmetric bistable potential. The chosen directionality can be either enhanced or suppressed if we consider polar actin filaments. To illustrate this point, we show in Fig. 8 how the drift velocity depends on the parameter characterizing the spatial asymmetry of the actin track. In particular, we see that on a polar filament with sufficient asymmetry our motor can be stopped and even steered in the opposite direction.

The next question concerns the compatibility of the proposed model with the minimal biochemical ATPase cycle shown in Fig. 1. The traditional identification of chemical and structural states, detailed in this figure, suggests that the motor must pass through the following four mechanical transients: "attached pre power stroke," "attached post power





FIG. 8. The dependence of the drift velocity v on the filament polarity $\Delta = \lambda_1 - \lambda_2$ in the model with coupling (6) at fixed temperature D = 0.01.

stroke," "detached post power stroke," and "detached pre power stroke." It is immediately clear that not all of these states can be reached by the model with coupling (6). Indeed, the detachment takes place when the "striking" element is positioned exactly between the two energy wells and therefore the power stroke cannot be completed in the attached state. As a result, the model reproduces reliably only two structural configurations: the attached pre-power-stroke state and the detached post-power-stroke state.

To capture the remaining states shown in Fig. 1 we must assume that the detachment, necessarily implying in our model the motion of the center of mass, is delayed until the power stroke is (almost) completed. Similarly, the attachment must take place only after the power-stroke element has been (almost fully) recharged. The necessary modification of the model, accounting for such two-way delays, is discussed in Sec. III.

III. HYSTERETIC COUPLING

To reproduce the whole Lymn-Taylor cycle, we postulate that the switching of the actin potential from the *on* to the *off* state takes place at different values of the variable y - x, depending on the *direction* of the conformational change (folding or unfolding). To this end, we replace the holonomic coupling (2) by a memory operator,

$$z\{x,y\} = \widehat{\Psi}\{y(t) - x(t)\},\tag{7}$$

whose output depends on whether the system is on the "striking" or on the "recharging" branch of the trajectory; see Fig. 9. Such memory structure can be also described by a rate-independent differential relation of the form

$$\dot{z} = Q(x, y, z)\dot{x} + R(x, y, z)\dot{y}, \tag{8}$$

where the implied nonintegrability makes the model nonholonomic. Indeed, if we introduce a vector variable $\mathbf{u} = (x, y, z)$ and neglect the time-dependent external noise we can rewrite the system of the governing equations in the form $\dot{\mathbf{u}} = \mathbf{F}(\mathbf{u})$, where **F** is no longer a gradient. The resulting Brownian motor can potentially advance even in the absence of the correlated



FIG. 9. The hysteresis operator $\widehat{\Psi}\{y(t) - x(t)\}\$ linking the degree of attachment *z* with the previous history of the power-stroke configuration y(t) - x(t).

noise by extracting energy directly from the nonholonomic control mechanism.

By using (7) we can now rewrite the energy of the system as a functional of its history y(t) and x(t),

$$G\{x, y\} = \widehat{\Psi}\{y(t) - x(t)\}\Phi(x) + V(y - x).$$
(9)

In the Langevin setting (4), the history dependence may mean that the underlying microscopic stochastic process is non-Markovian (due to, say, configurational pinning [50]) or that there are additional nonthermalized degrees of freedom that are not represented explicitly [51]. In general, it is well known that the realistic feedback implementations always involve delays [52].

To simulate hysteretic response numerically we used two versions of the same coupling function (6) shifted by δ with the branches $\Psi(y - x \pm \delta)$ identified sufficiently far away from the hysteresis domain; see Fig. 9. Our numerical experiments show that the performance of the model is not sensitive to the shape of the hysteresis loop and depends mostly on its width characterized by the small parameter δ .

In Fig. 10 we illustrate the "gait" of the motor with the hysteretic coupling (7). The center of mass advances in steps and during each step the power-stroke mechanism gets released and then gets recharged again, concurrently with attachment-detachment. By coupling the attached state with either the



FIG. 10. Stationary particle trajectories in the model with the hysteretic coupling (7). Different ways of biasing lead to different directions of drift and large hysteresis loops produce faster moving motors. Other parameters are D = 0.02 and A = 1.5.



FIG. 11. The dependence of the average velocity v on temperature *D* in the hysteretic model with $\delta = 0.5$.

pre- or post-power-stroke state, we can vary the directionality of the motion. The average velocity increases with the width of the hysteresis loop, which shows that the motor can extract more energy from the coupling mechanism system with longer delays.

The results of the parametric study of the model are summarized in Figs. 11 and 12. First, observe that the motor can now move even in the absence of the correlated noise, at A = 0, because the nonholonomic coupling (9) breaks the detailed balance by itself. At finite A the system can use both sources of energy (hysteretic loop and ac noise) and the resulting behavior is much richer than in the nonhysteretic model.

For instance, if the holonomic ratchet with a fixed coupling bias always advances in one direction, the nonholonomic ratchet can self-propel in both directions. At large *A* the hysteretic motor exhibits the same directionality as the nonhysteretic motor and the average velocity is only mildly affected by the presence of the hysteresis. At small *A* the situation changes and now the direction of the drift is controlled



FIG. 12. The dependence of the average velocity v on amplitude of the ac driving A in the hysteretic model with $\delta = 0.5$.



FIG. 13. Single-particle trajectories in the 3D space (y - x, z, x) and their projections on the plane (y - x, z): (a) nonhysteretic coupling and (b) hysteretic coupling. The parameters are D = 0.2, A = 0, and $\delta = 0.5$.

by the hysteresis and is reversed comparing to the case of a nonhysteretic motor. As we see, in the hysteretic powerstroke-driven ratchet different active mechanisms dominate at different values of A. This opens an interesting possibility for these molecular machines to flip "engines" and in this way reverse the directionality by simply changing the intensity of the external energy supply.

The A dependence of the drift velocity is shown in more detail in Fig. 12. At zero temperature the system is pinned and the drift is blocked until the driving amplitude reaches a threshold beyond which the system can work as a mechanical ratchet. At finite temperatures the pinning disappears because of the noise-induced barrier crossing. At small A the motor drifts in the direction opposite to the direction of the mechanical ratchet. The velocity of this drift shows a characteristic peak at finite A, revealing stochastic resonance. The current reversal, indicating the change of the mechanism from hysteresis dominated to correlation dominated, takes place near the depinning point, $A \sim 2.5$.

To illustrate the mechanism of the hysteresis-dominated drift, it is sufficient to consider the case when A = 0. This disables an alternative ac-driven ratchet mechanism. In Fig. 13 we compare two realizations of particle trajectories in the 3D space (x, y - x, z) for the model without hysteresis (2) and with hysteresis (7). The loops obtained by projecting these trajectories onto the 2D plane (y - x, z) describe the structure of the corresponding "strokes" in the configurational space. In the holonomic case (2) the area of the projected loop is equal to zero and we observe diffusion without drift [in Fig. 13(a) the average of x is equal to zero]. Instead, in the nonholonomic case (7), the projected trajectory spans a finite area and the drift velocity is finite [see Fig. 13(b)]. Similar dependence of the drift velocity on the area of the "stroke" is known in the theory of Stokes swimmers where nonholonomic control is also the factor responsible for the directional motion in "violation" of the scallop theorem [53].

The mechanical "stroke" in the space of internal variables z, y - x can be compared with the minimal biochemical actomyosin cycle shown in Fig. 1. The chemical states

constituting this cycle are identified with structural configurations (obtained from crystallographic reconstructions) in the following way [3]: A (attached, pre power stroke \rightarrow AM*ADP*P_i), B (attached, post power stroke \rightarrow AM*ADP), C (detached, post power stroke \rightarrow M*ATP), and D (detached, pre power stroke \rightarrow M*ADP*P_i). In our model the jump events are replaced by continuous transitions and the association of chemical states with particular regimes of stochastic dynamics is not straightforward.

In Fig. 14(a), we show a fragment of the averaged trajectory of a steadily advancing motor projected on the (x, y - x) plane. In Fig. 14(b) the same trajectory is shown in the (x, y - x, z) space with fast advances in the z direction intentionally schematized as jumps. By using the same letters A, B, C, and D as in Fig. 1 we establish a basic connection between the chemical and structural states and the transient mechanical configurations of the advancing motor.



FIG. 14. (a) A steady-state cycle in the hysteretic model projected on the x, y - x plane; the black line corresponds to f(t) > 0 and the gray line to f(t) < 0. (b) Representation of the same cycle in the z, x, y - x space with identification of the four chemical states A, B, C, and D constituting the Lymn-Taylor cycle shown in Fig. 1. The level sets represent the energy landscape G at z = 0 (detached state) and z = 1 (attached state). The parameters are D = 0.02, A = 1.5, and $\delta = 0.75$.



FIG. 15. Schematic representation of the power-stroke-driven motor carrying cargo: (a) pushing regime and (b) pulling regime.

Suppose that we start at point A corresponding to the end of the negative cycle of the ac driving f(t). The system is in the attached, pre-power-stroke state and z = 1. As the sign of the force f(t) changes, the motor undergoes a power stroke and reaches point B while remaining in the attached state. When the configurational variable y - x passes the detachment threshold, the myosin head detaches which leads to a transition from point B to B' on the plane z = 0. Since the positive cycle of the force f(t) continues, the motor completes the power stroke by moving from B' to point C. At this moment, the rocking force changes sign again, which leads to recharging of the power-stroke mechanism in the detached state, described in Fig. 1 as a transition from C to D. In point D, the variable y - x reaches the attachment threshold. The myosin head reattaches and the system moves to point D', where z = 1 again. The recharging continues in the attached state as the motor evolves from D' to a new state, A, shifted by one period.

As we see the chemical states constituting the minimal enzyme cycle can be linked to the mechanical configurations traversed by our stochastic dynamical system. The detailed mechanical picture, however, looks more complicated than in the simplest Lymn-Taylor scheme. It is clear that at least in some regimes one can use the Kramers approximation to perform a transition from our continuous dynamics to a description in terms of a discrete set of chemical reactions. However, it is also clear that more chemical states than in the minimal Lymn-Taylor model will be needed to describe the detailed mechanical "stroke."

So far we have been dealing with motors overcoming viscous friction but not carrying cargoes. The next step is to see how fast the same motor can move against an external force f_{ext} . Two different mechanical configurations of the motor carrying cargo correspond to the cases when $f_{ext} > 0, v < 0$ and $f_{ext} < 0, v > 0$; see Fig. 15. Since the nonhysteretic motor is designed to move to the left, the mechanical configuration shown in Fig. 15(a) can be somewhat arbitrarily characterized as "pushing." Given that the motor with the hysteretic coupling can move in both directions, the configuration shown in Fig. 15(b) can be then interpreted as "pulling." Since our motor does not have explicit leading and trailing edges, we assume that the force f_{ext} acts in both cases on the variable y, which amounts to tilting of the potential (9) along the y direction,

$$G\{x, y\} = \widehat{\Psi}\{y(t) - x(t)\}\Phi(x) + V(y - x) - yf_{\text{ext}}.$$
 (10)

We recall that the actual architecture of a half sarcomere is asymmetric and the forces are transmitted through passive cross-linkers imposing a particular polarity on the loading. Therefore, despite the ambiguity, the association of the two



FIG. 16. The force-velocity relation in the model with hysteretic coupling at different amplitudes of the ac driving A and different temperatures D. The hysteresis width is $\delta = 0.5$.

mechanical regimes shown in Fig. 15 with pushing and pulling is appropriate.

A stochastic system with energy (10) was studied numerically and in Fig. 16 we show the computed force-velocity relations. The light quadrants in the (f_{ext}, v) plane correspond to two domains of dissipative behavior where $R = f_{ext}v > 0$. Here the direction of the force agrees with the direction of motion and and the motor is being dragged by the applied load (while exhibiting both passive and active friction). The shaded quadrants indicate the two domains where the system is antidissipative and $R = f_{ext}v < 0$. In these regimes the motor produces work and the motion can be of two types: when the motor overcomes the opposing pushing force and drives the cargo ahead of itself ($f_{ext} > 0, v < 0$) and when it carries the cargo attached from behind acting against a pulling force $(f_{\text{ext}} < 0, v > 0)$. Since in the hysteretic model the current can be reversed by changing the amplitude of the ac noise A, our motor can perform both types of useful work.

Observe that at low temperatures the convexity properties of the force-velocity relations in active pushing and active pulling regimes differ. In the case of pulling, the typical force-velocity relation is reminiscent of the Hill's curve describing isotonic contractions [54]. In the case of pushing, the force-velocity relation can be characterized as convex-concave and such behavior has been also observed in muscle contraction experiments [55–57]. The difference between these force-velocity curves is due to the dominance of physically nonequivalent mechanisms in the corresponding parameter domains.

For instance, in the pushing regimes, the motor activity fully depends on ac driving and at large amplitudes of this driving it performs as a mechanical ratchet. Instead, in the pulling regimes, associated with small amplitudes of external driving, the motor advances because of the delayed feedback exemplified by the hysteretic mechanism. We may speculate that both mechanisms can be operative in actomyosin systems, which would then provide an explanation for occasionally counterintuitive drift directions. We also mention that dissimilarity of convexity properties of the force-velocity relations in pushing and pulling regimes has been recently discussed in the context of cell motility where actomyosin contractility is known to be one of the main driving forces [58]. The direct quantitative comparison is, however, premature since in our minimal setting the model deals with a single cross-bridge and still neglects important collective effects [24].

IV. NONPOTENTIAL MODELS

The performance of the power-stroke-driven ratchet can be considerably enhanced if the feedback between the power-stroke and the attachment-detachment mechanisms is made nonconservative even in the absence of hysteresis. This would happen, for instance, if the configurational state of the power-stroke element affected the position of a myosin head with respect to actin filament, while the reverse influence remained insignificant; in other words, if the coupling between the power-stroke element and the actin potential was one sided. In this case, instead of a passive control, we are dealing with an *active control* represented by a Maxwell demon-type mechanism [59,60].

The governing equations describing such ratchet can be written in the form

$$\dot{x} = -z\partial_x \Phi(x) - \partial_x V(y-x) - f(t) + \sqrt{2D}\xi_x(t)$$

$$\dot{y} = -\partial_y V(y-x) + f(t) + \sqrt{2D}\xi_y(t),$$
(11)

where the notations are the same as in (4). The results of the numerical study of the system (11) are summarized in Fig. 17.

The overall behavior of the nonpotential system (11) is similar to the behavior of the potential system with hysteretic coupling (9). Since the ratchet can now receive energy from the active controlling device [20,44], a nonzero drift takes place already at A = 0. The direction of the current can be again reversed by varying the amplitude of the driving. At large values of A, we obtain our usual mechanical ratchet which does not see the nonpotentiality of the model. At small A the ratchet





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FIG. 18. Temperature dependence of the drift velocity v in the nonpotential model (11) with hysteresis, $\delta = 1$.

exploits the nonpotentiality of the model in the essential way. As in the case of hysteretic system, the direction of the drift is now opposite to the one picked up by the mechanical ratchet. Notice also that at moderate values of *A* the directionality of the drift can be reversed by the variation of temperature.

The nonpotential ratchet shows the highest performance in combination with the hysteretic feedback (9); see Fig. 18. The behavior of such a hybrid system at A = 0 is similar to what we have seen in the case of the system with energy (9), which means that in this regime the response is dominated by hysteresis. As A increases we observe a new effect: Around $A \sim 1.5$ the system appears to be in a resonant state and works as a quasimechanical ratchet; however, now, the nonpotentiality is the principle driving factor; see Fig. 18. With further increase of A we observe a reversal of the current and the system enters the regime where the main driving force is again the ac noise. At large A the mechanical ratchet behavior prevails again; however, it fundamentally differs from the quasimechanical ratchet behavior observed around $A \sim 1.5$.

In Fig. 19 we illustrate the effect of the amplitude *A* on the drift velocity in more detail. In contrast to the potential case, the ratchet can now move at zero temperatures in both directions equally fast if the amplitude of the ac signal is chosen appropriately. The current reversal takes place in the narrow range of amplitudes *A* where the transition from a mechanical to a quasimechanical ratchet mechanism takes place.

At finite temperatures we see a complex interplay of all three active mechanisms. The detailed study of the underlying stochastic system, allowing one to precisely map the parametric domains where particular mechanisms dominate, will be presented elsewhere.

To better understand the effects of nonpotentiality we also compute the Péclet number $\text{Pe} = Lv/D_e$, characterizing the relative strength of the drift (over diffusion). The effective diffusion coefficient is defined by [61–63]

FIG. 17. Temperature dependence of the drift velocity v in the nonpotential model (11) without hysteresis.

$$D_e = \frac{1}{2} \lim_{t \to \infty} \frac{\langle [x(t) - \langle x(t) \rangle]^2 \rangle}{t}, \qquad (12)$$



FIG. 19. The dependence of the average velocity v on the amplitude A of the ac signal in the nonpotential model with hysteresis, $\delta = 1$.

so the stochastic transport is most coherent when the absolute value of the Péclet number number is larger than 1. From Fig. 20 we see that only in the nonpotential model the motion at small values of the driving amplitude *A* can be viewed as truly directional.

Suppose now that a load is attached to the motor with nonpotential hysteretic coupling. The typical force-velocity relations are shown in Fig. 21. As in the potential case, the motor can operate in two antidissipative regimes, either by working against a pushing force or by pulling a cargo. At both small and large values of A the behavior of the potential and the nonpotential motors is similar. Expectedly, an anomaly takes place in the pulling regime ($f_{\text{ext}} < 0, v > 0$) at $A \sim 1.5$ where the motor behaves as a quasimechanical ratchet. Here the nonpotentiality dominates and the force-velocity relation



FIG. 20. The Péclet number in the potential model with hysteresis ($\delta = 0.5$ as in Fig. 12) and in the nonpotential model with hysteresis ($\delta = 1$ as in Fig. 19); D = 0.1.



FIG. 21. The force-velocity relation in the nonpotential model with hysteresis at different temperatures *D* and different driving amplitudes *A*; $\delta = 1$.

shows an unusually sharp convexity change. It is interesting that in this regime the behavior near the stall force is reminiscent of the one observed in skeletal muscles [2].

V. DISCUSSION

In this paper, we developed a prototypical model of the power-stroke-driven actomyosin contraction. The mechanistic nature of the model is clear from the fact that the underlying stochastic dynamics is described by a set of continuous Langevin equations which are basically the equations of mechanics.

In the previous mechanistic representations of actomyosin systems the power stroke was undermined as a passive foldingunfolding mechanism while the attachment-detachment was given a primary role as the main driver of contraction. Since active sites are located inside motor domains, the external forces, representing the ATP activity, were typically introduced as conjugates to macroscopic positions of these domains and such ratchets were essentially attachment-detachment driven [64]. This conventional ratchet mechanism is complimentary to the one studied in the present paper where the thrust of the ATP activity has been shifted towards the internal variable characterizing the state of the power-stroke element.

To make a clear distinction between our model and the conventional models of Brownian ratchets we assumed that the actin track is nonpolar and that the bistable element is unbiased. The symmetry breaking was then achieved exclusively through the coupling of these two subsystems. In the more comprehensive models the polarity of the actin filament and the asymmetry of pre- and post-power-stroke states should be taken into consideration as well. This will contribute to the ratchet effect and improve the efficiency of energy transduction.

We discussed three different modalities of how a powerstroke-driven ratchet can receive energy of the ATP hydrolysis and presented mechanical analogs of the associated nonequilibrium chemical reservoirs. In the first, traditional, representation, a mechanical action of the chemical reaction was modeled by a correlated component of the noise. The second representation was based on the idea that the coupling between internal and external degrees of freedom is hysteretic. Here in contrast to what is usually observed in macroscopic systems, hysteresis was used as a source rather than a sink of energy. The third representation implied that the internal degrees of freedom have an inherently chemical origin and therefore the source of nonequilibrium is in the lack of potentiality of these forces.

We have shown that the use of the hysteretic design for the power-stroke-driven motor allows one to reproduce mechanistically the complete Lymn-Taylor cycle. This opens a way towards dynamic identification of the chemical states, known from the studies of the prototypical catalytic cycle in solution, with particular transient mechanical configurations of the actomyosin complex. Such identification is a precondition for the bioengineering reproduction of a wide range of cellular processes, where myosin cross-bridges play the dominant role, from movement of cells to cytokinesis. Given that the mechanisms involved in our model can be mimicked artificially at a supercellular scale, the proposed schematization of the contraction phenomenon can be viewed as a step towards building engineering devices imitating actomyosin enzymatic activity.

In our mechanical representation of the nonprocessive, single-legged motor an internal conformational change played the role of the main driving force. Since this is the way the processive motors are operating [37–39], our model brings these two groups of motors into the same class. To describe a processive dimeric motor in our framework, we need to

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associate the second leg with the variable y (see Fig. 3) and introduce the matching steric coupling in the potential,

$$G_{\dim}\{x, y\} = \hat{\Psi}\{y(t) - x(t)\}\Phi(x) + \hat{\Psi}\{x(t) - y(t)\}\Phi(y) + V(y - x).$$

Here to ensure the hand-over-hand motion [2] we flipped the sign of the argument in the hysteresis operator $\hat{\Psi}\{y(t) - x(t)\}$. In support of the idea that both processive and nonprocessive motors can be driven through a conformational change, we mention that the general shape of the force-velocity relations obtained in this paper is compatible with the available measurements not only for nonprocessive motors but also for processive motors [65–68].

The proposed model raises some challenging issues which need to be addressed in future work. One challenge is to understand the microscopic nature of the hysteretic element and of the active mechanism ensuring the nonpotential force structure. Another challenge is to find the optimal interaction of our three active mechanisms ensuring the highest performance of the motor. The third challenge is to study collective effects associated with activity of many elastically interacting power-stroke-driven motors. Here one can expect a variety of interesting regimes from coherent fluctuations [29,69–71] to self-tuning towards criticality [24,72,73].

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