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Viscoelasticity of Living Materials: Mechanics and Chemistry of Muscle as an Active Macromolecular System

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Abstract: At the molecular and cellular level, mechanics and chemistry are two aspects of the same macromolecular system. We present a bottom-up approach to such systems based on Kramers' diffusion theory of chemical reactions, the theory of polymer dynamics, and the recently developed models for molecular motors. Using muscle as an example, we develop a viscoelastic theory of muscle in terms of an simple equation for single motor protein movement. Both A.V. Hill's contractile component and A.F. Huxley's equation of sliding-filament motion are shown to be special cases of the general viscoelastic theory of the active material. Some disparity between the mechanical and the chemical views of cross-bridges and motor proteins are noted, and a duality between force and energy in discrete states and transitions of macromolecular systems is discussed.

Keyword: biomaterials, heat production, molecular motor, sliding filament, stochastic model

1 Introduction

In classical sciences, mechanics and chemistry are two well established disciplines, each with its own theoretical foundations and pedagogies. When dealing with macromolecules in living cells, however, theories and approaches from these two traditions intertwine, and mechanics and chemistry are two sides of the same coin. In particular, mechanics deals with movements and forces while chemistry deals with states and energies. Since a state of a macromolecule is defined in its conformational space in which submolecular movements occur, and force is simply the gradient of an energy function, a mathematical description of a macromolecule, its states, dynamics and functions, can be a powerful tool to integrate the two theories into a unifying view of macromolecular systems at a mesoscopic level [Qian (2000a, 2002)].

Muscle is one of the first living materials to have been studied mechanically. The study of muscle physiology and its molecular basis has been one of the most exciting stories of biochemistry and molecular biology. The understanding of muscle mechanics has gone through several important stages: viscoelastic theory and its generalization by A.V. Hill (1939), sliding filament theory of Huxley (1957), statistical thermodynamic theory of T.L. Hill (1974), and the recent theories based on molecular motors [Jülicher, Ajdari, and Prost (1997); Qian (1997, 2000b); Baker and Thomas (2000)].

The historical development clearly shows a movement away from mechanics and toward chemistry. But at the level of macromolecular motors, the chemistry and mechanics again become unified. In fact, the theory of sliding filaments in terms of motor proteins as cross-bridges is precisely a theory of viscoelastic living materials: As the energy source, the chemical reaction of ATP hydrolysis is built in as a part of the mechanical theory.

Through the studies of muscle physiology, the dialogue between the chemistry and the mechanics has led to the field of chemomechanics or mechanochemistry [White and Thorson (1973); Volkenstein (1977); Hibberd and Trentham (1986)]. This is the theoretical foundation of molecular and cellular biomechanics and tissue engineering. In this paper, I shall discuss two particular problems:

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(1) How the chemical approach to motor proteins based on the theories of Kramers' [Kramers (1940)] toegether with polymer dynamics [Doi and Edwards (1986)] and its generalizations leads to the viscoelasticity of active materials of A.V. Hill and chemomechanical equations such as those of Huxley.

(2) The duality of energy and force in macromolecular states and transitions. We show that there is an interesting disparity between considering motor proteins moving against a load with force-dependent chemical transitions, and treating cross-bridges with force-generating states. Inquiry into these different views on muscle and motor proteins leads to a deeper understanding of the mechanics and chemistry of macromolecular systems.

2 Muscle Mechanics and Simple Viscoelastic Model

Treating muscle as a mechanical system, one naturally considers it in analogy to a viscoelastic material with a pre-stress. A completely naive model would be a pre-stressed viscoelastic object moving in a highly viscous medium, with overdamped motion. That is $m\ddot{x}+\eta\dot{x}+k(x-x_0)=0$ in which $kx_0=F_{max}$ is the pre-stress and $\eta^2/(mk)\gg 1$. This leads to a force-velocity relation $F=F_{max}-\eta v$. The linear viscoelastic model with a pre-stressed spring in parallel with a dashpot [Voigt model, Fung (1965)] relates the the velocity, i.e., the speed of shortening, to the corresponding force, i.e., load [Gasser and Hill (1924)]. See Fig. 1.

However, there are major difficulties to considering a muscle as a traditional, passive viscoelastic material. Unlike a pre-stressed spring which stores and liberates energy reversibly, the mechanical energy in a muscle could not be reconverted to chemical energy and be used later on. If the muscle does not do work, the energy can only be released as heat. Therefore, the heat production of a muscle is higher than what is expected from a viscoelastic material. This is known as the Fenn effect [Fenn (1924)]. In an isometric measurement, i.e., when a muscle is held at constant length, there is no work being done but the muscle constantly produces heat. This is called maintenance heat. From a chemical standpoint, the isometric state of a muscle is not an chemical equilibrium, but a nonequilibrium steady state. Muscle is an open chemical system [Qian (2007)].

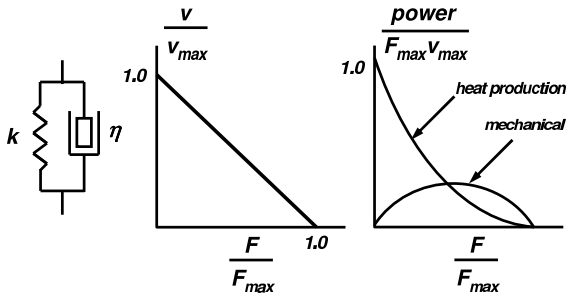

Figure 1: The force velocity relation according to a naive viscoelastic Voigt model $\eta v=F_{max}-F$. When $F=0$, $v_{max}=F_{max}/\eta$. The mechanical power per unit time is $Fv=F(F_{max}-F)/\eta$ and the heat production rate is ηv^2.

These considerations led A.V. Hill (1939) to propose a new kind of mechanical element called a contractile component (CC), together with an empirically determined steady state force-velocity relation

$$(F+a)(v+b)=c. \tag{1}$$

This model describes a decreasing viscosity coefficient with increasing force, sometimes referred to as "shear thinning".

3 Sliding Filament and Motor Proteins

The actin-myosin complex is the basic structural component of a muscle [Huxley (1986)]. The dynamic interaction between the motor protein myosin and its designated track, the actin filament, contributes to the mechanical behavior of muscle contraction [Huxley (1957)]. A comprehensive statistical thermodynamic theory for single motor-protein movement along its linear track has been developed. For recent reviews see Qian (2005); Kolomeisky and Fisher (2007). The theory provides a molecular basis for the "contractile component" in muscle contraction.

In the theory of a motor protein, both the stochastic dynamics of its internal conformation including biochemical reactions, $Y(t)$, and the stochastic movements of its center of mass along its track, $X(t)$, are described. Since both $X(t)$ and $Y(t)$ are stochastic, one is no long able to say "what are X and Y at time t", but rather one must say what are the probability of $X = x$ and of $Y = y$ at time t, in terms of a probability density function $P(x,y,t)$. This is the same approach used in Kramers' theory of chemical reactions [Kramers (1940)] and the theory of polymer dynamics [Doi and Edwards (1986)]. Qian (2002) has recently further developed this approach to account for active macromolecules in living matter as an open chemical system [Qian (2007)].

There are many different ways to realize a theory of motor proteins. Some treat the conformational space as discrete, other treat it as continuous. One can also consider the motion of a motor protein as continuous along an actin filament, or as jumping between discrete sites. We shall adopt the continuous representation for the movement of a motor protein along its track. Furthermore, for the simplicity of the discussion, we shall further assume that the internal conformational dynamics and biochemical reactions of the motor, i.e., $Y(t)$, is fast in comparison with the trasloaction movement $X(t)$. With this one assumption, a full set of equations for motor-protein dynamics and movements can be simplified into a single equation [Qian (2000b)]:

$$\eta\frac{\partial P(x,t)}{\partial t} = k_BT\frac{\partial^2 P(x,t)}{\partial x^2} + \frac{\partial}{\partial x}\left[\left(\frac{dE(x)}{dx} - F_{max} + F_{ext}\right)P(x,t)\right], \quad (2)$$

where x characterizes the position of the motor protein along its periodic track with period L, representing the periodic structure of an actin filament ($\sim$ 36nm). $P(x,t)$ is the probability density of the single motor protein at x at time t. η is a frictional coefficient, $E(x) = E(x+L)$ is the potential of mean force between the actin and myosin in the absence of ATP hydrolysis. In the presence of ATP hydrolysis, $E(x) - F_{max}x$ is the energy landscape in which the motor protein moves. The internal driving force for the motor protein is implicitly contained in the F_{max} term and the F_{ext} is the external load acting on the motor protein. Eq. 2 is the starting point of our present discussion.

The steady-state velocity of the motor protein can be obtained by solving Eq. 2 under a periodic boundary condition $P(x) = P(x+L)$:

$$v_{ss} = \frac{k_BTL}{\eta}\left(1 - e^{(F_{ext}-F_{max})L/k_BT}\right) \times \left\{\int_0^L R(x)e^{-(E(x)-F_{max}x+F_{ext}x)/k_BT}dx\right\}^{-1} \quad (3)$$

in which

$$R(x) = \int_x^L e^{(E(y)-F_{max}y+F_{ext}y)/k_BT}dy + e^{(F_{ext}-F_{max})L/k_BT}\int_0^x e^{(E(y)-F_{max}y+F_{ext}y)/k_BT}dy.$$

If we introduce dimensionless variables $\phi = e^{(F_{ext}-F_{max})L/k_BT}$ to replace F_{ext}, $\theta = x/L$, express energy function $E(x)$ in k_BT units, and v_{ss} in unit of $k_BT/(\eta L)$, then we have

$$\left(\frac{\eta L}{k_BT}\right)v_{ss}(\phi) = (1-\phi)\left\{\int_0^1 R(\theta)\phi^{-\theta}e^{-E(\theta)}d\theta\right\}^{-1} \quad (4)$$

in which

$$R(\theta) = \int_\theta^1 \phi^y e^{E(y)}dy + \phi\int_0^\theta \phi^y e^{E(y)}dy.$$

Eq. 4 provides the relationship between motor protein velocity and external load acting on the motor. It should be compared with Eq. 1. This relation is determined by the functional form of $E(x)$, i.e., the molecular interaction between single myosin molecular and the actin filament. With Eq. 4 in hand, we are now in a position to investigate the effect of the intermolecular energy on the viscoelastic properties of the contractile component (CC).

The most trivial case of Eq. 4 is when the intermolecular interaction has negligible effect: $E(x) \approx 0$. In this case, the motion of the motor

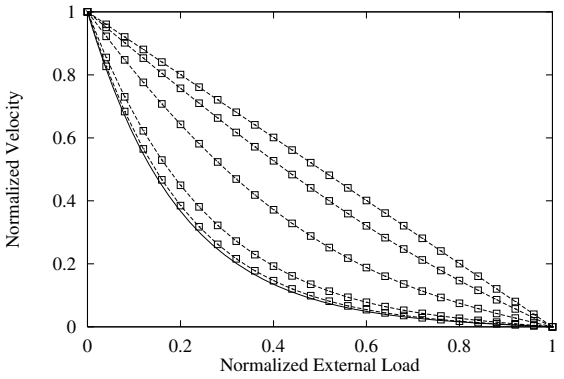

Figure 2: The effect of the height of the activation barrier on the viscoelasticity of motor units. The calculations are based on a quadratic ptoential $E(x) = 4\Delta G^{\ddagger}(x/L)(1-x/L)$. The transition state is located at the center where $x = L/2$. With varying F_{ext}, the location and the height of the transition state change. The peak of $E(x)$ is the transition state for $F_{ext} = F_{max}$. ($F_{max}L/k_BT$ = 10.) Five curves with symbols connected by dashed lines, from top to bottom, are for $\Delta G^{\ddagger}/(k_BT)$ = 0, 2.5, 5, 12.5, 50. The solid line is the asymptotic chemical limit based on transition state theory (see text). According to the transition-state theory, the shape of the normalized load-velocity curve is independent of the barrier height.

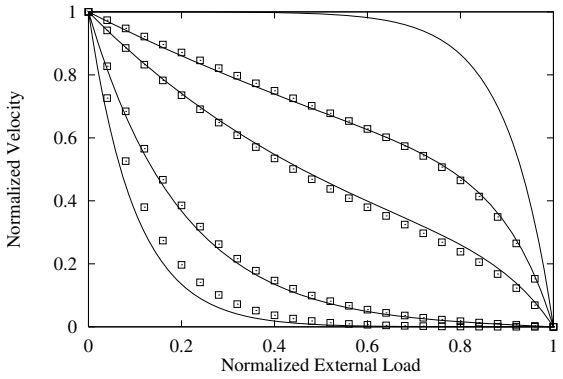

Figure 3: The effect of the position of the transition state on the viscoelasticity of motor units. The calculation is based on a piece-wise linear $E(x)$ with transition state at $x = \delta$, barrier height $\Delta G^{\ddagger}$ = $20k_BT$. Four curves with symbols, from top to bottom, are for δ/L = 0.0, 0.1, 0.5, 1.0. Solid lines are calculations based on transition state theory (Eq. 6): from top to bottom δ/L = 0.0, 0.075, 0.15, 0.5, 1.0. All calculations are with $F_{max}L/k_BT = 10$.

protein experiences an energy down-hill, due to ATP hydrolysis, with no significant energy barriers. This is the case of *mechanical limit*,

$$v_{ss} = \frac{F_{max} - F_{ext}}{\eta}.$$

This corresponds to the simple model of Gasser and Hill (1924) in Fig. 1.

If there is only a single dominant binding site for myosin on an actin filament per period L, then $E(x)$ has a dominant energy well and a single rate-limiting energy barrier within each period, corresponding to the binding site and the transition state, respectively. Figs. 2 and 3 show the effect of the height of the barrier and the location of the transition state on the viscoelasticity of the motor unit.

The model exhibits a set of rich behaviors. With increasing barrier height, the load-velocity curve becomes hyperbolic (Fig. 2), i.e., "shear thinning".

When the transition state appears "early", i.e, located near the n*th* well and far from the (n+1)*th* well , the load-velocity curve exhibits a negative curvature (concave, Fig. 3). When the transition state appears "late", the curve becomes convex. For very late transition state, the curve is quasi-linear [Qian (2000c)] with an apparent linear portion but a long flat tail. The significance of the last result is that, measuring a low steady-state velocity ($< 10\%\ v_{max}$) with corresponding experimental uncertainty, could give an apparent maximal force which is significantly lower than the true F_{max}. It has been shown [Fisher and Kolomeisky (1999); Qian (2000c)] that while the true F_{max} is a function of ATP concentration, the apparent maximal force is insensitive to the concentration.

When the activation barrier is sufficiently high, the load-velocity relationship is readily obtained from simple transition-state theory. We call this

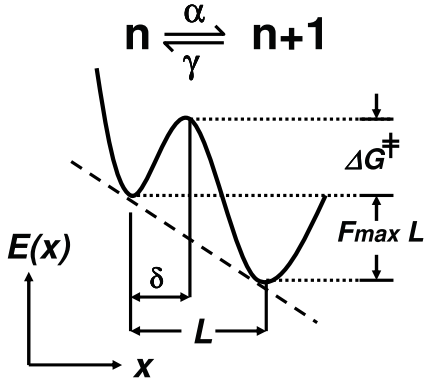

Figure 4: A schematic diagram showing the energy landscape in which a motor protein moves along its linear track. It assumes a single binding site per step (..., $n-1$, n, $n+1$, ...). When the $\Delta G^{\ddagger}$ is sufficiently large, there is a transition state at $x=\delta$ and the process is a jump process. However, if the $\Delta G^{\ddagger}$ is small, then the process is a diffusional. When an external load (F_{ext}) is applied, the energy function will be tilted toward the left. When $F_{ext}=F_{max}$, the two energy wells will be at an equal height and there will be no driving force for the motor to go from n to $n+1$. The driving force is implicitly contained in the α and γ which are functions of ATP, ADP, and Pi concentrations. Hence the driving force is a function of nucleotide concentrations in solution. When they are at their chemical equilibrium concentrations, $\alpha=\gamma$.

the *chemical limit*. This is schematically shown in Fig. 4 for a single step along the track. When there is an external load, the energy function will be tilted toward the left. We note in Fig. 4 that the external load F_{ext} decreases the forward rate constant α while it increases the backward rate constant γ:

$$\begin{aligned}\alpha(F_{ext}) &= \alpha(0)e^{-F_{ext}\delta/k_BT},\\ \gamma(F_{ext}) &= \gamma(0)e^{F_{ext}(L-\delta)/k_BT}\end{aligned} \tag{5}$$

where δ is the position of the transition-state. The thermodynamic driving force of the reaction is $F_{max}=(k_BT/L)\ln[\alpha(0)/\gamma(0)]$ and the steady-state velocity is $v_{ss}=(\alpha-\gamma)L$. We therefore immediately have:

$$v_{ss} = \kappa\left(e^{(F_{max}-F_{ext})\delta/k_BT}-e^{(F_{max}-F_{ext})(\delta-L)/k_BT}\right)L \tag{6}$$

where κ is a prefactor in the standard Kramers' rate theory.

Introducing the dimensionless variable ϕ, Eq. 6 can be written as

$$v_{ss}=\kappa L\frac{1-\phi}{\phi^{\delta/L}}. \tag{7}$$

This result for the chemical limit should be compared with Eq. 4: $k_BT/\eta L \leftrightarrow \kappa L$, $\phi^{\delta/L}\leftrightarrow\{...\}$. The former is simply the Einstein relationship if we identify κL^2 as the diffusion coefficient [Hill (1976)]. Eq. 7 gives a clear indication of how the position of the transition-state (δ) affects the viscoelastic properties of a molecular motor.

If $\delta=L/2$, Eq. 6 is further simplified into $2\kappa L\sinh[(F_{max}-F_{ext})/(2k_BT)]$ (the solid line in Fig. 2). If on the other hand $\delta=L$ representing a late transition state, then Eq. 6 is further simplified into

$$\begin{aligned}v_{ss} &= \kappa\left(e^{(F_{max}-F_{ext})L/k_BT}-1\right)L\\ &= \frac{\kappa L}{c}\left(c^{F_{ext}/F_{max}}-c\right)\end{aligned} \tag{8}$$

where $c=e^{-F_{max}L/k_BT}$. This equation has been previously obtained from a three-state chemical model for a single motor, with a *single rate-limiting step* assumption [Qian (2000c)].

Not shown in Fig. 3 is the load-velocity relation for $\delta<0$. In this case the curve is non-monotonic, which implies a certain instability [Thomas, Trintchina, Forero, Vogel, and Sokurenko (2002); Marshall, Long, Piper, Yago, McEver, and Zhu (2003)]. This possibility was first noted by Fisher and Kolomeisky (1999). The transition state preceding the "reactant" along a reaction coordinate is possible for a reaction in multidimensional space; the $E(x)$ in our model is a simplification based on the assumption of rapid biochemical reactions.

The results we present here demonstrate the simplest chemomechanical coupling. If the external

load is not a constant force, but, for example, due to an elastic cantilever or laser trap, then the model requires a more sophisticated mathematical treatment [Shapiro and Qian (1997); Qian and Shapiro (1999)] but it poses no additional conceptual difficulties. The model also provides a framework for calculating transient kinetics under varying external load.

I shall point out that the model we studied is not limited to chemomechanical energy transduction in motor proteins. A similar statistical mechanical model for the mechanical gating of mechanosensitive channels has been proposed in the past [Sachs and Lecar (1991)]. Our results can be applied equally well to other macromolecular mechanical systems.

4 Heat Production Rate

One of the important consequences of the stochastic chemical theory is that it provides a way to actually compute the heat production rate and the mechanical power of the muscle [Baker and Thomas (2000); Qian (2000b,c, 2004a)]. In general, heat is generated when a macromolecular system makes a complete cycle that contains ATP hydrolysis in its conformational space. When an active cycle produces no movement, it is futile. The futile cycle is the origin of the maintenance heat. If all active biochemical cycles are coupled to motor movements, then there will be no heat production when a motor protein is under isometric condition. Such systems are called *tightly coupled* between the hydrolysis and the movements [Qian (1997)].

The model given in Eq. 2 assumes rapid biochemical reactions including hydrolysis. It neglects all the futile cycles. Therefore, the the current model could not provide a realistic heat production calculation, but only its lower bound, for which we have

$$h_p \geq \frac{v_{ss}}{L} \cdot \int_0^L dx \left[k_B T \frac{dP}{dx} + \left(\frac{dE}{dx} - F_{max} + F_{ext} \right) P(x) \right] = \eta v_{ss}^2. \tag{9}$$

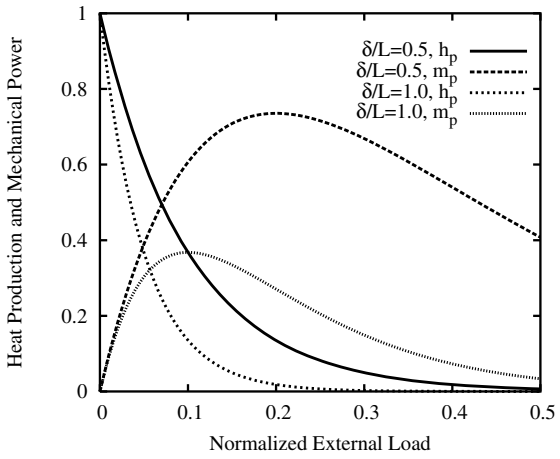

Figure 5: The mechanical power m_p and the lower bound of the heat production rate h_p for a motor protein in the chemical limit. The ordinate is in units $0.1 \times F_{max} v_{max}$. Other parameter used: $F_{max} L / k_B T = 10$.

The corresponding mechanical power is $m_p = v_{ss} \times F_{ext}$. Fig. 5 shows the m_p and the lower bound of h_p for a motor protein in its chemical limit, with $\delta / L = 0.5$ and 1.

5 From Single Motor to Sliding Filament

Huxley theory of muscle mechanics is based on the sliding of myosin filaments relative to actin filaments driven by interactions of myosin cross-bridges with the actin filaments [Huxley (1957)]. T.L. Hill (1974) has elucidated that Huxley's theory is in fact a mathematical model of an ensemble of individual cross-bridges connected by a linear, rigid filament. The viscoelastic theory of motor proteins presented above naturally lends itself to a theory of rigid, sliding filaments [Jülicher, Ajdari, and Prost (1997); Qian (2000b)]. In fact, one can *derive* equations such as Huxley's from an equation for a single motor proteins as follows.

To illustrate the basic idea of the derivation, let us consider two Brownian motors x_1 and x_2, each of which follows Eq. 2 on its own, but which are connected by a spring whose force is $\sigma(x_1 - x_2)$, where $\sigma(-x) = -\sigma(x)$. Then the joint probability

of the two motors, $p(x_1,x_2,t)$, satisfies:

$$\begin{aligned}&\frac{\partial p}{\partial t}\\ =&D\sum_{i=1,2}\frac{\partial^2 p}{\partial x_i^2}-\frac{\partial}{\partial x_1}\left(\frac{F(x_1)+\sigma(x_2-x_1)}{\eta}p\right)\\ &-\frac{\partial}{\partial x_2}\left(\frac{F(x_2)+\sigma(x_1-x_2)}{\eta}p\right).\end{aligned}\tag{10}$$

This system of two motors can be best understood in terms of a coordinate transformation developed by Qian (2004b). Let $y=(x_1+x_2)/2$ be the center of mass of the system, and $z=x_2-x_1$, then Eq. 10 becomes an equation for transformed $\widetilde{p}(y,z,t)$:

$$\begin{aligned}\frac{\partial\widetilde{p}}{\partial t}=\frac{D}{2}\frac{\partial^2\widetilde{p}}{\partial y^2}+2D\frac{\partial^2\widetilde{p}}{\partial z^2}-\frac{\partial}{\partial y}\left(\frac{\hat{F}\widetilde{p}}{2\eta}\right)\\ -\frac{\partial}{\partial z}\left(\frac{2\sigma(z)+f}{\eta}\widetilde{p}\right),\end{aligned}\tag{11}$$

in which $\hat{F}=F(y+z/2)+F(y-z/2)$ and $f=F(y+z/2)-F(y-z/2)$. The seemingly complicated Eq. 11 in fact has a simple mechanical interpretation: the center of mass follows a Brownian motion with diffusion coefficient $\frac{D}{2}$ and force $\hat{F}$; and the relative distance between x_1 and x_1 follows a Brownian motion with diffusion coefficient $2D$. Eq. 11 can be simplified if we follow the approach in [Qian (2000b, 2004b)] by integrating z and introducing conditional and marginal probabilities:

$$\widetilde{p}(z|y)=\frac{\widetilde{p}(y,z)}{p(y)},\quad p(y)=\int_0^\infty\widetilde{p}(y,z)dz.\tag{12}$$

Then we have

$$\frac{p(y,t)}{\partial t}=\frac{D}{2}\frac{\partial^2 p(y,t)}{\partial y^2}-\frac{\partial}{\partial y}\left(\frac{\overline{F}}{\eta}p(y,t)\right),\tag{13}$$

in which

$$\begin{aligned}&\overline{F}(y)=\\ &\frac{1}{2}\int_0^\infty\left(F(y+z/2)+F(y-z/2)\right)\widetilde{p}(z|y)dz.\end{aligned}\tag{14}$$

$\overline{F}(y)$ is in fact the mean force. If the spring connecting x_1 and x_2 is a rigid filament with length 2ℓ, then $\widetilde{p}(z|y)$ is a delta function, and $\overline{F}(y)=(F(y+\ell)+F(y-\ell))/2$.

The above method can be applied to a large ensemble of N motors uniformly distributed along a rigid filament. Then the motion of the entire filament is characterized by a diffusion coefficient of D/N and a mean force

$$\overline{F}\approx\frac{1}{L}\int_0^L F(x)dx.\tag{15}$$

Here we assumed that the motors are uniformly distributed over the periodic L [Hill (1974)]. For large N, the diffusion coefficient is essentially zero. Hence we obtain a first order partial differential equation. If one applies the above method to a system of equations for Brownian ratchet, then one obtains Huxley's equation. For more details, see [Jülicher, Ajdari, and Prost (1997); Qian (2000b)].

6 Chemical and Mechanical Views of Force Generation

The theories for motor proteins and for cross-bridges share many common features: both assume a set of discrete conformational states for a myosin molecule in terms of its interactions with an actin filament and nucleotides. Both have a set of rate constants which determine the transitions among the states. However, there is a disparity between the views of how force is generated by a cross-bridge and by a motor protein. In a motor model, a motor protein moves along its linear track against an external load [Qian (1997); Fisher and Kolomeisky (1999); Qian (2000c); Baker and Thomas (2000)]. In this approach, the force enters biochemical kinetics via *force-dependent rate constants*, as shown in Fig. 4 and Fig. 6A. On the other hand, discrete versions of the Huxley's cross-bridge theory often have the force associated with the states of a cross-bridge [Landesberg and Sideman (1994); Homsher, Lacktis, and Regnier (1997)]. It is widely considered that force is generated in various states.

Fig. 6 shows a duality in how to understand the force in a continuous energy landscape. The discrete models for motor proteins and cross-bridges

in fact provide complementary views of continuous motor protein/cross-bridge movement. To see this, consider Fig. 6A in which the rate constants between state n and $n+1$ are force-dependent. However, an alternative view exists: in Fig. 6B one considers the transitions from n to $(n-1)$ and from n to $(n+1)$. Then the different barrier heights of these two respective transitions define a *force associated with state n*.

A discrete state is a simplification of an energy well in the continuous energy landscape. When the energy barriers between the wells are large, this is an extremely good approximation for the system, as first demonstrated by Kramers (1940). Associated with a discrete state, there are energy and entropy that characterize, conceptually, the depth and the width of an energy well. The probability of being in an energy well is determined by both, i.e., the free energy. These are the basic concepts of equilibrium statistical chemistry. However, another important quantity, also associated with an energy well, which has not been widely appreciated is the *force* exerted on the discrete state. In Fig. 6B, this simply means the difference between the peak values of the energy barriers on the left and on the right, divided by the distance. *This is a force which biases the motion of the single molecule toward the right*! Therefore, there is a well-defined force associated with a discrete conformational state, even for a single molecule. (In a high-dimensional system, this force becomes a stress tensor as in solid mechanics.) In chemistry, one is taught that the ratio of the forward and backward rate constants *associated with a transition* is directly related to (free) energy of the reaction: $\Delta G = -k_B T \ln(\alpha/\gamma)$. One now sees that the ratio between forward and backward rate constants **associated with a state** is directly related to the force of the conformation: $F = \frac{k_B T}{L} \ln(\alpha/\gamma)$. There is a duality between these two equivalent views.

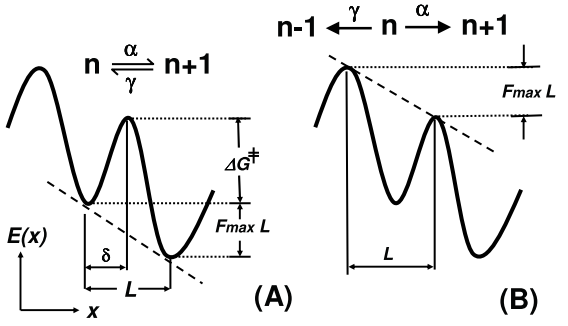

Figure 6: A periodic energy landscape for motor proteins. (A) The standard chemical view of molecular transition in terms of energy barrier crossing. $F_{max}L$ is usually denoted as ΔG between the two energy wells. It is related to the rate constants $\Delta G = -k_B T \ln(\alpha/\gamma)$. While in (A) one focuses on the forward and backward rate constants associated with the energy barrier between states n and $(n+1)$, in (B) one focuses on the forward and backward rate constants associated with two different energy barriers. In this view there is a force F_{max} associated with the discrete state n. One immediate insight is that the force associated with the state n varies with external load (not shown).

7 Equal Barrier and Equal Well Paradox

The above way of thinking also leads to another seeming paradox. Fig 7. shows two energy landscapes: one has equal barrier heights, and one with equal well levels. From the transition-state point of view from chemistry, the transitions between any two neighbouring states that share a same energy barrier have equal rates in (A), therefore equal probability in the long time limit; while in (B), the rate going leftward is greater than that going rightward between the two neighbouring states, hence the probability increases leftward. However, from the state-force point of view we developed, each state has a force going leftward in (A), while in (B) there are none. The transition-state view and the state-force view seem to be contradictory.

A resolution of this seeming paradox is in the meaning of "long time limit", which requires boundaries for the systems. With the possibility of reflection by the boundary, eventually there will be equal probability in all the energy wells in (A) but increasing probability leftward in (B). In (B), even though the rate of crossing the bar-

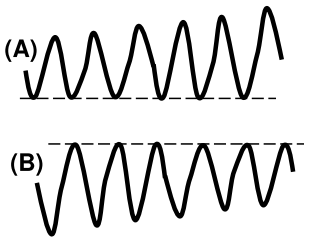

Figure 7: Is there a paradox? (A) The energy landscape with constant energy well indicates that the probabilities for all states are equal. But there is a bias in movement toward left. (B) There is no bias in movement but the probability increases leftward. If we denote the rightward and leftward rate constants leaving nth well by α_n and β_n, respectively, then we have in (A): $\alpha_n < \beta_n$, $\alpha_n = \beta_{n+1}$; and in (B): $\alpha_n = \beta_n$, $\alpha_n < \alpha_{n+1}$.

rier on one's left is the same as that on the right, one spends more time in a deeper well. The energy view is more appropriate for the equilibrium steady-state, while the state-force view is more appropriate for transient, stochastic movements. In fact, it is known that stationary probability distributions for systems in Fig. 7 are expressed in terms of $\frac{\alpha_n}{\beta_{n+1}}$, while fluxs and mean first passage times are expressed in terms of $\frac{\alpha_n}{\beta_n}$.

This situation can also be understood from an energy versus entropy perspective. The system shown in Fig. 7 can be represented in terms of a simple diffusion equation if we introduce $D(n\Delta x) = (\alpha_n + \beta_n)(\Delta x)^2/2$ and $V(n\Delta x) = (\alpha_n - \beta_n)\Delta x$ where Δx is the distance between two energy wells:

$$\frac{\partial u}{\partial t} = \frac{\partial}{\partial x}\left(\frac{\partial}{\partial x}(D(x)u) - V(x)u\right). \tag{16}$$

The stationary distribution with a reflecting boundary is

$$u_{ss}(x) \propto \frac{1}{D(x)} e^{\int (V(x)/D(x))dx}. \tag{17}$$

Hence, if $V(x) = 0$, the stationary distribution is determined by the inhomogeneous diffusion: The region with smaller diffusion will have higher probability. Of course, one can also obtained a different $D(n\Delta x) = (\alpha_n + \beta_{n+1})(\Delta x)^2/2$ and $V(n\Delta x) = (\alpha_n - \beta_{n+1})\Delta x$. In this case, the more appropriate diffusion equation becomes

$$\frac{\partial u}{\partial t} = \frac{\partial}{\partial x}\left(D(x)\frac{\partial}{\partial x}u - V(x)u\right). \tag{18}$$

See Ao, Kwon, and Qian (2007) for a discussion on the different interpretations of Eqs. 16 and 18.

8 Summary

At the molecular and cellular level, states and motions, and associated energies and forces, of macromolecules determine the material properties of living matters, such as a muscle. Traditional mechanics focuses on forces and movements of subcellular or submolecular components, while traditional chemistry focuses on the molecular states and their energies. These provide different views of the same macromolecular system. Recently developed theories of molecular motors [Jülicher, Ajdari, and Prost (1997); Qian (2000b); Bustamante, Keller, and Oster (2001); Kolomeisky and Fisher (2007)] show that one can obtain viscoelasticity of living materials, such a muscle, from a mesoscopic, stochastic theory based on Kramers' approach to chemical reactions [Kramers (1940)], and the theories of polymer dynamics [Doi and Edwards (1986)] and open chemical systems [Qian (2002, 2005, 2007)]. This paper discusses muscle viscoelasticity from such a mesoscopic approach. It is shown that A.V. Hill's contractile component and A.F. Huxley's equation for sliding-filament motions can both be derived. In the light of this integrative approach, we discussed the relationship between the force-dependent transition view of chemical motor proteins and force-generating state view of cross-bridges, and illustrate a duality between the force and energy in discrete states and transitions of macromolecular systems.

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