Biophysical Journal
Comment to the Editor

Biophysical Society

In defense of Huxley

INTRODUCTION

Models of muscle contraction fall into two broad categories: those that attempt to describe the molecules that power muscle contraction and those that posit relationships between macroscopic muscle properties. Huxley's 1957 model is an example of the former, where one keeps track of the average states and extensions of a large ensemble of myosin molecules interacting with an actin filament (1). A.V. Hill's 1938 model is an example of the latter, where measurements on frog muscle gave rise to relationships between muscle heat production, shortening length, shortening rate, and force (2). In the 1980s, as increased computer power drastically expanded how these models could be applied to measurements, researchers studying how muscles drive human or animal motion largely migrated to the macroscopic, "Hill" models. In parallel, as researchers learned more about myosin's biochemistry and single-molecule mechanics, researchers studying muscle (or myosin) function largely migrated to the molecular, "Huxley" models. More recently, as increased computing power continues to expand how models can be applied to measurements, a new class of "spatially explicit" models has emerged that can model each molecule and include the random noise inherent at the molecular scale (3), in contrast to Huxley models that describe average molecular properties with differential equations.

Over the years, there has been vigorous debate about which modeling approach is best for which applications (4). There are advantages and disadvantages to each approach, and while some applications favor one approach over another, it seems shortsighted to discount the results of any one approach. So, for example, while one might object that Hill models can show instabilities (5), they are nevertheless able to describe muscle forces in complex biomechanical tasks (6). The commentary from Prof. Josh Baker on our recent paper (7) makes the claim that any "corpuscular" (i.e., molecular) muscle model is both unphysical and cannot provide insight into human health. This criticism applies to our model as well as any Huxley or spatially explicit model. On the contrary, we believe these models do have a physical basis and have already provided insights into human health. We therefore address the criticism raised in the commentary.

To address Prof. Baker's criticism, we first provide a summary of our understanding of his argument, which we outline in the following four points.

(1) Models such as ours that attempt to span the molecular to the macroscopic scale ignore entropic effects.
(2) Our model does not account for the laws of thermodynamics and is, consequently, unconstrained.
(3) Our model is a mixed-scale model and is therefore unphysical, assuming on the one hand that myosin's force is generated by a single degree of freedom spring and on the other hand that the forces of all myosin molecules are balanced by another spring.
(4) Myosin, when part of an ensemble, undergoes a "thermodynamic" power stroke consistent with the second law of thermodynamics, and we assume a "molecular" power stroke.

In this response, we will provide evidence that our model is based on current equilibrium and nonequilibrium statistical mechanics of large, dilute molecules in solution. We will explain how the model accounts for entropy, is naturally constrained by the laws of thermodynamics, captures the potentially large number of myosin's degrees of freedom, and includes emergent ensemble effects. At the conclusion of our response, we will address Prof. Baker's final point that molecular muscle models, being based on incorrect physics, cannot provide any insight into human health.

THE PHYSICAL BASIS OF OUR MODEL

As a starting point for our model, suppose (like many molecular dynamics simulations) we consider myosin to be a set of N interacting particles of mass $m_1, m_2, \ldots, m_N$ with viscous drag $\zeta_1, \zeta_2, \ldots, \zeta_N$ at position $\boldsymbol{r}_1, \boldsymbol{r}_2, \ldots, \boldsymbol{r}_N$, all interacting with each other according to potential $V(\boldsymbol{r}_1, \boldsymbol{r}_2, \ldots, \boldsymbol{r}_N)$. Perhaps the most general governing equation for these particles in solution is the Chandrasekhar equation, a

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generalization of Liouville's theorem of the evolution of a conservative mechanical system in phase space to include Brownian motion (8). However, for large, dilute molecules in solution over typical timescales we care about, the Chandrasekhar equation reduces to the Smoluchowski equation (8,9), also called the Fokker-Planck equation (10):

$$\frac{\partial w}{\partial t} = \nabla\cdot(k_B T\mathbf{\Gamma}\nabla w + \mathbf{\Gamma}\nabla V w), \tag{1}$$

where $w(t,\boldsymbol{r}_1,\boldsymbol{r}_2,\ldots,\boldsymbol{r}_N)$ is the probability density of finding particle i at position $\boldsymbol{r}_i$ at time t, k_B is Boltzmann's constant, T is temperature, and $\mathbf{\Gamma}$ is a diagonal matrix whose entries are the inverse of each particle's viscous drag ($\Gamma_{ij} = \frac{1}{\zeta_i}\delta_{ij}$). Note that when $V = 0$ so that the particles do not interact, Eq. 1 reduces to Fick's second law, with each particle's diffusion constant defined by the Einstein relation $D_i = k_B T/\zeta_i$.

In our view, Eq. 1 is the foundation for modern equilibrium and nonequilibrium statistical mechanics for classical (i.e., nonquantum) systems. In particular, calculations from equilibrium statistical mechanics follow from the steady-state solution (see supporting materials and methods for an example). Given some assumptions about the interactions between particles, defined by the potential energy $V(\boldsymbol{r}_1,\boldsymbol{r}_2,\ldots,\boldsymbol{r}_N)$, we can apply Kramers' theory (11) and later generalizations (10) to derive chemical master equations whose rate constants depend on local properties of $V(\boldsymbol{r}_1,\boldsymbol{r}_2,\ldots,\boldsymbol{r}_N)$ near the minima that define each state and the saddles that define the transition states between them.

Criticism one is that attempts to span the molecular to macroscopic scale ignore entropic effects. However, equations derived from steady-state and non-steady-state solutions to Eq. 1 describe macroscopic effects with entropic contributions, e.g., the condensation of vapor (10) and the elasticity of a polymer (12). In the supporting materials and methods, we show that the steady-state solution to Eq. 1 can be used to derive the force-extension curve for a freely jointed chain, which is entirely due to entropy. Therefore, as far as we are aware, there is no entropy missing in Eq. 1.

Derivation of Huxley models (1) starts with a chemical master equation that accounts for the fact that when myosin binds to a moving actin filament, the myosin molecule stretches. Here, for example, is a two-state model describing a single myosin molecule interacting with an actin filament, where myosin is bound to actin in one state and unbound in the other:

$$\frac{\partial n}{\partial t} + \frac{dx}{dt}\frac{\partial n}{\partial \xi} = \kappa_a(\xi)\left(1 - \int_{-\infty}^{\infty} n d\xi\right) - k_d(\xi)n$$

$$\frac{d\xi}{dt} = \frac{dx}{dt}, \tag{2}$$

where $n(\xi,t)$ is the probability density of finding the myosin molecule bound with extension ξ at time t, $x(t)$ is the position of the actin filament, $\kappa_a(\xi)$ is the rate density of myosin attaching to actin with extension ξ, and $k_d(\xi)$ is the rate of myosin detaching from actin with extension ξ. Being a chemical master equation, it is possible to use Kramers' theory to derive Eq. 2, along with equations for $\kappa_a(\xi)$ and $k_d(\xi)$, from a molecular-mechanical system defined by a potential V (13). We can additionally write an equation for the expected force produced by this single molecule as a function of time

$$\langle F(t)\rangle = \int_{-\infty}^{\infty} f(\xi)n(\xi,t)d\xi, \tag{3}$$

where $f(\xi)$ is the force produced by a myosin molecule at that value of ξ.

The derivation of Eq. 2 requires some simplifying assumptions, e.g., that myosin may bind anywhere on actin, that actin is rigid, and that actin moves along a single degree of freedom. We concede that these assumptions are not correct and that violations of them may be important in understanding muscle, e.g., (3,14). However, to be tractable, every model must make simplifications. For each simplification, a modeler must balance, on the one hand, the likelihood the simplification renders the model incapable of explaining the data and, on the other hand, the complexity removed by making the assumption. That is, if one wishes to understand a particular observation, one must use a model that is "as simple as possible, but not simpler" (this quote, attributed to Albert Einstein, appears in (15)). In our current work (7), our model describes and predicts our measurements with reasonable success, so we are justified in making the assumptions. In future work, when our model is presented with data it cannot describe, as is the fate for any model, we will revisit these and other model assumptions. Though potentially incorrect, the assumptions do not render our model unphysical any more than neglecting friction and deformation in writing the equations of a pendulum is unphysical.

Criticism two is that our model is unconstrained by the laws of thermodynamics. The laws of thermodynamics are defined in terms of bulk properties and so do not directly apply to molecular models; however, they have molecular-scale analogs. For example, implicit in Eq. 1 are relationships between molecular fluctuations and energy dissipation (the fluctuation-dissipation theorem) and between the steady-state probability distribution and the potential energy (detailed balance), which are molecular-scale manifestations of the second law of thermodynamics (16). Note also that it is sometimes reasonable to violate these laws to simplify a model. For example, derivation of the Michaelis-Menten equation includes the assumption that the release of product from the enzyme is irreversible, which violates detailed balance. That is, while it is technically correct that product must rebind to the enzyme to satisfy detailed balance, neglecting this rare event is both mathematically

convenient and introduces only a small error. Similarly, in the current study (7), we assume that some reactions are irreversible. In our experiments, the concentration of hydrolysis products (ADP and inorganic phosphate) is sufficiently small such that reactions involving their release are rarely reversed. In neglecting these reversals, we simplify the model by decreasing the number of unknown parameters.

Part of criticism three is that we assume myosin's force is generated by a single degree of freedom spring. It is true that the function $f(\xi)$ in Eq. 3 defines how myosin produces force and, if this relationship were linear, could be thought of as a one-degree-of-freedom spring. However, this is a one-degree-of-freedom system because actin is assumed to move along one degree of freedom, not because myosin is assumed to have a single degree of freedom. In fact, we could use the expression for the force generated from a freely jointed chain to define $f(\xi)$ (17, 18) so that we make no assumptions about whether or not the spring is entropic or the number of myosin's degrees of freedom. Moreover, for small displacement, a linear relationship reasonably approximates $f(\xi)$ for a freely jointed chain, so our model's assumption of a linear relationship for $f(\xi)$ is similarly general. Finally, there is nothing unphysical about approximating a high-dimensional potential $V(\boldsymbol{r}_1, \boldsymbol{r}_2, \ldots, \boldsymbol{r}_N)$ with a low-dimensional free energy; this is the idea of a potential of mean force, e.g., (19,20).

As described above, Eq. 2 applies to a single myosin molecule interacting with a single actin filament. When simulating a myosin ensemble, it is useful to assume that the myosin molecules are sufficiently far apart that they do not attract or repel each other to an appreciable extent (more specifically, we mean that if the potential of one myosin is $V_1(\boldsymbol{r}_1, \boldsymbol{r}_2, \ldots)$ and the other is $V_2(\boldsymbol{s}_1, \boldsymbol{s}_2, \ldots)$, then we can approximate the overall potential $V(\boldsymbol{r}_1, \boldsymbol{r}_2, \ldots, \boldsymbol{s}_1, \boldsymbol{s}_2, \ldots) \approx V_1 + V_2$). Then, each molecule obeys Eq. 2, and since the equations are linear, we can write the average binding probability density of an ensemble of M myosin, $\overline{n} = \frac{1}{M}\sum_{i=1}^{M} n_i$, as

$$\frac{\partial \overline{n}}{\partial t} + \frac{dx}{dt}\frac{\partial \overline{n}}{\partial \xi} = \kappa_a(\xi)\left(1 - \int_{-\infty}^{\infty} \overline{n} d\xi\right) - k_d(\xi)\overline{n}$$

$$\frac{d\xi}{dt} = \frac{dx}{dt}. \tag{4}$$

Similarly, we can write the ensemble force $F = \sum_i^M \langle F_i(t) \rangle$ as

$$F = M \int_{-\infty}^{\infty} f(\xi)\overline{n}(\xi, t) d\xi. \tag{5}$$

In writing these expressions, we assume that each myosin molecule is the same as any other (so that, e.g., they could not be at different distances from the actin filament, they start in the same initial distribution, $n_i(\xi, 0) = n_j(\xi, 0)$, etc.).

Since the myosin molecules do not directly interact, they influence each other only through the motion of the actin filament. If, like Huxley (1), we assume that actin speed is constant ($\frac{dx}{dt} = v$), then the myosin molecules are independent. Solutions are then generally unique (21). Moreover, if we average together the simulation of M single molecules from Eq. 2, then we obtain the same solution as the ensemble average (Eq. 4). Thus, single-molecule measurements exactly predict ensemble measurements, and ensemble force scales linearly in myosin number. We believe this is what Prof. Baker calls a "molecular" power stroke, in that a molecule working as part of an ensemble generates the same work as a single molecule working in isolation.

Alternatively, if force on actin is constant, we must solve Eq. 4 subject to the constraint that Eq. 5 is a constant. Actin speed can then vary with time. Such a system can exhibit nonlinear behavior, including multiple stable solutions, oscillations, and hysteresis (22). We generally observe ensemble size effects, where the average velocity produced by a single molecule is not the same as the velocity produced by an ensemble (23). We believe this is what Prof. Baker calls a "thermodynamic" power stroke, in that a molecule working as part of an ensemble does not generate the same work as a single molecule working in isolation.

Criticism four is that our model assumes a "molecular" power stroke, which violates the second law of thermodynamics. It is true that specifying the velocity of actin violates the second law since its thermal fluctuations are ignored. However, we believe that it is still useful to consider how a myosin ensemble behaves as actin velocity is held constant in the same way it is useful to consider, say, the behavior of an ensemble of gas molecules as the volume of a piston changes at a constant rate. Regardless, we do not make this assumption in our model. Instead, to match the force produced immediately after a rapid stretch, our model requires a series elastic element (see also (24)). This series spring acts as a constraint on force, i.e., the force produced by myosin's interaction with actin must balance the force of the series spring, so that the model is in the "thermodynamic" power stroke regime.

The above provides at least a sketch of the physical basis of molecular muscle models, both Huxley and spatially explicit. For example, myosin in spatially explicit models typically obey an equation like Eq. 2, but the models include more complex coupling between myosin molecules than in Eq. 4, accounting for, e.g., actin elasticity, the position of binding sites, and so on (3, 14). Similar effects could also be included in Huxley models if, rather than assuming molecules do not interact, one applies a mean-field approximation. Alternatively, when the mean-field approximation does not hold, as is the case for submaximal activation where the system's behavior depends on the spacing between the attached myosin and not just the number, methods can be developed to generalize Eq. 4 (25). Thus, as far as we

are aware, there is no particular assumption in the above description that renders our model unphysical, but if there is, it seems likely that we could adapt our approach to account for it.

THE UTILITY OF MOLECULAR MUSCLE MODELS

Independent of this physical basis, our model and related molecular scale models successfully relate muscle function at one scale to another. We have shown, for example, that a model like Eq. 2 can explain single-molecule measurements in the laser trap, simulations of ~ 10 molecules coupled through a thermally fluctuating bead-actin-bead assembly can explain small ensemble force-velocity relations in the laser trap, simulations of ~ 100 molecules coupled through an actin filament can explain motility measurements, and these simulations converge to differential equations like Eq. 4 in the limit of large ensembles (23). These results are notable since the measurements, being constrained to have an average force, are in the "thermodynamic" power stroke regime so that molecules behave differently when isolated than when part of an ensemble (26). In fact, we do the same in our current study (7), but rather than determining model parameters based on fitting molecular-scale experiments, model parameters were determined from fits to our skinned fiber measurements. We show that better fits to the cellular data more successfully describe our molecular-scale data, supporting our claim that the model is predictive.

Such connections between the molecular and cellular scales of muscle contraction have clear implications for human health. Indeed, previous molecular models have explained the counterintuitive behavior of the heart drug omecamtiv mecarbil (27,28), successfully predicted that the drug mavacamten would improve function in cardiomyocytes from a patient with heart disease (29), explained how a small increase in 2′-deoxy-ATP can produce a large increase in ejection fraction in failing hearts (30), and related cellular force measurements to the molecular function of myosin binding protein C, a protein mutated in about a third of patients with familial hypertrophic cardiomyopathy (31). These are only a few examples of the insights molecular-scale modeling has already provided into human health.

CONCLUSIONS

In response to Prof. Baker's four criticisms, we have presented our view that 1) the "corpuscular" view of muscle contraction is based, not on the work of Boyle in the 17th century, but on the work of Chandrasekhar (8), Smoluchowski (9), Kramers (11), and others (10) in the 20th century and does not neglect entropy; 2) thermodynamic constraints, e.g., detailed balance and fluctuation-dissipation, exist in these models; 3) the models do not necessarily approximate myosin as having one degree of freedom (though such an approximation need not be unphysical); and 4) there is value in modeling situations both where actin's velocity is fixed and where the force on actin is fixed. We then addressed the criticism that molecular muscle models cannot provide insight into human health by presenting a few examples where they have done so. Connecting the molecular scale of muscle contraction to the function of a heart or the motion of a limb is an imposingly complex problem. Progress toward its solution has been made using a range of experimental and theoretical techniques. It is correct, but trivial, to claim that a modeling approach is wrong (since all models are wrong) or an experiment differs from the unmodified system (since one modifies a system by observing it). It is unfair to ignore the insights of one modeling approach because it is "more wrong" than another or one experimental approach because it is "more modified" than another. Though each approach has its benefits and drawbacks, continued success depends on using all techniques and integrating all results.

Though we disagree with Prof. Baker, we are grateful to him to have afforded us the opportunity to explain the physical basis of our model. Physical and mathematical aspects of muscle contraction have been relegated to the supplementary material of journal articles and private discussions at the sidelines of conferences. But muscle contraction is an interesting physical system, a large ensemble of molecules with local and global coupling between molecules (25), and an interesting mathematical system, with unique solutions at constant velocity (21) and classically nonlinear behavior at constant force (22). Open discussion of these and other physical/mathematical aspects of muscle contraction will broaden its appeal beyond the biology community, generate new modeling approaches, and provide new biological, physical, and mathematical insights.

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AUTHOR CONTRIBUTIONS

S.W. wrote the article with feedback from all authors.

SUPPORTING MATERIAL

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Supplemental information

In defense of Huxley

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Supplementary Material for "In defense of Huxley"

S. Walcott, et al.

The purpose of this Supplement is to apply the Smoluchowski equation (Eq. 1 in the main text) to a physical system with multiple "molecules" and derive an equation governing its "macroscopic" behavior. We choose a freely jointed chain as our physical molecular system, and the force-extension relationship as the macroscopic property we wish to derive. We chose this system for two reasons: first, the force-extension relationship for a freely jointed chain is entirely entropic, so if we can derive this relationship then the Smoluchowski equation presumably is not missing any entropy; second, the analysis presents some interesting points that we wish to highlight.

Suppose we have a freely jointed chain of N links in 3D. We anchor the first link, and define that point in 3D space to be $(0,0,0)$. We apply a force, $\boldsymbol{F} = F\hat{\boldsymbol{i}}$, directed along the x-axis and applied to the N^{th} molecule. To understand how this system will behave after it has settled into its final configurations, we apply the steady-state solution to the Smoluchowski equation:

$$w(\boldsymbol{r_1}, \boldsymbol{r_2}, \ldots) = C \exp\left(-\frac{V^0(\boldsymbol{r}_1, \boldsymbol{r_2}, \ldots) - F\hat{\boldsymbol{i}} \cdot \boldsymbol{r}_N}{k_B T}\right)$$

where $V^0(\boldsymbol{r}_1, \boldsymbol{r_2}, \ldots)$ is the potential that defines the interactions between each link in the chain (the overall potential is $V = V^0 - F\hat{\boldsymbol{i}} \cdot \boldsymbol{r}_N$), and the normalization constant

$$C = \frac{1}{\int_B \exp\left(-\frac{V^0(\boldsymbol{r}_1, \boldsymbol{r_2}, \ldots) - F\hat{\boldsymbol{i}} \cdot \boldsymbol{r}_N}{k_B T}\right) dV} \tag{1}$$

where B is the $3N$-dimensional space in which $\boldsymbol{r}_1, \boldsymbol{r_2}, \ldots$ reside.

Then, the expected stretch of the molecule, which we define as the position of $\boldsymbol{r}_N$ along the x-axis, is

$$\langle x \rangle = \frac{\int_B \hat{\boldsymbol{i}} \cdot \boldsymbol{r}_N \exp\left(-\frac{V^0(\boldsymbol{r}_1, \boldsymbol{r_2}, \ldots) - F\hat{\boldsymbol{i}} \cdot \boldsymbol{r}_N}{k_B T}\right) dV}{\int_B \exp\left(-\frac{V^0(\boldsymbol{r}_1, \boldsymbol{r_2}, \ldots) - F\hat{\boldsymbol{i}} \cdot \boldsymbol{r}_N}{k_B T}\right) dV}$$

At some distance $\boldsymbol{r}_1$ from the anchoring point at $(0,0,0)$, we have the first molecule. The potential energy for this molecule is 0 if $\|\boldsymbol{r}_1\| = \ell$ and infinity otherwise. The potential energy for the next molecule is 0 if $\|\boldsymbol{r}_1 - \boldsymbol{r}_2\| = \ell$ and infinity otherwise, and so on. Given this definition, we get that

$$\begin{aligned} \exp\left(-\frac{V^0(\boldsymbol{r}_1, \boldsymbol{r_2}, \ldots) - F\hat{\boldsymbol{i}} \cdot \boldsymbol{r}_N}{k_B T}\right) &= \exp\left(-\frac{V^0(\boldsymbol{r}_1, \boldsymbol{r_2}, \ldots)}{k_B T}\right) \exp\left(-\frac{F\hat{\boldsymbol{i}} \cdot \boldsymbol{r}_N}{k_B T}\right) \\ &= \left(\sum_{i=1}^{N} \delta(\|\boldsymbol{r}_{i-1} - \boldsymbol{r}_i\| - \ell)\right) \exp\left(-\frac{F\hat{\boldsymbol{i}} \cdot \boldsymbol{r}_N}{k_B T}\right) \end{aligned}$$

where we define $\boldsymbol{r}_0 = \boldsymbol{0}$.

We can then switch to spherical coordinates to eliminate the delta functions and the radial integrals to get

$$\langle x \rangle = \frac{\int_0^{2\pi} \int_0^{\pi} \cdots \int_0^{2\pi} \int_0^{\pi} \ell \left(\sum_{i=1}^{N} \cos(\theta_i)\sin(\phi_i)\right) \exp\left(-\frac{F\ell \sum_{i=1}^{N} \cos(\theta_i)\sin(\phi_i)}{k_B T}\right) \sin(\phi_1) d\phi_1 d\theta_1 \cdots \sin(\phi_N) d\phi_N d\theta_N}{\int_0^{2\pi} \int_0^{\pi} \cdots \int_0^{2\pi} \int_0^{\pi} \exp\left(-\frac{F\ell \sum_{i=1}^{N} \cos(\theta_i)\sin(\phi_i)}{k_B T}\right) \sin(\phi_1) d\phi_1 d\theta_1 \cdots \sin(\phi_N) d\phi_N d\theta_N} \tag{2}$$

We can turn the sum in the exponential in the denominator into a product of exponentials, then collect all the terms into independent integrals to obtain

$$\langle x \rangle = \frac{\int_0^{2\pi} \int_0^{\pi} \cdots \int_0^{2\pi} \int_0^{\pi} \ell \left(\sum_{i=1}^{N} \cos(\theta_i)\sin(\phi_i)\right) \exp\left(-\frac{F\ell \sum_{i=1}^{N} \cos(\theta_i)\sin(\phi_i)}{k_B T}\right) \sin(\phi_1) d\phi_1 d\theta_1 \cdots \sin(\phi_N) d\phi_N d\theta_N}{\left(\int_0^{2\pi} \int_0^{\pi} \exp\left(-\frac{F\ell \cos(\theta)\sin(\phi)}{k_B T}\right) \sin(\phi) d\phi d\theta\right)^N}$$

Similarly, in the numerator we can turn the sum in the exponential into a product of exponentials and multiply each term in the sum, then collect all the terms into independent integrals:

$$\begin{aligned}
&\int_0^{2\pi}\int_0^{\pi}\cdots\int_0^{2\pi}\int_0^{\pi}\ell\left(\sum_{i=1}^{N}\cos(\theta_i)\sin(\phi_i)\right)\exp\left(-\frac{F\ell\sum_{i=1}^{N}\cos(\theta_i)\sin(\phi_i)}{k_BT}\right)\sin(\phi_1)d\phi_1 d\theta_1\cdots\sin(\phi_N)d\phi_N d\theta_N \\
= &\int_0^{2\pi}\int_0^{\pi}\cdots\int_0^{2\pi}\int_0^{\pi}\ell\left(\cos(\theta_1)\sin(\phi_1)+\cdots+\cos(\theta_N)\sin(\phi_N)\right)\times\cdots \\
&\cdots\times\exp\left(-\frac{F\ell\cos(\theta_1)\sin(\phi_1)}{k_BT}\right)\cdots\exp\left(-\frac{F\ell\cos(\theta_N)\sin(\phi_N)}{k_BT}\right)\sin(\phi_1)d\phi_1 d\theta_1\cdots\sin(\phi_N)d\phi_N d\theta_N \\
= &\ N\int_0^{2\pi}\int_0^{\pi}\ell\cos(\theta)\sin(\phi)\exp\left(-\frac{F\ell\cos(\theta)\sin(\phi)}{k_BT}\right)\sin(\phi)d\phi d\theta\left(\int_0^{2\pi}\int_0^{\pi}\exp\left(-\frac{F\ell\cos(\theta)\sin(\phi)}{k_BT}\right)\sin(\phi)d\phi d\theta\right)^{N-1}
\end{aligned}$$

With these, the integral (Eq. 2) simplifies to

$$\langle x\rangle = \frac{\ell N\int_0^{2\pi}\int_0^{\pi}\left(\cos(\theta)\sin(\phi)\right)\exp\left(-\frac{F\ell\cos(\theta)\sin(\phi)}{k_BT}\right)\sin(\phi)d\phi d\theta}{\int_0^{2\pi}\int_0^{\pi}\exp\left(-\frac{F\ell\cos(\theta)\sin(\phi)}{k_BT}\right)\sin(\phi)d\phi d\theta} \tag{3}$$

Some comments:

1. Numerical integration yields a result that is identical, to within numerical error tolerance, of the classical result, $\langle x\rangle = \ell N\left(\coth\left(\frac{F\ell}{k_BT}\right)-\frac{k_BT}{F\ell}\right)$ [1, 2].

2. This equivalence between our results and classical results is not surprising. Each term in the equations relate to standard quantities from statistical mechanics. For example, Eq. 1 is the isothermal-isotension partition function [2].

3. We have calculated the average extension $\langle x\rangle$ (ξ when describing a myosin molecule) under a constant force field. If myosin were a freely jointed chain, this calculation would be approximately the inverse of the function relating force at a given extension, $f(\xi)$. However, the relation is only approximate because, if myosin were a freely jointed chain, then the end of the chain is constrained (unlike in the calculation above) [2, 3].

4. From a comparison between Eq. 2 and Eq. 3, we see that an N-link freely jointed chain is exactly equivalent to a single link of length $N\ell$ or, equivalently, N independent single links. This is not surprising, as force balance would suggest that each link in the chain experiences the same forces and should therefore behave identically. However, it's worth noting that a system with millions of degrees of freedom behaves exactly as a system with a single degree of freedom.

References

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