S2 Diode Model of Muscle Crossbridge Dynamics

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Abstract

This report explores the contribution of lateral myosin bending to the developed crossbridge force and power stroke. The equipartition theorem and Boltzmann distribution are used to calculate crossbridge force and displacement, consistent with experimental values. Negligible buckling strength of the S2-myosin link means that the muscle crossbridge is effectively a one-way force transducer, a mechanical diode, transmitting axial tension forces only. Crossbridge stiffness surfaces as an important factor. Power-stroke displacement is found to decrease with increasing stiffness, whereas axial force increases. The transverse thermal fluctuations of the myosin molecule are significant. Equipartition is used to calculate the mode amplitudes for myosin bending. Crossbridge axial force Fx and power stroke Δx develop from transverse in-plane fluctuations along the y and z axes. Single and double-headed actin-myosin attachment configurations are calculated in detail. Practical applications include the effects of temperature on the flexibility of the myosin molecule stiffness and tension, relevant to man-made fabrication of synthetic muscle using micro-machines. Scaling laws for the S2 bending amplitude depend on mode number, filament length, and stiffness, as (n)^2, (L)^2, and (E)^1.

Keywords: Actin-myosin; Muscle crossbridge; Axial force; Brownian motion; Stiffness; Scaling laws

Introduction

The muscle crossbridge structure is a highly efficient molecular machine. An understanding of the dynamics of crossbridge conformational changes are central to our understanding of the mechanism of chemo-mechanical transduction by motor proteins. The purpose of this report is to investigate the molecular dynamics of the skeletal muscle crossbridge, in particular, the contribution of thermal fluctuations of the S1 and S2 components of myosin. Basically an articulated molecule, as shown in Figure 1a, the myosin S1 segment is usually modelled as a 2, 3, or 4 position ratchet, similar to the escapement mechanism on a mechanical pendulum clock, generating force by rocking forward, as shown.

Reviews

Theories are many and varied in terms of explaining how the crossbridge generates axial force. Cooke [1] reviews various theoretical models for muscle crossbridge mechanics. Nie et al. [2] analyze the effect of Brownian motion on force generation in the muscle crossbridge. Greene [3-5] calculates thermal fluctuation effects on force generation and stiffness, finding values of 2 x 10^{-12} to 5 x 10^{-12} N/XB. Muscle physiology and crossbridge dynamics are reviewed by Cooke [1], McMahon [6], Carlson and Wilke [7], and McMahon and Greene [8].

Flexibility


Tension and compression

Adamovic et al. [16] measure directly the stretching and flexible bending stiffness of the LMM domain of myosin from scallop, finding values of 60-80 pN/nm and 0.010 pN/nm respectively, i.e., relatively compliant in bending. Kaya and Higuchi [17] using optical techniques measure directly the compression and tension characteristics of myosin, finding a small buckling load when strained negatively, with a working power stroke of 80 Å. Finer, Simmons and Spudich [18] measure a working step length of 110 Å and axial force per crossbridge of 3-4 pN. Dobbie et al. [19] measure a working step length of 110 Å and axial force per crossbridge of 3-4 pN. Greene [3-5] calculates thermal fluctuation effects on lever-arm flexibility of the S1-S2 junction, with values of 0.37 pN/nm stiffness. Golji et al. [20] model the model the S2 portion of myosin, finding axial displacements of 30-40 A°. Gittes et al. measure S2 buckling characteristics [21] in muscle fibers during quick release tension experiments.

Computer calculations

Huxley [22] reviews the mechanics of the muscle crossbridge. Slawnych, Seow, Huxley and Ford [23] develop a computer program to predict crossbridge performance. Billington et al. [24] report the thermal effects on lever-arm flexibility of the S1-S2 junction, with values of 0.37 pN/nm stiffness. Gittes et al. [25] model the molecular dynamics of α-Actinin (similar to but larger than F-actin) applying bending forces in the range 8 to 200 pN and torques of 50-500 pN-nm over a rapid time scale of 10 to 100 picoseconds. Pang [26] performs molecular dynamics calculations on a time scale of femtoseconds.

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Materials and Methods

Basic equations for bending and buckling of the myosin rod include actin F1 and myosin S2 bending and buckling, S2 mode amplitudes, and equipartition energy per mode [6]. As shown in Figure 1a, the x-axis is parallel to the developed force, the y-axis is vertical, and the z-axis is perpendicular to the xy-plane. Axial force Fx and power stroke Δx is produced by transverse in-plane fluctuations of S2 along the y and z axes. The origin of the coordinate system is at the S1-S2 junction. Myosin S2 buckling load is assumed minimal, Figure 1b, as measured [10a, 10b, 17a].

In-plane Δy and out-of-plane Δz fluctuations are independent of each other. The individual contributions are found by calculating the r.m.s. average,
\[ \Delta x = \sqrt{\Delta x^2 + \Delta z^2} \]  

(1)

Developed axial force results from integrating the Boltzmann distribution with the S1 spring stiffness in tension,
\[ Fx = \frac{Co}{Kx} \exp \left( \frac{-0.5 Kx^2}{kT} \right) dx \quad 0 < x < \infty \]  

(2)

where axial force F=Kx in tension for x>0, and F=0 for x<0 in compression, Figure 1b. The F-actin thin filament is also flexible in torsional mode [3]. The amplitudes Θn are found to scale as \( n^{-1} \), \( (EI)^{-1/2} \), and \( L^{1/2} \), where n is mode number, EI is actin bending stiffness, and L is filament length. Depending on conditions, the twisting modes can be as large as +/- 150. Similar scaling laws are found here for S2 bending, Table 1, showing scaling laws for S2 amplitude depends on filament length, mode number, and stiffness, Table 1.

Results

Harmonic mode amplitude for the over-tone sequence scales as \( (n\pi)^2 \), \( (L)^2 \), and \( (EI)^{-1} \) (Table 1; Figures 1 and 2). Power stroke for mode \( n \) scales as
\[ \Delta x / L o = 2.5 \left( \frac{A_n}{L} \right)^2 \]  

(3)

The first 3 principle modes (n=1, 2, 3) are shown in Figure 2 below, A1=+/−100 Å. Figure 3a shows the equipartition distribution of S1 axial position about its equilibrium point, calculated from Eq. (4) 0.5 Kt=0.5 K <x^2>. Figures 3b, 3c and 3d show force and displacement for the single and doubly-attached S1 myosin head depends strongly on crossbridge stiffness.

Crossbridge force is estimated at Fx=1.0 pN for the in-plane component,Fx,rs=1.4 pN for both in-plane and out-of-plane combined. Crossbridge power-stroke is estimated at dx=40 Å for the in-plane component, dx=56 Å for both the Δy and Δz fluctuations included. Minimal assumptions include [1] S2 link is inextensible with minimal buckling load and [2] experimental crossbridge compliance K is given by Eq. 4:
\[ \frac{dF}{dx} = 4 \times 10^{-4} \text{ N/m}, \quad K = 8 \times 10^{-4} \text{ N/m} \]  

for S1 double-head configuration

(4)

It is provided by S1 (Huxley and Simmons [27]). Muller et al. [28] calculate flexural details of the S2 link. An IBM PC-XT was used for the calculations, running MicroSoft Basic 3.2 at 4.77 MHz, then re-confirmed with an online Windows compatible version of QBASIC, running at 500-1,000 MHz, distributed by JustBasic.com [29]. Original calculations were made on an Apple II Computer running at 1 MHz. Modern computers, now 1,000 times faster, can perform the integrations in Eq. 2 in just 1-second, whereas previously 15-20 minutes were required.

Table 1: Scaling Effects for Thermal Oscillation Amplitude.
Discussion

Spider-Web monofilament model

Results presented here do not only apply to microscopic systems. For instance, a spider web stretched between two trees over a distance of 6 to 10 feet (2 to 3 meters) will fluctuate in the wind. The author has observed the n=1, 2, and 3 modes of these mono-filaments, buffeted by eddies in the wind on a still day, and the resulting bending of the leaf to which the filament is attached. This experimental observation, demonstrating the “clothesline effect”, may be important, as it represents the limiting case of zero bending stiffness, similar to the S2 segment of myosin. In other words, amplified axial force is developed by transverse flexing of the S2 filament.

Doubly attached myosin S1 head

The purpose of the second myosin (Figure 1a) head is still unknown [29-31]. Under some circumstances, both heads can co-attach, either to the same actin filament, or adjacent actin filaments, which effectively doubles the stiffness of the bridge, Figures 1b, 3b, 3c and 3d. From a thermodynamic point of view, the second head represents another ½ kT degree of freedom of the system. AC Power cable comparison. While power from random motion seems counter-intuitive, a familiar example serves to illustrate: fluctuating (+) and (-) voltages, after passing through a diode bridge, result in an average net (+) positive voltage. Likewise, AC power cables, in a wind-driven turbulent velocity field, result only in (+) positive cable tension, because cables cannot sustain buckling force in compression. Results presented here are a uni-directional tension-only mechanical model, hence the name “Myosin Diode Model”, because only positive forces can be transmitted through the S2-linkage.

Equipartition energy

The thermal fluctuations of the S1 motor head alone result in fractional pico-Newton forces on the S2 myosin and the actin filaments, considerably “under-powered” compared with the experimentally observed force per crossbridge. These force and displacement values correspond to ~ 0.5 kT of thermal energy and are comparable to the natural thermal fluctuations of the system. Note that the additional degrees of freedom of the S2 segment result in additional axial force from each independently oscillating mode, summed as per Eq. 1.

Applications

Results presented here show that during transverse thermal fluctuations of the myosin molecule, a significant axial crossbridge force and power stroke is developed from random transverse thermal motion (Figures 3b-3d). Practical applications include the effects of temperature on the flexibility of the myosin molecule [32,33]. Man-made fabrication of muscle is now possible, using micro-machines, so it is of interest to specify the role of Brownian motion on the mechanics of miniature molecular motors similar to the crossbridge [34,35]. In terms of the bioengineering design of these synthetic muscles, design objectives include determining the optimum length filament (equivalent to myosin), optimum stiffness, harmonic mode number, and optimum inter-filament spacing, for maximum crossbridge force, power stroke, and thermodynamic efficiency.
Figure 3d: Force F [pN] vs. stiffness K [N/m].

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Nomenclature
\[ \Delta x = \text{Crossbridge power stroke} = 40 \text{ to } 100 \text{ Å} \]
\[ K = \text{Crossbridge stiffness} = 4 \times 10^4 \text{ N/m (chevron)} \]
\[ F / XB = 2 \times 10^{-15} \text{ N/XB} = 2 \text{ pN} \]
\[ L_0 = \text{resting length of myosin} = 600 \text{ Å} \]
\[ 0.5 kT = \text{Equipartition energy, } k=1.38 \times 10^{-23} \text{ J/K} \]
\[ \exp(-U/kT) = \text{Boltzmann factor}, U=0.5 \text{ K } \times 2 \text{ elastic energy} \]
\[ C_0 \exp(-0.5 Kx^2 / kT) dx, \text{ Boltzmann constant} \]

References