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Supporting Material

Reversal of The Myosin Power Stroke Induced By Fast Stretching of Intact Skeletal Muscle Fibres

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Supplementary Material

S.1 Model Theory.

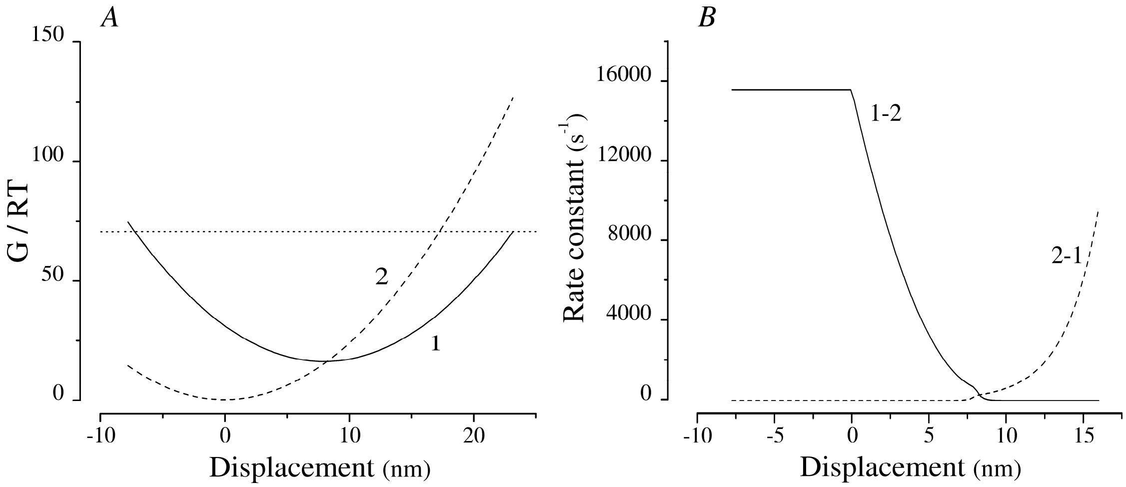

FIGURE 1s (*A*) Energy profiles of two attached cross-bridge states 1 and 2. (*B*) Forward and backward rate constant for the two attached cross-bridges states as function of displacement. Dotted line indicates energy level at which cross-bridges detach.

The model we used is formulated around that of Hill (1). The potential energy profiles and the rate constants assumed in the model are shown in Fig. 1s. Let $n_1(x)$ and $n_2(x)$ be the fractional occupancy of states 1 or 2 by actin-bound S1's, respectively, at a given x. At equilibrium, occupancy is related to the potential energy, $E(x)$, by the expression:

$$\frac{n_2(x)}{n_1(x)} = \exp\left(\frac{(E_1(x) - E_2(x))}{RT}\right) \qquad \text{(Eq.1)}$$

We now consider a region from x to $x+\Delta x$. If a waveform defining the fractional occupancy of state 2, $n_2(x,t)$, is sliding along the x axis, then the change in $n_2(x,t)$ over the distance Δx is given by:

$$\Delta n_2(x,t) = \Delta x\left(\frac{\partial n_2}{\partial x}\right)_x + \alpha_x(n_2(x,t))\Delta t \qquad \text{(Eq.2)}$$

The first right hand term represents the change in $n_2(x,t)$ produced by translation of the waveform along the x-axis, the second being the change in $n_2(x,t)$ due to chemical reactions occurring during Δt, where Δt is the time required to traverse distance Δx, and α_x is the rate of change in $n_2(x,t)$ with time at point x. If sliding occurs at a constant velocity, V, then dividing by Δt and letting Δx tend to its limit, dx, we have:

$$\frac{\partial n_2}{\partial t} = -V \frac{\partial n_2}{\partial x} + \alpha(x, n_2(x,t)) \qquad \text{(Eq.3)}$$

taking a convention that V is positive if motion is in the direction of increasing x, the translation produced by stretching the muscle. In the model used here, we assume that n_1+n_2 is constant throughout an applied stretch, so $n_1(x,t) = 1-n_2(x,t)$. If the rate constant for the transition from state 1 to state 2 is k_f, for state 2 to state 1 k_r, then the last term becomes

$$k_f(x)-(k_f(x)+k_r(x))n_2(x,t). \qquad \text{(Eq.4)}$$

The rate constants $k_f(x)$ and $k_r(x)$ are, to some extent, arbitrary as long as $k_f(x) / k_r(x)$ equals $n_2(x) / n_1(x)$ at equilibrium. We chose to define $k_f(x)$ as 0.01975 x^2-34.5 x+15,600 to provide a reasonable approximation to Fig. 4 of Eisenberg et al. (2) for $x < 8$ nm. For $x \geq 8$ nm, we allowed $k_f(x)$ to decline exponentially with a decay constant of -0.033 nm^{-1}. We then derived values for $k_r(x)$ from Eq. 1 using these values of $k_f(x)$. Equation 3 can be solved analytically for simple rate constant dependence on x, but since the expressions for $k_f(x)$ and $k_r(x)$ are complicated, we applied a numerical method solved by the method of characteristics (3). This consists of converting $n(x,t)$ into $n(\xi,t)$, where $\xi = x-Vt$, the position on the x axis occupied at zero time by a bridge currently positioned at x after time t. Applying this transformation to Eq. 2, we obtain:

$$\frac{\partial n_2}{\partial \xi}\frac{\partial \xi}{\partial t} + \frac{\partial n_2}{\partial t} = -V\left(\frac{\partial n_2}{\partial \xi}\frac{\partial \xi}{\partial x}\right) + k_f(\xi+Vt) - \left(k_f(\xi+Vt)+k_r(\xi+Vt)\right)n_2(\xi,t) \qquad \text{(Eq.5)}$$

since $\frac{\partial \xi}{\partial t}$ is $-V$ and $\frac{\partial \xi}{\partial x}$ is unity, this equation simplifies to:

$$\frac{\partial n_2}{\partial t} = k_f(\xi+Vt) - \left(k_f(\xi+Vt)+k_r(\xi+Vt)\right)n_2(\xi,t) \qquad \text{(Eq.6)}$$

To generate the force transients accompanying a stretch, we solved the integral:

$$P(t) = \frac{1}{b-a}\int_{a+Vt}^{b+Vt} K\left(n_2(x,t)x + n_1(x,t)(x-8)\right)\partial x \qquad \text{(Eq.7)}$$

to obtain total force at a series of time intervals, where a and b are the values of ξ between which cross-bridge formation is permitted. We took these as 4 and 12nm along the displacement axis of fig. 1s. At each time point, we computed the change in $n_2(x,t)$ by numerical integration over time of Eq. 6 for $x < l_r$, the rupture length (the x value at which rupture energy is reached for state 1 bridges) and derived $n_1(x,t)$ as $1-n_2(x,t)$. For $x \geq l_r$, state 1 bridges are assumed to detach very rapidly, so $n_1(x,t)$ becomes zero, and Eq. 6 reduces to:

$$\frac{\partial n_2}{\partial t} = -k_r(\xi+Vt)n_2(\xi,t) \qquad \text{(Eq.6a)}$$

We normalized tension to P_0 by dividing $P(t)$ by the integral evaluated at zero time. When a conditioning release was applied first, the release is assumed to occur as a step length change, and the $n(x,t)$ distributions during the recovery from the release were obtained as:

$$n_2(x,t) = \frac{k_f}{k_f+k_r}\left(1-\exp(-(k_f+k_r)t)\right)+n_2(x-\Delta x,0)\exp(-(k_f+k_r)t) \qquad \text{(Eq.7)}$$

where Δx is the displacement of the actin-bound S1 population by the release. The rate constant term in Eq. 6 and Eq. 6a must then be modified to k_r (ξ+ Δx +Vt), where t is measured from the onset of the stretch. The integrals were evaluated by a fifth order Runge-Kutta algorithm using adaptive step size control (4) written in Fortran 95, with an accuracy of 0.1%.

S.2 Acknowledgements.

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S.3 References.

1. Hill, T. L. 1974. Theoretical formalism for the sliding filament model of contraction of striated muscle. Part I. *Prog. Biophys. Mol. Biol.* 28:267-340.

2. Eisenberg, E., T. L. Hill, and Y. D. Chen. 1980. Cross-bridge model of muscle contraction. *Biophys. J.* 29:197-227.

3. Schoenberg, M. 1985. Equilibrium muscle cross-bridge behavior: theoretical considerations. *Biophys. J.* 48:467-475.

4. Press, W. H., B. P. Flannery, S. A. Teukolsky, and W. T. Vetterling. 1990. *Numerical Recipes: The Art of Scientific Computing*. Cambridge University Press, Cambridge, UK.