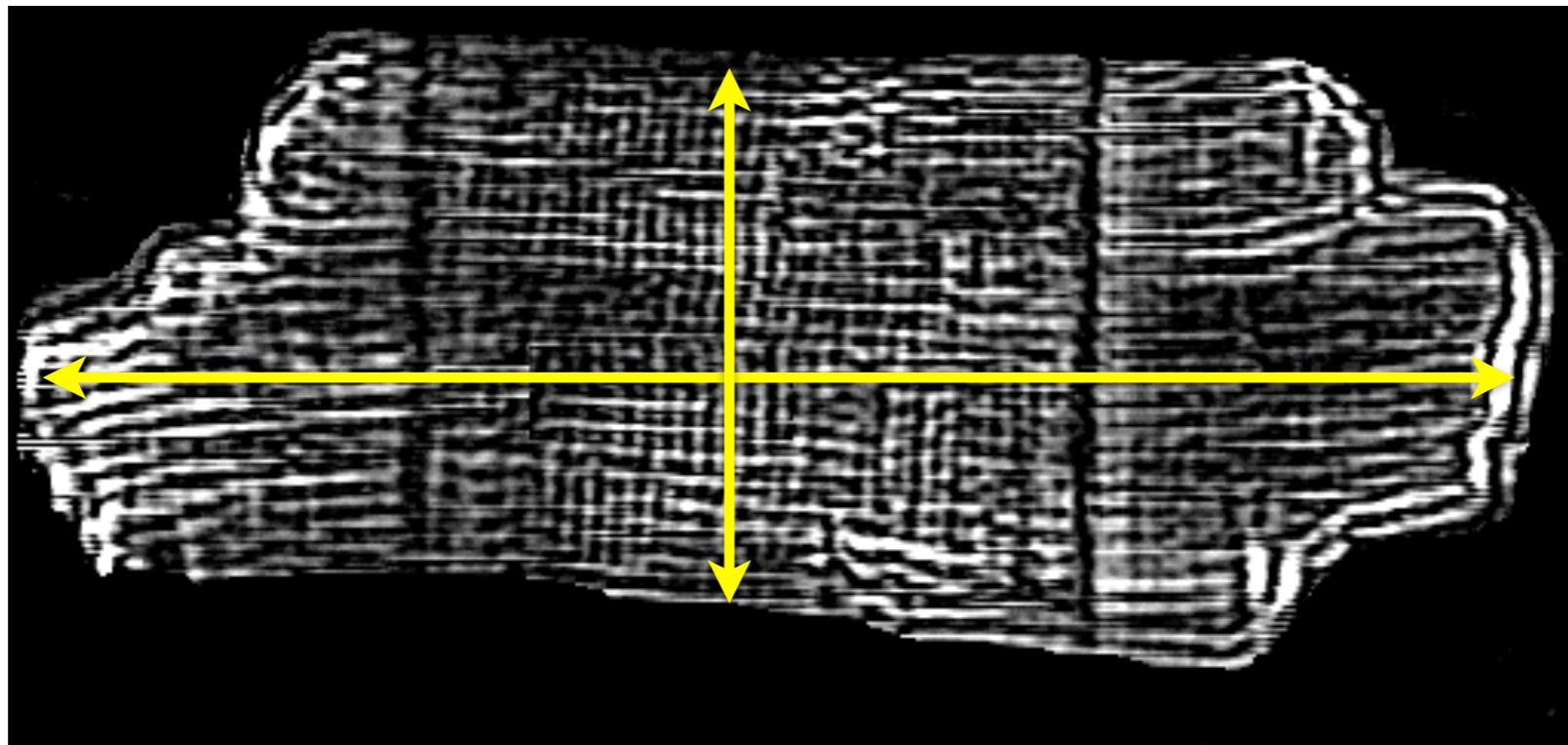


L11: Fundamental Cardiac Mechanics

K. McCabe

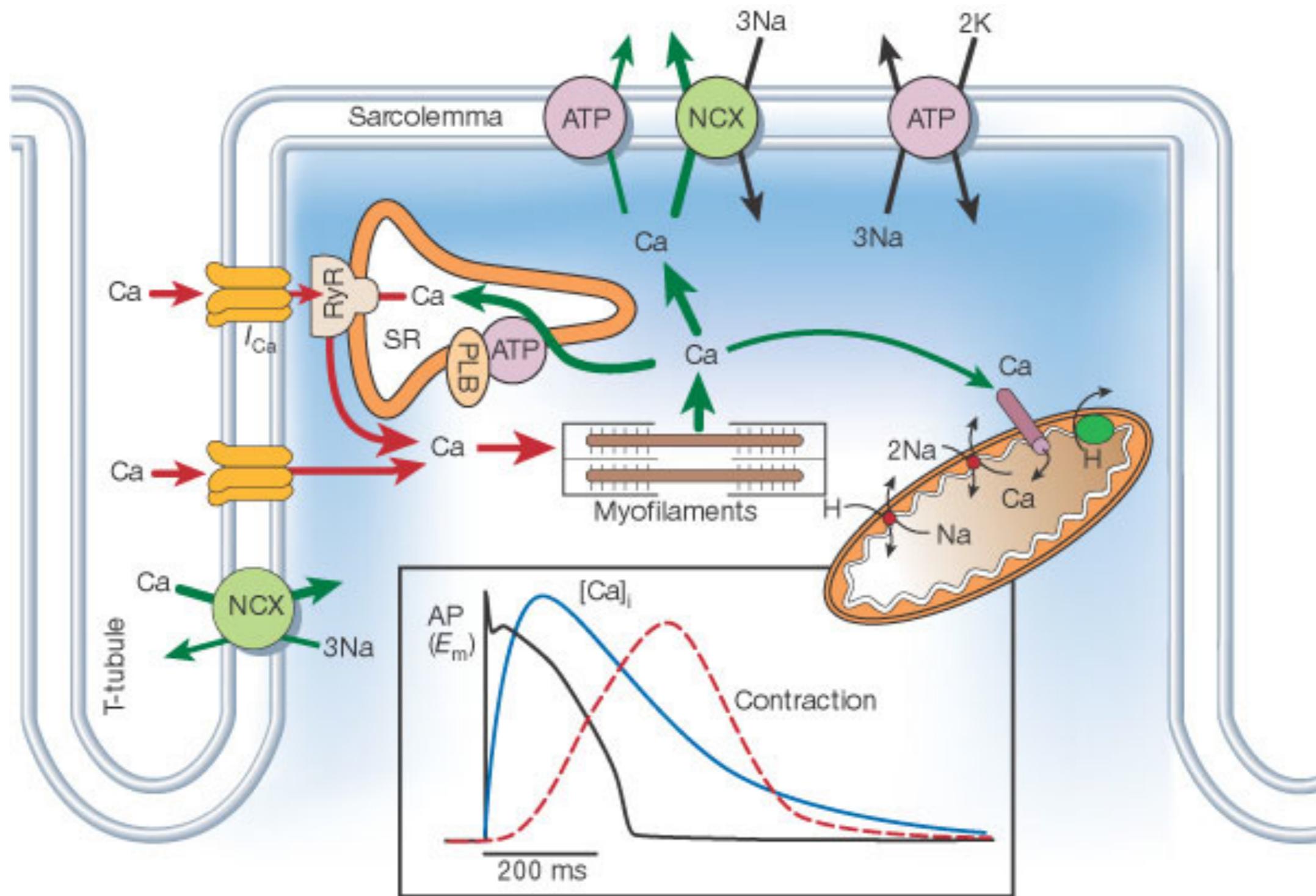
06/21/18

Cardiac Myocytes

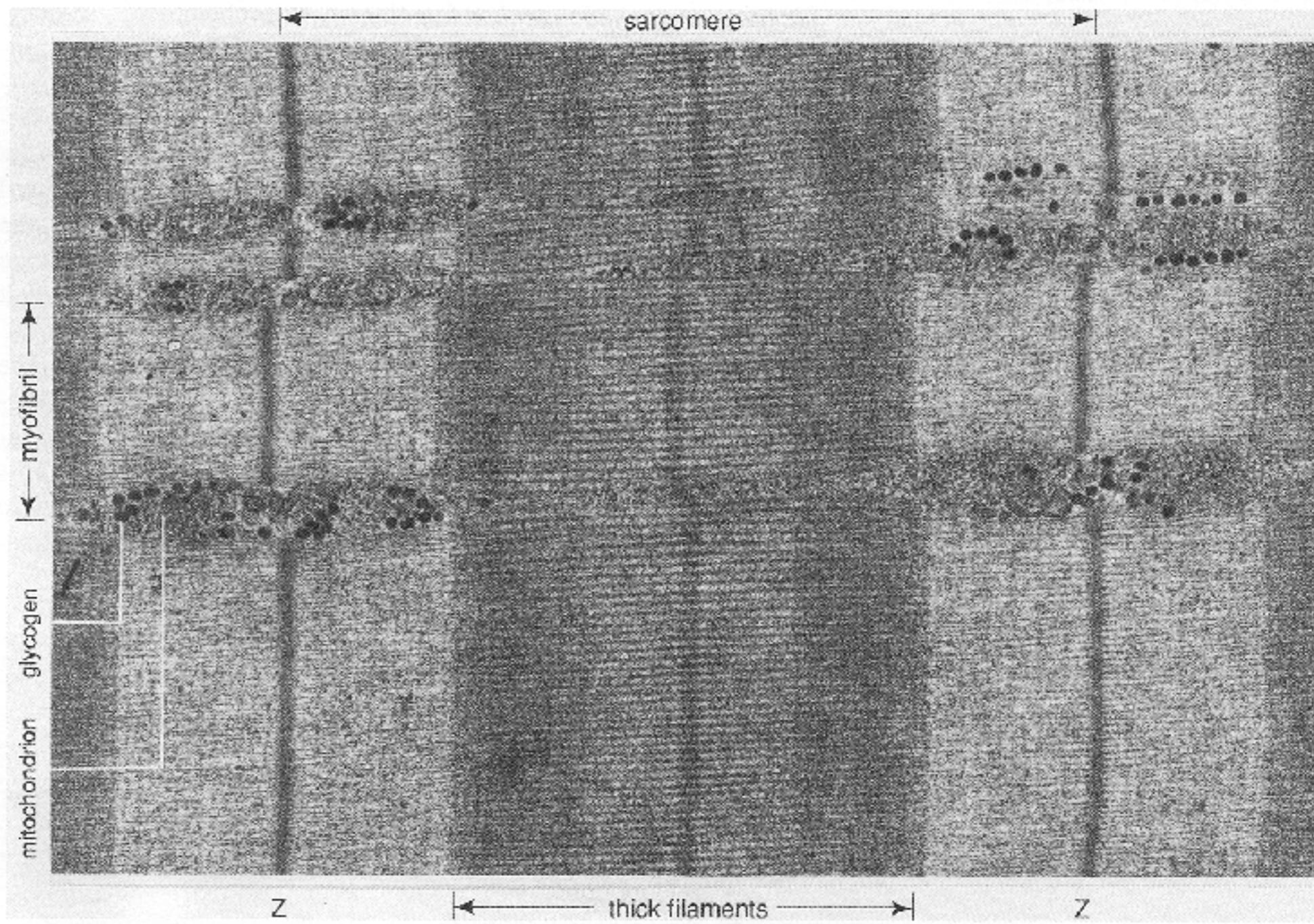


- Rod-shaped
- Striated
- 80-100 μm long
- 15-25 μm diameter

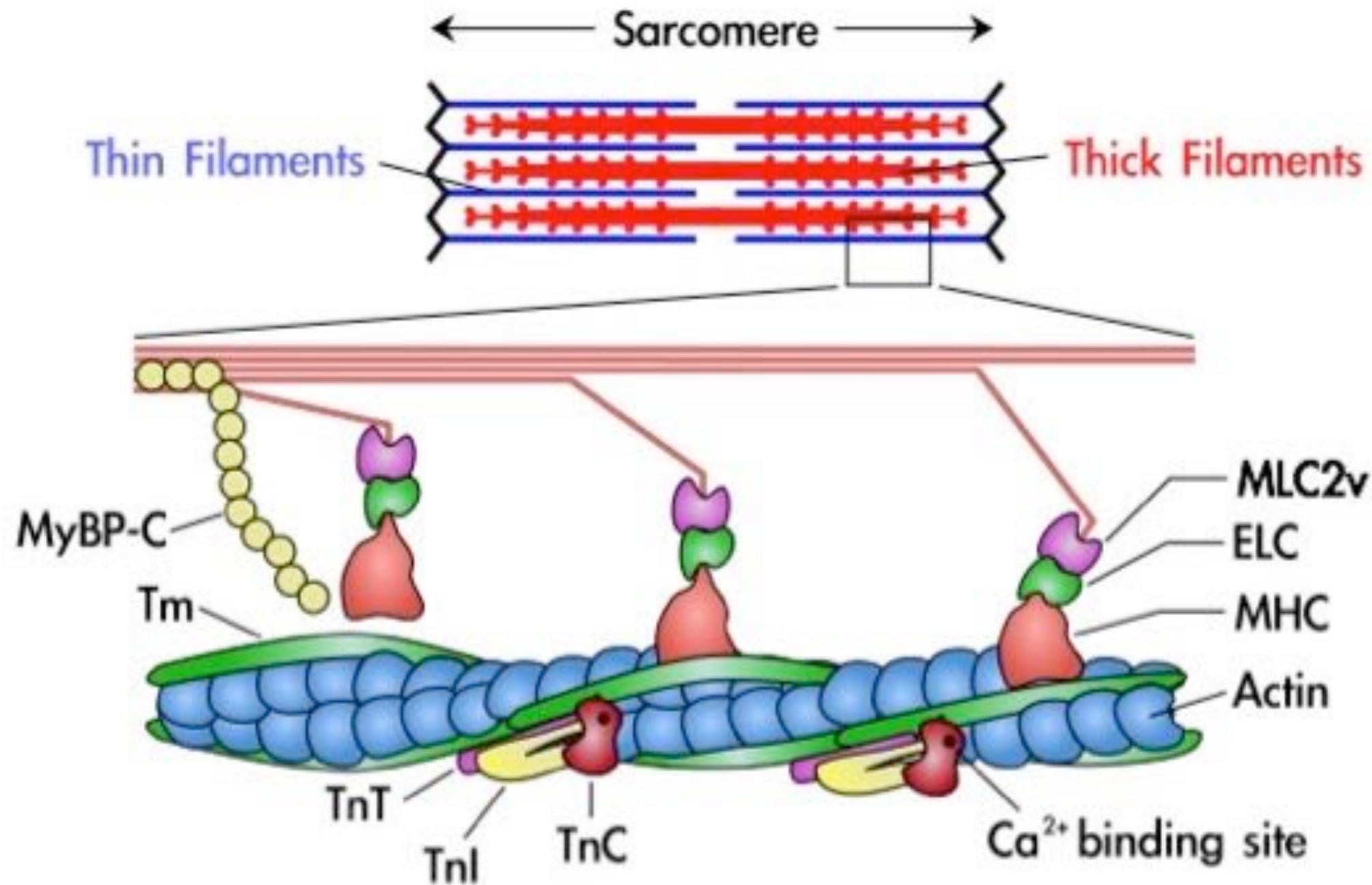
Excitation-Contraction Coupling



The Sarcomere

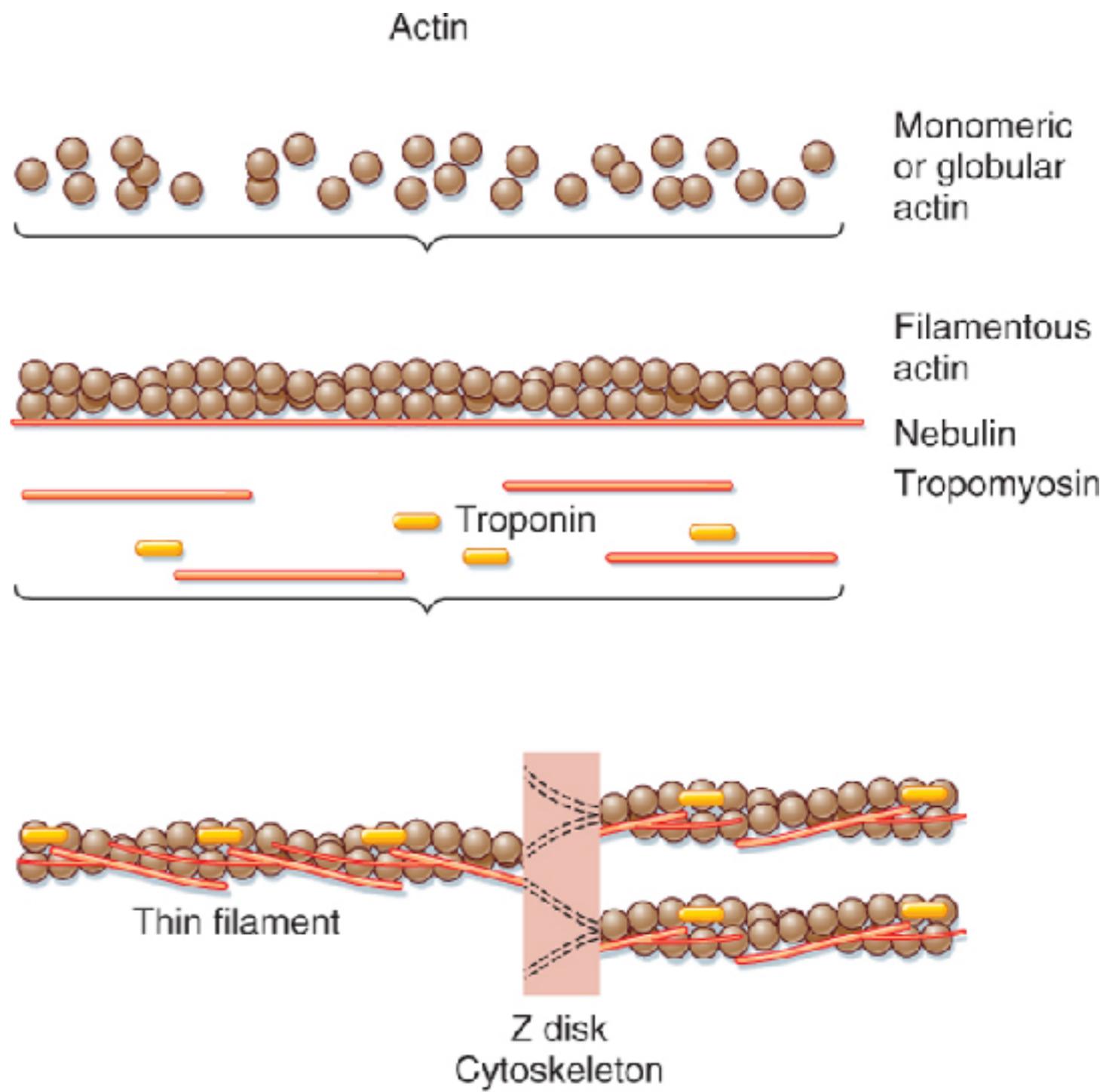


The Sarcomere



Actin

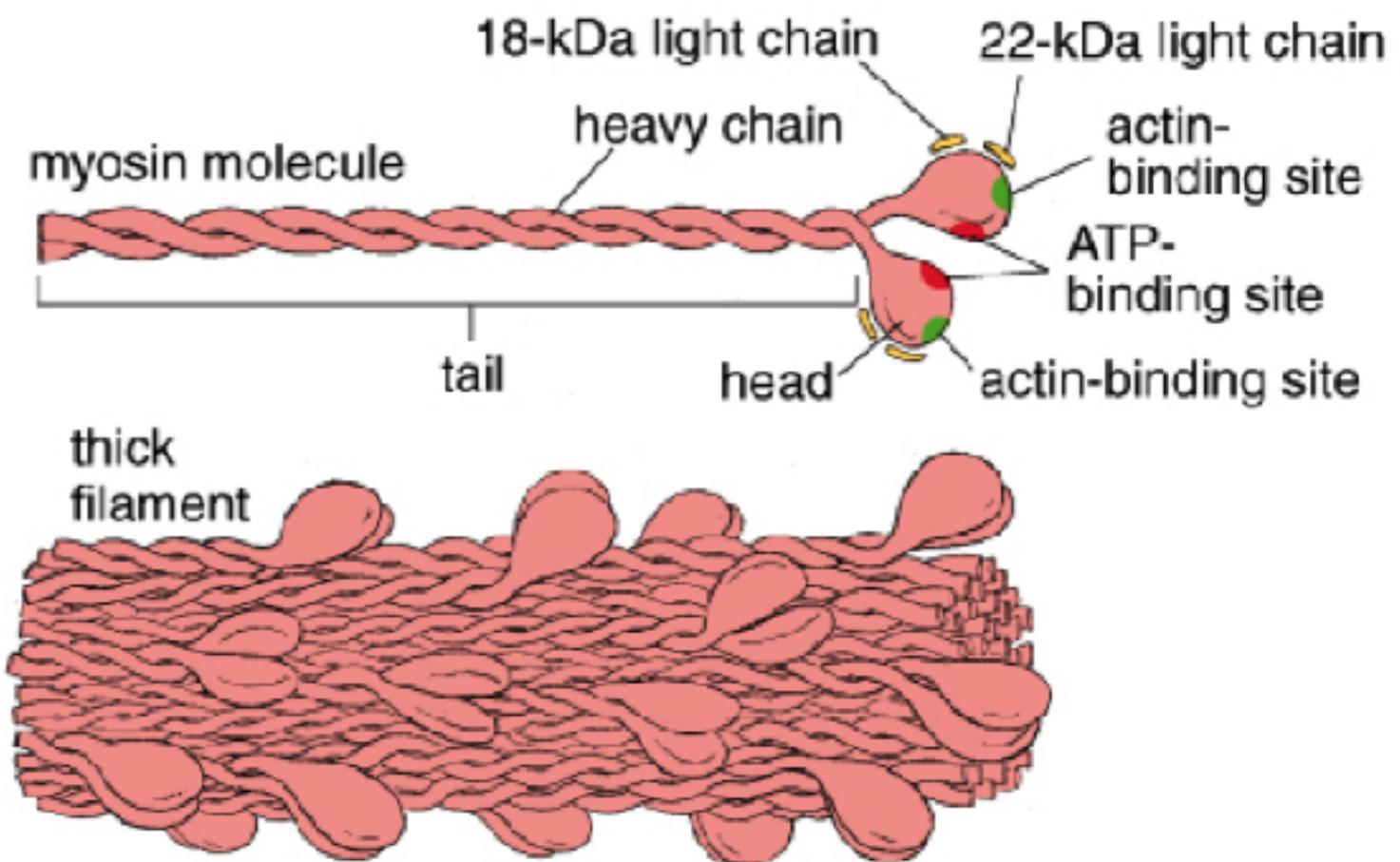
- F-actin molecule (7 nm diameter) formed from G-actin
- Twisted with a period ~37 nm into a double helix
- Nebulin is a large protein (600–900 kDa) that binds as many as 200 actin monomers and may control thin filament length



Koeppen & Stanton: Berne and Levy Physiology, 6th Edition.
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Myosin II

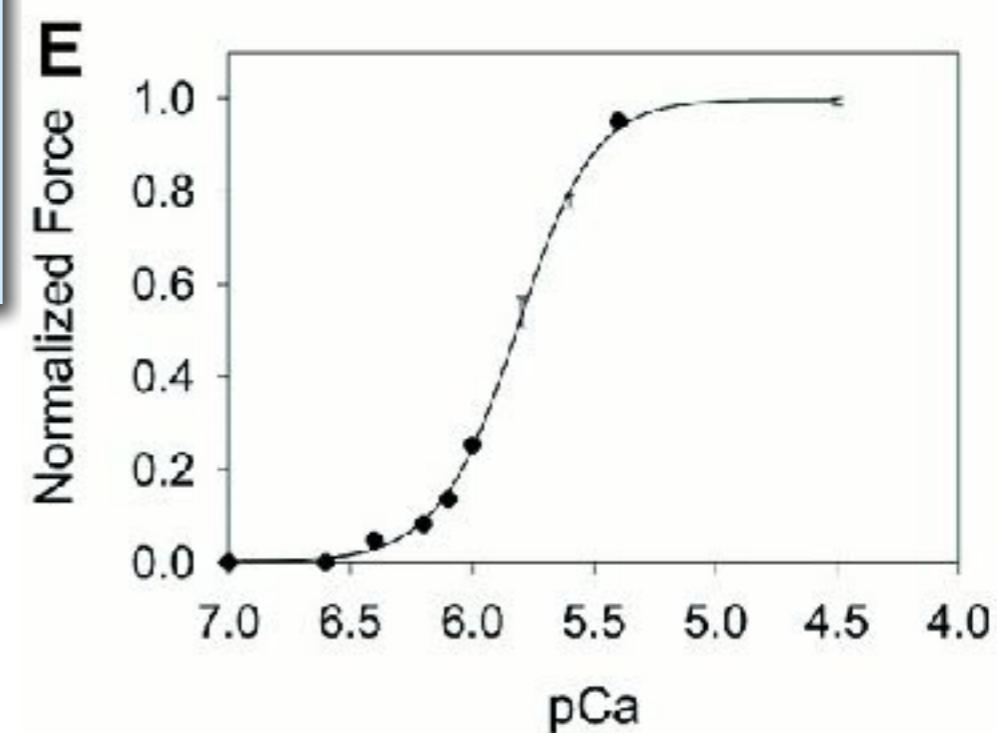
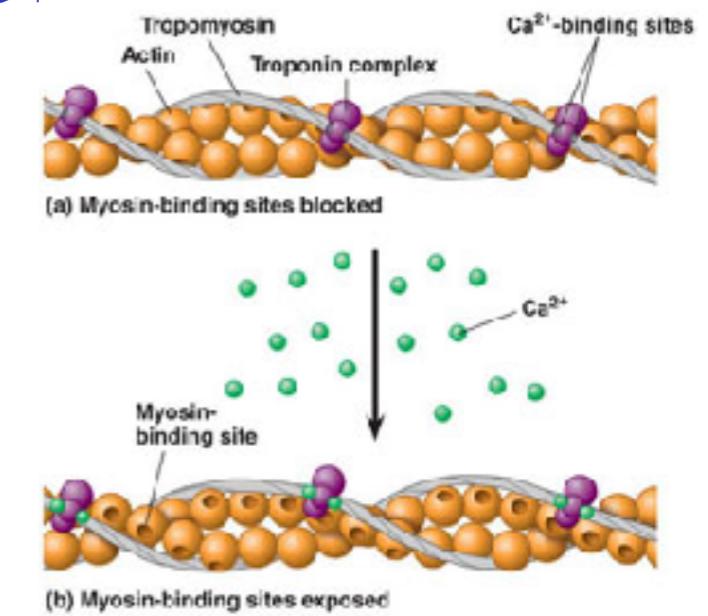
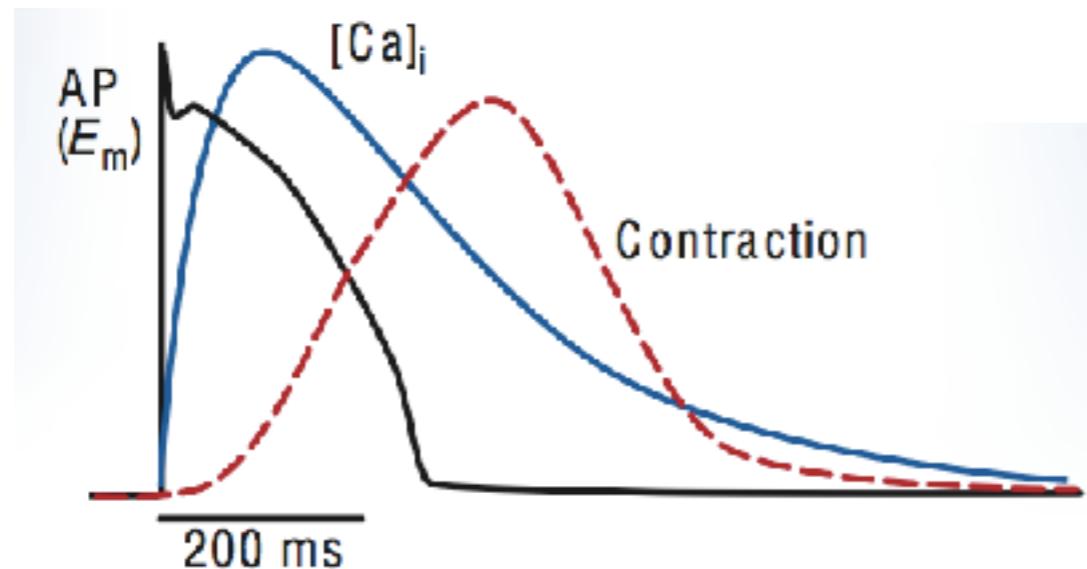
- Thick filament contains oligomerized myosin molecules
- Myosin subdomains:
 - Two myosin heavy chains
 - Two myosin light chains per heavy chain
 - One S1-head molecular motor domains per heavy chain
- Myosin heads protrude in pairs at 180°
- There are about 50 *pairs* of cross-bridges at each end of the thick filament
- Adjacent pairs along the thick filaments are rotated by 60 degrees
- 14.3 nm interval between pairs



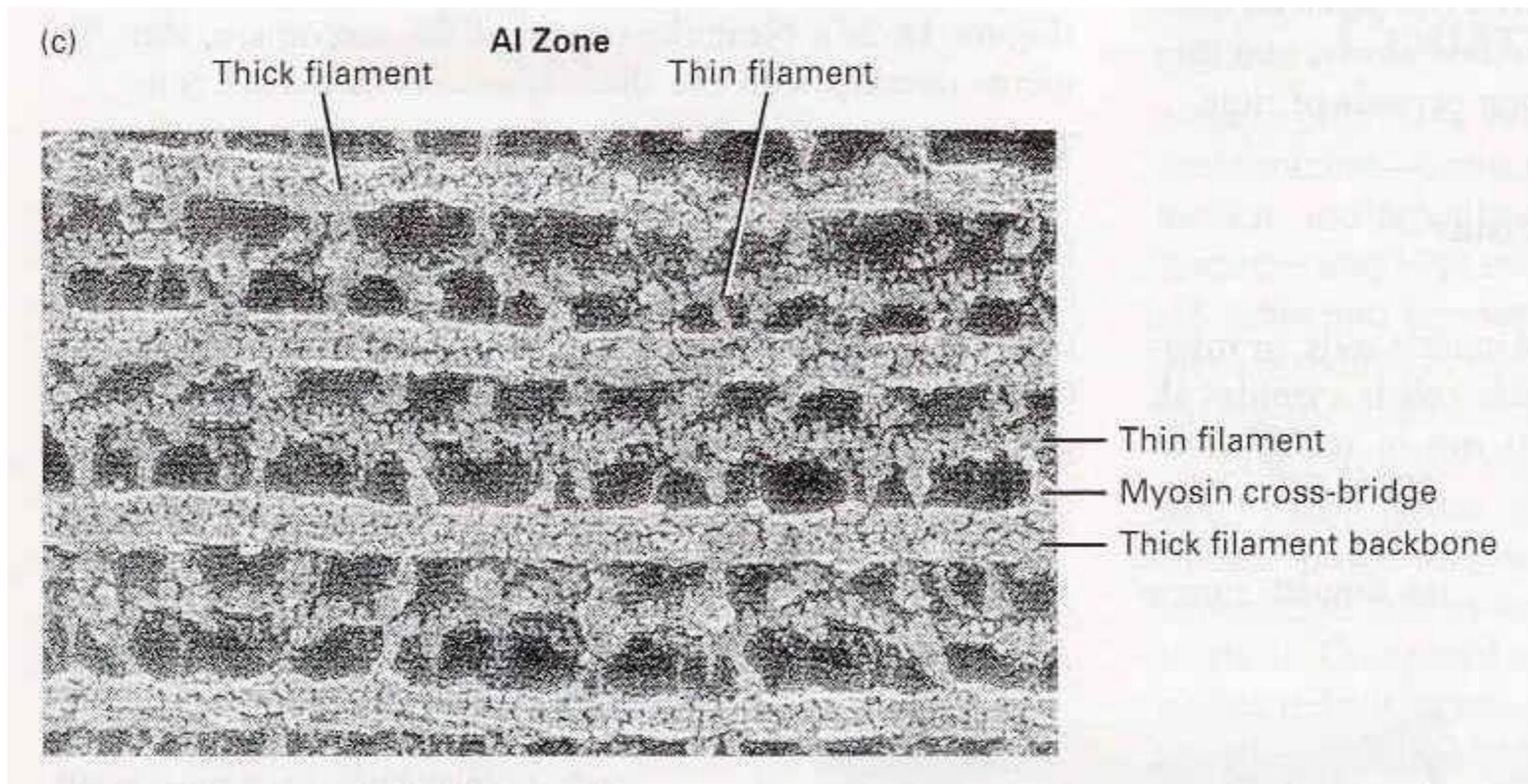
Unfig. 10.2. Thick filament.

Myofilament Activation

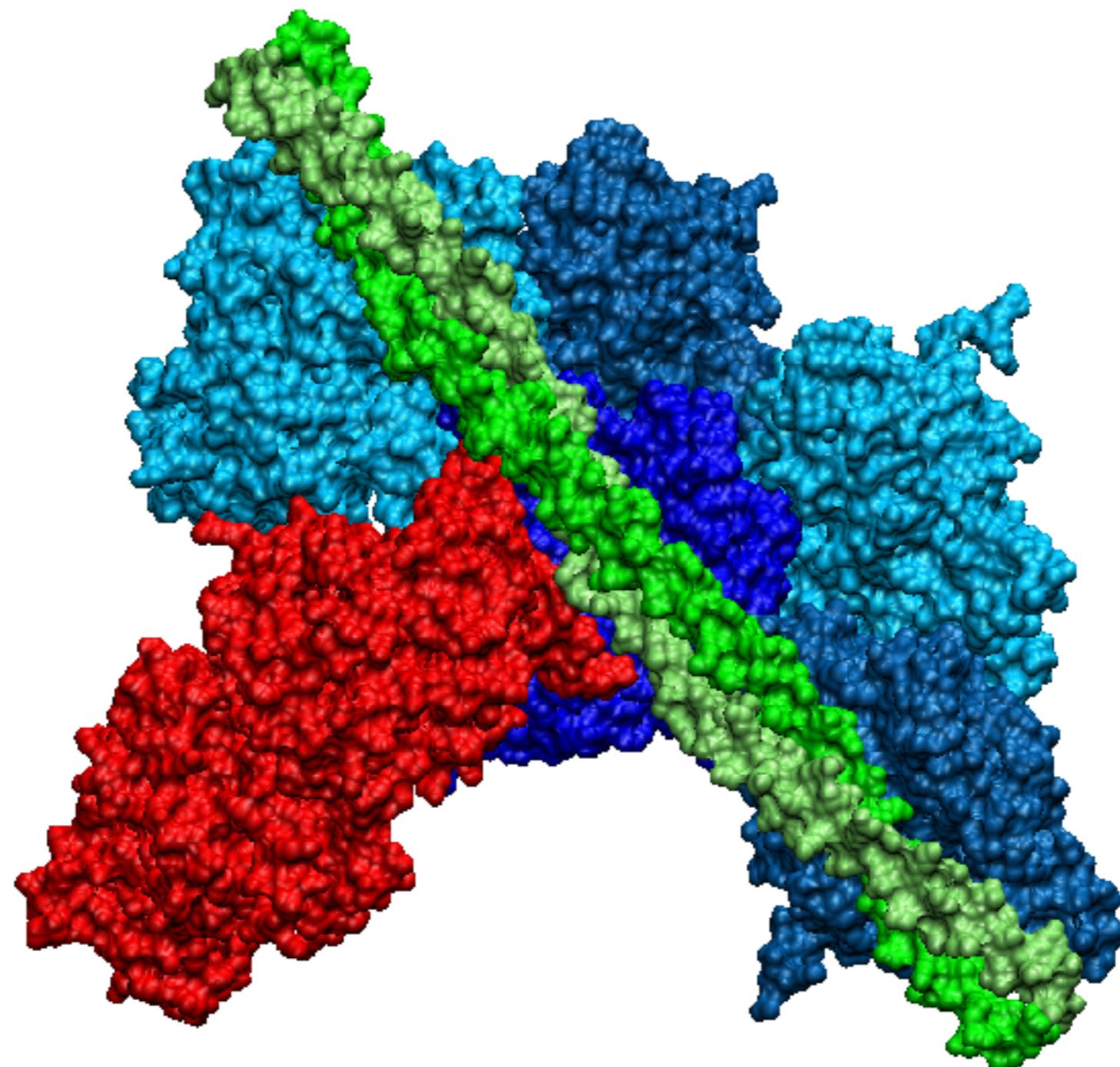
- Force-development is triggered by the intracellular $[Ca^{2+}]$ transient.
- Ca^{2+} binds to troponin-C sites, which are separated by neighboring troponin-C sites every 7 actin monomers
- Nearest neighbor cooperative activation



Crossbridge Formation

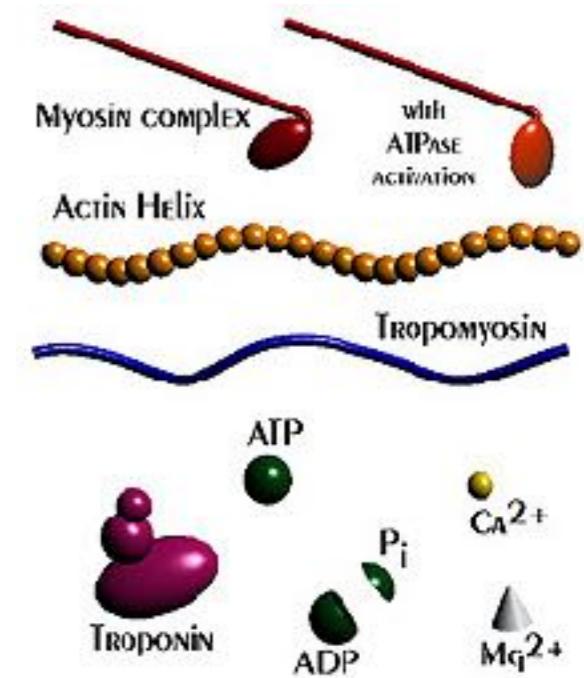
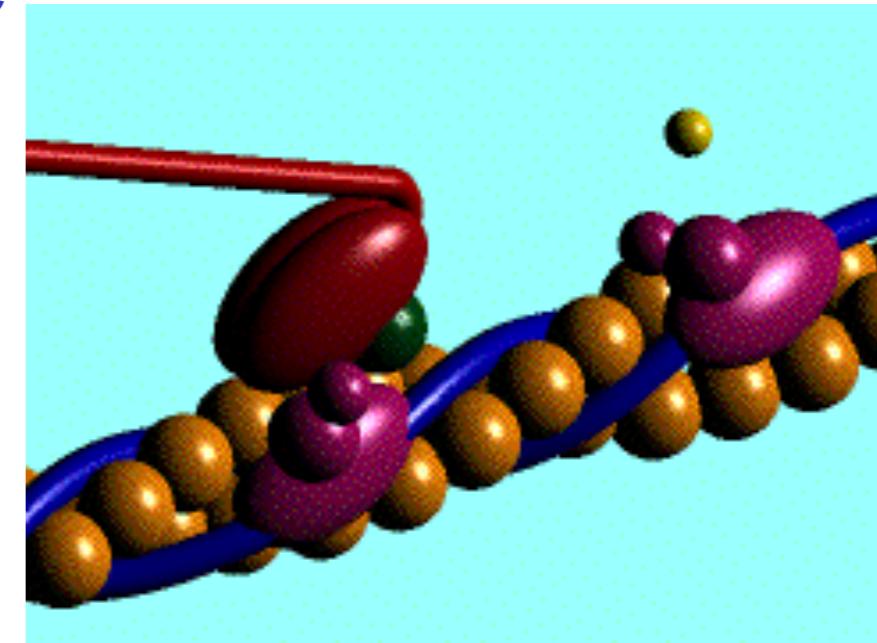
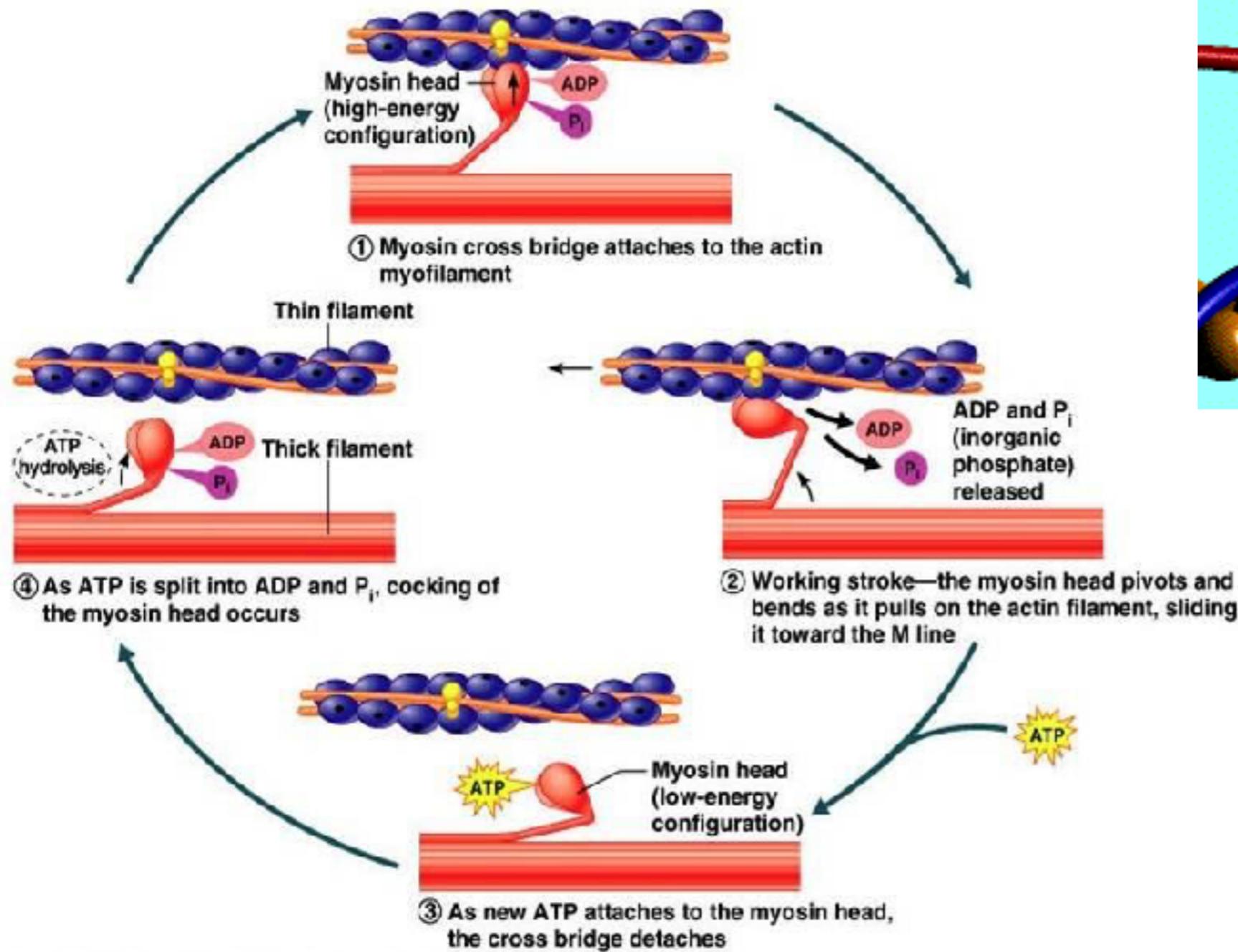


Myosin binding to actin



PDB: 4A7F (Behrmann 2012)

Crossbridge Cycle

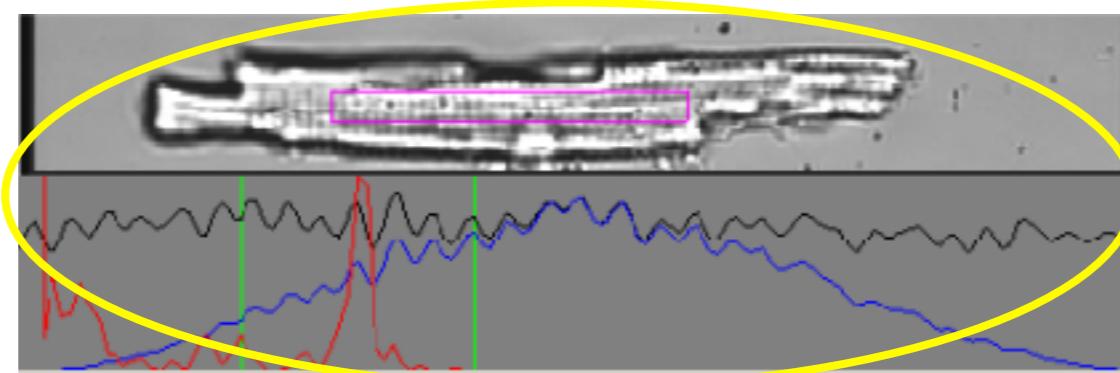
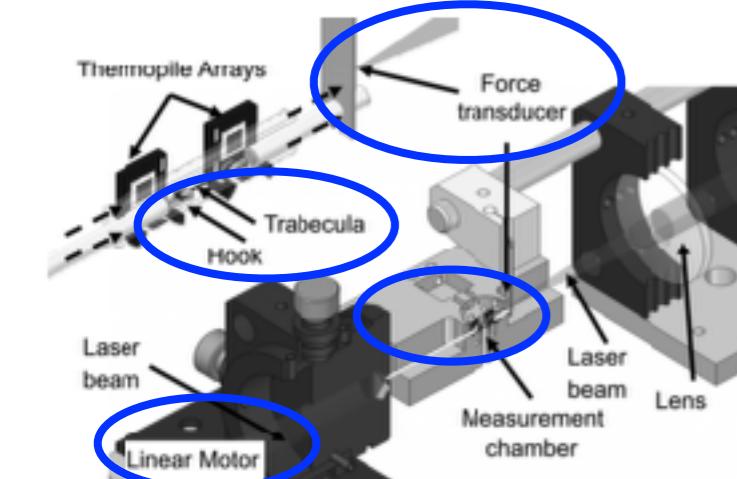
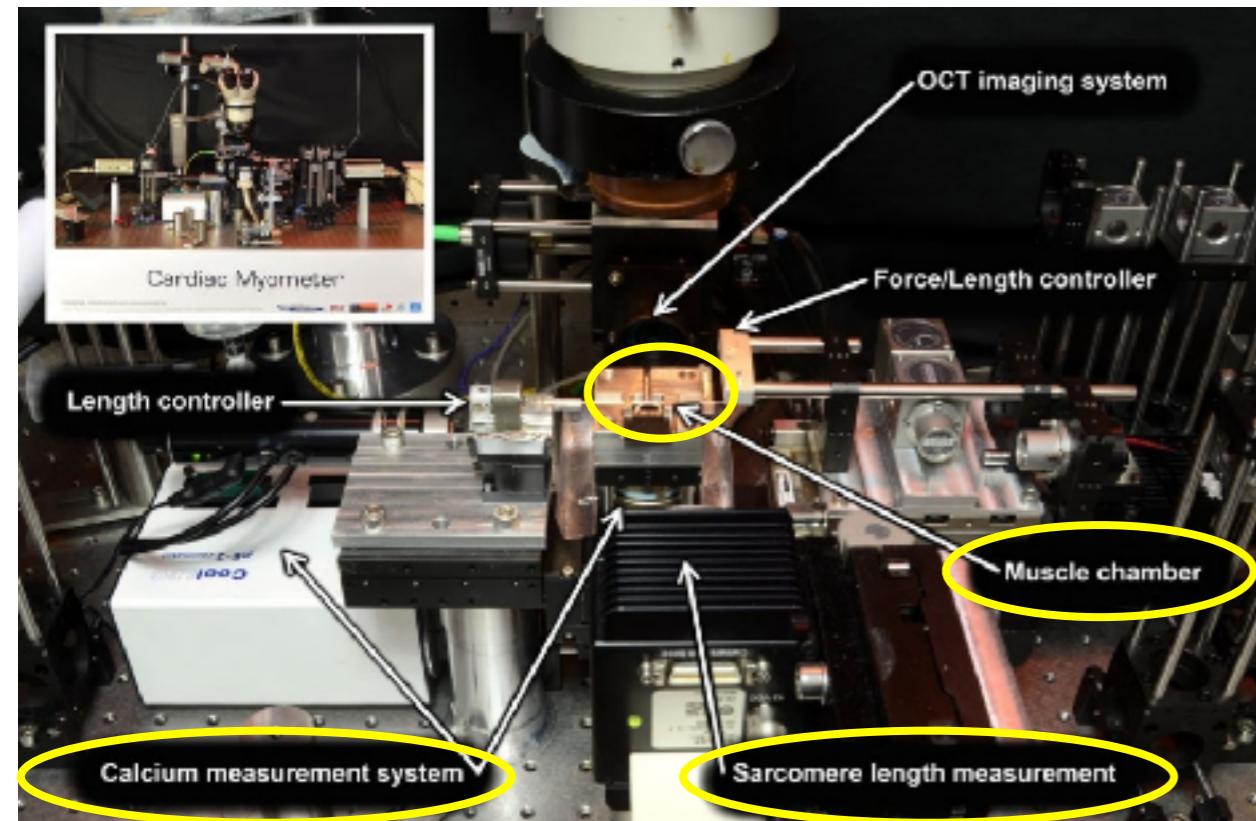


Primary Determinants of Force Production in Cardiac Muscle

- Intracellular calcium concentration
- Sarcomere length (SL)
- Rate of change in SL (velocity)



Cardiac Muscle Testing



Tissue chamber and preparation

- isolated right ventricular trabeculae
- $4000 \times 200 \times 90 \mu\text{m}$

Force transducers

- cantilever - laser interferometry
- piezoresistive 1 V/mN , capacitive 0.1 V/mN

Motor

- linear servomotor

Sarcomere length

- laser diffraction or Fourier imaging

Calcium

- ratiometric fluorescence imaging

Cardiac Muscle Testing

Cardiac muscle is much more difficult to test than skeletal muscle:

- tissue structure is complex and 3-D
- long uniform preparations with tendons attached are not available
- the best preparations are isolated *papillary muscles* (which hold atrioventricular valves closed during systole) and isolated *trabeculae*, which are more uniform but very small
- cardiac muscle branching scatters light making laser diffraction more difficult

Isometric testing

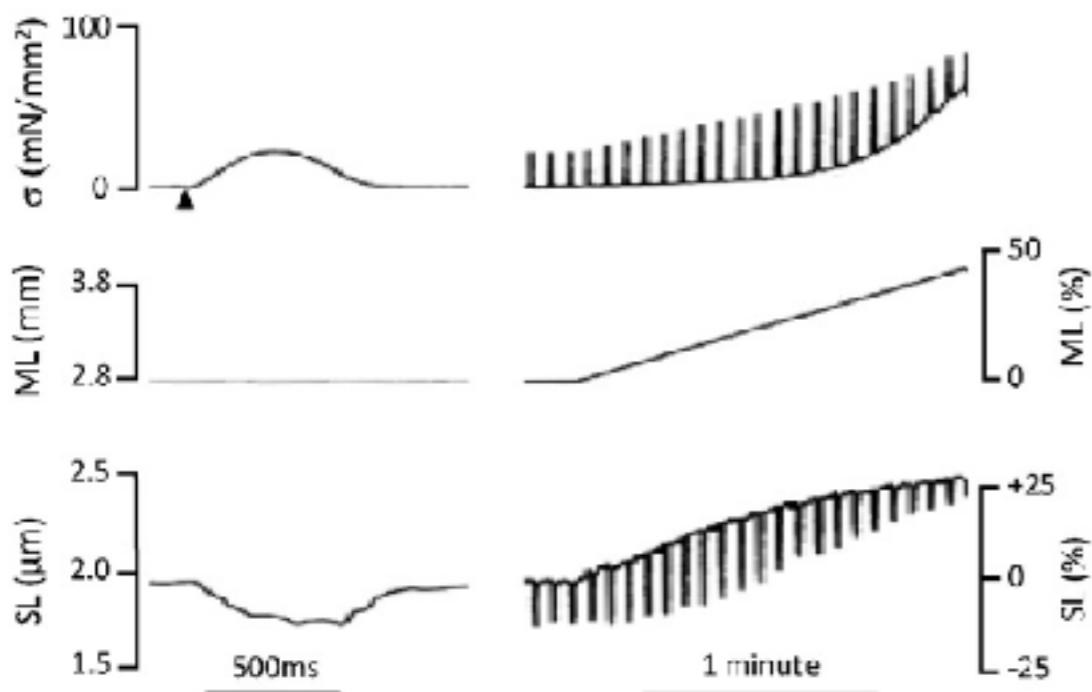


Fig. 1. Contractile response to increase in length. Stress (σ), force corrected for cross sectional area, and real-time laser diffraction derived sarcomere length (SL) was recorded from an isolated cat cardiac trabecula that was electrically stimulated at 0.2 Hz (arrow head); the middle panel shows muscle length (ML). The left panel shows a single twitch at an expanded time-scale at slack length. The right panel shows the contractile response to a slow ML ramp stretch to ~45%. The left scales depict absolute calibrations, while the right scales depict relative calibrations in percent normalized to slack length (ML% and SL%). Modified from [11].

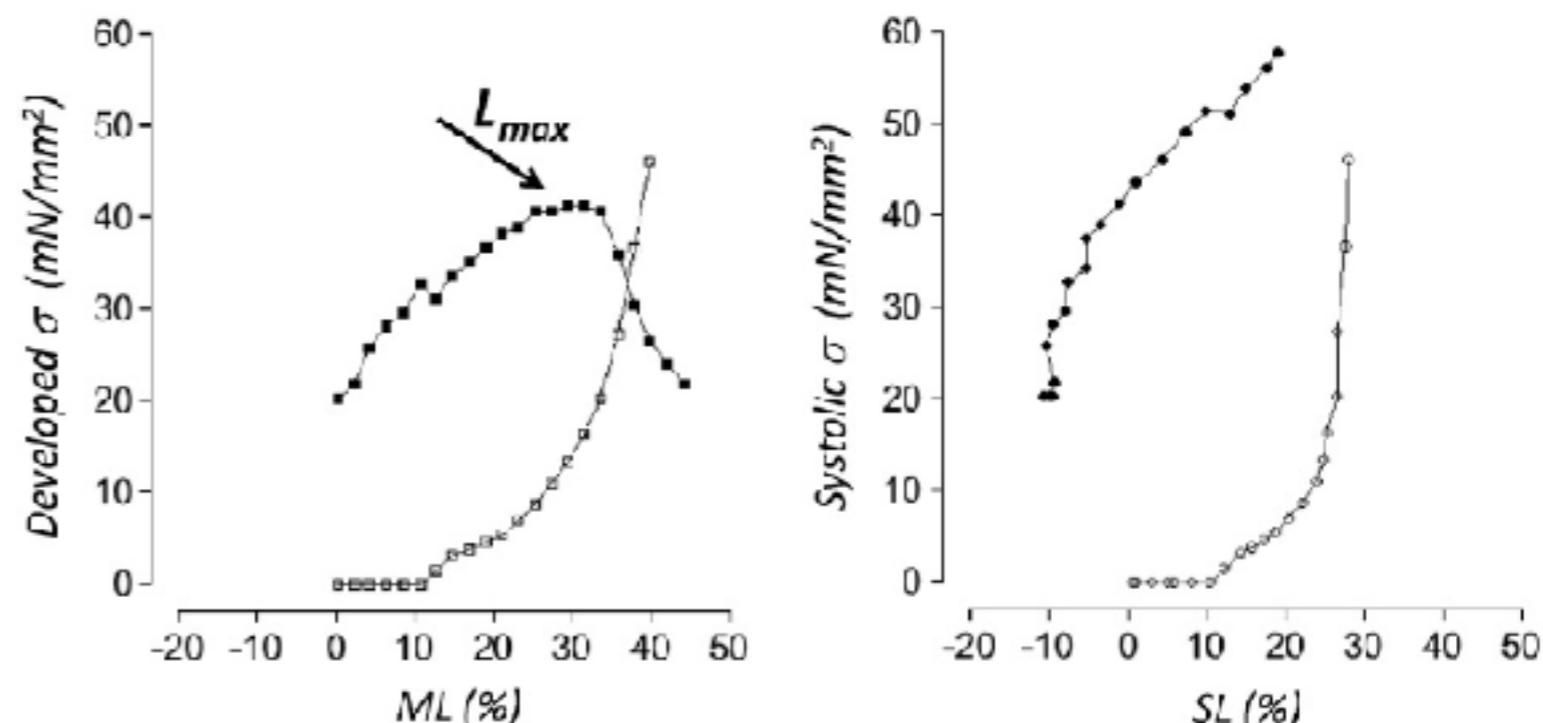
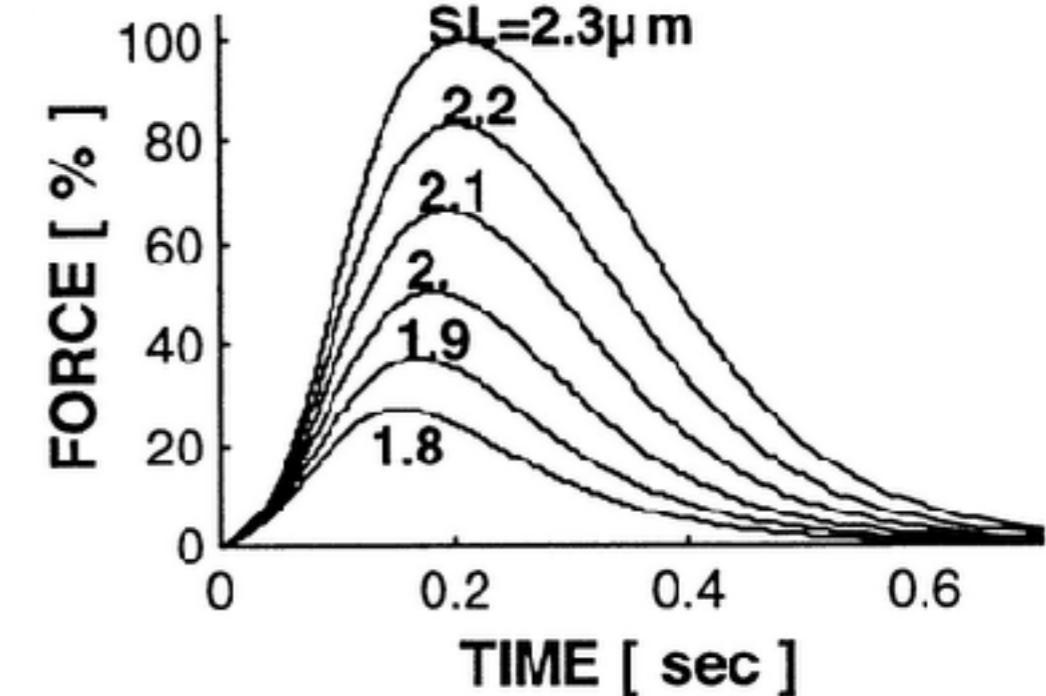
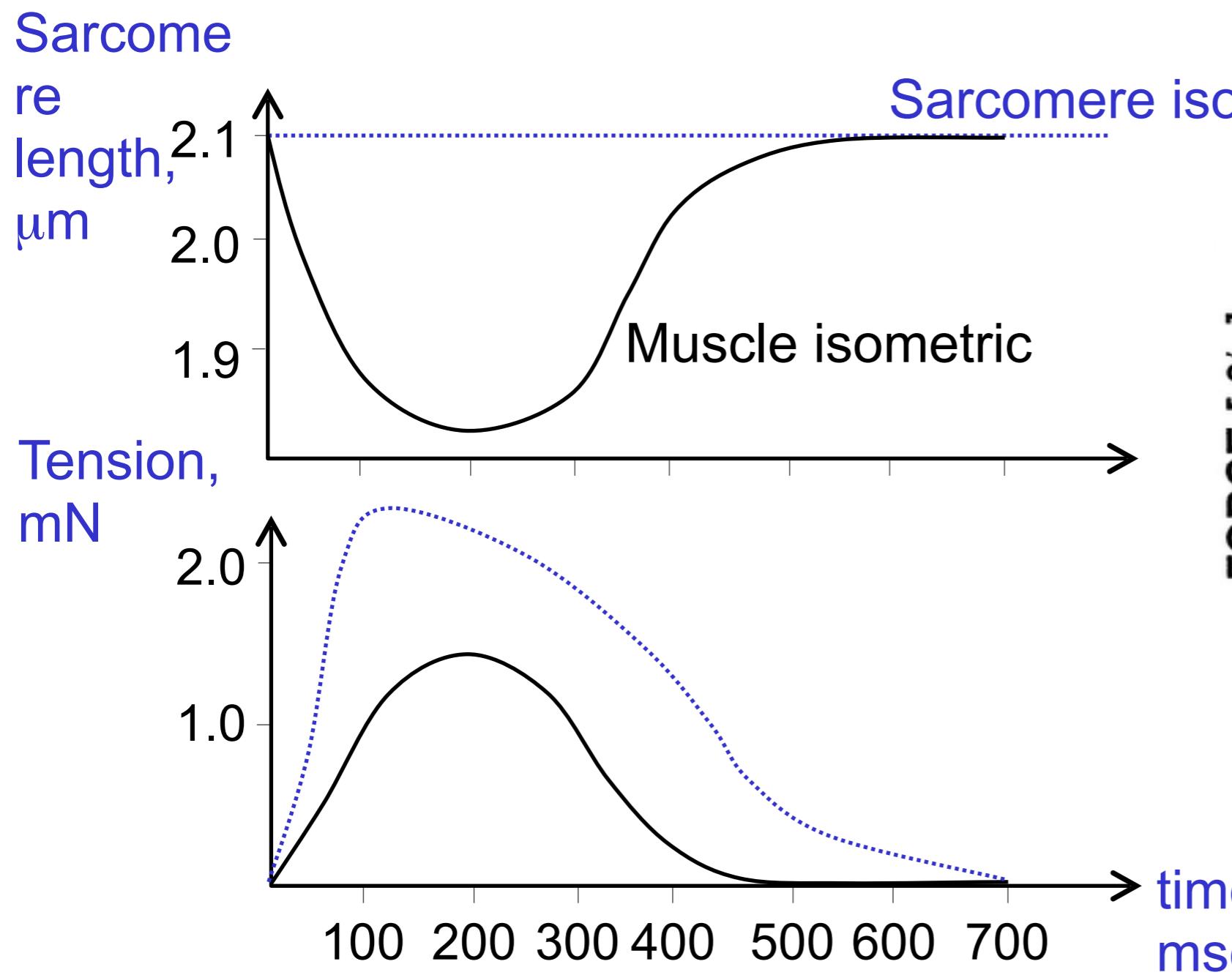


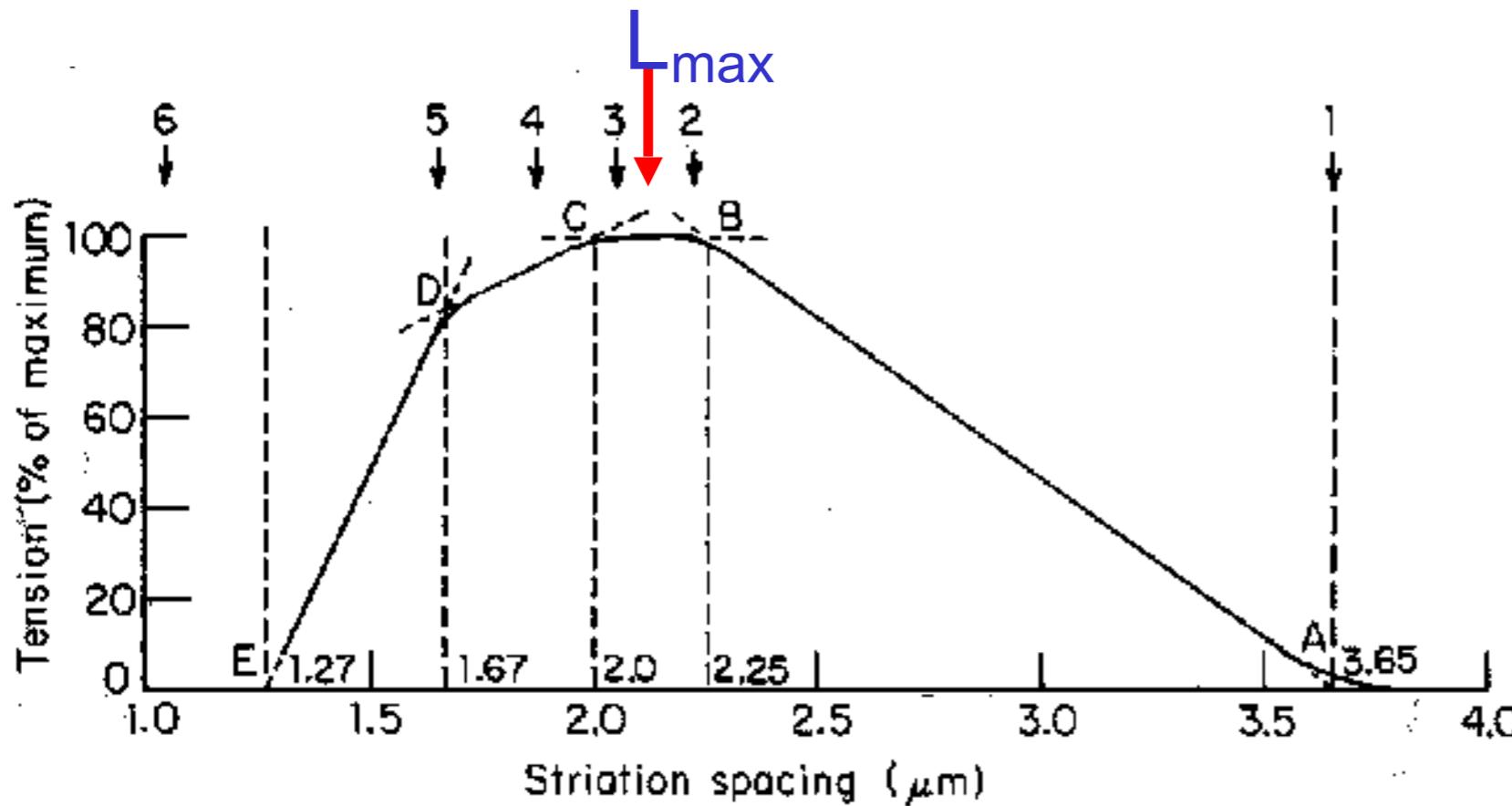
Fig. 2. Stress Sarcomere Length versus Stress Muscle length relationships. Analysis of the data shown in Fig. 1. The left panel shows the "traditional" ML based relationship between developed stress (peak twitch stress minus passive stress; closed squares) and passive stress (open squares), as function of normalized ML; maximum developed stress occurs at the optimal ML, L_{max} (arrow). The right panel shows SL based approach, that is, the relationship between systolic stress (peak twitch stress minus the passive stress that is recorded at the systolic SL; active (closed circles) and passive stress (open circles), as function of normalized SL. Unambiguous analysis of cardiac muscle mechanics requires measurement of real time sarcomere length.

At constant muscle length, muscle preparation shortens in the middle at the expense of lengthening at the damaged ends. de Tombe and ter Keurs (2016) *Journal of Molecular and Cellular Cardiology* 91: 148–150

Isometric Twitch Testing

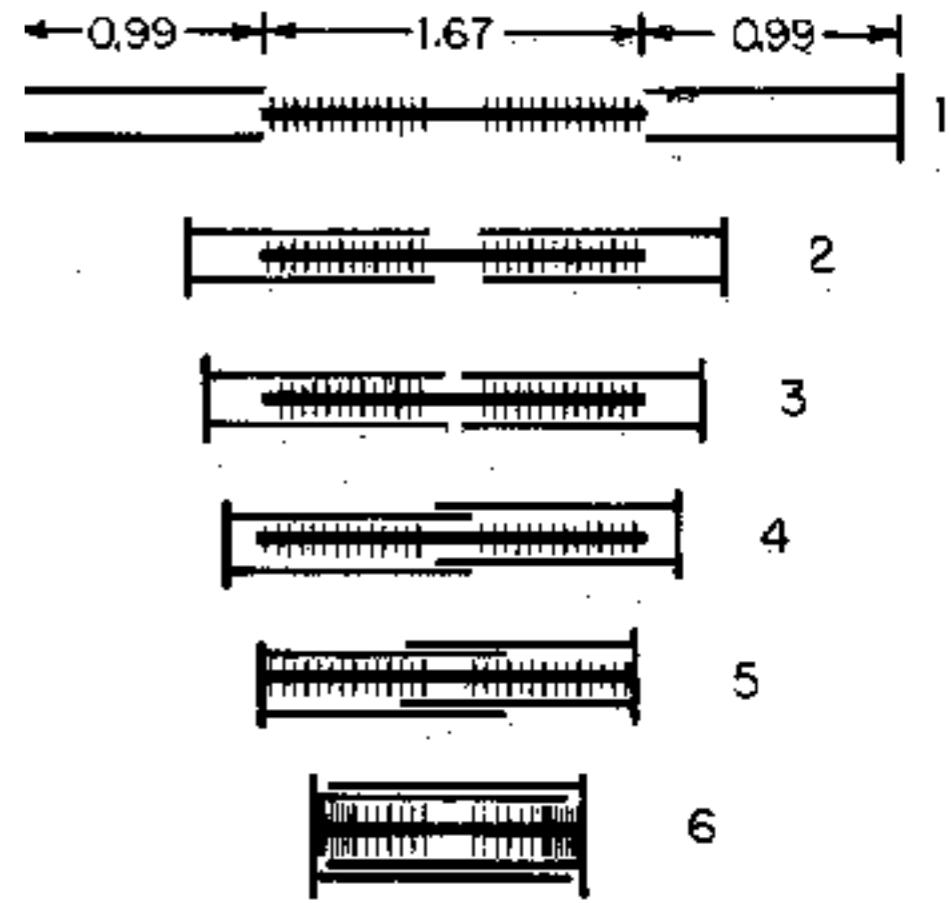


Isometric Tension: Sliding Filament Theory

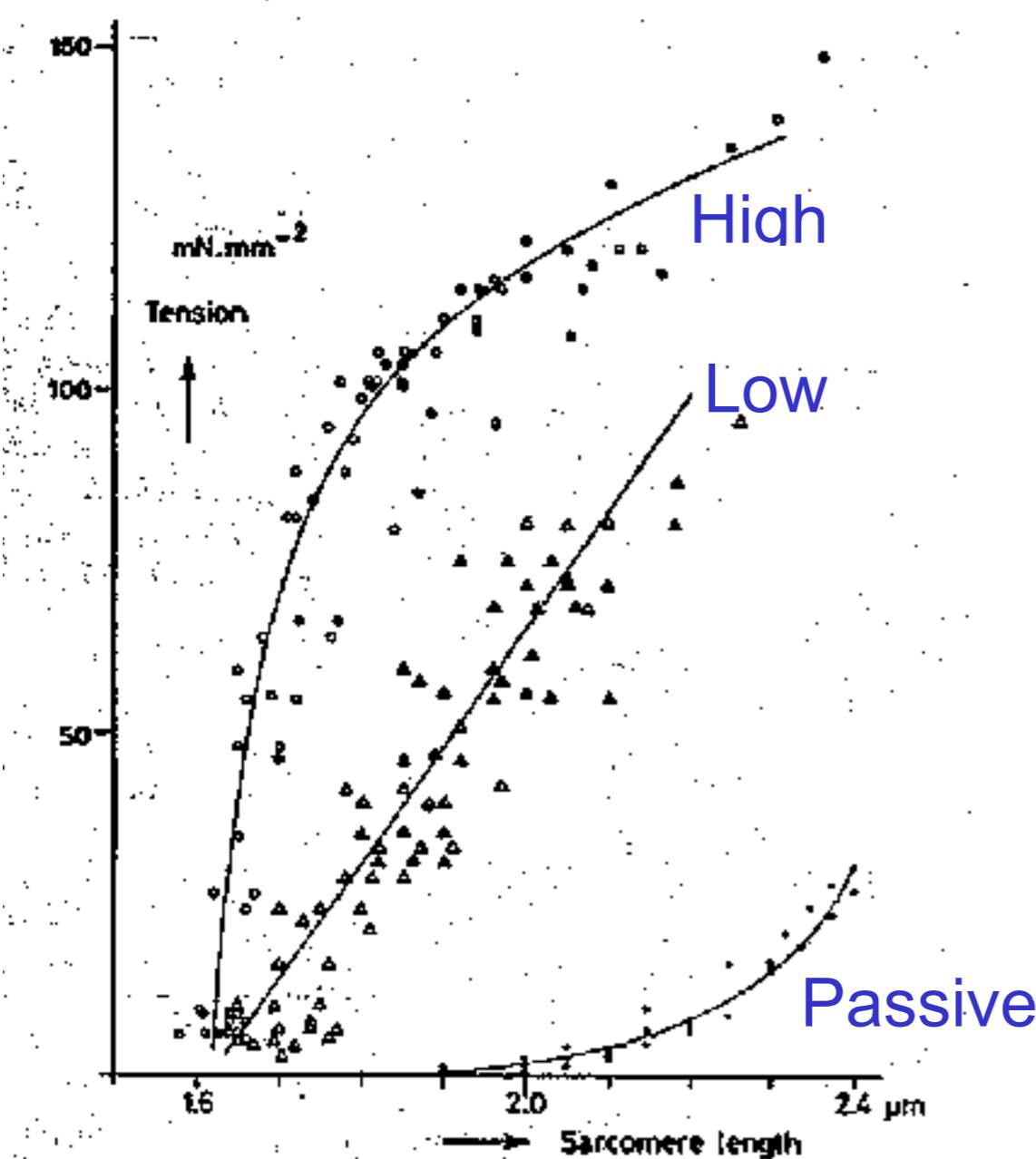


Developed tension versus length
for a single isometric fiber of frog
semitendinosus muscle

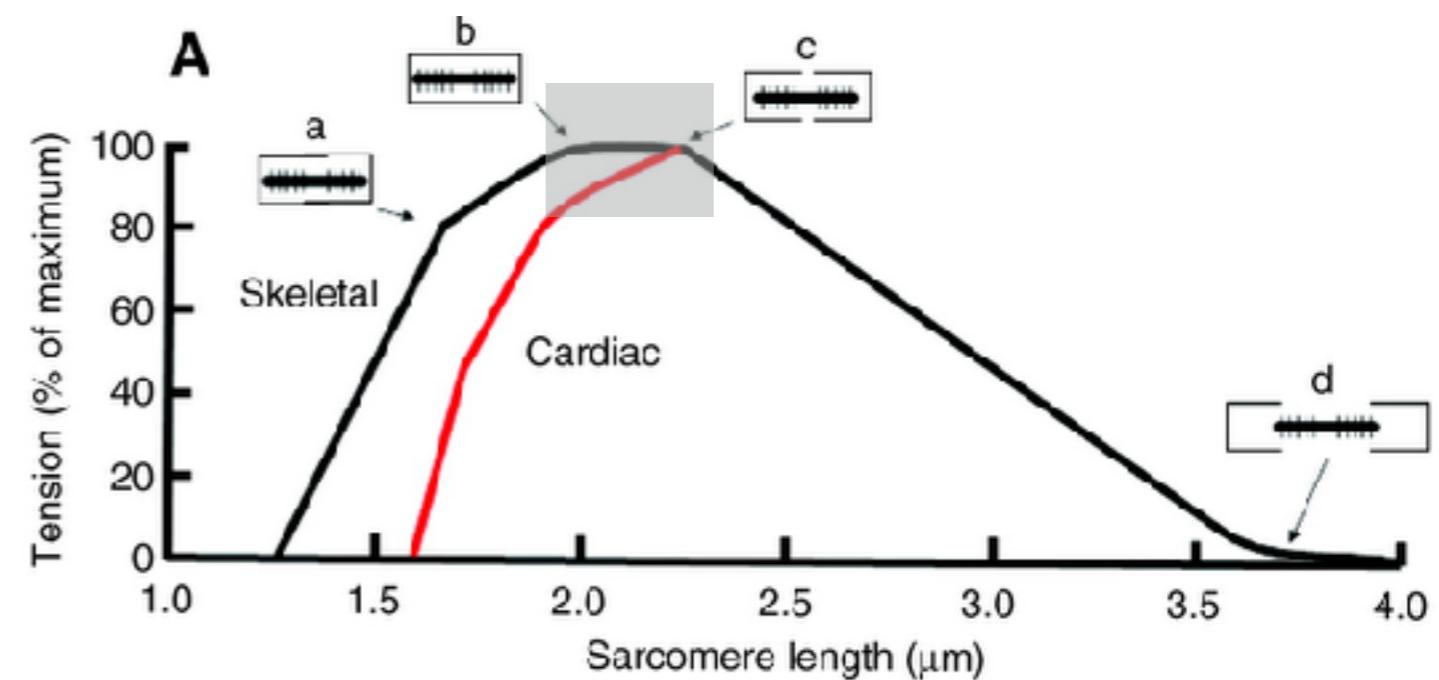
Sliding filament theory



Isometric Length-Peak Tension Curve

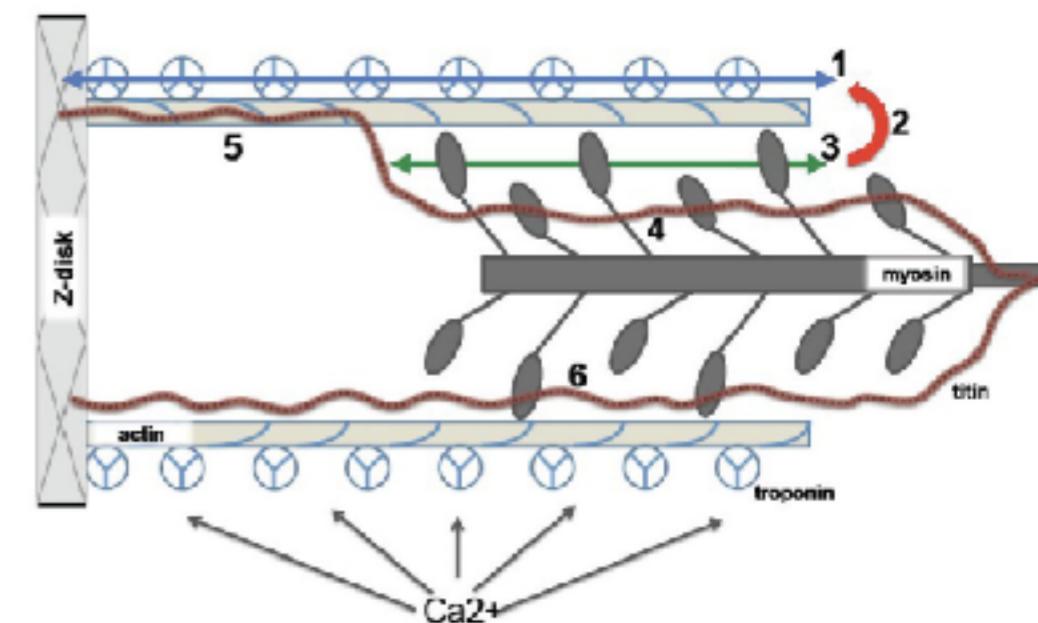
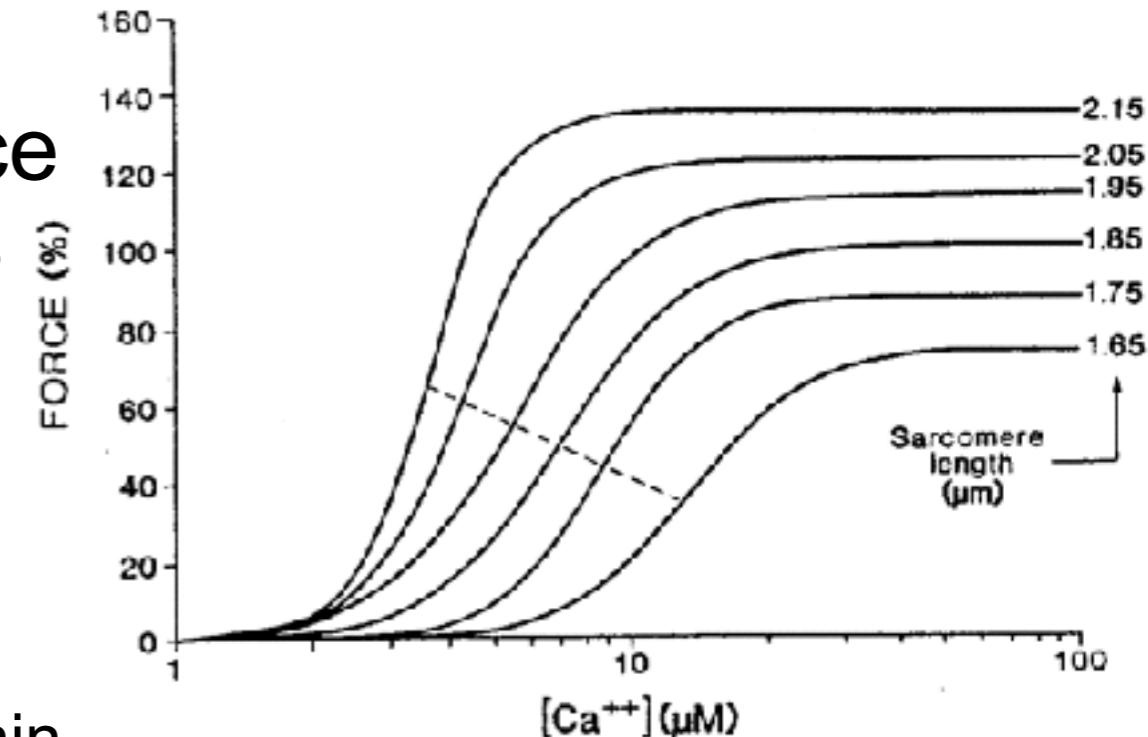


Peak developed isometric twitch tension (total-passive)



Length-Dependent Activation

- Intracellular calcium concentration required to achieve half maximal force decreases with increased sarcomere length
- The molecular mechanism is unknown but hypotheses include:
 - modulation of thin filament activation via troponin I due to troponin-troponin interactions (1)
 - modulation of thin filament activation via troponin I due to or actin-titin interactions (5)
 - modulation of myosin mediated cooperativity due to more cross bridges attached at higher SL (2, 3)
 - titin interaction with myosin (4,6)
 - Titin strain-mediated thick and thin filament rearrangement (Ait-Mou Y, et al, PNAS 2016)

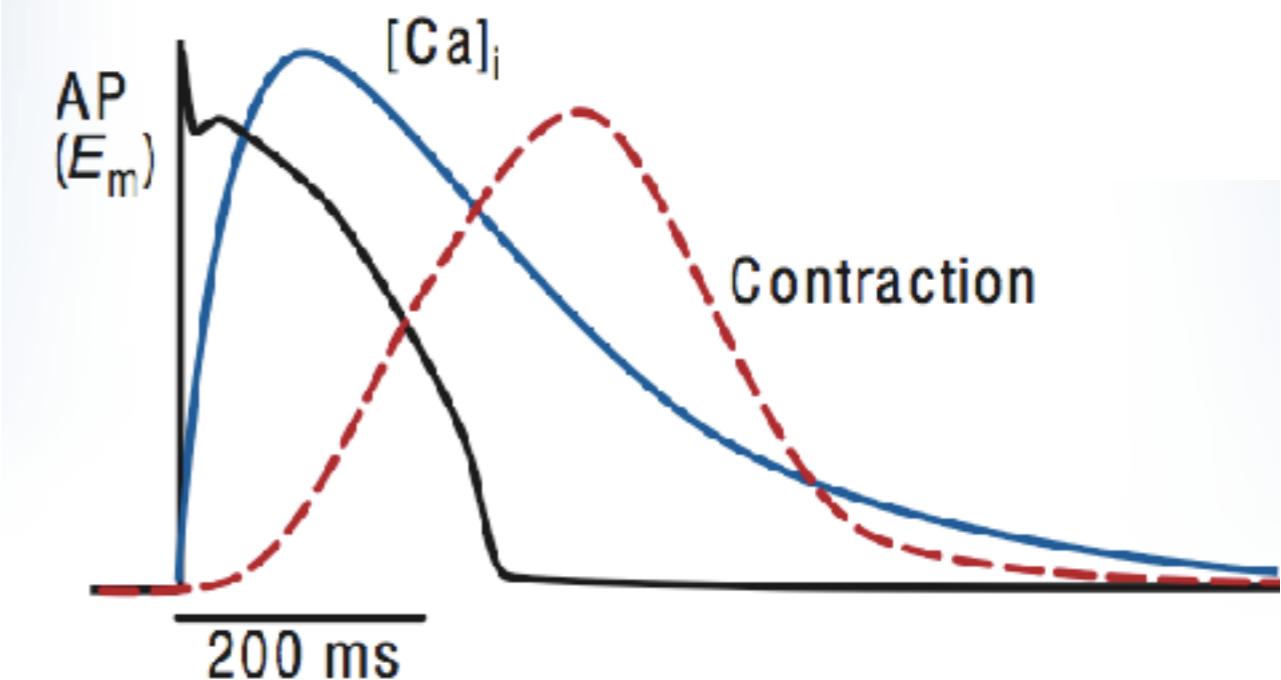
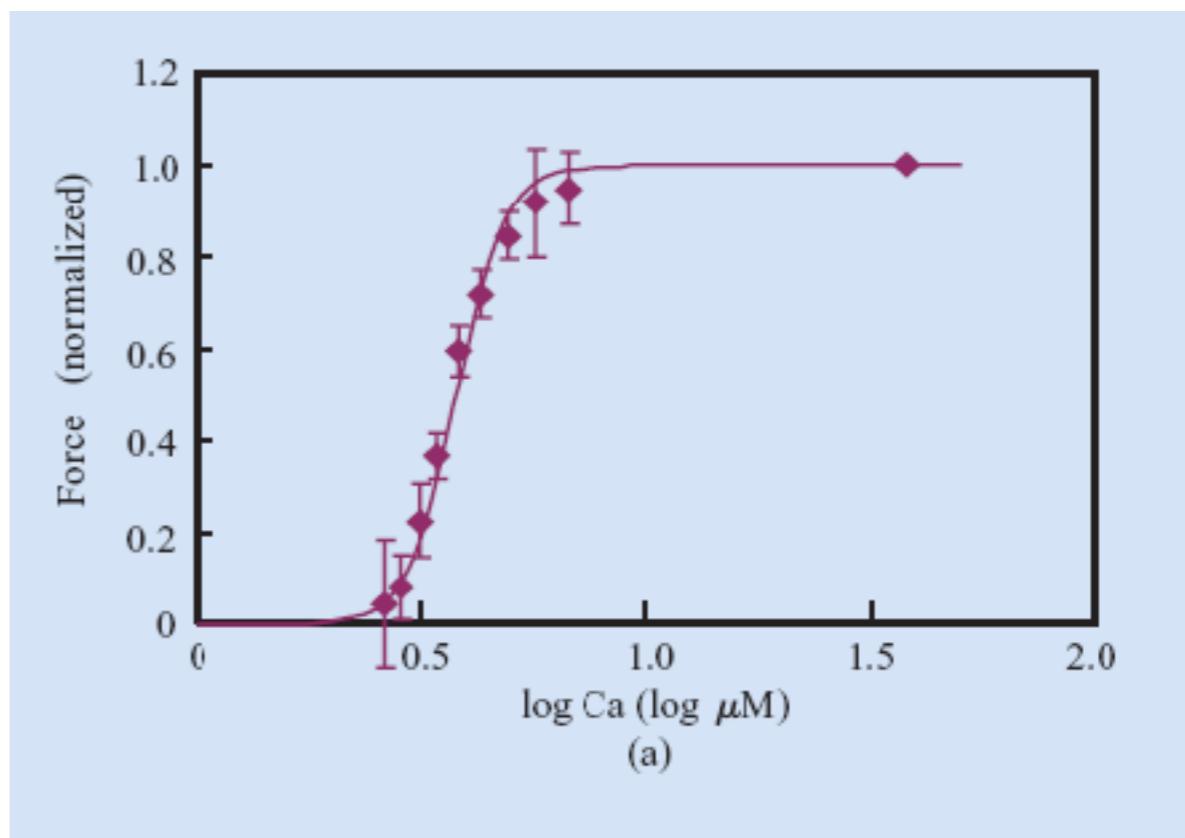


Cooperative Myofilament Activation

- Developed force is a steep nonlinear function of activator calcium (Ca) concentration.

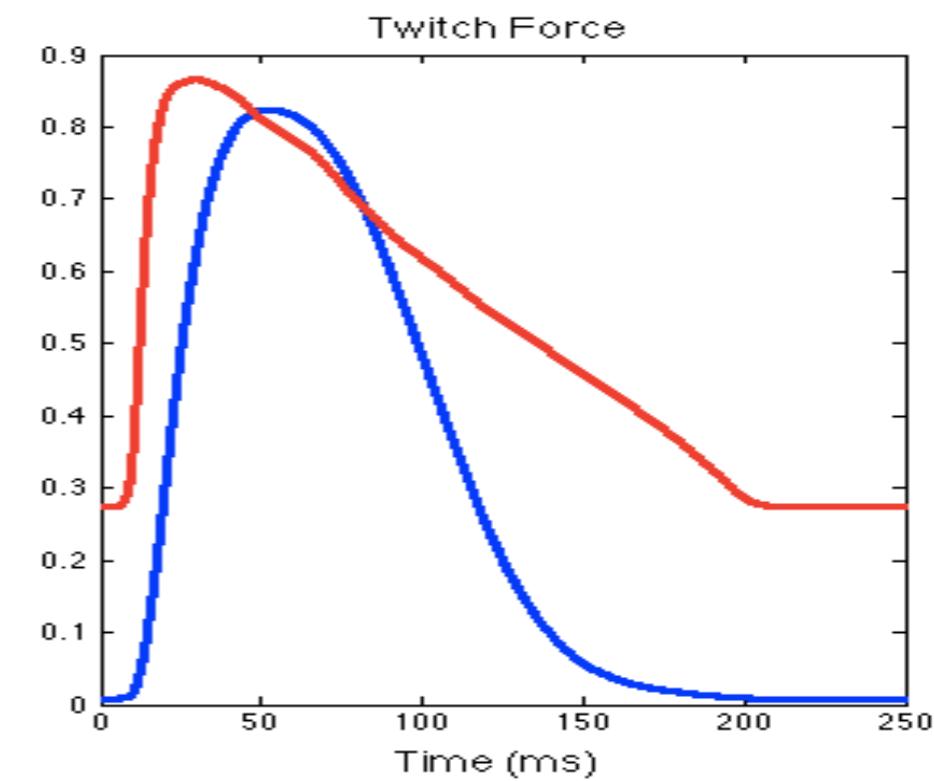
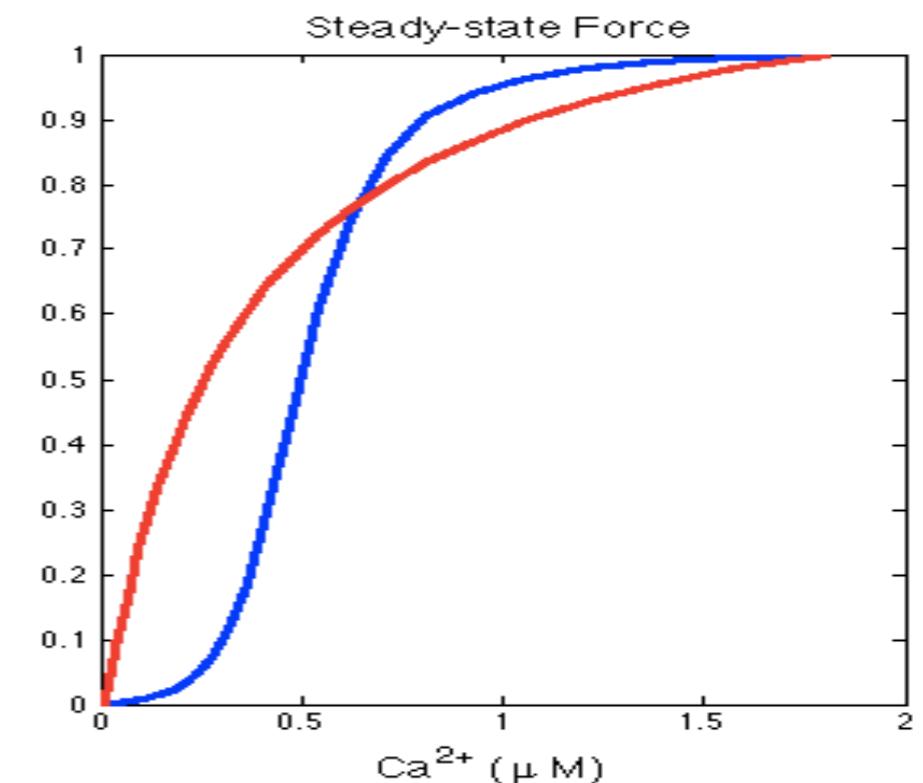
$$\frac{P}{P_0} = \frac{\text{Ca}^h}{\text{EC}_{50}^h + \text{Ca}^h}$$

- The steep calcium sensitivity produces a much larger change in force than the relative change in intracellular calcium
- Twitch forces rises faster than the calcium transient and falls slower



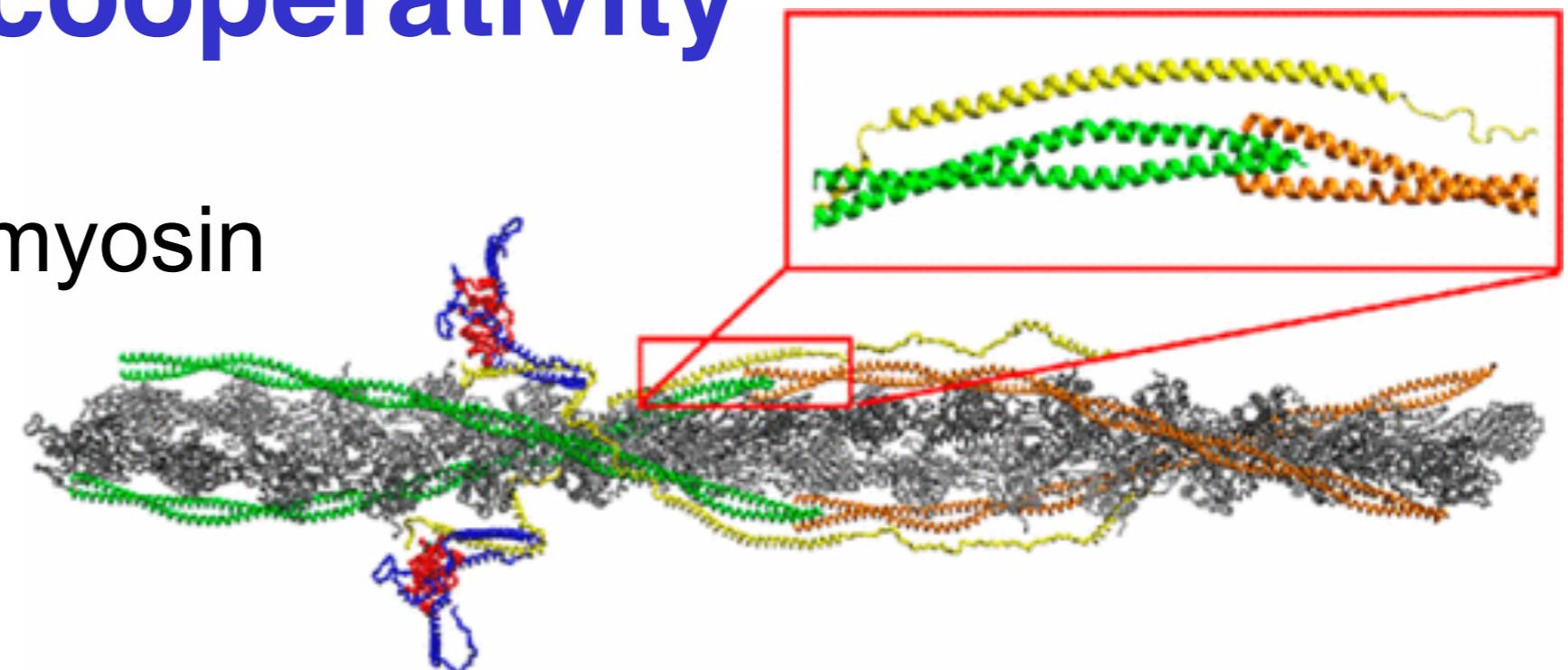
Cooperative Activation of Myofilaments by Ca^{2+}

- Inhibits force at diastolic $[\text{Ca}^{2+}]$
- Enhances force during *late* twitch and greatly impacts twitch dynamics

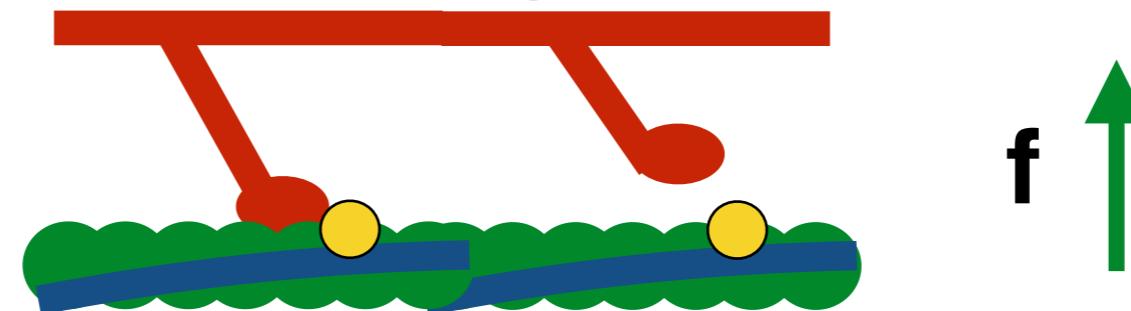


Mechanisms of myofilament cooperativity

- RU-RU (Tropomyosin Overlap)



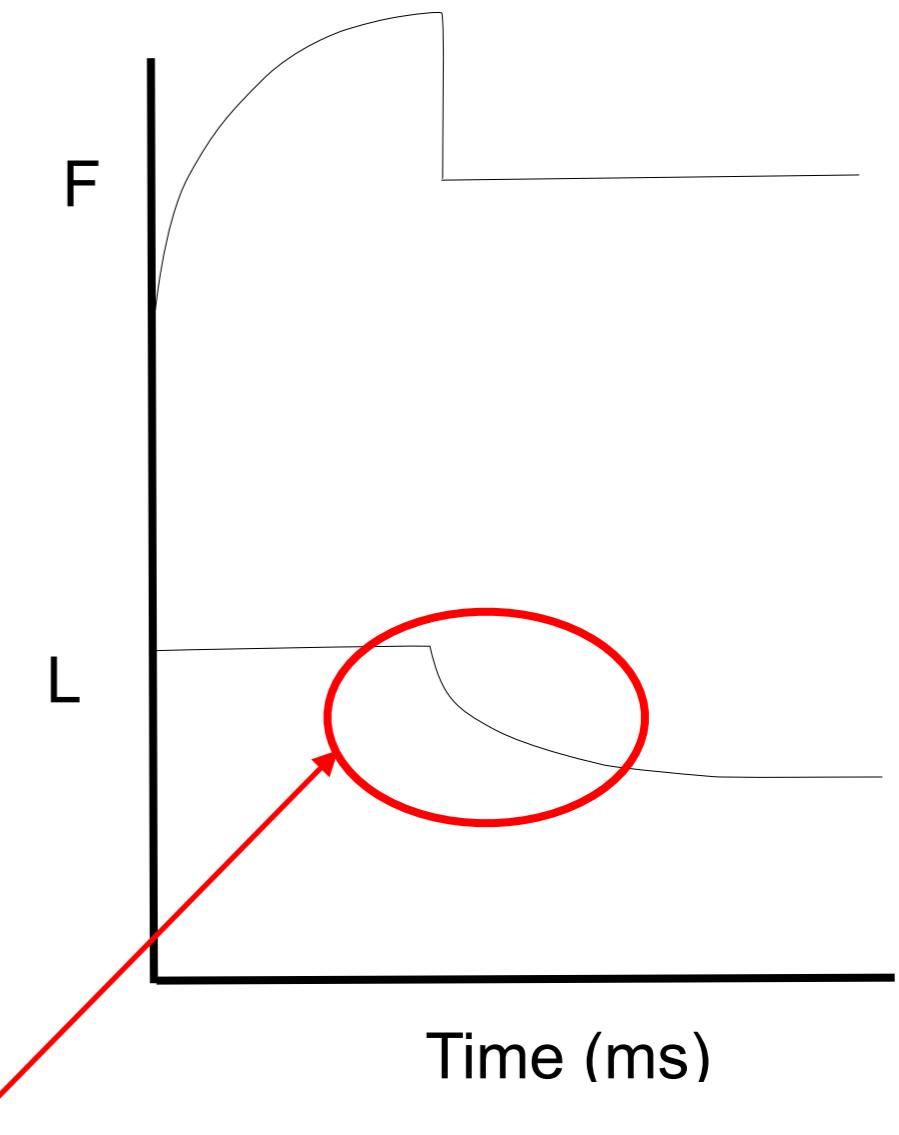
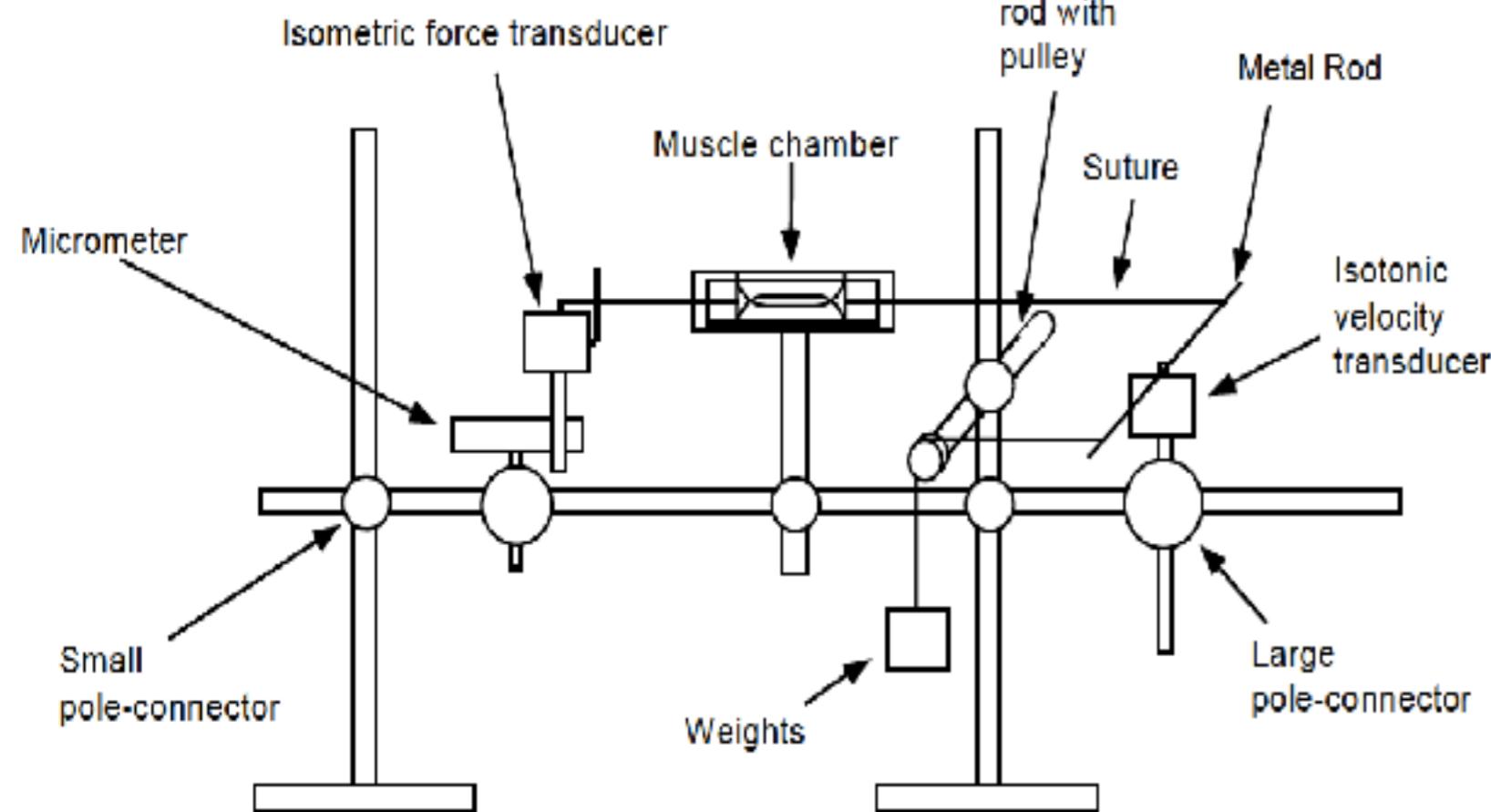
- XB-XB



- XB-RU



Isotonic (constant force) Test



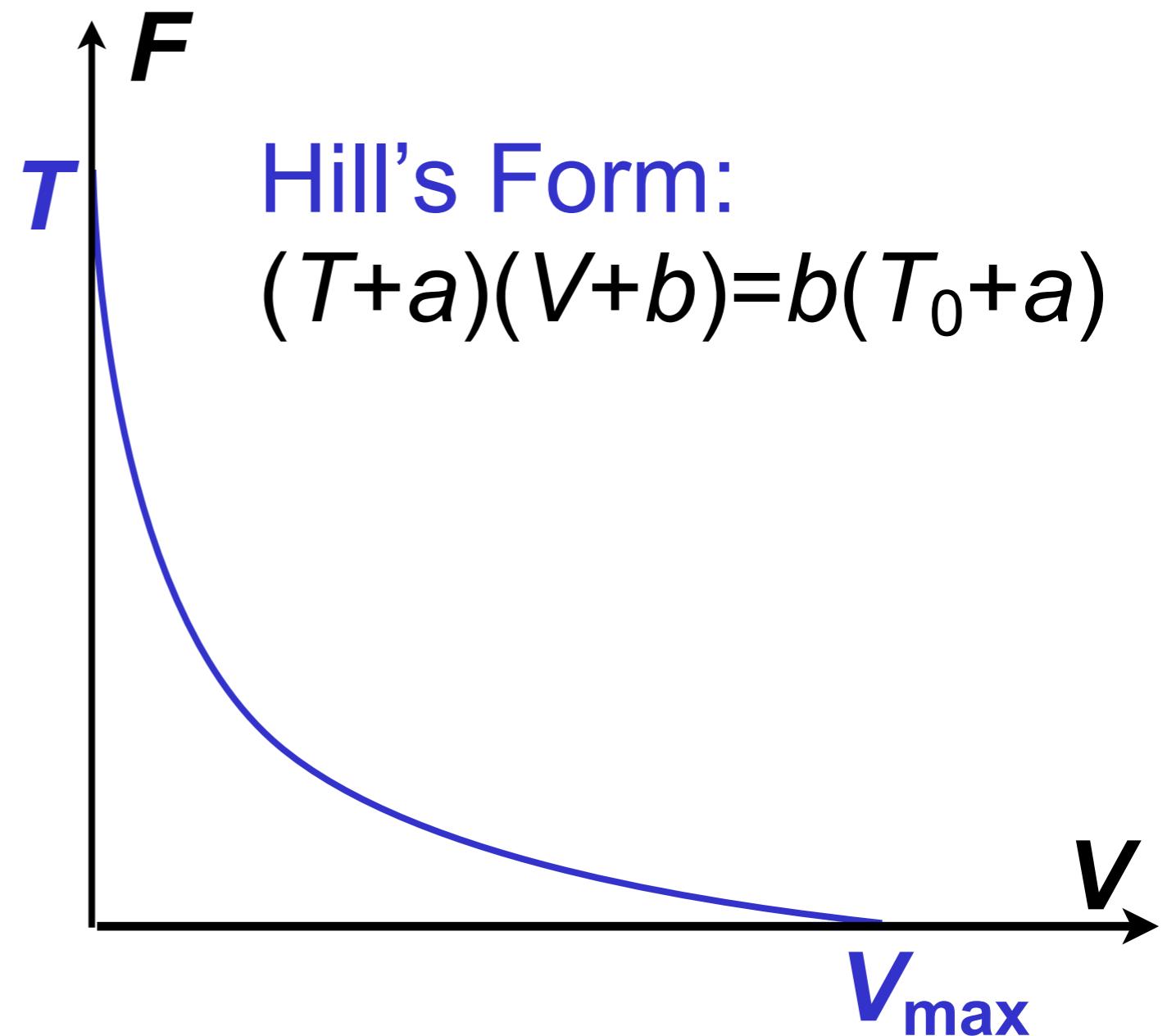
Hill's Force-Velocity Relation

Dimensionless forms:

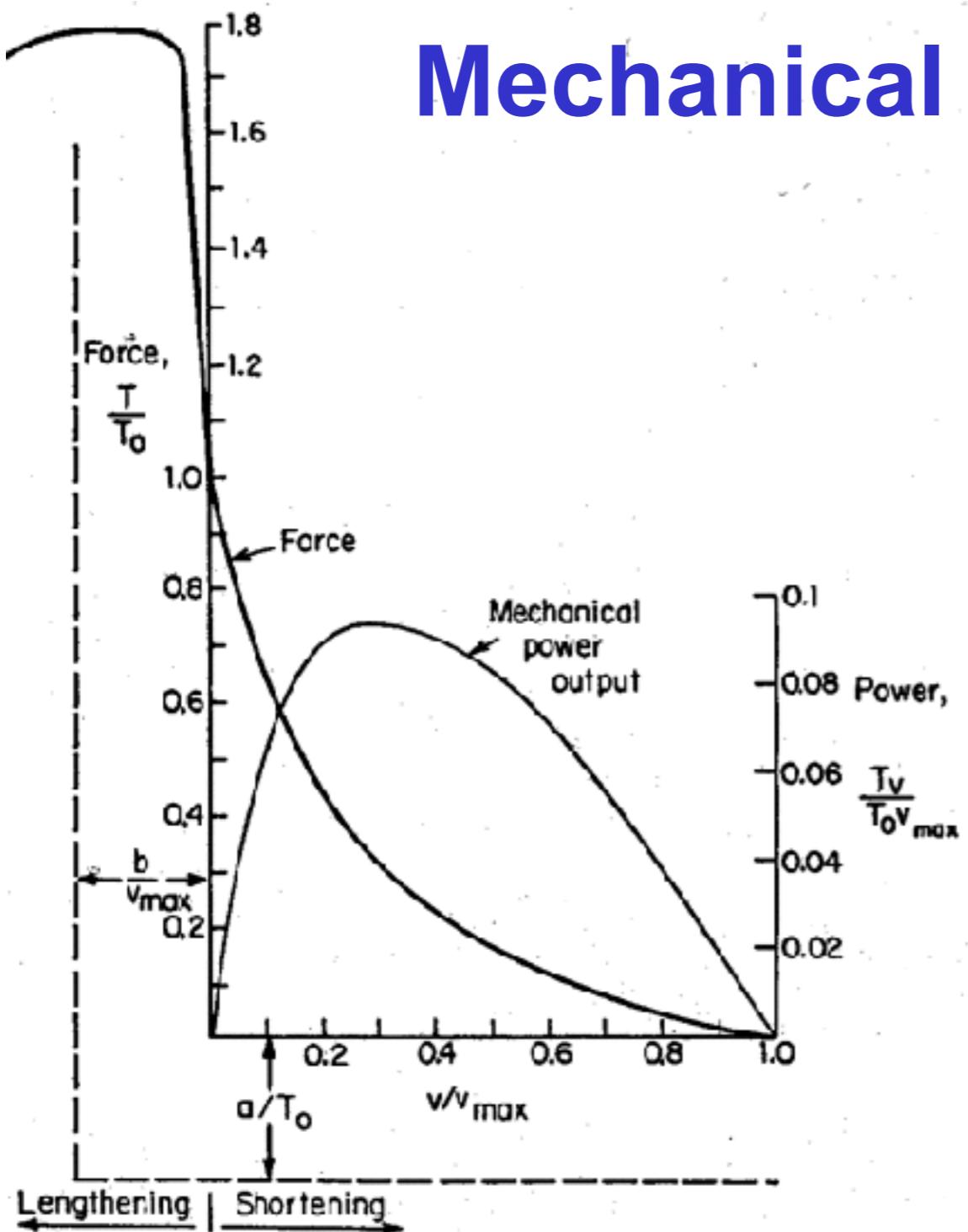
$$\frac{V}{V_{\max}} = \frac{1 - T/T_0}{1 + c(T/T_0)}$$

$$\frac{T}{T_0} = \frac{1 - V/V_{\max}}{1 + c(V/V_{\max})}$$

- $-a$, $-b$ = asymptotes
- T_0 = Isometric tension
- V_{\max} = unloaded shortening velocity
- $c = T_0/a$ (ranges from 1.2-4.0)



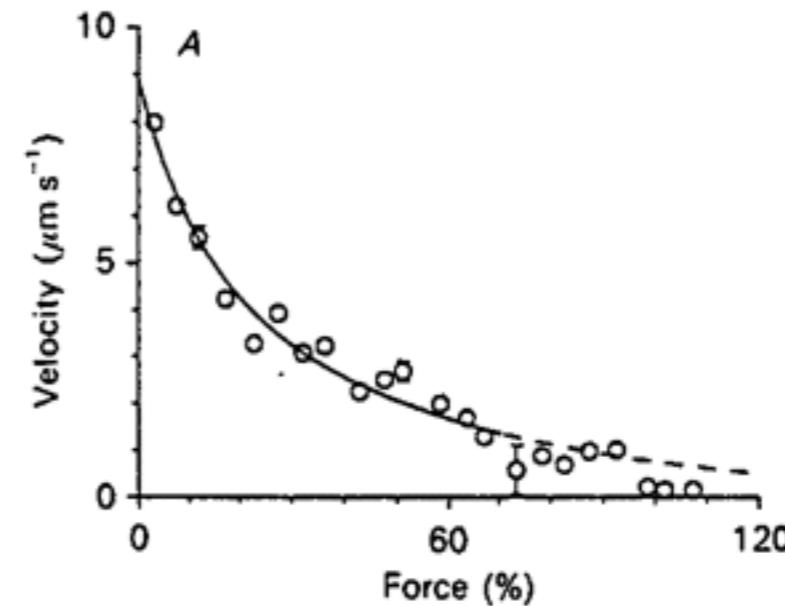
Mechanical Power Output



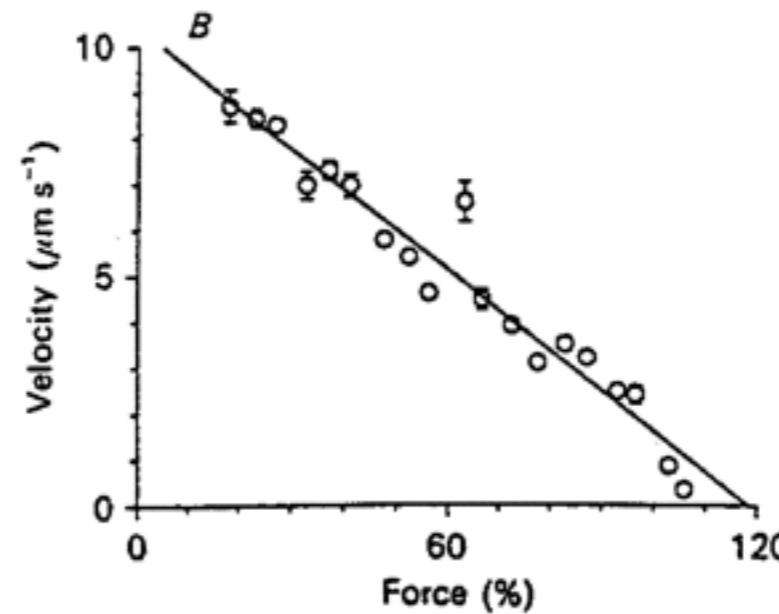
- Mechanical power output is the product of T and V
- The shortening part ($V>0$) of the curve was computed from Hill's equation with $c = 4$
- The asymptotes for Hill's hyperbola (broken lines) are parallel to the T/T_0 and V/V_{max} axes

Isotonic Force-Velocity Relation

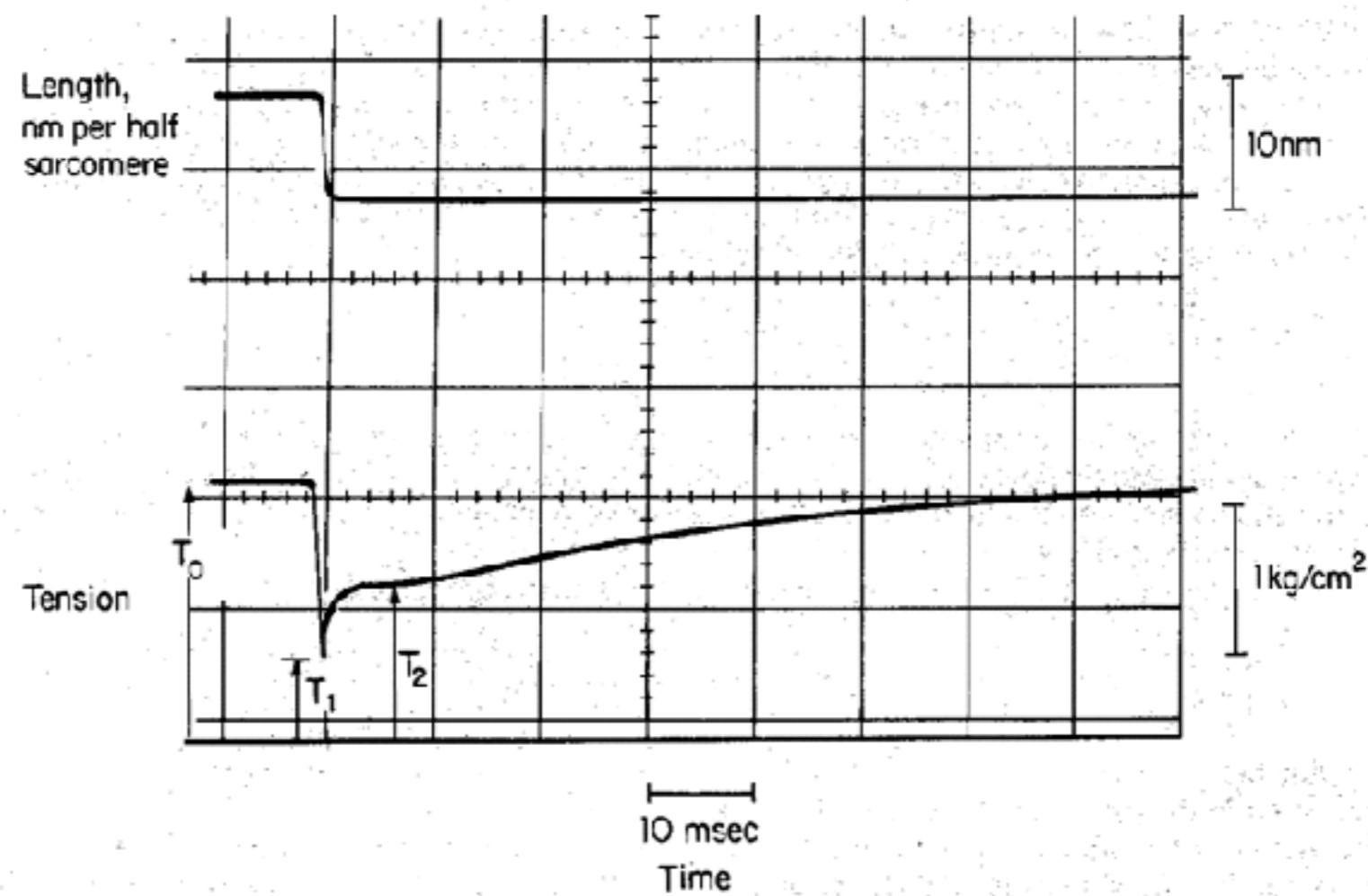
Isovelocity release experiment conducted during a twitch



Cardiac muscle force-velocity relation corrected for viscous forces of passive cardiac muscle which reduce shortening velocity



Small Length Step Response



Tetanized single frog muscle fiber at 0°C during a 1% shortening step lasting 1 ms

Cardiac Muscle: Summary

- *Cardiac muscle fibers* (cells) are short and rod-shaped but are connected by *intercalated disks* and collagen matrix into a spiral-wound *laminar fibrous architecture*
- The *cardiac sarcomere* is similar to the skeletal muscle sarcomere
- Cardiac muscle has a very slow twitch but it can not be tetanized because the *cardiac action potential* has a refractory period
- *Calcium* is the intracellular trigger for cardiac muscle contraction
- *Cardiac muscle testing* is much *more difficult* than skeletal muscle: *laser diffraction* has been used in trabeculae
- Cardiac muscle has relatively *high resting stiffness* due to more collagen and shorter titin isoforms.
- The *cardiac muscle isometric length-tension curve* has no real descending limb

Break

Modeling Contractile Mechanisms: Huxley 1957 Model

**With Slides Courtesy
Stuart Campbell, Yale and
J. Jeremy Rice**

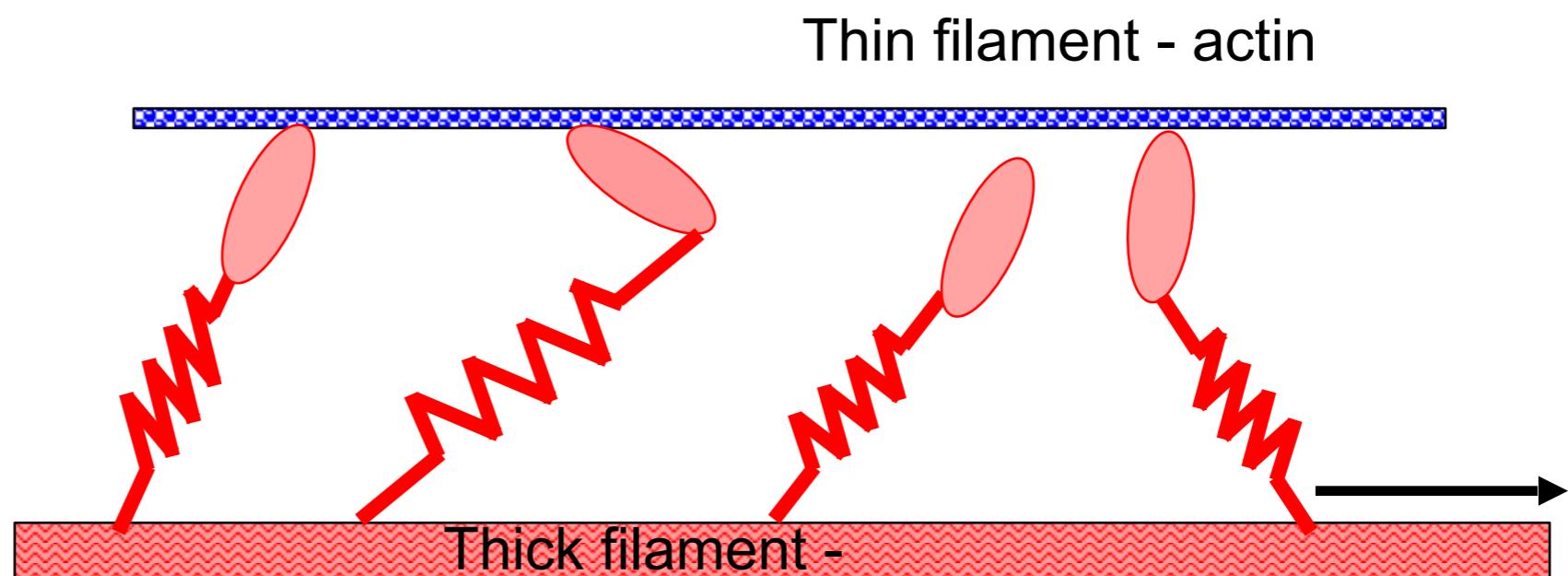
IBM T.J. Watson Research Center, P.O. Box 218, Yorktown Heights, NY 10598
johnrice@us.ibm.com
914-945-3728



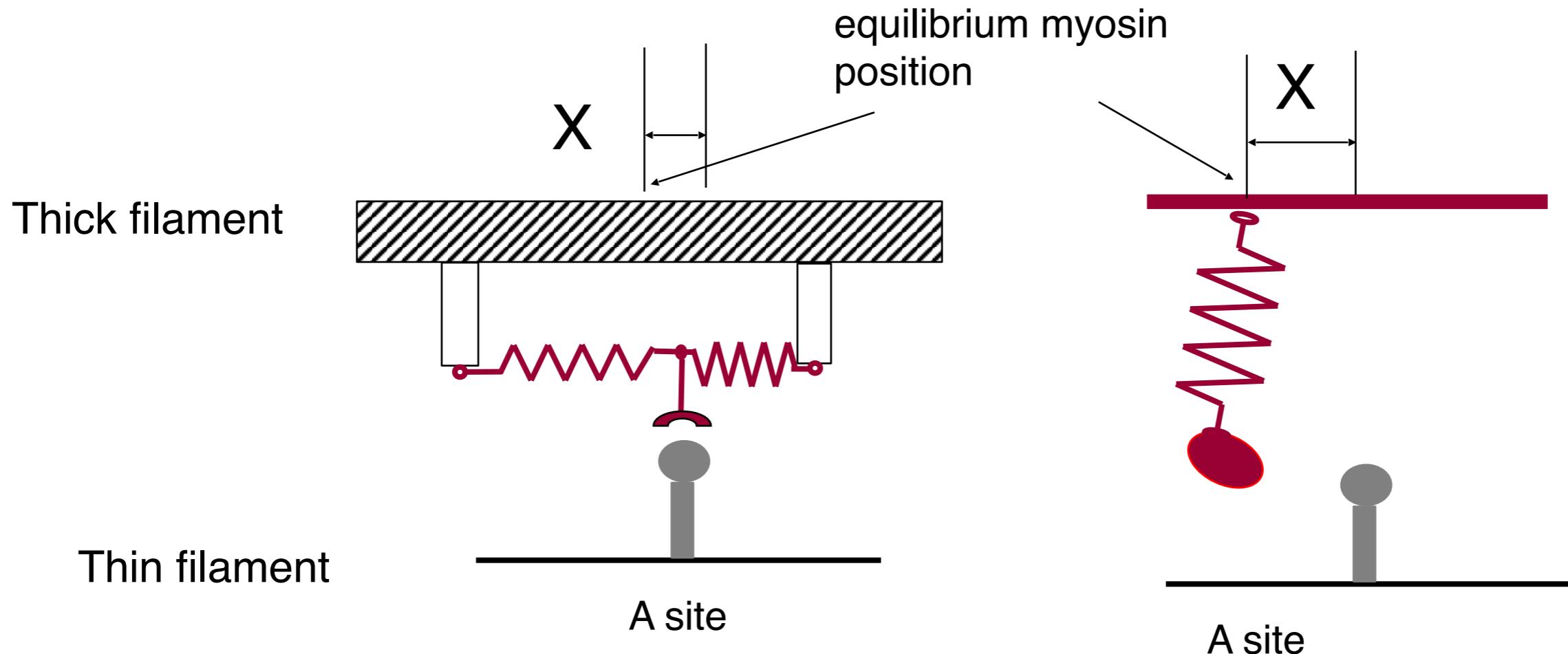
Derivation of Huxley '57 Model

Assumptions:

1. Contractile machinery only, not activation mechanisms
2. Plateau region of length-tension relation
3. Muscle fully activated
4. Constant velocity (a parameter of the model)
5. Crossbridges (XBs) always completes full cycle to detach and hydrolyzes 1 ATP in the process
6. A single myosin near every actin (A) site and interaction between this pair is independent of all other pairs of A sites and myosins

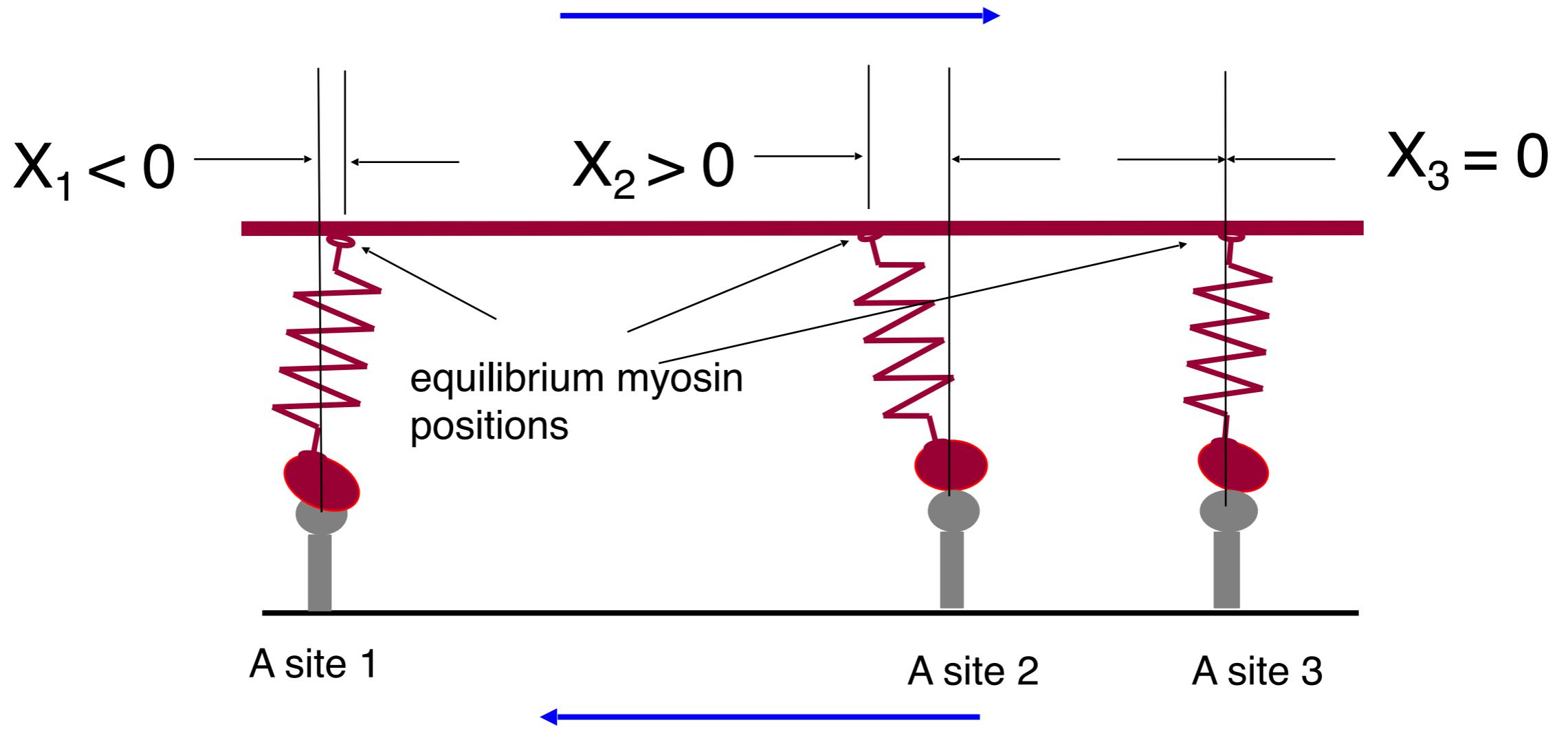


Setup for Huxley '57 model



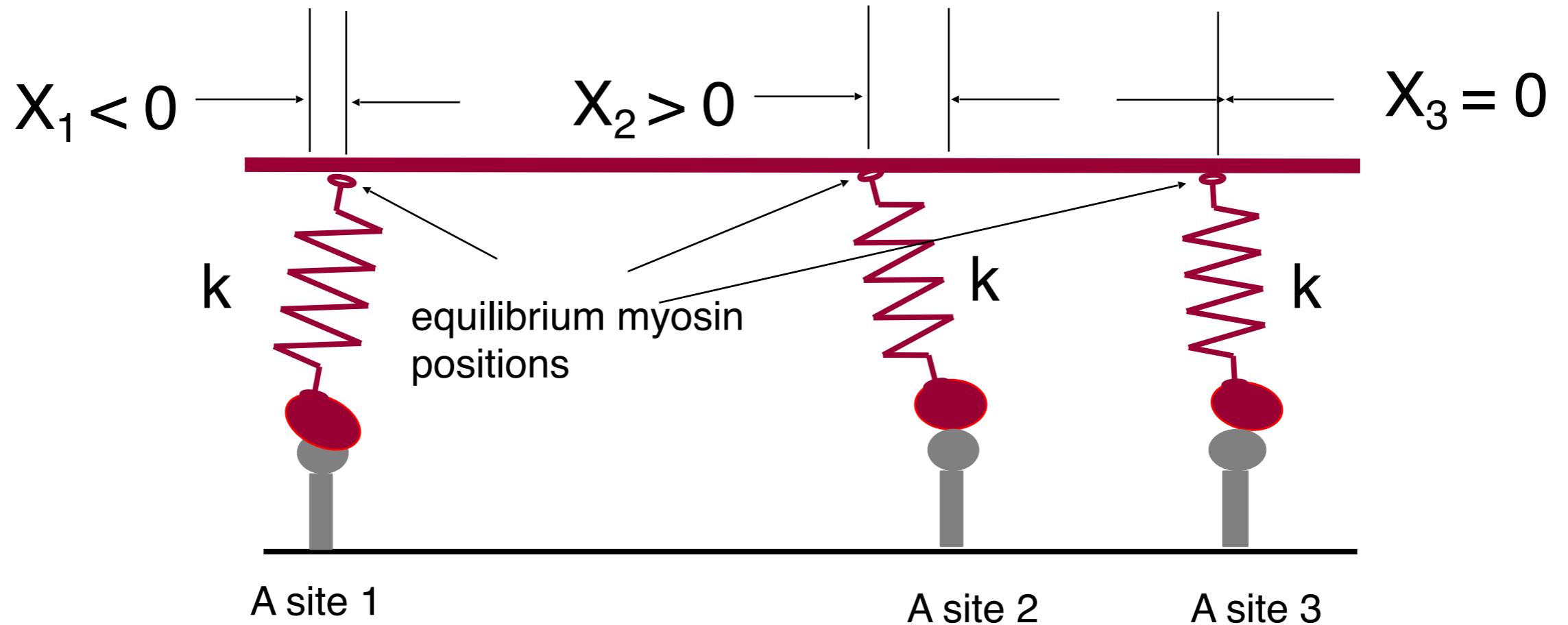
1D: consider model on left to be equivalent to model on right.
Model is built around XB binding sites called A sites on thin filament. Myosin heads from thick filament can bind to one and only one nearby A site.

Setup for Huxley '57 model



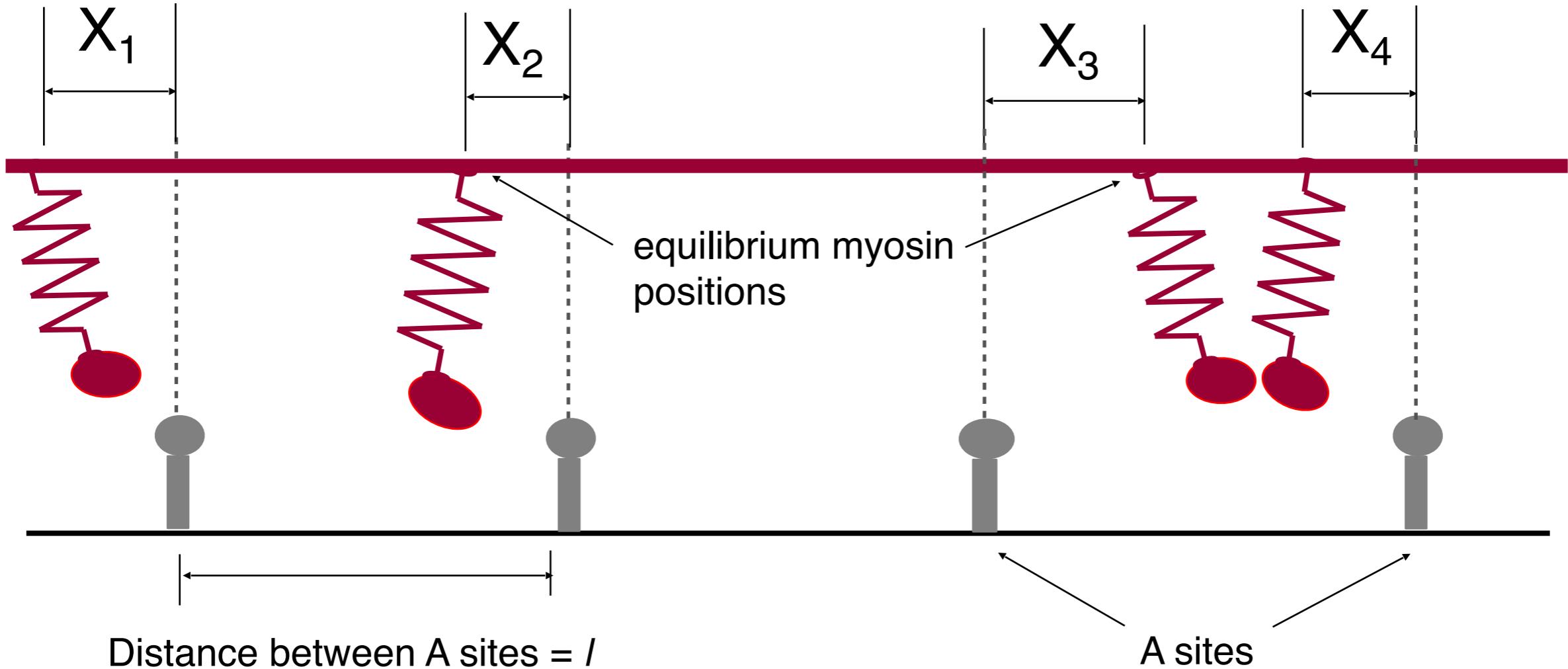
Forces are only considered in X direction parallel to thick and thin filaments. When an XB is bound to A site, force is generated due to the distortion of myosin from its equilibrium position. When A site is bound exactly at the equilibrium position (X_3), no force is generated.

Setup for Huxley '57 model



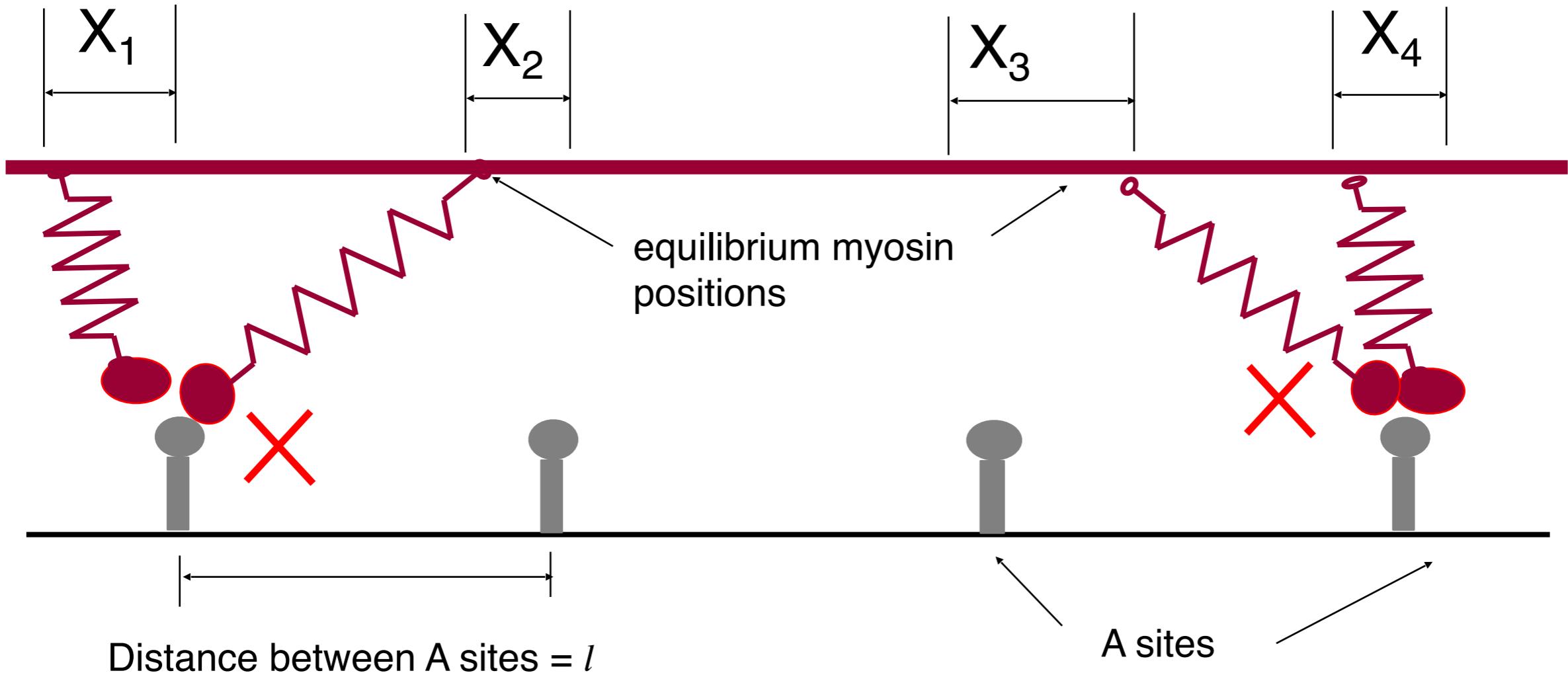
X_B is assumed to be a simple spring so that $T = kX$. For each A site with myosin bound, $T = kX$. Therefore, $T_1 < T_3 = 0 < T_2$.

Setup for Huxley '57 model



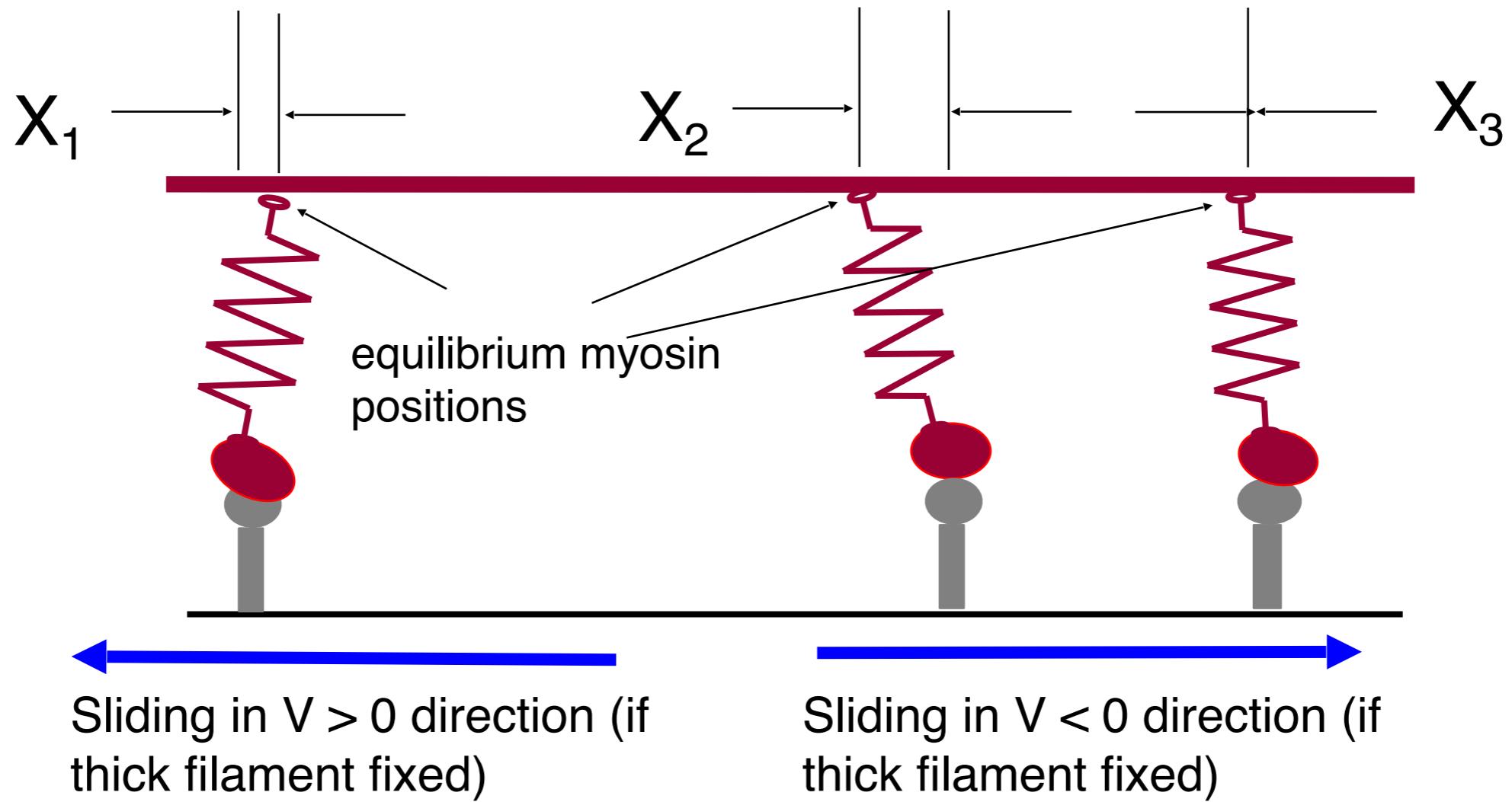
Model shows distance between A sites and equilibrium myosin positions. A whole population of A sites is assumed to sample equally all X values because A sites and equilibrium myosin positions are unequally spaced. (p.d.f is constant)

Setup for Huxley '57 model



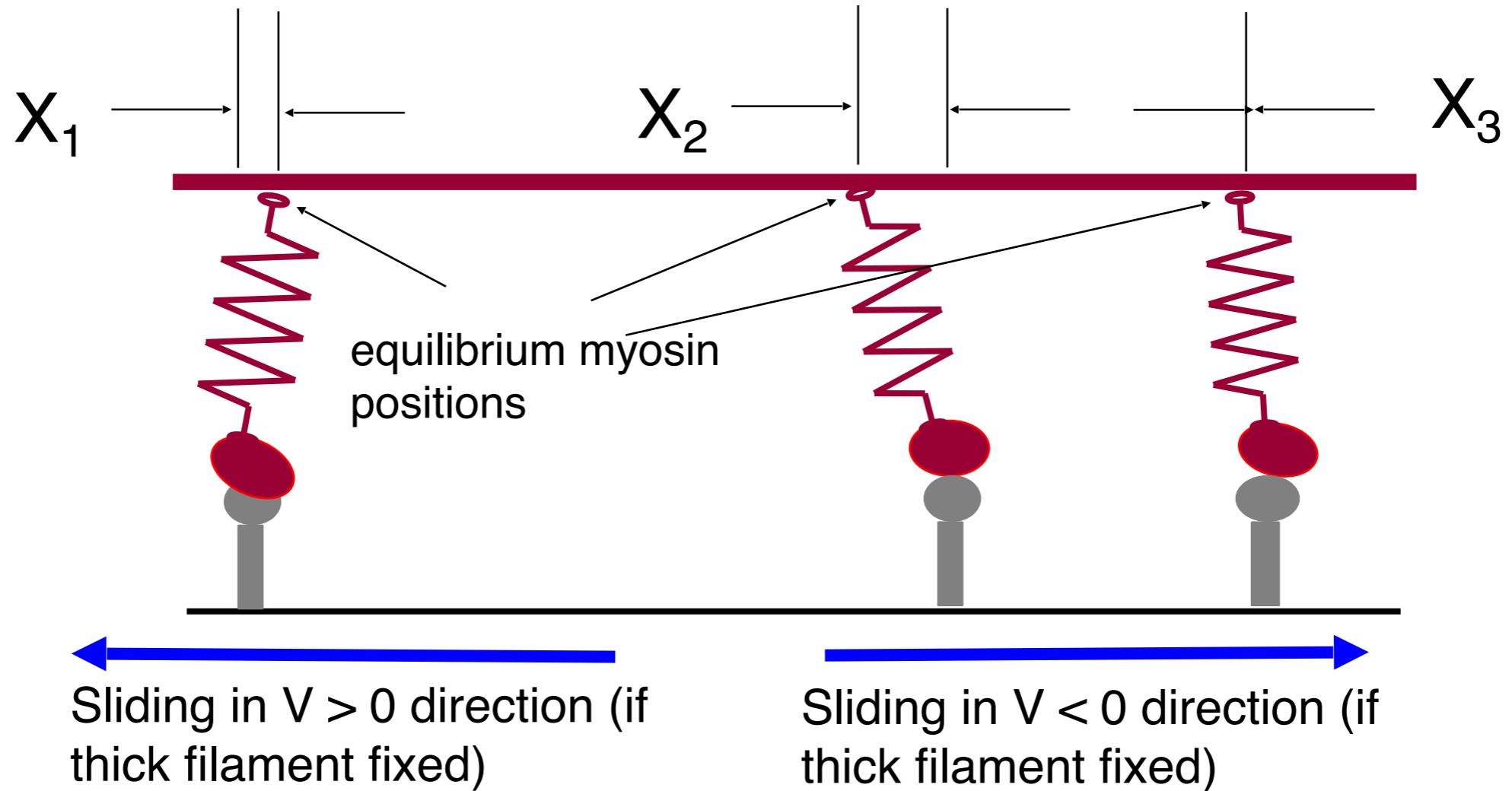
Model assumes distance l between A sites is large and interactions are with only one nearby myosin. Hence, each myosin can interact with only one A site at a time. Therefore, the cases shown above (for X_2 and X_3) cannot happen.

Setup for Huxley '57 model



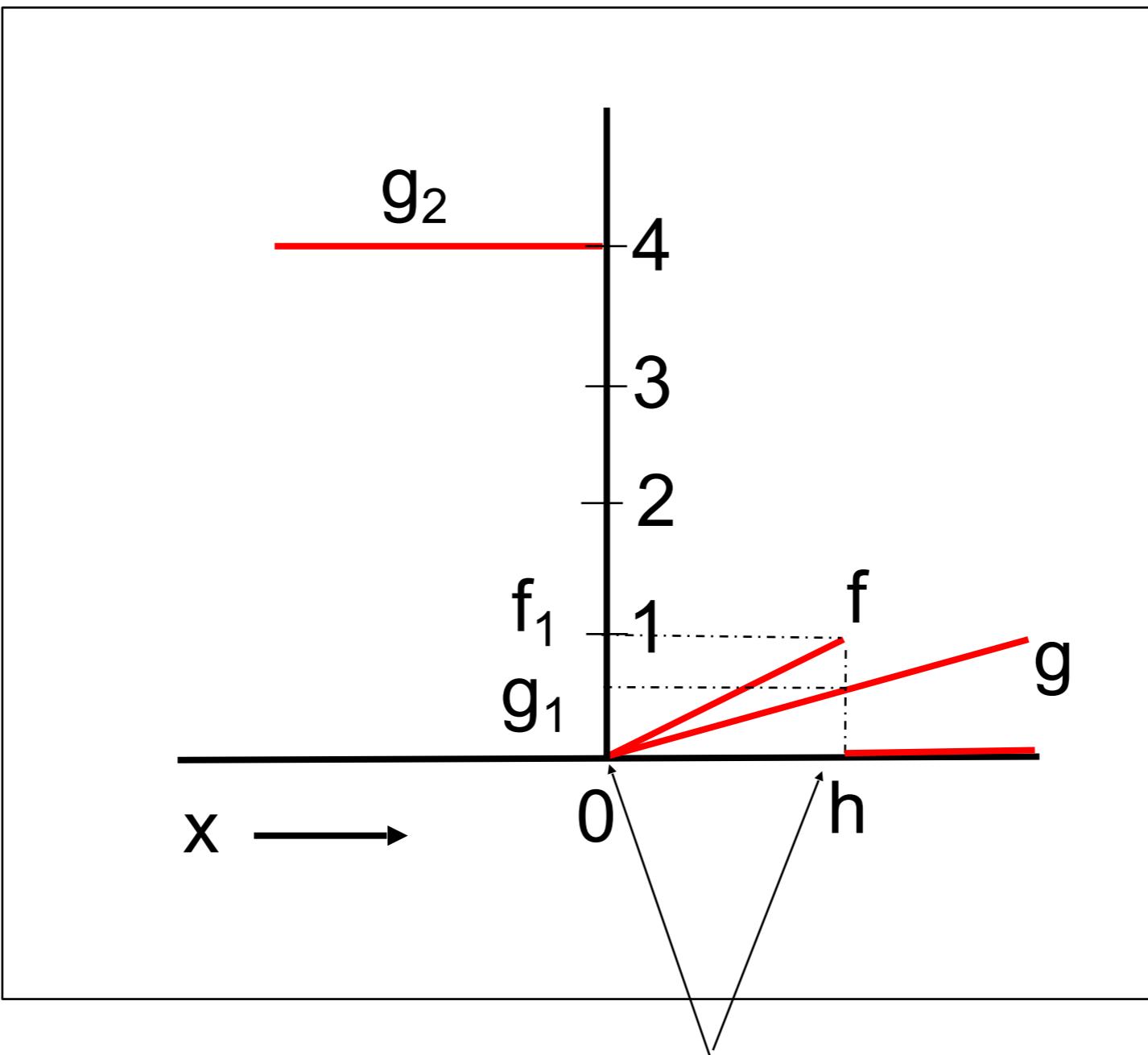
The thick and thin filaments slide past each other at a constant velocity V . We assume that the motion results from combined action of many force generators acting across the whole muscle, so the sliding velocity is not affected by the local attachment or detachment events. Note: velocity is a parameter in the model.

Setup for Huxley '57 model



As thick and thin filaments slide past each other at a constant velocity V , the relative position of A sites compared with the equilibrium myosin positions changes. Therefore, when $V > 0$, X_1 , X_2 and X_3 all decrease (get less positive or more negative) with time.

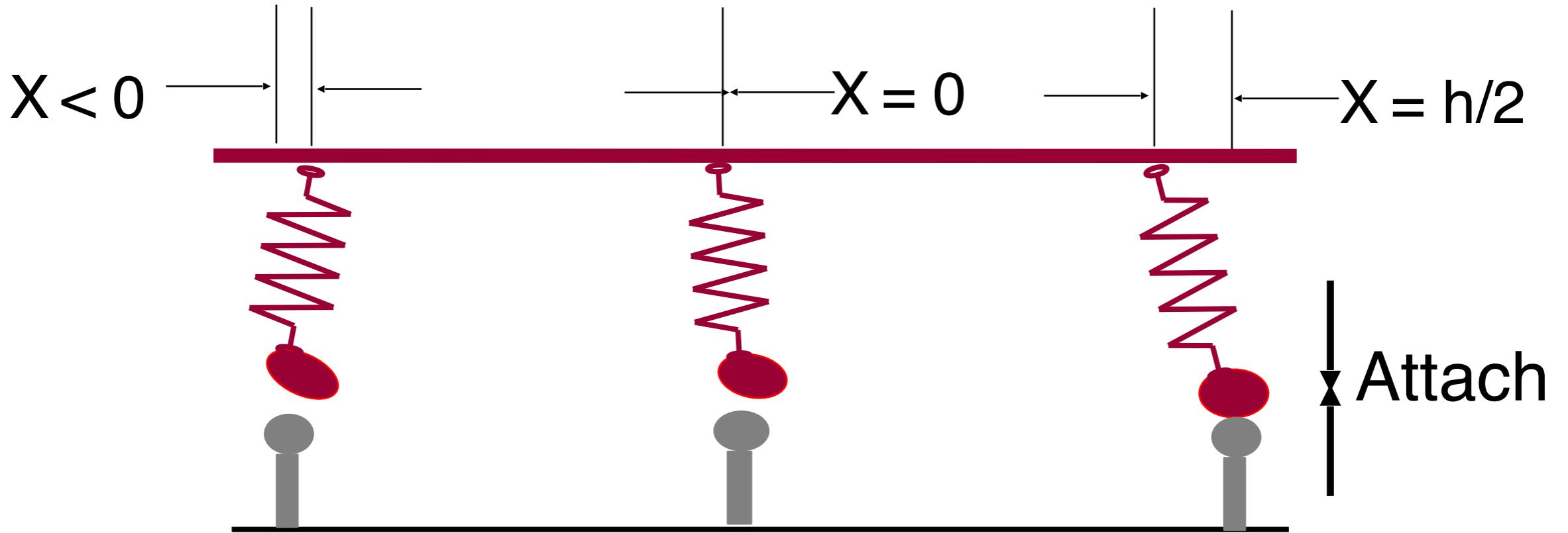
Attachment and detachment rates as functions of X



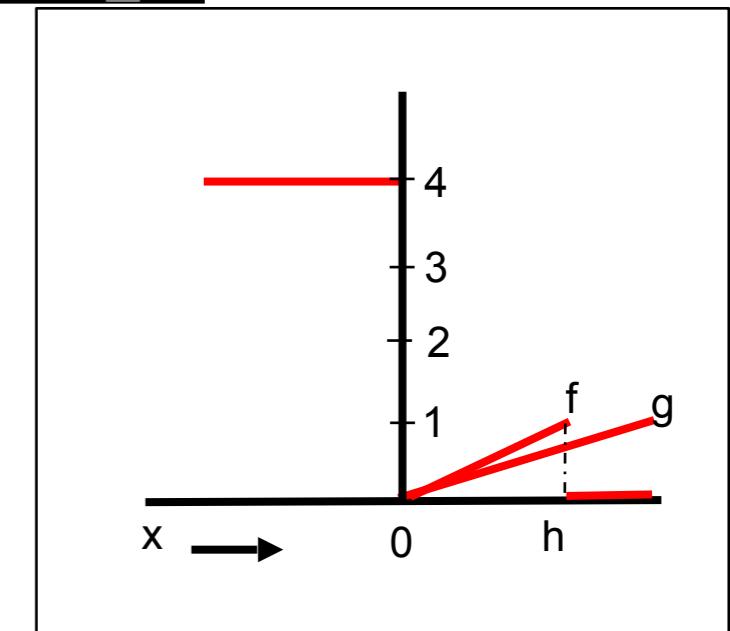
XB attach only in this range

XB can detach at any distortion

Attachment rates as function of X

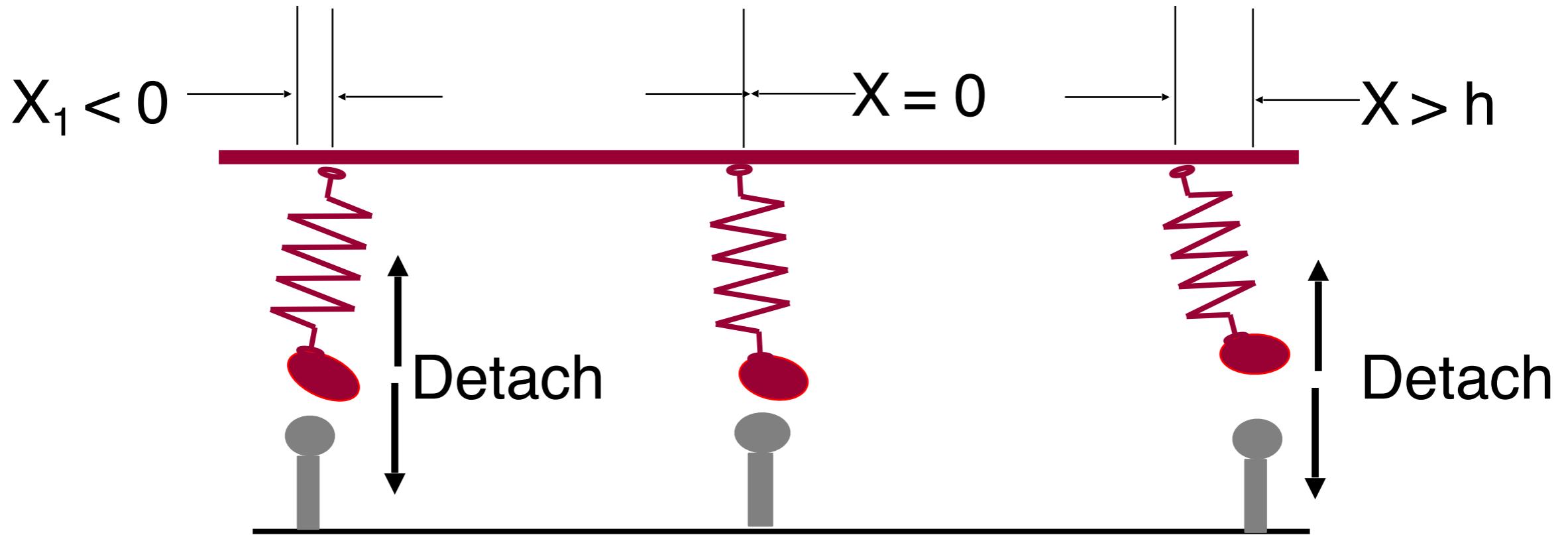


Attachment rate of myosin to A site is a function $f(X)$ of the distance between the A site and equilibrium myosin position. $f(X)$ increases linearly from $X = 0$ to $X = h$.

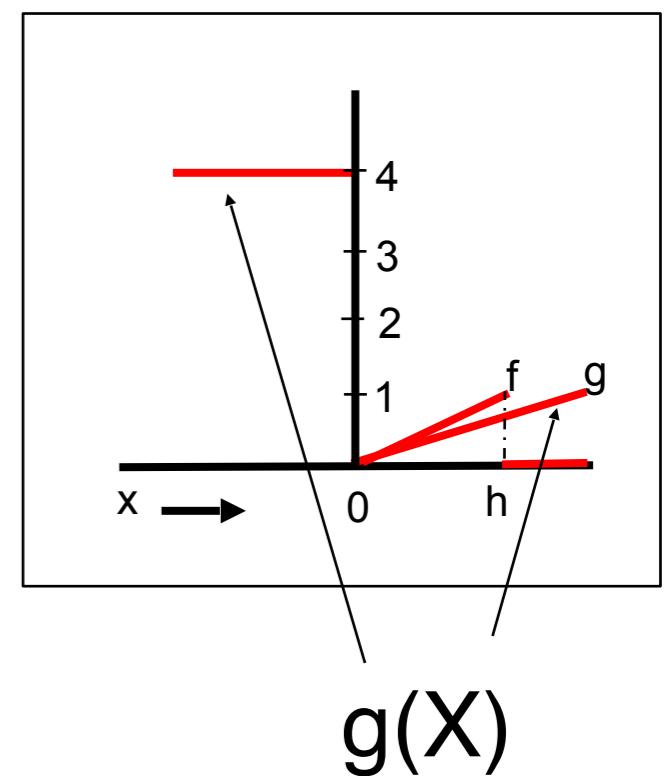


$f(X)$

Detachment rates as function of X



$g(X)$ is the myosin detachment rate as a function of the relative distance between the A site and equilibrium myosin position. In the positive range of X , $g(X)$ increases linearly. In the negative range, $g(X)$ is large so that the negative distortion XBs ("draggers") detach rapidly.



Let $n(x,t)$ be a conditional probability describing the likelihood that an XB is attached given that the A site is at displacement x from the nearest XB equilibrium position.

To be more rigorous:

$$n(x,t) = \lim_{\Delta x \rightarrow 0} \left[Pr \left\{ \begin{array}{l} A \text{ site has} \\ XB \text{ attached} \end{array} \middle| \begin{array}{l} A \text{ in range} \\ x \text{ to } x + \Delta x \end{array} \right\} \right]$$



Conditional probability vertical
bar means “given that”

A Note on Conditional Probability

We define a conditional probability as probability of an event A given that an event B has occurred. This is written as:

$$\Pr\{A|B\} = \frac{\Pr\{A \& B\}}{\Pr\{B\}}$$

This relation may make more intuitive sense when rearranged as:

$$\Pr\{A \& B\} = \Pr\{A|B\}\Pr\{B\}$$

For our system, a more intuitive function $\hat{n}(x,t)$ describes the probability that an A site is attached *and* the A site is between x and $x + \Delta x$

$$\hat{n}(x,t) = \lim_{\Delta x \rightarrow 0} \frac{1}{\Delta x} \left[\Pr \left\{ \begin{array}{l} \text{A site has} \\ \text{XB attached} \end{array} \right\} \& \left\{ \begin{array}{l} \text{A in range} \\ x \text{ to } x + \Delta x \end{array} \right\} \right]$$

Using probability theory $\Pr\{A \& B\} = \Pr\{A|B\}\Pr\{B\}$

Substitute limit above with product of limits

$$\hat{n}(x,t) = \lim_{\Delta x \rightarrow 0} \left[\Pr \left\{ \begin{array}{l} \text{A site has} \\ \text{XB attached} \end{array} \middle| \begin{array}{l} \text{A in range} \\ x \text{ to } x + \Delta x \end{array} \right\} \right] \cdot \lim_{\Delta x \rightarrow 0} \frac{1}{\Delta x} \left[\Pr \left\{ \begin{array}{l} \text{A in range} \\ x \text{ to } x + \Delta x \end{array} \right\} \right]$$

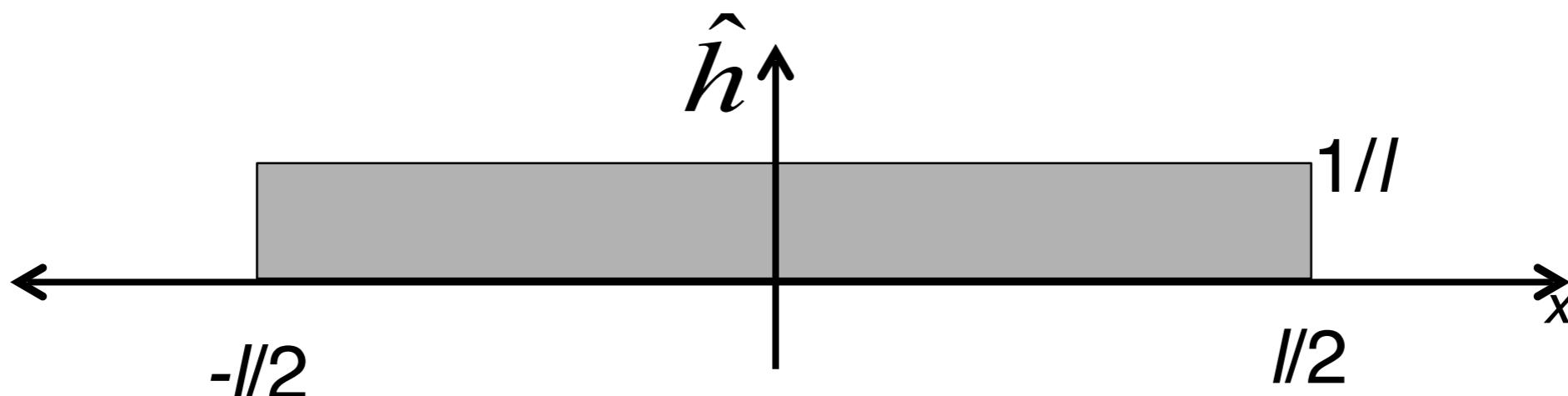
$\hat{n}(x,t) = n(x,t) \bullet \hat{h}(x,t)$

Conditional Probability Probability Density Function

$$\hat{n}(x, t) = n(x, t) \cdot \hat{h}(x, t)$$

\hat{h} is a probability density function describing the positions of A sites with respect to equilibrium XB positions

Model assumes \hat{h} is constant over all possible x values between $-l/2$ and $l/2$ as shown below:



Back to derivation:

For steady-state response: $\frac{dn(x,t)}{dt} = 0$

Apply chain rule: $\frac{\partial n}{\partial x} \frac{dx}{dt} + \frac{\partial n}{\partial t} \frac{dt}{dt} = 0$

We know that: $\frac{dx}{dt} = v$ $\frac{dt}{dt} = 1$

$$\frac{\partial n}{\partial x} v + \frac{\partial n}{\partial t} = 0$$

Rearrange to get: $-v \frac{\partial n}{\partial x} = \frac{\partial n}{\partial t}$

$$\frac{\partial n}{\partial t} = \text{rate of attachment to A site} - \text{rate of detachment from A site}$$

$$= f(x)[1 - n(x, t)] - g(x)n(x, t)$$

Consider steady state where $\frac{dn(x, t)}{dt} = 0$

\Rightarrow use $n(x)$ instead of $n(x, t)$

$$\frac{\partial n(x)}{\partial t} = f(x)[1 - n(x)] - g(x)n(x)$$

The diagram shows the steady-state equation $\frac{\partial n(x)}{\partial t} = f(x)[1 - n(x)] - g(x)n(x)$. Two red arrows point to specific terms: one arrow points to the term $[1 - n(x)]$, and another arrow points to the term $g(x)n(x)$.

Unattached A site fraction Attached A site fraction

Combine above results:

$$-\nu \frac{\partial n(x)}{\partial x} = \frac{\partial n(x)}{\partial t}$$

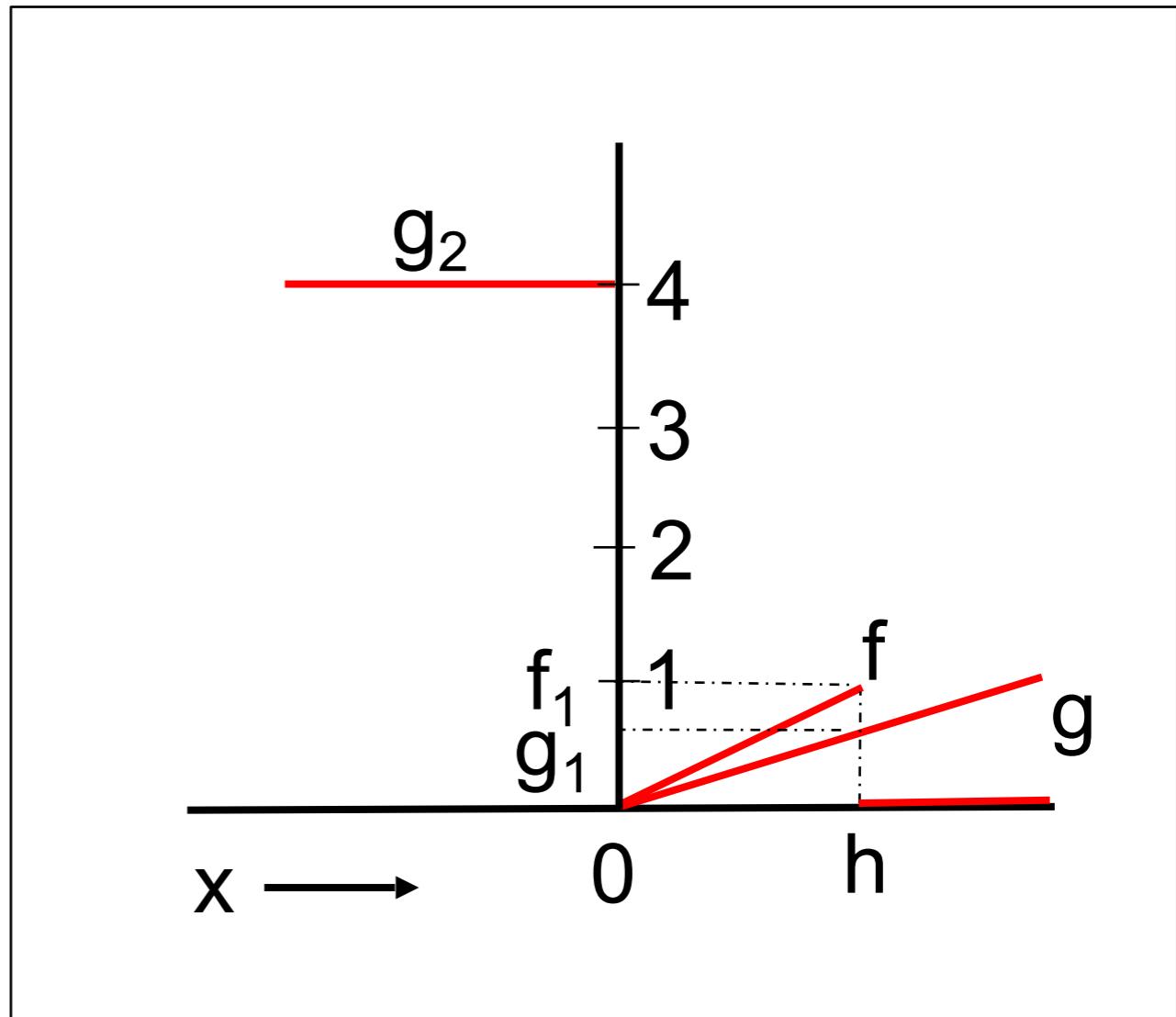
$$-\nu \frac{\partial n(x)}{\partial x} = f(x)[1 - n(x)] - g(x)n(x)$$

Can find solution for specific cases if we define $f(x)$ and $g(x)$ with units of s^{-1}

$$x < 0: \quad f(x) = 0 ; \quad g(x) = g_2$$

$$0 < x \leq h: \quad f(x) = \frac{f_1 x}{h} ; \quad g(x) = \frac{g_1 x}{h}$$

$$x > h: \quad f(x) = 0 ; \quad g(x) = \frac{g_1 x}{h}$$



Apply constraint that if $V \neq 0$ then solution is continuous at $x=0$ and $x=h$. One can write:

$$n(0^-) = n(0^+)$$

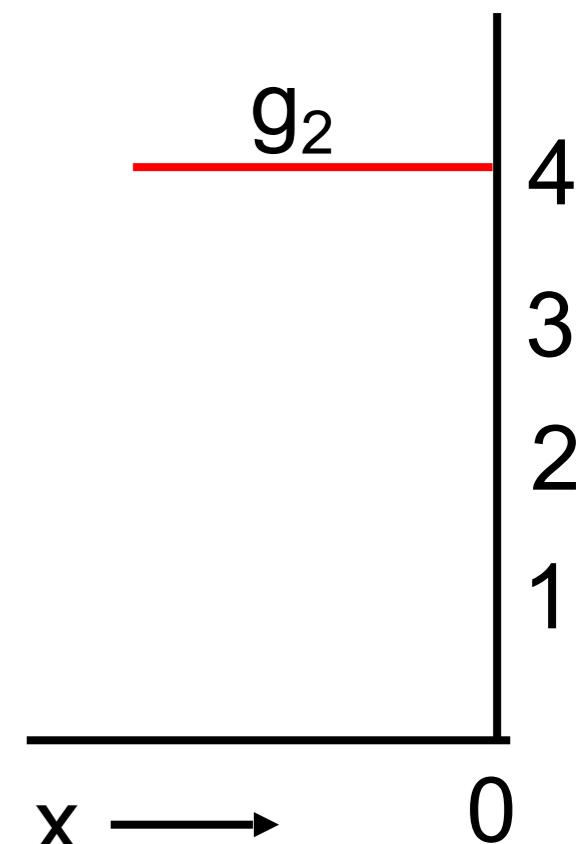
$$n(h^-) = n(h^+)$$

Now solve for three regions assuming $V > 0$:

Region 1 - $x < 0$: $f(x) = 0$; $g(x) = g_2$

$\frac{\partial n}{\partial x} = \frac{dn}{dx}$ in steady state where $\frac{dn(x,t)}{dt} = 0$

$$-\nu \frac{dn}{dx} = -g_2 n$$



$$\int \frac{dn}{n} = \int \frac{g_2}{\nu} dx$$

Integrate to get:

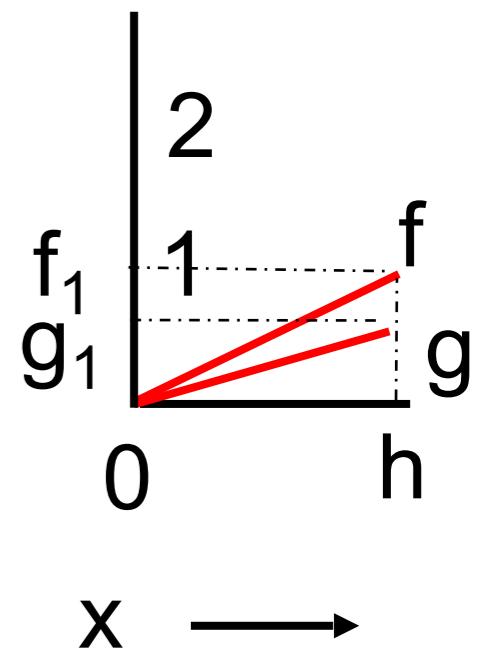
$$\ln n = \frac{g_2}{\nu} dx + C_0$$

$$n(x) = C_1 e^{\frac{g_2 x}{\nu}}$$

where $C_1 (= e^{C_0})$ is a constant T.B.D.

Region 2 - $0 < x \leq h$: $f(x) = \frac{f_1 x}{h}$; $g(x) = \frac{g_1 x}{h}$

$$-\nu \frac{dn}{dx} = \frac{f_1}{h} x(1-n) - \frac{g_1}{h} xn$$



$$-vh \frac{dn}{dx} = f_1 x(1-n) - g_1 x n$$

$$= f_1 x - (f_1 + g_1) x n$$

$$= x(f_1 + g_1) \left(\frac{f_1}{f_1 + g_1} - n \right)$$

Rearrange to get:

$$\frac{dn}{\left(-n + \frac{f_1}{f_1 + g_1} \right)} = \frac{f_1 + g_1}{vh} x dx$$

Integrate to get:

$$\ln\left(-n + \frac{f_1}{f_1 + g_1}\right) = \frac{f_1 + g_1}{vh} \frac{x^2}{2} + C_2$$

$$-n + \frac{f_1}{f_1 + g_1} = \exp\left\{\frac{f_1 + g_1}{vh} \frac{x^2}{2} + C_2\right\}$$

$$n = \frac{f_1}{f_1 + g_1} - C_3 \exp\left\{\frac{f_1 + g_1}{vh} \frac{x^2}{2}\right\}$$

where $C_3 = e^{C_2}$

Region 3 - $x > h : f(x) = 0 ; g(x) = \frac{g_1 x}{h}$

If we assume shortening then no crossbridges can be attached at $x > h$. This is equivalent to $n(x,t) = 0$ for $x > h$.

Now determine the constants using the continuity conditions:

$$n(h^+) = n(h^-)$$

Region 2: $0 = \frac{f_1}{f_1 + g_1} - C_3 \exp\left\{\frac{f_1 + g_1}{vh} \frac{x^2}{2}\right\}$

$$C_3 = \frac{f_1}{f_1 + g_1} \exp\left(-\frac{f_1 + g_1}{vh} \frac{h^2}{2}\right)$$

Substitute constant back into original equation (Region 2):

$$n(x) = \frac{f_1}{f_1 + g_1} \left[1 - e^{-\frac{f_1 + g_1}{2vh}(h^2 - x^2)} \right] \text{ for } 0 < x < h$$

Find C_1 using the other continuity condition: $n(0^-) = n(0^+)$

$$n(0^-) = C_1 e^{-\frac{0x}{v}} = C_1 \quad n(0^+) = \frac{f_1}{f_1 + g_1} \left[1 - e^{-\frac{f_1 + g_1}{2vh}h^2} \right]$$

$$C_1 = \frac{f_1}{f_1 + g_1} \left[1 - e^{-\frac{f_1 + g_1}{2vh}h^2} \right]$$

Substitute constant back into original equation (Region 1):

$$n(x) = \frac{f_1}{f_1 + g_1} \left[1 - e^{-\frac{f_1 + g_1}{2\nu h} h^2} \right] e^{-\frac{g_2 x}{\nu}} \text{ for } x < 0$$

Make a change of variables:

Define $\phi = \frac{h}{S}(f_1 + g_1)$ and $\nu = \frac{S}{2}V$

where S is a full sarcomere length ($\sim 2 \mu\text{m}$), $S/2$ is a half sarcomere length, and V is normalized velocity in half sarcomere lengths per second.

The three regions can now be defined as:

$$x < 0: \quad n(x) = \frac{f_1}{f_1 + g_1} \left[1 - e^{-\frac{\phi}{V}} \right] e^{\frac{g_2 x}{SV}}$$

$$0 < x < h: \quad n(x) = \frac{f_1}{f_1 + g_1} \left[1 - e^{\frac{(\frac{x^2}{h^2} - 1)\phi}{V}} \right]$$

$$x > h: \quad n(x) = 0$$

$$\text{where } \phi = \frac{h}{S}(f_1 + g_1) \quad \text{and} \quad \nu = \frac{S}{2}V$$

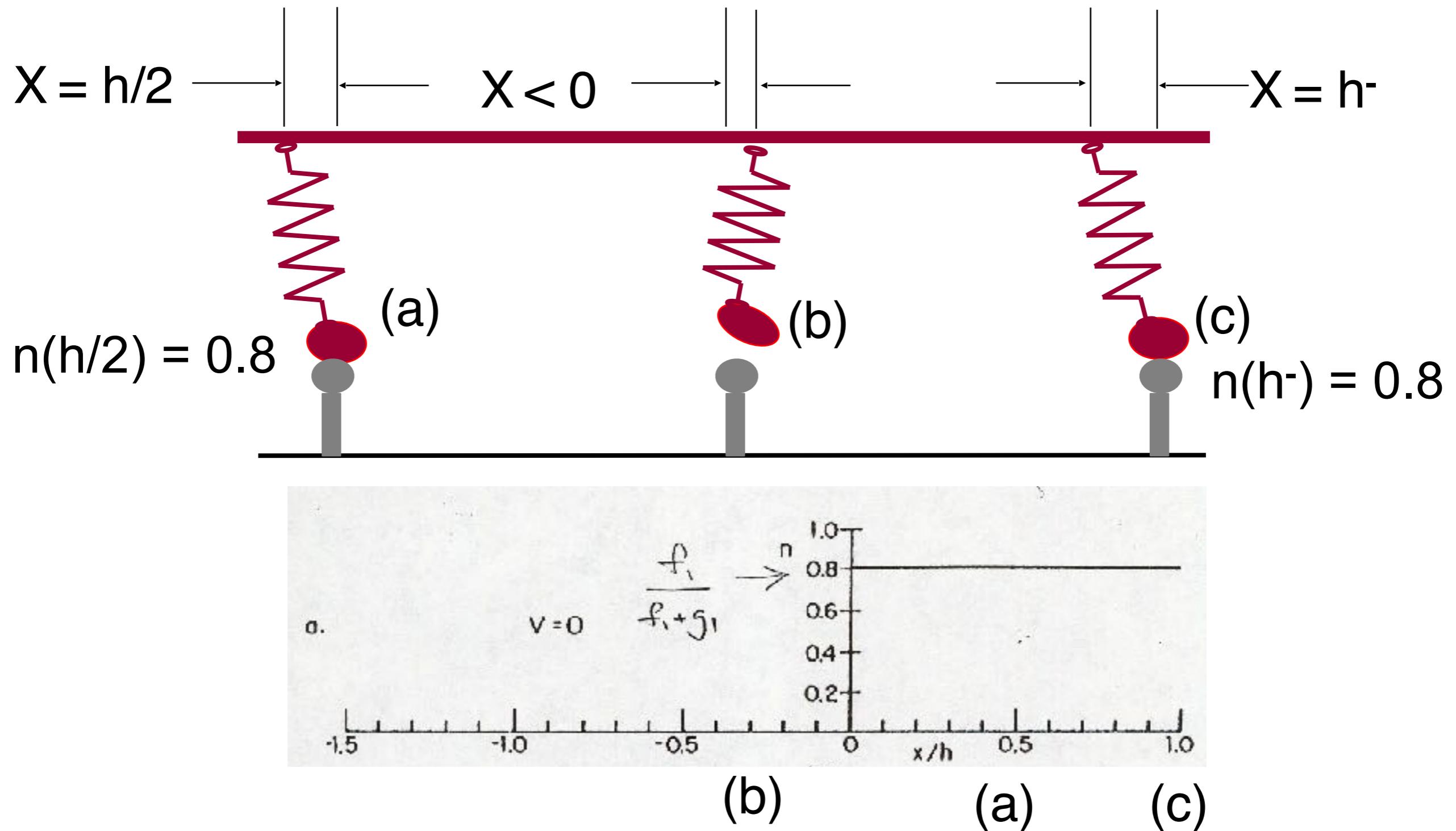
S is sarcomere length ($\sim 2 \mu\text{m}$), and V is normalized velocity in half sarcomere lengths per second.

Must define rates for XB cycling. Can use these ratios for best results:

$$\frac{g_1}{f_1 + g_1} = \frac{3}{16} \quad \frac{g_2}{f_1 + g_1} = 3.919$$

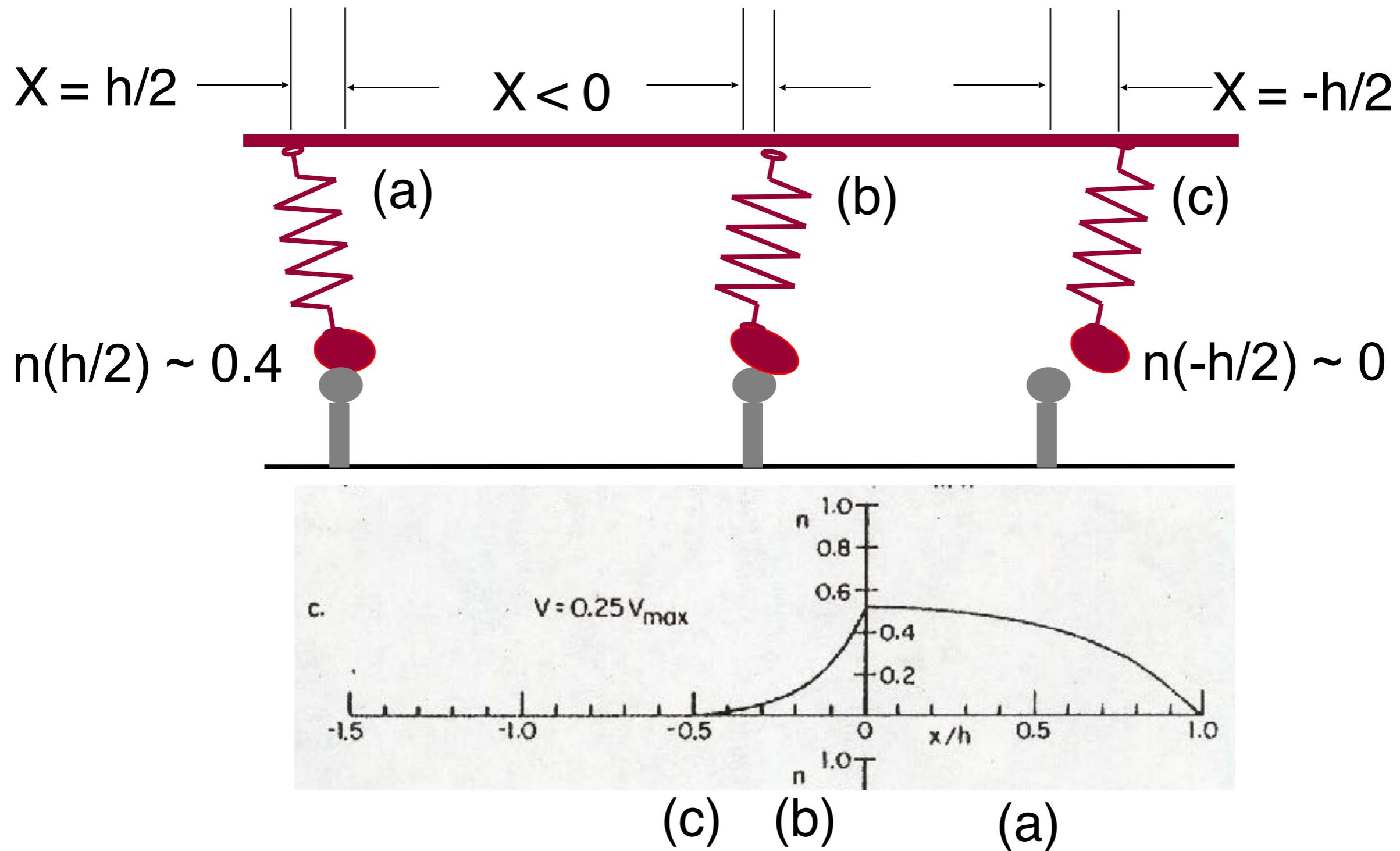
Inspect the “HuxleyModel” notebook, and use the Python code provided to explore the effect of myofilament sliding speed (V) on attachment probability (n)

Results for Huxley '57 model



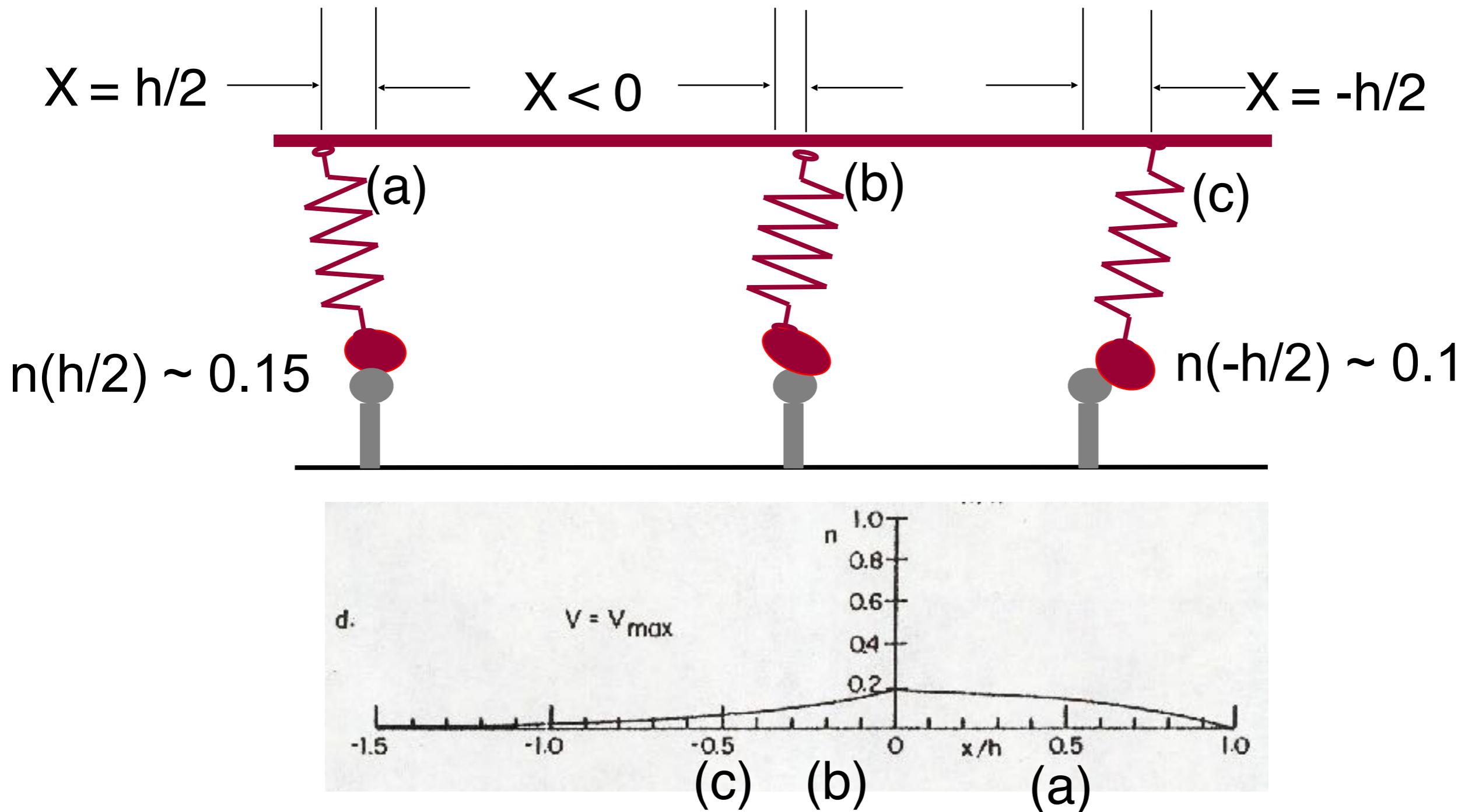
In isometric conditions ($V=0$), for given distances between $X = 0$ and $X = h$, there is a high probability of attachment of the A sites to the myosin. Attached XBs with positive distortion are "pullers".

Results for Huxley '57 model



As velocity increases ($V>0$), probability of attachment of the A site to the myosin can be above zero for $X<0$ because XB_s may attach between $X=0$ and $X=h$ and be dragged to negative distortions.

Results for Huxley '57 model



As velocity increases ($V>0$), the average distortion of the attached XBs decreases (less positive or more negative). At V_{max} the "pullers" ($X>0$, i.e. (a)) and "dragger" ($X<0$, i.e. (b)) cancel so that net tension $T = 0$. Detached XBs don't contribute.

To find the Force-Velocity relation, define force per single XB as

$$force_{XB} = kx$$

Expected value of tension for all A sites, both attached and detached:

Force of attached A site

$$\langle T_{XB} \rangle = \int_{-\infty}^{\infty} \left\{ kx \hat{n}(x) + 0 \cdot [\hat{h}(x) - \hat{n}(x)] \right\} dx$$

Attached A sites

Force of detached A site

Detached A sites

$$1 = \int_{-\infty}^{\infty} \left\{ \hat{n}(x) + [\hat{h}(x) - \hat{n}(x)] \right\} dx$$

True p.d.f. of all A site being at distance = x

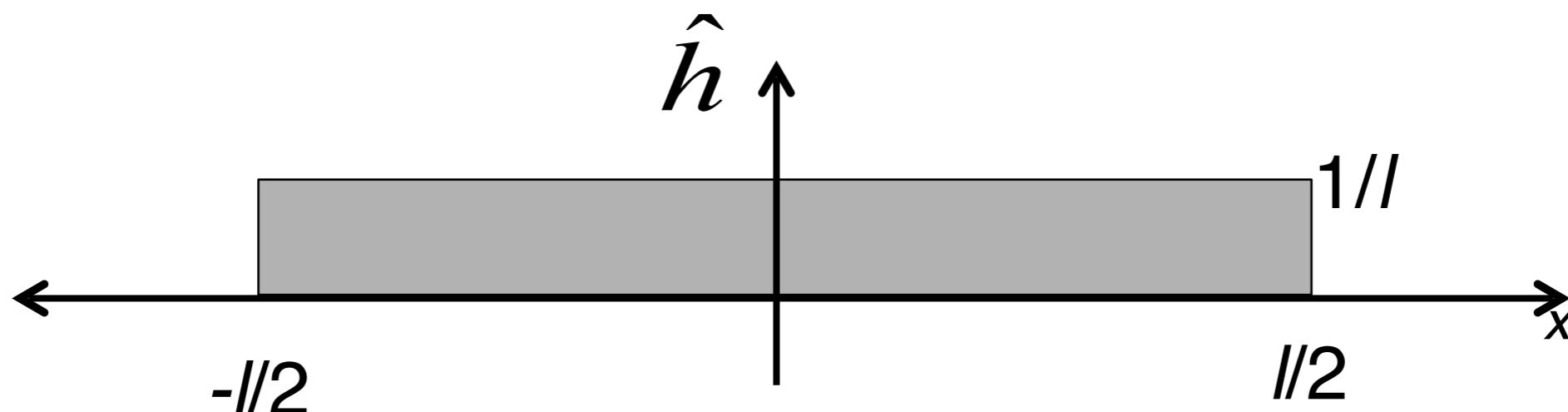
Recall these features of the model:

$$\hat{n}(x) = n(x) \cdot \hat{h}(x)$$

Conditional probability of an A site having an attached XB given its distance is x from the nearest equilibrium XB position

A p.d.f. describing likelihood of A sites being distance x from the nearest equilibrium XB position

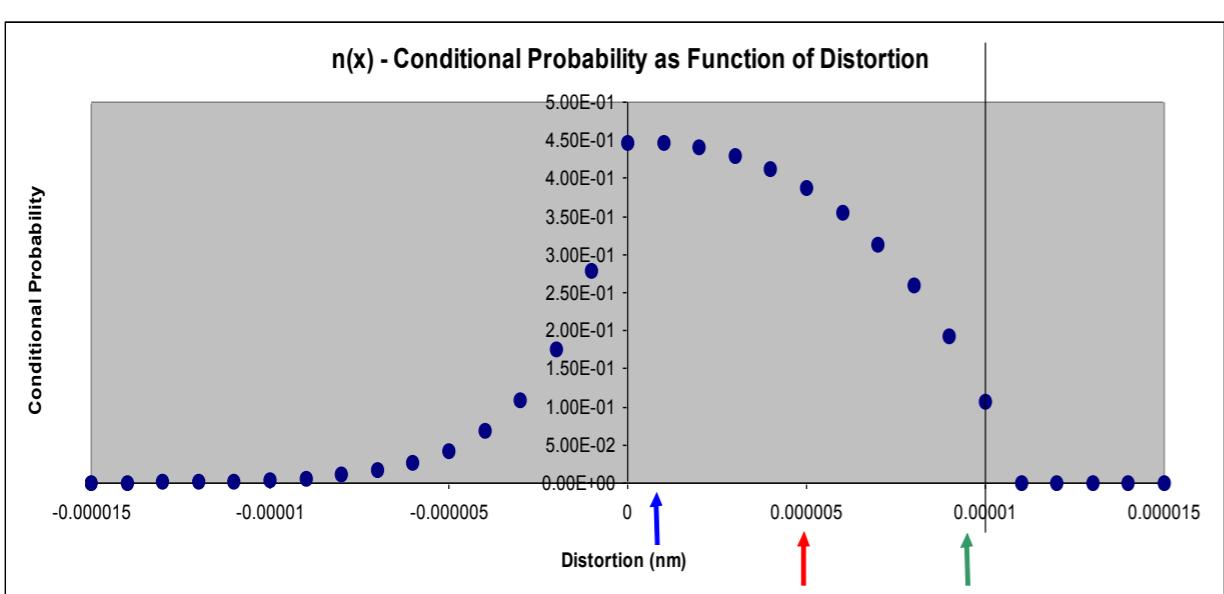
Model assumes \hat{h} is constant over all possible x values between $-l/2$ and $l/2$ as shown below:



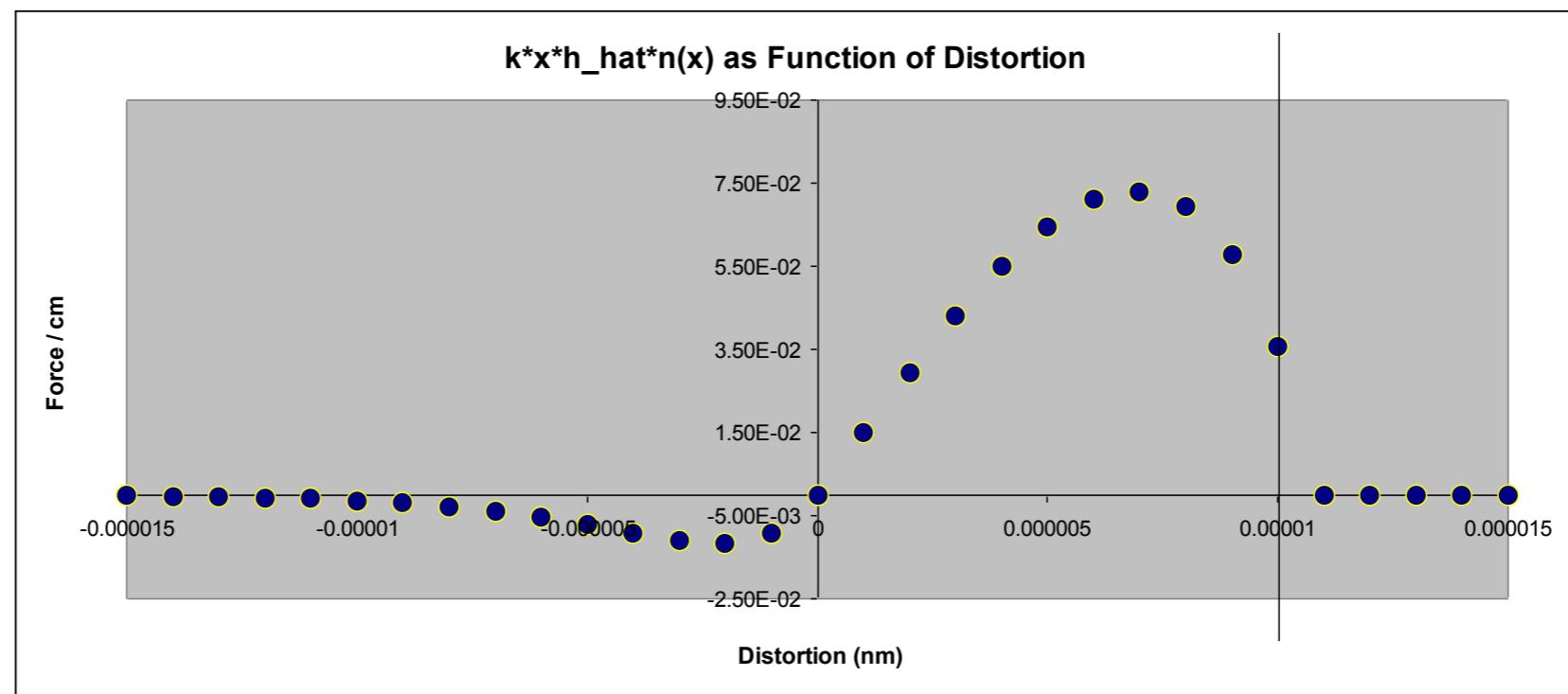
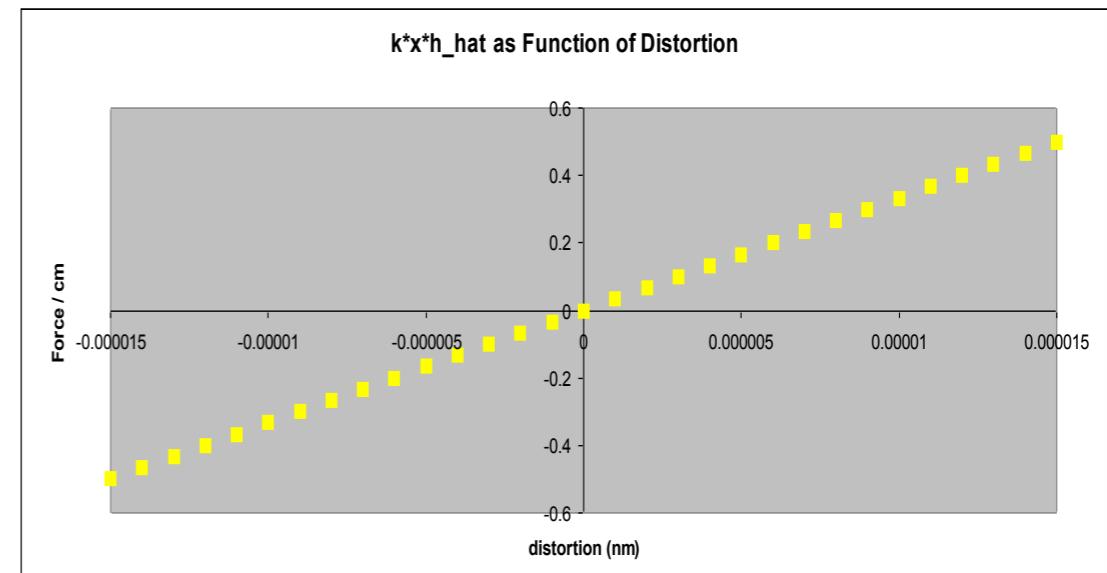
Multiply to help compute $\langle T_{XB} \rangle$

$n(x)$

$kx \bullet \hat{h}(x)$



X



Multiplying the terms produces:

$$\hat{n}(x) = \begin{cases} n(x)/l; & -l/2 < x < l/2 \\ 0 & ; \quad otherwise \end{cases}$$

Then substituting into expected value of force:

$$\begin{aligned} \langle T_{XB} \rangle &= \int_{-\infty}^{\infty} kx\hat{n}(x)dx \\ &= \int_{-l/2}^{l/2} \frac{kx}{l} n(x)dx \end{aligned}$$

Substitute for $n(x)$ and integrate to get:

$$\langle T_{XB} \rangle = \frac{f_1}{f_1 + g_1} \frac{kh^2}{2l} \left\{ 1 - \frac{V}{\phi} (1 - e^{-\frac{\phi}{V}}) \left[1 + \frac{1}{2} \left(\frac{f_1 + g_1}{g_2} \right)^2 \frac{V}{\phi} \right] \right\}$$

For isometric force, set $v=0$ to get:

$$\langle T_{XB}^{\max} \rangle = \frac{f_1}{f_1 + g_1} \frac{kh^2}{2l}$$

Now normalize force by isometric force to get:

$$T / T_{\max} = \frac{\langle T_{XB} \rangle}{\langle T_{XB}^{\max} \rangle} = \left\{ 1 - \frac{V}{\phi} \left(1 - e^{-\frac{\phi}{V}} \right) \left[1 + \frac{1}{2} \left(\frac{f_1 + g_1}{g_2} \right)^2 \frac{V}{\phi} \right] \right\}$$

$$\phi = \frac{h}{S} (f_1 + g_1)$$

These parameters give best fit to experimental data at right

$$\frac{g_1}{f_1 + g_1} = \frac{3}{16} \quad \frac{g_2}{f_1 + g_1} = 3.919$$

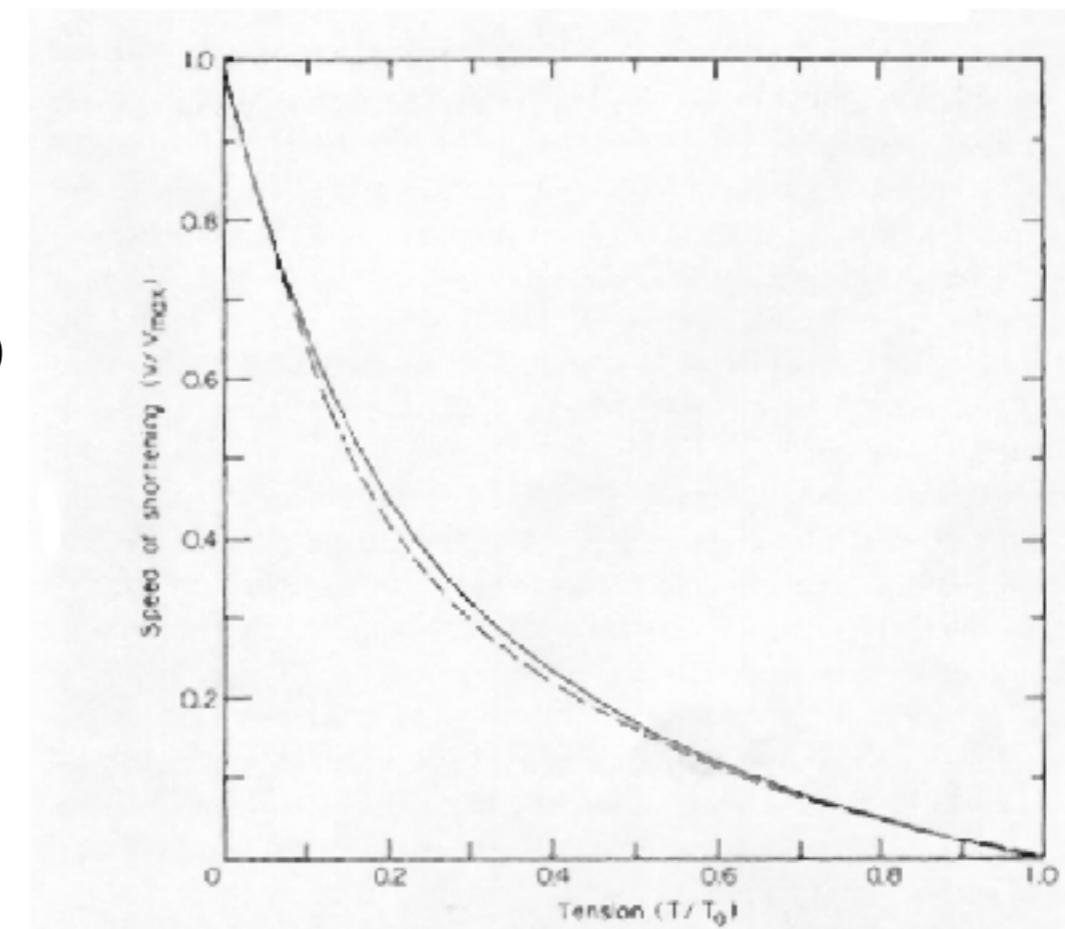


Fig. 4.5. Speed of shortening vs. tension. Solid line shows result of experiments (Hill equation, eq. 1.4 with $a/T_0 = 1/4$), broken line shows Huxley 1957 theory with constants chosen to provide best fit. From A. F. Huxley (1957).

Successes of model -

- Good framework for modeling XB cycling
- Reproduces observed Force-Velocity relationship
- Reproduces energy use vs. tension (tension-heat) relationship
- Superb first attempt given the knowledge in 1957

Problems -

- XB cycle is too simplistic
- Restrictive set of conditions
 - isotonic, constant velocity
 - full activation
- Cycling rate increases with lengthening causing usage in disagreement with experimental results increased ATP
- Overall ATP hydrolysis is too high

Other Cardiac Myofilament Models

Cross-Bridge Models

- Huxley-type cross-bridge models (PDEs)
 - extended with additional XB states, e.g. 5-state model (Pate and Cooke, 1989)
 - Allow more realistic ATP hydrolysis rates
 - Separate force-generation from XB binding
- Non-spatially explicit simplifications of XB cycling
 - Fading memory model (Hunter)
 - Distribution moment model (Zahalak)
 - Crossbridge distortion model (Razumova)

Myofilament Activation Models

- Models of cooperative thin filament activation
 - empirical models (Rice, Hunter)
 - mechanistic models of nearest neighbor interactions (Rice, Campbell)
 - XB-XB, RU-RU, XB-RU
- Models with length-dependent activation

Pate & Cooke, 1986

$$V dn_i(x)/dx = \sum_{\substack{j=1 \\ j \neq i}}^m R_{ji}(x) n_j(x) - \sum_{\substack{j=1 \\ j \neq i}}^m R_{ij}(x) n_i(x), \quad i = 1, \dots, m.$$

- To calculate reverse rates, use the Gibbs relation:

$$R_{ij}(x) = R_{ji}(x) \exp((A_i(x) - A_j(x))/kT)$$

Where A is the free energy of a state (i or j). Force per unit length can be calculated as:

$$F = 1/D \sum_i \int_a^b n_i(x) F_i(x) dx. \quad F_i(x) = k_i(x - a_i)$$

m = number of possible states

n = fraction of crossbridges in state *i* with distortion *x*

V = filament sliding velocity

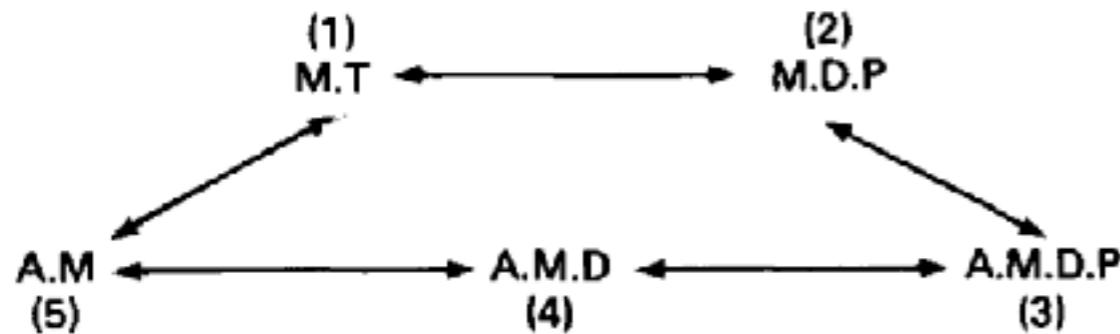
R_{ij} = Transition rate from state *i* to state *j*, function of distortion

D = length between myosin binding sites on actin

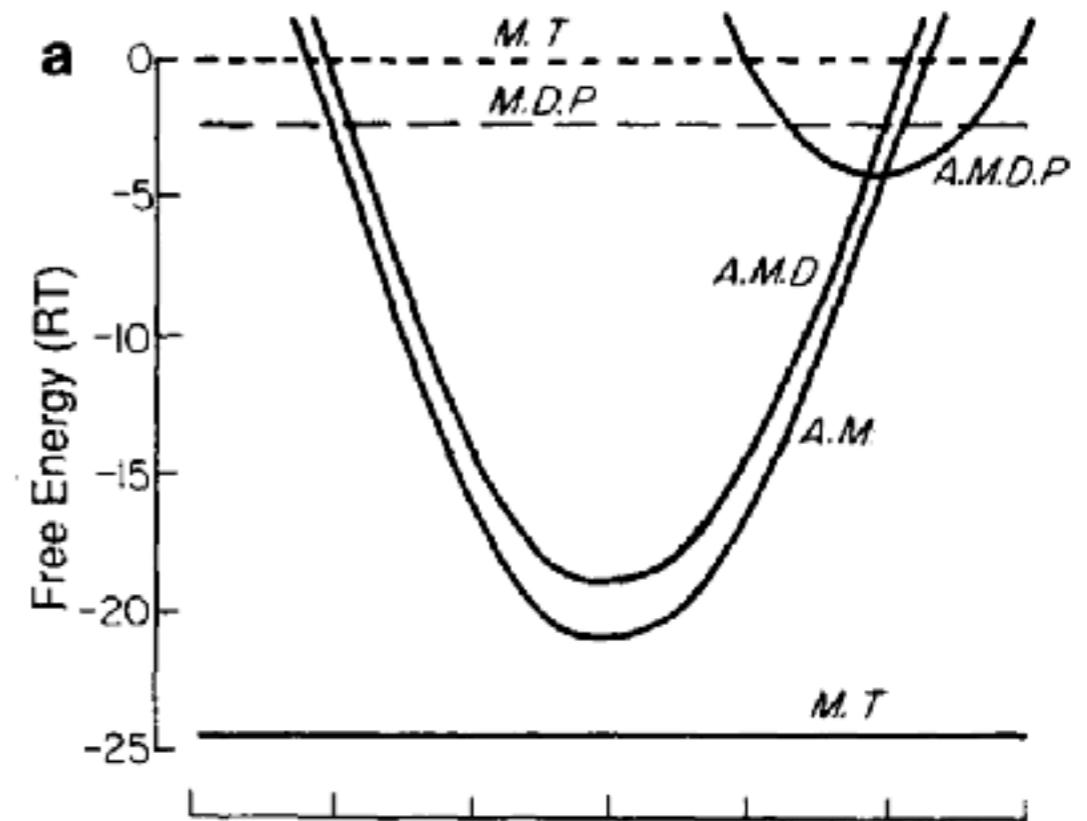
k – chosen to create reasonable force outputs

a_i = value of distortion producing 0 force

5-state model (Pate and Cooke, 1989)



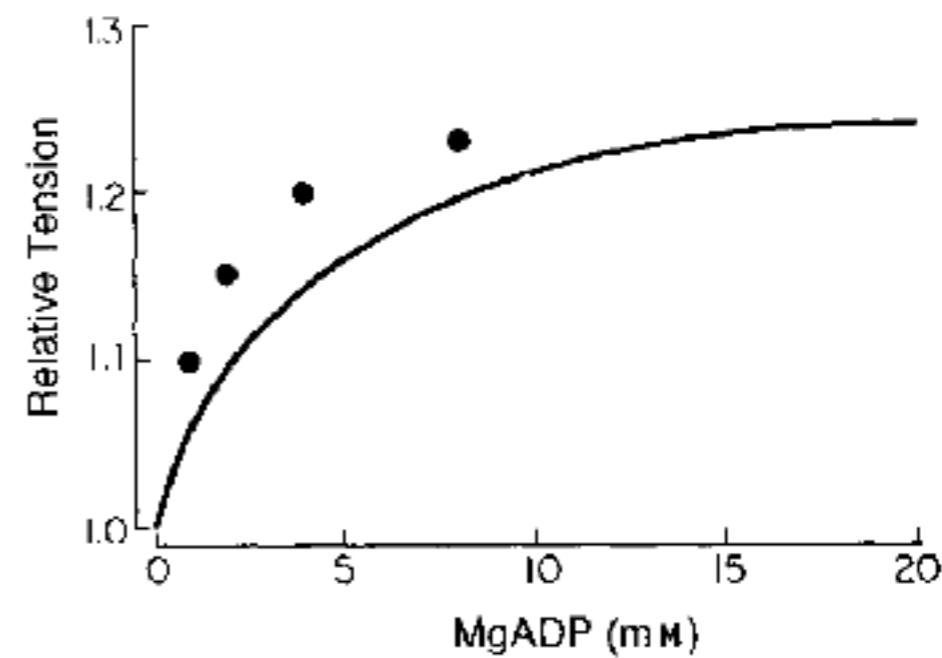
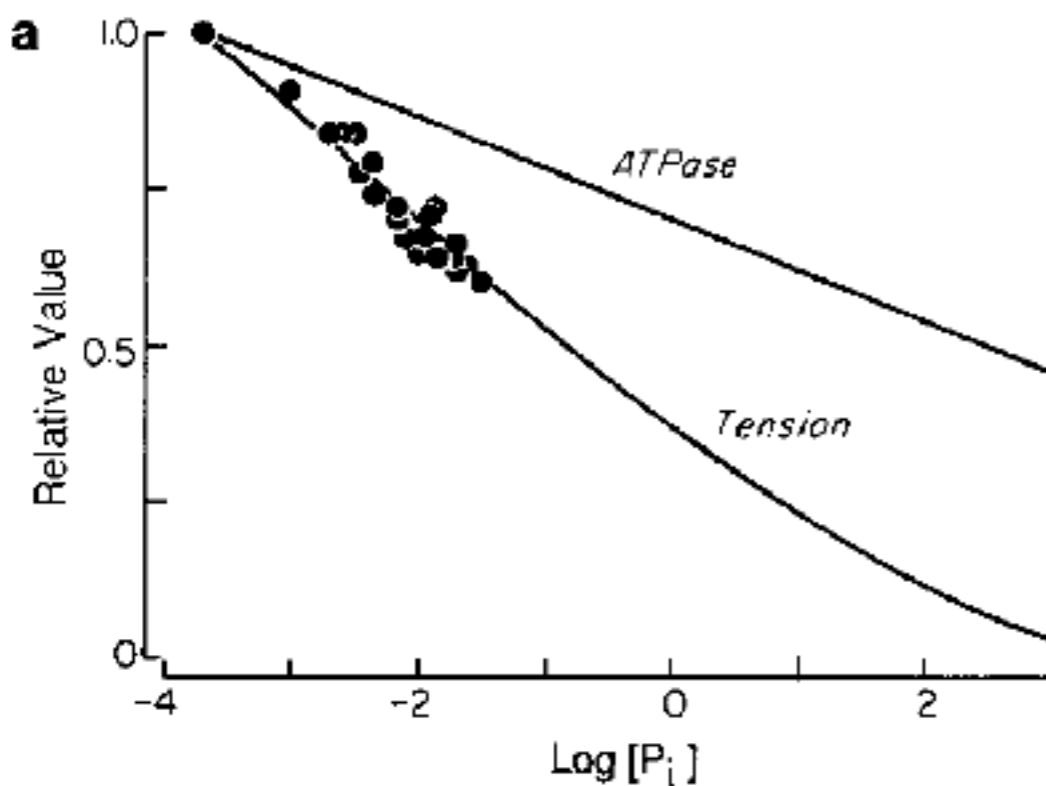
- M = Myosin
- A = Actin
- P = inorganic phosphate (Pi)
- D = ADP
- T = ATP



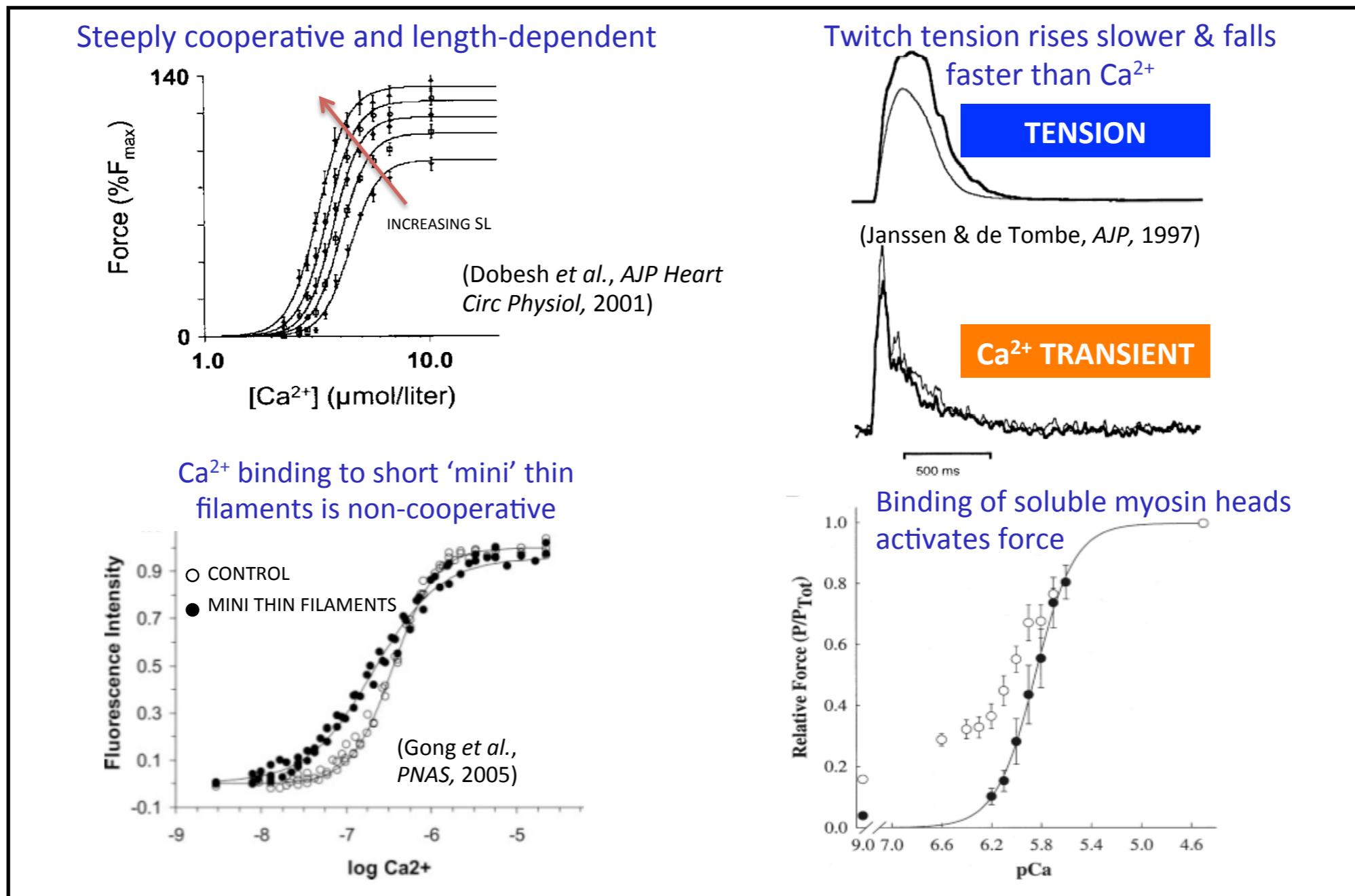
Free energy of all states as a function of crossbridge distortion

Takeaways

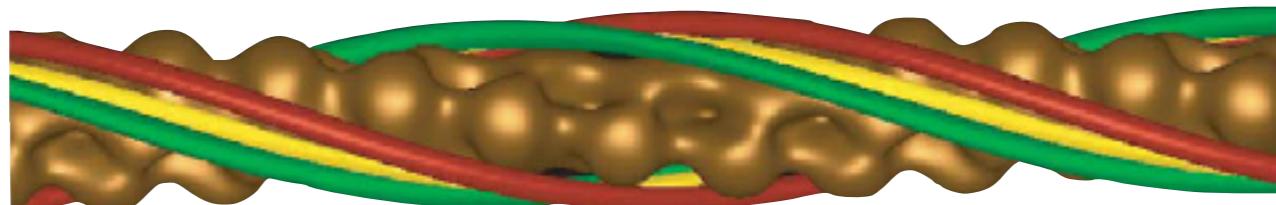
- Was able to predict a variety of experimental findings testing force development for different concentrations of ATP, ADP, and Pi
- Focuses only on crossbridge cycling, not thin filament activation



Properties of Cardiac Myofilament Activation

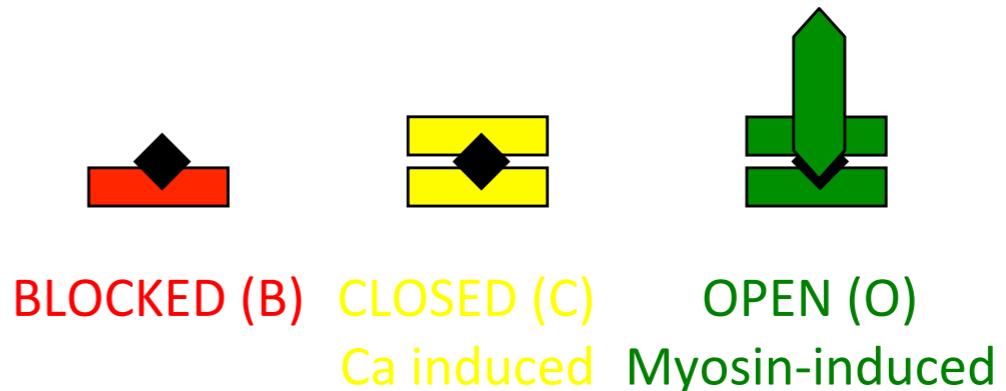


Nearest-Neighbor Interactions on the Thin Filament

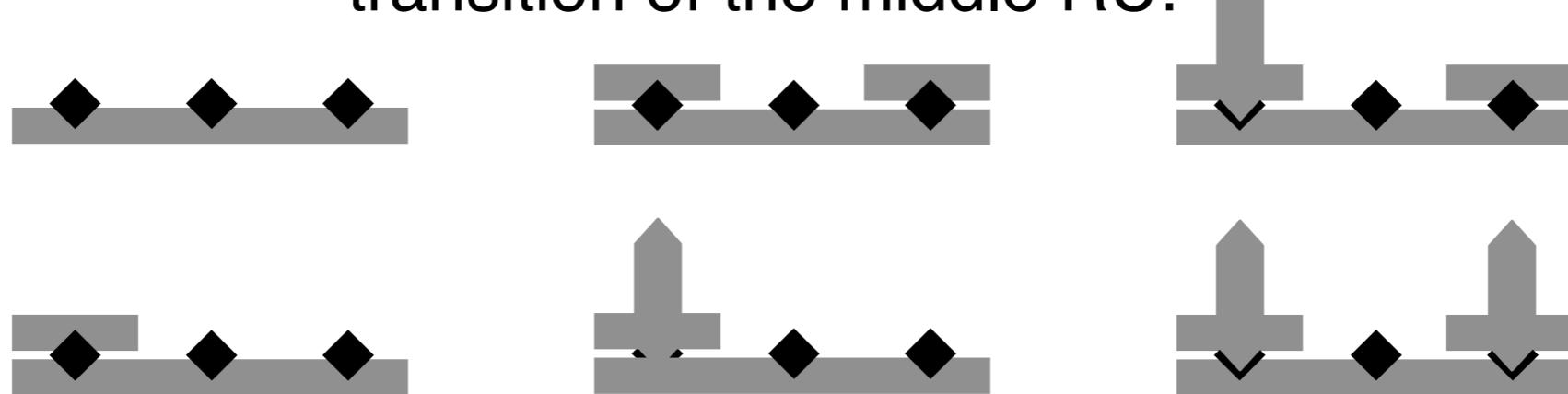


(Craig & Lehman, *J Mol Biol*, 2001)

Three possible states of tropomyosin in each regulatory unit:

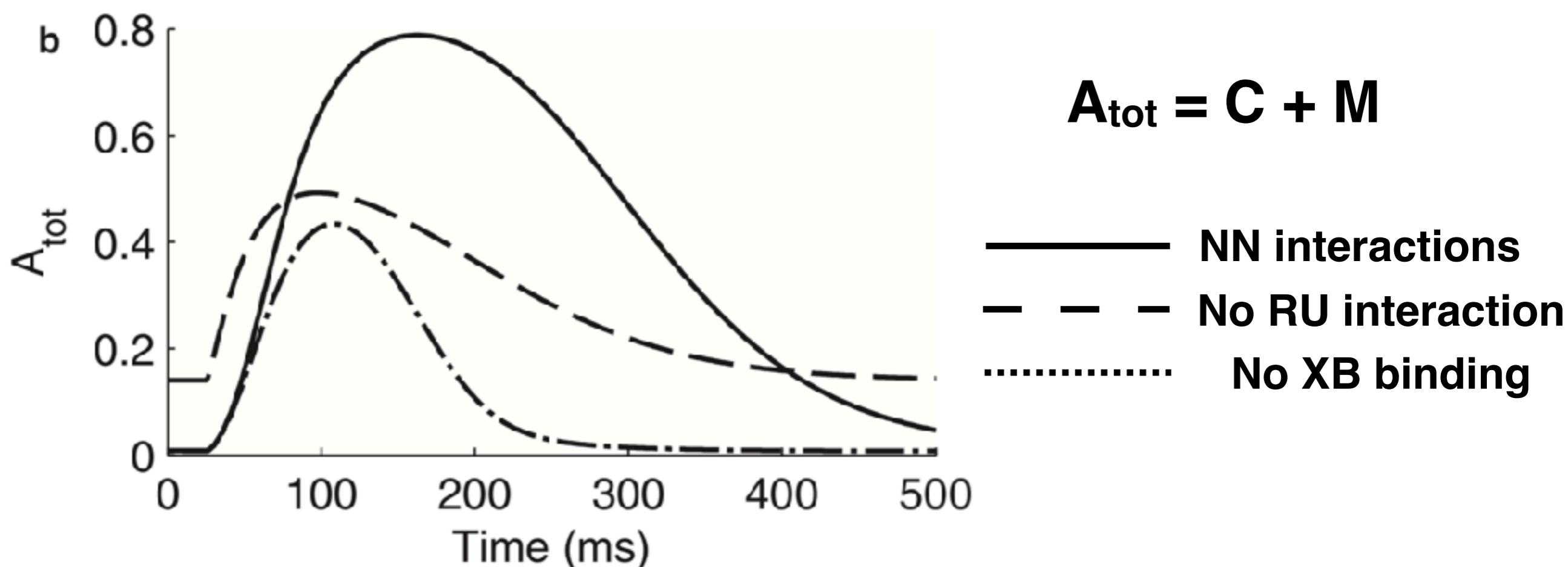
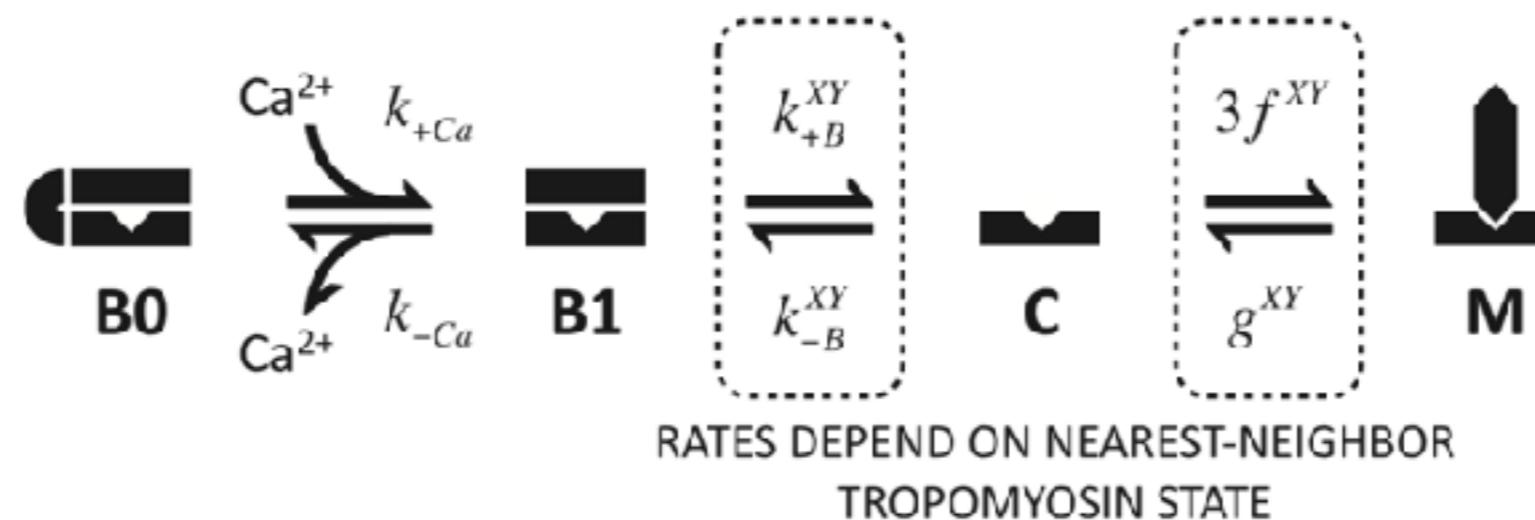


Six distinct nearest-neighbor configurations influence the transition of the middle RU:

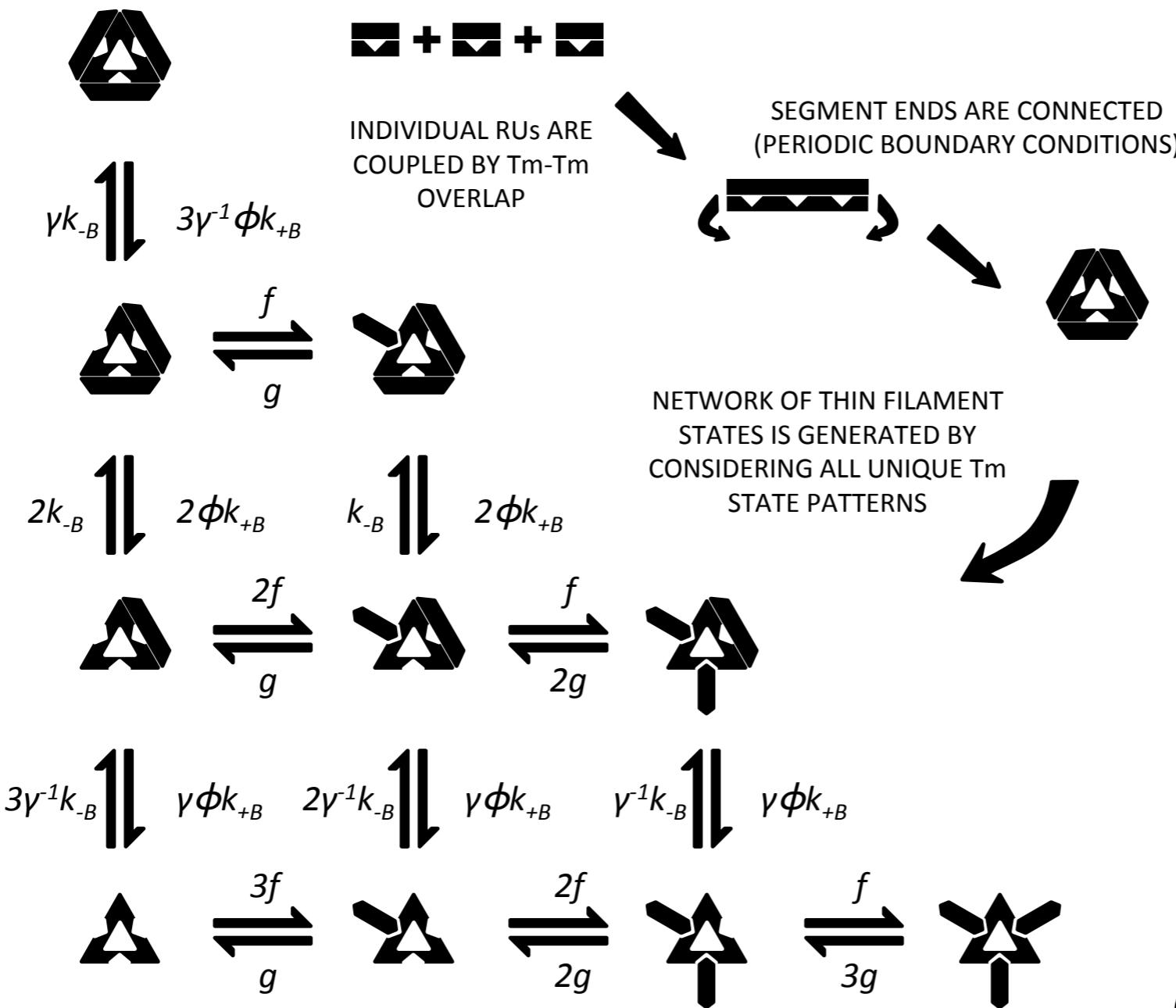


(Campbell et al., *Biophys J*, 2010)

Nearest-Neighbor Interactions on the Thin Filament



Incorporating Spatial detail into thin filament model

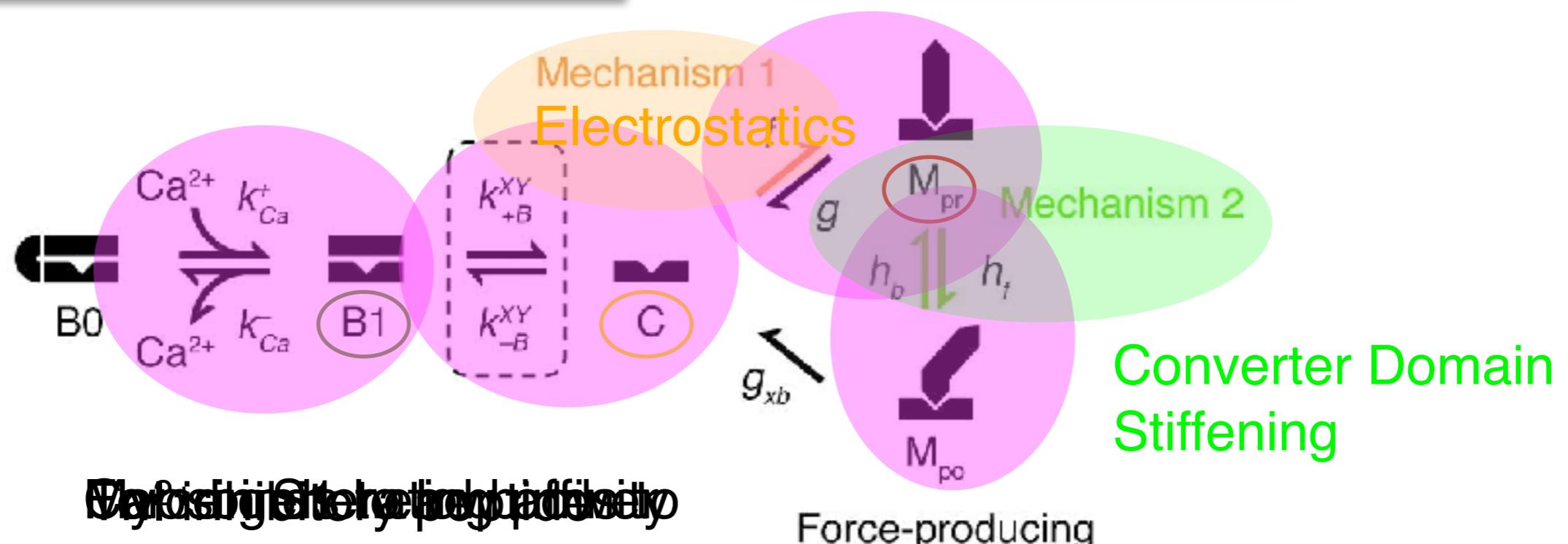
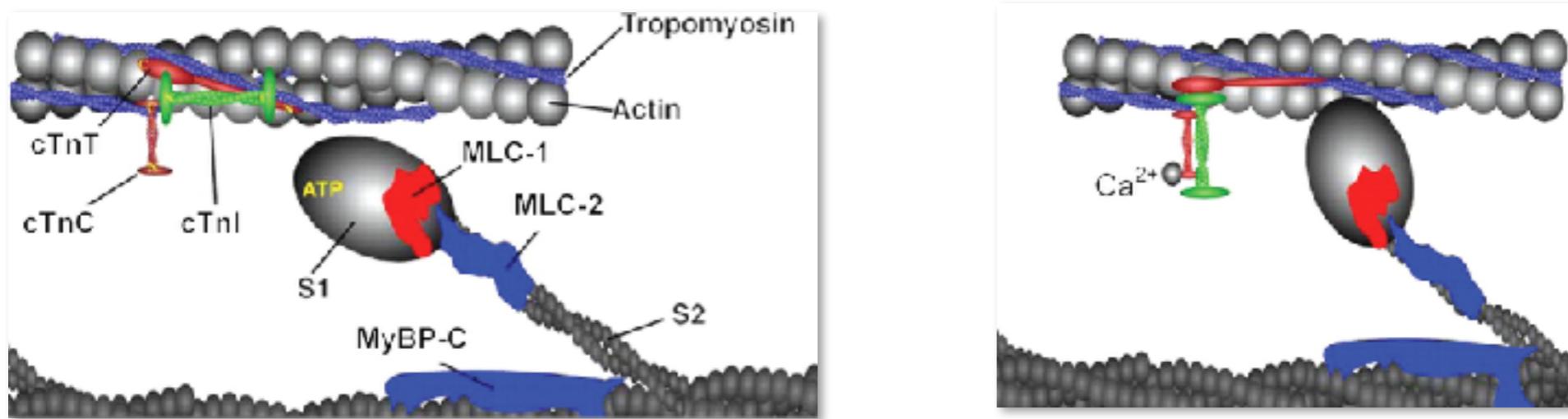


For n=3, there are
10 states and 12
thermodynamically
constrained
transitions

For n=26...

(

Models of Myofilament Activation



Myosin heads, being stiffened
at the C site, displace
tropomyosin to
displace ...

Modeling Cooperative Thin Filament Activation

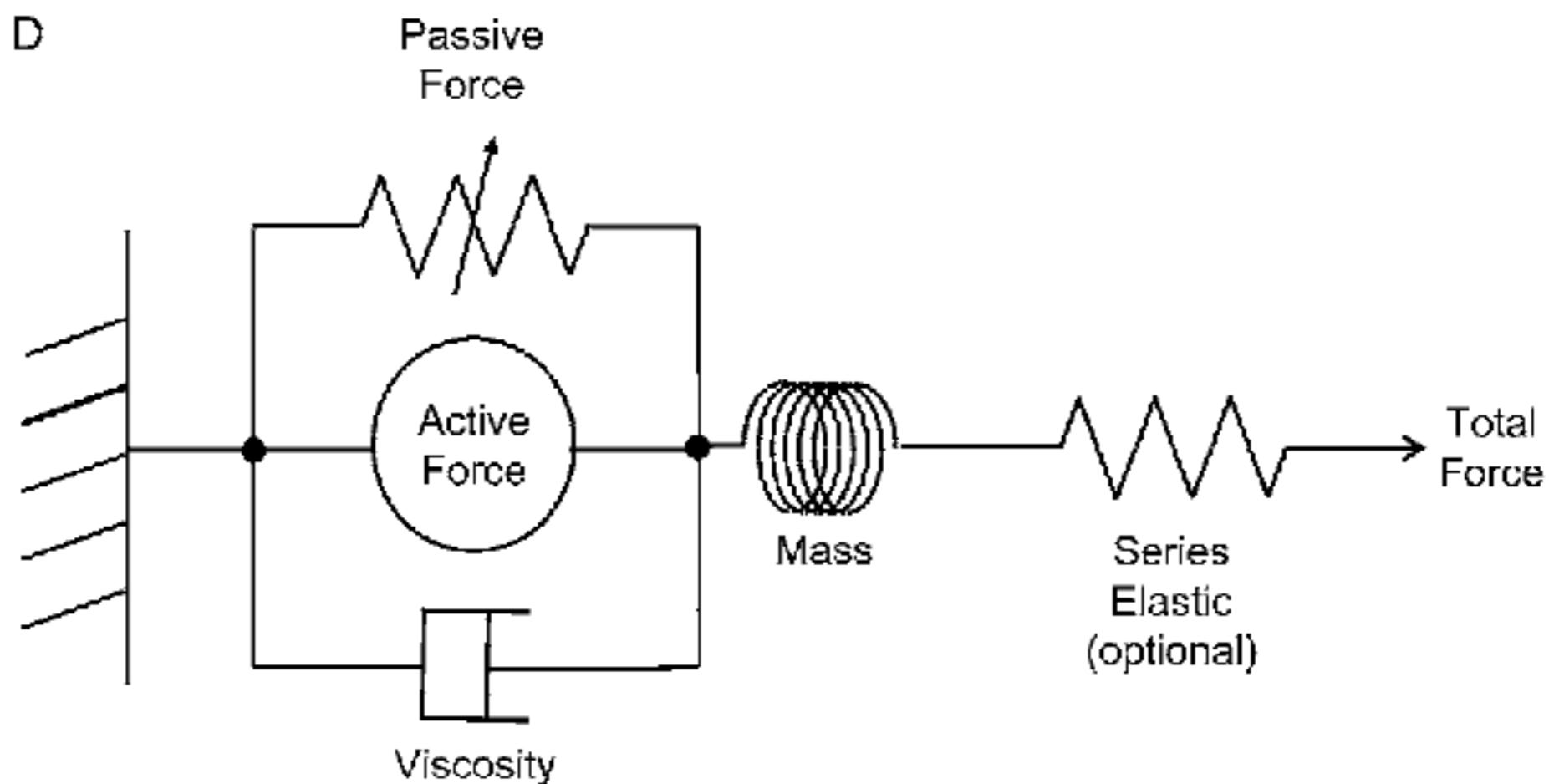
- RU-RU: nearest-neighbor interactions produced by the overlap of adjacent tropomyosin units along the thin filament
- XB-XB: binding of one myosin S1 head increases the binding rate of neighboring crossbridges
- RU-XB: cycling Ca^{2+} crossbridges have been shown to increase the Ca^{2+} affinity of troponin

Which of these mechanisms is sufficient/ necessary to accurately simulate experimental data?

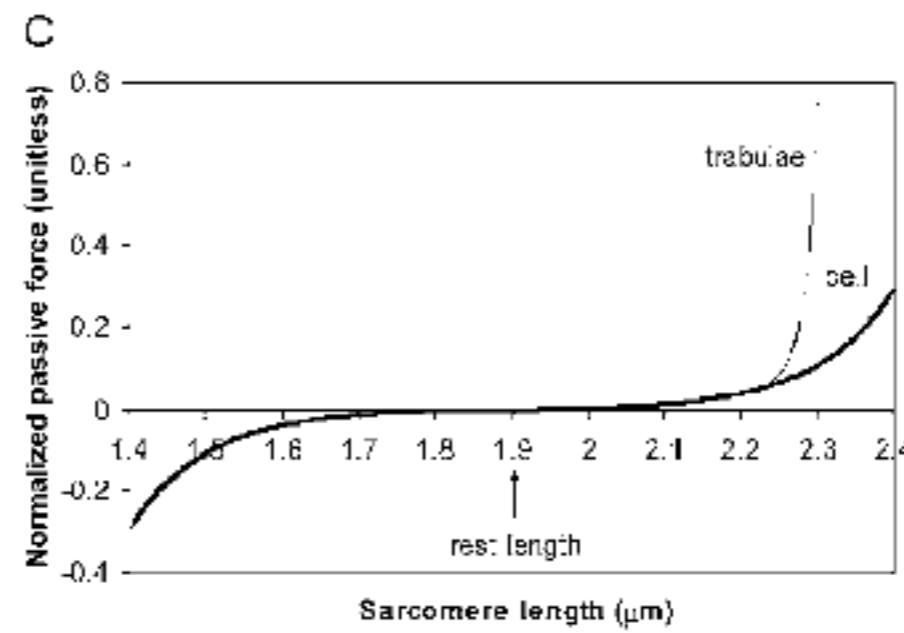
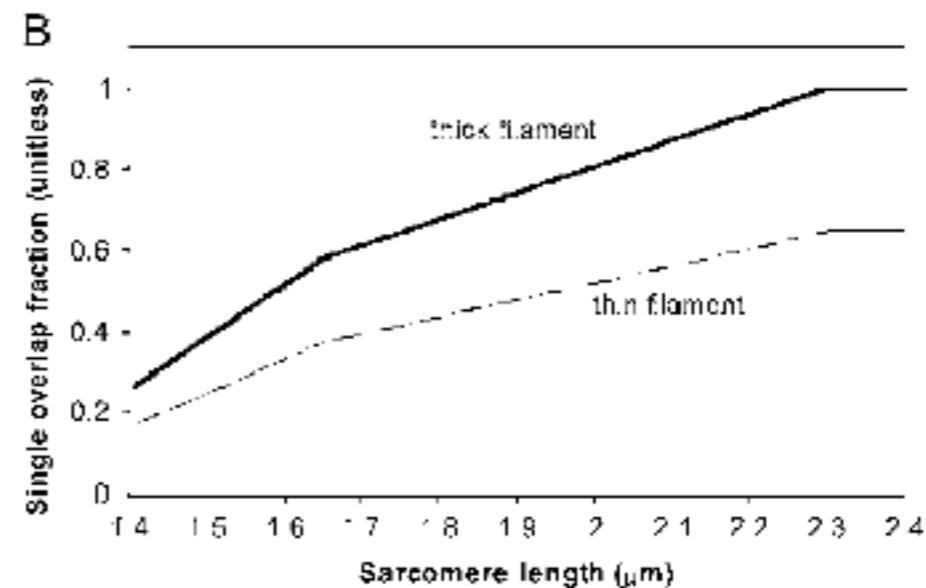
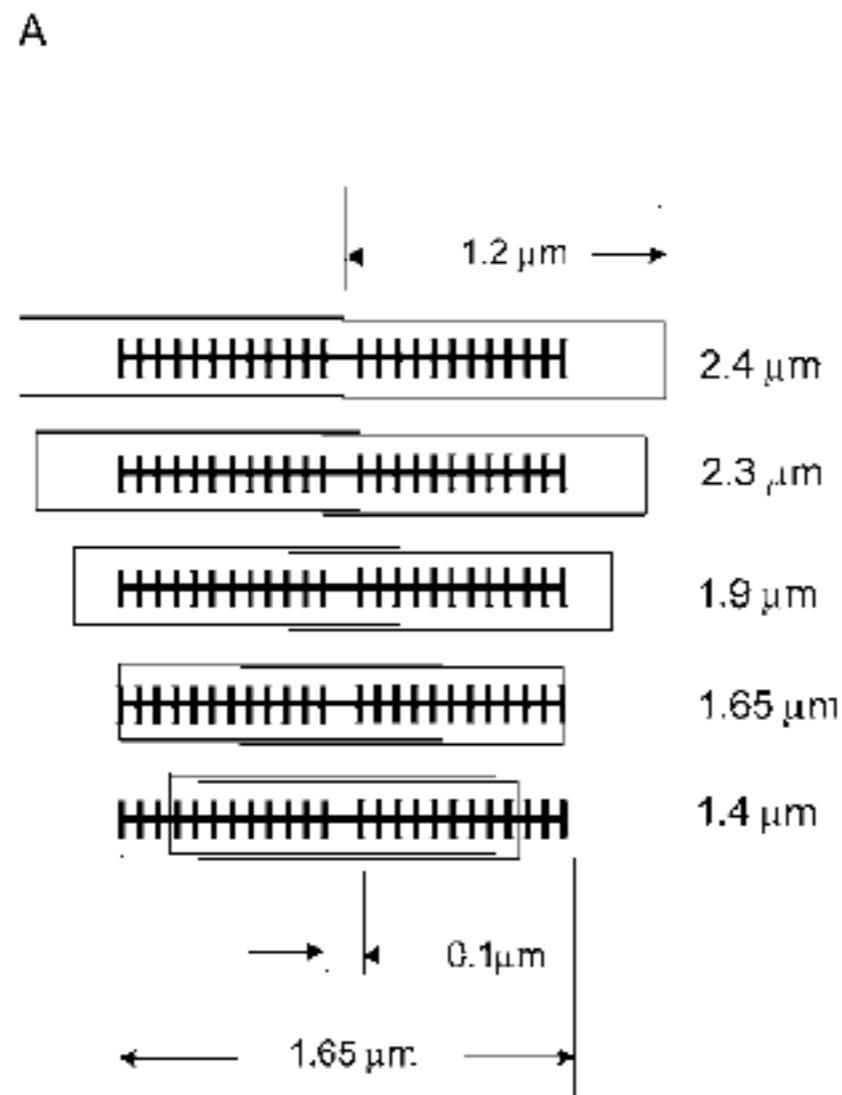
In order to fully model cooperativity, models must have explicit spatial consideration of nearest-neighbor cooperativity

Rice 2008

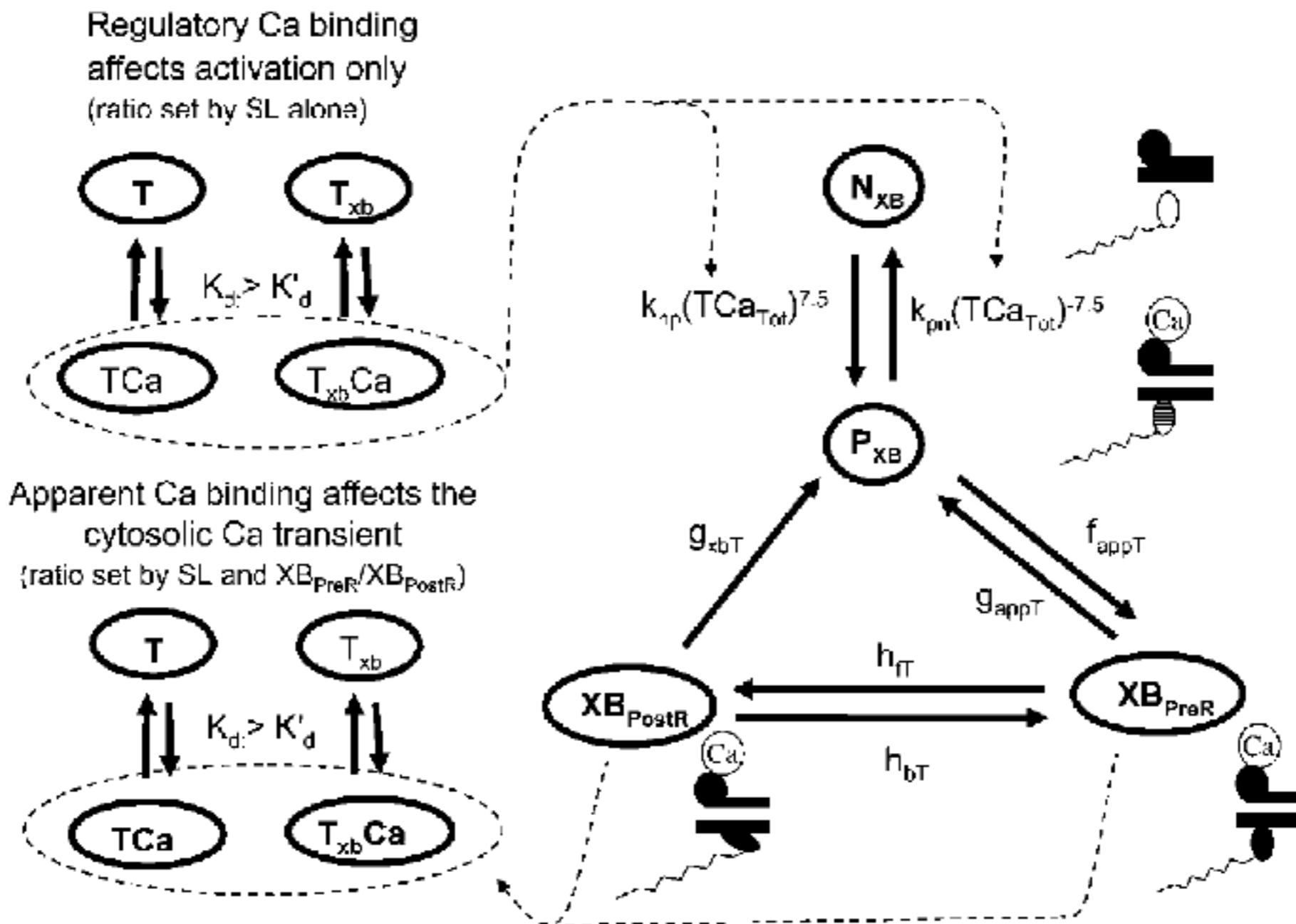
- Uses phenomenological approximations of biophysical processes to create an ODE model without mean-field approximations



Length Dependence -myofilament overlap



Model Formulation



Sarcomere Length Dependence

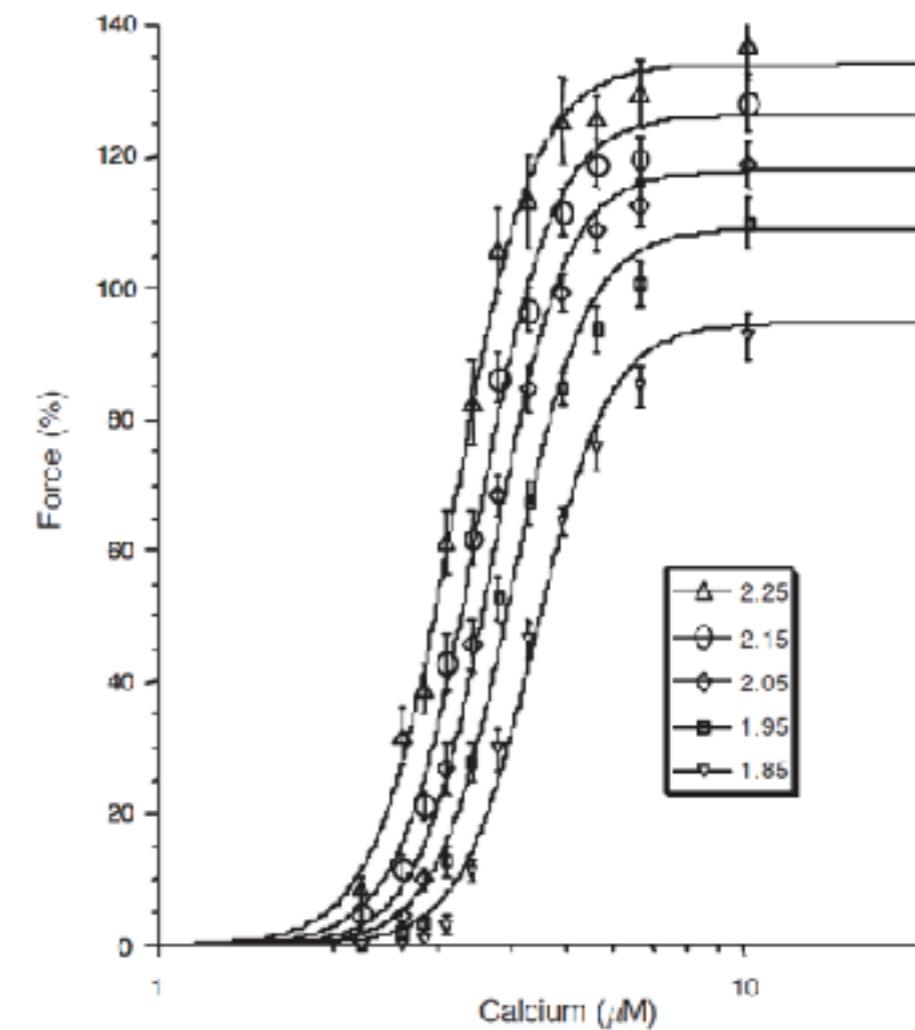
- The model alters Ca^{2+} binding rates using the overlap fraction as well as the fraction of strongly bound XBs:

$$Fract_{\text{SBXB}} = \frac{XB_{\text{PreR}} + XB_{\text{PostR}}}{XB_{\text{PreR}}^{\text{Max}} + XB_{\text{PostR}}^{\text{Max}}}.$$

$$\begin{aligned} Trop_{\text{Apparent}}(x) &= (1 - SOVF_{\text{thin}}(x)) \times Trop_L + SOVF_{\text{thin}}(x) \\ &\quad \times (Fract_{\text{SBXB}} \times Trop_H \\ &\quad + (1 - Fract_{\text{SBXB}}) \times Trop_L). \end{aligned}$$

Modeling Length Dependent Activation

- Change in maximum Force
 - Generally modeled as a linear relationship between SL and recruitable XBs
- Change in Ca^{2+} sensitivity
 - Often empirically modeled via a function linking SL to calcium binding rate or attachment rate ("f")



Length Dependence

- Included a length-sensing feature in the calculation of f :

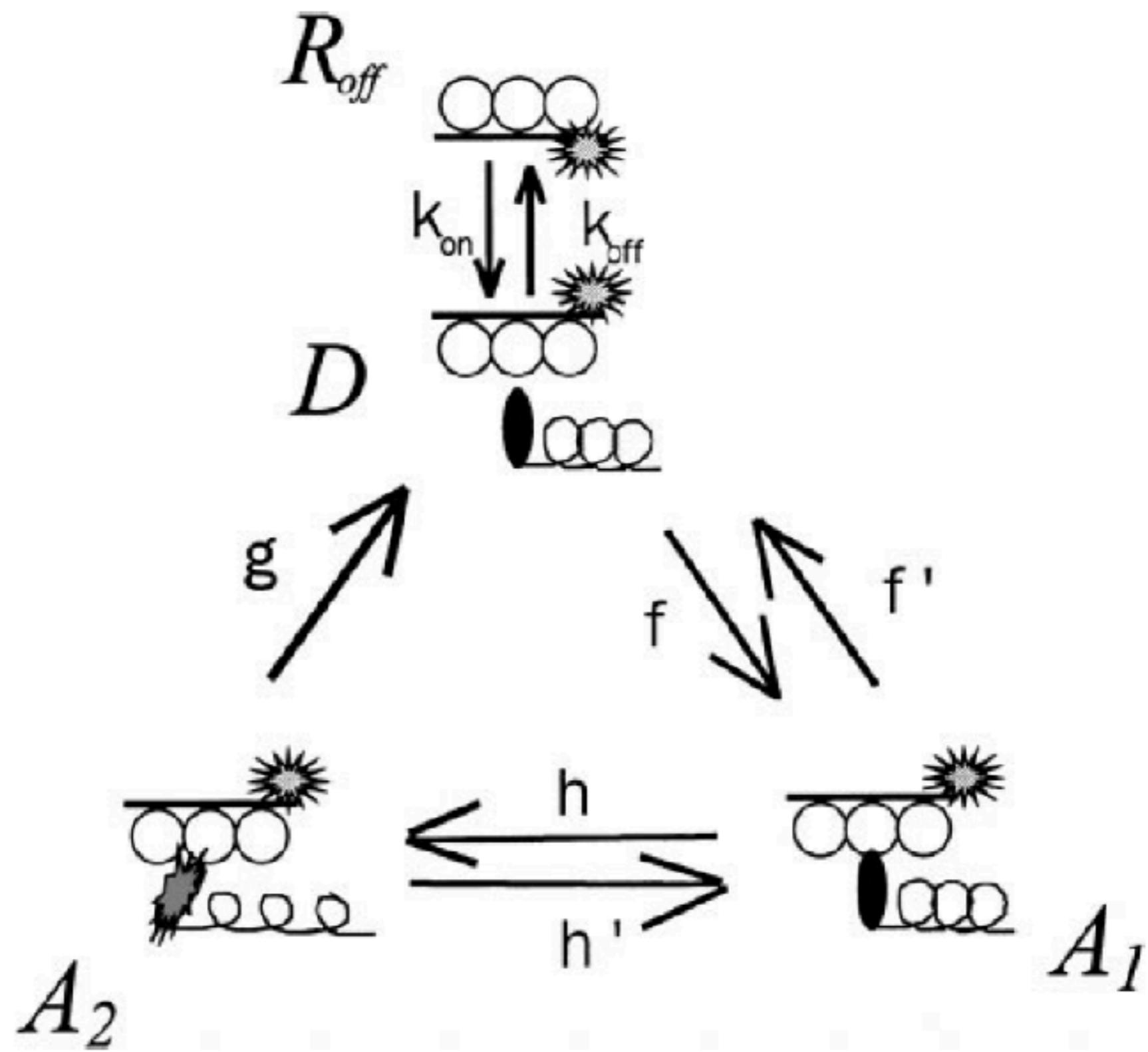
$$f_r = f_m \left(1 + \epsilon \frac{SL - SL_0}{SL_0} \right)$$

where ϵ scales the influence of length on f

- Estimated myofilament overlap by changing R_T (total number of XBs) based on SL .

Empirical formulation

Stiffness-Distortion model (Razumova, 2000)



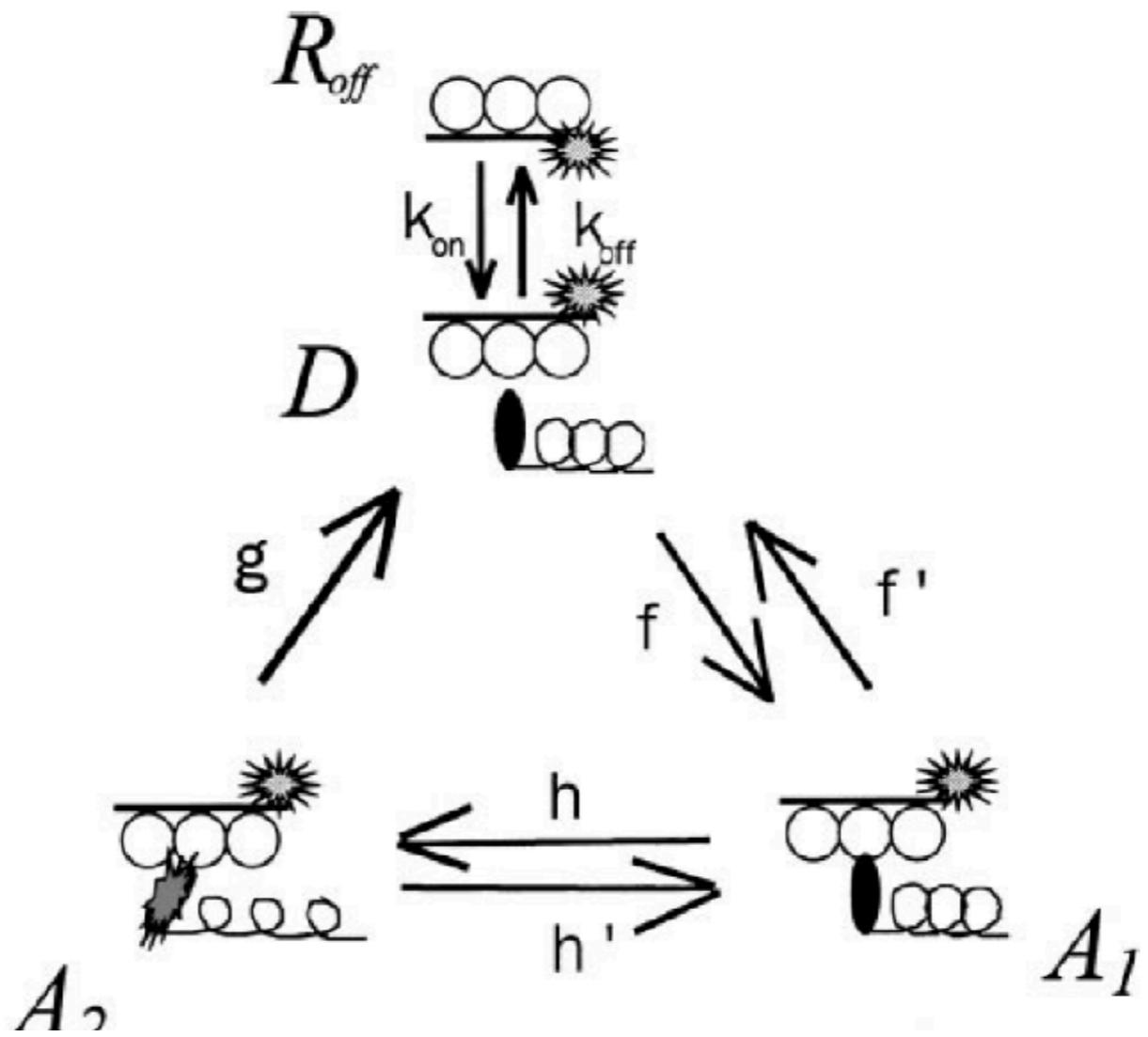
Initial Conditions

R_{off,0}	1
D₀	0
A₁₀	0
A₂₀	0

Parameters

RT	1
kon	400
koff	50
f	50
f'	400
h	8
h'	6
g	4

Stiffness-Distortion model (Razumova, 2000)



$$\dot{D}(t) = k_{on}R_{off}(t) + f'A_1(t) + gA_2(t) - (k_{off} + f)D(t)$$

$$\dot{A}_1(t) = fD(t) + h'A_2(t) - (f' + h)A_1(t)$$

$$\dot{A}_2(t) = hA_1(t) - (h' + g)A_2(t)$$

Cooperativity

- The model allows for the attachment rate f to be increased based on the attachment of neighboring XBs.

$$f = f_r \{1 + \lambda^{A_1} [e^{x_1/x_0(v-1)} - 1] + \lambda^{A_2} [e^{x_2/x_0(v-1)} - 1]\}^2$$

$$f = f_r + \left(\begin{array}{l} \text{contribution of neighboring sites,} \\ \text{neither of which has a} \\ \text{force-bearing cross bridge} \end{array} \right) + \left(\begin{array}{l} \text{contribution of neighboring sites,} \\ \text{one of which has a} \\ \text{force-bearing cross bridge} \end{array} \right) + \left(\begin{array}{l} \text{contribution of neighboring sites} \\ \text{both of which have a} \\ \text{force-bearing cross bridge} \end{array} \right)$$

λ^{A_1} and λ^{A_2} are the probabilities of finding a neighbor in one of the attached states

v is a number between 0 and 1 describing the influence of attached XBs on neighbors ($v=1$ when no cooperativity exists)

This is a largely empirical formulation.

Takeaways

- ODE system uses approximations of the PDEs that properly describe the detailed behavioral features of the system
- underlying thermodynamic constraints on kinetic relationships were not applied. Thus the distortion-dependent expressions are arbitrarily formulated.
- Uses mean-field approach: Assumes any individual unit in a population can be approximated by the mean behavior of the whole population of units