

Modeling Myofilament Dynamics

K.J. McCabe
19/06/25

simula

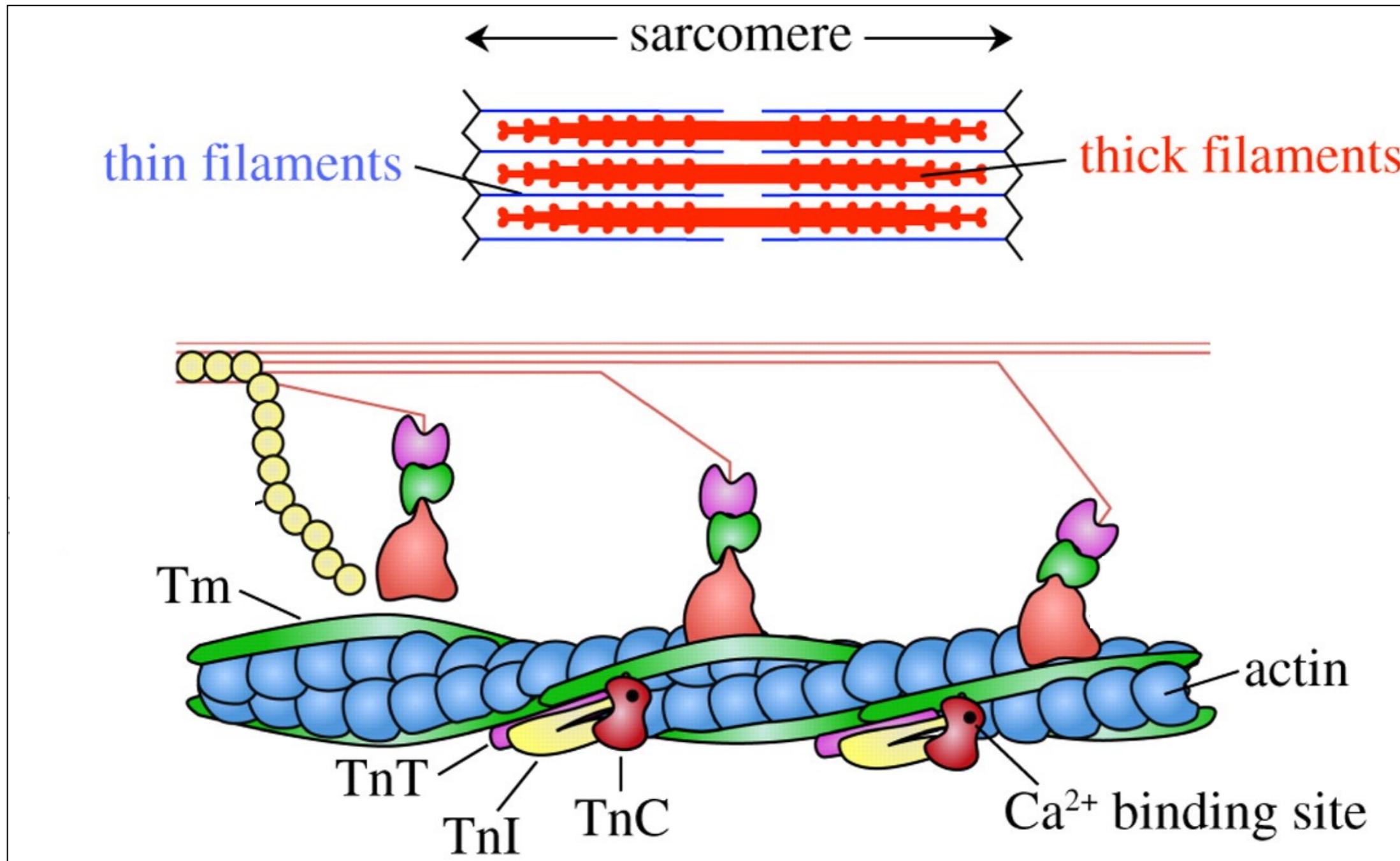


Simula-UiO-UCSD Research and PhD training programme

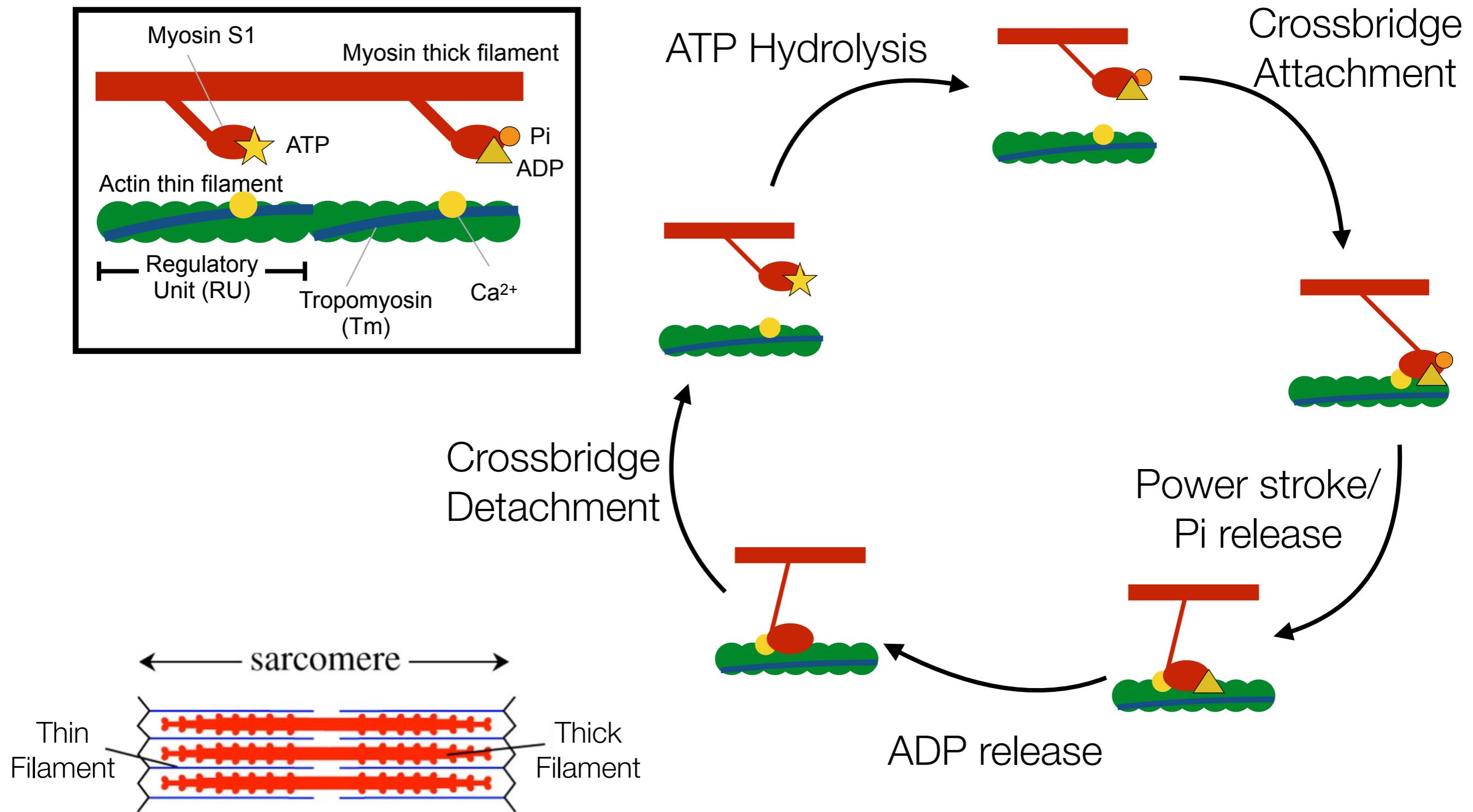
Agenda for this afternoon

- Huxley 1957 (first XB model)
- Coding Exercise - Razumova 1999 XB model
- Discussion: Rice 2008

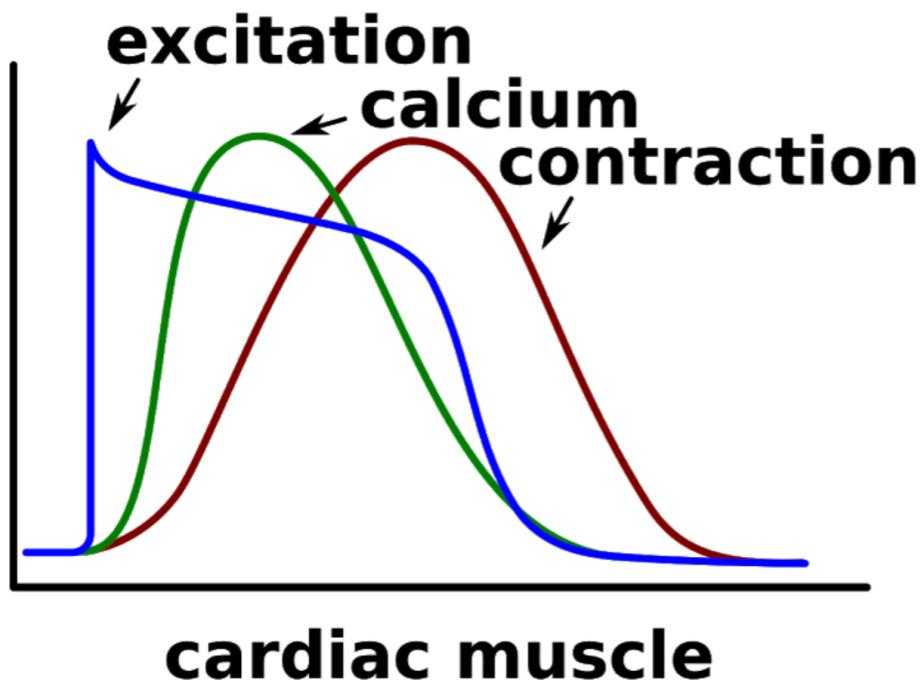
Thin filament activation



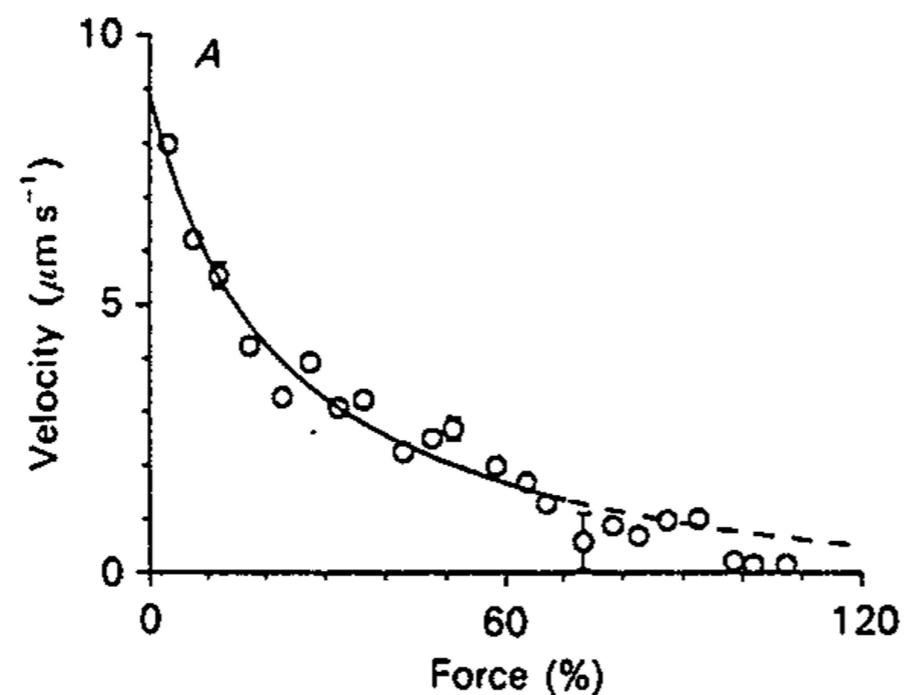
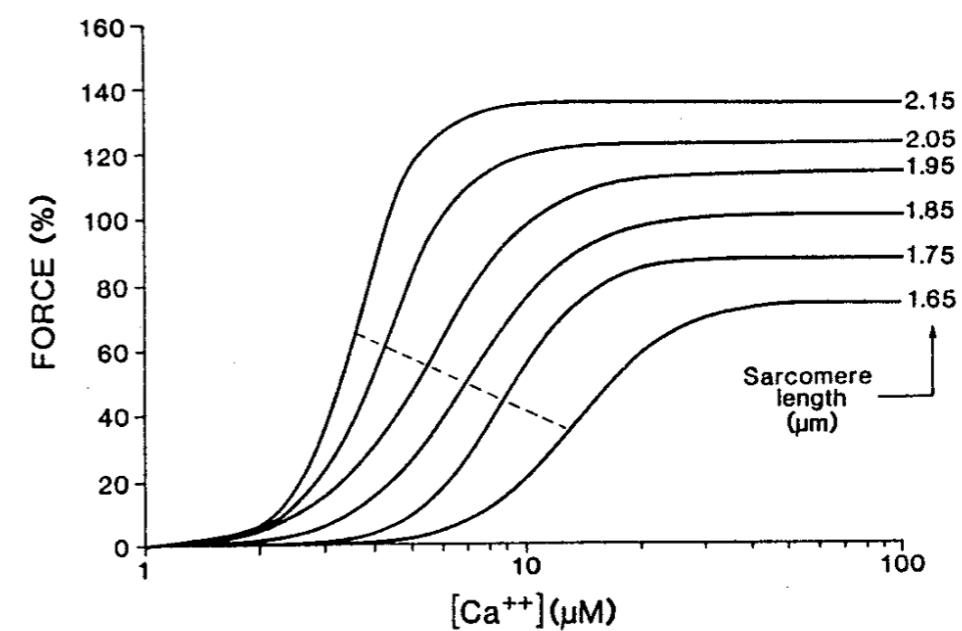
The Crossbridge cycle



Twitch tension rises slower & falls faster than Ca^{2+}



Cooperative, length Dependent activation



Inverse force-velocity relationship

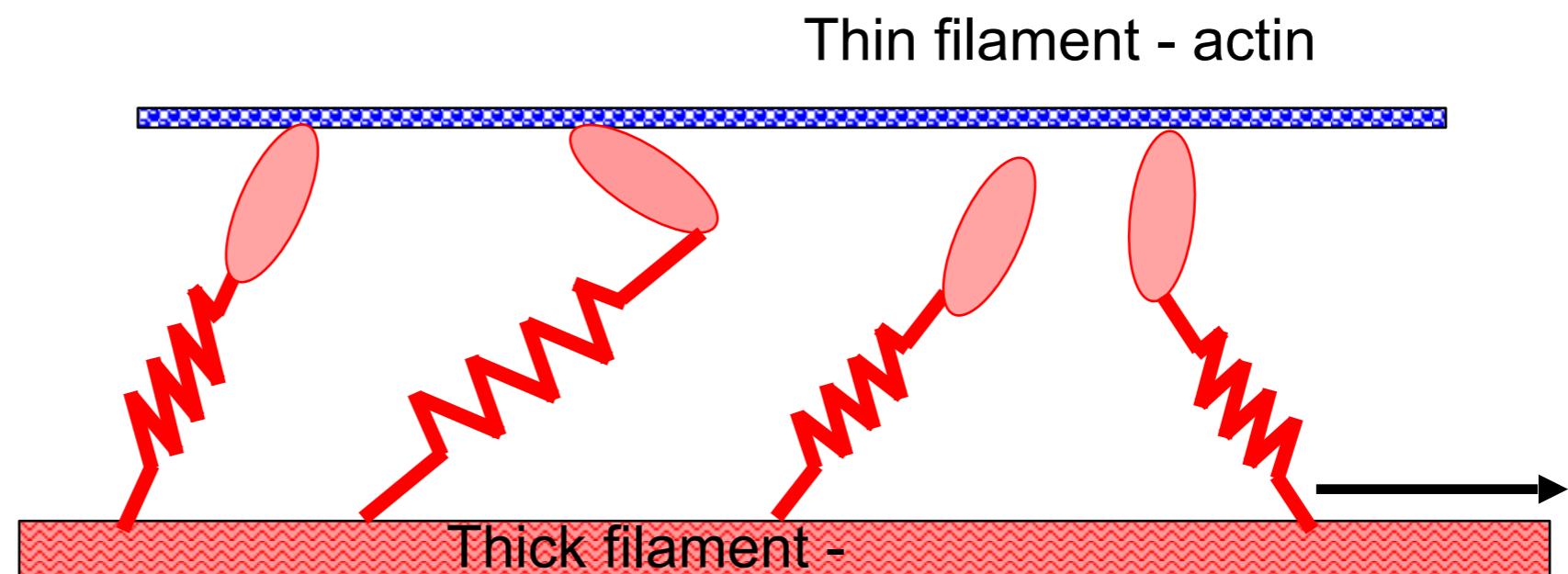
Modeling Contractile Mechanisms: Huxley 1957

**Slides adapted from
S.G. Campbell, J.J. Rice**

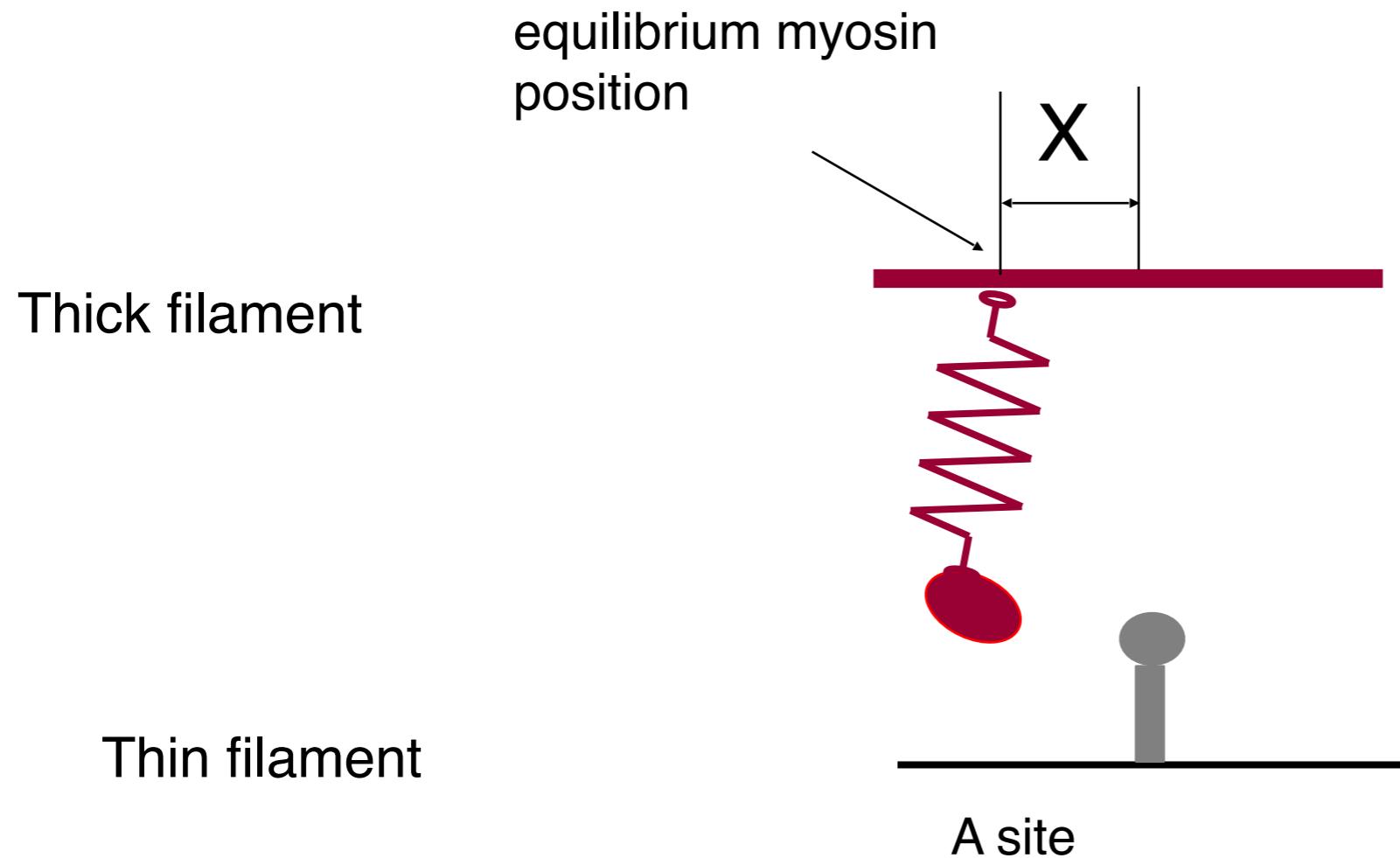
Derivation of Huxley '57 Model

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 complete full cycle to detach and hydrolyze 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

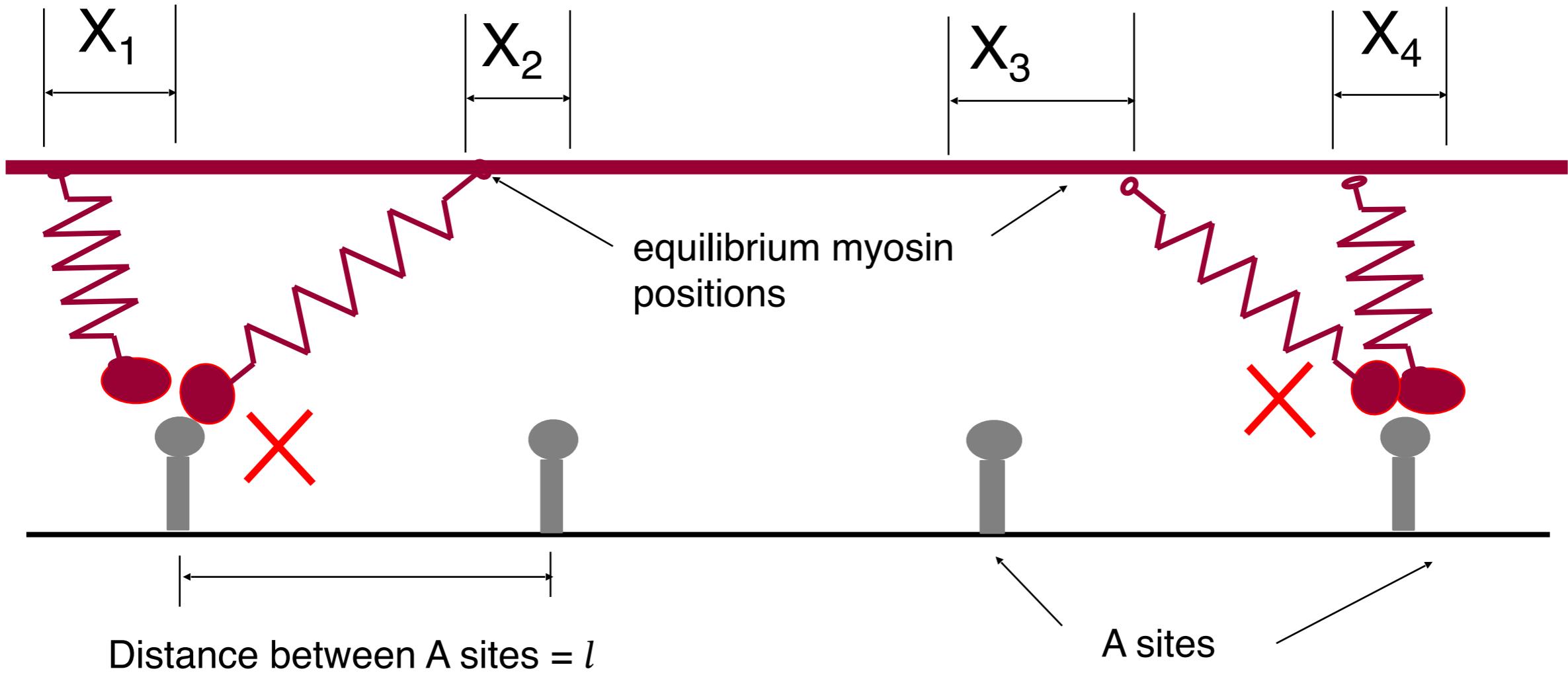


Setup for Huxley '57 model



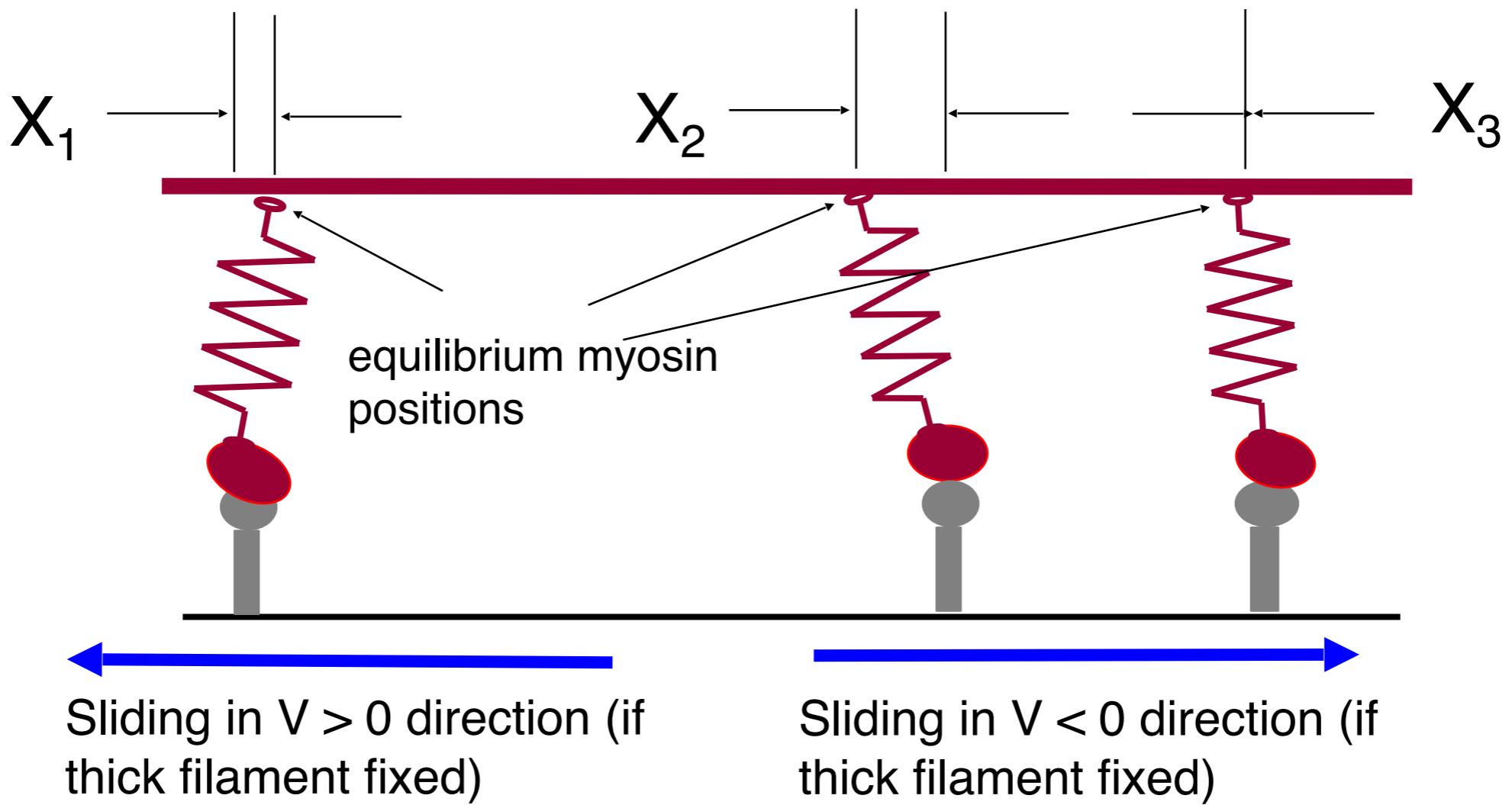
Model is built around XB binding sites called A sites on thin filament. Myosin heads from thick filament can bind to one *and only one* nearby A site.

Setup for Huxley '57 model



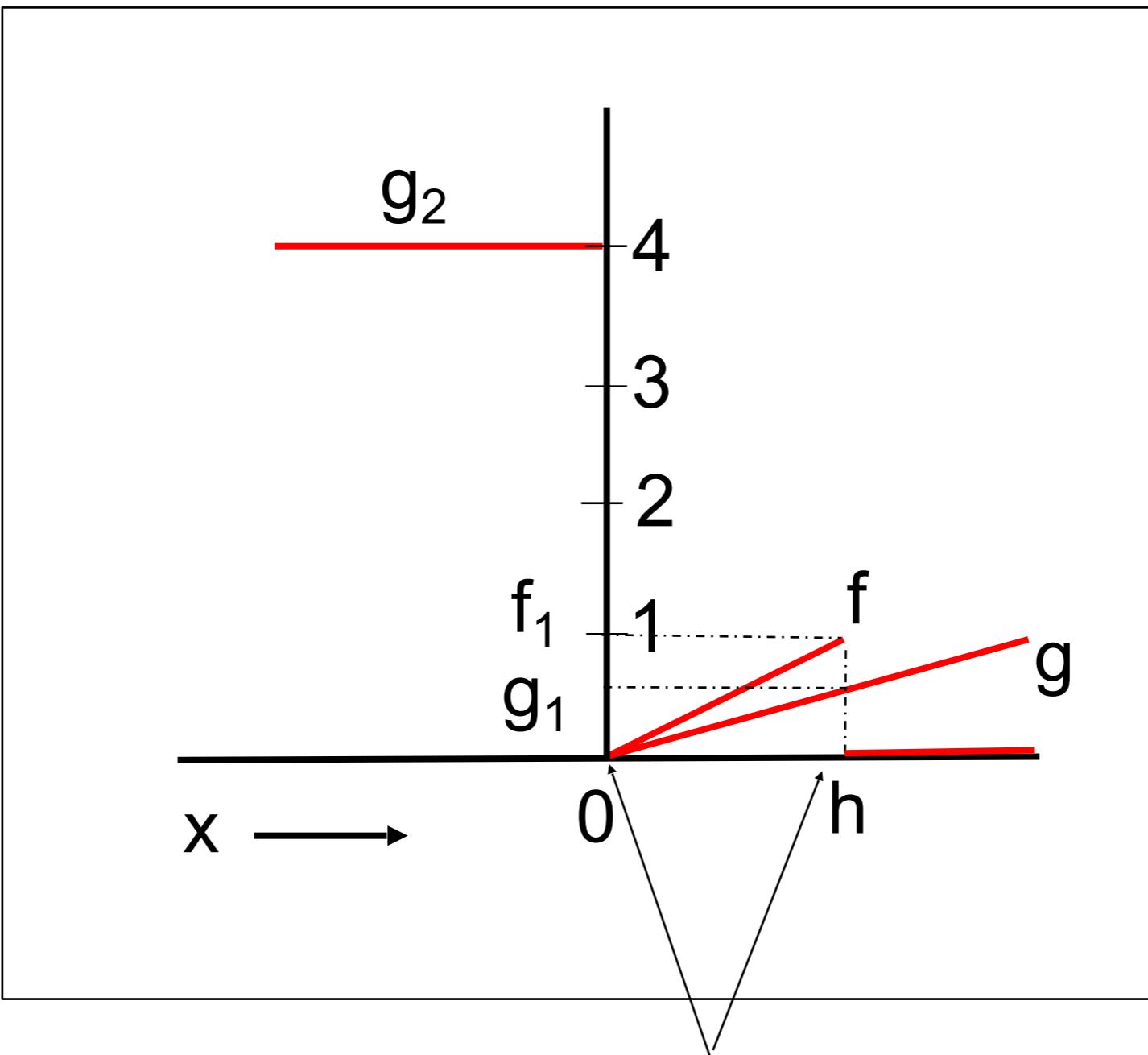
Model assumes interactions are with only one nearby myosin. Hence, each myosin can interact with only one A site at a time.

Setup for Huxley '57 model



The thick and thin filaments slide past each other at a constant velocity V . Sliding velocity is not affected by the local attachment or detachment events. Note: velocity is a parameter in the model.

Attachment and detachment rates as functions of X



XB attach only in this range

XB can detach at any distortion

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

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

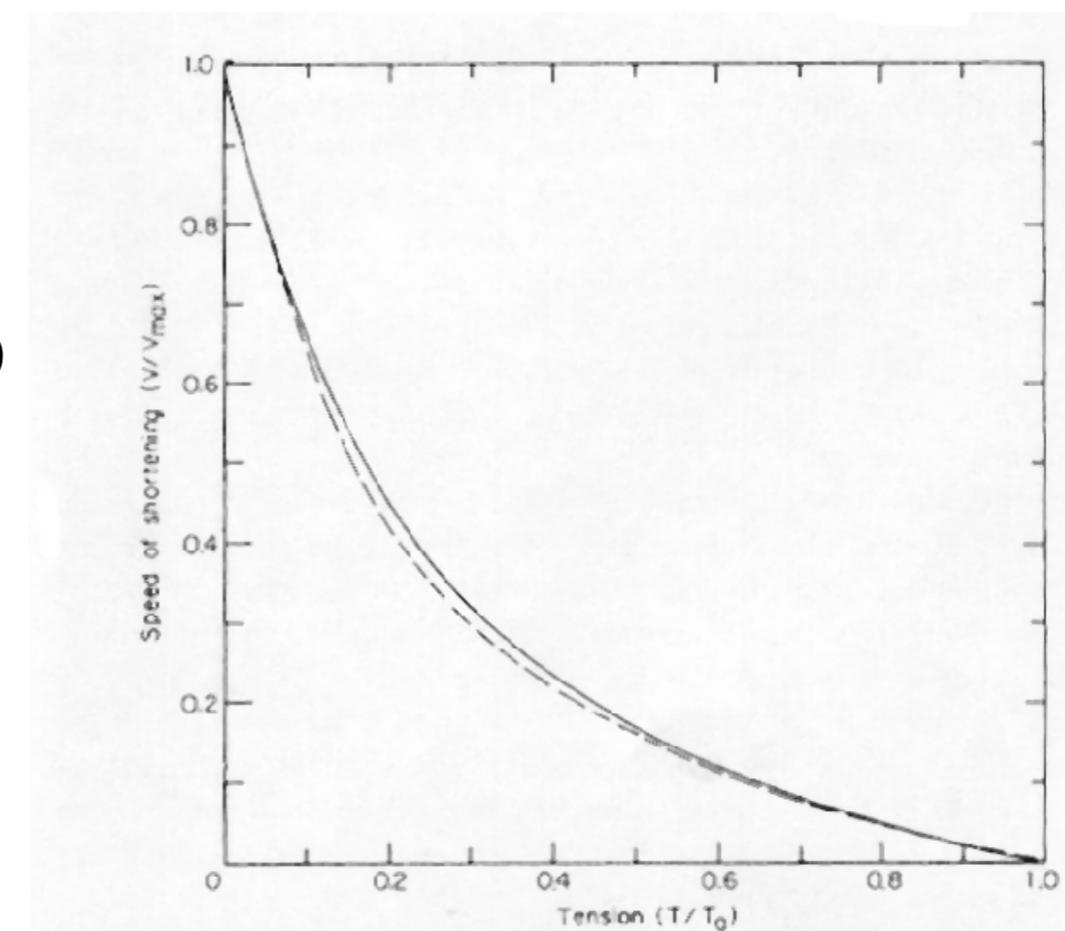


Fig. 4.5. Speed of shortening vs. tension. Solid line shows result of experiments (Hill equation, eq. 1.4 with $a/T_0 = 1/4$), broken line shows Huxley 1957 theory with constants chosen to provide best fit. From A. F. Huxley (1957).

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 increased ATP usage in disagreement with experimental results
- Overall ATP hydrolysis is too high

Other Cardiac Myofilament Models

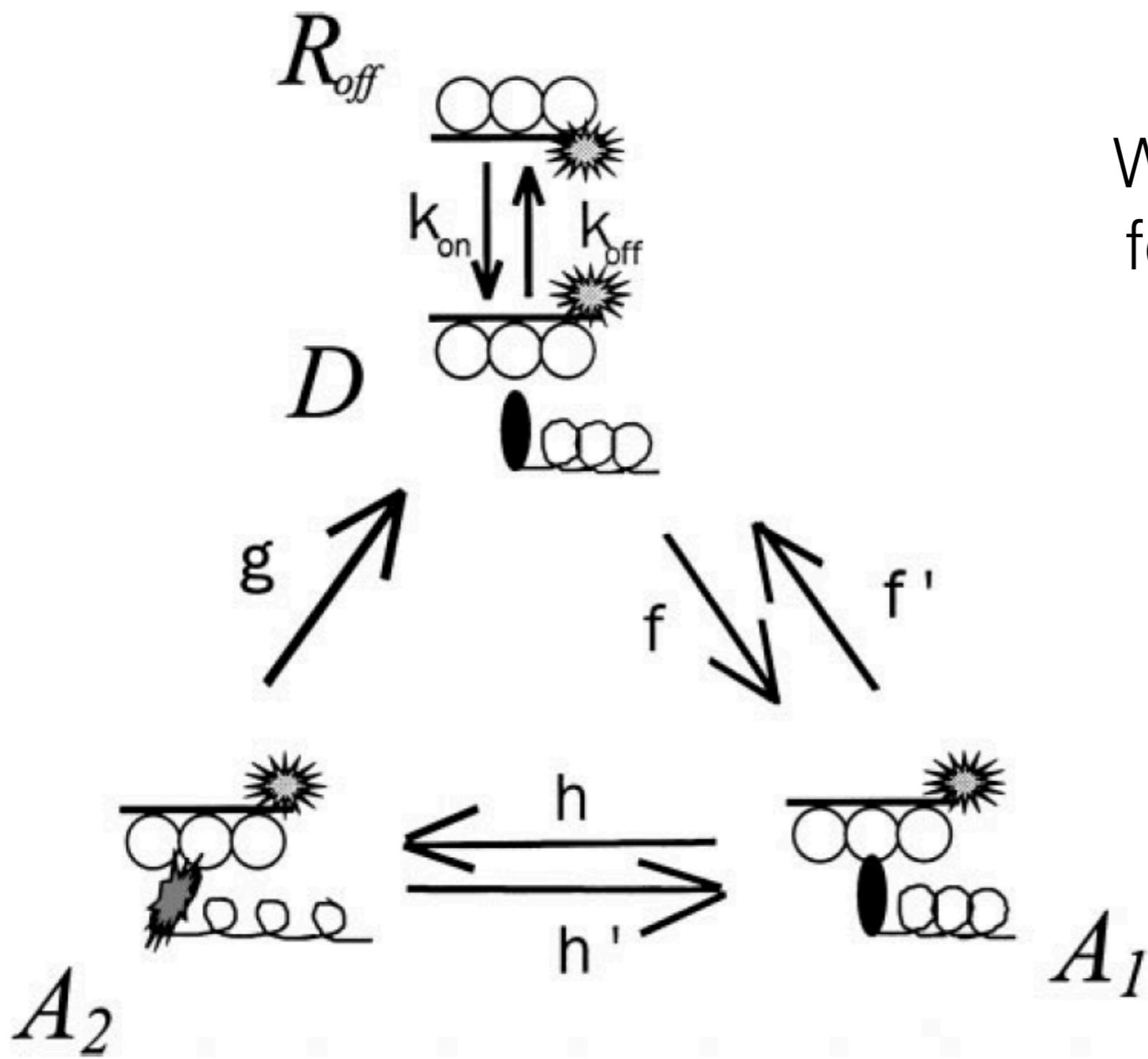
Cross-Bridge Models

- 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 mode (Razumova)

Myofilament Activation Models

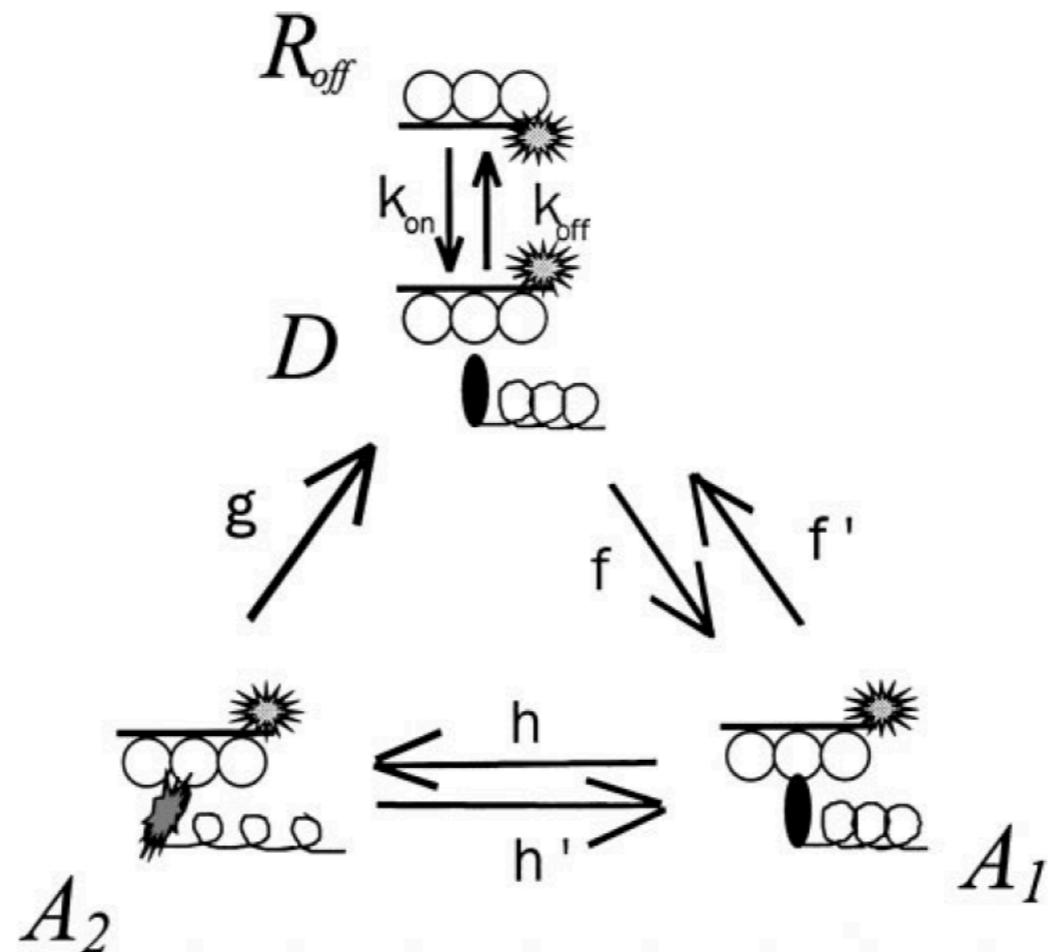
- Models of cooperative thin filament activation
 - empirical models (Rice, Hunter)
 - mechanistic models of nearest neighbor interactions (Rice, Campbell)
 - XB-XB, RU-RU, XB-RU
- Models with length-dependent activation

Stiffness-Distortion model (Razumova, 1999)



Write the ODEs
for this system

Stiffness-Distortion model (Razumova, 1999)



$$R_{off}(t) = R_T - D(t) - A_1(t) - A_2(t)$$

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

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

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

Try it!

- **Notebook: Part1_Razumova**
- **Constants:**

R_T = 1 #Total state occupation

k_on = 400 #Rate from nonpermissive to permissive

k_off = 50

f = 50 # attachment rate

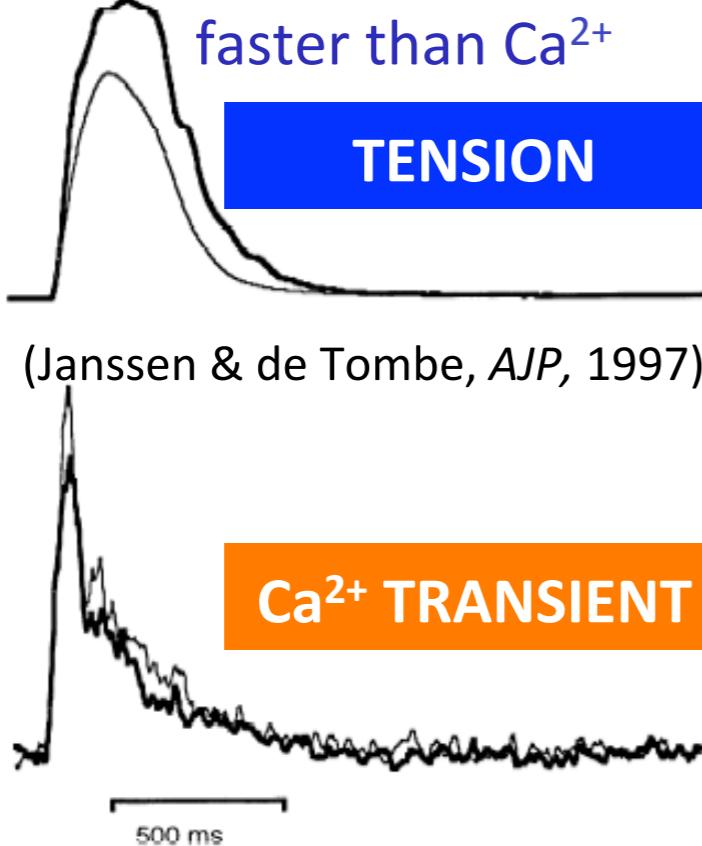
f_prime = 400

h = 8 #powerstroke rate

h_prime = 6

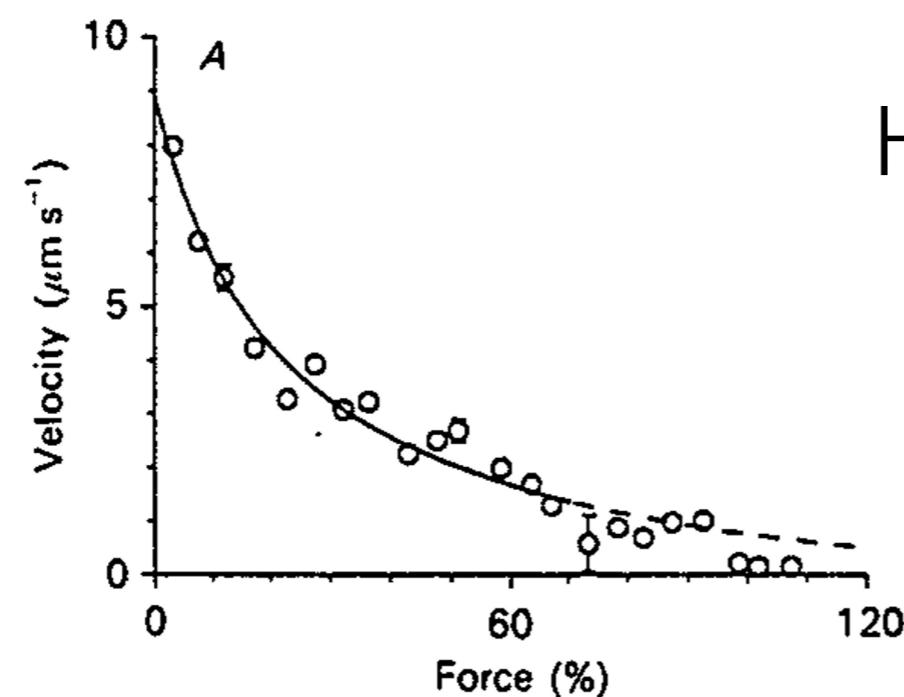
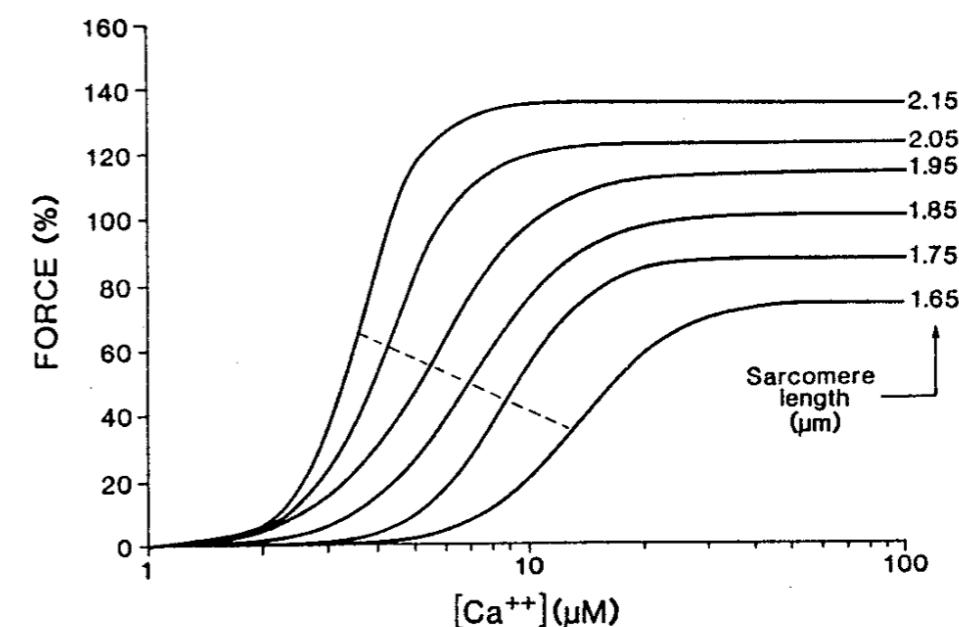
g = 4

Twitch tension rises slower & falls faster than Ca^{2+}



(Janssen & de Tombe, *AJP*, 1997)

Cooperative, length Dependent activation



Inverse force-velocity relationship

How must we alter this model to reproduce known muscle behaviour?

Step 1: Add Calcium dependence

$$k_{on}^u = k_{on}^0 + [k_{on}^{Ca} - k_{on}^0] \frac{Ca}{Ca_{50} + Ca}$$

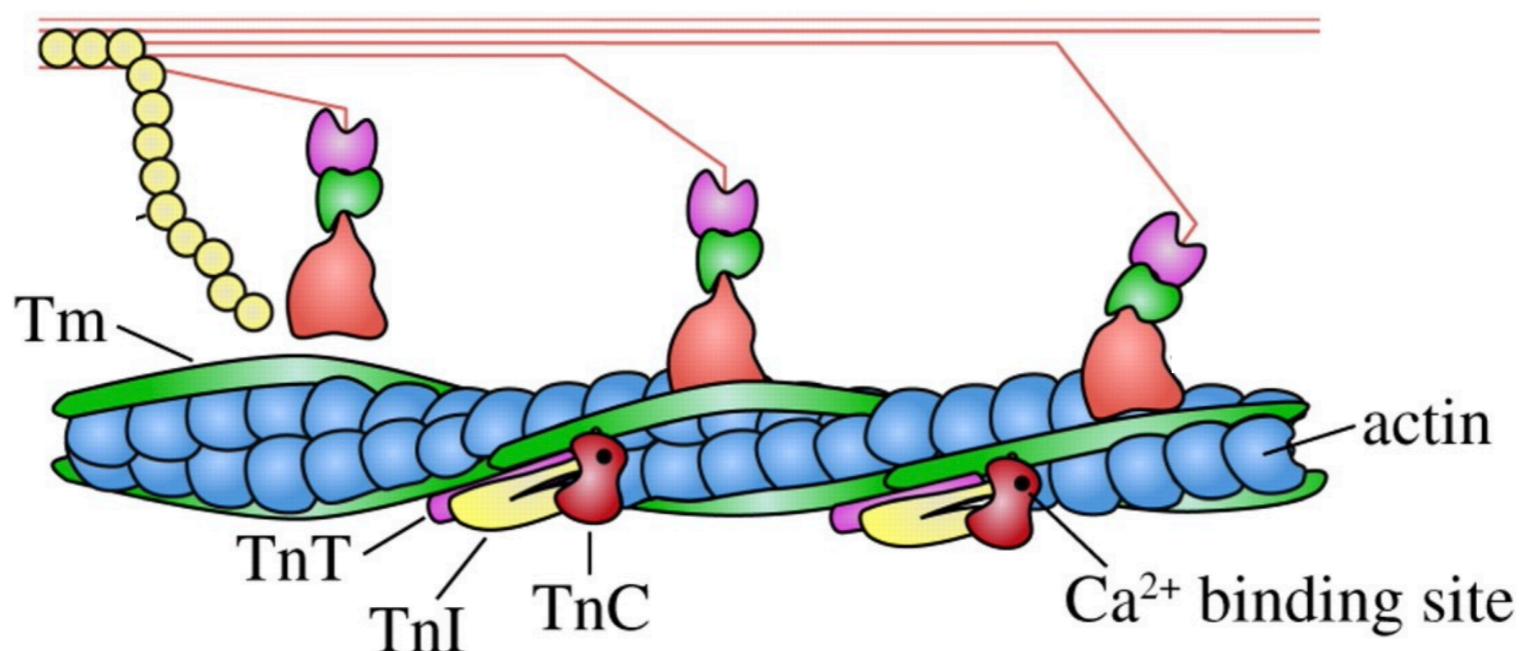
$$k_{off}^u = k_{off}^0 + [k_{off}^{Ca} - k_{off}^0] \frac{Ca}{Ca_{50} + Ca}$$

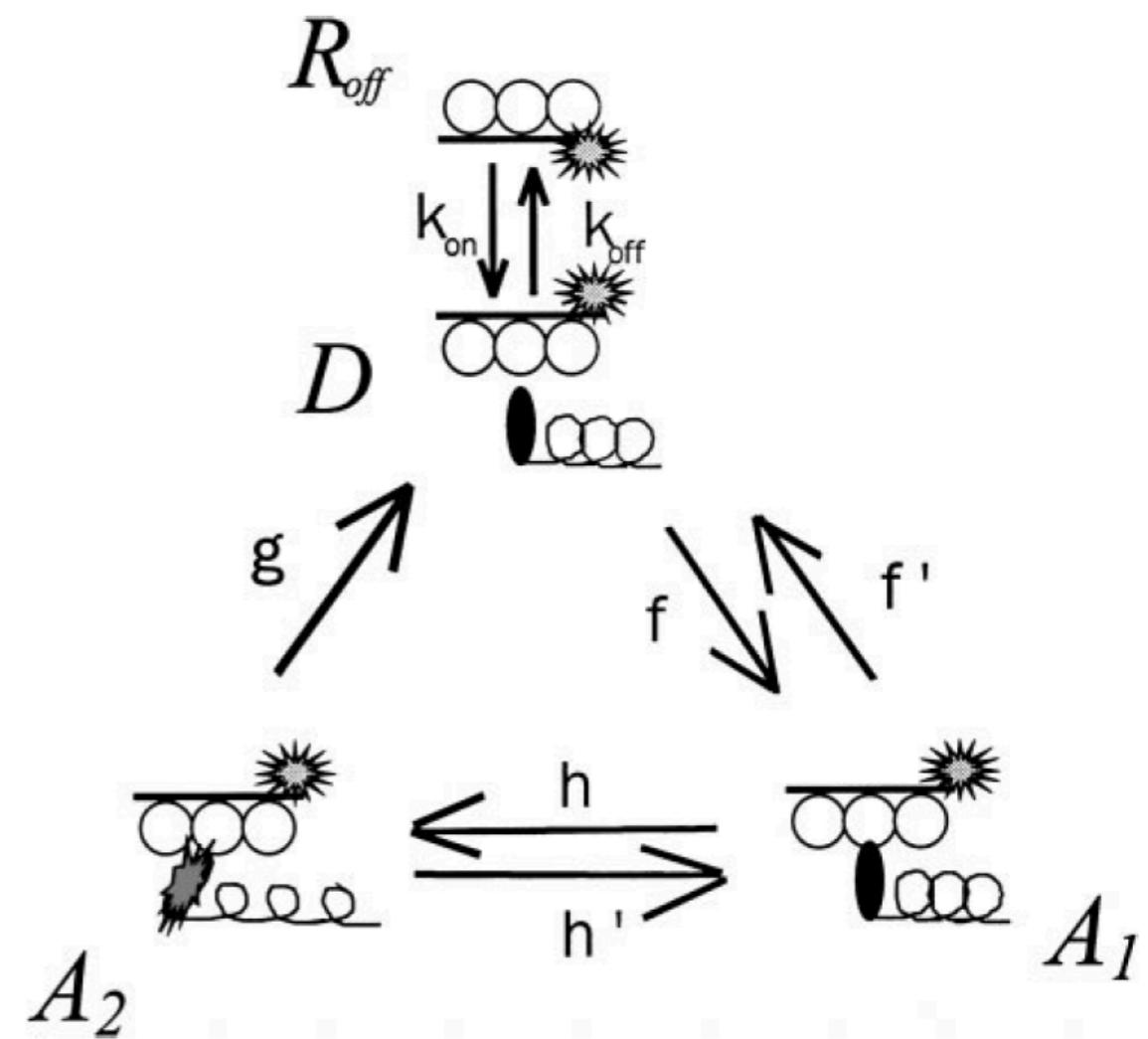
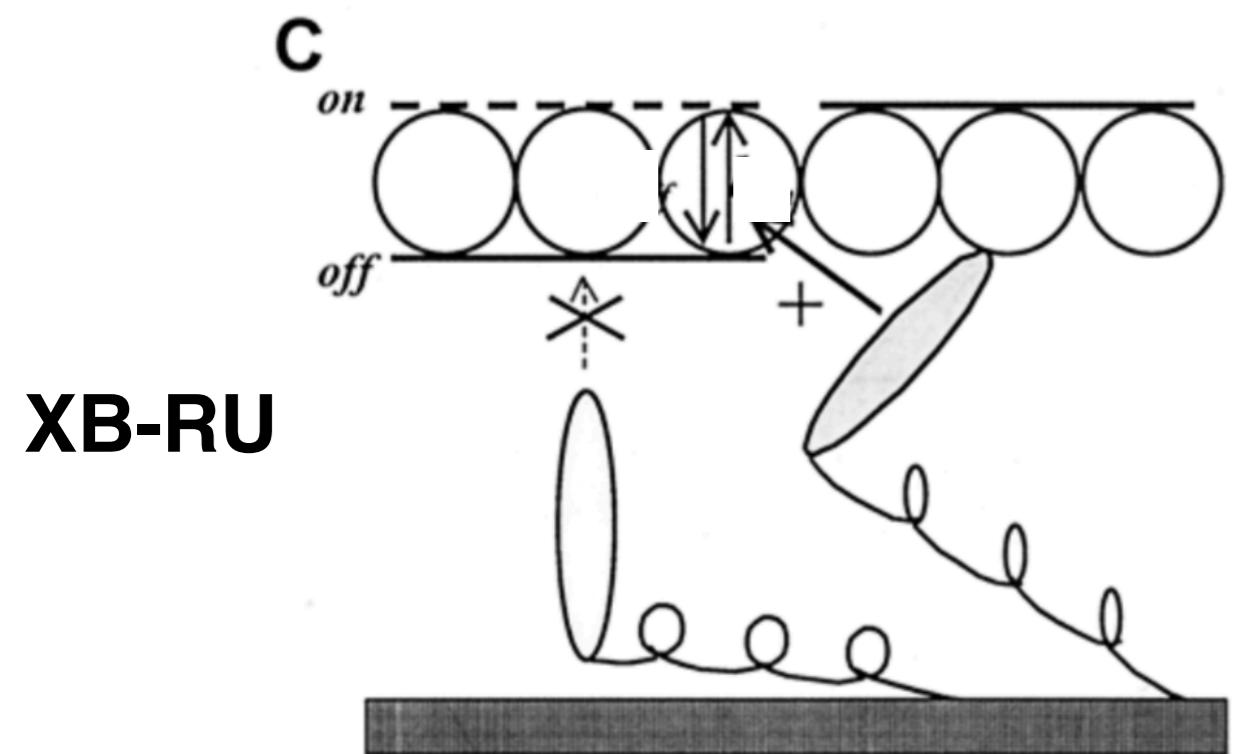
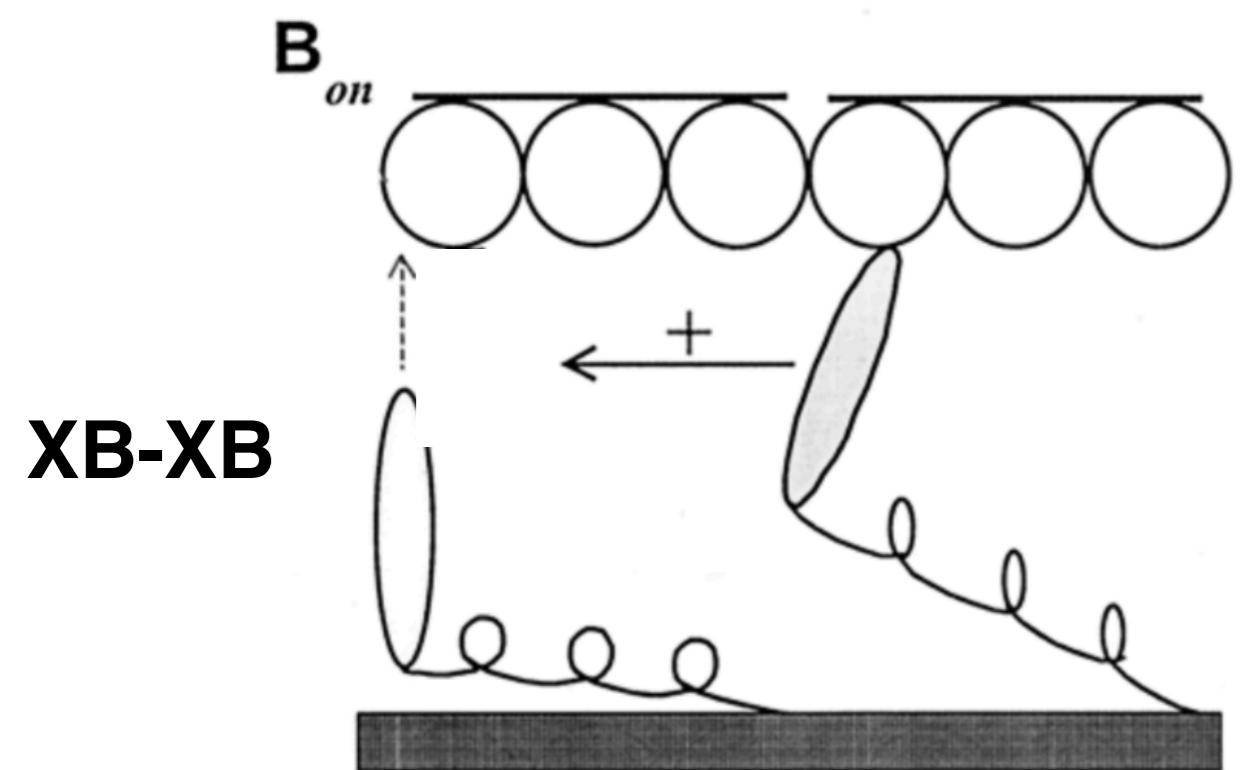
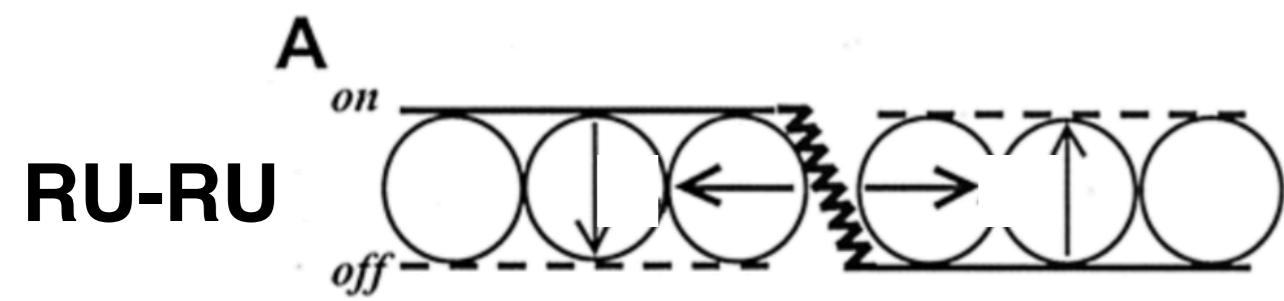
Notes here:

- $k_{on, off}^u$ - intermediate k values (further modification needed)
- Ca_{50} - [Ca] for 50% steady state force
- k^0, k^{Ca} - empirical constants

Step 2: Modeling Cooperative 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
- XB-RU: cycling crossbridges have been shown to increase the Ca^{2+} affinity of troponin





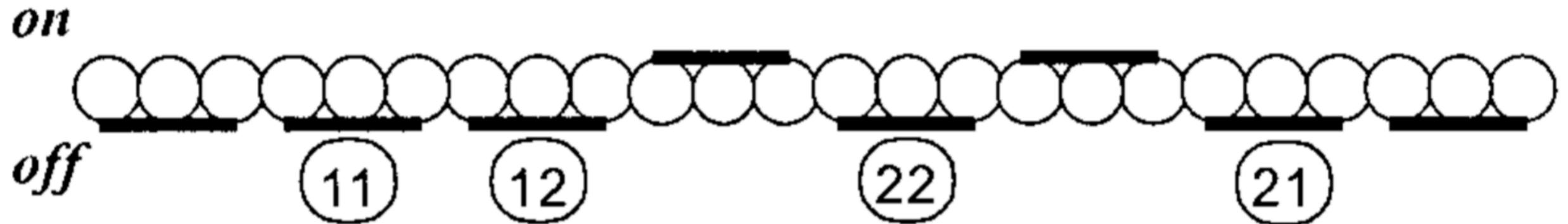
Defining state subpopulations

$$\lambda^{off} = \frac{R_{off}}{R_T} \quad \lambda^{on} = \frac{D + A_1 + A_2}{R_T} \quad \lambda^{cyc} = \lambda^{on}$$

$$\lambda^D = \frac{D}{R_T} \quad \lambda^{A_1} = \frac{A_1}{R_T} \quad \lambda^{A_2} = \frac{A_2}{R_T}$$

$$\lambda_{cyc}^{A_2} = \frac{A_2}{D + A_1 + A_2}$$

Step 2: Modeling RU-RU cooperativity



on/off transitions are represented using Boltzmann statistics:

$$k_{on}^* = k_a e^{-\frac{B_{12}^\#}{kT}}$$

Activation Energies

$$k_{off}^* = k_b e^{-\frac{B_{21}^\#}{kT}}$$

Absolute Temp.

Boltzmann Constant

Attempt frequency

Activation Energies

Absolute Temp.

Boltzmann Constant

Attempt frequency

For the whole population of RUs,

$$k_{\text{on}} = k_a \left\{ \begin{array}{l} \text{contribution by sites with} \\ \text{both neighbors "off"} \end{array} \right\} + \left[\begin{array}{l} \text{contribution by sites with} \\ \text{one neighbor "off" and one "on"} \end{array} \right] + \left[\begin{array}{l} \text{contribution by sites with} \\ \text{both neighbors "on"} \end{array} \right] \right\}$$

Attempt frequency

$$k_{\text{on}} = k_a \left(\lambda^{\text{off}} \lambda^{\text{off}} e^{-\frac{B_{12}^{11}}{\kappa T}} + \lambda^{\text{off}} \lambda^{\text{on}} e^{-\frac{B_{12}^{12}}{\kappa T}} + \lambda^{\text{on}} \lambda^{\text{off}} e^{-\frac{B_{12}^{21}}{\kappa T}} + \lambda^{\text{on}} \lambda^{\text{on}} e^{-\frac{B_{12}^{22}}{\kappa T}} \right)$$

$$k_{\text{on}} = k_a e^{-\frac{B_{12}^{11}}{\kappa T}} ((\lambda^{\text{off}})^2 + 2\lambda^{\text{on}} \lambda^{\text{off}} e^{-\frac{B_{12}^{21}-B_{12}^{11}}{\kappa T}} + (\lambda^{\text{on}})^2 e^{-\frac{B_{12}^{22}-B_{12}^{11}}{\kappa T}})$$

We can simplify further by considering the following relationship between activation energies:

$$B_{12}^{12} - B_{12}^{11} = -U$$

$$B_{12}^{12} - B_{12}^{22} = U$$

$$k_{on} = k_a e^{-\frac{B_{12}^{11}}{kT}} ((\lambda^{off})^2 + 2\lambda^{on}\lambda^{off}e^{\frac{U}{kT}} + (\lambda^{on})^2 e^{\frac{2U}{kT}})$$

$$k_{on} = k_{on}^u (\lambda^{off} + \lambda^{on} e^{\frac{U}{kT}})^2$$

* $k_{on}^u = k_a e^{-\frac{B_{12}^{11}}{kT}}$ is a reference k_{on} , [Ca]-dependent

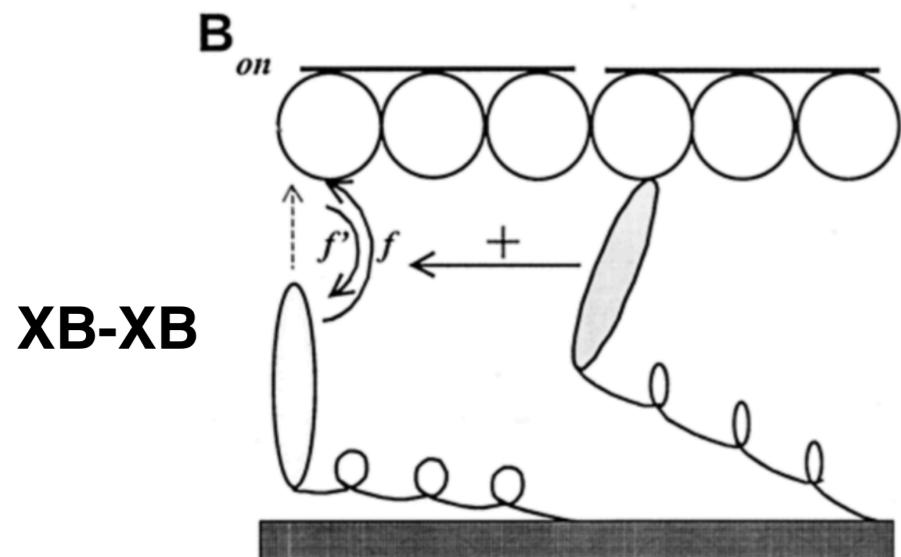
$$k_{on} = k_{on}^u (\lambda^{off} + \lambda^{on} e^{\frac{U}{kT}})^2$$

Define $u = e^{\frac{U}{kT}}$ And note $\lambda^{on} + \lambda^{off} = 1$

$$k_{on}^w = k_{on}^u [1 + \lambda^{on}(u - 1)]^2$$

We can similarly derive k_{off}^w :

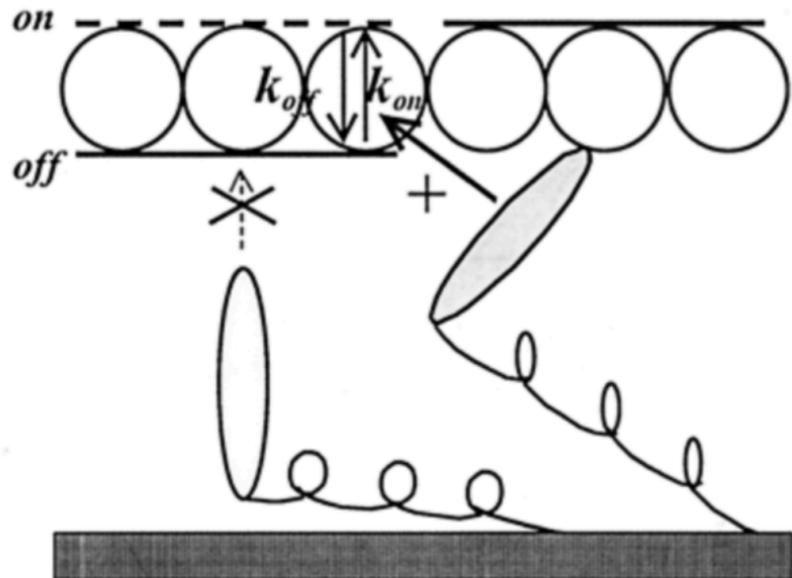
$$k_{off}^w = k_{off}^u [u - \lambda^{on}(u - 1)]^2$$



$$f = f_a \left\{ \begin{array}{l} \left[\text{contribution by sites with} \right. \\ \text{neighbors neither of which has a} \\ \text{force-bearing XB} \\ \left. \right] \\ + \left[\text{contribution by sites with} \right. \\ \text{neighbors one of which has a} \\ \text{force-bearing XB} \\ \left. \right] \\ + \left[\text{contribution by sites with} \right. \\ \text{neighbors both of which have a} \\ \text{force-bearing XB} \\ \left. \right] \end{array} \right\}$$

$$f = f_0 [1 + \lambda^{A_2} (e^{(v-1)} - 1)]^2$$

$$f' = f'_0 [1 + \lambda^{A_2} (e^{-(v-1)} - 1)]^2$$

C**XB-RU**

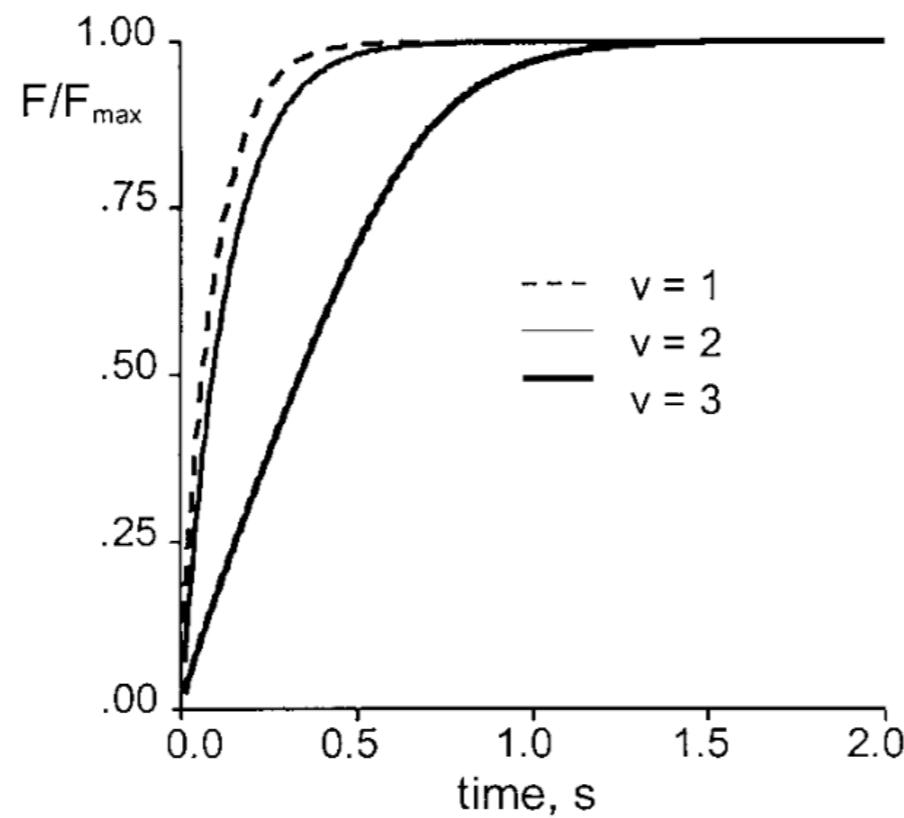
$$k_{on} = k_{on}^w [1 + \lambda^{A_2} (e^{(w-1)} - 1)]^2$$

$$k_{off} = k_{off}^w [1 + \lambda^{A_2} (e^{-(w-1)} - 1)]^2$$

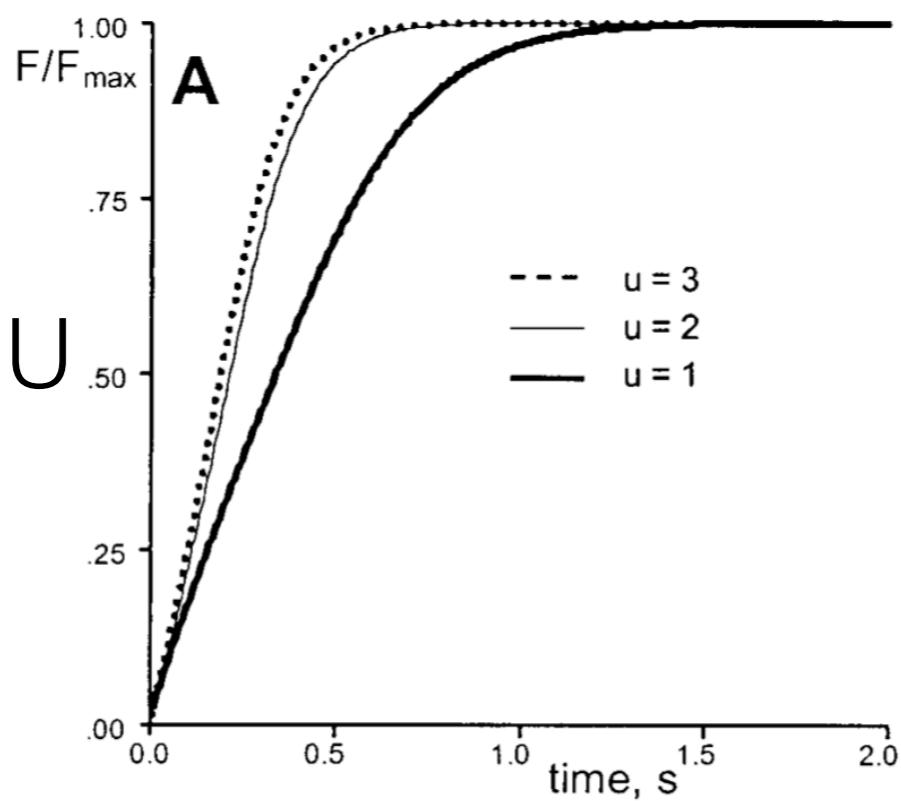
$$k_{on} = k_a \left\{ \begin{array}{l} \left[\text{contribution by sites with} \right. \\ \text{neighbors neither of which has a} \\ \text{force-bearing XB} \\ \left. \right] \\ + \left[\text{contribution by sites with} \right. \\ \text{neighbors one of which has a} \\ \text{force-bearing XB} \\ \left. \right] \\ + \left[\text{contribution by sites with} \right. \\ \text{neighbors both of which have a} \\ \text{force-bearing XB} \\ \left. \right] \end{array} \right\}$$

Let's Explore!

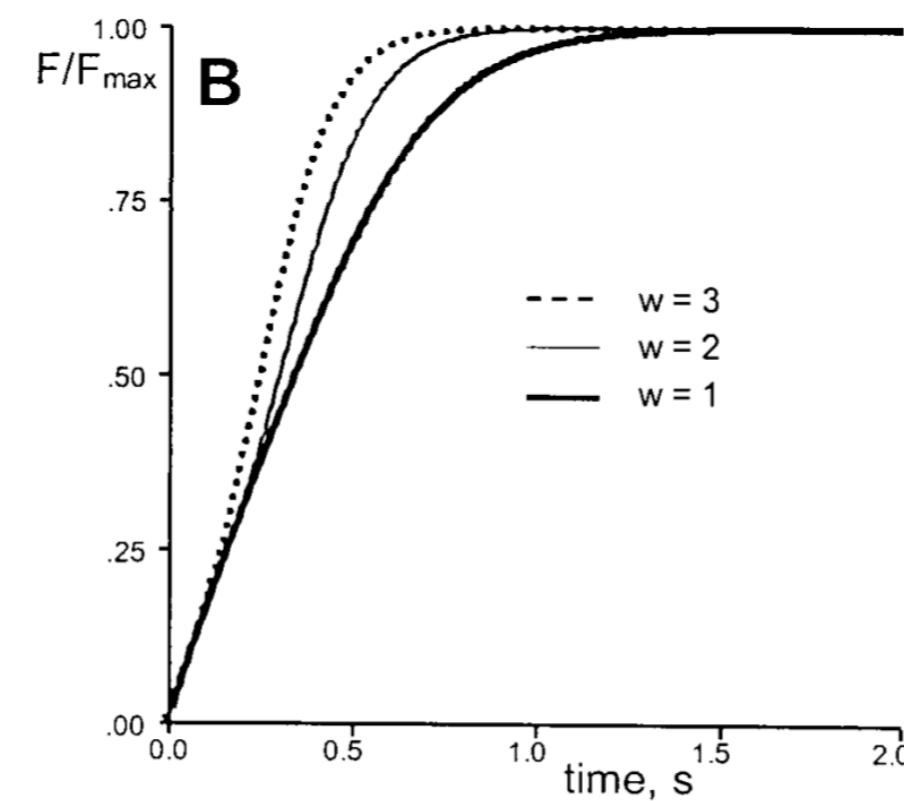
- Go to notebook Solved_Part2_Razumova.ipynb



XB-XB

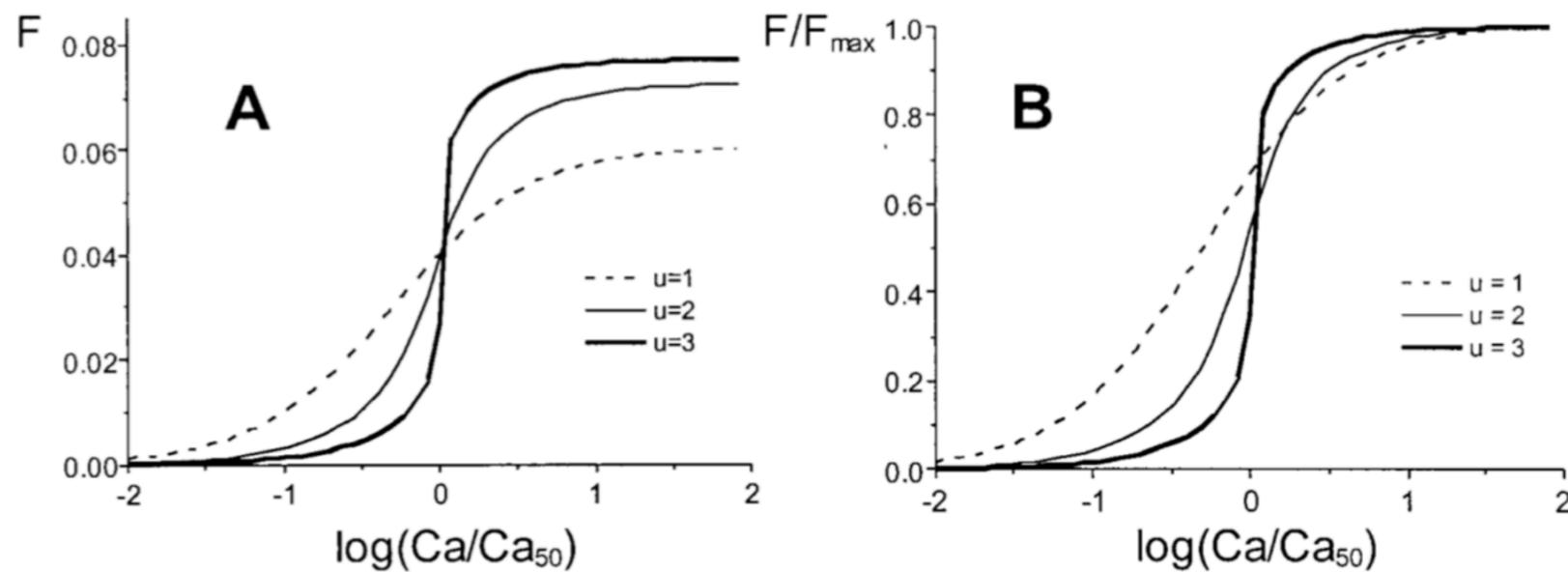


RU-RU

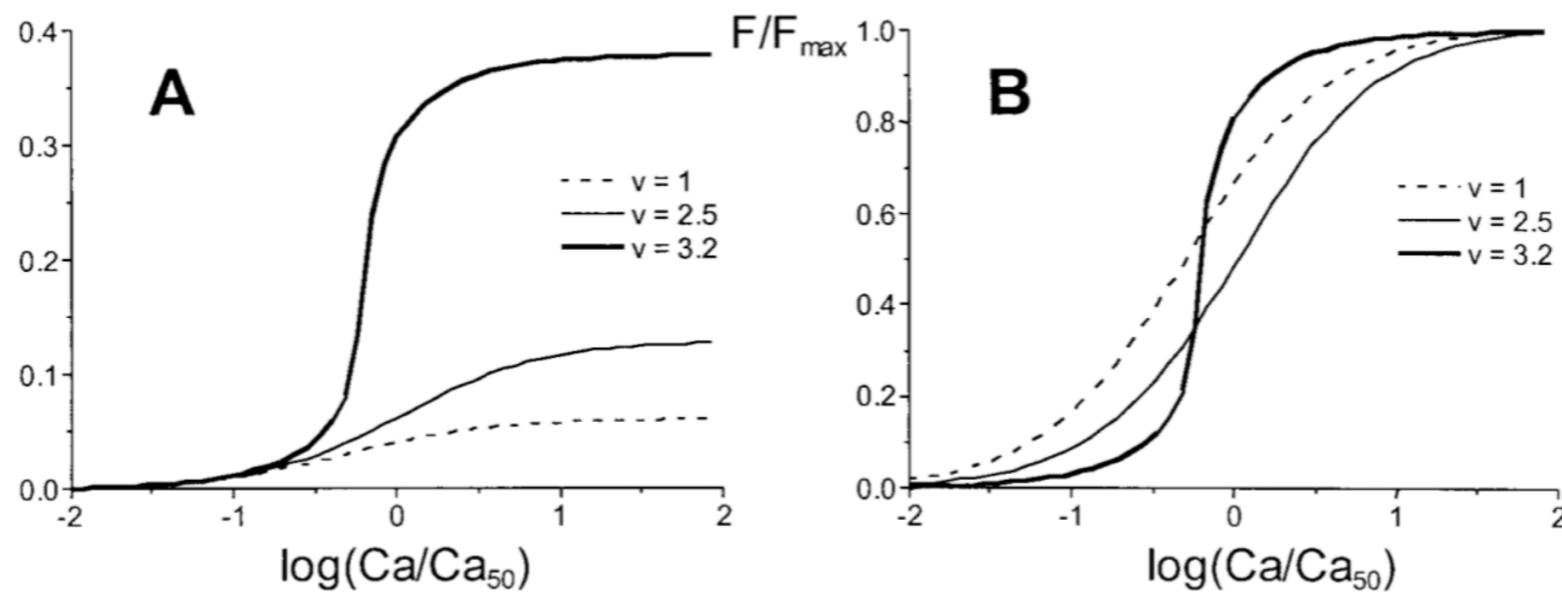


XB-RU

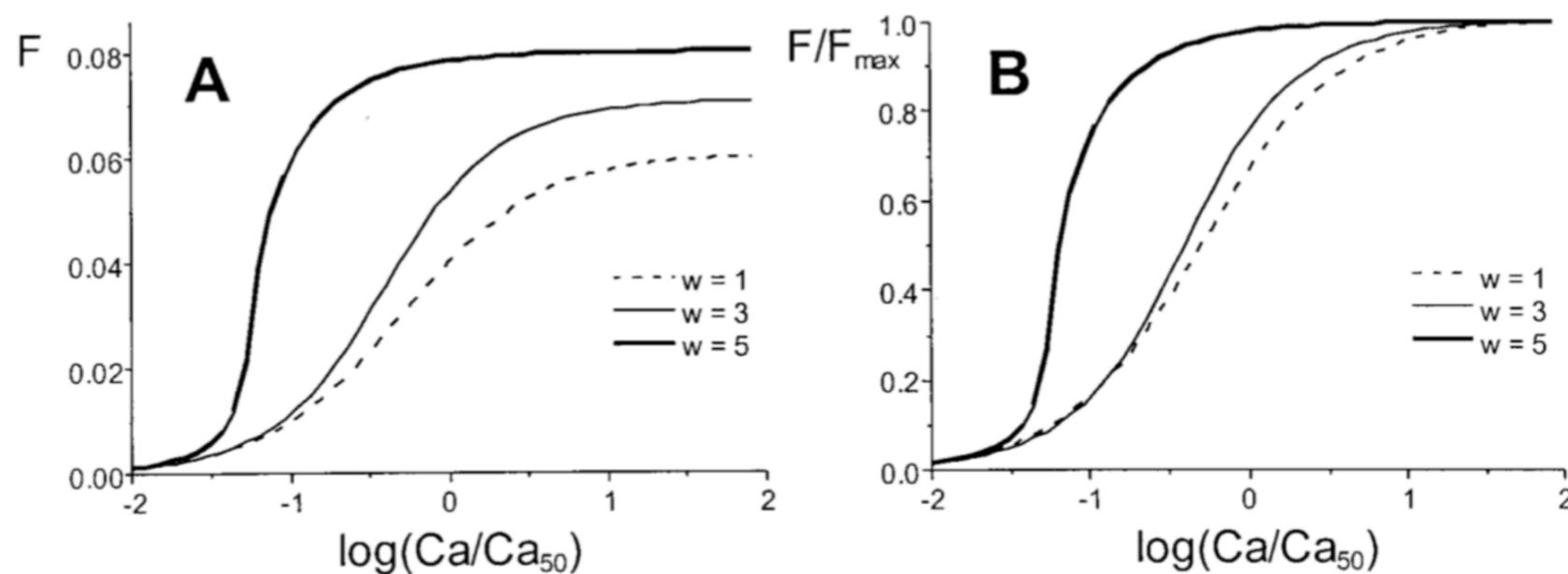
RU-RU



XB-XB

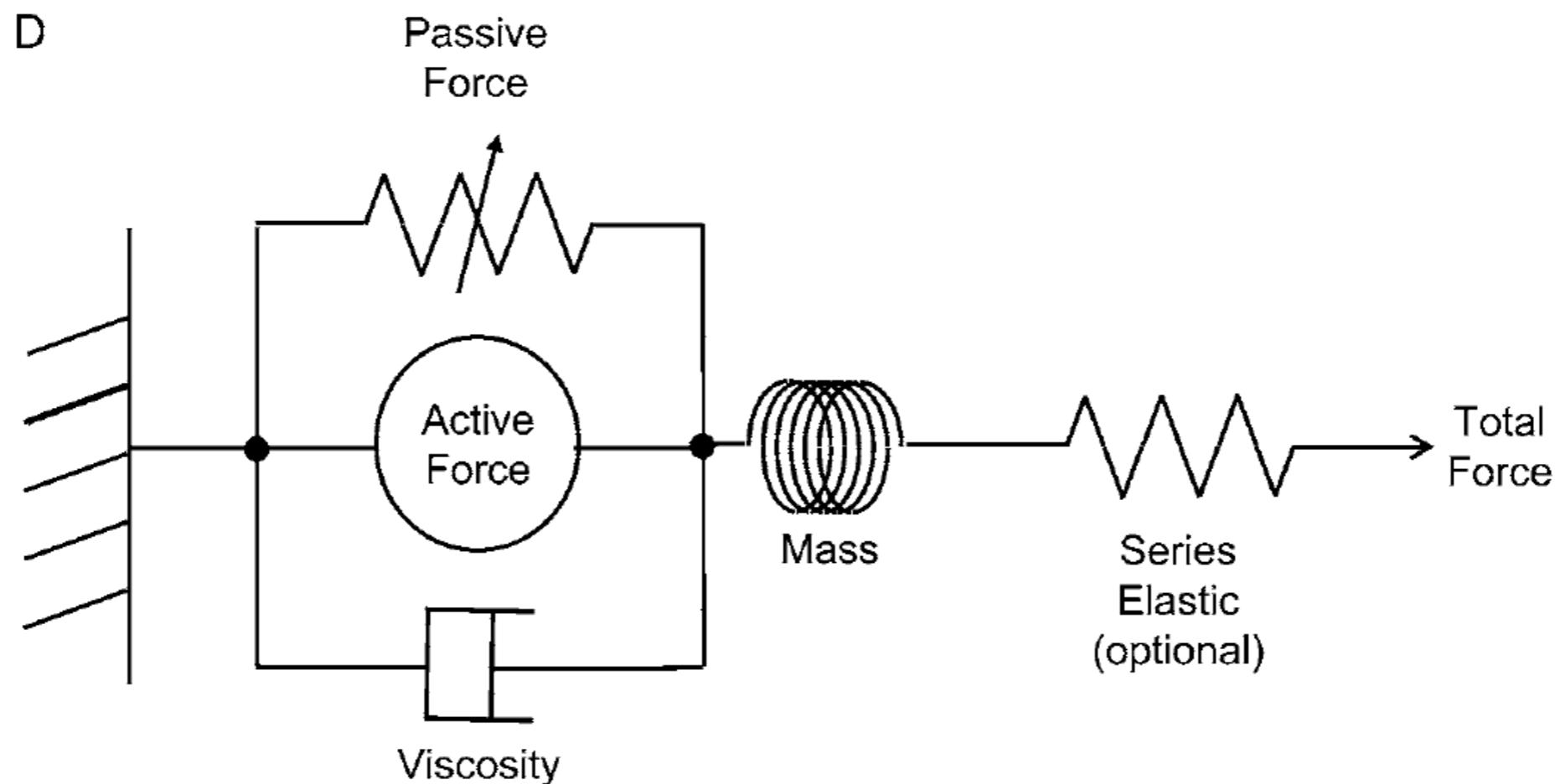


XB-RU



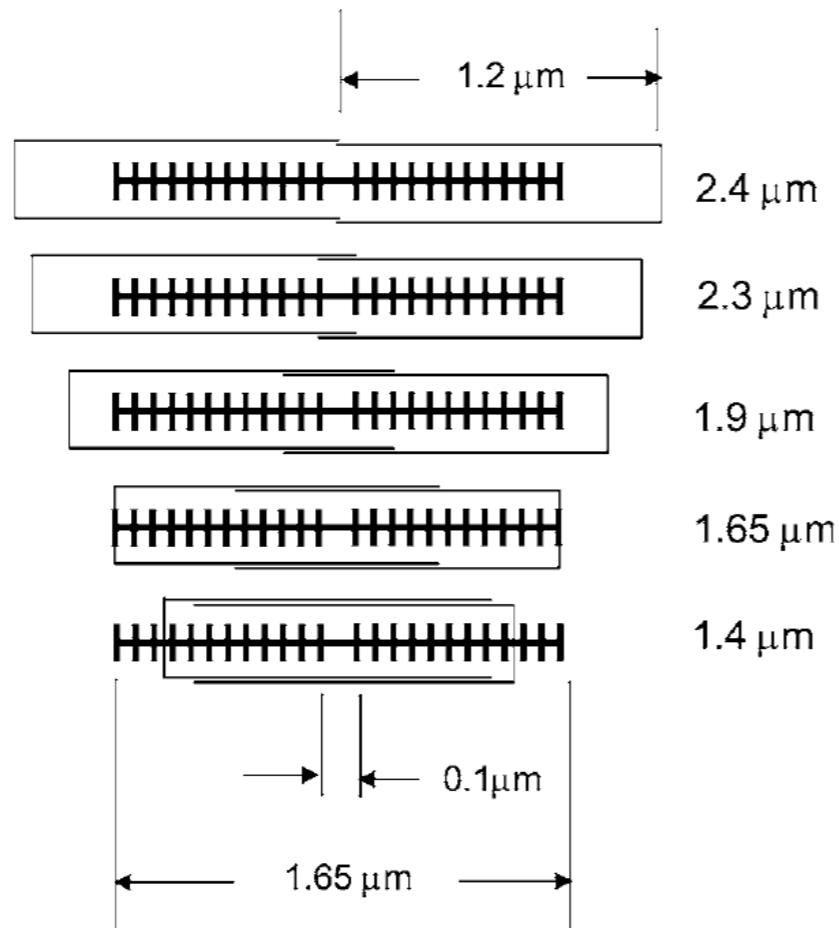
Rice 2008 (Biophysical Journal)

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

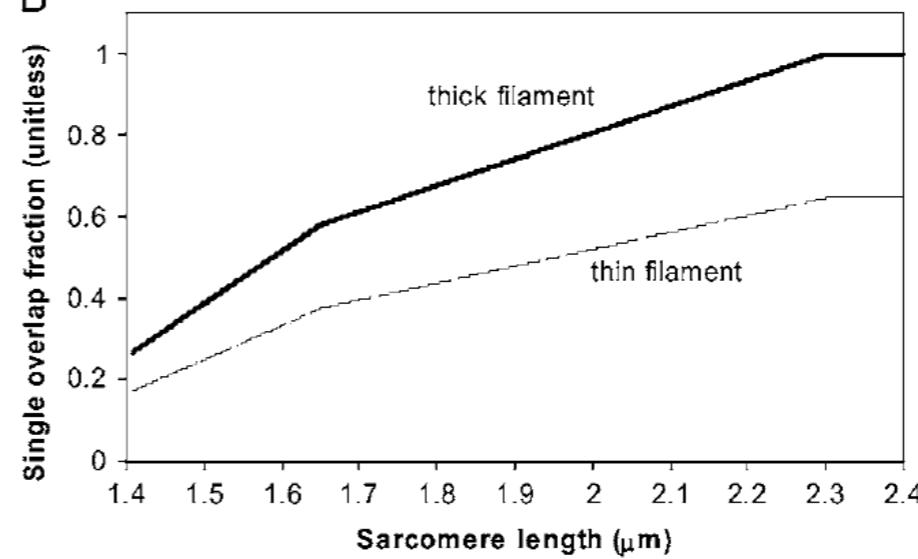


Length Dependence -myofilament overlap

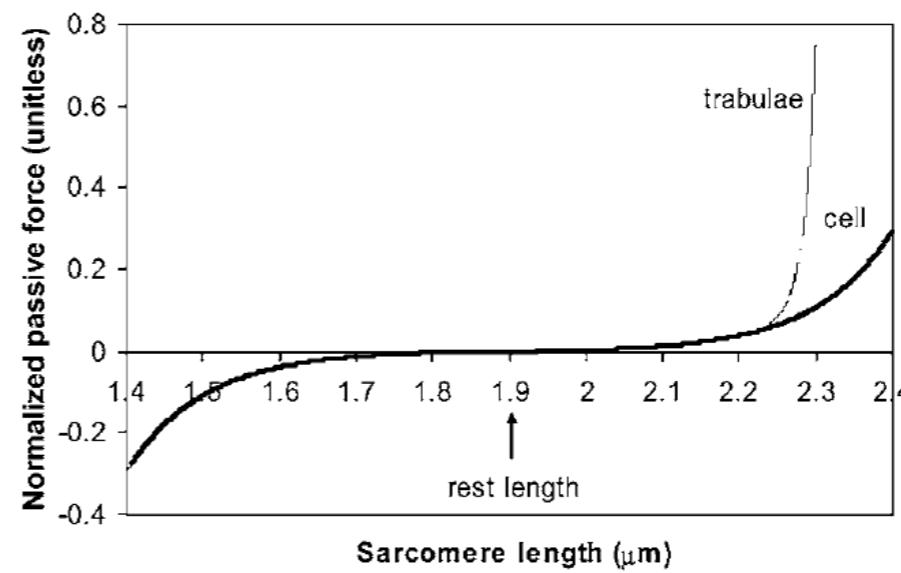
A



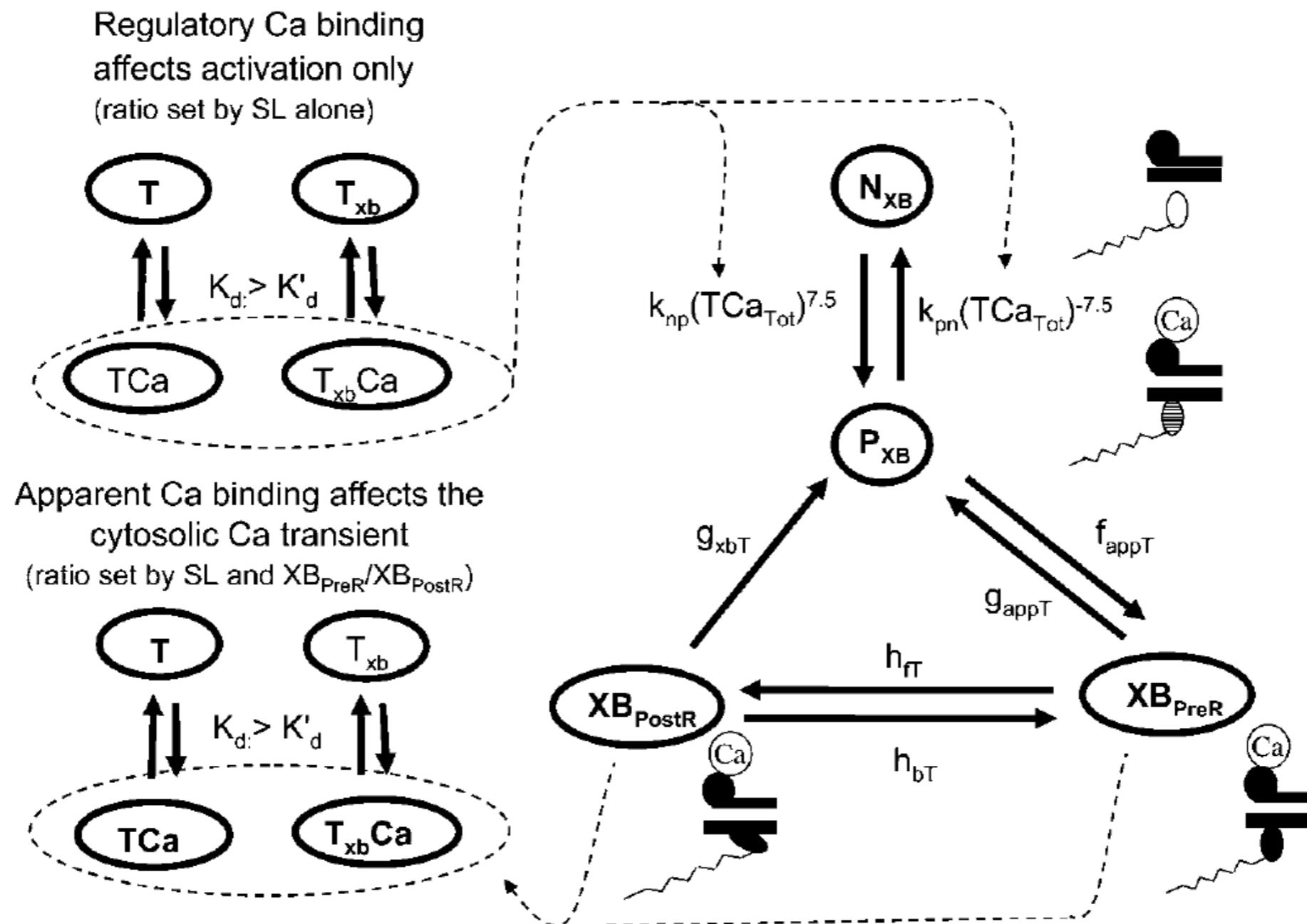
B



C



Model Formulation



Sarcomere Length Dependence

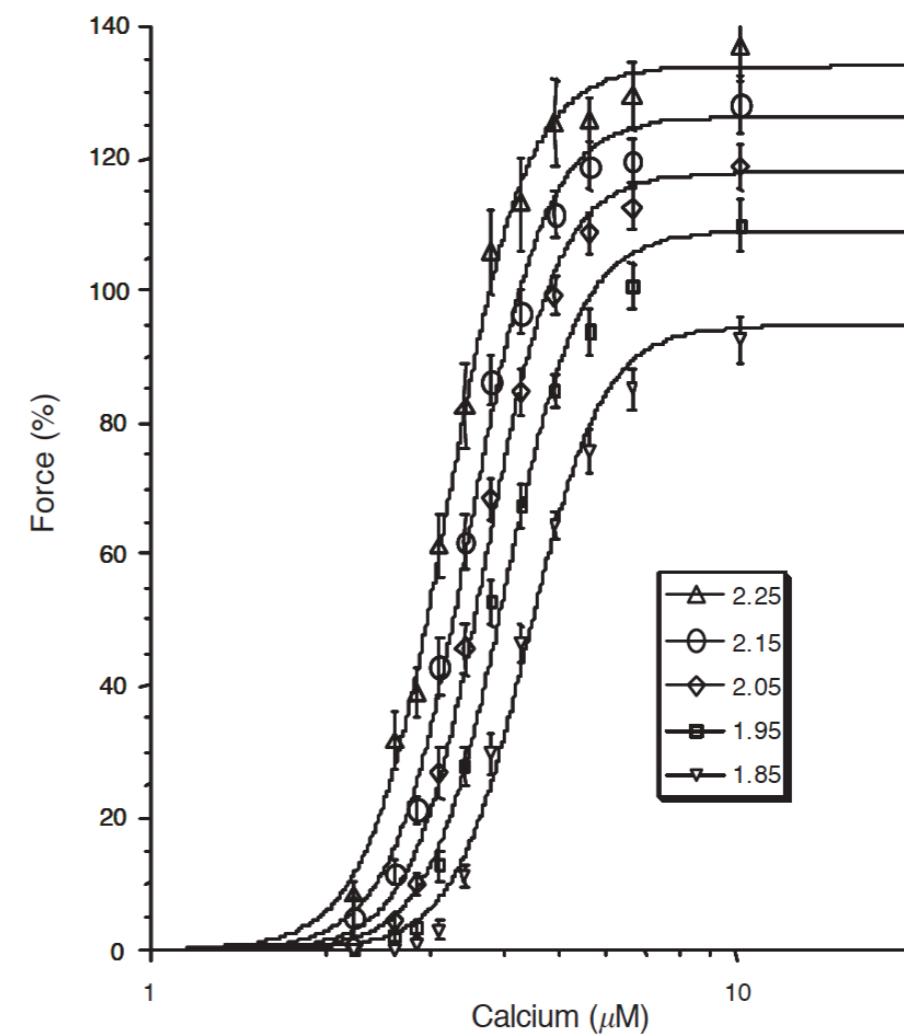
- The model alters Ca^{2+} binding rates using the overlap fraction as well as the fraction of strongly bound XBs:

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

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

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")



Cooperativity

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

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

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

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

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

This is a largely empirical formulation.

Length Dependence

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

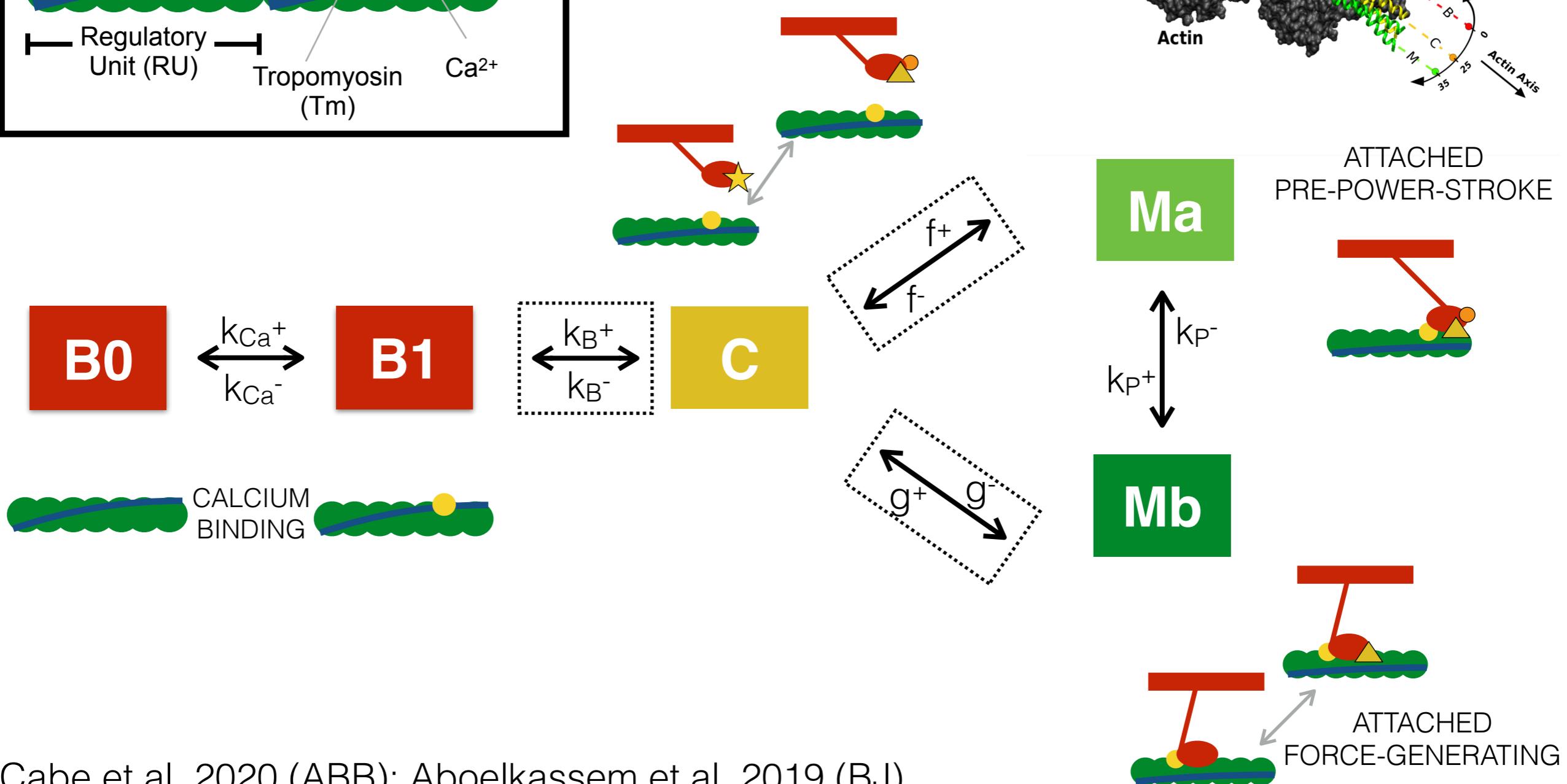
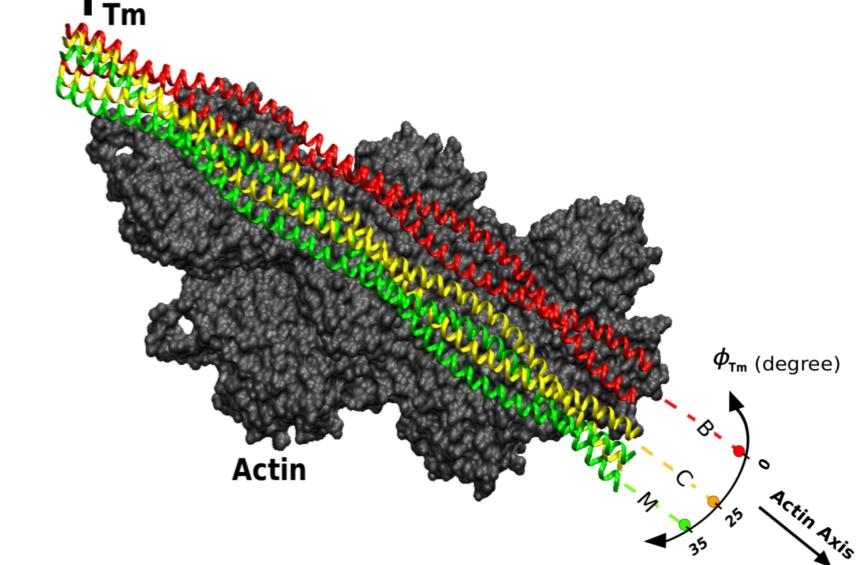
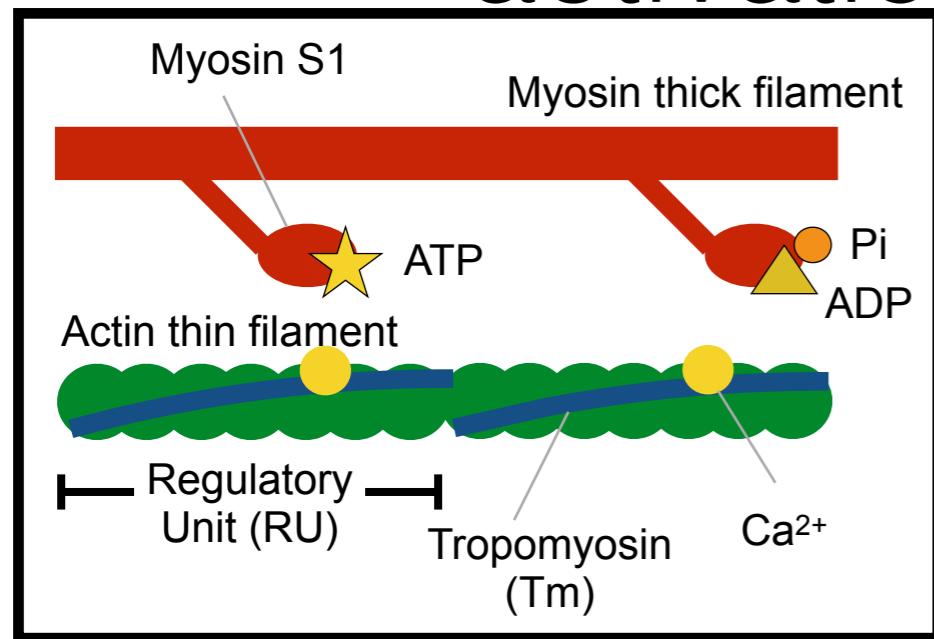
$$f_r = f_m \left(1 + \epsilon \frac{SL - SL_0}{SL_0} \right)$$

where ϵ scales the influence of length on f

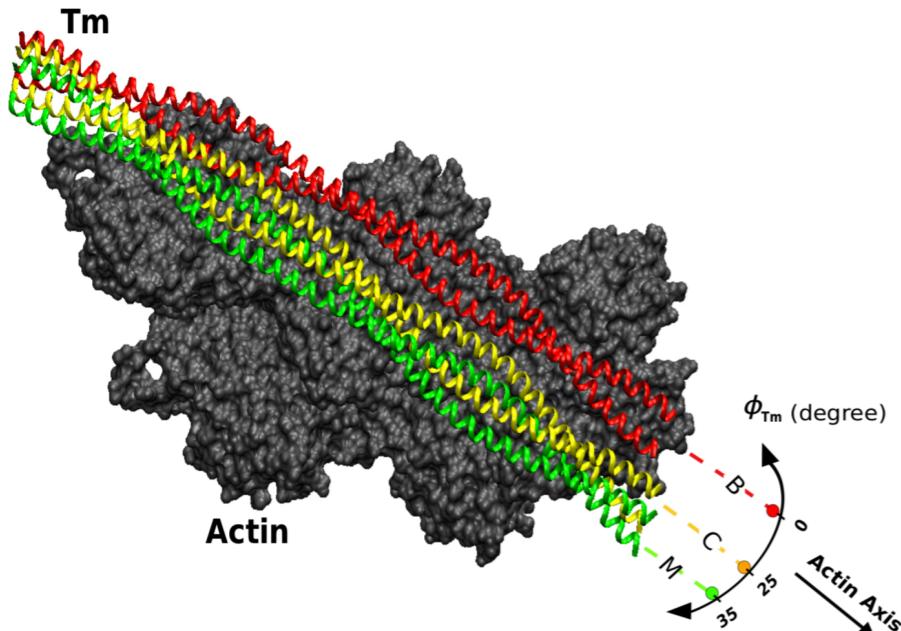
- Estimated myofilament overlap by changing R_T (total number of XBs) based on SL.

Empirical formulation

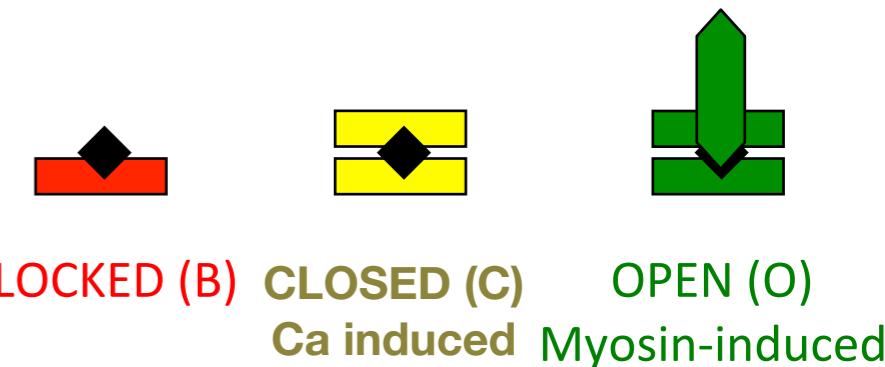
Stochastic Markov State Model for thin filament activation - spatially explicit



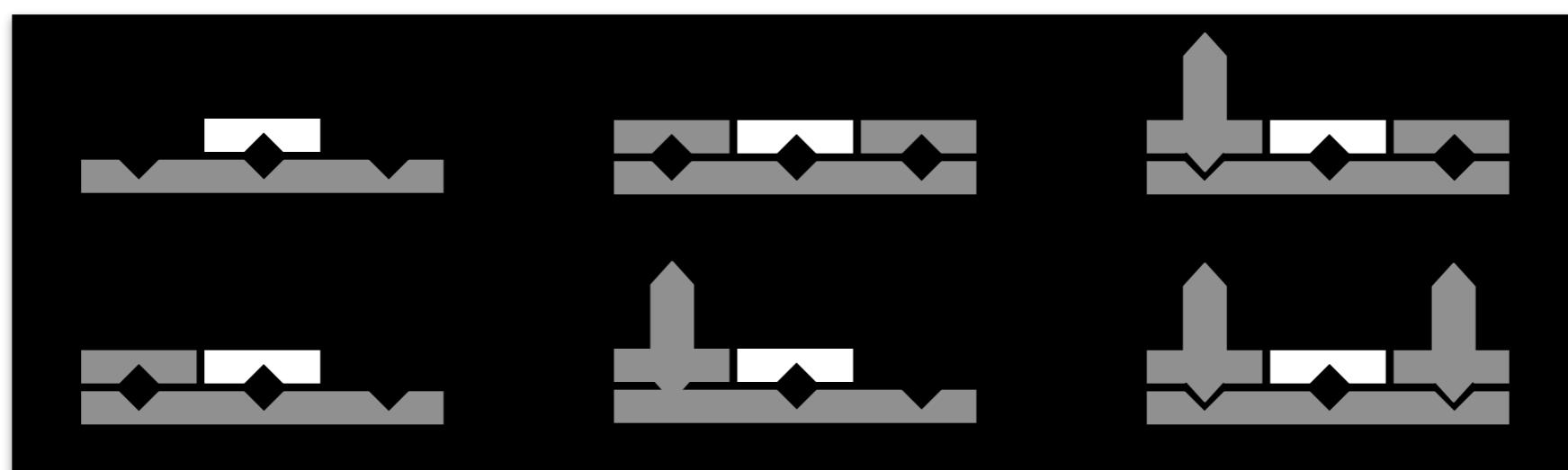
Nearest Neighbor interactions on the thin filament



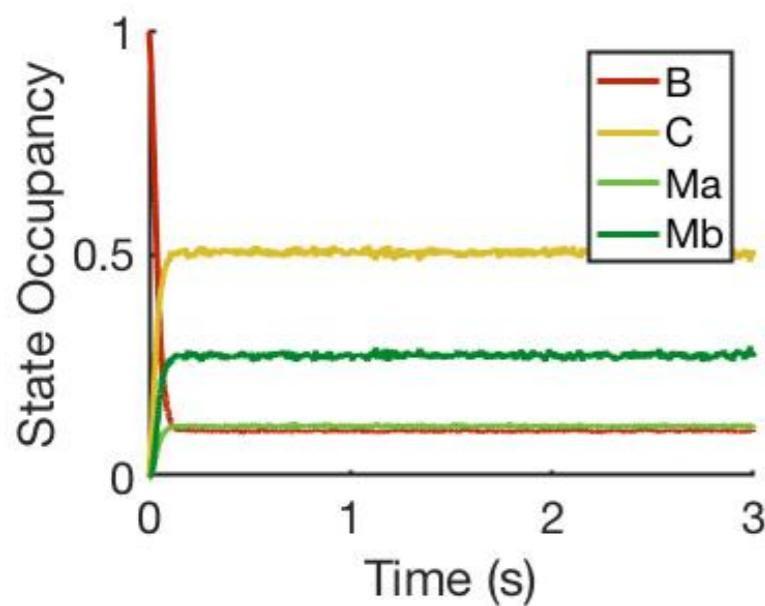
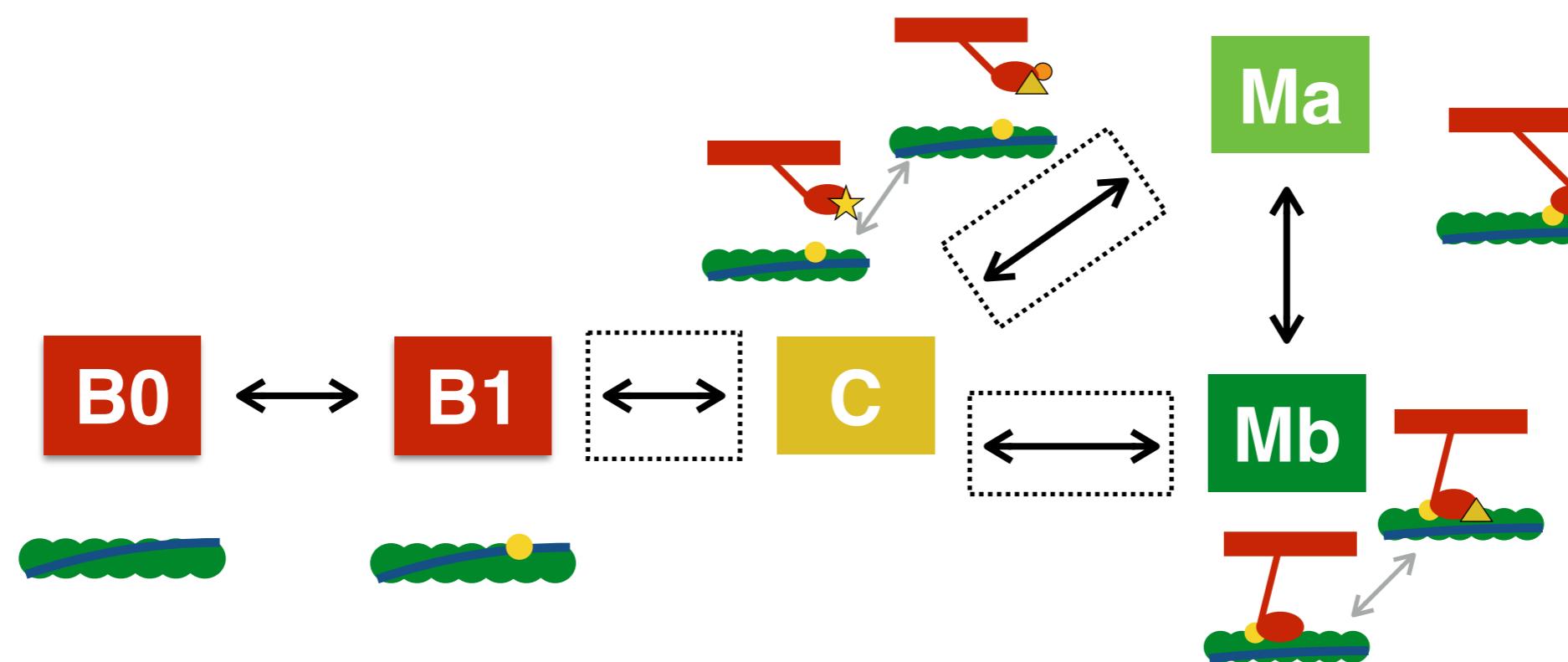
Three possible states
of tropomyosin in
each regulatory unit:



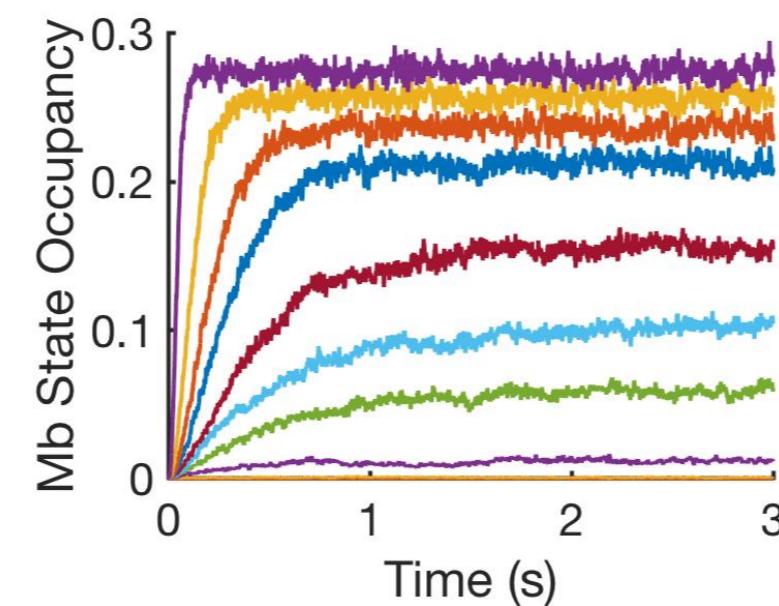
Six distinct nearest-neighbor configurations influence the transition of the middle RU:



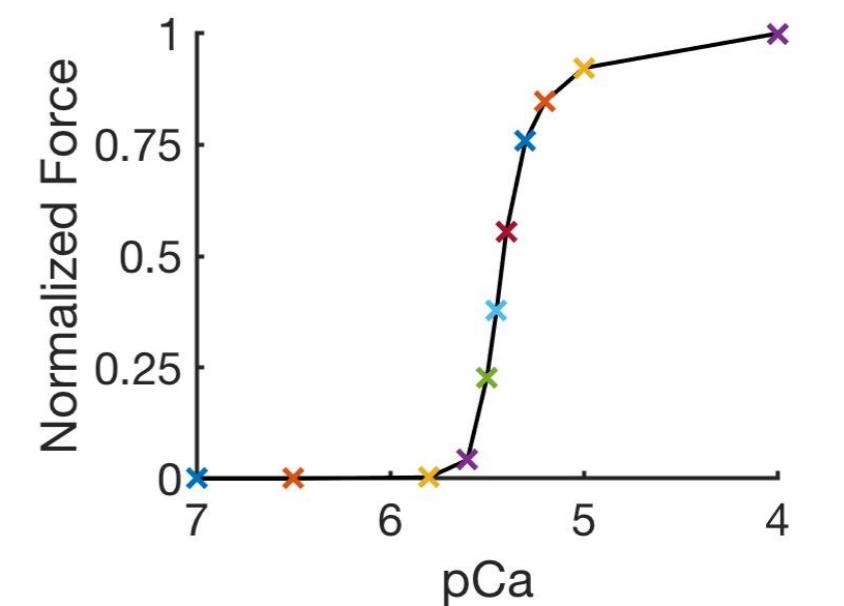
Sarcomere Markov Chain Model



Single $[\text{Ca}^{2+}]$



Force trace for
many $[\text{Ca}^{2+}]$



Average SS force used to
generate Force-pCa curve

Even more spatially explicit models exist
- balance of complexity vs. tractability

