**Dynamics of cross-bridge cycling, ATP hydrolysis, force generation, and deformation in cardiac muscle, Tewari et al. (2016) J Mol Cell Cardiol. 96:11-25, Model Documentation**

This document supplements the mathematical formulation of the model of Tewari et al. (2016) and serves as a guide to understand the associated computer code.

*Overall structure of model:*

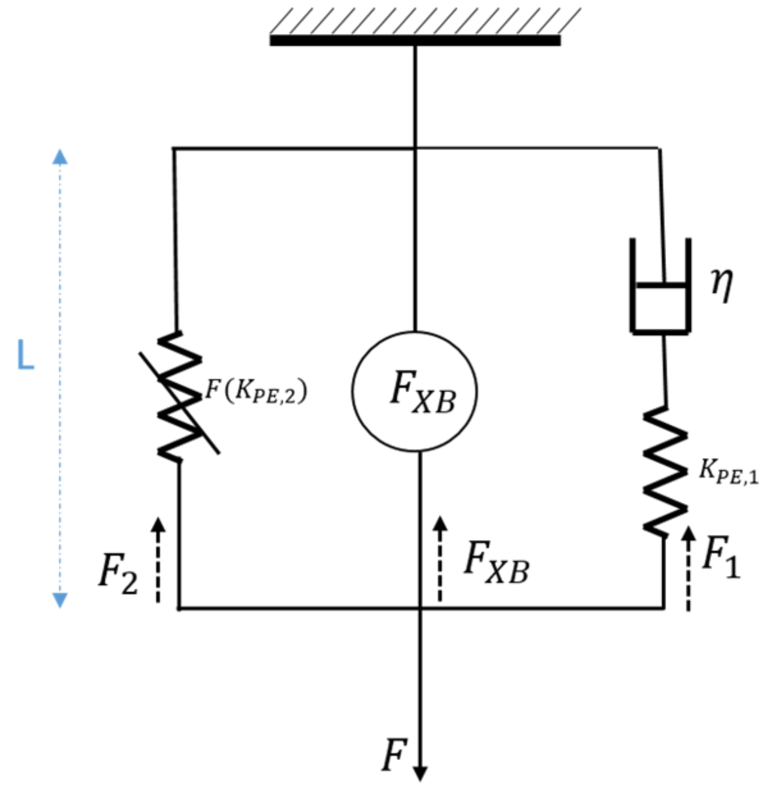



Figure 1. Cardiac muscle model.

In this model, $F_{XB}$ is the active force generated by the cross-bridge mechanics, $F_1$ and $F_2$ are passive forces associated with the muscle, and $F$ is the applied force. Overall force balance for the model yields

$$F(t) = F_{XB}(t) + F_1(t) + F_2(t). \tag{1}$$

The model has no mass (initial terms).

*Active and passive contributions to the force:*

The model for active force ($F_{XB}$) force due to cross bridge is

$$F_{XB}(t) = k_{stiff,1}\left(\int_{-\infty}^{+\infty} sp_2(t,s)ds + \int_{-\infty}^{+\infty} sp_3(t,s)ds\right) + k_{stiff,2}\,\Delta r \int_{-\infty}^{+\infty} p_3(t,s)ds, \tag{2}$$

where $k_{stiff,1}$ and $k_{stiff,2}$ are effective stiffness constants, $\Delta r$ is the cross bridge strain associated with ratcheting deformation, and $s$ is an independent variable representing strain in the population of attached cross-bridge states. Thus, the integrals in Equation (2) represent the following quantities:

$\frac{\int_{-\infty}^{+\infty} sp_2(t,s)ds}{\int_{-\infty}^{+\infty} p_2(t,s)ds}$ : average strain of attached cross bridges in model state 2

$\frac{\int_{-\infty}^{+\infty} sp_3(t,s)ds}{\int_{-\infty}^{+\infty} p_3(t,s)ds}$ : average strain of attached cross bridges in model state 3

$\int_{-\infty}^{+\infty} p_3(t,s)ds$ : fraction of cross bridges in model state 3

The spring and dashpot ($F_1$ and $\eta$) represent a linear Maxwell viscous model, governed by

$$\frac{dF_1}{dt} = K_{PE,1}(\frac{dL}{dt} - \frac{F_1}{\eta}) \tag{3}$$

How to get to equation (3):

Consider the $F_1$ branch in Fig. 1 that includes the dashpot (damper) and the spring.

Since the dashpot and the spring are in series, the forces transmitted through both elements are equal

$F_1 = F_\eta = F_{K_{PE,1}}$. (i)

Total strain $\Delta L$ is equal to sum of the strains $\Delta L = \Delta L_{K_{PE,1}} + \Delta L_\eta$. (ii)

For the spring and the dashpot (viscous element) we can write the force-displacement and the force-rate of displacement equations as following:

$F_{K_{PE,1}} = K_{PE,1}\, \Delta L_{K_{PE,1}}$ (iii)

$F_\eta = \eta \frac{\mathrm{d}L_\eta}{dt}$ (iv)

Now we obtain the rate of the change in lengths (L):

(the derivative of Equation (ii) and (iii) w.r.t time (t))

$\frac{\mathrm{d}L}{dt} = \frac{\mathrm{d}L_{K_{PE,1}}}{dt} + \frac{\mathrm{d}L_\eta}{dt}$ (v)

$\frac{\mathrm{d}L_{K_{PE,1}}}{dt} = \frac{1}{K_{PE,1}} \frac{\mathrm{d}F_{K_{PE,1}}}{dt}$ (vi)

Recalling Equations (i), (iv), and (vi), we can rewrite Equation (v):

$\frac{\mathrm{d}L}{dt} = \frac{1}{K_{PE,1}} \frac{\mathrm{d}F_1}{dt} + \frac{F_1}{\eta}$ (vii)

Rearranging equation (vii) we get equation 3:

$\frac{dF_1}{dt} = K_{PE,1}(\frac{dL}{dt} - \frac{F_1}{\eta})$ (viii)

$F_2$ is a nonlinear force:

$$F_2\,(L) = \begin{cases} \beta.K_{PE,1}\ \left[e^{\left(PExp_{titin}(L-SL_{rest})\right)} - 1\right]\ \ if\ L > SL_{rest} \\ -\beta.K_{PE,1}\ \left[e^{\left(PExp_{titin}(SL_{rest}-L)\right)} - 1\right]\ \ if\ L < SL_{rest} \end{cases} \tag{4}$$

Where $L$ is a sarcomere length[1].

To obtain a governing equation for length as a function of time, we rearrange Equation (3):

$$\frac{dL}{dt} = \frac{1}{K_{PE,1}}\left(\frac{dF_1}{dt}\right) + \frac{F_1}{\eta} \tag{5}$$

Substituting $F_1 = F - F_{XB} - F_2$ from Equation (1) we have

$$\frac{dL}{dt} = \frac{\dot{F}-\dot{F}_{XB}-\dot{F}_2}{K_{PE,1}} + \frac{F-F_{XB}-F_2}{\eta} \quad . \tag{6}$$

To simulate muscle dynamics according to Equation (6), we need to calculate $\dot{F}_{XB}$ taking the time derivative of the Equation (2):

$$\dot{F}_{XB} = \frac{dF_{XB}}{dt} = k_{stiff,1}\frac{d}{dt}\left(\int_{-\infty}^{+\infty} sp_2(t,s)ds + \int_{-\infty}^{+\infty} sp_3(t,s)ds\right) + k_{stiff,2}\,\Delta r\frac{d}{dt}\int_{-\infty}^{+\infty} p_3(t,s)ds \tag{7}$$

Using the moment definitions, this equation is written

$$\dot{F}_{XB} = k_{stiff,1}\left(\dot{p_2^1} + \dot{p_3^1}\right) + k_{stiff,2}\,\Delta r(\dot{p_3^0}). \tag{8}$$

Expressions for $\dot{p_3^0}$, $\dot{p_2^1}$ and $\dot{p_3^1}$ are obtained from Equation (11) in the paper:

$$\frac{dp_2^1}{dt} = v\,p_2^0 + \widetilde{k_1}(p_1^1 - \alpha_1 p_1^2) - k_{-1}(p_2^1 + \alpha_1 p_2^2) - k_2\,(p_2^1 - \alpha_2 p_2^2) + k_{-2}\,(p_3^1)$$

$$\frac{dp_3^1}{dt} = v\,p_3^0 + k_2\,(p_2^1 - \alpha_2 p_2^2) - k_{-2}\,(p_3^1) - k_3(p_3^1 - \alpha_3 s_3^2 p_3^1 + 2\alpha_3 s_3 p_3^2)$$

$$\frac{dp_3^0}{dt} = k_2\,(p_2^0 - \alpha_2 p_2^1 + 0.5 * \alpha_2^2 p_2^2) - k_{-2}\,(p_3^0) - k_3(p_3^0 - \alpha_3 s_3^2 p_3^0 + 2\alpha_3 s_3 p_3^1 + p_3^2) \tag{9}$$

(Note that for $i > 2$ we assume $p_k^i$ = 0.)

Substituting Equations (9) into Equation (8):

[1] Instead of x, SL and L which have been used interchangeably in the paper for sarcomere length, we use L for sarcomere length in this document.

$$\dot{F}_{XB} = k_{stiff,1} * \left( v\, p_2^0 + v\, p_3^0 + \widetilde{k_1}(p_1^1 - \alpha_1 p_1^2) - k_{-1}(p_2^1 + \alpha_1 p_2^2) + k_3 \left(p_3^1 - \alpha_3 s_3^2 p_3^1 + 2\alpha_3 s_3 p_3^2\right)\right) + k_{stiff,2}\, \Delta r\, (k_2 \left(p_2^0 - \alpha_2 p_2^1 + 0.5 * \alpha_2^2 p_2^2\right) - k_{-2}\left(p_3^0\right) - k_3 \left(p_3^0 - \alpha_3 s_3^2 p_3^0 + 2\alpha_3 s_3 p_3^1 + p_3^2\right)) \quad (10)$$

Recalling the velocity of sliding

$$v = \frac{dL}{dt}$$

We can cast the right-hand side of Equation (10) as having a velocity dependent term and velocity independent term:

$$\dot{F}_{XB} = A_{XB} + B_{XB} \frac{dL}{dt} \quad (11)$$

where the velocity-dependent term is

$$B_{XB} = k_{stiff,1}( p_2^0 + p_3^0). \quad (12)$$

Taking the derivative of $F_2$ with respect to time, we have

$$\dot{F}_2 = \frac{\partial F_2}{\partial L}\frac{dL}{dt} = (\beta. k_{PE,2})(PExp_{titin})\left[e^{(PExp_{titin}(L - SL_{rest}))}\right]\frac{dL}{dt} \quad (13)$$

Next, substituting Equation (11) into the Equation (6) yields

$$\frac{dL}{dt} = \frac{1}{k_{PE,1}}\left(\dot{F} - A_{XB} - B_{XB}\frac{dL}{dt} - \frac{\partial F_2}{\partial L}\frac{dL}{dt}\right) + \frac{1}{\eta}(F - F_{XB} - F_2)\ . \quad (14)$$

Rearranging we have

$$\frac{dL}{dt}\left(1 + \frac{B_{XB}}{k_{PE,1}} + \frac{1}{k_{PE,1}}\frac{\partial F_2}{\partial L}\right) = \frac{1}{k_{PE,1}}\left(\dot{F} - A_{XB}\right) + \frac{1}{\eta}(F - F_{XB} - F_2),$$

or

$$\frac{dL}{dt} = \frac{\frac{1}{k_{PE,1}}(\dot{F} - A_{XB}) + \frac{1}{\eta}(F - F_{XB} - F_2)}{\left(1 + \frac{B_{XB}}{k_{PE,1}} + \frac{1}{k_{PE,1}}\frac{\partial F_2}{\partial L}\right)}\ . \quad (15)$$

*Simulation of quick-release experiment:*

To simulate the quick-release experiment, the internal states of the cross bridges and the sarcomere length kinetics are simulated by integrating Equation (15) in parallel with Equation (3-6) from the paper, governing the cross-bridge kinetics:

$$\frac{dP}{dt} = k_{np}N(t) - k_{pn}P(t) + \tilde{k}_d\, \hat{p}_1(t,s) - k_a P(t) + \tilde{k}_3\, e^{\alpha_3 (s+s_3)^2} p_3(t,s) \quad (16)$$

$$\frac{\partial p_1}{\partial t} + \frac{dL}{dt}\frac{\partial p_1}{\partial s} = k_a \delta(s) P(t) - \tilde{k}_d\, p_1 - \tilde{k}_1\, e^{-\alpha_1 s}\, p_1 + k_{-1}\, e^{+\alpha_1 s}\, p_2$$

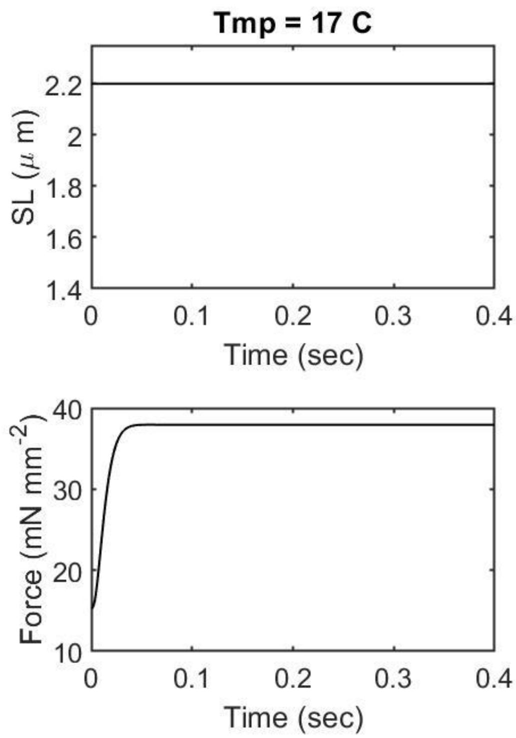
$$\frac{\partial p_2}{\partial t} + \frac{dL}{dt}\frac{\partial p_2}{\partial s} = \tilde{k}_1\, e^{-\alpha_1 s}\, p_1 - k_{-1}\, e^{+\alpha_1 s}\, p_2 - \; k_2\, e^{-\alpha_2 s}\, p_2 + \tilde{k}_{-2}\, p_3$$

$$\frac{\partial p_3}{\partial t} + \frac{dL}{dt}\frac{\partial p_3}{\partial s} = \; k_2\, e^{-\alpha_1 s}\, p_2 - \tilde{k}_{-2}\, p_3 - \tilde{k}_3\, e^{\alpha_3 (s+s_3)^2} p_3$$

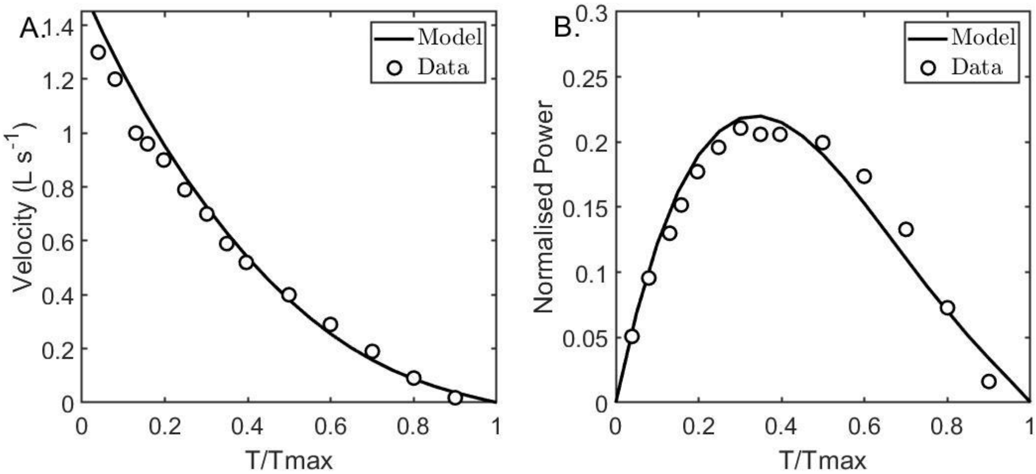
The initial state is obtained by holding the muscle at a fixed length $L_0$ = 2.2 μm, and integrating Equation (16) to reach a steady-state. Starting from this initial state, the applied force is reduced to a defined fraction of initial force, and the muscle dynamics simulated by integrating Equations (15) and (16).

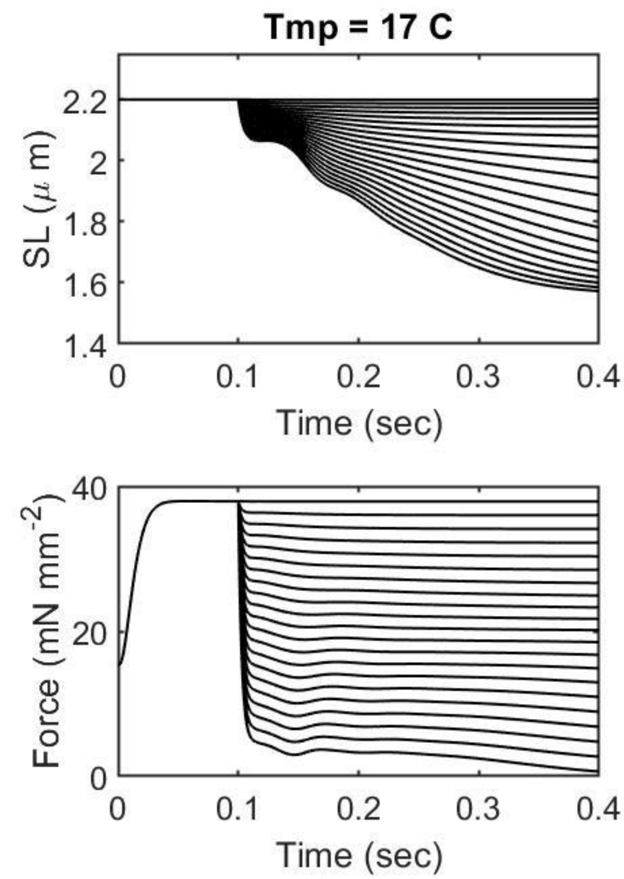
The following is the plot for the steady state force and fixed length of sarcomere. ($L_0$ = 2.2 μm)

The magnitude of the steady state has been used as an initial condition.




Following are the results with the above derivations




**Corrections on the original MATLAB code:**

1. In the original code, $p_3^2$ in Equation (10) was multiplied by $\alpha_3$ and the above derivation shows no coefficient for $p_3^2$. This typo, which negligible effects on the results, is fixed in the current (2019) distribution of the codes.
2. The Passive force subroutine has some typos for the passive force formulations. (Equations 2 and 13)

**Corrections in the paper:**

1. Equation (3) in the paper, should be (missing hat on $\hat{p}_1$ *and* $\hat{p}_3$)

$$\frac{dP}{dt} = k_{np}N(t) - k_{pn}P(t) + \tilde{k}_d\ \hat{p}_1(t,s) - \ k_a P(t) + \tilde{k}_3\ e^{\alpha_3(s+s_3)^2} p_3(t,s) \text{ -}$$

2. "$F$" in denominator of the LHS of the equation 12 of the paper should be changed to $\frac{dL}{dt}$

$$\frac{dL}{Ft} \rightarrow \frac{dL}{dt}$$

3. Page 23, Appendix D, line 11. "Panels C and D of Fig. D1" should be changed to "Panels B and D of Fig. D1"