Skeltal muscle FTU

We consider a 3 compartment voltage regulated/Ca^{2+} dependent Muscle cell ODE model. This model consists of Ca^{2+} conc. in the SR and the Myofibril space as described in Liu and Olson,2015 coupled with a Ca^{2+} dependent 4 state muscle contraction model as described in Razumova et al,2000.

Calcium Compartment model (Olsen and Liu 2014)

The concentration of free Ca^{2+}in the sarcoplasmic reticulum (SR) is given by

$$\frac{dC_{SR}}{dt} = -R(V) + V_{max}\frac{C_{MS}}{C_{MS} + K_{MS}} - L_p \tag{1}$$

where $R(V)$ is the Ca^{2+} release from the SR that depends on the strength of the nerve stimulation or applied input current and the resulting membrane voltage. Ca^{2+} uptake by SERCA is given by the second term on the rhs of the above equation. The leak parameter to capture the permeability of Ca^{2+} to leak from the SR is given by L_p. C_{MS}represents the concentration of free calcium in the myofibril space and is governed by the following

$$\begin{aligned}
\frac{dC_{MS}}{dt} &= R(V) + k_{t2}TC - k_{t1}C_{MS}T + k_{p2}PC - k_{p1}C_{MS}P - V_{max}\frac{C_{MS}}{C_{MS} + K_{MS}} + L_p \\
\frac{dTC}{dt} &= k_{t1}C_{MS} - k_{t2}TC \\
\frac{dPC}{dt} &= k_{p1}C_{MS}P - k_{p2}PC
\end{aligned}$$

We track the concentrations of the proteins and complexes: troponin T, parvalbumin P, troponin-Ca2+ complex TC and parvalbumin-Ca2+ complex PC. The fraction of receptors on the SR calcium release channel that are in an inactivated state is given by (Schneider and Simon, 1988)

$$\frac{dCaR}{dt} = \frac{k_f}{1 + \frac{K}{C_{MS}}} - k_r CaR - CaR\frac{k_f}{1 + \frac{K}{C_{MS}}} \tag{2}$$

The first term on the rhs describes the fraction of receptors that are bound to Ca2+ and transition to the inactivated state CaR. The second term describes inactivated Ca2+ bound receptor and the third term describes Ca2+ unbinding from the receptor. The total Ca^{2+} release from the SR $R(V)$ is given by

$$R(V) = R_{max}\left(\frac{1}{1 + \epsilon_2(1 + \epsilon_1)}\right)(1 - CaR) \tag{3}$$

where ϵ_i are functions of membrane potential V given by

$$\epsilon_i(V) = e^{\left(\bar{V}_{\epsilon_i} - V\right)/k_{\epsilon_i}} \tag{4}$$

where k and $\bar{V}$ orrespond to the steepness factor and mid-point voltage for transition respectively.

Membrane voltage (Olsen and Liu 2014)

The membrane voltahe is modeled by the governing equation

$$C_m\frac{dV}{dt} = -\left(I_{K_f} + I_{K_s} + I_{Na} + I_{Ca} + I_{Cl} + I_{leak}\right) + I_{input} \tag{5}$$

where I_j is the current in channel j, I_{leak} is a generic leak current and I_{input} is an input current.

Potassium current

Two potassium currents are considered a fast (I_{K_f}) and a slow current (I_{K_s}).

$$I_{K_f} = \bar{g_{kf}} n^4 \left(V - E_{K_f}\right)$$
$$I_{K_s} = \bar{g_{ks}} l^2 \left(V - E_{K_s}\right)$$

with gating variables n and l of the form

$$\frac{dn}{dt} = \alpha_n(V)(1-n) - \beta_n(V)n$$
$$\frac{dl}{dt} = \alpha_l(V)(1-l) - \beta_l(V)l$$
$$\alpha_k = \frac{\bar{\alpha_k}(V - \bar{V_k})}{1 - exp\left(-\frac{(V-\bar{V_k})}{\nu_k}\right)}$$
$$\beta_n = \frac{\bar{\beta_n}}{exp\left(\frac{(V-\bar{V_n})}{b_k}\right)}$$
$$\beta_l = \frac{\bar{\beta_l}(V - \bar{V_l})}{exp\left(\frac{(V-\bar{V_l})}{b_l}\right) - 1}$$

Sodium Current

Parametrers from experiments with striated skeletal muscle fibers were fitted to the standard Huxley sodium current

$$I_{Na} = \bar{g_{Na}} m_{Na}^3 h_{Na}(V - E_{Na})$$
$$\frac{dm_{Na}}{dt} = \alpha_{m1}(V)(1 - m_{Na}) - \beta_{m1}(V)m_{Na}$$
$$\beta_{m1} = \frac{\bar{\beta_{m1}}}{exp\left(\frac{(V-\bar{V_{m1}})}{b_{m1}}\right)}$$
$$\alpha_{m1} = \frac{\bar{\alpha_{m1}}(V - \bar{V_{m1}})}{1 - exp\left(-\frac{(V-\bar{V_{m1}})}{\nu_{m1}}\right)}$$
$$\frac{dh_{Na}}{dt} = \alpha_{h1}(V)(1 - h_{Na}) - \beta_{h1}(V)h_{Na}$$
$$\beta_{h1} = \frac{\bar{\beta_{h1}}}{1 + exp\left(-\frac{(V-\bar{V_{h1}})}{b_{h1}}\right)}$$
$$\alpha_{h1} = \frac{\bar{\alpha_{h1}}}{exp\left(\frac{(V-\bar{V_{h1}})}{\nu_{h1}}\right)}$$

Calcium current

Calcium channel kinetics is based in the model of Sanchez and Stefani 1970

$$
\begin{aligned}
I_{Ca} &= \bar{g_{Ca}} m_{Ca}^3 h_{Na} (V - E_{Na}) \\
\frac{dm_{Ca}}{dt} &= \alpha_{m2}(V)(1 - m_{Ca}) - \beta_{m2}(V) m_{Ca} \\
\beta_{m2} &= \bar{\beta_{m2}} exp\left(\frac{(\bar{V_{m2}} - V)}{b_{m2}}\right) \\
\alpha_{m2} &= \frac{\bar{\alpha_{m2}}(V - \bar{V_{m2}})}{1 - exp\left(\frac{(\bar{V_{m1}} - V)}{\nu_{m2}}\right)} \\
\frac{dh_{Ca}}{dt} &= \alpha_{h2}(V)(1 - h_{Ca}) - \beta_{h2}(V) h_{Ca} \\
\beta_{h1} &= \frac{\bar{\beta_{h2}}}{1 + exp\left(\frac{(\bar{V_{h2}} - V)}{b_{h2}}\right)} \\
\alpha_{h2} &= \bar{\alpha_{h2}} exp\left(\frac{(\bar{V_{h2}} - V)}{\nu_{h2}}\right)
\end{aligned}
$$

Chlorine current

The chlorine current is modelled by

$$
I_{Cl} = \bar{g_{Cl}} \left(\nu_{Cl} + \frac{1 - \nu_{Cl}}{1 + exp\left(\frac{\bar{V_{Cl}} - V}{k_{Cl}}\right)}\right)(V - E_{Cl}) \tag{6}
$$

The generic leak current is represented by

$$
I_{leak} = g_{leak}\,(V - E_{leak})\,. \tag{7}
$$

Finally the input current is given by

$$
I_{input} = \begin{cases} I_{app} & t_{on} \le t \le t_{off} \\ 0 & otherwise \end{cases} \tag{8}
$$

All parameters can be found in the original paper.

Contractile mechanism (Razumova et al 2000)

We adopt the reduced 4-state representation of the 8-state myofilament activation and crossbridge cycling model. This can be modelled by the following system

$$
\begin{aligned}
\frac{dD}{dt} &= k_{on} R_{off} - k_{off} D + g_s A_2 + g A_1 - f D \\
\frac{dA_1}{dt} &= f D + h_2 A_2 - g A_1 - h_1 A_1 \\
\frac{dA_2}{dt} &= h_1 A_1 - h_2 A_2 - g_s A_2
\end{aligned}
$$

where D, A_1 and A_2represent the detatched, attached and attached power stroke states respectively. R_{off} represents the off state tropomyosin-troponin regulatory unit, such that cross-bridge contraction is unable to occur. Via conservation of crossbridge units

$$
R_{off} = 1 - D - A_1 - A_2. \tag{9}
$$

The contractile force $F = A_1 + A_2$ with the fraction of cycling crossbridges that are generating force is given by

$$\lambda_{cyc} = \frac{A_2}{D + A_1 + A_2}. \tag{10}$$

All parameters can be found in the original papers.

References

[Liu and Olson, 2015] Liu, Weifan, and Sarah D. Olson. "Compartment calcium model of frog skeletal muscle during activation." Journal of theoretical biology 364 (2015): 139-153.

[Razumova et al, 2000] Razumova, Maria V., Anna E. Bukatina, and Kenneth B. Campbell. "Different myofilament nearest-neighbor interactions have distinctive effects on contractile behavior." Biophysical journal 78, no. 6 (2000): 3120-3137.