

The modeling procedure, including the equation derivation and parameter setting for the motoneuron and muscle fibers, was fully presented in our previous studies (Kim et al., 2014; Kim et al., 2015).

### 1. System equations used for the reduced motoneuron model

$$C_{m,S} \cdot \frac{dV_S}{dt} = -\sum I_{soma} - G_{m,S} \cdot (V_S - E_{Leak,S}) - \frac{G_C}{p} \cdot (V_S - V_D) + I_S \quad (1.1)$$

$$\sum I_{soma} = I_{Naf,S} + I_{Kdr,S} + I_{Can,S} + I_{K(Ca),S} + I_{Nap,S} + I_{H,S} + I_{syn,S}$$

$$C_{m,D} \cdot \frac{dV_D}{dt} = -\sum I_{dendrite} - G_{m,D} \cdot (V_D - E_{Leak,D}) - \frac{G_C}{1-p} \cdot (V_D - V_S) \quad (1.2)$$

$$\sum I_{dendrite} = I_{Naf,D} + I_{Kdr,D} + I_{Can,D} + I_{K(Ca),D} + I_{Nap,D} + I_{H,D} + I_{Cal,D} + I_{syn,D}$$

where the subscripts  $S$  and  $D$  indicate the soma and dendrites, respectively,  $V$  is the membrane potential,  $E_{Leak}$  is the reversal potential of the leak current,  $G$  and  $C$  indicate specific membrane conductance and capacitance,  $\sum I$  indicates transmembrane currents and  $I_S$  is intracellularly injected current at the soma.

#### 1.1 Inverse equations for the five cable parameters

$$G_{m,S} = \frac{1 - VA_{DS}^{DC}}{r_N (1 - VA_{SD}^{DC} VA_{DS}^{DC})} \quad (1.3)$$

$$G_{m,D} = \frac{p VA_{DS}^{DC} (1 - VA_{SD}^{DC})}{(1-p) r_N VA_{SD}^{DC} (1 - VA_{SD}^{DC} VA_{DS}^{DC})} \quad (1.4)$$

$$G_C = \frac{p VA_{DS}^{DC}}{r_N (1 - VA_{SD}^{DC} VA_{DS}^{DC})} \quad (1.5)$$

$$C_{m,D} = \frac{1}{\omega(1-p)} \sqrt{\frac{G_C^2}{(VA_{SD}^{AC})^2} - \{G_C + G_{m,D}(1-p)\}^2} \quad (1.6)$$

$$C_{m,S} = \frac{\tau_m \{p(1-p)\tau_m G_{m,S} G_{m,D} + p G_{m,S} (\tau_m G_C - C_{m,D}) + p^2 G_{m,S} C_{m,D} + (1-p)(\tau_m G_C G_{m,D} - G_C C_{m,D})\}}{p \{(1-p)(\tau_m G_{m,D} - C_{m,D}) + \tau_m G_C\}} \quad (1.7)$$

where  $VA$  indicates the voltage attenuation factor calculated between the soma and dendrites and  $r_N$  is the value of  $R_N$  normalized to the surface area of the somatic compartment. In the current version of PyMUS (PyMUS v2.0), the surface area for the somatic compartment,  $p$  and  $\omega$  were set to  $0.3157 \text{ m}^2$ ,  $0.5$  and  $2\pi \times 250 \text{ Hz}$ , respectively.

#### 1.2 Equations for the active currents

In the current version of PyMUS (PyMUS v2.0), the soma and dendrite have the same types of active membrane properties, except for the additional inclusion of low voltage activated L-type calcium current in the dendrite. All voltage gated ion channels were modeled based on the HH type formulation as follows:  $I_{Ion} = G_{Ion} \cdot m_{ion}^a \cdot h_{ion}^b \cdot (V - E_{Ion})$ , where  $G_{Ion}$  is the peak conductance of the specific ion current,  $m_{ion}$  and  $h_{ion}$  are the gating variables for activation and inactivation,  $a$  and  $b$  are the order of activation and inactivation, and  $E_{Ion}$  is the reversal potential for the ion of interest. The active mechanisms included in both the soma and the dendrite were indicated by the subscript  $X$  unless otherwise stated with the subscript  $S$  or  $D$  in the following equations.

Fast Na<sup>±</sup> current

$$\begin{aligned}
I_{Naf,X} &= G_{Naf,X} \cdot m_{naf}^3 \cdot h_{naf} \cdot (V_X - E_{Na,X}) \\
\frac{dm_{naf}}{dt} &= \alpha_m \cdot (1 - m_{naf}) - \beta_m \cdot m_{naf} \text{ where} \\
\alpha_m &= \frac{\alpha_{nafm1,X} \cdot (V_X + \alpha_{nafm2,X})}{\exp\left(-\frac{V_X + \alpha_{nafm2,X}}{\alpha_{nafm3,X}}\right) + \alpha_{nafm4,X}}, \quad \beta_m = \frac{\beta_{nafm1,X} \cdot (V_X - \beta_{nafm2,X})}{\exp\left(\frac{V_X - \beta_{nafm2,X}}{\beta_{nafm3,X}}\right) + \beta_{nafm4,X}} \\
\frac{dh_{naf}}{dt} &= \frac{h_\infty - h_{naf}}{\tau_h} \text{ where} \\
h_\infty &= \frac{1}{1 + \exp\left(\frac{V_X - \gamma_{nafh1,X}}{\gamma_{nafh2,X}}\right)}, \quad \tau_h = \frac{\gamma_{nafh6,X}}{\exp\left(\frac{V_S - \gamma_{nafh3,X}}{\gamma_{nafh4,X}}\right) + \exp\left(-\frac{V_S - \gamma_{nafh3,X}}{\gamma_{nafh5,X}}\right)}
\end{aligned} \tag{1.8}$$

Delayed rectifier K<sup>+</sup> current

$$\begin{aligned}
I_{Kdr,X} &= G_{Kdr,X} \cdot n_{kdr}^4 \cdot (V_X - E_{K,X}) \\
\frac{d(n_{kdr})}{dt} &= \frac{(n_\infty - n_{kdr})}{\tau_n} \text{ where} \\
n_\infty &= \frac{1}{1 + \exp\left(-\frac{V_X - \gamma_{kdrm1,X}}{\gamma_{kdrm2,X}}\right)}, \quad \tau_n = \frac{\gamma_{kdrm6,X}}{\exp\left(\frac{V_X - \gamma_{kdrm3,X}}{\gamma_{kdrm4,X}}\right) + \exp\left(-\frac{V_X - \gamma_{kdrm3,X}}{\gamma_{kdrm5,X}}\right)}
\end{aligned} \tag{1.9}$$

N-Type Ca<sup>2+</sup> current

$$\begin{aligned}
I_{Can,X} &= G_{Can,X} \cdot m_{can}^2 \cdot h_{can} \cdot (V_X - E_{Ca,X}) \\
\frac{d(m_{can})}{dt} &= \frac{m_\infty - m_{can}}{\tau_m} \text{ where } m_\infty = \frac{1}{1 + \exp\left(-\frac{V_X - \gamma_{canm1,X}}{\gamma_{canm2,X}}\right)}, \quad \tau_m = \gamma_{canm3,X} \\
\frac{d(h_{can})}{dt} &= \frac{h_\infty - h_{can}}{\tau_h} \text{ where } h_\infty = \frac{1}{1 + \exp\left(\frac{V_X - \gamma_{canh1,X}}{\gamma_{canh2,X}}\right)}, \quad \tau_h = \gamma_{canh3,X}
\end{aligned} \tag{1.10}$$

Ca<sup>2+</sup> concentration dynamics

$$\frac{d[Ca^{2+}]_{i,X}}{dt} = f_X (-\alpha_X \cdot I_{Can,X} - K_{Ca,X} \cdot [Ca^{2+}]_{i,X}) \tag{1.11}$$

Equilibrium potential for Ca<sup>2+</sup>

$$E_{Ca,X} = \frac{1000 \cdot R \cdot T}{Z_{Ca} \cdot F} \cdot \log\left(\frac{[Ca^{2+}]_{o,X}}{[Ca^{2+}]_{i,X}}\right) - 70 \tag{1.12}$$

where  $R=8.31441$  VC/mol·K,  $T=309.15$  K,  $Z_{Ca}=2$ ,  $F=96485.309$  C/mol with  $[Ca^{2+}]_o=2$  mM.

Calcium dependent K<sup>+</sup> current

$$I_{K(Ca),X} = G_{K(Ca),X} \cdot \frac{[Ca^{2+}]_{i,X}}{[Ca^{2+}]_{i,X} + K_{d,X}} \cdot (V_X - E_{K,X}) \quad (1.13)$$

Persistent Na<sup>+</sup> current:

$$I_{Nap,X} = G_{Nap,X} \cdot m_{nap}^3 \cdot (V_X - E_{Na,X}) \quad (1.14)$$

$$\frac{d(m_{nap})}{dt} = \alpha_m \cdot (1 - m_{nap}) - \beta_m \cdot m_{nap} \text{ where}$$

$$\alpha_m = \frac{\alpha_{napm1,X} \cdot (V_X - \alpha_{napm2,X})}{\exp\left(-\frac{V_X - \alpha_{napm2,X}}{\alpha_{napm3,X}}\right) + \alpha_{napm4,X}}, \quad \beta_m = \frac{\beta_{napm1,X} \cdot (V_X - \beta_{napm2,X})}{\exp\left(\frac{V_X - \beta_{napm2,X}}{\beta_{napm3,X}}\right) + \beta_{napm4,X}}$$

Hyperpolarization-activated mixed cation current

$$I_{H,X} = G_{H,X} \cdot m_h \cdot (V_X - E_{H,X}) \quad (1.15)$$

$$\frac{d(m_h)}{dt} = \frac{m_\infty - m_h}{\tau_m} \text{ where } m_\infty = \frac{1}{\exp\left(\frac{V_s + \gamma_{hm1,X}}{\gamma_{hm2,X}}\right)}, \quad \tau_m = \gamma_{hm3,X}$$

Synaptic current

$$I_{syn,X} = I_{esyn,X} + I_{isyn,X} \quad (1.16)$$

$$I_{esyn,X} = G_{esyn,X} \cdot (V_X - E_{esyn,X})$$

$$\frac{dG_{esyn,X}}{dt} = -\frac{1}{\tau_{esyn,X}} \cdot (G_{esyn,X} - G_{esyn0,X}) + \sqrt{\frac{2\sigma_{esyn,X}^2}{\tau_{esyn,X}}} \cdot \chi_1$$

$$I_{isyn,X} = G_{isyn,X} \cdot (V_X - E_{isyn,X})$$

$$\frac{dG_{isyn,X}}{dt} = -\frac{1}{\tau_{isyn,X}} \cdot (G_{isyn,X} - G_{isyn0,X}) + \sqrt{\frac{2\sigma_{isyn,X}^2}{\tau_{isyn,X}}} \cdot \chi_2$$

Dynamical variation in excitatory ( $G_{esyn,X}$ ) and inhibitory ( $G_{isyn,X}$ ) synaptic conductance with noise was formulated using the Ornstein-Uhlenbeck process, where  $G_{esyn0,X}$  and  $G_{isyn0,X}$  are the mean of  $G_{esyn,X}$  and  $G_{isyn,X}$ ,  $\tau$  is a time constant,  $\sigma$  is the standard deviation from the mean conductance and  $\chi$  is a random Gaussian noise process with a mean of 0 and a standard deviation of 1 (Destexhe et al., 2001).

Low voltage activation L-type Ca<sup>2+</sup> current

$$I_{Cal,D} = G_{Cal,D} \cdot l_{cal} \cdot (V_D - E_{Ca,D}) \quad (1.17)$$

$$\frac{dl_{cal}}{dt} = \frac{l_\infty - l_{cal}}{\tau_l} \text{ where } l_\infty = \frac{1}{1 + \exp\left(-\frac{V_D - \gamma_{calm1,D}}{\gamma_{calm2,D}}\right)}, \quad \tau_l = \gamma_{calm3,D}$$

## 2. System equations used for the muscle-tendon model

Module 1: The transformation of action potentials to calcium dynamics in the sarcoplasm

$$\frac{d[Ca_{SR}]}{dt} = -K1 \cdot CS_0 \cdot [Ca_{SR}] + (K1 \cdot [Ca_{SR}] + K2) \cdot [Ca_{SR}CS] - R + U \quad (2.1)$$

$$\frac{d[Ca_{SR}CS]}{dt} = K1 \cdot CS_0 \cdot [Ca_{SR}] - (K1 \cdot [Ca_{SR}] + K2) \cdot [Ca_{SR}CS] \quad (2.2)$$

where  $[Ca_{SR}]$ ,  $[Ca_{SR}CS]$  and  $CS_0$  indicate the concentration of free calcium ions,  $Ca^{2+}$  bound to calsequestrin and total calsequestrin in the sarcoplasmic reticulum (SR), respectively,  $K1$  and  $K2$  are the forward and backward constants for reaction kinetics between the  $Ca_{SR}$  and  $Ca_{SR}CS$  and the release ( $R$ ) of  $Ca^{2+}$  from the SR and the uptake ( $U$ ) of  $Ca^{2+}$  into the SR were mathematically modeled as

$$R = [Ca_{SR}] \cdot R_{\max} \cdot \sum_{i=1}^n \left( 1 - \exp\left(-\frac{t-t_i}{\tau_1}\right) \right) \cdot \exp\left(-\frac{t-t_i}{\tau_2}\right),$$

$$U = U_{\max} \cdot \left( \frac{[Ca_{SP}]^2 \cdot K^2}{1 + [Ca_{SP}] \cdot K + [Ca_{SP}]^2 \cdot K^2} \right)^2$$

$$\frac{d[Ca_{SP}]}{dt} = -(K3 \cdot B_0 + K5 \cdot T_0) \cdot [Ca_{SP}] + (K3 \cdot [Ca_{SP}] + K4) \cdot [Ca_{SP}B] + (K5 \cdot [Ca_{SP}] + K6) \cdot [Ca_{SP}T] + R - U \quad (2.3)$$

$$\frac{d[Ca_{SP}B]}{dt} = K3 \cdot B_0 \cdot [Ca_{SP}] - (K3 \cdot [Ca_{SP}] + K4) \cdot [Ca_{SP}B] \quad (2.4)$$

$$\frac{d[Ca_{SP}T]}{dt} = K5 \cdot T_0 \cdot [Ca_{SP}] - (K5 \cdot [Ca_{SP}] + K6) \cdot [Ca_{SP}T] \quad (2.5)$$

where  $[Ca_{SP}]$ ,  $[Ca_{SP}B]$ ,  $[Ca_{SP}T]$ ,  $B_0$  and  $T_0$  indicate the concentration of free calcium ions,  $Ca^{2+}$  bound to free calcium-buffering proteins ( $B$ ),  $Ca^{2+}$  bound to troponin ( $T$ ), total free calcium-buffering proteins and total troponin in the sarcoplasm ( $SP$ ), respectively and  $K3$ - $K6$  are the rate constants for chemical reactions between the  $Ca_{SP}$ ,  $B$ ,  $T$ ,  $Ca_{SP}B$  and  $Ca_{SP}T$  in which  $K5$  and  $K6$  were modulated as a function of muscle length ( $X_m$ ) and activation level ( $\tilde{A}$ ) under steady  $Ca^{2+}$  stimulation as follows,

$$K5 = K5_i \cdot \varphi(X_m), \begin{cases} \varphi(X_m) = \varphi_1 \cdot X_m + \varphi_2, & \text{for } X_m < \text{optimal length} \\ \varphi(X_m) = \varphi_3 \cdot X_m + \varphi_4, & \text{for } X_m \geq \text{optimal length} \end{cases},$$

$$K6 = \frac{K6_i}{1 + 5 \cdot \tilde{A}}$$

In the current version of PyMUS (PyMUS v2.0),  $CS_0$ ,  $B_0$  and  $T_0$  were set to 30 (mM), 0.43 (mM) and 70 ( $\mu$ M), respectively.

Module 2: The transformation of the sarcoplasmic calcium dynamics to muscle activation dynamics

$$A(t) = \frac{(\tilde{A})^{\alpha(t)}}{(1 + \beta \cdot \varphi(X_m)) \cdot (1 + \gamma \cdot V_m)} \quad (2.6)$$

where  $V_m$  is the time derivative of  $X_m$  and the  $\tilde{A}(t)$  and its exponent ( $\alpha(t)$ ) were mathematically modeled as

$$\frac{d\tilde{A}}{dt} = \frac{\tilde{A}_\infty - \tilde{A}}{\tau_{\tilde{A}}} \text{ where } \tilde{A}_\infty = 0.5 \cdot \left( 1 + \tanh \frac{[Ca_{sp}T]/T_0 - C1}{C2} \right), \tau_{\tilde{A}} = C3 \cdot \left( \cosh \frac{[Ca_{sp}T]/T_0 - C4}{2 \cdot C5} \right)^{-1}$$

$$\alpha(t) = \begin{cases} \alpha & \text{for isometric and isokinetic contraction} \\ \alpha + \alpha_1 \cdot \left( 1 + \tanh \frac{t - \alpha_2}{\alpha_3} \right) & \text{for dynamic contraction} \end{cases}$$

In the current version of PyMUS (PyMUS v2.0),  $\alpha$  and  $\alpha_1$ – $\alpha_3$  were set to 2, 4.77, 400 (ms) and 160 (ms), respectively. The  $\beta$  and  $\gamma$  were set to 0.47 and 0.001 (s/mm) for lengths shorter than the optimal length during muscle lengthening under dynamic contraction condition otherwise both were set to 0.

### Module 3: The transformation of muscle activation to muscle force

$$F = P_0 \cdot K_{SE} \cdot (\Delta X_m - \Delta X_{CE}) \quad (2.7)$$

where  $P_0$  is the peak force at the optimal length under full excitation in the isometric condition,  $K_{SE}$  is the stiffness of the serial element normalized by  $P_0$  and the length ( $X_{CE}$ ) of contractile element was calculated using the modified Hill-Mashma equations along with the length-tension relationship ( $g(X_m)$ ),

$$\frac{dX_{CE}}{dt} = \frac{-b_0 \cdot (P_0 \cdot g(X_m) \cdot A(t) - F)}{F + a_0 \cdot g(X_m) \cdot A(t)}, \text{ for } F \leq P_0 \cdot g(X_m) \cdot A(t)$$

$$\frac{dX_{CE}}{dt} = \frac{-d_0 \cdot (P_0 \cdot g(X_m) \cdot A(t) - F)}{2 \cdot P_0 \cdot g(X_m) \cdot A(t) - F + c_0 \cdot g(X_m) \cdot A(t)}, \text{ for } F > P_0 \cdot g(X_m) \cdot A(t)$$

$$g(X_m) = \exp \left\{ - \left( \frac{X_m - g_1}{g_2} \right)^2 \right\}$$

In the current version of PyMUS (PyMUS v2.0),  $a_0$  and  $c_0$  determined from  $P_0$ , length-tension and velocity-tension relationship for entire muscle were scaled by multiplying the ratio of new to default  $P_0$  for simulations of muscle units that may show various levels of  $P_0$ .

## References

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