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

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

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

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

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

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*

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

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

$$G_C=\frac{pVA_{\mathrm{DS}}{}^{DC}}{r_N\left(1-VA_{SD}{}^{DC}VA_{DS}{}^{DC}\right)} \quad (1.5)$$

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

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

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 ω were set to 0.3157 m^2, 0.5 and $2\pi\times250$ 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 $Na^{\pm}$ current

$$I_{Naf,X} = G_{Naf,X} \cdot {m_{naf}}^3 \cdot h_{naf} \cdot \left(V_X - E_{Na,X}\right) \tag{1.8}$$

$$\frac{dm_{naf}}{dt} = \alpha_m \cdot \left(1 - m_{naf}\right) - \beta_m \cdot m_{naf} \text{ where}$$

$$\alpha_m = \frac{\alpha_{nafm1,X} \cdot \left(V_X + \alpha_{nafm2,X}\right)}{\exp\left(-\frac{V_X + \alpha_{nafm2,X}}{\alpha_{nafm3,X}}\right) + \alpha_{nafm4,X}}, \quad \beta_m = \frac{\beta_{nafm1,X} \cdot \left(V_X - \beta_{nafm2,X}\right)}{\exp\left(\frac{V_X - \beta_{nafm2,X}}{\beta_{nafm3,X}}\right) + \beta_{nafm4,X}}$$

$$\frac{dh_{naf}}{dt} = \frac{h_\infty - h_{naf}}{\tau_h} \text{ where}$$

$$h_\infty = \frac{1}{1 + \exp\left(\frac{V_X - \gamma_{nafh1,X}}{\gamma_{nafh2,X}}\right)}, \quad \tau_h = \frac{\gamma_{nafh6,X}}{\exp\left(\frac{V_S - \gamma_{nafh3,X}}{\gamma_{nafh4,X}}\right) + \exp\left(-\frac{V_S - \gamma_{nafh3,X}}{\gamma_{nafh5,X}}\right)}$$

Delayed rectifier K^+ current

$$I_{Kdr,X} = G_{Kdr,X} \cdot {n_{kdr}}^4 \cdot (V_X - E_{K,X}) \tag{1.9}$$

$$\frac{d(n_{kdr})}{dt} = \frac{(n_\infty - n_{kdr})}{\tau_n} \text{ where}$$

$$n_\infty = \frac{1}{1 + \exp\left(-\frac{V_X - \gamma_{kdrm1,X}}{\gamma_{kdrm2,X}}\right)}, \quad \tau_n = \frac{\gamma_{kdrm6,X}}{\exp\left(\frac{V_X - \gamma_{kdrm3,X}}{\gamma_{kdrm4,X}}\right) + \exp\left(-\frac{V_X - \gamma_{kdrm3,X}}{\gamma_{kdrm5,X}}\right)}$$

N-Type Ca^{2+} current

$$I_{Can,X} = G_{Can,X} \cdot {m_{can}}^2 \cdot h_{can} \cdot (V_X - E_{Ca,X}) \tag{1.10}$$

$$\frac{d(m_{can})}{dt} = \frac{m_\infty - m_{can}}{\tau_m} \text{ where } m_\infty = \frac{1}{1 + \exp\left(-\frac{V_X - \gamma_{canm1,X}}{\gamma_{canm2,X}}\right)}, \quad \tau_m = \gamma_{canm3,X}$$

$$\frac{d(h_{can})}{dt} = \frac{h_\infty - h_{can}}{\tau_h} \text{ where } h_\infty = \frac{1}{1 + \exp\left(\frac{V_X - \gamma_{canh1,X}}{\gamma_{canh2,X}}\right)}, \quad \tau_h = \gamma_{canh3,X}$$

Ca^{2+} 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^{2+}

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

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+ 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^+ 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 $G_{isyn,X}$, τ is a time constant, σ is the standard deviation from the mean conductance and χ 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^{2+} 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,

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

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

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 (μM), respectively.

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

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

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

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

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

In the current version of PyMUS (PyMUS v2.0), α and α_1– α_3 were set to 2, 4.77, 400 (ms) and 160 (ms), respectively. The β and γ 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

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

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 ($g(X_m)$),

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

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

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

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.

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