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

1. System equations used for the reduced motoneuron model

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

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

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

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

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*

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

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

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

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

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

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 (see (Kim et al., 2009;Kim and Jones, 2012) for derivation of the inverse equations (1.3)-(1.7)). In the current version of PyMUS (PyMUS v2.0), the surface area for the somatic compartment, *p* and ω were set to 0.3157 m², 0.5 and 2π×250 Hz, respectively (see Figure 2 in (Kim et al., 2014) for the parameter setting).

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$^+$ current

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

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

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

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

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

Delayed rectifier K$^+$ current

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

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

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

N-Type Ca^{2+} current

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

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

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

Ca^{2+} concentration dynamics

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

Equilibrium potential for Ca^{2+}

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

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

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

Persistent Na$^+$ current:

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

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

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

Hyperpolarization-activated mixed cation current

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

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

Synaptic current

$$I_{syn,X} = I_{esyn,X} + I_{isyn,X} \tag{1.16}$$

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

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

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

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

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

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

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

The equations for I_{Naf}, I_{Kdr}, I_{CaN}, I_{Nap}, I_{CaL} and E_{Ca} were adopted from (McIntyre and Grill, 2002), $d[Ca^{2+}]_i/dt$ and $I_{K(Ca)}$ were from (Booth et al., 1997), and I_H was from (Powers et al., 2012).

2. System equations used for the muscle-tendon model

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

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

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

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

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

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

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

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

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

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 (see the Methods in (Kim et al., 2015) for the parameter setting).

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

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

where V_m is the time derivative of X_m and the $\tilde{A}(t)$ and its exponent ($\alpha(t)$) were mathematically modeled applying the Morris-Lecar formulation that has been used to mathematically represent the dynamics of gating variables underlying membrane excitability

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(Morris and Lecar, 1981),

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

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

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 (see Table 1 in (Kim et al., 2015) for the parameter setting).

Module 3: The transformation of muscle activation to muscle force

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

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 ($g(X_m)$),

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

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

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

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

Booth, V., Rinzel, J., and Kiehn, O. (1997). Compartmental model of vertebrate motoneurons for Ca2+-dependent spiking and plateau potentials under pharmacological treatment. *J Neurophysiol* 78**,** 3371-3385.

Destexhe, A., Rudolph, M., Fellous, J.M., and Sejnowski, T.J. (2001). Fluctuating synaptic conductances recreate in vivo-like activity in neocortical neurons. *Neuroscience* 107**,** 13-24.

Kim, H., and Jones, K.E. (2012). The retrograde frequency response of passive dendritic trees constrains the nonlinear firing behaviour of a reduced neuron model. *PLoS One* 7**,** e43654.

Kim, H., Jones, K.E., and Heckman, C.J. (2014). Asymmetry in signal propagation between the soma and dendrites plays a key role in determining dendritic excitability in motoneurons. *PLoS One* 9**,** e95454.

Kim, H., Major, L.A., and Jones, K.E. (2009). Derivation of cable parameters for a reduced model that retains asymmetric voltage attenuation of reconstructed spinal motor neuron dendrites. *J Comput Neurosci* 27**,** 321-336.

Kim, H., Sandercock, T.G., and Heckman, C.J. (2015). An action potential-driven model of soleus muscle activation dynamics for locomotor-like movements. *J Neural Eng* 12**,** 046025.

Mcintyre, C.C., and Grill, W.M. (2002). Extracellular stimulation of central neurons: influence of stimulus waveform and frequency on neuronal output. *J Neurophysiol* 88**,** 1592-1604.

Morris, C., and Lecar, H. (1981). Voltage oscillations in the barnacle giant muscle fiber. *Biophys J* 35**,** 193-213.

Powers, R.K., Elbasiouny, S.M., Rymer, W.Z., and Heckman, C.J. (2012). Contribution of intrinsic properties and synaptic inputs to motoneuron discharge patterns: a simulation study. *J Neurophysiol* 107**,** 808-823.