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Research article

Optogenetic actuation in ChR2-transduced fibroblasts alter excitation-contraction coupling and mechano-electric feedback in coupled cardiomyocytes: a computational modeling study

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Supplementary

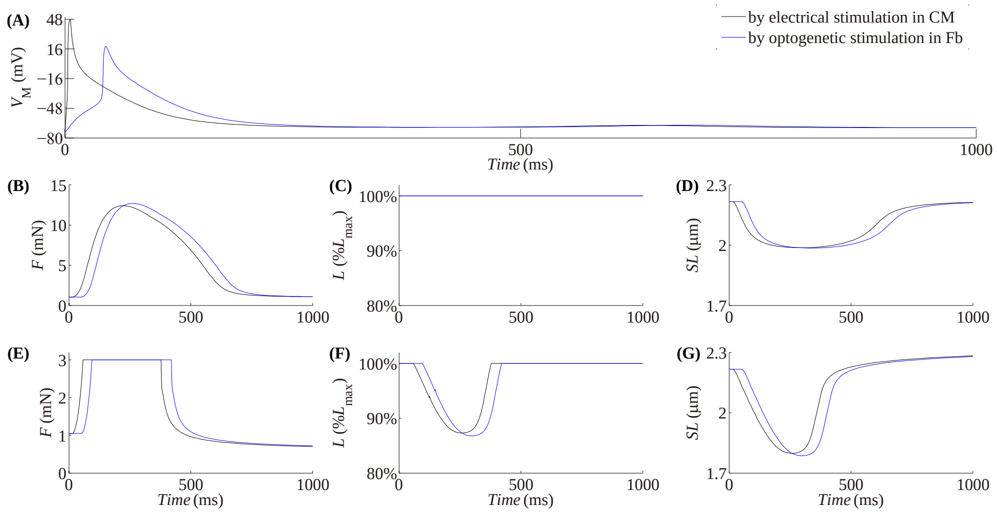

Figure S1. Membrane potentials and mechanical parameters in the CM. The electrical stimulation applied to the CM is a rectangular electrical pulse (6 ms, −15 pA/pF). The optogenetic stimulation applied to ChR2-tranduced Fbs is a light pulse (50 ms, 5 mW/mm^2). (A) V_M. (B-D) Time-dependent signals of isometric F, L and SL. (E-G) Time-dependent signals of isotonic F, L and SL applied an afterload of 3 mN.

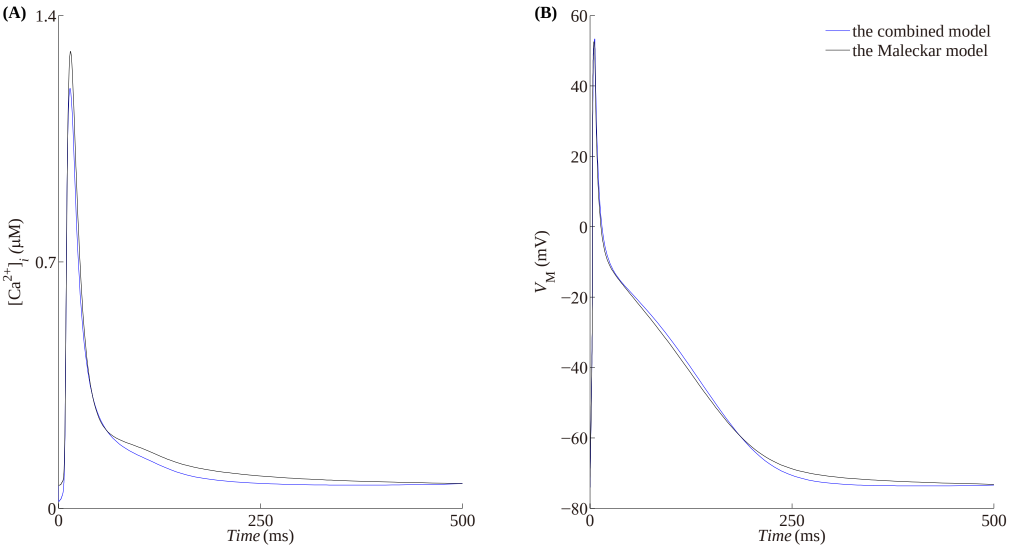

Figure S2. Illustration of [Ca^{2+}]$_i$ (A) and V_M (B) in the combined model and in the model of Maleckar et al. [1].

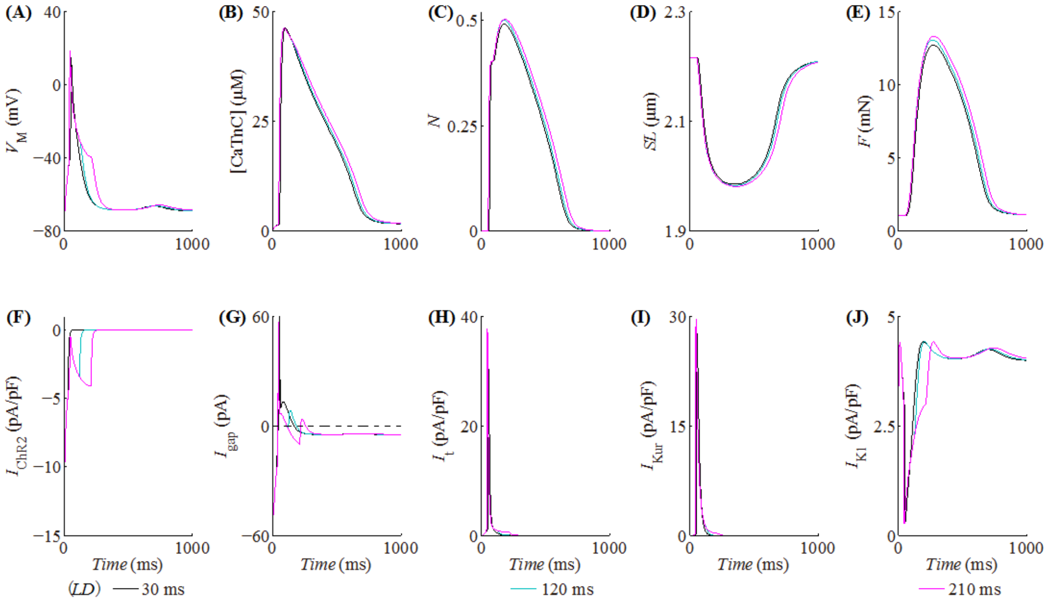

Figure S3. Electrophysiological and mechanical parameters (in isometric contraction) related to ECC at a LD of 30, 120 and 210 ms. LI is fixed to 5 mW/mm^2.

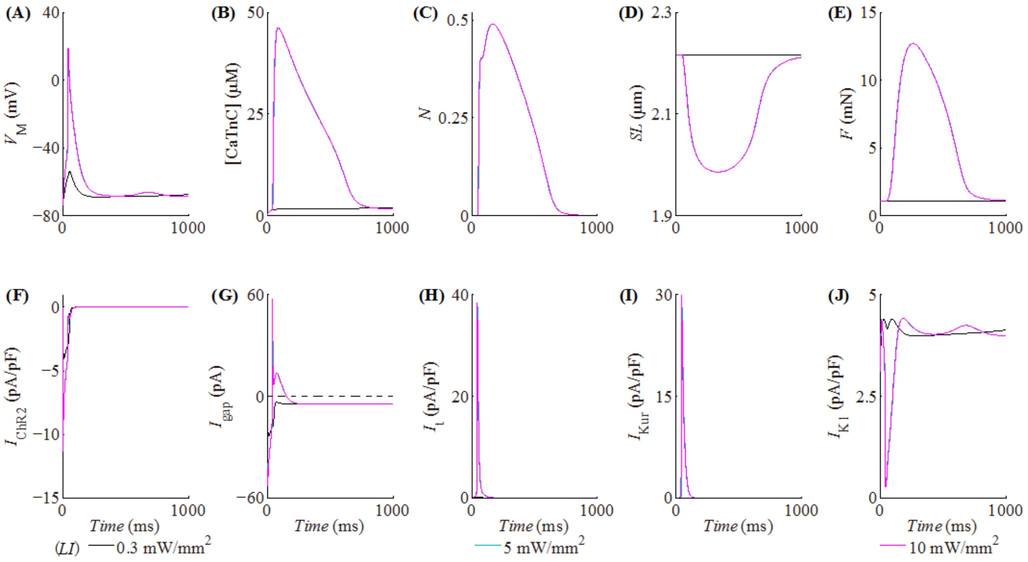

Figure S4. Electrophysiological and mechanical parameters (in isometric contraction) related to ECC at a LI of 0.3, 5 and 10 mW/mm^2. LD is fixed to 50 ms.

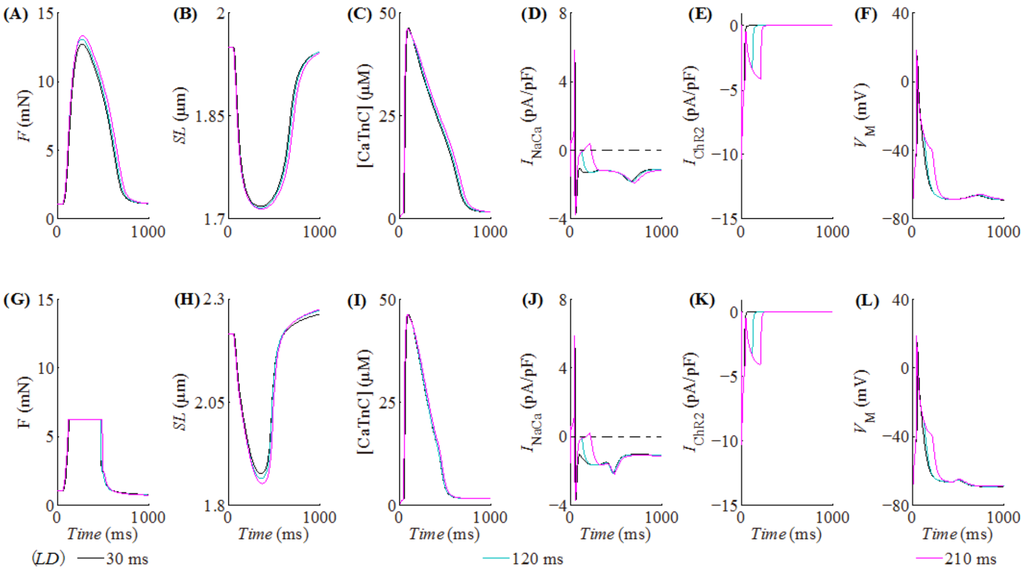

Figure S5. Electrophysiological and mechanical parameters (in isometric and isotonic contractions) related to MEF at a LD of 30, 120 and 210 ms. LI is fixed to 5 mW/mm^2.

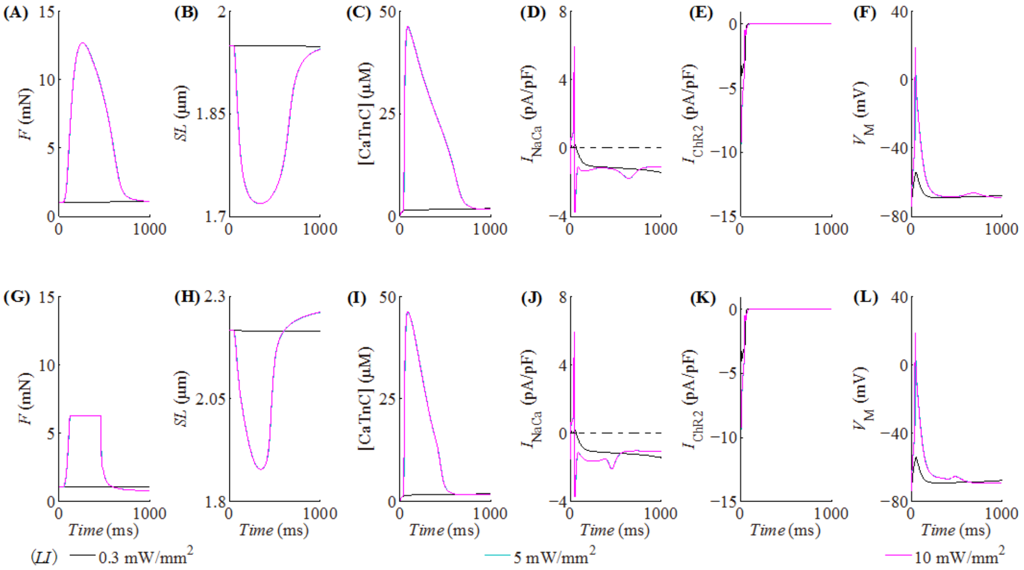

Figure S6. Electrophysiological and mechanical parameters (in isometric and isotonic contractions) related to MEF at a LI of 0.3, 5 and 10 mW/mm^2. LD is fixed to 50 ms.

Model Equations

Table 1 through 29 contained all the equations, parameters values and initial conditions necessary to carry out the simulations presented in this manuscript. Unless otherwise noted, the units are as follows: time in second (s), voltage in millivolt (mV), concentration in millimolar (mM), current in picoampere (pA), conductance in nanosiemens (nS), capacitance in picofarads (pF), volume in nanoliters (nL), temperature in kelvin (K), and sarcomere length in micron (μm).

As described in our manuscript, the model consists of three modules: the excitation-contraction coupling (ECC) module in the cardiomyocyte (CM), the optical module in fibroblasts (Fbs) and the CM-Fb coupling module.

Module 1: ECC in CM

This module consists of two blocks: an electrophysiological block and a mechanical block. The former is based on the 'Maleckar-Trayanova' (MT) ionic model, and the latter is based on an updated version of the 'Ekaterinburg-Oxford' (EO) model [1,2]. We replace the MT's description of Ca^{2+} buffering system with the EO's and modify the formulation of intracellular Ca^{2+} concentration. Then we integrate the two blocks to compose the ECC module.

1) Electrophysiological block

Table 1. Na^+ current: I_{Na}

$$I_{\mathrm{Na}} = P_{\mathrm{Na}} m^3 (0.9h_1 + 0.1h_2)[Na^+]_c V_{\mathrm{M}} \frac{\mathrm{F}^2}{\mathrm{RT}} \frac{\mathrm{e}^{(V_{\mathrm{M}}-E_{\mathrm{Na}})\mathrm{F/RT}} - 1.0}{\mathrm{e}^{V_{\mathrm{M}}\mathrm{F/RT}} - 1.0}$$

$$\bar{m} = \frac{1.0}{1.0 + \mathrm{e}^{(V_{\mathrm{M}}+27.12)/-8.21}} \qquad \bar{h} = \frac{1.0}{1.0 + \mathrm{e}^{(V_{\mathrm{M}}+63.6)/5.3}}$$

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \frac{\bar{m} - m}{\tau_m} \qquad \tau_m = 0.000042\mathrm{e}^{-\left((V_{\mathrm{M}}+25.57)/28.8\right)^2} + 0.000024$$

$$\frac{\mathrm{d}h_1}{\mathrm{d}t} = \frac{\bar{h} - h_1}{\tau_{h_1}} \qquad \tau_{h_1} = \frac{0.03}{1.0 + \mathrm{e}^{(V_{\mathrm{M}}+35.1)/3.2}} + 0.0003$$

$$\frac{\mathrm{d}h_2}{\mathrm{d}t} = \frac{\bar{h} - h_2}{\tau_{h_2}} \qquad \tau_{h_2} = \frac{0.12}{1.0 + \mathrm{e}^{(V_{\mathrm{M}}+35.1)/3.2}} + 0.003$$

Table 2. Ca^{2+} current: I_{CaL}

$$I_{\mathrm{CaL}} = \bar{g}_{\mathrm{CaL}} d_{\mathrm{L}} [f_{\mathrm{Ca}} f_{\mathrm{L1}} + (1 - f_{\mathrm{Ca}}) f_{\mathrm{L2}}] (V_{\mathrm{M}} - E_{\mathrm{Ca,app}})$$

$$\bar{d}_{\mathrm{L}} = \frac{1.0}{1.0 + \mathrm{e}^{(V_{\mathrm{M}}+9.0)/-5.8}} \qquad \bar{f}_{\mathrm{L}} = \frac{1.0}{1.0 + e^{(V_{\mathrm{M}}+27.4)/7.1}}$$

$$\frac{\mathrm{d}d_{\mathrm{L}}}{\mathrm{d}t} = \frac{\bar{d}_{\mathrm{L}} - d_{\mathrm{L}}}{\tau_{d_{\mathrm{L}}}} \qquad \tau_{d_{\mathrm{L}}} = 0.0027\mathrm{e}^{-\left((V_{\mathrm{M}}+35.0)/30.0\right)^2} + 0.002$$

$$\frac{\mathrm{d}f_{\mathrm{L1}}}{\mathrm{d}t}=\frac{\bar{f}_{\mathrm{L}}-f_{\mathrm{L1}}}{\tau_{f_{\mathrm{L1}}}} \qquad \tau_{f_{\mathrm{L1}}}=0.161\mathrm{e}^{-((V_{\mathrm{M}}+40.0)/14.4)^{2}}+0.01$$

$$\frac{\mathrm{d}f_{\mathrm{L2}}}{\mathrm{d}t}=\frac{\bar{f}_{\mathrm{L}}-f_{\mathrm{L2}}}{\tau_{f_{\mathrm{L2}}}} \qquad \tau_{f_{\mathrm{L2}}}=1.3323\mathrm{e}^{-((V_{\mathrm{M}}+40.0)/14.2)^{2}}+0.0626$$

$$f_{\mathrm{Ca}}=\frac{[\mathrm{Ca}^{2+}]_{\mathrm{d}}}{[\mathrm{Ca}^{2+}]_{\mathrm{d}}+k_{\mathrm{Ca}}}$$

Table 3. Transient and ultra-rapidly delayed rectifier K$^+$ currents: I_{t} and I_{Kur}

$$I_{\mathrm{t}}=\bar{g}_{\mathrm{t}}rs(V_{\mathrm{M}}-E_{\mathrm{K}})$$

$$\bar{r}=\frac{1.0}{1.0+\mathrm{e}^{(V_{\mathrm{M}}-1.0)/\text{-}11.0}} \qquad \bar{s}=\frac{1.0}{1.0+\mathrm{e}^{(V_{\mathrm{M}}+40.5)/11.5}}$$

$$\frac{\mathrm{d}r}{\mathrm{d}t}=\frac{\bar{r}-r}{\tau_{r}} \qquad \tau_{r}=0.0035\mathrm{e}^{-(V_{\mathrm{M}}/30.0)^{2}}+0.0015$$

$$\frac{\mathrm{d}s}{\mathrm{d}t}=\frac{\bar{s}-s}{\tau_{s}} \qquad \tau_{s}=0.025635\mathrm{e}^{-((V_{\mathrm{M}}+52.45)/15.89)^{2}}+0.01414$$

$$I_{\mathrm{Kur}}=\bar{g}_{\mathrm{Kur}}r_{\mathrm{Kur}}s_{\mathrm{Kur}}(V_{\mathrm{M}}-E_{\mathrm{K}})$$

$$\bar{r}_{\mathrm{Kur}}=\frac{1.0}{1.0+\mathrm{e}^{(V_{\mathrm{M}}+6.0)/\text{-}8.6}} \qquad \bar{s}_{\mathrm{Kur}}=\frac{1.0}{1.0+\mathrm{e}^{(V_{\mathrm{M}}+7.5)/10.0}}$$

$$\frac{\mathrm{d}r_{\mathrm{Kur}}}{\mathrm{d}t}=\frac{\bar{r}_{\mathrm{Kur}}-r_{\mathrm{Kur}}}{\tau_{r_{\mathrm{Kur}}}} \qquad \tau_{r_{\mathrm{Kur}}}=\frac{0.009}{1.0+\mathrm{e}^{(V_{\mathrm{M}}+5.0)/12.0}}+0.0005$$

$$\frac{\mathrm{d}s_{\mathrm{Kur}}}{\mathrm{d}t}=\frac{\bar{s}_{\mathrm{Kur}}-s_{\mathrm{Kur}}}{\tau_{s_{\mathrm{Kur}}}} \qquad \tau_{s_{\mathrm{Kur}}}=\frac{0.59}{1.0+\mathrm{e}^{(V_{\mathrm{M}}+60.0)/10.0}}+3.05$$

Table 4. Delayed rectifier K$^+$ currents: $I_{\mathrm{K,s}}$ and $I_{\mathrm{K,r}}$

$$I_{\mathrm{K,s}}=\bar{g}_{\mathrm{K,s}}n(V_{\mathrm{M}}-E_{\mathrm{K}})$$

$$\bar{n}=\frac{1.0}{1.0+\mathrm{e}^{(V_{\mathrm{M}}-19.9)/\text{-}12.7}} \qquad \tau_{n}=0.7+0.4\mathrm{e}^{-((V_{\mathrm{M}}-20.0)/20.0)^{2}}$$

$$\frac{\mathrm{d}n}{\mathrm{d}t}=\frac{\bar{n}-n}{\tau_{n}}$$

$$I_{\mathrm{K,r}}=\bar{g}_{\mathrm{K,r}}p_{\mathrm{a}}p_{\mathrm{i}}(V_{\mathrm{M}}-E_{\mathrm{K}})$$

$$\bar{p}_{\mathrm{a}}=\frac{1.0}{1.0+\mathrm{e}^{(V_{\mathrm{M}}+15.0)/\text{-}6.0}} \qquad p_{\mathrm{i}}=\frac{1.0}{1.0+\mathrm{e}^{(V_{\mathrm{M}}+55.0)/24.0}}$$

$$\frac{\mathrm{d}p_{\mathrm{a}}}{\mathrm{d}t}=\frac{\bar{p}_{\mathrm{a}}-p_{\mathrm{a}}}{\tau_{p_{\mathrm{a}}}} \qquad \tau_{p_{\mathrm{a}}}=0.03118+0.21718\mathrm{e}^{-((V_{\mathrm{M}}+20.1376)/22.1996)^{2}}$$

Table 5. Inward rectifier K$^+$ currents: I_{K1}

$$I_{\mathrm{K1}}=\bar{g}_{\mathrm{K1}}[\mathrm{K}^{+}]_{c}^{0.4457}\frac{V_{\mathrm{M}}-E_{\mathrm{K}}}{1.0+\mathrm{e}^{1.5(V_{\mathrm{M}}-E_{\mathrm{K}}+3.6)\mathrm{F/RT}}}$$

Table 6. Background inward currents: $I_{\mathrm{B,Na}}$ and $I_{\mathrm{B,Ca}}$

$$I_{\mathrm{B,Na}} = \bar{g}_{\mathrm{B,Na}}(V_{\mathrm{M}} - E_{\mathrm{Na}})$$

$$I_{\mathrm{B,Ca}} = \bar{g}_{\mathrm{B,Ca}}(V_{\mathrm{M}} - E_{\mathrm{Ca}})$$

Table 7. Pump and exchanger currents: I_{NaK}, I_{CaP}, and I_{NaCa}

$$I_{\mathrm{NaK}} = \bar{I}_{\mathrm{NaK}} \frac{[\mathrm{K}^+]_c}{[\mathrm{K}^+]_c + k_{\mathrm{NaK,K}}} \cdot \frac{[\mathrm{Na}^+]_i^{1.5}}{[\mathrm{Na}^+]_i^{1.5} + k_{\mathrm{NaK,Na}}^{1.5}} \cdot \frac{V_{\mathrm{M}} + 150.0}{V_{\mathrm{M}} + 200.0}$$

$$I_{\mathrm{CaP}} = \bar{I}_{\mathrm{CaP}} \frac{[\mathrm{Ca}^{2+}]_i}{[\mathrm{Ca}^{2+}]_i + k_{\mathrm{CaP}}}$$

$$I_{\mathrm{NaCa}} = k_{\mathrm{NaCa}} \frac{[\mathrm{Na}^+]_i^3 [\mathrm{Ca}^{2+}]_c \mathrm{e}^{\gamma V_{\mathrm{M}} \mathrm{F/RT}} - [\mathrm{Na}^+]_c^3 [\mathrm{Ca}^{2+}]_i \mathrm{e}^{(\gamma-1.0) V_{\mathrm{M}} \mathrm{F/RT}}}{1.0 + d_{\mathrm{NaCa}}\left([\mathrm{Na}^+]_c^3 [\mathrm{Ca}^{2+}]_i + [\mathrm{Na}^+]_i^3 [\mathrm{Ca}^{2+}]_c\right)}$$

Table 8. Intracellular ion concentrations: $[\mathrm{Na}^+]_i$, $[\mathrm{K}^+]_i$, and $[\mathrm{Ca}^{2+}]_i$

$$\frac{\mathrm{d}[\mathrm{Na}^+]_i}{\mathrm{d}t} = -\frac{I_{\mathrm{Na}} + I_{\mathrm{B,Na}} + 3I_{\mathrm{NaK}} + 3I_{\mathrm{NaCa}}}{\mathrm{Vol_i F}}$$

$$\frac{\mathrm{d}[\mathrm{K}^+]_i}{\mathrm{d}t} = -\frac{I_{\mathrm{t}} + I_{\mathrm{Kur}} + I_{\mathrm{K1}} + I_{\mathrm{K,s}} + I_{\mathrm{K,r}} - 2I_{\mathrm{NaK}}}{\mathrm{Vol_i F}}$$

$$\frac{\mathrm{d}[\mathrm{Ca}^{2+}]_i}{\mathrm{d}t} = -\frac{-I_{\mathrm{di}} + I_{\mathrm{B,Ca}} + I_{\mathrm{CaP}} - 2I_{\mathrm{NaCa}} + I_{\mathrm{up}} - I_{\mathrm{rel}}}{2\mathrm{Vol_i F}} - \left(\frac{\mathrm{d}[\mathrm{CaTnC}]}{\mathrm{d}t} + \frac{\mathrm{d}B_1}{\mathrm{d}t} + \frac{\mathrm{d}B_2}{\mathrm{d}t}\right)$$

$$\frac{\mathrm{d}[\mathrm{Ca}^{2+}]_d}{\mathrm{d}t} = -\frac{I_{\mathrm{CaL}} + I_{\mathrm{di}}}{2.0\ \mathrm{Vol_d F}}$$

$$I_{\mathrm{di}} = \left([\mathrm{Ca}^{2+}]_d - [\mathrm{Ca}^{2+}]_i\right) \frac{2\mathrm{F\ Vol_d}}{\tau_{\mathrm{di}}}$$

Table 9. Cleft space ion concentrations: $[\mathrm{Na}^+]_c$, $[\mathrm{K}^+]_c$, and $[\mathrm{Ca}^{2+}]_c$

$$\frac{\mathrm{d}[\mathrm{Na}^+]_c}{\mathrm{d}t} = \frac{[\mathrm{Na}^+]_{\mathrm{b}} - [\mathrm{Na}^+]_c}{\tau_{\mathrm{Na}}} + \frac{I_{\mathrm{Na}} + I_{\mathrm{B,Na}} + 3I_{\mathrm{NaK}} + 3I_{\mathrm{NaCa}}}{\mathrm{Vol_c F}}$$

$$\frac{\mathrm{d}[\mathrm{K}^+]_c}{\mathrm{d}t} = \frac{[\mathrm{K}^+]_{\mathrm{b}} - [\mathrm{K}^+]_c}{\tau_{\mathrm{K}}} + \frac{I_{\mathrm{t}} + I_{\mathrm{Kur}} + I_{\mathrm{K1}} + I_{\mathrm{K,s}} + I_{\mathrm{K,r}} - 2I_{\mathrm{NaK}}}{\mathrm{Vol_c F}}$$

$$\frac{\mathrm{d}[\mathrm{Ca}^{2+}]_c}{\mathrm{d}t} = \frac{[\mathrm{Ca}^{2+}]_{\mathrm{b}} - [\mathrm{Ca}^{2+}]_c}{\tau_{\mathrm{Ca}}} + \frac{I_{\mathrm{CaL}} + I_{\mathrm{B,Ca}} + I_{\mathrm{CaP}} - 2I_{\mathrm{NaCa}}}{2.0\ \mathrm{Vol_c F}}$$

Table 10. Intracellular Ca^{2+} buffering

$$\frac{\mathrm{d}B_1}{\mathrm{d}t} = b_{\mathrm{1on}} \cdot (B_{\mathrm{1tot}} - B_1) \cdot [\mathrm{Ca}^{2+}]_i - b_{\mathrm{1off}} \cdot B_1$$

$$\frac{\mathrm{d}B_2}{\mathrm{d}t} = b_{\mathrm{2on}} \cdot (B_{\mathrm{2tot}} - B_2) \cdot [\mathrm{Ca}^{2+}]_i - b_{\mathrm{2off}} \cdot B_2$$

Table 11. Ca^{2+} handling by the sarcoplasmic reticulum

$$I_{\mathrm{up}} = \bar{I}_{\mathrm{up}} \frac{[\mathrm{Ca}^{2+}]_i / k_{\mathrm{cyca}} - k_{\mathrm{xcs}}^2 [\mathrm{Ca}^{2+}]_{up} / k_{\mathrm{srca}}}{\left([\mathrm{Ca}^{2+}]_i + k_{\mathrm{cyca}}\right)/k_{\mathrm{cyca}} + k_{\mathrm{xcs}}\left([\mathrm{Ca}^{2+}]_{up} + k_{\mathrm{srca}}\right)/k_{\mathrm{srca}}}$$

$$I_{\mathrm{tr}} = \left([\mathrm{Ca}^{2+}]_{up} - [\mathrm{Ca}^{2+}]_{rel}\right) \frac{2\mathrm{F}\ \mathrm{Vol}_{\mathrm{rel}}}{\tau_{\mathrm{tr}}}$$

$$I_{\mathrm{rel}} = \alpha_{\mathrm{rel}} \left(\frac{F_2}{F_2 + 0.25}\right)^2 \left([\mathrm{Ca}^{2+}]_{rel} - [\mathrm{Ca}^{2+}]_i\right)$$

$$\frac{\mathrm{d}O_{\mathrm{Calse}}}{\mathrm{d}t} = 480.0[\mathrm{Ca}^{2+}]_{rel}(1.0 - O_{\mathrm{Calse}}) - 400.0 O_{\mathrm{Calse}}$$

$$\frac{\mathrm{d}[\mathrm{Ca}^{2+}]_{rel}}{\mathrm{d}t} = \frac{I_{\mathrm{tr}} - I_{\mathrm{rel}}}{2\mathrm{F}\ \mathrm{Vol}_{\mathrm{rel}}} - 31.0 \frac{\mathrm{d}O_{\mathrm{Calse}}}{\mathrm{d}t}$$

$$\frac{\mathrm{d}[\mathrm{Ca}^{2+}]_{up}}{\mathrm{d}t} = \frac{I_{\mathrm{up}} - I_{\mathrm{tr}}}{2\mathrm{F}\ \mathrm{Vol}_{\mathrm{up}}}$$

$$\frac{\mathrm{d}F_1}{\mathrm{d}t} = \mathrm{r}_{\mathrm{recov}}(1.0 - F_1 - F_2) - r_{\mathrm{act}} F_1$$

$$\frac{\mathrm{d}F_2}{\mathrm{d}t} = r_{\mathrm{act}} F_1 - r_{\mathrm{inact}} F_2$$

$$r_{\mathrm{act}} = 203.8\left[\left(\frac{[\mathrm{Ca}^{2+}]_i}{[\mathrm{Ca}^{2+}]_i + k_{\mathrm{rel,i}}}\right)^4 + \left(\frac{[\mathrm{Ca}^{2+}]_d}{[\mathrm{Ca}^{2+}]_d + k_{\mathrm{rel,d}}}\right)^4\right]$$

$$r_{\mathrm{inact}} = 33.96 + 339.6\left(\frac{[\mathrm{Ca}^{2+}]_i}{[\mathrm{Ca}^{2+}]_i + k_{\mathrm{rel,i}}}\right)^4$$

Table 12. Kinetics of CaTnC complexes

$$\frac{\mathrm{d}[\mathrm{CaTnC}]}{\mathrm{d}t} = a_{\mathrm{on}} \cdot (\mathrm{TnC}_{\mathrm{tot}} - [\mathrm{CaTnC}]) \cdot [\mathrm{Ca}^{2+}]_i - a_{\mathrm{off}} \cdot \mathrm{e}^{-k_{\mathrm{A}} \cdot [\mathrm{CaTnC}]} \cdot \Pi(N_{\mathrm{A}}) \cdot [\mathrm{CaTnC}]$$

$$\Pi(N_{\mathrm{A}}) = \begin{cases} 1 & \text{if } N_{\mathrm{A}} \leq 0 \\ \Pi_{\mathrm{min}}^{N_{\mathrm{A}}} & \text{if } N_{\mathrm{A}} \leq 1 \\ \Pi_{\mathrm{min}} & \text{otherwise} \end{cases}$$

$$N_{\mathrm{A}} = \frac{\mathrm{TnC}_{\mathrm{tot}} \cdot N}{L_{\mathrm{oz}} \cdot [\mathrm{CaTnC}]}$$

Table 13. Reversal potentials: E_{Na}, E_{K} and E_{Ca}

$$E_{\mathrm{Na}} = \frac{\mathrm{RT}}{\mathrm{F}} \log \frac{[\mathrm{Na}^+]_c}{[\mathrm{Na}^+]_i}$$

$$E_{\mathrm{K}} = \frac{\mathrm{RT}}{\mathrm{F}} \log \frac{[\mathrm{K}^+]_c}{[\mathrm{K}^+]_i}$$

$$E_{\mathrm{Ca}} = \frac{\mathrm{RT}}{2\mathrm{F}} \log \frac{[\mathrm{Ca}^{2+}]_c}{[\mathrm{Ca}^{2+}]_i}$$

2) Mechanical block

Table 14. Force

$$F_{\mathrm{CE}} = \lambda \cdot p_v \cdot N$$

$$F_{\mathrm{SE}} = \beta_1 \cdot \left(e^{\alpha_1 \cdot (l_2 - l_1)} - 1\right)$$

$$F_{\mathrm{PE}} = \beta_2 \cdot (e^{\alpha_2 \cdot l_2} - 1)$$

$$F_{\mathrm{XSE}} = \beta_3 \cdot (e^{\alpha_3 \cdot l_3} - 1)$$

$$F_{\mathrm{sample}} = F_{\mathrm{XSE}}$$

Table 15. Length

$$l = l_2 + l_3$$

$$\frac{\mathrm{d}l_1}{\mathrm{d}t} = v$$

$$\frac{\mathrm{d}l_2}{\mathrm{d}t} = w$$

$$\frac{\mathrm{d}l_3}{\mathrm{d}t} = \begin{cases} -w & \text{if isometry} \\ 0 & \text{if isotony} \end{cases}$$

Table 16. Contractile element (CE) velocity

$$alp_{\mathrm{p}} = \begin{cases} \alpha_{\mathrm{vp_l}} & \text{if } v \le 0 \\ \alpha_{\mathrm{vp_s}} & \text{otherwise} \end{cases}$$

$$k_{\mathrm{p_{vis}}} = \begin{cases} \beta_{\mathrm{vp_l}} \cdot \mathrm{e}^{\alpha_{\mathrm{vp_l}} \cdot l_1} & \text{if } v \le 0 \\ \beta_{\mathrm{vp_s}} \cdot \mathrm{e}^{\alpha_{\mathrm{vp_s}} \cdot l_1} & \text{otherwise} \end{cases}$$

$$\Phi_x = \begin{cases} -\dfrac{\lambda \cdot K_k \cdot p_v + alp_{\mathrm{p}} \cdot k_{\mathrm{p_{vis}}} \cdot v^2 + w \cdot (\alpha_2 \cdot \beta_2 \cdot \mathrm{e}^{\alpha_2 \cdot l_2} + \alpha_3 \cdot \beta_3 \cdot \mathrm{e}^{\alpha_3 \cdot l_3})}{\lambda \cdot N \cdot p_{\mathrm{prime}_v} + k_{\mathrm{p_{vis}}}} & \text{if isometry} \\ -\dfrac{\lambda \cdot K_k \cdot p_v + alp_{\mathrm{p}} \cdot k_{\mathrm{p_{vis}}} \cdot v^2 + w \cdot \alpha_2 \cdot \beta_2 \cdot \mathrm{e}^{\alpha_2 \cdot l_2}}{\lambda \cdot N \cdot p_{\mathrm{prime}_v} + k_{\mathrm{p_{vis}}}} & \text{if iso} \end{cases}$$

$$\frac{\mathrm{d}v}{\mathrm{d}t} = \Phi_x$$

Table 17. Parallel element (PE) velocity

$$alp_{\mathrm{s}} = \begin{cases} \alpha_{\mathrm{vs_l}} & \text{if } w \le v \\ \alpha_{\mathrm{vs_s}} & \text{otherwise} \end{cases}$$

$$k_{\mathrm{s_{vis}}} = \begin{cases} \beta_{\mathrm{vs_l}} \cdot \mathrm{e}^{\alpha_{\mathrm{vs_l}} \cdot (l_2 - l_1)} & \text{if } w \le v \\ \beta_{\mathrm{vs_s}} \cdot \mathrm{e}^{\alpha_{\mathrm{vs_s}} \cdot (l_2 - l_1)} & \text{otherwise} \end{cases}$$

$$\frac{\mathrm{d}w}{\mathrm{d}t} = \begin{cases} \dfrac{\Phi_x - alp_\mathrm{s} \cdot (w-v)^2 - \alpha_1 \cdot \beta_1 \cdot \mathrm{e}^{\alpha_1 \cdot (l_2 - l_1)} \cdot (w-v) + w \cdot (\alpha_2 \cdot \beta_2 \cdot \mathrm{e}^{\alpha_2 \cdot l_2} + \alpha_3 \cdot \beta_3 \cdot \mathrm{e}^{\alpha_3 \cdot l_3})}{k_{\mathrm{s}_\mathrm{vis}}} & \text{if isometry} \\ \dfrac{k_{\mathrm{s}_\mathrm{vis}} \cdot (\Phi_x - alp_\mathrm{s} \cdot (w-v)^2) - \alpha_1 \cdot \beta_1 \cdot \mathrm{e}^{\alpha_1 \cdot (l_2 - l_1)} \cdot (w-v) - w \cdot \alpha_2 \cdot \beta_2 \cdot \mathrm{e}^{\alpha_2 \cdot l_2}}{k_{\mathrm{s}_\mathrm{vis}}} & \text{if isotony} \end{cases}$$

Table 18. Average crossbridge force

$$v_1 = \frac{v_\mathrm{max}}{10}$$

$$\gamma_2 = \frac{a \cdot d_\mathrm{h} \cdot \left(\frac{v_1}{v_\mathrm{max}}\right)^2}{3a \cdot d_\mathrm{h} - \frac{(a+1) \cdot v_1}{v_\mathrm{max}}}$$

$$P_\mathrm{star} = \begin{cases} \dfrac{a \cdot \left(1 + \frac{v}{v_\mathrm{max}}\right)}{a - \frac{v}{v_\mathrm{max}}} & \text{if } v \le \\ 1 + d_\mathrm{h} - \dfrac{d_\mathrm{h}^2 \cdot a}{\frac{a \cdot d_\mathrm{h}}{\gamma_2} \cdot \left(\frac{v}{v_\mathrm{max}}\right)^2 + \frac{(a+1) \cdot v}{v_\mathrm{max}} + a \cdot d_\mathrm{h}} & \text{otherwise} \end{cases}$$

$$G_\mathrm{star} = \begin{cases} 1 + \dfrac{0.6v}{v_\mathrm{max}} & \text{if } v \le 0 \\ \dfrac{P_\mathrm{star}}{\frac{(0.4a+1) \cdot v}{a \cdot v_\mathrm{max}} + 1} & \text{if } 0 < v \le v_1 \\ \dfrac{P_\mathrm{star} \cdot \mathrm{e}^{-\alpha_\mathrm{G} \cdot \left(\frac{v - v_1}{v_\mathrm{max}}\right)^{\alpha_\mathrm{P}}}}{\frac{(0.4a+1) \cdot v}{a \cdot v_\mathrm{max}} + 1} & \text{otherwise} \end{cases}$$

$$\mathrm{case}_1 = \frac{a \cdot (0.4 + 0.4a)}{v_\mathrm{max} \cdot \big(0.4(a+1)\big)^2}$$

$$\mathrm{case}_2 = \frac{a \cdot \left(1 + 0.4a + \frac{1.2v}{v_\mathrm{max}} + 0.6\left(\frac{v}{v_\mathrm{max}}\right)^2\right)}{v_\mathrm{max} \cdot \left(\left(a - \frac{v}{v_\mathrm{max}}\right) \cdot \left(1 + \frac{0.6v}{v_\mathrm{max}}\right)\right)^2}$$

$$\mathrm{case}_3 = \frac{0.4a + 1}{a \cdot v_\mathrm{max}}$$

$$\mathrm{case}_4 = \frac{1}{v_\mathrm{max}} \cdot \mathrm{e}^{-\alpha_\mathrm{G} \cdot \left(\frac{v - v_1}{v_\mathrm{max}}\right)^{\alpha_\mathrm{P}}} \cdot \left(\frac{0.4a + 1}{a} + \alpha_\mathrm{G} \cdot \alpha_\mathrm{P} \cdot \left(1 + \frac{(0.4a+1) \cdot v}{a \cdot v_\mathrm{max}}\right) \cdot \left(\frac{v - v_1}{v_\mathrm{max}}\right)^{\alpha_\mathrm{P} - 1}\right)$$

$$p_{\text{prime}_v} = \begin{cases} \text{case}_1 & \text{if } v \le -v_{\max} \\ \text{case}_2 & \text{if } -v_{\max} < v \le 0 \\ \text{case}_3 & \text{if } 0 < v \le v_1 \\ \text{case}_4 & \text{otherwise} \end{cases}$$

$$p_v = \frac{P_{\text{star}}}{G_{\text{star}}}$$

Table 19. Crossbridge kinetics

$$M_{\text{A}} = \frac{\left(\frac{[\text{CaTnC}]}{\text{TnC}_{\text{tot}}}\right)^{\mu} \cdot \left(1 + k_{\upmu}^{\mu}\right)}{\left(\frac{[\text{CaTnC}]}{\text{TnC}_{\text{tot}}}\right)^{\mu} + k_{\upmu}^{\mu}}$$

$$temp_{n1} = g_1 \cdot l_1 + g_2$$

$$n_1 = \begin{cases} 0 & \text{if } temp_{n1} < 0 \\ temp_{n1} & \text{if } temp_{n1} < 1 \\ 1 & \text{otherwise} \end{cases}$$

$$L_{\text{oz}} = \begin{cases} \frac{l_1 + S_0}{0.46 + S_0} & \text{if } l_1 > 0.55 \\ S_0 + 0.55 & \text{otherwise} \end{cases}$$

$$v_{\text{st}} = x_{\text{st}} \cdot v_{\max}$$

$$q_v = \begin{cases} q_1 - \frac{q_2 \cdot v}{v_{\max}} & \text{if } v \le 0 \\ \frac{(q_4 - q_3) \cdot v}{v_{\text{st}}} + q_3 & \text{if } 0 < v \le v_{st} \\ \frac{q_4}{\left(1 + \frac{\beta_{\text{Q}} \cdot (v - v_{\text{st}})}{v_{\max}}\right)^{\alpha_{\text{Q}}}} & \text{otherwise} \end{cases}$$

$$k_{p_v} = \kappa \cdot \kappa_0 \cdot q_v \cdot m_0 \cdot G_{\text{star}}$$

$$k_{m_v} = \kappa_0 \cdot q_v \cdot (1 - \kappa \cdot m_0 \cdot G_{\text{star}})$$

$$K_{\kappa} = k_{p_v} \cdot M_{\text{A}} \cdot n_1 \cdot L_{\text{oz}} \cdot (1 - N) - k_{m_v} \cdot N$$

$$\frac{\mathrm{d}N}{\mathrm{d}t} = K_{\kappa}$$

Module 2: Optical activity in Fb

This module contains an electrophysiological model of atrial Fbs (represented by the Maleckar et al.) transduced with ChR2 currents (represented by Williams et al.) [3,4].

Table 20. Time- and voltage-dependent K$^+$ current: $I_{\mathrm{Kv\_Fb}}$

$$I_{\mathrm{Kv\_Fb}} = \bar{g}_{\mathrm{Kv,Fb}} r_{\mathrm{Kv}} s_{\mathrm{Kv}} \left(V_{\mathrm{Fb}} - E_{\mathrm{K,Fb}}\right)$$

$$\bar{r}_{\mathrm{Kv}} = \left(1.0 + \mathrm{e}^{-(V_{\mathrm{Fb}}+20.0)/11.0}\right)^{-1} \qquad \bar{s}_{\mathrm{Kv}} = \left(1.0 + \mathrm{e}^{(V_{\mathrm{Fb}}+23.0)/7.0}\right)^{-1}$$

$$\frac{\mathrm{d}r_{\mathrm{Kv}}}{\mathrm{d}t} = \frac{\bar{r}_{\mathrm{Kv}} - r_{\mathrm{Kv}}}{\tau_{r_{\mathrm{Kv}}}} \qquad \tau_{r_{\mathrm{Kv}}} = 0.0203 + 0.138 \cdot \mathrm{e}^{-\left((V_{\mathrm{Fb}}+20.0)/25.9\right)^2}$$

$$\frac{\mathrm{d}s_{\mathrm{Kv}}}{\mathrm{d}t} = \frac{\bar{s}_{\mathrm{Kv}} - s_{\mathrm{Kv}}}{\tau_{s_{\mathrm{Kv}}}} \qquad \tau_{s_{\mathrm{Kv}}} = 1.574 + 5.268 \cdot \mathrm{e}^{-\left((V_{\mathrm{Fb}}+23.0)/22.7\right)^2}$$

$$E_{\mathrm{K,Fb}} = \frac{\mathrm{RT}}{\mathrm{F}} \log \frac{[\mathrm{K}^+]_{\mathrm{c,Fb}}}{[\mathrm{K}^+]_{i,\mathrm{Fb}}}$$

Table 21. Time-independent inward-rectifying K$^+$ current: $I_{\mathrm{K1\_Fb}}$

$$I_{\mathrm{K1\_Fb}} = \bar{g}_{\mathrm{K1,Fb}} \left(\frac{\alpha_{\mathrm{K1}}}{\alpha_{\mathrm{K1}} + \beta_{\mathrm{K1}}}\right) \left(V_{\mathrm{Fb}} - E_{\mathrm{K,Fb}}\right)$$

$$\alpha_{\mathrm{K1}} = 0.1\left(1.0 + \mathrm{e}^{0.06\left(V_{\mathrm{Fb}} - E_{\mathrm{K,Fb}} - 200.0\right)}\right)^{-1}$$

$$\beta_{\mathrm{K1}} = \frac{3.0 \cdot \mathrm{e}^{0.0002\left(V_{\mathrm{Fb}} - E_{\mathrm{K,Fb}} + 100.0\right)} + \mathrm{e}^{0.1\left(V_{\mathrm{Fb}} - E_{\mathrm{K,Fb}} + 10.0\right)}}{1.0 + \mathrm{e}^{-0.5\left(V_{\mathrm{Fb}} - E_{\mathrm{K,Fb}}\right)}}$$

Table 22. Na$^+$-K$^+$ pump current: $I_{\mathrm{NaK\_Fb}}$

$$I_{\mathrm{NaK\_Fb}} = \bar{I}_{\mathrm{NaK,Fb}} \cdot \frac{[\mathrm{K}^+]_{\mathrm{c,Fb}}}{[\mathrm{K}^+]_{\mathrm{c,Fb}} + k_{\mathrm{mK,Fb}}} \cdot \left(\frac{[\mathrm{Na}^+]_{i,\mathrm{Fb}}}{[\mathrm{Na}^+]_{i,\mathrm{Fb}} + k_{\mathrm{mNa,Fb}}}\right)^{1.5} \cdot \frac{V_{\mathrm{Fb}} + 150.0}{V_{\mathrm{Fb}} + 200.0}$$

Table 23. Background inward current: $I_{\mathrm{B,Na\_Fb}}$

$$I_{\mathrm{B,Na\_Fb}} = \bar{g}_{\mathrm{B,Na,Fb}} \left(V_{\mathrm{Fb}} - E_{\mathrm{Na,Fb}}\right)$$

$$E_{\mathrm{Na,Fb}} = \frac{\mathrm{RT}}{\mathrm{F}} \log \frac{[\mathrm{Na}^+]_{\mathrm{c,Fb}}}{[\mathrm{Na}^+]_{i,\mathrm{Fb}}}$$

Table 24. Intracellular ion concentrations: $[\mathrm{Na}^+]_{i,\mathrm{Fb}}$, and $[\mathrm{K}^+]_{i,\mathrm{Fb}}$

$$\frac{\mathrm{d}[\mathrm{Na}^+]_{i,\mathrm{Fb}}}{\mathrm{d}t} = -\frac{I_{\mathrm{B,Na\_Fb}} + 3I_{\mathrm{NaK\_Fb}}}{\mathrm{Vol}_{\mathrm{i,Fb}}\mathrm{F}}$$

$$\frac{\mathrm{d}[\mathrm{K}^+]_{i,\mathrm{Fb}}}{\mathrm{d}t} = -\frac{I_{\mathrm{K1\_Fb}} + I_{\mathrm{Kv\_Fb}}}{\mathrm{Vol}_{\mathrm{i,Fb}}\mathrm{F}}$$

Table 25. Model of I_{ChR2}

$$I_{\mathrm{ChR2}} = \bar{g}_{\mathrm{ChR2}} \cdot G(V) \cdot (O_1 + 0.1O_2) \cdot (V_{\mathrm{Fb}} - E_{\mathrm{ChR2}})$$

$$O_1 + O_2 + C_1 + C_2 = 1$$

$$\frac{\mathrm{d}C_1}{\mathrm{d}t} = G_{\mathrm{r}} \cdot C_2 + G_{\mathrm{d1}} \cdot O_1 + k_1 \cdot C_1$$

$$\frac{\mathrm{d}O_1}{\mathrm{d}t} = k_1 \cdot C_1 - (G_{\mathrm{d1}} + e_{12}) \cdot O_1 + e_{21} \cdot O_2$$

$$\frac{\mathrm{d}O_2}{\mathrm{d}t} = k_2 \cdot C_2 - (G_{\mathrm{d2}} + e_{21}) \cdot O_2 + e_{12} \cdot O_1$$

$$\frac{\mathrm{d}C_2}{\mathrm{d}t} = G_{\mathrm{d2}} \cdot O_2 - (k_2 + G_{\mathrm{r}}) \cdot C_2$$

$$e_{12} = \left(0.011 + 0.005 \cdot \ln\left(1 + \frac{Irradiance}{0.024}\right)\right) \cdot 1000$$

$$e_{21} = \left(0.008 + 0.004 \cdot \ln\left(1 + \frac{Irradiance}{0.024}\right)\right) \cdot 1000$$

$$k_1 = \varepsilon_1 \cdot \sigma_{\mathrm{ret}} \cdot Irradiance \cdot \frac{\lambda_1}{w_{\mathrm{loss}} \cdot \mathrm{hc}} \cdot p$$

$$k_2 = \varepsilon_2 \cdot \sigma_{\mathrm{ret}} \cdot Irradiance \cdot \frac{\lambda_1}{w_{\mathrm{loss}} \cdot \mathrm{hc}} \cdot p$$

$$\frac{\mathrm{d}p}{\mathrm{d}t} = \frac{S0 - p}{\tau_{\mathrm{ChR2}}}$$

$$S0 = 0.5\big(1 + \tanh\big(120(100 \cdot Irradiance - 0.1)\big)\big)$$

$$G(V) = \frac{10.6408 - 14.6408\mathrm{e}^{-\frac{V_{\mathrm{Fb}}}{42.7671}}}{V_{\mathrm{Fb}}}$$

$$G_{\mathrm{d1}} = \left(0.075 + 0.043 \tanh\left(-\frac{V_{\mathrm{Fb}} + 20}{20}\right)\right) \cdot 1000$$

$$G_{\mathrm{r}} = (4.34 \times 10^{-5} \times \mathrm{e}^{-0.02115 V_{\mathrm{Fb}}}) \cdot 1000$$

Module 3: CM-Fb coupling

Table 26. Transmembrane potential of CM and Fb

$$\frac{\mathrm{d}V_{\mathrm{M}}}{\mathrm{d}t} = -\frac{1}{\mathrm{C_M}}\left[I_{\mathrm{M}} + \sum_{i=1}^{n} G_{\mathrm{gap}}(V_{\mathrm{M}} - V_{\mathrm{Fb}i})\right]$$

$$\frac{\mathrm{d}V_{\mathrm{Fb}i}}{\mathrm{d}t} = -\frac{1}{\mathrm{C_{Fb}}}\left[I_{\mathrm{Fb}i} + G_{\mathrm{gap}}(V_{\mathrm{Fb}i} - V_{\mathrm{M}})\right]$$

$$I_{\mathrm{M}} = I_{\mathrm{Na}} + I_{\mathrm{CaL}} + I_{\mathrm{t}} + I_{\mathrm{Kur}} + I_{\mathrm{K1}} + I_{\mathrm{K,r}} + I_{\mathrm{K,s}} + I_{\mathrm{B,Na}} + I_{\mathrm{B,Ca}} + I_{\mathrm{NaK}} + I_{\mathrm{CaP}} + I_{\mathrm{NaCa}}$$

$$I_{\mathrm{Fb}i} = I_{\mathrm{Kv\_Mfb}} + I_{\mathrm{K1\_Mfb}} + I_{\mathrm{NaK\_Mfb}} + I_{\mathrm{B,Na\_Mfb}} + I_{\mathrm{ChR2}}$$

Table 27. Parameter values

$[\mathrm{Na}^+]_\mathrm{b} = 130.0$ mM

$[\mathrm{K}^+]_\mathrm{b} = 5.4$ mM

$[\mathrm{Ca}^{2+}]_\mathrm{b} = 1.8$ mM

$E_{\mathrm{Ca,app}} = 60.0$ mV

$k_{\mathrm{Ca}} = 0.025$ mM

R = 8314.0 mJ/MK

$k_{\mathrm{NaCa}} = 0.0374842$ pA/(mM)^4

$\gamma = 0.45$

$d_{\mathrm{NaCa}} = 0.0003$ (mM)$^{-4}$

$\bar{I}_{\mathrm{up}} = 2800.0$ pA

$k_{\mathrm{cyca}} = 0.0003$ mM

$K_{\mathrm{srca}} = 0.5$ mM

$T = 306.15$ K
$F = 96487.0$ C/M
$C_M = 60$ pF
$Vol_i = 0.005884$ nL
$Vol_c = 0.136Vol_i$
$k_{CaP} = 0.0002$ mM
$Vol_d = 0.02Vol_i$
$Vol_{rel} = 0.0000441$ nL
$Vol_{up} = 0.0003969$ nL
$\tau_{Na} = 14.3$ s
$\tau_K = 10.0$ s
$\tau_{Ca} = 24.7$ s
$\tau_{di} = 0.01$ s
$\bar{I}_{NaK} = 68.55$ pA
$k_{NaK,K} = 1.0$ mM
$k_{NaK,Na} = 11.0$ mM
$\bar{I}_{CaP} = 4.0$ pA
$\alpha_{vp_l} = 16.0\ (\mu m)^{-1}$
$\alpha_{vp_s} = 16.0\ (\mu m)^{-1}$
$\beta_{vp_l} = 0.0015$ mN·s/μm
$\beta_{vp_s} = 0.0015$ mN·s/μm
$\alpha_{vs_l} = 39.0\ (\mu m)^{-1}$
$\alpha_{vs_s} = 46.0\ (\mu m)^{-1}$
$\beta_{vs_l} = 0.008$ mN·s/μm
$\beta_{vs_s} = 0.006$ mN·s/μm
$g_1 = 0.6\ (\mu m)^{-1}$
$g_2 = 0.52$
$TnC_{tot} = 0.07$ mM
$B_{1tot} = 0.08$ mM
$B_{2tot} = 0.1$ mM
$a_{on} = 70000.0\ (mM \cdot s)^{-1}$
$a_{off} = 200.0\ s^{-1}$
$b_{1on} = 100000.0\ (mM \cdot s)^{-1}$
$b_{1off} = 182.0\ s^{-1}$
$b_{2on} = 1000.0\ (mM \cdot s)^{-1}$
$b_{2off} = 3.0\ s^{-1}$
$\Pi_{min} = 0.03$
$S_0 = 1.14$ μm
$\alpha_G = 1.0$
$\alpha_P = 4.0$
$\alpha_Q = 10.0$
$\beta_Q = 5.0$
$k_A = 40.0\ (mM)^{-1}$

$K_{xcs} = 0.4$
$\tau_{tr} = 0.01$ s
$\alpha_{rel} = 200000.0\ pA\ (mM)^{-1}$
$k_{rel,i} = 0.0003$ mM
$k_{rel,d} = 0.003$ mM
$r_{recov} = 0.815\ s^{-1}$
$q_1 = 17.3\ s^{-1}$
$q_2 = 259.0\ s^{-1}$
$q_3 = 17.3\ s^{-1}$
$q_4 = 15.0\ s^{-1}$
$x_{st} = 0.964285$
$a = 0.25$
$\alpha_1 = 14.6\ (\mu m)^{-1}$
$\alpha_2 = 14.6\ (\mu m)^{-1}$
$\alpha_3 = 48.0\ (\mu m)^{-1}$
$\beta_1 = 0.84$ mN
$\beta_2 = 0.0018$ mN
$\beta_3 = 0.015$ mN
$d_h = 0.5$
$k_\mu = 0.6$
$\kappa = 0.705$
$\kappa_0 = 3.0$
$\lambda = 30.0$ mN
$m_0 = 0.9$
$\mu = 3.0$
$v_{max} = 5.5$ μm/s
$C_{Fb} = 6.3$ pF
$Vol_{i,Fb} = 0.00137$ nL
$[Na^+]_{c,Fb} = 130.011$ mM
$[K^+]_{c,Fb} = 5.3581$ mM
$k_{mK,Fb} = 1.0$ mmol
$k_{mNa,Fb} = 11.0$ mmol
$\bar{I}_{NaK,Fb} = 10.36$ pA
$E_{ChR2} = 0.0$ mV
$\varepsilon_1 = 0.8535$
$\varepsilon_1 = 0.14$
$\sigma_{ret} = 12.0 \times 10^{-20}\ m^2$
$\lambda_1 = 470.0$ nm
$w_{loss} = 1.3$
$hc = 1.986446 \times 10^{-50}\ kg \cdot m^3/s$
$G_{d2} = 50.0\ s^{-1}$
$\tau_{ChR2} = 0.0013$ s

Table 28. Maximum conductance values

$P_{\mathrm{Na}} = 0.0018$ nL/s
$\bar{g}_{\mathrm{CaL}} = 6.75$ nS
$\bar{g}_{\mathrm{t}} = 8.25$ nS
$\bar{g}_{\mathrm{Kur}} = 2.25$ nS
$\bar{g}_{\mathrm{K,s}} = 1.0$ nS
$\bar{g}_{\mathrm{K,r}} = 0.5$ nS
$\bar{g}_{\mathrm{K1}} = 3.1$ nS
$\bar{g}_{\mathrm{B,Na}} = 0.060599$ nS
$\bar{g}_{\mathrm{B,Ca}} = 0.078681$ nS
$\bar{g}_{\mathrm{Kv,Fb}} = 1.575$ nS
$\bar{g}_{\mathrm{K1,Fb}} = 3.038$ nS
$\bar{g}_{\mathrm{B,Na,Fb}} = 0.05985$ nS
$\bar{g}_{\mathrm{ChR2}} = 0.4$ nS/pF

Table 29. Initial conditions

$V_{\mathrm{M}} = -74.03$ mV
$[\mathrm{Na}^+]_c = 130.0221$ mM
$[\mathrm{K}^+]_c = 5.5602$ mM
$[\mathrm{Ca}^{2+}]_c = 1.8158$ mM
$[\mathrm{Na}^+]_i = 8.5168$ mM
$[\mathrm{K}^+]_i = 129.486$ mM
$[\mathrm{Ca}^{2+}]_i = 6.5\times10^{-5}$ mM
$[\mathrm{Ca}^{2+}]_d = 7.1\times10^{-5}$ mM
$[\mathrm{Ca}^{2+}]_{up} = 0.6492$ mM
$[\mathrm{Ca}^{2+}]_{rel} = 0.6326$ mM
$m = 3.289\times10^{-3}$
$h_1 = 0.8772$
$h_2 = 0.8739$
$d_{\mathrm{L}} = 1.4\times10^{-5}$
$f_{\mathrm{L1}} = 0.9986$
$f_{\mathrm{L2}} = 0.9986$
$r = 1.089\times10^{-3}$
$s = 0.9486$
$r_{\mathrm{Kur}} = 3.67\times10^{-4}$
$s_{\mathrm{Kur}} = 0.9673$
$n = 4.374\times10^{-3}$
$p_{\mathrm{a}} = 5.3\times10^{-5}$
$F_1 = 0.4701$
$F_2 = 0.0028$
$O_{\mathrm{Calse}} = 0.4315$
$[\mathrm{CaTnC}] = 0.00015$ mM
$B_1 = 0.0$ mM
$B_2 = 0.0$ mM
$v = 0.0$ µm/s
$w = 0.0$ µm/s
$[\mathrm{K}^+]_{i,\mathrm{Fb}} = 129.4349$ mM
$[\mathrm{Na}^+]_{i,\mathrm{Fb}} = 8.5547$ mM
$V_{\mathrm{Fb}} = -47.75$ mV
$r_{\mathrm{Kv}} = 0.0743$
$s_{\mathrm{Kv}} = 0.9717$
$O_1 = 0.0$
$O_2 = 0.0$
$C_1 = 1.0$
$C_2 = 0.0$
$p = 0.0$
$N = 7.455\times10^{-8}$
$l_1 = 0.436$ µm
$l_2 = 0.436$ µm
$l_3 = 0.089$ µm

Glossary

	Module 1: ECC in CM		
I_{Na}	Na^+ current	I_{di}	Ca^{2+} diffusion current from the diffusion-restricted subsarcolemmal space to the cytosol
I_{CaL}	L-type Ca^{2+} current	I_{up}	Sarcoplasmic reticulum Ca^{2+} uptake current
I_{t}	Transient outward K^+ current	I_{CaP}	Sarcolemmal Ca^{2+} pump current
I_{Kur}	Sustained outward K^+ current	I_{NaCa}	Na^+-Ca^{2+} exchange current
$I_{\mathrm{K,s}}$	Slow delayed rectifier K^+ current	I_{tr}	Sarcoplasmic reticulum Ca^{2+} translocation current (from uptake to release compartment)

$I_{\mathrm{K,r}}$	Rapid delayed rectifier K^+ current
I_{K1}	Inwardly rectifying K^+ current
$I_{\mathrm{B,Na}}$	Background Na^+ current
$I_{\mathrm{B,Ca}}$	Background Ca^{2+} current
I_{NaK}	Na^+-K^+ pump current
$[K^+]_c$	K^+ concentration in the extracellular cleft space
$[Ca^{2+}]_c$	Ca^{2+} concentration in the extracellular cleft space
$[Na^+]_i$	Na^+ concentration in the intracellular medium
$[K^+]_i$	K^+ concentration in the intracellular medium
$[Ca^{2+}]_i$	Ca^{2+} concentration in the intracellular medium
$[Ca^{2+}]_d$	Ca^{2+} concentration in the restricted subsarcolemmal space
$[Ca^{2+}]_{up}$	Ca^{2+} concentration in the sarcoplasmic reticulum uptake compartment
$[Ca^{2+}]_{rel}$	Ca^{2+} concentration in the sarcoplasmic reticulum release compartment
E_{Na}	Equilibrium (Nernst) potential for Na^+
E_{K}	Equilibrium (Nernst) potential for K^+
E_{Ca}	Equilibrium (Nernst) potential for Ca^{2+}
$E_{\mathrm{Ca,app}}$	Apparent reversal potential for I_{CaL}
$\bar{g}_{\mathrm{CaL}}$	Maximum conductance for I_{CaL}
$\bar{g}_{\mathrm{t}}$	Maximum conductance for I_{t}
$\bar{g}_{\mathrm{Kur}}$	Maximum conductance for I_{Kur}
$\bar{g}_{\mathrm{K,s}}$	Maximum conductance for $I_{\mathrm{K,s}}$
$\bar{g}_{\mathrm{K,r}}$	Maximum conductance for $I_{\mathrm{K,r}}$
$\bar{g}_{\mathrm{K1}}$	Maximum conductance for I_{K1}
$\bar{g}_{\mathrm{B,Na}}$	Maximum conductance for $I_{\mathrm{B,Na}}$
$\bar{g}_{\mathrm{B,Ca}}$	Maximum conductance for $I_{\mathrm{B,Ca}}$
m	Activation gating variable for I_{Na}
h_1, h_2	Fast and slow inactivation gating variables for I_{Na}
d_{L}	Activation gating variable for I_{CaL}
$f_{\mathrm{L1}}, f_{\mathrm{L2}}$	Fast and slow inactivation gating variables for I_{CaL}
f_{Ca}	$[Ca^{2+}]_d$-dependent ratio of fast (f_{L1}) to slow (f_{L2}) inactivation of I_{CaL}
k_{Ca}	Half-maximum Ca^{2+} binding concentration for f_{Ca}
I_{rel}	Sarcoplasmic reticulum Ca^{2+} release current
$[Na^+]_b$	Na^+ concentration in bulk (bathing) medium
$[K^+]_b$	K^+ concentration in bulk (bathing) medium
$[Ca^{2+}]_b$	Ca^{2+} concentration in bulk (bathing) medium
$[Na^+]_c$	Na^+ concentration in the extracellular cleft space
$\tau_{f_{\mathrm{L1}}}, \tau_{f_{\mathrm{L2}}}$	Fast and slow inactivation time constants for I_{CaL}
τ_r	Activation time constant for I_{t}
τ_s	Inactivation time constant for I_{t}
$\tau_{r_{\mathrm{Kur}}}$	Activation time constant for I_{Kur}
$\tau_{s_{\mathrm{Kur}}}$	Inactivation time constant for I_{Kur}
τ_n	Activation time constant for $I_{\mathrm{K,s}}$
$\tau_{p_{\mathrm{a}}}$	Activation time constant for $I_{\mathrm{K,r}}$
O_{Calse}	Fractional occupancy of the calsequestrin buffer (in the sarcoplasmic reticulum release compartment) by Ca^{2+}
R	Universal gas constant
T	Absolute temperature
F	Faraday's constant
C_{M}	Membrane capacitance of CM
V_{M}	Membrane voltage of CM
$\mathrm{Vol_c}$	Volume of the extracellular cleft space
$\mathrm{Vol_i}$	Total cytosolic volume
$\mathrm{Vol_d}$	Volume of the diffusion-restricted subsarcolemmal space
$\mathrm{Vol_{up}}$	Volume of the sarcoplasmic reticulum uptake compartment
$\mathrm{Vol_{rel}}$	Volume of the sarcoplasmic reticulum release compartment
τ_{Na}, τ_{K}, τ_{Ca}	Time constant of diffusion of Na^+, K^+, and Ca^{2+} from the bulk medium to the extracellular cleft space
τ_{di}	Time constant of diffusion from the restricted subsarcolemmal space to the cytosol
$\bar{I}_{\mathrm{NaK}}$	Maximum Na^+-K^+ pump current
$k_{\mathrm{NaK,K}}$	Half-maximum K^+ binding concentration for I_{NaK}
$k_{\mathrm{NaK,Na}}$	Half-maximum Na^+ binding concentration for I_{NaK}
$\bar{I}_{\mathrm{CaP}}$	Half-maximum Ca^{2+} binding concentration for I_{CaP}
k_{CaP}	Half-maximum Ca^{2+} binding concentration for I_{CaP}
k_{NaCa}	Scaling factor for I_{NaCa}

r	Activation gating variable for I_t
s	Inactivation gating variable for I_t
r_{Kur}	Activation gating variable for I_{Kur}
s_{Kur}	Inactivation gating variable for I_{Kur}
p_{i}	Inactivation gating variable (instantaneous) for $I_{\mathrm{K,r}}$
$\bar{m}, \bar{h}_1, \cdots$	Steady-state value of m, h_1, etc
F_1	Relative amount of "inactive precursor" in the I_{rel} formulation
F_2	Relative amount of "activator" in the I_{rel} formulation
P_{Na}	Relative permeability to Na^+
τ_{m}	Activation time constant for I_{Na}
τ_{h_1}, τ_{h_2}	Fast and slow inactivation time constants for I_{Na}
$\tau_{d_{\mathrm{L}}}$	Activation time constant for I_{CaL}
B_2	Concentration of Ca^{2+} bound with "slow" Ca^{2+} binding ligands
$b_{1\mathrm{on}}$	Rate constant for Ca^{2+} bound with "fast" Ca^{2+} binding ligands
$b_{2\mathrm{on}}$	Rate constant for Ca^{2+} bound with "slow" Ca^{2+} binding ligands
$b_{1\mathrm{off}}$	Maximum rate constant for unbound with "fast" Ca^{2+} binding ligands
$b_{2\mathrm{off}}$	Maximum rate constant for unbound with "slow" Ca^{2+} binding ligands
$B_{1\mathrm{tot}}$	Total concentration of Ca^{2+} bound with "fast" Ca^{2+} binding ligands
$B_{2\mathrm{tot}}$	Total concentration of Ca^{2+} bound with "slow" Ca^{2+} binding ligands
[CaTnC]	Ca^{2+}-troponin complexes concentration
$\mathrm{TnC}_{\mathrm{tot}}$	Total concentration of TnC
a_{on}	Rate constant for CaTnC association
a_{off}	Maximum rate constant for CaTnC dissociation
k_{A}	Cooperativity parameter
N_{A}	Average fraction of the attached cross-bridges per one CaTnC complex
$\Pi(N_{\mathrm{A}})$	Dependence defining cooperativity of the contractile proteins
Π_{min}	Parameter of $\Pi(N_{\mathrm{A}})$ function
r_{act}	Parameter of F_1 and F_2 function
r_{inact}	Parameter of F_1 and F_2 function
F_{CE}	Contractile element (sarcomere) (CE) force
F_{SE}	Serial elastic element (SE) force
F_{PE}	Parallel elastic element (PE) force
γ	Position of energy barrier controlling voltage dependence of I_{NaCa}
d_{NaCa}	Denominator constant for I_{NaCa}
$\bar{I}_{\mathrm{up}}$	Maximum sarcoplasmic reticulum uptake current
k_{cyca}	Half-maximum binding concentration for $[\mathrm{Ca}^{2+}]_i$ to I_{up}
k_{srca}	Half-maximum binding concentration for $[\mathrm{Ca}^{2+}]_{up}$ to I_{up}
k_{xcs}	Ratio of forward to back reactions for I_{up}
τ_{tr}	Time constant of diffusion of Ca^{2+} from sarcoplasmic reticulum uptake to release compartment
α_{rel}	Scaling factor for I_{rel}
$k_{\mathrm{rel,i}}$	Half-activation $[\mathrm{Ca}^{2+}]_i$ for I_{rel}
$k_{\mathrm{rel,d}}$	Half-activation $[\mathrm{Ca}^{2+}]_d$ for I_{rel}
r_{recov}	Recovery rate constant for the sarcoplasmic reticulum release channel
B_1	Concentration of Ca^{2+} bound with "fast" Ca^{2+} binding ligands
τ_{s_1}, τ_{s_2}	Rapidly and slowly recovering inactivation time constants for I_t
p_{a}	Activation gating variable for $I_{\mathrm{K,r}}$
n	Activation gating variable for $I_{\mathrm{K,s}}$
s_1, s_2	Rapidly and slowly recovering inactivation gating variables for I_t
alp_{p}	Parameter of Φ_x function
$\alpha_{\mathrm{vp_l}}$, $\alpha_{\mathrm{vp_s}}$, $\beta_{\mathrm{vp_l}}$,$\beta_{\mathrm{vp_s}}$	Constants of the dependencies of $k_{\mathrm{p_{vis}}}$ on the sarcomere length
$k_{\mathrm{p_{vis}}}$	Length-dependent coefficient of viscosity for damper viscous element
w	Velocity of PE deformation
Φ_x	Derivative of velocity of CE deformation
K_κ	Derivative of cross-bridges concentration
p_{prime_v}	Parameter of Φ_x function
alp_{s}	Parameter of w function
$\alpha_{\mathrm{vs_l}}$, $\alpha_{\mathrm{vs_s}}$, $\beta_{\mathrm{vs_l}}$, $\beta_{\mathrm{vs_s}}$	Constants of the dependencies of $k_{\mathrm{s_{vis}}}$ on the sarcomere length
$k_{\mathrm{s_{vis}}}$	Length-dependent coefficient of viscosity for damper viscous element
v_1	Parameter of p_v function
v_{max}	Parameter of p_v function
γ_2	Parameter of P_{star} function
a	Parameter of p_v function
d_{h}	Parameter of P_{star} function
P_{star}	Dependence of the steady-state

			sarcomere force on the sarcomere shortening/lengthening velocity
$\mathrm{F}_{\mathrm{XSE}}$	Extra serial elastic element (XSE) force	G_{star}	Dependence of the steady-state sarcomere stiffness on the velocity
F_{sample}	Sample force	α_{G}	Parameter of G_{star} function
l	Deviation of the sample length from its slack length	α_{P}	Parameter of G_{star} function
l_1	Deviation of contractile length from its slack length	case_1	Parameter of p_{prime_v} function
l_2	Deviation of parallel elastic element length from its slack length	case_2	Parameter of p_{prime_v} function
l_3	Deviation of extra series element length from its slack length	case_3	Parameter of p_{prime_v} function
α_1	Exponential coefficient of F_{SE}	case_4	Parameter of p_{prime_v} function
α_2	Exponential coefficient of F_{PE}	M_{A}	End-to-end interaction between adjacent tropomyosin segments in the case if both of them affected by the respective CaTnC complexes formation
α_3	Exponential coefficient of F_{XSE}	k_{μ}	Parameter of M_{A} function
β_1	Linear coefficient of F_{SE}	μ	Parameter of M_{A} function
β_2	Linear coefficient of F_{PE}	$temp_{n1}$	Parameter of n_1 function
β_3	Linear coefficient of F_{XSE}	g_1	Parameter of n_1 function
λ	Scale parameter of F_{CE}	g_2	Parameter of n_1 function
p_v	Steady-state dependence of an average crossbridge's force on the velocity of sarcomere shortening/lengthening	n_1	Probability of that a myosin head can find a vacant site on the actin filament
N	Cross-bridges concentration	v	Velocity of CE deformation
L_{oz}	Instantaneous length of thick and thin lament overlap zone	q_4	Parameter of q_v function
S_0	Parameter of L_{oz} function	α_{Q}	Parameter of q_v function
v_{st}	Parameter of q_v function	β_{Q}	Parameter of q_v function
x_{st}	Parameter of q_v function	k_{p_v}	Parameter of K_{κ} function
q_v	Stationary relation "stiffness-velocity" for the sample	κ	Function required for variation the ratio between rates of cross-bridge attachment and detachment
q_1	Parameter of q_v function	κ_0	Parameter of κ function
q_2	Parameter of q_v function	m_0	Fraction of strongly attached Xb in steady state isometric conditions
q_3	Parameter of q_v function	k_{m_v}	Parameter of K_{κ} function

Module 2: Optical activity in Fb

$I_{\mathrm{Kv\_Fb}}$	Time- and voltage-dependent K^+ current in Fb	E_{ChR2}	Reversal potential for ChR2
$I_{\mathrm{K1\_Fb}}$	Inward-rectifying K^+ current in Fb	O_1	Open state probability
$I_{\mathrm{NaK\_Fb}}$	Na^+-K^+ pump current in Fb	O_2	Open state probability
$I_{\mathrm{B,Na\_Fb}}$	Background Na^+ current in Fb	C_1	Closed state probability
$[\mathrm{Na}^+]_{\mathrm{c,Fb}}$	Na^+ concentration in the Fb's extracellular cleft space	C_2	Closed state probability
$[\mathrm{K}^+]_{\mathrm{c,Fb}}$	K^+ concentration in the Fb's extracellular cleft space	G_{r}	Rate constant for $C_2 \rightarrow C_1$ transition
$[\mathrm{Na}^+]_{i,\mathrm{Fb}}$	Na^+ concentration in the Fb's intracellular medium	G_{d1}	Rate constant for $O_1 \rightarrow C_1$ transition
$[\mathrm{K}^+]_{i,\mathrm{Fb}}$	K^+ concentration in the Fb's intracellular medium	k_1	Light-sensitive rate constant for $C_1 \rightarrow O_1$ transition
$E_{\mathrm{Na,Fb}}$	Equilibrium (Nernst) potential for Na^+ in Fb	e_{12}	Rate constant for $O_1 \rightarrow O_2$ transition
$E_{\mathrm{K,Fb}}$	Equilibrium (Nernst) potential for K^+	e_{21}	Rate constant for $O_2 \rightarrow O_1$ transition

	in Fb		
$\bar{g}_{\mathrm{Kv,Fb}}$	Maximum conductance for $I_{\mathrm{Kv\_Fb}}$	k_2	Light-sensitive rate constant for $C_2 \rightarrow O_2$ transition
$\bar{g}_{\mathrm{K1,Fb}}$	Maximum conductance for $I_{\mathrm{K1\_Fb}}$	G_{d2}	Rate constant for $O_2 \rightarrow C_2$ transition
$\bar{g}_{\mathrm{B,Na,Fb}}$	Maximum conductance for $I_{\mathrm{b,Na\_Fb}}$	$Irradiance$	Light irradiance
$\mathrm{Vol}_{\mathrm{i,Fb}}$	Total cytosolic volume of Fb	ε_1	Quantum efficiency for photon absorption from C_1
r_{Kv}	Activation gating variable for $I_{\mathrm{Kv\_Fb}}$	ε_2	Quantum efficiency for photon absorption from C_2
s_{Kv}	Inactivation gating variable for $I_{\mathrm{Kv\_Fb}}$	σ_{ret}	Absorption cross-section for retinal
$\tau_{r_{\mathrm{Kv}}}$	Activation time constant for $I_{\mathrm{Kv\_Fb}}$	λ_1	Wavelength of max absorption for retinal
$\tau_{s_{\mathrm{Kv}}}$	Inactivation time constant for $I_{\mathrm{Kv\_Fb}}$	w_{loss}	Scaling factor for losses of photons due to scattering or absorption
α_{K1}, β_{K1}	Fractional open probability of the $I_{\mathrm{K1\_Fb}}$ channel	hc	Product of Planck's constant and the speed of light
$\bar{I}_{\mathrm{NaK,Fb}}$	Maximum Na^+-K^+ pump current in Fb	p	State-variable, time- and irradiance-dependent activation function for ChR2
$k_{\mathrm{mK,Fb}}$	Half-maximum K^+ binding concentration for $I_{\mathrm{NaK,Fb}}$	$S0$	Parameter of p function
$k_{\mathrm{mNa,Fb}}$	Half-maximum Na^+ binding concentration for $I_{\mathrm{NaK,Fb}}$	τ_{ChR2}	Time constant of ChR2 activation
$\bar{r}_{\mathrm{Kv}}, \bar{s}_{\mathrm{Kv}}, \cdots$	Steady-state value of r_{Kv}, s_{Kv}, etc	I_{ChR2}	ChR2 current
C_{Fb}	Membrane capacitance of Fb	$\bar{g}_{\mathrm{ChR2}}$	Max conductance for I_{ChR2}
V_{Fb}	Membrane voltage of Fb	$G(V)$	Voltage-dependent rectification function
Module 3: CM-Fb coupling			
G_{gap}	Gap junctional conductance between Fb and CM	I_{M}	Net membrane current of the CM
n	Number of Fbs coupled to each CM	I_{Fb}	Net membrane current of the Fb

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