

# Supplementary Material

## Model Equations

Table 1 through 23 contained all the equations, parameters values and initial conditions necessary to carry out the simulations presented in this article. Unless otherwise noted, the units are as follows: time in seconds (s), voltage in millivolts (mV), concentration in millimoles/liter (mmol/L), current in picoamperes (pA), conductance in nanosiemens (nS), capacitance in picofarads (pF), volume in nanoliters (nL), and temperature in kelvin (K).

### Atrial Myocyte Model

The atrial myocyte model was represented by the Maleckar et al. mathematical model [1], which was based on a previous model of the adult human atrial myocyte action potential (AP), that of Nygren et al. [2]. The stimulus used to evoke an AP was a rectangular current pulse ( $I_{stim}$ ) with amplitude of 280 pA and duration of 6 ms. Equations of the stretch-activated current ( $I_{SAC}$ ) were taken from Kuijpers et al [3], which were assumed to be a nonselective cation current with a near-linear current-voltage relation on the basis of experimental observations [4]. When  $I_{SAC}$  was integrated in the myofibroblast-myocyte (Mfb-M) coupling, equations of intracellular ion concentrations of  $Na^+$ ,  $K^+$  and  $Ca^{2+}$  ( $[Na^+]_i$ ,  $[K^+]_i$ , and  $[Ca^{2+}]_i$ ) followed Table 12. Without  $I_{SAC}$  in Mfb-M coupling, they followed Table 8.

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

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$I_{Na} = P_{Na} m^3 (0.9 h_1 + 0.1 h_2) [Na^+]_c V_M \frac{F^2 e^{(V_M - E_{Na})F/RT} - 1.0}{RT e^{V_M F/RT} - 1.0}$	$\bar{h} = \frac{1.0}{1.0 + e^{(V_M + 63.6)/5.3}}$
$\bar{m} = \frac{1.0}{1.0 + e^{(V_M + 27.12)/-8.21}}$	$\tau_m = 0.000042 e^{-((V_M + 25.57)/28.8)^2} + 0.000024$
$\frac{dm}{dt} = \frac{\bar{m} - m}{\tau_m}$	$\tau_{h_1} = \frac{0.03}{1.0 + e^{(V_M + 35.1)/3.2}} + 0.0003$
$\frac{dh_1}{dt} = \frac{\bar{h} - h_1}{\tau_{h_1}}$	$\tau_{h_2} = \frac{0.12}{1.0 + e^{(V_M + 35.1)/3.2}} + 0.003$
$\frac{dh_2}{dt} = \frac{\bar{h} - h_2}{\tau_{h_2}}$	
$E_{Na} = \frac{RT}{F} \log \frac{[Na^+]_c}{[Na^+]_i}$	

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

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$$I_{CaL} = \bar{g}_{CaL} d_L [f_{Ca} f_{L1} + (1 - f_{Ca}) f_{L2}] (V_M - E_{Ca,app})$$

$$\bar{d}_L = \frac{1.0}{1.0 + e^{(V_M+9.0)/-5.8}}$$

$$\frac{dd_L}{dt} = \frac{\bar{d}_L - d_L}{\tau_{d_L}}$$

$$\bar{f}_{L1} = \frac{\bar{f}_L - f_{L1}}{\tau_{f_{L1}}}$$

$$\frac{df_{L1}}{dt} = \frac{\bar{f}_{L1} - f_{L1}}{\tau_{f_{L1}}}$$

$$\bar{f}_{L2} = \frac{\bar{f}_L - f_{L2}}{\tau_{f_{L2}}}$$

$$\frac{df_{L2}}{dt} = \frac{\bar{f}_{L2} - f_{L2}}{\tau_{f_{L2}}}$$

$$f_{Ca} = \frac{[Ca^{2+}]_d}{[Ca^{2+}]_d + k_{Ca}}$$

$$\bar{f}_L = \frac{1.0}{1.0 + e^{(V_M+27.4)/7.1}}$$

$$\tau_{d_L} = 0.0027e^{-((V_M+35.0)/30.0)^2} + 0.002$$

$$\tau_{f_{L1}} = 0.161e^{-((V_M+40.0)/14.4)^2} + 0.01$$

$$\tau_{f_{L2}} = 1.3323e^{-((V_M+40.0)/14.2)^2} + 0.0626$$

**Table 3. Transient and ultrarapidly delayed rectifier K<sup>+</sup> currents:  $I_t$  and  $I_{Kur}$**

$$I_t = \bar{g}_t r s (V_M - E_K)$$

$$\bar{r} = \frac{1.0}{1.0 + e^{(V_M-1.0)/-11.0}}$$

$$\frac{dr}{dt} = \frac{\bar{r} - r}{\tau_r}$$

$$\bar{s} = \frac{1.0}{1.0 + e^{(V_M+40.5)/11.5}}$$

$$\tau_r = 0.0035e^{-(V_M/30.0)^2} + 0.0015$$

$$\frac{ds}{dt} = \frac{\bar{s} - s}{\tau_s}$$

$$\tau_s = 0.025635e^{-((V_M+52.45)/15.89)^2} + 0.01414$$

$$I_{Kur} = \bar{g}_{Kur} r_{Kur} s_{Kur} (V_M - E_K)$$

$$\bar{r}_{Kur} = \frac{1.0}{1.0 + e^{(V_M+6.0)/-8.6}}$$

$$\frac{dr_{Kur}}{dt} = \frac{\bar{r}_{Kur} - r_{Kur}}{\tau_{r_{Kur}}}$$

$$\bar{s}_{Kur} = \frac{1.0}{1.0 + e^{(V_M+7.5)/10.0}}$$

$$\tau_{r_{Kur}} = \frac{0.009}{1.0 + e^{(V_M+5.0)/12.0}} + 0.0005$$

$$\frac{ds_{Kur}}{dt} = \frac{\bar{s}_{Kur} - s_{Kur}}{\tau_{s_{Kur}}}$$

$$\tau_{s_{Kur}} = \frac{0.59}{1.0 + e^{(V_M+60.0)/10.0}} + 3.05$$

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

**Table 4. Delayed rectifier K<sup>+</sup> currents:  $I_{K,s}$  and  $I_{K,r}$**

$$I_{K,s} = \bar{g}_{K,s} n (V_M - E_K)$$

$$\bar{n} = \frac{1.0}{1.0 + e^{(V_M-19.9)/-12.7}}$$

$$\frac{dn}{dt} = \frac{\bar{n} - n}{\tau_n}$$

$$\tau_n = 0.7 + 0.4e^{-((V_M-20.0)/20.0)^2}$$

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

$$I_{K,r} = \bar{g}_{K,r} p_a p_i (V_M - E_K)$$

$$\bar{p}_a = \frac{1.0}{1.0 + e^{(V_M+15.0)/-6.0}}$$

$$p_i = \frac{1.0}{1.0 + e^{(V_M+55.0)/24.0}}$$

$$\frac{dp_a}{dt} = \frac{\bar{p}_a - p_a}{\tau_{p_a}}$$

$$\tau_{p_a} = 0.03118 + 0.21718e^{-((V_M+20.1376)/22.1996)^2}$$

**Table 5. Inward rectifier K<sup>+</sup> currents:  $I_{K1}$** 

$$I_{K1} = \bar{g}_{K1} [K^+]_c^{0.4457} \frac{V_M - E_K}{1.0 + e^{1.5(V_M - E_K + 3.6)F/RT}}$$

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

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

$$I_{B,Na} = \bar{g}_{B,Na} (V_M - E_{Na}) \quad I_{B,Ca} = \bar{g}_{B,Ca} (V_M - E_{Ca})$$

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

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

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

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

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

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

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

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

$$\frac{d[Ca^{2+}]_i}{dt} = - \frac{-I_{di} + I_{B,Ca} + I_{CaP} - 2I_{NaCa} + I_{up} - I_{rel}}{2.0 Vol_i F} - \frac{dO}{dt}$$

$$\frac{dO}{dt} = 0.08 \frac{dO_{TC}}{dt} + 0.16 \frac{dO_{TMGC}}{dt} + 0.045 \frac{dO_c}{dt}$$

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

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

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

$$\frac{d[Na^+]_c}{dt} = \frac{[Na^+]_b - [Na^+]_c}{\tau_{Na}} + \frac{I_{Na} + I_{B,Na} + 3I_{NaK} + 3I_{NaCa}}{Vol_c F}$$

$$\frac{d[K^+]_c}{dt} = \frac{[K^+]_b - [K^+]_c}{\tau_K} + \frac{I_t + I_{Kur} + I_{K1} + I_{K,s} + I_{K,r} - 2I_{NaK}}{Vol_c F}$$

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

**Table 10. Intracellular Ca<sup>2+</sup> buffering**

$$\begin{aligned} \frac{dO_C}{dt} &= 200000.0[\text{Ca}^{2+}]_i(1.0 - O_C) - 476.0O_C \\ \frac{dO_{TC}}{dt} &= 78400.0[\text{Ca}^{2+}]_i(1.0 - O_{TC}) - 392.0O_{TC} \\ \frac{dO_{TMgC}}{dt} &= 200000.0[\text{Ca}^{2+}]_i(1.0 - O_{TMgC} - O_{TMgMg}) - 6.6O_{TMgC} \\ \frac{dO_{TMgMg}}{dt} &= 2000.0[\text{Mg}^{2+}]_i(1.0 - O_{TMgC} - O_{TMgMg}) - 666.0O_{TMgMg} \end{aligned}$$

**Table 11. Ca<sup>2+</sup> handling by the sarcoplasmic reticulum**

$$\begin{aligned} I_{up} &= \bar{I}_{up} \frac{[\text{Ca}^{2+}]_i/k_{cyca} - k_{xcs}^2[\text{Ca}^{2+}]_{up}/k_{srca}}{([\text{Ca}^{2+}]_i + k_{cyca})/k_{cyca} + k_{xcs}([\text{Ca}^{2+}]_{up} + k_{srca})/k_{srca}} \\ I_{tr} &= ([\text{Ca}^{2+}]_{up} - [\text{Ca}^{2+}]_{rel}) \frac{2F \text{Vol}_{rel}}{\tau_{tr}} \\ I_{rel} &= \alpha_{rel} \left( \frac{F_2}{F_2 + 0.25} \right)^2 ([\text{Ca}^{2+}]_{rel} - [\text{Ca}^{2+}]_i) \\ \frac{dO_{Calse}}{dt} &= 480.0[\text{Ca}^{2+}]_{rel}(1.0 - O_{Calse}) - 400.0O_{Calse} \\ \frac{d[\text{Ca}^{2+}]_{rel}}{dt} &= \frac{I_{tr} - I_{rel}}{2F \text{Vol}_{rel}} - 31.0 \frac{dO_{Calse}}{dt} \\ \frac{d[\text{Ca}^{2+}]_{up}}{dt} &= \frac{I_{up} - I_{tr}}{2F \text{Vol}_{up}} \\ \frac{dF_1}{dt} &= r_{recov}(1.0 - F_1 - F_2) - r_{act} F_1 \\ \frac{dF_2}{dt} &= r_{act} F_1 - r_{inact} F_2 \\ r_{act} &= 203.8 \left[ \left( \frac{[\text{Ca}^{2+}]_i}{[\text{Ca}^{2+}]_i + k_{rel,i}} \right)^4 + \left( \frac{[\text{Ca}^{2+}]_d}{[\text{Ca}^{2+}]_d + k_{rel,d}} \right)^4 \right] \\ r_{inact} &= 33.96 + 339.6 \left( \frac{[\text{Ca}^{2+}]_i}{[\text{Ca}^{2+}]_i + k_{rel,i}} \right)^4 \end{aligned}$$

**Table 12. Stretch-activated current: I<sub>SAC</sub>**

$$\begin{aligned} I_{SAC} &= I_{SAC,Na} + I_{SAC,K} + I_{SAC,Ca} \\ I_{SAC,Na} &= \bar{P}_{Na} g_{SAC} \frac{z_{Na}^2 F^2 V_M}{RT} \cdot \frac{[\text{Na}^+]_i - [\text{Na}^+]_c e^{-(z_{Na} F V_M)/RT}}{1.0 - e^{-(z_{Na} F V_M)/RT}} \\ I_{SAC,K} &= \bar{P}_K g_{SAC} \frac{z_K^2 F^2 V_M}{RT} \cdot \frac{[\text{K}^+]_i - [\text{K}^+]_c e^{-(z_K F V_M)/RT}}{1.0 - e^{-(z_K F V_M)/RT}} \\ I_{SAC,Ca} &= \bar{P}_{Ca} g_{SAC} \frac{z_{Ca}^2 F^2 V_M}{RT} \cdot \frac{[\text{Ca}^{2+}]_i - [\text{Ca}^{2+}]_c e^{-(z_{Ca} F V_M)/RT}}{1.0 - e^{-(z_{Ca} F V_M)/RT}} \end{aligned}$$

$$g_{SAC} = \frac{G_{SAC}}{1.0 + K_{SAC} e^{-(\alpha_{SAC}(\lambda-1))}}$$

$$\bar{P}_{Na} : \bar{P}_K : \bar{P}_{Ca} = 1:1:1$$

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

$$\frac{d[K^+]_i}{dt} = - \frac{I_t + I_{Kur} + I_{K1} + I_{Ks} + I_{Kr} - 2I_{NaK} + I_{SAC,K}}{Vol_i F}$$

$$\frac{d[Ca^{2+}]_i}{dt} = - \frac{-I_{di} + I_{B,Ca} + I_{CaP} - 2I_{NaCa} + I_{up} - I_{rel} + I_{SAC,Ca}}{2.0 Vol_i F} - \frac{dO}{dt}$$


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### Atrial Myofibroblast Model

The atrial Mfb model was represented by the MacCannell et al. mathematical model [5]. Mathematical formulations of the currents through voltage-gated sodium channels ( $I_{Na\_Mfb}$ ) and mechano-gated channels ( $I_{MGC\_Mfb}$ ) was based on experimental data from Chatelier et al. [6] and Kamkin et al. [7], respectively.

**Table 13. Time- and voltage-dependent K<sup>+</sup> current:  $I_{Kv\_Mfb}$**

$$I_{Kv\_Mfb} = \bar{g}_{Kv\_Mfb} r_{Kv} s_{Kv} (V_{Mfb} - E_{K,Mfb})$$

$$\bar{r}_{Kv} = (1.0 + e^{-(V_{Mfb}+20.0)/11.0})^{-1} \quad \bar{s}_{Kv} = (1.0 + e^{(V_{Mfb}+23.0)/7.0})^{-1}$$

$$\frac{dr_{Kv}}{dt} = \frac{\bar{r}_{Kv} - r_{Kv}}{\tau_{r_{Kv}}} \quad \tau_{r_{Kv}} = 0.0203 + 0.138 \cdot e^{-(V_{Mfb}+20.0)/25.9)^2}$$

$$\frac{ds_{Kv}}{dt} = \frac{\bar{s}_{Kv} - s_{Kv}}{\tau_{s_{Kv}}} \quad \tau_{s_{Kv}} = 1.574 + 5.268 \cdot e^{-(V_{Mfb}+23.0)/22.7)^2}$$

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


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**Table 14. Time-independent inward-rectifying K<sup>+</sup> current:  $I_{K1\_Mfb}$**

$$I_{K1\_Mfb} = \bar{g}_{K1,Mfb} (\alpha_{K1} / (\alpha_{K1} + \beta_{K1})) (V_{Mfb} - E_{K,Mfb})$$

$$\alpha_{K1} = 0.1 (1.0 + e^{0.06(V_{Mfb} - E_K - 200.0)})^{-1}$$

$$\beta_{K1} = \frac{3.0 \cdot e^{0.0002(V_{Mfb} - E_K + 100.0)} + e^{0.1(V_{Mfb} - E_K + 10.0)}}{1.0 + e^{-0.5(V_{Mfb} - E_K)}}$$

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


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**Table 15. Na<sup>+</sup>-K<sup>+</sup> pump current:  $I_{NaK\_Mfb}$**

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$$I_{\text{NaK\_Mfb}} = \bar{I}_{\text{NaK\_Mfb}} \cdot \frac{[\text{K}^+]_{\text{c,Mfb}}}{[\text{K}^+]_{\text{c,Mfb}} + k_{\text{mK}}} \cdot \frac{[\text{Na}^+]_{\text{i,Mfb}}^{1.5}}{[\text{Na}^+]_{\text{i,Mfb}}^{1.5} + k_{\text{mNa}}^{1.5}} \cdot \frac{V_{\text{Mfb}} + 150.0}{V_{\text{Mfb}} + 200.0}$$


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**Table 16. Background inward current:  $I_{\text{B,Na\_Mfb}}$**

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$$I_{\text{B,Na\_Mfb}} = \bar{g}_{\text{B,Na,Mfb}}(V_{\text{Mfb}} - E_{\text{Na,Mfb}})$$

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


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**Table 17.  $\text{Na}^+$  current:  $I_{\text{Na\_Mfb}}$**

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$$I_{\text{Na\_Mfb}} = \bar{g}_{\text{Na,Mfb}} m_{\text{Mfb}} j_{\text{Mfb}}^{0.12} (V_{\text{Mfb}} - E_{\text{Na,Mfb}})$$

$$\bar{m}_{\text{Mfb}} = \frac{-0.0102 - 1.0063}{1.0 + e^{(V_{\text{Mfb}} + 42.1)/10.53}} + 1.0063 \quad \bar{j}_{\text{Mfb}} = \frac{1.04 - 0.004}{1.0 + e^{(V_{\text{Mfb}} + 84.82)/9.4}} + 0.004$$

$$\frac{dm_{\text{Mfb}}}{dt} = \frac{\bar{m}_{\text{Mfb}} - m_{\text{Mfb}}}{\tau_{m_{\text{Mfb}}}} \quad \frac{dj_{\text{Mfb}}}{dt} = \frac{\bar{j}_{\text{Mfb}} - j_{\text{Mfb}}}{\tau_{j_{\text{Mfb}}}}$$

$$\tau_{m_{\text{Mfb}}} = \frac{1}{\alpha_{m_{\text{Mfb}}} + \beta_{m_{\text{Mfb}}}} \quad \tau_{j_{\text{Mfb}}} = \frac{1}{\alpha_{j_{\text{Mfb}}} + \beta_{j_{\text{Mfb}}}}$$

$$\alpha_{m_{\text{Mfb}}} = \begin{cases} 0.0077 \frac{V_{\text{Mfb}} + 68.19}{1.0 - e^{-0.18(V_{\text{Mfb}} + 68.19)}} \\ 0.0433, & \text{if } V_{\text{Mfb}} = -68.19 \end{cases}$$

$$\beta_{m_{\text{Mfb}}} = 0.004e^{-V_{\text{Mfb}}/11.98}$$

$$\alpha_{j_{\text{Mfb}}} = \begin{cases} (-14.5e^{0.17V_{\text{Mfb}}} + 1.8e^{1.56V_{\text{Mfb}}}) \cdot \frac{V_{\text{Mfb}} + 35.73}{1.0 + e^{3.31(V_{\text{Mfb}} + 3.86)}} \\ 0, & \text{if } V_{\text{Mfb}} \geq -40.0 \end{cases}$$

$$\beta_{j_{\text{Mfb}}} = \begin{cases} 5.05 \times 10^{-5} \frac{e^{-0.0995V_{\text{Mfb}}}}{1.0 + e^{-0.01(V_{\text{Mfb}} - 84.02)}} \\ 0.11 \frac{e^{-4.13 \times 10^{-4} V_{\text{Mfb}}}}{1.0 + e^{-0.09(V_{\text{Mfb}} + 42.44)}}, & \text{if } V_{\text{Mfb}} \geq -40.0 \end{cases}$$

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


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**Table 18. Mechano-gated channel mediated current:  $I_{\text{MGC\_Mfb}}$**

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$$I_{\text{MGC\_Mfb}} = \bar{g}_{\text{MGC,Mfb}} \cdot (V_{\text{Mfb}} - E_{\text{MGC,Mfb}})$$


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**Table 19. Intracellular ion concentrations:  $[\text{Na}^+]_{\text{i,Mfb}}$ ,  $[\text{K}^+]_{\text{i,Mfb}}$ , and  $[\text{Ca}^{2+}]_{\text{i,Mfb}}$**

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$$\text{Without } I_{\text{Na\_Mfb}}: \frac{d[\text{Na}^+]_{\text{i,Mfb}}}{dt} = -\frac{I_{\text{B,Na\_Mfb}} + 3I_{\text{NaK\_Mfb}}}{\text{Vol}_{\text{i,Mfb}}F}$$

$$\text{With } I_{\text{Na\_Mfb}}: \frac{d[\text{Na}^+]_{\text{i,Mfb}}}{dt} = -\frac{I_{\text{Na\_Mfb}} + I_{\text{B,Na\_Mfb}} + 3I_{\text{NaK\_Mfb}}}{\text{Vol}_{\text{i,Mfb}}F}$$


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$$\frac{d[K^+]_{i,Mfb}}{dt} = -\frac{I_{K1\_Mfb} + I_{Kv\_Mfb}}{Vol_{i,Mfb} F}$$

## Mfb-M electrical coupling

**Table 20. Transmembrane potential of myocyte and Mfb**

$$\frac{dV_M}{dt} = -\frac{1}{C_{m,M}} \left( I_M(V_M, t) + \sum_{i=1}^n G_{gap}(V_M - V_{Mfb,i}) \right)$$

$$\frac{dV_{Mfb,i}}{dt} = -\frac{1}{C_{m,Mfb}} \left( I_{Mfb,i}(V_{Mfb,i}, t) + G_{gap}(V_{Mfb,i} - V_M) \right)$$

Without  $I_{SAC}$ :  $I_M(V_M, t) =$

$$I_{Na} + I_{CaL} + I_t + I_{Kur} + I_{K1} + I_{K,r} + I_{K,s} + I_{B,Na} + I_{B,Ca} + I_{NaK} + I_{CaP} + I_{NaCa} - I_{Stim}$$

With  $I_{SAC}$ :  $I_M(V_M, t) =$

$$I_{Na} + I_{CaL} + I_t + I_{Kur} + I_{K1} + I_{K,r} + I_{K,s} + I_{B,Na} + I_{B,Ca} + I_{NaK} + I_{CaP} + I_{NaCa} + I_{SAC} - I_{Stim}$$

Without  $I_{Na\_Mfb}$  and  $I_{MGC\_Mfb}$ :  $I_{Mfb,i}(V_{Mfb,i}, t) = I_{Kv\_Mfb} + I_{K1\_Mfb} + I_{NaK\_Mfb} + I_{B,Na\_Mfb}$

With  $I_{Na\_Mfb}$  and  $I_{MGC\_Mfb}$ :  $I_{Mfb,i}(V_{Mfb,i}, t) =$

$$I_{Kv\_Mfb} + I_{K1\_Mfb} + I_{NaK\_Mfb} + I_{B,Na\_Mfb} + I_{Na\_Mfb} + I_{MGC\_Mfb}$$

**Table 21. Parameter values**

$$[Na^+]_b = 130.0 \text{ mmol/L}$$

$$[K^+]_b = 5.4 \text{ mmol/L}$$

$$[Ca^{2+}]_b = 1.8 \text{ mmol/L}$$

$$[Mg^{2+}]_i = 2.5 \text{ mmol/L}$$

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

$$k_{Ca} = 0.025 \text{ mmol/L}$$

$$R = 8314.0 \text{ mJ/molK}$$

$$T = 306.15 \text{ K}$$

$$F = 96487.0 \text{ C/mol}$$

$$C_{m,M} = 0.05 \text{ nF}$$

$$Vol_i = 0.005884 \text{ nL}$$

$$Vol_c = 0.136 Vol_i$$

$$Vol_d = 0.02 Vol_i$$

$$Vol_{rel} = 0.0000441 \text{ nL}$$

$$Vol_{up} = 0.0003969 \text{ nL}$$

$$\tau_{Na} = 14.3 \text{ s}$$

$$\tau_K = 10.0 \text{ s}$$

$$\tau_{Ca} = 24.7 \text{ s}$$

$$k_{CaP} = 0.0002 \text{ mmol/L}$$

$$k_{NaCa} = 0.0374842 \text{ pA/(mmol/L)}^4$$

$$\gamma = 0.45$$

$$d_{NaCa} = 0.0003 \text{ (mmol/L)}^{-4}$$

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

$$k_{cyca} = 0.0003 \text{ mmol/L}$$

$$K_{srca} = 0.5 \text{ mmol/L}$$

$$K_{xcs} = 0.4$$

$$\tau_{tr} = 0.01 \text{ s}$$

$$\alpha_{rel} = 200000.0 \text{ pA/L/mmol}$$

$$k_{rel,i} = 0.0003 \text{ mmol/L}$$

$$k_{rel,d} = 0.003 \text{ mmol/L}$$

$$r_{recov} = 0.815 \text{ s}^{-1}$$

$$K_{SAC} = 100$$

$$\alpha_{SAC} = 3$$

$$\lambda = 1.2$$

$$C_{m,Mfb} = 6.3 \text{ pF}$$

$$Vol_{i,Mfb} = 0.00137 \text{ nL}$$

$\tau_{dt} = 0.01 \text{ s}$	$[\text{Na}^+]_{c,\text{Mfb}} = 130.011 \text{ mmol/L}$
$\bar{I}_{\text{NaK}} = 68.55 \text{ pA}$	$[\text{K}^+]_{c,\text{Mfb}} = 5.3581 \text{ mmol/L}$
$k_{\text{NaK,K}} = 1.0 \text{ mmol/L}$	$k_{\text{mK}} = 1.0 \text{ mmol}$
$k_{\text{NaK,Na}} = 11.0 \text{ mmol/L}$	$k_{\text{mNa}} = 11.0 \text{ mmol}$
$\bar{I}_{\text{CaP}} = 4.0 \text{ pA}$	$\bar{I}_{\text{NaK,Mfb}} = 10.36 \text{ pA}$

**Table 22. Maximum conductance values**

$P_{\text{Na}} = 0.0018 \text{ nL/s}$	$\bar{g}_{\text{B,Ca}} = 0.078681 \text{ nS}$
$\bar{g}_{\text{CaL}} = 6.75 \text{ nS}$	$G_{\text{SAC}} = 0.015 \text{ } \mu\text{m/s}$
$\bar{g}_{\text{t}} = 8.25 \text{ nS}$	$\bar{g}_{\text{Kv,Mfb}} = 1.575 \text{ nS}$
$\bar{g}_{\text{Kur}} = 2.25 \text{ nS}$	$\bar{g}_{\text{K1,Mfb}} = 3.038 \text{ nS}$
$\bar{g}_{\text{Ks}} = 1.0 \text{ nS}$	$\bar{g}_{\text{B,Na,Mfb}} = 0.05985 \text{ nS}$
$\bar{g}_{\text{Kr}} = 0.5 \text{ nS}$	$\bar{g}_{\text{Na,Mfb}} = 0.756 \text{ nS}$
$\bar{g}_{\text{K1}} = 3.1 \text{ nS}$	$\bar{g}_{\text{MGC,Mfb}} = 0.043 \text{ nS}$
$\bar{g}_{\text{B,Na}} = 0.060599 \text{ nS}$	

**Table 23. Initial conditions**

$V_{\text{M}} = -74.2525 \text{ mV}$	$s_{\text{Kur}} = 0.9673$
$[\text{Na}^+]_{\text{c}} = 130.0221 \text{ mmol/L}$	$n = 4.374 \times 10^{-3}$
$[\text{K}^+]_{\text{c}} = 5.5602 \text{ mmol/L}$	$p_{\text{a}} = 5.3 \times 10^{-5}$
$[\text{Ca}^{2+}]_{\text{c}} = 1.8158 \text{ mmol/L}$	$F_1 = 0.4701$
$[\text{Na}^+]_{\text{i}} = 8.5168 \text{ mmol/L}$	$F_2 = 0.0028$
$[\text{K}^+]_{\text{i}} = 129.486 \text{ mmol/L}$	$O = 1.382$
$[\text{Ca}^{2+}]_{\text{i}} = 6.5 \times 10^{-5} \text{ mmol/L}$	$O_{\text{C}} = 0.0268$
$[\text{Ca}^{2+}]_{\text{d}} = 7.1 \times 10^{-5} \text{ mmol/L}$	$O_{\text{Calse}} = 0.4315$
$[\text{Ca}^{2+}]_{\text{up}} = 0.6492 \text{ mmol/L}$	$O_{\text{TC}} = 0.0129$
$[\text{Ca}^{2+}]_{\text{rel}} = 0.6326 \text{ mmol/L}$	$O_{\text{TMgC}} = 0.1904$
$m = 3.289 \times 10^{-3}$	$O_{\text{TMgMg}} = 0.7145$
$h_1 = 0.8772$	$[\text{K}^+]_{\text{i,Mfb}} = 129.4349 \text{ mmol/L}$
$h_2 = 0.8739$	$[\text{Na}^+]_{\text{i,Mfb}} = 8.5547 \text{ mmol/L}$
$d_{\text{L}} = 1.4 \times 10^{-5}$	$V_{\text{Mfb}} = -47.75 \text{ mV}$
$f_{\text{L1}} = 0.9986$	$r_{\text{Kv}} = 0.0743$
$f_{\text{L2}} = 0.9986$	$s_{\text{Kv}} = 0.9717$
$r = 1.089 \times 10^{-3}$	$m_{\text{Mfb}} = 3.0 \times 10^{-3}$
$s = 0.9486$	$j_{\text{Mfb}} = 0.9989$
$r_{\text{Kur}} = 3.67 \times 10^{-4}$	

## Glossary

	<b>Myocyte</b>	$\text{Vol}_{\text{i}}$	Total cytosolic volume
$I_{\text{Na}}$	$\text{Na}^+$ current	$\text{Vol}_{\text{d}}$	Volume of the diffusion-restricted subsarcolemmal space
$I_{\text{CaL}}$	L-type $\text{Ca}^{2+}$ current	$\text{Vol}_{\text{up}}$	Volume of the sarcoplasmic reticulum uptake compartment



$I_t$	Transient outward $K^+$ current	$Vol_{rel}$	Volume of the sarcoplasmic reticulum release compartment
$I_{Kur}$	Sustained outward $K^+$ current	$\tau_{Na^+}, \tau_K, \tau_{Ca^{2+}}$	Time constant of diffusion of $Na^+$ , $K^+$ , and $Ca^{2+}$ from the bulk medium to the extracellular cleft space
$I_{K,s}$	Slow delayed rectifier $K^+$ current	$\tau_{di}$	Time constant of diffusion from the restricted subsarcolemmal space to the cytosol
$I_{K,r}$	Rapid delayed rectifier $K^+$ current	$\bar{I}_{NaK}$	Maximum $Na^+$ - $K^+$ pump current
$I_{K1}$	Inwardly rectifying $K^+$ current	$k_{NaK,K}$	Half-maximum $K^+$ binding concentration for $I_{NaK}$
$I_{B,Na}$	Background $Na^+$ current	$k_{NaK,Na}$	Half-maximum $Na^+$ binding concentration for $I_{NaK}$
$I_{B,Ca}$	Background $Ca^{2+}$ current	$\bar{I}_{CaP}$	Half-maximum $Ca^{2+}$ binding concentration for $I_{CaP}$
$I_{NaK}$	$Na^+$ - $K^+$ pump current	$k_{NaCa}$	Scaling factor for $I_{NaCa}$
$I_{CaP}$	Sarcolemmal $Ca^{2+}$ pump current	$\gamma$	Position of energy barrier controlling voltage dependence of $I_{NaCa}$
$I_{NaCa}$	$Na^+$ - $Ca^{2+}$ exchange current	$d_{NaCa}$	Denominator constant for $I_{NaCa}$
$I_{di}$	$Ca^{2+}$ diffusion current from the diffusion-restricted subsarcolemmal space to the cytosol	$\bar{I}_{up}$	Maximum sarcoplasmic reticulum uptake current
$I_{up}$	Sarcoplasmic reticulum $Ca^{2+}$ uptake current	$k_{cyca}$	Half-maximum binding concentration for $[Ca^{2+}]_i$ to $I_{ub}$
$I_{tr}$	Sarcoplasmic reticulum $Ca^{2+}$ translocation current (from uptake to release compartment)	$k_{srca}$	Half-maximum binding concentration for $[Ca^{2+}]_{up}$ to $I_{up}$
$I_{rel}$	Sarcoplasmic reticulum $Ca^{2+}$ release current	$K_{xcs}$	Ratio of forward to back reactions for $I_{up}$
$[Na^+]_b$	$Na^+$ concentration in bulk (bathing) medium	$\tau_{tr}$	Time constant of diffusion of $Ca^{2+}$ from sarcoplasmic reticulum uptake to release compartment
$[K^+]_b$	$K^+$ concentration in bulk (bathing) medium	$\alpha_{rel}$	Scaling factor for $I_{rel}$
$[Ca^{2+}]_b$	$Ca^{2+}$ concentration in bulk (bathing) medium	$k_{rel,i}$	Half-activation $[Ca^{2+}]_i$ for $I_{rel}$
$[Na^+]_c$	$Na^+$ concentration in the extracellular cleft space	$k_{rel,d}$	Half-activation $[Ca^{2+}]_d$ for $I_{rel}$
$[K^+]_c$	$K^+$ concentration in the extracellular cleft space	$k_{recov}$	Recovery rate constant for the sarcoplasmic reticulum release channel
$[Ca^{2+}]_c$	$Ca^{2+}$ concentration in the extracellular cleft space	$I_{SAC}$	Stretch-activated current
$[Na^+]_i$	$Na^+$ concentration in the intracellular medium	$I_{SAC,Na}$	$Na^+$ contributes to $I_{sac}$
$[K^+]_i$	$K^+$ concentration in the intracellular medium	$I_{SAC,K}$	$K^+$ contributes to $I_{sac}$
$[Ca^{2+}]_i$	$Ca^{2+}$ concentration in the intracellular medium	$I_{SAC,Ca}$	$Ca^{2+}$ contributes to $I_{sac}$
$[Mg^{2+}]_i$	$Mg^{2+}$ concentration in the intracellular medium	$\bar{P}_{Na}$	Relative permeability to $Na^+$
$[Ca^{2+}]_d$	$Ca^{2+}$ concentration in the restricted subsarcolemmal space	$\bar{P}_K$	Relative permeability to $K^+$
$[Ca^{2+}]_{up}$	$Ca^{2+}$ concentration in the sarcoplasmic reticulum uptake compartment	$\bar{P}_{Ca}$	Relative permeability to $Ca^{2+}$
$[Ca^{2+}]_{rel}$	$Ca^{2+}$ concentration in the sarcoplasmic reticulum release compartment	$z_{Na}$	$Na^+$ valence
$E_{Na}$	Equilibrium (Nernst) potential for $Na^+$	$z_K$	$K^+$ valence
$E_K$	Equilibrium (Nernst) potential for $K^+$	$z_{Ca}$	$Ca^{2+}$ valence
$E_{Ca}$	Equilibrium (Nernst) potential for $Ca^{2+}$	$g_{SAC}$	Conductance for $I_{sac}$
$E_{Ca,app}$	Apparent reversal potential for $I_{CaL}$	$G_{SAC}$	Maximum conductance for $I_{sac}$
$P_{Na}$	Permeability for $I_{Na}$	$K_{SAC}$	Parameter to define the amount of current when the cell is not stretched
$\bar{g}_{CaL}$	Maximum conductance for $I_{CaL}$	$\alpha_{SAC}$	Parameter to describe the sensitivity to stretch
$\bar{g}_t$	Maximum conductance for $I_t$	$\lambda$	Stretch ratio
$\bar{g}_{Kur}$	Maximum conductance for $I_{Kur}$		<b>Myofibroblast</b>
$\bar{g}_{K,s}$	Maximum conductance for $I_{K,s}$	$I_{KV\_Mfb}$	Time- and voltage-dependent $K^+$ current
$\bar{g}_{K,r}$	Maximum conductance for $I_{K,r}$	$I_{K1\_Mfb}$	Inward-rectifying $K^+$ current

$\bar{g}_{K1}$	Maximum conductance for $I_{K1}$	$I_{NaK\_Mfb}$	Na <sup>+</sup> -K <sup>+</sup> pump current
$\bar{g}_{B,Na}$	Maximum conductance for $I_{B,Na}$	$I_{B,Na\_Mfb}$	Background Na <sup>+</sup> current
$\bar{g}_{B,Ca}$	Maximum conductance for $I_{B,Ca}$	$I_{Na\_Mfb}$	Na <sup>+</sup> current
$m$	Activation gating variable for $I_{Na}$	$I_{MGC\_Mfb}$	Mechano-gated current
$h_1, h_2$	Fast and slow inactivation gating variables for $I_{Na}$	$[Na^+]_{e,Mfb}$	Na <sup>+</sup> concentration in the extracellular cleft space
$d_L$	Activation gating variable for $I_{CaL}$	$[K^+]_{e,Mfb}$	K <sup>+</sup> concentration in the extracellular cleft space
$f_{L1}, f_{L2}$	Fast and slow inactivation gating variables for $I_{CaL}$	$[Na^+]_{i,Mfb}$	Na <sup>+</sup> concentration in the intracellular medium
$f_{Ca}$	[Ca <sup>2+</sup> ] <sub>i</sub> -dependent ratio of fast ( $f_{L1}$ ) to slow ( $f_{L2}$ ) inactivation of $I_{CaL}$	$[K^+]_{i,Mfb}$	K <sup>+</sup> concentration in the intracellular medium
$k_{Ca}$	Half-maximum Ca <sup>2+</sup> binding concentration for $f_{Ca}$	$E_{Na,Mfb}$	Equilibrium (Nernst) potential for Na <sup>+</sup>
$r$	Activation gating variable for $I_t$	$E_{K,Mfb}$	Equilibrium (Nernst) potential for K <sup>+</sup>
$s$	Inactivation gating variable for $I_t$	$E_{MGC,Mfb}$	Equilibrium (Nernst) potential for ion through mechano-gate channels
$s_1, s_2$	Rapidly and slowly recovering inactivation gating variables for $I_t$	$\bar{g}_{Kv,Mfb}$	Maximum conductance for $I_{Kv\_Mfb}$
$r_{Kur}$	Activation gating variable for $I_{Kur}$	$\bar{g}_{K1,Mfb}$	Maximum conductance for $I_{K1\_Mfb}$
$s_{Kur}$	Inactivation gating variable for $I_{Kur}$	$\bar{g}_{B,Na,Mfb}$	Maximum conductance for $I_{b,Na\_Mfb}$
$n$	Activation gating variable for $I_{K,s}$	$\bar{g}_{Na,Mfb}$	Maximum conductance for $I_{Na\_Mfb}$
$p_a$	Activation gating variable for $I_{K,r}$	$\bar{g}_{MGC,Mfb}$	Maximum conductance for $I_{MGC\_Mfb}$
$p_i$	Inactivation gating variable (instantaneous) for $I_{K,r}$	$r_{Kv}$	Activation gating variable for $I_{Kv\_Mfb}$
$\bar{m}, \bar{h}_1, \dots$	Steady-state value of $m, h_1$ , etc	$S_{Kv}$	Inactivation gating variable for $I_{Kv\_Mfb}$
$F_1$	Relative amount of "inactive precursor" in the $I_{rel}$ formulation	$\tau_{r_{Kv}}$	Activation time constant for $I_{Kv\_Mfb}$
$F_2$	Relative amount of "activator" in the $I_{rel}$ formulation	$\tau_{s_{Kv}}$	Inactivation time constant for $I_{Kv\_Mfb}$
$\tau_m$	Activation time constant for $I_{Na}$	$\alpha_{K1}, \beta_{K1}$	Fractional open probability of the $I_{K1\_Mfb}$ channel
$\tau_{h_1}, \tau_{h_2}$	Fast and slow inactivation time constants for $I_{Na}$	$\bar{I}_{NaK,max}$	Maximum Na <sup>+</sup> -K <sup>+</sup> pump current
$\tau_{d_L}$	Activation time constant for $I_{CaL}$	$k_{mK}$	Half-maximum K <sup>+</sup> binding concentration for $I_{NaK}$
$\tau_{f_{L1}}, \tau_{f_{L2}}$	Fast and slow inactivation time constants for $I_{CaL}$	$k_{mNa}$	Half-maximum Na <sup>+</sup> binding concentration for $I_{NaK}$
$\tau_r$	Activation time constant for $I_t$	$m_{Mfb}$	Activation gating variable for $I_{Na\_Mfb}$
$\tau_s$	Inactivation time constant for $I_t$	$j_{Mfb}$	Inactivation gating variable for $I_{Na\_Mfb}$
$\tau_{r_{Kur}}$	Activation time constant for $I_{Kur}$	$\tau_{m_{Mfb}}$	Activation time constant for $I_{Na\_Mfb}$
$\tau_{s_{Kur}}$	Inactivation time constant for $I_{Kur}$	$\tau_{j_{Mfb}}$	Inactivation time constant for $I_{Na\_Mfb}$
$\tau_n$	Activation time constant for $I_{K,s}$	$\alpha_{m_{Mfb}}, \alpha_{j_{Mfb}}$	Extrapolated rate coefficients
$\tau_{p_a}$	Activation time constant for $I_{K,r}$	$\beta_{m_{Mfb}}, \beta_{j_{Mfb}}$	
$O$	Buffer occupancy	$E_{Na,Mfb}$	Equilibrium (Nernst) potential for Na <sup>+</sup>
$O_C$	Fractional occupancy of the calmodulin buffer by Ca <sup>2+</sup>	$E_{K,Mfb}$	Equilibrium (Nernst) potential for K <sup>+</sup>
$O_{TC}$	Fractional occupancy of the troponin-Ca <sup>2+</sup> buffer by Ca <sup>2+</sup>	$E_{MGC,Mfb}$	Equilibrium (Nernst) potential for ion through mechano-gate channels
$O_{TMgC}$	Fractional occupancy of the troponin-Mg <sup>2+</sup> buffer by Ca <sup>2+</sup>	$\bar{r}_{Kv}, \bar{s}_{Kv}, \dots$	Steady-state value of $r_{Kv}, s_{Kv}$ , etc
$O_{TMgMg}$	Fractional occupancy of the troponin-Mg <sup>2+</sup> buffer by Mg <sup>2+</sup>	$C_{m,Mfb}$	Membrane capacitance
$O_{Calse}$	Fractional occupancy of the calsequestrin buffer (in the sarcoplasmic reticulum release compartment) by Ca <sup>2+</sup>	$V_{Mfb}$	Membrane voltage
$R$	Universal gas constant	<b>Mfb-M coupling</b>	
$T$	Absolute temperature	$G_{gap}$	Gap junctional conductance between Mfb and myocyte
$F$	Faraday's constant	$n$	Number of Mfbs per myocyte
$C_{m,M}$	Membrane capacitance	$I_M$	Net membrane current of the myocyte
		$I_{Mfb}$	Net membrane current of the Mfb

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