6.

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Apêndice 1

Formulação das correntes iônicas do modelo desenvolvido neste trabalho:

Corrente de Sódio Rápida:

Como no modelo de Shannon [46]

$$E_{Na} = \frac{RT}{F}\ln\left(\frac{[Na^+]_o}{[Na^+]_i}\right) \; ; \; G_{Na} = 10 \; ;$$

$$\alpha_m = \frac{0.32(V+47.13)}{1-e^{-0.1(V+47.13)}} \; ; \; \beta_m = 0.08e^{\frac{-V}{11}} \; ;$$

$$\alpha_h = \begin{cases} 0.135e^{\frac{(80+V)}{-6.8}} & para \quad V < -40 \\ 0 & para \quad V \geq -40 \end{cases} ;$$

$$\beta_h = \begin{cases} 3.56e^{0.079V} + 310000e^{0.35V} & para \quad V < -40 \\ \dfrac{1}{0.13\left(1+e^{\frac{(V+10.66)}{-11.1}}\right)} & para \quad V \geq -40 \end{cases} ;$$

$$\alpha_j = \begin{cases} (-127140e^{0.2444V} - 0.00003474e^{-0.0439V})\dfrac{V+37.78}{(1+e^{0.311(V+79.23)})} & para \quad V < -40 \\ 0 & para \quad V \geq -40 \end{cases}$$

;

$$\beta_j = \begin{cases} \dfrac{0.1212e^{-0.01052V}}{(1+e^{-0.1378(V+40.14)})} & para \quad V < -40 \\ 0 & para \quad V \geq -40 \end{cases} ;$$

$$I_{Na} = G_{Na} m^3 hj(V - E_{Na})$$

Corrente de potássio ativada rapidamente:

Como no modelo de Luo-Rudy [23] com modificações por Puglisi [41]

$$E_K = \frac{RT}{F}\ln\left(\frac{[K^+]_o}{[K^+]_i}\right);\ G_{Kr} = 0.035\sqrt{\frac{[K^+]_o}{5.4}};\ X_{r\infty} = \frac{1}{1+e^{\left(-\frac{V+50}{7.5}\right)}}$$

$$\tau_{xr} = \frac{1}{\frac{0.00138(V+7)}{1-e^{-0.123(V+7)}} + \frac{0.00061(V+10)}{e^{0.145(V+10)}-1}};\ R_K = \frac{1}{1+e^{\left(\frac{V+33}{22.4}\right)}}$$

$$I_{Kr} = G_{Kr} X_r R(V - E_K)$$

Corrente de potássio ativada lentamente:

Como no modelo de Luo-Rudy [23]

$$E_{Ks} = \frac{RT}{F}\ln\left(\frac{[K^+]_o + P_{Na,K}[Na^+]_o}{[K^+]_i + P_{Na,K}[Na^+]_i}\right);$$

$$P_{Na,K} = 0.01833;$$

$$G_{Ks} = 0.15\left(1 + \frac{0.8}{1+(\frac{0.2}{[Ca^{2+}]_i})^3}\right);$$

$$X_{1s\infty} = \frac{1}{1+e^{-\frac{(1.5-V)}{16.7}}};\ X_{2s\infty} = X_{1s\infty};$$

$$\tau_{x1s} = \frac{1}{\frac{0.0000719(V+30)}{1-e^{-0.148(V+30)}} + \frac{0.00031(V+30)}{-1+e^{0.0687(V+30)}}};$$

$\tau_{x2s} = 4\tau_{x1s}$;

$I_{Ks} = G_{Ks} X_{1s} X_{2s} (V - E_{Ks})$

Corrente de potássio independente do tempo:

Como no modelo de Luo-Rudy [23]

$E_{K1} = \frac{RT}{F} \ln\left(\frac{[K^+]_o}{[K^+]_i}\right)$; $G_{K1} = 0.540\sqrt{\frac{[K^+]_o}{5.4}}$;

$\alpha_{K1} = \frac{1.02}{1 + e^{0.2385(V - E_{K1} - 59.215)}}$;

$\beta_{K1} = \frac{0.06175 e^{(V - E_{K1} - 594.31)} + 0.0394564 e^{(V - E_{K1} + 5.476)}}{1 - 0.5143 e^{(V - E_{K1} + 4.753)}}$;

$K_1 = \frac{\alpha_{K1}}{\alpha_{K1} + \beta_{K1}}$;

$I_{K1} = G_{K1} K_1 (V - E_{K1})$

Corrente de potássio de Plateau:

Como no modelo de Luo-Rudy [23]

$K_p = \frac{1}{0.167224 e^{7.488 - V} + 1}$; $G_{Kp} = 0.008$;

$I_{Kp} = G_{Kp} K_p (V - E_K)$

Corrente transiente de saída:

Como no modelo de Shannon [46]

$G_{To,f} = 0.11$; $G_{To,s} = 0.04$; $R_{To} = \frac{1}{1 + e^{\left(\frac{V + 33.5}{10}\right)}}$;

$$X_{f\infty} = R_{To}\ ;\ X_{s\infty} = R_{To}\ ;\ Y_{f\infty} = \frac{1}{1+e^{\left(\frac{V+33.5}{10}\right)}};$$

$$\tau_{Xf} = 3.5e^{\left(\frac{V}{30}\right)^2} + 1.5\ ;\ \tau_{Yf} = \frac{20}{1+e^{\left(\frac{V+33.5}{10}\right)}} + 20;$$

$$\tau_{Xfs} = \frac{9}{1+e^{\left(\frac{V+3}{15}\right)}} + 0.5\ ;\ \tau_{Ys} = \frac{3000}{1+e^{\left(\frac{V+60}{10}\right)}} + 30;$$

Componente rápida da corrente transiente de sáida:

$$I_{To,f} = G_{To,f} X_f Y_f (V - E_K)$$

Componente lenta da corrente transiente de sáida:

$$I_{To,s} = G_{To,s} X_s \left(Y_s + 0.5 R_{To}\right)(V - E_K)$$

$$I_{To} = I_{To,f} + I_{To,s}$$

Corrente de cálcio que atravessa canais do tipo-L:

Como no modelo de Luo-Rudy [23]

$$d_\infty = \frac{1}{1+e^{-\frac{V-10}{6.24}}};\ f_{Ca} = \frac{1}{1+\frac{[Ca]_i}{K_{m,Ca}}}\ ;\ K_{m,Ca} = 0.006 mmol/L;$$

$$\tau_d = d_\infty \left(\frac{1 - e^{-\frac{V+14.5}{6}}}{0.035(V+14.5)} \right);\ f_\infty = \frac{1}{1+e^{\frac{V+35}{8.6}}} + \frac{0.6}{1+e^{\frac{50-V}{20}}};$$

$$\tau_f = \frac{1}{0.0197 e^{-(0.0337(V+14.5))^2} + 0.02}\ ;$$

$$\bar{I}_S = P_s Z_s^2 \left(\frac{VF^2}{RT}\right) \left(\frac{\left(\gamma_{[S]_i} [S]_i e^{\frac{Z_s VF}{RT}} - \gamma_{[S]_o} [S]_o \right)}{e^{\frac{Z_s VF}{RT}} - 1} \right),$$

Onde S inclui $[Ca^{2+}], [Na^+], [K^+]$ e

$$\gamma_{[Ca]_i} = 1 \qquad , \gamma_{[Ca]_o} = 0.341, \qquad \gamma_{[Na]_i} = \gamma_{[Na]_o} = \gamma_{[K]_i} = \gamma_{[K]_o} = 0.75;$$

$$P_{Ca} = 5.4 \cdot 10^{-4} \frac{\mu A}{\mu F}, \qquad P_{Na} = 6.75 \cdot 10^{-7} \frac{\mu A}{\mu F}, \qquad P_K = 1.93 \cdot 10^{-7} \frac{\mu A}{\mu F};$$

$$I_{L,Ca} = d \cdot f \cdot f_{Ca} \cdot \bar{I}_{Ca} \ ;$$

$$I_{L,CaNa} = d \cdot f \cdot f_{Ca} \cdot \bar{I}_{Na};$$

$$I_{L,CaK} = d \cdot f \cdot f_{Ca} \cdot \bar{I}_K;$$

$$I_{Ca,L} = I_{L,Ca} + I_{L,CaNa} + I_{L,CaK}$$

Corrente de cálcio que atravessa canais do tipo-T:

Como no modelo de Luo-Rudy [23]

$$G_{Ca,T} = 0.05, \ E_{Ca} = \frac{RT}{2F} \ln\left(\frac{[Ca^{2+}]_o}{[Ca^{2+}]_i}\right) ;$$

$$b_\infty = \frac{1}{1 + e^{-\frac{V+14}{10.8}}} \ ;$$

$$\tau_b = 3.7 + \frac{6.1}{1 + e^{\frac{V+25}{4.5}}} \ ;$$

$$g_\infty = \frac{1}{1 + e^{\frac{V+60}{5.6}}} \ ;$$

$$\tau_g = \begin{cases} -0.875(V+12) & para \quad V \le 0 \\ 12 & para \quad V > 0 \end{cases};$$

$$I_{Ca,T} = G_{Ca,T} b^2 g (V - E_{Ca})$$

Corrente da bomba sódio-potássio:

Como no modelo de Luo-Rudy [23]

$$\sigma = \frac{e^{-1+\frac{[Na^+]_o}{67.3}} - 1}{7} \; ; \; \bar{I}_{Na,K} = 1.5\frac{\mu A}{\mu F} \; ;$$

$$f_{Na,K} = \frac{1}{1+0.1245e^{-\frac{0.1VF}{RT}}} + 0.0365\sigma e^{-\frac{VF}{RT}} \; ;$$

$$K_{m,[Na]_i} = 1.2mmol/L; \qquad K_{m,[K]_o} = 1.5mmol/L;$$

$$I_{Na,K} = \bar{I}_{Na,K} \cdot f_{Na,K} \frac{1}{1+\frac{K_{m,[Na]_i}}{[Na^+]_i}} \cdot \frac{[K^+]_o}{[K^+]_o + K_{m,[K]_o}}$$

Corrente da bomba de cálcio do retículo sarcoplasmático:

Como no modelo de Luo-Rudy [23]

$$\bar{I}_{p,Ca} = 1.15\frac{\mu A}{\mu F} \; ; K_{m,pCa} = 0.005mmol/L \; ;$$

$$I_{p,Ca} = \frac{\bar{I}_{p,Ca}[Ca^{2+}]_i}{K_{m,pCa} + [Ca^{2+}]_i}$$

Corrente de fundo de cálcio:

Como no modelo de Luo-Rudy [23]

$$G_{Ca,b} = 0.003016 \; , \; E_{Ca,b} = \frac{RT}{2F}\ln\frac{[Ca^{2+}]_o}{[Ca^{2+}]_i} \; ;$$

$$I_{Ca,b} = G_{Ca,b}(V - E_{Ca,b})$$

Corrente de fundo de sódio:

Como no modelo de Luo-Rudy [23]

$$G_{Na,b} = 0.004 \; ;$$

$$I_{Na,b} = G_{Na,b}(V - E_{Na})$$

Fluxo pelo trocador sódio-cálcio:

Como no modelo de Luo-Rudy [23]

$$I_{NaCaX} = 0.00025e^{\frac{(0.15-1)VF}{RT}}\left(\frac{e^{\frac{VF}{RT}}([Na^+]_i)^3[Ca^{2+}]_o - ([Na^+]_o)^3[Ca^{2+}]_i}{1+0.0001e^{\frac{(0.15-1)VF}{RT}}\left(e^{\frac{VF}{RT}}([Na^+]_i)^3[Ca^{2+}]_o + ([Na^+]_o)^3[Ca^{2+}]_i\right)}\right)$$

Dinâmica do cálcio:

Como no modelo de Luo-Rudy [23]

$$G_{rel} = \frac{150}{1+e^{\left(\frac{I_{Ca,L}+I_{Ca,b}+I_{p,Ca}+I_{Ca,T}-2\cdot I_{NaCaX}+5}{0.9}\right)}};$$

$$RyR_{open} = \frac{1}{1+e^{\frac{4-t_r}{0.5}}};$$

$$RyR_{close} = 1-\frac{1}{1+e^{\frac{4-t_r}{0.5}}};$$

$$I_{rel} = G_{rel}\cdot RyR_{open}\cdot RyR_{close}\left([Ca^{2+}]_{JSR}-[Ca^{2+}]_i\right);$$

$$I_{up} = \bar{I}_{up}\frac{[Ca^{2+}]_i}{[Ca^{2+}]_i + K_{m,up}}\ ,\ \bar{I}_{up} = 0.00875,\ K_{m,up} = 0.00092\ ;$$

$$K_{leak} = \frac{\bar{I}_{up}}{[Ca^{2+}]_{NSR}}\ ;\ [Ca^{2+}]_{NSR_{initial}} = [Ca^{2+}]_{JSR_{initial}} = 1.179 mmol/L\ ;$$

$$I_{leak} = K_{leak}[Ca^{2+}]_{NSR};\ I_{tr} = \frac{[Ca^{2+}]_{NSR}-[Ca^{2+}]_{JSR}}{\tau_{tr}},$$

$$\tau_{tr} = 180, \qquad t_{r_{initial}} = 1000ms$$

Corrente total:

$$I_T = I_{Na} + I_{Na,b} + I_{Ca,L} + I_{NaCaX} + I_{pCa} + I_{Ca,T} + I_{Ca,b} + I_{Kr} + I_{Ks} + I_{K1} + I_{Kp} + I_{Na,K} + I_{To,f} + I_{To,s}$$