# 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:*

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

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

**Corrente de cálcio que atravessa canais do tipo-L:**

Como no modelo de Luo-Rudy [23]

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

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

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

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

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

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

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

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

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

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

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

**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]

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

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

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

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

**Corrente da bomba de cálcio do retículo sarcoplasmático:**

Como no modelo de Luo-Rudy [23]

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

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

**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]

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

**Dinâmica do cálcio:**

Como no modelo de Luo-Rudy [23]

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

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

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

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

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

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

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

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

**Corrente total:**

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