Modeling Gain and Gradedness of Ca^{2+} Release in the Functional Unit of the Cardiac Diadic Space

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$$J_{xfer} = \frac{1}{\tau_{xfer}}([Ca^{2+}]_{SS} - [Ca^{2+}]_{Myo}) \tag{1}$$

$$J_{tr} = \frac{1}{\tau_{tr}}([Ca^{2+}]_{NSR} - [Ca^{2+}]_{JSR}) \tag{2}$$

$$J_{DHPR} = -\frac{\overline{I}_{DHPR} DHPR_{open} A_{cap}}{2FV_{SS}} \tag{3}$$

$$\bar{I}_{DHPR} = \overline{P}_{Ca} 4 \frac{VF^2}{RT} \frac{0.001 e^{2VF/RT} - 0.341 [Ca^{2+}]_o}{e^{2VF/RT} - 1} \tag{4}$$

$$J_{RyR} = \sum_{i=1}^{8} \overline{J}_{RyR} RyR^{i}_{open} ([Ca]_{JSR} - [Ca]_{SS}) \tag{5}$$

$$\frac{d[Ca^{2+}]_{SS}}{dt} = \beta_{SS} (J_{DHPR} + J_{RyR} - \frac{V_{myo}}{V_{SS}} J_{xfer}) \tag{6}$$

$$\frac{d[Ca^{2+}]_{JSR}}{dt} = \beta_{JSR} (J_{tr} - \frac{V_{SS}}{V_{JSR}} J_{RyR}) \tag{7}$$

$$\beta_{SS} = \left(1 + \frac{[B]_{SR} K_{BSR}}{(K_{BSR} + [Ca^{2+}]_{SS})^2} + \frac{[B]_{SL} K_{BSL}}{(K_{BSL} + [Ca^{2+}]_{SS})^2} \right)^{-1} \tag{8}$$

$$\beta_{JSR} = \left(1 + \frac{[CSQN]_{total} K_{CSQN}}{(K_{CSQN} + [Ca^{2+}]_{JSR})^2} \right)^{-1} \tag{9}$$

Table 1 – DHPR transition probabilities

$$\gamma = 0.1875\ [Ca_{SS}]\ s^{-1}$$

$$\alpha = 400.0\, e^{(V+6)/25}\ s^{-1}$$

$$\beta = 50.0\, e^{-(V+6)/29}\ s^{-1}$$

$$\alpha' = \alpha\, a\ s^{-1}$$

$$\beta' = \frac{\beta}{b}\ s^{-1}$$

$$y_{\infty} = \frac{1}{1 + e^{(v+55)/7.5}} + \frac{0.1}{1 + e^{-(v-21)/6}}$$

$$\tau_{y} = 0.02 + \frac{0.04}{1 + e^{(V+30)/9.5}}$$

$$\omega = 10.0\ s^{-1}$$

$$a = 2.0$$

$$b = 2.0$$

$$f = 300.0\ s^{-1}$$

$$g = 2000.0\ s^{-1}$$

$$f' = 5.0\ s^{-1}$$

$$g' = 7000.0\ s^{-1}$$

Table 2 – RyR transition probabilities

$$k_{1,2} = \frac{3.0\times 10^{6}[Ca_{SS}]^{4}}{(7.66)^{4}+[Ca_{SS}]^{4}}\ s^{-1}$$

$$k_{2,1} = 2.5\times 10^{5}\ s^{-1}$$

$$k_{2,3} = \frac{3.0\times 10^{7}[Ca_{SS}]^{4}}{(7.66)^{4}+[Ca_{SS}]^{4}}\ s^{-1}$$

$$k_{3,2} = 9.6\times 10^{3}\ s^{-1}$$

$$k_{3,4} = \frac{3.0\times 10^{6}[Ca_{SS}]^{4}}{(7.66)^{4}+[Ca_{SS}]^{4}}\ s^{-1}$$

$$k_{4,3} = 1.3\times 10^{4}\ s^{-1}$$

$$k_{5,4} = \frac{198.0[Ca_{SS}]^{4}}{(7.66)^{4}+[Ca_{SS}]^{4}}\ s^{-1}$$

$$k_{4,5} = 66.67\ s^{-1}$$

$$k_{2,5} = \frac{3.0\times 10^{5}[Ca_{SS}]^{4}}{(7.66)^{4}+[Ca_{SS}]^{4}}\ s^{-1}$$

$$k_{5,2} = 1.235\ s^{-1}$$

$$k_{5,6} = \frac{3.0\times 10^{6}[Ca_{SS}]^{4}}{(7.66)^{4}+[Ca_{SS}]^{4}}\ s^{-1}$$

$$k_{6,5} = 3.0\times 10^{6}\ s^{-1}$$

Table 3 - Parameters

$V_{SS} = 2.03 \times 10^{-12}\ \mu L$

$V_{JSR} = 1.05 \times 10^{-10}\ \mu L$

$V_{myo} = 4.7 \times 10^{-9}\ \mu L$

$[Ca^{2+}]_{Myo} = 0.1\ \mu M$

$[Ca^{2+}]_{NSR} = 800\ \mu M$

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

$\tau_{tr} = 5.0\ ms$

$\tau_{xfer} = 0.0007\ ms$

$[B_{SR}] = 47.0\ \mu M$

$K_{BSR} = 0.87\ \mu M$

$[B_{SL}] = 1124.0\ \mu M$

$K_{BSL} = 8.7\ \mu M$

$[CSQN_{total}] = 15.0\ mM$

$K_{CSQN} = 0.8\ mM$

$F = 96500\ coul\,(mol\,e^{-})^{-1}$

$T = 310\ K$

$R = 8.314\ J\ mol^{-1}\ K^{-1}$

$\bar{J}_{RyR} = 3960.0\ s^{-1}$

$\bar{P}_{Ca} = 33.75 \times 10^{-4}\ cm\,s^{-1}$

$A_{cap} = 4.47 \times 10^{-9}\ cm^{2}$