Supporting Information

Dynamical effects of calcium-sensitive potassium currents on voltage and calcium alternans

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Mathematical model

We used a physiologically detailed mathematical model of the ventricular myocyte by Shiferaw et al (Shiferaw *et al.*, 2005) .

The fast sodium current (I_{Na}).

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

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

$$\frac{dm}{dt} = \alpha_m (1-m) - \beta_h m$$

$$\frac{dh}{dt} = \alpha_h (1-h) - \beta_h h$$

$$\frac{dj}{dt} = \alpha_j (1-j) - \beta_j j$$

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

$$\beta_m = 0.08 e^{-V/11}$$

$$\alpha_h = 0.135e^{(V+80)/-6.8}$$
$$\beta_h = \frac{7.5}{1+e^{-0.1(V+11)}}$$
$$\alpha_j = \frac{0.175e^{(V+100)/-23}}{1+e^{0.15(V+79)}}$$
$$\beta_j = \frac{0.3}{1+e^{-0.1(V+32)}}$$

The slow time constant of recovery of the sodium channel is given by $\tau_j = 1/(\alpha_j + \beta_j)$. For the tissue simulations we increase τ_j by a factor of 3 i.e. $\alpha_j \to \alpha_j / 3$ and $\beta_j \to \beta_j / 3$ in order to increase the steepness of the conduction velocity restitution.

The transient outward K^+ current (I_{to}):

$$I_{to} = g_{to} X_{to} Y_{to} (V - E_K)$$
$$E_K = \frac{RT}{F} \ln\left(\frac{[K^+]_o}{[K^+]_i}\right)$$
$$\frac{dX_{to}}{dt} = \alpha_{Xto}(1 - X_{to}) - \beta_{Xto} X_{to}$$
$$\frac{dY_{to}}{dt} = \alpha_{Yto}(1 - Y_{to}) - \beta_{Yto} Y_{to}$$
$$\alpha_{Xto} = 0.04516e^{0.0357V}$$
$$\beta_{Xto} = 0.0989e^{-0.063237}$$
$$\alpha_{Yto} = \frac{0.005415e^{(V+33.5)/-5}}{1+0.051335e^{(V+33.5)/-5}}$$
$$\beta_{Yto} = \frac{0.005415e^{(V+33.5)/5}}{1+0.051335e^{(V+33.5)/5}}$$

Inward rectifier K^+ current (I_{K1}):

$$I_{K1} = g_{K1} K_1^{\infty} \frac{[K^+]_o}{[K^+]_o + 13}(V - E_K)$$
$$K_1^{\infty} = \frac{1}{2+e^{1.62F/(RT)(V-E_K)}}$$

The Rapid component of the delayed rectifier K^+ current (I_{Kr}):

$$I_{Kr} = g_{Kr}\sqrt{\frac{[K^+]_o}{4}}x_{Kr}R(V)(V - E_K)$$

$$R(V) = \frac{1}{1+2.5e^{0.1(V+28)}}$$

$$\frac{dx_{Kr}}{dt} = \frac{x_{Kr}^{\infty} - x_{Kr}}{\tau_{Kr}}$$

$$x_{Kr}^{\infty} = \frac{1}{1+e^{-2.182-0.1819V}}$$

$$\tau_{Kr} = 43 + \frac{1}{e^{-5.495+0.1601V} + e^{-7.677-0.0128V}}$$

The slow component of the delayed rectifier K^+ current (I_{Ks}):

For I_{SK2} simulations, we used Shiferaw et al (Shiferaw *et al.*, 2005) I_{Ks}, which does not have a Ca-sensitive component. This ensures that negative $Ca_i \rightarrow V_m$ coupling is due to I_{SK2}

$$I_{Ks} = g_{Ks}x_{Ks}^2(V - E_{Ks})$$

$$\frac{dx_{Ks}}{dt} = \frac{x_{Ks}^{\infty} - x_{Ks}}{\tau_{Ks}}$$

$$x_{Ks}^{\infty} = \frac{1}{1+e^{-(V-16)/13.6}}$$

$$\tau_{Ks} = \frac{1}{\left(\frac{0.0000719(V-10)}{1-e^{-0.148(V-10)}} + \frac{0.00031(V-10)}{-1+e^{0.0687(V-10)}}\right)}$$

$$E_{Ks} = \frac{RT}{F}\ln\left(\frac{[K^+]_o + 0.01833[Na^+]_o}{[K^+]_i + 0.01833[Na^+]_i}\right)$$

For I_{Ks} simulations, we used Mahajan et al (Mahajan *et al.*, 2008) I_{Ks}

$$I_{Ks} = g_{Ks} x_{s1} x_{s2} q_{Ks} \left(V - E_{Ks}\right)$$

$$q_{Ks} = 1 + \frac{0.8}{\left(1 + \left(\frac{Km}{c_s}\right)^3\right)}$$

$$\frac{dx_{s1}}{dt} = \frac{x_s^{\infty} - x_{s1}}{\tau_{xs1}}$$

$$\frac{dx_{s2}}{dt} = \frac{x_s^{\infty} - x_{s2}}{\tau_{xs2}}$$

$$x_s^{\infty} = \frac{1}{1 + e^{-(V-1.5)/16.7}}$$

$$\tau_{xs1} = \frac{1}{\left(\frac{0.0000719(V+30)}{1 - e^{-0.148(V+30)}} + \frac{0.00031(V+30)}{-1 + e^{0.0687(V+30)}}\right)}$$

$$\tau_{xs2} = 4.\tau_{xs1}$$

$$E_{Ks} = \frac{RT}{F} \ln\left(\frac{[K^+]_o + 0.01833[Na^+]_o}{[K^+]_i + 0.01833[Na^+]_i}\right).$$

The plateau potassium current (I_{Kp}):

$$I_{Kp} = g_{Kp} K_{Kp}(V)\left(V - E_K\right)$$

$$K_{Kp}(V) = \frac{1}{1 + e^{(7.488-V)/5.98}}$$

The sodium-calcium exchanger (J_{NaCa}):

$$J_{NaCa} = g_{naca} \frac{1}{K_{m,Na}^3 + [Na^+]_o^3} \frac{1}{K_{m,Ca} + [Ca^{2+}]_o} \frac{e^{\xi a}[Na^+]_i^3[Ca^{2+}]_o - e^{(\xi-1)a}[Na^+]_o^3 c_s}{1 + k_{sat} e^{(\xi-1)a}}.$$

The L-type Ca_i current flux (J_{Ca}):

$$J_{Ca} = -g_{Ca} d \cdot f \cdot f_{Ca} \cdot i_{Ca}$$
$$\frac{df}{dt} = \frac{f_\infty - f}{\tau_f}$$
$$\frac{d(d)}{dt} = \frac{d_\infty - d}{\tau_d}$$
$$\frac{df_{Ca}}{dt} = \frac{f_{Ca}^\infty - f_{Ca}}{\tau_{fca}}$$
$$f_\infty = \frac{1}{1+e^{((V+35)/8.6)}}$$
$$d_\infty = \frac{1}{1+e^{(-(V+5)/6.24)}}$$
$$f_{Ca}^\infty = \frac{1}{1+\left(c_s/\tilde{c}_s\right)^\gamma}$$
$$i_{Ca} = \frac{4VF^2}{RT}\left(\frac{c_s e^{2a} - 0.341[Ca^{2+}]_o}{e^{2a}-1}\right)$$

with $a = VF/RT$.

The SR Ca_i release vs. SR Ca_i load relationship:

$$Q(c_j') = \begin{cases} 0 & 0 < c_j' < 50, \\ 1.5\left(c_j' - 50\right) & 50 < c_j' < 110, \\ uc_j' + s & c_j' > 110, \end{cases}$$

where the flux $Q(c_j')$ is in units of 10^{-6} μM/ms, and where $s = 90 - 110u$.

SERCA pump:

In order for the formation of spatially discordant alternans, fluctuations in Ca cycling is crucial. We used fluctuations due to the finite number of SERCA channels in the cell following Sato et al.(Sato *et al.*, 2006) In this model, each SERCA pump is modeled as a two state system with closed (C) and open (O) states that obey

$$C \underset{k_-}{\overset{k_+}{\leftrightharpoons}} O \quad , \tag{1}$$

where the open rate is $k_+ c_i^2$ and the closed rate is a constant k_-. Here, the open rate is taken to be a function of the diastolic Ca concentration c_i. Given this reaction scheme then the total uptake current is

$$J_{up}(t) = N_{up} \cdot p \cdot i_{up}, \tag{2}$$

where i_{up} is the single channel flux in the open state, p is the fraction of SERCA channels open, and where N_{up} is the total number of SERCA channels within a sarcomere. Following Fox et al.(Fox & Lu, 1994) the fraction of open SERCA channels is approximated by the Langevin equation

$$\frac{dp}{dt} = k_+ c_i^2 (1-p) - k_- p + \eta(t) \ , \tag{3}$$

where $\eta(t)$ is a noise term that satisfies

$$\langle \eta(t)\eta(t') \rangle = \frac{k_+ c_i^2 (1-p) + k_- p}{N_{up}} \ \delta(t-t') \ . \tag{4}$$

This approach accounts for the stochastic fluctuations of Ca cycling due to the finite number of SERCA pumps in the cell. Spatially discordant alternans can be formed by Turing instability (Sato *et al.*, 2006) or competition between diffusion and fluctuations (Sato *et al.*, 2014). For these mechanisms, stochasticity in the model is essential. We used the stochastic SERCA pump for tissue simulations. For the single cell simulations, we used the deterministic SERCA pump model (i.e. $N_{up} \to \infty$)(Sato *et al.*, 2006) or competition between diffusion and fluctuations . For these mechanisms, stochasticity in the model is essential. We used the stochastic SERCA pump for tissue simulations. For the single cell simulations, we used the deterministic SERCA pump model (i.e. $N_{up} \to \infty$)

Nonlinear buffering:

Instantaneous buffering of calcium to SR, calmodulin, and Troponin C sites in the submembrane and bulk myoplasm are accounted for by the functions

$$\beta_s = \left(1 + \frac{B_{SR} K_{SR}}{(c_s + K_{SR})^2} + \frac{B_{cd} K_{cd}}{(c_s + K_{cd})^2} + \frac{B_T K_T}{(c_s + K_T)^2} \right)^{-1} ,$$

$$\beta_i = \left(1 + \frac{B_{SR} K_{SR}}{(c_i + K_{SR})^2} + \frac{B_{cd} K_{cd}}{(c_i + K_{cd})^2} + \frac{B_T K_T}{(c_i + K_T)^2} \right)^{-1} .$$

TABLES

Table 1: cytosolic buffering parameters

Parameter	Definition	Value
B_T	Total concentration of Troponin C	70 μmol/l cytosol
B_{SR}	Total concentration of SR binding sites	47 μmol/l cytosol
B_{Cd}	Total concentration of Calmodulin binding sites	24 μmol/l cytosol
K_T	Dissociation constant for Troponin C	0.6 μM
K_{SR}	Dissociation constant for SR binding sites	0.6 μM
K_{Cd}	Dissociation constant for Calmodulin binding sites	7 μM

Table 2: SR release parameters

Parameter	Definition	Value
τ_r	Spark lifetime	20 ms
τ_a	NSR-JSR diffusion time constant	50 ms
g	Release current strength	7.5×10^4 sparks/μM
u	Release slope	1.5~18 ms^{-1}

Table 3: Exchanger and uptake parameters

Parameter	Definition	Value
c_{up}	Uptake threshold	0.5 μM
v_{up}	Strength of exchanger	0.25 μM/ms
g_{NaCa}	Luo-Rudy II constant	6 μM/ms
k_{sat}	Luo-Rudy II constant	0.1
ξ	Luo-Rudy II constant	0.35
$K_{m,Na}$	Luo-Rudy II constant	87.5 mM
$K_{m,Ca}$	Luo-Rudy II constant	1.38 mM

Table 4: Physical constants and ionic concentrations

Parameter	Definition	Value
C_m	Cell capacitance	1.66×10^{-4} μF
v_i	Cell volume	2.58×10^{-5} μl
v_s	Submembrane volume	$0.1v_i$
F	Faraday constant	96.5 C/mmol
R	Universal gas constant	8.315 $Jmol^{-1}K^{-1}$
T	Temperature	308 K
$[Na^+]_i$	Internal sodium concentration	10 mM
$[Na^+]_o$	External sodium concentration	140 mM
$[K^+]_i$	Internal potassium concentration	149.4 mM
$[K^+]_o$	External potassium concentration	4.0 mM
$[Ca^{2+}]_o$	External calcium concentration	1.8 mM

Table 5: Ion current conductance

Parameter	Definition	Value
g_{Na}	Peak I_{Na} conductance	12 mS/μF
g_{to}	Peak I_{to} conductance	0.1 mS/μF
g_{K1}	Peak I_{K1} conductance	2.8 mS/μF
g_{Kr}	Peak I_{Kr} conductance	0.0136 mS/μF
g_{Ks}	Peak I_{Ks} conductance	0.0245 mS/μF
g_{Kp}	Peak I_{Kp} conductance	0.00221 mS/μF

Table 6: L-type Ca channel parameters

Parameter	Definition	Value
g_{Ca}	Adjustable strength of J_{Ca}	1.46×10^{-3} μMl/C/ms
τ_f	Voltage dependent inactivation gate constant	30~200 ms
γ	Exponent for Ca-induced inactivation	0.7
$\widetilde{c}_s$	Calcium inactivation threshold	1.0 μM
τ_d	Voltage dependent activation gate time constant	5 ms
τ_{fca}	Calcium-induced inactivation gate time constant	20 ms

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