Biophysical Journal, Volume 96

Supporting Material

Biophysically-Based Mathematical Modelling of Interstitial Cells of Cajal Slow Wave Activity Generated From a Discrete Unitary Potential Basis

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SLOW WAVE MODEL
SUPPLEMENTARY MATERIALS

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MODEL STATE VARIABLES

Pacemaker Unit State Variables

C_{S1} – Subspace 1 [Ca^{2+}]
C_{S2} – Subspace 1 [Ca^{2+}]
C_{ER} – Endoplasmic Reticulum [Ca^{2+}]
C_{MT} – Mitochondrial [Ca^{2+}]
N_{S1} – Subspace 1 [Na^{+}]
H – IP_3R Control Variable
ζ – IP_3R Recovery Variable

Whole Cell Current Gating Variables

d_{T} – $I_{Ca(T)}$ Activation Rate
f_{T} – $I_{Ca(T)}$ Inactivation Rate
O_{T} – $I_{Ca(T)}$ Open Probability
$d_{v1.1}$ – $I_{K(v1.1)}$ Activation
$f_{v1.1}$ – $I_{K(v1.1)}$ Inactivation
d_{ERG} – $I_{K(ERG)}$ Activation

Global Variables

V_{m} – Membrane Potential
C_{Cy} – Bulk Cytoplasmic [Ca^{2+}]

MODEL CONDUCTANCES

Pacemaker Unit Conductances

Plasma Membrane Conductances

I_{Ca} – Inward Ca^{2+} Current
I_{Na} – Inward Na^{+} Current
I_{NSCC} – Non-Selective Cation Conductance
I_{PM} – Plasma Membrane Ca^{2+}-ATPase
I_{NaP} – Outward Na^{+} Pump

Intracellular Ca^{2+} Fluxes

J_{SERCA} – Sarco-Endoplasmic Reticulum Ca^{2+}-ATPase
J_{IPR} – IP_3 Receptor Ca^{2+} Flux
J_{MCU} – Mitochondrial Ca^{2+} Uniporter
J_{NCX} – Mitochondrial $\text{Na}^{+}/\text{Ca}^{2+}$ Exchanger
J_{S1S2} – Subspace 1/Subspace 2 Ca^{2+} Diffusion
J_{S2Cy} – Subspace 2/Bulk Cytoplasmic Ca^{2+} Diffusion

Bulk Cytoplasmic Subspace Conductances

Plasma Membrane Conductances

$I_{\text{Ca(T)}}$ – T-Type Ca^{2+} Current
$I_{\text{Ca(Ext)}}$ – Ca^{2+} Extrusion Pump
$I_{\text{K(v1.1)}}$ – K(v1.1) K^{+} Current
$I_{\text{K(ERG)}}$ – Ether-a-go-go K^{+} Current
I_{KB} – Background K^{+} Current
I_{L} – Non-Selective Inward Current

Intracellular Ca^{2+} Fluxes

J_{Cy} – Bulk Cytoplasmic Intracellular Ca^{2+} Flux

PACEMAKER UNIT MODEL EQUATIONS

Plasma Membrane Conductances

Ca^{2+} Currents

$$I_{\mathrm{Ca}} = g_{\mathrm{Ca}}\left(V_{\mathrm{m}} - E_{\mathrm{Ca}}\right) \tag{S1}$$

$$g_{\mathrm{Ca}} = \hat{g}_{\mathrm{Ca}} e^{k_{\mathrm{Ca}} V_{\mathrm{m}}} \tag{S2}$$

$$I_{\mathrm{PM}} = g_{\mathrm{PM}}\left(\frac{C_{\mathrm{S1}}{}^{2}}{K_{\mathrm{PM}}{}^{2} + C_{\mathrm{S1}}{}^{2}}\right) \tag{S3}$$

Na^{+} Currents

$$I_{\mathrm{Na}} = g_{\mathrm{Na}}\left(V_{\mathrm{m}} - E_{\mathrm{Na}}\right) \tag{S4}$$

$$I_{\mathrm{NaP}} = g_{\mathrm{NaP}}\left(\frac{N_{\mathrm{S1}}{}^{h_{\mathrm{NaP}}}}{K_{\mathrm{NaP}}{}^{h_{\mathrm{NaP}}} + N_{\mathrm{S1}}{}^{h_{\mathrm{NaP}}}}\right)\left(E_{\mathrm{NaP}} - V_{\mathrm{m}}\right) \tag{S5}$$

Non-Selective Cation Current

$$I_{\mathrm{NSCC(Z)}} = g_{\mathrm{NSCC(Z)}}\left(V_{\mathrm{m}} - E_{\mathrm{NSCC}}\right) \tag{S6}$$

$$g_{\mathrm{NSCC(Z)}} = \hat{g}_{\mathrm{NSCC(Z)}}\left(\frac{K_{\mathrm{NSCC}}{}^{h_{\mathrm{NSCC}}}}{K_{\mathrm{NSCC}}{}^{h_{\mathrm{NSCC}}} + C_{S1}{}^{h_{\mathrm{NSCC}}}}\right) \tag{S7}$$

where Z = Ca or Na

Nernst Potentials

$$E_{\mathrm{Ca}} = \frac{RT}{Z_{\mathrm{Ca}}F}\log_{e}\left(\frac{C_{\mathrm{O}}}{C_{\mathrm{S1}}}\right) \tag{S8}$$

$$E_{\mathrm{Na}} = \frac{RT}{Z_{\mathrm{Na}}F}\log_{e}\left(\frac{N_{\mathrm{O}}}{N_{\mathrm{S1}}}\right) \tag{S9}$$

Conductance Rate Scale Factor

$$V_{\mathrm{Scale}} = \frac{n_{\mathrm{PU(Base)}}}{n_{\mathrm{PU}}} \tag{S10}$$

Aggregate Plasma Membrane Conductances

$$I_{\mathrm{iCa}} = V_{\mathrm{Scale}}\left(I_{\mathrm{Ca}} + I_{\mathrm{PM}} + I_{\mathrm{NSCC(Ca)}}\right) \tag{S11}$$

$$I_{\text{iNa}} = V_{\text{Scale}}\left(I_{\text{Na}} + I_{\text{NaP}} + I_{\text{NSCC(Na)}}\right) \tag{S12}$$

$$I_{\text{ion}_{\text{PU}}}(i) = I_{\text{iCa}} + I_{\text{iNa}} \tag{S13}$$

Intracellular Ca^{2+} Fluxes

ER Ca^{2+} Fluxes

$$J_{\text{SERCA}} = \frac{V_{\text{SERCA}}\left(C_{\text{S1}} - A_2 C_{\text{ER}}\right)}{1 + A_4 C_{\text{S1}} + A_5 C_{\text{ER}} + A_6 C_{\text{S1}} C_{\text{ER}}} \tag{S14}$$

$$J_{\text{IPR}} = k_{\text{IPR}}\left(\frac{P\phi_1 H}{P\phi_1 + \phi_{-1}}\right)^4 \left(C_{\text{ER}} - C_{\text{S2}}\right) \tag{S15}$$

Mitochondrial Ca^{2+} Fluxes

$$J_{\text{MCU}} = V_{\text{MCU}}\left(\frac{{C_{\text{S2}}}^2}{{K_{\text{MCU}}}^2 + {C_{\text{S2}}}^2}\right)\varepsilon_{\text{INH}} \tag{S16}$$

$$\varepsilon_{\text{INH}} = \frac{{K_{\text{INH}}}^{h_{\text{INH}}}}{{K_{\text{INH}}}^{h_{\text{INH}}} + {C_{\text{MT}}}^{h_{\text{INH}}}} \tag{S17}$$

$$J_{\text{NCX}} = V_{\text{NCX}}\left(\frac{C_{\text{MT}}}{K_{\text{NCX}} + C_{\text{MT}}}\right) \tag{S18}$$

Inter-Compartmental Volume Ca^{2+} Diffusion

$$J_{\text{S1S2}_{(i)}} = \mu_{\text{S1S2}_{(i)}}\left(C_{\text{S2}_{(i)}} - C_{\text{S1}_{(i)}}\right) \tag{S19}$$

$$\mu_{\text{S1S2}_{(i)}} = \mu_{\text{A}} + \left(\mu_{\text{B}} - \mu_{\text{A}}\right)\left[\frac{i-1}{n_{\text{PU}} - 1}\right] \tag{S20}$$

$$J_{\text{S2Cy}_{(i)}} = \mu_{\text{S2Cy}_{(i)}}\left(C_{\text{Cy}} - C_{\text{S2}_{(i)}}\right) \tag{S21}$$

NB –μ_{S2Cy} values (for n_{PU} = 5-10, 15, 20 & 25) are given in Table S5

IP$_3$R Rate Equations

$$\phi_1 = \frac{k_1 R_1 + r_2 C_{\text{S2}}}{R_1 + C_{\text{S2}}} \tag{S22}$$

$$\phi_{-1} = \frac{\left(k_{-1} + r_{-2}\right)R_3}{R_3 + C_{\text{S2}}} \tag{S23}$$

$$\phi_2 = \frac{k_2 R_3 + r_4 C_{\text{S2}}}{R_3 + C_{\text{S2}}} \tag{S24}$$

$$\phi_3 = \frac{g_{\phi_3}\zeta}{\left[1+\left(\frac{K_{\phi_3}(\mathrm{act})}{C_{\mathrm{S2}}}\right)^{h_{\phi_3(\mathrm{act})}}\right]\left[1+\left(\frac{C_{\mathrm{S2}}}{K_{\phi_3}(\mathrm{inh})}\right)^{h_{\phi_3(\mathrm{inh})}}\right]} \tag{S25}$$

IP$_3$R Recovery Variable Equations

$$\frac{d\zeta}{dt} = \alpha_\zeta(1-\zeta) - \beta_\zeta\zeta \tag{S26}$$

$$\alpha_\zeta = g_\alpha \tag{S27}$$

$$\beta_\zeta = g_\beta \frac{{C_{\mathrm{S2}}}^{h_\beta}}{{C_{\mathrm{S2}}}^{h_\beta} + {K_\beta}^{h_\beta}} \tag{S28}$$

Mitochondrial Ca^{2+} Buffering Rate

$$f_{\mathrm{m}} = \frac{1}{1+\frac{K_{\mathrm{m}}B_{\mathrm{m}}}{(K_{\mathrm{m}}+C_{\mathrm{MT}})^2}} \tag{S29}$$

Compartmental Volume Ratio

$$\lambda_{\mathrm{X/Y}} = \frac{\gamma_{\mathrm{X}}}{\gamma_{\mathrm{Y}}} \tag{S30}$$

where X, Y = S$_1$, S$_2$, ER or MT

State Variable Derivatives

$$\frac{dC_{\mathrm{S1}}}{dt} = J_{\mathrm{S1S2}} + \lambda_{\mathrm{MT/S_1}}J_{\mathrm{NCX}} - \left(\frac{\delta_{\mathrm{S(PU)}}}{V_{\mathrm{Scale}}Z_{\mathrm{Ca}}}\right)I_{\mathrm{iCa}} - \lambda_{\mathrm{ER/S_1}}J_{\mathrm{SERCA}} \tag{S31}$$

$$\frac{dC_{\mathrm{S2}}}{dt} = J_{\mathrm{S2Cy}} + \lambda_{\mathrm{ER/S_2}}J_{\mathrm{IPR}} - \lambda_{\mathrm{S_1/S_2}}J_{\mathrm{S1S2}} - \lambda_{\mathrm{MT/S_2}}J_{\mathrm{MCU}} \tag{S32}$$

$$\frac{dC_{\mathrm{ER}}}{dt} = J_{\mathrm{SERCA}} - J_{\mathrm{IPR}} \tag{S33}$$

$$\frac{dC_{\mathrm{MT}}}{dt} = f_{\mathrm{m}}(J_{\mathrm{MCU}} - J_{\mathrm{NCX}}) \tag{S34}$$

$$\frac{dN_{\mathrm{S1}}}{dt} = -\left(\frac{\delta_{\mathrm{S(PU)}}}{V_{\mathrm{Scale}}Z_{\mathrm{Na}}}\right)I_{\mathrm{iNa}} \tag{S35}$$

$$\frac{dH}{dt} = \phi_3(1-H) - \left(\frac{P\phi_1\phi_2}{P\phi_1+\phi_{-1}}\right)H \tag{S36}$$

BULK CYTOPLASMIC SUBSPACE MODEL EQUATIONS

Plasma Membrane Conductances

Ca^{2+} Currents

$$I_{\mathrm{Ca(T)}} = g_{\mathrm{Ca(T)}} O_{\mathrm{T}} \left(V_{\mathrm{m}} - E_{\mathrm{Ca(T)}} \right) \tag{S37}$$

$$I_{\mathrm{Ca(Ext)}} = g_{\mathrm{Ca(Ext)}} \left(\frac{C_{\mathrm{Cy}}}{K_{\mathrm{Ca(Ext)}} + C_{\mathrm{Cy}}} \right) \tag{S38}$$

K^{+} Currents

$$I_{\mathrm{K(v1.1)}} = g_{\mathrm{K(v1.1)}} d_{\mathrm{v1.1}} f_{\mathrm{v1.1}} \left(V_{\mathrm{m}} - E_{\mathrm{K}} \right) \tag{S39}$$

$$I_{\mathrm{K(ERG)}} = g_{\mathrm{K(ERG)}} d_{\mathrm{ERG}} \left(V_{\mathrm{m}} - E_{\mathrm{K}} \right) \tag{S40}$$

$$I_{\mathrm{K(B)}} = g_{\mathrm{K(B)}} \left(V_{\mathrm{m}} - E_{\mathrm{K(B)}} \right) \tag{S41}$$

Other Currents

$$I_{\mathrm{L}} = g_{\mathrm{L}} \left(V_{\mathrm{m}} - E_{\mathrm{L}} \right) \tag{S42}$$

Nernst Potentials

$$E_{\mathrm{K}} = \frac{RT}{Z_{\mathrm{K}} F} \log_e \left(\frac{K_{\mathrm{O}}}{K_{\mathrm{i}}} \right) \tag{S43}$$

Aggregate Currents

$$I_{\mathrm{ion_{Cy}}} = I_{\mathrm{Ca(T)}} + I_{\mathrm{Ca(Ext)}} + I_{\mathrm{K(v1.1)}} + I_{\mathrm{K(ERG)}} + I_{\mathrm{K(B)}} + I_{\mathrm{L}} \tag{S44}$$

Intracellular Ca^{2+} Fluxes

$$J_{\mathrm{Cy}} = \mu_{\mathrm{Cy}} \left(C_{\infty} - C_{\mathrm{Cy}} \right) \tag{S45}$$

Ionic Current Gating Differential Equations

$I_{Ca(T)}$ Current

$$\frac{dO_{\mathrm{T}}}{dt} = \alpha_{\mathrm{OT}} d_{\mathrm{T}} f_{\mathrm{T}} - \beta_{\mathrm{OT}} O_{\mathrm{T}} \tag{S46}$$

$$\frac{dX_{\mathrm{T}}}{dt} = \frac{X_{\mathrm{T}\infty} - X_{\mathrm{T}}}{\tau_{\mathrm{XT}}} \tag{S47}$$

for $X = d$ or f

$$X_{\mathrm{T}\infty} = \frac{1}{1 + e^{k_{\mathrm{XT}}(V_m - V_{\mathrm{XT}})}} \tag{S48}$$

$$\tau_{\mathrm{dT}} = A_{\mathrm{dT}(1)} \tag{S49}$$

$$\tau_{\mathrm{fT}} = A_{\mathrm{fT}(1)} + \frac{\left(A_{\mathrm{fT}(2)} - A_{\mathrm{fT}(1)}\right)}{1 + e^{A_{\mathrm{fT}(3)}\left(V_{\mathrm{m}} - A_{\mathrm{fT}(4)}\right)}} \tag{S50}$$

K^+ Currents

$$\frac{dX}{dt} = \alpha_{\mathrm{X}}(1 - X) - \beta_{\mathrm{X}} X \tag{S51}$$

for $X = d_{\mathrm{v1.1}}, f_{\mathrm{v1.1}}, d_{\mathrm{ERG}}$

$$\alpha_{\mathrm{X}} = A_{\mathrm{X}(1)}\left[\frac{A_{\mathrm{X}(2)}}{1 + e^{A_{\mathrm{X}(3)}\left(V_{\mathrm{m}} - A_{\mathrm{X}(4)}\right)}} + \left(1 - A_{\mathrm{X}(2)}\right)\right] \tag{S52}$$

$$\beta_{\mathrm{X}} = A_{\mathrm{X}(1)}\left[A_{\mathrm{X}(2)} - \frac{A_{\mathrm{X}(2)}}{1 + e^{A_{\mathrm{X}(3)}\left(V_{\mathrm{m}} - A_{\mathrm{X}(4)}\right)}}\right] \tag{S53}$$

Global State Variable Derivatives

$$\frac{dV_{\mathrm{m}}}{dt} = -\frac{1}{C_{\mathrm{m}}}\left[I_{\mathrm{ion}_{\mathrm{Cy}}} + \sum_{i=1}^{n_{\mathrm{PU}}} I_{\mathrm{ion}_{\mathrm{PU}}}(i)\right] \tag{S54}$$

$$\frac{dC_{\mathrm{Cy}}}{dt} = J_{\mathrm{Cy}} - \lambda_{\mathrm{S2Cy}} \sum_{i=1}^{n_{\mathrm{PU}}} J_{\mathrm{S2Cy}_{(i)}} - \left(\frac{\delta_{\mathrm{S(Cy)}}}{Z_{\mathrm{Ca}}}\right)\left[I_{\mathrm{Ca(T)}} + I_{\mathrm{Ca(Ext)}}\right] \tag{S55}$$

PACEMAKER UNIT MODEL PARAMETERS

Plasma Membrane Conductances							
Ca^{2+} Currents							
$\hat{g}_{Ca}$	0.074 pS	S2	F_{UP}^{*}	k_{Ca}	0.013 mV^{-1}	S2	F_{UP}^{**}
g_{PM}	675 fA	S3	F_{UP}^{*}	K_{PM}	1 μM	S3	(1)
Na^{+} Currents							
g_{Na}	13.5 pS	S4	F_{UP}^{**}	g_{NaP}	187.5 pS	S5	F_{UP}^{*}
E_{NaP}	10 mV	S5	$(2)^{**}$	K_{NaP}	1 x 10^{4} μM	S5	F_{UP}
h_{NaP}	4	S5	F_{UP}				
Non-Selective Cation Conductance							
E_{NSCC}	0 mV	S6	(3)	$\hat{g}_{NSCC(Ca)}$	0.1 pS	S7	F_{UP}^{*}
$\hat{g}_{NSCC(Na)}$	160 pS	S7	F_{UP}^{*}	K_{NSCC}	0.12 μM	S7	F_{UP}
h_{NSCC}	4	S7	(3)				
Intracellular Ca^{2+} Fluxes							
Endoplasmic Reticulum Ca^{2+} Conductances							
k_{IPR}	2000 s^{-1}	S15	F_{UP}	V_{SERCA}	1 x 10^{5} s^{-1}	S14	F_{UP}
A_2	6 x 10^{-4}	S14	F_{UP}	A_4	3.57 μM^{-1}	S14	(4)
A_5	2.7 x 10^{-5} μM^{-1}	S14	(4)	A_6	2.31 x 10^{-5} μM^{-2}	S14	(4)
Mitochondrial Ca^{2+} Conductances							
V_{MCU}	800 μM s^{-1}	S16	F_{UP}	K_{MCU}	10 μM	S16	(5)
K_{INH}	10 μM	S17	F_{UP}	h_{INH}	4	S17	F_{UP}
V_{NCX}	3 μM s^{-1}	S18	F_{UP}^{*}	K_{NCX}	0.30 μM	S18	(6)
K_m	0.01 μM	S29	F_{UP}	B_m	1000 μM	S29	F_{UP}
Intracellular Ca^{2+} Diffusion Rates							
μ_A	0.30 s^{-1}	S20	F_{UP}	μ_B	0.24 s^{-1}	S20	F_{UP}
IP_3R Rate Parameters							
Instantaneous Rate Equations							
k_1	0 s^{-1}	S22	F_{UP}	k_{-1}	6.4 s^{-1}	S23	F_{UP}
k_2	4 s^{-1}	S24	F_{UP}	r_2	250 s^{-1}	S22	F_{UP}
r_{-2}	0 μM s^{-1}	S23	F_{UP}	r_4	750 s^{-1}	S24	F_{UP}
R_1	36 μM	S22	(7)	R_3	300 μM	S23,S24	(7)
ϕ_3 Rate Parameters							
$g_{\phi3}$	4.5 s^{-1}	S25	F_{UP}	$K_{\phi3(act)}$	0.1 μM	S25	F_{UP}
$K_{\phi3(inh)}$	0.5 μM	S25	F_{UP}	$h_{\phi3(act)}$	3	S25	F_{UP}
$h_{\phi3(inh)}$	3	S25	F_{UP}				
ζ Rate Parameters							
g_{α}	0.85 s^{-1}	S27	F_{UP}	g_{β}	1.5 x 10^{3} s^{-1}	S28	F_{UP}
K_{β}	0.35 μM	S28	F_{UP}	h_{β}	4	S28	F_{UP}

Table S1 – Pacemaker Unit Model Equation Parameters

Numbers in parenthesis denotes literary reference. F_{UP} denotes that parameter was fitted to reproduce unitary potential characteristics (see “Parameter Estimation” from Ref. (8)).
* denotes parameter was modified from original model.
** denotes parameter was added to model framework.

WHOLE CELL CURRENT EQUATION PARAMETERS

Plasma Membrane Conductances							
Ca^{2+} Currents							
$g_{Ca(T)}$	800 pS	S37	F_{SW}	$E_{Ca(T)}$	17 mV	S37	(8)
$g_{Ca(Ext)}$	100 fA	S38	F_{SW}	$K_{Ca(Ext)}$	1.0 µM	S38	F_{SW}
K^{+} Currents							
$g_{K(v1.1)}$	10 pS	S39	F_{SW}	$g_{K(ERG)}$	6 pS	S40	F_{SW}
$g_{K(B)}$	13.5 pS	S41	F_{SW}	$E_{K(B)}$	-70 mV	S41	F_{SW}
Other Currents							
g_{L}	0.8 pS	S42	F_{SW}	E_{L}	0 mV	S42	(3)
Intracellular Ca^{2+} Fluxes							
μ_{Cy}	1.3 s^{-1}	S45	F_{SW}	C_{∞}	0.12 µM	S45	F_{SW}
Gating Variable Rate Equations							
O_T Rate Equations							
α_{OT}	240 s^{-1}	S46	F_{SW}	β_{OT}	72 s^{-1}	S46	F_{SW}
d_T Rate Equations							
k_{dT}	-0.60 mV^{-1}	S48	(9)	V_{dT}	-53 mV	S48	(9)
$A_{dT(1)}$	0.0025 s	S49	(9)				
f_T Rate Equations							
k_{fT}	1 mV^{-1}	S48	(9)	V_{fT}	-65 mV	S48	(9)
$A_{fT(1)}$	0.019 s	S50	(9)	$A_{fT(2)}$	6.75 s	S50	(9)
$A_{fT(3)}$	2 mV^{-1}	S50	(9)	$A_{fT(4)}$	-40 mV	S50	(9)
$d_{v1.1}$ Rate Equations							
$A_{dv(1)}$	1000 s^{-1}	S52,S53	(10)	$A_{dv(2)}$	0.80	S52,S53	(10)
$A_{dv(3)}$	-0.13 mV^{-1}	S52,S53	(10)	$A_{dv(4)}$	25 mV	S52,S53	(10)
$f_{v1.1}$ Rate Equations							
$A_{fv(1)}$	333 s^{-1}	S52,S53	(10)	$A_{fv(2)}$	0.10	S52,S53	(10)
$A_{fv(3)}$	0.23 mV^{-1}	S52,S53	(10)	$A_{fv(4)}$	44.8 mV	S52,S53	(10)
d_{ERG} Rate Equations							
$A_{dERG(1)}$	1000 s^{-1}	S52,S53	(10)	$A_{dERG(2)}$	0.70	S52,S53	(10)
$A_{dERG(3)}$	-0.56 mV^{-1}	S52,S53	(10)	$A_{dERG(4)}$	30 mV	S52,S53	(10)

Table S2 – Whole Cell Current Model Equation Parameters

Numbers in parenthesis denotes literary reference. FSW denotes that parameter was fitted to reproduce slow wave characteristics (see “Parameter Estimation” section in manuscript).

CELL CONSTANTS AND GLOBAL PARAMETERS

Universal Constants							
	R	8.31 x 10^{3} aJ zmol^{-1} K^{-1}	S8,S9,S43		T	310.16 K	S8,S9,S43
	F	9.649 x 10^{-2} fC zmol^{-1}	S8,S9,S43				
Ion/Metabolite Concentrations							
	C_{O}	1.8 x 10^{3} μM	S8		N_{O}	140 x 10^{3} μM	S9
	K_{O}	5.4 x 10^{3} μM	S43		K_{i}	145 x 10^{3} μM	S43
	P	1 μM	S15,S36				
Ion Valency							
	Z_{Ca}	2	S8,S31,S55		Z_{Na}	1	S9,S35
	Z_{K}	1	S43				
Compartmental Volume Ratios							
	γ_{S1}	100	S30		γ_{S2}	1	S30
	γ_{ER}	20	S30		γ_{MT}	200	S30
	γ_{Cy}	1000	S30				
Cell Constants							
	$\delta_{\text{S(Cy)}}$	2 x 10^{-3} μM C^{-1}	S55		$\delta_{\text{S(PU)}}$	9.25 μM C^{-1}	S31,S35
	C_{m}	20 pF	S54		$n_{\text{PU(Base)}}$	50	S10

Table S3 – Model Cell Constants and Other Global Parameters

INITIAL STATE VARIABLE VALUES

Pacemaker Unit State Variables				
	C_{S1}	0.120 μM	C_{S2}	0.023 μM
	C_{ER}	200 μM	C_{MT}	0.200 μM
	N_{S1}	1.01 x 10^{4} μM	H	0.200
	ζ	0.300		
Whole Cell Current Gating Variables				
	d_{T}	0.010	f_{T}	0.001
	O_{T}	0.000	$d_{\text{v1.1}}$	0.000
	$f_{\text{v1.1}}$	1.000	d_{ERG}	0.000
Global Variables				
	V_{m}	-70 mV	C_{Cy}	0.12 μM

Table S4 – Model State Variable Initial Values

SUBSPACE 2/BULK CYTOPLASM Ca^{2+} DIFFUSION RATES

PU #	$n_{PU} = 5$	$n_{PU} = 6$	$n_{PU} = 7$	$n_{PU} = 8$	$n_{PU} = 9$	$n_{PU} = 10$	$n_{PU} = 15$	$n_{PU} = 20$	$n_{PU} = 25$
1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
2	0.4788	0.4133	0.4071	0.3662	0.3520	0.3361	0.2150	0.1544	0.1136
3	0.6843	0.5577	0.4752	0.4253	0.3850	0.3658	0.4367	0.3260	0.2489
4	0.9335	0.7464	0.6244	0.5441	0.4829	0.4357	0.5096	0.4981	0.3872
5	1.1673	0.9389	0.7818	0.6750	0.5935	0.5351	0.4565	0.4844	0.5217
6		1.1184	0.9388	0.8062	0.7095	0.6366	0.5033	0.4455	0.5672
7			1.0827	0.9357	0.8240	0.7386	0.5390	0.4628	0.4886
8				1.0545	0.9325	0.8361	0.6042	0.5127	0.4790
9					1.0336	0.9320	0.6642	0.5458	0.5179
10						1.0185	0.7348	0.5831	0.5282
11							0.7977	0.6366	0.5536
12							0.8619	0.6802	0.5883
13							0.9241	0.7256	0.6200
14							0.9812	0.7694	0.6541
15							1.0344	0.8221	0.6935
16								0.8690	0.7305
17								0.9096	0.7684
18								0.9550	0.8036
19								0.9965	0.8343
20								1.0347	0.8712
21									0.9092
22									0.9435
23									0.9768
24									1.0079
25									1.0361

Table S5 – Subspace 2/Bulk Cytoplasmic (μ_{S2Cy}) Ca^{2+} Diffusion Rates

DOSE-RESPONSE SIMULATIONS

The following is of the dose-response simulations that have been included in the supplementary materials:

Figure 1 – Decreased $[Ca^{2+}]_O$
Figure 2 – Decreased $[Na^{+}]_O$
Figure 3 – Increased $[K^{+}]_O$
Figure 4 – Varying $[IP_3]$
Figure 5 – J_{NCX} Inhibition
Figure 6 – $I_{K(ERG)}$ Inhibition

The format of each dose-response simulation figure is comprised of 9 subplots (*A*-*I*). The subplots *A*-*H* are seperated into two columns, the first column illustrating the simulated V_m response and the second the pacemaker unit discharge rastergram. Each row, within this subplot group, is the response generated by the proportional change in the target parameter (see Table 5 of the manuscript) which indicated by the key given in subplot *I*. The final subplot (*I*) shows the change in the slow wave characteristic values from control conditions, a list of which is given below:

- MDP (mV) ,
- Amplitude (mV) ,
- $\{dV_m/dt\}_{max}$ (mV s^{-1}) , and
- Frequency (cpm)

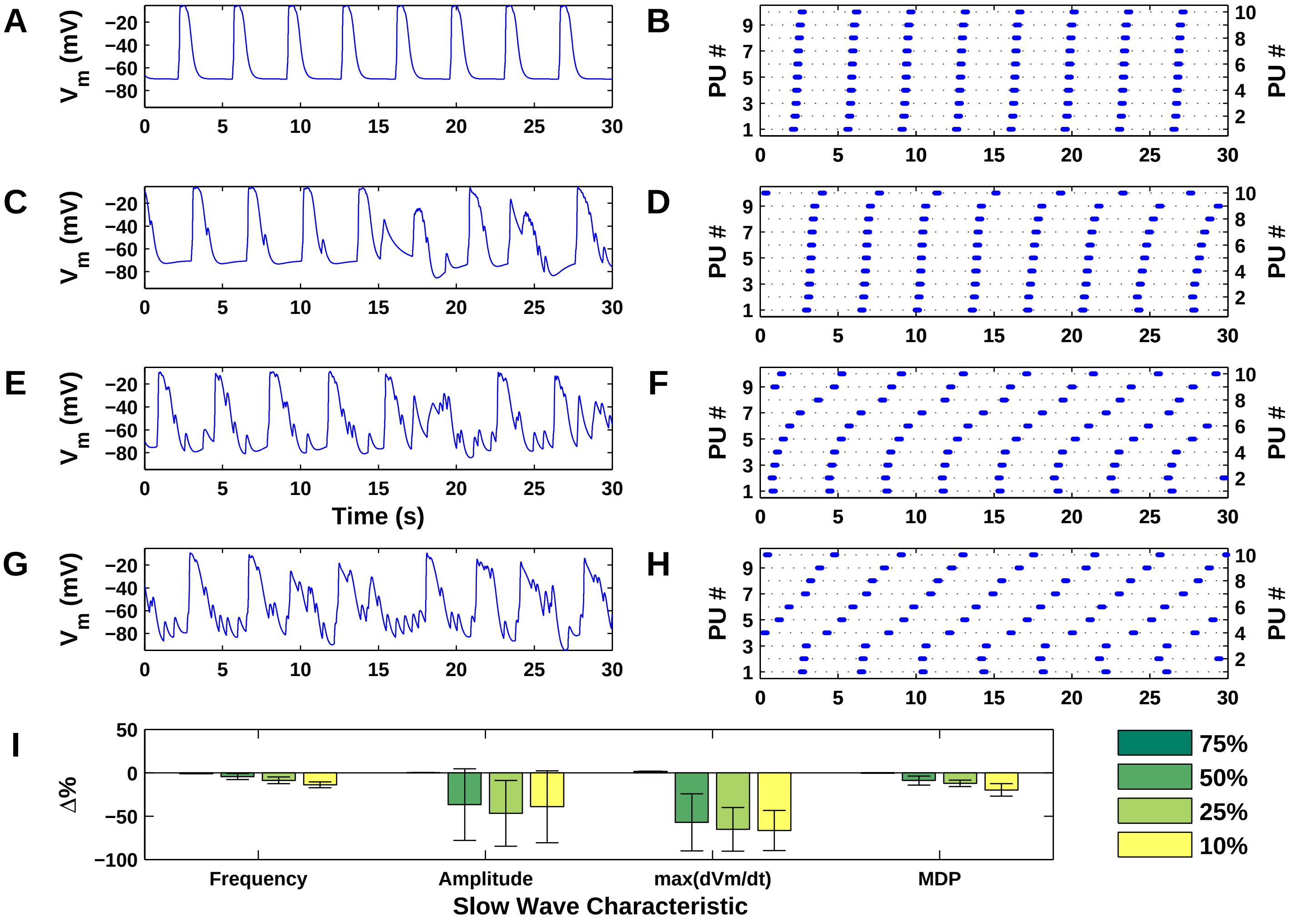

Figure S1 – Decreased Extracellular [Ca^{2+}] Dose Response Simulation

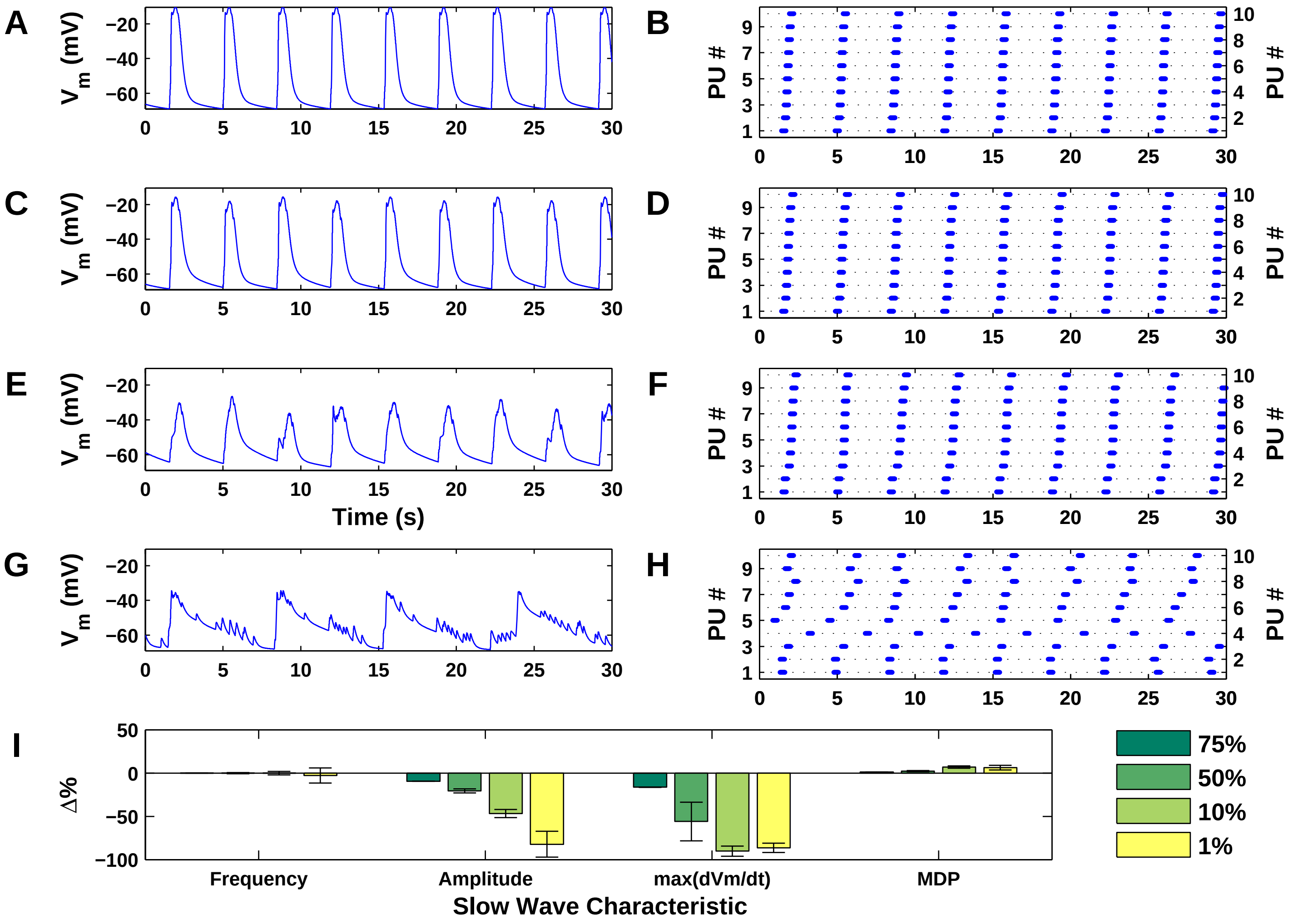

Figure S2 – Decreased Extracellular [Na$^+$] Dose Response Simulations

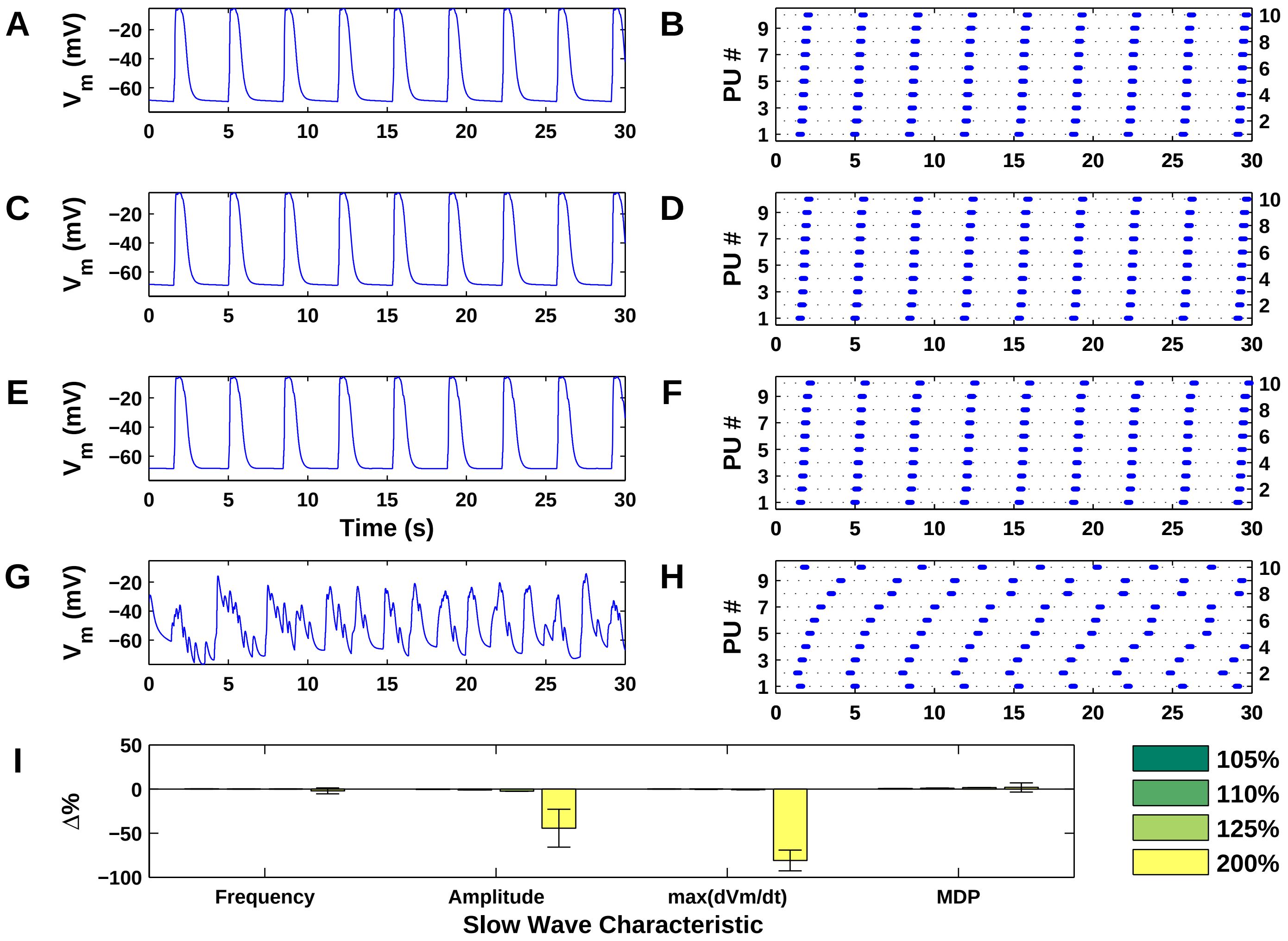

Figure S3 – Increase Extracellular [K$^+$] Dose Response Simulations

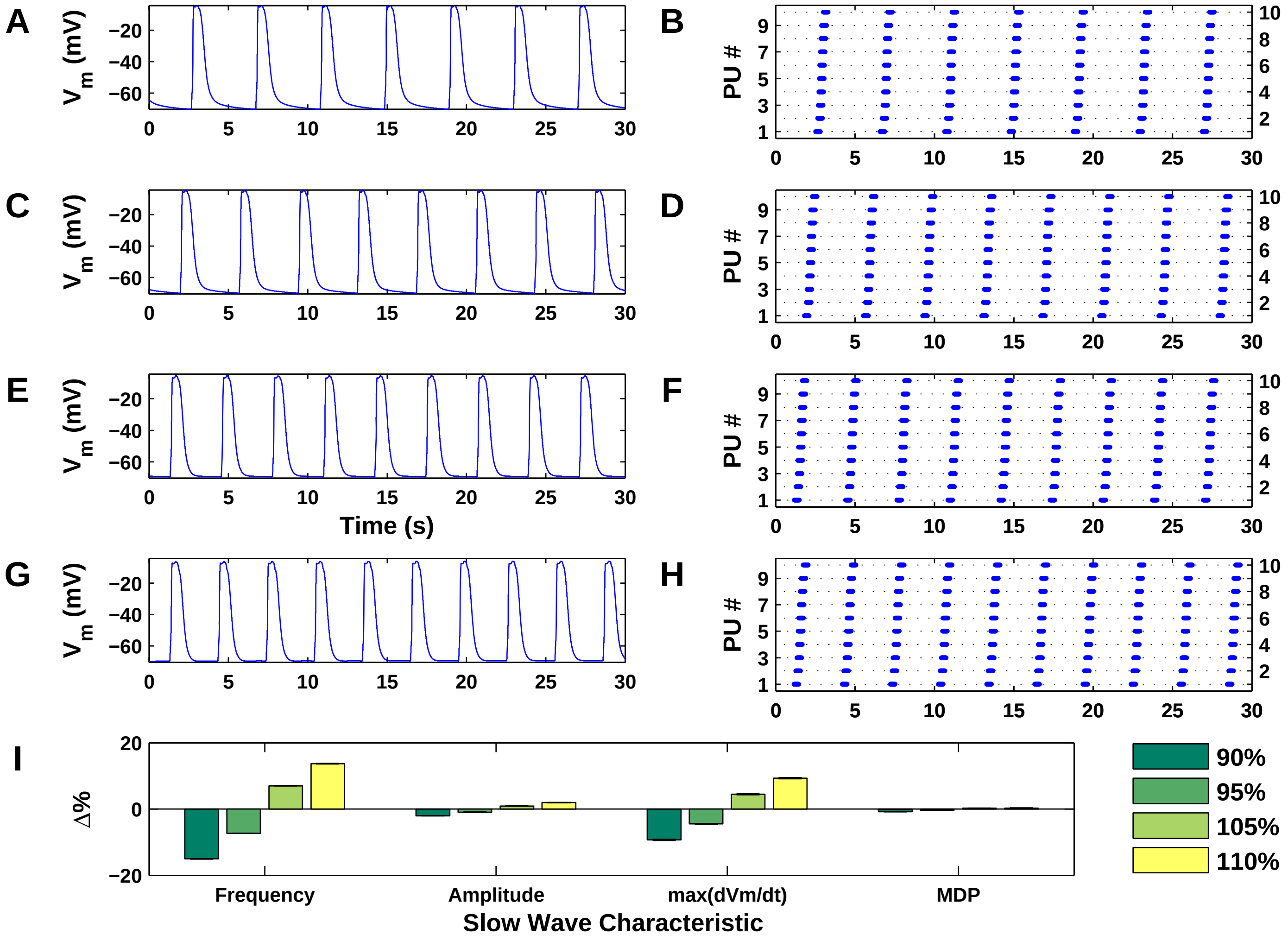

Figure S4 – Varying [IP$_3$] Dose Response Simulations

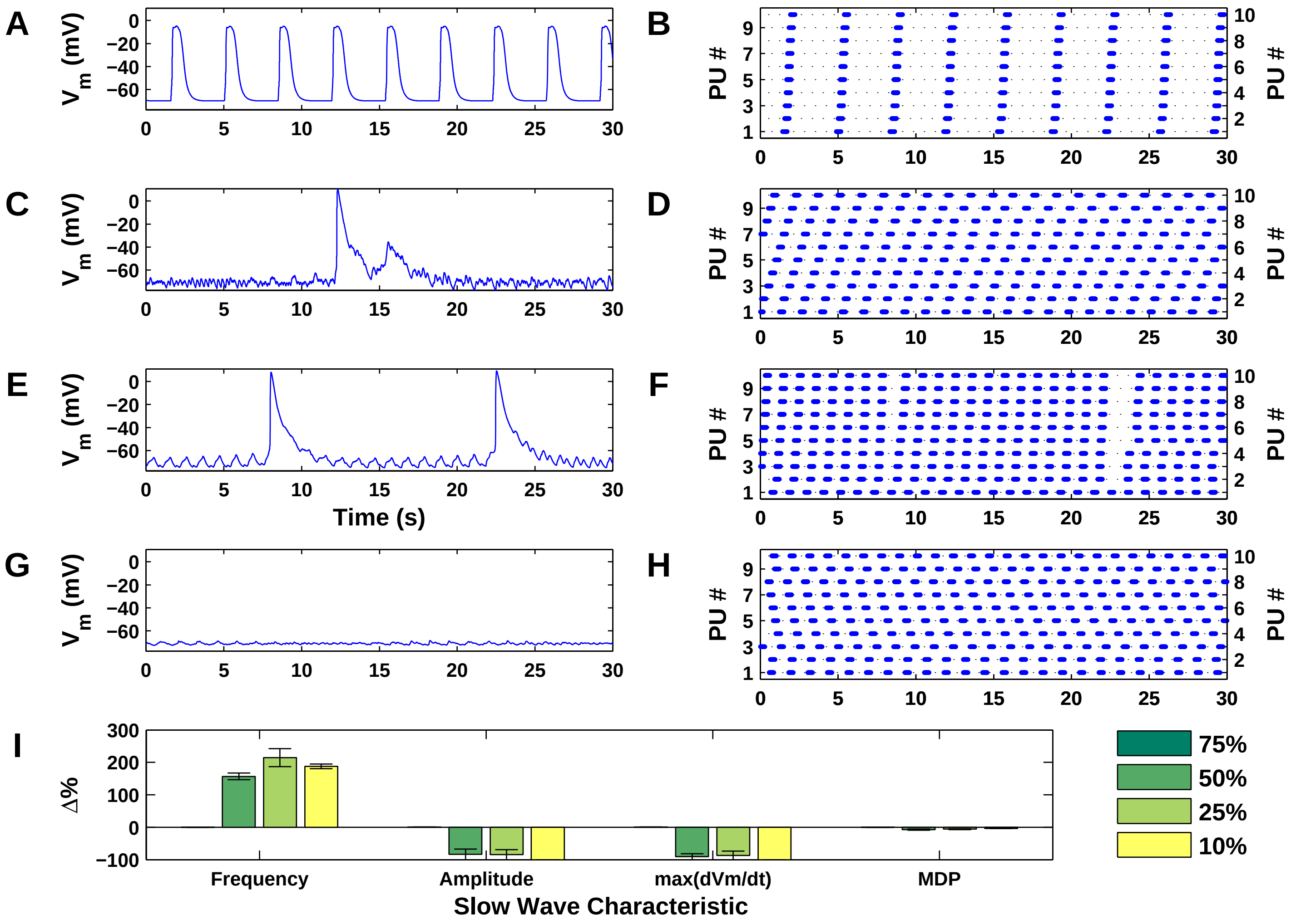

Figure S5 – J_{NCX} Inhibition Dose Response Simulations

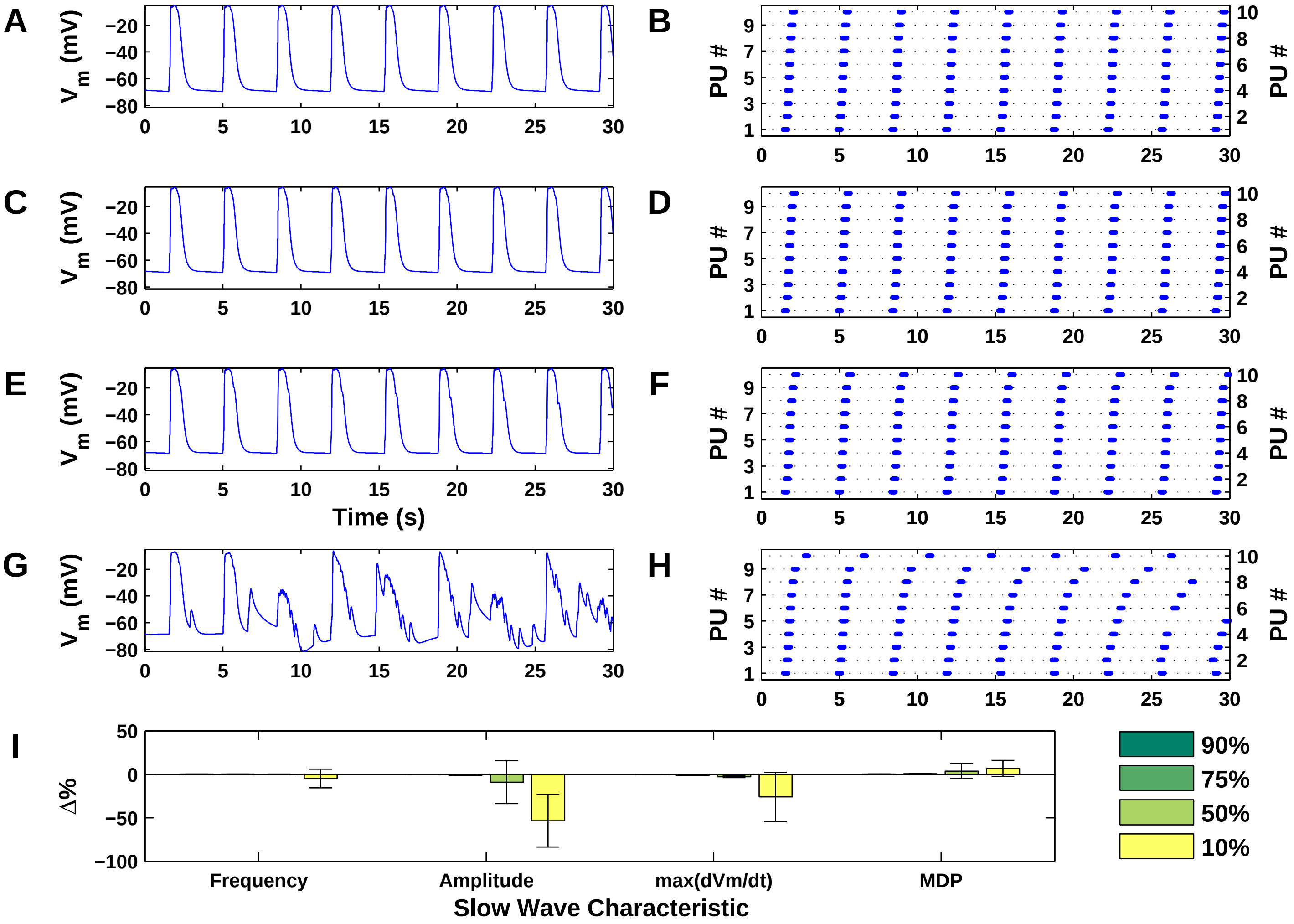

Figure S6 – $I_{K(ERG)}$ Inhibition Dose Response Simulations

PACEMAKER UNIT FIRING DISTRIBUTION

Inverse Distribution Function

The cumulative distribution function, $\psi(t)$ that describes pacemaker unit discharge over time is given by the 2-parameter Boltzmann function as follows:

$$\psi(t) = \frac{1}{1 + e^{-k_\psi (t - T_\psi)}} \tag{S.A1}$$

Therefore, in order to determine the time at which a proportion, P_x, of the pacemaker unit population has fired, we invert $\psi(t)$ as follows:

$$t = \psi^{-1}(P_x) = T_\psi - \frac{1}{k_\psi} \log_e \left(\frac{1}{P_x} - 1 \right) \tag{S.A2}$$

Pacemaker Unit Firing Probability

If a pacemaker unit population is comprised of n_PU units, then each pacemaker unit represents a proportion of $1/n_\mathrm{PU}$ of the entire population. Therefore, the proportion of the population which has fired after the discharge of i pacemaker units is given by the equation:

$$P_{x(i)} = \frac{i}{n_{PU}} \tag{S.A3}$$

Note that as we are making a discrete approximation to a continuous distribution, this proportion is fixed as the midpoint of the interval over which it represents (i.e., $1/n_\mathrm{PU}$).

$$\text{i.e.} \quad P_{x(i)} = \frac{i}{n_{PU}} - \frac{1}{2n_{PU}} = \frac{2i-1}{2n_{PU}} \tag{S.A4}$$

Substituting eqn. (S.A4) into eqn. (S.A2) therefore gives the time at which the i^th pacemaker unit will discharge:

$$t_i = T_\psi - \frac{1}{k_\psi} \log_e \left(\frac{2n_{PU}}{2i-1} - 1 \right) \tag{S.A5}$$

Pacemaker Cycle Landmark

As $\Psi(t)$ can be shifted in time to coincide with any arbitrary landmark point within the slow wave cycle, then the value of T_Ψ is also arbitrary. Therefore, ψ(t) was fixed such that the firing of the first pacemaker unit was set at $t = 0$. This is due to the fact that this is a landmark point which is common to any pacemaker unit population, independent of size. Subtituting $t = 0$ into eqn. (S.A5) and rearranging gives:

$$T_{\psi} = \frac{1}{k_{\psi}} \log_e \left(\frac{1}{P_{x(1)}} - 1 \right) \tag{S.A6}$$

From eqn. (S.A4), we know that $P_{x(1)} = 1/(2n_{PU})$. Therefore, substituting eqn. (S.A4) into (S.A6) gives the following equation which describes T_{ψ} as a function of n_{PU}:

$$T_{\psi} = \frac{1}{k_{\psi}} \log_e (2n_{PU} - 1) \tag{S.A7}$$

Pacemaker Unit Firing Time Distribution

Substituting eqn. (S.A7) into eqn. (S.A5) gives the final equation describing the time at which the i^{th} pacemaker unit, from a population of n_{PU} units, will discharge as follows:

$$\boxed{t_i = \frac{1}{k_{\psi}} \left[\log_e (2n_{PU} - 1) - \log_e \left(\frac{2n_{PU}}{2i - 1} - 1 \right) \right]} \tag{S.A8}$$

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