

**Supplementary Material S1 Text: Model Description**

Arrhythmia Mechanisms and Spontaneous Calcium  
Release: Bi-directional Coupling Between Re-entrant and  
Focal Excitation

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# 1. Spatial $\text{Ca}^{2+}$ cycling model

This section describes the spatial  $\text{Ca}^{2+}$  cycling model, a simplified and efficient version of a previously developed model [1].

## Variables

Table S1:  $\text{Ca}^{2+}$  handling model variables

Parameter	Description	Unit
$[Ca^{2+}]_{ds}$	Average $\text{Ca}^{2+}$ concentration in the dyadic cleft	$\mu\text{M}$
$^m[Ca^{2+}]_{ds}$	$\text{Ca}^{2+}$ concentration in dyad in CRU $m$	$\mu\text{M}$
$[Ca^{2+}]_{rbSS}$	Average $\text{Ca}^{2+}$ concentration in the subspace	$\mu\text{M}$
$^m[Ca^{2+}]_{rbSS}$	$\text{Ca}^{2+}$ concentration in subspace in CRU $m$	$\mu\text{M}$
$[Ca^{2+}]_{cyto}$	Average $\text{Ca}^{2+}$ concentration in the bulk cytoplasm	$\mu\text{M}$
$^m[Ca^{2+}]_{cyto}$	$\text{Ca}^{2+}$ concentration in cytoplasm in CRU $m$	$\mu\text{M}$
$[Ca^{2+}]_{nSR}$	Average $\text{Ca}^{2+}$ concentration in the network SR	$\mu\text{M}$
$^m[Ca^{2+}]_{nSR}$	$\text{Ca}^{2+}$ concentration in network SR in CRU $m$	$\mu\text{M}$
$[Ca^{2+}]_{jSR}$	Average $\text{Ca}^{2+}$ concentration in the junctional SR	$\mu\text{M}$
$^m[Ca^{2+}]_{jSR}$	$\text{Ca}^{2+}$ concentration in junctional SR in CRU $m$	$\mu\text{M}$
$^mJ_{rel} \mid J_{rel}$	Release flux in dyad $m \mid$ Whole cell average release flux	$\mu\text{M}.\text{ms}^{-1}$
$^mJ_{CaL} \mid I_{CaL}$	LTCC flux in dyad $m \mid$ Whole cell current	$\mu\text{M}.\text{ms}^{-1} \mid \text{pA/pF}$
$^mJ_{up} \mid J_{up}$	SR Uptake flux in CRU $m \mid$ Whole cell SR update flux	$\mu\text{M}.\text{ms}^{-1}$
$^mJ_{leak} \mid J_{leak}$	SR leak flux in CRU $m \mid$ Whole cell SR leak flux	$\mu\text{M}.\text{ms}^{-1}$
$^mJ_{ds}$	Flux from dyad $m$ to rbSS voxel at $m$	$\mu\text{M}.\text{ms}^{-1}$
$^mJ_{ss}$	Flux from rbSS to cytoplasm voxel $m$	$\mu\text{M}.\text{ms}^{-1}$
$^mJ_{jSR}$	Flux from network to junctional SR at dyad $m$	$\mu\text{M}.\text{ms}^{-1}$
$^mJ_{trpn}$	Trpn buffering flux at CRU $m$	$\mu\text{M}.\text{ms}^{-1}$
$^mJ_{NaCa} \mid I_{NaCa}$	Sodium- $\text{Ca}^{2+}$ exchanger flux in CRU $m \mid$ Whole cell current	$\mu\text{M}.\text{ms}^{-1} \mid \text{pA/pF}$
$^mJ_{pCa} \mid I_{pCa}$	PMCA $\text{Ca}^{2+}$ pump flux in in CRU $m \mid$ Whole cell current	$\mu\text{M}.\text{ms}^{-1} \mid \text{pA/pF}$
$J_{Cab} \mid I_{Cab}$	Background $\text{Ca}^{2+}$ current flux in voxel $p \mid$ Whole cell current	$\mu\text{M}.\text{ms}^{-1} \mid \text{pA/pF}$
$^m\beta_{cyto}$	Instantaneous buffering in the cytoplasm in CRU $m$	-
$^m\beta_{jSR}$	Instantaneous buffering in the junctional SR in CRU $m$	-
$^mn_{o\_gr}$	Number of open RyRs in dyad $m$	-
$^mCA$	Number of RyRs in the <u>C</u> losed <u>A</u> ctivated state, dyad $m$	-
$^mOA$	Number of RyRs in the <u>O</u> pen <u>A</u> ctivated state, dyad $m$	-
$^mCI$	Number of RyRs in the <u>C</u> losed <u>I</u> nactivated state, dyad $m$	-
$^mOI$	Number of RyRs in the <u>O</u> pen <u>I</u> nactivated state, dyad $m$	-
$csqn$	Free calsequestrin concentration	$\text{mM}$
$^mM$	Proportion of csqn in monomer state, dyad $m$	-
$^md_1$	LTCC activation gate state 1, dyad $m$	-
$^md_2$	LTCC activation gate state 2, dyad $m$	-
$^md_3$	LTCC activation gate state 3, dyad $m$	-
$^mf_1$	LTCC voltage-dependent inactivation state 1, dyad $m$	-
$^mf_2$	LTCC voltage-dependent inactivation state 2, dyad $m$	-
$^mf_{ca1}$	LTCC $\text{Ca}^{2+}$ -dependent inactivation state 1, dyad $m$	-
$^mf_{ca2}$	LTCC $\text{Ca}^{2+}$ -dependent inactivation state 2, dyad $m$	-
$V_m$	Membrane potential	$\text{mV}$

## Fundamental equations for $Ca^{2+}$ concentration

$$\frac{d[Ca^{2+}]_i}{dt} = \beta_i \left( \mathbf{D}\nabla^2[Ca^{2+}]_i + \phi_i + (v_{ss}/v_i)J_{ss} \right) \quad (1)$$

$$\frac{d[Ca^{2+}]_{ss}}{dt} = \mathbf{D}\nabla^2[Ca^{2+}]_{ss} + \phi_{ss} - J_{ss} + (v_{ds}/v_{ss})J_{ds} \quad (2)$$

$$\frac{d[Ca^{2+}]_{nSR}}{dt} = \beta_{nSR} \left( \mathbf{D}\nabla^2[Ca^{2+}]_{nSR} + \phi_{nSR} - (v_{jsr}/v_{nSR})J_{jsr} \right) \quad (3)$$

$$\frac{d[Ca^{2+}]_{ds}}{dt} = \phi_{ds} - J_{ds} \quad (4)$$

$$\frac{d[Ca^{2+}]_{JSR}}{dt} = \phi_{JSR} + J_{jsr} \quad (5)$$

Where transfer between compartments is given by:

$$J_{ss} = \left( [Ca^{2+}]_{ss} - [Ca^{2+}]_i \right) \tau_{ss}^{-1} \quad (6)$$

$$J_{ds} = \left( [Ca^{2+}]_{ds} - [Ca^{2+}]_{ss} \right) \tau_{ds}^{-1} \quad (7)$$

$$J_{jsr} = \left( [Ca^{2+}]_{nSR} - [Ca^{2+}]_{JSR} \right) \tau_{ds}^{-1} \quad (8)$$

And the reaction terms are:

$$\phi_i = J_{NaCa} + J_{pCa} + J_{CaB} - (J_{up} - J_{leak}) - J_{trpn} \quad (9)$$

$$\phi_{nSR} = (J_{up} - J_{leak})(v_i/v_{nSR}) \quad (10)$$

$$\phi_{ss} = J_{NaCa_{ss}} \quad (11)$$

$$\phi_{ds} = J_{rel} + J_{CaL} \quad (12)$$

$$\phi_{JSR} = -J_{rel}(v_{ds}/v_{JSR}) \quad (13)$$

Spatial diffusion is described by a 6-node nearest neighbours finite difference approximation:

$$\mathbf{D}\nabla^2[Ca^{2+}]_x \approx J_{Ca\_diff\_x} = \sum_{i=1}^{i=3} \left( \frac{e_i+1[Ca^{2+}]_x + e_i-1[Ca^{2+}]_x - 2e_i[Ca^{2+}]_x}{\tau_{x,e_i}} \right) \quad (14)$$

Where  $e_i$  refers to the three dimensions (x,y,z).

Due to the small volume of the dyadic cleft, an analytical description can be found for the dyadic cleft  $Ca^{2+}$  concentration under the approximation that the volume reaches its steady-state concentration within the time-step,  $\Delta t$ . Thus, by setting:

$$\frac{d[Ca^{2+}]_{ds}}{dt} = 0 \quad (15)$$

An approximation for equation (4) can be obtained as [2]:

$$[Ca^{2+}]_{ds} = [Ca^{2+}]_{ss} + \frac{\tau_{ds} \cdot \left( {}^n k_{rel} \cdot [Ca^{2+}]_{jSR} + {}^n J_{CaL} \right)}{(1 + \tau_{ds} \cdot {}^n k_{rel})} \quad (16)$$

**Table S2: Cell structure and diffusion parameters**

Parameter	Description	Value
$v_i$	Cytoplasm volume per CRU	$1.0 \mu m^3$
$v_{nSR}$	Network SR volume per CRU	$0.05 \mu m^3$
$v_{SS}$	Sub-space volume per CRU	$0.0175 \mu m^3$
$\langle v_{ds} \rangle$	Average volume of individual dyad	$1.712 \times 10^{-3} \mu m^3$
$v_{jSR}$	Volume individual jSR	$0.015 \mu m^3$
$\tau_{ds}$	Time constant diffusion from dyad to SS	$0.022 \text{ ms}$
$\tau_{ss}$	Time constant diffusion from SS to cytoplasm	$0.1 \text{ ms}$
$\tau_{jSR}$	Time constant diffusion from nSR to jSR	$5 \text{ ms}$
$\tau_{i,transverse}$	Time constant of transverse cytoplasm diffusion	$2.3 \text{ ms}$
$\tau_{i,longitudinal}$	Time constant of longitudinal cytoplasm diffusion	$2.9 \text{ ms}$
$\tau_{ss,transverse}$	Time constant of transverse subspace diffusion	$1.35 \text{ ms}^*$
$\tau_{ss,longitudinal}$	Time constant of longitudinal subspace diffusion	$2.20 \text{ ms}^*$
$\tau_{nSR,transverse}$	Time constant of transverse nSR diffusion	$7 \text{ ms}$
$\tau_{nSR,longitudinal}$	Time constant of longitudinal nSR diffusion	$14 \text{ ms}$

\* varied in different conditions. These are control model values

## Reaction terms

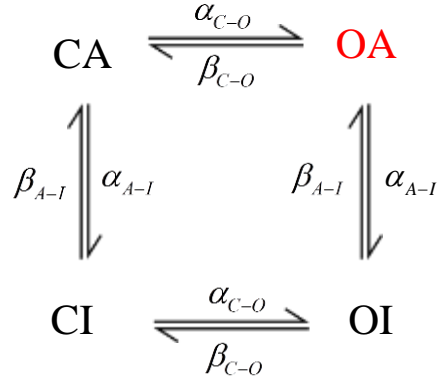
The formulations for the reaction terms (Equations (9-13)) are described below:

### Intracellular $Ca^{2+}$ release, $J_{rel}$

$${}^m J_{rel} = {}^m k_{rel} \left( {}^m [Ca^{2+}]_{jSR} - {}^m [Ca^{2+}]_{ds} \right) \quad (17)$$

$${}^m k_{rel} = {}^m n_{o\_RyR} \cdot g_{RyR} \cdot {}^m v_{ds}^{-1} \quad (18)$$

${}^m n_{o\_RyR}$  is the number of open RyR channels in dyad  $m$ . RyR dynamics is described by a 4-state Markov Chain model. The model is similar to Stern et al [3] and Restrepo et al [4], with a functional monomer induced inactivation based on the csqn dynamics described by Gaur-Rudy [5].



$$\frac{d {}^m\text{CA}}{dt} = {}^m\text{OA} \cdot \beta_{C-O} + {}^m\text{CI} \cdot \beta_{A-I} - {}^m\text{CA} \cdot (\alpha_{C-O} + \alpha_{A-I}) \quad (19)$$

$$\frac{d {}^m\text{OA}}{dt} = {}^m\text{CA} \cdot \alpha_{C-O} + {}^m\text{OI} \cdot \beta_{A-I} - {}^m\text{OA} \cdot (\beta_{C-O} + \alpha_{A-I}) \quad (20)$$

$$\frac{d {}^m\text{CI}}{dt} = {}^m\text{OI} \cdot \beta_{C-O} + {}^m\text{C} \cdot \alpha_{A-I} - {}^m\text{CI} \cdot (\alpha_{C-O} + \beta_{A-I}) \quad (21)$$

$$\frac{d {}^m\text{OI}}{dt} = {}^m\text{CI} \cdot \alpha_{C-O} + {}^m\text{OA} \cdot \alpha_{A-I} - {}^m\text{OI} \cdot (\beta_{C-O} + \beta_{A-I}) \quad (22)$$

Where:

$$\alpha_{C-O} = k_a \left( {}^m[\text{Ca}^{2+}]_{ds} \right)^H \quad (23)$$

$$\beta_{C-O} = k_b \quad (24)$$

$$\alpha_{A-I} = (1 - {}^m\text{Mi}_{ss}) / \tau_{\text{Mi},1} \quad (25)$$

$$\beta_{A-I} = {}^m\text{Mi}_{ss} / \tau_{\text{Mi},2} \quad (26)$$

$${}^m\text{Mi}_{ss} = 1 / \left( 1 + e^{({}^mM - 0.5) / 0.04167} \right) \quad (27)$$

$$\frac{dM}{dt} = \alpha_M (1 - M) + \beta_M M \quad (28)$$

$$\alpha_M = M_{ss} / \tau_{M,1} \quad (29)$$

$$\beta_M = (1 - M_{ss}) / \tau_{M,2} \quad (30)$$

$$M_{ss} = 1 / (1 + e^{(-6.5 \cdot (csqn - 6.37))}) \quad (31)$$

$$csqn = B_{csqn} \cdot K_{mcsqn} / \left( {}^m[\text{Ca}^{2+}]_{jSR} + K_{mcsqn} \right) \quad (32)$$

In this model,  $OA$  is the only state in which a flux occurs. Thus,  ${}^m n_{o\_RyR}$  is equal to the number of channels in dyad  $m$  which are in state  $OA$  (red text in schematic).

### L-type $Ca^{2+}$ channel flux, $J_{CaL}$

The flux through the L-type Calcium Current is defined as:

$${}^m J_{CaL} = -{}^m n_{o\_LTCC} {}^m \bar{J}_{CaL} \quad (33)$$

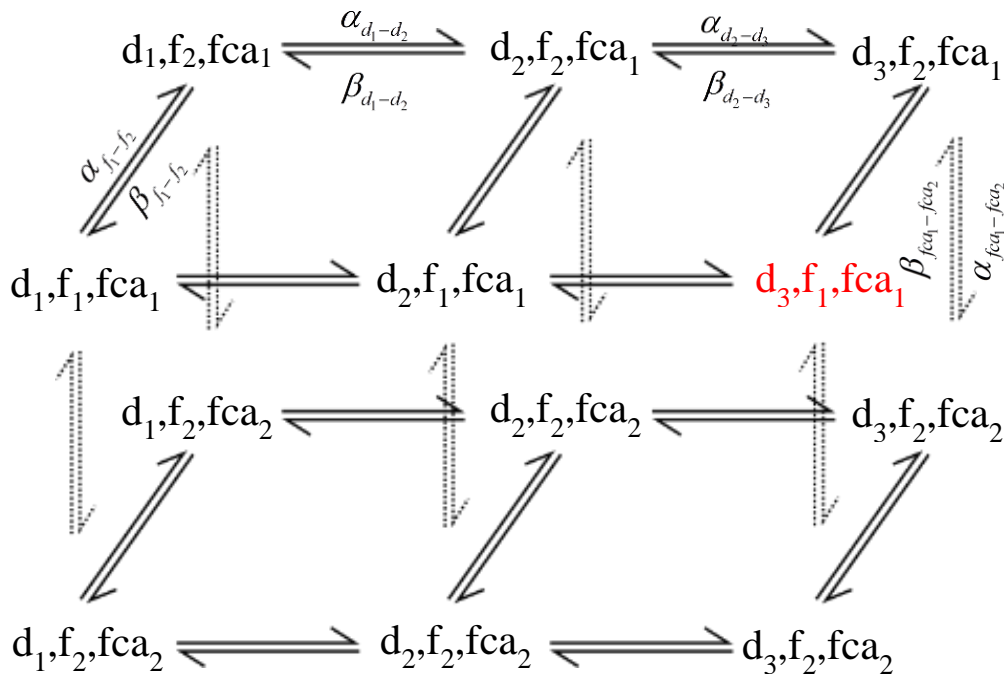
Where  ${}^m n_{o\_LTCC}$  is the number of open LTCC channels in dyad  $m$  (defined below) and  $\bar{J}_{CaL}$  is the maximal flux rate per channel [6]:

$${}^m \bar{J}_{CaL} = 4P_{Ca} zF \frac{\frac{1}{2} \gamma_{Ca} {}^m [Ca^{2+}]_{ds} e^{2z} - \gamma_{Ca} [Ca^{2+}]_o}{e^{2z} - 1} \quad (34)$$

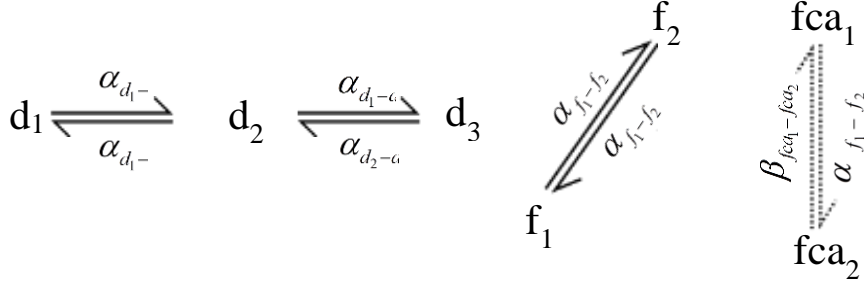
$$z = \frac{V_m F}{RT} \quad (35)$$

Where  $[Ca^{2+}]_o$  is the extracellular  $Ca^{2+}$  concentration,  $P_{Ca}$  is the maximum permeability of an individual LTCC and  $F$  is the Faraday constant.

The LTCCs are described by a Markov Chain construction of a Hodgkin-Huxley model [6,7]



Which is equivalent to the three gate Hodgkin-Huxley model:



And thus described by:

$$\frac{d(d_1)}{dt} = d_2 \beta_{d_1-d_2} - d_1 \alpha_{d_1-d_2} \quad (36)$$

$$\frac{d(d_2)}{dt} = d_1 \alpha_{d_1-d_2} + d_3 \beta_{d_2-d_3} - d_2 (\beta_{d_1-d_2} + \alpha_{d_2-d_3}) \quad (37)$$

$$\frac{d(d_3)}{dt} = d_2 \alpha_{d_2-d_3} - d_3 \beta_{d_2-d_3} \quad (38)$$

$$\frac{d(f_1)}{dt} = f_2 \beta_{f_1-f_2} - f_1 \alpha_{f_1-f_2} \quad (39)$$

$$\frac{d(fca_1)}{dt} = fca_2 \beta_{fca_1-fca_2} - fca_1 \alpha_{fca_1-fca_2} \quad (40)$$

Where the transition rates for each variable couplet, ( $x = d_1-d_2, f_1-f_2, fca_1-fca_2$ ) are defined from the steady-state and time constant in the standard way:

$$\alpha_x = x_{ss} / \tau_x \quad (41)$$

$$\beta_x = (1 - x_{ss}) / \tau_x \quad (42)$$

And:

$$\alpha_{d_2-d_3} = k_{d2d3} \quad (43)$$

$$\beta_{d_2-d_3} = k_{d3d2} \quad (44)$$

$$d_{ss} = 1 / \left( 1 + e^{(-(V_m - 5)/6.24)} \right) \quad (45)$$

$$f_{ss} = 1 - 1 / \left( 1 + e^{((V_m + 32.06)/8.6)} \right) \quad (46)$$

$$\tau_d = d_{ss} \cdot \left( 1 - e^{(-(V_m - 5)/6.24)} \right) / (0.035(V_m - 5)) \quad (47)$$

$$\tau_f = 2 / \left( 0.0197 e^{-([0.0337(V_m + 7)]^2 + 0.02)} \right) \quad (48)$$

$$fca_{ss} = 1 - 1 / \left( 1 + \left( {}^m[Ca^{2+}]_{ds} / \bar{Ca} \right)^2 \right) \quad (49)$$



Note that the steady states of the inactivation gates ( $f, f_{ca}$ ) are inverse to those in the standard Hodgkin-Huxley model because in this Markov description  $f_2$  is the inactivated state, equivalent to  $(1-f)$  in the standard description (and  $f_1$  is equivalent to  $f$ ).

**Table S3: RyR and LTCC flux parameters**

Parameter	Description	Value
$g_{Rr}$	Maximal flux rate through the RyRs	$2.05 \times 10^{-4} \mu\text{m}^3 \text{ms}^{-1}$
$P_{Ca}$	Maximum permeability of LTCC	$11.9 \mu\text{mol C}^{-1} \text{ms}^{-1}$
$\gamma_{Ca}$	Activity Coefficient LTCC	0.341
$N_{RyR}$	Number of RyRs per dyad*	100
$H$	RyR Open rate $\text{Ca}^{2+}$ power	2.5
$k_a$	RyR activation rate constant	$1.58 \times 10^{-4} \mu\text{M}^{-2.5} \text{ms}^{-1}$
$k_b$	RyR deactivation rate constant	$1.0 \text{ms}^{-1}$
$\tau_{M,1}$	Time constant of monomer binding	25 ms
$\tau_{Mi,1}$	Time constant of monomer inactivation	30 ms
$\tau_{M,2}$	Time constant monomer unbinding	156 ms
$\tau_{Mi,2}$	Time constant of de-inactivation	75 ms
$N_{LTCC}$	Number of L-type $\text{Ca}^{2+}$ channels per dyad*	15
$k_{d2d3}$	Rate constant for transition $d_2-d_3$	$0.3 \text{ms}^{-1}$
$k_{d3d2}$	Rate constant for transition $d_3-d_2$	$6.0 \text{ms}^{-1}$
$\tau_{fca}$	Time constant for $\text{Ca}^{2+}$ induced inactivation	15 ms
$\bar{Ca}$	$\text{Ca}^{2+}$ constant for $\text{Ca}^{2+}$ induced inactivation	$6.0 \mu\text{M}$
$[Ca^{2+}]_o$	Extracellular $\text{Ca}^{2+}$ concentration	1.8 mM

#### Intracellular uptake and leak, $J_{up}$ and $J_{leak}$

These equations are based on Restrepo et al [4] and preceding studies [8,9].

$${}^m J_{up} = g_{up} \frac{\left( {}^m [Ca^{2+}]_i / K_{cyto} \right)^2 - \left( {}^m [Ca^{2+}]_{nSR} / K_{nSR} \right)^2}{1 + \left( {}^m [Ca^{2+}]_i / K_{cyto} \right)^2 + \left( {}^m [Ca^{2+}]_{nSR} / K_{nSR} \right)^2} \quad (50)$$

$${}^m J_{leak} = g_{leak} \frac{{}^m [Ca^{2+}]_{nSR}^2}{{}^m [Ca^{2+}]_{nSR}^2 + K_{leak}^2} \left( {}^m [Ca^{2+}]_{nSR} - {}^m [Ca^{2+}]_i \right) \quad (51)$$

**Table S4:  $\text{Ca}^{2+}$  uptake and leak parameters**

Parameter	Description	Value
$g_{up}$	Maximal flux rate of $J_{up}$	$0.339 \mu\text{M} \cdot \text{ms}^{-1}$
$K_{cyto}$	Cytoplasm constant for $J_{up}$	$0.15 \mu\text{M}$
$K_{nSR}$	Network SR constant for $J_{up}$	$1700 \mu\text{M}$
$g_{leak}$	Maximal flux rate of $J_{leak}$	$1.412 \times 10^{-5} \text{ms}^{-1}$
$K_{leak}$	$J_{leak}$ constant	$450 \mu\text{M}$

### Membrane fluxes, $J_{NaCa}$ , $J_{pCa}$ and $J_{CaB}$

These equations are based on Restrepo et al [4] and preceding studies [8,9].

$${}^m J_{NaCa} = \frac{K_a g_{NaCa} v_{vox}^{-1} \left( e^{\eta z} [Na^+]_i [Ca^{2+}]_o - e^{(\eta-1)z} [Na^+]_o {}^m [Ca^{2+}]_{cyto} \right)}{(t_1 + t_2 + t_3)(1 + K_{sat} e^{(\eta-1)z})} \quad (52)$$

$${}^m J_{pCa} = \left( v_i^{-1} g_{pCa} {}^m [Ca^{2+}]_i \right) / \left( K_{mpCa} + {}^m [Ca^{2+}]_i \right) \quad (53)$$

$${}^m J_{CaB} = v_{vox}^{-1} g_{CaB} (V_m - E_{r,Ca}) \quad (54)$$

Where

$$t_1 = K_{mCai} [Na^+]_o^3 \left( 1 + \left( [Na^+]_i / K_{mNai} \right)^3 \right) \quad (55)$$

$$t_2 = K_{mNao}^3 {}^m [Ca^{2+}]_i \left( 1 + \left( {}^m [Ca^{2+}]_i / K_{mCai} \right) \right) \quad (56)$$

$$t_3 = K_{mCao} [Na^+]_i^3 + [Na^+]_i^3 [Ca^{2+}]_o + [Na^+]_o^3 {}^m [Ca^{2+}]_i \quad (57)$$

$$K_a = \left[ 1 + \left( K_{da} / {}^m [Ca^{2+}]_i \right) \right] \quad (58)$$

$$z = \frac{V_m F}{RT} \quad (59)$$

**Table S5: Membrane flux parameters**

Parameter	Description	Value
$g_{NaCa}$	Maximal flux rate of Sodium-Ca <sup>2+</sup> exchanger	0.3726 $\mu\text{m}^3 \cdot \mu\text{M} \cdot \text{ms}^{-1}$
$K_{da}$	Ca <sup>2+</sup> scaling constant	0.11 $\mu\text{M}$
$\eta$	Voltage sensitivity coefficient	0.35
$K_{sat}$	Saturation constant	0.27
$K_{mcai}$	Intracellular Ca <sup>2+</sup> constant	3.59 $\mu\text{M}$
$K_{mcao}$	Extracellular Ca <sup>2+</sup> constant	1.3 mM
$K_{mmai}$	Intracellular Na <sup>+</sup> constant	12.3 mM
$K_{mmao}$	Extracellular Na <sup>+</sup> constant	87.5 mM
$g_{pca}$	Maximal flux rate of PMCA Ca <sup>2+</sup> pump	1.37 x10 <sup>-3</sup> $\mu\text{m}^3 \cdot \mu\text{M} \cdot \text{ms}^{-1}$
$g_{cab}$	Maximal flux rate of background Ca <sup>2+</sup> current	1.82 x10 <sup>-5</sup> $\mu\text{m}^3 \cdot \mu\text{M} \cdot \text{ms}^{-1} \cdot \text{mV}^{-1}$
$[Na^+]_i$	Intracellular Na <sup>+</sup> concentration	7.95 mM
$[Na^+]_o$	Extracellular Na <sup>+</sup> concentration	136 mM

## Ca<sup>2+</sup> Buffering

### Instantaneous buffering in the cytoplasm

Instantaneous buffering in the cytoplasm follows that of previous models, e.g., Restrepo et al [4] and Nivala et al. [10], based on [11]. At each voxel,  $n$ , the buffering term is given by:

$${}^m\beta_{cyto} = \left[ 1 + \sum_x \frac{B_x K_x}{\left( {}^m[Ca^{2+}]_{cyto} + K_x \right)^2} \right]^{-1} \quad (60)$$

Where  $x$  refers to four buffering processes: Calmodulin, SR sites, Myosin (Ca) and Myosin (Mg).

### Instantaneous buffering in the jSR

Buffering in the jSR follows that of the previous study Gaur-Rudy [5]:

$${}^m\beta_{jSR} = \left[ 1 + \frac{B_{csqn} K_{mcsqn}}{\left( {}^m[Ca^{2+}]_{jSR} + K_{mcsqn} \right)^2} \right]^{-1} \quad (61)$$

### Troponin buffering and force

Troponin buffering and force generation is from the Gauthier et al model [12,13]:

$${}^nJ_{trpn} = \frac{dH_{trpn,Ca}}{dt} + \frac{dL_{trpn,Ca}}{dt} \quad (62)$$

$$\frac{d{}^nH_{trpn,Ca}}{dt} = k_{H,trpn}^+ {}^n[Ca^{2+}]_{cyto} (B_{H,trpn} - H_{trpn,Ca}) - k_{H,trpn}^- H_{trpn,Ca} \quad (63)$$

$$\frac{d{}^nL_{trpn,Ca}}{dt} = k_{L,trpn}^+ {}^n[Ca^{2+}]_{cyto} (B_{L,trpn} - L_{trpn,Ca}) - k_{L,trpn}^- \left( 1 - \frac{2}{3} F_{norm} \right) L_{trpn,Ca} \quad (64)$$

Where  $F_{norm}$  is the normalised force:

$$F_{norm} = \left( \frac{P_1 + N_1 + 2P_2 + 3P_3}{P_1^{\max} + 2P_2^{\max} + 3P_3^{\max}} \right) \quad (65)$$

And:

$$\phi = 1 + \frac{2.3 - SL}{(2.3 - 1.7)^{1.6}} \quad (66)$$

$$f_{01} = 3f_{XB} \quad (67)$$

$$f_{12} = 10f_{XB} \quad (68)$$

$$f_{23} = 7f_{XB} \quad (69)$$

$$g_{01} = g_{XB} \quad (70)$$

$$g_{12} = 2g_{XB} \quad (71)$$

$$g_{23} = 3g_{XB} \quad (72)$$

$$g_{01,SL} = 1\phi g_{XB,\min} \quad (73)$$

$$g_{12,SL} = 2\phi g_{XB,\min} \quad (74)$$

$$g_{23,SL} = 3\phi g_{XB,\min} \quad (75)$$

$$K_{TRPN}^{Ca} = \frac{k_{L,TRPN}^-}{k_{L,TRPN}^+} \quad (76)$$

$$N_{TRPN} = 3.5SL - 2.0 \quad (77)$$

$$K_{1/2}^{TRPN} = \left[ 1 + \frac{K_{TRPN}^{Ca}}{1.4 \times 10^{-3} - 8 \times 10^{-4} ((SL - 1.7)/0.6)} \right]^{-1} \quad (78)$$

$$k_{np,TRPN} = k_{pn,TRPN} \left( \frac{\left[ \frac{TRPN_{Ca}^L}{K_{1/2}^{TRPN}} \right]^{N_{TRPN}}}{K_{1/2}^{TRPN} TRPN_{tot}^L} \right) \quad (79)$$

$$\sum Paths = g_{01}g_{12}g_{23} + f_{01}g_{12}g_{23} + f_{01}f_{12}g_{23} + f_{01}f_{12}f_{23} \quad (80)$$

$$P_1^{\max} = \frac{f_{01}g_{12}g_{23}}{\sum Paths} \quad (81)$$

$$P_2^{\max} = \frac{f_{01}f_{12}g_{23}}{\sum Paths} \quad (82)$$

$$P_3^{\max} = \frac{f_{01}f_{12}f_{23}}{\sum Paths} \quad (83)$$

$$\frac{dP_0}{dt} = -(k_{pn,TRPN} + f_{01})P_0 + k_{np,TRPN}N_0 + g_{01,SL}P_1 \quad (84)$$

$$\frac{dP_1}{dt} = -(k_{pn,TRPN} + f_{12} + g_{01,SL})P_1 + k_{np,TRPN}N_1 + f_{01}P_0 + g_{12,SL}P_1 \quad (85)$$

$$\frac{dP_2}{dt} = -(f_{23} + g_{12,SL})P_2 + f_{12}P_1 + g_{23,SL}P_3 \quad (86)$$

$$\frac{dP_3}{dt} = -g_{23,SL}P_3 + f_{23,SL}P_2 \quad (87)$$

$$\frac{dN_1}{dt} = k_{pn,TRPN}P_1 - (k_{np,TRPN} + g_{01,SL})N_1 \quad (88)$$

$$\frac{dN_0}{dt} = \frac{dP_0}{dt} - \frac{dP_1}{dt} - \frac{dP_2}{dt} - \frac{dP_3}{dt} - \frac{dN_1}{dt} \quad (89)$$

**Table S6: Ca<sup>2+</sup> buffering parameters**

Parameter	Description	Value
$K_{CAM}$	Dissociation constant for calmodulin	7.0 $\mu\text{M}$
$B_{CAM}$	Total concentration buffering sites	24.0 $\mu\text{M}$
$K_{SR}$	Dissociation constant for SR sites	0.6 $\mu\text{M}$
$B_{SR}$	Total concentration buffering sites	47.0 $\mu\text{M}$
$K_{M,Ca}$	Dissociation constant for Myosin (Ca)	0.033 $\mu\text{M}$
$B_{M,Ca}$	Total concentration buffering sites	140.0 $\mu\text{M}$
$K_{M,Mg}$	Dissociation constant for Myosin (Mg)	3.64 $\mu\text{M}$
$B_{M,Mg}$	Total concentration buffering sites	140 $\mu\text{M}$
$K_{mcqn}$	Dissociation constant for csqn	0.8 mM
$B_{csqn}$	Total concentration buffering sites	10 mM
$k_{+H, trpn}$	On rate for troponin high affinity sites	100 mM <sup>-1</sup> ms <sup>-1</sup>
$k_{-H, trpn}$	Off rate for troponin high affinity sites	1.0 x10 <sup>-3</sup> ms <sup>-1</sup>
$k_{+L, trpn}$	On rate for troponin low affinity sites	100 mM <sup>-1</sup> ms <sup>-1</sup>
$k_{-L, trpn}$	Off rate for troponin low affinity sites	4.0 x 10 <sup>-2</sup> ms <sup>-1</sup>
$B_{H, trpn}$	Total high affinity sites on troponin	0.14 mM
$B_{L, trpn}$	Total low affinity sites on troponin	0.7 mM
$f_{XB}$	Weak to strong cross bridge transition rate	0.05 ms <sup>-1</sup>
$g_{XB, min}$	Maximum strong to weak rate	0.1 ms <sup>-1</sup>
$SL$	Sarcomere length	2.15 $\mu\text{m}$
$K_{pn, TRPN}$	Permissive to non-permissive transition rate	0.04 ms <sup>-1</sup>

## 2. The 0D, deterministic model

Except for the RyR, the deterministic model comprises the same components as the 3D cell model for one CRU, with the LTCC dynamics solved by the forward-Euler method. However, due to the poor capitulation of CICR by deterministic solutions to the RyR model, adjustments were performed: The dyadic Ca<sup>2+</sup> concentration seen by the RyRs was solved to be dependent only on  $I_{CaL}$ , allowing more continuous behaviour in RyR opening, and  $k_a$  set to  $2.37 \times 10^{-3} \mu\text{M}^{-2.5} \text{ms}^{-1}$ . The open transition rate is therefore given as:

$$\alpha_{C-O} = k_a \left( {}^n [Ca^{2+}]_{SS} + \tau_{ds} \cdot {}^n J_{CaL} \right)^H \quad (90)$$

## 3. Hybrid-minimal AP model

The hybrid-minimal model was designed to give a controllable AP while maintaining physiological ion current magnitudes for integration with the calcium dependent currents of the 3D and 0D calcium handling models. In addition to the calcium currents, the model comprises:

Phase-0 depolarising current ( $I_{p0d}$ ): modelled exactly the same as the LRd  $I_{Na}$  formulation [6].

Phase-1 repolarising current ( $I_{p1r}$ ):

$$I_{p1r} = g_{p1r} \cdot va_{p1r} \cdot vi_{p1r} \cdot (V_m + 88) \quad (91)$$

$$va_{p1r_{ss}} = 1 / \left( 1 + e^{-(V_m - 1)/11.0} \right) \quad (92)$$

$$vi_{p1r_{ss}} = 1 / \left( 1 + e^{(V_m + 40)/11.5} \right) \quad (93)$$

$$va_{p1r_{\tau}} = 3.5e^{-(V_m/30)^2} + 1.5 \quad (94)$$

$$va_{p1r_{\tau}} = 25.6e^{-(V_m + 52)/15)^2} + 14 \quad (95)$$

Phase-2 repolarising current ( $I_{p2r}$ ):

$$I_{p2r} = g_{p2r} \cdot va_{p2r} \cdot vi_{p2r} \cdot (V_m + 88) \quad (96)$$

$$va_{p2r\_ss} = 1 / \left( 1 + e^{-(V_m + 6)/8.6} \right) \quad (97)$$

$$vi_{p2r\_ss} = 1 / \left( 1 + e^{(V_m + 7.5)/10} \right) \quad (98)$$

$$va_{p2r\_t} = 9e^{-(V_m + 5)/12} + 0.5 \quad (99)$$

$$va_{p2r\_t} = 590e^{-(V_m + 60)/10} + 3000 \quad (100)$$

Phase-3 repolarising current ( $I_{p3r}$ ):

$$I_{p3r} = g_{p3r} \cdot va_{p3r} \cdot vti_{p3r} \cdot (V_m + 88) \quad (101)$$

$$va_{p3r\_ss} = 1 / \left( 1 + e^{-(V_m + 14)/6.5} \right) \quad (102)$$

$$vti_{p3r} = 1 / \left( 1 + e^{(V_m + 15)/22.4} \right) \quad (103)$$

$$va_{p3r\_a} = 0.0003(V_m + 14) / \left( 1 + e^{-(V_m + 14)/5} \right) \quad (104)$$

$$va_{p3r\_b} = 0.000074(V_m - 3.3) / \left( e^{-(V_m - 3.3)/5} - 1 \right) \quad (105)$$

$$va_{p3r\_t} = 1 / \left( va_{p3r\_a} + va_{p3r\_b} \right) \quad (106)$$

Phase-4 repolarising current ( $I_{p4r}$ ):

$$I_{p4r} = g_{p4r} \cdot \left( 1 + 0.07e^{(V_m + 80)} \right)^{-1} \cdot (V_m + 88) \quad (107)$$

**Table S7: Minimal model heterogeneity parameters**

Parameter	Vent EPI	Vent M	Vent ENDO	Atria RA
$g_{p0d}$ (s/mF)	16	16	16	16
$g_{p1r}$ (s/mF)	0.081	0.081	0.081	0.289
$g_{p2r}$ (s/mF)	0.0034	0.0034	0.0034	0.0204
$g_{p3r}$ (s/mF)	0.05	0.03	0.045	0.0125
$g_{p4r}$ (s/mF)	0.3	0.3	0.3	0.15

## 4. Non-specific remodelling and ISO models

Representative (but non-specific) models were included for isoprenaline (ISO, sympathetic response which enhances CICR) and two types of pro-SCRE general disease remodelling mimicking features observed in conditions such as AF and HF: (i) SERCA was up-regulated and NCX was down-regulated ( $R_{SERCA/NCX}$ ); (ii) the SR- $Ca^{2+}$  threshold for release was lowered through increased inter-CRU coupling ( $R_{CRU-CRU}$ ).

Remodelling 1 – “ $R_{\text{SERCA/NCX}}$ ”:

**Table S8: Scaling factors and voltage shifts for remodelling model  $R_{\text{SERCA/NCX}}$**

Parameter	EPI	ENDO	M	RA	ORD	Col
$g_{\text{K1}}/g_{\text{p4r}}$	0.5	0.5	0.5	0.25	0.5	0.5
$I_{\text{K1}}$ V-shift	10 mV	10 mV	10 mV	10 mV	10 mV	10 mV
$g_{\text{CaL}}$	0.5	0.5	0.5	2	0.5	0.5
$g_{\text{Kr}}/g_{\text{p3r}}$	1.5	1.5	1.5	0.5	0.666	1.5
$g_{\text{Na}}/g_{\text{p0d}}$	0.5	0.5	0.5	0.5	0.5	0.5
$I_{\text{NCX\_max}}$	0.5	0.5	0.5	0.5	0.5	0.5
$J_{\text{up\_max}}$	1.5	1.5	1.5	1.5	1.25	1.5

Remodelling 2 – “ $R_{\text{CRU-CRU}}$ ” simply involved setting the time constants of sub-space coupling to 1.0 and 1.5 ms.

ISO:

**Table S9: Scaling factors ISO model**

Parameter	EPI	ENDO	M	RA	ORD	Col
$g_{\text{to}}/g_{\text{p1r}}$	1	1	1	1.5	1	1.5
$g_{\text{Kur}}/g_{\text{p2r}}$	2	2	2	1.5	1	1.5
$g_{\text{k}}/g_{\text{p3r}}$	2	2	2	1	2	1.5
$J_{\text{up\_max}}$	2	2	2	1.2	1.75	1.7
$I_{\text{CaL}} - k_{\text{d2d3}}$	2	2	2	2	2	2

## 5. Tissue models

Tissue simulations were performed using the homogeneous, isotropic approximation to the monodomain equation describing spatial coupling of the membrane potential:

$$\mathbf{D} \nabla^2 {}^i V_m \approx \frac{D}{\Delta x^2} \sum_{i=1}^{i=3} \left( {}^{e_i+1} V_m + {}^{e_i-1} V_m - 2 {}^i V_m \right) \quad (108)$$

Where  ${}^i V_m$  is the membrane potential at the relevant cell, the subscript  $i$  refers to the three spatial-dimensions,  $D$  is the isotropic diffusion coefficient,  $\Delta x$  is the spatial step and  $\nabla^2$  is the spatial Laplacian operator in 3D.

The basic 2D idealised tissue model, used for analysis of the emergence of focal excitation and the impact of SCRE variability on the focal-SR- $\text{Ca}^{2+}$  relationship, comprised a grid of  $100 \times 100$  cells with a spatial resolution of 0.2 mm and an isotropic diffusion coefficient,  $D$ , of  $0.1 \text{ mm}^2/\text{ms}$ , giving a conduction velocity of 0.56 m/s. Re-entrant (and matched pacing) simulations were performed in a larger tissue model of either  $200 \times 200$  or  $400 \times 400$  cells, at a spatial resolution of 0.25 mm.  $D$  ranged from  $0.1 \text{ mm}^2/\text{ms}$  (control) to  $0.05 \text{ mm}^2/\text{ms}$  (most reduced), giving conduction velocities of 0.54-0.34 m/s. The idealised model of the heterogeneous ventricular transmural strand, used in the investigation of SCRE and conduction block, comprised a sheet of  $200 \times 100$  cells, with heterogeneity evenly distributed in the x-direction (ratio of 1:1:1 ENDO:M:EPI); the remaining parameters were identical to the basic sheet described above.

Parameters for the anatomically detailed tissue models are as follows: (1) human ventricular wedge reconstruction – spatial step = 0.3 mm,  $D = 0.04 \text{ mm}^2/\text{ms}$  and conduction velocity = 0.26 m/s; (2) whole canine ventricle – spatial step = 0.5 mm,  $D = 0.1 \text{ mm}^2/\text{ms}$  and conduction velocity = 0.39 m/s; (3) whole human atria – spatial step = 0.33 mm,  $D = 0.3 \text{ mm}^2/\text{ms}$  and conduction velocity = 0.98 m/s. All conduction velocities were calculated using the hybrid minimal cell model.

## 6. Spontaneous release functions

### RyR waveforms

The  $N_{RyR\_O}$  waveforms can be grouped into two primary types: spike-like associated with short, large-amplitude release, and plateau-like associated with long, small-amplitude release. For the spike-like morphology, the waveform can be well approximated with the simple function:

$$N_{RyR\_O} = N_{RyR\_O}^{peak} \left[ \left( 1 + e^{-(t-t_1)/k_1} \right) \left( 1 + e^{-(t-t_2)/k_2} \right) \right]^{-1} \quad (109)$$

$$t_1 = t_i + 0.5(t_p - t_i) \quad (110)$$

$$t_2 = t_p + 0.5(t_f - t_p) \quad (111)$$

$$k_1 = 0.1689(t_p - t_i) + 0.00255 \quad (112)$$

$$k_2 = 0.1689(t_f - t_p) + 0.00255 \quad (113)$$

where  $t_i$  is the initiation time of the SCORE,  $t_f$  is the end time (duration,  $\lambda$ , thus  $= t_f - t_i$ ),  $t_p$  is the time of the peak of the waveform and  $N_{RyR\_O}^{peak}$  is the peak of open proportion RyR. The function for the plateau-like waveform (corresponding to durations longer than 300 ms) is derived from the same parameters:

$$N_{RyR\_O} = N_{RyR\_O}^{plateau} \left[ \left( 1 + e^{-(t-(t_i+17.5))/5.946} \right) \left( 1 + e^{(t-(t_f-17.5))/5.946} \right) \right]^{-1} + \left( N_{RyR\_O}^{peak} - N_{RyR\_O}^{plateau} \right) \left[ \left( 1 + e^{-(t-(t_p-25))/5.946} \right) \left( 1 + e^{(t-(t_p+17.5))/5.946} \right) \right]^{-1} \quad (114)$$

Where  $N_{RyR\_O}^{plateau}$  is the amplitude of the plateau. This equation assumes the same form for the spike occurring within the plateau, with its upstroke time being 50 ms and its decay time 35ms;  $t_i^{spike}$  therefore corresponds to  $t_p - 50$  (and its half maximal activation time  $t_p - 25$ ).

The waveform is therefore completely described by four-five parameters: (1) initiation time,  $t_i$ ; (2) duration ( $\lambda = t_f - t_i$ ); (3) peak time,  $t_p$ ; and (4-5) amplitude ( $N_{RyR\_O}^{peak}$ ,  $N_{RyR\_O}^{plateau}$ ). In order to maintain physiological waveforms and randomly sample the parameter values from appropriate distributions, the nature of stochastic variation of these four parameters is discussed below.

### Parameter distributions

(1) -  $t_i$ : The probability density functions for the initiation time associated with each SR- $Ca^{2+}$  value do not demonstrate a normal distribution, but rather a skewed distribution. The cumulative frequency is well approximated by the use of two simple sigmoidal functions, maintaining the desire for restraint in the number of parameters and allowing simple and intuitive controllability:

$$F(t_i) = \begin{cases} F_1(t_i) = \left( 2CF_{t_i, Sep} \right) \left( 1 + e^{-(t_i - t_{i, sep})/k_{F1}} \right)^{-1} & t_i < t_{i, Sep} \\ F_2(t_i) = \left( 2(1 - CF_{t_i, Sep}) \right) \left( 1 + e^{-(t_i - t_{i, sep})/k_{F2}} \right)^{-1} - 1 + 2CF_{t_i, Sep} & t_i \geq t_{i, Sep} \end{cases} \quad (115)$$

The distribution for  $t_i$  is therefore determined by four parameters: the initiation time corresponding to the point where the functions are separated ( $t_{i, Sep}$ ); the cumulative frequency at this point ( $CF_{t_i, Sep} = F(t_i) |_{t_i = t_{i, Sep}}$ ), and the gradient parameter of each function ( $k_{F1}$ ,  $k_{F2}$  - corresponding to the width of the distribution either side of  $t_{i, Sep}$ ).



(2) -  $\lambda$ : The distributions for the duration are also non-normal, and well approximated by two sigmoidal functions describing the cumulative frequency for half of the data either side of the median duration ( $MD$ ):

$$F(MD) = \begin{cases} F_{D1}(MD) = \left(1 + e^{-(\lambda - MD)/0.261DW_1}\right)^{-1} & \lambda < MD \\ F_{D2}(MD) = \left(1 + e^{-(\lambda - MD)/0.261DW_2}\right)^{-1} & \lambda \geq MD \end{cases} \quad (116)$$

Where the widths ( $DW_1, DW_2$ , in ms) are a function of the  $MD$ , given by:

$$DW_1 = A_{DW1} \left(1 + e^{-(MD - a_{DW1})/k_{DW1}}\right)^{-1} + DW_1^{\min} \quad (117)$$

$$DW_2 = A_{DW2} \left(1 + e^{-(MD - a_{DW2})/k_{DW2}}\right)^{-1} + DW_2^{\min} \quad (118)$$

Default parameters are given in Table S10. The duration distribution is therefore completely described by the median,  $MD$ . Note that the widths ( $DW_1, DW_2$ ) could also be specified directly for complete control over the variability in duration. Note also that, at individual conditions (such as SR- $\text{Ca}^{2+}$  concentration) there is no strong correlation between  $t_i$  and  $\lambda$  and thus it is reasonable to sample these parameters independently (Figure S1).

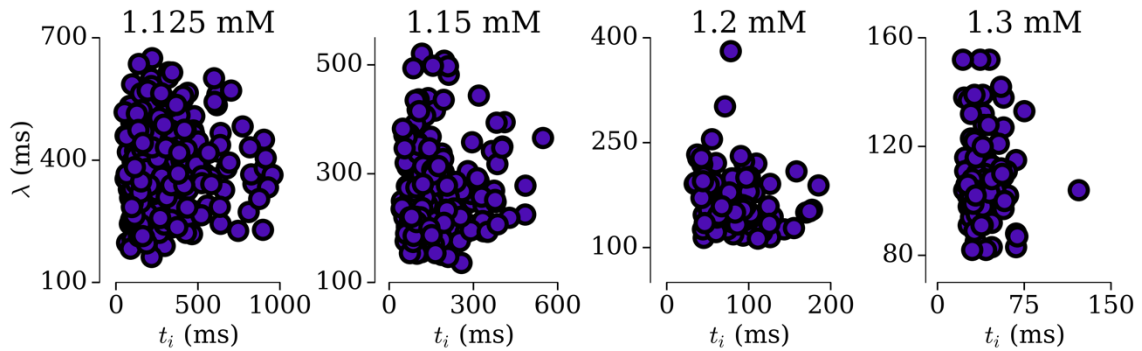
(3) -  $t_p$ : The timing of the peak varies approximately evenly within the duration of the waveform, occurring between 25 ms after the initiation ( $t_i$ ) and 52 ms before the final time ( $t_f$ ).

(4) -  $N_{\text{RyR}_O}^{\text{peak}}, N_{\text{RyR}_O}^{\text{plateau}}$ : The amplitude correlates strongly with duration,  $\lambda$ :

$$\langle N_{\text{RyR}_O}^{\text{peak}} \rangle = 692.99\lambda^{-1.6} + 0.059 \quad (119)$$

$$\langle N_{\text{RyR}_O}^{\text{plateau}} \rangle = 31.09(0.01\lambda)^{-7.39} + 0.034 \quad \text{if } \lambda > 300\text{ms} \quad (120)$$

With small variance ( $\pm 0.025; \pm 0.125N_{\text{RyR}_O}^{\text{plateau}}$ ). Note that it would not be appropriate to define the amplitude independently from the duration, due to the correlation between these two parameters corresponding to the total amount of  $\text{Ca}^{2+}$  released.



**Figure S1: Independence of  $t_i$  and  $\lambda$  parameters.**  $t_i$  and  $\lambda$  plotted against each other for distributions emerging at multiple SR- $\text{Ca}^{2+}$  concentrations (panel titles). Note that while the distributions are not normal, the two parameters exhibit no strong correlation to each other.

## The Direct Control SRF model

With this setup, therefore, all parameters of the waveform are derived from two primary waveform properties: the initiation time,  $t_i$ , and the duration,  $\lambda$ , which also determine the peak time and amplitude; the distributions describing the variability of these properties is entirely described by 5-7 parameters ( $t_i = f(t_{i\_sep}, CF_{t_{i\_sep}}, k_{F1}, k_{F2})$ ;  $\lambda = f(MD, DW_1, DW_2)$  where  $DW_1, DW_2 = f(MD)$  or specified). For the simplest implementation of SCORE in 0D models, the user Direct Control model, SRF variability and morphology can therefore be described by simply defining these 5-7 parameters (as well as a probability of SCORE) in order to reproduce single conditions (for example, fit to a single dataset).

## The Dynamic Fit SRF model

The Dynamic Fit SRF model was derived through correlation of the parameters defining the  $t_i$  and  $\lambda$  distributions with the primary environment variable controlling SCORE: the SR- $Ca^{2+}$  concentration (Figure S2). Relation to this single variable was chosen for practicality and simplicity of the resulting equations, which is in particularly valuable for reproducing variable  $Ca^{2+}$  handling system states.

The probability that an SCORE occurs at a given SR- $Ca^{2+}$  is well-approximated by a sigmoidal function:

$$P(SCR) = \left( 1 + e^{-([Ca^{2+}]_{SR} - SCR_{threshold})/k_{P(SCR)}} \right)^{-1} \quad (121)$$

The SR- $Ca^{2+}$  dependence of  $t_{i\_sep}$  and  $CF_{t_{i\_sep}}$  can be approximated by the following functions:

$$t_{i\_sep} = A_{t_{i\_sep}} e^{-([Ca^{2+}]_{SR} - a_{t_{i\_sep}})/k_{t_{i\_sep}}} + t_{i\_sep}^{\min} \quad (122)$$

$$CF_{t_{i\_sep}} = A_{CF} \left( 1 + e^{-([Ca^{2+}]_{SR} - a_{CF})/k_{CF}} \right)^{-1} + 0.05 \quad (123)$$

The gradient parameters for  $F_1(t_i)$  and  $F_2(t_i)$ ,  $k_{F1}$  and  $k_{F2}$ , are then approximated by the following functions:

$$k_{F1} = A_{k_{F1}} e^{-([Ca^{2+}]_{SR} - a_{k_{F1}})/k_{k_{F1}}} + k_{F1}^{\min} \quad (124)$$

$$k_{F2} = A_{k_{F2}} [Ca^{2+}]_{SR}^{H1_{k_{F2}}} + B_{k_{F2}} [Ca^{2+}]_{SR}^{H2_{k_{F2}}} + k_{F2}^{\min} \quad (125)$$

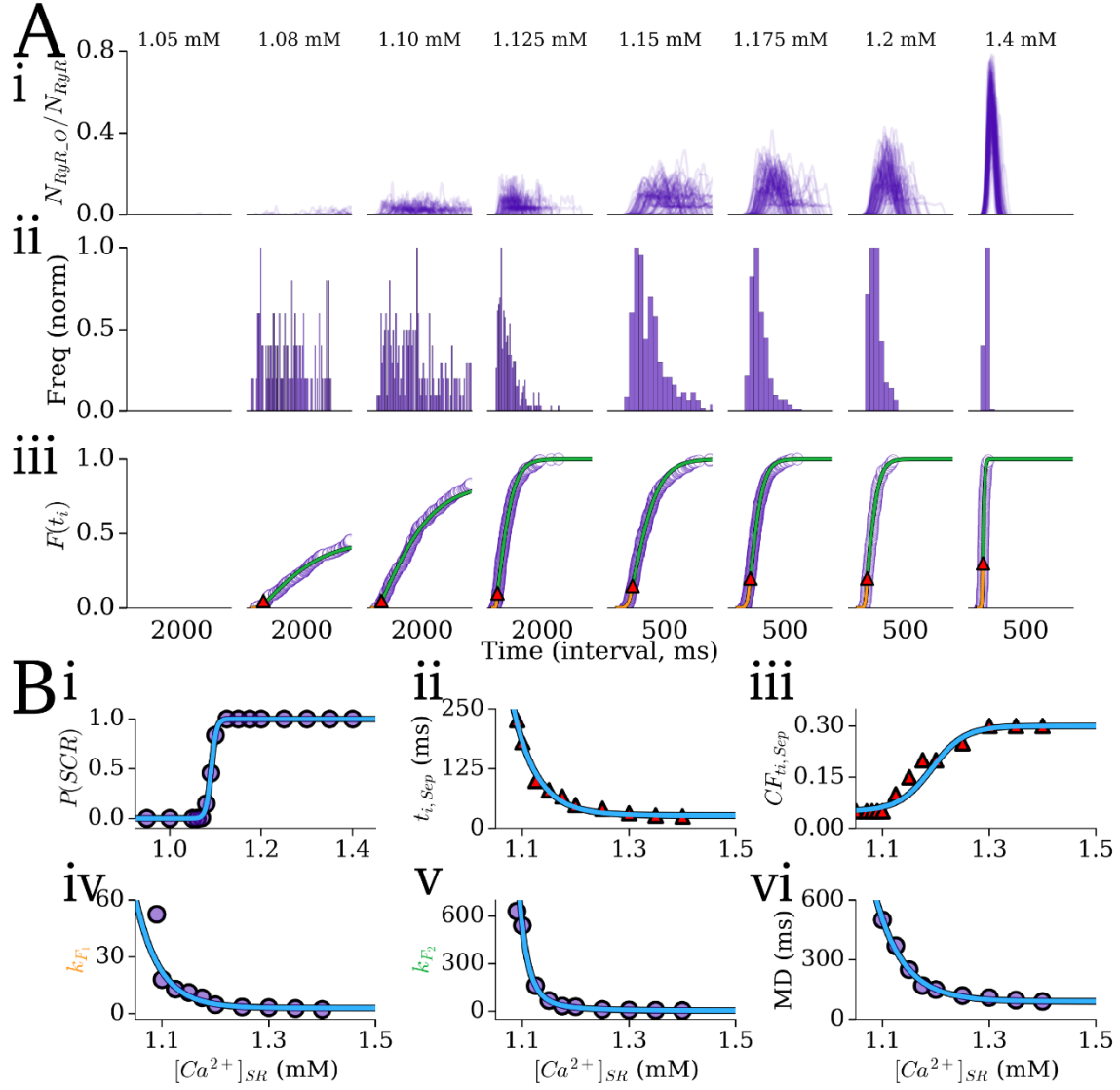
And finally, the MD also correlates well with the SR- $Ca^{2+}$ :

$$MD = A_{MD} e^{-([Ca^{2+}]_{SR} - a_{MD})/k_{MD}} + MD^{\min} \quad (126)$$

Parameters for the fit achieved for the different model conditions are given in Table S10.

**Table S10:** Spontaneous release function variables SR- $\text{Ca}^{2+}$  dependence parameters, Dynamic Fit model

Symbol	Parameter	Value control	Value $R_{\text{SERCA/NCX}}$	Value $R_{\text{CRU-CRU}}$
$SCR_{\text{threshold}}$	SR- $\text{Ca}^{2+}$ threshold for SCRE (mM)	1.091	0.993	0.963
$k_P(\text{SCR})$	Gradient parameter for $P(\text{SCR})$	0.0058	0.007	0.0075
$A_{i,\text{Sep}}$	Coefficient for $i_{i,\text{Sep}}$ function	37.78	27.62	65.047
$a_{i,\text{Sep}}$	$i_{i,\text{Sep}}$ exponent $[\text{Ca}^{2+}]_{\text{SR}}$ reference parameter	1.157	1.096	1.017
$k_{i,\text{Sep}}$	$i_{i,\text{Sep}}$ exponent $[\text{Ca}^{2+}]_{\text{SR}}$ gradient parameter	0.041	0.0581	0.0674
$i_{i,\text{Sep}}^{\text{min}}$	Minimal value for $i_{i,\text{Sep}}$	31.83	18	27
$A_{\text{CF}}$	Coefficient for $\text{CF}_{i,\text{Sep}}$ function	0.25	0.25	0.15
$a_{\text{CF}}$	$\text{CF}_{i,\text{Sep}}$ exponent $[\text{Ca}^{2+}]_{\text{SR}}$ reference parameter	1.192	1.124	0.99
$k_{\text{CF}}$	$\text{CF}_{i,\text{Sep}}$ exponent $[\text{Ca}^{2+}]_{\text{SR}}$ gradient parameter	0.0311	0.0481	0.0111
$A_{k_{\text{F1}}}$	Coefficient for $k_{\text{F1}}$ function	8.619	3.955	10.93
$a_{k_{\text{F1}}}$	$k_{\text{F1}}$ exponent $[\text{Ca}^{2+}]_{\text{SR}}$ reference parameter	1.136	1.1	1.04
$k_{k_{\text{F1}}}$	$k_{\text{F1}}$ exponent $[\text{Ca}^{2+}]_{\text{SR}}$ gradient parameter	0.0449	0.0704	0.0659
$k_{\text{F1}}^{\text{min}}$	Minimal value for $k_{\text{F1}}$	2.967	1.532	1.529
$A_{k_{\text{F2}}}$	1 <sup>st</sup> coefficient for $k_{\text{F2}}$ function	583.6	173.361	181.12
$B_{k_{\text{F2}}}$	2 <sup>nd</sup> coefficient for $k_{\text{F2}}$ function	295149	338.742	0
$H1_{k_{\text{F2}}}$	$[\text{Ca}^{2+}]_{\text{SR}}$ power for 1 <sup>st</sup> term $k_{\text{F2}}$ function	-18.979	-21.099	-31.02
$H2_{k_{\text{F2}}}$	$[\text{Ca}^{2+}]_{\text{SR}}$ power for 2 <sup>nd</sup> term $k_{\text{F2}}$ function	-68.306	-118.771	N/A
$k_{\text{F2}}^{\text{min}}$	Minimal value for $k_{\text{F2}}$	5	3.9	6.7
$A_{\text{MD}}$	Coefficient of median duration (MD) function	208.57	801.86	136.86
$a_{\text{MD}}$	$\text{MD}$ exponent $[\text{Ca}^{2+}]_{\text{SR}}$ reference parameter	1.136	.953	1.0312
$k_{\text{MD}}$	$\text{MD}$ exponent $[\text{Ca}^{2+}]_{\text{SR}}$ gradient parameter	0.0526	0.063	0.0854
$\text{MD}^{\text{min}}$	Minimal value of MD	90	90	64.12
$A_{\text{DW1}}$	Coefficient for $\text{DW}_1$ function	276.72	273.53	155.61
$a_{\text{DW1}}$	$\text{DW}_1$ exponent MD reference parameter	324.11	268.012	223.98
$k_{\text{DW1}}$	$\text{DW}_1$ exponent MD gradient parameter	70.67	40.24	57.27
$\text{DW}_1^{\text{min}}$	Minimal value of $\text{DW}_1$	40	48.26	40
$A_{\text{DW2}}$	Coefficient for $\text{DW}_2$ function	233.26	369.44	109.18
$a_{\text{DW2}}$	$\text{DW}_2$ exponent MD reference parameter	160.74	188.14	140.46
$k_{\text{DW2}}$	$\text{DW}_2$ exponent MD gradient parameter	14.6	18.72	10.7
$\text{DW}_2^{\text{min}}$	Minimal value of $\text{DW}_2$	53	60.56	70.422



**Figure S2: Derivation of the Dynamic SRF parameters in the control model.** A – RyR waveforms from 100 simulations of the  $\text{Ca}^{2+}$  clamp protocol (i) over eight steps of SR- $\text{Ca}^{2+}$  (panel titles), and corresponding initiation time distributions (ii) and cumulative frequency plots (iii) from 250 simulations at each SR- $\text{Ca}^{2+}$ . The values given on the  $x$ -axis refer to the total time interval of the plot, not absolute values. The two fitting functions ( $F_1(t_i)$  and  $F_2(t_i)$ , orange and green; see Figure 4) and their separation point (red triangular marker) are shown. B – Summary data (purple dots, red triangles) and the fit from the relevant functions (blue line) against SR- $\text{Ca}^{2+}$  for: (i) probability of whole-cell SCORE; (ii) initiation time corresponding to the separation point,  $t_{i,\text{Sep}}$ ; (iii) the normalised cumulative frequency at this point,  $CF_{t_{i,\text{Sep}}} = F(t_i) |_{t_i=t_{i,\text{Sep}}}$ ; (iv) the  $k$  parameter for  $F_1(t_i)$  and (v) for  $F_2(t_i)$ ; (vi) the median duration,  $MD$ .

### The General Dynamic SRF model

Primary equations for the parameters are:

$$CaSR_{\min} = CaSR_{\text{threshold}} - 0.5CaSR_{P\_range} \quad (127)$$

$$P(\text{SCR}) = \left[ 1 + \exp\left(-([Ca^{2+}]_{SR} - CaSR_{\text{threshold}}) / 0.1CaSR_{P\_range}\right) \right]^{-1} \quad (128)$$

$$t_{i,\text{Sep}} = (t_{i,\text{Sep}}^{\max} - t_{i,\text{Sep}}^{\min}) e^{\left(-5([Ca^{2+}]_{SR} - CaSR_{\min}) / (CaSR_{\max} - CaSR_{\min})\right)} + t_{i,\text{Sep}}^{\min} \quad (129)$$

$$MD = (MD^{\max} - MD^{\min}) e^{\left(-5 \left( (Ca^{2+})_{SR} - CaSR_{\min} \right) / (CaSR_{\max} - CaSR_{\min}) \right)} + MD^{\min} \quad (130)$$

$$k_{F_1} = 0.145 \left[ (t_{i,width}^{\max} - t_{i,width}^{\min}) \left[ (t_{i,sep} - t_{i,sep}^{\min}) / (t_{i,sep}^{\max} - t_{i,sep}^{\min}) \right]^{H_{width}} + t_{i,width}^{\min} \right] \quad (131)$$

$$k_{F_2} = 1.5k_{F_1} \quad (132)$$

$$DW_1 = (\lambda_{width}^{\max} - \lambda_{width}^{\min}) \left[ (MD - MD^{\min}) / (MD^{\max} - MD^{\min}) \right]^{H_{width}} + \lambda_{width}^{\min} \quad (133)$$

$$DW_2 = DW_1 \quad (134)$$

Where the following may be defined by the user: (i) - The threshold for SCORE ( $CaSR_{\text{threshold}}$ ); (ii) - The SR- $Ca^{2+}$  range over which  $P(\text{SCR})$  varies from 0 to 1 ( $CaSR_{\text{p\_range}}$ ); (iii) - The maximal SR- $Ca^{2+}$  above which SCORE distributions converge ( $CaSR_{\text{max}}$ ); (iv) - The minimum and maximum  $t_{i,sep}$  and  $MD$  ( $t_{i,sep}^{\min}$ ,  $t_{i,sep}^{\max}$ ,  $MD^{\min}$ ,  $MD^{\max}$ ); (v) - The  $t_i$  and  $\lambda$  distribution widths at these extremes ( $t_{i,width}^{\min}$ ,  $t_{i,width}^{\max}$ ,  $\lambda_{width}^{\min}$ ,  $\lambda_{width}^{\max}$ ); And (vi) - the non-linearity of width variance ( $H_{width}$ );  $CF_{t_i,sep}$  was set to 0.4.

Parameter sets used in the study, for the investigation of variability on SR- $Ca^{2+}$ -TA relationship (General 1-5) and generalisation of the approach by implementation in the Grandi et al. human atrial cell model [14] and parameterisation to the data of Workman et al. 2012 [15] are:

**Table S11:** SR- $Ca^{2+}$  dependence parameters, General Dynamic model.

Parameter	General_1	2	3	4	5	Grandi	Workman
$CaSR_{\text{threshold}}$	1.1	1.05	1.00	1.15	1.2	0.6	0.72
$CaSR_{\text{p\_range}}$	0.05	0.05	0.05	0.05	0.05	0.01	0.01
$CaSR_{\text{max}}$	1.7	1.65	1.6	1.75	1.8	0.7	1.07
$t_{i,sep}^{\min}$	30	30	30	30	30	200	45
$t_{i,sep}^{\max}$	870	870	870	870	870	1000	940
$MD^{\min}$	50	50	50	50	50	100	75
$MD^{\max}$	800	800	800	800	800	800	250
$t_{i,width}^{\min}$	20	20	20	20	20	150	8
$t_{i,width}^{\max}$	1000	1000	1000	1000	1000	800	262
$\lambda_{width}^{\min}$	20	20	20	20	20	50	15
$\lambda_{width}^{\max}$	300	300	300	300	300	300	150

## Inverse functions

Initiation time,  $t_i$ ; inverse function of equation (115):

$$t_i = \begin{cases} -k_{F_1} \cdot \ln \left( \frac{2CF_{t_i,sep}}{rand} - 1 \right) + t_{i,sep} & rand < CF_{t_i,sep} \\ -k_{F_2} \cdot \ln \left( \frac{2(1 - CF_{t_i,sep})}{rand + 1 - 2CF_{t_i,sep}} - 1 \right) + t_{i,sep} & rand \geq CF_{t_i,sep} \end{cases} \quad (135)$$

Duration,  $\lambda$ ; inverse function of equation (116):

$$\lambda = \begin{cases} 0.261DW_1 \cdot \ln(rand^{-1} - 1) + MD & rand < 0.5 \\ 0.261DW_2 \cdot \ln(rand^{-1} - 1) + MD & rand \geq 0.5 \end{cases} \quad (136)$$

Peak time,  $t_p$ , following a uniform distribution approximation:

$$t_p = 25 + rand(\lambda - 52) + t_i \quad (137)$$

$N_{RyR\_O}^{peak}$ ,  $N_{RyR\_O}^{plateau}$  are determined from  $\lambda$  directly from their definition functions (eqns 119-120) and  $\pm rand \times$  simple variance magnitude of 0.05 and  $0.25N_{RyR\_O}^{plateau}$ , respectively.

### Implementation with the 0D model

These SRF were implemented within the 0D cell models using a simple algorithm (Figure 6 MS): the input parameters ( $P(SCR)$ ,  $t_{i,sep}$ ,  $CF_{i,sep}$ ,  $k_{F1}$ ,  $k_{F2}$ ,  $MD$ ; see previous section: Parameter distributions) are defined at a certain time (see below) and then the waveform parameters ( $t_i$  and  $\lambda$ , which in turn define  $t_p$  and  $N_{RyR\_O}^{peak}$ ; see previous section: Parameter distributions) are randomly sampled from the associated inverse functions (equations 135-137 above). When the SRF have been initiated (i.e.,  $t > t_i$  and  $N_{RyR\_O}^{SRF}$  is  $> 0$ ), the  $N_{RyR\_O}$  in the cell model is set to this value and the model thus evolves as if the equivalent SCORE was occurring in the 3D cell model.

For the simplest implementation of the SRF, the Direct Control model, this calculation is determined at the time of cellular excitation, setting  $t_i$  and  $\lambda$  based on the distributions defined by user input parameters ( $P(SCR)$ ,  $t_{i,sep}$ ,  $CF_{i,sep}$ ,  $k_{F1}$ ,  $k_{F2}$ ,  $MD$ ) and five random numbers input into the corresponding inverse functions: first, a random number between 0 and 1 is generated and compared to the probability of release,  $P(SCR)$ ; if  $rand < P(SCR)$ , then the input parameters are used to determine the inverse functions (equations 28-30) and 4 more random numbers determine the actual SRF waveform parameters; if  $rand > P(SCR)$ , then no SRF parameters are set. Note that the  $t_{i,sep}$  must be set relative to excitation time. The model will set SRF parameters based on these single distributions with every cellular excitation (note that the parameters may give an SCORE timing later than the next stimulated excitation, in which case it will be reset on the next excitation).

For the Dynamic Fit model, the calculation is performed multiple times, dynamically determined during the simulation: After an initial stimulated AP, when the RyR availability has recovered above a set threshold, the SR- $Ca^{2+}$  is input to first define the probability of release,  $P(SCR)$ , from equation (22) and the same process is followed as described above, with the remaining input parameters defined from the SR- $Ca^{2+}$  according to the appropriate functions [equations 23-27]. If the SR- $Ca^{2+}$  concentration changes more than by a predefined value (e.g., 0.01 mM) before the SCORE has been initiated, then the parameters are recalculated based on this new SR- $Ca^{2+}$ . SRF parameters are not calculated during excitation (i.e., when the RyR availability is low) but recalculated upon RyR recovery.

The implementation with the 0D cell model required scaling of  $I_{NCX}$  and  $K_{rel}$  when SCORE was modelled, due to localised activity differing from proportional global activity:

$$I_{NCX\_mult} = 0.4 / \left(1 + e^{(\lambda-176)/46}\right) + 0.25 \quad (138)$$

$$K_{rel\_mult} = 0.35 / \left(1 + e^{(\lambda-113)/18}\right) + 0.4 \quad (139)$$

In the case that a SCORE initiates a triggered action potential, the total proportion of RyRs available to be triggered during excitation is adjusted to account for those which have already undergone release during the event:

$$N_{RyR\_O} = N_{RyR} \cdot N_{RyR\_O\_det} \cdot \left(1 - 0.75 N_{RyR\_ac\_SRF}\right) \quad (140)$$

Where

$$N_{RyR\_ac\_SRF} = (t - t_i) / \lambda \quad (141)$$

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