

# Supplemental Materials

## Ionic Mechanisms of Propagated Repolarization in a One-Dimensional Strand of Human Ventricular Myocyte Model

Yukiko Himeno <sup>1\*</sup>, Yixin Zhang <sup>1</sup>, Suzuka Enomoto <sup>1</sup>, Hiroto Nomura <sup>1</sup>, Natsuki Yamamoto <sup>1</sup>, Shotaro Kiyokawa <sup>1</sup>, Mirei Ujihara <sup>1</sup>, Yuttamol Muangkram <sup>1</sup>, Akinori Noma <sup>1</sup> and Akira Amano <sup>1</sup>

<sup>1</sup> Department of Bioinformatics, College of Life Sciences, Ritsumeikan University, Japan

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## 1. Abbreviations

**Table S1.** Abbreviations in model equations

Membrane excitation	
$V_m$	membrane potential (mV)
$I_{tot\_cell}$	total current of ion channels and exchangers (pA/pF)
$I_{tot\_X\_a}$	total current of ion 'X' channels and exchangers at space 'a' (pA/pF)
$I_{app\_blk}$	current applied through a patch electrode (pA/pF)
$E_X$	reversal potential of ion 'X', determined from the slope conductance of $I_X$ - $V_m$ relationship, or by the Nernst equation (mV)
$C_m$	membrane capacitance (pF)
$G_I$	conductance of current 'I' (pA/mV/pF)
$GHK_{X\_a}$	a modified Goldman-Hodgkin-Katz equation of ion 'X' at a space 'a' (mM)
$k, \alpha, \beta, \nu$	rate constant (/ms)
$K_{d\_X}$	dissociation constant for ion 'X' (/mM)
$P_{I(X)}$	converting factor of current 'I' from $GHK_X$ (pA/mM/pF)
$v_{cyc\_T}$	turnover rate of transporter 'T' (/ms)
$p(S)_{(a)}$	probability of state 'S' in a scheme of state transitions at a space 'a'
$p(O)_{I(a)}$	open probability of current 'I' at space 'a'
$V_X$	total volume of space 'X' ( $\mu\text{m}^3$ )
$[X_{total}]_a$	total concentration of substance 'X' at space 'a' (mM)
$[X_{free}]_a$	free concentration of substance 'X' at space 'a' (mM)
$[X]_a$	concentration of ion 'X' at space 'a' (mM)
$J_X$	total flux of ion 'X' (amol/ms)
$z_X$	valence of ion 'X'
$\frac{d[X]_a}{dt}$	rate of change of 'X' concentration at space 'a' (mM/ms)

## 2. Model parameters

### Physical constants

**Table S2.** Physical constants

$R$	8.3143	C · mV/mmol/K
$T$	310	K
$F$	96.4867	C/mmol

## Ion concentrations

**Table S3.** Ionic composition of external solution

$[K^+]_o$	4.5	mM
$[Na^+]_o$	140	mM
$[Ca^{2+}]_o$	1.8	mM

## Substrates

**Table S4.** Substrates

$[H^+]_{cyt}$	0.0001	mM
$[Mg^{2+}]_{cyt}$	0.8	mM
$[SPM]$	5	mM

## Cell volume

**Table S5.** Cell compartments

Cell configuration ( $V_{cell}$ )	$120 \cdot 37.62 \cdot 8.4$	fL
Bulk space ( $V_{blk}$ )	$0.68 \cdot V_{cell}$	fL
Intermediate zone ( $V_{iz}$ )	$0.035 \cdot V_{cell}$	fL
Junction space ( $V_{jnc}$ )	$0.008 \cdot V_{cell}$	fL
Cytsol volume ( $V_{cyt}$ )	$0.723 \cdot V_{cell}$	fL
Total SR space ( $V_{SRt}$ )	$0.06 \cdot V_{cell}$	fL
SR releasing site volume ( $V_{SRrl}$ )	$0.2 \cdot V_{SRt}$	fL
SR uptake site volume ( $V_{SRup}$ )	$0.8 \cdot V_{SRt}$	fL
Input capacitance ( $C_m$ )	192.46	pF

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

The detailed set of buffer species (1) used in the GPB model was adopted after several simplifications as described in our previous paper (2). In short, we deleted the myosin, Na<sup>+</sup> and Mg<sup>2+</sup> buffers, and fixed [Mg<sup>2+</sup>]. The low affinity binding of Ca<sup>2+</sup> to troponin (TnCl) was replaced by a contraction model (3) and the amount of the high affinity site (TnCh) was adjusted.

**Table S6.** Ca<sup>2+</sup> buffer

$CaM$	calmodulin (mM)
$CaMCa$	CaM-calcium complex (mM)
$[B_{total}CaM]$	total buffer concentration of CaM, 0.0216 (mM)

<i>TnCh</i>	troponin C with a high affinity
<i>TnChCa</i>	TnCh-calcium complex
$[B_{total}TnCh]$	total buffer concentration of TnCh, 0.108 (mM)
<i>SRCa</i>	calcium buffer by SR membrane-Calcium complex
$[B_{total}SR]$	total buffer concentration on SR membrane, 0.01539 (mM)
$[Ca^{2+}]_{SRrl}$	total calcium concentration in release site of the SR (mM)
$[Ca^{2+}]_{SRrl}$	free calcium concentration in release site of the SR (mM)
$[B_{total}H]_{iz}$	total sarcolemmal calcium buffer concentration with a high affinity in iz space, 0.2178 (mM)
$[B_{total}L]_{iz}$	total sarcolemmal calcium buffer concentration with a low affinity in iz space, 0.6078 (mM)
$[B_{total}H]_{jnc}$	total sarcolemmal calcium buffer concentration with a high affinity in jnc space, 0.398 (mM)
$[B_{total}L]_{jnc}$	total sarcolemmal calcium buffer concentration with a low affinity in jnc space, 1.1095 (mM)
<i>L<sub>b</sub></i>	calcium-sarcolemmal buffer complex with a low affinity
<i>H<sub>b</sub></i>	calcium-sarcolemmal buffer complex with a high affinity
<i>B<sub>total</sub>CSQN</i>	total buffer concentration of calsequestrin, 3.0 (mM)

### Bulk space (*blk*)

$$\frac{d[CaMca]}{dt} = k_{on\_CaM} \cdot [Ca^{2+}]_{blk} \cdot ([B_{total}CaM] - [CaMca]) - k_{off\_CaM} \cdot [CaMca]$$

$$k_{off\_CaM} = 0.238, k_{on\_CaM} = 34$$

$$\frac{d[TnChCa]}{dt} = k_{on\_TnCh} \cdot [Ca^{2+}]_{blk} \cdot ([B_{total}TnCh] - [TnChCa]) - k_{off\_TnCh} \cdot [TnChCa]$$

$$k_{off\_TnCh} = 0.000032, k_{on\_TnCh} = 2.37$$

$$\frac{d[SRCa]}{dt} = k_{on\_SR} \cdot [Ca^{2+}]_{blk} \cdot ([B_{total}SR] - [SRCa]) - k_{off\_SR} \cdot [SRCa]$$

$$k_{off\_SR} = 0.06, k_{on\_SR} = 100$$

### Intermediate zone (*iz*)

$$[L_{free}]_{iz} = \frac{[B_{total}L]_{iz}}{1 + \frac{[Ca^{2+}]_{iz}}{K_{dL_{iz}}}}$$

$$K_{dL_{iz}} = \frac{k_{off\_L_{iz}}}{k_{on\_L_{iz}}}, k_{off\_L_{iz}} = 1.3, k_{on\_L_{iz}} = 100$$

$$[H_{free}]_{iz} = \frac{[B_{total}H]_{iz}}{1 + \frac{[Ca^{2+}]_{iz}}{K_{dH_{iz}}}}$$

$$K_{dH_{iz}} = \frac{k_{off\_H_{iz}}}{k_{on\_H_{iz}}}, k_{off\_H_{iz}} = 0.03, k_{on\_H_{iz}} = 100$$

$$[Ca^{2+}]_{iz} = \frac{[Ca_{tot}]_{iz}}{1 + \frac{[L_{free}]_{iz}}{K_{dL_{iz}}} + \frac{[H_{free}]_{iz}}{K_{dH_{iz}}}}$$

### Junctional space (*jnc*)

$$[L_{free}]_{jnc} = \frac{[B_{totalL}]_{jnc}}{1 + \frac{[Ca^{2+}]_{jnc}}{K_{dL_{jnc}}}}$$

$$K_{dL_{jnc}} = \frac{k_{off\_L\_jnc}}{k_{on\_L\_jnc}}, k_{off\_L\_jnc} = 1.3, k_{on\_L\_jnc} = 100$$

$$[H_{free}]_{jnc} = \frac{[B_{totalH}]_{jnc}}{1 + \frac{[Ca^{2+}]_{jnc}}{K_{dH_{jnc}}}}$$

$$K_{dH_{jnc}} = \frac{k_{off\_H\_jnc}}{k_{on\_H\_jnc}}, k_{off\_H\_jnc} = 0.03, k_{on\_H\_jnc} = 100$$

$$[Ca^{2+}]_{jnc} = \frac{[Ca_{tot}]_{jnc}}{1 + \frac{[L_{free}]_{jnc}}{K_{dL_{jnc}}} + \frac{[H_{free}]_{jnc}}{K_{dH_{jnc}}}}$$

### Release site of the SR (*SRrl*)

$$K_{d\_CSQN\_Ca} = \frac{k_{off\_CSQN}}{k_{on\_CSQN}}$$

$$k_{off\_CSQN} = 65, k_{on\_CSQN} = 100$$

$$a = 1$$

$$b = [B_{totalCSQN}] - [Ca_{total}]_{SRrl} + K_{d\_CSQN\_Ca}$$

$$c = -K_{d\_CSQN\_Ca} \cdot [Ca_{total}]_{SRrl}$$

$$[Ca^{2+}]_{SRrl} = \frac{-b + \sqrt{b^2 - 4 \cdot a \cdot c}}{2 \cdot a}$$

### Boundary $Ca^{2+}$ diffusion

#### $Ca^{2+}$ transfer between cytosolic compartments

$$J_{Ca\_jnciz} = G_{dCa\_jnciz} \cdot ([Ca^{2+}]_{jnc} - [Ca^{2+}]_{iz})$$

$$G_{dCa\_jnciz} = 3395.88 \cdot fL \cdot ms^{-1}$$

$$J_{Ca\_izblk} = G_{dCa\_izblk} \cdot ([Ca^{2+}]_{iz} - [Ca^{2+}]_{blk})$$

$$G_{dCa\_izblk} = 3507.78 \cdot fL \cdot ms^{-1}$$

#### $Ca^{2+}$ transfer from SR uptake site to release site

$$J_{trans\_SR} = P_{trans} \cdot ([Ca^{2+}]_{SRup} - [Ca^{2+}]_{SRrl})$$

$$P_{trans} = 4.8037$$

## 3. Rate of change in the membrane potential and ion concentrations

### Membrane potential

$$\frac{dv_m}{dt} = -(I_{tot\_cell} + I_{app}) \quad (\text{Eq. S1})$$

$$I_{tot\_cell} = I_{tot\_Na} + I_{tot\_Ca} + I_{tot\_K} \quad (\text{Eq. S2})$$

$$I_{tot\_Ca} = I_{tot\_Ca\_jnc} + I_{tot\_Ca\_iz} + I_{tot\_Ca\_blk} \quad (\text{Eq. S3})$$

$$I_{tot\_Ca\_jnc} = I_{CaL\_Ca\_LR} + I_{CaL\_Ca\_L0} \quad (\text{Eq. S4})$$

$$I_{tot\_Ca\_iz} = I_{CaL\_Ca\_iz} + I_{PMCA\_iz} + I_{NCX\_Ca\_iz} + I_{Cab\_iz} \quad (\text{Eq. S5})$$

$$I_{tot\_Ca\_blk} = I_{CaL\_Ca\_blk} + I_{PMCA\_blk} + I_{NCX\_Ca\_blk} + I_{Cab\_Ca\_blk} \quad (\text{Eq. S6})$$

$$I_{tot\_Na} = (I_{CaL\_Na\_jnc} + I_{CaL\_Na\_iz} + I_{CaL\_Na\_blk}) + (I_{NCX\_Na\_iz} + I_{NCX\_Na\_blk}) \quad (\text{Eq. S7})$$

$$+ (I_{Ks\_Na\_iz} + I_{Ks\_Na\_blk}) + I_{NaT\_Na} + I_{NaL\_Na} + I_{NaK\_Na} + I_{Kto\_Na} + I_{bNSC\_Na} \\ + (I_{LCCa\_Na\_iz} + I_{LCCa\_Na\_blk})$$

$$I_{tot\_K} = (I_{CaL\_K\_jnc} + I_{CaL\_K\_iz} + I_{CaL\_K\_blk}) + I_{NaT\_K} + I_{NaL\_K} + I_{K1\_K} + I_{Kr\_K} \quad (\text{Eq. S8})$$

$$+ (I_{Ks\_K\_iz} + I_{Ks\_K\_blk}) + I_{Kto\_K} + I_{Kpl} + I_{NaK\_K} + I_{KATP\_K\_cyt} + I_{bNSC\_K}$$

$$+ (I_{LCCa\_K\_iz} + I_{LCCa\_K\_blk})$$

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### Ion concentrations

$$\frac{d[Ca_{total}^{2+}]_{jnc}}{dt} = -\frac{I_{tot\_Ca\_jnc} \cdot C_m}{V_{jnc} \cdot 2 \cdot F} + \frac{J_{Ca\_rel}}{V_{jnc}} - \frac{J_{Ca\_jnciz}}{V_{jnc}} \quad (\text{Eq. S9})$$

$$\frac{d[Ca_{total}^{2+}]_{iz}}{dt} = -\frac{I_{tot\_Ca\_iz} \cdot C_m}{V_{iz} \cdot 2 \cdot F} + \frac{J_{Ca\_jnciz}}{V_{iz}} - \frac{J_{Ca\_izblk}}{V_{iz}} \quad (\text{Eq. S10})$$

$$\frac{d[Ca_{total}^{2+}]_{blk}}{dt} = -\frac{I_{tot\_Ca\_blk} \cdot C_m}{V_{blk} \cdot 2 \cdot F} + \frac{J_{Ca\_SERCA}}{V_{blk}} - \frac{J_{Ca\_izblk}}{V_{blk}} \quad (\text{Eq. S11})$$

$$\frac{d[Ca^{2+}]_{SRup}}{dt} = -\frac{J_{SERCA}}{V_{SRup}} - \frac{J_{trans\_SR}}{V_{SRup}} \quad (\text{Eq. S12})$$

$$\frac{d[Ca_{total}^{2+}]_{SRrl}}{dt} = -\frac{J_{trans\_SR}}{V_{SRrl}} - \frac{J_{rel\_SR}}{V_{SRrl}} \quad (\text{Eq. S13})$$

$$\frac{d[Na^+]_i}{dt} = -\frac{I_{tot\_Na} \cdot C_m}{V_{cyt} \cdot F} \quad (\text{Eq. S14})$$

$$\frac{d[K^+]_i}{dt} = -\frac{(I_{tot\_K} + I_{app}) \cdot C_m}{V_{cyt} \cdot F} \quad (\text{Eq. S15})$$

Free  $Ca^{2+}$  concentrations as calculated below are used as intracellular  $Ca^{2+}$  concentrations in each compartment.

$$[Ca_{free}^{2+}]_{jnc} = [Ca_{total}^{2+}]_{jnc} - ([L_{bind}]_{jnc} + [H_{bind}]_{jnc})$$

$$[L_{bind}]_{jnc} = [B_{total}L]_{jnc} - [L_{free}]_{jnc}$$

$$[H_{bind}]_{jnc} = [B_{total}H]_{jnc} - [H_{free}]_{jnc}$$

$$[Ca_{free}^{2+}]_{iz} = [Ca_{total}^{2+}]_{iz} - ([L_{bind}]_{iz} + [H_{bind}]_{iz})$$

$$[L_{bind}]_{iz} = [B_{total}L]_{iz} - [L_{free}]_{iz}$$

$$[H_{bind}]_{iz} = [B_{total}H]_{iz} - [H_{free}]_{iz}$$

$$[Ca_{free}^{2+}]_{blk} = [Ca_{total}^{2+}]_{blk} - ([CaMCA] + [TnChCa] + [SRCa] + nCaBS \cdot \frac{(cMDP+cAMPpW+cAMDs+cAMT+cMDPr)}{1000})$$

## 4. Ion channels and transporters

### GHK equation

The magnitudes of ion channel currents were described by the ohmic equation or by the GHK equation. In the latter case, the term to convert mM to pA (permeability times zF) in the original GHK equation was represented by a lumped converting factor, P in a unit of pA·mM<sup>-1</sup>, because of unknown total number of channels within a cell and single channel ion permeability. Then, the fully-activated current amplitude (I) for an ion X was given by,

$$I = P \cdot GHK_X$$

where  $GHK_X$  is,

$$GHK_X = \frac{z_X F V_m}{RT} \cdot \frac{([X]_i - [X]_o \cdot \exp(\frac{-z_X F V_m}{RT}))}{(1 - \exp(\frac{-z_X F V_m}{RT}))}$$

Nernst equation

$$E_X = \frac{R \cdot T}{z_X \cdot F} \cdot \log \left( \frac{[X]_o}{[X]_i} \right)$$

### L-type Ca<sup>2+</sup> current (I<sub>CaL</sub>, LCC)

The model developed by Himeno *et al.*(4) was used after adjusting P<sub>CaL\_Ca</sub>, which was multiplied by 2.1. I<sub>CaL</sub> is composed of Ca<sup>2+</sup>, Na<sup>+</sup> and K<sup>+</sup> components, which are described with GHK<sub>X</sub> for each cation.

$$I_{CaL} = (I_{CaL\_Ca\_jnc} + I_{CaL\_Na\_jnc} + I_{CaL\_K\_jnc}) + (I_{CaL\_Ca\_iz} + I_{CaL\_Na\_iz} + I_{CaL\_K\_iz}) \quad (\text{Eq. S16})$$

$$+ (I_{CaL\_Ca\_blk} + I_{CaL\_Na\_blk} + I_{CaL\_K\_blk})$$

$$I_{CaL\_X\_a} = f_{CaL\_a} \cdot P_{CaL\_X} \cdot GHK_{X\_a} \cdot pO_{LCC\_a} \cdot \frac{1}{1 + \left( \frac{1.4}{[MgATP\_cyl]} \right)^3} \quad (\text{Eq. S17})$$

$$pO_{LCC\_a} = Y_{ooo} + Y_{ooc} \quad a = (blk, iz, jnc) \quad X = (Ca, Na, K) \quad (\text{Eq. S18})$$

**fraction of I<sub>CaL</sub>**

$$f_{CaL\_jnc} = 0.75, \quad f_{CaL\_blk} = 0.1, \quad f_{CaL\_iz} = 0.15$$

**Converting factors**

$$P_{CaL\_Ca} = 14.21 \cdot C_m$$

$$P_{CaL\_Na} = 0.0000185 \cdot P_{CaL\_Ca}$$

$$P_{CaL\_K} = 0.000367 \cdot P_{CaL\_Ca}$$

**Rate constants for V<sub>m</sub>-gate(α<sub>+</sub>, α<sub>-</sub>) and Ca<sup>2+</sup>-gate(ε<sub>+</sub>, ε<sub>-</sub>)**

$$\alpha_+ = \frac{1}{3.734 \cdot \exp\left(\frac{-V_m}{8.5}\right) + 0.35 \cdot \exp\left(\frac{-V_m}{3500}\right)} \quad (\text{Eq. S19})$$

$$\alpha_- = \frac{1}{4.65 \cdot \exp\left(\frac{V_m}{15}\right) + 1.363 \cdot \exp\left(\frac{V_m}{100}\right)} \quad (\text{Eq. S20})$$

$$\varepsilon_+ = \frac{[Ca^{2+}]_{nd} \cdot \alpha_+}{T_L \cdot K_L} \quad (\text{Eq. S21})$$

$$\varepsilon_- = \frac{1}{8084 \cdot \exp\left(\frac{Vm}{10}\right) + 158 \cdot \exp\left(\frac{Vm}{1000}\right)} + \frac{1}{134736 \cdot \exp\left(-\frac{Vm}{5}\right) + 337 \cdot \exp\left(-\frac{Vm}{2000}\right)} \quad (\text{Eq. S22})$$

### Sodium current( $I_{Na}$ )

The model developed by Asakura *et al.* (2) was used. To facilitate calculation of rapid gating kinetics of the current, integration of the parameters was conducted using Rush-Larsen method(5). The whole cell  $I_{Na}$  was given by a sum of  $I_{NaT}$  and  $I_{NaL}$  with a fraction( $f_L$ ) of 0.13125 for  $I_{NaL}$ . The current was carried by both  $Na^+$  and  $K^+$  at ratio of permeability,  $P_{Na}/P_K$ , of 10.

$$I_{Na} = I_{NaT} + I_{NaL} \quad (\text{Eq. S23})$$

$$f_L = 0.13125, P_{Na} = 8.1072 \cdot C_m \text{ (pA/mM)}$$

### Transient component( $I_{NaT}$ )

$$I_{NaT} = (1 - f_L) \cdot P_{Na} \cdot (GHK_{Na} + 0.1 \cdot GHK_K) \cdot p(O)_{NaT} \quad (\text{Eq. S24})$$

$$\frac{dp(C)_{NaT}}{dt} = k_{OC} \cdot p(O)_{NaT} + k_{I2C} \cdot p(I_2)_{NaT} + k_{Isb} \cdot p(I_s)_{NaT} - \quad (\text{Eq. S25})$$

$$(k_{Isf} + f_{C\_Na} \cdot (k_{C2O} + k_{C2I2})) \cdot p(C)_{NaT}$$

$$\frac{dp(O)_{NaT}}{dt} = k_{I2O} \cdot p(I_2)_{NaT} + f_{C\_Na} \cdot k_{C2O} \cdot p(C)_{NaT} - (k_{OC} + k_{OI2}) \cdot p(O)_{NaT} \quad (\text{Eq. S26})$$

$$\frac{dp(I_2)_{NaT}}{dt} = f_{C\_Na} \cdot k_{C2I2} \cdot p(C)_{NaT} + k_{OI2} \cdot p(O)_{NaT} + k_{Isb} \cdot p(I_s)_{NaT} \quad (\text{Eq. S27})$$

$$-(k_{I2C} + k_{I2O} + k_{Isf}) \cdot p(I_2)_{NaT}$$

$$\frac{dp(I_s)_{NaT}}{dt} = k_{Isf} \cdot p(I_2)_{NaT} + k_{Isf} \cdot p(C)_{NaT} - 2 \cdot k_{Isb} \cdot p(I_s)_{NaT} \quad (\text{Eq. S28})$$

$$f_{C\_Na} = \frac{C_2}{(C_1 + C_2)} = \frac{1}{1 + \exp\left(-\frac{Vm + 48}{7}\right)} \quad (\text{Eq. S29})$$

$$k_{C2O} = \frac{0.5}{0.0025 \cdot \exp\left(\frac{Vm}{-8.0}\right) + 0.15 \cdot \exp\left(\frac{Vm}{-100.0}\right)} \quad (\text{Eq. S30})$$

$$k_{OC} = \frac{0.5}{30.0 \cdot \exp\left(\frac{Vm}{12.0}\right) + 0.53 \cdot \exp\left(\frac{Vm}{50.0}\right)} \quad (\text{Eq. S31})$$

$$k_{OI2} = \frac{1}{0.0433 \cdot \exp\left(\frac{Vm}{-27.0}\right) + 0.34 \cdot \exp\left(\frac{Vm}{-2000.0}\right)} \quad (\text{Eq. S32})$$

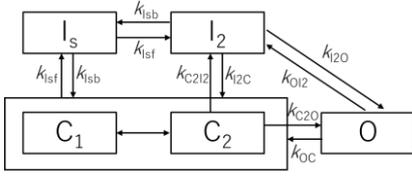
$$k_{I2O} = 0.0001312$$

$$k_{C2I2} = \frac{0.5}{1.0 + \frac{k_{I2O} \cdot k_{OC}}{k_{OI2} \cdot k_{C2O}}} \quad (\text{Eq. S33})$$

$$k_{I2C} = 0.5 - k_{C2I2} \quad (\text{Eq. S34})$$

$$k_{Isb} = \frac{1}{300000.0 \cdot \exp\left(\frac{Vm}{10.0}\right) + 50000.0 \cdot \exp\left(\frac{Vm}{16.0}\right)} \quad (\text{Eq. S35})$$

$$k_{Isf} = \frac{1}{0.016 \cdot \exp\left(\frac{Vm}{-9.9}\right) + 8.0 \cdot \exp\left(\frac{Vm}{-45.0}\right)} \quad (\text{Eq. S36})$$



Scheme 1.  $I_{NaT}$  model

### Late component ( $I_{NaL}$ )

The  $k_{I1I2}$ ,  $k_{O1I}$ ,  $k_{I1O}$ ,  $k_{I1C}$  and  $k_{C2I1}$  are specific for  $I_{NaL}$ , and other rate constants are the same as in  $I_{NaL}$ .

$$I_{NaL} = f_L \cdot P_{Na} \cdot (GHK_{Na} + 0.1 \cdot GHK_K) \cdot p(O)_{NaL} \quad (\text{Eq. S37})$$

$$\frac{dp(C)_{NaL}}{dt} = k_{OC} \cdot p(O)_{NaL} + k_{I1C} \cdot p(I_1)_{NaL} + k_{I2C} \cdot p(I_2)_{NaL} + k_{Isb} \cdot p(I_s)_{NaL} \quad (\text{Eq. S38})$$

$$- (k_{Isf} + f_{C\_Na} \cdot (k_{C2O} + k_{C2I2} + k_{C2I1})) \cdot p(C)_{NaL}$$

$$\frac{dp(O)_{NaL}}{dt} = k_{I1O} \cdot p(I_1)_{NaL} + f_{C\_Na} \cdot k_{C2O} \cdot p(C)_{NaL} - (k_{OC} + k_{O1I}) \cdot p(O)_{NaL} \quad (\text{Eq. S39})$$

$$\frac{dp(I_1)_{NaL}}{dt} = k_{O1I} \cdot p(O)_{NaL} + f_{C\_Na} \cdot k_{C2I1} \cdot p(C)_{NaL} - (k_{I1O} + k_{I1C} + k_{I1I2}) \cdot p(I_1)_{NaL} \quad (\text{Eq. S40})$$

$$\frac{dp(I_2)_{NaL}}{dt} = f_{C\_Na} \cdot k_{C2I2} \cdot p(C)_{NaL} + k_{I1I2} \cdot p(I_1)_{NaL} + k_{Isb} \cdot p(I_s)_{NaL} \quad (\text{Eq. S41})$$

$$- (k_{I2C} + k_{Isf}) \cdot p(I_2)_{NaL}$$

$$\frac{dp(I_s)_{NaL}}{dt} = k_{Isf} \cdot p(I_2)_{NaL} + k_{Isf} \cdot p(C)_{NaL} - 2 \cdot k_{Isb} \cdot p(I_s)_{NaL} \quad (\text{Eq. S42})$$

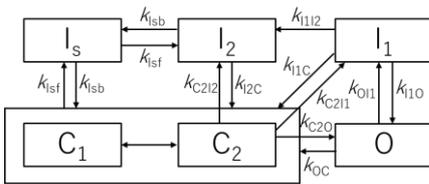
$$k_{I1I2} = 0.00534$$

$$k_{O1I} = k_{O12}$$

$$k_{I1O} = 0.01$$

$$k_{I1C} = k_{I2C}$$

$$k_{C2I1} = k_{C2I2}$$



Scheme 2.  $I_{NaL}$  model

### Inward rectifier potassium current ( $I_{K1}$ )

The model developed by Yan and Ishihara (6) and Ishihara and Yan (7) was used after adjusting the amplitude of  $I_{K1}$  to obtain repolarizing rate of  $\sim 1$  V/s. The gating in this model was described by two modes: in mode 1,  $Mg^{2+}$  and spermine blocks the channel in a competitive manner, while in mode 2, spermine instantaneously blocks the channel in a  $V_m$ -dependent

manner.

$$I_{K1} = G_{K1} \cdot x_{K1} \cdot (V_m - E_k) \cdot p(O)_{K1} \quad G_{K1} = 1.353 \cdot C_m \quad (\text{Eq. S43})$$

$$x_{K1} = \frac{\left(\frac{[K^+]_o}{4.5}\right)^{0.4}}{1.0 + \exp\left(\frac{[K^+]_o - 2.2}{0.6}\right)} \quad (\text{Eq. S44})$$

$$p(O)_{K1} = p_{mode1} + p_{mode2} \quad (\text{Eq. S45})$$

$$p_{mode1} = f_{mode1} \cdot (1 - p_{spm}) \cdot (p_{Mg} + \frac{2}{3} \cdot p_{Mg1} \cdot \frac{1}{3} \cdot p_{Mg2}) \quad (\text{Eq. S46})$$

$$f_{mode1} = 0.9$$

$$p_{mode2} = \frac{(1 - f_{mode1})}{1.0 + \frac{[SPM]}{40.0 \cdot \exp\left(\frac{V_m - E_k}{9.1}\right)}} \quad (\text{Eq. S47})$$

### The Mg<sup>2+</sup>-block in the mode1

$$p_{Mg} = f_o \cdot f_o \cdot f_o \quad (\text{Eq. S48})$$

$$p_{Mg1} = 3.0 \cdot f_o \cdot f_o \cdot f_B \quad (\text{Eq. S49})$$

$$p_{Mg2} = 3.0 \cdot f_o \cdot f_B \cdot f_B \quad (\text{Eq. S50})$$

$$f_o = \frac{\alpha_{Mg}}{\alpha_{Mg} + \beta_{Mg}}, \quad f_B = \frac{\beta_{Mg}}{\alpha_{Mg} + \beta_{Mg}} \quad (\text{Eq. S51})$$

$$\alpha_{Mg} = 12.0 \cdot \exp(-0.025 \cdot (V_m - E_k)) \quad (\text{Eq. S52})$$

$$\beta_{Mg} = 28 \cdot [Mg^{2+}]_{cyt} \cdot \exp(0.025 \cdot (V_m - E_k)) \quad (\text{Eq. S53})$$

### The SPM-block in the mode2

$$\frac{dP_{spm}}{dt} = \beta_{SPM} \cdot p_{Mg} \cdot (1 - P_{spm}) - \alpha_{SPM} \cdot P_{spm} \quad (\text{Eq. S54})$$

$$\alpha_{SPM} = \frac{0.17 \cdot \exp(-0.07 \cdot (V_m - E_k) + 8[Mg^{2+}]_{cyt})}{1.0 + 0.01 \cdot \exp(0.12 \cdot (V_m - E_k) + 8[Mg^{2+}]_{cyt})} \quad (\text{Eq. S53})$$

$$\beta_{Mg} = \frac{0.28 \cdot [SPM] \cdot \exp(0.15 \cdot (V_m - E_k) + 8[Mg^{2+}]_{cyt})}{1.0 + 0.01 \cdot \exp(0.13 \cdot (V_m - E_k) + 8[Mg^{2+}]_{cyt})} \quad (\text{Eq. S54})$$

### Delayed rectifier K<sup>+</sup> current, fast component (I<sub>Kr</sub>)

The model was taken from Asakura *et al.* (2) was used after adjusting the conductance of I<sub>Kr</sub>, G<sub>Kr</sub>. The current amplitude is described with an ohmic equation.

$$I_{Kr} = G_{Kr} \cdot (V_m - E_k) \cdot p(O)_{Kr} \cdot \left(\frac{[K^+]_o}{4.5}\right)^{0.2} \quad (\text{Eq. S55})$$

$$G_{Kr} = 0.02 \cdot 0.83 \cdot 1.6 \cdot C_m$$

The open probability of the channel is described with three gating parameters, y<sub>1</sub>, y<sub>2</sub> and y<sub>3</sub>.

$$p(O)_{Kr} = (0.6 \cdot y_1 + 0.4 \cdot y_2) \cdot y_3 \quad (\text{Eq. S56})$$

$$\frac{dy_1}{dt} = \alpha_{y1} \cdot (1.0 - y_1) - \beta_{y1} \cdot y_1 \quad (\text{Eq. S57})$$

$$\frac{dy_2}{dt} = \alpha_{y2} \cdot (1.0 - y_2) - \beta_{y2} \cdot y_2 \quad (\text{Eq. S58})$$

$$\frac{dy_3}{dt} = \alpha_{y3} \cdot (1.0 - y_3) - \beta_{y3} \cdot y_3 \quad (\text{Eq. S59})$$

$$\alpha_{y1} = \frac{1.0}{35.0 \cdot \exp\left(-\frac{V_m}{10.5}\right) + 75.0 \cdot \exp\left(-\frac{V_m}{100.0}\right)} \quad (\text{Eq. S60})$$

$$\beta_{y1} = \frac{1.0}{470.0 \cdot \exp\left(\frac{V_m}{8.3}\right) + 220.0 \cdot \exp\left(\frac{V_m}{29.0}\right)} \quad (\text{Eq. S61})$$

$$\alpha_{y2} = \frac{1.0}{350.0 \cdot \exp\left(-\frac{V_m}{10.5}\right) + 300.0 \cdot \exp\left(-\frac{V_m}{100.0}\right)} \quad (\text{Eq. S62})$$

$$\beta_{y2} = \frac{1.0}{1850.0 \cdot \exp\left(\frac{V_m}{8.3}\right) + 2200.0 \cdot \exp\left(\frac{V_m}{29.0}\right)} \quad (\text{Eq. S63})$$

$$\alpha_{y3} = \frac{1.0}{0.015 \cdot \exp\left(\frac{V_m}{6.0}\right) + 7.0 \cdot \exp\left(\frac{V_m}{60.0}\right)} \quad (\text{Eq. S64})$$

$$\beta_{y3} = \frac{1.0}{0.114 \cdot \exp\left(-\frac{V_m}{9.2}\right) + 2.3 \cdot \exp\left(-\frac{V_m}{1000.0}\right)} \quad (\text{Eq. S65})$$

### Delayed rectifier K<sup>+</sup> current, slow component (I<sub>Ks</sub>)

The model developed by Asakura *et al.*(2) was used after adjusting P<sub>Ks,K</sub>. I<sub>Ks</sub> is composed of K<sup>+</sup> and Na<sup>+</sup> components described with the modified GHK equations. The permeability ratio is P<sub>Na</sub>/P<sub>K</sub>=0.04.

$$I_{Ks} = (I_{Ks,K_{iz}} + I_{Ks,Na_{iz}}) + (I_{Ks,K_{blk}} + I_{Ks,Na_{blk}}) \quad (\text{Eq. S66})$$

$$I_{Ks,X,a} = f_{Ks,a} \cdot P_{Ks,X} \cdot GHK_X \cdot p(O)_{Ks,a} \quad a = (blk, iz), X = (K, Na) \quad (\text{Eq. S67})$$

### Converting factors

$$P_{Ks,K} = 0.9$$

$$P_{Ks,Na} = 0.04 \cdot P_{Ks,K}$$

Ten percent of the channel population is distributed to *jnc*, and the rest in *blk*.

$$f_{Ks_{iz}} = 0.1$$

$$f_{Ks_{blk}} = 0.9$$

$$p(O)_{Ks,a} = (p(O_v))^2 \cdot (0.99 \cdot p_a(O_c) + 0.01) \quad (\text{Eq. S68})$$

A basal active fraction of 1% was assumed in the Ca<sup>2+</sup> gate.

### Voltage gate

$$\frac{dp(O_v)}{dt} = \alpha_1 \cdot (1.0 - p(O_v)) - \beta_1 \cdot p(O_v) \quad (\text{Eq. S69})$$

$$\alpha_1 = \frac{1.0}{150.0 \cdot \exp\left(-\frac{V_m}{25.0}\right) + 900.0 \cdot \exp\left(-\frac{V_m}{200.0}\right)} \quad (\text{Eq. S70})$$

$$\beta_1 = \frac{1.0}{1000.0 \cdot \exp\left(\frac{Vm}{13.0}\right) + 220.0 \cdot \exp\left(\frac{Vm}{50.0}\right)} \quad (\text{Eq. S71})$$

Calcium gate

The Ca<sup>2+</sup>-dependent activation gate was represented with a three-state scheme; sequential C<sub>1</sub>, C<sub>2</sub> and O<sub>c</sub> states. Ca<sup>2+</sup>-binding reaction was couples with the transition from C<sub>2</sub> to O<sub>c</sub>.  $\alpha_{2a}$  was slightly changed from 2.24.

$$\frac{dp_a(O_c)}{dt} = \alpha_{2a} \cdot p_a(C_2) - \beta_2 \cdot p_a(O_c) \quad (\text{Eq. S72})$$

$$\frac{dp_a(C_2)}{dt} = \alpha_3 \cdot p_a(C_1) - \beta_3 \cdot p_a(C_2) - \alpha_{2a} \cdot p_a(C_2) + \beta_2 \cdot p_a(O_c) \quad (\text{Eq. S73})$$

$$p_a(C_1) = 1 - p_a(C_2) - p_a(O_c) \quad a = (blk, iz) \quad (\text{Eq. S74})$$

$$\alpha_{2a} = 2.25 \cdot [Ca^{2+}]_a$$

$$\beta_2 = 0.000296$$

$$\alpha_3 = 0.0003$$

$$\beta_3 = 0.03$$

### Transient outward K<sup>+</sup> current(I<sub>Kto</sub>)

The model was taken from Asakura *et al.* (2) was used after adjusting P<sub>Kto,K</sub>.

The magnitude of I<sub>Kto</sub> is composed of K<sup>+</sup> and Na<sup>+</sup> components described with GHK and a pNa/pK ratio = 0.09. The conductance as well as the gating were determined separately for the endo(Endo)- and epi(Epi)-cardium. In the present study, the Endo model was used. Replacement by Epi I<sub>Kto</sub> model for the Endo type in the cell model well reconstructed the Epi AP(not shown).

$$I_{Kto} = I_{Kto\_Na} + I_{Kto\_K} \quad (\text{Eq. S75})$$

$$I_{Kto\_X} = P_{Kto\_X} \cdot GHK_X \cdot p(O)_{Kto} \quad X = (K, Na) \quad (\text{Eq. S76})$$

Converting factors in Asakura *et al.* (2014) model were multiplied by 0.73.

$$P_{Kto\_K} = 0.01825 \cdot 0.73(\text{Endo}) \cdot C_m, \quad 0.08553 \cdot 0.73 \cdot C_m(\text{Epi})$$

$$P_{Kto\_Na} = 0.09 \cdot P_{Kto\_K}(\text{End and Epi})$$

The gating is determined by an activation gate (y1) and inactivation gate (y2), both of which are described by the two-state gating scheme.

$$p(O)_{Kto} = y_{1Kto} \cdot y_{2Kto} \quad (\text{Eq. S77})$$

$$\frac{dy_{1Kto}}{dt} = \alpha_{y1Kto} \cdot (1.0 - y_{1Kto}) - \beta_{y1Kto} \cdot y_{1Kto} \quad (\text{Eq. S78})$$

$$\frac{dy_{2Kto}}{dt} = \alpha_{y2Kto} \cdot (1.0 - y_{2Kto}) - \beta_{y2Kto} \cdot y_{2Kto} \quad (\text{Eq. S79})$$

### Endocardium

$$\alpha_{y1Kto} = \frac{1.0}{9.0 \cdot \exp\left(-\frac{V_m}{20.0}\right)} \quad (\text{Eq. S80})$$

$$\beta_{y1Kto} = \frac{1.0}{2.1 \cdot \exp\left(\frac{V_m}{60.0}\right)} \quad (\text{Eq. S81})$$

$$\alpha_{y2Kto} = \frac{1.0}{950.0 \cdot \exp\left(\frac{V_m}{500.0}\right)} \quad (\text{Eq. S83})$$

$$\beta_{y2Kto} = \frac{1.0}{40.0 \cdot \exp\left(-\frac{V_m}{9.0}\right)} + 13.0 \cdot \exp\left(-\frac{V_m}{1000.0}\right) \quad (\text{Eq. S84})$$

### Epicardium

$$\alpha_{y1Kto} = \frac{1.0}{9.0 \cdot \text{Exp}\left(-\frac{V_m}{20.0}\right)} \quad (\text{Eq. S86})$$

$$\beta_{y1Kto} = \frac{1.0}{2.1 \cdot \text{Exp}\left(\frac{V_m}{36.5}\right)} \quad (\text{Eq. S87})$$

$$\alpha_{y2Kto} = \frac{1.0}{365.0 \cdot \text{Exp}\left(\frac{V_m}{8.65}\right) + 9.4 \cdot \text{Exp}\left(\frac{V_m}{5000.0}\right)} \quad (\text{Eq. S88})$$

$$\beta_{y2Kto} = \frac{1.0}{4.0 \cdot \text{Exp}\left(-\frac{V_m}{8.5}\right) + 8.0 \cdot \text{Exp}\left(-\frac{V_m}{5000.0}\right)} \quad (\text{Eq. S89})$$

### Time-independent current

All equations for these currents were taken from Takeuchi *et al.* (8) as described in Asakura *et al.*(2)

### Voltage-dependent potassium current (plateau current)( $I_{Kpl}$ )

$P_{Kpl}$  in the original model was multiplied by 0.4.

$$I_{Kpl} = P_{Kpl} \cdot p(O)_{kpl} \cdot GHK_K \quad (\text{Eq. S90})$$

$$P_{Kpl} = 0.000043 \cdot 0.4 \cdot C_m \cdot \left(\frac{[K^+]_o}{5.4}\right)^{0.16} \quad (\text{Eq. S91})$$

$$p(O)_{kpl} = \frac{V_m}{1 - \exp\left(-\frac{V_m}{13.0}\right)} \quad (\text{Eq. S92})$$

### Background calcium current( $I_{Cab}$ )

$P_{Cab}$  in the original model was multiplied by 0.1.

$$I_{Cab} = I_{Cab_{iz}} + I_{Cab_{blk}} \quad (\text{Eq. S93})$$

$$I_{Cab_a} = P_{Cab_a} \cdot f_{Cab_a} \cdot GHK_{Ca}, \quad a = (blk, iz) \quad (\text{Eq. S94})$$

$$P_{Cab_a} = 0.0006822 \cdot 0.1 \cdot C_m$$

### Fraction of $I_{Cab}$

$$f_{cab\_iz} = 0.1, \quad f_{cab\_blk} = 0.9$$

### Background non-selective cation current( $I_{bNSC}$ )

$$I_{bNSC} = P_{bNSC\_K} + P_{bNSC\_Na} \quad (\text{Eq. S95})$$

$$I_{bNS\_X} = P_{bNSC\_X} \cdot GHK_X, \quad X = (K, Na) \quad (\text{Eq. S96})$$

$$P_{bNSC\_K} = 0.00014 \cdot C_m, \quad P_{bNSC\_Na} = 0.00035 \cdot C_m$$

### Calcium-activated background cation current( $I_{I(Ca)}$ )

$$I_{I(Ca)} = I_{I(Ca)\_Na\_iz} + I_{I(Ca)\_K\_iz} + I_{I(Ca)\_Na\_blk} + I_{I(Ca)\_K\_blk} \quad (\text{Eq. S97})$$

$$I_{I(Ca)\_X\_a} = P_{I(Ca)\_X} \cdot f_{I(Ca)\_a} \cdot GHK_X \cdot p(O)_a \quad X = (Na, K), \quad a = (blk, iz) \quad (\text{Eq. S98})$$

$$P_{I(Ca)\_Na} = 0.00273 \cdot C_m$$

$$P_{I(Ca)\_K} = P_{I(Ca)\_Na}$$

$$p(O)_a = \frac{1.0}{1.0 + \left( \frac{0.0012}{[Ca^{2+}]_a} \right)^3} \quad (\text{Eq. S99})$$

### Fraction of $I_{I(Ca)}$

$$f_{I(Ca)\_iz} = 0.1, \quad f_{I(Ca)\_blk} = 0.9$$

### ATP-sensitive potassium current( $I_{KATP}$ )

$$I_{KATP} = G_{KATP} \cdot (V_m - E_K) \cdot p(O)_{KATP} \cdot x_{IKATP} \quad (\text{Eq. S100})$$

$$G_{KATP} = 17.674 \cdot C_m$$

$$p(O)_{KATP} = \frac{0.8}{1.0 + \left( \frac{[ATP]_{cyt}}{0.1} \right)^2} \quad (\text{Eq. S101})$$

$$x_{IKATP} = 0.0236 \cdot ([K^+]_o)^{0.24} \quad (\text{Eq. S102})$$

### Na<sup>+</sup>/K<sup>+</sup> pump current( $I_{NaK}$ )

The Na<sup>+</sup>/K<sup>+</sup> pump model developed by Oka *et al.* (9) on the framework of Smith and Crampin (10) was used after adjusting Amp<sub>NaK</sub>.

$$I_{NaK} = Amp_{NaK} \cdot V_{cyt\_NaK} \quad (\text{Eq. S103})$$

$$Amp_{NaK} = 25.1779 \cdot C_m$$

$$V_{cyt\_NaK} = V_{step1} \quad (\text{Eq. S104})$$

$$V_{step1} = \alpha_1^+ \cdot P_{1\_6} - \alpha_1^- \cdot P_7 \quad (\text{Eq. S105})$$

$$V_{step2} = \alpha_2^+ \cdot P_7 - \alpha_2^- \cdot P_{8\_13} \quad (\text{Eq. S106})$$

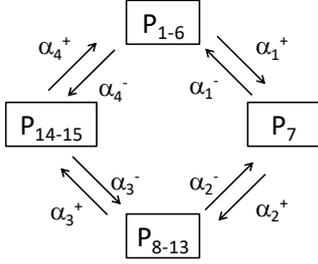
$$V_{step3} = \alpha_3^+ \cdot P_{8\_13} - \alpha_3^- \cdot P_{14\_15} \quad (\text{Eq. S107})$$

$$V_{step4} = \alpha_4^+ \cdot P_{14\_15} - \alpha_4^- \cdot P_{1\_6} \quad (\text{Eq. S108})$$

$$I_{NaK\_Na} = Stoi_{NaK\_Na} \cdot I_{NaK} \quad Stoi_{NaK\_Na} = 3 \quad (\text{Eq. S109})$$

$$I_{NaK\_K} = Stoi_{NaK\_K} \cdot I_{NaK} \quad Stoi_{NaK\_K} = -2 \quad (\text{Eq. S110})$$

The state transition is described by the four-state model.



Scheme 3. Na/K pump model

$$\frac{d(P_{1,6})}{dt} = -\alpha_1^+ \cdot P_{1,6} + \alpha_1^- \cdot P_7 + \alpha_4^+ \cdot P_{14,15} - \alpha_4^- \cdot P_{1,6} \quad (\text{Eq. S111})$$

$$\frac{d(P_7)}{dt} = -\alpha_2^+ \cdot P_7 + \alpha_2^- \cdot P_{8,13} + \alpha_1^+ \cdot P_{1,6} - \alpha_1^- \cdot P_7 \quad (\text{Eq. S112})$$

$$\frac{d(P_{8,13})}{dt} = -\alpha_3^+ \cdot P_{8,13} + \alpha_3^- \cdot P_{14,15} + \alpha_2^+ \cdot P_7 - \alpha_2^- \cdot P_{8,13}$$

(Eq. S113)

$$P_{14,15} = 1 - P_{1,6} - P_7 - P_{8,13} \quad (\text{Eq. S114})$$

#### Rate constants

$$\alpha_1^+ = \frac{k_1^+ \overline{\text{Na}_i}^3}{(1 + \overline{\text{Na}_i})^3 + (1 + \overline{K_i})^2 - 1} \quad (\text{Eq. S115})$$

$$\alpha_2^+ = k_2^+$$

$$\alpha_3^+ = \frac{k_3^+ \overline{K_o}^2}{(1 + \overline{\text{Na}_o})^3 + (1 + \overline{K_o})^2 - 1} \quad (\text{Eq. S116})$$

$$\alpha_4^+ = \frac{k_4^+ \overline{\text{MgATP}}}{1 + \overline{\text{MgATP}}} \quad (\text{Eq. S117})$$

$$\alpha_1^- = k_1^- [\text{MgATP}]_{\text{cyt}} \quad (\text{Eq. S118})$$

$$\alpha_2^- = \frac{k_2^- \overline{\text{Na}_o}^3}{(1 + \overline{\text{Na}_o})^3 + (1 + \overline{K_o})^2 - 1} \quad (\text{Eq. S119})$$

$$\alpha_3^- = \frac{k_3^- [P_i][H^+]}{1 + \overline{\text{MgATP}}} \quad (\text{Eq. S120})$$

$$\alpha_4^- = \frac{k_4^- \overline{K_i}^2}{(1 + \overline{\text{Na}_i})^3 + (1 + \overline{K_i})^2 - 1} \quad (\text{Eq. S121})$$

$$k_1^+ = 0.72, k_1^- = 0.08, k_2^+ = 0.08, k_2^- = 0.008, k_3^+ = 4, k_3^- = 8000, k_4^+ = 0.3, k_4^- = 0.2$$

$$\overline{\text{Na}_i} = \frac{[\text{Na}^+]_i}{K_{d,\text{Na}_i}} \quad (\text{Eq. S122})$$

$$\overline{Na}_o = \frac{[Na^+]_o}{K_{d,Na_o}} \quad (\text{Eq. S123})$$

$$\overline{K}_i = \frac{[K^+]_i}{K_{d,K_i}} \quad (\text{Eq. S124})$$

$$\overline{K}_o = \frac{[K^+]_o}{K_{d,K_o}} \quad (\text{Eq. S125})$$

$$\overline{MgATP} = \frac{[MgATP]_{cyt}}{K_{d,MgATP}} \quad (\text{Eq. S126})$$

$$K_{d,Na_o} = K_{d,Na_o}^0 \cdot \text{Exp} \frac{\Delta_{Na_o} \cdot FV_m}{RT} \quad (\text{Eq. S127})$$

$$K_{d,Na_i} = K_{d,Na_i}^0 \cdot \text{Exp} \frac{\Delta_{Na_i} \cdot FV_m}{RT} \quad (\text{Eq. S128})$$

$$K_{d,K_o} = K_{d,K_o}^0 \cdot \text{Exp} \frac{\Delta_{K_o} \cdot FV_m}{RT} \quad (\text{Eq. S129})$$

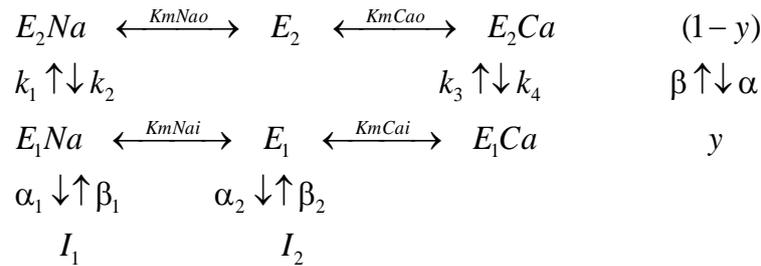
$$K_{d,K_i} = K_{d,K_i}^0 \cdot \text{Exp} \frac{\Delta_{K_i} \cdot FV_m}{RT} \quad (\text{Eq. S130})$$

$$K_{d,Na_i}^0 = 5, K_{d,Na_o}^0 = 26.8, K_{d,K_i}^0 = 18.8, K_{d,K_o}^0 = 0.8, K_{d,MgATP} = 0.6$$

$$\Delta_{Na_i} = -0.14, \Delta_{Na_o} = 0.44, \Delta_{K_i} = -0.14, \Delta_{K_o} = 0.23$$

### Na<sup>+</sup>/Ca<sup>+</sup> exchange current (I<sub>NCX</sub>)

The NCX model developed by Takeuchi *et al.* (8) was used after adjusting the amplitude factor Amp<sub>NCX</sub>.



Scheme 4. NCX model

$$a = (blk, iz)$$

$$I_{NCX} = I_{NCX_{iz}} + I_{NCX_{blk}} \quad (\text{Eq. S131})$$

$$f_{NCX_{iz}} = 0.1, \quad f_{NCX_{blk}} = 0.9$$

$$I_{NCX_{Na_a}} = 3 \cdot I_{NCX_a} \quad (\text{Eq. S132})$$

$$I_{NCX_{Ca_a}} = -2 \cdot I_{NCX_a} \quad (\text{Eq. S133})$$

$$I_{NCX_a} = f_{NCX_a} \cdot \text{Amp}_{NCX} \cdot V_{cyc-NCX_a} \quad (\text{Eq. S134})$$

$$\begin{aligned} Amp_{NCX} &= 61.06 \cdot 0.5 \cdot C_m \\ V_{cyl\_NCX\_a} &= k_1 \cdot q_a(E_1Na) \cdot q(E_1)_{NCX\_a} - k_2 \cdot q_a(E_2Na) \cdot q(E_2)_{NCX\_a} \end{aligned} \quad (\text{Eq. S135})$$

### Fraction of $I_{NCX}$

$$f_{NCX\_iz} = 0.1, \quad f_{NCX\_blk} = 0.9$$

$$\begin{aligned} \frac{dp(E_1)_{NCX\_a}}{dt} &= p(E_2)_{NCX\_a} \cdot \alpha_E + p(I_1)_{NCX\_a} \cdot \beta_{1\_a} + p(I_2)_{NCX\_a} \cdot \beta_{2\_a} \\ &\quad - p(E_1)_{NCX\_a} \cdot (\beta_{E_a} + \alpha_{1\_X} + \alpha_{2\_X}) \end{aligned} \quad (\text{Eq. S136})$$

$$\frac{dp(I_1)_{NCX\_a}}{dt} = p(E_1)_{NCX\_a} \cdot \alpha_{1\_a} - p(I_1)_{NCX\_a} \cdot \beta_{1\_a} \quad (\text{Eq. S137})$$

$$\frac{dp(I_2)_{NCX\_a}}{dt} = p(E_1)_{NCX\_a} \cdot \alpha_{2\_a} - p(I_2)_{NCX\_a} \cdot \beta_{2\_a} \quad (\text{Eq. S138})$$

$$p(E_2)_{NCX\_a} = 1 - p(E_1)_{NCX\_a} - p(I_1)_{NCX\_a} - p(I_2)_{NCX\_a} \quad (\text{Eq. S139})$$

$$q_a(E_1Na) = \frac{1.0}{\left(1.0 + \left(\frac{K_{m,Na}i}{[Na^+]_i}\right)^3\right) \cdot \left(1.0 + \frac{[Ca^{2+}]_a}{K_{m,Ca}i}\right)} \quad (\text{Eq. S140})$$

$$q_a(E_1Ca) = \frac{1.0}{\left(1.0 + \frac{K_{m,Ca}i}{[Ca^{2+}]_a}\right) \cdot \left(1.0 + \left(\frac{[Na^+]_i}{K_{m,Na}i}\right)^3\right)} \quad (\text{Eq. S141})$$

$$q(E_2Na) = \frac{1.0}{\left(1.0 + \left(\frac{K_{m,Na}o}{[Na^+]_o}\right)^3\right) \cdot \left(1.0 + \frac{[Ca^{2+}]_a}{K_{m,Ca}o}\right)} \quad (\text{Eq. S142})$$

$$q(E_2Ca) = \frac{1.0}{\left(1.0 + \frac{K_{m,Ca}o}{[Ca^{2+}]_a}\right) \cdot \left(1.0 + \left(\frac{[Na^+]_o}{K_{m,Na}o}\right)^3\right)} \quad (\text{Eq. S143})$$

$$\alpha_{1\_a} = q_a(E_1Na) \cdot (f_{caina\_a} \cdot \alpha_{1\_on} + (1 - f_{caina\_a}) \cdot \alpha_{1\_off}) \quad (\text{Eq. S144})$$

$$\beta_{1\_a} = f_{caina\_a} \cdot \beta_{1\_on} + (1 - f_{caina\_a}) \cdot \beta_{1\_off} \quad (\text{Eq. S145})$$

$$\alpha_{2\_a} = f_{caina\_a} \cdot \alpha_{2\_on} + (1 - f_{caina\_a}) \cdot \alpha_{2\_off} \quad (\text{Eq. S146})$$

$$\beta_{2\_a} = f_{caina\_a} \cdot \beta_{2\_on} + (1 - f_{caina\_a}) \cdot \beta_{2\_off} \quad (\text{Eq. S147})$$

$$\alpha_{1\_on} = 0.002, \quad \alpha_{1\_off} = 0.0015, \quad \beta_{1\_on} = 0.0012, \quad \beta_{1\_off} = 0.0000005$$

$$\alpha_{2\_on} = 0.00006, \quad \alpha_{2\_off} = 0.02, \quad \beta_{2\_on} = 0.18, \quad \beta_{2\_off} = 0.0002$$

$$\alpha_E = k_2 \cdot q(E_1Na) + k_4 \cdot q(E_2Ca) \quad (\text{Eq. S148})$$

$$\beta_{E\_a} = k_1 \cdot q_a(E_1Na) + k_3 \cdot q_a(E_2Ca) \quad (\text{Eq. S149})$$

$$k_1 = \exp\left(\frac{0.32 \cdot F \cdot V_m}{R \cdot T}\right) \quad (\text{Eq. S150})$$

$$k_2 = \exp\left(\frac{(0.32-1) \cdot F \cdot V_m}{R \cdot T}\right) \quad (\text{Eq. S151})$$

$$k_3 = 1.0, \quad k_4 = 1.0$$

$$f_{Caina\_a} = \frac{[Ca^{2+}]_a}{[Ca^{2+}]_a + K_{m,act}} \quad (\text{Eq. S153})$$

$$K_{m,act} = 0.004$$

$$K_{m,Nao} = 87.5, \quad K_{m,Nai} = 20.74854, \quad K_{m,Cao} = 1.38, \quad K_{m,Cai} = 0.0184$$

### Plasma membrane Ca<sup>2+</sup>-ATPase current (I<sub>PMCA</sub>)

The model equation used in Grandi *et al.* (11) was used for *iz* and *blk* after adjusting the amplitude factor Amp<sub>PMCA</sub>. H<sup>+</sup> was neglected for convenience.

$$I_{PMCA} = I_{PMCA\_iz} + I_{PMCA\_blk} \quad (\text{Eq. S154})$$

$$I_{PMCA\_a} = f_{PMCA\_a} \cdot Amp_{PMCA} \cdot \frac{([Ca^{2+}]_a)^{1.6}}{(K_m)^{1.6} + ([Ca^{2+}])^{1.6}} \quad (\text{Eq. S155})$$

$$a = (blk, iz)$$

$$f_{PMCA\_iz} = 0.1, \quad f_{PMCA\_blk} = 0.9, \quad Amp_{PMCA} = 0.19 \cdot C_m, \quad K_m = 0.0005$$

### CaRU

#### LCC

The tightly coupled LCC-RyR kinetic model developed by Hinch *et al.* (12) was used after decreasing  $P_{RyR}$  to 5191 from 5967.67 (fL/ms). The new LCC model is described in the section of the L-type Ca<sup>2+</sup> current.

#### RyR channel

The state transition of a RyR is defined by the two-state transition with the activation rate,  $k_{co}$  and deactivation rate  $k_{oc}$ .  $Q_{10}$  is a temperature factor ( $Q_{10}=3$ )

$$k_{co} = Q_{10} \cdot \frac{0.4}{1 + \left(\frac{0.025}{[Ca^{2+}]_{nd}}\right)^{2.7}} \quad (\text{Eq. S156})$$

The  $[Ca^{2+}]_{nd}$  for the activation is,

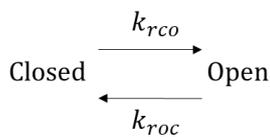
$$[Ca^{2+}]_{nd} = Ca_{L0} \text{ for LCC-dependent activation of a RyR}$$

$$[Ca^{2+}]_{nd} = Ca_{00} \text{ for spontaneous activation of a RyR}$$

$$k_{oc} = Q_{10} \cdot 0.5664 \quad (\text{Eq. S157})$$

$$f_t = \frac{k_{co}}{k_{co} + k_{oc}} \quad (\text{Eq. S158})$$

The state transition of couplon at the regenerative step is also described by the two-state transition scheme.



Scheme 5. Two-state model

The activation rate  $k_{rco}$  and the deactivation rate  $k_{roc}$  are,

$$k_{rco} = f_n \cdot f_t \cdot k_{co} \cdot (sloc0 + [Ca^{2+}]_{SRrl}) \quad (\text{Eq. S159})$$

$$f_n = 7, sloc0 = 0.1$$

$[Ca^{2+}]_{nd} = Ca_{LR}$  for LCC-dependent activation,

$[Ca^{2+}]_{nd} = Ca_{OR}$  for RyR-dependent spontaneous activation,

$$k_{roc} = k_{co} \cdot pC^{((N_{RyR}-1) \cdot 0.74)} \quad pC = \frac{k_{oc}}{k_{oc} + f_t \cdot \frac{k_{rco}}{f_n}} \quad (\text{Eq. S160})$$

The  $f_t$  is calculated using  $Ca_{00}$ .  $N_{RyR}$  is the number of RyRs in a couplon and assumed to be 10.

The  $[Ca^{2+}]_{nd}$  is defined as  $Ca_{00}$ ,  $Ca_{OR}$ ,  $Ca_{LO}$  or  $Ca_{LR}$ .

LCC closed; RyR closed:

$$Ca_{00} = [Ca^{2+}]_{jnc} \quad (\text{Eq. S161})$$

LCC closed; RyR open:

$$Ca_{OR} = \frac{Ca_{00} + f_R \cdot [Ca^{2+}]_{SRrl}}{1 + f_R} \quad (\text{Eq. S162})$$

$$f_R = 0.31$$

LCC open; RyR closed:

$$Ca_{LO} = \frac{Ca_{00} + f_L \cdot \frac{\delta V \cdot e^{-\delta V}}{1 - e^{-\delta V}} [Ca^{2+}]_o}{(1 + f_L \cdot \frac{\delta V}{1 - e^{-\delta V}})} \quad (\text{Eq. S163})$$

$$f_L = 0.014$$

LCC open; RyR open:

$$Ca_{LR} = \frac{Ca_{00} + f_R \cdot [Ca^{2+}]_{SRrl} + f_L \cdot \frac{\delta V \cdot e^{-\delta V}}{1 - e^{-\delta V}} [Ca^{2+}]_o}{1 + f_R + f_L \cdot \frac{\delta V}{1 - e^{-\delta V}}} \quad (\text{Eq. S164})$$

$$\delta = \frac{2 \cdot F}{R \cdot T} \quad (\text{Eq. S165})$$

$$p(O)_t = p(O) + p(O)_{base} \quad (\text{Eq. S166})$$

$$p(O)_{base} = 0.000075$$

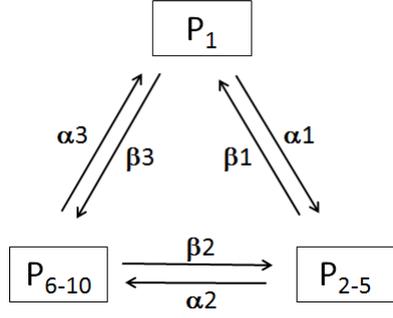
$$p(O) = Y_{ooo} + Y_{coo} + Y_{cco} + Y_{oco} \quad (\text{Eq. S167})$$

$$J_{Ca\_rel} = P_{RyR} \cdot p(O)_t \cdot ([Ca^{2+}]_{SRrl} - [Ca^{2+}]_{jnc}) \cdot Sc_{cell} \quad (\text{Eq. S168})$$

$$P_{RyR} = 5191 (f_L \cdot ms^{-1}) \quad (\text{whole cell})$$

### Sarcoplasmic reticulum $Ca^{2+}$ pump (SERCA) current ( $J_{SERCA}$ )

The three-state model developed by Trans *et al.* (13) was used after several minor modifications as described Asakura *et al.* (2). The limiting amplitude of  $J_{SERCA}$ ,  $amp_{SERCA}$ , was modified.



Scheme 6. SERCA model

$$J_{SERCA} = \frac{ampSERCA \cdot V_{cyc}}{2 \cdot F \cdot 1000} \cdot Sc_{cell} \quad (\text{Eq. S169})$$

$$ampSERCA = 106444.8 \text{ (mmol} \cdot \text{ms}^{-1}\text{)}$$

$$V_{cyc} = \frac{6.86 \cdot (\alpha1 \cdot \alpha2 \cdot \alpha3 - \beta1 \cdot \beta2 \cdot \beta3)}{\alpha2 \cdot \alpha3 + \beta1 \cdot \beta2 + \alpha1 \cdot \alpha3 + \beta2 \cdot \alpha1 + \beta2 \cdot \beta3 + \alpha1 \cdot \alpha2 + \beta3 \cdot \beta1 + \beta3 \cdot \alpha2} \quad (\text{Eq. S170})$$

$$\alpha1 = 25900 \cdot [MgATP]_{cyt} \quad (\text{Eq. S171})$$

$$\alpha2 = \frac{2540}{1 + \left( \frac{Kd_{Cai}}{[Ca_{free}^{2+}]_{blk}} \right)^{1.7}} \quad (\text{Eq. S172})$$

$$\alpha3 = \frac{5.35}{1 + \left( \frac{[Ca^{2+}]_{SRup}}{Kd_{Casr}} \right)^{1.7}} \quad (\text{Eq. S173})$$

$$\beta1 = \frac{0.1972}{1 + \left( \frac{[Ca_{free}^{2+}]_{blk}}{Kd_{Cai}} \right)^{1.7}} \quad (\text{Eq. S174})$$

$$\beta2 = \frac{25435 \cdot [MgADP]_{cyt}}{1 + \left( \frac{Kd_{Casr}}{[Ca^{2+}]_{SRup}} \right)^{1.7}} \quad (\text{Eq. S175})$$

$$\beta3 = 149 \cdot [Pi] \quad (\text{Eq. S176})$$

$$Kd_{Cai} = 0.0027 \text{ (mM)}, Kd_{Casr} = 1.378 \text{ (mM)}$$

## 5. Contraction

The original model Negroni and Lascano (14) was used. Six states of troponin systems (TS), each system composed by 3 adjacent troponin-propomyosin regulatory units acting cooperatively: free TS; Ca<sup>2+</sup> bound to TS without attached CBs (TSCa<sub>3</sub>), Ca<sup>2+</sup> bound to TS with attached CBs in the weak state (TSCa<sub>3w</sub>), Ca<sup>2+</sup> bound to TS without attached CBs in the power state (TSCa<sub>3s</sub>), TS without Ca<sup>2+</sup> with attached CBs in the power state (TS<sub>s</sub>) and TS without Ca<sup>2+</sup> with attached CBs in the weak state (TS<sub>w</sub>).

The rate of ATP hydrolysis by myosin ATPase (ATP<sub>contraction</sub>) is calculated by Eq.S177;

$$\frac{dATP_{contraction}}{dt} = ratioATP \cdot (Y_p \cdot [TSCa_w] + Z_q \cdot [TS_w]) \cdot V_{cell} \quad (\text{Eq. S177})$$

where ratioATP is the stoichiometry of myosin ATPase for each troponin contraction.

### Dynamics of the eCB elongation(h)

All equations to calculate the eCB dynamics are the same as in the original model of Negroni and Lascano (14). The half sarcomere length (halfSL) was represented as a sum of the elongation of the equivalent crossbridge (eCB) and the rest X for each of the powered and weakly-bound eCBs.  $h_p$  and  $h_w$  represent elongation of the elastic component of the strong-bound CB state and weak-bound CB state.

$$X_p = halfSL - h_p \quad (\text{Eq. S178})$$

$$X_w = halfSL - h_w \quad (\text{Eq. S179})$$

The rate of change in X(dX/dt) is,

$$\frac{dX_p}{dt} = B \cdot (h_p - h_{pr}) \quad (\text{Eq. S180})$$

$$\frac{dX_w}{dt} = B \cdot (h_w - h_{wr}) \quad (\text{Eq. S181})$$

Rated parameters are given in Table S7, and  $A_p$  and  $A_w$  are the stiffness summed for each type eCBs within a cell. The  $L_e$  and  $K_e$  are the spring constant of the parallel elastic component.

### Developed tension

#### CB force

CB force ( $F_b$ ) is given by the sum of weak CB force ( $F_{bw}$ ) and powered CB force ( $F_{bp}$ ).

$$F_b = F_{bw} + F_{bp} \quad (\text{Eq. S182})$$

$$F_{bw} = n_{CaBS} \cdot A_w \cdot ([TSCa_{3w}] + [TS_w]) \cdot h_w \quad (\text{Eq. S183})$$

$$F_{bp} = n_{CaBS} \cdot A_p \cdot ([TSCa_{3s}] + [TS_s]) \cdot h_p \quad (\text{Eq. S184})$$

#### The force of the parallel elastic element

$$F_p = K_e \cdot (L_{hSL} - L_0)^5 + L_e \cdot (L_{hSL} - L_0) \quad (\text{Eq. S185})$$

#### The detachment rates of CB

$$g = Z_a \cdot Y_v \cdot (1 - e^{-\gamma \cdot (h_w - h_{wr})^2}) \quad (\text{Eq. S186})$$

$$g_d = Y_d \cdot Y_c \cdot (L - L_c)^2 + Y_{vd} \cdot (1 - e^{-\gamma \cdot (h_w - h_{wr})^2}) \quad (\text{Eq. S187})$$

$$F_h = \begin{cases} 0.1; h_w > h_{wr} \\ 1; h_w \leq h_{wr} \end{cases} \quad (\text{Eq. S188})$$

#### Calculation of state transitions of the model

$Y_b, Z_b, f, g, Y_p, Z_p, Y_r, Z_r, Y_q, Z_q$  and  $g_d$  are rate constants of the reaction.

$$\frac{d[TSCa_3]}{dt} = Y_b \cdot [TS] \cdot ([Ca_{free}^{2+}]_{blk} \cdot 1000)^3 - Z_b \cdot [TSCa_3] + g \cdot [TSCa_{3w}] - f \cdot [TSCa_3] \text{eff} \quad (\text{Eq. S189})$$

$$\frac{d[TSCa_{3w}]}{dt} = f \cdot [TSCa_3] \text{eff} - g \cdot [TSCa_{3w}] + Z_p \cdot [TSCa_{3s}] - Y_p \cdot [TSCa_{3w}] \quad (\text{Eq. S190})$$

$$\frac{d[TSCa_{3s}]}{dt} = Y_p \cdot [TSCa_{3w}] - Z_p \cdot [TSCa_{3s}] + Z_r \cdot [TS_s] \cdot \left( [Ca_{free}^{2+}]_{blk} \cdot 1000 \right)^3 - Y_r \cdot [TSCa_{3s}] \quad (\text{Eq. S191})$$

$$\frac{d[TS_s]}{dt} = Y_r \cdot [TSCa_{3s}] - Z_r \cdot [TS_s] \cdot \left( [Ca_{free}^{2+}]_{blk} \cdot 1000 \right)^3 + Z_q \cdot [TS_w] - Y_q \cdot [TS_s] \quad (\text{Eq. S192})$$

$$\frac{d[TS_w]}{dt} = Y_q \cdot [TS_s] - Z_q \cdot [TS_w] - g_d \cdot [TS_w] \quad (\text{Eq. S193})$$

$$[TS] = [TS_{tot}] - [TSCa_3] - [TSCa_{3w}] - [TSCa_{3s}] - [TS_s] - [TS_w] \quad (\text{Eq. S194})$$

$$[TSCa_3]_{eff} = e^{-R(L-La)^2} \cdot [TSCa_3] \quad (\text{Eq. S195})$$

**Table S7.** Parameters in Hybrid model

Parameter	Hybrid model	Units
$A_p$	2700	$mNmm^{-2}\mu m^{-1}\mu M^{-1}$
$A_w$	540	$mNmm^{-2}\mu m^{-1}\mu M^{-1}$
$B_p$	0.5	$ms^{-1}$
$B_w$	0.2	$ms^{-1}$
$\gamma$	28000	$\mu m^{-2}$
f	0.0023	$ms^{-1}$
$h_{pr}$	0.006	$\mu m$
$h_{wr}$	0.0001	$\mu m$
$K_e$	105000	$mNmm^{-2}\mu m^{-5}$
$L_a$	1.15	$\mu m$
$L_e$	10	$mNmm^{-2}\mu m^{-1}$
$[TS_{tot}]$	23	$\mu M$
$n_{CaBS}$	3	unitless
R	15	$\mu m^{-2}$
$Y_b$	0.1816	$\mu M^{-3}ms^{-1}$
$Y_c$	1.0	$ms^{-1}\mu m^{-2}$
$Y_d$	0.0333	$ms^{-1}$
$Y_p$	0.1397	$ms^{-1}$
$Y_q$	0.2328	$ms^{-1}$
$Y_r$	0.1397	$ms^{-1}$
$Y_v$	1.5	$ms^{-1}$
$Z_a$	0.0023	$ms^{-1}$
$Z_b$	0.1397	$ms^{-1}$
$Z_p$	0.2095	$ms^{-1}$

$Z_q$	0.3724	$ms^{-1}$
$Z_r$	7.2626	$ms^{-1}$

$A_p$	parameter describing the bridge force of the power work state
$A_w$	parameter describing the bridge force of the weak state
$B$	parameter describing equivalent CB kinetics
$CB$	attached cross-bridge
$f$	kinetic reaction constant for the CB attaching step
$F_b$	total CB force
$F_{bp}$	CB force of attached CB in power states
$F_{bw}$	CB force of attached CB in weak states
$F_h$	parameter for asymmetry
$F_p$	parallel force
$g$	parameter representing CB detachment step from $cAM_{DPw}$
$\gamma$	parameter describing $Y_v$ detachment pathway
$h_p$	mean elongation of attached CBs in power work state
$h_w$	mean elongation of attached CBs in weak state
$h_{pr}$	steady elongation of attached CBs in power work state
$h_{wr}$	steady elongation of attached CBs in weak state
$K_e$	parameter describing the parallel elastic element
$L_{hSL}$	half sarcomere length
$L_0$	parameter describing the parallel elastic element
$L_a$	parameter constraining the $[cM_{DP}]$ , giving effective $[cM_{DP}]$
$L_e$	parameter describing the parallel elastic element
$n_{CaBS}$	number $nCa^{2+}$ of CBs for a single TS
$R_a$	parameter describing the kurtosis of the curve
$X_p$	non-elastic portion of the contractile element equals to $L_{hSL} - h_p$
$X_w$	non-elastic portion of the contractile element equals to $L_{hSL} - h_w$

## 6. Metabolic parameters

**Table S8.** Values of the model parameters

Parameters	Values	Units
$[Pi_{free}]_{cyt}$	0.50872066859173026	$mM$
$[AMP]_{cyt}$	0.00033459021041526427	$mM$
$[ADP_{free}]_{cyt}$	0.0022536111580301241	$mM$

$[MgADP]_{cyt}$	0.025978226605534577	<i>mM</i>
$[ATP_{free}]_{cyt}$	0.039789862258604494	<i>mM</i>
$[MgATP]_{cyt}$	6.631643709767415	<i>mM</i>
$[Cr]_{cyt}$	12.6772372798697	<i>mM</i>

### ATP consumption:

$$v_{cons} = \frac{dATP_{membrane}}{dt} + \frac{dATP_{contraction}}{dt} \quad (\text{Eq. S196})$$

$$\frac{dATP_{membrane}}{dt} = \frac{dATP_{NaK} + dATP_{PMCA\_blk} + dATP_{PMCA\_iz} + dATP_{SERCA}}{v_{cyt}} \quad (\text{Eq. S197})$$

## 7. Initial values of HuVEC model

$$V_m = -91.4466885079348$$

$$V_o = 0$$

$$V_i = V_m + V_o$$

$$TnChCa = 0.110742559707052 * 0.9$$

$$CaMCA = 0.000228581865602447 * 0.9$$

$$bufferSRCa = 0.00172960014640511 * 0.9$$

$$Lb\_jnc = 0.0218215322629436$$

$$Lb\_iz = 0.0075621764602356$$

$$Hb\_jnc = 0.185094540066232$$

$$Hb\_iz = 0.0769149150028914$$

$$Nai = 6.66894310282034$$

$$Ki = 139.238265011042$$

$$Catot\_jnc = 0.207176351449979$$

$$Catot\_iz = 0.084640522722006$$

$$Catot\_blk = 0.11279654524634$$

$$Ca\_SRup = 0.761077662687456$$

$$Catot\_SRrl = 2.21876221622152$$

$$O\_TM = 0.000000706725155695262$$

$$I2\_TM = 0.0117704053067285$$

$$Is\_TM = 0.304002781414015$$

Is\_LSM = 0.2  
I2\_LSM = 0  
C\_LSM = 1.0 - Is\_LSM - I2\_LSM  
fixzero\_INaLslowgate = 0

Yco\_iz = 0.992251726297519  
Yoc\_iz = 0.000000024556270151713  
Yoo\_iz = 0.00000314564543512061  
Yco\_blk = 0.992424981547859  
Yoc\_blk = 0.0000000240070147854924  
Yoo\_blk = 0.00000314619469048683

Yooo = 0.00000172489315884865  
Yooc = 0.00000142034754677507  
Ycoo = 0.0000138422676498755  
Ycoc = 0.992110534408681  
Ycco = 0.0000000953816272498217  
Yoco = 0.00000000000156949238162028  
Yocc = 0.0000000249594301562175

y1\_IKr = 0.0000440909425988806  
y2\_IKr = 0.000003386  
y3\_IKr = 0.999363731

paraxs1\_iz = 0.277482694590328  
paraxs2\_iz = 0.000131110342877451  
paraxs1\_blk = 0.277482694590328  
paraxs2\_blk = 0.000131110342877451

Ov\_IKs = 0.01  
C2IKs\_iz = 0.2  
OcIKs\_iz = 0.01  
C2IKs\_blk = 0.2  
OcIKs\_blk = 0.01

a\_IKto = 0.000793627635934239

y1\_IKto = 0.999756080468878

y2\_IKto = 0.575995954010486

Pbspm = 0.594875991179992

E1NCX\_iz = 0.238718640001014

I1NCX\_iz = 0.13771129457898

I2NCX\_iz = 0.622892868847556

E1NCX\_blk = 0.111872123711613

I1NCX\_blk = 0.203023555446362

I2NCX\_blk = 0.684869019924837

P1\_6\_NaK = 0.435289193632868

P7\_NaK = 0.0831770174499825

P8\_13\_NaK = 0.281082409575779

halfSL = 1.09840500012898

Fb = 0.0502092089156129

Fp = 4.94926096641491

TSCa3 = 0.00899891910620064

TSCa3W = 0.000369547640656701

TSCa3S = 0.000153834503967436

TSS = 0.000876347322180234

TSW = 0.000492054058977473

hw = 0.000100147615113241

hp = 0.00600014761511324

ATPt\_cyt = 6.67701543987464

ADPt\_cyt = 0.0227671477707

Pi\_cyt = 0.381130087573153

PCr\_cyt = 13.9261301893242

ATPt\_mit = 6.20328024045349

Pi\_mit = 2.23625256468335

NADH\_mit = 1.60566548407208

H\_mit = 0.0000285579652594013

K\_mit = 117.80018539511  
UQr\_mit = 0.201994111666095  
ctCrd\_mit = 0.0448941156153114  
dpsi = -159.077387598919

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