Text S1

Supplementary Material for "NHE Inhibition Does Not Improve Na^+ or Ca^{2+} Overload During Reperfusion: Using Modeling to Illuminate the Mechanisms Underlying a Therapeutic Failure."

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Symbols and Values

Abbreviation	Parameter	Units	Constant Value
A_{cap}	capacitive area	cm^2	0.0001534 [1]
aa_{AE}	transition rate (AE)	N/A	N/A
aa_{CHE}	transition rate (CHE)	N/A	N/A
aa_{NBC}	transition rate (NBC)	N/A	N/A
aa_{NHE}	transition rate (NHE)	N/A	N/A
[ADP]	ADP concentration	mM	N/A
α_h	opening rate constant for h gate	ms^{-1}	N/A
α_j	opening rate constant for j gate	ms^{-1}	N/A
α_{K1}	rate constant for I_{K1} inactivation	ms^{-1}	N/A
α_m	opening rate constant for m gate	ms^{-1}	N/A
α_p	opening rate constant for p gate	ms^{-1}	N/A
α^{+}_{NaK1}	forward rate constant (NaK)	s^{-1}	N/A
α^{-}_{NaK1}	reverse rate constant (NaK)	s^{-1}	N/A
α^{+}_{NaK2}	forward rate constant (NaK)	s^{-1}	N/A
α^{-}_{NaK2}	reverse rate constant (NaK)	s^{-1}	N/A
α^{+}_{NaK3}	forward rate constant (NaK)	s^{-1}	N/A
α^{-}_{NaK3}	reverse rate constant (NaK)	s^{-1}	N/A
α^{+}_{NaK4}	forward rate constant (NaK)	s^{-1}	N/A
α^{-}_{NaK4}	reverse rate constant (NaK)	s^{-1}	N/A
$\alpha^{+}_{1,SERCA}$	apparent forward rate constant	s^{-1}	N/A
$\alpha^{-}_{1,SERCA}$	apparent reverse rate constant	s^{-1}	N/A
$\alpha^{+}_{2,SERCA}$	apparent forward rate constant	s^{-1}	N/A
$\alpha^{-}_{2,SERCA}$	apparent reverse rate constant	s^{-1}	N/A
$\alpha^{+}_{3,SERCA}$	apparent forward rate constant	s^{-1}	N/A
$\alpha^{-}_{3,SERCA}$	apparent reverse rate constant	s^{-1}	N/A
[AMP]	AMP concentration	mM	N/A
[$Anion^{-}$]	concentration of conjugate anions due to metabolic acidosis	mM	N/A
[ATP]	ATP concentration	mM	N/A
$[\widetilde{ATP}]$	apparent concentration of enzyme-bound ion (NaK)	N/A	N/A
b	$I_{Ca,t}$ activation gate	N/A	N/A
b_∞	steady state value for b gate	N/A	N/A
bb_{AE}	transition rate (AE)	N/A	N/A
bb_{CHE}	transition rate (CHE)	N/A	N/A
bb_{NBC}	transition rate (NBC)	N/A	N/A

Table S1: Note: numbers in brackets refer to citations in the biblography at the end of this supplement.

Abbreviation	Parameter	Units	Constant Value
bb_{NHE}	transition rate (NHE)	N/A	N/A
β_{cai}	Ca^{2+} buffering	N/A	N/A
β_{CMDN}	calmodulin buffering power	N/A	N/A
β_{CSQN}	calsequestrin buffering power	N/A	N/A
β_e	extracellular intrinsic (non-CO_2) buffering capacity	N/A	N/A
β_h	closing rate constant for h gate	ms^{-1}	N/A
β_i	intracellular intrinsic (non-CO_2) buffering capacity	N/A	N/A
β_j	closing rate constant for j gate	ms^{-1}	N/A
β_{K1}	rate constant for I_{K1} inactivation	ms^{-1}	N/A
β_m	closing rate constant for m gate	ms^{-1}	N/A
β_p	closing rate constant for p gate	ms^{-1}	N/A
β_{TRPN}	troponin buffering powering power	N/A	N/A
c_{ADP}	closed prob. because two ADP molecules not bound to one subunit	N/A	N/A
$[Ca_i^{2+}]$	intracellular Ca^{2+} concentration	mM	N/A
$[Ca_o^{2+}]$	extracellular Ca^{2+} concentration	mM	N/A
$\widetilde{Ca}_{i,SERCA}$	apparent Ca^{2+} binding to SERCA in myoplasm	N/A	N/A
$\widetilde{Ca}_{SR,SERCA}$	apparent Ca^{2+} binding to SERCA in SR	N/A	N/A
cc_{AE}	transition rate (AE)	N/A	N/A
cc_{CHE}	transition rate (CHE)	N/A	N/A
cc_{NBC}	transition rate (NBC)	N/A	N/A
cc_{NHE}	transition rate (NHE)	N/A	N/A
$[Cl_e^-]$	extracellular chloride concentration	mM	146.7 [2]
$[Cl_i^-]$	intracellular chloride concentration	mM	N/A
C_m	membrane capacitance	uF/cm^2	1.0 [1]
[CMDN]	concentration of Ca^{2+} bound to calmodulin	mM	N/A
$\overline{[CMDN]}$	max $[Ca^{2+}]$ bound to calmodulin	mM	0.050 [1]
$[CO_{2,e}]$	extracellular carbon dioxide concentration	mM	N/A
CO_{2sol}	carbon dioxide solubility	mM	0.03253 [1]
$[CO_{2,i}]$	intracellular carbon dioxide concentration	mM	N/A
[Cr]	creatine concentration	mM	N/A
[CSQN]	concentration of Ca^{2+} bound to calsequestrin	mM	N/A
csqnth	threshold for Ca^{2+}release from CSQN due to JSR overload	mM	8.75 [1]
$\overline{[CSQN]}$	max $[Ca^{2+}]$ bound to calsequestrin	mM	10.0 [1]
cyc_{NaK}	clockwise steady-state cycle rate (NaK)	s^{-1}	N/A
cyc_{SERCA}	SERCA cycling rate	s^{-1}	N/A
C_0	constant used in calculating voltage by charge diff. method	mM	N/A
c1	scaling factor for I_{NaCa}	uA/uF	0.00015
c2	half-saturation concentration for NaCa exchanger	mM	0.0001 [1]
d	$I_{Ca(L)}$ activation gate	N/A	N/A
d_∞	steady state value for d gate	N/A	N/A
dd_{AE}	transition rate (AE)	N/A	N/A
dd_{CHE}	transition rate (CHE)	N/A	N/A
dd_{NBC}	transition rate (NBC)	N/A	N/A
dd_{NHE}	transition rate (NHE)	N/A	N/A
Δt	time step	ms	0.005
$density_{NaK}$	density of NaK pump enzymes in sarcolemma	um^{-2}	7450.0 [3]
$dI_{Ca,total}$	rate of Ca^{2+} flux across membrane	uA/(uF*ms)	N/A
dvdtnew	change in V between time steps	mV/ms	N/A
E_{Ca}	Ca^{2+} reversal potential	mV	N/A
E_K	K^+ reversal potential	mV	N/A

Abbreviation	Parameter	Units	Constant Value
E_{Ks}	K^+ reversal potential for I_{Ks}	mV	N/A
E_{Na}	Na^+ reversal potential	mV	N/A
F	Faraday's constant	C/mol	96485.0 [1]
f	$I_{Ca(L)}$ inactivation gate	N/A	N/A
f_∞	steady state value for f gate	N/A	N/A
f_{ADP}	open probability due to ADP binding	N/A	N/A
f'_{ADP}	open probability due to ADP binding	N/A	N/A
f_{ATP}	fraction of channels open because no ATP binding	N/A	N/A
f_{Ca}	$I_{Ca(L)}$ Ca^{2+} dependent inactivation gate	N/A	N/A
$f_{Ca,ATP}$	relative $I_{Ca(L)}$ channel availability	N/A	N/A
$f_{K(ATP)}$	open probability (no ATP or two ADP bound to subunit)	N/A	N/A
$fac_{H,RYR}$	pH-dependent modification of RYR activity	N/A	N/A
fac_{NaCa}	pH-dependent modification of NaCa activity	N/A	N/A
factorNaKdel	determines voltage dependence of binding reactions	N/A	-0.17952 [3]
flag	Boolean variable used to test for dvdtmax	N/A	N/A
g	$I_{Ca,t}$ inactivation gate	N/A	N/A
g_∞	steady state value for g gate	N/A	N/A
$g_{Ca,b}$	max. $I_{Ca,b}$ conductance	mS/uF	0.003016 [1]
$g_{Ca,t}$	max. $I_{Ca,t}$ conductance	mS/uF	0.05 [1]
$g_{K(ATP)}$	$I_{K(ATP)}$ channel conductance	mS/uF	N/A
g_{Kp}	I_{Kp} channel conductance	mS/uF	0.00552 [1]
g_{Kr}	I_{Kr} channel conductance	mS/uF	N/A
g_{Ks}	I_{Ks} channel conductance	mS/uF	N/A
g_{K1}	I_{K1} channel conductance	mS/uF	N/A
g_{maxrel}	max. rate constant of Ca^{2+} release from JSR	ms^{-1}	37.5 [1]
g_{Na}	max. I_{Na} conductance	mS/uF	16.0 (14.4 ischemia) [4]
$g_{Na,b}$	max. $I_{Na,b}$ conductance	mS/uF	0.002 [1]
$g_{relbarjsrol}$	rate constant of Ca^{2+} release from JSR due to overload	ms^{-1}	4.0 [1]
$g_{reljsrol}$	rate of constant Ca^{2+} release from JSR due to CICR	ms^{-1}	N/A
gacai	intracellular Ca^{2+} activity coefficient	N/A	1.0 [1]
gacao	extracellular Ca^{2+} activity coefficient	N/A	0.341 [1]
gaki	intracellular K^+ activity coefficient	N/A	0.75 [1]
gako	extracellular K^+ activity coefficient	N/A	0.75 [1]
gammas	energy barrier controlling voltage dependence of NaCa	N/A	0.12 [1]
ganai	intracellular Na^+ activity coefficient	N/A	0.75 [1]
ganao	extracellular Na^+ activity coefficient	N/A	0.75 [1]
h	I_{Na} inactivation gate	N/A	N/A
h_∞	steady state value for h gate	N/A	N/A
$[H_e^+]$	extracellular proton concentration	mM	N/A
$[H_i^+]$	intracellular proton concentration	mM	N/A
$\widetilde{H}_{SERCA}$	apparent proton binding to SERCA in SR	N/A	N/A
$\widetilde{H}_{i,SERCA}$	apparent proton binding to SERCA in myoplasm	N/A	N/A
$\widetilde{H}_{1,SERCA}$	apparent proton binding to SERCA in myoplasm	N/A	N/A
$\widetilde{H}_{SR,SERCA}$	apparent proton binding to SERCA in SR	N/A	N/A
$[HCO^-_{3,e}]$	extracellular bicarbonate concentration	mM	N/A
$[HCO^-_{3,i}]$	intracellular bicarbonate concentration	mM	N/A
$[Hib_{ref}]$	concentration of protons bound to intrinsic buffers at start	mM	N/A
$[Hib_1]$	concentration of protons bound to first generic intrinsic buffer	mM	N/A
$[Hib_2]$	concentration of protons bound to second generic intrinsic buffer	mM	N/A

Abbreviation	Parameter	Units	Constant Value
$\bar{I}_{Ca}$	max. Ca^{2+} current through $I_{Ca(L)}$	uA/uF	N/A
$I_{Ca,b}$	background Ca^{2+} current	uA/uF	N/A
$I_{Ca(L)}$	L-type Ca^{2+} current	uA/uF	N/A
$I_{Ca(L),K}$	K^+ flux through $I_{Ca(L)}$	uA/uF	N/A
$I_{Ca(L),Na}$	Na^+ flux through $I_{Ca(L)}$	uA/uF	N/A
$I_{Ca,t}$	T-type Ca^{2+} current	uA/uF	N/A
$I_{Ca,total}$	total Ca^{2+} flux across cell membrane	uA/uF	N/A
I_{Cl}	Cl^- current	uA/uF	N/A
$I_{Cl,total}$	total Cl^- flux across cell membrane	uA/uF	N/A
$\bar{I}_{K}$	max. K^+ current through $I_{Ca(L)}$	uA/uF	N/A
$I_{K(ATP)}$	ATP-inactivated K^+ current	uA/uF	N/A
I_{Kp}	plateau K^+ current	uA/uF	N/A
I_{Kr}	rapid delayed K^+ rectifier current	uA/uF	N/A
I_{Ks}	slow delayed K^+ rectifier current	uA/uF	N/A
I_{K1}	time-independent K^+ rectifier current	uA/uF	N/A
$I_{K,total}$	total K^+ flux across cell membrane	uA/uF	N/A
I_{leak}	Ca^{2+} leakage from NSR to myoplasm	mM/ms	N/A
I_{Na}	fast inward sodium current	uA/uF	N/A
$\bar{I}_{Na}$	max. Na^+ current through $I_{Ca(L)}$	uA/uF	N/A
$I_{Na,b}$	background sodium current	uA/uF	N/A
I_{NaCa}	current through NaCa exchanger	uA/uF	N/A
I_{NaK}	current through the NaK pump	uA/cm^2	N/A
$I_{Na,l}$	late sodium current	uA/uf	N/A
$I_{Na,total}$	total Na^+ flux across cell membrane	uA/uF	N/A
$I_{p(Ca)}$	Ca^{2+} pump current	uA/uF	N/A
$\bar{I}_{p(Ca)}$	max. $I_{p(Ca)}$ current	uA/uF	1.65
$I_{relcicr}$	Ca^{2+} release from JSR to myoplasm due to CICR	mM/ms	N/A
$I_{reljsrol}$	Ca^{2+} release from JSR to myoplasm due to overload	mM/ms	N/A
I_{stim}	stimulus current	uA/uF	-80.0 [1]
I_{tr}	translocation of Ca^{2+} from NSR to JSR	mM/ms	N/A
$\bar{I}_{up}$	max. flux through SERCA	mM/ms	0.00875 [1]
$[ib_1]$	concentration of first generic intrinsic buffer	mM	84.22 [1]
$[ib_2]$	concentration of second generic intrinsic buffer	mM	29.38 [1]
j	I_{Na} inactivation gate	N/A	N/A
j_∞	steady state value for j gate	N/A	N/A
[JSR]	Ca^{2+} concentration in JSR	mM	N/A
jsr_{magrel}	magnitude of Ca^{2+} release	N/A	N/A
jsr_{off}	deactivation of Ca^{2+} release from JSR	N/A	N/A
jsr_{on}	activation of Ca^{2+} release from JSR	N/A	N/A
$k_{AE,cl}$	dissociation constant (AE)	mM	983.50 [1]
$k_{AE,hco3}$	dissociation constant (AE)	mM	110.64 [1]
$K_{AE,he}$	dissociation constant (AE)	mM	0.000312 [1]
$K_{AE,hi}$	dissociation constant (AE)	mM	0.0000267 [1]
k^+_{AE1}	forward rate constant (AE)	ms^{-1}	20,789.9 [1]
k^-_{AE1}	reverse rate constant (AE)	ms^{-1}	21,118.2 [1]
k^+_{AE2}	forward rate constant (AE)	ms^{-1}	21,256.54 [1]
k^-_{AE2}	reverse rate constant (AE)	ms^{-1}	21592.21 [1]
k_{ATP}	$k_{1/2}$ for the binding of ATP to $I_{Ca(L)}$ channels	mM	1.4 [5]
$k_{CHE,cl}$	dissociation constant (CHE)	mM	17,970.36 [1]
$k_{CHE,oh}$	dissociation constant (CHE)	mM	0.0008907 [1]

Abbreviation	Parameter	Units	Constant Value
k^+_{CHE1}	forward rate constant (CHE)	ms^{-1}	14,975.6 [1]
k^-_{CHE1}	reverse rate constant (CHE)	ms^{-1}	257.4 [1]
k^+_{CHE2}	forward rate constant (CHE)	ms^{-1}	4,084.9 [1]
k^-_{CHE2}	reverse rate constant (CHE)	ms^{-1}	70.20 [1]
$K_{d,Cai,SERCA}$	K_d for Ca^{2+} binding to SERCA in myoplasm	mM	0.91 [6]
$K_{d,CaSR,SERCA}$	K_d for Ca^{2+} binding to SERCA in SERCA	mM	2.24 [6]
$K_{d,H,SERCA}$	K_d for proton binding to SERCA in SR	mM	0.0000724 [6]
$K_{d,Hi,SERCA}$	K_d for proton binding to SERCA in myoplasm	mM^2	0.00354 [6]
$K_{d,HSR,SERCA}$	K_d for proton binding to SERCA in SR	mM^2	0.0000000105 [6]
$K_{d,H1,SERCA}$	K_d for proton binding to SERCA in myoplasm	mM	0.0000109 [6]
$K_{dNaK,atp}$	dissociation constant (NaK)	mM	2.9263 [3]
$K_{dNaK,ke}$	dissociation constant (NaK)	mM	6.80234 [3]
$K_{dNaK,ki}$	dissociation constant (NaK)	mM	255.13 [3]
$K_{dNaK,kpi}$	inorganic phosphate binding constant (NaK)	mM	292.0 [3]
$K_{dNaK,nae1}$	voltage partitioning of dissociation of 'first' Na^+ ion	mM	N/A
$K_{dNaK,nai1}$	voltage partitioning of dissociation of 'first' Na^+ ion	mM	N/A
$K_{dNaK,nae2}$	voltage-independent dissoc. constant for 'other two' Na^+ ions	mM	356.01 [3]
$K_{dNaK,nai2}$	voltage-independent dissoc. constant for 'other two' Na^+ ions	mM	154.39 [3]
$K_{dNaK,napi}$	inorganic phosphate binding constant (NaK)	mM	224.0 [3]
$K^0_{dNaK,nae}$	dissoc. constant of 'first' Na^+ ion at 0mV	mM	141.27 [3]
$K^0_{dNaK,nai}$	dissoc. constant of 'first' Na^+ ion at 0mV	mM	$0.12x10^{-7}$ [3]
$[\widetilde{K}_e]$	apparent concentration of enzyme-bound ion (NaK)	N/A	N/A
k^+_{hyd}	forward reaction rate for CO_2 hyrdolysis	$mM^{-1}s^{-1}$	0.000365 [1]
k^-_{hyd}	reverse reaction rate for CO_2 hyrdolysis	$mM^{-1}s^{-1}$	0.481 [1]
$[K^+_i]$	intracellular K^+ concentration	mM	N/A
$[\widetilde{K}_i]$	apparent concentration of enzyme-bound ion (NaK)	N/A	N/A
kin	I_{K1} inactivation	N/A	N/A
k_{leak}	rate constant of Ca^{2+} leakage from NSR	ms^{-1}	N/A
$k_{m,Ca}$	half-saturation concentration ($I_{Ca(L)}$)	mM	0.006 [1]
$k_{m,CMDN}$	equilibrium constant of buffering for calmodulin	mM	0.00238 [1]
$k_{m,CSQN}$	equilibrium constant of buffering for calsequestrin	mM	0.8 [1]
$k_{mp(Ca)}$	half-saturation concentration of sarcolemmal Ca^{2+} pump	mM	0.0005 [1]
$k_{m,TRPN}$	equilibrium constant of buffering for troponin	mM	0.0005 [1]
$k_{m,TRPNapp}$	apparent binding constant	mM	N/A
$k_{NBC,hco3}$	dissociation constant (NBC)	mM	0.008017 [1]
$K_{NBC,he}$	dissociation constant (NBC)	mM	0.0000653 [1]
$K_{NBC,hi}$	dissociation constant (NBC)	mM	0.000183 [1]
$k_{NBC,na}$	dissociation constant (NBC)	mM	4,866.11 [1]
k^+_{NBC1}	forward rate constant (NBC)	ms^{-1}	3,597.7 [1]
k^-_{NBC1}	reverse rate constant (NBC)	ms^{-1}	598.4 [1]
k^+_{NBC2}	forward rate constant (NBC)	ms^{-1}	5.12 [1]
k^-_{NBC2}	reverse rate constant (NBC)	ms^{-1}	0.8516 [1]
$k_{NHE,h}$	dissociation constant (NHE)	mM	0.000165 [1]
K_{NHE}	dissociation constant (NHE)	mM	0.0003438 [1]
$k_{NHE,na}$	dissociation constant (NHE)	mM	33.58 [1]
k^+_{NHE1}	forward rate constant (NHE)	ms^{-1}	197.5 [1]
k^-_{NHE1}	reverse rate constant (NHE)	ms^{-1}	725.5 [1]
k^+_{NHE2}	forward rate constant (NHE)	ms^{-1}	44.0 [1]
k^-_{NHE2}	reverse rate constant (NHE)	ms^{-1}	161.63 [1]
$[K^+_o]$	extracellular K^+ concentration	mM	N/A

Abbreviation	Parameter	Units	Constant Value
kp	K^+ "plateau" factor	N/A	N/A
$k^+_{1,SERCA}$	forward rate constant (SERCA)	$mM^{-1}s^{-1}$	25,900 [6]
$k^-_{1,SERCA}$	reverse rate constant (SERCA)	$mM^{-1}s^{-1}$	2 [6]
$k^+_{2,SERCA}$	forward rate constant (SERCA)	s^{-1}	2,540 [6]
$k^-_{2,SERCA}$	reverse rate constant (SERCA)	$mM^{-1}s^{-1}$	67,200 [6]
$k^+_{3,SERCA}$	forward rate constant (SERCA)	s^{-1}	20.5 [6]
$k^-_{3,SERCA}$	reverse rate constant (SERCA)	$mM^{-1}s^{-1}$	149 [6]
Lp	hydraulic conductivity of membrane	$L*N^{-1}*s^{-1}$	$1.21x10^{-10}$ [3]
m	I_{Na} activation gate	N/A	N/A
m_∞	steady state value for m gate	N/A	N/A
$modifier_{Inal}$	modifier to determine $I_{Na,l}$ max.conductance	N/A	0.0007 (0.00018 ischemia) [4]
$modifier_{NHE}$	factor to simulate NHE inhibition	N/A	N/A
$n_{AE,he}$	Hill coefficient for binding of extracellular protons to AE	N/A	1.44 [1]
$n_{AE,hi}$	Hill coefficient for binding of intracellular protons to AE	N/A	5.11 [1]
$n_{H,NaCa}$	Hill coefficient for binding of protons to NaCa exchanger	N/A	0.75
$n_{H,RYR}$	Hill coefficient for protons inhibiting RYR	N/A	1.8668 [1]
$n_{H,TRPN}$	Hill coefficient for binding of protons to troponin	N/A	1.6524 [1]
$n_{NBC,he}$	Hill coefficient for binding of extracellular protons to NBC	N/A	2.18 [1]
$n_{NBC,hi}$	Hill coefficient for binding of intracellular protons to NBC	N/A	2.91 [1]
$n_{NHE,he}$	Hill coefficient for binding of extracellular protons to NHE	N/A	1.00 [7]
$n_{NHE,hi}$	Hill coefficient for binding of intracellular protons to NHE	N/A	3.18 [1]
n_{SERCA}	number of H^+ transported via SERCA for every 2 Ca^{2+}	N/A	2.0 [6]
$[\widetilde{Na}_{e,1}]$	apparent concentration of enzyme-bound ion (NaK)	N/A	N/A
$[\widetilde{Na}_{e,2}]$	apparent concentration of enzyme-bound ion (NaK)	N/A	N/A
$[Na^+_i]$	intracellular Na^+ concentration	mM	N/A
$[\widetilde{Na}_{i,1}]$	apparent concentration of enzyme-bound ion (NaK)	N/A	N/A
$[\widetilde{Na}_{i,2}]$	apparent concentration of enzyme-bound ion (NaK)	N/A	N/A
$[Na^+_o]$	extracellular Na^+ concentration	mM	N/A
[NSR]	Ca^{2+} concentration in NSR	mM	N/A
$[\overline{NSR}]$	max. $[Ca^{2+}]$ in NSR	mM	15.0 [1]
$[OH^-_e]$	extracellular hydroxide concentration	mM	N/A
$[OH^-_i]$	intracellular hydroxide concentration	mM	N/A
p	$I_{Na,l}$ activation gate	N/A	N/A
p_∞	steady state value for p gate	N/A	N/A
p_{atm}	atmospheric pressure	mmHg	760
p_{Ca}	permeability of membrane to Ca^{2+}	cm/s	0.00054 [1]
p_{Cl}	membrane permeability to Cl^- ions	cm/ms	0.0000001 [1]
p_K	permeability of membrane to K^+	cm/s	0.000000193 [1]
p_{Na}	permeability of membrane to Na^+	cm/s	0.000000675 [1]
[PCr]	phosphocreatine concentration	mM	N/A
pH_e	extracellular pH	N/A	N/A
pH_i	intracellular pH	N/A	N/A
pH_{ref}	reference pH value ("normal" pH)	N/A	7.15
$[Pi_{free}]$	concentration of free inorganic phosphate	mM	N/A
$[Pi_{NaK}]$	concentration of free inorganic phosphate bound to NaK	mM	N/A
$[Pi_{total}]$	concentration of total phosphate	mM	35.312184 [3]
$pK_{dNaK,hpi}$	pK for inorganic phosphate binding to NaK	N/A	6.77 [3]
$pK_{H,NaCa}$	pK for protons inhibiting NaCa exchanger	N/A	7.00
$pK_{H,RYR}$	pK for protons inhibiting RYR	N/A	6.6396 [1]

Abbreviation	Parameter	Units	Constant Value
$pK_{H,TRPN}$	pK for protons binding to troponin	N/A	6.7914 [1]
pK1	pK for proton binding to first generic intrinsic buffer	N/A	6.03 [1]
pK2	pK for proton binding to second generic intrinsic buffer	N/A	7.57 [1]
$ppCO_2$	carbon dioxide partial pressure	$mmHg^{-1}$	0.03 [1]
prnak	Na^+/K^+ permeability ratio	N/A	0.01833 [1]
$\prod_e$	extracellular osmolarity	mOsm	310 [3]
$\prod_i$	intracellular osmolarity	mOsm	N/A
$[Proton_{ref}]$	concentration of free intracellular protons at simulation start	mM	N/A
R	universal gas constant	J/(K*kmol)	8314.0 [1]
$rate^+_{NaK1}$	baseline rate constant (NaK)	s^{-1}	1664.12 [3]
$rate^-_{NaK1}$	baseline rate constant (NaK)	$s^{-1}mM^{-1}$	264.15 [3]
$rate^+_{NaK2}$	baseline rate constant (NaK)	s^{-1}	110.42 [3]
$rate^-_{NaK2}$	baseline rate constant (NaK)	s^{-1}	14.04 [3]
$rate^+_{NaK3}$	baseline rate constant (NaK)	s^{-1}	2314.26 [3]
$rate^-_{NaK3}$	baseline rate constant (NaK)	$s^{-1}mM^{-2}$	7599999.5 [3]
$rate^+_{NaK4}$	baseline rate constant (NaK)	s^{-1}	462.38 [3]
$rate^-_{NaK4}$	baseline rate constant (NaK)	s^{-1}	1702.53 [3]
rkinac	time-independent I_{Kr} inactivation gate	N/A	N/A
reg_{AE}	modification of AE flux by extra- and intracellular protons	N/A	N/A
reg_{NBC}	modification of NBC flux by extra- and intracellular protons	N/A	N/A
reg_{NHE}	modification of NHE flux by intracellular protons	N/A	N/A
$s1_{AE}$	state occupancy probability (AE)	N/A	N/A
$s1_{CHE}$	state occupancy probability (CHE)	N/A	N/A
$s1_{NBC}$	state occupancy probability (NBC)	N/A	N/A
$s1_{NHE}$	state occupancy probability (NHE)	N/A	N/A
$s6_{AE}$	state occupancy probability (AE)	N/A	N/A
$s6_{CHE}$	state occupancy probability (CHE)	N/A	N/A
$s6_{NBC}$	state occupancy probability (NBC)	N/A	N/A
$s6_{NHE}$	state occupancy probability (NHE)	N/A	N/A
t	ischemic time	min.	N/A
t_{cicr}	Ca^{2+}-induced Ca^{2+} release timer	ms	N/A
t_{jsrol}	counter for Ca^{2+} release from JSR due to overload	ms	N/A
τ_b	time constant for b gate	ms	N/A
τ_d	time constant for d gate	ms	N/A
τ_f	time constant for f gate	ms	N/A
τ_g	time constant for g gate	ms	N/A
τ_h	time constant for h gate	ms	N/A
τ_j	time constant for j gate	ms	N/A
τ_m	time constant for m gate	ms	N/A
τ_{off}	time constant of deactivation of Ca^{2+} release from JSR	ms	0.5 [1]
τ_{on}	time constant of activation of Ca^{2+} release from JSR	ms	0.5 [1]
τ_p	time constant for p gate	ms	N/A
τ_{tr}	time constant of Ca^{2+} transfer from NSR to JSR	ms	180.0 [1]
τ_{xr}	time constant for xr gate	ms	N/A
τ_{xs1}	time constant for xs1 gate	ms	N/A
τ_{xs2}	time constant for xs2 gate	ms	N/A
temp	temperature	K	310.0 [1]
[TRPN]	concentration of Ca^{2+} bound to troponin	mM	N/A
$[\overline{TRPN}]$	max. $[Ca^{2+}]$ bound to troponin	mM	0.070 [1]
V	membrane voltage	mV	N/A
V_{AE}	flux through anion exchanger	$mM*uL*ms^{-1}$	N/A

Abbreviation	Parameter	Units	Constant Value
V_{CHE}	flux through chloride-hydroxide exchanger	mM*uL*ms^{-1}	N/A
V_{CO_2}	carbon dioxide flux across membrane	mM*uL*ms^{-1}	N/A
$V_{hyd,e}$	reaction rate for extracellular CO_2 hydrolysis	mM*uL*ms^{-1}	N/A
$V_{hyd,i}$	reaction rate for intracellular CO_2 hydrolysis	mM*uL*ms^{-1}	N/A
V_{H_2O}	movement of water across membrane	uL*cm^{-2}*ms^{-1}	N/A
V_{NBC}	flux through sodium-bicarbonate symporter	mM*uL*ms^{-1}	N/A
V_{NHE}	flux through sodium-hydrogen exchanger	mM*uL*ms^{-1}	N/A
V_{SERCA}	SERCA flux	mM/ms	N/A
Vol_{cell}	total cell volume	uL	N/A
$Vol_{external}$	extracellular compartment volume	uL	N/A
Vol_{jsr}	JSR volume	uL	N/A
Vol_{myo}	myoplasm volume	uL	N/A
Vol_{nsr}	NSR volume	uL	N/A
Vol_{sr}	SR volume	uL	N/A
Vol_{total}	total cell volume	uL	43.182x10^{-6} [3]
xr	I_{Kr} inactivation gate	N/A	N/A
xr_{∞}	steady state value for xr gate	N/A	N/A
xs1	I_{Ks} inactivation gate	N/A	N/A
$xs1_{\infty}$	steady state value for xs1 gate	N/A	N/A
xs2	I_{Ks} inactivation gate	N/A	N/A
$xs2_{\infty}$	steady state value for xs2 gate	N/A	N/A
$[X_e^{zi-}]$	concentration of extracellular impermeable osmolytes	nM	N/A
$[X_i^{zi-}]$	concentration of intracellular impermeable osmolytes	nM	N/A
z_{Ca}	Ca^{2+} valence	N/A	2.0
z_{Cl}	Cl^- valence	N/A	-1.0
z_K	K^+ valence	N/A	1.0
z_{Na}	Na^+ valence	N/A	1.0

Model Equations

$\mathbf{I_{Na}}$

$$\alpha_{\mathrm{m}} = 0.32 * \frac{\mathrm{V} + 47.13}{1 - \exp(-0.1 * (\mathrm{V} + 47.13))} \tag{S.1}$$

$$\beta_{\mathrm{m}} = 0.08 * \exp\left(\frac{-\mathrm{V}}{11.0}\right) \tag{S.2}$$

$$\tau_{\mathrm{m}} = \frac{1}{\alpha_{\mathrm{m}} + \beta_{\mathrm{m}}} \tag{S.3}$$

$$\mathrm{m}_{\infty} = \alpha_{\mathrm{m}} * \tau_{\mathrm{m}} \tag{S.4}$$

$$\mathrm{m_t} = \mathrm{m}_{\infty} - (\mathrm{m}_{\infty} - \mathrm{m_{t\text{-}\Delta t}}) * \exp\left(\frac{-\Delta \mathrm{t}}{\tau_{\mathrm{m}}}\right) \tag{S.5}$$

$$\alpha_{\mathrm{h}} = 0.135 * \exp\left(\frac{-\mathrm{V} - 80.0}{6.8}\right) \tag{S.6}$$

$$\beta_{\mathrm{h}} = \frac{7.5}{1 + \exp(-0.1 * (\mathrm{V} + 11.0))} \tag{S.7}$$

$$\tau_{\mathrm{h}} = \frac{1}{\alpha_{\mathrm{h}} + \beta_{\mathrm{h}}} \tag{S.8}$$

$$\mathrm{h}_{\infty} = \alpha_{\mathrm{h}} * \tau_{\mathrm{h}} \tag{S.9}$$

$$\mathrm{h_t} = \mathrm{h}_{\infty} - (\mathrm{h}_{\infty} - \mathrm{h_{t\text{-}\Delta t}}) * \exp\left(\frac{-\Delta \mathrm{t}}{\tau_{\mathrm{h}}}\right) \tag{S.10}$$

$$\alpha_{\mathrm{j}} = \frac{0.175 * \exp\left(\frac{-\mathrm{V} - 100.0}{23.0}\right)}{1.0 + \exp(0.15 * (\mathrm{V} + 79.0))} \tag{S.11}$$

$$\beta_{\mathrm{j}} = \frac{0.3}{1 + \exp(-0.1 * (\mathrm{V} + 32.0))} \tag{S.12}$$

$$\tau_{\mathrm{j}} = \frac{1}{\alpha_{\mathrm{j}} + \beta_{\mathrm{j}}} \tag{S.13}$$

$$\mathrm{j}_{\infty} = \alpha_{\mathrm{j}} * \tau_{\mathrm{j}} \tag{S.14}$$

$$\mathrm{j_t} = \mathrm{j}_{\infty} - (\mathrm{j}_{\infty} - \mathrm{j_{t\text{-}\Delta t}}) * \exp\left(\frac{-\Delta \mathrm{t}}{\tau_{\mathrm{j}}}\right) \tag{S.15}$$

$$\mathrm{I_{Na}} = \mathrm{g_{Na}} * \mathrm{m}^3 * \mathrm{h} * \mathrm{j} * (\mathrm{V} - \mathrm{E_{Na}}) \tag{S.16}$$

$I_{Na,b}$

$$I_{Na,b} = g_{Na,b} * (V - E_{Na}) \tag{S.17}$$

$I_{Na,l}$

$$\alpha_p = 19.0 * \exp\left(\frac{V}{16.5}\right) \tag{S.18}$$

$$\beta_p = 0.2 * \exp\left(\frac{-V}{20.0}\right) \tag{S.19}$$

$$\tau_p = \frac{1}{\alpha_p + \beta_p} \tag{S.20}$$

$$p_\infty = \alpha_p * \tau_p \tag{S.21}$$

$$p_t = p_\infty - (p_\infty - p_{t\text{-}\Delta t}) * \exp\left(\frac{-\Delta t}{\tau_p}\right) \tag{S.22}$$

$$I_{Na,l} = \text{modifier}_{Inal} * g_{Na} * p^3 * (V - E_{Na}) \tag{S.23}$$

$I_{Ca(L)}$

$$d_\infty = \frac{1}{1 + \exp\left(\frac{-V - 10}{6.24}\right)} \tag{S.24}$$

$$\tau_d = d_\infty * \frac{1 - \exp\left(\frac{-V - 10}{6.24}\right)}{0.035 * (V + 10)} \tag{S.25}$$

$$d_t = d_\infty - (d_\infty - d_{t\text{-}\Delta t}) * \exp\left(\frac{-\Delta t}{\tau_d}\right) \tag{S.26}$$

$$f_\infty = \frac{1}{1 + \exp\left(\frac{V + 32}{8}\right)} + \frac{0.6}{1 + \exp\left(\frac{50 - V}{20}\right)} \tag{S.27}$$

$$\tau_f = \frac{1}{(0.0197 * \exp(-((0.0337 * (V + 10)) * (0.0337 * (V + 10))))) + 0.02)} \tag{S.28}$$

$$f_t = f_\infty - (f_\infty - f_{t\text{-}\Delta t}) * \exp\left(\frac{-\Delta t}{\tau_f}\right) \tag{S.29}$$

$$f_{Ca,ATP} = \frac{1}{1 + \left(\frac{k_{ATP}}{[ATP]}\right)^{2.6}} \tag{S.30}$$

$$f_{Ca} = \frac{1}{1 + \frac{[Ca_i^{2+}]}{k_{m,Ca}}} \tag{S.31}$$

$$\bar{I}_{Ca} = p_{Ca} * z_{Ca} * z_{Ca} * \frac{V * F * F}{R * temp} * \frac{gacai * [Ca_i^{2+}] * \exp\left(\frac{z_{Ca} * V * F}{R * temp}\right) - gacao * [Ca_o^{2+}]}{\exp\left(\frac{z_{Ca} * V * F}{R * temp}\right) - 1} \tag{S.32}$$

$$\bar{I}_{Na} = p_{Na} * z_{Na} * z_{Na} * \frac{V * F * F}{R * temp} * \frac{ganai * [Na_i^{+}] * \exp\left(\frac{z_{Na} * V * F}{R * temp}\right) - ganao * [Na_o^{+}]}{\exp\left(\frac{z_{Na} * V * F}{R * temp}\right) - 1} \tag{S.33}$$

$$\bar{I}_{K} = p_{K} * z_{K} * z_{K} * \frac{V * F * F}{R * temp} * \frac{gaki * [K_i^{+}] * \exp\left(\frac{z_{K} * V * F}{R * temp}\right) - gako * [K_o^{+}]}{\exp\left(\frac{z_{K} * V * F}{R * temp}\right) - 1} \tag{S.34}$$

$$I_{Ca(L)} = f_{Ca,ATP} * d * f * f_{Ca} * \bar{I}_{Ca} \tag{S.35}$$

$$I_{Ca(L),Na} = f_{Ca,ATP} * d * f * f_{Ca} * \bar{I}_{Na} \tag{S.36}$$

$$I_{Ca(L),K} = f_{Ca,ATP} * d * f * f_{Ca} * \bar{I}_{K} \tag{S.37}$$

$I_{Ca,t}$

$$b_\infty = \frac{1}{1 + \exp\left(\frac{-V - 14}{10.8}\right)} \tag{S.38}$$

$$\tau_b = 3.7 + \frac{6.1}{1 + \exp\left(\frac{V + 25.0}{4.5}\right)} \tag{S.39}$$

$$b_t = b_\infty - (b_\infty - b_{t\text{-}\Delta t}) * \exp\left(\frac{-\Delta t}{\tau_b}\right) \tag{S.40}$$

$$g_\infty = \frac{1}{1 + \exp\left(\frac{V + 60.0}{5.6}\right)} \tag{S.41}$$

If $V \leq 0.0$:

$$\tau_g = -0.875 * V + 12.0 \tag{S.42}$$

Otherwise:

$$\tau_g = 12.0 \tag{S.43}$$

$$g_t = g_\infty - (g_\infty - g_{t\text{-}\Delta t}) * \exp\left(\frac{-\Delta t}{\tau_g}\right) \tag{S.44}$$

$$I_{Ca,t} = g_{Ca,t} * b^2 * g * (V - E_{Ca}) \tag{S.45}$$

$I_{p(Ca)}$

$$I_{p(Ca)} = \frac{\bar{I}_{p(Ca)} * Ca_i^{2+}}{k_{mp(Ca)} + Ca_i^{2+}} \tag{S.46}$$

$I_{Ca,b}$

$$I_{Ca,b} = g_{Ca,b} * (V - E_{Ca}) \tag{S.47}$$

JSR

$$I_{tr} = \frac{[nsr] - [jsr]}{\tau_{tr}} \tag{S.48}$$

$$dI_{Ca,total} = \frac{I_{Ca,total\ t} - I_{Ca,total\ t\text{-}\Delta t}}{\Delta t} \tag{S.49}$$

$$jsr_{on} = \frac{1}{1 + \exp\left(\frac{-t_{cicr} + 4.0}{\tau_{on}}\right)} \tag{S.50}$$

$$jsr_{off} = 1 - \frac{1}{1 + \exp\left(\frac{-t_{cicr} + 4.0}{\tau_{off}}\right)} \tag{S.51}$$

$$\mathrm{jsr_{magrel}} = \frac{1}{1 + \exp\left(\frac{\mathrm{I_{Ca,total}} + 5.0}{0.9}\right)} \tag{S.52}$$

$$\mathrm{fac_{H,RYR}} = \frac{\left(\frac{1 + 10^{\mathrm{n_{H,RYR}}(\text{-}7.4763 + \mathrm{pK_{H,RYR}})}}{1 + 10^{\mathrm{n_{H,RYR}}(\text{-}\mathrm{pH_i} + \mathrm{pK_{H,RYR}})}}\right)}{\left(\frac{1 + 10^{\mathrm{n_{H,RYR}}(\text{-}7.4763 + \mathrm{pK_{H,RYR}})}}{1 + 10^{\mathrm{n_{H,RYR}}(\text{-}\mathrm{pH_{ref}} + \mathrm{pK_{H,RYR}})}}\right)} \tag{S.53}$$

$$\mathrm{I_{relcicr}} = \mathrm{fac_{H,RYR}} * \mathrm{g_{maxrel}} * \mathrm{jsr_{on}} * \mathrm{jsr_{off}} * \mathrm{jsr_{magrel}} * ([\mathrm{JSR}] - [\mathrm{Ca_i^{2+}}]) \tag{S.54}$$

$$\mathrm{g_{reljsrol}} = \mathrm{g_{relbarjsrol}} * \left(1 - \exp\left(\frac{-\mathrm{t_{jsrol}}}{\mathrm{tau_{on}}}\right)\right) * \exp\left(\frac{-\mathrm{t_{\text{-}tjsrol}}}{\mathrm{tau_{off}}}\right) \tag{S.55}$$

$$\mathrm{I_{reljsrol}} = \mathrm{g_{reljsrol}} * ([\mathrm{JSR}] - [\mathrm{Ca_i^{2+}}]) \tag{S.56}$$

$$\frac{\mathrm{d}[\mathrm{JSR}]}{\mathrm{dt}} = \frac{\mathrm{I_{tr}} - \mathrm{I_{relcicr}} - \mathrm{I_{reljsrol}}}{\beta_{\mathrm{CSQN}}} \tag{S.57}$$

NSR

$$\mathrm{k_{leak}} = \frac{\bar{\mathrm{I}}_{\mathrm{up}}}{[\overline{\mathrm{NSR}}]} \tag{S.58}$$

$$\mathrm{I_{leak}} = \mathrm{k_{leak}} * [\mathrm{NSR}] \tag{S.59}$$

$$\frac{\mathrm{d}[\mathrm{NSR}]}{\mathrm{dt}} = \mathrm{V_{SERCA}} - \mathrm{I_{leak}} - \mathrm{I_{tr}}\left(\frac{\mathrm{Vol_{jsr}}}{\mathrm{Vol_{nsr}}}\right) \tag{S.60}$$

SERCA

$$\widetilde{\mathrm{Ca}}_{\mathrm{i,SERCA}} = \frac{[\mathrm{Ca_i^{2+}}]}{\mathrm{K_{d,Cai,SERCA}}} \tag{S.61}$$

$$\widetilde{\mathrm{Ca}}_{\mathrm{SR,SERCA}} = \frac{[\mathrm{NSR}]}{\mathrm{K_{d,CaSR,SERCA}}} \tag{S.62}$$

$$\widetilde{\mathrm{H}}_{\mathrm{i,SERCA}} = \frac{[\mathrm{H_i^{+}}]^{\mathrm{n_{SERCA}}}}{\mathrm{K_{d,Hi,SERCA}}} \tag{S.63}$$

$$\widetilde{\mathrm{H}}_{\mathrm{SR,SERCA}} = \frac{[\mathrm{H}_{\mathrm{i}}^{+}]^{\mathrm{n_{SERCA}}}}{\mathrm{K_{d,HSR,SERCA}}} \tag{S.64}$$

$$\widetilde{\mathrm{H}}_{\mathrm{1,SERCA}} = \frac{[\mathrm{H}]^{+}}{\mathrm{K_{d,H1,SERCA}}} \tag{S.65}$$

$$\widetilde{\mathrm{H}}_{\mathrm{SERCA}} = \frac{[\mathrm{H}]^{+}}{\mathrm{K_{d,H,SERCA}}} \tag{S.66}$$

$$\alpha_{\mathrm{1,SERCA}}^{+} = \mathrm{k}_{\mathrm{1,SERCA}}^{+}[\mathrm{ATP}] \tag{S.67}$$

$$\alpha_{\mathrm{2,SERCA}}^{+} = \frac{\mathrm{k}_{\mathrm{2,SERCA}}^{+}\widetilde{\mathrm{Ca}}_{\mathrm{i,SERCA}}^{2}}{\widetilde{\mathrm{Ca}}_{\mathrm{i,SERCA}}^{2}(1+\widetilde{\mathrm{H}}_{\mathrm{i,SERCA}}) + \widetilde{\mathrm{H}}_{\mathrm{i,SERCA}}(1+\widetilde{\mathrm{H}}_{\mathrm{1,SERCA}})} \tag{S.68}$$

$$\alpha_{\mathrm{3,SERCA}}^{+} = \frac{\mathrm{k}_{\mathrm{3,SERCA}}^{+}\widetilde{\mathrm{H}}_{\mathrm{SR,SERCA}}}{\widetilde{\mathrm{H}}_{\mathrm{SERCA}}(1+\widetilde{\mathrm{Ca}}_{\mathrm{SR,SERCA}}^{2}) + \widetilde{\mathrm{H}}_{\mathrm{SR,SERCA}}(1+\widetilde{\mathrm{H}}_{\mathrm{SERCA}})} \tag{S.69}$$

$$\alpha_{\mathrm{1,SERCA}}^{-} = \frac{\mathrm{k}_{\mathrm{1}}^{-}\widetilde{\mathrm{H}}_{\mathrm{i,SERCA}}}{\widetilde{\mathrm{Ca}}_{\mathrm{i,SERCA}}^{2}(1+\widetilde{\mathrm{H}}_{\mathrm{i,SERCA}}) + \widetilde{\mathrm{H}}_{\mathrm{i,SERCA}}(1+\widetilde{\mathrm{H}}_{\mathrm{1,SERCA}})} \tag{S.70}$$

$$\alpha_{\mathrm{2,SERCA}}^{-} = \frac{\mathrm{k}_{\mathrm{2,SERCA}}^{-}[\mathrm{ADP}]\widetilde{\mathrm{Ca}}_{\mathrm{SR,SERCA}}^{2}\widetilde{\mathrm{H}}_{\mathrm{SR,SERCA}}}{\widetilde{\mathrm{H}}_{\mathrm{SERCA}}(1+\widetilde{\mathrm{Ca}}_{\mathrm{SR,SERCA}}^{2}) + \widetilde{\mathrm{H}}_{\mathrm{SR,SERCA}}(1+\widetilde{\mathrm{H}}_{\mathrm{SERCA}})} \tag{S.71}$$

$$\alpha_{\mathrm{3,SERCA}}^{-} = \mathrm{k}_{\mathrm{3,SERCA}}^{-}[\mathrm{Pi_{free}}] \tag{S.72}$$

$$\begin{aligned}\Sigma_3 = {} & \alpha_{\mathrm{2,SERCA}}^{+}\alpha_{\mathrm{3,SERCA}}^{+} + \alpha_{\mathrm{1,SERCA}}^{-}\alpha_{\mathrm{3,SERCA}}^{+} + \alpha_{\mathrm{1,SERCA}}^{-}\alpha_{\mathrm{2,SERCA}}^{-} + \\ & \alpha_{\mathrm{1,SERCA}}^{+}\alpha_{\mathrm{3,SERCA}}^{+} + \alpha_{\mathrm{2,SERCA}}^{-}\alpha_{\mathrm{1,SERCA}}^{+} + \alpha_{\mathrm{2,SERCA}}^{-}\alpha_{\mathrm{3,SERCA}}^{-} + \\ & \alpha_{\mathrm{1,SERCA}}^{+}\alpha_{\mathrm{2,SERCA}}^{+} + \alpha_{\mathrm{3,SERCA}}^{-}\alpha_{\mathrm{1,SERCA}}^{-} + \alpha_{\mathrm{3,SERCA}}^{-}\alpha_{\mathrm{2,SERCA}}^{+}\end{aligned} \tag{S.73}$$

$$\mathrm{cyc_{SERCA}} = \frac{\alpha_{\mathrm{1,SERCA}}^{+}\alpha_{\mathrm{2,SERCA}}^{+}\alpha_{\mathrm{3,SERCA}}^{+} - \alpha_{\mathrm{1,SERCA}}^{-}\alpha_{\mathrm{2,SERCA}}^{-}\alpha_{\mathrm{3,SERCA}}^{-}}{\Sigma_3} \tag{S.74}$$

$$\mathrm{V_{SERCA}} = 0.00820 * \mathrm{cyc_{SERCA}} \tag{S.75}$$

Ca^{2+} Buffering

$$k_{m,TRPNapp} = k_{m,TRPN}\left(\frac{1+10^{n_{H,TRPN}(\text{-}pH_i+pK_{H,TRPN})}}{1+10^{n_{H,TRPN}(\text{-}pH_{ref}+pK_{H,TRPN})}}\right) \tag{S.76}$$

$$\beta_{TRPN} = 1+\frac{[\overline{TRPN}]*k_{m,TRPNapp}}{([Ca_i^{2+}]+k_{m,TRPNapp})^2} \tag{S.77}$$

$$[TRPN] = [\overline{TRPN}]\left(\frac{[Ca_i^{2+}]}{[Ca_i^{2+}]+k_{m,TRPNapp}}\right) \tag{S.78}$$

$$\beta_{CSQN} = 1+\frac{[\overline{CSQN}]*k_{m,CSQN}}{([JSR]+k_{m,CSQN})^2} \tag{S.79}$$

$$[CSQN] = [\overline{CSQN}]\left(\frac{[JSR]}{[JSR]+k_{m,CSQN}}\right) \tag{S.80}$$

$$\beta_{CMDN} = 1+\frac{[\overline{CMDN}]*k_{m,CMDN}}{([Ca_i^{2+}]+k_{m,CMDN})^2} \tag{S.81}$$

$$[CMDN] = [\overline{CMDN}]\left(\frac{[Ca_i^{2+}]}{[Ca_i^{2+}]+k_{m,CMDN}}\right) \tag{S.82}$$

I_{Kr}

$$rkinac = \frac{1}{1+\exp\left(\frac{V+9}{22.4}\right)} \tag{S.83}$$

$$g_{Kr} = 0.02614\sqrt{\frac{[K_o^+]}{5.4}} \tag{S.84}$$

$$xr_\infty = \frac{1}{1+\exp\left(\frac{-V-21.5}{7.5}\right)} \tag{S.85}$$

$$\tau_{xr} = \frac{1}{\frac{0.00138*(V+14.2)}{(1-\exp(-0.123*(V+14.2)))}+\frac{0.00061*(V+38.9)}{(\exp(0.145*(V+38.9))-1)}} \tag{S.86}$$

$$xr_t = xr_\infty-(xr_\infty-xr_{t\text{-}\Delta t})*\exp\left(\frac{-\Delta t}{\tau_{xr}}\right) \tag{S.87}$$

$$I_{Kr} = g_{Kr}*xr*rkinac*(V-E_K) \tag{S.88}$$

$\mathbf{I_{Ks}}$

$$g_{Ks} = 0.433 \left(1 + \left(\frac{0.6}{1 + \left(\frac{0.000038}{[Ca_i^{2+}]} \right)^{1.4}} \right) \right) \tag{S.89}$$

$$xs1_{\infty} = \frac{1}{1 + \exp\left(\frac{-V + 1.5}{16.7} \right)} \tag{S.90}$$

$$\tau_{xs1} = \frac{1}{\frac{0.0000719 * (V + 30)}{(1 - \exp(-0.148 * (V + 30)))} + \frac{0.000131 * (V + 30)}{(\exp(0.0687 * (V + 30)) - 1)}} \tag{S.91}$$

$$xs1_t = xs1_{\infty} - (xs1_{\infty} - xs1_{t\text{-}\Delta t}) * \exp\left(\frac{-\Delta t}{\tau_{xs1}} \right) \tag{S.92}$$

$$xs2_{\infty} = \frac{1}{1 + \exp\left(\frac{-V + 1.5}{16.7} \right)} \tag{S.93}$$

$$\tau_{xs2} = \frac{4}{\frac{0.0000719 * (V + 30)}{(1 - \exp(-0.148 * (V + 30)))} + \frac{0.000131 * (V + 30)}{(\exp(0.0687 * (V + 30)) - 1)}} \tag{S.94}$$

$$xs2_t = xs2_{\infty} - (xs2_{\infty} - xs2_{t\text{-}\Delta t}) * \exp\left(\frac{-\Delta t}{\tau_{xs2}} \right) \tag{S.95}$$

$$I_{Ks} = g_{Ks} * xs1 * xs2 * (V - E_{Ks}) \tag{S.96}$$

$\mathbf{I_{K1}}$

$$\alpha_{K1} = \frac{1.02}{1 + \exp(0.2385(V - E_K - 59.215))} \tag{S.97}$$

$$\beta_{K1} = \frac{0.49124 * \exp(0.08032 * (V - E_K + 5.476)) + \exp(0.06175 * (V - E_K - 594.31))}{1 + \exp(-0.5143 * (V - E_K + 4.753))} \tag{S.98}$$

$$kin = \frac{\alpha_{K1}}{\alpha_{K1} + \beta_{K1}} \tag{S.99}$$

$$g_{K1} = 0.75\sqrt{\frac{[K_o^+]}{5.4}} \tag{S.100}$$

$$I_{K1} = g_{K1} * kin * (V - E_K) \tag{S.101}$$

I_{Kp}

$$kp = \frac{1}{1 + \exp\left(\frac{7.488 - V}{5.98}\right)} \tag{S.102}$$

$$I_{Kp} = g_{Kp} * kp * (V - E_K) \tag{S.103}$$

$I_{K(ATP)}$

$$f_{ATP} = \left(1 - \frac{[ATP]}{[ATP] + 12.0}\right)^4 \tag{S.104}$$

$$f'_{ADP} = \left(\frac{[ADP]}{[ADP] + 421.05}\right)^2 \tag{S.105}$$

$$c_{ADP} = 1 - f'_{ADP} \tag{S.106}$$

$$f_{ADP} = 1 - c_{ADP}^4 \tag{S.107}$$

$$f_{K(ATP)} = 0.08 * f_{ATP} * (1 - f_{ADP}) + 0.89 * f_{ATP} * f_{ADP} \tag{S.108}$$

$$g_{K(ATP)} = 0.4 * f_{K(ATP)} * \left(\frac{[K_o^+]}{4.5}\right)^{0.24} \tag{S.109}$$

$$I_{K(ATP)} = g_{K(ATP)} * (V - E_K) \tag{S.110}$$

Na-Ca Exchange

$$fac_{NaCa} = \frac{1 + 10^{n_{H,NaCa}(\text{-}pH_{ref} + pK_{H,NaCa})}}{1 + 10^{n_{H,NaCa}(\text{-}pH_i + pK_{H,NaCa})}} \tag{S.111}$$

$$I_{NaCa} = c1 * fac_{NaCa} * \exp\left(\frac{(gammas - 1) * V * F}{R * temp}\right) * \left(\frac{\exp\left(\frac{V * F}{R * temp}\right)[Na_i^+]^3 * [Ca_o^{2+}] - [Na_o^+]^3 * [Ca_i^{2+}]}{1 + c2 * \exp\left(\frac{(gammas - 1) * V * F}{R * temp}\right) * \exp\left(\frac{V * F}{R * temp}\right) * [Na_i^+]^3 * [Ca_o^{2+}] + [Na_o^+]^3 * [Ca_i^{2+}]}\right) \tag{S.112}$$

NaK Pump

$$\mathrm{K_{dNaK,nae1}} = \mathrm{K^0_{dNaK,nae}} * \exp\left(\frac{(1+\mathrm{factorNaKdel}) * \mathrm{F} * \mathrm{V}}{\mathrm{R} * \mathrm{temp}}\right) \tag{S.113}$$

$$\mathrm{K_{dNaK,nai1}} = \mathrm{K^0_{dNaK,nai}} * \exp\left(\frac{(1+\mathrm{factorNaKdel}) * \mathrm{F} * \mathrm{V}}{\mathrm{R} * \mathrm{temp}}\right) \tag{S.114}$$

$$[\widetilde{\mathrm{Na}}_{\mathrm{e},1}] = \frac{[\mathrm{Na_o^+}]}{\mathrm{K_{dNaK,nae1}}} \tag{S.115}$$

$$[\widetilde{\mathrm{Na}}_{\mathrm{i},1}] = \frac{[\mathrm{Na_i^+}]}{\mathrm{K_{dNaK,nai1}}} \tag{S.116}$$

$$[\widetilde{\mathrm{Na}}_{\mathrm{e},2}] = \frac{[\mathrm{Na_o^+}]}{\mathrm{K_{dNaK,nae2}}} \tag{S.117}$$

$$[\widetilde{\mathrm{Na}}_{\mathrm{i},2}] = \frac{[\mathrm{Na_i^+}]}{\mathrm{K_{dNaK,nai2}}} \tag{S.118}$$

$$[\widetilde{\mathrm{K}}_{\mathrm{e}}] = \frac{[\mathrm{K_o^+}]}{\mathrm{K_{dNaK,ke}}} \tag{S.119}$$

$$[\widetilde{\mathrm{K}}_{\mathrm{i}}] = \frac{[\mathrm{K_i^+}]}{\mathrm{K_{dNaK,ki}}} \tag{S.120}$$

$$[\widetilde{\mathrm{ATP}}] = \frac{[\mathrm{ATP}]}{\mathrm{K_{dNaK,atp}}} \tag{S.121}$$

$$[\mathrm{Pi_{NaK}}] = \left(\frac{[\mathrm{Pi_{free}}]}{1 + \frac{[\mathrm{K_i^+}]}{\mathrm{K_{dNak,kpi}}} + \frac{[\mathrm{H_i^+}]}{10^{3\text{-}\mathrm{pK_{dNaK,hpi}}}} + \frac{[\mathrm{Na_i^+}]}{\mathrm{K_{dNaK,napi}}}}\right) \tag{S.122}$$

$$\alpha^+_{\mathrm{NaK1}} = \mathrm{rate^+_{NaK1}} * [\widetilde{\mathrm{Na}}_{\mathrm{i},1}] * \frac{[\widetilde{\mathrm{Na}}_{\mathrm{i},2}]^2}{(1+[\widetilde{\mathrm{Na}}_{\mathrm{i},1}]) * (1+[\widetilde{\mathrm{Na}}_{\mathrm{i},2}])^2 + (1+[\widetilde{\mathrm{K}}_{\mathrm{i}}])^2 - 1} \tag{S.123}$$

$$\alpha^+_{\mathrm{NaK2}} = \mathrm{rate^+_{NaK2}} \tag{S.124}$$

$$\alpha^+_{\mathrm{NaK3}} = \mathrm{rate^+_{NaK3}} * \frac{[\widetilde{\mathrm{K}}_{\mathrm{e}}]^2}{(1+[\widetilde{\mathrm{Na}}_{\mathrm{e},1}]) * (1+[\widetilde{\mathrm{Na}}_{\mathrm{e},2}])^2 + (1+[\widetilde{\mathrm{K}}_{\mathrm{e}}])^2 - 1} \tag{S.125}$$

$$\alpha^{+}_{\mathrm{NaK4}} = \mathrm{rate}^{+}_{\mathrm{NaK4}} * \frac{[\widetilde{\mathrm{ATP}}]}{1 + [\widetilde{\mathrm{ATP}}]} \tag{S.126}$$

$$\alpha^{-}_{\mathrm{NaK1}} = \mathrm{rate}^{-}_{\mathrm{NaK1}} * [\mathrm{ADP}] \tag{S.127}$$

$$\alpha^{-}_{\mathrm{NaK2}} = \mathrm{rate}^{-}_{\mathrm{NaK2}} * \frac{[\widetilde{\mathrm{Na}}_{\mathrm{e},1}] * [\widetilde{\mathrm{Na}}_{\mathrm{e},2}]^2}{(1 + [\widetilde{\mathrm{Na}}_{\mathrm{e},1}]) * (1 + [\widetilde{\mathrm{Na}}_{\mathrm{e},2}])^2 + (1 + [\widetilde{\mathrm{K}}_{\mathrm{e}}])^2 - 1} \tag{S.128}$$

$$\alpha^{-}_{\mathrm{NaK3}} = \mathrm{rate}^{-}_{\mathrm{NaK3}} * \frac{[\mathrm{Pi}_{\mathrm{NaK}}] * [\mathrm{H}^{+}_{\mathrm{i}}]}{1 + [\widetilde{\mathrm{ATP}}]} \tag{S.129}$$

$$\alpha^{-}_{\mathrm{NaK4}} = \mathrm{rate}^{-}_{\mathrm{NaK4}} * \frac{[\widetilde{\mathrm{K}}_{\mathrm{i}}]^2}{(1 + [\widetilde{\mathrm{Na}}_{\mathrm{i},1}]) * (1 + [\widetilde{\mathrm{Na}}_{\mathrm{i},2}])^2 + (1 + [\widetilde{\mathrm{K}}_{\mathrm{i}}])^2 - 1} \tag{S.130}$$

$$\begin{aligned}\Sigma_{\mathrm{NaK}} = {} & \alpha^{-}_{\mathrm{NaK1}}\alpha^{-}_{\mathrm{NaK2}}\alpha^{-}_{\mathrm{NaK3}} + \alpha^{-}_{\mathrm{NaK1}}\alpha^{-}_{\mathrm{NaK2}}\alpha^{+}_{\mathrm{NaK4}} + \alpha^{-}_{\mathrm{NaK1}}\alpha^{+}_{\mathrm{NaK3}}\alpha^{+}_{\mathrm{NaK4}} + \alpha^{+}_{\mathrm{NaK2}}\alpha^{+}_{\mathrm{NaK3}}\alpha^{+}_{\mathrm{NaK4}} + \\ & \alpha^{-}_{\mathrm{NaK2}}\alpha^{-}_{\mathrm{NaK3}}\alpha^{-}_{\mathrm{NaK4}} + \alpha^{+}_{\mathrm{NaK1}}\alpha^{-}_{\mathrm{NaK2}}\alpha^{-}_{\mathrm{NaK3}} + \alpha^{+}_{\mathrm{NaK1}}\alpha^{-}_{\mathrm{NaK2}}\alpha^{+}_{\mathrm{NaK4}} + \alpha^{+}_{\mathrm{NaK1}}\alpha^{+}_{\mathrm{NaK3}}\alpha^{+}_{\mathrm{NaK4}} + \\ & \alpha^{-}_{\mathrm{NaK1}}\alpha^{-}_{\mathrm{NaK3}}\alpha^{-}_{\mathrm{NaK4}} + \alpha^{+}_{\mathrm{NaK2}}\alpha^{-}_{\mathrm{NaK3}}\alpha^{-}_{\mathrm{NaK4}} + \alpha^{+}_{\mathrm{NaK1}}\alpha^{+}_{\mathrm{NaK2}}\alpha^{-}_{\mathrm{NaK3}} + \alpha^{+}_{\mathrm{NaK1}}\alpha^{+}_{\mathrm{NaK2}}\alpha^{+}_{\mathrm{NaK4}} + \\ & \alpha^{-}_{\mathrm{NaK1}}\alpha^{-}_{\mathrm{NaK2}}\alpha^{-}_{\mathrm{NaK4}} + \alpha^{-}_{\mathrm{NaK1}}\alpha^{+}_{\mathrm{NaK3}}\alpha^{-}_{\mathrm{NaK4}} + \alpha^{+}_{\mathrm{NaK2}}\alpha^{+}_{\mathrm{NaK3}}\alpha^{-}_{\mathrm{NaK4}} + \alpha^{+}_{\mathrm{NaK1}}\alpha^{+}_{\mathrm{NaK2}}\alpha^{+}_{\mathrm{NaK3}}\end{aligned} \tag{S.131}$$

$$\mathrm{cyc}_{\mathrm{NaK}} = \frac{\alpha^{+}_{\mathrm{NaK1}}\alpha^{+}_{\mathrm{NaK2}}\alpha^{+}_{\mathrm{NaK3}}\alpha^{+}_{\mathrm{NaK4}} - \alpha^{-}_{\mathrm{NaK1}}\alpha^{-}_{\mathrm{NaK2}}\alpha^{-}_{\mathrm{NaK3}}\alpha^{-}_{\mathrm{NaK4}}}{\Sigma_{\mathrm{NaK}}} \tag{S.132}$$

$$\mathrm{I}_{\mathrm{NaK}} = .000016 * \mathrm{density}_{\mathrm{NaK}} * \mathrm{cyc}_{\mathrm{NaK}} \tag{S.133}$$

$\mathbf{I_{Cl}}$

$$\mathrm{I}_{\mathrm{Cl}} = \mathrm{p}_{\mathrm{Cl}} * \frac{\mathrm{F}^2 * \mathrm{V}}{\mathrm{R} * \mathrm{temp}} * \frac{[\mathrm{Cl}^{-}_{\mathrm{i}}] - [\mathrm{Cl}^{-}_{\mathrm{e}}] * \exp\left(\frac{\mathrm{F} * \mathrm{V}}{\mathrm{R} * \mathrm{temp}}\right)}{1 - \exp\left(\frac{\mathrm{F} * \mathrm{V}}{\mathrm{R} * \mathrm{temp}}\right)} \tag{S.134}$$

Anion Exchanger

$$\mathrm{aa}_{\mathrm{AE}} = 1 + \frac{\mathrm{k}_{\mathrm{AE,hco3}}}{[\mathrm{HCO}^{-}_{3,\mathrm{e}}]} + \frac{\mathrm{k}_{\mathrm{AE,hco3}} * [\mathrm{Cl}^{-}_{\mathrm{e}}]}{[\mathrm{HCO}^{-}_{3,\mathrm{e}}] * \mathrm{k}_{\mathrm{AE,cl}}} \tag{S.135}$$

$$\mathrm{bb}_{\mathrm{AE}} = 1 + \frac{\mathrm{k}_{\mathrm{AE,cl}}}{[\mathrm{Cl}^{-}_{\mathrm{e}}]} + \frac{\mathrm{k}_{\mathrm{AE,cl}} * [\mathrm{HCO}^{-}_{3,\mathrm{e}}]}{[\mathrm{Cl}^{-}_{\mathrm{e}}] * \mathrm{k}_{\mathrm{AE,hco3}}} \tag{S.136}$$

$$cc_{AE} = 1 + \frac{k_{AE,cl}}{[Cl^-_i]} + \frac{k_{AE,cl} * [HCO^-_{3,i}]}{[Cl^-_i] * k_{AE,hco3}} \tag{S.137}$$

$$dd_{AE} = 1 + \frac{k_{AE,hco3}}{[HCO^-_{3,i}]} + \frac{k_{AE,hco3} * [Cl^-_i]}{[HCO^-_{3,i}] * k_{AE,cl}} \tag{S.138}$$

$$s1_{AE} = \frac{1}{aa_{AE} + dd_{AE} * \dfrac{k^+_{AE1} + k^+_{AE2}\left(\dfrac{aa_{AE}}{bb_{AE}}\right)}{k^-_{AE1} + k^-_{AE2}\left(\dfrac{dd_{AE}}{cc_{AE}}\right)}} \tag{S.139}$$

$$s6_{AE} = \frac{1}{dd_{AE} + aa_{AE} * \dfrac{k^-_{AE1} + k^-_{AE2}\left(\dfrac{dd_{AE}}{cc_{AE}}\right)}{k^+_{AE1} + k^+_{AE2}\left(\dfrac{aa_{AE}}{bb_{AE}}\right)}} \tag{S.140}$$

$$reg_{AE} = \left(\frac{K^{n_{AE,hi}}_{AE,hi}}{([H^+_i]^{n_{AE,hi}} + K^{n_{AE,hi}}_{AE,hi})}\right) * \left(\frac{[H^+_e]^{n_{AE,he}}}{([H^+_e]^{n_{AE,he}} + K^{n_{AE,he}}_{AE,he})}\right) \tag{S.141}$$

$$V_{AE} = Vol_{myo} * reg_{AE} * \frac{k^-_{AE1} * s6_{AE} - k^+_{AE1} * s1_{AE}}{60,000} \tag{S.142}$$

Sodium-Bicarbonate Symporter

$$aa_{NBC} = 1 + \frac{[Na^+_o]}{k_{NBC,na}} + \frac{[Na^+_o] * [HCO^-_{3,e}]}{k_{NBC,na} * k_{NBC,hco3}} \tag{S.143}$$

$$bb_{NBC} = 1 + \frac{k_{NBC,hco3}}{[HCO^-_{3,e}]} + \frac{k_{NBC,na} * k_{NBC,hco3}}{[HCO^-_{3,e}] * [Na^+_o]} \tag{S.144}$$

$$cc_{NBC} = 1 + \frac{k_{NBC,hco3}}{[HCO^-_{3,i}]} + \frac{k_{NBC,na} * k_{NBC,hco3}}{[HCO^-_{3,i}] * [Na^+_i]} \tag{S.145}$$

$$dd_{NBC} = 1 + \frac{[Na^+_i]}{k_{NBC,na}} + \frac{[Na^+_i] * [HCO^-_{3,i}]}{k_{NBC,na} * k_{NBC,hco3}} \tag{S.146}$$

$$s1_{NBC} = \frac{1}{aa_{NBC} + dd_{NBC} * \dfrac{k^+_{NBC1} + k^+_{NBC2}\left(\dfrac{aa_{NBC}}{bb_{NBC}}\right)}{k^-_{NBC1} + k^-_{NBC2}\left(\dfrac{dd_{NBC}}{cc_{NBC}}\right)}} \tag{S.147}$$

$$s6_{NBC} = \frac{1}{dd_{NBC} + aa_{NBC} * \frac{k^-_{NBC1} + k^-_{NBC2}\left(\frac{dd_{NBC}}{cc_{NBC}}\right)}{k^+_{NBC1} + k^+_{NBC2}\left(\frac{aa_{NBC}}{bb_{NBC}}\right)}} \tag{S.148}$$

$$reg_{NBC} = \left(\frac{[H^+_i]^{n_{NBC,hi}}}{([H^+_i]^{n_{NBC,hi}} + K^{n_{NBC,hi}}_{NBC,hi})}\right) * \left(1 - \left(\frac{[H^+_e]^{n_{NBC,he}}}{([H^+_e]^{n_{NBC,he}} + K^{n_{NBC,he}}_{NBC,he})}\right)\right) \tag{S.149}$$

$$V_{NBC} = Vol_{myo} * reg_{NBC} * \frac{k^-_{NBC1} * s6_{NBC} - k^+_{NBC1} * s1_{NBC}}{60,000} \tag{S.150}$$

Chloride-Hydroxide Exhanger

$$aa_{CHE} = 1 + \frac{k_{CHE,oh}}{[OH^-_e]} + \frac{k_{CHE,oh} * [Cl^-_e]}{[OH^-_e] * k_{CHE,cl}} \tag{S.151}$$

$$bb_{CHE} = 1 + \frac{k_{CHE,cl}}{[Cl^-_e]} + \frac{k_{CHE,cl} * [OH^-_e]}{[Cl^-_e] * k_{CHE,oh}} \tag{S.152}$$

$$cc_{CHE} = 1 + \frac{k_{CHE,cl}}{[Cl^-_i]} + \frac{k_{CHE,cl} * [OH^-_i]}{[Cl^-_i] * k_{CHE,oh}} \tag{S.153}$$

$$dd_{CHE} = 1 + \frac{k_{CHE,oh}}{[OH^-_i]} + \frac{k_{CHE,oh} * [Cl^-_i]}{[OH^-_i] * k_{CHE,cl}} \tag{S.154}$$

$$s1_{CHE} = \frac{1}{aa_{CHE} + dd_{CHE} * \frac{k^+_{CHE1} + k^+_{CHE2}\left(\frac{aa_{CHE}}{bb_{CHE}}\right)}{k^-_{CHE1} + k^-_{CHE2}\left(\frac{dd_{CHE}}{cc_{CHE}}\right)}} \tag{S.155}$$

$$s6_{CHE} = \frac{1}{dd_{CHE} + aa_{CHE} * \frac{k^-_{CHE1} + k^-_{CHE2}\left(\frac{dd_{CHE}}{cc_{CHE}}\right)}{k^+_{CHE1} + k^+_{CHE2}\left(\frac{aa_{CHE}}{bb_{CHE}}\right)}} \tag{S.156}$$

$$V_{CHE} = Vol_{myo} * \frac{k^-_{CHE1} * s6_{CHE} - k^+_{CHE1} * s1_{CHE}}{60,000} \tag{S.157}$$

Sodium-Hydrogen Exchanger

$$\mathrm{aa_{NHE}} = 1 + \frac{\mathrm{k_{NHE,h}}}{[\mathrm{H_e^+}]} + \frac{\mathrm{k_{NHE,h}} * [\mathrm{Na_o^+}]}{[\mathrm{H_e^+}] * \mathrm{k_{NHE,na}}} \tag{S.158}$$

$$\mathrm{bb_{NHE}} = 1 + \frac{\mathrm{k_{NHE,na}}}{[\mathrm{Na_o^+}]} + \frac{\mathrm{k_{NHE,na}} * [\mathrm{H_e^+}]}{[\mathrm{Na_o^+}] * \mathrm{k_{NHE,h}}} \tag{S.159}$$

$$\mathrm{cc_{NHE}} = 1 + \frac{\mathrm{k_{NHE,na}}}{[\mathrm{Na_i^+}]} + \frac{\mathrm{k_{NHE,na}} * [\mathrm{H_i^+}]}{[\mathrm{Na_i^+}] * \mathrm{k_{NHE,h}}} \tag{S.160}$$

$$\mathrm{dd_{NHE}} = 1 + \frac{\mathrm{k_{NHE,h}}}{[\mathrm{H_i^+}]} + \frac{\mathrm{k_{NHE,h}} * [\mathrm{Na_i^+}]}{[\mathrm{H_i^+}] * \mathrm{k_{NHE,na}}} \tag{S.161}$$

$$\mathrm{s1_{NHE}} = \frac{1}{\mathrm{aa_{NHE}} + \mathrm{dd_{NHE}} * \dfrac{\mathrm{k_{NHE1}^+} + \mathrm{k_{NHE2}^+}\left(\dfrac{\mathrm{aa_{NHE}}}{\mathrm{bb_{NHE}}}\right)}{\mathrm{k_{NHE1}^-} + \mathrm{k_{NHE2}^-}\left(\dfrac{\mathrm{dd_{NHE}}}{\mathrm{cc_{NHE}}}\right)}} \tag{S.162}$$

$$\mathrm{s6_{NHE}} = \frac{1}{\mathrm{dd_{NHE}} + \mathrm{aa_{NHE}} * \dfrac{\mathrm{k_{NHE1}^-} + \mathrm{k_{NHE2}^-}\left(\dfrac{\mathrm{dd_{NHE}}}{\mathrm{cc_{NHE}}}\right)}{\mathrm{k_{NHE1}^+} + \mathrm{k_{NHE2}^+}\left(\dfrac{\mathrm{aa_{NHE}}}{\mathrm{bb_{NHE}}}\right)}} \tag{S.163}$$

$$\mathrm{reg_{NHE}} = \left(\frac{[\mathrm{H_i^+}]^{\mathrm{n_{NHE,hi}}}}{([\mathrm{H_i^+}]^{\mathrm{n_{NHE,hi}}} + \mathrm{K_{NHE}^{n_{NHE,hi}}})}\right) * \left(1 - \frac{[\mathrm{H_e^+}]^{\mathrm{n_{NHE,he}}}}{([\mathrm{H_e^+}]^{\mathrm{n_{NHE,he}}} + \mathrm{K_{NHE}^{n_{NHE,he}}})}\right) \tag{S.164}$$

$$\mathrm{V_{NHE}} = \mathrm{modifier_{NHE}} * \mathrm{Vol_{myo}} * \mathrm{reg_{NHE}} * \frac{\mathrm{k_{NHE1}^-} * \mathrm{s6_{NHE}} - \mathrm{k_{NHE1}^+} * \mathrm{s1_{NHE}}}{60,000} \tag{S.165}$$

Carbon Dioxide

$$\mathrm{V_{CO_2}} = 1.17 * \mathrm{Vol_{myo}} * ([\mathrm{CO_{2,e}}] - [\mathrm{CO_{2,i}}]) \tag{S.166}$$

$$\mathrm{V_{hyd,e}} = \mathrm{Vol_{external}}(\mathrm{k_{hyd}^+}[\mathrm{CO_{2,e}}] - \mathrm{k_{hyd}^-}[\mathrm{HCO_{3,e}^-}][\mathrm{H_e^+}]) \tag{S.167}$$

$$\mathrm{V_{hyd,i}} = (\mathrm{Vol_{myo}} + \mathrm{Vol_{sr}}) * (\mathrm{k_{hyd}^+}[\mathrm{CO_{2,i}}] - \mathrm{k_{hyd}^-}[\mathrm{HCO_{3,i}^-}] * [\mathrm{H_i^+}]) \tag{S.168}$$

$$\frac{d[CO_{2,i}]}{dt} = \frac{V_{CO2}}{Vol_{myo}} - \frac{V_{hyd,i}}{Vol_{myo} + Vol_{sr}} \tag{S.169}$$

During pre-ischemia, $[CO_{2,e}]$ is constant:

$$[CO_{2,e}] = ppCO_2 * CO_{2sol} * p_{atm} \tag{S.170}$$

During ischemia:

$$[CO_{2,e}]_t = [CO_{2,e}]_{t\text{-}\Delta t} - \frac{V_{CO2} + V_{hyd,e}}{Vol_{external}}\Delta t \tag{S.171}$$

During reperfusion:

$$[CO_{2,e}]_t = [CO_{2,e}]_{t\text{-}\Delta t} - \frac{[CO_{2,e}]_{t\text{-}\Delta t} - [CO_{2,e}]_{preischemic}}{3.75x10^4}\Delta t \tag{S.172}$$

Bicarbonate

$$\frac{d[HCO^-_{3,i}]}{dt} = \frac{V_{hyd,i}}{Vol_{myo} + Vol_{sr}} + \frac{V_{NBC} - V_{AE}}{Vol_{myo}} \tag{S.173}$$

During pre-ischemia, $[HCO^-_{3,e}]$ is constant. During ischemia:

$$[HCO^-_{3,e}]_t = [HCO^-_{3,e}]_{t\text{-}\Delta t} + \frac{V_{hyd,e} - V_{NBC} + V_{AE}}{Vol_{external}}\Delta t \tag{S.174}$$

During reperfusion:

$$[HCO^-_{3,e}]_t = [HCO^-_{3,e}]_{t\text{-}\Delta t} - \frac{[HCO^-_{3,e}]_{t\text{-}\Delta t} - [HCO^-_{3,e}]_{preischemic}}{3.75x10^4}\Delta t \tag{S.175}$$

pH

$$\beta_e = \log_{10}\left(10^{-pHe} + \frac{[ib_1] * 10^{(pK1\text{-}pHe)}}{(1 + 10^{(pK1\text{-}pHe)})^2} + \frac{[ib_2] * 10^{(pK2\text{-}pHe)}}{(1 + 10^{(pK2\text{-}pHe)})^2}\right) \tag{S.176}$$

$$\beta_i = \log_{10}\left(10^{-pHi} + \frac{[ib_1] * 10^{(pK1\text{-}pHi)}}{(1 + 10^{(pK1\text{-}pHi)})^2} + \frac{[ib_2] * 10^{(pK2\text{-}pHi)}}{(1 + 10^{(pK2\text{-}pHi)})^2}\right) \tag{S.177}$$

During pre-ischemia, pH_e is constant. During ischemia:

$$pH_{e,\,t} = pH_{e,\,t\text{-}\Delta t} - \frac{1}{\beta_e}\left(\frac{V_{NHE} - V_{CHE} + V_{hyd,e}}{Vol_{external}}\right)\Delta t \tag{S.178}$$

During reperfusion:

$$pH_{e,\,t} = pH_{e,\,t\text{-}\Delta t} + \frac{(7.40 - pH_{e,\,t\text{-}\Delta t})}{1.5x10^5}\Delta t \tag{S.179}$$

During pre-ischemia and reperfusion:

$$pH_{i,\,t} = pH_{i,\,t\text{-}\Delta t} - \frac{1}{\beta_i}\left(\frac{-V_{NHE} + V_{CHE}}{Vol_{myo}} + \frac{V_{hyd,i}}{Vol_{myo} + Vol_{sr}}\right)\Delta t \tag{S.180}$$

During ischemia:

$$pH_i = 6.18507 - 0.56697e^{-0.19015t} + 1.5377e^{-0.18462t} \tag{S.181}$$

Ion Concentrations

$$[H_e^+] = 10^{(3\text{-}pH_e)} \tag{S.182}$$

$$[H_i^+] = 10^{(3\text{-}pH_i)} \tag{S.183}$$

$$[OH_e^-] = 10^{(-11+pH_e)} \tag{S.184}$$

$$[OH_i^-] = 10^{(-11+pH_i)} \tag{S.185}$$

$$I_{Na,total} = I_{Na} + I_{Na,b} + I_{Na,l} + I_{Ca(L),Na} + 3 * I_{NaK} + 3 * I_{NaCa} \tag{S.186}$$

$$I_{K,total} = I_{Kr} + I_{Ks} + I_{K1} + I_{Kp} + I_{K(ATP)} + I_{Ca(L),K} - 2 * I_{NaK} \tag{S.187}$$

$$I_{Ca,total} = I_{Ca(L)} + I_{Ca,b} + I_{Ca,t} + I_{p(Ca)} - 2 * I_{NaCa} \tag{S.188}$$

$$I_{Cl,total} = I_{Cl} \tag{S.189}$$

$$\frac{d[Na_i^+]}{dt} = \frac{-I_{Na,total} * C_m * A_{cap}}{F * z_{Na} * Vol_{myo}} + \frac{V_{NHE} + V_{NBC}}{Vol_{myo}} \tag{S.190}$$

$$\frac{d[K_i^+]}{dt} = \frac{-(I_{K,total} + I_{stim}) * C_m * A_{cap}}{F * z_K * Vol_{myo}}, \tag{S.191}$$

$$\beta_{cai} = \beta_{TRPN} + \beta_{CMDN} - 1 \tag{S.192}$$

$$\frac{d[Ca_i^{2+}]}{dt} = -\frac{1}{\beta_{cai}} \left(\frac{I_{Ca,total} * C_m * A_{cap}}{F * z_{Ca} * Vol_{myo}} + \left((V_{SERCA} - I_{leak}) \frac{Vol_{nsr}}{Vol_{myo}} \right) - \left((I_{relcicr} + I_{reljsrol}) \frac{Vol_{jsr}}{Vol_{myo}} \right) \right) \tag{S.193}$$

$$\frac{d[Cl_i^-]}{dt} = \frac{-I_{Cl,total} * C_m * A_{cap}}{F * z_{Cl} * Vol_{myo}} + \frac{V_{CHE} + V_{AE}}{Vol_{myo}} \tag{S.194}$$

During pre-ischemia, $[Na^+{}_o]$, $[K^+{}_o]$, and $[Ca^{2+}{}_o]$ are constant. During ischemia:

$$[Na_o^+]_t = [Na_o^+]_{t\text{-}\Delta t} + \left(\frac{I_{Na,total} * C_m * A_{cap}}{F * z_{Na} * Vol_{external}} - \frac{V_{NHE} + V_{NBC}}{Vol_{external}} \right) \Delta t \tag{S.195}$$

$$[K_o^+]_t = [K_o^+]_{t\text{-}\Delta t} + \frac{I_{K,total} * C_m * A_{cap}}{F * z_K * Vol_{external}} \Delta t \tag{S.196}$$

$$[Ca_o^{2+}]_t = [Ca_o^{2+}]_{t\text{-}\Delta} t + \frac{I_{Ca,total} * C_m * A_{cap}}{F * z_{Ca} * Vol_{external}} \Delta t \tag{S.197}$$

During reperfusion:

$$[Na_o^+]_t = [Na_o^+]_{t\text{-}\Delta t} - \frac{[Na_o^+]_{t\text{-}\Delta t} - [Na_o^+]_{preischemic}}{3.75x10^4} \Delta t \tag{S.198}$$

$$[K_o^+]_t = [K_o^+]_{t\text{-}\Delta t} - \frac{[K_o^+]_{t\text{-}\Delta t} - [K_o^+]_{preischemic}}{3.75x10^4} \Delta t \tag{S.199}$$

$$[Ca_o^{2+}]_t = [Ca_o^{2+}]_{t\text{-}\Delta t} - \frac{[Ca_o^{2+}]_{t\text{-}\Delta t} - [Ca_o^{2+}]_{preischemic}}{3.75x10^4} \Delta t \tag{S.200}$$

Volume Regulation

During pre-ischemia, $\prod_i$ is constant at 310.0. During ischemia:

$$\prod_i = 310 + t \tag{S.201}$$

During reperfusion:

$$\prod_{i,\ t} = \prod_{i,\ t\text{-}\Delta 1} - \frac{\prod_{i,\ t\text{-}\Delta t} - 310}{3.75x10^4 ms} \Delta t \tag{S.202}$$

Calculated once at beginning of simulation:

$$X_e^{zi\text{-}} = Vol_{external} * \left(\prod_e -[Na_o^+] - [K_o^+] - [Ca_o^{2+}] - [Cl_e^-] \right) \tag{S.203}$$

During ischemia and reperfusion (constant during pre-ishemia):

$$X_i^{zi\text{-}} = Vol_{myo} * \left(\prod_i -[Na_i^+] - [K_i^+] - [Ca_i^{2+}] - [Cl_i^-] \right) \tag{S.204}$$

$$V_{H_2O} = 10 * Lp * R * temp * (([Na_i^+] + [K_i^+] + [Ca_i^{2+}] + [Cl_i^-] + \frac{[X_i^{zi\text{-}}]}{Vol_{myo}}) - ([Na_o^+] + [K_o^+] + [Ca_o^{2+}] + [Cl_e^-] + \frac{[X_e^{zi\text{-}}]}{Vol_{external}})) \tag{S.205}$$

$$dVol_{cell} = A_{cap} * V_{H_2O} * \Delta t \tag{S.206}$$

$$Vol_{myo} = Vol_{cell} * 0.68 \tag{S.207}$$

$$Vol_{sr} = Vol_{cell} * 0.06 \tag{S.208}$$

$$Vol_{nsr} = Vol_{cell} * 0.0552 \tag{S.209}$$

$$Vol_{jsr} = Vol_{cell} * 0.0048 \tag{S.210}$$

$$Vol_{external} = Vol_{total} - Vol_{cell} \tag{S.211}$$

Voltage Calculations

Calculate $\text{Proton}_{\text{ref}}$ and Hib_{ref} at beginning of simulation:

$$[\text{Proton}_{\text{ref}}] = 10^{3\text{-pH}_\text{i}} \tag{S.212}$$

$$[\text{Hib}_{\text{ref}}] = \frac{[\text{ib}_1] * 10^{\text{-pH}_\text{i}}}{10^{\text{-pH}_\text{i}} + 10^{\text{-pK1}}} + \frac{[\text{ib}_2] * 10^{\text{-pH}_\text{i}}}{10^{\text{-pH}_\text{i}} + 10^{\text{-pK2}}} \tag{S.213}$$

$$[\text{Hib}_1] = \frac{[\text{ib}_1] * 10^{\text{-pHi}}}{10^{\text{-pHi}} + 10^{\text{-pK1}}} \tag{S.214}$$

$$[\text{Hib}_2] = \frac{[\text{ib}_2] * 10^{\text{-pHi}}}{10^{\text{-pHi}} + 10^{\text{-pK2}}} \tag{S.215}$$

$$[\text{Anion}^{\text{-}}] = (10^{3\text{-pHi}} - [\text{Proton}_{\text{ref}}]) + ([\text{Hib}_1] + [\text{Hib}_2] - [\text{Hib}_{\text{ref}}]) \tag{S.216}$$

$$\begin{aligned} \text{C}_0 = -\frac{\text{V} * \text{A}_{\text{cap}} * \text{C}_\text{m}}{\text{Vol}_{\text{myo}} * \text{F}} + [\text{Na}_\text{i}^+] + [\text{K}_\text{i}^+] - [\text{Cl}_\text{i}^-] - [\text{HCO}_{3,\text{i}}^-] + ([\text{Proton}_{\text{ref}}] - [\text{Hib}_{\text{ref}}]) - [\text{OH}_\text{i}^-] - [\text{Anion}^{\text{-}}] + \\ \text{z}_{\text{Ca}} * \left(([\text{Ca}_\text{i}^{2+}] + [\text{TRPN}] + [\text{CMDN}]) + [\text{NSR}] * \left(\frac{\text{Vol}_{\text{nsr}}}{\text{Vol}_{\text{myo}}} \right) + ([\text{JSR} + [\text{CSQN}]) * \left(\frac{\text{Vol}_{\text{jsr}}}{\text{Vol}_{\text{myo}}} \right) \right) \end{aligned} \tag{S.217}$$

$$\begin{aligned} \text{V} = \frac{\text{Vol}_{\text{myo}} * \text{F}}{\text{A}_{\text{cap}} * \text{C}_\text{m}} * (- \text{C}_0 + [\text{Na}_\text{i}^+] + [\text{K}_\text{i}^+] - [\text{Cl}_\text{i}^-] - [\text{HCO}_{3,\text{i}}^-] + ([\text{Proton}_{\text{ref}}] - [\text{Hib}_{\text{ref}}]) - [\text{OH}_\text{i}^-] - [\text{Anion}^{\text{-}}] + \\ \text{z}_{\text{Ca}} * \left(([\text{Ca}_\text{i}^{2+}] + [\text{TRPN}] + [\text{CMDN}]) + [\text{NSR}] * \left(\frac{\text{Vol}_{\text{nsr}}}{\text{Vol}_{\text{myo}}} \right) + ([\text{JSR} + [\text{CSQN}]) * \left(\frac{\text{Vol}_{\text{jsr}}}{\text{Vol}_{\text{myo}}} \right) \right)) \end{aligned} \tag{S.218}$$

$$\text{dvdtnew} = \frac{\text{V}_\text{t} - \text{V}_{\Delta\text{t}}}{\Delta\text{t}} \tag{S.219}$$

Phosphometabolites

During pre-ischemia, all metabolites are held at their initial values. During ischemia:

$$[\text{ATP}] = 0.0006549\text{t}^3 - 0.02305\text{t}^2 - 0.104837\text{t} + 7.216 \tag{S.220}$$

$$[\text{PCr}] = -0.01259 + 12.339\text{e}^{\text{-0.92559t}} + 0.96819\text{e}^{\text{-0.078496t}} \tag{S.221}$$

During reperfusion:

$$[\text{ATP}]_\text{t} = [\text{ATP}]_{\text{t-}\Delta\text{t}} - \frac{[\text{ATP}]_{\text{t-}\Delta\text{t}} - 0.4[\text{ATP}_{\text{preischemic}}]}{5\text{x}10^3\text{ms}}\Delta\text{t} \tag{S.222}$$

$$[\mathrm{PCr}]_{\mathrm{t}} = [\mathrm{PCr}]_{\mathrm{t\text{-}\Delta t}} - \frac{[\mathrm{PCr}]_{\mathrm{t\text{-}\Delta t}} - 0.75[\mathrm{ion}_{\mathrm{preischemic}}]}{5\mathrm{x}10^{3}\mathrm{ms}}\Delta \mathrm{t} \tag{S.223}$$

During ischemia and reperfusion:

$$[\mathrm{Cr}] = 22.2 - [\mathrm{PCr}] \tag{S.224}$$

$$[\mathrm{ADP}] = \frac{[\mathrm{ATP}] * [\mathrm{Cr}]}{[\mathrm{PCr}] * [\mathrm{H}_{\mathrm{i}}^{+}] * 1.66\mathrm{x}10^{6}} \tag{S.225}$$

$$[\mathrm{AMP}] = \frac{[\mathrm{ADP}] * [\mathrm{ADP}] * 1.05}{[\mathrm{ATP}]} \tag{S.226}$$

$$[\mathrm{Pi}_{\mathrm{free}}] = [\mathrm{Pi}_{\mathrm{total}} - (3 * [\mathrm{ATP}] + 2 * [\mathrm{ATP}] + [\mathrm{AMP}] + [\mathrm{PCr}]) \tag{S.227}$$

Miscellaneous

$$\mathrm{E}_{\mathrm{Na}} = \frac{\mathrm{R} * \mathrm{temp}}{\mathrm{F}} * \log\left(\frac{[\mathrm{Na}_{\mathrm{o}}^{+}]}{[\mathrm{Na}_{\mathrm{i}}^{+}]}\right) \tag{S.228}$$

$$\mathrm{E}_{\mathrm{Ca}} = \frac{\mathrm{R} * \mathrm{temp}}{2 * \mathrm{F}} * \log\left(\frac{[\mathrm{Ca}_{\mathrm{o}}^{2+}]}{[\mathrm{Ca}_{\mathrm{i}}^{2+}]}\right) \tag{S.229}$$

$$\mathrm{E}_{\mathrm{K}} = \frac{\mathrm{R} * \mathrm{temp}}{\mathrm{F}} * \log\left(\frac{[\mathrm{K}_{\mathrm{o}}^{+}]}{[\mathrm{K}_{\mathrm{i}}^{+}]}\right) \tag{S.230}$$

$$\mathrm{E}_{\mathrm{Ks}} = \frac{\mathrm{R} * \mathrm{temp}}{\mathrm{F}} * \log\left(\frac{[\mathrm{K}_{\mathrm{o}}^{+}] + \mathrm{prnak} * [\mathrm{Na}_{\mathrm{o}}^{+}]}{[\mathrm{K}_{\mathrm{i}}^{+}] + \mathrm{prnak} * [\mathrm{Na}_{\mathrm{i}}^{+}]}\right) \tag{S.231}$$

If dvdtnew > 10.0 AND $\mathrm{t}_{\mathrm{cicr}}$ > 10.0 AND flag = true, then set flag = false.

If V > -35.0 AND $\mathrm{dI}_{\mathrm{Ca,total\ t}} > \mathrm{dI}_{\mathrm{Ca,total\ t\text{-}\Delta t}}$ AND flag = false, then:
set flag = true
set $\mathrm{t}_{\mathrm{cicr}} = 0$

If [CSQN] $\geq$ csqnth AND $\mathrm{t}_{\mathrm{jsrol}} \geq 50$, then reset $\mathrm{t}_{\mathrm{jsrol}} = 0$.

Notes on experimental data used in determination of model parameters

The following pertains to model parameters cited from [1]:

AE, CHE, NBC, and NHE:

[8]: guinea pig papillary muscle and sheep Purkinje fiber, 34-37 degrees C.

[9]: isolated rabbit ventricular myocytes, 35-37 degrees C.

[10]: isolated guinea pig ventricular myocytes, 37 degrees C.

[11]: isolated guinea pig ventricular myocytes, 37 degrees C.

[12]: sheep Purkinje fiber, 37 degrees C.

[7]: sheep Purkinje fiber, 37 degrees C.

pH Dependence of SR Calcium Release:

[13]: canine cardiac muscle SR fractions.

pH Dependence of Na-Ca Exchange:

[14]: guinea pig ventricular cell excised pathches.

pH Dependence of Calcium Binding to Troponin:

[15]: canine cardiac myofibrils, 22 degrees C.

[16]: XL1 cells transformed with mouse Troponin I cDNA.

pH Regulation:

[17]: squid giant axon, 23 degrees C.

[18]: isolated guinea pig ventricular myocytes, 37 degrees C.

[10]: isolated guinea pig ventricular myocytes, 37 degrees C.

The following pertains to model parameters cited from [3]:

NaK Pump:

Parameter values were adjusted to correspond to a temperature of 37 degrees C using a Q_{10} of 2.6.

$rate^{+}_{NaK1}$, $rate^{-}_{NaK1}$, sensitivity to $[Na^{+}_{o}]$ and [ADP] [19]: isolated rat myocytes, 23 degrees C.

$rate^{+}_{NaK2}$, $rate^{-}_{NaK2}$ [20]: rabbit kidney fragments adsorbed on lipid bilayers, 20 degrees C.

$rate^{-}_{NaK3}$ [21]: porcine kidney outer medulla, 37 degrees C.

$rate^{+}_{NaK4}$, $rate^{-}_{NaK4}$ [22]: rabbit kidney outer medulla, 37 degrees C.

$density_{NaK}$ [23]: isolated guinea pig and rat myocytes, 35 degrees C.

Sensitivity to $[Na^{+}_{i}]$ [24]: rabbit ventricular myocytes, 22 degrees C.

Sensitivity to membrane potential and $[K^{+}_{o}]$ [25]: guinea pig membrane excised patches, 36 degrees C.

Sensitivity to changes in [ATP] [26]: guinea pig excised patches.

Other experimental data sets used:

[27–29]: isolated guinea pig ventricular myocytes, 36 degrees C.

$I_{K(ATP)}$:

[30]: guinea pig ventricular myocytes, 36 degrees C.

[31]: guinea pig isolated ventricular myocytes, room temperature.

[32]: COSm6 cells transfected with mouse Kir6.2, 20-22 degrees C.

[33]: COSm6 cells transfected with mouse Kir6.2, 25 degrees C.

[34]: HEK cells transfected with Kir6.2 and SUR1.

[35]: mouse $I_{K(ATP)}$ isolted from pancreatic beta and HIT cells.

[36]: *Xenopus* oocytes transfected with mouse Kir6.2 and rat SUR1.

[37]: COS-7 cells transfected with hamster SUR1, 20-24 degrees C.

Volume Regulation:

[38]: slices of canine left ventricle and papillary muscle, 37 degrees C.

[39]: porcine, transmural biopsies from intact beating heart.

pH and phosphometabolites:

ATP, PCr, and pH [40]: perfused guinea pig hearts, 37 degrees C.

ATP, PCr, and Cr [41]: guinea pig isolated myocytes, atria, and saline perfused hearts, 37 degrees C.

P_i [42]: perfused guinea pig hearts.

The following pertains to model parameters cited from [6]:

Data from three studies were used to constrain model parameters:

[43]: $Ca^{2+}{}_i$ uptake versus pH (Fig. 5); mouse SERCA2a microsomes, experiments performed at 37 degrees C, [ATP] = 3mM, [ADP] = 0mM, $[P_i]$ = 0mM, $[Ca^{2+}{}_i]$ = 0mM, $[Ca^{2+}{}_{SR}]$ = 0.001mM.

[43]: $Ca^{2+}{}_i$ uptake versus $[Ca^{2+}{}_i]$ at different pH (Fig. 4); mouse SERCA2a microsomes, experiments performed at 37 degrees C, [ATP] = 3mM, [ADP] = 0mM, $[P_i]$ = 0mM, $[Ca^{2+}{}_i]$ = variable, $[Ca^{2+}{}_{SR}]$ = 0mM.

[44]: level of back phosphorylation versus $[P_i]$ (Fig. 6); rabbit SERCA1a nonnative cell experession, 25 degrees C, pH 6, [ATP] = 0mM, [ADP] = 0mM, $[P_i]$ = variable, $[Ca^{2+}{}_i]$ = 0mM, $[Ca^{2+}{}_{SR}]$ = 0mM.

[45]: ATPase activity versus ATP and ADP (Fig. 7), rabbit SERCA1a solubilized SR fragments, 10 degrees C, pH 7, [ATP] = variable, [ADP] = variable, $[P_i]$ = 0mM, $[Ca^{2+}{}_i]$ = 5mM, $[Ca^{2+}{}_{SR}]$ = 5mM.

In the absence of reliable Q_{10} data, the authors in [6] chose normalize the data to a maximum cycle rate of 5 s^{-1} under the following "optimal" conditions: pH = 7.2, [ATP] = 5mM, [ADP] = 0mM, $[P_i]$ = 0mM, $[Ca^{2+}{}_i]$ = 0mM, $[Ca^{2+}{}_{SR}]$ = 10uM.

The following pertains to model parameters cited from [5]:

The experiments used to determine $k_{1/2}$ for ATP binding and the Hill coefficient of 2.6 were performed using isolated guinea pig ventricular cells at a temperature between 35 and 36 degrees C [30].

The following pertains to model parameters cited from [4]:

The data used to inform alterations in sodium conductance and late sodium current came from experiments performed on isolated guinea pig myocytes at 37 degrees C [46].

Summary of Ischemia and Reperfusion Simulation Protocols

During pre-ischemia, extracellular species and pH are held constant, the assumption being that they are in equilibrium with a much larger volume. During ischemia, when the extracellular compartment is assumed to be isolated, concentrations and pH in the extracellular compartment are allowed to vary as described by the equations cited in the table below and in Supplement 2. Also, a variable representing intracellular osmolarity is increased, favoring inward water flux, thereby increasing and decreasing the intra- and extracellular volumes, respectively. During reperfusion, when extracellular fluid is washed out and replaced with "normal" fluid from the surrounding non-ischemia tissue, we return the values representing extracellular species concentration and pH to normal over a specified time. Intracellular osmolarity is returned to normal, as well.

Also, during ischemia a decrease in intracellular pH, as well as the concentrations of ATP and phosphocreatine, are imposed on the system per the equations cited in the table below.

	Ischemia	Reperfusion
pH_i	Prescribed by Eq. S181	Calculated by Eq. S180
pH_e	Calculated by Eq. S178	Prescribed by Eq. S179
$[CO_{2,e}]$	Calculated by Eq. S171	Prescribed by Eq. S172
$[HCO^-_{3,e}]$	Calculated by Eq. S174	Prescribed by Eq. S175
$[Na^+_o]$	Calculated by Eq. S195	Prescribed by Eq. 198
$[K^+_o]$	Calculated by Eq. S196	Prescribed by Eq. 199
$[Ca^{2+}_o]$	Calculated by Eq. S197	Prescribed by Eq. 200
$\prod_i$	Prescribed by Eq. S201	Prescribed by Eq. S202
[ATP]	Prescribed by Eq. S220	Prescribed by Eq. S222
[PCr]	Prescribed by Eq. S221	Prescribed by Eq. S223
$\text{modifier}_{\text{Inal}}$	0.00018	0.00007
g_{Na}	14.4 mS/uF	16.0 mS/uF

Table S2: Summary of ischemia and reperfusion protocols.

Data from several different experimental sources were cited in the manuscript. Details of the relevant experimental methods are provided below.

The experiments cited in discussions of intracellular pH (including Figure 3A in the manuscript), ATP and PCr [40] were performed with Langendorff-perfused female guinea pig hearts. Experiments are performed at at temperature of 37 degrees Celsius and whole hearts were perfused with standard Krebs-Henseleit buffer. Changes in pH and phosphometabolite concentrations were determined by NMR spectroscopy. Global ischemia was induced by clamping the perfusion line.

Figure 3B in the manuscript cites control data from experiments detailed in [47]. Male guinea pig hearts were used and a temperature of 37 degrees Celsius was maintained during perfusion of whole hearts. pH measurements before, during, and after global ischemia were made using a pH electrode inserted into the left ventricle. Hearts were spontaneously beating and perfused with Krebs-Henseleit solution of the following composition (in mM): NaCl 118, KCl 4.7, $CaCl_2$ 2.5, $MgSO_4$ 1.2, KH_2PO_4 1.2, $NaHCO_3$ 25, and glucose 10. Buffer was aerated with 95 percent oxygen/5 percent CO_2 (pH 7.5)

Figure 3C in the manuscript and discussions of intracellular sodium and calcium cite data from experiments performed with guinea pig hearts [48]. Calcium and sodium measurements using fluorescent dyes were made from the left ventricles of intact hearts. Hearts were perfused at a temperature of 37.2 degrees Celsius with Krebs-Ringer solution equilibrated with 97 percent oxygen/3 percent carbon dioxide (pH 7.39) and composed of the following (in mM): 137 Na^+, 5 K^+, 1.2 Mg^{2+}, 2.5 Ca^{2+}, 134 Cl^-, 15.5 HCO_3^-, 1.2 $H_2PO_4^-$, 11.5 glucose, 2 pyruvate, 16 mannitol, 0.05 EDTA, 0.1 probenecid, and 5U/l insulin.

The porcine experiment cited in the discussion of extracellular pH recovery [49] consisted of using pH-sensitive electrodes inserted into the LAD of hearts in live anesthetized pigs, ventilated to maintain arterial oxygen saturation greater than 95 percent, arterial P_{CO_2} 35-45 mm Hg, and arterial pH at 7.35-7.45. Within the same discussion, canine data was referenced from a study [50] in which pH measurements were made using a blood gas analyzer from coronary venous blood samples. The dogs in this study were anesthetized and the arterial pH, P_{O_2} and P_{CO_2} before the start of experimental protocols were 7.40, 104 mm Hg, and 37.5 mm Hg, respectively.

The estimate of how much time is required for extracellular ions to return to preischemic concentrations comes from measurements of extracellular potassium made in Langendorff-perfused guinea pig hearts [51]. Ischemia was induced by clamping of the aorta. Ion concentrations were made either by flame photometry or an ion-selective probe. The temperature range was 31-33 degrees Celsius, although temperature was reported to remain constant during individual experiments. Perfusion fluid contained washed bovine erythrocytes (hemoglobin concentration of 8 g/100 ml), dextran (mol wt of 70,000, 4 g/100 ml), insulin (1 U/l), heparin (400 U/l) and Tyrode's solution of the following composition (in mM): Na^+ 149, K^+ 4.5, Mg^{2+} 0.49, Ca^{2+} 1.8, Cl^- 145.8, HCO_3^- 11.9, $H_2PO_4^-$ 0.4, and glucose, 20. pH was between 7.34 and 7.37.

Figure Legends

Figure S1.

Analysis of sodium influx under three different conditions. (A) Sodium influx through all seven components in the model quantified as the change in concentration per minute that would occur in the absence of equivalent efflux via the sodium-potassium exchanger. (B) Percentage of total sodium influx through each of the seven components. For each of the three conditions, the model was allowed to reach steady state and sodium current through each of the seven components was analyzed for the last minute of the simulation. The model was either paced continuously at a rate of 1 Hz under pre-ischemic conditions (blue), was left at rest under pre-ischemic conditions (red), or was left at rest with intracellular pH set to 6.9 (green). As was expected, total sodium influx was highest when the cell was paced, and was higher at rest during mild acidosis than normal pH, due in part to increased flux through the sodium-hydrogen exchanger (NHE) and sodium-bicarbonate symporter (NBC)under acidosis. Also, as expected, there was less sodium-calcium exchange (NCX) activity when the cell was at rest, and even less when the resting cell experienced a lower pH. Other abbreviations: fast inward sodium current (INa), background sodium current (INa,b), late sodium current (INa,l), and sodium current through the L-type calcium channel (Ilcana).

Figure S2.

Intracellular sodium concentration profiles from simulations performed with the aim or investigating strategies that may improve $[Na]_i$ overload during reperfusion. The default ischemia-reperfusion simulation is provided as a reference (black). In the simulation shown in blue, ATP concentration was allowed to recover to the preischemic value during reperfusion (using the same constant), as opposed to being restricted to a maximum recovery of 40 percent of the preischemic value. In the simulation shown in green, NaK exchanger activity was doubled, starting at the moment of initial reperfusion. Both strategies markedly reduced the amount of $[Na]_i$ overload during reperfusion.

Figure S3.

Results of a sensitivity analysis of the sodium-potassium exchanger. For each simulation, one of 20 fixed parameters was deviated 10 percent above or below the default value and the model was run until it reached steady state, at which point the intracellular sodium concentration was recorded. Sensitivity values are reported for each of the 20 parameters. The value on the vertical axis represents the percent change in steady state concentration that results when a given parameter is increased by 1 percent. For example, the most sensitive parameter, the binding constant named $K_{\mathrm{dNaK,nai2}}$, would cause a 0.62 percent increase in steady state sodium concentration when increased by 1 percent. Parameter names, values, units, and meanings can be found in Supplement 1: Symbols and Values.

Figure S4.

The relationship between pacing frequency and steady state intracellular sodium concentration in two models and experimental data. Steady state sodium concentrations at different frequencies are compared between the present model (blue), the LRd model of guinea pig cardiomyocyte physiology (red), and data obtained from guinea pig papillary muscle (Wang *et al*, 1998) (black). Numbers for the LRd results and Wang experimental data were extracted from Figure 4 of [52] using DigitizeIt software (share-it!, Denmark).

Figure S5.

Extracellular pH (A) and intracellular sodium concentration (B) during simulated ischemia (gray region) and reperfusion. Identical conditions were simulated with versions of the model that lacked allosteric NHE regulation by extracellular protons (black) and with extracellular regulation implemented (blue). The cell was constantly simulated at a rate of 3 Hz in both simulations. Experimental studies suggest that after 20 minutes of ischemia, extracellular pH decreases to about 6.0 (see Figure 3 in the manuscript). Implementation of extracellular NHE regulation, in which flux is reduced as extracellular pH decreases, improves the extracellular pH profile of our model, reaching approximately 5.8 after 20 minutes of ischemia, (up from approximately 5.4), and exhibiting a less steep decrease in early ischemia, consistent with the data shown in Figure 3. However, at this pacing frequency, the initial accumulation of intracellular sodium during early ischemia is lost as extracellular acidosis develops and NHE flux decreases.

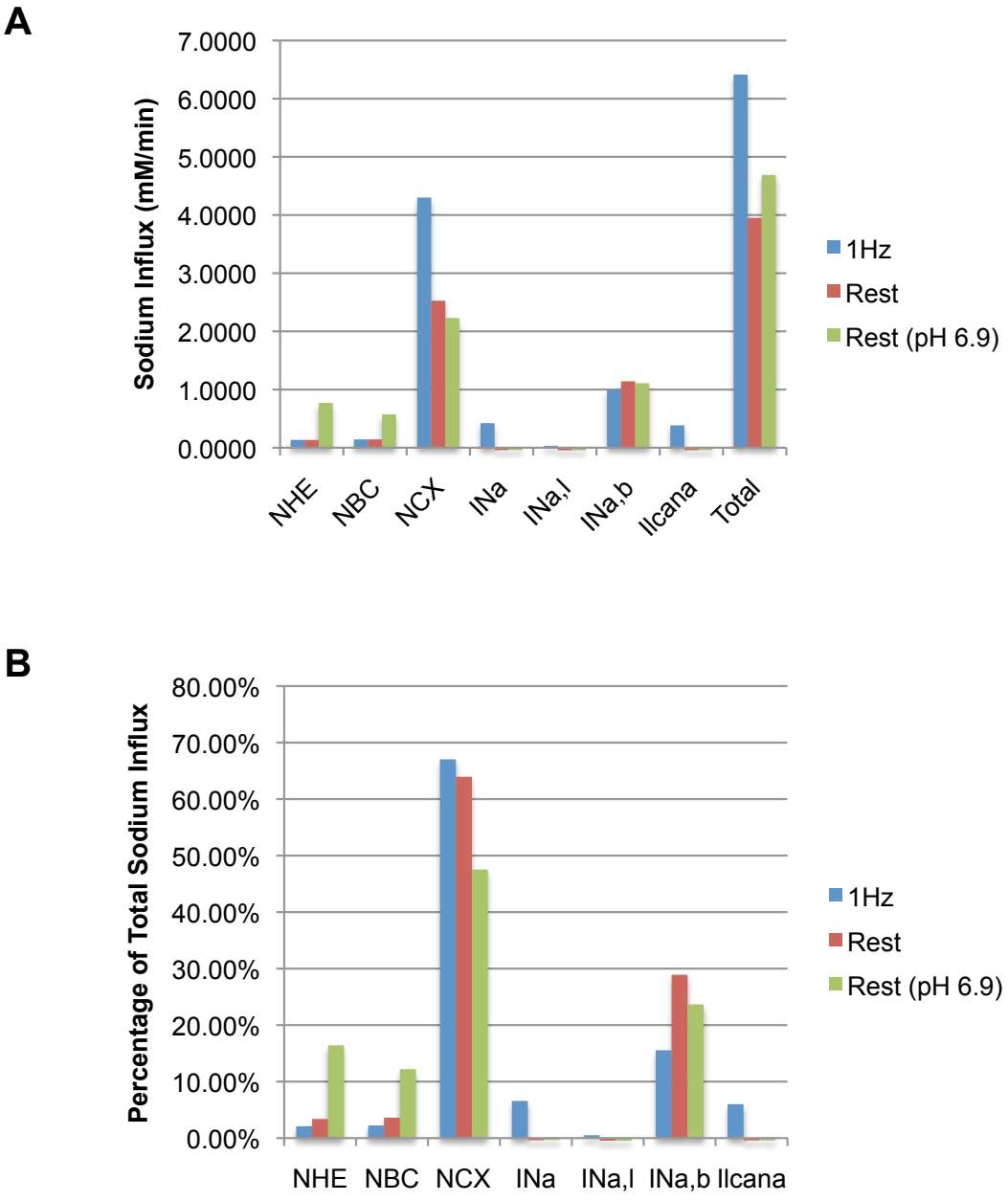

A
Sodium Influx (mM/min)
7.0000
6.0000
5.0000
4.0000
3.0000
2.0000
1.0000
0.0000
NHE
NBC
NCX
INa
INa,l
INa,b
Ilcana
Total
1Hz
Rest
Rest (pH 6.9)
B
Percentage of Total Sodium Influx
80.00%
70.00%
60.00%
50.00%
40.00%
30.00%
20.00%
10.00%
0.00%
NHE
NBC
NCX
INa
INa,l
INa,b
Ilcana
1Hz
Rest
Rest (pH 6.9)

Figure S1:

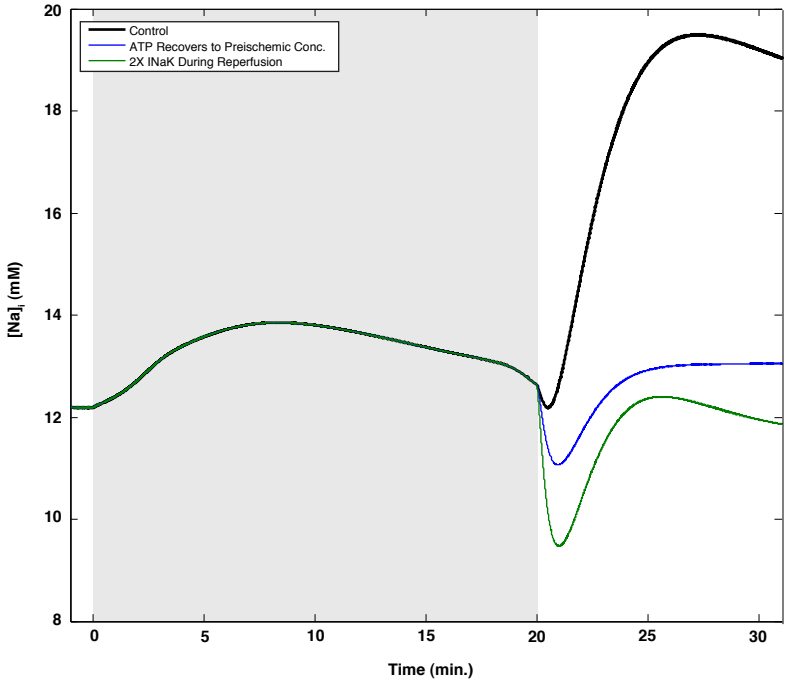
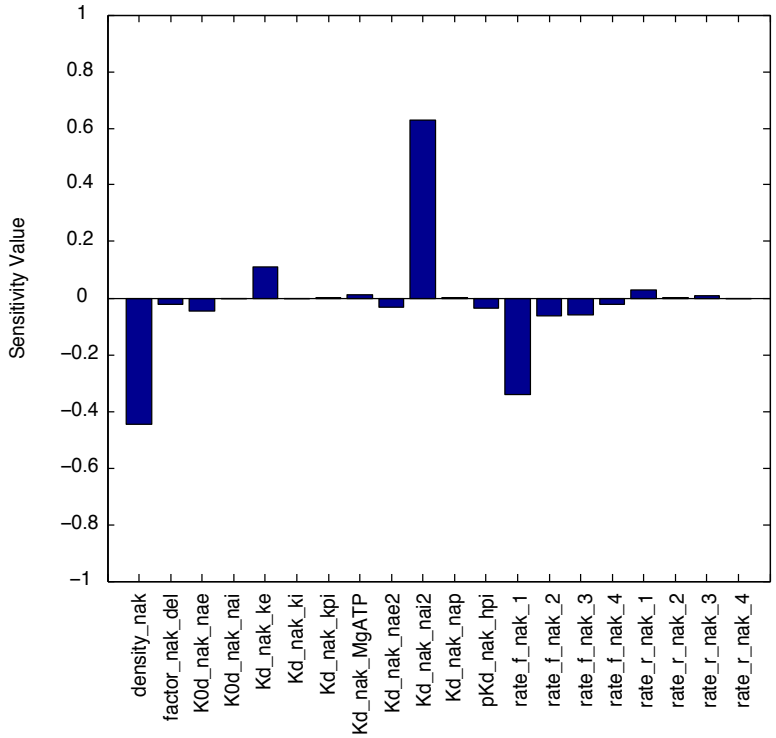

Control
ATP Recovers to Preischemic Conc.
2X INaK During Reperfusion
20
18
16
14
12
10
8
0
5
10
15
20
25
30
[Na]i (mM)
Time (min.)

Figure S2:


Sensitivity Value
1
0.8
0.6
0.4
0.2
0
−0.2
−0.4
−0.6
−0.8
−1
density_nak
factor_nak_del
K0d_nak_nae
K0d_nak_nai
Kd_nak_ke
Kd_nak_ki
Kd_nak_kpi
Kd_nak_MgATP
Kd_nak_nae2
Kd_nak_nai2
Kd_nak_nap
pKd_nak_hpi
rate_f_nak_1
rate_f_nak_2
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rate_r_nak_4

Figure S3:

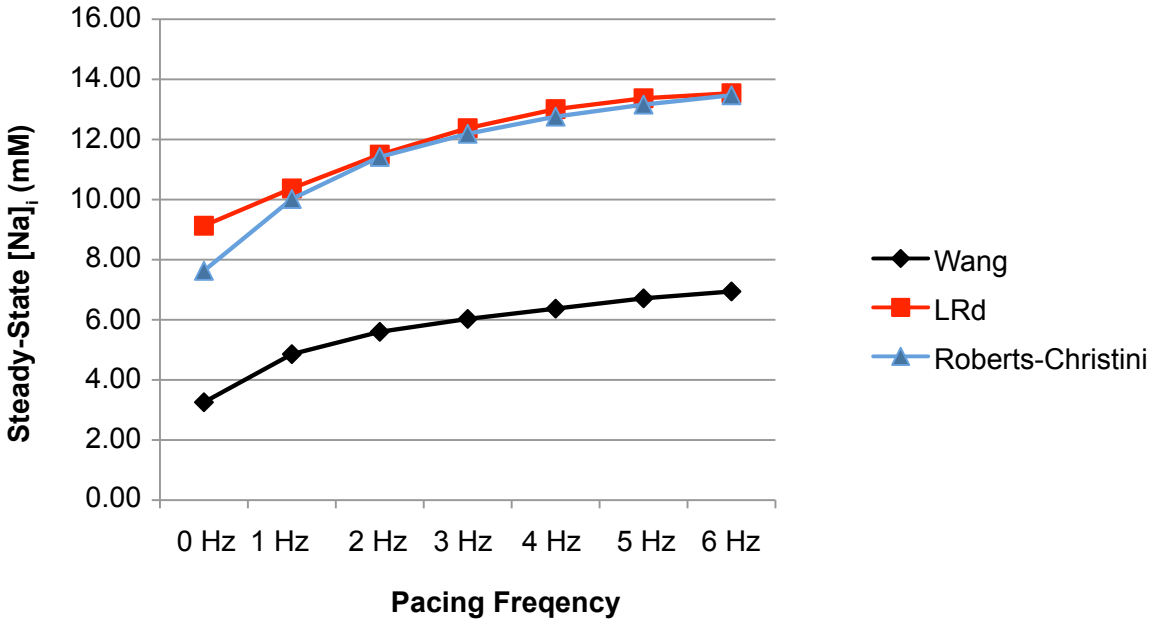
16.00
14.00
12.00
10.00
8.00
6.00
4.00
2.00
0.00
Steady-State [Na]i (mM)
0 Hz
1 Hz
2 Hz
3 Hz
4 Hz
5 Hz
6 Hz
Pacing Freqency
Wang
LRd
Roberts-Christini

Figure S4:

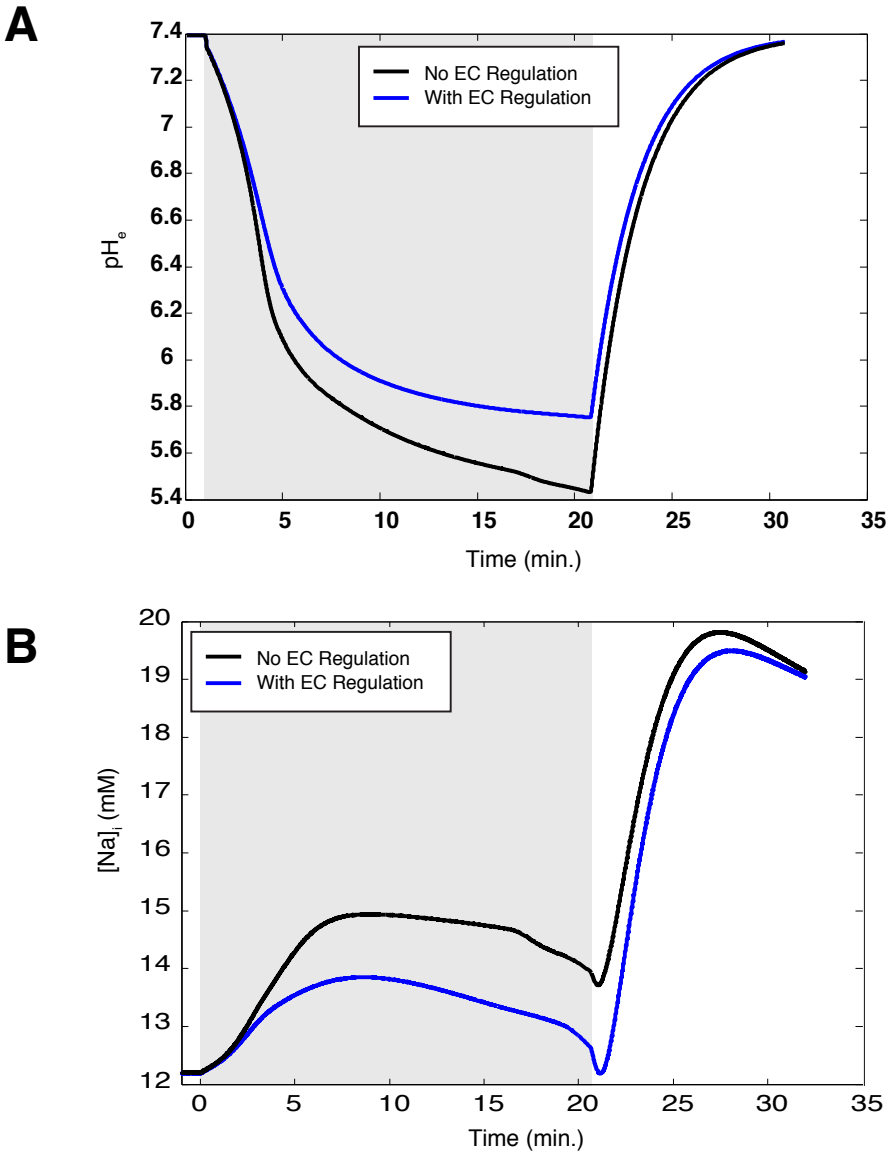
A
7.4
7.2
7
6.8
6.6
6.4
6.2
6
5.8
5.6
5.4
pH_e
No EC Regulation
With EC Regulation
0
5
10
15
20
25
30
35
Time (min.)
B
20
19
18
17
16
15
14
13
12
[Na]_i (mM)
No EC Regulation
With EC Regulation
0
5
10
15
20
25
30
35
Time (min.)

Figure S5:

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