Neurovascular Coupling Equations for Code version 2.0

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Todo list

Chapter 1

Notes for reading

The following notes, definitions and equations provide the reader with a comprehensive guide to version 1.2 of NVU. The document is set out in sections where each section contains the equations for each compartment, namely neuron, synaptic cleft, astrocyte, perivascular space, smooth muscle cell, endothelial cell, extracellular space and finally the lumen. The reader will find multiple definitions and equations but by dividing the document into sections corresponding to compartments it is hoped that a more clear understanding is obtained. Concentrations as written on the left-hand-side of the o.d.e. are given by the notation of N_j where j can be any specii such as $Na^+$of Ca^{2+}. True concentrations are written with square brackets as in $[Ca^{2+}]_n$. In point of fact they are equivalent.

Subscripts on variable such as concentrations denote the compartment, n=neuron, k=astrocyte, s=synaptic cleft, i=smooth muscle cell, j=endothelial cell, e = extracellular space. Concentrations with "hats" denote those in the ER/SR stores.

Some notes on the comparison with the Zheng data [35]

The present model is assumed to be a synaptically driven NVC rather than a neuro-modulated /arousal driven NVC. In the neuro-modulatory state norepinepherine induces robust Ca2+ astrocyte variations via G protein coupled pathway/receptors. In discussion with KC Brennan and Punam (Postdoc in KC's lab) they suggested the following

- **need to have AMPA channel in the post synapse neuron compartment or that the stimulus would be large. This channel provides Na^+in/out of the post-synaptic neuron. However it does not affect the production of NO but it does provide variations in Na^+in the ECS/synaptic cleft which can, through EAAT channels allow influx of Na^+into the astrocyte which supports the astrocytic Na^+/ K^+ATP-ase pump. [18]**

- **NCX channel (Na^+K^+exchanger)**

- **need to have $K_{IR}4.1$ in the astrocyte (important for setting the membrane potential) rather than the present K+ channel**

- **Nanna Macauly (Univ Copenhagen) shows that in the astrocyte the relative weighting of Na/K ATPase pump is greater than $K_{IR}4.1$ is greater than NKCC1**

- **possibly need VOCC in Astrocyte.**

This essentially models the K+ handling in the astrocyte. With respect to Zheng (2010) data the stimulus is large, very large. Hence there may be some other neuro-stimuli pathways involved such as norepinepherine, both cholinergic and norginergic as part of the arousal response. This could be the reason why the CBF increases in the Zheng data after 6-8 seconds when the stimulus is greater than 15 seconds. OR it could be the NO pathway as originally thought.

1.0.1 Version 1.2 /2.0 difference

The basic difference between version 1.2 and version 2.0 is the new neuron model. This is based on the work of Chang et al [2] and that of Kager et al [19]. For this version the neuron model has 4 compartments; i) soma/axon, ii) dendrite , iii) post synaptic terminal and extracellular space (ECS). Ion channels for Na^+, and K^+efflux into the ECS. $K^+$is buffered in the ECS and a portion of the K^+flux is passed into the synaptic cleft compartment. On reaching a certain concentration of K^+in the synaptic cleft glutamate is pumped into the synaptic cleft . This glutamate is taken up by both the post-synaptic neuron and the astrocyte. The neuron is stimulated by injection of a current of specified value into the soma/axon compartment.

In addition Nitric Oxide is derived from the NMDA receptor where glutamate mediates Ca^{2+}flux into the post-synaptic neuron. This $Ca^{2+}$is combined with calmodulin to produce eNOS and finally NO. Schematic of the full set of pathways is shown in Figure 1.1

1.1 Global Constants

F	Faraday's constant	96500 C mole^{-1}
T	Temperature	300 K
R_{gas}	Gas constant	8.315 J mole K^{-1}

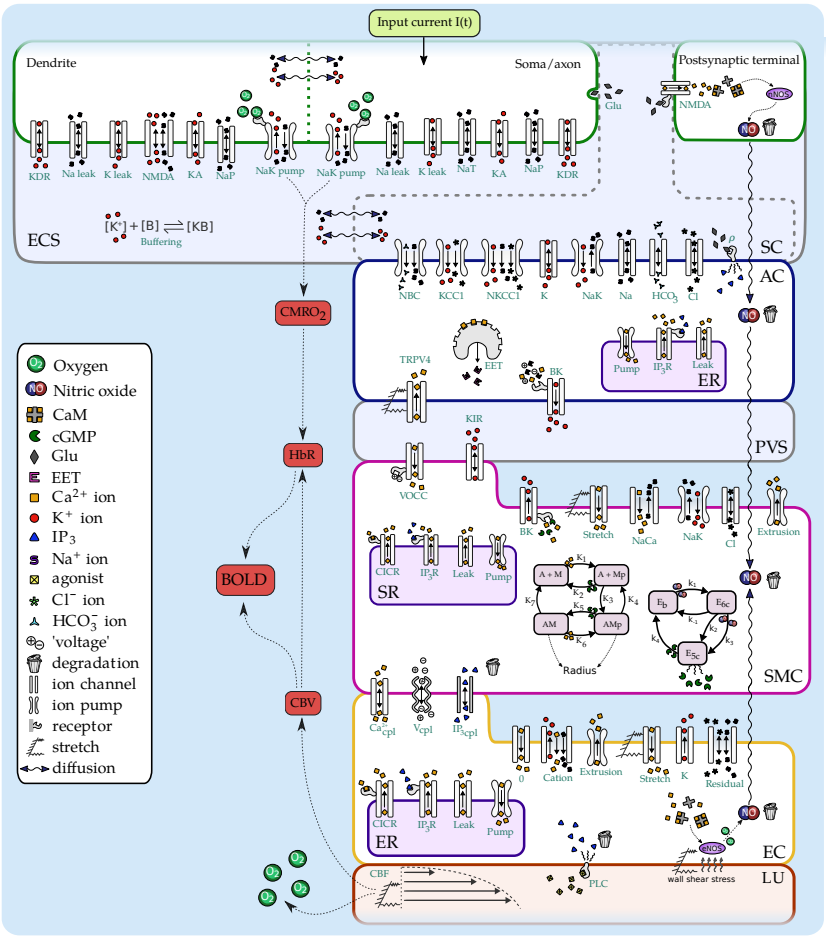

Figure 1.1: Schematic of version 1.2

1.1.1 The Neuron Model

Ion channels,Cross membrane currents and the Na^+/K^+ exchange pump

The soma compartment has two sodium ion channels namely the persistent sodium and sodium leak channels and three potassium channels namely delayed rectifier potassium channel, transient potassium channel and potassium leak channel . In addition to these the dendrite compartment also has an N-methyl-D-aspartate(NMDA) receptor mediated channel which can allow both the sodium and potassium currents to flow through it. The cross-membrane currents of all the ion channels except the leak ion channel were modelled using the Goldman-Hodgkin-Katz(GHK) equation given as

$$I_{Ion,GHK} = m^p h^q \frac{g_{Ion,GHK} F v_m [[Ion]_i - exp(\frac{-v_m}{\phi})[Ion]_e]}{\phi[1 - exp(\frac{-v_m}{\phi})]} \tag{1.1.1}$$

where $I_{Ion,GHK}$ is the current of a particular ion through an ion channel, $g_{Ion,GHK}$ is the maximal conductance value and permeability is absorbed into this parameter, v_m is the membrane potential, $\phi = PT/F$ where P is the universal gas constant , T the absolute temperature and F Faraday's constant, $[Ion]_i$ and $[Ion]_e$ are the concentrations of a particular ion inside and outside the membrane respectively. The conductance is channel specific and concentration of ion is compartment specific. The electrically excitable property of the neuron is simulated using the classical Hodgkin Huxley kinetic description [17]. The variables m and h are the fraction of activation and inactivation gates in the open state respectively. The parameters p and q are the number of individual activation and inactivation gates per channel respectively. The rate at which the activation gates open and close in response to the membrane potential is modelled according to the equation

$$\frac{\mathrm{d}m}{\mathrm{d}t} = \frac{m_\infty(v_m) - m}{\tau_m(v_m)} \tag{1.1.2}$$

where

$$m_\infty(v_m) = \frac{\alpha_m(v_m)}{\alpha_m(v_m) + \beta_m(v_m)} \tag{1.1.3}$$

and

$$\tau_m(v_m) = \frac{1}{\alpha_m(v_m) + \beta_m(v_m)} \tag{1.1.4}$$

The function $m_\infty(v_m)$ is called the steady-state activation curve. The value of m tends asymptotically to the steady state if voltage is held constant for a sufficient length of time. The function τ_m is the characteristic time curve of the activation gate describing the variation of the characteristic time scale with of the membrane potential. The rate functions α and β are usually determined through a mix of theoretical and empirical considerations and they are of the form

$$\alpha(v_m) = a_0 \exp(\frac{-\delta v_m}{s}) \tag{1.1.5}$$

$$\beta(v_m) = b_0 \exp(\frac{(1-\delta) v_m}{s}) \tag{1.1.6}$$

where a_0, b_0, and δ are positive constants, with $0 \leq \delta \leq 1$. A gate that tends to open on depolarization will have $s < 0$, while a gate that tends to open on hyperpolarisation will have $s > 0$ [32]. These exponential forms are modified to fit the experimental data using curve fitting. The expressions used in the neuron model that describe the voltage-dependent rate functions are based on a model of hippocamppal pyramidal cells [31] and morphological parameters are based on reconstructed hippocampal neurons [1]. The sodium, potassium and chlorine leak currents are calculated by a Hodgkin-Huxley(HH) model given by

$$I_{Ion,HH} = g_{Ion,HH}(v_m - E_{Ion}) \tag{1.1.7}$$

where $g_{Ion,HH}$ is the constant conductance for the specific ion and E_{Ion} is the Nernst potential for the specific ion and is given by

$$E_{Ion} = \frac{PT}{zF} log \frac{[Ion]_e}{[Ion]_i} \tag{1.1.8}$$

here z is the valence of the ionic species. The primary role of the Na^+/K^+ ATPase exchange pump in the neuronal membrane is to restore ionic concentrations to their homeostatic state during neural activation. The Na^+/K^+ ATPase pump is a transmembrane protein with two extracellular binding sites for potassium, three intracellular binding sites for sodium, and a single intracellular binding site for ATP. The pump moves out three intracellular sodium ions and two extracellular potassium ions against their electrochemical gradients and hence the need for ATP (energy). Both the soma and dendrite compartments have a Na^+/K^+ exchange pump. Since the energy in the form of ATP is highly dependent on tissue oxygen concentration, the exchange pump current in the neuronal membrane is modelled as a variable dependent on the availability of oxygen. The potassium and sodium pump currents in the soma and dendrite are given by $I_{*,K,pump} = -2I_{*,pump}$ and $I_{*,Na,pump} = 3I_{*,pump}$ respectively($*$ is either s for somatic or d for dendritic). The total current due to the sodium/potassium exchange pump in the soma and dendrite is given by

$$I_{*,pump} = I_{max}\gamma_{*,pump,1}([K^+]_e, [Na^+]_i, *)\gamma_{*,pump,2}([O_2]) \tag{1.1.9}$$

where I_{max} is the maximum pumping rate of the Na^+/K^+ exchange pump with

$$\gamma_{*,pump,1}([K^+]_e, [Na^+]_i, *) = \left(1 + \frac{[K^+]_{e,0}}{[K^+]_e}\right)^{-2} \left(1 + \frac{[Na^+]_{i,0}}{[Na^+]_{i,*}}\right)^{-3} \tag{1.1.10}$$

where $[K^+]_{e,0}$ and $[Na^+]_{i,0}$ are the baseline concentrations of extracellular potassium and intracellular sodium respectively. This expression describes that the action of the pump depends on the concentrations of extracellular potassium and intracellular sodium. The second pump represents the oxygen dependent production of ATP by the mitochondria[5, 16] taking the form

$$\gamma_{*,pump,2}([O_2]) = 2\left(1 + \frac{[O_2]_0}{(1-G)[O_2] + G[O_2]_0}\right)^{-1} \tag{1.1.11}$$

in this case $[O_2]$ is the tissue oxygen concentration encompassing the neurovascular unit, $[O_2]_0$ is the initial equilibrium value of oxygen concentration and G is the percentage of ATP production that is independent of oxygen. This expression indicates that the pumping rate will be reduced whenever there is a decrease in the oxygen level in the tissue.

Membrane potential and Ionic concentration

In reality the membrane potential depends on the membrane potential difference and concentration gradients. Here, the membrane potential of the soma and dendrite is calculated

based on the assumption that the flow of ions between the two compartments is only due to the difference in membrane potential between them. The total cross membrane currents are the sum of the voltage dependent sodium and potassium currents, sodium, potassium and chlorine leak currents, and the sodium-potassium exchange current. The membrane potentials of the neuronal compartments are governed by the differential equations of the form

$$C_m \frac{\mathrm{d}v_{m,s}}{\mathrm{d}t} = -I_{s,tot} + \frac{1}{2R_a\delta_d^2}(v_{m,d} - v_{m,s}) + I_{stim} \tag{1.1.12}$$

$$C_m \frac{\mathrm{d}v_{m,d}}{\mathrm{d}t} = -I_{d,tot} + \frac{1}{2R_a\delta_d^2}(v_{m,s} - v_{m,d}) \tag{1.1.13}$$

here C_m is the membrane capacitance per unit surface area, R_a is the input resistance of the effective dendritic tree, δ_d is the half length of the effective dendritic tree,$v_{m,s}$ and $v_{m,d}$ are the membrane potentials of soma and dendrite respectively. I_{stim} is the stimulating current in Gaussian form whose mean, variance and amplitude can be allowed to vary. $I_{s,tot}$ and $I_{s,tot}$ are the total cross-membrane ionic currents per unit surface area for soma and dendrite written as

$$I_{*,tot} = I_{*,Na,tot} + I_{*,K,tot} + I_{*,Cl,tot} \tag{1.1.14}$$

The rates of change of ionic concentration in the soma and dendrite are due to the membrane currents and the exchange between the soma and dendrite. The exchange between the somatic and dendritic compartments is modelled by a flux proportional to the difference between their ion concentrations. The equation describing the rate of change of ions in the soma is again of the general form

$$\frac{\mathrm{d}[Ion]_{i,s}}{\mathrm{d}t} = -\frac{A_s}{FV_s} I_{s,Ion,tot} + \frac{D_{Ion}(V_d + V_s)}{2\delta_d^2 V_s}([Ion]_{i,d} - [Ion]_{i,s}) \tag{1.1.15}$$

The notation, D_{Ion} , is the ion diffusion coefficient in aqueous solution taking into account tortuosity and volume fraction [27]. The quantities A_s and A_d are the surface areas of the soma and dendrite respectively in the total fixed volume given by the sum of the fixed somatic volume V_s, dendritic volumeV_d, and extracellular volume,V_e. The equation describing the rate of change of ions in the dendrite is

$$\frac{\mathrm{d}[Ion]_{i,d}}{\mathrm{d}t} = -\frac{A_d}{FV_d} I_{d,Ion,tot} + \frac{D_{Ion}(V_s + V_d)}{2\delta_d^2 V_d}([Ion]_{i,s} - [Ion]_{i,d}) \tag{1.1.16}$$

The local rates of change of the extracellular space ions are due to the membrane currents from the soma and dendrite. To ensure electro-neutrality, the initial extracellular concentration of the anion Cl^- is chosen to be equal to the sum of the concentration of cations Na^+ and K^+ in the extracellular space. Also, the initial intracellular concentration of chlorine is chosen in such a way that its Nernst potential matches a resting membrane potential of -70 mV. The existence of immobile anions has been assumed in the soma and

dendrites to achieve intracellular electro-neutrality.The equations describing the rate of change of ions in the extracellular compartment is given by

$$\frac{\mathrm{d}[Ion]_e}{\mathrm{d}t} = \frac{1}{f_e F}\left(\frac{A_s I_{s,Ion,tot}}{V_s} + \frac{A_d I_{d,Ion,tot}}{V_d}\right) \tag{1.1.17}$$

where extracellular space volume fraction is given by $f_e = V_e/(V_s + V_d)$. The extracellular space volume was defined as 15% of the intracellular space volume based on published data [24, 25].

Chapter 2

State variables, initial values and parameter values

In the actual Matlab code the state variables are defined as follows

v_{sa} : membrane potential of soma/axon, mV v_d :membrane potential of dendrite, mV K_{sa} : K+ concentration of soma/axon, mM K_d : K+ concentration of dendrite, mM Na_d : Na+ concentration of dendrite, mM K_e : K+ concentration of ECS, mM Na_e :Na+ concentration of ECS, mM $Buff_e$: Buffer concentration for K+ buffering in ECS, mM

Gating variables m1 : Activation gating variable, soma/axon NaP channel (Na+) m2 : Activation gating variable, soma/axon KDR channel (K+) m3 : Activation gating variable, soma/axon KA channel (K+) m4 : Activation gating variable, dendrite NaP channel (Na+) m5 : Activation gating variable, dendrite NMDA channel (Na+) m6 : Activation gating variable, dendrite KDR channel (K+) m7 : Activation gating variable, dendrite KA channel (K+) m8 : Activation gating variable, soma/axon NaT channel (Na+)

h1 : Inactivation gating variable, soma/axon NaP channel (Na+) h2 : Inactivation gating variable, soma/axon KA channel (K+) h3 : Inactivation gating variable, dendrite NaP channel (Na+) h4 : Inactivation gating variable, dendrite NMDA channel (Na+) h5 : Inactivation gating variable, dendrite KA channel (K+) h6 : Inactivation gating variable, soma/axon NaT channel (Na+)

NO pathway Ca_n :Ca^{2+}in the post-synaptic neuron $nNOS_act_n$:activated NOS in the post-synaptic neuron NO_n : Nitric Oxide in the post-synaptic neuron

Table 2.1: Initial resting values and other parameter values of the neuron model, from Chang et al[2]

Parameters	**Values**	**Units**	**Description**
v_m	-70	mV	membrane petential
$[K^+]_e$	3.5	mM	extracellular space potassium ion concentration
$[K^+]_i$	133.5	mM	intracellular potassium ion concentration of neuron
$[Na^+]_e$	140	mM	extracellular space sodium ion concentration
$[Na^+]_i$	10	mM	intracellular sodium ion concentration of neuron
$[O_2]_0$	2×10^{-2}	mM	baseline concentration of oxygen in the tissue
B_0	0.9	$ml/100mg/s$	baseline cerebral blood flow
$[O_2]_b$	4×10^{-2}	mM	blood oxygen concentration
J_0	2.5×10^{-2}	mM/s	steady state change in oxygen concentration due to cerebral blood flow
R_a	1.83×10^5	Ω	input resistance of dendritic tree
δ_d	4.5×10^{-2}	cm	half-length of dendrite
A_s	1.586×10^{-5}	cm^2	surface area of soma
A_d	2.6732×10^{-4}	cm^2	surface area of dendrite
V_s	2.160×10^{-9}	cm^3	volume of soma
V_d	5.614×10^{-9}	cm^3	volume of dendrite
S_e	4.1179×10^{-6}	cm	volume to surface area ratio of the extracellular space
C_m	7.5×10^{-5}	$s/\Omega cm^2$	membrane capacitance
I_{max}	1.48×10^{-3}	mA/cm^2	Na^+/K^+-ATPase rate
D_{Na^+}	1.33×10^{-5}	cm^2/s	Sodium diffusion coefficient
D_{K^+}	1.96×10^{-5}	cm^2/s	Potassium diffusion coefficient
D_{Cl^-}	2.03×10^{-5}	cm^2/s	Chlorine diffusion coefficient

Table 2.2: Rate expressions and parameter values used in the voltage dependent channel currents of the neuron model, from Chang et al[2]

Currents mA/cm^2	$g_{Ion,GHK}$ $mAcm$	**Gates** $m^p h^q$	**Voltage dependent rate functions**
$I_{Na,P}$	2×10^{-6}	$m^2 h$	$\alpha_m = \frac{1}{6(1+exp[-(0.143E_m+5.67)])}$ $\beta_m = \frac{exp[-(0.143E_m+5.67)]}{6(1+exp[-(0.143E_m+5.67)])}$ $\alpha_h = 5.12 \times 10^{-8} exp[-(0.056E_m + 2.94)]$ $\beta_h = \frac{1.6 \times 10^{-6}}{1+exp[-(0.2E_m+1.25)]}$
$I_{K,DR}$	10×10^{-5}	m^2	$\alpha_m = 0.016 \frac{E_m+34.9}{1-exp[-(0.2E_m+6.98)]}$ $\beta_m = 0.25 exp[-(0.25E_m + 1.25)]$
$I_{K,A}$	1×10^{-5}	$m^2 h$	$\alpha_m = 0.02 \frac{E_m+56.9}{1-exp[-(0.1E_m+5.69)]}$ $\beta_m = 0.0175 \frac{E_m+29.9}{exp(0.1E_m+2.99)-1}$ $\alpha_h = 0.016 exp[-(0.056E_m + 4.61)]$ $\beta_h = \frac{0.5}{1+exp[-(0.2E_m+11.98)]}$
I_{NMDA}	1×10^{-5}	mh	$\alpha_m = \frac{0.5}{1+exp\left(\frac{13.5-[K^+]}{1.42}\right)}$ $\beta_m = 0.5 - \alpha_m$ $\alpha_h = \frac{1}{2000\left(1+exp\left[\frac{[K^+]_e-6.75}{0.71}\right]\right)}$ $\beta_h = 5 \times 10^{-5} - \alpha_h$

Chapter 3

Equations for each compartment

3.1 Neuron

3.1.1 Nernst potential for Na,K ions in soma and dendrite (Cl constant)

$$E_{Na_{sa}} = \frac{RT}{F} ln(\frac{Na_e}{Na_{sa}}) \tag{3.1.1}$$

$$E_{K_{sa}} = \frac{RT}{F} ln(\frac{K_e}{K_{sa}}) \tag{3.1.2}$$

$$E_{Na_d} = \frac{RT}{F} ln(\frac{Na_e}{Na_d}) \tag{3.1.3}$$

$$E_{K_d} = \frac{RT}{F} ln(\frac{K_e}{K_d}) \tag{3.1.4}$$

3.1.2 Leak fluxes of Na,K,Cl in soma and dendrite using HH

$$J_{Naleak_{sa}} = g_{Naleak_{sa}}(v_{sa} - E_{Na_{sa}}) \tag{3.1.5}$$

$$J_{Kleak_{sa}} = g_{Kleak_{sa}}(v_{sa} - E_{K_{sa}}) \tag{3.1.6}$$

$$J_{Naleak_d} = g_{Naleak_d}(v_d - E_{Na_d}) \tag{3.1.7}$$

$$J_{Kleak_d} = g_{Kleak_d}(v_d - E_{K_d}) \tag{3.1.8}$$

$$\tag{3.1.9}$$

3.1.3 Dendrite (with subscript d)

Na flux through NaP channel in dendrite using GHK

$$m4_\alpha = \frac{1}{6(1+exp(-((0.143v_d)+5.67)))} \tag{3.1.10}$$

$$m4_\beta = \frac{exp(-((0.143v_d)+5.67))}{6(1+exp(-((0.143v_d)+5.67)))} \tag{3.1.11}$$

$$h3\alpha = 5.12e-8exp(-((0.056v_d)+2.94)) \tag{3.1.12}$$

$$h3\beta = \frac{1.6e-6}{1+exp(-(((0.2*v_d))+8))} \tag{3.1.13}$$

$$J_{NaP_d} = (m4^2 h3 g_{NaP} F v_d \frac{(Na_d - (exp(\frac{-v_d F}{RT})Na_e)))}{(\frac{RT}{F}(1-exp(\frac{-v_d F}{RT})))} \tag{3.1.14}$$

$$\tag{3.1.15}$$

The parameters whose values are 0.143 and 5.67 have a high influence on the K^+in the ECS.

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Na/K flux through NMDA channel in dendrite using GHK

$$m5_\alpha = \frac{0.5}{1+exp(\frac{13.5-K_e}{1.42})} \tag{3.1.16}$$

$$m5_\beta = 0.5 - m5_\alpha \tag{3.1.17}$$

$$h4_\alpha = \frac{1}{2000*(1+exp(\frac{K_e-6.75}{0.71}))} \tag{3.1.18}$$

$$h4_\beta = 5\times10^{-4} - h4_\alpha \tag{3.1.19}$$

$$J_{NMDA_{K_d}} = M(v,Mg)((m5h4 g_{NMDA} F v_d \frac{(K_d - (exp(\frac{v_d F}{RT})K_e)))}{(\frac{RT}{F}(1-exp(\frac{-v_d F}{RT})))} \tag{3.1.20}$$

$$M(v,Mg) = \frac{1}{(1+0.33Mg \quad exp(-(0.07v_d+0.7)))} \tag{3.1.21}$$

K flux through KDR channel in dendrite using GHK

$$m6_\alpha = \frac{0.016((v_d+34.9)}{(1-exp(-((0.2*v_d)+6.98))))} \tag{3.1.22}$$

$$m6_\beta = 0.25exp(-((0.025*v_d)+1.25)) \tag{3.1.23}$$

$$J_{KDR_d} = m6^2 g_{KDR} F v_d \frac{(K_d - (exp(\frac{-v_d F}{RT})K_e))}{(\frac{RT}{F}(1-\frac{-v_d F}{RT}))} \tag{3.1.24}$$

K flux through KA channel in dendrite using GHK

$$m7_\alpha = \frac{0.02((v_d + 56.9)}{(1 - exp(-((0.1v_d) + 5.69))))} \tag{3.1.25}$$

$$m7_\beta = \frac{0.0175((v_d + 29.9)}{(exp(((0.1 * v_d) + 2.99)) - 1))} \tag{3.1.26}$$

$$h5_\alpha = 0.016exp(-((0.056v_d) + 4.61)) \tag{3.1.27}$$

$$h5_\beta = \frac{0.5}{(1 + exp(-((0.2 * v_d) + 11.98)))} \tag{3.1.28}$$

$$J_{KA_d} = m7^2 h5 g_{KA} F v_d \frac{(K_d - (exp(\frac{-v_d F}{RT})K_e))}{(\frac{RT}{F}(1 - \frac{-v_d F}{RT}))} \tag{3.1.29}$$

3.1.4 Soma/Axon (with subscript sa)

Na flux through NaP channel in soma using GHK

$$m1_\alpha = \frac{1}{6(1 + exp(-(0.143v_{sa} + 5.67)))} \tag{3.1.30}$$

$$m1_\beta = \frac{exp(-0.143v_{sa} + 5.67)}{6(1 + exp(-(0.143v_{sa} + 5.67)))} \tag{3.1.31}$$

$$h1_\alpha = 5.12 \times 10^{-8} exp(-(0.056v_{sa} + 2.94)) \tag{3.1.32}$$

$$h1_\beta = \frac{1.6 \times 10^{-6}}{1 + exp(-(0.2v_{sa} + 8))} \tag{3.1.33}$$

$$J_{NaP_{sa}} = m1^2 h1 g_{NaP} F v_{sa} \frac{(Na_{sa} - (exp(\frac{-v_{sa} F}{RT})Na_e))}{(\frac{RT}{F}(1 - \frac{-v_{sa} F}{RT}))} \tag{3.1.34}$$

The parameters whose values are 0.143 ND 5.67 have a high influence on the K^+in the ECS.

Na flux through NaT channel in soma using GHK

$$m8_\alpha = \frac{0.32(-v_{sa} - 51.9)}{exp(-0.25v_{sa} - 12.975) - 1} \tag{3.1.35}$$

$$m8_\beta = \frac{0.28(v_{sa} + 24.89)}{(exp(0.2v_{sa} + 4.978) - 1))} \tag{3.1.36}$$

$$h6_\alpha = 0.128exp(-(0.056v_{sa} + 2.94)) \tag{3.1.37}$$

$$h6_\beta = \frac{4}{(1 + exp(-(0.2v_{sa} + 6)))} \tag{3.1.38}$$

$$J_{NaT_{sa}} = m8^3 h6 g_{NaT} F v_{sa} \frac{(Na_{sa} - (exp(\frac{-v_{sa} F}{RT})Na_e))}{(\frac{RT}{F}(1 - \frac{-v_{sa} F}{RT}))} \tag{3.1.39}$$

$$\tag{3.1.40}$$

The parameter whose value is 51.9 has a high influence on the K^+in the ECS.

K flux through KDR channel in soma using GHK

$$m2_{\alpha} = \frac{0.016((v_{sa}+34.9)}{(1-exp(-((0.2v_{sa})+6.98))))} \tag{3.1.41}$$

$$m2_{\beta} = 0.25exp(-((0.025v_{sa})+1.25)) \tag{3.1.42}$$

$$J_{KDR_{sa}} = m2^2 gKDRFv_{sa}\frac{(K_{sa}-(exp(\frac{-v_{sa}F}{RT})K_e))}{(\frac{RT}{F}(1-\frac{-v_{sa}F}{RT}))} \tag{3.1.43}$$

$$\tag{3.1.44}$$

K flux through KA channel in soma using GHK input current

$$m3_{\alpha} = \frac{0.02(v_{sa}+56.9)}{(1-exp(-(0.1v_{sa}+5.69)))} \tag{3.1.45}$$

$$m3_{\beta} = \frac{0.0175(v_{sa}+29.9)}{(exp(0.1v_{sa}+2.99)-1))} \tag{3.1.46}$$

$$h2_{\alpha} = 0.016exp(-(0.056v_{sa}+4.61)) \tag{3.1.47}$$

$$h2_{\beta} = \frac{0.5}{1+exp(-(0.2v_{sa}+11.98))} \tag{3.1.48}$$

$$J_{KA_{sa}} = m3^2 h2g_{KA}Fv_{sa}\frac{(K_{sa}-(exp(\frac{-v_{sa}F}{RT})K_e))}{(\frac{RT}{F}(1-\frac{-v_{sa}F}{RT}))} \tag{3.1.49}$$

$$\tag{3.1.50}$$

flux through the NaK-ATPase pump

$$J_{pump1_{sa}} = (1+(\frac{K_{init_e}}{K_e}))^{-2}(1+(\frac{Na_{init_{sa}}}{Na_{sa}}))^{-3} \tag{3.1.51}$$

$$J_{pump1init_{sa}} = 0.0312 \tag{3.1.52}$$

$$J_{pump1_d} = (1+(\frac{K_{init_e}}{K_e}))^{-2}(1+(\frac{Na_{init_d}}{Na_d}))^{-3} \tag{3.1.53}$$

$$J_{pump1init_d} = 0.0312 \tag{3.1.54}$$

$$\tag{3.1.55}$$

Determine whether there is limited oxygen: O2switch=0 ATP is plentiful, O2switch=1 ATP is limited (oxygen-limited regime)

$$
\begin{aligned}
O2_p &= O2_0(1 - O2_{switch}) + O2O2_{switch} && (3.1.56)\\
J_{pump2} &= 2(1 + \frac{O2_0}{(1-\alpha)O2_p + \alpha O2_0})^{-1} && (3.1.57)\\
J_{pump_{sa}} &= Imax J_{pump_{sa}} J_{pump2} && (3.1.58)\\
J_{pump_d} &= Imax J_{pump_d} J_{pump2} && (3.1.59)\\
J_{Napump_{sa}} &= 3J_{pump_{sa}} && (3.1.60)\\
J_{Kpump_{sa}} &= -2J_{pump_{sa}} && (3.1.61)\\
J_{Napump_d} &= 3J_{pump_d} && (3.1.62)\\
J_{Kpump_d} &= -2J_{pump_d} && (3.1.63)\\
& && (3.1.64)
\end{aligned}
$$

3.1.5 Total ion fluxes

Total ion fluxes in soma

$$
\begin{aligned}
J_{Na_{tot_{sa}}} &= J_{NaP_{sa}} + J_{Naleak_{sa}} + J_{Napump_{sa}} + J_{NaT_{sa}} && (3.1.65)\\
J_{K_{tot_{sa}}} &= J_{KDR_{sa}} + J_{KA_{sa}} + J_{Kleak_{sa}} + J_{Kpump_{sa}} && (3.1.66)\\
J_{leak_{tot_{sa}}} &= g_{leak_{sa}}(v_{sa} - E_{Cl_{sa}}) && (3.1.67)\\
& && (3.1.68)
\end{aligned}
$$

Total ion fluxes in dendrite

$$
\begin{aligned}
J_{Na_{tot_d}} &= J_{NaP_d} + J_{Naleak_d} + J_{Napump_d} + J_{Na_{NMDA_d}} && (3.1.69)\\
J_{K_{tot_d}} &= J_{KDR_d} + J_{KA_d} + J_{Kleak_d} + J_{Kpump_d} + J_{K_{NMDA_d}} && (3.1.70)\\
J_{leak_{tot_d}} &= g_{leak_d}(v_d - E_{Cl_d}) && (3.1.71)\\
& && (3.1.72)
\end{aligned}
$$

Total ion fluxes in soma and dendrite

$$
\begin{aligned}
J_{tot_{sa}} &= J_{Na_{tot_{sa}}} + J_{K_{tot_{sa}}} + J_{leak_{tot_{sa}}} && (3.1.73)\\
J_{tot_d} &= J_{Na_{tot_d}} + J_{K_{tot_d}} + J_{leak_{tot_d}} && (3.1.74)\\
& && (3.1.75)
\end{aligned}
$$

Tissue oxygen

$$
\begin{aligned}
J_{pump2_0} &= 0.0952 && (3.1.76)\\
J_{pump2_{O2_0}} &= 1 && (3.1.77)\\
CBF &= CBF_{init}\frac{R^4}{R^4_{init}} && (3.1.78)\\
& && (3.1.79)
\end{aligned}
$$

Note The pump functions could look like this
$J_{pump2_0} = 2(1 + \frac{O2_0}{(((1-\alpha_{O2})O2_0)+\alpha_{O2}O2_0))})^{-1}$

$$J_{pump2_{O2_0}} = 2 * (1 + O2_0./(((1 - p.alpha_O2) * p.O2_0) + p.alpha_O2 * p.O2_0)).^{-1}$$

NO pathway, post-synaptic neuron

Glutamate input: vesicle released when the extracellular $K^+$is over 5.5 mM (Ke_{switch})

$$w_{NR2A} = \frac{Glu}{(K_{mA} + Glu)} \tag{3.1.80}$$

$$w_{NR2B} = \frac{Glu}{(K_{mB} + Glu)} \tag{3.1.81}$$

$$I_{Ca} = -4v_n G_M \frac{P_{Ca}}{P_M} \frac{(\frac{Ca_{ex}}{M}))}{(1 + exp(-80(v_n + 0.02)))} \frac{(exp(2v_n \frac{F}{RT})))}{(1 - exp(2v_n \frac{F}{RT})))} \tag{3.1.82}$$

$$I_{Ca_{tot}} = I_{Ca}(n_{NR2A} w_{NR2A} + n_{NR2B} w_{NR2B}) \tag{3.1.83}$$

$$CaM = \frac{Ca_n}{m_c} \tag{3.1.84}$$

$$\tau_{nk} = \frac{x_{nk}^2}{2D_{cNO}} \tag{3.1.85}$$

$$p_{NO_n} = NO_{switch} nNOS_{act_n} V_{max_{NO_n}} \frac{O2_n}{K_{mO2_n} + O2_n} \frac{LArg_n}{K_{mArg_n} + LArg_n} \tag{3.1.86}$$

$$c_{NO_n} = k_{O2_n} NO_n^2 O2_n \tag{3.1.87}$$

$$d_{NO_n} = \frac{NO_k - NO_n}{\tau_{nk}} \tag{3.1.88}$$

$$\tag{3.1.89}$$

NO_{switch} **turns the NO Pathway on or off**

3.2 Conservation equations for neuron compartment

change in membrane potential

$$\frac{dv_{sa}}{dt} = \frac{1}{C_m}(-J_{tot_{sa}} + \frac{1}{2Ra \quad dhod^2}(v_d - v_{sa}) + inputcurrent(t)) \tag{3.2.1}$$

$$\frac{dv_d}{dt} = \frac{1}{C_m}(-J_{tot_d} + \frac{1}{2Ra \quad dhod^2}(v_{sa} - v_d)) \tag{3.2.2}$$

$$\tag{3.2.3}$$

change in concentration of Na,K in the soma

$$\frac{dNa_{sa}}{dt} = \frac{-A_s}{FV_s} J_{Na_{tot_{sa}}} + \frac{D_{Na}(V_d + V_s)}{2dhod^2 V_s}(Na_d - Na_{sa}) \tag{3.2.4}$$

$$\frac{dK_{sa}}{dt} = \frac{-A_s}{FV_s} J_{K_{tot_{sa}}} + \frac{D_K(V_d + V_s)}{2dhod^2 V_s}(K_d - K_{sa}) \tag{3.2.5}$$

$$\tag{3.2.6}$$

change in concentration of Na,K in the dendrite

$$\frac{dNa_d}{dt} = \frac{-A_d}{FV_d} J_{Na_{tot_d}} + \frac{D_{Na}(V_d + V_s)}{2dhod^2 V_s}(Na_{sa} - Na_d) \tag{3.2.7}$$

$$\frac{dK_d}{dt} = \frac{-A_d}{FV_d} J_{K_{tot_d}} + \frac{D_K(V_d + V_s)}{2dhod^2 V_s}(K_{sa} - K_d) \tag{3.2.8}$$

$$\tag{3.2.9}$$

change in tissue oxygen

$$\frac{dO_2}{dt} = J_{O2_{vascular}} - J_{O2_{background}} - J_{O2_{pump}} \tag{3.2.10}$$

$$\tag{3.2.11}$$

Change in activation gating variables m

$$\frac{dm_i}{dt} = 1000(m_{i_\alpha}(1 - m_i) - m_\beta m_i) \quad i = 1..8 \tag{3.2.12}$$

$$\tag{3.2.13}$$

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$$\frac{dh_i}{dt} = 1000(h_{i_\alpha}(1 - h_i) - h_\beta h_i) \quad i = 1..6 \tag{3.2.14}$$

$$\tag{3.2.15}$$

NO pathway

$$\frac{dCa_n}{dt} = \frac{(\frac{I_{Ca_{tot}}}{2FV_{spine}} - (k_{ex}(Ca_n - Ca_{rest})))}{1 + \lambda_{buf}} \tag{3.2.16}$$

$$\frac{dnNOS_{act_n}}{dt} = \frac{V_{maxNOS} CaM}{K_{actNOS} + CaM} - mu2_n nNOS_{act_n} \tag{3.2.17}$$

$$\tag{3.2.18}$$

3.3 Extra Cellular Space (ECS with subscript e)

change in buffer for K+ in the extracellular space

$$\frac{dBuff_e}{dt} = \frac{\mu K_e(B_0 - Buff_e)}{1 + exp(-((K_e - 5.5)./1.09))} - \mu Buff_e \tag{3.3.1}$$

$$\tag{3.3.2}$$

change in concentration of Na,K in the extracellular space

$$\frac{dNa_e}{dt} = \frac{1}{Ff_e}(\frac{A_s J_{Na_{tot_{sa}}}}{V_s} + \frac{A_d J_{Na_{tot_d}}}{V_d}) \tag{3.3.3}$$

$$\frac{dK_e}{dt} = \frac{1}{Ff_e}(\frac{A_s J_{K_{tot_{sa}}}}{V_s} + \frac{A_d J_{K_{tot_d}}}{V_d}) \tag{3.3.4}$$

$$J_{K_{NEtoSC}} = SC_{coup}\frac{dK_e}{dt} \tag{3.3.5}$$

$$\tag{3.3.6}$$

The variable $J_{K_{NEtoSC}}$ is used in the astrocyte module to evaluate the rate of change of K^+in the synaptic cleft. At present the model does not compute $J_{Na_{NEtoSC}}$ give by

$$J_{K_{NEtoSC}} = SC_{coup}\frac{dNa_e}{dt} \tag{3.3.7}$$

$$\tag{3.3.8}$$

But assumes that the Na^+flux is equal to the K^+flux.

we need to fix this bug to include $J_{Na_{NEtoSC}}$

3.4 Postsynaptic Neuron (with subscript n)

these equations below seem somewhat different from the actual version 2 code (see above). **Check with Allanah**

Differential equations

Rate of change of cytosolic Ca^{2+}concentration ($\mu M\,s^{-1}$) due to NMDA receptors mediated by Glutamate :

$$\frac{\mathrm{d}[\mathrm{Ca}^{2+}]_n}{\mathrm{d}t} = \frac{I_{\mathrm{Ca,tot}}/(2FV_{\mathrm{spine}}) - \kappa_{\mathrm{ex}}([\mathrm{Ca}^{2+}]_n - [\mathrm{Ca}^{2+}]_{\mathrm{rest}})}{1+\lambda_{\mathrm{buf}}} \tag{3.4.1}$$

Rate of change of activated nNOS ($\mu M\,s^{-1}$):

$$\frac{\mathrm{d}[\mathrm{nNOS_{act}}]_n}{\mathrm{d}t} = \frac{V_{\mathrm{max,nNOS}}[\mathrm{CaM}]_n}{K_{\mathrm{m,nNOS}}+[\mathrm{CaM}]_n} - \mu_{\mathrm{deact},n}[\mathrm{nNOS_{act}}]_n \tag{3.4.2}$$

Rate of change of neuronal NO ($\mu M\,s^{-1}$):

$$\frac{\mathrm{d}[\mathrm{NO}]_n}{\mathrm{d}t} = p_{\mathrm{NO},n} - c_{\mathrm{NO},n} + d_{\mathrm{NO},n} \tag{3.4.3}$$

NO production flux ($\mu M\,s^{-1}$):

$$p_{\mathrm{NO},n} = V_{\mathrm{max,NO},n}[\mathrm{nNOS_{act}}]_n \frac{[\mathrm{O_2}]_n}{K_{\mathrm{m,O2},n}+[\mathrm{O_2}]_n}\frac{[\mathrm{L\text{-}Arg}]_n}{K_{\mathrm{m,L\text{-}Arg},n}+[\mathrm{L\text{-}Arg}]_n} \tag{3.4.4}$$

NO consumption flux ($\mu M\,s^{-1}$):

$$c_{\mathrm{NO},n} = k_{\mathrm{O2},n}[\mathrm{NO}]_n^2[\mathrm{O_2}]_n \tag{3.4.5}$$

NO diffusive flux ($\mu M\,s^{-1}$):

$$d_{\mathrm{NO},n} = \frac{[\mathrm{NO}]_k - [\mathrm{NO}]_n}{\tau_{nk}} \tag{3.4.6}$$

Time for NO to diffuse between the centres of the NE and the AC (s):

$$\tau_{nk} = \frac{x_{nk}^2}{2D_{\mathrm{c,NO}}} \tag{3.4.7}$$

[1] model estimation

V_{spine}	dentritic spine volume	8×10^{-8} nL	[29]
κ_{ex}	decay rate constant of internal Ca^{2+} concentration	1.6×10^{3} s^{-1}	[29]
$[Ca^{2+}]_{\text{rest}}$	resting internal calcium concentration	0.1 µM	[29]
λ_{buf}	buffer capacity	20 (dim.less)	[29]
$V_{\text{max,nNOS}}$	maximum nNOS activation rate	25×10^{-3} µM	M.E.[1]
$K_{\text{m,nNOS}}$	Michaelis constant	9.27×10^{-2}	[15]
$\mu_{\text{deact},n}$	rate constant at which nNOS is deactivated	0.0167 s^{-1}	[6]
$K_{\text{m},A}$	Michaelis constant	650 µM	[29]
$K_{\text{m},B}$	Michaelis constant	2800 µM	[29]
v_n	neuronal membrane potential	-0.04 V	M.E. but see Kager et al model maybe -0.05 -or -0.06 V
G_{M}	conductance of NMDA receptor	4.6×10^{4} fS	[29]
$P_{\text{Ca}}/P_{\text{M}}$	ratio of NMDA receptor permeability to Ca^{2+} to permeability to monovalent ions	3.6 (dim.less)	[29]
$[Ca^{2+}]_{\text{ex}}$	external calcium concentration	2×10^{3} µM	[29]
[M]	concentration of monovalent ions	1.3×10^{5} µM	[29]
α_v	voltage-dependent Mg^{2+} block parameter	-80 V^{-1}	[29]
β_v	voltage-dependent Mg^{2+} block parameter	0.02 V	[29]
$n_{\text{NR2},A}$	average number of NR2A NMDA receptors	0.63 (dim.less)	[29]
$n_{\text{NR2},B}$	average number of NR2A NMDA receptors	11 (dim.less)	[29]
Q_1	Ca^{2+}-CaM binding constant	1.9×10^{5} μM^{-1}	[7]
Q_2	Ca^{2+}-CaM binding constant	2.1×10^{5} μM^{-1}	[7]
Q_3	Ca^{2+}-CaM binding constant	0.4×10^{5} μM^{-1}	[7]
Q_4	Ca^{2+}-CaM binding constant	0.26×10^{5} μM^{-1}	[7]
$V_{\text{max,NO},n}$	maximum catalytic rate of neuronal NO production	4.22 s^{-1}	[3]
$[O_2]_n$	O_2 concentration in the neuron	200 µM	M.E.
$K_{\text{m,O2},n}$	Michaelis constant for nNOS for O_2	243 µM	[4]
$[\text{L-Arg}]_n$	L-Arg concentration in the neuron	100 µM	[4]
$K_{\text{m,L-Arg},n}$	Michaelis constant for nNOS for L-Arg	1.5 µM	[3]
$k_{\text{O2},n}$	O_2 reaction rate constant	9.6×10^{-6} μM^{-2} s^{-1}	[20]
x_{nk}	distance between centres of NE and AC	25 µm	M.E.
$D_{\text{c,NO}}$	NO diffusion coefficient	3300 $\mu m^2 s^{-1}$	[23]

Algebraic equations

Fraction of open NR2A NMDA receptors (dim.less):

$$w_{\mathrm{NR2},A} = \frac{[\mathrm{Glu}]_{sc}}{K_{\mathrm{m},A} + [\mathrm{Glu}]_{sc}} \tag{3.4.8}$$

Fraction of open NR2B NMDA receptors (dim.less):

$$w_{\mathrm{NR2},B} = \frac{[\mathrm{Glu}]_{sc}}{K_{\mathrm{m},B} + [\mathrm{Glu}]_{sc}} \tag{3.4.9}$$

Inward calcium current per open NMDA receptor (fA):

$$I_{\mathrm{Ca}} = \frac{4v_n G_{\mathrm{M}}(P_{\mathrm{Ca}}/P_{\mathrm{M}})([\mathrm{Ca}^{2+}]_{\mathrm{ex}}/[\mathrm{M}])}{1+\exp(\alpha_v(v_n+\beta_v))} \frac{\exp(2v_nF/(R_{\mathrm{gas}}T))}{1-\exp(2v_nF/(R_{\mathrm{gas}}T))} \tag{3.4.10}$$

Total inward calcium current for all open NMDA receptors per synapse (fA):

$$I_{\mathrm{Ca,tot}} = (n_{\mathrm{NR2},A}w_{\mathrm{NR2},A} + n_{\mathrm{NR2},B}w_{\mathrm{NR2},B})I_{\mathrm{Ca}} \tag{3.4.11}$$

Sum of all the states of bound calcium with respect to free calcium (dim.less):

$$\phi_{\mathrm{mc}} = 1 + Q_1[\mathrm{Ca}^{2+}]_n + Q_1Q_2[\mathrm{Ca}^{2+}]_n^2 + Q_1Q_2Q_3[\mathrm{Ca}^{2+}]_n^3 + Q_1Q_2Q_3Q_4[\mathrm{Ca}^{2+}]_n^4 \tag{3.4.12}$$

Number of calcium ions bound per calmodulin (dim.less):

$$m_c = \frac{[\mathrm{Ca}^{2+}]_n}{\phi_{\mathrm{mc}}} \frac{\mathrm{d}\phi_{\mathrm{mc}}}{\mathrm{d}[\mathrm{Ca}^{2+}]_n} \tag{3.4.13}$$

This equation could be simplified considerably as noted by

$$m_c = \frac{[\mathrm{Ca}^{2+}]_n}{\phi_{\mathrm{mc}}} \frac{\mathrm{d}\phi_{\mathrm{mc}}}{\mathrm{d}[\mathrm{Ca}^{2+}]_n} \tag{3.4.14}$$

$$= \frac{\sum_{i=1}^{4}(i(\Pi_{j=1}^{i}Q_i))[\mathrm{Ca}^{2+}]^i}{1+\sum_{i=1}^{4}((\Pi_{j=1}^{i}Q_i)[\mathrm{Ca}^{2+}]^i)} \simeq 4 \tag{3.4.15}$$

This is due to the size of the constants Q_i's being of the order 10^5.

Calcium-calmodulin complex concentration (µM):

$$[\mathrm{CaM}]_n = \frac{[\mathrm{Ca}^{2+}]_n}{m_c} \simeq \frac{[\mathrm{Ca}^{2+}]_n}{4} \tag{3.4.16}$$

3.5 BOLD Signal

$$f_{out} = CBV^{\frac{1}{d}} + \frac{\tau_{TAT}}{\tau_{MTT}+\tau_{TAT}}\left(\frac{CBF}{CBF_{init}} - CBV^{\frac{1}{d}}\right) \tag{3.5.1}$$

$$CMRO2 = J_{O2_{background}} + J_{O2_{pump}} \tag{3.5.2}$$

$$CMRO2_{init} = CBF_{init}P_{02} \tag{3.5.3}$$

$$OEF = CMRO2\frac{E_0}{CBF} \tag{3.5.4}$$

$$BOLD = V_0(a_1(1-HBR) - a_2(1-CBV)) \tag{3.5.5}$$

$$\tag{3.5.6}$$

3.6 Synaptic Cleft (with subscript s)

check for the diffusion of K^+into the ECS

Glutamate flux from presynapse neuron

The neuron model (pre-synapse) provides input into the synaptic cleft for three species, that of Na^+, $K^+$and Glu. The post-synapse model uses Gluas an input to provide Ca^{2+}which allows neuronal NOto be formed from $eNOS_{act}$.

Glu concentration in the synaptic cleft (µM):

$$[Glu]_{sc}(t) = [Glu]_{\max}\left(0.5\tanh\left(t-t_0\right) - 0.5\tanh\left(t-t_2\right)\right) \tag{3.6.1}$$

or more succinctly

$$\rho = \rho_{min} + \frac{\rho_{max}-\rho_{min}}{2}\left(\tanh\left(t-t_0\right) - \tanh\left(t-t_2\right)\right)$$

$[\mathrm{Glu}]_{\max}$ is the maximum glutamate concentration = 1846 µM[29] The ratio of bound to unbound receptors (mGluR) of glutamate is dependent on the synaptic glutamate release and is given by

$$\rho = \rho_{min} + \frac{\rho_{max}-\rho_{min}}{\mathrm{Glu}_{max}}[\mathrm{Glu}]_{sc}(t)$$

The ratio of total G-protein due to mGluR binding to the asytocyte is given by

$$G = \frac{\rho+\delta}{K_G+\rho+\delta} \tag{3.6.2}$$

The G is needed in the flux of IP_3 into the astrocyte as part of the Ca^{2+}pathway.

δ	ratio of activities of unbound and bound receptors	1.235×10^{-2}
K_G	G protein disassociation constant	8.82

Flux of $Na^+$and K^+into the synaptic cleft We assume that the flux from the neuron into the synaptic space is equal to a fraction of the flux from neuron into the extracellular space. The fraction is equal to the volume ratio of the synaptic space to the extracellular space.

what about diffusion into the ECS for both $Na^+$and K^+?

K^+ concentration in the SC

$$\frac{\mathrm{d}N_{K_s}}{\mathrm{d}t} = k_C f(t) - \frac{\mathrm{d}N_{K_k}}{\mathrm{d}t} + J_{BK_k} + \frac{R_s}{\tau_s}\left\{[\mathrm{K}^+]_e - [\mathrm{K}^+]_s\right\} \tag{3.6.3}$$

τ_s is defined in equation **??** and has a value of 2.8 secs. $[K^+]_e$ is the potassium concentration in the ECS and $[K^+]_s$is the potassium concentration in the synaptic cleft. Na^+ concentration in the SC

$$\frac{dN_{Na_s}}{dt} = -k_C f(t) - \frac{dN_{Na_k}}{dt} \tag{3.6.4}$$

HCO_3 concentration in the SC

$$\frac{dN_{HCO_{3_s}}}{dt} = -\frac{dN_{HCO_{3_k}}}{dt} \tag{3.6.5}$$

k_C	Input scaling parameter	7.35×10^{-5} µM m s^{-1}	[28]

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Cl concentration in the synaptic cleft is derived by assuming electro-neutrality:

$$[Cl^{-1}]_s = [Na^+]_s + [K^+]_s - [HCO_3^{-1}]_s \tag{3.6.6}$$

3.7 Astrocyte (with subscript k)

Rate of change of astrocytic NO concentration ($\mu M\,s^{-1}$):

$$\frac{d[NO]_k}{dt} = p_{NO,k} - c_{NO,k} + d_{NO,k} \tag{3.7.1}$$

Algebraic equations

NO production flux ($\mu M\,s^{-1}$):

$$p_{NO,k} = 0 \tag{3.7.2}$$

NO consumption flux ($\mu M\,s^{-1}$):

$$c_{NO,k} = k_{O2,k}[NO]_k^2[O_2]_k \tag{3.7.3}$$

NO diffusive flux ($\mu M\,s^{-1}$):

$$d_{NO,k} = \frac{[NO]_n - [NO]_k}{\tau_{nk}} + \frac{[NO]_i - [NO]_k}{\tau_{ki}} \tag{3.7.4}$$

Time for NO to diffuse between the centres of the AC and the SMC (s):

$$\tau_{ki} = \frac{x_{ki}^2}{2D_{c,NO}} \tag{3.7.5}$$

K^+ concentration in the AC :

$$\frac{dN_{K_k}}{dt} = -J_{K_k} + 2J_{NaK_k} + J_{NKCC1_k} + J_{KCC1_k} - J_{BK_k} \tag{3.7.6}$$

$k_{O2,k}$	O_2 reaction rate constant	$9.6\times10^{-6}\mu M^{-2}s^{-1}$	[20]	
x_{ki}	distance between centres of AC and SMC compartments	25 µm	model assumption	
$[O_2]_k$	oxygen concentration in the astrocyte	200 µM	M.E.	

K^+ flux through the Ca^{2+}mediated BK channel :

$$J_{BK_k} = \frac{g_{BK_k}}{F} w_k \left(v_k - E_{BK_k}\right) \tag{3.7.7}$$

Open probability of the BK channel (s^{-1}):

$$\frac{\mathrm{d}w_k}{\mathrm{d}t} = \phi_w \left(w_\infty - w_k\right) \tag{3.7.8}$$

$$\phi_w = \psi_n cosh(\frac{v_k - v_3}{2v_4}) \tag{3.7.9}$$

$$v_3 = -\frac{v_5}{2} tanh[\frac{[Ca^{2+}]_k - Ca_3}{Ca_4}] + v_6 \tag{3.7.10}$$

ψ_n	characteristic time scale for BK channel	$2.664s^{-1}$
v_4	measure of the spread of w_∞	8 millivolts
v_5	shift in w_∞ as a function of Ca^{2+}	15 millivolts
v_6	BK open probability constant	-55 millivolts
Ca_3	BK open probability constant	0.4 µM
Ca_4	BK open probability constant	0.35 µM
EET_{shift}	EET dependent voltage shift	2 mV M^{-1}

Equilibrium state BK-channel as a function of the concentration of EET in the astrocytic cytosol:

$$w_\infty = 0.5\left(1 + \tanh\left(\frac{v_k EET_{shift}[EET]_k - v_3}{v_4}\right)\right) \tag{3.7.11}$$

Na^+ concentration in the AC :

$$\frac{\mathrm{d}N_{Na_k}}{\mathrm{d}t} = -J_{Na_k} - 3J_{NaK_k} + J_{NKCC1_k} + J_{NBC_k} \tag{3.7.12}$$

HCO_3 concentration in the AC :

$$\frac{\mathrm{d}N_{HCO_{3_k}}}{\mathrm{d}t} = 2J_{NBC_k} \tag{3.7.13}$$

Cl concentration in the AC :

$$\frac{\mathrm{d}N_{Cl_k}}{\mathrm{d}t} = \frac{\mathrm{d}N_{Na_k}}{\mathrm{d}t} + \frac{\mathrm{d}N_{K_k}}{\mathrm{d}t} - \frac{\mathrm{d}N_{HCO_{3_k}}}{\mathrm{d}t} \tag{3.7.14}$$

IP_3 concentration in the AC :

$$\frac{\mathrm{d}N_{i_k}}{\mathrm{d}t} = r_h G - k_{deg}[IP_3]_k \tag{3.7.15}$$

G is determined by equation 3.6.2.

r_h	Max rate of IP_3 production in AC due to glu receptors	4.8 µM
k_{deg}	Rate constant for IP_3 degradation in AC	1.25 s^{-1}

The astrocytic cytosolic Ca2+ comes from both the ER through various channels and from the PVS via the TRPV4 channel:

Cytosolic Ca^{2+} concentration in the AC :

$$\frac{\mathrm{d}N_{Ca_k}}{\mathrm{d}t} = B_{cyt}(J_{IP3_k} - J_{pump_k} + J_{ERleak_k} + \frac{J_{TRPV_k}}{r_{buff}}) \tag{3.7.16}$$

r_{buff} has the value 0.05 as a way of estimating the buffering at the astrocytic process close to the arteriole.

If r_{buff} is in fact buffering then shouldn't it be greater than unity rather than 0.05?

Ca^{2+} concentration in the ER of the AC :

$$\frac{\mathrm{d}N_{Ca_{ER}}}{\mathrm{d}t} = -B_{cyt}\frac{J_{IP3_k} - J_{pump_k} + J_{ERleak_k}}{VR_{ER_{cyt}}} \tag{3.7.17}$$

$$B_{cyt} = (1 + BK_{end} + \frac{K_{ex}B_{ex}}{K_{ex} + [\mathrm{Ca}^{2+}]_k})^{-1} \tag{3.7.18}$$

B_{ex}	concentration of exogenous buffer	11.35 µM	
K_{ex}	disassociation constant for exogenous buffer	0.26 µM	
BK_{end}	Ratio of endogenous buffer conc to disassociation constant	40	
r_{buff}	exogenous buffering constant at the end astrocytic process	0.05	estimated value
K_{inh}	dissociation constant for IP3R	0.1 µM	
k_{on}	Rate of Ca^{2+}binding to the inhibitory site of the IP3R	2 $\mu M\, s^{-1}$	
K_{act}	dissociation constant for binding to the activation site of IP3R	0.17 µM	
K_i	dissociation constant for IP3 binding to the IP3R	0.03 µM	
K_{ex}	dissociation constant for exogenous buffer	0.26 µM	
k_{pump}	Ca^{2+}uptake pump dissociation constant	0.24 µM	

$$J_{IP3_k} = J_{max}[(\frac{i_k}{i_k + K_i})(\frac{[\mathrm{Ca}^{2+}]_k}{[\mathrm{Ca}^{2+}]_k + K_{act}})h_k]^3(1 - \frac{[\mathrm{Ca}^{2+}]_k}{Ca_{ER}}) \tag{3.7.19}$$

h_k is the activation/inactivation variable for the IP3R binding

$$\frac{\mathrm{d}h_k}{\mathrm{d}t} = k_{on}(K_{inh} - ([\mathrm{Ca}^{2+}]_k + K_{inh})h_k) \tag{3.7.20}$$

$$J_{ERleak} = P_L(1 - \frac{c_k}{Ca_{ER}}) \tag{3.7.21}$$

$$J_{pump_k} = V_{max}\frac{{[\mathrm{Ca}^{2+}]_k}^2}{{[\mathrm{Ca}^{2+}]_k}^2 + k_{pump}^2} \tag{3.7.22}$$

EET concentration in the AC :

$$\frac{\mathrm{d}N_{EET_k}}{\mathrm{d}t} = V_{eet}max([\mathrm{Ca}^{2+}]_k - {\mathrm{Ca}^{2+}}_{min}, 0) - k_{eet}[\mathrm{EET}]_k \tag{3.7.23}$$

${\mathrm{Ca}^{2+}}_{min}$	minimum Ca^{2+}required for EETproduction	0.1 µM
V_{eet}	EETmax production rate	72 µM s^{-1}
k_{eet}	Ca^{2+}uptake pump dissociation constant	0.24 µM

Membrane voltage of the AC (mV):

Should really have a time-dependent o.d.e. here for the membrane potential

$$v_k = \frac{g_{Na_k}E_{Na_k} + g_{K_k}E_{K_k} + g_{TRPV}E_{TRPV_k} + g_{Cl_k}E_{Cl_k} + g_{NBC_k}E_{NBC_k} + g_{BK_k}w_kE_{BK_k} - J_{NaK_k}F \times 10^3}{g_{Na_k} + g_{K_k} + g_{Cl_k} + g_{NBC_k} + g_{BK_k}w_k + g_{TRPV}m_k} \tag{3.7.24}$$

Nernst potential for the potassium channel (in mV):

$$E_{K_k} = \frac{R_gT}{z_KF}ln\left(\frac{[\mathrm{K}^+]_s}{[\mathrm{K}^+]_k}\right) \tag{3.7.25}$$

Nernst potential for the sodium channel (in mV):

$$E_{Na_k} = \frac{R_gT}{z_{Na}F}ln\left(\frac{[\mathrm{Na}^+]_s}{[\mathrm{Na}^+]_k}\right) \tag{3.7.26}$$

Nernst potential for the chloride channel (in mV):

$$E_{Cl_k} = \frac{R_gT}{z_{Cl}F}ln\left(\frac{[\mathrm{Cl}^{-1}]_s}{[\mathrm{Cl}^{-1}]_k}\right) \tag{3.7.27}$$

Nernst potential for the NBC channel (in mV):

$$E_{NBC_k} = \frac{R_gT}{z_{NBC}F}ln\left(\frac{[\mathrm{Na}^+]_s{[\mathrm{HCO}_3^{-1}]_s}^2}{[\mathrm{Na}^+]_k{[\mathrm{HCO}_3^{-1}]_k}^2}\right) \tag{3.7.28}$$

Nernst potential for the BK channel (in mV):

$$E_{BK_k} = \frac{R_g T}{z_K F} ln\left(\frac{[K^+]_p}{[\mathrm{K}^+]_k}\right) \tag{3.7.29}$$

g_{Cl_k}	Specific ion conductance of chloride	0.879 $\Omega^{-1}\mathrm{m}^{-2}$	[28]
z_K	Valence of a potassium ion	1	
z_{Na}	Valence of a sodium ion	1	
z_{Cl}	Valence of a chloride ion	-1	
z_{NBC}	Effective valence of the NBC cotransporter complex	-1	

TRPV4 channel

Ca^{2+}concentration in the AC (times the AC volume-area ratio R_k; in µM m):

Need Ca^{2+}conservation equation check with Allanah about the format of the TRPV4 flux into the astrocyte and from the PVS.

the Ca^{2+} flux through the TRPV4 channel is given by

$$J_{TRPV_k} = -g_{TRPV} m_k (v_k - E_{TRPV_k}) \tag{3.7.30}$$

$$\frac{\mathrm{d}m_k}{\mathrm{d}t} = \phi_m \left(m_\infty - m_k\right) \tag{3.7.31}$$

$$\phi_m = \frac{1}{t_{TRPV}} \tag{3.7.32}$$

$$E_{TRPV_k} = \frac{RT}{z_{Ca} F} log(\frac{[\mathrm{Ca}^{2+}]_p}{[\mathrm{Ca}^{2+}]_k}) \tag{3.7.33}$$

$$\tag{3.7.34}$$

The equilibrium state of the TRPV4 channel is:

$$m_{\infty_k} = \frac{1}{1 + exp(-\frac{\theta - \theta_0}{\kappa_k})} \frac{1}{1 + H_{Ca_k}} (H_{Ca_k} + tanh(\frac{v_k - v_{1,TRPV}}{v_{2,TRPV}})) \tag{3.7.35}$$

$$H_{[\mathrm{Ca}^{2+}]_k} = \frac{[\mathrm{Ca}^{2+}]_k}{\gamma_{Cai}} + \frac{[\mathrm{Ca}^{2+}]_p}{\gamma_{Cae}} \tag{3.7.36}$$

$$\theta = \frac{R - R_{passive}}{R_{passive}} \tag{3.7.37}$$

$$\tag{3.7.38}$$

3.7.1 Fluxes into and out of the astrocyte

K^+ flux

$$J_{K_k} = \frac{g_{K_k}}{F}(v_k - E_{K_k}) \tag{3.7.39}$$

θ_0	strain required for half activation of TRPV4 channel	0.1	[33]
κ_k	TRPV4 strain scaling constant	0.1	[33]
$\nu_{1,TRPV}$	TRPV4 channel voltage gating constant	0.12 mV	
$\nu_{2,TRPV}$	TRPV4 channel voltage gating constant	0.013 mV	
γ_{Cai}	Ca^{2+}constant	0.01 µM	
γ_{Cae}	Ca^{2+}constant	200 µM	
$R_{passive}$	vessel radius when no stress applied	20 μm	estimate
t_{TRPV}	characteristic time constant for the TRPV4 channel	0.9 s	estimate

Na^+ flux

$$J_{Na_k} = \frac{g_{Na_k}}{F}(v_k - E_{Na_k}) \tag{3.7.40}$$

Na^+ and HCO_3 flux through the NBC channel

$$J_{NBC_k} = \frac{g_{NBC_k}}{F}\left(v_k - E_{NBC_k}\right) \tag{3.7.41}$$

Cl and K^+ flux through the KCC1 channel

$$J_{KCC1_k} = C_{input}\frac{g_{KCC1_k}}{F}\frac{R_gT}{F}ln\left(\frac{K_sCl_s}{K_kCl_k}\right) \tag{3.7.42}$$

Na^+, K^+ and Cl flux through the NKCC1 channel

$$J_{NKCC1_k} = C_{input}\frac{g_{NKCC1_k}}{F}\frac{R_gT}{F}ln\left(\frac{Na_sK_sCl_s{}^2}{Na_kK_kCl_k{}^2}\right) \tag{3.7.43}$$

Flux through the sodium potassium pump

$$J_{NaK_k} = J_{NaK_{max}}\frac{Na_k{}^{1.5}}{Na_k{}^{1.5} + K_{Na_k}{}^{1.5}}\frac{K_s}{K_s + K_{K_s}} \tag{3.7.44}$$

what are the definitions and values of K_{Na_k}, K_{K_s}

3.8 Perivascular Space (with subscript p)

K^+ concentration in the PVS (in µM):

$$\frac{\mathrm{d}K_p}{\mathrm{d}t} = \frac{J_{BK_k}}{R_kR_{pa}} + \frac{J_{KIR_i}}{R_{ps}} + \frac{J_{TRPV_k}}{R_kR_{pa}} \tag{3.8.1}$$

The ODE for the PVS Ca^{2+} concentration is

$$\frac{\mathrm{d}Ca_p}{\mathrm{d}t} = -\frac{J_{TRPV_k}}{VR_{pa}} + \frac{J_{VOCC_i}}{VR_{ps}} - Ca_{decay_k}(Ca_p - Ca_{min_k}) \tag{3.8.2}$$

$$\tag{3.8.3}$$

F	Faraday's constant	9.649×10^4 C mol^{-1}	
R_g	Gas constant	8.315 J mol^{-1}K^{-1}	
T	Temperature	300 K	
g_{K_k}	Specific ion conductance of potassium	40×10^3 Ω^{-1}m^{-2}	[28]
g_{Na_k}	Specific ion conductance of sodium	1.314×10^3 Ω^{-1}m^{-2}	[28]
K_{Na_k}		40×10^3 Ω^{-1}m^{-2}	[28]
g_{Na_k}	Specific ion conductance of sodium	1.314×10^3 Ω^{-1}m^{-2}	[28]
g_{NBC_k}	Specific ion conductance of the NBC cotransporter	7.57×10^2 Ω^{-1}m^{-2}	[28]
g_{KCC1_k}	Specific ion conductance of the KCC1 cotransporter	10 Ω^{-1}m^{-2}	[28]
g_{NKCC1_k}	Specific ion conductance of the NKCC1 cotransporter	55.4 Ω^{-1}m^{-2}	[28]
$J_{NaK_{max}}$	Maximum flux through the NaKATPase pump	1.42×10^{-3} µM ms^{-1}	[28]
g_{BK_k}	Specific ion conductance of the BK channel	1.16×10^3 Ω^{-1}m^{-2}	[11]
C_{input}	Block function to switch the channel on and off	0 ; 1 [-]	

R_{pa}	Volume ratio of PVS to AC	10^{-3} [-]	[26]
R_{ps}	Volume ratio of PVS to SMC	10^{-3} [-]	[26]
Ca_{decay_k}	Rate of decay of Ca^{2+}in the PVS	0.5 s^{-1}	
Ca_{min_k}	steady state value of Ca^{2+}in PVS	2 mM	

3.9 Smooth Muscle Cell

Cytosolic [Ca^{2+}] in the SMC (in µM):

$$\frac{\mathrm{d}[Ca^{2+}]_i}{\mathrm{d}t} = J_{IP_{3i}} - J_{SR_{uptake_i}} + J_{CICR_i} - J_{extrusion_i} + J_{SR_{leak_i}} \dots \\ -J_{VOCC_i} + J_{Na/Ca_i} - 0.1J_{stretch_i} + J^{SMC-EC}_{Ca^{2+}-coupling_i} \tag{3.9.1}$$

[Ca^{2+}] in the SR of the SMC (in µM):

$$\frac{\mathrm{d}[\widehat{Ca}^{2+}]_i}{\mathrm{d}t} = J_{SR_{uptake_i}} - J_{CICR_i} - J_{SR_{leak_i}} \tag{3.9.2}$$

Membrane potential of the SMC (in mV):

$$\frac{\mathrm{d}v_i}{\mathrm{d}t} = \gamma_i(-J_{Na/K_i} - J_{Cl_i} - 2J_{VOCC_i} - J_{Na/Ca_i} - J_{K_i} \dots \\ -J_{stretch_i} - J_{KIR_i}) + V^{SMC-EC}_{coupling_i} \tag{3.9.3}$$

IP_3 concentration of the SMC (in µM):

$$\frac{\mathrm{d}[IP_3]_i}{\mathrm{d}t} = J^{SMC-EC}_{IP_3-coupling_i} - J_{degrad_i} \tag{3.9.4}$$

Open state probability of calcium and cGMP -activated potassium channels :

$$\frac{\mathrm{d}w_i}{\mathrm{d}t} = \lambda_i\,(K_{act_i} - w_i) \tag{3.9.5}$$

Equilibrium distribution of open channel states for the BK channel (dim.less), see Dormanns et al. [9]:

$$K_{act_i} = \frac{([\mathrm{Ca}^{2+}]_i + c_{\mathrm{w},i})^2}{([\mathrm{Ca}^{2+}]_i + c_{\mathrm{w},i})^2 + \beta_i \exp(v_{\mathrm{Ca3},i} - v_i/R_{\mathrm{K},i})} \tag{3.9.6}$$

Translation factor, regulatory effect of cGMP on the BK channel open probability (µM):

$$c_{\mathrm{w},i} = \frac{1}{2}\left[1 + tanh(\frac{[cGMP] - cGMP_1}{cGMP_2})\right] \tag{3.9.7}$$

Release of calcium from IP_3 sensitive stores in the SMC (in µM s^{-1}):

$$J_{IP_{3i}} = F_i \frac{[IP_3]_i^2}{K_{ri}^2 + [IP_3]_i^2} \tag{3.9.8}$$

F_i	Maximal rate of activation-dependent calcium influx	0.23 µM s^{-1}	[22]
K_{ri}	Half-saturation constant for agonist-dependent calcium entry	1 µM	[22]
$cGMP_1$	shift parameter for cGMP regulatory effect	10.75 µM	ME
$cGMP_2$	scaling parameter for cGMP regulatory effect	0.668 µM	ME
$R_{K,i}$	scaling parameter for membrane voltage regulatory effect on K_{act_i}	??? mV	ME

Uptake of calcium into the sarcoplasmic reticulum (in µM s^{-1}):

$$J_{SR_{uptake_i}} = B_i \frac{[Ca^{2+}]_i^2}{c_{bi}^2 + [Ca^{2+}]_i^2} \tag{3.9.9}$$

B_i	SR uptake rate constant	2.025 µM s^{-1}	[22]
c_{bi}	Half-point of the SR ATPase activation sigmoidal	1.0 µM	[22]

Calcium-induced calcium release (CICR; in µM s^{-1}):

$$J_{CICR_i} = C_i \frac{[\widehat{Ca}^{2+}]_i^2}{s_{ci}^2 + [\widehat{Ca}^{2+}]_i^2} \frac{[Ca^{2+}]_i^4}{c_{ci}^4 + [Ca^{2+}]_i^4} \tag{3.9.10}$$

C_i	CICR rate constant	55 µM s^{-1}	[22]
s_{ci}	Half-point of the CICR Ca^{2+} efflux sigmoidal	2.0 µM	[22]
c_{ci}	Half-point of the CICR activation sigmoidal	0.9 µM	[22]

D_i	Rate constant for Ca^{2+} extrusion by the ATPase pump	0.24 s^{-1}	[22]
v_d	Intercept of voltage dependence of extrusion ATPase	-100.0 mV	[22]
R_{di}	Slope of voltage dependence of extrusion ATPase.	250.0 mV	[22]

Calcium extrusion by Ca^{2+}-ATPase pumps (in µM s^{-1}):

$$J_{extrusion_i} = D_i[Ca^{2+}]_i \left(1 + \frac{v_i - v_d}{R_{di}}\right) \tag{3.9.11}$$

Leak current from the SR (in µM s^{-1}):

$$J_{SR_{leak_i}} = L_i[\widehat{Ca}^{2+}]_i \tag{3.9.12}$$

L_i	Leak from SR rate constant	0.025 s^{-1}	[22]

Calcium influx through VOCCs (in µM s^{-1}):

$$J_{VOCC_i} = G_{Cai} \frac{v_i - v_{Ca_{1i}}}{1 + exp(-\left[\left(v_i - v_{Ca_{2i}}\right)/R_{Cai}\right])} \tag{3.9.13}$$

G_{Cai}	Whole-cell conductance for VOCCs	1.29×10^{-3} µM $mV^{-1}s^{-1}$	[22]
$v_{Ca_{1i}}$	Reversal potential for VOCCs	100.0 mV	[22]
$v_{Ca_{2i}}$	Half-point of the VOCC activation sigmoidal	-24.0 mV	[22]
R_{Cai}	Maximum slope of the VOCC activation sigmoidal	8.5 mV	[22]

Flux of calcium exchanging with sodium in the Na^+Ca^{2+} exchange (in µM s^{-1}):

$$J_{Na/Ca_i} = G_{Na/Ca_i} \frac{[Ca^{2+}]_i}{[Ca^{2+}]_i + c_{Na/Cai}} \left(v_i - v_{Na/Ca_i}\right) \tag{3.9.14}$$

$G_{Na/Cai}$	Whole-cell conductance for Na^+/Ca^{2+} exchange	3.16×10^{-3} µM $mV^{-1}s^{-1}$	[22]
$c_{Na/Cai}$	Half-point for activation of Na^+/Ca^{2+} exchange by Ca^{2+}	0.5 µM	[22]
$v_{Na/Cai}$	Reversal potential for the Na^+/Ca^{2+} exchanger	-30.0 mV	[22]

Calcium flux through the stretch-activated channels in the SMC (in µM s^{-1}):

$$J_{stretch_i} = \frac{G_{stretch}}{1 + exp\left(-\alpha_{stretch}\left(\frac{\Delta pR}{h} - \sigma_0\right)\right)} \left(v_i - E_{SAC}\right) \tag{3.9.15}$$

$G_{stretch}$	Whole cell conductance for SACs	6.1×10^{-3} µM $mV^{-1}s^{-1}$	[22]
$\alpha_{stretch}$	Slope of stress dependence of the SAC activation sigmoidal	7.4×10^{-3} $mmHg^{-1}$	[22]
Δp	Pressure difference	30 mmHg	ME
σ_0	Half-point of the SAC activation sigmoidal	500 mmHg	[22]
E_{SAC}	Reversal potential for SACs	-18 mV	[22]

Flux through the sodium potassium pump (in µM s^{-1}):

$$J_{NaK_i} = F_{NaK} \tag{3.9.16}$$

F_{NaK}	Rate of the potassium influx by the sodium potassium pump	4.32×10^{-2} µM s^{-1}	[22]

Chloride flux through the chloride channel (in µM s^{-1}):

$$J_{Cl_i} = G_{Cli}\left(v_i - v_{Cli}\right) \tag{3.9.17}$$

G_{Cli}	Whole-cell conductance for Cl^- current	1.34×10^{-3} µM $mV^{-1}s^{-1}$	[22]
v_{Cli}	Reversal potential for Cl^- channels.	-25.0 mV	[22]

Potassium flux through potassium channel (in µM s^{-1}):

$$J_{K_i} = G_{Ki} w_i \left(v_i - E_{K_i}\right) \tag{3.9.18}$$

G_{Ki}	Whole-cell conductance for K^+ efflux.	4.46×10^{-3} µM $mV^{-1}s^{-1}$	[22]
vK_i	Nernst potential	-94 mV	[22]

Flux through KIR channels in the SMC (in µM s^{-1}):

$$J_{KIR_i} = \frac{F_{KIR_i} g_{KIR_i}}{\gamma_i}(v_i - v_{KIR_i}) \tag{3.9.19}$$

why do we have $\frac{F_{KIR_i}}{\gamma_i}$ when they have both the same dimensions but one value F_{KIR_i} is 750 and the other γ_i is 1970 ?

Nernst potential of the KIR channel in the SMC (in mV):

$$v_{KIR_i} = z_1 K_p - z_2 \tag{3.9.20}$$

Conductance of KIR channel (in µM mV^{-1} s^{-1}):

$$g_{KIR_i} = exp(z_5 v_i + z_3 K_p - z_4) \tag{3.9.21}$$

c_{wi}	Translation factor for Ca^{2+} dependence of K_{Ca} channel activation sigmoidal.	0.0 µM	[22]
β_i	Translation factor for membrane potential dependence of K_{Ca} channel activation sigmoidal.	0.13 $µM^2$	[22]
$v_{Ca_{3i}}$	Half-point for the K_{Ca} channel activation sigmoidal.	-27 mV	[22]
R_{Ki}	Maximum slope of the K_{Ca} activation sigmoidal.	12 mV	[22]
z_1	Model estimation for membrane voltage KIR channel	4.5×10^3 mV $µM^{-1}$	[10]
z_2	Model estimation for membrane voltage KIR channel	112 mV	[10]
z_3	Model estimation for the KIR channel conductance	4.2×10^2 $mV^{-1}s^{-1}$	[10]
z_4	Model estimation for the KIR channel conductance	12.6 µM $mV^{-1}s^{-1}$	[10]
z_5	Model estimation for the KIR channel conductance	-7.4×10^{-2} µM $mV^{-2}s^{-1}$	[10]

F_{KIR_i}	Scaling factor of potassium efflux through the KIR channel	750 mV $µM^{-1}$

IP_3 degradation (in µM s^{-1}):

$$J_{degrad_i} = k_{di} I_i \tag{3.9.22}$$

k_{di}	Rate constant of IP_3 degradation	0.1 s^{-1}	[22]

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Coupling

Heterocellular electrical coupling between SMCs en ECs (in mV s^{-1}):

$$V_{coupling_i}^{SMC-EC} = -G_{coup}(v_i - v_j) \tag{3.9.23}$$

Heterocellular IP_3 coupling between SMCs and ECs (in µM s^{-1}):

$$J_{IP_3-coupling_i}^{SMC-EC} = -P_{IP_3}([IP_3]_i - [IP_3]_j) \tag{3.9.24}$$

Calcium coupling with EC (in µM s^{-1}):

$$J_{Ca^{2+}-coupling_i}^{SMC-EC} = -P_{Ca^{2+}}([Ca^{2+}]_i - [Ca^{2+}]_j) \tag{3.9.25}$$

K^+ concentration in the SMC (in µM):

G_{coup}	Heterocellular electrical coupling coefficient	0.5 s^{-1}	ME
P_{IP_3}	Heterocellular IP_3 coupling coefficient	0.05 s^{-1}	[22]
$P_{Ca^{2+}}$	Heterocellular $P_{Ca^{2+}}$ coupling coefficient	0.05 s^{-1}	[22]

We should note here that the membrane potential coupling $V_{coupling_i}^{SMC-EC}$ is an approximation that assumes the gradient of concentrations is negligible and hence only the membrane potential diffusion term is non-zero determined from the electro-diffusion theory.

$$\frac{\mathrm{d}[K_i^+]}{\mathrm{d}t} = J_{Na/K_i} - J_{KIR_i} - J_{K_i} \tag{3.9.26}$$

γ_i	Change in membrane potential by a scaling factor	1970 mV μM^{-1}	[22]
λ_i	Rate constant for opening	45.0 s^{-1}	[22]

Rate of change of NO concentration in the SMC (µM s^{-1}):

$$\frac{\mathrm{d}[\mathrm{NO}]_i}{\mathrm{d}t} = p_{\mathrm{NO},i} - c_{\mathrm{NO},i} + d_{\mathrm{NO},i} \tag{3.9.27}$$

Rate of change of fraction of sGC in the basal state (s^{-1}):

$$\frac{\mathrm{d}E_b}{\mathrm{d}t} = -k_1 E_b[\mathrm{NO}]_i + k_{-1}E_{6c} + k_4 E_{5c} \tag{3.9.28}$$

Rate of change of fraction of sGC in the intermediate form (s^{-1}):

$$\frac{\mathrm{d}E_{6c}}{\mathrm{d}t} = k_1 E_b[\mathrm{NO}]_i - (k_{-1} + k_2)E_{6c} - k_3 E_{6c}[\mathrm{NO}]_i \tag{3.9.29}$$

Rate of change of cGMP concentration (µM s^{-1}):

$$\frac{\mathrm{d}[\mathrm{cGMP}]_i}{\mathrm{d}t} = V_{\mathrm{max,sGC}}E_{5c} - \frac{V_{\mathrm{max,pde}}[\mathrm{cGMP}]_i}{K_{\mathrm{m,pde}} + [\mathrm{cGMP}]_i} \tag{3.9.30}$$

Maximum cGMP production rate (µM s^{-1}):

$$V_{\mathrm{max,pde}} = k_{\mathrm{pde}}[\mathrm{cGMP}]_i \tag{3.9.31}$$

Algebraic equations

NO production flux ($\mu M\,s^{-1}$):

$$p_{\mathrm{NO},i} = 0 \tag{3.9.32}$$

NO consumption flux ($\mu M\,s^{-1}$):

$$c_{\mathrm{NO},i} = k_{\mathrm{dno}}[\mathrm{NO}]_i \tag{3.9.33}$$

NO diffusive flux ($\mu M\,s^{-1}$):

$$d_{\mathrm{NO},i} = \frac{[\mathrm{NO}]_k - [\mathrm{NO}]_i}{\tau_{ki}} + \frac{[\mathrm{NO}]_j - [\mathrm{NO}]_i}{\tau_{ij}} \tag{3.9.34}$$

$$\tau_{i,j} = \frac{x_{K,i}^2}{2D_{NO}} \tag{3.9.35}$$

$$x_{K,i} = 25\mu m \tag{3.9.36}$$

$$\tag{3.9.37}$$

sGC kinetics rate constant (s^{-1}):

$$k_4 = C_4[\mathrm{cGMP}]_i^{m_4} \tag{3.9.38}$$

Fraction of sGC in the fully activated form (dim.less):

$$E_{5c} = 1 - E_b - E_{6c} \tag{3.9.39}$$

Regulatory effect of cGMP on myosin dephosphorylation (dim.less):

$$R_{\mathrm{cGMP}} = \frac{[\mathrm{cGMP}]_i^2}{K_{\mathrm{m,mlcp}}^2 + [\mathrm{cGMP}]_i^2} \tag{3.9.40}$$

Rate constants for dephosphorylation (s^{-1}) in the Hia and Murphy 4-state latch model, see Dormanns et al. [8]:

$$K_{2c} = K_{5c} = \delta_i \left(k_{\mathrm{mlpc,b}} + k_{\mathrm{mlpc,c}} R_{\mathrm{cGMP}}\right) \tag{3.9.41}$$

Equilibrium distribution of open channel states for the BK channel flux into the ECS (dim.less), see Dormanns et al. [9]:

$$K_{\mathrm{act},i} = \frac{([\mathrm{Ca}^{2+}]_i + c_{\mathrm{w},i})^2}{([\mathrm{Ca}^{2+}]_i + c_{\mathrm{w},i})^2 + \beta_i \exp(v_{\mathrm{Ca3},i} - v_i/R_{\mathrm{K},i})} \tag{3.9.42}$$

Translation factor, regulatory effect of cGMP on the BK channel open probability (μM)):

$$c_{\mathrm{w},i} = \frac{c_{w,max}}{2}[1 + tanh(\frac{[\mathrm{cGMP}_i] - \epsilon_i}{\alpha_i})] \tag{3.9.43}$$

Time for NO to diffuse between the centres of the SMC and the EC (s):

$$\tau_{ij} = \frac{x_{ij}^2}{2D_{\mathrm{c,NO}}} \tag{3.9.44}$$

k_{-1}	sGC kinetics rate constant	100 s^{-1}	[34]
k_1	sGC kinetics rate constant	$2{\times}10^3$ μM^{-1} s^{-1}	[34]
k_2	sGC kinetics rate constant	0.1 s^{-1}	[34]
k_3	sGC kinetics rate constant	3 μM^{-1} s^{-1}	[34]
$V_{\mathrm{max,sGC}}$	maximal cGMP production rate	0.8520 $\mu M\, s^{-1}$	[34]
$K_{\mathrm{m,pde}}$	Michaelis constant	2 µM	[34]
k_{dno}	lumped NO consumption rate constant reflecting the activity of various NO scavengers	0.01 s^{-1}	[34]
C_4	constant	0.011 s^{-1} μM^{-2}	[34]
m_4	cGMP feedback strength	2 (dim.less)	[34]
$K_{\mathrm{m,mlcp}}$	Hill coefficient	5.5 µM	[34]
δ_i	constant to fit data	58.1395 (dim.less)	[13], fit
$k_{\mathrm{mlpc,b}}$	basal MLC dephosphorylation rate constant	0.0086 s^{-1}	[34]
$k_{\mathrm{mlpc,c}}$	first-order rate constant for cGMP-regulated MLC dephosphorylation	0.0327 s^{-1}	[34]
α_i	constant to fit data	0.665 µM	[30]
β_i	translation factor for membrane potential dependence of K_{Ca} channel activation sigmoidal	0.13 μM^2	[22]
$c_{w,max}$	constant to fit data	1 $\mu M\, s^{-1}$	[30]
ϵ_i	constant to fit data	10.75 µM	[30]
$[Ca^{2+}]_i$	calcium concentration in the SMC cytosol	var.	see Dormanns et al. [9]
$v_{\mathrm{Ca3},i}$	half-point for the K_{Ca} channel activation sigmoidal.	-27 mV	[22]
v_i	SMC membrane potential	var.	see [9]
$R_{\mathrm{K},i}$	Maximum slope of the K_{Ca} activation sigmoidal	12 mV	[22]
k_{pde}	phosphodiesterase rate constant	0.0195 s^{-1}	[34]

3.9.1 The Contraction Model

Fraction of free phosphorylated cross-bridges (dimensionless):

$$\frac{\mathrm{d}[Mp]}{\mathrm{d}t} = K_4[AMp] + K_1[M] - (K_2 + K_3)[Mp] \tag{3.9.45}$$

Fraction of attached phosphorylated cross-bridges (dimensionless):

$$\frac{\mathrm{d}[AMp]}{\mathrm{d}t} = K_3[Mp] + K_6[AM] - (K_4 + K_5)[AMp] \tag{3.9.46}$$

Fraction of attached dephosphorylated cross-bridges (dimensionless):

$$\frac{\mathrm{d}[AM]}{\mathrm{d}t} = K_5[AMp] - (K_7 + K_6)[AM] \tag{3.9.47}$$

Fraction of free non-phosphorylated cross-bridges (dimensionless):

$$[M] = 1 - [AM] - [AMp] - [Mp] \tag{3.9.48}$$

Rate constants that represent phosphorylation of M to Mp and of AM to AMp by the active myosin light chain kinase (MLCK), respectively (in s^{-1}):

$$K_1 = K_6 = \gamma_{cross}[Ca^{2+}]_i^{n_{cross}} \tag{3.9.49}$$

K_2	Rate constant for dephosphorylation (of Mp to M) by myosin light-chain phosphatase (MLCP)	0.5 s^{-1}	[14]
K_3	Rate constants representing the attachment/detachment of fast cycling phosphorylated crossbridges	0.4 s^{-1}	[14]
K_4	Rate constants representing the attachment/detachment of fast cycling phosphorylated crossbridges	0.1 s^{-1}	[14]
K_5	Rate constant for dephosphorylation (of AMp to AM) by myosin light-chain phosphatase (MLCP)	0.5 s^{-1}	[14]
K_7	Rate constant for latch-bridge detachment	0.1 s^{-1}	[14]
γ_{cross}	Sensitivity of the contractile apparatus to calcium	17 μM^{-3} s^{-1}	[21]
n_{cross}	Fraction constant of the phosphorylation crossbridge	3 [−]	[21]

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3.9.2 The Mechanical Model

Wall thickness of the vessel (in µm):

$$h = -R + \sqrt{R^2 + 2R_{0_{pas}}h_{0_{pas}} + h_{0_{pas}}^2} \tag{3.9.50}$$

Fraction of attached myosin cross-bridges (dimensionless):

$$F_r = [AM_p] + [AM] \tag{3.9.51}$$

Vessel radius (in µm):

$$\frac{\mathrm{d}R}{\mathrm{d}t} = \frac{R_{0_{pas}}}{\eta}\left(\frac{RP_T}{h} - E(F_r)\frac{R - R_0(F_r)}{R_0(F_r)}\right) \tag{3.9.52}$$

with:

$$E(F_r) = E_{pas} + F_r\left(E_{act} - E_{pas}\right) \tag{3.9.53}$$

$$R_0(F_r) = R_{0_{pas}} + F_r(\alpha - 1)R_{0_{pas}} \tag{3.9.54}$$

η	viscosity	10^4 Pa s	[22]
$R_{0_{pas}}$	Radius of the vessel when passive and no stress is applied	20 µm	ME
P_T	Transmural pressure	4×10^3 Pa	ME
E_{pas}	Young's moduli for the passive vessel	66×10^3 Pa	[12]
E_{act}	Additional component of the Young's moduli when vessel is active	167×10^3 Pa	[12]
α	Scaling factor initial radius	0.6	[12]

3.10 Endothelial Cell

Endothelial cell

Cytosolic Ca^{2+} concentration in the EC (in µM):

$$\begin{aligned}\frac{\mathrm{d}[Ca^{2+}]_j}{\mathrm{d}t} &= J_{IP_{3j}} - J_{ER_{uptake_j}} + J_{CICR_j} - J_{extrusion_j} \cdots \\ &+ J_{ER_{leak_j}} + J_{cation_j} + J_{0_j} - J_{stretch_j} - J^{SMC-EC}_{Ca^{2+}-coupling_j}\end{aligned} \tag{3.10.1}$$

Ca^{2+} concentration in the ER in the EC (in µM):

$$\frac{\mathrm{d}[\widehat{Ca}^{2+}]_j}{\mathrm{d}t} = J_{SR_{uptake_j}} - J_{CICR_j} - J_{SR_{leak_j}} \tag{3.10.2}$$

Membrane potential of the EC (in mV):

$$\frac{\mathrm{d}v_j}{\mathrm{d}t} = -\frac{1}{C_{m_j}}(J_{K_j} + J_{R_j}) + V^{SMC-EC}_{coupling_j} \tag{3.10.3}$$

IP_3 concentration of the EC (in µM):

$$\frac{\mathrm{d}[IP_3]_j}{\mathrm{d}t} = J_{EC,IP_3} - J_{degrad_j} - J^{SMC-EC}_{IP_3-coupling_j} \tag{3.10.4}$$

Coupling

Heterocellular electrical coupling between SMCs en ECs (in mV s^{-1}):

$$V^{SMC-EC}_{coupling_i} = -G_{coup}(v_i - v_j) \tag{3.10.5}$$

Heterocellular IP_3 coupling between SMCs and ECs (in µM s^{-1}):

$$J^{SMC-EC}_{IP_3-coupling_i} = -P_{IP_3}([IP_3]_i - [IP_3]_j) \tag{3.10.6}$$

Calcium coupling with EC (in µM s^{-1}):

$$J^{SMC-EC}_{Ca^{2+}-coupling_i} = -P_{Ca^{2+}}([Ca^{2+}]_i - [Ca^{2+}]_j) \tag{3.10.7}$$

G_{coup}	Heterocellular electrical coupling coefficient	0.5 s^{-1}	ME
P_{IP_3}	Heterocellular IP_3 coupling coefficient	0.05 s^{-1}	[22]
$P_{Ca^{2+}}$	Heterocellular $P_{Ca^{2+}}$ coupling coefficient	0.05 s^{-1}	[22]

C_{m_j}	Membrane capacitance	25.8 pF	[22]
J_{EC,IP_3}	IP_3 production rate	µM s^{-1}	[22]

$$\frac{\mathrm{d}[\mathrm{eNOS_{act}}]_j}{\mathrm{d}t} = \gamma_{\mathrm{eNOS}} \frac{K_{\mathrm{dis}}[\mathrm{Ca^{2+}}]_j}{K_{\mathrm{m,eNOS}} + [\mathrm{Ca^{2+}}]_j} + (1 - \gamma_{\mathrm{eNOS}}) g_{\max} F_{\mathrm{wss}} - \mu_{\mathrm{deact},j}[\mathrm{eNOS_{act}}]_j \tag{3.10.8}$$

$$\frac{\mathrm{d}[\mathrm{NO}]_j}{\mathrm{d}t} = p_{\mathrm{NO},j} - c_{\mathrm{NO},j} + d_{\mathrm{NO},j} \tag{3.10.9}$$

NO production flux (µM s^{-1}):

$$p_{\mathrm{NO},j} = V_{\max,\mathrm{NO},j}[\mathrm{eNOS_{act}}]_j \frac{[\mathrm{O_2}]_j}{K_{\mathrm{m,O2},j} + [\mathrm{O_2}]_j} \frac{[\text{L-Arg}]_j}{K_{\mathrm{m,L\text{-}Arg},j} + [\text{L-Arg}]_j} \tag{3.10.10}$$

NO consumption flux (µM s^{-1}):

$$c_{\mathrm{NO},j} = k_{\mathrm{O2},j}[\mathrm{NO}]_j^2[\mathrm{O_2}]_j \tag{3.10.11}$$

NO diffusive flux (µM s^{-1}):

$$d_{\mathrm{NO},j} = \frac{[\mathrm{NO}]_i - [\mathrm{NO}]_j}{\tau_{ij}} - \frac{4D_{\mathrm{c,NO}}[\mathrm{NO}]_j}{r^2} \tag{3.10.12}$$

$$\tau_{ij} = \frac{x^2}{2D_{NO}} \tag{3.10.13}$$

$$x = 3.75\mu m \tag{3.10.14}$$

Endothelial cell

Release of calcium from IP_3-sensitive stores in the EC (in µM s^{-1}):

$$J_{IP_{3j}} = F_j \frac{[IP_3]_j^2}{K_{rj}^2 + [IP_3]_j^2} \tag{3.10.15}$$

Uptake of calcium into the endoplasmic reticulum (in µM s^{-1}):

$$J_{ER_{uptake_j}} = B_j \frac{[Ca^{2+}]_j^2}{c_{bj}^2 + [Ca^{2+}]_j^2} \tag{3.10.16}$$

F_j	Maximal rate of activation-dependent calcium influx	0.23 µM s^{-1}	[22]
K_{rj}	Half-saturation constant for agonist-dependent calcium entry	1 µM	[22]

B_j	ER uptake rate constant	0.5 µM s^{-1}	[22]
c_{bj}	Half-point of the SR ATPase activation sigmoidal	1.0 µM	[22]

Calcium-induced calcium release (CICR; in µM s^{-1}):

$$J_{CICR_j} = C_j \frac{[\widehat{Ca}^{2+}]_j^2}{s_{cj}^2 + [\widehat{Ca}^{2+}]_j^2} \frac{[Ca^{2+}]_j^4}{c_{cj}^4 + [Ca^{2+}]_j^4} \tag{3.10.17}$$

C_j	CICR rate constant	5 µM s^{-1}	[22]
s_{cj}	Half-point of the CICR Ca^{2+} efflux sigmoidal	2.0 µM	[22]
c_{cj}	Half-point of the CICR activation sigmoidal	0.9 µM	[22]

Calcium extrusion by Ca^{2+}-ATPase pumps (in µM s^{-1}):

$$J_{extrusion_j} = D_j [Ca^{2+}]_j \tag{3.10.18}$$

D_j	Rate constant for Ca^{2+} extrusion by the ATPase pump	0.24 s^{-1}	[21]

Calcium flux through the stretch-activated channels in the EC (in µM s^{-1}):

$$J_{stretch_j} = \frac{G_{stretch}}{1 + e^{-\alpha_{stretch}(\sigma - \sigma_0)}} (v_j - E_{SAC}) = \frac{G_{stretch}}{1 + e^{-\alpha_{stretch}\left(\frac{\Delta pR}{h} - \sigma_0\right)}} (v_j - E_{SAC}) \tag{3.10.19}$$

$G_{stretch}$	The whole cell conductance for SACs	6.1×10^{-3} µM $mV^{-1}s^{-1}$	[22]
$\alpha_{stretch}$	Slope of stress dependence of the SAC activation sigmoidal	7.4×10^{-3} $mmHg^{-1}$	[22]
Δp	Pressure difference	30 mmHg	ME
σ_0	Half-point of the SAC activation sigmoidal	500 mmHg	[22]
E_{SAC}	The reversal potential for SACs	-18 mV	[22]

Leak current from the ER (in µM s^{-1}):

$$J_{ER_{leak_j}} = L_j [\widehat{Ca}^{2+}]_j \tag{3.10.20}$$

L_j	Rate constant for Ca^{2+} leak from the ER	0.025 s^{-1}	[22]

Calcium influx through nonselective cation channels (in µM s^{-1}):

$$J_{cation_j} = G_{cat_j}(E_{Ca_j} - v_j)\frac{1}{2}\left(1 + \tanh\left(\frac{\log_{10}[Ca^{2+}]_j - m_{3_{cat_j}}}{m_{4_{cat_j}}}\right)\right) \tag{3.10.21}$$

G_{catj}	Whole-cell cation channel conductivity	6.6×10^{-4} µM $mV^{-1}s^{-1}$	[22]
E_{Caj}	Ca^{2+} equilibrium potential	50 mV	[22]
$m_{3_{catj}}$	Model constant	-0.18 µM	[22]
$m_{4_{catj}}$	Model constant	0.37 µM	[22]

Potassium efflux through the $J_{BK_{Caj}}$ channel and the $J_{SK_{Caj}}$ channel (in µM s^{-1}):

$$J_{K_j} = G_{totj}(v_j - v_{Kj})\left(J_{BK_{Caj}} + J_{SK_{Caj}}\right) \tag{3.10.22}$$

G_{totj}	Total potassium channel conductivity.	6927 pS	[22]
v_{Kj}	K^+ equilibrium potential	-80.0 mV	[22]

Potassium efflux through the $J_{BK_{Caj}}$ channel (in µM s^{-1}):

$$J_{BK_{Caj}} = 0.2\left(1 + \tanh\left(\frac{(\log_{10}[Ca^{2+}]_j - c)(v_j - b_j) - a_{1j}}{m_{3bj}(v_j + a_{2j}(\log_{10}[Ca^{2+}]_j - c) - b_j)^2 + m_{4bj}}\right)\right) \tag{3.10.23}$$

Potassium efflux through the $J_{SK_{Caj}}$ channel (in µM s^{-1}):

$$J_{SK_{Caj}} = 0.3\left(1 + \tanh\left(\frac{\log_{10}[Ca^{2+}]_j - m_{3sj}}{m_{4sj}}\right)\right) \tag{3.10.24}$$

c	Model constant, further explanation see reference	-0.4 µM	[22]
b_j	Model constant, further explanation see reference	-80.8 mV	[22]
a_{1j}	Model constant, further explanation see reference	53.3 µM mV	[22]
a_{2j}	Model constant, further explanation see reference	53.3 mV μM^{-1}	[22]
m_{3bj}	Model constant, further explanation see reference	1.32×10^{-3} µM mV^{-1}	[22]
m_{4bj}	Model constant, further explanation see reference	0.30 µM mV	[22]
m_{3sj}	Model constant, further explanation see reference	-0.28 µM	[22]
m_{4sj}	Model constant, further explanation see reference	0.389 µM	[22]

Residual current regrouping chloride and sodium current flux (in µM s^{-1}):

$$J_{R_j} = G_{R_j}(v_j - v_{restj}) \tag{3.10.25}$$

G_{R_j}	Residual current conductivity	955 pS	[22]
v_{restj}	Membrane resting potential	-31.1 mV	[22]

IP_3 degradation (in µM s^{-1}):

$$J_{degrad_j} = k_{dj}[IP_3]_j \tag{3.10.26}$$

k_{dj}	Rate constant of IP_3 degradation	0.1 s^{-1}	[22]

$$J_{0_j} = 0.029 \mu M s^{-1} \tag{3.10.27}$$

Algebraic equations

Fraction of the elastic strain energy stored within the membrane (dim.less):

$$F_{\text{wss}} = \frac{1}{1 + \alpha_{\text{wss}} \exp(-W_{\text{wss}})} - \frac{1}{1 + \alpha_{\text{wss}}} \tag{3.10.28}$$

Strain energy density (Pa):

$$W_{\text{wss}} = W_0 \frac{(\tau_{\text{wss}} + \sqrt{16\delta_{\text{wss}}^2 + \tau_{\text{wss}}^2} - 4\delta_{\text{wss}})^2}{\tau_{\text{wss}} + \sqrt{16\delta_{\text{wss}}^2 + \tau_{\text{wss}}^2}} \tag{3.10.29}$$

Wall shear stress (Pa):

$$\tau_{\text{wss}} = \frac{r\Delta P}{2L} \tag{3.10.30}$$

3.11 Lumen

γ_{eNOS}	relative strength of the Ca^{2+}-dependent pathway for the eNOS activation	0.1 (dim.less)	[6]
$\mu_{\mathrm{deact},j}$	eNOS-caveolin association rate	0.0167 s^{-1}	[6]
K_{dis}	eNOS-caveolin disassociation rate	0.09 $\mu M\,s^{-1}$	[6]
$[Ca^{2+}]_j$	calcium concentration in the EC cytosol	var.	see Dormanns et al. [9]
$K_{\mathrm{m,eNOS}}$	Michaelis constant	0.45 µM	[6]
g_{max}	maximum wall-shear-stress-induced eNOS activation	0.06 $\mu M\,s^{-1}$	[6]
α_{wss}	zero shear open channel constant	2 (dim.less)	[6]
W_0	shear gating constant	1.4 Pa^{-1}	[6]
δ_{wss}	membrane shear modulus	2.86 Pa	[6]
r	radius of arteriole	var.	see Dormanns et al. [9]
$V_{\mathrm{max,NO},j}$	maximum catalytic rate of NO production	1.22 s^{-1}	[3]
$[O_2]_j$	O_2 concentration in the EC	200 µM	M.E.
$K_{\mathrm{m,O2},j}$	Michaelis constant for eNOS for O_2	7.7 µM	[3]
$[\mathrm{L\text{-}Arg}]_j$	L-Arg concentration in the neuron	100 µM	[3]
$K_{\mathrm{m,L\text{-}Arg},j}$	Michaelis constant for eNOS for L-Arg	1.5 µM	[3]
$\Delta P/L$	pressure drop over length of arteriole	9.1×10^4 Pa m^{-1}	M.E.
$k_{\mathrm{O2},j}$	O_2 reaction rate constant	9.6×10^{-6} $\mu M^{-2}\,s^{-1}$	[20]

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