

Neurovascular Coupling Equations for Code version 1.2

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0.1 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^+ or Ca^{2+} . True concentrations are written with square brackets as in $[\text{Ca}^{2+}]_n$. In point of fact they are equivalent. Figure ?? shows a schematic of the ion channels, pumps and pathways.

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.

0.2 Global Constants

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

For version 1.2 there are essentially three fluxes from the pre-synapse entering the synaptic cleft, 1) K^+ , 2) Na^+ , and Glu(glutamate). 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

0.3 Synaptic Cleft (with subscript s)

check for the diffusion of K^+ into the ECS

Glutamate flux from presynapse neuron

need to note here what the input into the synaptic cleft models for this simple neuron model.

The ratio of bound to unbound receptors (mGluR) of glutamate is dependent on the synaptic glutamate release and is given by

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

Glu concentration in the synaptic cleft (μM):

$$[\text{Glu}]_{sc}(t) = [\text{Glu}]_{\max} (0.5 \tanh(t - t_0) - 0.5 \tanh(t - t_2)) \quad (0.3.1)$$

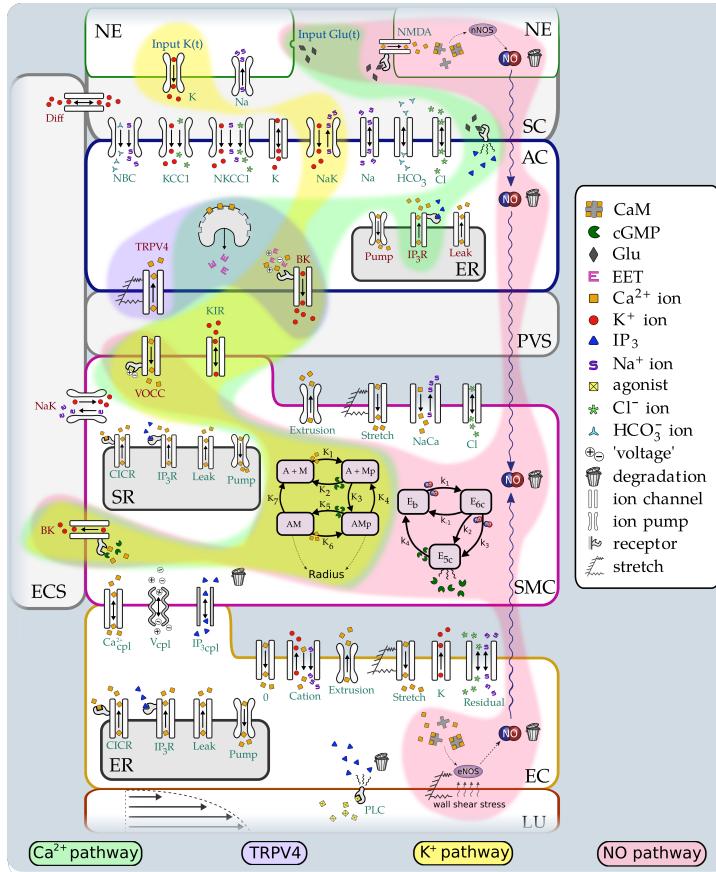


Figure 1: Schematic of version 1.2

or more succinctly

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

[Glu]_{max} is the maximum glutamate concentration = 1846 μM[18]

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

$$G = \frac{\rho + \delta}{K_G + \rho + \delta} \quad (0.3.2)$$

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

K⁺ and Na⁺ Input signals

This signal provides the neuronal K⁺ flux into the synaptic cleft. Taken from the Ostby model [17]

For $t < t_0$ and $t > t_3$:

$$f(t) = 0 \quad (0.3.3)$$

For $t_0 \leq t \leq t_1$:

$$f(t) = F_{input} \frac{(\alpha + \beta - 1)!}{(\alpha - 1)!(\beta - 1)!} \left(\frac{1t_\beta - (t - t_0)}{\Delta t} \right)^{\beta-1} \left(\frac{t - t_0}{\Delta t} \right)^{\alpha-1} \quad (0.3.4)$$

the function f(t) should be non-dimensional however the component given by

$\left(\frac{1 - (t - t_0)}{\Delta t} \right)^{\beta-1}$ dimensionally incorrect !!

30

For $t_1 \leq t \leq t_2$:

$$f(t) = 0 \quad (0.3.5)$$

For $t_2 \leq t \leq t_3$:

$$f(t) = -F_{input} \quad (0.3.6)$$

t_0	Start of neuronal pulse	variable see [5]
t_1	End of neuronal pulse	variable see [5]
t_2	Start of back-buffering	variable see [5]
t_3	End of back-buffering	variable see [5]
t_β	parameter	1 to ensure correct dimensionality
F_{input}	Amplitude scaling factor	2.5
α	Beta-distribution constant	2
β	Beta-distribution constant	5
Δt	Time-scaling factor	ME ¹

Scaling

This is also from the Ostby model [17] where the cell volume is a function of the flux across the membrane AC (astrocyte) volume-area ratio (in m), R_k :

$$\frac{dR_k}{dt} = L_p([Na^+]_k + [K^+]_k + [Cl^{-1}]_k + [HCO_3^{-1}]_k - [Na^+]_s - [K^+]_s - [Cl^{-1}]_s - [HCO_3^{-1}]_s + \frac{X_k}{R_k})$$

¹Model Estimation

(0.3.7)

SC (synaptic cleft) volume-surface ratio (in m):

$$R_s = R_{tot} - R_k \quad (0.3.8)$$

L_p	Total water permeability per unit area of the astrocyte	$2.1 \times 10^{-9} \text{ m } \mu\text{M}^{-1}\text{s}^{-1}$	[17]
X_k	Number of negatively charged impermeable ions trapped within the astrocyte divided by the astrocyte membrane area	$12.41 \times 10^{-3} \mu\text{M m}$	[17]
R_{tot}	Total volume surface ratio AC+SC	$8.79 \times 10^{-8} \text{ m}$	[17]

The volume surface area ratios do not change significantly and thus we may treat them as constants. So that $R_k \neq R_s$ are constants. R_k initially has the value of 6.28×10^{-8} meters. This value varies from 6.2 to 7 in the simulation but treating it as a constant makes virtually no difference.

K^+ concentration in the SC

$$\frac{dN_{K_s}}{dt} = k_C f(t) - \frac{dN_{K_k}}{dt} \quad (0.3.9)$$

Na^+ concentration in the SC

$$\frac{dN_{Na_s}}{dt} = -k_C f(t) - \frac{dN_{Na_k}}{dt} \quad (0.3.10)$$

HCO_3 concentration in the SC

$$\frac{dN_{HCO_3s}}{dt} = -\frac{dN_{HCO_3k}}{dt} \quad (0.3.11)$$

k_C	Input scaling parameter	$7.35 \times 10^{-5} \mu\text{M m s}^{-1}$	[17]
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Cl concentration in the synaptic cleft is derived by assuming electro-neutrality:

$$[\text{Cl}^{-1}]_s = [\text{Na}^+]_s + [\text{K}^+]_s - [\text{HCO}_3^{-1}]_s \quad (0.3.12)$$

0.4 Postsynaptic Neuron (with subscript n)

Differential equations

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

$$\frac{d[\text{Ca}^{2+}]_n}{dt} = \frac{I_{\text{Ca,tot}}/(2FV_{\text{spine}}) - \kappa_{\text{ex}}([\text{Ca}^{2+}]_n - [\text{Ca}^{2+}]_{\text{rest}})}{1 + \lambda_{\text{buf}}} \quad (0.4.1)$$

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

$$\frac{d[\text{nNOS}_{\text{act}}]_n}{dt} = \frac{V_{\text{max,nNOS}}[\text{CaM}]_n}{K_{\text{m,nNOS}} + [\text{CaM}]_n} - \mu_{\text{deact},n}[\text{nNOS}_{\text{act}}]_n \quad (0.4.2)$$

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

$$\frac{d[\text{NO}]_n}{dt} = p_{\text{NO},n} - c_{\text{NO},n} + d_{\text{NO},n} \quad (0.4.3)$$

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

$$p_{\text{NO},n} = V_{\text{max,NO},n}[\text{nNOS}_{\text{act}}]_n \frac{[\text{O}_2]_n}{K_{\text{m,O}_2,n} + [\text{O}_2]_n} \frac{[\text{L-Arg}]_n}{K_{\text{m,L-Arg},n} + [\text{L-Arg}]_n} \quad (0.4.4)$$

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

$$c_{\text{NO},n} = k_{\text{O}_2,n}[\text{NO}]_n^2[\text{O}_2]_n \quad (0.4.5)$$

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

$$d_{\text{NO},n} = \frac{[\text{NO}]_k - [\text{NO}]_n}{\tau_{nk}} \quad (0.4.6)$$

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

$$\tau_{nk} = \frac{x_{nk}^2}{2D_{\text{c,NO}}} \quad (0.4.7)$$

Algebraic equations

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

$$w_{\text{NR2,A}} = \frac{[\text{Glu}]_{sc}}{K_{\text{m,A}} + [\text{Glu}]_{sc}} \quad (0.4.8)$$

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

$$w_{\text{NR2,B}} = \frac{[\text{Glu}]_{sc}}{K_{\text{m,B}} + [\text{Glu}]_{sc}} \quad (0.4.9)$$

Inward calcium current per open NMDA receptor (fA):

$$I_{\text{Ca}} = \frac{4v_n G_{\text{M}}(P_{\text{Ca}}/P_{\text{M}})([\text{Ca}^{2+}]_{\text{ex}}/[M])}{1 + \exp(\alpha_v(v_n + \beta_v))} \frac{\exp(2v_n F/(R_{\text{gas}}T))}{1 - \exp(2v_n F/(R_{\text{gas}}T))} \quad (0.4.10)$$

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

$$I_{\text{Ca,tot}} = (n_{\text{NR2,A}} w_{\text{NR2,A}} + n_{\text{NR2,B}} w_{\text{NR2,B}}) I_{\text{Ca}} \quad (0.4.11)$$

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

$$\phi_{mc} = 1 + Q_1[Ca^{2+}]_n + Q_1Q_2[Ca^{2+}]_n^2 + Q_1Q_2Q_3[Ca^{2+}]_n^3 + Q_1Q_2Q_3Q_4[Ca^{2+}]_n^4 \quad (0.4.12)$$

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

$$m_c = \frac{[Ca^{2+}]_n}{\phi_{mc}} \frac{d\phi_{mc}}{d[Ca^{2+}]_n} \quad (0.4.13)$$

This equation could be simplified considerably as noted by

$$m_c = \frac{[Ca^{2+}]_n}{\phi_{mc}} \frac{d\phi_{mc}}{d[Ca^{2+}]_n} \quad (0.4.14)$$

$$= \frac{\sum_{i=1}^4 (i(\prod_{j=1}^i Q_j)) [Ca^{2+}]^i}{1 + \sum_{i=1}^4 ((\prod_{j=1}^i Q_j) [Ca^{2+}]^i)} \simeq 4 \quad (0.4.15)$$

⁴⁰ This is due to the size of the constants Q_i 's being of the order 10^5 .

Calcium-calmodulin complex concentration (μM):

$$[CaM]_n = \frac{[Ca^{2+}]_n}{m_c} \simeq \frac{[Ca^{2+}]_n}{4} \quad (0.4.16)$$

0.5 Astrocyte (with subscript k)

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

$$\frac{d[NO]_k}{dt} = p_{NO,k} - c_{NO,k} + d_{NO,k} \quad (0.5.1)$$

Algebraic equations

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

$$p_{NO,k} = 0 \quad (0.5.2)$$

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

$$c_{NO,k} = k_{O2,k} [NO]_k^2 [O_2]_k \quad (0.5.3)$$

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

$$d_{NO,k} = \frac{[NO]_n - [NO]_k}{\tau_{nk}} + \frac{[NO]_i - [NO]_k}{\tau_{ki}} \quad (0.5.4)$$

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

$$\tau_{ki} = \frac{x_{ki}^2}{2D_{c,NO}} \quad (0.5.5)$$

V_{spine}	dendritic spine volume	$8 \times 10^{-8} \text{ nL}$	[18]
κ_{ex}	decay rate constant of internal Ca^{2+} concentration	$1.6 \times 10^3 \text{ s}^{-1}$	[18]
$[\text{Ca}^{2+}]_{\text{rest}}$	resting internal calcium concentration	0.1 μM	[18]
λ_{buf}	buffer capacity	20 (dim.less)	[18]
$V_{\text{max,nNOS}}$	maximum nNOS activation rate	$25 \times 10^{-3} \mu\text{M}$	M.E. ²
$K_{\text{m,nNOS}}$	Michaelis constant	9.27×10^{-2}	[11]
$\mu_{\text{deact},n}$	rate constant at which nNOS is deactivated	0.0167 s^{-1}	[3]
$K_{\text{m},A}$	Michaelis constant	650 μM	[18]
$K_{\text{m},B}$	Michaelis constant	2800 μM	[18]
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	$4.6 \times 10^4 \text{ fS}$	[18]
P_{Ca}/P_M	ratio of NMDA receptor permeability to Ca^{2+} to permeability to monovalent ions	3.6 (dim.less)	[18]
$[\text{Ca}^{2+}]_{\text{ex}}$	external calcium concentration	$2 \times 10^3 \mu\text{M}$	[18]
$[\text{M}]$	concentration of monovalent ions	$1.3 \times 10^5 \mu\text{M}$	[18]
α_v	voltage-dependent Mg^{2+} block parameter	-80 V^{-1}	[18]
β_v	voltage-dependent Mg^{2+} block parameter	0.02 V	[18]
$n_{\text{NR2},A}$	average number of NR2A NMDA receptors	0.63 (dim.less)	[18]
$n_{\text{NR2},B}$	average number of NR2B NMDA receptors	11 (dim.less)	[18]
Q_1	Ca^{2+} -CaM binding constant	$1.9 \times 10^5 \mu\text{M}^{-1}$	[4]
Q_2	Ca^{2+} -CaM binding constant	$2.1 \times 10^5 \mu\text{M}^{-1}$	[4]
Q_3	Ca^{2+} -CaM binding constant	$0.4 \times 10^5 \mu\text{M}^{-1}$	[4]
Q_4	Ca^{2+} -CaM binding constant	$0.26 \times 10^5 \mu\text{M}^{-1}$	[4]
$V_{\text{max,NO},n}$	maximum catalytic rate of neuronal NO production	4.22 s^{-1}	[1]
$[\text{O}_2]_n$	O_2 concentration in the neuron	200 μM	M.E.
$K_{\text{m,O2},n}$	Michaelis constant for nNOS for O_2	243 μM	[2]
$[\text{L-Arg}]_n$	L-Arg concentration in the neuron	100 μM	[2]
$K_{\text{m,L-Arg},n}$	Michaelis constant for nNOS for L-Arg	1.5 μM	[1]
$k_{\text{O2},n}$	O_2 reaction rate constant	$9.6 \times 10^{-6} \frac{\mu\text{M}^{-2}}{\text{s}^{-1}}$	[12]
x_{nk}	distance between centres of NE and AC	25 μm	M.E.
$D_{\text{c,NO}}$	NO diffusion coefficient	$3300 \frac{\mu\text{m}^2}{\text{s}}$	[15]

$k_{O_2,k}$	O ₂ reaction rate constant	$9.6 \times 10^{-6} \mu\text{M}^{-2}\text{s}^{-1}$	[12]
x_{ki}	distance between centres of AC and SMC compartments	25 μm	model assumption
$[\text{O}_2]_k$	oxygen concentration in the astrocyte	200 μM	M.E.

K⁺ concentration in the AC :

$$\frac{dN_{K_k}}{dt} = -J_{K_k} + 2J_{NaK_k} + J_{NKCC1_k} + J_{KCC1_k} - J_{BK_k} \quad (0.5.6)$$

K⁺ flux through the BK channel :

$$J_{BK_k} = \frac{g_{BK_k}}{F} w_k (v_k - E_{BK_k}) \quad (0.5.7)$$

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

$$\frac{dw_k}{dt} = \phi_w (w_\infty - w_k) \quad (0.5.8)$$

$$\phi_w = \psi_n \cosh\left(\frac{v_k - v_3}{2v_4}\right) \quad (0.5.9)$$

$$v_3 = -\frac{v_5}{2} \tanh\left[\frac{[\text{Ca}^{2+}]_k - Ca_3}{Ca_4}\right] + v_6 \quad (0.5.10)$$

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}

⁴⁵ **Equilibrium state BK-channel as a function of the concentration of EET in the astrocytic cytosol:**

$$w_\infty = 0.5 \left(1 + \tanh\left(\frac{v_k EET_{shift} [EET]_k - v_3}{v_4}\right) \right) \quad (0.5.11)$$

Na⁺ concentration in the AC :

$$\frac{dN_{Na_k}}{dt} = -J_{Na_k} - 3J_{NaK_k} + J_{NKCC1_k} + J_{NBC_k} \quad (0.5.12)$$

²model estimation

HCO₃ concentration in the AC :

$$\frac{dN_{HCO_{3k}}}{dt} = 2J_{NBC_k} \quad (0.5.13)$$

Cl concentration in the AC :

$$\frac{dN_{Cl_k}}{dt} = \frac{dN_{Na_k}}{dt} + \frac{dN_{K_k}}{dt} - \frac{dN_{HCO_{3k}}}{dt} \quad (0.5.14)$$

IP₃ concentration in the AC :

$$\frac{dN_{i_k}}{dt} = r_h G - k_{deg} i_k \quad (0.5.15)$$

G is determined by equation 0.3.2.

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 Ca²⁺ concentration in the AC :

$$\frac{dN_{Ca_k}}{dt} = B_{cyt}(J_{IP3k} - J_{pump_k} + J_{ERleak_k} + \frac{J_{TRPV_k}}{r_{buf}}) \quad (0.5.16)$$

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

Ca²⁺ concentration in the ER of the AC :

$$\frac{dN_{Ca_{ER}}}{dt} = -B_{cyt} \frac{J_{IP3k} - J_{pump_k} + J_{ERleak_k}}{VR_{ER_{cyt}}} \quad (0.5.17)$$

$$B_{cyt} = (1 + BK_{end} + \frac{K_{ex}B_{ex}}{K_{ex} + [Ca^{2+}]_k})^{-1} \quad (0.5.18)$$

$$J_{IP3k} = J_{max}[(\frac{i_k}{i_k + K_i})(\frac{[Ca^{2+}]_k}{[Ca^{2+}]_k + K_{act}})h_k]^3(1 - \frac{[Ca^{2+}]_k}{Ca_{ER}}) \quad (0.5.19)$$

h_k is the activation/inactivation variable for the IP3R binding

$$\frac{dh_k}{dt} = k_{on}(K_{inh} - ([Ca^{2+}]_k + K_{inh})h_k) \quad (0.5.20)$$

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	$2 \mu\text{M s}^{-1}$
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

$$J_{ERleak} = P_L \left(1 - \frac{c_k}{Ca_{ER}}\right) \quad (0.5.21)$$

$$J_{pump_k} = V_{max} \frac{[\text{Ca}^{2+}]_k^2}{[\text{Ca}^{2+}]_k^2 + k_{pump}^2} \quad (0.5.22)$$

EET concentration in the AC :

$$\frac{dN_{EET_k}}{dt} = V_{eet} \max([\text{Ca}^{2+}]_k - \text{Ca}^{2+}_{min}, 0) - k_{eet} [\text{EET}]_k \quad (0.5.23)$$

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

55 Membrane voltage of the AC (mV):

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

$$v_k = \frac{g_{Na_k} E_{Na_k} + g_{K_k} E_{K_k} + g_{TRPV} E_{TRPV_k} + g_{Cl_k} E_{Cl_k} + g_{NBC_k} E_{NBC_k} + g_{BK_k} w_k E_{BK_k} - J_{NaK_k} F \times 10^3}{g_{Na_k} + g_{K_k} + g_{Cl_k} + g_{NBC_k} + g_{BK_k} w_k + g_{TRPV} m_k} \quad (0.5.24)$$

Nernst potential for the potassium channel (in mV):

$$E_{K_k} = \frac{R_g T}{z_K F} \ln \left(\frac{[\text{K}^+]_s}{[\text{K}^+]_k} \right) \quad (0.5.25)$$

Nernst potential for the sodium channel (in mV):

$$E_{Na_k} = \frac{R_g T}{z_{Na} F} \ln \left(\frac{[Na^+]_s}{[Na^+]_k} \right) \quad (0.5.26)$$

Nernst potential for the chloride channel (in mV):

$$E_{Cl_k} = \frac{R_g T}{z_{Cl} F} \ln \left(\frac{[Cl^{-1}]_s}{[Cl^{-1}]_k} \right) \quad (0.5.27)$$

Nernst potential for the NBC channel (in mV):

$$E_{NBC_k} = \frac{R_g T}{z_{NBC} F} \ln \left(\frac{[Na^+]_s [HCO_3^{-1}]_s^2}{[Na^+]_k [HCO_3^{-1}]_k^2} \right) \quad (0.5.28)$$

Nernst potential for the BK channel (in mV):

$$E_{BK_k} = \frac{R_g T}{z_K F} \ln \left(\frac{[K^+]_p}{[K^+]_k} \right) \quad (0.5.29)$$

g_{Cl_k}	Specific ion conductance of chloride	$0.879 \Omega^{-1} m^{-2}$	[17]
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

Ca²⁺ concentration in the AC (times the AC volume-area ratio R_k ; in μM m):

Need Ca²⁺ conservation equation check with Allanah about the format of the TRPV4 flux into the astrocyte and from the PVS.

the Ca²⁺ flux through the TRPV4 channel is given by

$$J_{TRPV_k} = -g_{TRPV} m_k (v_k - E_{TRPV_k}) \quad (0.5.30)$$

$$\frac{dm_k}{dt} = \phi_m (m_\infty - m_k) \quad (0.5.31)$$

$$\phi_m = \frac{1}{t_{TRPV}} \quad (0.5.32)$$

$$E_{TRPV_k} = \frac{RT}{z_{Ca} F} \log \left(\frac{[Ca^{2+}]_p}{[Ca^{2+}]_k} \right) \quad (0.5.33)$$

$$(0.5.34)$$

The equilibrium state of the TRPV4 channel is:

$$m_{\infty_k} = \frac{1}{1 + \exp(-\frac{\theta - \theta_0}{\kappa_k})} \frac{1}{1 + H_{Ca_k}} (H_{Ca_k} + \tanh(\frac{v_k - v_{1,TRPV}}{v_{2,TRPV}})) \quad (0.5.35)$$

$$H_{[\text{Ca}^{2+}]_k} = \frac{[\text{Ca}^{2+}]_k}{\gamma_{Cai}} + \frac{[\text{Ca}^{2+}]_p}{\gamma_{Cae}} \quad (0.5.36)$$

$$\theta = \frac{R - R_{passive}}{R_{passive}} \quad (0.5.37)$$

(0.5.38)

θ_0	strain required for half activation of TRPV4 channel	0.1	[?]
κ_k	TRPV4 strain scaling constant	0.1	[?]
$\nu_{1,TRPV}$	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

0.5.1 Fluxes into and out of the astrocyte

K^+ flux

$$J_{K_k} = \frac{g_{K_k}}{F} (v_k - E_{K_k}) \quad (0.5.39)$$

Na^+ flux

$$J_{Na_k} = \frac{g_{Na_k}}{F} (v_k - E_{Na_k}) \quad (0.5.40)$$

Na^+ and HCO_3^- flux through the NBC channel

$$J_{NBC_k} = \frac{g_{NBC_k}}{F} (v_k - E_{NBC_k}) \quad (0.5.41)$$

Cl and K^+ flux through the KCC1 channel

$$J_{KCC1_k} = C_{input} \frac{g_{KCC1_k}}{F} \frac{R_g T}{F} \ln \left(\frac{K_s Cl_s}{K_k Cl_k} \right) \quad (0.5.42)$$

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

$$J_{NKCC1_k} = C_{input} \frac{g_{NKCC1_k}}{F} \frac{R_g T}{F} \ln \left(\frac{Na_s K_s Cl_s^2}{Na_k K_k Cl_k^2} \right) \quad (0.5.43)$$

Flux through the sodium potassium pump

$$J_{NaK_k} = J_{NaK_{max}} \frac{Na_k^{1.5}}{Na_k^{1.5} + K_{Na_k}^{1.5}} \frac{K_s}{K_s + K_{K_s}} \quad (0.5.44)$$

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

F	Faraday's constant	$9.649 \times 10^4 \text{ C mol}^{-1}$	
R_g	Gas constant	$8.315 \text{ J mol}^{-1}\text{K}^{-1}$	
T	Temperature	300 K	
g_{K_k}	Specific ion conductance of potassium	$40 \times 10^3 \Omega^{-1}\text{m}^{-2}$	[17]
g_{Na_k}	Specific ion conductance of sodium	$1.314 \times 10^3 \Omega^{-1}\text{m}^{-2}$	[17]
K_{Na_k}		$40 \times 10^3 \Omega^{-1}\text{m}^{-2}$	[17]
g_{Na_k}	Specific ion conductance of sodium	$1.314 \times 10^3 \Omega^{-1}\text{m}^{-2}$	[17]
g_{NBC_k}	Specific ion conductance of the NBC cotransporter	$7.57 \times 10^2 \Omega^{-1}\text{m}^{-2}$	[17]
g_{KCC1_k}	Specific ion conductance of the KCC1 cotransporter	$10 \Omega^{-1}\text{m}^{-2}$	[17]
g_{NKCC1_k}	Specific ion conductance of the NKCC1 cotransporter	$55.4 \Omega^{-1}\text{m}^{-2}$	[17]
$J_{NaK_{max}}$	Maximum flux through the NaKATPase pump	$1.42 \times 10^{-3} \mu\text{M ms}^{-1}$	[17]
g_{BK_k}	Specific ion conductance of the BK channel	$1.16 \times 10^3 \Omega^{-1}\text{m}^{-2}$	[7]
C_{input}	Block function to switch the channel on and off	0 ; 1 [-]	

0.6 Perivascular Space (with subscript p)

K^+ concentration in the PVS (in μM):

$$\frac{dK_p}{dt} = \frac{J_{BK_k}}{R_k R_{pa}} + \frac{J_{KIR_i}}{R_{ps}} + \frac{J_{TRPV_k}}{R_k R_{pa}} \quad (0.6.1)$$

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

$$\frac{dC_{ap}}{dt} = -\frac{J_{TRPV_k}}{VR_{pa}} + \frac{J_{VOCC_i}}{VR_{ps}} - Ca_{decay_k}(Ca_p - Ca_{min_k}) \quad (0.6.2)$$

(0.6.3)

R_{pa}	Volume ratio of PVS to AC	$10^{-3} [-]$	[16]
R_{ps}	Volume ratio of PVS to SMC	$10^{-3} [-]$	[16]
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	

note that R_k is now a constant defined as unity, see neuron model of Ostby

0.7 Smooth Muscle Cell

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

$$\begin{aligned} \frac{d[Ca^{2+}]_i}{dt} = & J_{IP_{3i}} - J_{SR_{uptake_i}} + J_{CICR_i} - J_{extrusion_i} + J_{SR_{leak_i}} \dots \\ & - J_{VOCC_i} + J_{Na/Ca_i} - 0.1 J_{stretch_i} + J_{Ca^{2+}-coupling_i}^{SMC-EC} \end{aligned} \quad (0.7.1)$$

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

$$\frac{d[\widehat{Ca}^{2+}]_i}{dt} = J_{SR_{uptake_i}} - J_{CICR_i} - J_{SR_{leak_i}} \quad (0.7.2)$$

Membrane potential of the SMC (in mV):

$$\frac{dv_i}{dt} = \gamma_i(-J_{Na/K_i} - J_{Cl_i} - 2J_{VOCC_i} - J_{Na/Ca_i} - J_{K_i} \dots \\ - J_{stretch_i} - J_{KIR_i}) + V_{coupling_i}^{SMC-EC} \quad (0.7.3)$$

IP_3 concentration om the SMC (in μM):

$$\frac{d[IP_3]_i}{dt} = J_{IP_3-coupling_i}^{SMC-EC} - J_{degrad_i} \quad (0.7.4)$$

what is the definition and value of γ_i ? and what is $R_{K,i}$? see below in equation for K_{act_i}

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

$$\frac{dw_i}{dt} = \lambda_i (K_{act_i} - w_i) \quad (0.7.5)$$

Equilibrium distribution of open channel states for the BK channel (dim.less), see Dommans et al. [5]:

$$K_{act_i} = \frac{([Ca^{2+}]_i + c_{w,i})^2}{([Ca^{2+}]_i + c_{w,i})^2 + \beta_i \exp(v_{Ca3,i} - v_i/R_{K,i})} \quad (0.7.6)$$

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

$$c_{w,i} = \frac{1}{2} \left[1 + \tanh\left(\frac{[cGMP] - cGMP_1}{cGMP_2}\right) \right] \quad (0.7.7)$$

Release of calcium from IP_3 sensitive stores in the SMC (in $\mu M s^{-1}$):

$$J_{IP_3i} = F_i \frac{[IP_3]_i^2}{K_{ri}^2 + [IP_3]_i^2} \quad (0.7.8)$$

Uptake of calcium into the sarcoplasmic reticulum (in $\mu M s^{-1}$):

$$J_{SR_{uptake_i}} = B_i \frac{[Ca^{2+}]_i^2}{c_{bi}^2 + [Ca^{2+}]_i^2} \quad (0.7.9)$$

Calcium-induced calcium release (CICR; in $\mu M s^{-1}$):

$$J_{CICR_i} = C_i \frac{[\widehat{Ca}^{2+}]_i^2}{s_{ci}^2 + [\widehat{Ca}^{2+}]_i^2} \frac{[Ca^{2+}]_i^4}{c_{ci}^4 + [Ca^{2+}]_i^4} \quad (0.7.10)$$

F_i	Maximal rate of activation-dependent calcium influx	0.23 $\mu\text{M s}^{-1}$	[14]
K_{ri}	Half-saturation constant for agonist-dependent calcium entry	1 μM	[14]
$cGMP_1$	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
B_i	SR uptake rate constant	2.025 $\mu\text{M s}^{-1}$	[14]
c_{bi}	Half-point of the SR ATPase activation sigmoidal	1.0 μM	[14]
C_i	CICR rate constant	55 $\mu\text{M s}^{-1}$	[14]
s_{ci}	Half-point of the CICR Ca^{2+} efflux sigmoidal	2.0 μM	[14]
c_{ci}	Half-point of the CICR activation sigmoidal	0.9 μM	[14]

Calcium extrusion by Ca^{2+} -ATPase pumps (in $\mu\text{M s}^{-1}$):

$$J_{extrusion_i} = D_i[\text{Ca}^{2+}]_i \left(1 + \frac{v_i - v_d}{R_{di}} \right) \quad (0.7.11)$$

D_i	Rate constant for Ca^{2+} extrusion by the ATPase pump	0.24 s^{-1}	[14]
v_d	Intercept of voltage dependence of extrusion ATPase	-100.0 mV	[14]
R_{di}	Slope of voltage dependence of extrusion ATPase.	250.0 mV	[14]

Leak current from the SR (in $\mu\text{M s}^{-1}$):

$$J_{SR_{leak_i}} = L_i[\widehat{\text{Ca}}^{2+}]_i \quad (0.7.12)$$

L_i	Leak from SR rate constant	0.025 s^{-1}	[14]
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Calcium influx through VOCCs (in $\mu\text{M s}^{-1}$):

$$J_{VOCC_i} = G_{Cai} \frac{v_i - v_{Ca_{1i}}}{1 + \exp(-[(v_i - v_{Ca_{2i}})/R_{Cai}])} \quad (0.7.13)$$

G_{Cai}	Whole-cell conductance for VOCCs	$1.29 \times 10^{-3} \text{ } \mu\text{M mV}^{-1}\text{s}^{-1}$	[14]
$v_{Ca_{1i}}$	Reversal potential for VOCCs	100.0 mV	[14]
$v_{Ca_{2i}}$	Half-point of the VOCC activation sigmoidal	-24.0 mV	[14]
R_{Cai}	Maximum slope of the VOCC activation sigmoidal	8.5 mV	[14]

Flux of calcium exchanging with sodium in the $\text{Na}^+/\text{Ca}^{2+}$ exchange (in $\mu\text{M s}^{-1}$):

$$J_{\text{Na}/\text{Ca}_i} = G_{\text{Na}/\text{Ca}_i} \frac{[\text{Ca}^{2+}]_i}{[\text{Ca}^{2+}]_i + c_{\text{Na}/\text{Ca}_i}} (v_i - v_{\text{Na}/\text{Ca}_i}) \quad (0.7.14)$$

$G_{\text{Na}/\text{Ca}_i}$	Whole-cell conductance for $\text{Na}^+/\text{Ca}^{2+}$ exchange	$3.16 \times 10^{-3} \text{ } \mu\text{M mV}^{-1}\text{s}^{-1}$	[14]
$c_{\text{Na}/\text{Ca}_i}$	Half-point for activation of $\text{Na}^+/\text{Ca}^{2+}$ exchange by Ca^{2+}	0.5 μM	[14]
$v_{\text{Na}/\text{Ca}_i}$	Reversal potential for the $\text{Na}^+/\text{Ca}^{2+}$ exchanger	-30.0 mV	[14]

Calcium flux through the stretch-activated channels in the SMC (in $\mu\text{M s}^{-1}$):

$$J_{\text{stretch}_i} = \frac{G_{\text{stretch}}}{1 + \exp\left(-\alpha_{\text{stretch}}\left(\frac{\Delta p R}{h} - \sigma_0\right)\right)} (v_i - E_{SAC}) \quad (0.7.15)$$

G_{stretch}	Whole cell conductance for SACs	$6.1 \times 10^{-3} \text{ } \mu\text{M mV}^{-1}\text{s}^{-1}$	[14]
α_{stretch}	Slope of stress dependence of the SAC activation sigmoidal	$7.4 \times 10^{-3} \text{ mmHg}^{-1}$	[14]
Δp	Pressure difference	30 mmHg	ME
σ_0	Half-point of the SAC activation sigmoidal	500 mmHg	[14]
E_{SAC}	Reversal potential for SACs	-18 mV	[14]

Flux through the sodium potassium pump (in $\mu\text{M s}^{-1}$):

$$J_{\text{Na}K_i} = F_{\text{Na}K} \quad (0.7.16)$$

$F_{\text{Na}K}$	Rate of the potassium influx by the sodium potassium pump	$4.32 \times 10^{-2} \text{ } \mu\text{M s}^{-1}$	[14]
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Chloride flux through the chloride channel (in $\mu\text{M s}^{-1}$):

$$J_{Cl_i} = G_{Cl_i} (v_i - v_{Cl_i}) \quad (0.7.17)$$

Potassium flux through potassium channel (in $\mu\text{M s}^{-1}$):

$$J_{K_i} = G_{K_i} w_i (v_i - v_{K_i}) \quad (0.7.18)$$

G_{Cl_i}	Whole-cell conductance for Cl^- current	$1.34 \times 10^{-3} \text{ } \mu\text{M mV}^{-1}\text{s}^{-1}$	[14]
v_{Cl_i}	Reversal potential for Cl^- channels.	-25.0 mV	[14]
G_{K_i}	Whole-cell conductance for K^+ efflux.	$4.46 \times 10^{-3} \text{ } \mu\text{M mV}^{-1}\text{s}^{-1}$	[14]
v_{K_i}	Nernst potential	-94 mV	[14]

Flux through KIR channels in the SMC (in $\mu\text{M s}^{-1}$):

$$J_{KIR_i} = \frac{F_{KIR_i} g_{KIR_i}}{\gamma_i} (v_i - v_{KIR_i}) \quad (0.7.19)$$

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

$$v_{KIR_i} = z_1 K_p - z_2 \quad (0.7.20)$$

Conductance of KIR channel (in $\mu\text{M mV}^{-1} \text{ s}^{-1}$):

$$g_{KIR_i} = \exp(z_5 v_i + z_3 K_p - z_4) \quad (0.7.21)$$

c_{wi}	Translation factor for Ca^{2+} dependence of K_{Ca} channel activation sigmoidal.	0.0 μM	[14]
β_i	Translation factor for membrane potential dependence of K_{Ca} channel activation sigmoidal.	0.13 μM^2	[14]
$v_{Ca_{3i}}$	Half-point for the K_{Ca} channel activation sigmoidal.	-27 mV	[14]
R_{Ki}	Maximum slope of the K_{Ca} activation sigmoidal.	12 mV	[14]
z_1	Model estimation for membrane voltage KIR channel	$4.5 \times 10^3 \text{ mV } \mu\text{M}^{-1}$	[6]
z_2	Model estimation for membrane voltage KIR channel	112 mV	[6]
z_3	Model estimation for the KIR channel conductance	$4.2 \times 10^2 \text{ mV}^{-1}\text{s}^{-1}$	[6]
z_4	Model estimation for the KIR channel conductance	$12.6 \text{ } \mu\text{M mV}^{-1}\text{s}^{-1}$	[6]
z_5	Model estimation for the KIR channel conductance	$-7.4 \times 10^{-2} \text{ } \mu\text{M mV}^{-2}\text{s}^{-1}$	[6]

F_{KIR_i}	Scaling factor of potassium efflux through the KIR channel	750 mV μM^{-1}	[7]
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IP_3 degradation (in $\mu\text{M s}^{-1}$):

$$J_{degrad_i} = k_{di} I_i \quad (0.7.22)$$

k_{di}	Rate constant of IP_3 degradation	0.1 s^{-1}	[14]
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Coupling

Heterocellular electrical coupling between SMCs en ECs (in mV s⁻¹):

$$V_{coupling_i}^{SMC-EC} = -G_{coup}(v_i - v_j) \quad (0.7.23)$$

Heterocellular IP₃ coupling between SMCs and ECs (in μM s⁻¹):

$$J_{IP_3-coupling_i}^{SMC-EC} = -P_{IP_3}([IP_3]_i - [IP_3]_j) \quad (0.7.24)$$

Calcium coupling with EC (in μM s⁻¹):

$$J_{Ca^{2+}-coupling_i}^{SMC-EC} = -P_{Ca^{2+}}([Ca^{2+}]_i - [Ca^{2+}]_j) \quad (0.7.25)$$

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	[14]
$P_{Ca^{2+}}$	Heterocellular $P_{Ca^{2+}}$ coupling coefficient	0.05 s ⁻¹	[14]

We should note here that the membrane potential coupling $V_{coupling_i}^{SMC-EC}$ is an approximation that does not include electrodiffusion.

$$\frac{d[K_i^+]}{dt} = J_{Na/K_i} - J_{KIR_i} - J_{K_i} \quad (0.7.26)$$

γ_i	Change in membrane potential by a scaling factor	1970 mV μM ⁻¹	[14]
λ_i	Rate constant for opening	45.0 s ⁻¹	[14]

Rate of change of NO concentration in the SMC (μM s⁻¹):

$$\frac{d[NO]_i}{dt} = p_{NO,i} - c_{NO,i} + d_{NO,i} \quad (0.7.27)$$

Rate of change of fraction of sGC in the basal state (s⁻¹):

$$\frac{dE_b}{dt} = -k_1 E_b [NO]_i + k_{-1} E_{6c} + k_4 E_{5c} \quad (0.7.28)$$

Rate of change of fraction of sGC in the intermediate form (s⁻¹):

$$\frac{dE_{6c}}{dt} = k_1 E_b [NO]_i - (k_{-1} + k_2) E_{6c} - k_3 E_{6c} [NO]_i \quad (0.7.29)$$

Rate of change of cGMP concentration (μM s⁻¹):

$$\frac{d[cGMP]_i}{dt} = V_{max,sGC} E_{5c} - \frac{V_{max,pde} [cGMP]_i}{K_{m,pde} + [cGMP]_i} \quad (0.7.30)$$

Maximum cGMP production rate (μM s⁻¹):

$$V_{max,pde} = k_{pde} [cGMP]_i \quad (0.7.31)$$

Algebraic equations

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

$$p_{\text{NO},i} = 0 \quad (0.7.32)$$

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

$$c_{\text{NO},i} = k_{\text{dno}}[\text{NO}]_i \quad (0.7.33)$$

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

$$d_{\text{NO},i} = \frac{[\text{NO}]_k - [\text{NO}]_i}{\tau_{ki}} + \frac{[\text{NO}]_j - [\text{NO}]_i}{\tau_{ij}} \quad (0.7.34)$$

$$\tau_{i,j} = \frac{x_{K,i}^2}{2D_{\text{NO}}} \quad (0.7.35)$$

$$x_{K,i} = 25\mu\text{m} \quad (0.7.36)$$

$$(0.7.37)$$

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

$$k_4 = C_4[\text{cGMP}]_i^{m_4} \quad (0.7.38)$$

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

$$E_{5c} = 1 - E_b - E_{6c} \quad (0.7.39)$$

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

$$R_{\text{cGMP}} = \frac{[\text{cGMP}]_i^2}{K_{\text{m,mrcp}}^2 + [\text{cGMP}]_i^2} \quad (0.7.40)$$

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

$$K_{2c} = K_{5c} = \delta_i (k_{\text{mlpc,b}} + k_{\text{mlpc,c}} R_{\text{cGMP}}) \quad (0.7.41)$$

Equilibrium distribution of open channel states for the BK channel flux into the ECS (dim.less), see Dormanns et al. [5]:

$$K_{\text{act},i} = \frac{([\text{Ca}^{2+}]_i + c_{w,i})^2}{([\text{Ca}^{2+}]_i + c_{w,i})^2 + \beta_i \exp(v_{\text{Ca3},i} - v_i/R_{\text{K},i})} \quad (0.7.42)$$

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

$$c_{w,i} = \frac{c_{w,max}}{2} [1 + \tanh(\frac{[\text{cGMP}]_i - \epsilon_i}{\alpha_i})] \quad (0.7.43)$$

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

$$\tau_{ij} = \frac{x_{ij}^2}{2D_{\text{c,NO}}} \quad (0.7.44)$$

k_{-1}	sGC kinetics rate constant	100 s^{-1}	[20]
k_1	sGC kinetics rate constant	$2 \times 10^3 \text{ } \mu\text{M}^{-1} \text{ s}^{-1}$	[20]
k_2	sGC kinetics rate constant	0.1 s^{-1}	[20]
k_3	sGC kinetics rate constant	$3 \text{ } \mu\text{M}^{-1} \text{ s}^{-1}$	[20]
$V_{\max,\text{sGC}}$	maximal cGMP production rate	$0.8520 \text{ } \mu\text{M s}^{-1}$	[20]
$K_{\text{m,pde}}$	Michaelis constant	$2 \text{ } \mu\text{M}$	[20]
k_{dno}	lumped NO consumption rate constant reflecting the activity of various NO scavengers	0.01 s^{-1}	[20]
C_4	constant	$0.011 \text{ } \mu\text{M}^{-2} \text{ s}^{-1}$	[20]
m_4	cGMP feedback strength	2 (dim.less)	[20]
$K_{\text{m,mlcp}}$	Hill coefficient	$5.5 \text{ } \mu\text{M}$	[20]
δ_i	constant to fit data	$58.1395 \text{ (dim.less)}$	[9], fit
$k_{\text{mlpc,b}}$	basal MLC dephosphorylation rate constant	0.0086 s^{-1}	[20]
$k_{\text{mlpc,c}}$	first-order rate constant for cGMP-regulated MLC dephosphorylation	0.0327 s^{-1}	[20]
α_i	constant to fit data	$0.665 \text{ } \mu\text{M}$	[19]
β_i	translation factor for membrane potential dependence of K_{Ca} channel activation sigmoidal	$0.13 \text{ } \mu\text{M}^2$	[14]
$c_{w,max}$	constant to fit data	$1 \text{ } \mu\text{M s}^{-1}$	[19]
ϵ_i	constant to fit data	$10.75 \text{ } \mu\text{M}$	[19]
$[\text{Ca}^{2+}]_i$	calcium concentration in the SMC cytosol	var.	see Dommanns et al. [5]
$v_{\text{Ca3},i}$	half-point for the K_{Ca} channel activation sigmoidal	-27 mV	[14]
v_i	SMC membrane potential	var.	see [5]
$R_{K,i}$	Maximum slope of the K_{Ca} activation sigmoidal	12 mV	[14]
k_{pde}	phosphodiesterase rate constant	0.0195 s^{-1}	[20]

0.7.1 The Contraction Model

Fraction of free phosphorylated cross-bridges (dimensionless):

$$\frac{d[MP]}{dt} = K_4[AMP] + K_1[M] - (K_2 + K_3)[Mp] \quad (0.7.45)$$

Fraction of attached phosphorylated cross-bridges (dimensionless):

$$\frac{d[AMP]}{dt} = K_3[Mp] + K_6[AM] - (K_4 + K_5)[AMP] \quad (0.7.46)$$

Fraction of attached dephosphorylated cross-bridges (dimensionless):

$$\frac{d[AM]}{dt} = K_5[AMP] - (K_7 + K_6)[AM] \quad (0.7.47)$$

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

$$[M] = 1 - [AM] - [AMP] - [Mp] \quad (0.7.48)$$

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}):

$$K_1 = K_6 = \gamma_{cross} [Ca^{2+}]_i^{n_{cross}} \quad (0.7.49)$$

K_2	Rate constant for dephosphorylation (of Mp to M) by myosin light-chain phosphatase (MLCP)	0.5 s^{-1}	[10]
K_3	Rate constants representing the attachment/detachment of fast cycling phosphorylated crossbridges	0.4 s^{-1}	[10]
K_4	Rate constants representing the attachment/detachment of fast cycling phosphorylated crossbridges	0.1 s^{-1}	[10]
K_5	Rate constant for dephosphorylation (of AMP to AM) by myosin light-chain phosphatase (MLCP)	0.5 s^{-1}	[10]
K_7	Rate constant for latch-bridge detachment	0.1 s^{-1}	[10]
γ_{cross}	Sensitivity of the contractile apparatus to calcium	$17\text{ }\mu\text{M}^{-3}\text{ s}^{-1}$	[13]
n_{cross}	Fraction constant of the phosphorylation crossbridge	3 [-]	[13]

80

0.7.2 The Mechanical Model

Wall thickness of the vessel (in μm):

$$h = -R + \sqrt{R^2 + 2R_{0pas}h_{0pas} + h_{0pas}^2} \quad (0.7.50)$$

Fraction of attached myosin cross-bridges (dimensionless):

$$F_r = [AM_p] + [AM] \quad (0.7.51)$$

Vessel radius (in μm):

$$\frac{dR}{dt} = \frac{R_{0pas}}{\eta} \left(\frac{RP_T}{h} - E(F_r) \frac{R - R_0(F_r)}{R_0(F_r)} \right) \quad (0.7.52)$$

with:

$$E(F_r) = E_{pas} + F_r(E_{act} - E_{pas}) \quad (0.7.53)$$

$$R_0(F_r) = R_{0pas} + F_r(\alpha - 1)R_{0pas} \quad (0.7.54)$$

η	viscosity	10^4 Pa s	[14]
$R_{0_{pas}}$	Radius of the vessel when passive and no stress is applied	$20 \mu\text{m}$	ME
P_T	Transmural pressure	4×10^3 Pa	ME
E_{pas}	Young's moduli for the passive vessel	66×10^3 Pa	[8]
E_{act}	Additional component of the Young's moduli when vessel is active	167×10^3 Pa	[8]
α	Scaling factor initial radius	0.6	[8]

0.8 Endothelial Cell

Endothelial cell

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

$$\frac{d[\text{Ca}^{2+}]_j}{dt} = J_{IP_{3j}} - J_{ER_{uptake_j}} + J_{CICR_j} - J_{extrusion_j} \dots + J_{ER_{leak_j}} + J_{cation_j} + J_{0j} - J_{stretch_j} - J_{Ca^{2+}-coupling_j}^{SMC-EC} \quad (0.8.1)$$

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

$$\frac{d[\widehat{\text{Ca}}^{2+}]_j}{dt} = J_{SR_{uptake_j}} - J_{CICR_j} - J_{SR_{leak_j}} \quad (0.8.2)$$

Membrane potential of the EC (in mV):

$$\frac{dv_j}{dt} = -\frac{1}{C_{m_j}}(J_{K_j} + J_{R_j}) + V_{coupling_j}^{SMC-EC} \quad (0.8.3)$$

IP_3 concentration of the EC (in μM):

$$\frac{d[IP_3]_j}{dt} = J_{EC,IP_3} - J_{degrad_j} - J_{IP_3-coupling_j}^{SMC-EC} \quad (0.8.4)$$

Coupling

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

$$V_{coupling_i}^{SMC-EC} = -G_{coup}(v_i - v_j) \quad (0.8.5)$$

Heterocellular IP_3 coupling between SMCs and ECs (in $\mu\text{M s}^{-1}$):

$$J_{IP_3-coupling_i}^{SMC-EC} = -P_{IP_3}([IP_3]_i - [IP_3]_j) \quad (0.8.6)$$

Calcium coupling with EC (in $\mu\text{M s}^{-1}$):

$$J_{Ca^{2+}-coupling_i}^{SMC-EC} = -P_{Ca^{2+}}([Ca^{2+}]_i - [Ca^{2+}]_j) \quad (0.8.7)$$

G_{coup}	Heterocellular electrical coupling coefficient	0.5 s ⁻¹	ME
P_{IP_3}	Heterocellular IP ₃ coupling coefficient	0.05 s ⁻¹	[14]
$P_{Ca^{2+}}$	Heterocellular $P_{Ca^{2+}}$ coupling coefficient	0.05 s ⁻¹	[14]
C_{m_j}	Membrane capacitance	25.8 pF	[14]
J_{EC,IP_3}	IP ₃ production rate	$\mu\text{M s}^{-1}$	[14]

$$\frac{d[\text{eNOS}_{\text{act}}]_j}{dt} = \gamma_{\text{eNOS}} \frac{K_{\text{dis}} [\text{Ca}^{2+}]_j}{K_{\text{m,eNOS}} + [\text{Ca}^{2+}]_j} + (1 - \gamma_{\text{eNOS}}) g_{\max} F_{\text{wss}} - \mu_{\text{deact},j} [\text{eNOS}_{\text{act}}]_j \quad (0.8.8)$$

$$\frac{d[\text{NO}]_j}{dt} = p_{\text{NO},j} - c_{\text{NO},j} + d_{\text{NO},j} \quad (0.8.9)$$

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

$$p_{\text{NO},j} = V_{\max,\text{NO},j} [\text{eNOS}_{\text{act}}]_j \frac{[\text{O}_2]_j}{K_{\text{m,O}_2,j} + [\text{O}_2]_j} \frac{[\text{L-Arg}]_j}{K_{\text{m,L-Arg},j} + [\text{L-Arg}]_j} \quad (0.8.10)$$

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

$$c_{\text{NO},j} = k_{\text{O}_2,j} [\text{NO}]_j^2 [\text{O}_2]_j \quad (0.8.11)$$

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

$$d_{\text{NO},j} = \frac{[\text{NO}]_i - [\text{NO}]_j}{\tau_{ij}} - \frac{4D_{\text{c,NO}} [\text{NO}]_j}{r^2} \quad (0.8.12)$$

85

definition of τ_{ij} ??

$$\tau_{ij} = \frac{x^2}{2D_{\text{NO}}} \quad (0.8.13)$$

$$x = 3.75\mu\text{m} \quad (0.8.14)$$

Endothelial cell

Release of calcium from IP₃-sensitive stores in the EC (in $\mu\text{M s}^{-1}$):

$$J_{IP_3,j} = F_j \frac{[IP_3]_j^2}{K_{rj}^2 + [IP_3]_j^2} \quad (0.8.15)$$

F_j	Maximal rate of activation-dependent calcium influx	0.23 $\mu\text{M s}^{-1}$	[14]
K_{rj}	Half-saturation constant for agonist-dependent calcium entry	1 μM	[14]
B_j	ER uptake rate constant	0.5 $\mu\text{M s}^{-1}$	[14]
c_{bj}	Half-point of the SR ATPase activation sigmoidal	1.0 μM	[14]

Uptake of calcium into the endoplasmic reticulum (in $\mu\text{M s}^{-1}$):

$$J_{ER_{uptake_j}} = B_j \frac{[Ca^{2+}]_j^2}{c_{bj}^2 + [Ca^{2+}]_j^2} \quad (0.8.16)$$

Calcium-induced calcium release (CICR; in $\mu\text{M s}^{-1}$):

$$J_{CICR_j} = C_j \frac{[\widehat{Ca}^{2+}]_j^2}{s_{cj}^2 + [\widehat{Ca}^{2+}]_j^2} \frac{[Ca^{2+}]_j^4}{c_{cj}^4 + [Ca^{2+}]_j^4} \quad (0.8.17)$$

C_j	CICR rate constant	5 $\mu\text{M s}^{-1}$	[14]
s_{cj}	Half-point of the CICR Ca^{2+} efflux sigmoidal	2.0 μM	[14]
c_{cj}	Half-point of the CICR activation sigmoidal	0.9 μM	[14]

Calcium extrusion by Ca^{2+} -ATPase pumps (in $\mu\text{M s}^{-1}$):

$$J_{extrusion_j} = D_j [Ca^{2+}]_j \quad (0.8.18)$$

D_j	Rate constant for Ca^{2+} extrusion by the ATPase pump	0.24 s^{-1}	[13]
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Calcium flux through the stretch-activated channels in the EC (in $\mu\text{M s}^{-1}$):

$$J_{stretch_j} = \frac{G_{stretch}}{1 + e^{-\alpha_{stretch}(\sigma - \sigma_0)}} (v_j - E_{SAC}) = \frac{G_{stretch}}{1 + e^{-\alpha_{stretch}(\frac{\Delta p_R}{h} - \sigma_0)}} (v_j - E_{SAC}) \quad (0.8.19)$$

Leak current from the ER (in $\mu\text{M s}^{-1}$):

$$J_{ER_{leak_j}} = L_j [\widehat{Ca}^{2+}]_j \quad (0.8.20)$$

$G_{stretch}$	The whole cell conductance for SACs	$6.1 \times 10^{-3} \text{ } \mu\text{M mV}^{-1}\text{s}^{-1}$	[14]
$\alpha_{stretch}$	Slope of stress dependence of the SAC activation sigmoidal	$7.4 \times 10^{-3} \text{ mmHg}^{-1}$	[14]
Δp	Pressure difference	30 mmHg	ME
σ_0	Half-point of the SAC activation sigmoidal	500 mmHg	[14]
E_{SAC}	The reversal potential for SACs	-18 mV	[14]
L_j	Rate constant for Ca^{2+} leak from the ER	0.025 s ⁻¹	[14]
G_{catj}	Whole-cell cation channel conductivity	$6.6 \times 10^{-4} \text{ } \mu\text{M mV}^{-1}\text{s}^{-1}$	[14]
E_{Ca_j}	Ca^{2+} equilibrium potential	50 mV	[14]
$m_{3_{catj}}$	Model constant	-0.18 μM	[14]
$m_{4_{catj}}$	Model constant	0.37 μM	[14]

Calcium influx through nonselective cation channels (in $\mu\text{M s}^{-1}$):

$$J_{cation_j} = G_{catj}(E_{Ca_j} - v_j) \frac{1}{2} \left(1 + \tanh \left(\frac{\log_{10}[\text{Ca}^{2+}]_j - m_{3_{catj}}}{m_{4_{catj}}} \right) \right) \quad (0.8.21)$$

Potassium efflux through the $J_{BK_{Ca_j}}$ channel and the $J_{SK_{Ca_j}}$ channel (in $\mu\text{M s}^{-1}$):

$$J_{K_j} = G_{totj}(v_j - v_{Kj})(J_{BK_{Ca_j}} + J_{SK_{Ca_j}}) \quad (0.8.22)$$

G_{totj}	Total potassium channel conductivity.	6927 pS	[14]
v_{Kj}	K^+ equilibrium potential	-80.0 mV	[14]

Potassium efflux through the $J_{BK_{Ca_j}}$ channel (in $\mu\text{M s}^{-1}$):

$$J_{BK_{Ca_j}} = 0.2 \left(1 + \tanh \left(\frac{(\log_{10}[\text{Ca}^{2+}]_j - c)(v_j - b_j) - a_{1j}}{m_{3bj}(v_j + a_{2j}(\log_{10}[\text{Ca}^{2+}]_j - c) - b_j)^2 + m_{4bj}} \right) \right) \quad (0.8.23)$$

Potassium efflux through the $J_{SK_{Ca_j}}$ channel (in $\mu\text{M s}^{-1}$):

$$J_{SK_{Ca_j}} = 0.3 \left(1 + \tanh \left(\frac{\log_{10}[\text{Ca}^{2+}]_j - m_{3sj}}{m_{4sj}} \right) \right) \quad (0.8.24)$$

Residual current regrouping chloride and sodium current flux (in $\mu\text{M s}^{-1}$):

$$J_{R_j} = G_{R_j}(v_j - v_{restj}) \quad (0.8.25)$$

IP₃ degradation (in $\mu\text{M s}^{-1}$):

$$J_{degrad_j} = k_{dj}[\text{IP}_3]_j \quad (0.8.26)$$

$$J_{0_j} = 0.029 \mu\text{Ms}^{-1} \quad (0.8.27)$$

c	Model constant, further explanation see reference	-0.4 pM	[14]
b_j	Model constant, further explanation see reference	-80.8 mV	[14]
a_{1j}	Model constant, further explanation see reference	53.3 $\mu\text{M mV}$	[14]
a_{2j}	Model constant, further explanation see reference	53.3 $\text{mV } \mu\text{M}^{-1}$	[14]
m_{3bj}	Model constant, further explanation see reference	$1.32 \times 10^{-3} \mu\text{M mV}^{-1}$	[14]
m_{4bj}	Model constant, further explanation see reference	0.30 $\mu\text{M mV}$	[14]
m_{3sj}	Model constant, further explanation see reference	-0.28 μM	[14]
m_{4sj}	Model constant, further explanation see reference	0.389 μM	[14]
G_{R_j}	Residual current conductivity	955 pS	[14]
v_{restj}	Membrane resting potential	-31.1 mV	[14]
k_{dj}	Rate constant of IP_3 degradation	0.1 s^{-1}	[14]

Algebraic equations

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

$$F_{\text{wss}} = \frac{1}{1 + \alpha_{\text{wss}} \exp(-W_{\text{wss}})} - \frac{1}{1 + \alpha_{\text{wss}}} \quad (0.8.28)$$

Strain energy density (Pa):

$$W_{\text{wss}} = W_0 \frac{(\tau_{\text{wss}} + \sqrt{16\delta_{\text{wss}}^2 + \tau_{\text{wss}}^2} - 4\delta_{\text{wss}})^2}{\tau_{\text{wss}} + \sqrt{16\delta_{\text{wss}}^2 + \tau_{\text{wss}}^2}} \quad (0.8.29)$$

Wall shear stress (Pa):

$$\tau_{\text{wss}} = \frac{r \Delta P}{2L} \quad (0.8.30)$$

0.9 Extracellular Space

diffusion, NaK and BK fluxes defined here

$$\frac{d[K]_e}{dt} = -VRJ_{diff} + J_K - J_{NaK} \quad (0.9.1)$$

where

$$J_{diff} = \frac{1}{\tau_s}(K_e - K_s) \quad (0.9.2)$$

$$J_K = G_K w_i(v_i - E_K) \quad (0.9.3)$$

$$J_{NaK} = F_{NaK} \quad (0.9.4)$$

$$(0.9.5)$$

γ_{eNOS}	relative strength of the Ca^{2+} -dependent pathway for the eNOS activation	0.1 (dim.less)	[3]
$\mu_{deact,j}$	eNOS-caveolin association rate	0.0167 s^{-1}	[3]
K_{dis}	eNOS-caveolin disassociation rate	$0.09 \text{ } \mu\text{M s}^{-1}$	[3]
$[\text{Ca}^{2+}]_j$	calcium concentration in the EC cytosol	var.	see Dormanns et al. [5]
$K_{m,eNOS}$	Michaelis constant	$0.45 \text{ } \mu\text{M}$	[3]
g_{max}	maximum wall-shear-stress-induced eNOS activation	$0.06 \text{ } \mu\text{M s}^{-1}$	[3]
α_{wss}	zero shear open channel constant	2 (dim.less)	[3]
W_0	shear gating constant	1.4 Pa^{-1}	[3]
δ_{wss}	membrane shear modulus	2.86 Pa	[3]
r	radius of arteriole	var.	see Dormanns et al. [5]
$V_{max,\text{NO},j}$	maximum catalytic rate of NO production	1.22 s^{-1}	[1]
$[\text{O}_2]_j$	O_2 concentration in the EC	$200 \text{ } \mu\text{M}$	M.E.
$K_{m,\text{O}_2,j}$	Michaelis constant for eNOS for O_2	$7.7 \text{ } \mu\text{M}$	[1]
$[\text{L-Arg}]_j$	L-Arg concentration in the neuron	$100 \text{ } \mu\text{M}$	[1]
$K_{m,\text{L-Arg},j}$	Michaelis constant for eNOS for L-Arg	$1.5 \text{ } \mu\text{M}$	[1]
$\Delta P/L$	pressure drop over length of arteriole	$9.1 \times 10^4 \text{ Pa m}^{-1}$	M.E.
$k_{\text{O}_2,j}$	O_2 reaction rate constant	$9.6 \times 10^{-6} \text{ } \mu\text{M}^{-2} \text{ s}^{-1}$	[12]

and

$$\tau_s = \frac{(\Delta x_s)^2}{2D_K} \quad (0.9.6)$$

$$D_K = \frac{D_{free}}{\lambda_0^2} \quad (0.9.7)$$

here Δx_s is the effective diffusion distance and D_{free} is the diffusion coefficient of potassium in a free medium, λ_0 the tortuosity factor since diffusion is hindered by the narrow confines of the extracellular space. At this time volume ratios are used only for the transfer of potassium from the synaptic cleft to the ECS.

Δx_s	10^{-4}	m	average distance across two adjacent astrocyte arms
D_{free}	4.58×10^{-9}	$\text{m}^2 \text{s}^{-1}$	potassium diffusion coefficient in free media
λ_0	1.6	non-dimensional	tortuosity factor
G_K	4.46×10^{-3}	$\mu\text{MmV}^{-1}\text{s}^{-1}$	whole SMC conductance for K^+ efflux
E_K	-94	mV	Mernst potential for the SMC BK channel
F_{NaK}	4.32×10^{-2}	μuMs^{-1}	rate of K^+ influx by the sodium/potassium pump.

0.10 Lumen

Conservation Equations

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