Supplementary Material

Improvement of the BOLD signal in a biophysical neurovascular unit model

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1 Model Overview

The neurogliovascular unit (NGVU) model formulated in this work builds on the lineage of biophysical models from the Tim David group [Farr, David, 2011], [Dormanns et al., 2015], [Kenny et al., 2018], [Mathias et al., 2018] and on our own previous publications on neurovascular coupling [Loshkarev, Postnov, 2020], [Loshkarev, Postnov, 2021], [Loshkarev, Postnov, 2025]. The full model consists of **73 coupled ordinary differential equations** that describe the dynamics of neuronal activity, glial signalling, vascular mechanics, and the resulting BOLD response. All equations are listed in Table 1 together with their initial values; full lists of parameters are provided in Sec. 4.

The model structure is summarised schematically in Fig. 1.

The 73 differential equations cover the following compartments and processes (numbering refers to Table 1):

- **Eqs. 1–2** – Cerebral blood volume (CBV) and deoxyhaemoglobin (HbR) dynamics for BOLD signal modelling, linking oxygen consumption to vascular responses (balloon-Buxton model).
- **Eqs. 3–31** – Two-compartment neuron model (soma/axon and dendrite) with membrane potentials, intracellular Na^+/K^+ concentrations, voltage-gated ion channel gating variables, calcium signalling, neuronal nitric oxide synthase (nNOS) activation, NO production, oxygen dynamics, volume regulation, and the **metabolic-inertia state** $CMRO_{2,n}$ that filters the instantaneous oxygen consumption used by the balloon (introduced in this work).
- **Eqs. 9–11** – Extracellular K^+, Na^+, and buffer concentrations (shared extracellular space).
- **Eqs. 32–35, 40–46, 49–51** – Astrocytic intracellular ions (Na^+, K^+, HCO_3^-, Cl^-), membrane potential, calcium dynamics with IP_3 signalling and ER calcium store, BK channel gating, EET production, TRPV channel dynamics, and volume regulation.
- **Eqs. 36–38** – Na^+, K^+, and HCO_3^- in the synaptic/perisynaptic space.
- **Eqs. 39, 47** – K^+ and Ca^{2+} in the perivascular space surrounding arterioles, critical for astrocyte-to-vessel signalling.
- **Eqs. 44, 48, 52–53** – Gliotransmitter and neuromodulator signalling: IP_3, NO in astrocyte, glutamate, and norepinephrine dynamics for intercellular communication.
- **Eqs. 54–63** – Smooth muscle cell (SMC) membrane potential, intracellular Ca^{2+} and SR Ca^{2+} store, K^+ concentration, BK channel gating, IP_3 dynamics, NO concentration, and the NO-cGMP-PKG signalling cascade.
- **Eqs. 64–69** – Endothelial cell (EC) membrane potential, intracellular Ca^{2+} and ER Ca^{2+} store, IP_3 dynamics, endothelial NOS (eNOS) activation, and NO production.
- **Eqs. 70–73** – Four-state crossbridge model for smooth muscle contraction (myosin phosphorylation states M, M$\mathbb{P}$, AM$\mathbb{P}$, AM) and vessel-radius mechanics.

2 Inter-compartment Coupling

The compartments are bidirectionally coupled through the following mechanisms:

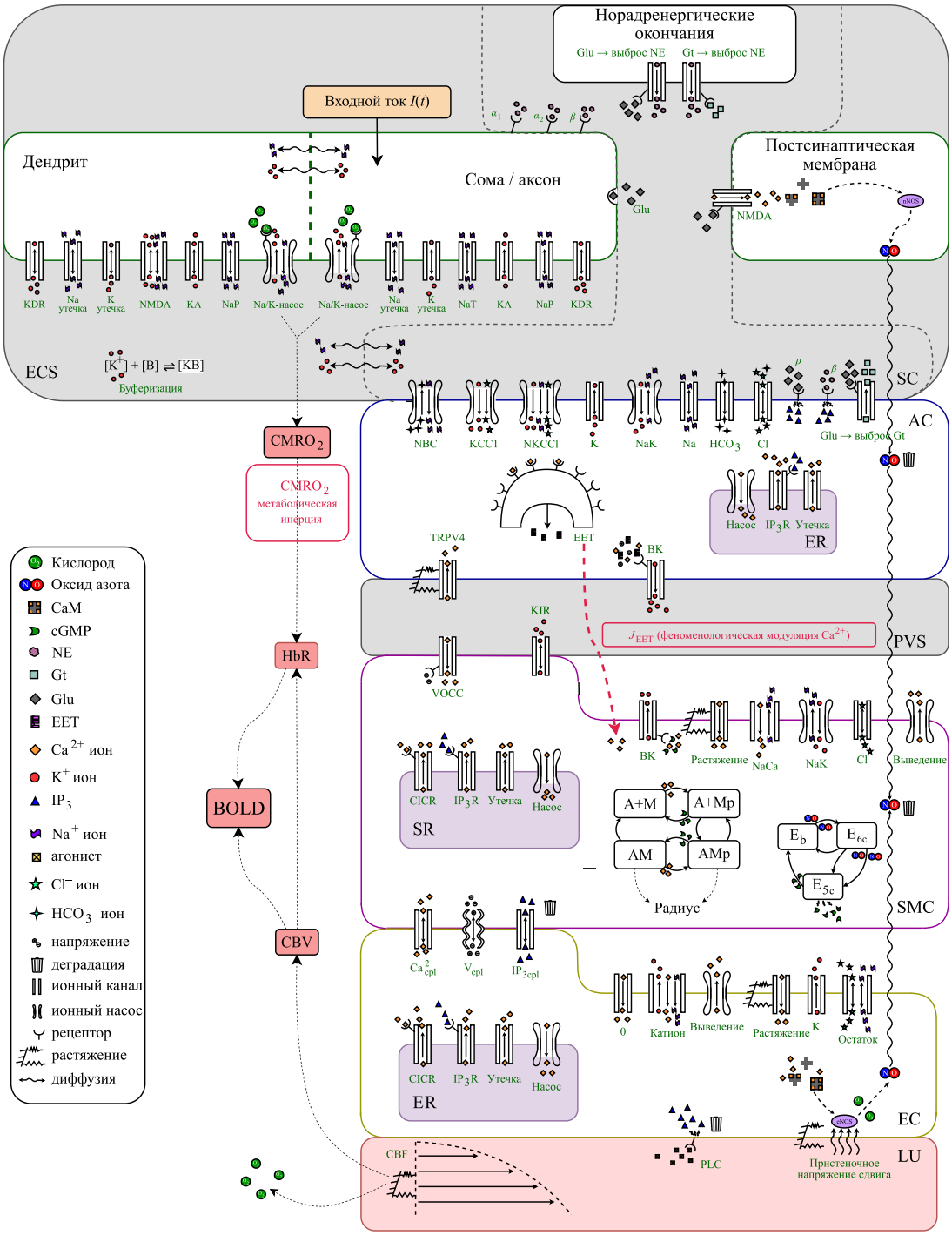


Figure 1: Schematic of the neurogliovascular unit model. Neuronal activation drives potassium and glutamate release; astrocytic calcium triggers EET and BK-channel pathways; smooth muscle cell electrophysiology and crossbridge dynamics control vessel radius; the resulting cerebral blood flow drives the balloon model that produces BOLD.

- **Ion fluxes:** Neuronal activity releases K^+ to the extracellular space; astrocytes buffer K^+ via uptake and spatial redistribution to the perivascular space; perivascular K^+ hyperpolarises smooth muscle.
- **Metabolic coupling:** Neuronal oxygen consumption drives the hemodynamic response. In this work an additional first-order metabolic-inertia filter ($CMRO_{2,n}$) was introduced to decouple instantaneous neuronal demand from the smoother vascular metabolic signal that feeds the balloon model.
- **Vasoactive signalling:** Multiple parallel pathways regulate vessel diameter: (1) K^+-mediated hyperpolarisation through KIR channels (with conductance $F_{KIR,i}$ doubled in this work), (2) astrocytic EET release (a phenomenological coupling term added in this work to provide sustained dilation), (3) NO diffusion from neurons and endothelium, (4) myogenic tone, and (5) wall shear stress sensing by endothelium.
- **Ca^{2+} signalling:** IP_3-mediated Ca^{2+} release in astrocytes and endothelium; voltage-operated Ca^{2+} entry in neurons, astrocytes, and smooth muscle; calcium-induced calcium release in smooth muscle and endothelium.
- **Mechanics:** The Hai–Murphy four-state crossbridge model converts SMC calcium into actin/myosin engagement; the crossbridge time scale was accelerated ($w_{Mech} = 3.2$) to reproduce a canonical BOLD overshoot.
- **Volume regulation:** Osmotic gradients from ion redistribution drive water movement and volume changes in neurons, astrocytes, and the extracellular space.
- **Neuromodulation:** Norepinephrine modulates astrocytic IP_3 production via α_1-adrenergic receptors, affecting Ca^{2+} signalling and downstream vasoactive responses.

3 Complete ODE System

Table 1 lists every ordinary differential equation in the model, with the variable, the right-hand side, and the initial value used for the steady-state baseline. The table is auto-generated from the Python source (see Sec. 5) and has been checked against it.

Table 1: Complete list of differential equations in the NVU model

No.	Variable	Equation	Initial Value
Neuron			
1	CBV	$\frac{dCBV}{dt} = \frac{\frac{CBF}{CBF_{init}} - CBV^{\frac{1}{d}}}{\tau_{MTT} + \tau_{TAT}}$	1.3167 -
2	HbR	$\frac{dHbR}{dt} = \frac{cmro_{2forhbr} - \frac{HbRf_{out}}{CBV}}{\tau_{MTT}}$	0.6665 -
3	v_{sa}	$\frac{dv_{sa}}{dt} = \frac{-J_{totsa} + input_{current} + \frac{v_d - v_{sa}}{2Radhod^2}}{Cm}$	-70.0337 mV
4	v_d	$\frac{dv_d}{dt} = \frac{-J_{totd} + input_{currentdendrite} + \frac{-v_d + v_{sa}}{2Radhod^2}}{Cm}$	-70.0195 mV
5	K_{sa}	$\frac{dK_{sa}}{dt} = -\frac{AsJ_{Ktotsa}10^{12}}{Faradvolume_{sa}} + \frac{D_K 10^{12}\,(K_d - K_{sa})\left(Vd + \frac{volume_{sa}}{10^{12}}\right)}{2dhod^2 volume_{sa}}$	134.186 mM
6	Na_{sa}	$\frac{dNa_{sa}}{dt} = -\frac{AsJ_{Natotsa}10^{12}}{Faradvolume_{sa}} + \frac{D_{Na}10^{12}\,(Na_d - Na_{sa})\left(Vd + \frac{volume_{sa}}{10^{12}}\right)}{2dhod^2 volume_{sa}}$	9.2691 mM
7	K_d	$\frac{dK_d}{dt} = -\frac{AdJ_{Ktotd}}{FaradVd} + \frac{D_K\,(-K_d + K_{sa})\left(Vd + \frac{volume_{sa}}{10^{12}}\right)}{2Vddhod^2}$	134.42 mM
8	Na_d	$\frac{dNa_d}{dt} = -\frac{AdJ_{Natotd}}{FaradVd} + \frac{D_{Na}\,(-Na_d + Na_{sa})\left(Vd + \frac{volume_{sa}}{10^{12}}\right)}{2Vddhod^2}$	9.3203 mM
9	K_e	$\frac{dK_e}{dt} = dKedt$	3.493 mM
10	Na_e	$\frac{dNa_e}{dt} = flu_{diffNa} + \frac{\frac{AdJ_{Natotd}}{Vd} + \frac{AsJ_{Natotsa}10^{12}}{volume_{sa}}}{Faradecs_{tosomaanddendratio}}$	150 mM

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No.	Variable	Equation	Initial Value
11	$Buff_e$	$\frac{dBuff_e}{dt} = dBuff_e$	165.981 mM
12	$O2$	$\frac{dO2}{dt} = -J_{O2background} - J_{O2pump} + J_{O2vascular}$	0.0281 mM
13	$m1$	$\frac{dm1}{dt} = -1000 m_1 m1beta + 1000 m1alpha\,(1 - m_1)$	0.01281 -
14	$m2$	$\frac{dm2}{dt} = -1000 m_2 m2beta + 1000 m2alpha\,(1 - m_2)$	0.001209 -
15	$m3$	$\frac{dm3}{dt} = -1000 m_3 m3beta + 1000 m3alpha\,(1 - m_3)$	0.119 -
16	$m4$	$\frac{dm4}{dt} = -1000 m_4 m4beta + 1000 m4alpha\,(1 - m_4)$	0.01284 -
17	$m5$	$\frac{dm5}{dt} = -1000 m_5 m5beta + 1000 m5alpha\,(1 - m_5)$	0.000869 -
18	$m6$	$\frac{dm6}{dt} = -1000 m_6 m6beta + 1000 m6alpha\,(1 - m_6)$	0.001213 -
19	$m7$	$\frac{dm7}{dt} = -1000 m_7 m7beta + 1000 m7alpha\,(1 - m_7)$	0.1191 -
20	$m8$	$\frac{dm8}{dt} = -1000 m_8 m8beta + 1000 m8alpha\,(1 - m_8)$	0.004962 -
21	$h1$	$\frac{dh1}{dt} = -1000 h_1 h1beta + 1000 h1alpha\,(1 - h_1)$	0.9718 -
22	$h2$	$\frac{dh2}{dt} = -1000 h_2 h2beta + 1000 h2alpha\,(1 - h_2)$	0.1214 -
23	$h3$	$\frac{dh3}{dt} = -1000 h_3 h3beta + 1000 h3alpha\,(1 - h_3)$	0.9718 -
24	$h4$	$\frac{dh4}{dt} = -1000 h_4 h4beta + 1000 h4alpha\,(1 - h_4)$	0.9899 -

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No.	Variable	Equation	Initial Value
25	$h5$	$\frac{dh5}{dt} = -1000h_5h5beta + 1000h5alpha\,(1-h_5)$	0.121 -
26	$h6$	$\frac{dh6}{dt} = -1000h_6h6beta + 1000h6alpha\,(1-h_6)$	0.9961 -
27	Ca_n	$\frac{dCa_n}{dt} = \frac{-k_{ex}\,(Ca_n - Ca_{rest}) + \frac{I_{Catot}}{2FV_{spine}}}{\lambda_{buf}+1}$	0.1 μM
28	$nNOS_{act_n}$	$\frac{dnNOS_{act_n}}{dt} = \frac{CaMV_{maxNOS}}{CaM + K_{actNOS}} - \mu_{2n}nNOS_{actn}$	0.318 μM
29	NO_n	$\frac{dNO_n}{dt} = -c_{NOn} + d_{NOn} + p_{NOn}$	0.1671 μM
30	$volume_{sa}$	$\frac{dvolume_{sa}}{dt} = \frac{-volume_{sa} + volume_{saeq}}{\tau_{volumechangesa}}$	2160 μM**3
31	$CMRO2_n$	$\frac{dCMRO2_n}{dt} = \frac{-CMRO_{2n} + cmro_{2ratio}}{\tau_{eff}}$	1 -
Astrocyte			
32	Na_k	$\frac{dNa_k}{dt} = J_{NBCk} + J_{NKCC1k} - 3J_{NaCak} - 3J_{NaKk} - J_{Nak} + flu_{gapNa}$	18268 μM
33	K_k	$\frac{dK_k}{dt} = -J_{BKk} + J_{KCC1k} - J_{KIRk} - J_{Kk} + J_{NKCC1k} + 2J_{NaKk} + flu_{gapK}$	92708 μM
34	$HCO3_k$	$\frac{dHCO3_k}{dt} = 2J_{NBCk} + flu_{gapHCO3}$	9131 μM
35	Cl_k	$\frac{dCl_k}{dt} = 2dCa_{kdt} - dHCO_{3kdt} + dK_{kdt} + dNa_{kdt}$	7733 μM
36	Na_s	$\frac{dNa_s}{dt} = J_{NaNEtoSCk} + \frac{-J_{NBCk} - J_{NKCC1k} + 3J_{NaKk} + J_{Nak}}{VR_{sa}}$	150255 μM
37	K_s	$\frac{dK_s}{dt} = J_{KNEtoSCk} + \frac{-J_{KCC1k} + J_{KIRk} + J_{Kk} - J_{NKCC1k} - 2J_{NaKk}}{VR_{sa}}$	2837 μM

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No.	Variable	Equation	Initial Value
38	$HCO3_s$	$\frac{dHCO3_s}{dt} = -\frac{2J_{NBCk}}{VR_{sa}}$	16881 μM
39	K_p	$\frac{dK_p}{dt} = \frac{J_{BKk}}{VR_{pa}} + \frac{J_{KIRi}}{VR_{ps}} - R_{decay}\left(K_p - K_{pmin}\right)$	3045.1 μM
40	w_k	$\frac{dw_k}{dt} = \phi_w\left(w_{inf} - w_k\right)$	0.0001703 -
41	Ca_k	$\frac{dCa_k}{dt} = B_{cyt}\left(J_{ERleak} + J_{IP3} + J_{NaCak} + \frac{J_{TRPVk}}{r_{buff}} - J_{VOCCk} - J_{pump} + flu_{gapCa}\right)$	0.1612 μM
42	s_k	$\frac{ds_k}{dt} = -\frac{B_{cyt}\left(J_{ERleak} + J_{IP3} - J_{pump}\right)}{VR_{ERcyt}}$	480.8 μM
43	h_k	$\frac{dh_k}{dt} = k_{on}\left(K_{inh} - h_k\left(Ca_k + K_{inh}\right)\right)$	0.3828 -
44	I_k	$\frac{dI_k}{dt} = -I_k k_{deg} + r_h\left(G + G_{noradrenaline}\right)$	0.048299 μM
45	eet_k	$\frac{deet_k}{dt} = V_{eet}\max\left(0, Ca_k - Ca_{kmin}\right) - eet_k k_{eet}$	0.6123 μM
46	m_k	$\frac{dm_k}{dt} = \frac{trpv_{switch}\left(-m_k + minf_k\right)}{t_{TRPVk}}$	0.571 -
47	Ca_p	$\frac{dCa_p}{dt} = -Ca_{decayk}\left(Ca_p - Capmin_k\right) + \frac{J_{VOCCi}}{VR_{ps}} + \frac{-J_{TRPVk} + J_{VOCCk}}{VR_{pa}}$	1746.4 μM
48	NO_k	$\frac{dNO_k}{dt} = -c_{NOk} + d_{NOk} + p_{NOk}$	0.1106 μM
49	v_k	$\frac{dv_k}{dt} = \gamma_i\left(-J_{BKk} - J_{Clk} - J_{Kk} - J_{NBCk} - J_{NaKk} - J_{Nak} + 2J_{TRPVk} + 2flu_{gapCa} - flu_{gapCl} - flu_{gapHCO3} + flu_{gapK} + flu_{gapNa}\right)$	-88.9 mV
50	$volume_k$	$\frac{dvolume_k}{dt} = \frac{-volume_k + volume_{keq}}{\tau_{volumechangek}}$	2160 μm**3

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No.	Variable	Equation	Initial Value
51	$volume_p$	$\frac{dvolume_p}{dt} = \frac{-volume_p + volume_{peq}}{\tau_{volumechangep}}$	2.16 μm**3
52	Gt	$\frac{dGt}{dt} = Gt_{diff} + \frac{SVR_{AVF} k_{gt}}{1 + \frac{k_m^2}{Ca_k^2}} - \frac{-GT_{amb} + Gt}{\tau_{GT}}$	0 mM
53	$Norepinephrine_s$	$\frac{dNorepinephrine_s}{dt} = J_{NA} + NA_{diff} + \frac{NA_{amb} - Norepinephrine_s}{\tau_{NA}}$	0 mM
SMCEC			
54	Ca_i	$\frac{dCa_i}{dt} = J_{CICRi} + J_{Cacoupi} - J_{EETi} + J_{IP3i} + J_{NaCai} + J_{SRleaki} - J_{SRuptakei} - J_{VOCCi} - J_{extrusioni} - 0.1 J_{stretchi}$	0.2637 μM
55	s_i	$\frac{ds_i}{dt} = -J_{CICRi} - J_{SRleaki} + J_{SRuptakei}$	1.1686 μM
56	v_i	$\frac{dv_i}{dt} = V_{coupi} + \gamma_i \left(-J_{Cli} - J_{KIRi} - J_{Ki} - J_{NaCai} - J_{NaKi} - 2J_{VOCCi} - J_{stretchi}\right)$	-34.7 mV
57	w_i	$\frac{dw_i}{dt} = \lambda_i \left(K_{acti} - w_i\right)$	0.2206 -
58	I_i	$\frac{dI_i}{dt} = J_{IP3coupi} - J_{degradi}$	0.275 μM
59	K_i	$\frac{dK_i}{dt} = -J_{KIRi} - J_{Ki} + J_{NaKi}$	99994.8 μM
60	NO_i	$\frac{dNO_i}{dt} = -c_{NOi} + d_{NOi} + p_{NOi}$	0.0541 μM
61	E_b	$\frac{dE_b}{dt} = E_{5c} k_4 + E_{6c} k_1 - E_b NO_i k_1$	0.4077 -
62	E_{6c}	$\frac{dE_{6c}}{dt} = -E_{6c} NO_i k_3 - E_{6c} \left(k_2 + k_1\right) + E_b NO_i k_1$	0.4396 -
63	$cGMP_i$	$\frac{dcGMP_i}{dt} = E_{5c} V_{maxsGC} - \frac{V_{maxpde} cGMP_i}{K_{mpde} + cGMP_i}$	8.2826 μM

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No.	Variable	Equation	Initial Value
64	Ca_j	$\frac{dCa_j}{dt} = J_{0j} + J_{CICRj} - J_{Cacoupi} + J_{ERleakj} - J_{ERuptakej} + J_{IP3j} + J_{cationj} - J_{extrusionj} - J_{stretchj}$	0.8331 μM
65	s_j	$\frac{ds_j}{dt} = -J_{CICRj} - J_{ERleakj} + J_{ERuptakej}$	0.6266 μM
66	v_j	$\frac{dv_j}{dt} = -V_{coupi} - \frac{J_{Kj} + J_{Rj}}{C_{mj}}$	-68.27 mV
67	I_j	$\frac{dI_j}{dt} = -J_{IP3coupi} + J_{PLC} - J_{degradj}$	0.825 μM
68	$eNOS_{act_j}$	$\frac{deNOS_{act_j}}{dt} = Act_{eNOSCa} gam_{eNOS} + Act_{eNOSwss} (1 - gam_{eNOS}) - eNOS_{actj} \mu_{2j}$	0.4479 μM
69	NO_j	$\frac{dNO_j}{dt} = -c_{NOj} + d_{NOj} + p_{NOj}$	0.0528 μM
WallMechanics			
70	Mp	$\frac{dMp}{dt} = wallMech\,(AMpK_4 + K_1M - Mp\,(K_2 + K_3))$	0.0842 -
71	AMp	$\frac{dAMp}{dt} = wallMech\,(AMK_6 - AMp\,(K_4 + K_5) + K_3Mp)$	0.0622 -
72	AM	$\frac{dAM}{dt} = wallMech\,(-AM\,(K_6 + K_7) + AMpK_5)$	0.2746 -
73	R	$\frac{dR}{dt} = \frac{R_{0passive}\left(-\frac{E(R-R_0)}{R_0} + \frac{Rtrans_p}{h}\right)}{\eta}$	2.297e-05 m

4 Detailed Model Specification

This section provides the complete specification of every model parameter, initial condition, and equation, sliced by component. The 73 ODEs and the ∼300 parameters are auto-extracted from the Python source.

Each subsystem below provides:

- Initial conditions table – all dynamic variables with values, units, and descriptions
- Parameters table – all constants and parameters with values, units, and descriptions

4.1 Neuron and Extracellular Space

Neuron and ECS initial conditions:

Table 2: Neuron and ECS initial conditions

Parameter	Value	Unit	Description
CBV	1.3167	–	Cerebral blood volume
HbR	0.6665	–	Deoxyhemoglobin (HbR) concentration
v_{sa}	-70.0337	mV	membrane potential of soma/axon
v_d	-70.0195	mV	membrane potential of dendrite
K_{sa}	134.1858	mM	K+ concentration of soma/axon
Na_{sa}	9.2691	mM	Na+ concentration of soma/axon
K_d	134.4198	mM	K+ concentration of dendrite
Na_d	9.3203	mM	Na+ concentration of dendrite
K_e	3.493	mM	K+ concentration of ECS
Na_e	150	mM	Na+ concentration of ECS
$Buff_e$	165.9812	mM	Buffer concentration for K+ buffering in ECS
$O2$	0.0281	mM	Tissue oxygen concentration
$m1$	0.01281	–	Activation gating variable, soma/axon NaP channel (Na+)
$m2$	0.001209	–	Activation gating variable, soma/axon KDR channel (K+)
$m3$	0.1190	–	Activation gating variable, soma/axon KA channel (K+)
$m4$	0.01284	–	Activation gating variable, dendrite NaP channel (Na+)
$m5$	0.000869	–	Activation gating variable, dendrite NMDA channel (Na+)
$m6$	0.001213	–	Activation gating variable, dendrite KDR channel (K+)
$m7$	0.1191	–	Activation gating variable, dendrite KA channel (K+)
$m8$	0.004962	–	Activation gating variable, soma/axon NaT channel (Na+)
$h1$	0.9718	–	Inactivation gating variable, soma/axon NaP channel (Na+)

$h2$	0.1214	–	Inactivation gating variable, soma/axon KA channel (K+)
$h3$	0.9718	–	Inactivation gating variable, dendrite NaP channel (Na+)
$h4$	0.9899	–	Inactivation gating variable, dendrite NMDA channel (Na+)
$h5$	0.1210	–	Inactivation gating variable, dendrite KA channel (K+)
$h6$	0.9961	–	Inactivation gating variable, soma/axon NaT channel (Na+)
Ca_n	0.1	μM	Ca2+ concentration in the neuron
$nNOS_{act\,n}$	0.318	μM	Activated neuronal NO synthase (nNOS)
NO_n	0.1671	μM	NO concentration in the neuron
$volume_{sa}$	2160	$\mu M**3$	Volume of the neuron
$CMRO2_n$	1.0	–	Normalized CMRO2 with metabolic inertia (1.0 = equilibrium)

Neuron and ECS parameters:

Table 3: Neuron and ECS initial conditions

Parameter	Value	Unit	Description
$start_{pulse}$	100	s	Start time of input current
end_{pulse}	120	s	The end of input current
$CurrentType$	1	–	Type of current input. 1: normal, 2: two stimulations, 3: obtained from data, 4: data + LC pain pathway
$GluSwitch$	1	–	Turn on glutamate input (for NO and Ca2+ pathways)
$NOswitch$	1	–	Turn on Nitric Oxide production
$O2switch$	1	–	0: ATP is plentiful, 1: ATP is limited (oxygen-limited regime, default)
Glu_{max}	1846	μM	Maximum glutamate concentration, Santucci2008
Glu_{slope}	0.1	mM	Slope of glutamate sigmoidal (M.E.)
Ke_{switch}	5.5	mM	Threshold past which glutamate vesicle is released (M.E.)
$Istrength$	0.022	$mAcm**-2$	Max strength of current input to soma-axon
$Istrength_{dendrite}$	0.0	$mAcm**-2$	Max strength of current input to dendrite (default 0 for backward compatibility)

SC_{coup}	11.5	–	Coupling scaling factor, values can range between 1.06 to 14.95 according to estimation from experimental data of Ventura and Harris, Maximum dilation at 9.5
tau_{MTT}	3	s	Mean transit time
tau_{TAT}	20	s	Transient adjustment time constant
d	0.4	–	Empirical relation between CBF and CBV
a_1	3.4	–	Weight for HbR change (Buxton)
a_2	1	–	Weight for CBV change
V_0	0.03	–	Resting venous blood volume fraction
E_0	0.4	–	Baseline oxygen extraction fraction
tau_{CMRO2}	0	s	Metabolic inertia time constant (0 = disabled, instantaneous CMRO2)
$tau_{CMRO2\,rise}$	0	s	CMRO2 rise time constant (0 = use tau_CMRO2 for both directions)
$use_{buxton\,balloon}$	False	–	Use pure Buxton 1998 balloon model instead of Kenny formula
F	9.65e4	$Cmol**-1$	Faraday's constant
R_{gas}	8.315	$Jmol**-1K**-1$	Gas constant
T	300	K	Temperature
$lengtht1$	10	s	Duration for t_1 calculation (time offset from t_0)
$E_{Cl\,sa}$	-70	mV	Nernst potential for Cl- in soma
$E_{Cl\,d}$	-70	mV	Nernst potential for Cl- in dendrite
Ra	1.83e5	$ohms$	Input resistance of dendritic tree
$dhod$	4.5e-2	cm	Half length of dendrite
As	1.586e-5	$cm**2$	Surface area of soma/axon
Ad	2.6732e-4	$cm2$	Surface area of dendrite
Vs	2.16e-9	$cm3$	Volume of soma
Vd	5.614e-9	$cm3$	Volume of dendrite
fe	0.15	–	ECS to neuron ratio
Cm	7.5e-7	$scm**-2/ohms$	Membrane capacitance
$Farad$	96.485	$C/mmol$	Faraday constant
ph	26.6995	$mV?$	RT/F
Mu	8e-4	m/s	Buffer rate
$B0$	500	mM	Effective total buffer concentration
$gNaP_{GHk}$	2e-6	–	NaP channel conductance
$gKDR_{GHk}$	10e-5	–	KDR channel conductance

gKA_{GHk}	1e-5	–	KA channel conductance
$gNMDA_{GHk}$	1e-5	–	NMDA channel conductance
$gNaT_{GHk}$	10e-5	–	NaT channel conductance
$gNaleak_{sa}$	6.2378e-5	$Scm**-2$	Conductance of Na+ leak channel on soma/axon
$gKleak_{sa}$	2.1989e-4	$Scm**-2$	Conductance of K+ leak channel on soma/axon
$gleak_{sa}$	6.2378e-4	$Scm**-2$	Conductance of general leak channel on soma/axon
$gNaleak_{d}$	6.2961e-5	$Scm**-2$	Conductance of Na+ leak channel on dendrite
$gKleak_{d}$	2.1987e-4	$Scm**-2$	Conductance of K+ leak channel on dendrite
$gleak_{d}$	6.2961e-4	$Scm**-2$	Conductance of general leak channel on dendrite
$Imax$	0.078	$mAcm**-2$	0.013 6, Maximum rate of Na+/K+ ATP-ase pump
$O2_0$	0.02	mM	Equilibrium tissue oxygen level
$alpha_{O2}$	0.05	–	percentage of ATP production independent of O2
D_{Na}	1.33e-5	$cm**2/s$	Intracellular diffusion rate of Na+
D_K	1.96e-5	$cm**2/s$	Intracellular diffusion rate of K+
$K_{init\ e}$	2.9	mM	Equilibrium K_e
$Na_{init\ sa}$	10	mM	Equilibrium Na_sa
$Na_{init\ d}$	10	mM	Equilibrium Na_d
R_{init}	1.9341e-5	m	Vessel radius when passive and no stress is applied
CBF_{init}	3.2e-2	–	Steady state CBF
$O2_b$	4e-2	mM	Blood oxygen level
$gamma_{O2}$	0.10	–	Fraction of the total oxygen consumption at steady state
Mg	1.2	$mML**-1$	Equilibrium magnesium
$J_{0\,CBF}$	0.032	$mMs**-1$	Equilibrium change in oxygen concentration due to CBF
m_c	4	–	Number of Ca2+ bound per calmodulin (approximated as parameter, originally an algebraic variable that changed from 3.999 to 4)
K_{mA}	650	μM	Michaelis constant - fit to Santucci2008
K_{mB}	2800	μM	Michaelis constant - fit to Santucci2008
v_n	-0.04	V	the neuronal membrane potential, assumed to be approximately constant in this model
G_M	46000	fS	Conductance of NMDA receptor (was 46 pS)

$P_{Ca\,P\,M}$	3.6	$-$	The relative conductance of the NMDA channel to Ca2+ compared to monovalent ions (Ratio of Ca2+ permeability to monovalent ion permeability)
Ca_{ex}	2e3	μM	External Ca2+ concentration (in Comerford and David2008: 1.5 mM!)
M	1.3e5	μM	The concentration of monovalent ions in the neuron
n_{NR2A}	0.63	$-$	Average number of NR2A NMDA receptors per synapse (Santucci2008)
n_{NR2B}	11	$-$	Average number of NR2B NMDA receptors per synapse (Santucci2008)
$V_{max\,NO\,n}$	4.22	$s**-1$	Maximum catalytic rate of neuronal NO production (Chen2006) - obtained from fig 6 and equ 17 and 18
$O2_n$	200	μM	O2 concentration in the neuron (M.E.)
$K_{mO2\,n}$	243	μM	Michaelis constant for NNOS for LArg (Chen2006)
$LArg_n$	100	μM	L-Arg concentration in the neuron
$K_{mArg\,n}$	1.5	μM	Michaelis constant for nNOS for O2
$k_{O2\,n}$	9.6e-6	$\mu M**-2s**-1$	O2 reaction rate constant (Kavdia2002)
x_{nk}	25	μM	Distance between centers of neuron and astrocyte
D_{cNO}	3300	$\mu M**2s**-1$	Diffusion coefficient NO (Malinski1993)
V_{spine}	8e-8	nL	Volume of the neuronal dendritic spine Santucci2008
k_{ex}	1600	$s**-1$	Decay rate constant of internal Ca2+ concentration Santucci2008
Ca_{rest}	0.1	μM	Resting calcium concentration (in Comerford and David2008: 2.830 mM in Santucci2008P: 0.1 μM)
$lambda_{buf}$	20	$-$	Buffer capacity Santucci2008
V_{maxNOS}	25e-3	$\mu M s**-1$	Maximum nNOS activation rate
K_{actNOS}	9.27e-2	μM	Michaelis constant
$mu2_n$	0.0167	$s**-1$	Rate constant at which the nNOS is deactivated Comerford2008
dt	0.001	s	
Cl_e	124.7	mM	, from Ullah

$impermeants_e$	57507	$mM * \mu m * *3$	, from Ullah
$tau_{volume\ change\ sa}$	15	–	Rate controlling the speed of convergence towards equilibrium volume
$Cl_{sa\ ions}$	21816	$mM * \mu m * *3$	Cl_i 2160, where Cl_i = 10.1 mM, from Ullah
$impermeants_{sa}$	440500	$mM * \mu m * *3$	(Ullah)
$gaussian_{current\ mean}$	0	$mAcm**-2$	Mean of Gaussian noise current
$gaussian_{current\ variation}$	0	$mAcm**-2$	Standard deviation of Gaussian noise current
$gaussian_{current\ variations\ per\ second}$	0	Hz	Number of current variations per second
NA_{rest}	0	μM	Resting norepinephrine concentration
$neuron_{NE\ alpha1\ interaction}$	1	–	Interaction term for alpha1 receptor
$neuron_{NE\ alpha2\ interaction}$	1	–	Interaction term for alpha2 receptor
$neuron_{NE\ beta\ interaction}$	1	–	Interaction term for beta receptor
$do_{stop\ current\ by\ K\ e\ level}$	False	–	Stop current when K_e reaches a certain level
$stop_{current\ by\ K\ e\ level}$	5.5	mM	Stop current when K_e reaches this level. Works only if do_stop_current_by_K_e_level is True
$stim_{index}$	1	–	Experimental stimulus duration index (value 1 for 8-s stimulus from options 2, 8, 16)
isi_{index}	6	–	Experimental ISI index (value 6 for 8-s ISI from options 0.6, 1, 2, 3, 4, 6, 8)

Neuron and ECS parameters post-initialization

$lengthpulse = end_{pulse} - start_{pulse}$ **[s]**
$t_0 = start_{pulse}$
$t_1 = t_0 + lengtht1$
$t_2 = t_0 + lengthpulse$
$t_3 = t_1 + lengthpulse$

Neuron and ECS equations

Nernst potential for Na,K ions in soma and dendrite (Cl constant) [mV]
$E_{Na\ sa} = ph * log(Na_e/Na_{sa})$
$E_{K\ sa} = ph * log(K_e/K_{sa})$

$E_{Na\,d} = ph * log(Na_e/Na_d)$
$E_{K\,d} = ph * log(K_e/K_d)$

Ion fluxes

Leak fluxes of Na,K,Cl in soma/axon or dendrite using HH [mA cm-2]**
$J_{Naleak\,sa} = gNaleak_{sa} * (v_{sa} - E_{Na\,sa})$
$J_{Kleak\,sa} = gKleak_{sa} * (v_{sa} - E_{K\,sa})$
$J_{Naleak\,d} = gNaleak_d * (v_d - E_{Na\,d})$
$J_{Kleak\,d} = gKleak_d * (v_d - E_{K\,d})$

Na flux through NaP channel in soma using GHK

Rate functions for the activation m and deactivation h gating variables [ms-1]**
$m1alpha = 1/(6 * (1 + exp(-((0.143 * v_{sa}) + 5.67))))$
$m1beta = exp(-((0.143 * v_{sa}) + 5.67))/(6 * (1 + exp(-((0.143 * v_{sa}) + 5.67))))$
$h1alpha = 5.12e - 8 * exp(-((0.056 * v_{sa}) + 2.94))$
$h1beta = 1.6e - 6/(1 + exp(-(((0.2 * v_{sa})) + 8)))$
Na+ current through NaP channel in soma/axon [mA cm-2]**
$J_{NaP\,sa} = (m1 * *2 * h1 * gNaP_{GHk} * Farad * v_{sa} * (Na_{sa} - (exp(-v_{sa}/ph) * Na_e)))/(ph * (1 - exp(-v_{sa}/ph)))$

Na+ flux through NaT channel in soma using GHK

$m8alpha = 0.32 * ((-v_{sa} - 51.9)/(exp(-(0.25 * v_{sa} + 12.975)) - 1))$
$m8beta = 0.28 * ((v_{sa} + 24.89)/(exp(0.2 * v_{sa} + 4.978) - 1))$
$h6alpha = 0.128 * exp(-(0.056 * v_{sa} + 2.94))$
$h6beta = 4/(1 + exp(-(0.2 * v_{sa} + 6)))$
Na+ current through NaT channel in soma/axon [mA cm-2]**
$J_{NaT\,sa} = (m8 * *3 * h6 * gNaT_{GHk} * Farad * v_{sa} * (Na_{sa} - (exp(-v_{sa}/ph) * Na_e)))/(ph * (1 - exp(-v_{sa}/ph)))$

K+ flux through KDR channel in soma using GHK

$m2alpha = 0.016 * ((v_{sa} + 34.9)/(1 - exp(-((0.2 * v_{sa}) + 6.98))))$
$m2beta = 0.25 * exp(-((0.025 * v_{sa}) + 1.25))$
K+ current through KDR channel in the soma/axon [mA cm-2]**
$J_{KDR\,sa} = (m2 * *2 * gKDR_{GHk} * Farad * v_{sa} * (K_{sa} - (exp(-v_{sa}/ph) * K_e)))/(ph * (1 - exp(-v_{sa}/ph)))$

K+ flux through KA channel in soma using GHKinput_current

$m3alpha = 0.02 * ((v_{sa} + 56.9)/(1 - exp(-((0.1 * v_{sa}) + 5.69))))$
$m3beta = 0.0175 * ((v_{sa} + 29.9)/(exp(((0.1 * v_{sa}) + 2.99)) - 1))$
$h2alpha = 0.016 * exp(-((0.056 * v_{sa}) + 4.61))$
$h2beta = 0.5/(1 + exp(-((0.2 * v_{sa}) + 11.98)))$
K+ current through KA channel in the soma/axon [mA cm-2]**
$J_{KA\,sa} = (m3 * *2 * h2 * gKA_{GHk} * Farad * v_{sa} * (K_{sa} - (exp(-v_{sa}/ph) * K_e)))/(ph * (1 - exp(-v_{sa}/ph)))$

Na+ flux through NaP channel in dendrite using GHK

$m4alpha = 1/(6 * (1 + exp(-((0.143 * v_d) + 5.67))))$
$m4beta = exp(-((0.143 * v_d) + 5.67))/(6 * (1 + exp(-((0.143 * v_d) + 5.67))))$
$h3alpha = 5.12e - 8 * exp(-((0.056 * v_d) + 2.94))$
$h3beta = 1.6e - 6/(1 + exp(-(((0.2 * v_d)) + 8)))$
Na+ current through NDA channel in dendrite [mA cm-2]**
$J_{NaP\,d} = (m4 * *2 * h3 * gNaP_{GHk} * Farad * v_d * (Na_d - (exp(-v_d/ph) * Na_e)))/(ph * (1 - exp(-v_d/ph)))$

Na+/K+ flux through NMDA channel in dendrite using GHK

$m5alpha = 0.5/(1 + exp((13.5 - K_e)/1.42))$
$m5beta = 0.5 - m5alpha$
$h4alpha = 1/(2000 * (1 + exp((K_e - 6.75)/0.71)))$
$h4beta = 5e - 4 - h4alpha$
K+ current through N-methyl-D-aspartate (NMDA) channel in the dendrite [mA cm-2]**
$J_{NMDA\,K\,d} = ((m5 * h4 * gNMDA_{GHk} * Farad * v_d * (K_d - (exp(-v_d/ph) * K_e)))/(ph * (1 - exp(-v_d/ph))))/(1 + 0.33 * Mg * exp(-(0.07 * v_d + 0.7)))$
$J_{NMDA\,Na\,d} = ((m5 * h4 * gNMDA_{GHk} * Farad * v_d * (Na_d - (exp(-v_d/ph) * Na_e)))/(ph * (1 - exp(-v_d/ph))))/(1 + 0.33 * Mg * exp(-(0.07 * v_d + 0.7)))$

K+ flux through KDR channel in dendrite using GHK

$m6alpha = 0.016 * ((v_d + 34.9)/(1 - exp(-((0.2 * v_d) + 6.98))))$
$m6beta = 0.25 * exp(-((0.025 * v_d) + 1.25))$
K+ current through KDR channel in the dendrite [mA cm-2]**
$J_{KDR\,d} = (m6 * *2 * gKDR_{GHk} * Farad * v_d * (K_d - (exp(-v_d/ph) * K_e)))/(ph * (1 - exp(-v_d/ph)))$

K+ flux through KA channel in dendrite using GHK

$m7alpha = 0.02 * ((v_d + 56.9)/(1 - exp(-((0.1 * v_d) + 5.69))))$
$m7beta = 0.0175 * ((v_d + 29.9)/(exp(((0.1 * v_d) + 2.99)) - 1))$

$h5alpha = 0.016 * exp(-((0.056 * v_d) + 4.61))$
$h5beta = 0.5/(1 + exp(-((0.2 * v_d) + 11.98)))$
K+ current through KA channel in the dendrite [mA cm-2]**
$J_{KA\,d} = (m7**2*h5*gKA_{GHk}*Farad*v_d*(K_d-(exp(-v_d/ph)*K_e)))/(ph*(1-exp(-v_d/ph)))$

Oxygen independent term of the ATP-ase pump in both the soma/axon or dendrite (flux through the NaK-ATPase pump) [-]
$J_{pump1\,sa} = (1 + (K_{init\,e}/K_e)) * *(-2) * (1 + (Na_{init\,sa}/Na_{sa})) * *(-3)$
Steady state pump rate in the soma/axon [-]
$J_{pump1init\,sa} = 0.0312$ **(1 + (K_init_e / K_init_e))**(-2) * (1 + (Na_init_sa / Na_init_sa))**(-3)**
$J_{pump1\,d} = (1 + (K_{init\,e}/K_e)) * *(-2) * (1 + (Na_{init\,d}/Na_d)) * *(-3)$
Steady state pump rate in the dendrite [-]
$J_{pump1init\,d} = 0.0312$ **(1 + (K_init_e / K_init_e))**(-2) * (1 + (Na_init_d / Na_init_d))**(-3)**

Determine whether there is limited oxygen: O2switch=0 ATP is plentiful, O2switch=1 ATP is limited (oxygen-limited regime) [?]
$O2_p = O2_0 * (1 - O2switch) + O2 * O2switch$
Oxygen dependent term of the ATP-ase pump [-]
$J_{pump2} = 2 * (1 + O2_0/(((1 - alpha_{O2}) * O2_p) + alpha_{O2} * O2_0)) * *(-1)$

Na+/K+ ATP-ase pump flux in soma/axon or dendrite [mA cm-2]**
$J_{pump\,sa} = Imax * J_{pump1\,sa} * J_{pump2}$
$J_{pump\,d} = Imax * J_{pump1\,d} * J_{pump2}$

Na+ and K+ currents through Na+/K+ ATP-ase pump in soma axon or dendrite [mA cm-2]**
$J_{Napump\,sa} = 3 * J_{pump\,sa}$
$J_{Kpump\,sa} = -2 * J_{pump\,sa}$
$J_{Napump\,d} = 3 * J_{pump\,d}$
$J_{Kpump\,d} = -2 * J_{pump\,d}$

Total ion fluxes

Total ion fluxes in soma [mA cm-2]**
$J_{Na\,tot\,sa} = J_{NaP\,sa} + J_{Naleak\,sa} + J_{Napump\,sa} + J_{NaT\,sa}$
$J_{K\,tot\,sa} = J_{KDR\,sa} + J_{KA\,sa} + J_{Kleak\,sa} + J_{Kpump\,sa}$
General leak in the soma/axon [mA cm-2]**
$J_{leak\,tot\,sa} = gleak_{sa} * (v_{sa} - E_{Cl\,sa})$

Total ion fluxes in dendrite [mA cm-2]**
$J_{Na\,tot\,d} = J_{NaP\,d} + J_{Naleak\,d} + J_{Napump\,d} + J_{NMDA\,Na\,d}$
$J_{K\,tot\,d} = J_{KDR\,d} + J_{KA\,d} + J_{Kleak\,d} + J_{Kpump\,d} + J_{NMDA\,K\,d}$
General leak in the dendrite [mA cm-2]**
$J_{leak\,tot\,d} = gleak_d * (v_d - E_{Cl\,d})$ **leak**

Total ion fluxes in soma and dendrite [mA cm-2]**
$J_{tot\,sa} = J_{Na\,tot\,sa} + J_{K\,tot\,sa} + J_{leak\,tot\,sa}$

$J_{tot\,d} = J_{Na\,tot\,d} + J_{K\,tot\,d} + J_{leak\,tot\,d}$

Tissue oxygen

$J_{pump2\,0}$ = 0.0952 **2 * (1 + O2_0 / (((1 - alpha_O2) * 0) + alpha_O2 * O2_0))**(-1)**
$J_{pump2\,O2\,0}$ = 1 **2 * (1 + O2_0 / (((1 - alpha_O2) * O2_0) + alpha_O2 * O2_0))**(-1)**
The normalized pump rate [-]
$P_{02} = (J_{pump2} - J_{pump2\,0})/(J_{pump2\,O2\,0} - J_{pump2\,0})$
The cerebral blood flow [-]
$CBF = CBF_{init} * (R**4/R_{init}**4)$
The vascular supply of oxygen [mM s-1]**
$J_{O2\,vascular} = CBF * ((O2_b - O2)/(O2_b - O2_0))$
The background oxygen consumption [mM s-1]**
$J_{O2\,background} = CBF_{init} * P_{02} * (1 - gamma_{O2})$
The tissue oxygen consumption dur to the ATP-ase pump [mM s-1]**
$J_{O2\,pump} = CBF_{init} * P_{02} * gamma_{O2} * ((J_{pump1\,sa} + J_{pump1\,d})/(J_{pump1init\,sa} + J_{pump1init\,d}))$
The change in oxygen concentration due to cerebral blood flow (CBF) [mM s1]**
$J_{O2\,CBF} = J_{0\,CBF} * CBF/CBF_{init}$

BOLD

The time dependent outflow from the venous compartment [-]
$if\,use_{buxton\,balloon}$:
$f_{out} = CBV**(1/d)$
$else$:
$f_{out} = CBV**(1/d) + tau_{TAT} * (1/(tau_{MTT} + tau_{TAT}) * (CBF/CBF_{init} - CBV**(1/d)))$
The cerebral metabolic rate of oxygen consumption [mM s-1]**
$CMRO2 = J_{O2\,background} + J_{O2\,pump}$
The equilibrium value of CMRO2 [mM s-1]**
$CMRO2_{init} = CBF_{init} * P_{02}$
The oxygen extraction fraction [-]
$OEF = CMRO2 * E_0/CBF$
The BOLD signal change from its steady state value
$BOLD = V_0 * (a_1 * (1 - HbR) - a_2 * (1 - CBV))$

Glutamate input: vesicle released when the extracellular K+ is over 5.5 mM (Ke_switch)

Fraction of open NR2A NMDA receptors [-]
$w_{NR2A} = Glu/(K_{mA} + Glu)$
Fraction of open NR2B NMDA receptors [-]
$w_{NR2B} = Glu/(K_{mB} + Glu)$

Inward Ca2+ current per open NMDA receptor [fA]

$I_{Ca} = (-4 * v_n * G_M * P_{Ca\,P\,M} * (Ca_{ex}/M))/(1 + exp(-80 * (v_n + 0.02))) * (exp(2 * v_n * F/(R_{gas} * T)))/(1 - exp(2 * v_n * F/(R_{gas} * T)))$
Total inward Ca2+ current for all open NMDA receptors per synapse [fA]
$I_{Ca\,tot} = I_{Ca} * (n_{NR2A} * w_{NR2A} + n_{NR2B} * w_{NR2B})$

Ca2+-calmodulin complex concentration [μM]
$CaM = Ca_n/m_c$
Time for NO to diffuse between the centres of the neuron and the astrocyte [s]
$tau_{nk} = x_{nk} * *2/(2 * D_{cNO})$

Neuronal NO production flux [μM/s]
$p_{NO\,n} = NOswitch * (nNOS_{act\,n} * V_{max\,NO\,n} * O2_n/(K_{mO2\,n} + O2_n) * LArg_n/(K_{mArg\,n} + LArg_n))$
Neuronal NO consumption flux [μM/s]
$c_{NO\,n} = k_{O2\,n} * NO_n * *2 * O2_n$
Neuronal NO diffusive flux [μM/s]
$d_{NO\,n} = (NO_k - NO_n)/tau_{nk}$

ECS electrodiffusion TEST
$Delta_{K\,e} = 3.493 - K_e$
$average_{K\,e} = (3.493 + K_e)/2$
$Delta_{Na\,e} = 150 - Na_e$
$average_{Na\,e} = (150 + Na_e)/2$
$Delta_{v\,e} = -(8.315 * 300)/96.485 * (1 * 3.6e-9 * Delta_{K\,e} + 1 * 2.4e-9 * Delta_{Na\,e})/(1 * 3.6e-9 * average_{K\,e} + 1 * 2.4e-9 * average_{Na\,e})$
$flu_{diff\,Fick\,K} = (3.6e-9/(1.24e-4) * *2) * (Delta_{K\,e})$
$flu_{diff\,Fick\,Na} = (2.4e-9/(1.24e-4) * *2) * (Delta_{Na\,e})$
$flu_{diff\,el\,K} = (3.6e-9/(1.24e-4) * *2) * (((1 * 96.485)/(8.315 * 300)) * (average_{K\,e} * Delta_{v\,e}))$
$flu_{diff\,el\,Na} = (2.4e-9/(1.24e-4) * *2) * (((1 * 96.485)/(8.315 * 300)) * (average_{Na\,e} * Delta_{v\,e}))$

$flu_{diff\,K} = flu_{diff\,Fick\,K} + flu_{diff\,el\,K}$
$flu_{diff\,Na} = flu_{diff\,Fick\,Na} + flu_{diff\,el\,Na}$

Volume changes equations

Total num of ions in cells changing volume, like in Ullah's model [mM μm3]**
$n_{total\,ions} = neuron_{ions} + astrocyte_{ions} + sc_{ions} + ecs_{ions} + pvs_{ions}$
Equilibrium neuron volume [μm3]**
$volume_{sa\,eq} = total_{volume} * neuron_{ions}/n_{total\,ions}$

$input_{current} = input_{current(t)}$
$if\,do_{stop\,current\,by\,K\,e\,level} and K_e > stop_{current\,by\,K\,e\,level}:$
$input_{current} = 0$

$input_{current\,dendrite} = input_{current\,dendrite(t)}$
$if\,do_{stop\,current\,by\,K\,e\,level} and K_e > stop_{current\,by\,K\,e\,level}:$
$input_{current\,dendrite} = 0$

K_e optional injection
$K_{e\,injection} = 0$

$for injection in K_{to\ ecs\ injections}$:
$K_{e\ injection} += injection.inject_{if\ conditions\ true(current\ time=t)}$

Conservation equations

The membrane potential of the soma/axon and dendrite [mV]
$d[v_{sa}]/dt = 1/Cm * (-J_{tot\ sa} + 1/(2 * Ra * dhod * *2) * (v_d - v_{sa}) + input_{current})$
$d[v_d]/dt = 1/Cm * (-J_{tot\ d} + 1/(2 * Ra * dhod * *2) * (v_{sa} - v_d) + input_{current\ dendrite})$

The change in the ion concentrations (K+ and Na+) in the soma/axon [mM]
$if enable_{volume\ changes\ dependencies}$:
$d[Na_{sa}]/dt = -As/(Farad * volume_{sa}/1e12) * J_{Na\ tot\ sa} + D_{Na} * (Vd + volume_{sa}/1e12)/(2 * dhod * *2 * volume_{sa}/1e12) * (Na_d - Na_{sa})$
$d[K_{sa}]/dt = -As/(Farad * volume_{sa}/1e12) * J_{K\ tot\ sa} + D_K * (Vd + volume_{sa}/1e12)/(2 * dhod * *2 * volume_{sa}/1e12) * (K_d - K_{sa})$
$else$:
$d[Na_{sa}]/dt = -As/(Farad * Vs) * J_{Na\ tot\ sa} + D_{Na} * (Vd + Vs)/(2 * dhod * *2 * Vs) * (Na_d - Na_{sa})$
$d[K_{sa}]/dt = -As/(Farad * Vs) * J_{K\ tot\ sa} + D_K * (Vd + Vs)/(2 * dhod * *2 * Vs) * (K_d - K_{sa})$

change in concentration of Na,K in the dendrite [mM]
$if enable_{volume\ changes\ dependencies}$:
$d[Na_d]/dt = -Ad/(Farad * Vd) * J_{Na\ tot\ d} + D_{Na} * (volume_{sa}/1e12 + Vd)/(2 * dhod * *2 * Vd) * (Na_{sa} - Na_d)$
$d[K_d]/dt = -Ad/(Farad * Vd) * J_{K\ tot\ d} + D_K * (volume_{sa}/1e12 + Vd)/(2 * dhod * *2 * Vd) * (K_{sa} - K_d)$
$else$:
$d[Na_d]/dt = -Ad/(Farad * Vd) * J_{Na\ tot\ d} + D_{Na} * (Vs + Vd)/(2 * dhod * *2 * Vd) * (Na_{sa} - Na_d)$
$d[K_d]/dt = -Ad/(Farad * Vd) * J_{K\ tot\ d} + D_K * (Vs + Vd)/(2 * dhod * *2 * Vd) * (K_{sa} - K_d)$

change in buffer for K+ in the extracellular space [mM]
$d[Buff_e]/dt = dBuff_e$

change in concentration of Na,K in the extracellular space (ECS) [mM]
$if enable_{volume\ changes\ dependencies}$:
$d[Na_e]/dt = 1/(Farad * ecs_{to\ soma\ and\ dend\ ratio}) * (((As * J_{Na\ tot\ sa})/(volume_{sa}/1e12)) + ((Ad * J_{Na\ tot\ d})/Vd)) + flu_{diff\ Na}$
$else$:
$d[Na_e]/dt = 1/(Farad * fe) * (((As * J_{Na\ tot\ sa})/Vs) + ((Ad * J_{Na\ tot\ d})/Vd)) + flu_{diff\ Na}$
$d[K_e]/dt = dKedt$

change in tissue oxygen concentration [mM]
$d[O2]/dt = J_{O2\ vascular} - J_{O2\ background} - J_{O2\ pump}$

change in non dimensional cerebral blood volume (CBV) (BOLD response) [-]
$if use_{buxton\ balloon}$:
$d[CBV]/dt = 1/tau_{MTT} * (CBF/CBF_{init} - CBV * *(1/d))$
$else$:
$d[CBV]/dt = 1/(tau_{MTT} + tau_{TAT}) * (CBF/CBF_{init} - CBV * *(1/d))$

Metabolic inertia: smooth CMRO2 ratio for HbR dynamics
$cmro2_{ratio} = CMRO2/CMRO2_{init}$
$if tau_{CMRO2} > 0:$
$if cmro2_{ratio} > CMRO2_n:$ **CMRO2 rising**
$tau_{eff} = tau_{CMRO2\,rise} if tau_{CMRO2\,rise} > 0 else tau_{CMRO2}$
$else:$ **CMRO2 falling**
$tau_{eff} = tau_{CMRO2}$
$d[CMRO2_n]/dt = (cmro2_{ratio} - CMRO2_n)/tau_{eff}$
$cmro2_{for\,hbr} = CMRO2_n$
$else:$
$d[CMRO2_n]/dt = 0$
$cmro2_{for\,hbr} = cmro2_{ratio}$

change in deoxyhemoglobin (HbR) concentration [-]
$d[HbR]/dt = 1/tau_{MTT} * (cmro2_{for\,hbr} - HbR/CBV * f_{out})$

Change in activation gating variables m [-]
$d[m1]/dt = 1000 * ((m1alpha * (1 - m1)) - (m1beta * m1))$
$d[m2]/dt = 1000 * ((m2alpha * (1 - m2)) - (m2beta * m2))$
$d[m3]/dt = 1000 * ((m3alpha * (1 - m3)) - (m3beta * m3))$
$d[m4]/dt = 1000 * ((m4alpha * (1 - m4)) - (m4beta * m4))$
$d[m5]/dt = 1000 * ((m5alpha * (1 - m5)) - (m5beta * m5))$
$d[m6]/dt = 1000 * ((m6alpha * (1 - m6)) - (m6beta * m6))$
$d[m7]/dt = 1000 * ((m7alpha * (1 - m7)) - (m7beta * m7))$
$d[m8]/dt = 1000 * ((m8alpha * (1 - m8)) - (m8beta * m8))$

Change in inactivation gating variables h [-]
$d[h1]/dt = 1000 * ((h1alpha * (1 - h1)) - (h1beta * h1))$
$d[h2]/dt = 1000 * ((h2alpha * (1 - h2)) - (h2beta * h2))$
$d[h3]/dt = 1000 * ((h3alpha * (1 - h3)) - (h3beta * h3))$
$d[h4]/dt = 1000 * ((h4alpha * (1 - h4)) - (h4beta * h4))$
$d[h5]/dt = 1000 * ((h5alpha * (1 - h5)) - (h5beta * h5))$
$d[h6]/dt = 1000 * ((h6alpha * (1 - h6)) - (h6beta * h6))$

Ca2+ concentration in the neuron [μM]
$d[Ca_n]/dt = (I_{Ca\,tot}/(2 * F * V_{spine}) - (k_{ex} * (Ca_n - Ca_{rest})))/(1 + lambda_{buf})$
Activated neuronal NO synthase (nNOS) [μM]
$d[nNOS_{act\,n}]/dt = V_{maxNOS} * CaM/(K_{actNOS} + CaM) - mu2_n * nNOS_{act\,n}$
NO concentration in the neuron
$d[NO_n]/dt = p_{NO\,n} - c_{NO\,n} + d_{NO\,n}$
Change in the volume of the neuron [μm3]**
$d[volume_{sa}]/dt = (volume_{sa\,eq} - volume_{sa})/tau_{volume\,change\,sa}$

Neuron and ECS equations

Nernst potential for Na,K ions in soma and dendrite (Cl constant) [mV]

$E_{Na\,sa} = ph * log(Na_e/Na_{sa})$
$E_{K\,sa} = ph * log(K_e/K_{sa})$
$E_{Na\,d} = ph * log(Na_e/Na_d)$
$E_{K\,d} = ph * log(K_e/K_d)$

Ion fluxes

Leak fluxes of Na,K,Cl in soma/axon or dendrite using HH [mA cm-2]**
$J_{Naleak\,sa} = gNaleak_{sa} * (v_{sa} - E_{Na\,sa})$
$J_{Kleak\,sa} = gKleak_{sa} * (v_{sa} - E_{K\,sa})$
$J_{Naleak\,d} = gNaleak_d * (v_d - E_{Na\,d})$
$J_{Kleak\,d} = gKleak_d * (v_d - E_{K\,d})$

Na flux through NaP channel in soma using GHK

Rate functions for the activation m and deactivation h gating variables [ms-1]**
$m1alpha = 1/(6 * (1 + exp(-((0.143 * v_{sa}) + 5.67))))$
$m1beta = exp(-((0.143 * v_{sa}) + 5.67))/(6 * (1 + exp(-((0.143 * v_{sa}) + 5.67))))$
$h1alpha = 5.12e - 8 * exp(-((0.056 * v_{sa}) + 2.94))$
$h1beta = 1.6e - 6/(1 + exp(-(((0.2 * v_{sa})) + 8)))$
Na+ current through NaP channel in soma/axon [mA cm-2]**
$J_{NaP\,sa} = (m1 * *2 * h1 * gNaP_{GHk} * Farad * v_{sa} * (Na_{sa} - (exp(-v_{sa}/ph) * Na_e)))/(ph * (1 - exp(-v_{sa}/ph)))$

Na+ flux through NaT channel in soma using GHK

$m8alpha = 0.32 * ((-v_{sa} - 51.9)/(exp(-(0.25 * v_{sa} + 12.975)) - 1))$
$m8beta = 0.28 * ((v_{sa} + 24.89)/(exp(0.2 * v_{sa} + 4.978) - 1))$
$h6alpha = 0.128 * exp(-(0.056 * v_{sa} + 2.94))$
$h6beta = 4/(1 + exp(-(0.2 * v_{sa} + 6)))$
Na+ current through NaT channel in soma/axon [mA cm-2]**
$J_{NaT\,sa} = (m8 * *3 * h6 * gNaT_{GHk} * Farad * v_{sa} * (Na_{sa} - (exp(-v_{sa}/ph) * Na_e)))/(ph * (1 - exp(-v_{sa}/ph)))$

K+ flux through KDR channel in soma using GHK

$m2alpha = 0.016 * ((v_{sa} + 34.9)/(1 - exp(-((0.2 * v_{sa}) + 6.98))))$
$m2beta = 0.25 * exp(-((0.025 * v_{sa}) + 1.25))$
K+ current through KDR channel in the soma/axon [mA cm-2]**
$J_{KDR\,sa} = (m2 * *2 * gKDR_{GHk} * Farad * v_{sa} * (K_{sa} - (exp(-v_{sa}/ph) * K_e)))/(ph * (1 - exp(-v_{sa}/ph)))$

K+ flux through KA channel in soma using GHKinput_current

$m3alpha = 0.02 * ((v_{sa} + 56.9)/(1 - exp(-((0.1 * v_{sa}) + 5.69))))$
$m3beta = 0.0175 * ((v_{sa} + 29.9)/(exp(((0.1 * v_{sa}) + 2.99)) - 1))$
$h2alpha = 0.016 * exp(-((0.056 * v_{sa}) + 4.61))$
$h2beta = 0.5/(1 + exp(-((0.2 * v_{sa}) + 11.98)))$
K+ current through KA channel in the soma/axon [mA cm-2]**
$J_{KA\,sa} = (m3 * *2 * h2 * gKA_{GHk} * Farad * v_{sa} * (K_{sa} - (exp(-v_{sa}/ph) * K_e)))/(ph * (1 - exp(-v_{sa}/ph)))$

Na+ flux through NaP channel in dendrite using GHK

$m4alpha = 1/(6 * (1 + exp(-((0.143 * v_d) + 5.67))))$
$m4beta = exp(-((0.143 * v_d) + 5.67))/(6 * (1 + exp(-((0.143 * v_d) + 5.67))))$
$h3alpha = 5.12e - 8 * exp(-((0.056 * v_d) + 2.94))$
$h3beta = 1.6e - 6/(1 + exp(-(((0.2 * v_d)) + 8)))$
Na+ current through NDA channel in dendrite [mA cm-2]**
$J_{NaP\,d} = (m4 * *2 * h3 * gNaP_{GHk} * Farad * v_d * (Na_d - (exp(-v_d/ph) * Na_e)))/(ph * (1 - exp(-v_d/ph)))$

Na+/K+ flux through NMDA channel in dendrite using GHK

$m5alpha = 0.5/(1 + exp((13.5 - K_e)/1.42))$
$m5beta = 0.5 - m5alpha$
$h4alpha = 1/(2000 * (1 + exp((K_e - 6.75)/0.71)))$
$h4beta = 5e - 4 - h4alpha$
K+ current through N-methyl-D-aspartate (NMDA) channel in the dendrite [mA cm-2]**
$J_{NMDA\,K\,d} = ((m5 * h4 * gNMDA_{GHk} * Farad * v_d * (K_d - (exp(-v_d/ph) * K_e)))/(ph * (1 - exp(-v_d/ph))))/(1 + 0.33 * Mg * exp(-(0.07 * v_d + 0.7)))$
$J_{NMDA\,Na\,d} = ((m5 * h4 * gNMDA_{GHk} * Farad * v_d * (Na_d - (exp(-v_d/ph) * Na_e)))/(ph * (1 - exp(-v_d/ph))))/(1 + 0.33 * Mg * exp(-(0.07 * v_d + 0.7)))$

K+ flux through KDR channel in dendrite using GHK

$m6alpha = 0.016 * ((v_d + 34.9)/(1 - exp(-((0.2 * v_d) + 6.98))))$
$m6beta = 0.25 * exp(-((0.025 * v_d) + 1.25))$
K+ current through KDR channel in the dendrite [mA cm-2]**
$J_{KDR\,d} = (m6 * *2 * gKDR_{GHk} * Farad * v_d * (K_d - (exp(-v_d/ph) * K_e)))/(ph * (1 - exp(-v_d/ph)))$

K+ flux through KA channel in dendrite using GHK

$m7alpha = 0.02 * ((v_d + 56.9)/(1 - exp(-((0.1 * v_d) + 5.69))))$
$m7beta = 0.0175 * ((v_d + 29.9)/(exp(((0.1 * v_d) + 2.99)) - 1))$
$h5alpha = 0.016 * exp(-((0.056 * v_d) + 4.61))$
$h5beta = 0.5/(1 + exp(-((0.2 * v_d) + 11.98)))$
K+ current through KA channel in the dendrite [mA cm-2]**
$J_{KA\,d} = (m7**2*h5*gKA_{GHk}*Farad*v_d*(K_d-(exp(-v_d/ph)*K_e)))/(ph*(1-exp(-v_d/ph)))$

Oxygen independent term of the ATP-ase pump in both the soma/axon or dendrite (flux through the NaK-ATPase pump) [-]
$J_{pump1\,sa} = (1 + (K_{init\,e}/K_e)) **(-2) * (1 + (Na_{init\,sa}/Na_{sa})) **(-3)$
Steady state pump rate in the soma/axon [-]
$J_{pump1init\,sa} = 0.0312$ **(1 + (K_init_e / K_init_e))**(-2) * (1 + (Na_init_sa / Na_init_sa))**(-3)**
$J_{pump1\,d} = (1 + (K_{init\,e}/K_e)) **(-2) * (1 + (Na_{init\,d}/Na_d)) **(-3)$
Steady state pump rate in the dendrite [-]
$J_{pump1init\,d} = 0.0312$ **(1 + (K_init_e / K_init_e))**(-2) * (1 + (Na_init_d / Na_init_d))**(-3)**

Determine whether there is limited oxygen: O2switch=0 ATP is plentiful, O2switch=1 ATP is limited (oxygen-limited regime) [?]
$O2_p = O2_0 * (1 - O2switch) + O2 * O2switch$
Oxygen dependent term of the ATP-ase pump [-]
$J_{pump2} = 2 * (1 + O2_0/(((1 - alpha_{O2}) * O2_p) + alpha_{O2} * O2_0)) **(-1)$

Na+/K+ ATP-ase pump flux in soma/axon or dendrite [mA cm-2]**
$J_{pump\,sa} = Imax * J_{pump1\,sa} * J_{pump2}$
$J_{pump\,d} = Imax * J_{pump1\,d} * J_{pump2}$

Na+ and K+ currents through Na+/K+ ATP-ase pump in soma axon or dendrite [mA cm-2]**
$J_{Napump\,sa} = 3 * J_{pump\,sa}$
$J_{Kpump\,sa} = -2 * J_{pump\,sa}$
$J_{Napump\,d} = 3 * J_{pump\,d}$
$J_{Kpump\,d} = -2 * J_{pump\,d}$

Total ion fluxes

Total ion fluxes in soma [mA cm-2]**
$J_{Na\,tot\,sa} = J_{NaP\,sa} + J_{Naleak\,sa} + J_{Napump\,sa} + J_{NaT\,sa}$
$J_{K\,tot\,sa} = J_{KDR\,sa} + J_{KA\,sa} + J_{Kleak\,sa} + J_{Kpump\,sa}$
General leak in the soma/axon [mA cm-2]**
$J_{leak\,tot\,sa} = gleak_{sa} * (v_{sa} - E_{Cl\,sa})$

Total ion fluxes in dendrite [mA cm-2]**
$J_{Na\,tot\,d} = J_{NaP\,d} + J_{Naleak\,d} + J_{Napump\,d} + J_{NMDA\,Na\,d}$
$J_{K\,tot\,d} = J_{KDR\,d} + J_{KA\,d} + J_{Kleak\,d} + J_{Kpump\,d} + J_{NMDA\,K\,d}$
General leak in the dendrite [mA cm-2]**
$J_{leak\,tot\,d} = gleak_d * (v_d - E_{Cl\,d})$ **leak**

Total ion fluxes in soma and dendrite [mA cm-2]**
$J_{tot\ sa} = J_{Na\ tot\ sa} + J_{K\ tot\ sa} + J_{leak\ tot\ sa}$
$J_{tot\ d} = J_{Na\ tot\ d} + J_{K\ tot\ d} + J_{leak\ tot\ d}$

Tissue oxygen

$J_{pump2\,0} = 0.0952$ **2 * (1 + O2_0 / (((1 - alpha_O2) * 0) + alpha_O2 * O2_0))**(-1)**
$J_{pump2\,O2\,0} = 1$ **2 * (1 + O2_0 / (((1 - alpha_O2) * O2_0) + alpha_O2 * O2_0))**(-1)**
The normalized pump rate [-]
$P_{02} = (J_{pump2} - J_{pump2\,0})/(J_{pump2\,O2\,0} - J_{pump2\,0})$
The cerebral blood flow [-]
$CBF = CBF_{init} * (R**4/R_{init}**4)$
The vascular supply of oxygen [mM s-1]**
$J_{O2\,vascular} = CBF * ((O2_b - O2)/(O2_b - O2_0))$
The background oxygen consumption [mM s-1]**
$J_{O2\,background} = CBF_{init} * P_{02} * (1 - gamma_{O2})$
The tissue oxygen consumption dur to the ATP-ase pump [mM s-1]**
$J_{O2\,pump} = CBF_{init} * P_{02} * gamma_{O2} * ((J_{pump1\ sa} + J_{pump1\ d})/(J_{pump1init\ sa} + J_{pump1init\ d}))$
The change in oxygen concentration due to cerebral blood flow (CBF) [mM s1]**
$J_{O2\,CBF} = J_{0\,CBF} * CBF/CBF_{init}$

BOLD

The time dependent outflow from the venous compartment [-]
$if use_{buxton\ balloon}$:
$f_{out} = CBV**(1/d)$
$else$:
$f_{out} = CBV**(1/d) + tau_{TAT} * (1/(tau_{MTT} + tau_{TAT}) * (CBF/CBF_{init} - CBV**(1/d)))$
The cerebral metabolic rate of oxygen consumption [mM s-1]**
$CMRO2 = J_{O2\,background} + J_{O2\,pump}$
The equilibrium value of CMRO2 [mM s-1]**
$CMRO2_{init} = CBF_{init} * P_{02}$
The oxygen extraction fraction [-]
$OEF = CMRO2 * E_0/CBF$
The BOLD signal change from its steady state value
$BOLD = V_0 * (a_1 * (1 - HbR) - a_2 * (1 - CBV))$

Glutamate input: vesicle released when the extracellular K+ is over 5.5 mM (Ke_switch)

Fraction of open NR2A NMDA receptors [-]
$w_{NR2A} = Glu/(K_{mA} + Glu)$
Fraction of open NR2B NMDA receptors [-]
$w_{NR2B} = Glu/(K_{mB} + Glu)$

Inward Ca2+ current per open NMDA receptor [fA]
$I_{Ca} = (-4 * v_n * G_M * P_{Ca\,P\,M} * (Ca_{ex}/M))/(1 + exp(-80 * (v_n + 0.02))) * (exp(2 * v_n * F/(R_{gas} * T)))/(1 - exp(2 * v_n * F/(R_{gas} * T)))$
Total inward Ca2+ current for all open NMDA receptors per synapse [fA]
$I_{Ca\,tot} = I_{Ca} * (n_{NR2A} * w_{NR2A} + n_{NR2B} * w_{NR2B})$

Ca2+-calmodulin complex concentration [μM]
$CaM = Ca_n/m_c$
Time for NO to diffuse between the centres of the neuron and the astrocyte [s]
$tau_{nk} = x_{nk} * *2/(2 * D_{cNO})$

Neuronal NO production flux [μM/s]
$p_{NO\,n} = NOswitch * (nNOS_{act\,n} * V_{max\,NO\,n} * O2_n/(K_{mO2\,n} + O2_n) * LArg_n/(K_{mArg\,n} + LArg_n))$
Neuronal NO consumption flux [μM/s]
$c_{NO\,n} = k_{O2\,n} * NO_n * *2 * O2_n$
Neuronal NO diffusive flux [μM/s]
$d_{NO\,n} = (NO_k - NO_n)/tau_{nk}$

ECS electrodiffusion TEST
$Delta_{K\,e} = 3.493 - K_e$
$average_{K\,e} = (3.493 + K_e)/2$
$Delta_{Na\,e} = 150 - Na_e$
$average_{Na\,e} = (150 + Na_e)/2$
$Delta_{v\,e} = -(8.315 * 300)/96.485 * (1 * 3.6e-9 * Delta_{K\,e} + 1 * 2.4e-9 * Delta_{Na\,e})/(1 * 3.6e-9 * average_{K\,e} + 1 * 2.4e-9 * average_{Na\,e})$
$flu_{diff\,Fick\,K} = (3.6e-9/(1.24e-4) * *2) * (Delta_{K\,e})$
$flu_{diff\,Fick\,Na} = (2.4e-9/(1.24e-4) * *2) * (Delta_{Na\,e})$
$flu_{diff\,el\,K} = (3.6e-9/(1.24e-4) * *2) * (((1 * 96.485)/(8.315 * 300)) * (average_{K\,e} * Delta_{v\,e}))$
$flu_{diff\,el\,Na} = (2.4e-9/(1.24e-4) * *2) * (((1 * 96.485)/(8.315 * 300)) * (average_{Na\,e} * Delta_{v\,e}))$

$flu_{diff\,K} = flu_{diff\,Fick\,K} + flu_{diff\,el\,K}$
$flu_{diff\,Na} = flu_{diff\,Fick\,Na} + flu_{diff\,el\,Na}$

Volume changes equations

Total num of ions in cells changing volume, like in Ullah's model [mM μm3]**
$n_{total\,ions} = neuron_{ions} + astrocyte_{ions} + sc_{ions} + ecs_{ions} + pvs_{ions}$
Equilibrium neuron volume [μm3]**
$volume_{sa\,eq} = total_{volume} * neuron_{ions}/n_{total\,ions}$

$input_{current} = input_{current(t)}$
$if\,do_{stop\,current\,by\,K\,e\,level} and K_e > stop_{current\,by\,K\,e\,level}:$
$input_{current} = 0$

$input_{current\,dendrite} = input_{current\,dendrite(t)}$
$if\,do_{stop\,current\,by\,K\,e\,level} and K_e > stop_{current\,by\,K\,e\,level}:$
$input_{current\,dendrite} = 0$

K_e optional injection
$K_{e\,injection} = 0$
$for injection in K_{to\,ecs\,injections}:$
$K_{e\,injection} += injection.inject_{if\ conditions\ true(current\ time=t)}$

Conservation equations

The membrane potential of the soma/axon and dendrite [mV]
$d[v_{sa}]/dt = 1/Cm * (-J_{tot\,sa} + 1/(2 * Ra * dhod * *2) * (v_d - v_{sa}) + input_{current})$
$d[v_d]/dt = 1/Cm * (-J_{tot\,d} + 1/(2 * Ra * dhod * *2) * (v_{sa} - v_d) + input_{current\,dendrite})$

The change in the ion concentrations (K+ and Na+) in the soma/axon [mM]
$if enable_{volume\,changes\,dependencies}:$
$d[Na_{sa}]/dt = -As/(Farad * volume_{sa}/1e12) * J_{Na\,tot\,sa} + D_{Na} * (Vd + volume_{sa}/1e12)/(2 * dhod * *2 * volume_{sa}/1e12) * (Na_d - Na_{sa})$
$d[K_{sa}]/dt = -As/(Farad * volume_{sa}/1e12) * J_{K\,tot\,sa} + D_K * (Vd + volume_{sa}/1e12)/(2 * dhod * *2 * volume_{sa}/1e12) * (K_d - K_{sa})$
$else:$
$d[Na_{sa}]/dt = -As/(Farad * Vs) * J_{Na\,tot\,sa} + D_{Na} * (Vd + Vs)/(2 * dhod * *2 * Vs) * (Na_d - Na_{sa})$
$d[K_{sa}]/dt = -As/(Farad * Vs) * J_{K\,tot\,sa} + D_K * (Vd + Vs)/(2 * dhod * *2 * Vs) * (K_d - K_{sa})$

change in concentration of Na,K in the dendrite [mM]
$if enable_{volume\,changes\,dependencies}:$
$d[Na_d]/dt = -Ad/(Farad * Vd) * J_{Na\,tot\,d} + D_{Na} * (volume_{sa}/1e12 + Vd)/(2 * dhod * *2 * Vd) * (Na_{sa} - Na_d)$
$d[K_d]/dt = -Ad/(Farad * Vd) * J_{K\,tot\,d} + D_K * (volume_{sa}/1e12 + Vd)/(2 * dhod * *2 * Vd) * (K_{sa} - K_d)$
$else:$
$d[Na_d]/dt = -Ad/(Farad * Vd) * J_{Na\,tot\,d} + D_{Na} * (Vs + Vd)/(2 * dhod * *2 * Vd) * (Na_{sa} - Na_d)$
$d[K_d]/dt = -Ad/(Farad * Vd) * J_{K\,tot\,d} + D_K * (Vs + Vd)/(2 * dhod * *2 * Vd) * (K_{sa} - K_d)$

change in buffer for K+ in the extracellular space [mM]
$d[Buff_e]/dt = dBuff_e$

change in concentration of Na,K in the extracellular space (ECS) [mM]
$if enable_{volume\,changes\,dependencies}:$
$d[Na_e]/dt = 1/(Farad * ecs_{to\ soma\ and\ dend\ ratio}) * (((As * J_{Na\,tot\,sa})/(volume_{sa}/1e12)) + ((Ad * J_{Na\,tot\,d})/Vd)) + flu_{diff\ Na}$
$else:$
$d[Na_e]/dt = 1/(Farad * fe) * (((As * J_{Na\,tot\,sa})/Vs) + ((Ad * J_{Na\,tot\,d})/Vd)) + flu_{diff\ Na}$
$d[K_e]/dt = dKedt$

change in tissue oxygen concentration [mM]
$d[O2]/dt = J_{O2\,vascular} - J_{O2\,background} - J_{O2\,pump}$

change in non dimensional cerebral blood volume (CBV) (BOLD response) [-]
$if use_{buxton\,balloon}:$
$d[CBV]/dt = 1/tau_{MTT} * (CBF/CBF_{init} - CBV * *(1/d))$

$else:$
$d[CBV]/dt = 1/(tau_{MTT} + tau_{TAT}) * (CBF/CBF_{init} - CBV**(1/d))$
Metabolic inertia: smooth CMRO2 ratio for HbR dynamics
$cmro2_{ratio} = CMRO2/CMRO2_{init}$
$if tau_{CMRO2} > 0:$
$if cmro2_{ratio} > CMRO2_n:$ **CMRO2 rising**
$tau_{eff} = tau_{CMRO2\,rise} if tau_{CMRO2\,rise} > 0 else tau_{CMRO2}$
$else:$ **CMRO2 falling**
$tau_{eff} = tau_{CMRO2}$
$d[CMRO2_n]/dt = (cmro2_{ratio} - CMRO2_n)/tau_{eff}$
$cmro2_{for\,hbr} = CMRO2_n$
$else:$
$d[CMRO2_n]/dt = 0$
$cmro2_{for\,hbr} = cmro2_{ratio}$

change in deoxyhemoglobin (HbR) concentration [-]
$d[HbR]/dt = 1/tau_{MTT} * (cmro2_{for\,hbr} - HbR/CBV * f_{out})$

Change in activation gating variables m [-]
$d[m1]/dt = 1000 * ((m1alpha * (1 - m1)) - (m1beta * m1))$
$d[m2]/dt = 1000 * ((m2alpha * (1 - m2)) - (m2beta * m2))$
$d[m3]/dt = 1000 * ((m3alpha * (1 - m3)) - (m3beta * m3))$
$d[m4]/dt = 1000 * ((m4alpha * (1 - m4)) - (m4beta * m4))$
$d[m5]/dt = 1000 * ((m5alpha * (1 - m5)) - (m5beta * m5))$
$d[m6]/dt = 1000 * ((m6alpha * (1 - m6)) - (m6beta * m6))$
$d[m7]/dt = 1000 * ((m7alpha * (1 - m7)) - (m7beta * m7))$
$d[m8]/dt = 1000 * ((m8alpha * (1 - m8)) - (m8beta * m8))$

Change in inactivation gating variables h [-]
$d[h1]/dt = 1000 * ((h1alpha * (1 - h1)) - (h1beta * h1))$
$d[h2]/dt = 1000 * ((h2alpha * (1 - h2)) - (h2beta * h2))$
$d[h3]/dt = 1000 * ((h3alpha * (1 - h3)) - (h3beta * h3))$
$d[h4]/dt = 1000 * ((h4alpha * (1 - h4)) - (h4beta * h4))$
$d[h5]/dt = 1000 * ((h5alpha * (1 - h5)) - (h5beta * h5))$
$d[h6]/dt = 1000 * ((h6alpha * (1 - h6)) - (h6beta * h6))$

Ca2+ concentration in the neuron [μM]
$d[Ca_n]/dt = (I_{Ca\,tot}/(2 * F * V_{spine}) - (k_{ex} * (Ca_n - Ca_{rest})))/(1 + lambda_{buf})$
Activated neuronal NO synthase (nNOS) [μM]
$d[nNOS_{act\,n}]/dt = V_{maxNOS} * CaM/(K_{actNOS} + CaM) - mu2_n * nNOS_{act\,n}$
NO concentration in the neuron
$d[NO_n]/dt = p_{NO\,n} - c_{NO\,n} + d_{NO\,n}$
Change in the volume of the neuron [μm3]**
$d[volume_{sa}]/dt = (volume_{sa\,eq} - volume_{sa})/tau_{volume\,change\,sa}$

4.2 Astrocyte, Synaptic Cleft, and Perivascular Space

Astrocyte, Synaptic cleft, and Perivascular space initial conditions:

Table 4: Neuron and ECS initial conditions

Parameter	Value	Unit	Description
Na_k	18268	μM	Na+ concentration in the astrocyte
K_k	92708	μM	K+ concentration in the astrocyte
$HCO3_k$	9131	μM	HCO3 concentration in the astrocyte
Cl_k	7733	μM	Cl concentration in the astrocyte
Na_s	150255	μM	Na+ concentration in the SC
K_s	2837	μM	K+ concentration in the synaptic cleft (SC)
$HCO3_s$	16881	μM	HCO3- concentration in the SC
K_p	3045.1	μM	K+ concentration in the PVS
w_k	1.703e-4	–	The open probability of the big potassium (BK) channel
Ca_k	0.1612	μM	The astrocytic cytosolic Ca2+ concentration
s_k	480.8	μM	The Ca2+ concentration in the astrocytic endoplasmic reticulum (ER)
h_k	0.3828	–	The inactivation variable of the astrocytic IP3R channel
I_k	0.048299	μM	The astrocytic inositol triphosphate (IP3) concentration
eet_k	0.6123	μM	The astrocytic epoxyeicosatrienoic acid (EET) concentration
m_k	0.5710	–	TRPV open probability, the trpv_switch can switch the turn the channel on or off.
Ca_p	1746.4	μM	Ca2+ concentration in the PVS
NO_k	0.1106	μM	NO concentration in the astrocyte
v_k	-88.9	mV	Membrane potential of the astrocyte (AC)
$volume_k$	2160	$\mu m**3$	Astrocyte volume
$volume_p$	2.160	$\mu m**3$	PVS volume
Gt	0	mM	Gliotransmitter dynamics
$Norepinephrine_s$	0	mM	Noradrenaline concentration in the synaptic cleft (SC)

Astrocyte, Synaptic cleft, and Perivascular space parameters:

Table 5: Neuron and ECS initial conditions

Parameter	Value	Unit	Description
$gamma_i$	1970	$mV/\mu M$	Change in membrane potential by a scaling factor
z_1	4.5e-3	$mV\mu M * *-1$	
z_2	112	mV	
z_3	4.2e-4	?	
z_4	12.6	?	
z_5	-7.4e-2	?	
$F_{KIR\,k}$	750	–	
$G_{NaCa\,k}$	3.16e-3	$\mu MmV * *-1s**-1$	
$c_{NaCa\,k}$	0.5	μM	
$v_{NaCa\,k}$	-30	mV	
$G_{Ca\,k}$	1.29e-3	$\mu MmV * *-1s**-1$	VOCC whole cell conductance
$v_{Ca1\,k}$	100	mV	VOCC reversal potential
$v_{Ca2\,k}$	-24	mV	Half point of the VOCC activation sigmoidal
$R_{Ca\,k}$	8.5	mV	Maximum slope of the VOCC activation sigmoidal
$G_{BK\,k}$	10.25	?	g_BK_k : float = 225 1e-12 / 3.7e-9: float = 6.08e-2
$G_{K\,k}$	6907.77	–	Specific ion conductance of K+ (40)
$G_{Na\,k}$	226.94	–	Specific ion conductance of Na+ (1.314)
$G_{NBC\,k}$	130.74	–	Specific ion conductance of the NBC cotransporter (7.57e-1)
$G_{KCC1\,k}$	1.728	–	Specific ion cnoductance of the KCCL cotransporter (1e-2)
$G_{NKCC1\,k}$	9.568	–	Specific ion conductance of the NKCCl cotransporter (5.54e-2)
$G_{Cl\,k}$	151.93	–	Specific ion conductance of Cl- (8.797e-1)
$J_{NaK\,max}$	2.3667e4	$\mu Ms**-1$	Maximum flux through the Na+/K+ ATP-ase pump 1.42e-3
$rhoSwitch$	1	–	
$GluSwitch$	1	–	
$trpv_{switch}$	1	–	Turn on TRPV4 Ca2+ channel from AC to PVS
Mu	8e-4	m/s	
$B0$	500	mM	Effective total buffer concentration
rho_{min}	0.1	–	Minimum ratio of bound to unbound IP3 receptors(one vesicle, Santucci2008)
rho_{max}	0.7	–	Maximum ratio of bound to unbound IP3 receptors

Glu_{max}	1846	μM	Maximum glutamate concentration (one vesicle), Santucci2008
Glu_{min}	0	μM	Minimum glutamate concentration
$theta_{L\,Glu}$	1	?	slope of Glu input
$theta_{R\,Glu}$	1	?	slope of Glu input
GT_{amb}	0	μM	Steady-state gliotransmitter concentration
Gt_{diff}	0.1	$\mu M s**-1$	Coupling coefficient for gliotransmitter diffusion
tau_{GT}	5	s	Gliotransmitter loss rate time constant
SVR_{AVF}	1	$-$	Surface to volume ratio parameter SVR(AVF(x,y))
k_{gt}	1	$\mu M s**-1$	Gliotransmitter production rate through Ca2+
k_m	0.1612	μM	Dissociation constant of Ca2+ stimulation of gliotransmitter
v_4	8	mV	A measure of the spread of w_inf
v_5	15	mV	Determines the range of the shift of w_inf as Ca2+ varies
v_6	-55	mV	Voltage associated with the opening of half the population, shifts the range of w_inf
Ca_4	0.35	μM	BK open probability Ca2+ constant
VR_{se}	1	$-$?	
VR_{pe}	0.001	$-$?	
tau	0.7	s?	
$tau2$	2.8	s?	
R_s	2.79e-8	m	Synaptic cleft volume / surface area ratio
R_k	6e-8	m	Astrocyte volume / surface area ratio
R_{tot}	8.79e-8	m	Total volume / surface area ratio
Amp	0.7	$-$?	
$base$	0.1	$-$?	
$theta_L$	1	s?	
$theta_R$	1	s?	
$delta$	1.235e-2	$-$	Ratio of the activities of the unbound and bound receptors
BK_{switch}	-2.5e-10	$-$	
$VR_{ER\,cyt}$	0.185	$-$	Volume ratio between ER and astrocytic cytosol
k_{on}	2	$\mu M**-1s** - 1$	Rate of Ca2+ binding to the inhibitory site on the IP3R
K_{inh}	0.1	μM	Disassociation constant for IP3R

r_h	4.8	μM	Maximum rate of IP3 production in astrocyte due to glutamate receptors
k_{deg}	1.25	$s**-1$	Rate constant for IP3 degradation in astrocyte
V_{eet}	72	μM	EET production rate
k_{eet}	7.2	μM	EET degradation rate
$Ca_{k\,min}$	0.1	μM	Minimum Ca2+ concentration required for EET production
Ca_3	0.4	μM	BK open probability Ca2+ constant
eet_{shift}	2	mV	
K_I	0.03	μM	Disassociation constant for IP3 binding to an IP3R
$Capmin_k$	2000	μM	Steady state value of Ca2+ in PVS
$C_{astr\,k}$	40	pF	
$gam_{cae\,k}$	200	μM	Ca2+ concentration constant
$gam_{cai\,k}$	0.01	μM	Ca2+ concentration constant
$epshalf_k$	0.1	–	Strain required for half activation of the TRPV4 channel
$kappa_k$	0.1	–	TRPV4 channel strain constant
$v1_{TRPV\,k}$	120	mV	TRPV4 channel voltage gating constant
$v2_{TRPV\,k}$	13	mV	TRPV4 channel voltage gating constant
$t_{TRPV\,k}$	0.9	s	Characteristic time constant for m_k
$R_{0\,passive\,k}$	20e-6	μm	Vessel radius when passive and no stress is applied
$Ca_{decay\,k}$	0.5	$s**-1$	Rate of decay of Ca2+ in PVS
$G_{TRPV\,k}$	50	pS	TRPV4 whole cell conductance
r_{buff}	0.05	–	Rate at which Ca2+ from the TRPV4 channel at the endfoot is buffered compared to rest of channels on the astrocyte body
$volume_i$	2160	$\mu m**3$	SMC volume
VR_{pa}	0.001	–	Initial volume ratio between PVS and astrocyte
VR_{ps}	0.001	–	Initial volume ratio between PVS and SMC
$volume_p$	2.160	$\mu m**3$	PVS volume, 0.001 is PVS to astrocyte ratio (volume_i VR_ps)
R_{decay}	0.15	$s**-1$	Rate of decay of K+ in PVS
$K_{p\,min}$	3e3	μM	Steady state value of K+ in PVS
$F_{NaK\,i}$	4.32e-2	$\mu M s**-1$	
$K_{e\,for\,balance}$	3493	μM	
F	9.65e4	$Cmol**-1$	Faraday's constant

R_g	8.315	$Jmol**-1K**-1$	Gas constant
T	300	K	Temperature
$K_{Na\,k}$	10000	μM	Na+/K+ ATP-ase pump constant
$K_{K\,s}$	1500	μM	Na+/K+ ATP-ase pump constant
$A_{ef\,k}$	3.7e-9	$m2$	
J_{max}	2880	$\mu Ms**-1$	Maximum rate of Ca2+ through the IP3 mediated channel
K_{act}	0.17	μM	Disassociation constant for Ca2+ binding to an activation site on an IP3R
P_L	0.0804	μM	ER leak channel steady state balance constant
V_{max}	20	$\mu Ms**-1$	Maximum rate of Ca2+ uptake pump on the ER
k_{pump}	0.24	μM	Ca2+ uptake pump disassociation constant
z_K	1	$-$	
z_{Na}	1	$-$	
z_{Cl}	-1	$-$	
z_{NBC}	-1	$-$	
z_{Ca}	2	$-$	
BK_{end}	40	$-$	Ratio of endogeneous buffer concentration to dissasociation constant
K_{ex}	0.26	μM	Disassociation constant of exogenous buffer
B_{ex}	11.35	μM	Concentration of exogenous buffer
K_G	8.82	μM	G-protein disassociation constant
psi_w	2.664	$s**-1$	A characteristic time for the open probability of the BK channel
ph	26.6995	$RT/Farad$	where Farad is C/mmol, also used in Neuron.m
D_{cNO}	3300	$\mu M**2s**-1$	Diffusion coefficient NO (Malinski1993)
x_{nk}	25	μM	Distance between centers of neuron and astrocyte (M.E.)
x_{ki}	25	μM	Distance between centers of astrocyte and SMC compartments (M.E.)
$k_{O2\,k}$	9.6e-6	$\mu M**-2s**-1$	O2 reaction rate constant (Kavdia2002)
$O2_k$	200	μM	O2 concentration in the astrocyte (M.E.)

$volume_{sc\,0}$	5e-3	$\mu M * *3$	Volume of the synaptic cleft (Rusakov https://www.sciencedirect.com/science/article/pii/S0006349501758468)
$tau_{volume\ change\ k}$	15	–	Rate controlling the speed of astrocyte volume convergence towards equilibrium volume
$impermeants_k$	495500	$mM * \mu m * *3$	from Ullah, 2160 is initial volume, the other number is balancing coefficient
$tau_{volume\ change\ p}$	15	–	Rate controlling the speed of PVS volume convergence towards equilibrium volume
$diffusion_{ecs\ pvs}$	3e-8	–	Rate of diffusion between ECS and PVS
$are_{noradrenaline\ pathways\ active}$	False	–	Enable noradrenaline receptor-mediated pathways
$do_{force\ norepinephrine\ value}$	False	–	Force constant norepinephrine value during simulation
$forced_{norepinephrine\ value}$	2	mM	Constant norepinephrine value when forcing is enabled
$forced_{norepinephrine\ start}$	0	s	Start time for forced norepinephrine value
$forced_{norepinephrine\ end}$	0	s	End time for forced norepinephrine value
$do_{enable\ norepinephrine\ reuptake\ inhibition}$	False	–	Enable norepinephrine reuptake inhibition
r_{NA}	0.0002	$mMs**-1$	Normal baseline norepinephrine influx
r_{NG}	0.00050	$s**-1$	Normal glutamate influence
r_{NGt}	0.00020	$s**-1$	Normal gliotransmitter influence

Astrocyte, Synaptic cleft, and Perivascular space shared equations

$external_{volume} = total_{volume} - volume_k - volume_{sa}$
$volume_{sc} = external_{volume} * sc_{volume\ share}$
$astrocyte_{concentrations} = K_k + Na_k + Cl_k + Ca_k + HCO3_k + NO_k$
$pvs_{concentrations} = K_p + Ca_p$
$Cl_s = Na_s + K_s - HCO3_s$
$sc_{concentrations} = K_s + Na_s + HCO3_s + Cl_s$
$astrocyte_{ions} = astrocyte_{concentrations}/1000 * volume_k + impermeants_k$
$sc_{ions} = sc_{concentrations}/1000 * volume_{sc}$
$pvs_{ions} = pvs_{concentrations}/1000 * volume_p + 761$
$J_{K\ ECS\ to\ PVS} = diffusion_{ecs\ pvs} * (K_e * 10 * *3 - K_p)$

$if\ do_{force\ norepinephrine\ value}$:
$Norepinephrine_s = 0$
$if\ forced_{norepinephrine\ start} \leq t < forced_{norepinephrine\ end}$:
$Norepinephrine_s = forced_{norepinephrine\ value}$

Astrocyte, Synaptic cleft, and Perivascular space equations

Synaptic Cleft:

Cl- concentration in the SC, electroneutrality condition [μM]
$Cl_s = Na_s + K_s - HCO3_s$

Volume / surface area ratio of SC to AC [-]
$VR_{sa} = R_s/R_k$

Input of K+ to the SC (assuming that the SC is a small part of the ECS and everything that happens to the ECS also happens to the SC)
$J_{K\,NEtoSC\,k} = J_{K\,NEtoSC} * 1e3$ **Convert from mM/s to μM/s**
$J_{Na\,NEtoSC\,k} = J_{Na\,NEtoSC} * 1e3$ **Convert from mM/s to μM/s**

Astrocyte

Nernst potentials [mV]

Nernst potential for the K+ channel [mV]
$E_{K\,k} = ph/z_K * log(K_s/K_k)$
Nernst potential for the Na+ channel [mV]
$E_{Na\,k} = ph/z_{Na} * log(Na_s/Na_k)$
Nernst potential for the Cl- channel [mV]
$E_{Cl\,k} = ph/z_{Cl} * log(Cl_s/Cl_k)$
Nernst potential for the NBC channel [mV]
$E_{NBC\,k} = ph/z_{NBC} * log((Na_s * HCO3_s **2)/(Na_k * HCO3_k **2))$
Nernst potential for the BK channel [mV]
$E_{BK\,k} = ph/z_K * log(K_p/K_k)$
Nernst potential for the TRPV4 channel [mV]
$E_{TRPV\,k} = ph/z_{Ca} * log(Ca_p/Ca_k)$

Fluxes

Flux through the Sodium Potassium (Na+/K+) ATP-ase pump [μM/s]
$J_{NaK\,k} = J_{NaK\,max} * Na_k **1.5/(Na_k **1.5 + K_{Na\,k} **1.5) * K_s/(K_s + K_{K\,s})$
K+ flux through the BK channel [μM/s]
$J_{BK\,k} = G_{BK\,k} * w_k * (v_k - E_{BK\,k})$

Volume ratio of PVS to Astrocyte
$VR_{pa} = volume_p/volume_k$
Volume ratio of PVS to SMCEC
$VR_{ps} = volume_p/volume_i$
K+ influx into the PVS [μM/s]

$if enable_{volume\ changes\ dependencies}$:
$J_{BK\,p} = J_{BK\,k}/VR_{pa}$
$else$:
$J_{BK\,p} = J_{BK\,k}/VR_{pa}$
K+ flux throgh the K+ channel [μM/s]
$J_{K\,k} = G_{K\,k} * (v_k - E_{K\,k})$
Na+ flux through the K+ channel [μM/s]
$J_{Na\,k} = G_{Na\,k} * (v_k - E_{Na\,k})$
Na+ and HCO3- flux through the NBC channel [μM/s]
$J_{NBC\,k} = G_{NBC\,k} * (v_k - E_{NBC\,k})$
Cl- and K+ flux through the KCCl channel [μM/s]
$J_{KCC1\,k} = G_{KCC1\,k} * ph * log((K_s * Cl_s)/(K_k * Cl_k))$
Na+, K+ and Cl- flux through the NKCCl channel [μM/s]
$J_{NKCC1\,k} = G_{NKCC1\,k} * ph * log((Na_s * K_s * Cl_s * *2)/(Na_k * K_k * Cl_k * *2))$
Cl- flux through the Cl- channel [μM s1]**
$J_{Cl\,k} = G_{Cl\,k} * (v_k - E_{Cl\,k})$

New fluxes

$v_{KIR\,k} = z_1 * K_s - z_2$
$G_{KIR\,k} = exp(z_5 * v_k + z_3 * K_s - z_4)$
$J_{KIR\,k} = 0$ **F_KIR_k * G_KIR_k / gamma_i * (v_k - v_KIR_k)**

$J_{NaCa\,k} = 0$ **G_NaCa_k * Ca_k / (Ca_k + c_NaCa_k) * (v_k - v_NaCa_k)**
The flux of Ca2+ through the voltage operated Ca2+ channel (VOCC) which connects the SMC to the PCS [μM/s]
$J_{VOCC\,k} = 0$ **G_Ca_k * (v_k - v_Ca1_k) / (1 + exp(-(v_k - v_Ca2_k) / R_Ca_k))**

Calcium Equations

Fluxes

The flux of Ca2+ through the IP3R channel [μM/s]
$J_{IP3} = J_{max} * (I_k/(I_k + K_I) * Ca_k/(Ca_k + K_{act}) * h_k) * *3 * (1 - Ca_k/s_k)$
The flux of Ca2+ through the leak channel [μM/s]
$J_{ER\,leak} = P_L * (1 - Ca_k/s_k)$
The flux of Ca2+ through the uptake pump [μM/s]
$J_{pump} = V_{max} * Ca_k * *2/(Ca_k * *2 + k_{pump} * *2)$

The flux of Ca2+ through the TRPV4 channel [μM/s]
$I_{TRPV\,k} = G_{TRPV\,k} * m_k * (v_k - E_{TRPV\,k})$

$J_{TRPV\,k} = -I_{TRPV\,k}/(z_{Ca} * C_{astr\,k} * gamma_i)$

The ratio of bound to unbound metabotropic receptors on the astrocytic process adjacent to the SC [-]
$rho = rho_{min} + (rho_{max} - rho_{min})/Glu_{max} * Glu$
$rho_{noradrenaline} = (rho_{max} - rho_{min})/Glu_{max} * min(Norepinephrine_s * 1000, Glu_{max})$

Other equations

Fast Ca2+ buffering is described within the steady state approximation [-]
$B_{cyt} = 1/(1 + BK_{end} + K_{ex} * B_{ex}/(K_{ex} + Ca_k) * *2)$
The ratio of active to toal G-protein due to metabotropic glutamate receptor (mGluR) binding on the astrocyte endfoot surround the SC [-]
The inclusion of d allows for there to be background activity even in the absence of ligand binding (i.e. unbound receptors can still activate a small amount of G-protein). This behaviour is more fully described in the work of Lemon et al. (2003).
$G = (rho + delta)/(K_G + rho + delta)$
The ratio of active to total G-protein due to metabotropic noradrenaline receptor (alpha1R) [-]
$if rho_{noradrenaline} == 0 or not are_{noradrenaline\,pathways\,active}:$
$G_{noradrenaline} = 0$
$else:$
$G_{noradrenaline} = (rho_{noradrenaline} + delta)/(K_G + rho_{noradrenaline} + delta)$

The voltage associated with half open probability [mV]
$v_3 = v_6 - v_5/2 * tanh((Ca_k - Ca_3)/Ca_4)$

Parent Ca2+ equations
Equilibrium state BK-channel [-]
BK channel equations are taken from Gonzalez-Fernandez and Ermentrout (1994). Work by Lu et al. (2001) shows that both EETs and EET-derived dihydroxyeicosatrienoic acids (DHETs) act as potent activators of BK channels, where DHETs were shown to shift the voltage at which the channel open probability was half-maximal. We therefore incorporate a EET-dependent voltage shift (eet shift) into the relationship given by Gonzalez-Fernandez and Ermentrout (1994), to get n 1 , the equilibrium distribution of openings for the BK channel:
$w_{inf} = 0.5 * (1 + tanh((v_k + eet_{shift} * eet_k - v_3)/v_4))$
The time constant associated with the opening of the BK-channel [s-1]**
the time constant associated with the opening of BK channels, f n , is based on statistical considerations (Ehrenstein and Lecar, 1977). In this case, c n is a characteristic time and v 3 incorporates a calcium-dependent shift on the distribution of BK channel open states with respect to membrane voltage. v 3 is the voltage associated with the opening of half the population and v 4 is a measure of the spread of the distribution. v 5 determines the range of the shift of n 1 , as calcium varies.
$phi_w = psi_w * cosh((v_k - v_3)/(2 * v_4))$

TRPV Channel open probability equations

The Ca2+ inhibitory term [-]
$H_{Ca\,k} = Ca_k/gam_{cai\,k} + Ca_p/gam_{cae\,k}$
The strain on the perivascular endfoot of the astrocyte [-]
$eta = (R - R_{0\,passive\,k})/(R_{0\,passive\,k})$
The material strain gating term [-]
$gamma_m = 1/(1 + exp(-(eta - epshalf_k)/kappa_k))$
The equilibrium state of the TRPV4 channel [-]
$minf_k = gamma_m * ((1/(1 + H_{Ca\,k})) * (H_{Ca\,k} + tanh((v_k - v1_{TRPV\,k})/v2_{TRPV\,k})))$

Time for NO to diffuse between the centres of the neuron and the astrocyte [s]
$tau_{nk} = x_{nk} * *2/(2 * D_{cNO})$
Time for NO to diffuse between the centres of the astrocyte and the SMC [s]
$tau_{ki} = x_{ki} * *2/(2 * D_{cNO})$
Astrocyte NO production flux [μM/s]
$p_{NO\,k} = 0$
Astrocyte NO consumption flux [μM/s]
$c_{NO\,k} = k_{O2\,k} * NO_k * *2 * O2_k$
Astrocyte NO diffusive flux [μM/s]
$d_{NO\,k} = (NO_n - NO_k)/tau_{nk} + (NO_i - NO_k)/tau_{ki}$

Temp gap junction for bug testing

$flu_{gap\,K} = 0$ **((3.1e-9 / (1.24e-4)**2) * (92708 - K_k) + ((96.485 * 1)/(8.315 * 300)) * 0.5*(92708+K_k)*(-88.9-v_k))**

$flu_{gap\,diff\,Na} = (3.1e-9/(1.24e-4) * *2) * (18268 + 18268 + 18268 + 18268 - 4 * Na_k)$
$flu_{gap\,electro1\,Na} = ((3.1e-9 * 96.485 * 1)/((1.24e-4) * *2 * 8.315 * 300)) * (Na_k * (-88.9 + -88.9 + -88.9 + -88.9 - 4 * v_k))$
$flu_{gap\,Na} = 0$ **(flu_gap_diff_Na + flu_gap_electro1_Na)**

$flu_{gap\,diff\,Cl} = (3.1e-9/(1.24e-4) * *2) * (18268 + 18268 + 18268 + 18268 - 4 * Cl_k)$
$flu_{gap\,electro1\,Cl} = ((3.1e-9 * 96.485 * -1)/((1.24e-4) * *2 * 8.315 * 300)) * (Cl_k * (-88.9 + -88.9 + -88.9 + -88.9 - 4 * v_k))$
$flu_{gap\,Cl} = 0$ **(flu_gap_diff_Cl + flu_gap_electro1_Cl)**

$flu_{gap\,diff\,HCO3} = (3.1e-9/(1.24e-4) * *2) * (9131 + 9131 + 9131 + 9131 - 4 * HCO3_k)$
$flu_{gap\,electro1\,HCO3} = ((3.1e-9 * 96.485 * -1)/((1.24e-4) * *2 * 8.315 * 300)) * (HCO3_k * (-88.9 + -88.9 + -88.9 + -88.9 - 4 * v_k))$
$flu_{gap\,HCO3} = 0$ **(flu_gap_diff_HCO3 + flu_gap_electro1_HCO3)**

$flu_{gap\,diff\,Ca} = (3.1e-9/(1.24e-4) * *2) * (0.1612 + 0.1612 + 0.1612 + 0.1612 - 4 * Ca_k)$
$flu_{gap\,electro1\,Ca} = ((3.1e-9 * 96.485 * 2)/((1.24e-4) * *2 * 8.315 * 300)) * (Ca_k * (-88.9 + -88.9 + -88.9 + -88.9 - 4 * v_k))$
$flu_{gap\,Ca} = 0$ **(flu_gap_diff_Ca + flu_gap_electro1_Ca)**

$dvkdt = gamma_i * (-J_{BK\,k} - J_{K\,k} - J_{Cl\,k} - J_{NBC\,k} - J_{Na\,k} - J_{NaK\,k} + 2 * J_{TRPV\,k} + flu_{gap\,K} + flu_{gap\,Na} - flu_{gap\,Cl} - flu_{gap\,HCO3} + 2 * flu_{gap\,Ca})$

Volume changes equations

$n_{total\,ions} = astrocyte_{ions} + sc_{ions} + neuron_{ions} + ecs_{ions} + pvs_{ions}$
Astrocyte equilibrium volume [μm3]**
$volume_{k\,eq} = total_{volume} * astrocyte_{ions}/n_{total\,ions}$
$volume_{p\,eq} = total_{volume} * pvs_{ions}/n_{total\,ions}$

$Glu_{amb} = 0$ **[mM] Steady-state Glu**
$J_{NA} = r_{NA} + r_{NG} * (Glu - Glu_{amb}) + r_{NGt} * (Gt - GT_{amb})$
$NA_{amb} = 0$ **[mM] Steady-state (ambient) NA**
$tau_{NA} = 1.8$ **[s]**
$NA_{diff} = 0.0004$ **0.4 [mMs**-1] Coupling coefficient for NA**

Conservation Equations

The astrocyte membrane voltage changes due to fluxes of ions leaving the astrocyte, namely: the potassium flux through BK channels (J BK k) and a general leak flux (J leak k —not to be confused with J ER leak). where C ast is the astrocyte cell membrane capacitance
Noradrenaline concentration in the synaptic cleft (SC) [mM]
$if not do_{enable\,norepinephrine\,reuptake\,inhibition}$:
$d[Norepinephrine_s]/dt = J_{NA} + (NA_{amb} - Norepinephrine_s)/tau_{NA} + NA_{diff}$
$else$:
$d[Norepinephrine_s]/dt = J_{NA} + NA_{diff}$

Gliotransmitter dynamics
$d[Gt]/dt = SVR_{AVF} * k_{gt}/(1 + (k_m/Ca_k) * *2) - (Gt - GT_{amb})/tau_{GT} + Gt_{diff}$

Membrane potential of the astrocyte (AC) [mV]
$d[v_k]/dt = gamma_i * (-J_{BK\,k} - J_{K\,k} - J_{Cl\,k} - J_{NBC\,k} - J_{Na\,k} - J_{NaK\,k} + 2 * J_{TRPV\,k} + flu_{gap\,K} + flu_{gap\,Na} - flu_{gap\,Cl} - flu_{gap\,HCO3} + 2 * flu_{gap\,Ca})$

Differential Equations in the Astrocyte

K + concentration in the astrocyte [μM]
$d[K_k]/dt = -J_{K\,k} + 2 * J_{NaK\,k} + J_{NKCC1\,k} + J_{KCC1\,k} - J_{BK\,k} - J_{KIR\,k} + flu_{gap\,K}$
Na + concentration in the astrocyte [μM]
$d[Na_k]/dt = -J_{Na\,k} - 3 * J_{NaK\,k} + J_{NKCC1\,k} + J_{NBC\,k} - 3 * J_{NaCa\,k} + flu_{gap\,Na}$
HCO3- concentration in the astrocyte [μM]
$d[HCO3_k]/dt = 2 * J_{NBC\,k} + flu_{gap\,HCO3}$
Cl- concentration in the astrocyte [μM]
$d[Cl_k]/dt = d[Na_{k]} + d[K_{k]} - d[HCO3_{k]} + 2 * d[Ca_{k]}$

Differential Calcium Equations in Astrocyte

Calcium moves between the cytosol and the endoplasmic reticulum (ER), and the cytosol and the extracellular space surrounding the astrocyte, by several mechanisms. We denote the calcium flux from the ER to the cytosolic volume through IP 3 receptors (IP 3 R) by J IP 3 , the leakage flux from the ER to the cytosol as J ER leak and the ATP-dependent pump flux from cytoplasm to ER as J pump . The constant B cyt is a steady state approximation for buffering in the cytosol

The astrocytic cytosolic Ca2+ concentration [μM]

$d[Ca_k]/dt = B_{cyt} * (J_{IP3} - J_{pump} + J_{ER\,leak} + J_{NaCa\,k} - J_{VOCC\,k} + J_{TRPV\,k}/r_{buff} + flu_{gap\,Ca})$

s k , the concentration of calcium in the ER, was assumed to be constant in the original model (Bennett et al., 2008). where VR ERcyt is the ratio of ER (stores) volume to cytosolic volume.

The Ca2+ concentration in the astrocytic endoplasmic reticulum (ER) [μM]

$d[s_k]/dt = -(B_{cyt} * (J_{IP3} - J_{pump} + J_{ER\,leak}))/(VR_{ER\,cyt})$

Here k on is the rate of Ca2+ binding to the inhibitory site on the IP 3 R and K inh is the corresponding dissociation constant

The inactivation variable of the astrocytic IP3R channel [-]

$d[h_k]/dt = k_{on} * (K_{inh} - (Ca_k + K_{inh}) * h_k)$

The astrocytic inositol trisphosphate (IP3) concentration [μM]

$d[I_k]/dt = r_h * (G + G_{noradrenaline}) - k_{deg} * I_k$

The open probability of the transient receptor potential vanniloid-related 4 (TRPV4) channel that can switch it on or off [-]

$d[m_k]/dt = trpv_{switch} * ((minf_k - m_k)/t_{TRPV\,k})$

The astrocytic epoxyeicosatrienoic acid (EET) concentration (μM)

k_eet degradation is assumed to follow the first-order kinetics.

$d[eet_k]/dt = V_{eet} * max(Ca_k - Ca_{k\,min,}0) - k_{eet} * eet_k$

The open probability of the big potassium (BK) channel [-]

The time course of the fraction of BK channel open states, n, is described, after Morris and Lecar (1981), by the first-order kinetics of opening

$d[w_k]/dt = phi_w * (w_{inf} - w_k)$

Differential Equations in the Perivascular space

K+ concentration in the PVS [μM]

We adopt a simple model for the concentration of potassium in this perivascular space at this stage—assuming that the accumulating potassium is removed by a potassium-dependent decay term. Potassium enters the perivascular space via astrocyte BK channels and SMC KIR channels, with corresponding fluxes denoted by J BK k and J KIR k , respectively. The balance of these fluxes, along with the decay term, gives the following differential equation

$if enable_{volume\ changes\ dependencies}$:

$d[K_p]/dt = J_{BK\,k}/VR_{pa} + J_{KIR\,i}/VR_{ps} - R_{decay} * (K_p - K_{p\,min})$ **+ J__K__ECS__to__PVS**

$else$:

$d[K_p]/dt = J_{BK\,k}/VR_{pa} + J_{KIR\,i}/VR_{ps} - R_{decay} * (K_p - K_{p\,min})$

Ca2+ concentration in the PVS [μM]

$d[Ca_p]/dt = (-J_{TRPV\,k} + J_{VOCC\,k})/VR_{pa} + J_{VOCC\,i}/VR_{ps} - Ca_{decay\,k} * (Ca_p - Capmin_k)$
calcium concentration in PVS

Differential Equations in the Synaptic Cleft

Potassium is released into this space by the neurons only during neuronal activation, and is constantly removed from the space via the Na–K pump positioned on the top "arm" of the astrocyte. The smooth "pulse" of potassium release during neuronal activation is represented by J K s , and the Na–K pump flux is denoted by J NaK s .
K + concentration in the synaptic cleft (SC) [μM]
$d[K_s]/dt = 1/VR_{sa} * (J_{K\,k} - 2 * J_{NaK\,k} - J_{NKCC1\,k} - J_{KCC1\,k} + J_{KIR\,k}) + J_{K\,NEtoSC\,k}$
Na + concentration in the SC [μM]
$d[Na_s]/dt = 1/VR_{sa} * (J_{Na\,k} + 3 * J_{NaK\,k} - J_{NKCC1\,k} - J_{NBC\,k}) + J_{Na\,NEtoSC\,k}$
HCO3- concentration in the SC [μM]
$d[HCO3_s]/dt = 1/VR_{sa} * (-2 * J_{NBC\,k})$

NO concentration in the astrocyte [μM]
$d[NO_k]/dt = p_{NO\,k} - c_{NO\,k} + d_{NO\,k}$

Volume changes

Astrocyte volume [μm3]**
$d[volume_k]/dt = (volume_{k\,eq} - volume_k)/tau_{volume\,change\,k}$
PVS volume [μm3]**
$d[volume_p]/dt = (volume_{p\,eq} - volume_p)/tau_{volume\,change\,p}$

4.3 Smooth Muscle Cell and Endothelial Cell

Smooth muscle cell and Endothelial cell initial conditions:

Table 6: Neuron and ECS initial conditions

Parameter	Value	Unit	Description
Ca_i	0.2637	μM	Cytosolic Ca2+ in the SMC
s_i	1.1686	μM	Ca2+ in the sarcoplasmic reticulum (SR) of the SMC
v_i	-34.7	mV	Membrane potential of the SMC
w_i	0.2206	–	Open state probability of Ca2+ - activated K+ channels
I_i	0.275	μM	IP3 concentration in the SMC
K_i	99994.8	μM	K+ concentration in the SMC
NO_i	0.0541	μM	NO concentration in the SMC
E_b	0.4077	–	Fraction of soluble guanylyl cyclase (sGC) in the basal state

E_{6c}	0.4396	$-$	Fraction of sGC in the intermediate form
$cGMP_i$	8.2826	μM	Concentration of cGMP in the SMC
Ca_j	0.8331	μM	Cytosolic Ca2+ concentration in the EC
s_j	0.6266	μM	Ca2+ concentration in the ER in the EC
v_j	-68.27	mV	Membrane potential of the EC
I_j	0.825	μM	IP3 concentration of the EC
$eNOS_{act\,j}$	0.4479	μM	Activated endothelial NO synthase (eNOS)
NO_j	0.0528	μM	NO concentration in the EC

Smooth muscle cell and Endothelial cell parameters:

Table 7: Neuron and ECS initial conditions

Parameter	Value	Unit	Description
$NOswitch$	1	$-$	
$gamma_i$	1970	$mV\mu M * *-1$	
$lambda_i$	45	$s**-1$	Rate constant for opening
$C_{m\,j}$	25.8	pF	Membrane capacitance
J_{PLC}	0.11	$\mu Ms**-1$	IP3 production rate
$J_{0\,j}$	0.029	$\mu Ms**-1$	Constant Ca influx (EC)
F_i	0.23	$\mu Ms**-1$	Maximal rate of activation-dependent Ca2+ influx, IP3/RYR channel strength
$K_{r\,i}$	1	μM	Half-saturation constant for agonist-dependent Ca2+ entry
B_i	2.025	$\mu Ms**-1$	SR updake rate constant (SERCA pump strength)
$c_{b\,i}$	1.0	μM	
C_i	55	$\mu Ms**-1$	CICR rate constant
$s_{c\,i}$	2.0	μM	Half-point of the CICR Ca2+ efflux sigmoidal
$c_{c\,i}$	0.9	μM	Half-point of the CICR activation sigmoidal
D_i	0.24	$s**-1$	Rate constant for Ca2+ extrusion by the ATP-ase pump
v_d	-100	mV	Intercept of voltage dependence of extrusion ATP-ase
$R_{d\,i}$	250	mV	Slope of voltage dependence of extrusion ATP-ase
L_i	0.025	$s**-1$	Leak from SR rate constant
$G_{Ca\,i}$	1.29e-3	$\mu MmV * *-1s**-1$	Whole-cell conductance for VOCCs
$v_{Ca1\,i}$	100	mV	Reversal potential for VOCCs

$v_{Ca2\,i}$	-24	mV	Half-point of the VOCC activation sigmoidal
$R_{Ca\,i}$	8.5	mV	Maximum slope of the VOCC activation sigmoidal
$G_{NaCa\,i}$	3.16e-3	$\mu MmV * *-1s**-1$	Whole-cell conductance for Na+/Ca2+ exchange
$c_{NaCa\,i}$	0.5	μM	Half-point for activation of Na+/Ca2+ exchange by Ca2+
$v_{NaCa\,i}$	-30	mV	Reversal potential for the Na+/Ca2+ exchanger
$G_{stretch}$	6.1e-3	$\mu MmV * *-1s**-1$	Whole cell conductance for stretch activated channels (SACs) (Also EC parameter)
$alpha_{stretch}$	7.4e-3	$mmHg**-1$	Slope of stress dependence of the SAC activation sigmoidal (Also EC parameter)
$trans_{p\,mmHg}$	30	$mmHg$	Pressure difference over vessel (Also EC parameter) (transmural pressure)
$sigma_0$	500	$mmHg$	Half-point of the SAC activation sigmoidal (Also EC parameter)
E_{SAC}	-18	mV	Reversal potential for SACs (Also EC parameter)
$F_{NaK\,i}$	4.32e-2	$\mu Ms**-1$	Rate of the K+ influx by the Na+/K+ pump
$G_{Cl\,i}$	1.34e-3	$\mu MmV * *-1s**-1$	Whole-cell conductance for Cl-current
$v_{Cl\,i}$	-25	mV	Reversal potential for Cl- channels
$G_{K\,i}$	4.46e-3	$\mu MmV * *-1s**-1$	Whole-cell conductance for K+ efflux
$v_{K\,i}$	-94	mV	Nernst potential
$F_{KIR\,i}$	7.5e2	$-$	Scaling factor of K+ efflux through the KIR channel
$k_{d\,i}$	0.1	$s**-1$	Rate constant of IP3 degradation
$G_{EET\,i}$	0.0	$\mu Ms**-1$	Max rate of effective Ca2+ reduction (0 = disabled). Calibrated: 0.03
$K_{EET\,i}$	0.9	μM	Effective half-activation EET concentration (model parameter, not measured EC50)
F_j	0.23	$\mu Ms**-1$	Maximal rate of activation-dependent Ca2+ influx
$K_{r\,j}$	1	μM	Half-saturation constant for agonist-dependent Ca2+ entry
B_j	0.5	$\mu Ms**-1$	ER uptake rate constant
$c_{b\,j}$	1	μM	Half-point of the SR ATP-ase activation sigmoidal
C_j	5	$\mu Ms**-1$	CICR rate constant

$s_{c\,j}$	2	μM	Half-point of the CICR Ca2+ efflux sigmoidal
$c_{c\,j}$	0.9	μM	Half-point of the CICR activation sigmoidal
D_j	0.24	$s**-1$	Rate constant for Ca2+ extrusion by the ATP-ase pump
L_j	0.025	$s**-1$	Rate constant for Ca2+ leak from the ER
$G_{cat\,j}$	6.6e-4	μMmV $**-1s**-1$	Whole-cell cation channel conductivity
$E_{Ca\,j}$	50	mV	Ca2+ equilibrium potential
$m_{3\,cat\,j}$	-0.18	μM	Model constant, further explanations at Koenigsberger, M., Sauser, R., Bény, J.-L. J. L., and Meister, J.-J. J. J.-J. (2006). Effects of arterial wall stress on vasomotion. Biophysical journal, 91(September):1663–1674.
$m_{4\,cat\,j}$	0.37	μM	Model constant, further explanations at Koenigsberger, M., Sauser, R., Bény, J.-L. J. L., and Meister, J.-J. J. J.-J. (2006). Effects of arterial wall stress on vasomotion. Biophysical journal, 91(September):1663–1674.
$G_{tot\,j}$	6927	$pmho$	Total K+ channel conductivity
$v_{K\,j}$	-80	$mmho$	K+ equilibrium potential
c	-0.4	μM	Model constant, further explanations at Koenigsberger, M., Sauser, R., Bény, J.-L. J. L., and Meister, J.-J. J. J.-J. (2006). Effects of arterial wall stress on vasomotion. Biophysical journal, 91(September):1663–1674.
bb_j	-80.8	mV	Model constant, further explanations at Koenigsberger, M., Sauser, R., Bény, J.-L. J. L., and Meister, J.-J. J. J.-J. (2006). Effects of arterial wall stress on vasomotion. Biophysical journal, 91(September):1663–1674.
$a_{1\,j}$	53.3	μMmV	Model constant, further explanations at Koenigsberger, M., Sauser, R., Bény, J.-L. J. L., and Meister, J.-J. J. J.-J. (2006). Effects of arterial wall stress on vasomotion. Biophysical journal, 91(September):1663–1674.

$a_{2\,j}$	53.3	$mV\mu M * * -1$	Model constant, further explanations at Koenigsberger, M., Sauser, R., Bény, J.-L. J. L., and Meister, J.-J. J. J.-J. (2006). Effects of arterial wall stress on vasomotion. Biophysical journal, 91(September):1663–1674.
$m_{3b\,j}$	1.32e-3	$\mu M mV * * -1$	Model constant, further explanations at Koenigsberger, M., Sauser, R., Bény, J.-L. J. L., and Meister, J.-J. J. J.-J. (2006). Effects of arterial wall stress on vasomotion. Biophysical journal, 91(September):1663–1674.
$m_{4b\,j}$	0.3	$\mu M mV$	Model constant, further explanations at Koenigsberger, M., Sauser, R., Bény, J.-L. J. L., and Meister, J.-J. J. J.-J. (2006). Effects of arterial wall stress on vasomotion. Biophysical journal, 91(September):1663–1674.
$m_{3s\,j}$	-0.28	μM	Model constant, further explanations at Koenigsberger, M., Sauser, R., Bény, J.-L. J. L., and Meister, J.-J. J. J.-J. (2006). Effects of arterial wall stress on vasomotion. Biophysical journal, 91(September):1663–1674.
$m_{4s\,j}$	0.389	μM	Model constant, further explanations at Koenigsberger, M., Sauser, R., Bény, J.-L. J. L., and Meister, J.-J. J. J.-J. (2006). Effects of arterial wall stress on vasomotion. Biophysical journal, 91(September):1663–1674.
$G_{R\,j}$	955	$pomh$	Residual current conductivity
$v_{rest\,j}$	-31.1	mV	Membrane resting potential
$k_{d\,j}$	0.1	$s**-1$	Rate constant of IP3 degradation
P_{Ca}	0.05	$s**-1$	Heterocellular P_Ca coupling coefficient
P_{IP3}	0.05	$s**-1$	Heterocellular IP3 coupling coefficient
G_{coup}	0.5	$s**-1$	Heterocellular electrical coupling coefficient
$beta_i$	0.13	$\mu M**2$	Translation factor for v_i dependence of K_act_i sigmoidal
$v_{Ca3\,i}$	-27	mV	Half-point for the K_Ca activation sigmoidal
$R_{K\,i}$	12	mV	Maximum slope of the K_Ca activation sigmoidal

z_1	4.5e-3	$mV\mu M * * -1$	Model estimation for the membrane voltage KIR channel
z_2	112	mV	Model estimation for membrane voltage KIR channel
z_3	4.2e-4	$\mu M * * -1$	Model estimation for the KIR channel conductance
z_4	12.6	$-$	Model estimation for the KIR channel conductance
z_5	-7.4e-2	$mV * * -1$	Model estimation for the KIR channel conductance
$beta_{w\,i}$	1	μM	Constant to fit data
$alpha_{w\,i}$	10.75	μM	Constant to fit data
$eps_{w\,i}$	0.668	μM	Constant to fit data
D_{cNO}	3300	$\mu M * *2s * * -1$	NO diffusion coefficient (Malinski1993)
$K_{mArg\,j}$	1.5	μM	Michaelis constant for L-Arg
$K_{mO2\,j}$	7.7	μM	Michaelis constant for eNOS for O2 (Chen2006)
k_{dno}	0.01	$s * * -1$	Constant reflecting the activity of various NO scavengers
$K_{m\,mlcp}$	5.5	μM	Hill coefficient
$V_{NOj\,max}$	1.22	$s * * -1$	Maximum catalytic rate of NO production (Chen2006) - obtained from fig 6 and equ 17 and 18
$O2_j$	200	μM	O2 concentration in the EC (ME)
$LArg_j$	100	μM	L-Arg concentration in the neuron
k_{O2}	9.6e-6	$\mu M * *-2s * * -1$	O2 reaction rate constant
W_0	1.4	$Pa * * -1$	shear gating constant (Comerford2008)
$delta_{wss}$	2.86	Pa	the membrane shear modulus (Comerford2008)
k_1	100	$s * * -1$	sGC kinetics rate constant
$k1$	2e3	$\mu M * *-1s * * -1$	sGC kinetics rate constant
$k2$	0.1	$s * * -1$	sGC kinetics rate constant
$k3$	3	$\mu M * *-1s * * -1$	sGC kinetics rate constant
$V_{max\,sGC}$	0.8520	?	Maximal cGMP production rate
k_{pde}	0.0195	$s * * -1$	Phosphodiesterase rate constant
C_4	0.011	$s * *-1\mu M * * -2$	sGC rate scaling constant
$K_{m\,pde}$	2	μM	Michaelis constant
gam_{eNOS}	0.1	$-$	Relative strength of the Ca2+ dependent pathway for eNOS activation
$mu2_j$	0.0167	$s * * -1$	eNOS-caveolin association rate

K_{dis}	9e-2	$\mu Ms**-1$	eNOS-caveolin disassociation rate
K_{eNOS}	4.5e-1	μM	
g_{max}	0.06	$\mu Ms**-1$	Maximum wall-shear-stress-induced eNOS activation
alp	2	$-$	Zero shear open channel constant (Comerford2008) in Wiesner1997 alp = 3
$delta_{p\,L}$	9.1e4	?	Pressure drop over length of arteriole (M.E.)
x_{ki}	25	μM	Distance between centers of astrocyte and SMC compartments (M.E.)
x_{ij}	3.75	μM	Distance between centres of SMC and EC compartments (Kavdia2002)
r_l	25	μM	Lumen radius
F	9.65e4	$Cmol**-1$	Faraday's constant
R_{gas}	8.315	$Jmol**-1K**-1$	Gas constant
T	300	K	Temperature

Smooth muscle cell and Endothelial cell shared equations

Regulatory effect of cGMP on myosin dephosphorylation [-]
$R_{cGMP2} = cGMP_i**2/(cGMP_i**2 + K_{m\,mlcp}**2)$

Nernst potential of the KIR channel in the SMC [mV]
$v_{KIR\,i} = z_1 * K_p - z_2$
Conductance of KIR channel [μM mV-1 s**-1]**
$g_{KIR\,i} = exp(z_5 * v_i + z_3 * K_p - z_4)$
Flux through inward rectifying K+ (KIR) channels in the SMC [μM s-1]**
$J_{KIR\,i} = F_{KIR\,i} * g_{KIR\,i}/gamma_i * (v_i - v_{KIR\,i})$
The flux of Ca 2+ through the voltage operated Ca2+ channel (VOCC) which connects the smooth muscle cell (SMC) to the PVS [μM s-1]**
$J_{VOCC\,i} = G_{Ca\,i} * (v_i - v_{Ca1\,i})/(1 + exp(-(v_i - v_{Ca2\,i})/R_{Ca\,i}))$

Smooth muscle cell and Endothelial cell equations

Initalize inputs and parameters

SMC fluxes

Release of Ca2+ from IP3 sensitive stores in the SMC [μM s-1]**
$J_{IP3\,i} = F_i * I_i**2/(K_{r\,i}**2 + I_i**2)$
Uptake of Ca2+ into the SR (SERCA pump) [μM s-1]**
$J_{SR\,uptake\,i} = B_i * Ca_i**2/(c_{b\,i}**2 + Ca_i**2)$

Ca2+ induced Ca2+ release (CICR) [μM s-1]**
$J_{CICR\,i} = C_i * s_i * *2/(s_{c\,i} * *2 + s_i * *2) * Ca_i * *4/(c_{c\,i} * *4 + Ca_i * *4)$
Ca2+ extrusion by Ca2+-ATP-ase pumps [μM s-1]**
$J_{extrusion\,i} = D_i * Ca_i * (1 + (v_i - v_d)/R_{d\,i})$
Leak current from the SR [μM s-1]**
$J_{SR\,leak\,i} = L_i * s_i$

Flux of Ca2+ exchanging with Na+ in the Na+/Ca2+ exchange [μM s-1]**
$J_{NaCa\,i} = G_{NaCa\,i} * Ca_i/(Ca_i + c_{NaCa\,i}) * (v_i - v_{NaCa\,i})$
Ca2+ flux through the stretch-activated channels in the SMC [μM s-1]**
$J_{stretch\,i} = G_{stretch}/(1 + exp(-alpha_{stretch} * (trans_{p\,mmHg} * R/h - sigma_0))) * (v_i - E_{SAC})$
Cl- flux through the Cl- channel [μM s-1]**
$J_{Cl\,i} = G_{Cl\,i} * (v_i - v_{Cl\,i})$
Flux through the Na+/K+ pump [μM s-1]**
$J_{NaK\,i} = F_{NaK\,i}$
Nernst potential

Flux through inward rectifying K+ (KIR) channels in the SMC [μM s-1]**
$J_{K\,i} = G_{K\,i} * w_i * (v_i - v_{K\,i})$
Equation with this dynamic v_K_i leads to unstable outcomes. Needs further balances and tests if it is to be used

EET-mediated vasodilation – phenomenological reduction of SMC Ca2+.
Physiological mechanism: astrocyte EET - > TRPV4 Ca2+ sparklets - > RyR sparks - > BK_Ca
activation - > V_m hyperpolarization - > reduced VOCC/Ca_V1.2 influx - > lower global Ca_i
(Earley et al. 2005, Circ Res 97:1270; Tran/Institoris et al. 2022, Nature Neurosci).
Implemented here as an effective Ca_i sink (reduced-order approximation) rather than
explicitly routing through the V_m/VOCC chain. A more mechanistic alternative would be
to attenuate J_VOCC_i or add a hyperpolarizing current to v_i. Hill coefficient n=2
represents the multi-step cascade steepness. K_EET_i is an effective potency parameter,
not a directly measured EC50 — literature supports submicromolar EET activity (300 nM
11,12-EET activates TRPV4 in arterial SMCs; Earley et al. 2005).
$J_{EET\,i} = G_{EET\,i} * eet_k * *2/(eet_k * *2 + K_{EET\,i} * *2)$

IP3 degradation [μM s-1]**
$J_{degrad\,i} = k_{d\,i} * I_i$

EC fluxes

Release of Ca2+ from IP3-sensitive stores in the EC [μM s-1]**
$J_{IP3\,j} = F_j * I_j * *2/(K_{r\,j} * *2 + I_j * *2)$

Uptake of Ca2+ into the endoplasmic reticulum [μM s-1]**
$J_{ER\,uptake\,j} = B_j * Ca_j * *2/(c_{b\,j} * *2 + Ca_j * *2)$
CICR [μM s-1]**
$J_{CICR\,j} = C_j * s_j * *2/(s_{c\,j} * *2 + s_j * *2) * Ca_j * *4/(c_{c\,j} * *4 + Ca_j * *4)$
Ca2+ extrusion by Ca2+-ATP-ase pumps [μM s-1]**
$J_{extrusion\,j} = D_j * Ca_j$
Ca2+ flux through the stretch-activated channels in the EC [μM s-1]**
$J_{stretch\,j} = G_{stretch}/(1 + exp(-alpha_{stretch} * (trans_{p\,mmHg} * R/h - sigma a_0))) * (v_j - E_{SAC})$
Leak current from the ER [μM s-1]**
$J_{ER\,leak\,j} = L_j * s_j$
Ca2+ influx through nonselective cation channels [μM s-1]**
$J_{cation\,j} = G_{cat\,j} * (E_{Ca\,j} - v_j) * 0.5 * (1 + tanh((nlog10(Ca_j) - m_{3\,cat\,j})/m_{4\,cat\,j}))$
K+ efflux through the BK_Ca_j channel [-]
$J_{BK\,Ca\,j} = 0.2 * (1 + tanh(((nlog10(Ca_j) - c) * (v_j - bb_j) - a_{1\,j})/(m_{3b\,j} * (v_j + a_{2\,j} * (nlog10(Ca_j) - c) - bb_j) * *2 + m_{4b\,j})))$
K+ efflux through the SK_Ca_j channel [-]
$J_{SK\,Ca\,j} = 0.3 * (1 + tanh((nlog10(Ca_j) - m_{3s\,j})/m_{4s\,j}))$
K+ current through the BK_Ca_j channel and the SK_Ca_j channel [fA]
$J_{K\,j} = G_{tot\,j} * (v_j - v_{K\,j}) * (J_{BK\,Ca\,j} + J_{SK\,Ca\,j})$
Residual current regrouping Cl- and Na+ current flux [fA]
$J_{R\,j} = G_{R\,j} * (v_j - v_{rest\,j})$
IP3 degradation [μM s-1]**
$J_{degrad\,j} = k_{d\,j} * I_j$

Coupling

Heterocellular electrical coupling between SMCs and endothelial cells (ECs) [mV s-1]**
$V_{coup\,i} = -G_{coup} * (v_i - v_j)$
Heterocellular IP3 coupling between SMCs and ECs [μM s-1]**
$J_{IP3\,coup\,i} = -P_{IP3} * (I_i - I_j)$
Ca2+ coupling between SMCs and ECs [μM s-1]**
$J_{Ca\,coup\,i} = -P_{Ca} * (Ca_i - Ca_j)$

Translation factor, regulatory effect of cyclic guanosine monophosphate (cGMP) on the BK channel open probability [μM]
$c_{w\,i} = beta_{w\,i}/2 * (1 + tanh((cGMP_i - alpha_{w\,i})/eps_{w\,i}))$

Equilibrium distribution of open channel states for the SMC BK channels [-]
$K_{act\,i} = (Ca_i + c_{w\,i}) * *2/((Ca_i + c_{w\,i}) * *2 + beta_i * exp(-(v_i - v_{Ca3\,i})/R_{K\,i}))$

Wall shear stress (from Dormanns 2016) [Pa]
$tau_{wss} = R/2 * delta_{p\,L}$

Time for NO to diffuse between the centres of the astrocyte and the SMC [s]
$tau_{ki} = x_{ki} * *2/(2 * D_{cNO})$
Time for NO to diffuse between the centres of the SMC and the EC [s]
$tau_{ij} = x_{ij} * *2/(2 * D_{cNO})$
SMC NO production flux [μM/s]

$p_{NO\,i} = 0$
SMC NO consumption flux [μM/s]
$c_{NO\,i} = k_{dno} * NO_i$
SMC NO diffusive flux [μM/s]
$d_{NO\,i} = (NO_k - NO_i)/tau_{ki} + (NO_j - NO_i)/tau_{ij}$

sGC kinetics rate constant [s-1]**
$k4 = C_4 * cGMP_i * *2$
Fraction of sGC in the fully activated form [-]
$E_{5c} = 1 - E_b - E_{6c}$

Maximum cGMP production rate [μM/s]
$V_{max\,pde} = k_{pde} * cGMP_i$

O2 concentration in EC (Oxygen in EC taken as O2 from lumen (diffusion very fast so plausible!) instead of constant, in μM) [μM]
$O2_j = O2 * 1e3$
EC NO production flux [μM/s]
$p_{NO\,j} = NOswitch * (V_{NOj\,max} * eNOS_{act\,j} * O2_j/(K_{mO2\,j} + O2_j) * LArg_j/(K_{mArg\,j} + LArg_j))$
EC NO consumption flux [μM/s]
$c_{NO\,j} = k_{O2} * NO_j * *2 * O2_j$

$J_{lumen} = -NO_j * 4 * D_{cNO}/(r_l * *2)$
EC NO diffusive flux [μM/s]
$d_{NO\,j} = (NO_i - NO_j)/tau_{ij} + J_{lumen}$

Strain energy density [-]
$W_{wss} = W_0 * (tau_{wss} + nsqrt(16 * delta_{wss} * *2 + tau_{wss} * *2) - 4 * delta_{wss}) * *2/(tau_{wss} + nsqrt(16 * delta_{wss} * *2 + tau_{wss} * *2))$
Fraction of the elastic strain energy stored within the membrane [-]
$F_{wss} = 1/(1 + alp * exp(-W_{wss})) - 1/(1 + alp)$

$Act_{eNOS\,Ca} = K_{dis} * Ca_j/(K_{eNOS} + Ca_j)$
$Act_{eNOS\,wss} = g_{max} * F_{wss}$

Differential Equations

Smooth muscle cell

Cytosolic Ca2+ in the SMC [μM]
$d[Ca_i]/dt = J_{IP3\,i} - J_{SR\,uptake\,i} - J_{extrusion\,i} + J_{SR\,leak\,i} - J_{VOCC\,i} + J_{CICR\,i} + J_{NaCa\,i} - 0.1 * J_{stretch\,i} + J_{Ca\,coup\,i} - J_{EET\,i}$
Ca2+ in the sarcoplasmic reticulum (SR) of the SMC [μM]
$d[s_i]/dt = J_{SR\,uptake\,i} - J_{CICR\,i} - J_{SR\,leak\,i}$
Membrane potential of the SMC [mV]
$d[v_i]/dt = gamma_i * (-J_{NaK\,i} - J_{Cl\,i} - 2 * J_{VOCC\,i} - J_{NaCa\,i} - J_{K\,i} - J_{stretch\,i} - J_{KIR\,i}) + V_{coup\,i}$
Open state probability of Ca2+-activated K+ channels [-]

$d[w_i]/dt = lambda_i * (K_{act\,i} - w_i)$
IP3 concentration in the SMC [μM]
$d[I_i]/dt = J_{IP3\,coup\,i} - J_{degrad\,i}$
K+ concentration in the SMC [μM]
$d[K_i]/dt = J_{NaK\,i} - J_{KIR\,i} - J_{K\,i}$

Endothelial Cell

Cytosolic Ca2+ concentration in the EC [μM]
$d[Ca_j]/dt = J_{IP3\,j} - J_{ER\,uptake\,j} + J_{CICR\,j} - J_{extrusion\,j} + J_{ER\,leak\,j} + J_{cation\,j} + J_{0\,j} - J_{stretch\,j} - J_{Ca\,coup\,i}$
Ca2+ concentration in the ER in the EC [μM]
$d[s_j]/dt = J_{ER\,uptake\,j} - J_{CICR\,j} - J_{ER\,leak\,j}$
Membrane potential of the EC [mV]
$d[v_j]/dt = -1/C_{m\,j} * (J_{K\,j} + J_{R\,j}) - V_{coup\,i}$
IP3 concentration of the EC [μM]
$d[I_j]/dt = J_{PLC} - J_{degrad\,j} - J_{IP3\,coup\,i}$ **J_PLC or input_plc(t)**

NO concentration in the SMC
$d[NO_i]/dt = p_{NO\,i} - c_{NO\,i} + d_{NO\,i}$
Fraction of soluble guanylyl cyclase (sGC) in the basal state [-]
$d[E_b]/dt = -k1 * E_b * NO_i + k_1 * E_{6c} + k4 * E_{5c}$
Fraction of sGC in the intermediate form [-]
$d[E_{6c}]/dt = k1 * E_b * NO_i - (k_1 + k2) * E_{6c} - k3 * E_{6c} * NO_i$
Concentration of cGMP in the SMC [μM]
$d[cGMP_i]/dt = V_{max\,sGC} * E_{5c} - V_{max\,pde} * cGMP_i/(K_{m\,pde} + cGMP_i)$
Activated endothelial NO synthase (eNOS) [μM]
$d[eNOS_{act\,j}]/dt = (gam_{eNOS} * Act_{eNOS\,Ca} + (1 - gam_{eNOS}) * Act_{eNOS\,wss} - mu2_j * eNOS_{act\,j})$
NO concentration in the EC [μM]
$d[NO_j]/dt = p_{NO\,j} - c_{NO\,j} + d_{NO\,j}$

4.4 Wall Mechanics

Wall mechanics initial conditions:

Table 8: Neuron and ECS initial conditions

Parameter	Value	Unit	Description
Mp	0.0842	–	Fraction of free phosphorylated cross-bridges
AMp	0.0622	–	Fraction of attached phosphorylated cross-bridges
AM	0.2746	–	Fraction of attached dephosphorylated cross-bridges
R	22.97e-6	m	Vessel radius

Wall mechanics parameters:

Table 9: Neuron and ECS initial conditions

Parameter	Value	Unit	Description
$wallMech$	1.7	–	Scaling constant for wall mechanics
$delta_{wall\,k}$	58.1395	–	Constant to fit data
K_3	0.4	$s**-1$	
K_4	0.1	$s**-1$	
K_7	0.1	$s**-1$	
$gamma_{cross}$	17	$\mu M**-3s**-1$	
n_{cross}	3	–	Fraction constant of the phosphorylation cross-bridge
eta	1e4	Pas	Viscosity
$R_{0\,passive}$	20e-6	m	Vessel radius when passive and no stress is applied
$trans_p$	4000	Pa	transmural pressure
$E_{passive}$	66e3	Pa	
E_{active}	233e3	Pa	Young's moduli for the active vessel
$alpha_{wall}$	0.6	–	Scaling factor for initial radius
$k_{mlcp\,b}$	0.0086	$s**-1$	Basal MLC dephosphorylation rate constant
$k_{mlcp\,c}$	0.0327	$s**-1$	First-order rate constant for cGMP regulated MLC dephosphorylation

Wall mechanics shared equations

Wall thickness of the vessel [μm]
$h = 0.1 * R$

Wall mechanics equations

Contraction Equations

Equations describing the motion of the arterial wall are modified from the model of Kudryashov and Chernyavskii (2008).
Rate constants for phosphorylation of M to Mp and of AM to AMp [s-1]**
$K_1 = gamma_{cross} * Ca_i * *n_{cross}$
$K_6 = K_1$
Rate constants for dephosphorylation of Mp to M and of AMp to AM [s-1]**
$K_2 = delta_{wall\,k} * k_{mlcp\,b} + delta_{wall\,k} * k_{mlcp\,c} * R_{cGMP2}$
$K_5 = K_2$

Fraction of free non-phosphorylated cross-bridges [-]

$M = 1 - AM - AMp - Mp$

Fraction of free phosphorylated cross-bridges [-]
$d[Mp]/dt = wallMech * (K_4 * AMp + K_1 * M - (K_2 + K_3) * Mp)$
Fraction of attached phosphorylated cross-bridges [-]
$d[AMp]/dt = wallMech * (K_3 * Mp + K_6 * AM - (K_4 + K_5) * AMp)$
Fraction of attached dephosphorylated cross-bridges [-]
$d[AM]/dt = wallMech * (K_5 * AMp - (K_7 + K_6) * AM)$

Mechanical Equations

Fraction of attached myosin cross-bridges [-]
The cellular calcium concentration and the subsequent develop- ment of myosin–actin cross-bridges in SMCs is related by the cross- bridge phosphorylation and latch-state model of Hai and Murphy (1988). In their model, an elevation of calcium induces contraction through the formation of crossbridges between myosin and actin. Myosin can be in four possible states: free non-phosphorylated crossbridges [M], free phosphorylated crossbridges [Mp], attached phosphorylated crossbridges [Amp], and attached dephosphorylated crossbridges [AM]. It is the fraction of myosin in the two attached states that determines the active stress, and hence contraction that can be effected in the arteriolar wall. Kudryashov and Chernyavskii (2008) define the active force on smooth muscle due to muscular tonus as k 2 F (where k 2 is a constant and F is the concentration of contracting actin–myosin laments). For our model, we instead define F A as the total fraction of attached crossbridges
$F_r = AMp + AM$
Young's modulus [Pa]
$E = E_{passive} + F_r * (E_{active} - E_{passive})$
Initial radius [μM]
$R_0 = R_{0\,passive} + F_r * (alpha_{wall} - 1) * R_{0\,passive}$

Vessel radius [μm]
$d[R]/dt = R_{0\,passive}/eta * (R * trans_p/h - E * (R - R_0)/R_0)$

4.5 Global Parameters

Global parameters:

Table 10: Neuron and ECS initial conditions

Parameter	Value	Unit	Description
$seconds_{to\ simulate}$	1000	s	
$max_{ode\ step}$	0.1	–	
$integration_{method}$	BDF	–	use BDF or Radau, others are much slower
$enable_{volume\ changes\ dependencies}$	True	–	

NVU post-initialization parameters parameters post-initialization

$volume_{ecs\ and\ sc\ 0} = volume_{sc\ 0} + volume_{ecs\ 0}$
$total_{volume} = volume_{sa\ 0} + volume_{k\ 0} + volume_{ecs\ and\ sc\ 0} + volume_{p\ 0}$
$sc_{volume\ share} = volume_{sc\ 0}/volume_{ecs\ and\ sc\ 0}$
$ecs_{volume\ share} = (1 - sc_{volume\ share})$

5 Numerical Implementation

The model is implemented in Python 3.11 using NumPy and SciPy. Time integration uses the BDF solver (`scipy.integrate.solve_ivp`, `method="BDF"`) with adaptive time-stepping and a maximum step size of 0.1 s. The parameter sweep that underlies the figures of the main article was run at the SciPy default tolerances (`rtol` $= 10^{-3}$, `atol` $= 10^{-6}$); the maximum step size of 0.1 s, not the tolerance, is the binding accuracy constraint here. Individual runs repeated with `rtol` $= 10^{-6}$ reproduce the reported BOLD metrics to within 0.02 percentage points, which we take as a convergence check. A typical 300 s simulation completes in approximately 12 minutes on a single CPU core.

Initial conditions represent the steady-state values listed in the "Initial Value" column of Table 1. Before each stimulation experiment the model is allowed to relax to its dynamic equilibrium for 90 s of simulated time; the stimulus is then applied between $t = 100$ s and $t = 100 + T_{\text{stim}}$ s.

Three design choices work against runaway behaviour: (i) every module has been previously developed and tested in the published modelling literature; (ii) saturating functional forms (hyperbolic tangents, Hill kinetics) are used on the right-hand sides of the ODEs in place of unbounded linear couplings; and (iii) all parameter values are kept within the physiologically plausible range. No signs of structural instability were observed across the $\sim$165 simulation cases reported in the main article.

6 Уравнения модифицированных сигнальных путей

Ниже приведены уравнения сигнальных путей, которые были модифицированы в настоящей работе или необходимы для понимания её результатов. Этот материал вынесен из основного текста статьи, чтобы не перегружать изложение.

Путь EET-управляемой вазодилатации

Этот сигнальный путь представляет собой многоступенчатый каскад, в котором эпоксиэйкозатриеновые кислоты, производимые астроцитом, активируют каналы TRPV4 на мембране ГМК, вызывая локальные кальциевые транзиенты, которые запускают всплески Ca^{2+} через рианодиновые рецепторы (RyR); те, в свою очередь, активируют каналы BK_{Ca} и гиперполяризуют мембрану, что снижает глобальную цитозольную концентрацию Ca^{2+} и приводит к расслаблению миоцита [Earley et al., 2005; Dabertrand et al., 2013]. EET — один из нескольких астроцит-производных медиаторов (наряду с простагландинами и 20-HETE), вовлечённых в устойчивое нейроваскулярное сопряжение [Girouard et al., 2010; Institoris et al., 2022]. В модели этот путь обеспечивает длительную вазодилатацию при продолжительной нейронной активности, дополняя кратковременный K^+/KIR-отклик.

Каскад реализован с использованием функции Хилла с коэффициентом $n = 2$:

$$J_{\mathrm{EET},i} = G_{\mathrm{EET},i}\,\frac{\mathrm{eet}_k^2}{\mathrm{eet}_k^2 + K_{\mathrm{EET},i}^2}, \tag{1}$$

где $G_{\mathrm{EET},i}$ — эффективный коэффициент связи (мкМ c^{-1}), $K_{\mathrm{EET},i} = 0{,}9$ мкМ — эффективная концентрация полуактивации. Концентрация EET eet_k определяется динамикой кальция в астроците:

$$\frac{d\,\mathrm{eet}_k}{dt} = V_{\mathrm{eet}}\ \max(\mathrm{Ca}_k - \mathrm{Ca}_{k,\min},\,0) - k_{\mathrm{eet}}\,\mathrm{eet}_k, \tag{2}$$

где V_{eet} — скорость продукции EET, $\mathrm{Ca}_{k,\min}$ — пороговая концентрация Ca^{2+} для продукции EET, k_{eet} — скорость деградации. Слагаемое $J_{\mathrm{EET},i}$ вычитается из уравнения для цитозольной концентрации Ca^{2+} в ГМК:

$$\frac{d\,\mathrm{Ca}_i}{dt} = J_{\mathrm{IP3},i} - J_{\mathrm{SRup},i} - J_{\mathrm{ext},i} + J_{\mathrm{SRleak},i} - J_{\mathrm{VOCC},i} + \\ + J_{\mathrm{CICR},i} + J_{\mathrm{NaCa},i} - 0.1\,J_{\mathrm{str},i} + J_{\mathrm{Ca,coup},i} - J_{\mathrm{EET},i}, \tag{3}$$

где $J_{\mathrm{CICR},i}$ обозначает кальций-индуцированное высвобождение кальция, $J_{\mathrm{VOCC},i}$ — поток через потенциал-зависимые кальциевые каналы, остальные слагаемые представляют соответственно IP_3-опосредованное высвобождение, захват SERCA, вынос через плазматическую мембрану, утечку из саркоплазматического ретикулума, Na^+/Ca^{2+}-обмен, каналы, активируемые растяжением, и гетероклеточное сопряжение [Koenigsberger et al., 2006].

KIR-канал и мембранный потенциал ГМК

Калиевый канал внутреннего выпрямления (KIR) на мембране ГМК реагирует на периваскулярную концентрацию K^+ (K_p) и обеспечивает быстрый путь вазодилатации:

$$J_{\mathrm{KIR},i} = F_{\mathrm{KIR},i}\,\frac{g_{\mathrm{KIR},i}}{\gamma_i}\,(v_i - v_{\mathrm{KIR},i}), \tag{4}$$

где

$$v_{\mathrm{KIR},i} = z_1 K_p - z_2, \qquad g_{\mathrm{KIR},i} = \exp(z_5 v_i + z_3 K_p - z_4),$$

$F_{\mathrm{KIR},i}$ — масштабирующий коэффициент (по умолчанию 750, в финальной конфигурации 1500), $\gamma_i = 1970$ мВ мкМ$^{-1}$ — фактор мембранной ёмкости, $z_1, \ldots, z_5$ — эмпирические константы, полученные подгонкой к экспериментальным данным по KIR-току ГМК внутримозговых артериол [Filosa et al., 2006; Dormanns et al., 2015]. Мембранный потенциал ГМК описывается уравнением:

$$\frac{dv_i}{dt} = \gamma_i \left(-J_{\mathrm{NaK},i} - J_{\mathrm{Cl},i} - 2J_{\mathrm{VOCC},i} - J_{\mathrm{NaCa},i} - J_{K,i} - J_{\mathrm{str},i} - J_{\mathrm{KIR},i}\right) + V_{\mathrm{coup},i}. \tag{5}$$

Динамика поперечных мостиков

Сокращение сосуда описывается моделью поперечных мостиков Хая–Мёрфи с четырьмя состояниями [Hai, Murphy, 1988], описывающей фосфорилирование и прикрепление миозиновых мостиков. Доли свободных фосфорилированных (M_p), прикреплённых фосфорилированных (AM_p) и прикреплённых дефосфорилированных (AM) мостиков удовлетворяют уравнениям:

$$\begin{aligned}
\frac{dM_p}{dt} &= w_{\mathrm{Mech}} \left(K_4\, AM_p + K_1\, M - (K_2 + K_3)\, M_p\right), \\
\frac{dAM_p}{dt} &= w_{\mathrm{Mech}} \left(K_3\, M_p + K_6\, AM - (K_4 + K_5)\, AM_p\right), \\
\frac{dAM}{dt} &= w_{\mathrm{Mech}} \left(K_5\, AM_p - (K_7 + K_6)\, AM\right),
\end{aligned} \tag{6}$$

где $M = 1 - AM - AM_p - M_p$ — доля свободных нефосфорилированных мостиков, $K_1 = K_6 = \gamma_\times \,\mathrm{Ca}_i^{n_\times}$ — Ca^{2+}-зависимая скорость фосфорилирования, w_{Mech} — масштабирующая константа, определяющая общую скорость цикла поперечных мостиков (по умолчанию 1,7, в финальной конфигурации 3,2). Доля прикреплённых мостиков $F_r = AM_p + AM$ определяет активное напряжение, от которого зависит радиус сосуда R:

$$\frac{dR}{dt} = \frac{R_{0,\mathrm{pass}}}{\eta} \left(\frac{R\, P_{\mathrm{trans}}}{h} - E\, \frac{R - R_0}{R_0}\right), \tag{7}$$

где $E = E_{\mathrm{pass}} + F_r(E_{\mathrm{act}} - E_{\mathrm{pass}})$ — модуль Юнга, интерполированный между пассивным и активным состояниями, $R_0 = R_{0,\mathrm{pass}} + F_r(\alpha - 1)R_{0,\mathrm{pass}}$ — ненапряжённый радиус, $h = 0{,}1R$ — толщина стенки, η — вязкость, P_{trans} — трансмуральное давление.

Гемодинамические уравнения

В модели зависимость церебрального кровотока от радиуса сосуда задаётся степенным соотношением с показателем 4, нормированным на референтные значения $\mathrm{CBF}_{\mathrm{init}}$ и R_{init} [Mathias et al., 2018]:

$$\mathrm{CBF} = \mathrm{CBF}_{\mathrm{init}} \left(\frac{R}{R_{\mathrm{init}}}\right)^4. \tag{8}$$

Венозная баллонная модель связывает CBV, дезоксигемоглобин (HbR) и BOLD:

$$\frac{d\,\mathrm{CBV}}{dt} = \frac{1}{\tau_{\mathrm{MTT}} + \tau_{\mathrm{TAT}}} \left(\frac{\mathrm{CBF}}{\mathrm{CBF}_{\mathrm{init}}} - \mathrm{CBV}^{1/d}\right), \tag{9}$$

$$\frac{d\,\mathrm{HbR}}{dt} = \frac{1}{\tau_{\mathrm{MTT}}}\left(\mathrm{CMRO}_{2,n} - \frac{\mathrm{HbR}}{\mathrm{CBV}}\,f_{\mathrm{out}}\right), \tag{10}$$

где d — показатель Грубба, связывающий CBV и CBF, τ_{MTT} — среднее время прохождения, τ_{TAT} — постоянная времени переходной вязкоупругой перестройки венозного компартмента, $f_{\mathrm{out}} = \mathrm{CBV}^{1/d} + \tau_{\mathrm{TAT}} \cdot (\mathrm{CBF}/\mathrm{CBF}_{\mathrm{init}} - \mathrm{CBV}^{1/d})/(\tau_{\mathrm{MTT}} + \tau_{\mathrm{TAT}})$ — венозный отток, $\mathrm{CMRO}_{2,n}$ — безразмерная фильтрованная по фильтру низких частот нормированная скорость метаболизма кислорода (определена в ур. (12)). Сигнал BOLD рассчитывается по формуле [Buxton et al., 2004]:

$$\mathrm{BOLD} = V_0\,(a_1\,(1 - \mathrm{HbR}) - a_2\,(1 - \mathrm{CBV})), \tag{11}$$

с $V_0 = 0.03$, $a_1 = 3.4$, $a_2 = 1.0$.

Метаболическая инерция

По окончании стимула требуется некоторое время и метаболические ресурсы на восстановление ионных градиентов, рециркуляцию нейромедиаторов и пополнение запасов гликогена [Hua et al., 2011; van Zijl et al., 2012]. К мгновенному отношению $\mathrm{CMRO}_2/\mathrm{CMRO}_{2,\mathrm{init}}$ применяется фильтр низких частот первого порядка, дающий фильтрованную нормированную величину $\mathrm{CMRO}_{2,n}$:

$$\frac{d\,\mathrm{CMRO}_{2,n}}{dt} = \frac{\mathrm{CMRO}_2/\mathrm{CMRO}_{2,\mathrm{init}} - \mathrm{CMRO}_{2,n}}{\tau_{\mathrm{CMRO}_2}}. \tag{12}$$

Здесь CMRO_2 и $\mathrm{CMRO}_{2,\mathrm{init}}$ имеют размерность [мМ $\mathrm{с}^{-1}$]; их отношение $\mathrm{CMRO}_2/\mathrm{CMRO}_{2,\mathrm{init}}$ безразмерно, и $\mathrm{CMRO}_{2,n}$ — его фильтрованная версия (также безразмерна). τ_{CMRO_2} [с] — временная постоянная метаболической инерции. В исходной модели Кенни/Матиаса этот фильтр отсутствует: отношение $\mathrm{CMRO}_2/\mathrm{CMRO}_{2,\mathrm{init}}$ используется в уравнении HbR напрямую. В настоящей работе вводится уравнение (12) с $\tau_{\mathrm{CMRO}_2} > 0$, что замедляет отклик метаболизма на стимул. В калиброванной конфигурации $\tau_{\mathrm{CMRO}_2} = 20$ с, в финальной — $\tau_{\mathrm{CMRO}_2} = 8$ с.

Калибровка параметров

Значение τ_{CMRO_2} на каждом этапе подбиралось эмпирически, как и остальные параметры калибровки; вместе с тем его влияние на форму сигнала BOLD имеет ясный механизм. В уравнении баланса деоксигемоглобина (ур. (10)) слагаемое $\mathrm{CMRO}_{2,n}$ играет роль источника (метаболическая генерация HbR за счёт потребления кислорода), а второе слагаемое — роль стока (вымывание HbR венозным кровотоком). От τ_{CMRO_2} зависит только источник; сосудистая ветвь (CBF, CBV) параметрически от τ_{CMRO_2} не зависит. Тем самым τ_{CMRO_2} определяет лишь то, насколько быстро метаболический источник HbR отслеживает изменение кровотока. При $\tau_{\mathrm{CMRO}_2} = 20$ с (Этап I) источник нарастает медленно и отстаёт от быстрого увеличения кровотока: HbR вымывается сильнее, а сигнал BOLD оказывается завышенным. В прямом сравнительном расчёте при прочих равных условиях $\tau_{\mathrm{CMRO}_2} = 20$ с даёт пик +7,4% и плато +5,8% против +5,5% и +3,5% при $\tau_{\mathrm{CMRO}_2} = 8$ с, причём сосудистые переменные CBF и CBV в обоих расчётах практически совпадают. Уменьшение до $\tau_{\mathrm{CMRO}_2} = 8$ с (Этап II) приближает скорость метаболического источника к скорости сосудистого отклика и восстанавливает корректные амплитуды пика и плато.

Значение τ_{CMRO_2} подобрано по форме модельного отклика, а не выведено из независимых данных. Отметим лишь, что оно согласуется по порядку величины с характерными временами постстимульного восстановления ионных градиентов $\mathrm{Na}^+/\mathrm{K}^+$-АТФазой — единицы

секунд [van Zijl et al., 2012], — которыми и определяется сохраняющееся после стимула потребление кислорода.

7 Факторное сравнение вкладов KIR и поперечных мостиков

Расчёт выполнен при одном сочетании условий стимуляции ($I = 0{,}020$ мА см$^{-2}$, длительность стимула 20 с). Во всех четырёх прогонах прочие параметры финальной конфигурации и настройки решателя (BDF, max_step = 0,1 с) совпадают; различаются только $F_{\mathrm{KIR},i}$ и w_{Mech}.

Таблица 11: Метрики отклика BOLD в четырёх ячейках факторного плана. Уровень в конце стимуляции усреднён по последним 5 с стимула; отношение овершута — $(V_{\mathrm{peak}} - V_{\mathrm{late}})/V_{\mathrm{late}} \times 100\%$.

конфигурация	$F_{\mathrm{KIR},i}$	w_{Mech}	пик, %	время пика, с	уровень в конце стимуляции, %	отношение овершута, %	постстим. снижение, %
базовая	750	1,7	+4,31	12,7	+4,07	5,9	−1,20
только KIR	1500	1,7	+3,69	11,6	+3,12	18,4	−0,64
только мостики	750	3,2	+6,07	6,8	+4,58	32,4	−3,28
совместная (финальная)	1500	3,2	+5,46	6,9	+3,45	58,1	−2,35

Ускорение динамики поперечных мостиков само по себе даёт каноническое время достижения пика (6,8 с при исходном $F_{\mathrm{KIR},i} = 750$); усиление KIR для этого не требуется и даже несколько снижает амплитуду пика. Вклад $F_{\mathrm{KIR},i}$ состоит в понижении уровня в конце стимуляции, за счёт чего и формируется отношение овершута. Тем самым прежняя формулировка о том, что оба изменения являются «необходимыми и достаточными», некорректна.

В качестве контроля совместная конфигурация воспроизвела ранее выполненный независимый расчёт с точностью до машинного нуля. Вывод ограничен одним сочетанием условий стимуляции; кроме того, изменение $F_{\mathrm{KIR},i}$ смещает исходную рабочую точку (базовый уровень BOLD выше на 6,6%), поэтому сравнение по этому фактору проводится не при полностью совпадающем базовом состоянии.

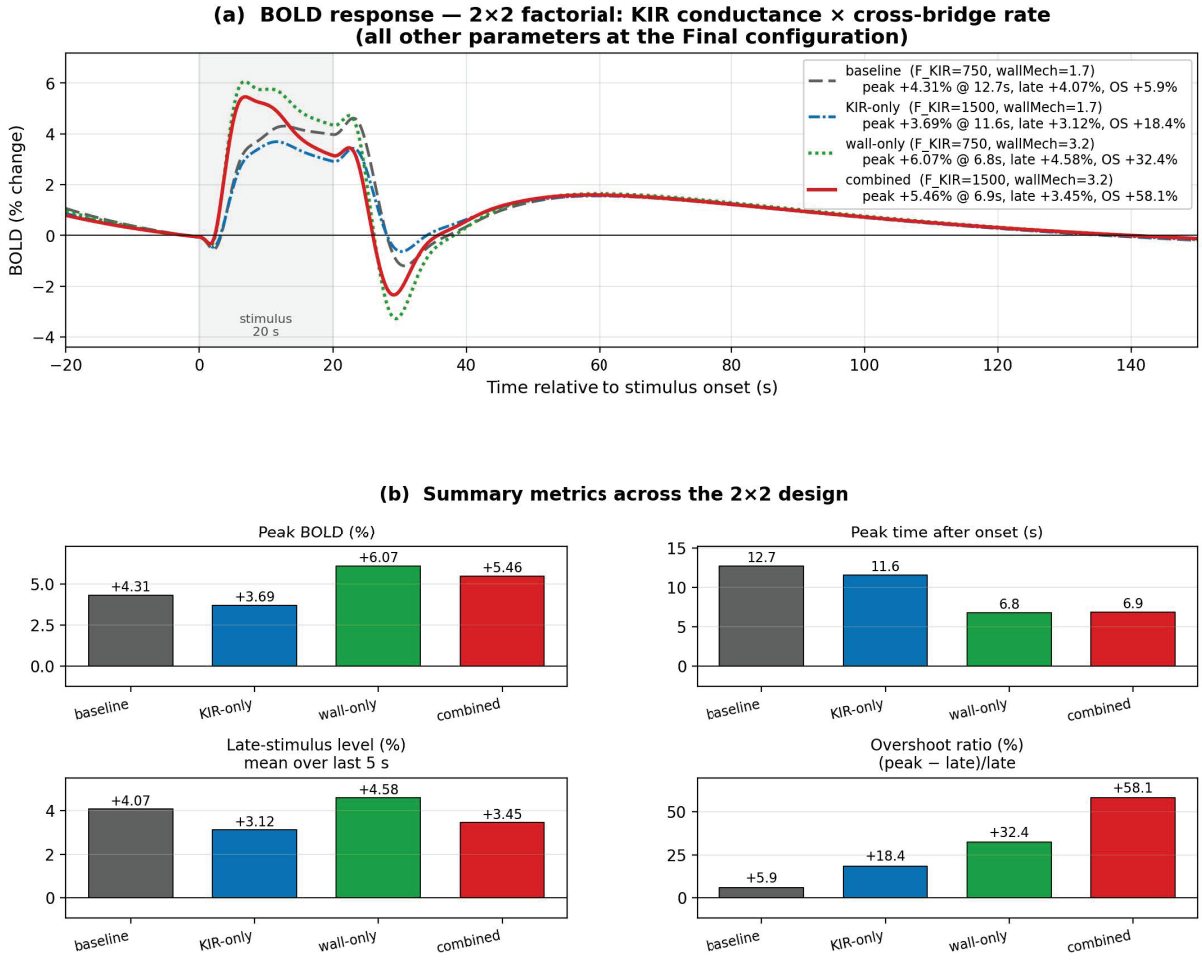


Рис. 2: Полное факторное сравнение 2×2: влияние $F_{\mathrm{KIR},i}$ и w_{Mech} на форму отклика BOLD. Финальная конфигурация, $I = 0{,}020$ мА см$^{-2}$, стимул 20 с.

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