Global Sensitivity Analysis of High Dimensional Neuroscience Models: An Example of Neurovascular Coupling Supplementary material: Model equations and parameters

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The single neurovascular unit (NVU) model originally developed by Farr and David [3] and later extended by Dormanns et al. [2], Dormanns et al. [1], Mathias et al. [6], Kenny et al. [4], and (Elshin ref) contains 67 ordinary differential equations (ODEs) plus a large number of algebraic variables and parameters. The equations and parameters are divided into sections corresponding to different compartments and pathways of the model. The following parameters are given for ordinary neurovascular coupling (NVC) conditions.

1. Global Constants

Parameter	Description	Value
F	Faraday's constant	96.485 C mmol^{-1}
R_g	Gas constant	8.315 J mol^{-1} K^{-1}
T	Temperature constant	300 K
ϕ	R_gT/F	26.7 mV
z_K	Ionic valence for potassium (K^+)	1
z_{Na}	Ionic valence for sodium (Na^+)	1
z_{Cl}	Ionic valence for chlorine (Cl^-)	-1
z_{NBC}	Effective valence of the NBC cotransporter complex	-1
z_{Ca}	Ionic valence for calcium (Ca^{2+})	2

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2. Neuron and Extracellular Space

2.1. Input to the model

The input current to the soma (mA cm^{-2}):

$$I_{stim} = \begin{cases} 0 & t < t_0 \\ I_{strength} & t_0 \leq t \leq t_f \\ 0 & t_f < t \end{cases} \tag{1}$$

2.2. ODEs

The membrane potential of the soma/axon (v_{sa}) and dendrite (v_d) (mV):

$$C_m \frac{dv_{sa}}{dt} = -I_{tot_{sa}} + \frac{1}{2R_a\delta_d^2}(v_d - v_{sa}) + I_{stim} \tag{2}$$

$$C_m \frac{dv_d}{dt} = -I_{tot_d} + \frac{1}{2R_a\delta_d^2}(v_{sa} - v_d) \tag{3}$$

The ion concentrations (K$^+$ and Na$^+$) in the soma/axon (mM):

$$\frac{dK_{sa}}{dt} = -\frac{A_s}{FV_s} I_{K,tot_{sa}} + \frac{D_{K,n}(V_d + V_s)}{2\delta_d^2 V_s}(K_d - K_{sa}) \tag{4}$$

$$\frac{dNa_{sa}}{dt} = -\frac{A_s}{FV_s} I_{Na,tot_{sa}} + \frac{D_{Na,n}(V_d + V_s)}{2\delta_d^2 V_s}(Na_d - Na_{sa}) \tag{5}$$

The ion concentrations (K$^+$ and Na$^+$) in the dendrite (mM):

$$\frac{dK_d}{dt} = -\frac{A_d}{FV_d} I_{K,tot_d} + \frac{D_{K,n}(V_d + V_s)}{2\delta_d^2 V_d}(K_d - K_d) \tag{6}$$

$$\frac{dNa_d}{dt} = -\frac{A_d}{FV_d} I_{Na,tot_d} + \frac{D_{Na,n}(V_d + V_s)}{2\delta_d^2 V_d}(Na_d - Na_d) \tag{7}$$

The K$^+$ and Na$^+$ ion concentrations in the extracellular space (ECS) (mM):

$$\frac{dNa_e}{dt} = \frac{1}{Ff_e}\left(\frac{A_s I_{Na,tot_{sa}}}{V_s} + \frac{A_d I_{Na,tot_d}}{V_d}\right) \tag{8}$$

$$\frac{dK_e}{dt} = \frac{1}{Ff_e}\left(\frac{A_s I_{K,tot_{sa}}}{V_s} + \frac{A_d I_{K,tot_d}}{V_d}\right) - \frac{d\text{Buff}_e}{dt} \tag{9}$$

The buffer concentration in the ECS (Buff$_e$) (mM):

$$\frac{d\text{Buff}_e}{dt} = \mu(B_0 - \text{Buff}_e)\frac{K_e}{1 + \exp\left(\frac{-(K_e - 5.5)}{1.09}\right)} - \mu\text{Buff}_e \tag{10}$$

Activation gating variable m_* (for m_1 to m_8) (-):

$$\frac{dm_*}{dt} = (\alpha_{m_*}(1 - m_*) - \beta_{m_*} m_*) \tag{11}$$

Deactivation gating variable h_* (for h_1 to h_6) (-):

$$\frac{dh_*}{dt} = (\alpha_{h_*}(1 - h_*) - \beta_{h_*} h_*) \tag{12}$$

The tissue oxygen concentration (mM):

$$\frac{dO_2}{dt} = J_{O_2\, vascular} - J_{O_2\, background} - J_{O_2\, pump} \tag{13}$$

2.3. Algebraic Variables

Total current of ions in soma/axon or dendrite (*) (mA cm^{-2}):

$$I_{tot_*} = I_{K,tot_*} + I_{Na,tot_*} + I_{leak_*} \tag{14}$$

Total current of K$^+$ in soma/axon (mA cm^{-2}):

$$I_{K,tot_{sa}} = I_{KDR_{sa}} + I_{KA_{sa}} + I_{K,leak_{sa}} + I_{pump,K_{sa}} \tag{15}$$

Total current of K$^+$ in dendrite (mA cm^{-2}):

$$I_{K,tot_d} = I_{KDR_d} + I_{KA_d} + I_{K,leak_d} + I_{pump,K_d} + I_{NMDA,K_d} \tag{16}$$

Total current of Na$^+$ in soma/axon (mA cm^{-2}):

$$I_{Na,tot_{sa}} = I_{NaP_{sa}} + I_{NaT_{sa}} + I_{Na,leak_{sa}} + I_{pump,Na_{sa}} \tag{17}$$

Total current of Na$^+$ in dendrite (mA cm^{-2}):

$$I_{Na,tot_d} = I_{NaP_d} + I_{Na,leak_d} + I_{pump,Na_d} + I_{NMDA,Na_d} \tag{18}$$

K$^+$ current through Na$^+$/K$^+$ adenosine triphosphate (ATP)-ase pump in the soma/axon or dendrite (*) (mA cm^{-2}):

$$I_{pump,K_*} = -2\, I_{pump_*} \tag{19}$$

Na$^+$ current through Na$^+$/K$^+$ ATP-ase pump in soma/axon or dendrite (*) (mA cm^{-2}):

$$I_{pump,Na_*} = 3\, I_{pump_*} \tag{20}$$

Na$^+$/K$^+$ ATP-ase pump flux in soma/axon or dendrite (*) (mA cm^{-2}):

$$I_{pump_*} = I_{max} J_{pump1_*} J_{pump2}(O_2) \tag{21}$$

Oxygen independent term of the ATP-ase pump in both the soma/axon or dendrite (*) (-):

$$J_{pump1_*} = \left(1 + \frac{K_{e,0}}{K_e}\right)^{-2} \left(1 + \frac{Na_{*,0}}{Na_*}\right)^{-3} \tag{22}$$

Oxygen dependent term of the ATP-ase pump (-):

$$J_{pump2}(O_2) = 2\left(1 + \frac{O2_0}{(1-\alpha_{O2})\,O_2 + \alpha_{O2}\,O2_0}\right)^{-1} \tag{23}$$

The vascular supply of oxygen (mM s^{-1}):

$$J_{O_2\,vascular} = J\frac{O2_b - O_2}{O2_b - O2_0} \tag{24}$$

The background oxygen consumption (mM s^{-1}):

$$J_{O_2\,background} = J_0 P_{O2}(1-\gamma_{O2}) \tag{25}$$

The tissue oxygen consumption due to the ATP-ase pump (mM s^{-1}):

$$J_{O_2\,pump} = J_0 P_{O2}\gamma_{O2}\frac{J_{pump1_{sa}} + J_{pump1_d}}{J_{pump1_{sa_0}} + J_{pump1_{d_0}}} \tag{26}$$

The change in oxygen concentration due to cerebral blood flow (CBF) (mM s^{-1}):

$$J = J_0\frac{\text{CBF}}{\text{CBF}_{init}} \tag{27}$$

The cerebral blood flow (-):

$$\text{CBF} = \text{CBF}_{init}\frac{R^4}{R^4_{init}} \tag{28}$$

The normalised pump rate (-):

$$P_{O2} = \frac{J_{pump2}(O_2) - J_{pump2}(0)}{J_{pump2}(O2_0) - J_{pump2}(0)} \tag{29}$$

Leak currents of K$^+$, Na$^+$ and general leak in the soma/axon or dendrite (mA cm^{-2}):

$$I_{K,leak_*} = g_{K,leak_*}(v_* - E_{K_*}) \tag{30}$$

$$I_{Na,leak_*} = g_{Na,leak_*}(v_* - E_{Na_*}) \tag{31}$$

$$I_{leak_*} = g_{leak_*}(v_* - E_{leak_*}) \tag{32}$$

Nernst potential for K$^+$ and Na$^+$ in the soma/axon or dendrite (*), (mV):

$$E_{K_*} = \frac{\phi}{z_K}\ln\left(\frac{K_e}{K_*}\right) \tag{33}$$

$$E_{Na_*} = \frac{\phi}{z_{Na}}\ln\left(\frac{Na_e}{Na_*}\right) \tag{34}$$

K$^+$ current through KDR channel in the soma/axon (mA cm^{-2}):

$$I_{KDR_{sa}} = m_2^2\,\frac{g_{KDR} F v_{sa}\left(K_{sa} - \exp\left(\frac{-v_{sa}}{\phi}\right)K_e\right)}{\phi\left(1-\exp\left(\frac{-v_{sa}}{\phi}\right)\right)} \tag{35}$$

K^+ current through KA channel in the soma/axon (mA cm^{-2}):

$$I_{KA_{sa}} = m_3^2\ h_2\ \frac{g_{KA} F v_{sa} \left(K_{sa} - \exp\left(\frac{-v_{sa}}{\phi}\right) K_e \right)}{\phi \left(1 - \exp\left(\frac{-v_{sa}}{\phi}\right)\right)} \tag{36}$$

K^+ current through KDR channel in the dendrite (mA cm^{-2}):

$$I_{KDR_d} = m_6^2\ \frac{g_{KDR} F v_d \left(K_d - \exp\left(\frac{-v_d}{\phi}\right) K_e \right)}{\phi \left(1 - \exp\left(\frac{-v_d}{\phi}\right)\right)} \tag{37}$$

K^+ current through KA channel in the dendrite (mA cm^{-2}):

$$I_{KA_d} = m_7^2\ h_5\ \frac{g_{KA} F v_d \left(K_d - \exp\left(\frac{-v_d}{\phi}\right) K_e \right)}{\phi \left(1 - \exp\left(\frac{-v_d}{\phi}\right)\right)} \tag{38}$$

K^+ current through N-methyl-D-aspartate (NMDA) channel in the dendrite (mA cm^{-2}):

$$I_{NMDA,K_d} = m_5\ h_4\ \frac{g_{NMDA} F v_d \left(K_d - \exp\left(\frac{-v_d}{\phi}\right) K_e \right)}{\phi \left(1 - \exp\left(\frac{-v_d}{\phi}\right)\right) \left(1 + 0.33\ [Mg]_0 \exp(-0.07 v_d - 0.7)\right)} \tag{39}$$

Na^+ current through NaP channel in soma/axon (mA cm^{-2}):

$$I_{NaP,Na_{sa}} = m_1^2\ h_1\ \frac{g_{NaP} F v_{sa} \left(Na_{sa} - \exp\left(\frac{-v_{sa}}{\phi}\right) Na_e \right)}{\phi \left(1 - \exp\left(\frac{-v_{sa}}{\phi}\right)\right)} \tag{40}$$

Na^+ current through NaT channel in soma/axon (mA cm^{-2}):

$$I_{NaT,Na_{sa}} = m_8^3\ h_6\ \frac{g_{NaT} F v_{sa} \left(Na_{sa} - \exp\left(\frac{-v_{sa}}{\phi}\right) Na_e \right)}{\phi \left(1 - \exp\left(\frac{-v_{sa}}{\phi}\right)\right)} \tag{41}$$

Na^+ current through NaP channel in dendrite (mA cm^{-2}):

$$I_{NaP,Na_d} = m_4^2\ h_3\ \frac{g_{NaP} F v_d \left(Na_d - \exp\left(\frac{-v_d}{\phi}\right) Na_e \right)}{\phi \left(1 - \exp\left(\frac{-v_d}{\phi}\right)\right)} \tag{42}$$

Na^+ current through NMDA channel in dendrite (mA cm^{-2}):

$$I_{NMDA,Na_d} = m_5\ h_4\ \frac{g_{NMDA} F v_d \left(Na_d - \exp\left(\frac{-v_d}{\phi}\right) Na_e \right)}{\phi \left(1 - \exp\left(\frac{-v_d}{\phi}\right)\right) \left(1 + 0.33\ [Mg]_0 \exp(-0.07 v_d - 0.7)\right)} \tag{43}$$

Rate functions for the activation m and deactivation h gating variables (s^{-1}):

$$\alpha_{m_1} = \frac{1000}{6} \frac{1}{1 + \exp(-(0.143 v_{sa} + 5.67))} \tag{44}$$

$$\beta_{m_1} = \frac{1000}{6} - \alpha_{m_1} \tag{45}$$

$$\alpha_{m_2} = 16\frac{v_{sa}+34.9}{1-\exp(-(0.2v_{sa}+6.98))} \tag{46}$$

$$\beta_{m_2} = 250\exp(-(0.025v_{sa}+1.25)) \tag{47}$$

$$\alpha_{m_3} = 20\frac{v_{sa}+56.9}{1-\exp(-(0.1v_{sa}+5.69))} \tag{48}$$

$$\beta_{m_3} = 17.5\frac{v_{sa}+29.9}{\exp(0.1v_{sa}+2.99)-1} \tag{49}$$

$$\alpha_{m_4} = \frac{1000}{6}\frac{1}{1+\exp(-(0.143v_d+5.67))} \tag{50}$$

$$\beta_{m_4} = \frac{1000}{6} - \alpha_{m_4} \tag{51}$$

$$\alpha_{m_5} = 500\frac{1}{1+\exp(\frac{13.5-K_e}{1.42})} \tag{52}$$

$$\beta_{m_5} = 500 - \alpha_{m_5} \tag{53}$$

$$\alpha_{m_6} = 16\frac{v_d+34.9}{1-\exp(-(0.2v_d+6.98))} \tag{54}$$

$$\beta_{m_6} = 250\exp(-(0.025v_d+1.25)) \tag{55}$$

$$\alpha_{m_7} = 20\frac{v_d+56.9}{1-\exp(-(0.1v_d+5.69))} \tag{56}$$

$$\beta_{m_7} = 17.5\frac{v_d+29.9}{\exp(0.1v_d+2.99)-1} \tag{57}$$

$$\alpha_{m_8} = 320\frac{-v_{sa}-51.9}{\exp(-(0.25v_{sa}+12.975))-1} \tag{58}$$

$$\beta_{m_8} = 280\frac{v_{sa}+24.89}{\exp(0.2v_{sa}+4.978)-1} \tag{59}$$

$$\alpha_{h_1} = 5.12\times10^{-5}\exp(-(0.056v_{sa}+2.94)) \tag{60}$$

$$\beta_{h_1} = 1.6\times10^{-3}\frac{1}{1+\exp(-(0.2v_{sa}+8))} \tag{61}$$

$$\alpha_{h_2} = 16\exp(-(0.056v_{sa}+4.61)) \tag{62}$$

$$\beta_{h_2} = 500\frac{1}{1+\exp(-(0.2v_{sa}+11.98))} \tag{63}$$

$$\alpha_{h_3} = 5.12\times10^{-5}\exp(-(0.056v_d+2.94)) \tag{64}$$

$$\beta_{h_3} = 1.6\times10^{-3}\frac{1}{1+\exp(-(0.2v_d+8))} \tag{65}$$

$$\alpha_{h_4} = 0.5\frac{1}{\left(1+\exp\left(\frac{K_e-6.75}{0.71}\right)\right)} \tag{66}$$

$$\beta_{h_4} = 0.5 - \alpha_{h_4} \tag{67}$$

$$\alpha_{h_5} = 16\exp(-(0.056v_d + 4.61)) \tag{68}$$

$$\beta_{h_5} = 500\frac{1}{1+\exp(-(0.2v_d + 11.98))} \tag{69}$$

$$\alpha_{h_6} = 128\exp(-(0.056v_{sa} + 2.94)) \tag{70}$$

$$\beta_{h_6} = 4\times10^3\frac{1}{1+\exp(-(0.2v_{sa} + 6))} \tag{71}$$

Parameter	Description	Value
$I_{strength}$	Amplitude of input current	0.022 mA cm^{-2}
t_0	Start time of input current	0 s
t_f	Final time of input current	20 s
$O2_b$	Blood oxygen level	0.04 mM
$O2_0$	Equilibrium tissue oxygen level	0.02 mM
γ_{O2}	Fraction of the total oxygen consumption at steady state	0.1
J_0	Equilibrium change in oxygen concentration due to CBF	0.032 mM s^{-1}
CBF$_{init}$	Equilibrium CBF	0.032
$J_{pump1_{sa_0}}$	Steady state pump rate in the soma/axon	0.0312
$J_{pump1_{d_0}}$	Steady state pump rate in the dendrite	0.0312
R_{init}	Vessel radius when passive and no stress is applied	20 μm
α_{O2}	Fraction of oxygen independent ATP production	0.05
$J_{pump2}(0)$	Pump rate when oxygen concentration is 0	0.0952
$J_{pump2}(O2_0)$	Pump rate when oxygen is at equilibrium	1
$K_{e,0}$	Equilibrium K_e	2.9 mM
$Na_{sa,0}$	Equilibrium Na_{sa}	10 mM
$Na_{d,0}$	Equilibrium Na_d	10 mM
C_m	Membrane capacitance	7.5$\times$10^{-7} S cm^{-2} s
R_a	Input resistance of dendritic tree	1.83$\times$10^5 Ω
δ_d	Half length of dendrite	4.5$\times$10^{-2} cm
A_s	Soma/axon surface area	1.586$\times$10^{-5} cm^2
A_d	Dendrite surface area	2.6732$\times$10^{-4} cm^2
V_s	Soma/axon volume	2.16$\times$10^{-9} cm^3
V_d	Dendrite volume	5.614$\times$10^{-9} cm^3
f_e	ECS to neuron volume ratio	0.15
$D_{Na,n}$	Intracellular diffusion rate of Na$^+$	1.33$\times$10^{-5} cm^2 s^{-1}
$D_{K,n}$	Intracellular diffusion rate of K$^+$	1.96$\times$10^{-5} cm^2 s^{-1}
$g_{K,leak_{sa}}$	Conductance of K$^+$ leak channel on soma/axon	2.1989 $\times$ 10^{-4} S cm^{-2}

$g_{Na,leak_{sa}}$	Conductance of Na^+ leak channel on soma/axon	6.2378×10^{-5} S cm^{-2}
$g_{leak_{sa}}$	Conductance of general leak channel on soma/axon	6.2378×10^{-4} S cm^{-2}
$g_{K,leak_d}$	Conductance of K^+ leak channel on dendrite	2.1987×10^{-4} S cm^{-2}
$g_{Na,leak_d}$	Conductance of Na^+ leak channel on dendrite	6.2961×10^{-5} S cm^{-2}
g_{leak_d}	Conductance of general leak channel on dendrite	6.2961×10^{-4} S cm^{-2}
$E_{leak_{sa}}$	Nernst potential for general leak in the soma/axon	-70 mV
E_{leak_d}	Nernst potential for general leak in the dendrite	-70 mV
g_{KDR}	KDR channel conductance	10^{-4} S cm^{-2}
g_{KA}	KA channel conductance	10^{-5} S cm^{-2}
g_{NMDA}	NMDA channel conductance	10^{-5} S cm^{-2}
g_{NaP}	NaP channel conductance	2×10^{-6} S cm^{-2}
g_{NaT}	NaT channel conductance	10^{-5} S cm^{-2}
$[Mg]_0$	Equilibrium magnesium	1.2 mM L^{-1}
I_{max}	Maximum rate of Na^+/K^+ ATP-ase pump	0.078 mA cm^{-2}
μ	Buffer rate	8×10^{-4} ms^{-1}
B_0	Effective total buffer concentration	500 mM

Table 2: Parameters of the neuron and extracellular space submodel, for references see Mathias et al. [6].

3. Blood-oxygen-level dependent (BOLD) response

3.1. ODEs

The non dimensional cerebral blood volume (CBV) (-):

$$\frac{d\text{CBV}}{dt} = \frac{1}{\tau_{MTT} + \tau_{TAT}} \left(\frac{\text{CBF}}{\text{CBF}_{init}} - \text{CBV}^d \right) \tag{72}$$

The non dimensional deoxyhemoglobin (HbR) concentration (-):

$$\frac{d\text{HbR}}{dt} = \frac{1}{\tau_{MTT}} \left(\frac{\text{CMRO}_2}{\text{CMRO}_{2_0}} - \frac{\text{HbR}}{\text{CBV}} f_{out} \right) \tag{73}$$

3.2. Algebraic Variables

The non dimensional normalised total hemoglobin (HbT) concentration (-):

$$\text{HbT}_N = \frac{\text{CBF}_N \text{HbR}_N}{\text{CMRO}_{2_N}} \tag{74}$$

where the normalised CBF is given by $\text{CBF}_N = \text{CBF}/\text{CBF}(0)$ and $\text{CBF}(0)$ is the steady state value, similarly for HbR and CMRO_{2_N}.

The non dimensional normalised oxyhemoglobin (HbO) concentration (-):

$$\text{HbO}_N = \text{HbT}_N - \text{HbR}_N + 1 \tag{75}$$

The time dependent outflow from the venous compartment (-):

$$f_{out} = \text{CBV}^d + \tau_{TAT} \frac{d\text{CBV}}{dt} \tag{76}$$

The cerebral metabolic rate of oxygen consumption (mM s^{-1}):

$$\text{CMRO}_2 = J_{O_2\,background} + J_{O_2\,pump} \tag{77}$$

The equilibrium value of CMRO_2 (mM s^{-1}):

$$\text{CMRO}_{2_0} = J_0 P_{02} \tag{78}$$

The oxygen extraction fraction (-):

$$E = E_0 \frac{\text{CMRO}_2}{J} \tag{79}$$

The BOLD signal change from its steady state value (-):

$$\Delta BOLD \approx V_0 \left(a_1 \left[1 - \text{HbR}_N \right] + a_2 \left[\text{CBV}_N - 1 \right] \right) \tag{80}$$

Parameter	Description	Value
τ_{MTT}	Mean transit time	3 s
τ_{TAT}	Transient adjustment time constant	20 s
CBF_{init}	Steady state CBF	0.032
d	Empirical relation between CBF and CBV	2.5
a_1	Weight for HbR change	3.4
a_2	Weight for CBV change	1
V_0	Resting venous blood volume fraction	0.03
E_0	Baseline oxygen extraction fraction	0.4

Table 3: Parameters of the BOLD submodel, for references see Mathias et al. [6].

4. Synaptic Cleft and Astrocyte

4.1. ODEs

K^+ concentration in the synaptic cleft (SC) (μM):

$$\frac{dK_s}{dt} = \frac{1}{VR_{sk}} \left(J_{K_k} - 2J_{NaK_k} - J_{NKCC1_k} - J_{KCC1_k} \right) + J_{NEtoSC} \tag{81}$$

Na^+ concentration in the SC (μM):

$$\frac{dNa_s}{dt} = \frac{1}{VR_{sk}} \left(J_{Na_k} + 3 * J_{NaK_k} - J_{NKCC1_k} - J_{NBC_k} \right) - J_{NEtoSC} \tag{82}$$

HCO_3^- concentration in the SC (μM):

$$\frac{dHCO_{3_s}}{dt} = \frac{1}{VR_{sk}}\left(-2J_{NBC_k}\right) \tag{83}$$

K^+ concentration in the astrocyte (μM):

$$\frac{dK_k}{dt} = -J_{K_k} + 2J_{NaK_k} + J_{NKCC1_k} + J_{KCC1_k} - J_{BK_k} \tag{84}$$

Na^+ concentration in the astrocyte (μM):

$$\frac{dNa_k}{dt} = -J_{Na_k} - 3J_{NaK_k} + J_{NKCC1_k} + J_{NBC_k} \tag{85}$$

HCO_3^- concentration in the astrocyte (μM):

$$\frac{dHCO_{3_k}}{dt} = 2J_{NBC_k} \tag{86}$$

Cl^- concentration in the astrocyte (μM):

$$\frac{dCl_k}{dt} = \frac{dNa_k}{dt} + \frac{dK_k}{dt} - \frac{dHCO_{3_k}}{dt} + 2\frac{dCa_k}{dt} \tag{87}$$

The astrocytic cytosolic Ca^{2+} concentration (μM):

$$\frac{dCa_k}{dt} = B_{cyt}\left(J_{IP3_k} - J_{pump_k} + J_{ERleak_k} - \frac{J_{TRPV_k}}{r_{buff}}\right) \tag{88}$$

The astrocytic inositol trisphosphate (IP_3) concentration (μM):

$$\frac{dIP3_k}{dt} = r_h G - k_{deg}\, IP3_k \tag{89}$$

The astrocytic epoxyeicosatrienoic acid (EET) concentration (μM):

$$\frac{deet_k}{dt} = V_{eet}\max(Ca_k - c_{k_{min}}, 0) - k_{eet}eet_k \tag{90}$$

The Ca^{2+} concentration in the astrocytic endoplasmic reticulum (ER) (μM):

$$\frac{ds_k}{dt} = \frac{-B_{cyt}}{VR_{ERcyt}}\left(J_{IP3_k} - J_{pump_k} + J_{ERleak_k}\right) \tag{91}$$

Membrane potential of the astrocyte (AC) (mV):

$$\frac{dv_k}{dt} = \gamma_j(-J_{BK_k} - J_{K_k} - J_{Cl_k} - J_{NBC_k} - J_{Na_k} - J_{NaK_k} - 2J_{TRPV_k}) \tag{92}$$

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

$$\frac{dw_k}{dt} = \phi_n(w_\infty - w_k) \tag{93}$$

The inactivation variable h_k of the astrocytic IP_3R channel (-):

$$\frac{dh_k}{dt} = k_{on}\left[K_{inh} - (Ca_k + K_{inh})h_k\right] \tag{94}$$

4.2. Algebraic Variables

The glutamate concentration in the SC (μM):

$$Glu = \frac{Glu_{max}}{2}\left(1 + \tanh\left(\frac{K_e - K_{e_{switch}}}{Glu_{slope}}\right)\right) \tag{95}$$

The flux of K^+ into the SC based on the extracellular K^+ (μMs^{-1}):

$$J_{NEtoSC} = c_{unit}k_{syn}\frac{dK_e}{dt} \tag{96}$$

Cl^- concentration in the SC (μM):

$$Cl_s = Na_s + K_s - HCO_{3_s} \tag{97}$$

Cl^- flux through the Cl^- channel (μM s^{-1}):

$$J_{Cl_k} = G_{Cl_k}(v_k - E_{Cl_k}) \tag{98}$$

K^+ flux through the K^+ channel (μM s^{-1}):

$$J_{K_k} = G_{K_k}(v_k - E_{K_k}) \tag{99}$$

Na^+ flux through the Na^+ channel (μM s^{-1}):

$$J_{Na_k} = G_{Na_k}(v_k - E_{Na_k}) \tag{100}$$

Na^+ and HCO_3^- flux through the NBC channel (μM s^{-1}):

$$J_{NBC_k} = G_{NBC_k}\left(v_k - E_{NBC_k}\right) \tag{101}$$

Cl^- and K^+ flux through the KCC1 channel (μM s^{-1}):

$$J_{KCC1_k} = G_{KCC1_k}\phi \ln\left(\frac{K_s Cl_s}{K_k Cl_k}\right) \tag{102}$$

Na^+, K^+ and Cl^- flux through the NKCC1 channel (μM s^{-1}):

$$J_{NKCC1_k} = G_{NKCC1_k}\phi \ln\left(\frac{Na_s K_s {Cl_s}^2}{Na_k K_k {Cl_k}^2}\right) \tag{103}$$

Flux through the Na^+/K^+ ATP-ase pump (μM s^{-1}):

$$J_{NaK_k} = J_{NaK_{max}}\frac{{Na_k}^{1.5}}{{Na_k}^{1.5} + {K_{Na_k}}^{1.5}}\frac{K_s}{K_s + K_{K_s}} \tag{104}$$

K^+ flux through the BK channel (μM s^{-1}):

$$J_{BK_k} = G_{BK_k}w_k\left(v_k - E_{BK_k}\right) \tag{105}$$

Nernst potential for the K^+ channel (mV):

$$E_{K_k} = \frac{\phi}{z_K}\ln\left(\frac{K_s}{K_k}\right) \tag{106}$$

Nernst potential for the Na^+ channel (mV):

$$E_{Na_k} = \frac{\phi}{z_{Na}} \ln\left(\frac{Na_s}{Na_k}\right) \tag{107}$$

Nernst potential for the Cl^- channel (mV):

$$E_{Cl_k} = \frac{\phi}{z_{Cl}} \ln\left(\frac{Cl_s}{Cl_k}\right) \tag{108}$$

Nernst potential for the NBC channel (mV):

$$E_{NBC_k} = \frac{\phi}{z_{NBC}} \ln\left(\frac{Na_s HCO_{3_s}{}^2}{Na_k HCO_{3_k}{}^2}\right) \tag{109}$$

Nernst potential for the BK channel (mV):

$$E_{BK_k} = \frac{\phi}{z_K} \ln\left(\frac{K_p}{K_k}\right) \tag{110}$$

Equilibrium state BK-channel (-):

$$w_\infty = 0.5\left(1 + \tanh\left(\frac{v_k + v_6}{v_4}\right)\right) \tag{111}$$

The time constant associated with the opening of the BK channel (s^{-1}):

$$\phi_n = \psi_n \cosh\left(\frac{v_k - v_3}{2v_4}\right) \tag{112}$$

The equilibrium state of the BK channel (-):

$$w_\infty = \frac{1}{2}\left(1 + \tanh\left(\frac{v_k + eet_{shift} eet_k - v_3}{v_4}\right)\right) \tag{113}$$

The voltage associated with half open probability (mV):

$$v_3 = -\frac{v_5}{2} \tanh\left(\frac{Ca_k - Ca_3}{Ca_4}\right) + v_6 \tag{114}$$

The ratio ρ of bound to unbound metabotropic receptors on the astrocytic process adjacent to the SC (-):

$$\rho = \rho_{\text{min}} + \frac{\rho_{\text{max}} - \rho_{\text{min}}}{Glu_{max}} Glu \tag{115}$$

The ratio G of active to total G-protein due to metabotropic glutamate receptor (mGluR) binding on the astrocyte endfoot surround the SC (-):

$$G = \frac{\rho + \delta_G}{K_G + \rho + \delta_G} \tag{116}$$

Fast Ca^{2+} buffering is described within the steady state approximation (-):

$$B_{cyt} = \left(1 + BK_{end} + \frac{K_{ex} B_{ex}}{(K_{ex} + Ca_k)^2}\right)^{-1} \tag{117}$$

The flux of Ca^{2+} through the IP_3R channel (μM s^{-1}):

$$J_{IP3_k} = J_{max}\left[\left(\frac{IP3_k}{IP3_k + K_i}\right)\left(\frac{Ca_k}{Ca_k + K_{act_k}}\right)h_k\right]^3\left(1 - \frac{Ca_k}{s_k}\right) \tag{118}$$

The flux of Ca^{2+} through the uptake pump (μM s^{-1}):

$$J_{pump_k} = V_{max}\frac{Ca_k^2}{Ca_k^2 + k_{pump}^2} \tag{119}$$

The flux of Ca^{2+} through the leak channel (μM s^{-1}):

$$J_{ERleak_k} = P_L\left(1 - \frac{Ca_k}{s_k}\right) \tag{120}$$

Parameter	Description	Value
VR_{sk}	Volume ratio between the SC and astrocyte	0.465
Glu_{max}	Maximum glutamate concentration (one vesicle)	1846 μM
$K_{e_{switch}}$	Threshold past which glutamate vesicle is released	5.5 mM
Glu_{slope}	Slope of glutamate sigmoidal	0.1 mM
c_{unit}	Constant to convert from mM to μM	10^3
k_{syn}	The number of active synapses per astrocytic process	11.5
γ_j	Change in membrane potential by a scaling factor	1970 mV μM $^{-1}$
G_{K_k}	Specific ion conductance of K^+	6907.77 μM mV^{-1} s^{-1}
G_{Na_k}	Specific ion conductance of Na^+	226.94 μM mV^{-1} s^{-1}
G_{NBC_k}	Specific ion conductance of the NBC cotransporter	130.74 μM mV^{-1} s^{-1}
G_{KCC1_k}	Specific ion conductance of the KCC1 cotransporter	1.728 μM mV^{-1} s^{-1}
G_{NKCC1_k}	Specific ion conductance of the NKCC1 cotransporter	9.568 μM mV^{-1} s^{-1}
G_{BK_k}	Specific ion conductance of the BK channel	10.25 μM mV^{-1} s^{-1}
G_{Cl_k}	Specific ion conductance of Cl^-	151.93 μM mV^{-1} s^{-1}
$J_{NaK_{max}}$	Maximum flux through the Na^+/K^+ ATP-ase pump	2.37$\times 10^4$ μM s^{-1}
K_{Na_k}	Na^+/K^+ ATP-ase pump constant	10×10^3 μM
K_{K_s}	Na^+/K^+ ATP-ase pump constant	1.5×10^3 μM
v_6	Voltage associated with the opening of half the population	22 mV
v_4	A measure of the spread of w_∞	14.5 mV
ψ_w	A characteristic time for the open probability of the BK channel	2.664 s^{-1}
$\rho_{\min}$	Minimum ratio of bound to unbound IP_3 receptors	0.1
$\rho_{\max}$	Maximum ratio of bound to unbound IP_3 receptors	0.7
δ_G	Ratio of the activities of the unbound and bound receptors	1.235×10^{-2}
K_G	G-protein disassociation constant	8.82
r_h	Maximum rate of IP_3 production in astrocyte due to glutamate receptors	4.8 μM s^{-1}
k_{deg}	Rate constant for IP_3 degradation in astrocyte	1.25 s^{-1}
r_{buff}	Rate of Ca^{2+} buffering at the endfoot compared to the astrocyte body	0.05
VR_{ERcyt}	Volume ratio between ER and astrocytic cytosol	0.185

BK_{end}	Ratio of endogenous buffer concentration to disassociation constant	40
K_{ex}	Disassociation constant of exogenous buffer	0.26 μM
B_{ex}	Concentration of exogenous buffer	11.35 μM
J_{max}	Maximum rate of Ca^{2+} through the IP_3 mediated channel	2880 μM s^{-1}
K_i	Disassociation constant for IP_3 binding to an IP_3R	0.03 μM
K_{act_k}	Disassociation constant for Ca^{2+} binding to an activation site on an IP_3R	0.17 μM
k_{on}	Rate of Ca^{2+} binding to the inhibitory site on the IP_3R	2 μM $^{-1}$ s^{-1}
K_{inh}	Disassociation constant of IP_3R	0.1 μM
V_{max}	Maximum rate of Ca^{2+} uptake pump on the ER	20 μM s^{-1}
k_{pump}	Ca^{2+} uptake pump disassociation constant	0.24 μM
P_L	ER leak channel steady state balance constant	0.0804 μM s^{-1}
V_{eet}	EET production rate	72 s^{-1}
$c_{k_{min}}$	Minimum Ca^{2+} concentration required for EET production	0.1 μM
k_{eet}	EET degradation rate	7.2 s^{-1}
ψ_n	Characteristic time for the opening of the BK channel	2.664 s^{-1}
v_4	Measure of the spread of w_∞	8 mV
eet_{shift}	Describes the EET dependent voltage shift	2 mV μM $^{-1}$
v_5	Determines the range of the shift of w_∞ as Ca^{2+} varies	15 mV
v_6	Shifts the range of w_∞	-55 mV
Ca_3	BK open probability Ca^{2+} constant	0.4 μM
Ca_4	BK open probability Ca^{2+} constant	0.35 μM

Table 4: Parameters of the astrocyte and SC submodel, for references see Dormanns et al. [2], Kenny et al. [4].

5. Perivascular space (PVS)

5.1. ODEs

K^+ concentration in the PVS (μM):

$$\frac{dK_p}{dt} = \frac{J_{BK_k}}{VR_{pk}} + \frac{J_{KIR_i}}{VR_{pi}} - K_{decay_p}(K_p - K_{min_p}) \tag{121}$$

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

$$\frac{dCa_p}{dt} = \frac{J_{TRPV_k}}{VR_{pk}} + \frac{J_{VOCC_i}}{VR_{pi}} - Ca_{decay_p}(Ca_p - Ca_{min_p}) \tag{122}$$

The open probability of the transient receptor potential vanniloid-related 4 (TRPV4) channel (-):

$$\frac{dm_k}{dt} = \frac{m_{\infty_k} - m_k}{t_{TRPV_k}} \tag{123}$$

5.2. Algebraic Variables

The flux of Ca^{2+} through the voltage operated Ca^{2+} channel (VOCC) which connects the smooth muscle cell (SMC) to the PVS (μM s^{-1}):

$$J_{VOCC_i} = G_{Cai} \frac{v_i - v_{Ca1}}{1 + \exp\left[-(v_i - v_{Ca2})/R_{Cai}\right]} \tag{124}$$

The flux of Ca^{2+} through the TRPV4 channel (μM s^{-1}):

$$J_{TRPV_k} = G_{TRPV_k} m_k (v_k - E_{TRPV_k}) \tag{125}$$

The Nernst potential of the TRPV4 channel (mV):

$$E_{TRPV_k} = \frac{\phi}{z_{Ca}} \ln\left(\frac{Ca_p}{Ca_k}\right) \tag{126}$$

The equilibrium state of the TRPV4 channel (-):

$$m_{\infty_k} = \Gamma_m \left[\frac{1}{1 + H_{Ca_k}} \left(H_{Ca_k} + \tanh\left(\frac{v_k - v_{1,TRPV}}{v_{2,TRPV}}\right)\right)\right] \tag{127}$$

The material strain gating term (-):

$$\Gamma_m = \frac{1}{1 + \exp\left(-\frac{\eta - \eta_0}{\kappa_k}\right)} \tag{128}$$

The strain on the perivascular endfoot of the astrocyte (-)

$$\eta = \frac{R - R_{init}}{R_{init}} \tag{129}$$

The Ca^{2+} inhibitory term (-)

$$H_{Ca_k} = \frac{Ca_k}{\gamma_{Cai}} + \frac{Ca_p}{\gamma_{Cae}} \tag{130}$$

Parameter	Description	Value
VR_{pk}	Volume ratio between PVS and astrocyte	0.001
VR_{pi}	Volume ratio between PVS and SMC	0.001
K_{decay_p}	Rate of decay of K^+ in PVS	0.15 s^{-1}
K_{min_p}	Steady state value of K^+ in PVS	3×10^3 μM
Ca_{decay_p}	Rate of decay of Ca^{2+} in PVS	0.5 s^{-1}
Ca_{min_p}	Steady state value of Ca^{2+} in PVS	2×10^3 μM
G_{Cai}	VOCC whole cell conductance	1.29×10^{-3} μM mV^{-1} s^{-1}
v_{Ca1}	VOCC reversal potential	100 mV
v_{Ca2}	Half point of the VOCC activation sigmoidal	-24 mV
R_{Cai}	Maximum slope of the VOCC activation sigmoidal	8.5 mV
G_{TRPV_k}	TRPV4 whole cell conductance	3.15×10^{-4} μM mV^{-1} s^{-1}
t_{TRPV_k}	Characteristic time constant for m_k	0.9 s
η_0	Strain required for half activation of the TRPV4 channel	0.1

κ_k	TRPV4 channel strain constant	0.1
$v_{1,TRPV}$	TRPV4 channel voltage gating constant	120 mV
$v_{2,TRPV}$	TRPV4 channel voltage gating constant	13 mV
γ_{Cai}	Ca^{2+} concentration constant	0.01 μM
γ_{Cae}	Ca^{2+} concentration constant	200 μM

Table 5: Parameters of the PVS compartment, for references see Dormanns et al. [2], Kenny et al. [4].

6. SMC

6.1. ODEs

Cytosolic Ca^{2+} in the SMC (μM):

$$\frac{dCa_i}{dt} = J_{IP_{3i}} - J_{SR_{uptake_i}} + J_{CICR_i} - J_{extrusion_i} + J_{SR_{leak_i}} \dots \\ -J_{VOCC_i} + J_{Na/Ca_i} - 0.1 J_{stretch_i} + J^{SMC-EC}_{Ca^{2+}-coupling_i} \tag{131}$$

Ca^{2+} in the sarcoplasmic reticulum (SR) of the SMC (μM):

$$\frac{ds_i}{dt} = J_{SR_{uptake_i}} - J_{CICR_i} - J_{SR_{leak_i}} \tag{132}$$

Membrane potential of the SMC (mV):

$$\frac{dv_i}{dt} = \gamma_j(-J_{NaK_i} - J_{Cl_i} - 2J_{VOCC_i} - J_{Na/Ca_i} - J_{K_i} - J_{stretch_i} - J_{KIR_i}) + V^{SMC-EC}_{coupling_i} \tag{133}$$

Open state probability of Ca^{2+}-activated K^+ channels (-):

$$\frac{dw_i}{dt} = \lambda_i \left(K_{act_i} - w_i\right) \tag{134}$$

IP_3 concentration in the SMC (μM):

$$\frac{dIP3_i}{dt} = J^{SMC-EC}_{IP_3-coupling_i} - J_{degrad_i} \tag{135}$$

K^+ concentration in the SMC (μM):

$$\frac{dK_i}{dt} = J_{NaK_i} - J_{KIR_i} - J_{K_i} \tag{136}$$

6.2. Algebraic Variables

Release of Ca^{2+} from IP_3 sensitive stores in the SMC (μM s^{-1}):

$$J_{IP3_i} = F_i \frac{IP3_i^2}{K_{ri}^2 + IP3_i^2} \tag{137}$$

Uptake of Ca^{2+} into the SR (μM s^{-1}):

$$J_{SR_{uptake_i}} = B_i \frac{Ca_i^2}{c_{bi}^2 + Ca_i^2} \tag{138}$$

Ca^{2+} induced Ca^{2+} release (CICR) (μM s^{-1}):

$$J_{CICR_i} = C_i \frac{s_i^2}{s_{ci}^2 + \ s_i^2} \frac{Ca_i^4}{c_{ci}^4 + Ca_i^4} \tag{139}$$

Ca^{2+} extrusion by Ca^{2+}-ATP-ase pumps (μM s^{-1}):

$$J_{extrusion_i} = D_i Ca_i \left(1 + \frac{v_i - v_d}{R_{di}}\right) \tag{140}$$

Leak current from the SR (μM s^{-1}):

$$J_{SR_{leak_i}} = L_i s_i \tag{141}$$

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

$$J_{Na/Ca_i} = G_{Na/Ca_i} \frac{Ca_i}{Ca_i + c_{Na/Cai}} \left(v_i - v_{Na/Ca_i}\right) \tag{142}$$

Ca^{2+} flux through the stretch-activated channels in the SMC (μM s^{-1}):

$$J_{stretch_i} = \frac{G_{stretch}}{1 + \exp\left(-\alpha_{stretch}\left(\frac{\Delta pR}{h} - \sigma_0\right)\right)} \left(v_i - E_{SAC}\right) \tag{143}$$

Flux through the Na^{+}/K^{+} pump (μM s^{-1}):

$$J_{NaK_i} = F_{NaK} \tag{144}$$

Cl^{-} flux through the Cl^{-} channel (μM s^{-1}):

$$J_{Cl_i} = G_{Cli}\left(v_i - v_{Cli}\right) \tag{145}$$

K^{+} flux through K^{+} channel (μM s^{-1}):

$$J_{K_i} = G_{Ki} w_i \left(v_i - v_{K_i}\right) \tag{146}$$

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

$$J_{KIR_i} = G_{KIR_i}(v_i - v_{KIR_i}) \tag{147}$$

IP_3 degradation (μM s^{-1}):

$$J_{degrad_i} = k_{di} I_i \tag{148}$$

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

$$v_{KIR_i} = z_1 K_p - z_2 \tag{149}$$

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

$$G_{KIR_i} = F_{KIR_i} \exp(z_5 v_i + z_3 K_p - z_4) \tag{150}$$

Equilibrium distribution of open channel states for the SMC BK channels (-):

$$K_{act_i} = \frac{\left(Ca_i + c_{w,i}\right)^2}{\left(Ca_i + c_{w,i}\right)^2 + \alpha_{act_i} \exp(-\left(\left[v_i - v_{Ca_3 i}\right]/R_{Ki}\right))} \tag{151}$$

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

$$c_{\mathrm{w},i} = \frac{\beta_{w,i}}{2}(1 + \tanh\left(\frac{\text{cGMP}_i - \alpha_{w,i}}{\epsilon_{w,i}}\right)) \tag{152}$$

Heterocellular electrical coupling between SMCs and endothelial cells (ECs) (mV s^{-1}):

$$V^{SMC-EC}_{coupling_i} = -G_{coup}(v_i - v_j) \tag{153}$$

Heterocellular IP$_3$ coupling between SMCs and ECs (μM s^{-1}):

$$J^{SMC-EC}_{IP_3-coupling_i} = -P_{IP_3}(IP3_i - IP3_j) \tag{154}$$

Ca^{2+} coupling between SMCs and ECs (μM s^{-1}):

$$J^{SMC-EC}_{Ca^{2+}-coupling_i} = -P_{Ca^{2+}}(Ca_i - Ca_j) \tag{155}$$

Parameter	Description	Value
λ_i	Rate constant for opening	45 s^{-1}
F_i	Maximal rate of activation-dependent Ca^{2+} influx	0.23 μM s^{-1}
K_{ri}	Half-saturation constant for agonist-dependent Ca^{2+} entry	1 μM
B_i	SR uptake rate constant	2.025 μM s^{-1}
c_{bi}	Half-point of the SR ATP-ase activation sigmoidal	1 μM
C_i	CICR rate constant	55 μM s^{-1}
s_{ci}	Half-point of the CICR Ca^{2+} efflux sigmoidal	2 μM
c_{ci}	Half-point of the CICR activation sigmoidal	0.9 μM
D_i	Rate constant for Ca^{2+} extrusion by the ATP-ase pump	0.24 s^{-1}
v_d	Intercept of voltage dependence of extrusion ATP-ase	-100 mV
R_{di}	Slope of voltage dependence of extrusion ATP-ase	250 mV
L_i	Leak from SR rate constant	0.025 s^{-1}
G_{Cai}	Whole-cell conductance for VOCCs	1.29$\times$10^{-3} μM mV^{-1} s^{-1}
$v_{Ca_{1i}}$	Reversal potential for VOCCs	100 mV
$v_{Ca_{2i}}$	Half-point of the VOCC activation sigmoidal	-24 mV
R_{Cai}	Maximum slope of the VOCC activation sigmoidal	8.5 mV
$G_{Na/Cai}$	Whole-cell conductance for Na$^+$/Ca^{2+} exchange	3.16$\times$10^{-3} μM mV^{-1} s^{-1}
$c_{Na/Cai}$	Half-point for activation of Na$^+$/Ca^{2+} exchange by Ca^{2+}	0.5 μM
$v_{Na/Cai}$	Reversal potential for the Na$^+$/Ca^{2+} exchanger	-30 mV
$G_{stretch}$	Whole cell conductance for stretch activated channels (SACs)	6.1$\times$10^{-3} μM mV^{-1} s^{-1}
$\alpha_{stretch}$	Slope of stress dependence of the SAC activation sigmoidal	7.4$\times$10^{-3} mmHg^{-1}
Δp	Pressure difference over vessel	30 mmHg
σ_0	Half-point of the SAC activation sigmoidal	500 mmHg
E_{SAC}	Reversal potential for SACs	-18 mV
F_{NaK}	Rate of the K$^+$ influx by the Na$^+$/K$^+$ pump	4.32$\times$10^{-2} μM s^{-1}

G_{Cli}	Whole-cell conductance for Cl^- current	1.34×10^{-3} μM mV^{-1} s^{-1}
v_{Cli}	Reversal potential for Cl^- channels	-25 mV
G_{Ki}	Whole-cell conductance for K^+ efflux	4.46×10^{-3} μM mV^{-1} s^{-1}
v_{K_i}	Nernst potential	-94 mV
F_{KIR_i}	Scaling factor of K^+ efflux through the KIR channel	0.381 μM mV^{-1} s^{-1}
k_{di}	Rate constant of IP_3 degradation	0.1 s^{-1}
α_{act_i}	Translation factor for v_i dependence of K_{act_i} sigmoidal	0.13 μM ^{2}
$v_{Ca_{3i}}$	Half-point for the K_{Ca} channel activation sigmoidal	-27 mV
R_{Ki}	Maximum slope of the K_{Ca} activation sigmoidal	12 mV
z_1	Model estimation for membrane voltage KIR channel	4.5×10^3 mV μM $^{-1}$
z_2	Model estimation for membrane voltage KIR channel	112 mV
z_3	Model estimation for the KIR channel conductance	4.2×10^{-4} μM $^{-1}$
z_4	Model estimation for the KIR channel conductance	12.6
z_5	Model estimation for the KIR channel conductance	-7.4×10^{-2} mV^{-1}
$\beta_{w,i}$	Constant to fit data	1 μM
$\alpha_{w,i}$	Constant to fit data	10.75 μM
$\epsilon_{w,i}$	Constant to fit data	0.668 μM
G_{coup}	Heterocellular electrical coupling coefficient	0.5 s^{-1}
P_{IP_3}	Heterocellular IP_3 coupling coefficient	0.05 s^{-1}
$P_{Ca^{2+}}$	Heterocellular $P_{Ca^{2+}}$ coupling coefficient	0.05 s^{-1}

Table 6: Parameters of the SMC compartment, for references see Dormanns et al. [2].

7. EC

7.1. ODEs

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

$$\begin{aligned}\frac{dCa_j}{dt} &= J_{IP_{3j}} - J_{ER_{uptake_j}} + J_{CICR_j} - J_{extrusion_j} \dots \\ &+ J_{ER_{leak_j}} + J_{cation_j} + J_{0_j} - J_{stretch_j} - J^{SMC-EC}_{Ca^{2+}-coupling_j}\end{aligned} \tag{156}$$

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

$$\frac{ds_j}{dt} = J_{ER_{uptake_j}} - J_{CICR_j} - J_{ER_{leak_j}} \tag{157}$$

Membrane potential of the EC (mV):

$$\frac{dv_j}{dt} = -\frac{1}{C_{m_j}}(I_{K_j} + I_{R_j}) - V^{SMC-EC}_{coupling_j} \tag{158}$$

IP_3 concentration of the EC (μM):

$$\frac{dIP3_j}{dt} = J_{PLC} - J_{degrad_j} - J^{SMC-EC}_{IP_3-coupling_j} \tag{159}$$

7.2. Algebraic Variables

Release of Ca^{2+} from IP_3-sensitive stores in the EC (μM s^{-1}):

$$J_{IP_{3j}} = F_j \frac{IP3_j^2}{K_{rj}^2 + IP3_j^2} \tag{160}$$

Uptake of Ca^{2+} into the endoplasmic reticulum (μM s^{-1}):

$$J_{ER_{uptake_j}} = B_j \frac{Ca_j^2}{c_{bj}^2 + Ca_j^2} \tag{161}$$

CICR (μM s^{-1}):

$$J_{CICR_j} = C_j \frac{s_j^2}{s_{cj}^2 + s_j^2} \frac{Ca_j^4}{c_{cj}^4 + Ca_j^4} \tag{162}$$

Ca^{2+} extrusion by Ca^{2+}-ATP-ase pumps (μM s^{-1}):

$$J_{extrusion_j} = D_j Ca_j \tag{163}$$

Ca^{2+} flux through the stretch-activated channels in the EC (μM s^{-1}):

$$J_{stretch_j} = \frac{G_{stretch}}{1 + \exp\left(-\alpha_{stretch}\left(\frac{\Delta pR}{h} - \sigma_0\right)\right)} (v_j - E_{SAC}) \tag{164}$$

Leak current from the ER (μM s^{-1}):

$$J_{ER_{leak_j}} = L_j s_j \tag{165}$$

Ca^{2+} influx through nonselective cation channels (μM s^{-1}):

$$J_{cation_j} = G_{cat_j}(E_{Ca_j} - v_j)\frac{1}{2}\left(1 + \tanh\left(\frac{\log_{10}(Ca_j/c_{log}) - m_{3_{cat_j}}}{m_{4_{cat_j}}}\right)\right) \tag{166}$$

K^+ current through the BK_{Caj} channel and the SK_{Caj} channel (fA):

$$I_{K_j} = G_{totj}(v_j - v_{Kj})\left(I_{BK_{Caj}} + I_{SK_{Caj}}\right) \tag{167}$$

K^+ efflux through the BK_{Caj} channel (-):

$$I_{BK_{Caj}} = 0.2\left(1 + \tanh\left(\frac{(\log_{10}(Ca_j/c_{log}) - c)(v_j - b_j) - a_{1j}}{m_{3bj}(v_j + a_{2j}(\log_{10}(Ca_j/c_{log}) - c) - b_j)^2 + m_{4bj}}\right)\right) \tag{168}$$

K^+ efflux through the SK_{Caj} channel (-):

$$I_{SK_{Caj}} = 0.3\left(1 + \tanh\left(\frac{\log_{10}(Ca_j/c_{log}) - m_{3sj}}{m_{4sj}}\right)\right) \tag{169}$$

Residual current regrouping Cl^- and Na^+ current flux (fA):

$$I_{R_j} = G_{R_j}(v_j - v_{restj}) \tag{170}$$

IP_3 degradation (μM s^{-1}):

$$J_{degrad_j} = k_{dj} IP3_j \tag{171}$$

Parameter	Description	Value
J_{0_j}	Constant Ca^{2+} influx	0.029 μM s^{-1}
C_{m_j}	Membrane capacitance	25.8 pF
J_{PLC}	IP_3 production rate	0.11 μM s^{-1}
F_j	Maximal rate of activation-dependent Ca^{2+} influx	0.23 μM s^{-1}
K_{rj}	Half-saturation constant for agonist-dependent Ca^{2+} entry	1 μM
B_j	ER uptake rate constant	0.5 μM s^{-1}
c_{bj}	Half-point of the SR ATP-ase activation sigmoidal	1 μM
C_j	CICR rate constant	5 μM s^{-1}
s_{cj}	Half-point of the CICR Ca^{2+} efflux sigmoidal	2 μM
c_{cj}	Half-point of the CICR activation sigmoidal	0.9 μM
D_j	Rate constant for Ca^{2+} extrusion by the ATP-ase pump	0.24 s^{-1}
L_j	Rate constant for Ca^{2+} leak from the ER	0.025 s^{-1}
G_{catj}	Whole-cell cation channel conductivity	6.6×10^{-4} μM mV^{-1} s^{-1}
E_{Caj}	Ca^{2+} equilibrium potential	50 mV
c_{log}	Log constant	1 μM
G_{totj}	Total K^+ channel conductivity	6927 pS
v_{Kj}	K^+ equilibrium potential	-80 mV
$m_{3_{catj}}$	Model constant, further explanation see [5]	-0.18
$m_{4_{catj}}$	Model constant, further explanation see [5]	0.37
c	Model constant, further explanation see [5]	-0.4
b_j	Model constant, further explanation see [5]	-80.8 mV
a_{1j}	Model constant, further explanation see [5]	53.3 mV
a_{2j}	Model constant, further explanation see [5]	53.3 mV
m_{3bj}	Model constant, further explanation see [5]	1.32×10^{-3} mV^{-1}
m_{4bj}	Model constant, further explanation see [5]	0.30 mV
m_{3sj}	Model constant, further explanation see [5]	-0.28
m_{4sj}	Model constant, further explanation see [5]	0.389
G_{R_j}	Residual current conductivity	955 pS
v_{restj}	Membrane resting potential	-31.1 mV
k_{dj}	Rate constant of IP_3 degradation	0.1 s^{-1}

Table 7: Parameters of the EC compartment, for references see Dormanns et al. [2].

8. Nitric oxide (NO) pathway

8.1. ODEs

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

$$\frac{dCa_n}{dt} = \frac{1}{1+\lambda_{\text{buf}}}\left(\frac{I_{\text{Ca,tot}}}{2FV_{\text{spine}}} - \kappa_{\text{ex}}(Ca_n - [Ca]_{\text{rest}})\right) \tag{172}$$

Activated neuronal NO synthase (nNOS) (μM):

$$\frac{d[\text{nNOS}]_n}{dt} = \frac{V_{\text{max,nNOS}}[\text{CaM}]_n}{K_{\text{m,nNOS}} + [\text{CaM}]_n} - \mu_{\text{deact},n}[\text{nNOS}]_n \tag{173}$$

NO concentration in the neuron (μM):

$$\frac{d\text{NO}_n}{dt} = p_{NO,n} - c_{NO,n} + d_{NO,n} \tag{174}$$

NO concentration in the astrocyte (μM):

$$\frac{d\text{NO}_k}{dt} = p_{NO,k} - c_{NO,k} + d_{NO,k} \tag{175}$$

NO concentration in the SMC (μM):

$$\frac{d\text{NO}_i}{dt} = p_{NO,i} - c_{NO,i} + d_{NO,i} \tag{176}$$

Activated endothelial NO synthase (eNOS) (μM):

$$\frac{d[\text{eNOS}]_j}{dt} = \gamma_{\text{eNOS}}\frac{K_{\text{dis}}Ca_j}{K_{\text{m,eNOS}} + Ca_j} + (1 - \gamma_{\text{eNOS}})g_{\max}F_{\text{wss}} - \mu_{\text{deact},j}[\text{eNOS}]_j \tag{177}$$

NO concentration in the EC (μM):

$$\frac{d\text{NO}_j}{dt} = p_{NO,j} - c_{NO,j} + d_{NO,j} \tag{178}$$

Fraction of soluble guanylyl cyclase (sGC) in the basal state (-):

$$\frac{dE_b}{dt} = -k_1 E_b\text{NO}_i + k_{-1}E_{6c} + k_4 E_{5c} \tag{179}$$

Fraction of sGC in the intermediate form (-):

$$\frac{dE_{6c}}{dt} = k_1 E_b\text{NO}_i - (k_{-1} + k_2)E_{6c} - k_3 E_{6c}\text{NO}_i \tag{180}$$

Concentration of cGMP in the SMC (μM):

$$\frac{d\text{cGMP}_i}{dt} = V_{\text{max,sGC}}E_{5c} - V_{\text{max,pde}}\frac{\text{cGMP}_i}{K_{\text{m,pde}} + \text{cGMP}_i} \tag{181}$$

8.2. Algebraic Variables

Fraction of open NR2A NMDA receptors (-):

$$w_{\text{NR2},A} = \frac{Glu}{K_{m,A} + Glu} \tag{182}$$

Fraction of open NR2B NMDA receptors (-):

$$w_{\text{NR2},B} = \frac{Glu}{K_{\text{m},B} + Glu} \tag{183}$$

Inward Ca^{2+} current per open NMDA receptor (fA):

$$I_{\text{Ca}} = \frac{4v_n G_{\text{M}}(P_{\text{Ca}}/P_{\text{M}})([Ca]_{\text{ex}}/[\text{M}])}{1+\exp(\alpha_v(v_n+\beta_v))} \frac{\exp(2v_n/\phi))}{1-\exp(2v_n/\phi))} \tag{184}$$

Total inward Ca^{2+} current for all open NMDA receptors per synapse (fA):

$$I_{\text{Ca,tot}} = (n_{\text{NR2},A} w_{\text{NR2},A} + n_{\text{NR2},B} w_{\text{NR2},B}) I_{\text{Ca}} \tag{185}$$

Ca^{2+}-calmodulin complex concentration (μM):

$$[\text{CaM}]_n = \frac{Ca_n}{m_c} \tag{186}$$

Neuronal NO production flux (μM s^{-1}):

$$p_{NO,n} = V_{\text{max,NO},n}[\text{nNOS}]_n \frac{[O_2]_n}{K_{\text{m,O2},n}+[O_2]_n} \frac{[LArg]_n}{K_{\text{m,LArg},n}+[LArg]_n} \tag{187}$$

Neuronal NO consumption flux (μM s^{-1}):

$$c_{NO,n} = k_{\text{O2},n}[\text{NO}]_n^2[O_2]_n \tag{188}$$

Neuronal NO diffusive flux (μM s^{-1}):

$$d_{NO,n} = \frac{[\text{NO}]_k - [\text{NO}]_n}{\tau_{nk}} \tag{189}$$

Time for NO to diffuse between the centres of the neuron and the astrocyte (s):

$$\tau_{nk} = \frac{x_{nk}^2}{2D_{\text{c,NO}}} \tag{190}$$

Astrocytic NO production flux (μM s^{-1}):

$$p_{NO,k} = 0 \tag{191}$$

Astrocytic NO consumption flux (μM s^{-1}):

$$c_{NO,k} = k_{\text{O2},k}[\text{NO}]_k^2[O_2]_k \tag{192}$$

Astrocytic NO diffusive flux (μM s^{-1}):

$$d_{NO,k} = \frac{[\text{NO}]_n - [\text{NO}]_k}{\tau_{nk}} + \frac{[\text{NO}]_i - [\text{NO}]_k}{\tau_{ki}} \tag{193}$$

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

$$\tau_{ki} = \frac{x_{ki}^2}{2D_{\text{c,NO}}} \tag{194}$$

SMC NO production flux (μM s^{-1}):

$$p_{NO,i} = 0 \tag{195}$$

SMC NO consumption flux (μM s^{-1}):

$$c_{NO,i} = k_{\text{dno}}[\text{NO}]_i \tag{196}$$

SMC NO diffusive flux (μM s^{-1}):

$$d_{NO,i} = \frac{[\text{NO}]_k - [\text{NO}]_i}{\tau_{ki}} + \frac{[\text{NO}]_j - [\text{NO}]_i}{\tau_{ij}} \tag{197}$$

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

$$k_4 = C_4[\text{cGMP}]_i^2 \tag{198}$$

Fraction of sGC in the fully activated form (-):

$$E_{5c} = 1 - E_b - E_{6c} \tag{199}$$

Regulatory effect of cGMP on myosin dephosphorylation (-):

$$R_{\text{cGMP}} = \frac{[\text{cGMP}]_i^2}{K_{\text{m,mlcp}}^2 + [\text{cGMP}]_i^2} \tag{200}$$

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

$$V_{\text{max,pde}} = k_{\text{pde}}[\text{cGMP}]_i \tag{201}$$

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

$$\tau_{ij} = \frac{x_{ij}^2}{2D_{\text{c,NO}}} \tag{202}$$

Fraction of the elastic strain energy stored within the membrane (-):

$$F_{\text{wss}} = \frac{1}{1 + \alpha_{\text{wss}} \exp(-W_{\text{wss}})} - \frac{1}{1 + \alpha_{\text{wss}}} \tag{203}$$

Strain energy density (-):

$$W_{\text{wss}} = W_0 \frac{(\tau_{\text{wss}} + \sqrt{16\delta_{\text{wss}}^2 + \tau_{\text{wss}}^2} - 4\delta_{\text{wss}})^2}{\tau_{\text{wss}} + \sqrt{16\delta_{\text{wss}}^2 + \tau_{\text{wss}}^2}} \tag{204}$$

Wall shear stress (Pa):

$$\tau_{\text{wss}} = \frac{R\Delta P}{2L} \tag{205}$$

O_2 concentration in the EC (μM):

$$[O_2]_j = c_{unit}\, O_2 \tag{206}$$

EC NO production flux (μM s^{-1}):

$$p_{NO,j} = V_{\text{max,NO},j}[\text{eNOS}]_j \frac{[O_2]_j}{K_{\text{m,O2},j} + [O_2]_j} \frac{[LArg]_j}{K_{\text{m,L-Arg},j} + [LArg]_j} \tag{207}$$

EC NO consumption flux (μM s^{-1}):

$$c_{NO,j} = k_{\text{O2},j}[\text{NO}]_j^2[O_2]_j \tag{208}$$

EC NO diffusive flux (μM s^{-1}):

$$d_{NO,j} = \frac{[\text{NO}]_i - [\text{NO}]_j}{\tau_{ij}} - \frac{4D_{\text{c,NO}}[\text{NO}]_j}{r_l^2} \tag{209}$$

Parameter	Description	Value
$[\mathrm{Glu}]_{\max}$	Maximum glutamate concentration	1846 μM
V_{spine}	Dendritic spine volume	8×10^{-5} pL
κ_{ex}	Decay rate constant of internal Ca^{2+} concentration	1.6×10^{3} s^{-1}
$[Ca]_{\text{rest}}$	Resting internal Ca^{2+} concentration	0.1 μM
λ_{buf}	Buffer capacity	20
$V_{\text{max,nNOS}}$	Maximum nNOS activation rate	25×10^{-3} μM s^{-1}
$K_{\text{m,nNOS}}$	Michaelis constant	9.27×10^{-2} μM
$\mu_{\text{deact},n}$	Rate constant at which nNOS is deactivated	0.0167 s^{-1}
$K_{\text{m},A}$	Michaelis constant	650 μM
$K_{\text{m},B}$	Michaelis constant	2800 μM
v_n	Neuronal membrane potential	-40 mV
G_{M}	Conductance of NMDA receptor	46 pS
$P_{\text{Ca}}/P_{\text{M}}$	Ratio of Ca^{2+} permeability to monovalent ion permeability	3.6
$[Ca]_{\text{ex}}$	External Ca^{2+} concentration	2×10^{3} μM
[M]	Concentration of monovalent ions	1.3×10^{5} μM
α_v	Voltage-dependent Mg^{2+} block parameter	-0.08 mV^{-1}
β_v	Voltage-dependent Mg^{2+} block parameter	20 mV
$n_{\text{NR2},A}$	Average number of NR2A NMDA receptors	0.63
$n_{\text{NR2},B}$	Average number of NR2B NMDA receptors	11
m_c	Number of Ca^{2+} ions bound per calmodulin	4
$V_{\text{max,NO},n}$	Maximum catalytic rate of neuronal NO production	4.22 s^{-1}
$[O_2]_n$	O_2 concentration in the neuron	200 μM
$K_{\text{m,O2},n}$	Michaelis constant for nNOS for O_2	243 μM
$[LArg]_n$	L-Arg concentration in the neuron	100 μM
$K_{\text{m,LArg},n}$	Michaelis constant for nNOS for LArg	1.5 μM
$k_{\text{O2},n}$	O_2 reaction rate constant	9.6×10^{-6} μM $^{-2}$ s^{-1}
x_{nk}	Distance between centres of neuron and astrocyte	25 μm
$k_{\text{O2},k}$	O_2 reaction rate constant	$9.6 \times 10^{-6}\mu$M $^{-2}$s^{-1}
$[O_2]_k$	O_2 concentration in the astrocyte	200 μM
x_{ki}	Distance between centres of astrocyte and SMC compartments	25 μm
k_{-1}	sGC kinetics rate constant	100 s^{-1}
k_1	sGC kinetics rate constant	2×10^{3} μM $^{-1}$ s^{-1}
k_2	sGC kinetics rate constant	0.1 s^{-1}
k_3	sGC kinetics rate constant	3 μM $^{-1}$ s^{-1}
$V_{\text{max,sGC}}$	Maximal cGMP production rate	0.8520 μM s^{-1}
$K_{\text{m,pde}}$	Michaelis constant	2 μM
k_{dno}	Constant reflecting the activity of various NO scavengers	0.01 s^{-1}
C_4	sGC rate scaling constant	0.011 μM $^{-2}$ s^{-1}
$K_{\text{m,mlcp}}$	Hill coefficient	5.5 μM

$v_{\text{Ca3},i}$	Half-point for the K_{Ca} channel activation sigmoidal	-27 mV
$R_{\text{K},i}$	Maximum slope of the K_{Ca} activation sigmoidal	12 mV
k_{pde}	Phosphodiesterase rate constant	0.0195 s^{-1}
x_{ij}	Distance between centres of SMC and EC compartments	3.75 μm
γ_{eNOS}	Relative strength of the Ca^{2+} dependent pathway for eNOS activation	0.1
$\mu_{\text{deact},j}$	eNOS-caveolin association rate	0.0167 s^{-1}
K_{dis}	eNOS-caveolin disassociation rate	0.09 $\mu\text{M s}^{-1}$
$K_{\text{m,eNOS}}$	Michaelis constant	0.45 μM
$g_{\max}$	Maximum wall-shear-stress-induced eNOS activation	0.06 $\mu\text{M s}^{-1}$
α_{wss}	Zero shear open channel constant	2
W_0	Shear gating constant	1.4 Pa^{-1}
δ_{wss}	Membrane shear modulus	2.86 Pa
$V_{\text{max,NO},j}$	Maximum catalytic rate of NO production	1.22 s^{-1}
$K_{\text{m,O2},j}$	Michaelis constant for eNOS for O_2	7.7 μM
$[LArg]_j$	L-Arg concentration in the neuron	100 μM
$K_{\text{m,L-Arg},j}$	Michaelis constant for L-Arg	1.5 μM
$\Delta P/L$	Pressure drop over length of arteriole	9.1×10^{-2} Pa μm^{-1}
$k_{\text{O2},j}$	O_2 reaction rate constant	9.6×10^{-6} $\mu\text{M}^{-2}\,\text{s}^{-1}$
$D_{\text{c,NO}}$	NO diffusion coefficient	3300 $\mu\text{m}^{2}\text{s}^{-1}$
r_l	Constant of lumen radius	25 μm

Table 8: Parameters of the NO submodel, for references see Dormanns et al. [1].

9. Wall mechanics

9.1. ODEs

Fraction of free phosphorylated cross-bridges (-):

$$\frac{d[Mp]}{dt} = \chi_w \left(K_4[AMp] + K_1[M] - (K_2 + K_3)[Mp]\right) \tag{210}$$

Fraction of attached phosphorylated cross-bridges (-):

$$\frac{d[AMp]}{dt} = \chi_w \left(K_3[Mp] + K_6[AM] - (K_4 + K_5)[AMp]\right) \tag{211}$$

Fraction of attached dephosphorylated cross-bridges (-):

$$\frac{d[AM]}{dt} = \chi_w \left(K_5[AMp] - (K_7 + K_6)[AM]\right) \tag{212}$$

Vessel radius (μm):

$$\frac{dR}{dt} = \frac{R_{init}}{\eta}\left(\frac{RP_T}{h} - E\frac{R - R_0}{R_0}\right) \tag{213}$$

9.2. Algebraic Variables

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

$$[M] = 1 - [AM] - [AMp] - [Mp] \tag{214}$$

Rate constants for phosphorylation of M to Mp and of AM to AMp (s^{-1}):

$$K_1 = K_6 = \gamma_{cross} Ca_i^{n_{cross}} \tag{215}$$

Rate constants for dephosphorylation of Mp to M and of AMp to AM (s^{-1}):

$$K_2 = K_5 = \delta_K \left(k_{\text{mlpc,b}} + k_{\text{mlpc,c}} R_{\text{cGMP}} \right) \tag{216}$$

Wall thickness of the vessel (in μm):

$$h = 0.1R \tag{217}$$

Fraction of attached myosin cross-bridges (-):

$$F_r = [AM_p] + [AM] \tag{218}$$

Young's modulus (Pa):

$$E = E_{pas} + F_r \left(E_{act} - E_{pas} \right) \tag{219}$$

Initial radius (μm):

$$R_0 = R_{init} + F_r(\alpha - 1)R_{init} \tag{220}$$

Parameter	Description	Value
χ_w	Scaling constant for wall mechanics	1.7
K_3	Rate constant for attachment of phosphorylated crossbridges	0.4 s^{-1}
K_4	Rate constant for detachment of phosphorylated crossbridges	0.1 s^{-1}
K_7	Rate constant for detachment of dephosphorylated crossbridges	0.1 s^{-1}
γ_{cross}	Sensitivity of the contractile apparatus to Ca^{2+}	17 $\mu M^{-3} s^{-1}$
n_{cross}	Fraction constant of the phosphorylation crossbridge	3
δ_K	Constant to fit data	58.14
$k_{\text{mlpc,b}}$	Basal MLC dephosphorylation rate constant	8.6×10^{-3} s^{-1}
$k_{\text{mlpc,c}}$	First-order rate constant for cGMP regulated MLC dephosphorylation	32.7×10^{-3} s^{-1}
η	Viscosity	10^4 Pa s
P_T	Transmural pressure	4×10^3 Pa
E_{pas}	Young's moduli for the passive vessel	66×10^3 Pa
E_{act}	Young's moduli for the active vessel	233×10^3 Pa
α	Scaling factor for initial radius	0.6

Table 9: Parameters of the wall mechanics submodel, for references see Dormanns et al. [2].

10. Tissue Slice Model

10.1. ODEs

K^+ concentration in the astrocyte of NVU block i with four neighbours j (μM):

$$\frac{dK_k^i}{dt} = \sum_j Q_{K,j\to i} - J_{K_k}^i + 2J_{NaK_k}^i + J_{NKCC1_k}^i + J_{KCC1_k}^i \tag{221}$$

Membrane potential in the astrocyte of NVU block i with four neighbours j (mV):

$$\frac{dv_k^i}{dt} = \gamma_j \left[\sum_j z_K Q_{K,j\to i} - J_{BK_k}^i - J_{K_k}^i - J_{Cl_k}^i - J_{NBC_k}^i - J_{Na_k}^i - J_{NaK_k}^i - 2J_{TRPV_k}^i\right] \tag{222}$$

K^+ concentration in the ECS of NVU block i with four neighbours j (mM):

$$\frac{dK_e^i}{dt} = \sum_j Q_{K,j\to i}^e + \frac{1}{Ff_e}\left(\frac{A_s I_{K,tot_{sa}}^i}{V_s} + \frac{A_d I_{K,tot_d}^i}{V_d}\right) - \frac{d\text{Buff}_e^i}{dt} \tag{223}$$

Na^+ concentration in the ECS of NVU block i with four neighbours j (mM):

$$\frac{dNa_e^i}{dt} = \sum_j Q_{Na,j\to i}^e + \frac{1}{Ff_e}\left(\frac{A_s I_{Na,tot_{sa}}^i}{V_s} + \frac{A_d I_{Na,tot_d}^i}{V_d}\right) \tag{224}$$

10.2. Algebraic Variables

Rate of change of K_k in NVU block i due to gap junctional flux from neighbour j (μM s^{-1}):

$$Q_{K,j\to i} = \frac{D_{gap}}{\Delta x^2}\left((K_k^j - K_K^i) + \frac{z_K F}{RT}\frac{K_k^i + K_k^j}{2}(v_k^j - v_k^i)\right) \tag{225}$$

Rate of change of K_e and Na_e in NVU block i due to extracellular electrodiffusion from neighbour j (mM s^{-1}):

$$Q_{K,j\to i}^e = \frac{D_{K,e}}{\Delta x^2}\left[(K_e^j - K_e^i) - z_K\left(\frac{K_e^i + K_e^j}{2}\right)\left(\frac{z_K D_{K,e}(K_e^j - K_e^i) + z_{Na} D_{Na,e}(Na_e^j - Na_e^i)}{z_K^2 D_{K,e}\frac{K_e^i + K_e^j}{2} + z_{Na}^2 D_{Na,e}\frac{Na_e^i + Na_e^j}{2}}\right)\right] \tag{226}$$

$$Q_{Na,j\to i}^e = \frac{D_{Na,e}}{\Delta x^2}\left[(Na_e^j - Na_e^i) - z_{Na}\left(\frac{Na_e^i + Na_e^j}{2}\right)\left(\frac{z_K D_{K,e}(K_e^j - K_e^i) + z_{Na} D_{Na,e}(Na_e^j - Na_e^i)}{z_K^2 D_{K,e}\frac{K_e^i + K_e^j}{2} + z_{Na}^2 D_{Na,e}\frac{Na_e^i + Na_e^j}{2}}\right)\right] \tag{227}$$

Parameter	Description	Value
D_{gap}	Astrocytic gap junction diffusion coefficient	3.1×10^{-9} m^2 s^{-1}
Δx^2	Width of one NVU block	1.24×10^{-4} m
$D_{K,e}$	Extracellular K^+ diffusion coefficient	3.8×10^{-9} m^2 s^{-1}
$D_{Na,e}$	Extracellular Na^+ diffusion coefficient	2.5×10^{-9} m^2 s^{-1}

Table 10: Parameters of the large scale tissue slice model.

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