K^+ Pathway for Code version 2.0

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Todo list

Chapter 1

Notes for reading

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

1.0.1 Version 1.2 /2.0 difference

The basic difference between version 1.2 and version 2.0 is the new neuron model. This is based on the work of Chang et al [1] and that of Kager et al [9]. For this version the neuron model has 4 compartments; i) soma/axon, ii) dendrite , iii) post synaptic terminal and extracellular space (ECS). Ion channels for Na^+, and K^+efflux into the ECS. $\mathrm{K}^+$is buffered in the ECS and a portion of the K^+flux is passed into the synaptic cleft compartment. On reaching a certain concentration of K^+in the synaptic cleft glutamate is pumped into the synaptic cleft . This glutamate is taken up by both the post-synaptic neuron and the astrocyte. The neuron is stimulated by injection of a current of specified value into the soma/axon compartment.

Schematic of the full set of pathways is shown in Figure **??**

1.1 Global Constants

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

Chapter 2

State variables, initial values and parameter values

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

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

Gating variables

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

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

NO pathway

- Ca_n :Ca^{2+}in the post-synaptic neuron $nNOS_a ct_n$:activated NOS in the post-synaptic neuron NO_n : Nitric Oxide in the post-synaptic neuron

Table 2.1: Initial resting values and other parameter values of the neuron model, from Chang et al[1]

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

Table 2.2: Rate expressions and parameter values used in the voltage dependent channel currents of the neuron model, from Chang et al[1]

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

Chapter 3

Equations for each compartment

3.1 Neuron

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

$$E_{K_{sa}} = \frac{RT}{F} ln(\frac{K_e}{K_{sa}}) \tag{3.1.1}$$

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

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

$$J_{Kleak_{sa}} = g_{Kleak_{sa}}(v_{sa} - E_{K_{sa}}) \tag{3.1.3}$$

$$J_{Kleak_d} = g_{Kleak_d}(v_d - E_{K_d}) \tag{3.1.4}$$

$$\tag{3.1.5}$$

$$J_K leak_s a = p.gKleak_s a * (v_s a - E_{K_{sa}}); \qquad J_K leak_d = p.gKleak_d * (v_d - E_{K_d});$$

3.1.3 Dendrite (with subscript d)

Na flux through NaP channel in dendrite using GHK

$$m4_{\alpha} = \frac{1}{6(1+exp(-((0.143v_d)+5.67)))} \tag{3.1.6}$$

$$m4_{\beta} = \frac{exp(-((0.143v_d)+5.67))}{6(1+exp(-((0.143v_d)+5.67)))} \tag{3.1.7}$$

$$h3\alpha = 5.12e-8exp(-((0.056v_d)+2.94)) \tag{3.1.8}$$

$$h3\beta = \frac{1.6e-6}{1+exp(-(((0.2*v_d))+8))} \tag{3.1.9}$$

$$J_{NaP_d} = (m4^2h3g_{NaP}Fv_d\frac{(Na_d-(exp(\frac{-v_dF}{RT})Na_e)))}{(\frac{RT}{F}(1-exp(\frac{-v_dF}{RT})))} \tag{3.1.10}$$

$$\tag{3.1.11}$$

$$J_{NMDA_{K_d}} = M(v,Mg)((m5h4g_{NMDA}Fv_d\frac{(K_d-(exp(\frac{v_dF}{RT})K_e)))}{(\frac{RT}{F}(1-exp(\frac{-v_dF}{RT})))} \tag{3.1.12}$$

$$M(v,Mg) = \frac{1}{(1+0.33}Mg \quad exp(-(0.07v_d+0.7))) \tag{3.1.13}$$

$J_NMDA_{K_d} = ((m5.*h4.*p.gNMDA_GHk*p.Farad.*v_d.*(K_d-(exp(-v_d/p.ph).*K_e))))./(p.ph*(1-exp(-v_d/p.p$

K flux through KDR channel in dendrite using GHK

$$m6_{\alpha} = \frac{0.016((v_d+34.9)}{(1-exp(-((0.2*v_d)+6.98))))} \tag{3.1.14}$$

$$m6_{\beta} = 0.25exp(-((0.025*v_d)+1.25)) \tag{3.1.15}$$

$$J_{KDR_d} = m6^2g_{KDR}Fv_d\frac{(K_d-(exp(\frac{-v_dF}{RT})K_e))}{(\frac{RT}{F}(1-\frac{-v_dF}{RT}))} \tag{3.1.16}$$

K flux through KA channel in dendrite using GHK

$$m7_{\alpha} = \frac{0.02((v_d+56.9)}{(1-exp(-((0.1v_d)+5.69))))} \tag{3.1.17}$$

$$m7_{\beta} = \frac{0.0175((v_d+29.9)}{(exp(((0.1*v_d)+2.99))-1))} \tag{3.1.18}$$

$$h5_{\alpha} = 0.016exp(-((0.056v_d)+4.61)) \tag{3.1.19}$$

$$h5_{\beta} = \frac{0.5}{(1+exp(-((0.2*v_d)+11.98)))} \tag{3.1.20}$$

$$J_{KA_d} = m7^2h5g_{KA}Fv_d\frac{(K_d-(exp(\frac{-v_dF}{RT})K_e))}{(\frac{RT}{F}(1-\frac{-v_dF}{RT}))} \tag{3.1.21}$$

3.1.4 Soma/Axon (with subscript sa)

K flux through KDR channel in soma using GHK

$$m2_\alpha = \frac{0.016((v_{sa} + 34.9)}{(1 - exp(-((0.2v_{sa}) + 6.98))))} \tag{3.1.22}$$

$$m2_\beta = 0.25exp(-((0.025v_{sa}) + 1.25)) \tag{3.1.23}$$

$$J_{KDR_{sa}} = m2^2 g_{KDR} F v_{sa} \frac{(K_{sa} - (exp(\frac{-v_{sa}F}{RT})K_e))}{(\frac{RT}{F}(1 - \frac{-v_{sa}F}{RT}))} \tag{3.1.24}$$

$$\tag{3.1.25}$$

K flux through KA channel in soma using GHK input current

$$m3_\alpha = \frac{0.02(v_{sa} + 56.9)}{(1 - exp(-(0.1v_{sa} + 5.69)))} \tag{3.1.26}$$

$$m3_\beta = \frac{0.0175(v_{sa} + 29.9)}{(exp(0.1v_{sa} + 2.99) - 1))} \tag{3.1.27}$$

$$h2_\alpha = 0.016exp(-(0.056v_{sa} + 4.61)) \tag{3.1.28}$$

$$h2_\beta = \frac{0.5}{1 + exp(-(0.2v_{sa} + 11.98))} \tag{3.1.29}$$

$$J_{KA_{sa}} = m3^2 h2 g_{KA} F v_{sa} \frac{(K_{sa} - (exp(\frac{-v_{sa}F}{RT})K_e))}{(\frac{RT}{F}(1 - \frac{-v_{sa}F}{RT}))} \tag{3.1.30}$$

$$\tag{3.1.31}$$

flux through the NaK-ATPase pump

$$J_{pump1_{sa}} = (1 + (\frac{K_{init_e}}{K_e}))^{-2}(1 + (\frac{Na_{init_{sa}}}{Na_{sa}}))^{-3} \tag{3.1.32}$$

$$J_{pump1init_{sa}} = 0.0312 \tag{3.1.33}$$

$$J_{pump1_d} = (1 + (\frac{K_{init_e}}{K_e}))^{-2}(1 + (\frac{Na_{init_d}}{Na_d}))^{-3} \tag{3.1.34}$$

$$J_{pump1init_d} = 0.0132 \tag{3.1.35}$$

$$\tag{3.1.36}$$

3.1.5 Total ion fluxes

I have kept this in to make code easier to understand. It has no explicit parameters in it for the K^+ pathway

Total ion fluxes in soma

$$J_{Na_{tot_{sa}}} = J_{NaP_{sa}} + J_{Naleak_{sa}} + J_{Napump_{sa}} + J_{NaT_{sa}} \tag{3.1.37}$$

$$J_{K_{tot_{sa}}} = J_{KDR_{sa}} + J_{KA_{sa}} + J_{Kleak_{sa}} + J_{Kpump_{sa}} \tag{3.1.38}$$

$$J_{leak_{tot_{sa}}} = g_{leak_{sa}}(v_{sa} - E_{Cl_{sa}}) \tag{3.1.39}$$

$$\tag{3.1.40}$$

Total ion fluxes in dendrite

$$J_{Na_{tot_d}} = J_{NaP_d} + J_{Naleak_d} + J_{Napump_d} + J_{Na_{NMDA_d}} \tag{3.1.41}$$
$$J_{K_{tot_d}} = J_{KDR_d} + J_{KA_d} + J_{Kleak_d} + J_{Kpump_d} + J_{K_{NMDA_d}} \tag{3.1.42}$$
$$J_{leak_{tot_d}} = g_{leak_d}(v_d - E_{Cl_d}) \tag{3.1.43}$$
$$\tag{3.1.44}$$

Total ion fluxes in soma and dendrite

$$J_{tot_{sa}} = J_{Na_{tot_{sa}}} + J_{K_{tot_{sa}}} + J_{leak_{tot_{sa}}} \tag{3.1.45}$$
$$J_{tot_d} = J_{Na_{tot_d}} + J_{K_{tot_d}} + J_{leak_{tot_d}} \tag{3.1.46}$$
$$\tag{3.1.47}$$

Tissue oxygen

$$J_{pump2_0} = 0.0952 \tag{3.1.48}$$
$$J_{pump2_{O2_0}} = 1 \tag{3.1.49}$$
$$CBF = CBF_{init}\frac{R^4}{R_{init}^4} \tag{3.1.50}$$
$$\tag{3.1.51}$$

Note The pump functions could look like this
$J_{pump2_0} = 2(1 + \frac{O2_0}{(((1-\alpha_{O2})O2_0)+\alpha_{O2}O2_0))})^{-1}$
$J_{pump2_{O2_0}} = 2 * (1 + O2_0./(((1 - p.alpha_O 2) * p.O2_0) + p.alpha_O 2 * p.O2_0)).^{-1}$

3.2 Conservation equations for neuron compartment

change in concentration of Na,K in the soma

$$\frac{dK_{sa}}{dt} = \frac{-A_s}{FV_s}J_{K_{tot_{sa}}} + \frac{D_k(V_d + V_s)}{2dhod^2V_s}(K_d - K_{sa}) \tag{3.2.1}$$
$$\tag{3.2.2}$$

change in concentration of Na,K in the dendrite

$$\frac{dK_d}{dt} = \frac{-A_d}{FV_d}J_{K_{tot_{sa}}} + \frac{D_k(V_d + V_s)}{2dhod^2V_s}(K_{sa} - K_d) \tag{3.2.3}$$
$$\tag{3.2.4}$$

3.3 Extra Cellular Space (ECS with subscript e)

change in buffer for K+ in the extracellular space

$$\frac{dBuff_e}{dt} = \frac{\mu K_e(B_0 - Buff_e)}{1 + exp(-((K_e - 5.5)./1.09))} - \mu Buff_e \tag{3.3.1}$$
$$\tag{3.3.2}$$

change in concentration of Na,K in the extracellular space

$$\frac{dK_e}{dt} = \frac{1}{F f_e}\left(\frac{A_s J_{K_{tot_{sa}}}}{V_s} + \frac{A_d J_{K_{tot_d}}}{V_d}\right) \tag{3.3.3}$$

$$\tag{3.3.4}$$

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

K^+ concentration in the SC

$$\frac{\mathrm{d}N_{K_s}}{\mathrm{d}t} = k_C f(t) - \frac{\mathrm{d}N_{K_k}}{\mathrm{d}t} + J_{BK_k} + \frac{R_s}{\tau_s}\left\{[\mathrm{K}^+]_e - [\mathrm{K}^+]_s\right\} \tag{3.3.5}$$

τ_s is defined in equation 3.8.5 and has a value of 2.8 secs. $[\mathrm{K}^+]_e$ is the potassium concentration in the ECS and $[\mathrm{K}^+]_s$ is the potassium concentration in the synaptic cleft. Na^+ concentration in the SC

$$\frac{\mathrm{d}N_{Na_s}}{\mathrm{d}t} = -k_C f(t) - \frac{\mathrm{d}N_{Na_k}}{\mathrm{d}t} \tag{3.3.6}$$

HCO_3 concentration in the SC

$$\frac{\mathrm{d}N_{HCO_{3_s}}}{\mathrm{d}t} = -\frac{\mathrm{d}N_{HCO_{3_k}}}{\mathrm{d}t} \tag{3.3.7}$$

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

$$[\mathrm{Cl}^{-1}]_s = [\mathrm{Na}^+]_s + [\mathrm{K}^+]_s - [\mathrm{HCO}_3^{-1}]_s \tag{3.3.8}$$

3.4 Astrocyte (with subscript k)

K^+ concentration in the AC :

$$\frac{\mathrm{d}N_{K_k}}{\mathrm{d}t} = -J_{K_k} + 2J_{NaK_k} + J_{NKCC1_k} + J_{KCC1_k} - J_{BK_k} \tag{3.4.1}$$

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

$$J_{BK_k} = \frac{g_{BK_k}}{F} w_k \left(v_k - E_{BK_k}\right) \tag{3.4.2}$$

g_{BK_k} is evaluated in the code using

```
g_BK_k␣=␣p.G_BK_k*1e-12␣/␣p.A_ef_k;␣the␣value␣␣p.G_BK_k
```

is 225 (as listed in the parameter list in Astrocyte.m)

[1] model estimation

V_{spine}	dentritic spine volume	8×10^{-8} nL	[15]
κ_{ex}	decay rate constant of internal Ca^{2+} concentration	1.6×10^{3} s^{-1}	[15]
$[Ca^{2+}]_{\mathrm{rest}}$	resting internal calcium concentration	0.1 µM	[15]
λ_{buf}	buffer capacity	20 (dim.less)	[15]
$V_{\mathrm{max,nNOS}}$	maximum nNOS activation rate	25×10^{-3} µM	M.E.[1]
$K_{\mathrm{m,nNOS}}$	Michaelis constant	9.27×10^{-2}	[8]
$\mu_{\mathrm{deact},n}$	rate constant at which nNOS is deactivated	0.0167 s^{-1}	[4]
$K_{\mathrm{m},A}$	Michaelis constant	650 µM	[15]
$K_{\mathrm{m},B}$	Michaelis constant	2800 µM	[15]
v_n	neuronal membrane potential	-0.04 V	M.E. but see Kager et al model maybe -0.05 -or -0.06 V
G_{M}	conductance of NMDA receptor	4.6×10^{4} fS	[15]
$P_{\mathrm{Ca}}/P_{\mathrm{M}}$	ratio of NMDA receptor permeability to Ca^{2+} to permeability to monovalent ions	3.6 (dim.less)	[15]
$[Ca^{2+}]_{\mathrm{ex}}$	external calcium concentration	2×10^{3} µM	[15]
$[\mathrm{M}]$	concentration of monovalent ions	1.3×10^{5} µM	[15]
α_v	voltage-dependent Mg^{2+} block parameter	-80 V^{-1}	[15]
β_v	voltage-dependent Mg^{2+} block parameter	0.02 V	[15]
$n_{\mathrm{NR2},A}$	average number of NR2A NMDA receptors	0.63 (dim.less)	[15]
$n_{\mathrm{NR2},B}$	average number of NR2A NMDA receptors	11 (dim.less)	[15]
Q_1	Ca^{2+}-CaM binding constant	1.9×10^{5} μM^{-1}	[5]
Q_2	Ca^{2+}-CaM binding constant	2.1×10^{5} μM^{-1}	[5]
Q_3	Ca^{2+}-CaM binding constant	0.4×10^{5} μM^{-1}	[5]
Q_4	Ca^{2+}-CaM binding constant	0.26×10^{5} μM^{-1}	[5]
$V_{\mathrm{max,NO},n}$	maximum catalytic rate of neuronal NO production	4.22 s^{-1}	[2]
$[O_2]_n$	O_2 concentration in the neuron	200 µM	M.E.
$K_{\mathrm{m,O2},n}$	Michaelis constant for nNOS for O_2	243 µM	[3]
$[\mathrm{L\text{-}Arg}]_n$	L-Arg concentration in the neuron	100 µM	[3]
$K_{\mathrm{m,L\text{-}Arg},n}$	Michaelis constant for nNOS for L-Arg	1.5 µM	[2]
$k_{\mathrm{O2},n}$	O_2 reaction rate constant	9.6×10^{-6} μM^{-2} s^{-1}	[10]
x_{nk}	distance between centres of NE and AC	25 µm	M.E.
$D_{\mathrm{c,NO}}$	NO diffusion coefficient	3300 $\mu m^2 s^{-1}$	[12]

k_C	Input scaling parameter	$7.35{\times}10^{-5}$ µM m s^{-1}	[14]

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

$$\frac{\mathrm{d}w_k}{\mathrm{d}t} = \phi_w\left(w_\infty - w_k\right) \tag{3.4.3}$$

$$\phi_w = \psi_n cosh(\frac{v_k - v_3}{2v_4}) \tag{3.4.4}$$

$$v_3 = -\frac{v_5}{2} tanh[\frac{[\mathrm{Ca}^{2+}]_k - Ca_3}{Ca_4}] + v_6 \tag{3.4.5}$$

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

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

$$w_\infty = 0.5\left(1 + \tanh\left(\frac{v_k EET_{shift}[EET]_k - v_3}{v_4}\right)\right) \tag{3.4.6}$$

3.4.1 Fluxes into and out of the astrocyte

K^+ flux

$$J_{K_k} = \frac{g_{K_k}}{F}(v_k - E_{K_k}) \tag{3.4.7}$$

Cl and K^+ flux through the KCC1 channel

$$J_{KCC1_k} = C_{input}\frac{g_{KCC1_k}}{F}\frac{R_g T}{F} ln\left(\frac{K_s Cl_s}{K_k Cl_k}\right) \tag{3.4.8}$$

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

$$J_{NKCC1_k} = C_{input}\frac{g_{NKCC1_k}}{F}\frac{R_g T}{F} ln\left(\frac{Na_s K_s {Cl_s}^2}{Na_k K_k {Cl_k}^2}\right) \tag{3.4.9}$$

Flux through the sodium potassium pump

$$J_{NaK_k} = J_{NaK_{max}}\frac{{Na_k}^{1.5}}{{Na_k}^{1.5} + {K_{Na_k}}^{1.5}}\frac{K_s}{K_s + K_{K_s}} \tag{3.4.10}$$

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

F	Faraday's constant	9.649×10^4 C mol^{-1}	
R_g	Gas constant	8.315 J mol^{-1}K^{-1}	
T	Temperature	300 K	
g_{K_k}	Specific ion conductance of potassium	40×10^3 Ω^{-1}m^{-2}	[14]
g_{Na_k}	Specific ion conductance of sodium	1.314×10^3 Ω^{-1}m^{-2}	[14]
K_{Na_k}		40×10^3 Ω^{-1}m^{-2}	[14]
g_{Na_k}	Specific ion conductance of sodium	1.314×10^3 Ω^{-1}m^{-2}	[14]
g_{NBC_k}	Specific ion conductance of the NBC cotransporter	7.57×10^2 Ω^{-1}m^{-2}	[14]
g_{KCC1_k}	Specific ion conductance of the KCC1 cotransporter	10 Ω^{-1}m^{-2}	[14]
g_{NKCC1_k}	Specific ion conductance of the NKCC1 cotransporter	55.4 Ω^{-1}m^{-2}	[14]
$J_{NaK_{max}}$	Maximum flux through the NaKATPase pump	1.42×10^{-3} µM ms^{-1}	[14]
g_{BK_k}	Specific ion conductance of the BK channel	1.16×10^3 Ω^{-1}m^{-2}	[7]
C_{input}	Block function to switch the channel on and off	0 ; 1 [-]	

3.5 Perivascular Space (with subscript p)

K^+ concentration in the PVS (in µM):

$$\frac{\mathrm{d}K_p}{\mathrm{d}t} = \frac{J_{BK_k}}{R_k R_{pa}} + \frac{J_{KIR_i}}{R_{ps}} + \frac{J_{TRPV_k}}{R_k R_{pa}} \tag{3.5.1}$$

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

$$\frac{\mathrm{d}Ca_p}{\mathrm{d}t} = -\frac{J_{TRPV_k}}{VR_{pa}} + \frac{J_{VOCC_i}}{VR_{ps}} - Ca_{decay_k}(Ca_p - Ca_{min_k}) \tag{3.5.2}$$

$$\tag{3.5.3}$$

R_{pa}	Volume ratio of PVS to AC	10^{-3} [-]	[13]
R_{ps}	Volume ratio of PVS to SMC	10^{-3} [-]	[13]
Ca_{decay_k}	Rate of decay of Ca^{2+}in the PVS	0.5 s^{-1}	
Ca_{min_k}	steady state value of Ca^{2+}in PVS	2 mM	

3.6 Smooth Muscle Cell

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

$$J_{NaK_i} = F_{NaK} \tag{3.6.1}$$

F_{NaK}	Rate of the potassium influx by the sodium potassium pump	4.32×10^{-2} µM s^{-1}	[11]

G_{Cli}	Whole-cell conductance for Cl^- current	1.34×10^{-3} µM $mV^{-1}s^{-1}$	[11]
v_{Cli}	Reversal potential for Cl^- channels.	-25.0 mV	[11]

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

$$J_{K_i} = G_{Ki} w_i \left(v_i - E_{K_i}\right) \tag{3.6.2}$$

G_{Ki}	Whole-cell conductance for K^+ efflux.	4.46×10^{-3} µM $mV^{-1}s^{-1}$	[11]
vK_i	Nernst potential	-94 mV	[11]

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

$$J_{KIR_i} = \frac{F_{KIR_i} g_{KIR_i}}{\gamma_i} \left(v_i - v_{KIR_i}\right) \tag{3.6.3}$$

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

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

$$v_{KIR_i} = z_1 K_p - z_2 \tag{3.6.4}$$

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

$$g_{KIR_i} = exp(z_5 v_i + z_3 K_p - z_4) \tag{3.6.5}$$

c_{wi}	Translation factor for Ca^{2+} dependence of K_{Ca} channel activation sigmoidal.	0.0 µM	[11]
β_i	Translation factor for membrane potential dependence of K_{Ca} channel activation sigmoidal.	0.13 $µM^2$	[11]
$v_{Ca_{3i}}$	Half-point for the K_{Ca} channel activation sigmoidal.	-27 mV	[11]
R_{Ki}	Maximum slope of the K_{Ca} activation sigmoidal.	12 mV	[11]
z_1	Model estimation for membrane voltage KIR channel	4.5×10^3 mV $µM^{-1}$	[6]
z_2	Model estimation for membrane voltage KIR channel	112 mV	[6]
z_3	Model estimation for the KIR channel conductance	4.2×10^2 $mV^{-1}s^{-1}$	[6]
z_4	Model estimation for the KIR channel conductance	12.6 µM $mV^{-1}s^{-1}$	[6]
z_5	Model estimation for the KIR channel conductance	-7.4×10^{-2} µM $mV^{-2}s^{-1}$	[6]

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

IP$_3$ degradation (in µM s^{-1}):

$$J_{degrad_i} = k_{di} I_i \tag{3.6.6}$$

k_{di}	Rate constant of IP$_3$ degradation	0.1 s^{-1}	[11]

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

K^+ concentration in the SMC (in µM):

$$\frac{\mathrm{d}[K_i^+]}{\mathrm{d}t} = J_{Na/K_i} - J_{KIR_i} - J_{K_i} \tag{3.6.7}$$

γ_i	Change in membrane potential by a scaling factor	1970 mV µM^{-1}	[11]
λ_i	Rate constant for opening	45.0 s^{-1}	[11]

3.7 Endothelial Cell

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

$$J_{K_j} = G_{totj}(v_j - v_{Kj})\left(J_{BK_{Caj}} + J_{SK_{Caj}}\right) \tag{3.7.1}$$

G_{totj}	Total potassium channel conductivity.	6927 pS	[11]
v_{Kj}	K^+ equilibrium potential	-80.0 mV	[11]

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

$$J_{BK_{Caj}} = 0.2\left(1 + \tanh\left(\frac{(\log_{10}[Ca^{2+}]_j - c)(v_j - b_j) - a_{1j}}{m_{3bj}(v_j + a_{2j}(\log_{10}[Ca^{2+}]_j - c) - b_j)^2 + m_{4bj}}\right)\right) \tag{3.7.2}$$

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

$$J_{SK_{Caj}} = 0.3\left(1 + \tanh\left(\frac{\log_{10}[Ca^{2+}]_j - m_{3sj}}{m_{4sj}}\right)\right) \tag{3.7.3}$$

c	Model constant, further explanation see reference	-0.4 µM	[11]
b_j	Model constant, further explanation see reference	-80.8 mV	[11]
a_{1j}	Model constant, further explanation see reference	53.3 µM mV	[11]
a_{2j}	Model constant, further explanation see reference	53.3 mV µM^{-1}	[11]
m_{3bj}	Model constant, further explanation see reference	1.32×10^{-3} µM mV^{-1}	[11]
m_{4bj}	Model constant, further explanation see reference	0.30 µM mV	[11]
m_{3sj}	Model constant, further explanation see reference	-0.28 µM	[11]
m_{4sj}	Model constant, further explanation see reference	0.389 µM	[11]

3.8 Extracellular Space

diffusion, NaK and BK fluxes defined here

$$\frac{d[K]_e}{dt} = -VRJ_{diff} + J_K - J_{NaK} \tag{3.8.1}$$

where

$$J_{diff} = \frac{1}{\tau_s}(K_e - K_s) \tag{3.8.2}$$

$$J_K = G_K w_i (v_i - E_K) \tag{3.8.3}$$

$$J_{NaK} = F_{NaK} \tag{3.8.4}$$

The flux J_K and the open probability w_i are defined in equations **??** to **??**. and

$$\tau_s = \frac{(\Delta x_s)^2}{2D_K} \tag{3.8.5}$$

$$D_K = \frac{D_{free}}{\lambda_0^2} \tag{3.8.6}$$

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

3.9 Lumen

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

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