The Nitric Oxide Pathway and Parameter Values in Code version 2.0

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Todo list

Chapter 1

Notes for reading

This report provides the basic equations and parameters for the NO pathway in the NVU 2.0 The following notes, definitions and equations provide the reader with a comprehensive guide to version 1.2 of NVU. The document is set out in sections where each section contains the equations for each compartment, namely neuron, synaptic cleft, astrocyte, perivascular space, smooth muscle cell, endothelial cell, extracellular space and finally the lumen. The reader will find multiple definitions and equations but by dividing the document into sections corresponding to compartments it is hoped that a more clear understanding is obtained. Concentrations as written on the left-hand-side of the o.d.e. are given by the notation of N_j where j can be any specii such as $Na^+$of Ca^{2+}. True concentrations are written with square brackets as in $[Ca^{2+}]_n$. In point of fact they are equivalent.

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

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

In addition neuronal Nitric Oxide is derived from the NMDA receptor where glutamate mediates Ca^{2+}flux into the post-synaptic neuron. This $Ca^{2+}$is combined with calmodulin to form activated neuronal Nitric Oxide synthase which then combines with $O_2$and L-Arginine to produce finally NO. Schematic of the full set of pathways is shown in Figure 1.1

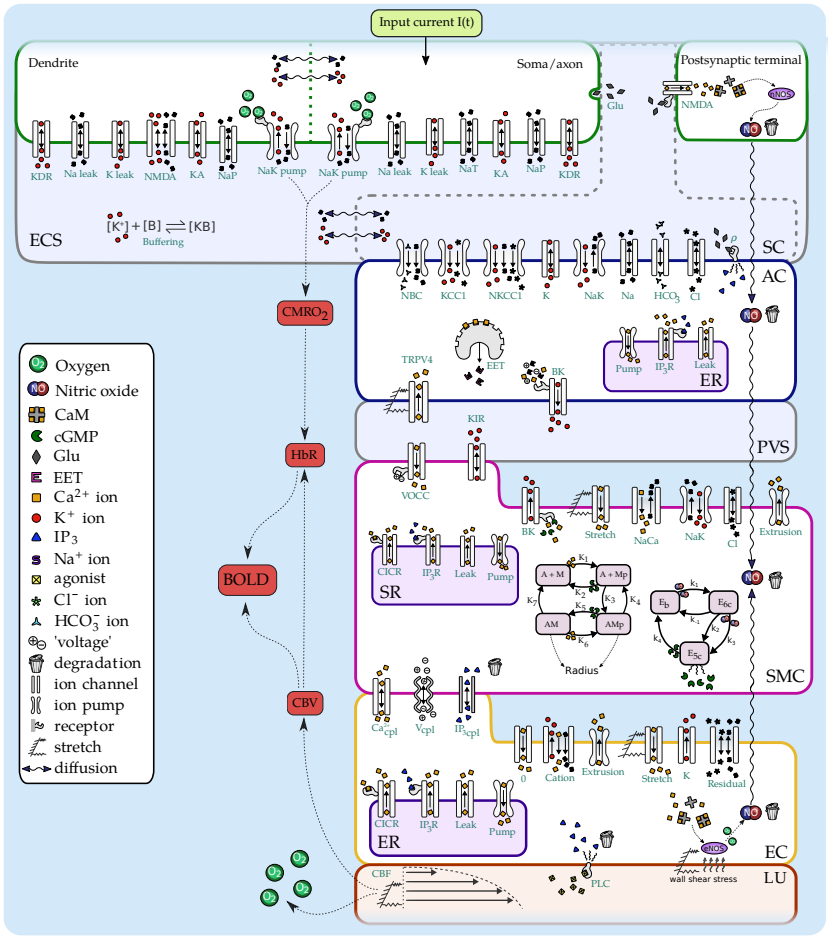

Figure 1.1: Schematic of version 1.2

The NO derived from the endothelial cell is mediated by the WSS and the stretch channel providing Ca^{2+}which combines with Calmodulin and in a similar manner to nNOS. eNOS is mediated by O_2 and L-Arginine to form NO. The NO is then diffused to smooth muscle cell as is the neuronally derived NO diffused to the astrocyte and thence the SMC.

The full description of the NO pathway is that given in [2].

The work of Zheng et al [10] showed that as the stimulus period increased the resulting CBF profile showed a concave form. Figure 1.2 is a sketch of the stimulus , the K^+in the ECS and the resulting CBF profile. We think that the first part of the concavity is due to the neuron parameters which to some extent provide the driver for the K^+in the ECS and synaptic cleft. The second half of the concave profile could be a number of phenomena but we first try to the Nitric Oxide pathway, hence this document.

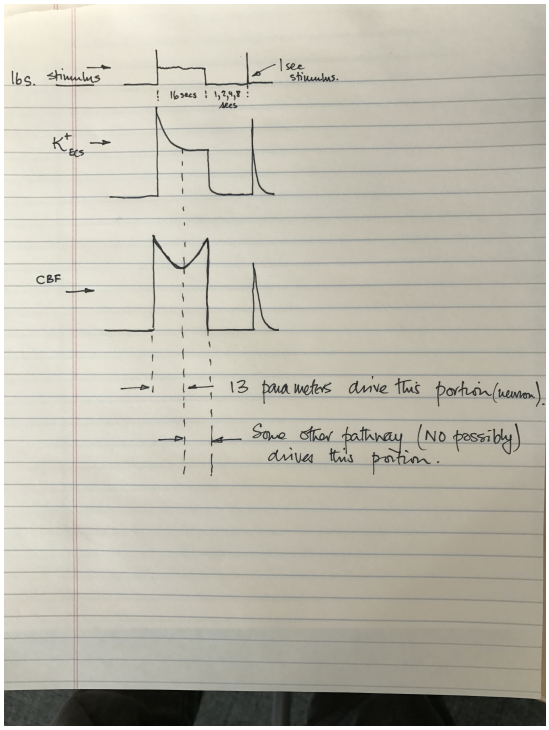

Figure 1.2: Sketch of 16 second stimulus, K^+in the ECS and resulting concave CBF. The second pulse is due to the stimulus profile after the 16 second conditioning block.

Chapter 2

Basic Equations

2.1 Global Constants

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

2.2 NO pathway

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

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

$$Glu = 0.5Glu_{switch} \quad Glu_{max}(1 + tanh(\frac{(K_e - K_{e_{switch}})}{Glu_{slope}})) \tag{2.2.1}$$

(2.2.2)

Glu_{switch} **turns the Glutamate pathway on (=1) or off (=0).**

$$w_{NR2A} = \frac{Glu}{(K_{mA} + Glu)} \tag{2.2.3}$$

$$w_{NR2B} = \frac{Glu}{(K_{mB} + Glu)} \tag{2.2.4}$$

$$I_{Ca} = -4v_n G_M \frac{P_{Ca}}{P_M} \frac{(\frac{Ca_{ex}}{M}))}{(1 + exp(-80(v_n + 0.02)))} \frac{(exp(2v_n \frac{F}{RT})))}{(1 - exp(2v_n \frac{F}{RT})))} \tag{2.2.5}$$

$$I_{Ca_{tot}} = I_{Ca}(n_{NR2A} w_{NR2A} + n_{NR2B} w_{NR2B}) \tag{2.2.6}$$

$$CaM = \frac{Ca_n}{m_c} \tag{2.2.7}$$

$$\tau_{nk} = \frac{x_{nk}^2}{2D_{cNO}} \tag{2.2.8}$$

$$\tag{2.2.9}$$

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

$$p_{NO_n} = NO_{switch} nNOS_{act_n} V_{max_{NO_n}} \frac{O2_n}{K_{mO2_n} + O2_n} \frac{LArg_n}{K_{mArg_n} + LArg_n} \tag{2.2.10}$$

$$\tag{2.2.11}$$

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

$$c_{NO_n} = k_{O2_n} (NO_n)^2 O2_n \tag{2.2.12}$$

$$\tag{2.2.13}$$

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

$$d_{NO_n} = \frac{NO_k - NO_n}{\tau_{nk}} \tag{2.2.14}$$

$$\tag{2.2.15}$$

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

Chapter 3

Conservation equations

3.1 post-synaptic neuron

$$\frac{d[Ca]_n}{dt} = \frac{(\frac{I_{Ca_{tot}}}{2FV_{spine}} - (k_{ex}(Ca_n - Ca_{rest})))}{1 + \lambda_{buf}} \tag{3.1.1}$$

$$\frac{d[nNOS_{act}]_n}{dt} = \frac{V_{maxNOS}CaM}{K_{actNOS} + CaM} - \mu_{2_n} nNOS_{act_n} \tag{3.1.2}$$

$$\tag{3.1.3}$$

3.2 Astrocyte

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

$$\frac{\mathrm{d[NO]}_k}{\mathrm{d}t} = p_{\mathrm{NO},k} - c_{\mathrm{NO},k} + d_{\mathrm{NO},k} \tag{3.2.1}$$

Algebraic equations

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

$$p_{\mathrm{NO},k} = 0 \tag{3.2.2}$$

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

$$c_{\mathrm{NO},k} = k_{\mathrm{O2},k}[\mathrm{NO}]_k^2[\mathrm{O_2}]_k \tag{3.2.3}$$

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

$$d_{\mathrm{NO},k} = \frac{[\mathrm{NO}]_n - [\mathrm{NO}]_k}{\tau_{nk}} + \frac{[\mathrm{NO}]_i - [\mathrm{NO}]_k}{\tau_{ki}} \tag{3.2.4}$$

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

$$\tau_{ki} = \frac{x_{ki}^2}{2D_{\mathrm{c,NO}}} \tag{3.2.5}$$

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

3.3 Smooth Muscle cell

Rate of change of NO concentration in the SMC ($\mu\mathrm{M\,s^{-1}}$):

$$\frac{\mathrm{d}[\mathrm{NO}]_i}{\mathrm{d}t} = p_{\mathrm{NO},i} - c_{\mathrm{NO},i} + d_{\mathrm{NO},i} \tag{3.3.1}$$

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

$$\frac{\mathrm{d}E_b}{\mathrm{d}t} = -k_1 E_b [\mathrm{NO}]_i + k_{-1} E_{6c} + k_4 E_{5c} \tag{3.3.2}$$

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

$$\frac{\mathrm{d}E_{6c}}{\mathrm{d}t} = k_1 E_b [\mathrm{NO}]_i - (k_{-1} + k_2) E_{6c} - k_3 E_{6c} [\mathrm{NO}]_i \tag{3.3.3}$$

Rate of change of cGMP concentration ($\mu\mathrm{M\,s^{-1}}$):

$$\frac{\mathrm{d}[\mathrm{cGMP}]_i}{\mathrm{d}t} = V_{\mathrm{max,sGC}} E_{5c} - \frac{V_{\mathrm{max,pde}} [\mathrm{cGMP}]_i}{K_{\mathrm{m,pde}} + [\mathrm{cGMP}]_i} \tag{3.3.4}$$

Maximum cGMP production rate ($\mu\mathrm{M\,s^{-1}}$):

$$V_{\mathrm{max,pde}} = k_{\mathrm{pde}} [\mathrm{cGMP}]_i \tag{3.3.5}$$

Algebraic equations

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

$$p_{\mathrm{NO},i} = 0 \tag{3.3.6}$$

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

$$c_{\mathrm{NO},i} = k_{\mathrm{dno}} [\mathrm{NO}]_i \tag{3.3.7}$$

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

$$d_{\mathrm{NO},i} = \frac{[\mathrm{NO}]_k - [\mathrm{NO}]_i}{\tau_{ki}} + \frac{[\mathrm{NO}]_j - [\mathrm{NO}]_i}{\tau_{ij}} \tag{3.3.8}$$

$$\tau_{i,j} = \frac{x_{K,i}^2}{2D_{NO}} \tag{3.3.9}$$

$$x_{K,i} = 25\mu m \tag{3.3.10}$$

$$\tag{3.3.11}$$

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

$$k_4 = C_4[\text{cGMP}]_i^{m_4} \tag{3.3.12}$$

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

$$E_{5c} = 1 - E_b - E_{6c} \tag{3.3.13}$$

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

$$R_{\text{cGMP}} = \frac{[\text{cGMP}]_i^2}{K_{\text{m,mlcp}}^2 + [\text{cGMP}]_i^2} \tag{3.3.14}$$

Rate constants for dephosphorylation (s^{-1}) in the Hia and Murphy 4-state latch model, see Dormanns et al. [2]:

$$K_{2c} = K_{5c} = \delta_i \left(k_{\text{mlpc,b}} + k_{\text{mlpc,c}} R_{\text{cGMP}}\right) \tag{3.3.15}$$

Equilibrium distribution of open channel states for the BK channel flux into the ECS (dim.less), see Dormanns et al. [3]:

$$K_{\text{act},i} = \frac{([\text{Ca}^{2+}]_i + c_{\text{w},i})^2}{([\text{Ca}^{2+}]_i + c_{\text{w},i})^2 + \beta_i \exp(v_{\text{Ca3},i} - v_i/R_{\text{K},i})} \tag{3.3.16}$$

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

$$c_{\text{w},i} = \frac{c_{w,max}}{2}[1 + tanh(\frac{[\text{cGMP}_i] - \epsilon_i}{\alpha_i})] \tag{3.3.17}$$

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

$$\tau_{ij} = \frac{x_{ij}^2}{2D_{\text{c,NO}}} \tag{3.3.18}$$

3.4 Endothelial Cell

$$\frac{\text{d}[\text{eNOS}_{\text{act}}]_j}{\text{d}t} = \gamma_{\text{eNOS}} \frac{K_{\text{dis}}[\text{Ca}^{2+}]_j}{K_{\text{m,eNOS}} + [\text{Ca}^{2+}]_j} + (1 - \gamma_{\text{eNOS}}) g_{\max} F_{\text{wss}} - \mu_{\text{deact},j}[\text{eNOS}_{\text{act}}]_j \tag{3.4.1}$$

$$\frac{\mathrm{d}[\mathrm{NO}]_j}{\mathrm{d}t} = p_{\mathrm{NO},j} - c_{\mathrm{NO},j} + d_{\mathrm{NO},j} \tag{3.4.2}$$

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

$$p_{\mathrm{NO},j} = V_{\mathrm{max,NO},j}[\mathrm{eNOS_{act}}]_j \frac{[\mathrm{O_2}]_j}{K_{\mathrm{m,O2},j} + [\mathrm{O_2}]_j} \frac{[\text{L-Arg}]_j}{K_{\mathrm{m,L\text{-}Arg},j} + [\text{L-Arg}]_j} \tag{3.4.3}$$

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

$$c_{\mathrm{NO},j} = k_{\mathrm{O2},j}[\mathrm{NO}]_j^2[\mathrm{O_2}]_j \tag{3.4.4}$$

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

$$d_{\mathrm{NO},j} = \frac{[\mathrm{NO}]_i - [\mathrm{NO}]_j}{\tau_{ij}} - \frac{4D_{\mathrm{c,NO}}[\mathrm{NO}]_j}{r^2} \tag{3.4.5}$$

$$\tau_{ij} = \frac{x^2}{2D_{NO}} \tag{3.4.6}$$

$$x = 3.75\mu m \tag{3.4.7}$$

Algebraic equations

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

$$F_{\mathrm{wss}} = \frac{1}{1 + \alpha_{\mathrm{wss}} \exp(-W_{\mathrm{wss}})} - \frac{1}{1 + \alpha_{\mathrm{wss}}} \tag{3.4.8}$$

Strain energy density (Pa):

$$W_{\mathrm{wss}} = W_0 \frac{(\tau_{\mathrm{wss}} + \sqrt{16\delta_{\mathrm{wss}}^2 + \tau_{\mathrm{wss}}^2} - 4\delta_{\mathrm{wss}})^2}{\tau_{\mathrm{wss}} + \sqrt{16\delta_{\mathrm{wss}}^2 + \tau_{\mathrm{wss}}^2}} \tag{3.4.9}$$

Wall shear stress (Pa):

$$\tau_{\mathrm{wss}} = \frac{r\Delta P}{2L} \tag{3.4.10}$$

Chapter 4

parameter listing

NO pathway in Neuron

- Parameter ('m_c', 4); **DON'T CHANGE THIS !!!** [-] Number of Ca2+ bound per calmodulin (approximated as parameter, originally an algebraic variable that changed from 3.999 to 4)

- Parameter ('K_{mA}', 650); [uM] - fit to Santucci2008

- Parameter ('K_{mB}', 2800); [uM] - fit to Santucci2008

- Parameter ('v_n', -0.04); [V] ; **DON'T CHANGE THIS !!!**the neuronal membrane potential , assumed to be approx constant in this model

- Parameter ('G_M', 46000); [fS]! was 46 pS! ; the conductance of the NMDA channel to Ca2+ compared

- Parameter ('$P_{Ca_{P_M}}$', 3.6); [-] ; the relative conductance of the NMDA channel to Ca2+ compared to monovalent ions

- Parameter ('Ca_{ex}', 2e3); [microM] ; the external calcium concentration (in Comerford+David2008: 1.5 mM!)

- Parameter ('M', 1.3e5); [microM] ; the concentration of monovalent ions in the neuron

k_{-1}	sGC kinetics rate constant	100 s^{-1}	[9]
k_1	sGC kinetics rate constant	$2{\times}10^3$ μM^{-1} s^{-1}	[9]
k_2	sGC kinetics rate constant	0.1 s^{-1}	[9]
k_3	sGC kinetics rate constant	3 μM^{-1} s^{-1}	[9]
$V_{\mathrm{max,sGC}}$	maximal cGMP production rate	0.8520 $\mu M\, s^{-1}$	[9]
$K_{\mathrm{m,pde}}$	Michaelis constant	2 µM	[9]
k_{dno}	lumped NO consumption rate constant reflecting the activity of various NO scavengers	0.01 s^{-1}	[9]
C_4	constant	0.011 s^{-1} μM^{-2}	[9]
m_4	cGMP feedback strength	2 (dim.less)	[9]
$K_{\mathrm{m,mlcp}}$	Hill coefficient	5.5 µM	[9]
δ_i	constant to fit data	58.1395 (dim.less)	[4], fit
$k_{\mathrm{mlpc,b}}$	basal MLC dephosphorylation rate constant	0.0086 s^{-1}	[9]
$k_{\mathrm{mlpc,c}}$	first-order rate constant for cGMP-regulated MLC dephosphorylation	0.0327 s^{-1}	[9]
α_i	constant to fit data	0.665 µM	[8]
β_i	translation factor for membrane potential dependence of K_{Ca} channel activation sigmoidal	0.13 μM^2	[7]
$c_{w,max}$	constant to fit data	1 $\mu M\, s^{-1}$	[8]
ϵ_i	constant to fit data	10.75 µM	[8]
$[\mathrm{Ca}^{2+}]_i$	calcium concentration in the SMC cytosol	var.	see Dormanns et al. [3]
$v_{\mathrm{Ca3},i}$	half-point for the K_{Ca} channel activation sigmoidal.	-27 mV	[7]
v_i	SMC membrane potential	var.	see [3]
$R_{\mathrm{K},i}$	Maximum slope of the K_{Ca} activation sigmoidal	12 mV	[7]
k_{pde}	phosphodiesterase rate constant	0.0195 s^{-1}	[9]

- Parameter ('n_{NR2A}', 0.63); [-] ; average number of NR2A NMDA receptors per synapse (Santucci2008)

- Parameter ('n_{NR2B}', 11); [-] ; average number of NR2B NMDA receptors per synapse (Santucci2008)

- Parameter ('$V_{max_{NO_n}}$', 4.22); [s^-1] ; maximum catalytic rate of NO production (Chen2006) - obtained from fig 6 and equ 17 and 18

- Parameter ('$O2_n$', 200); [uM] ; tissue O2 concentration in the neuron (M.E.)

- Parameter ('K_{mO2_n}', 243); [uM] ; Chen2006
- Parameter ('$LArg_n$', 100); [uM] ;
- Parameter ('K_{mArg_n}', 1.5); [uM] ;
- Parameter ('k_{O2_n}', 9.6e-6); [uM^-2s^-1] ;
- Parameter ('x'_{nk}, 25); [um] ; (M.E.)
- Parameter ('D_{cNO}', 3300); [um^2s^-1] ; Diffusion coefficient NO (Malinski1993)
- Parameter ('V_{spine}', 8e-8); [nL] ; volume of the neuronal dendritic spine Santucci2008
- Parameter ('k_{ex}', 1600); [s^-1] ; decay rate constant of internal calcium concentration Santucci2008
- Parameter ('Ca_{rest}', 0.1); [uM] ; resting calcium concentration (in Comerford and David2008: 2.830 mM; in Santucci2008P: 0.1 μM)
- Parameter ('$lambda_{buf}$', 20); [-] ; buffer capacity Santucci2008
- Parameter ('V_{maxNOS}', 25e-3); [] ; M.E.
- Parameter ('K_{actNOS}', 9.27e-2); [uM] ;
- Parameter ('$mu2_n$', 0.0167); [s^-1] ; rate constant at which the nNOS is deactivated Comerford2008

NO pathway parameters in Astrocyte

- Parameter ('D_{cNO}', 3300); [um^2s^-1] ; Diffusion coefficient NO (Malinski1993)
- Parameter ('x_{nk}', 25); [um] ; (M.E.)
- Parameter ('x_{ki}', 25); [um] ; (M.E.)
- Parameter ('k_{O2_k}', 9.6e-6); [uM^-2s^-1] ; (Kavdia2002)

- Parameter ('$O2_k$', 200); [uM] ; (M.E.)

NO pathway parameters in Smooth Muscle Cell and Endothelial Cell

- Parameter ('D_{cNO}', 3300); [um^2s^-1] ; Diffusion coefficient NO (Malinski1993)

- Parameter ('K_{mArg_j}', 1.5); [] ;

- Parameter ('K_{mO2_j}', 7.7); [] ; Chen2006

- Parameter ('k_{dno}', 0.01); [s^{-1}] ;

- Parameter ('$K_{m_{mlcp}}$', 5.5); [uM] ;

- Parameter ('$V_{NOj_{max}}$', 1.22); [s^{-1}] ; maximum catalytic rate of NO production (Chen2006) - obtained from fig 6 and equ 17 and 18

- Parameter ('$O2_j$', 200); [uM] ; O2 concentration in the EC (ME)

- Parameter ('$LArg_j$', 100); [uM] ;

- Parameter ('k_{O2}', 9.6e-6); [uM^-2s^{-1}] ;

- Parameter ('W_0', 1.4); [Pa^{-1}] ; shear gating constant (Comerford2008)

- Parameter ('$delta_{wss}$', 2.86); [Pa] ; the membrane shear modulus (Comerford2008)

- Parameter ('k_1', 100); [s^{-1}] ;

- Parameter ('k1', 2e3); [$uM^{-1}s^{-1}$] ;

- Parameter ('k2', 0.1); [s^{-1}] ;

- Parameter ('k3', 3); [$uM^{-1}s^{-1}$] ;

- Parameter ('$V_{max_{sGC}}$', 0.8520); [] ;

- Parameter ('k_{pde}', 0.0195); [s^{-1}] ;
- Parameter ('C_4', 0.011); [$s^{-1} microM^{-2}$] ;
- Parameter ('$K_{m_{pde}}$, 2); [uM] ;
- Parameter ('gam_{eNOS}', 0.1); [-] ;
- Parameter ('$mu2_j$', 0.0167); [s^{-1}] ;
- Parameter ('K_{dis}', 9e-2); [uMs^{-1}] ;
- Parameter ('K_{eNOS}', 4.5e-1); [uM] ;
- Parameter ('g_{max}', 0.06); [uM s^{-1}] ;
- Parameter ('alp', 2); [-] ; zero shear open channel constant (Comerford2008); in Wiesner1997: alp = 3
- Parameter ('$delta_{p_L}$', 9.1e4); 9.1e4: ME
- Parameter ('x_{ki}', 25); [um] (M.E.)
- Parameter ('x_{ij}', 3.75); [um] (Kavdia2002)

Bibliography

[1] **Chang, J. C.; Brennan, K. C.; He, D.; Huang, H.; Miura, R. M.; Wilson, P. L. and Wylie, J. J.** (**2013**): A Mathematical Model of the Metabolic and Perfusion Effects on Cortical Spreading Depression, PloS one, Vol. 8, No. 8 p. e70469.

[2] **Dormanns, K.; Brown, R. and David, T.** (**2016**): The role of nitric oxide in neurovascular coupling, Journal of Theoretical Biology, Vol. 394 pp. 1–17.

[3] **Dormanns, K.; van Disseldorp, E.; Brown, R. and David, T.** (**2015**): Neurovascular coupling and the influence of luminal agonists via the endothelium, Journal of Theoretical Biology, Vol. 364 pp. 49–70.

[4] **Hai, C. M. and Murphy, R. a.** (**1988**): Cross-bridge phosphorylation and regulation of latch state in smooth muscle Cross-bridge phosphorylation and regulation of latch state in smooth muscle, American Journal of Cell Physiology, Vol. 254 pp. C99–C106.

[5] **Kager, H.; Wadman, W. J. and Somjen, G. G.** (**2000**): Simulated seizures and spreading depression in a neuron model incorporating interstitial space and ion concentrations., Journal of neurophysiology, Vol. 84, No. 1 pp. 495–512.

[6] **Kavdia, M.; Tsoukias, N. M. and Popel, A. S.** (**2002**): Model of nitric oxide diffusion in an arteriole: impact of hemoglobin-based blood substitutes., American Journal of Physiology, Heart and Circulatory Physiology, Vol. 282, No. 6 pp. H2245–H2253.

[7] **Koenigsberger, M.; Sauser, R.; Bény, J.-L. and Meister, J.-J.** (**2006**): Effects of arterial wall stress on vasomotion., Biophysical journal, Vol. 91, No. 5 pp. 1663–1674.

[8] **Stockand, J. D. and Sansom, S. C.** (**1996**): Mechanism of activation by cGMP-dependent protein kinase of large Ca2+-activated K+ channels in mesangial cells.

[9] **Yang, J.; Clark, J. W.; Bryan, R. M. and Robertson, C. S.** (**2005**): Mathematical modeling of the nitric oxide/cGMP pathway in the vascular smooth muscle cell., American Journal of Physiology, Heart and Circulatory Physiology, Vol. 289, No. 2 pp. H886–H897.

[10] **Zheng, Y.; Pan, Y.; Harris, S.; Billings, S.; Coca, D.; Berwick, J.; Jones, M.; Kennerley, A.; Johnston, D.; Martin, C.; Devonshire, I. M. and Mayhew, J.** (**2010**): A dynamic model of neurovascular coupling: Implications for blood vessel dilation and constriction, NeuroImage, Vol. 52, No. 3 pp. 1135–1147.