

# Neurovascular Unit Model

## Documentation for Code “OO-NVU Version 2.0”

A merged NVC model of a neuron, astrocyte, smooth muscle cell,  
endothelial cell and the mechanical vessel response.

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# 1 Release notes

## 1.1 Changes to the previous version

This is where changes should be listed.

## 1.2 Corrections

A mistake was discovered in NVU1.0 for the equation used to describe the  $K^+$  concentration in the synaptic cleft. The original equation subtracted the change in astrocytic  $K^+$  concentration from the  $K^+$  influx from the neuron. This was incorrect since not all channels lead from the astrocyte to the synaptic cleft. The BK-channel describes the flux from the astrocyte to the perivascular space, and therefore this flux was added to the equation. Fortunately, this mistake led to very small changes, and it did not significantly change the model outcomes. Figure 1 shows the old and the corrected results for the flux through the BK-channel, and it is clear that they practically overlap.

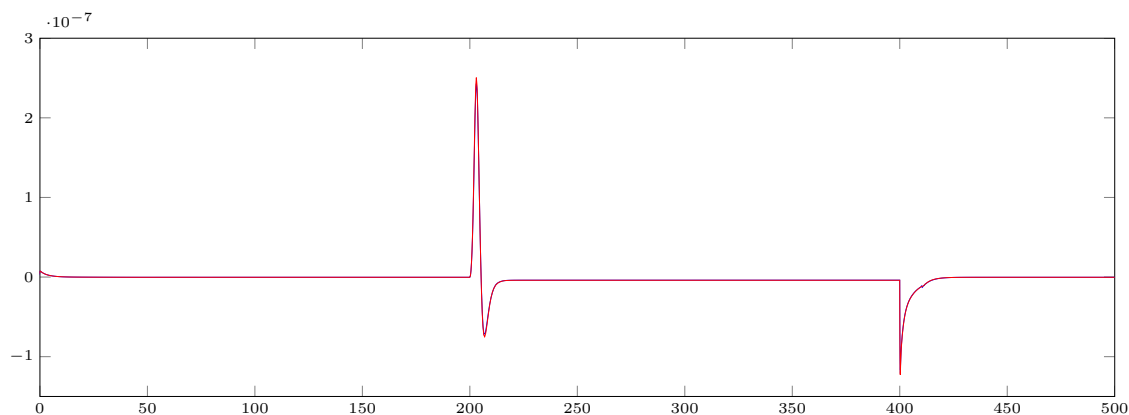


Figure 1: The flux through the BK-channel in  $\mu M$  m/s for the old (blue) and corrected (red) simulation

## 2 Code Structure

The three core classes, the `Astrocyte`, `SMCEC` and `WallMechanics`, correspond to the components of the NVU model, namely the astrocyte model, the SMC and EC model, and the mechanical contraction cell model. For a given model component, all fluxes and ODEs are grouped together in the code of the corresponding class. The `NVU` class uses the three core component classes to collect the state variable and derivatives values and pass them to the `ode15s` solver for stiff problems. All classes in OO-NVU code are subclasses of the MATLAB's `handle` class which makes them appear as reference object to avoid unnecessary object duplication on assignment. Figure 2 shows the public interfaces for all OO-NVU classes.

For a proper OO development and complexity management in the future the `Astrocyte`, `SMCEC` and the `WallMechanics` classes should have a common superclass with the shared interface (at least) and functionality. –Kon

The following features apply to the `Astrocyte`, `SMCEC` and `WallMechanics` classes:

1. The core classes rely on the class constructors to initialise the parameters with the help of the class-specific function `parse_inputs(varargin)`. The constructors also initialise the variable indices, initial conditions and the output indices.
2. In every core class the `rhs` method contains the algebraic and state variables, as well as the corresponding equations.
3. The `shared(self, ~, u)` method, where present, provides the access to the shared algebraic or state variables used as input variables in the other model components where appropriate.

The code in the file `nvu_script.m` provides a number of use-cases for running the NVU model. The code Listing 1 shows an example of setting the options for the ODE solver `ode15s` specifying the `odeopts` parameter, however the code works well with default tolerances. The `simulate()` method of the `NVU` class start the simulation.

Listing 1: Initialisation of the NVU model components.

```
1 odeopts = odeset('RelTol', 1e-03, 'AbsTol', 1e-03, 'MaxStep', 1, ...  
    'Vectorized', 1);  
2  
3 nv = NVU(Astrocyte(), ...  
4 WallMechanics(), ...  
5 SMCEC('J_PLC', 0.18), ...  
6 'odeopts', odeopts);  
7  
8 nv.simulate()
```

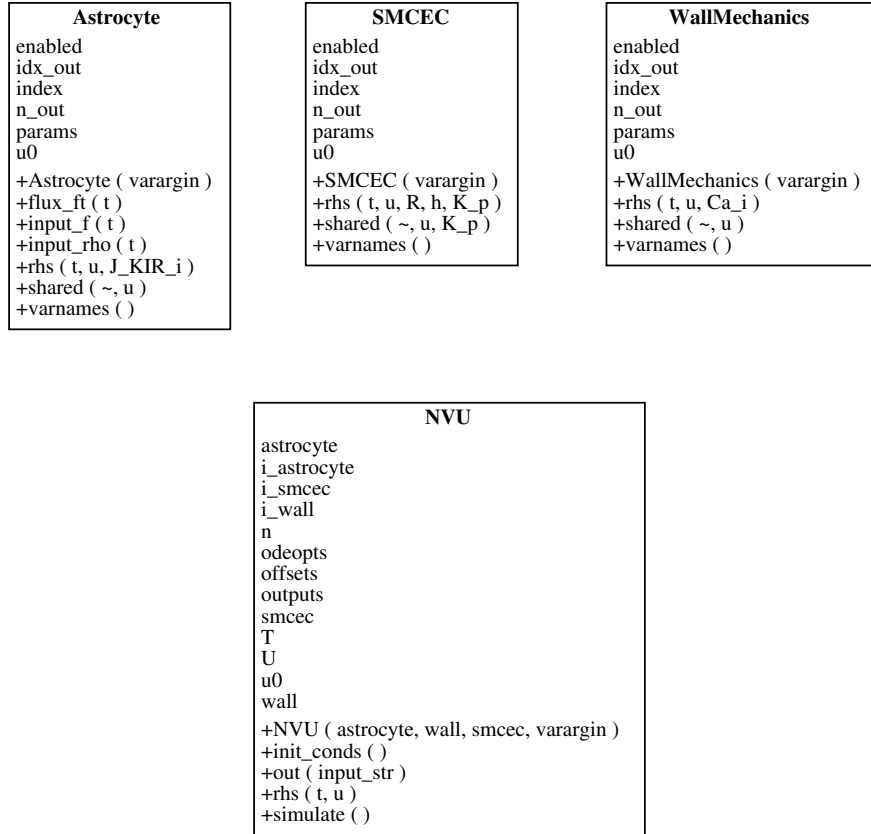


Figure 2: UML class diagram for the OO NVU code.

This is the first draft of this section. Suggestions as to what needs to be expanded further? Include more code listings? –Kon

Remove the code structure files used in the previous documentation version when this version is done. –Kon

### 3 Introduction

#### 3.1 Neurovascular Unit

The cerebral cortex, a highly complex component of the human brain and part of the grey matter (*substantia grisea*), mainly consists of neurons (NEs), unmyelinated axons and glial cells such as astrocytes (ACs). It forms the outer layer of *cerebrum* and *cerebellum* and is veined with capillary blood vessels that provide the brain tissue with glucose and oxygen (Shipp [9]). These arterioles are surrounded by endothelial cells (ECs) that form a thin layer on the interior surface of arterioles (*intima*). The outer layer of the arteriole consists of smooth muscle cells (SMCs), which are aligned in circumferential direction. They define the contractile unit of the vessel and regulate its diameter by contraction and dilation.

A neurovascular unit (NVU) defined in this research includes one cell of each of the described types and is graphically pictured in Figure 4.

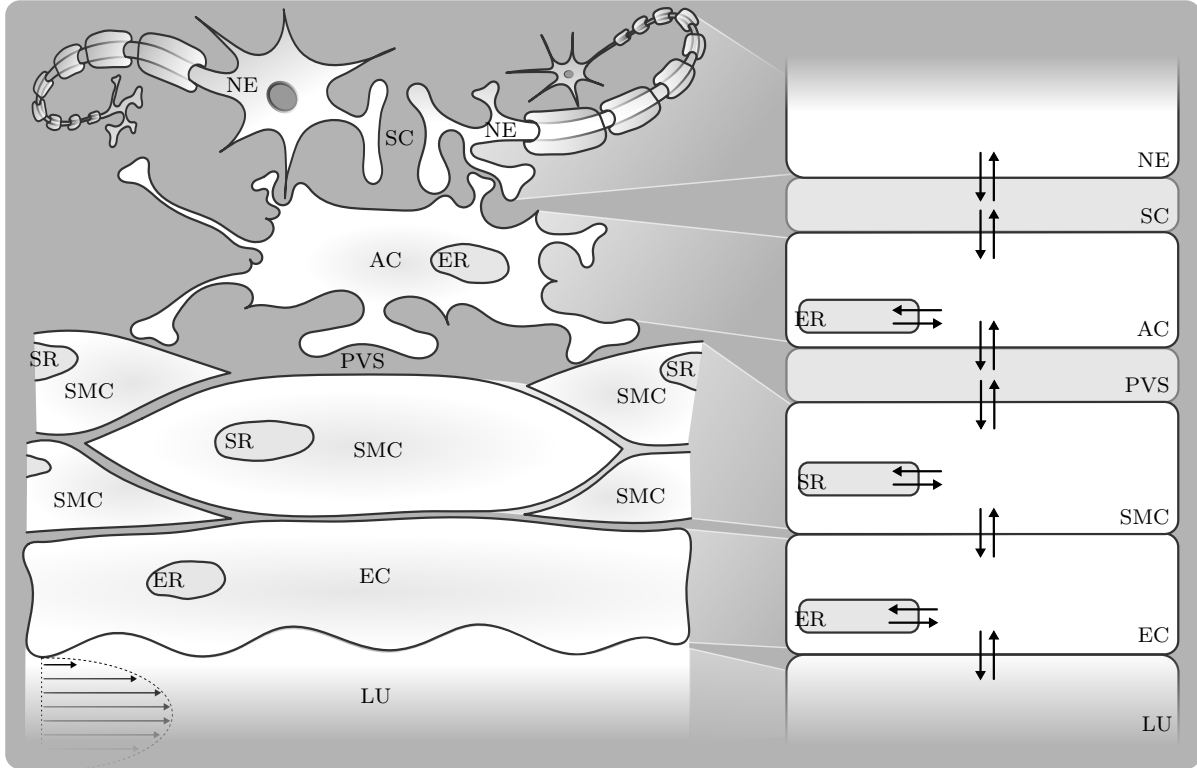


Figure 3: **Overview of different cells and domains that form a neurovascular unit.** NE - Neuron, SC - Synaptic Cleft, AC - Astrocyte, ER - Endoplasmic Reticulum, PVS - Perivascular Space, SMC - Smooth Muscle Cell, SR - Sarcoplasmic Reticulum, EC - Endothelial Cell, LU - Lumen with indicated blood flow. Intercellular communication via the exchange of ions is indicated by arrows.

Each of the cell types and the spaces in between play an important role within the process of neurovascular coupling (NVC, see Section 3.2). The synaptic cleft (SC) is the space between an axon terminal and dendrite of two different NEs in which neurotransmitters are released. It is enclosed by the star-shaped AC that can take up released neurotransmitters. Protoplasmic ACs are polarized cells which can temporarily buffer extracellular  $K^+$ , which is one of the key mechanisms within NVC. The astrocytic endoplasmatic reticulum (ER), an isolated space in the cytosol, contains  $IP_3$ -sensitive  $Ca^{2+}$  channels, which can release  $Ca^{2+}$ -ions into the cytosol. The perivascular space (PVS) is located between the end feet of an AC and the arteriole. In the PVS, ion exchange occurs between the arterial wall and the AC. The ECs form a monolayer on the luminal side of the vessel in which all cells are aligned in the direction of the flow. It prevents passive diffusion of bigger molecules, while small ones, such as  $O_2$ ,  $Ca^{2+}$  or  $IP_3$ , can pass through. It also functions as an active organ sensing wall shear stress which plays an important role in the NO-mediated pathway. Together with the SMC layer the endothelium forms the blood brain barrier (BBB), the physical frontier between brain tissue and blood vessel. SMC contraction occurs by actin and myosin filaments forming cross-bridges. The rate of contraction is dependent on the SMC cytosolic  $Ca^{2+}$  concentration.

### 3.2 Neurovascular Coupling

Neurovascular coupling (NVC), or functional hyperaemia, describes the local vasodilation and -contraction due to neuronal activation. The change in the vessel diameter (vasoreactivity) controls the blood flow and thereby the cerebral supply of oxygen and glucose.

Each cell type plays an important specific role during the process of NVC. Communication between cells is based on an exchange of ions through pumps and channels. These ion fluxes contribute to changes in cytosolic and intercellular species concentration and cell membrane potentials.

There are several pathways that can lead to vasocontraction or -dilation and are mediated by different signalling molecules, such as  $K^+$ ,  $Ca^{2+}$ , EET, NO and 20-HETE. Neurotransmitters are released by the NE into the SC and can bind to receptors on dendrites of other neurons and astrocytes. This leads to a cascade of chemical reactions and the opening and closing of ion channels which influences the fluxes and concentrations.

### 3.3 Mathematical Approach

The physiological models are based on a set of differential equations that describe the mass conservation of ions and molecules passing from one cell or domain to another. The simulations describe time-dependent ion fluxes and changes in membrane potential modelled by reaction rates that describe the kinetics which are physiologically validated by experimental data from the literature. This approach assumes homogeneous behaviour of a variable in a certain subdomain i.e. the spatial gradient of a variable in every subdomain is negligible.

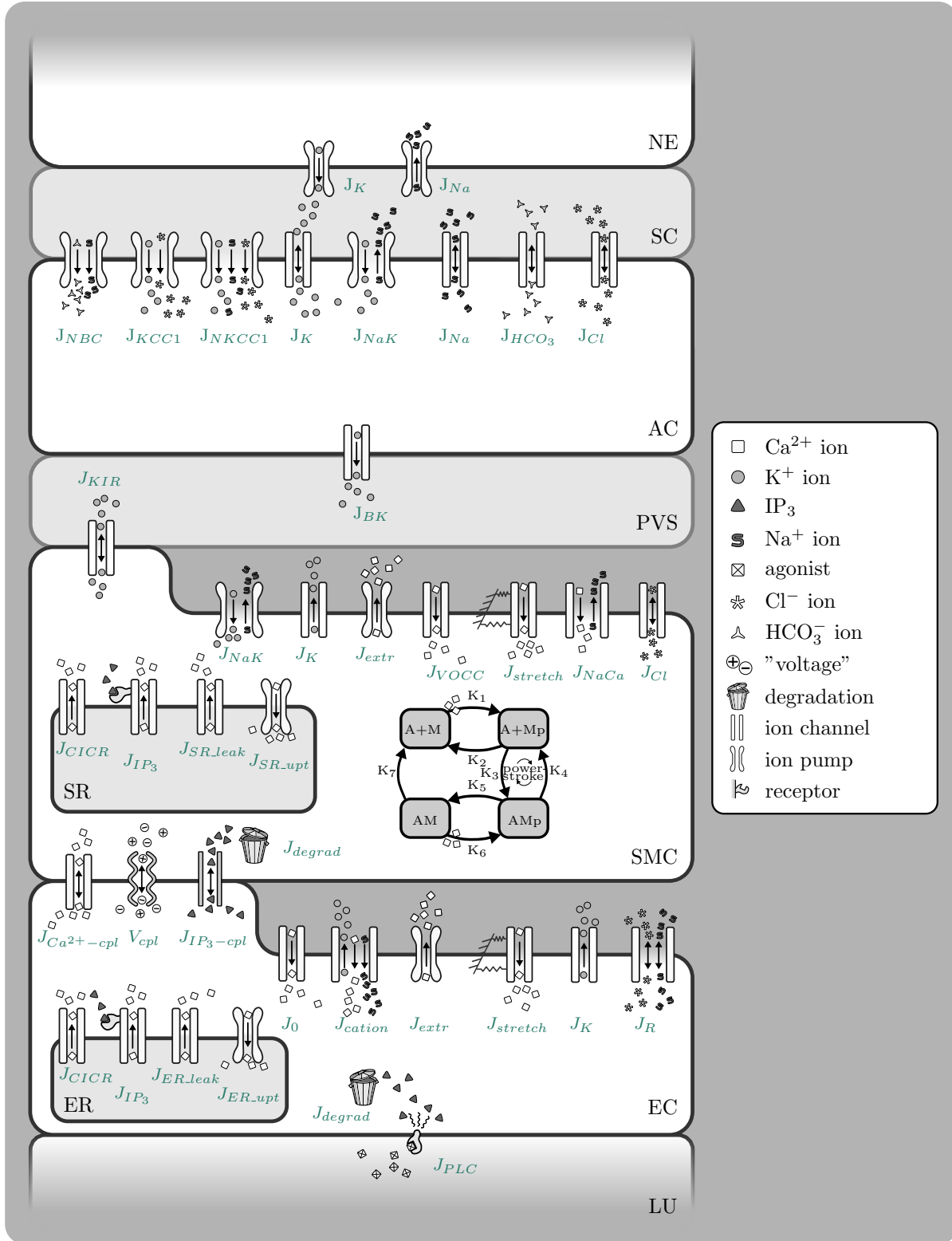


Figure 4: **Overview of model.** NE - Neuron, SC - Synaptic Cleft, AC - Astrocyte, ER - Endoplasmic Reticulum, PVS - Perivascular Space, SMC - Smooth Muscle Cell, SR - Sarcoplasmic Reticulum, EC - Endothelial Cell, LU - Lumen.



## 4 Results

### 4.1 OO-NVU 2.0

#### Potassium input signal (figure 5)

At the top the neuronal  $K^+$  input signal is shown. This input signal is pumped into the SC by the NE. As a result of that, there is more  $K^+$  taken up by the AC in the beginning of the input pulse, and released at the end of the input pulse. In the second graph the membrane potential of the AC is shown over time. When the  $K^+$  concentration in the SC is increased the membrane voltage depolarises and when the  $K^+$  concentration in the SC decreases the membrane potential repolarises again. In the third graph the fluxes into the PVS are shown. In blue the flux by the astrocytic BK channel, and in green the flux by the KIR channel in the SMC is shown. The drop in the middle of the KIR flux is caused because the SMC becomes in a oscillatory state and therefore the efflux by the KIR channel follows the  $Ca^{2+}$  waves inside the SMC. The bottom figure shows the  $K^+$  concentration in the PVS.

#### Neurovascular Coupling Overview (figure 6)

This figure describes the main pathway from the synaptic cleft to the radius change. It starts with a  $K^+$  concentration in the synaptic cleft, followed by the flux trough the BK-channel determined in the astrocyte, leading to an increased  $K^+$  concentration in the perivascular space. This causes an increased  $K^+$  influx trough the KIR channel, changing the membrane voltage of the SMC. The  $Ca^{2+}$  flux through the VOCC increases, decreasing the  $Ca^{2+}$  concentration in the SMC and thereby inducing vasodilation.

#### AC State Variables (figure 7)

The graphs display the concentrations of  $K^+$ ,  $Ca^{2+}$ , Cl and  $HCO_3$  in the astrocyte and  $K^+$  in the SC and PVS. These concentrations, together with the membrane voltage contribute to the opening of the BK-channel in their own way. The open state of the BK channel determines the potassium flux from the astrocyte to the perivascular spcace, where it induces vascular contraction.

#### AC Fluxes (figure 8)

All ion fluxes that enter or leave the astrocyte.

#### SMC EC State Variables and Coupling (figure 9)

The graphs in this figure shows the solutions of the differential equations of the SMC and EC, including the intracellular  $Ca^{2+}$  concentration, the  $IP_3$  concentration, the sarcoplasmic (SMC) or endoplasmic (EC)  $Ca^{2+}$  concentration, the membrane voltage and the coupling fluxes between EC and SMC.

### **SMC Fluxes (figure 10)**

In these figures the coupling and the fluxes in the SMC are shown. When one of the fluxes is negative, it means that the direction of the flux is in the opposite than it is defined in the equations. These figures show that when the neuronal signal is given, the VOCC closes and that the SMC contracts.

### **EC Fluxes (figure 11)**

All ion fluxes that enter or leave the EC.

### **Contraction Model and Radius (figure 12)**

In this figure the fraction of the four states (M, Mp, AMp, AM) of myosin in the SMC are shown at the top. At the bottom left the fraction of attached cross bridged myosin (the sum of AM and AMp) is shown. And at the bottom right the radius is plotted over time. The increase in vessel diameter is in the expected order of magnitude.

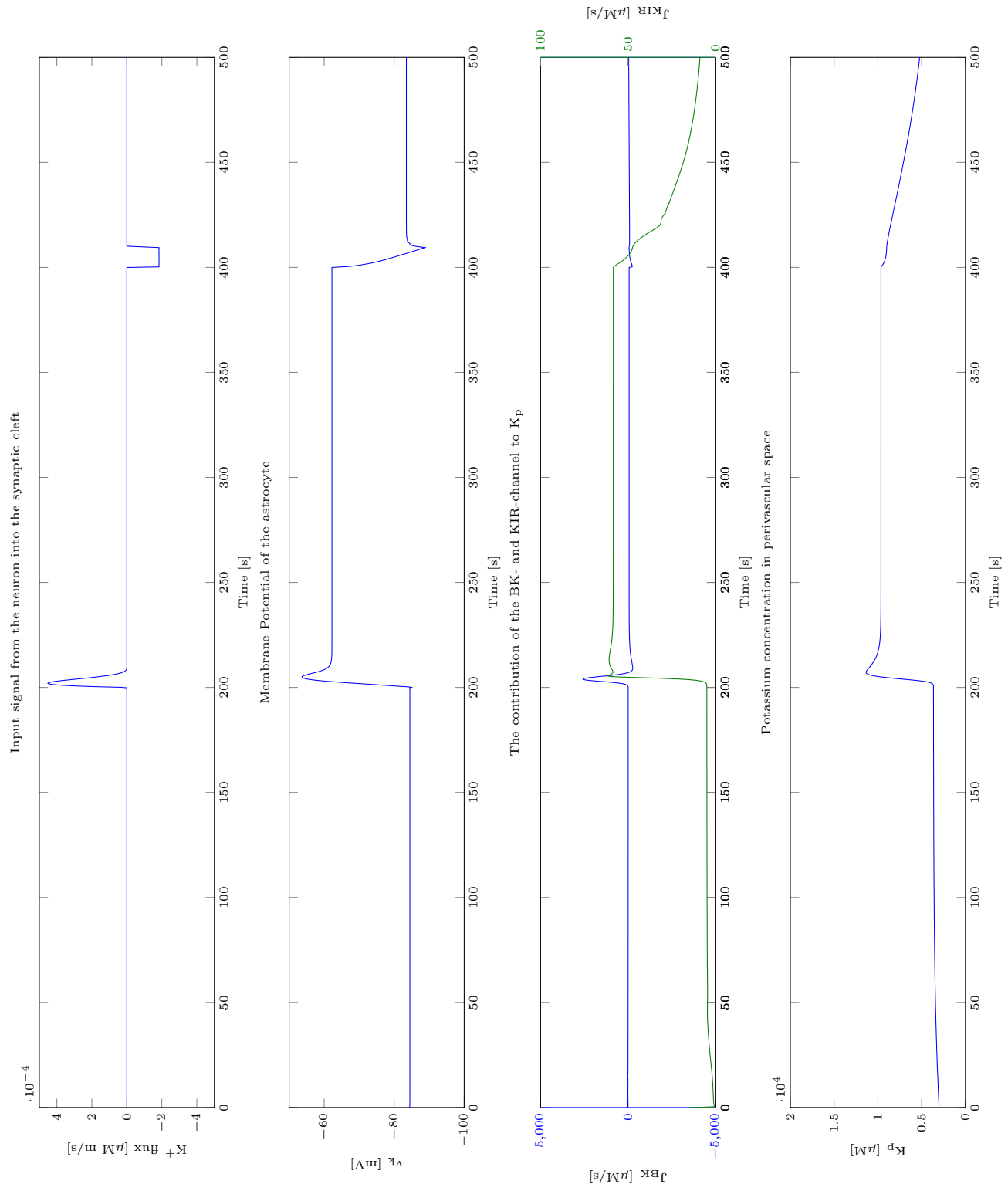


Figure 5: The input signal.

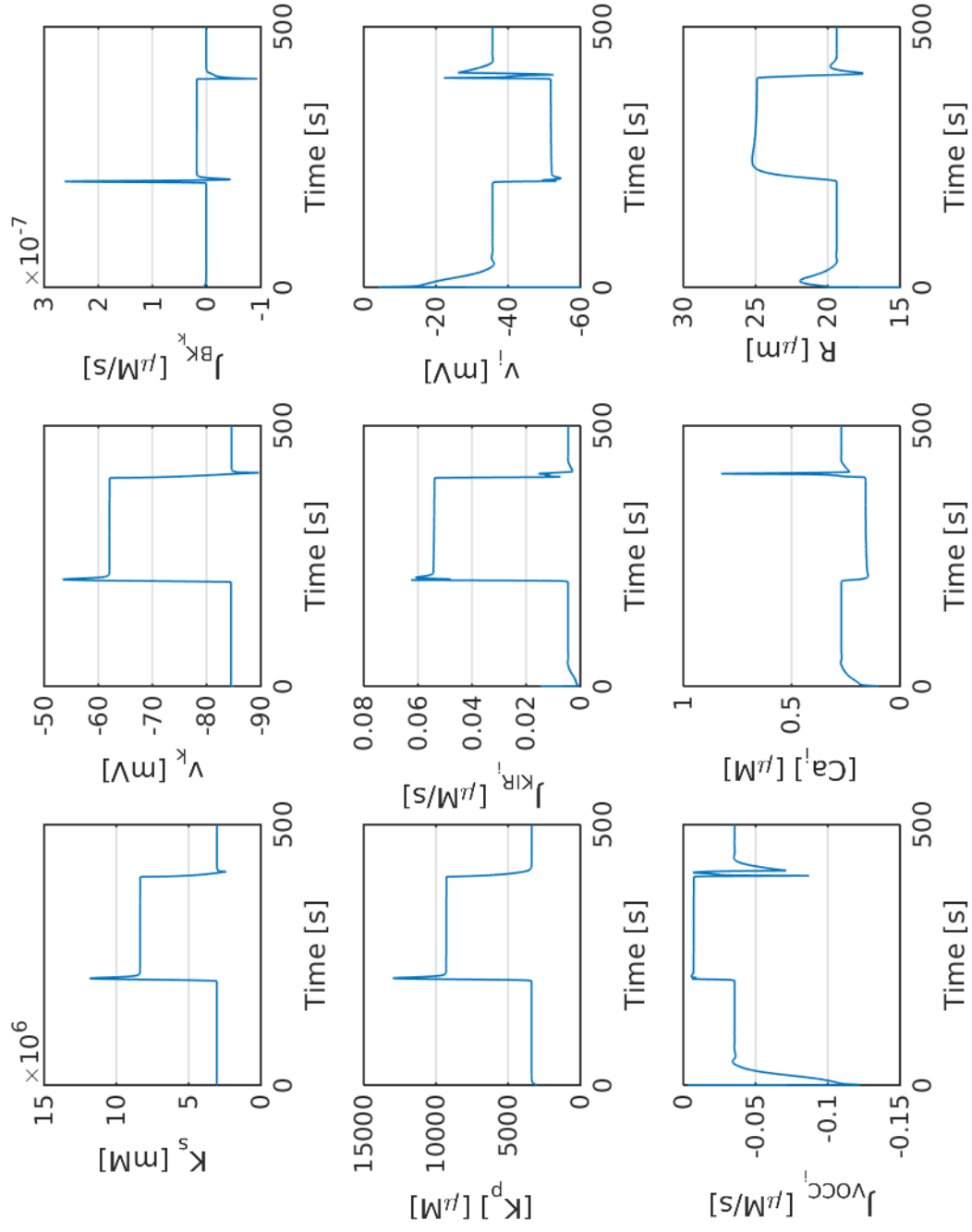


Figure 6: Neurovascular Coupling Overview.

AC State Variables.png

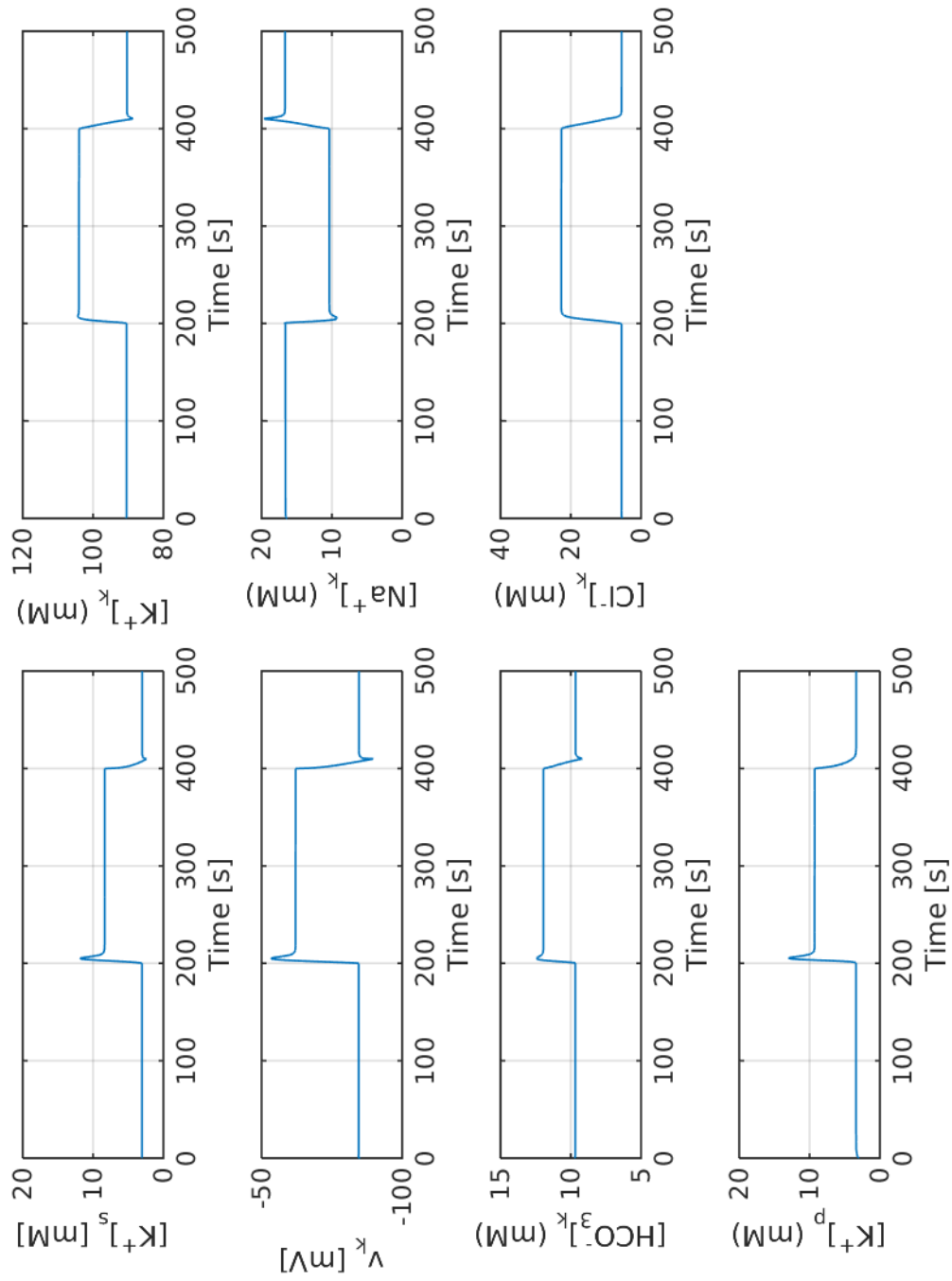


Figure 7: AC State Variables.

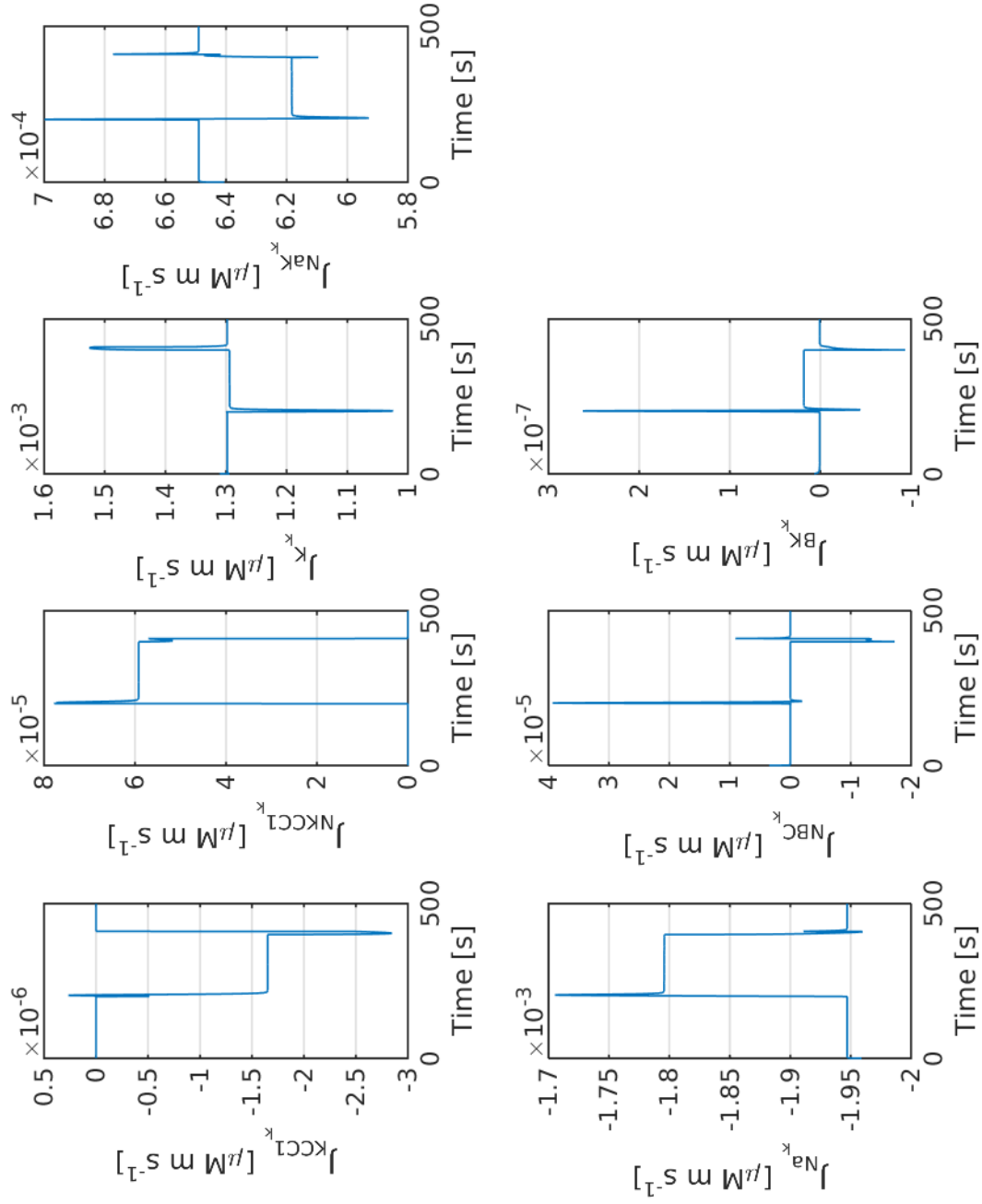


Figure 8: AC Fluxes.

SMC EC State Variables and Coupling.png

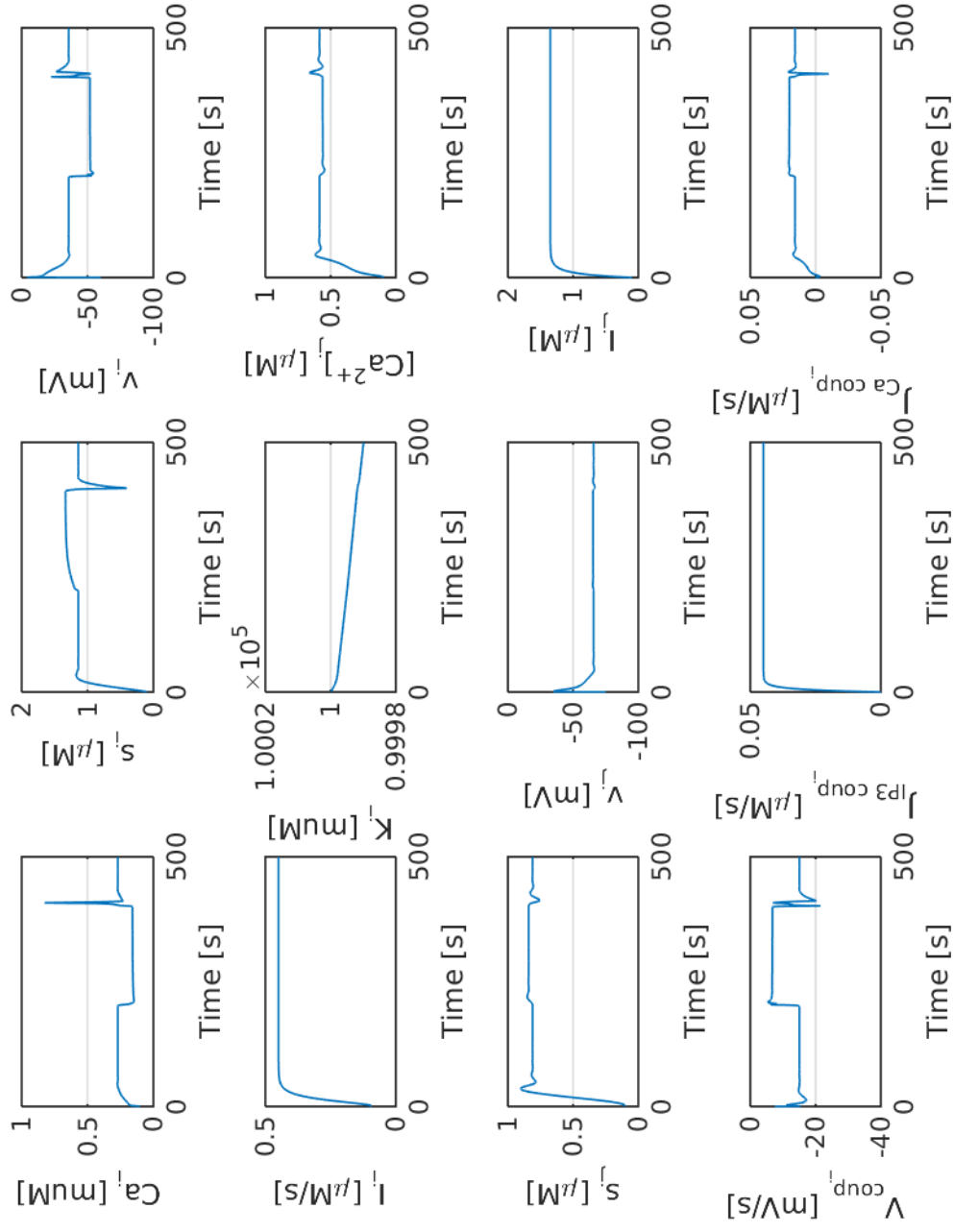


Figure 9: SMC EC State Variables and Coupling.

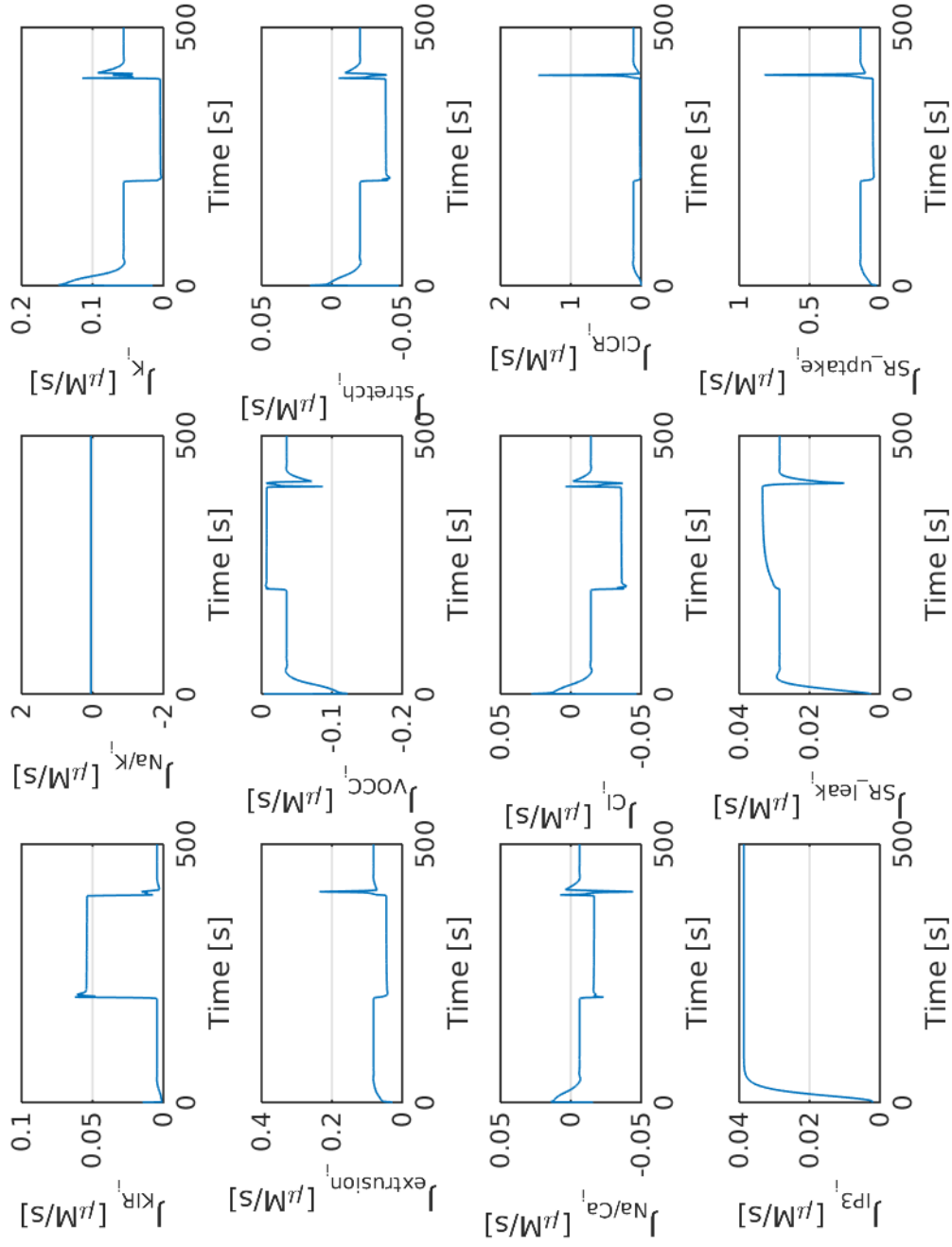


Figure 10: SMC Fluxes.



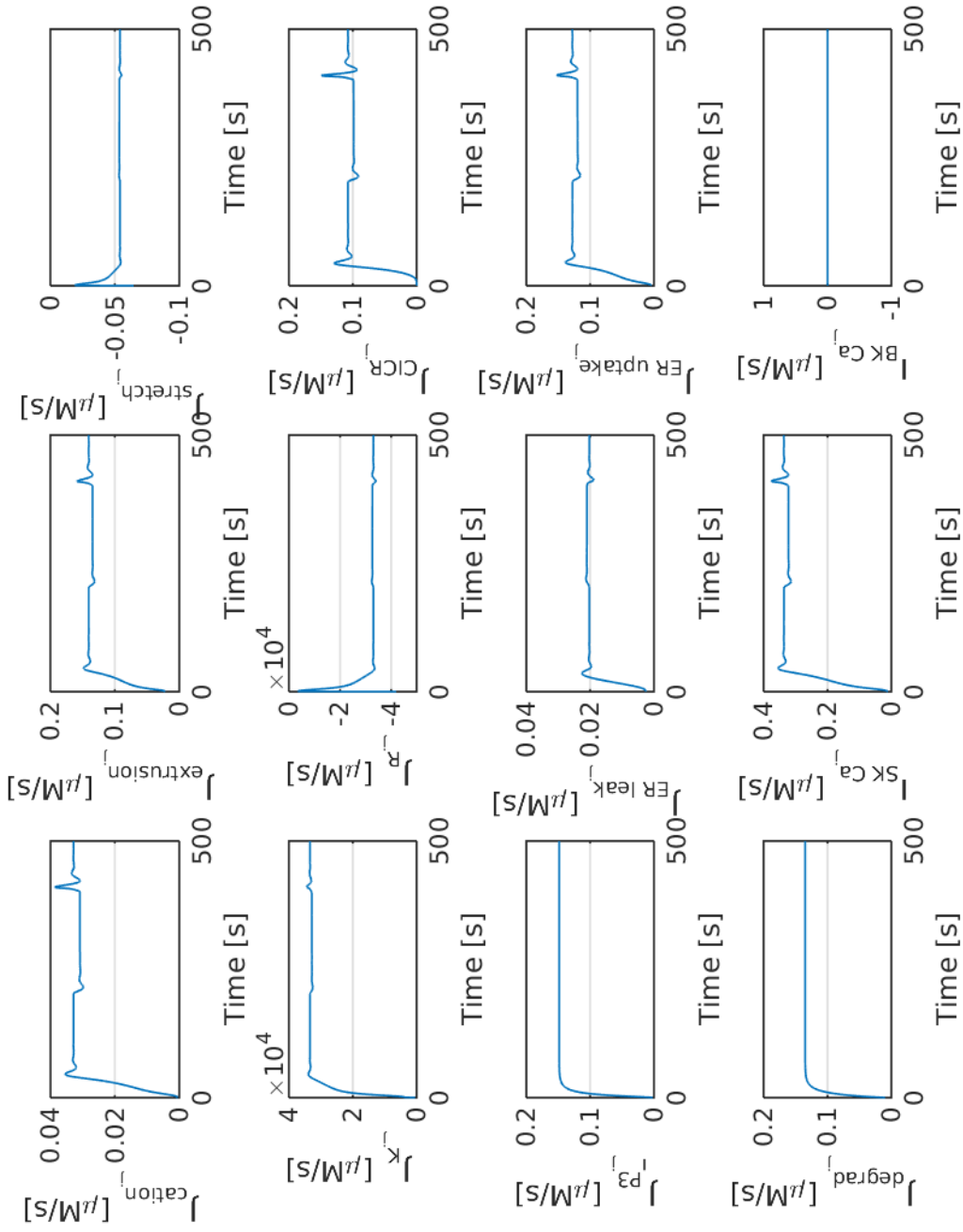


Figure 11: EC Fluxes.

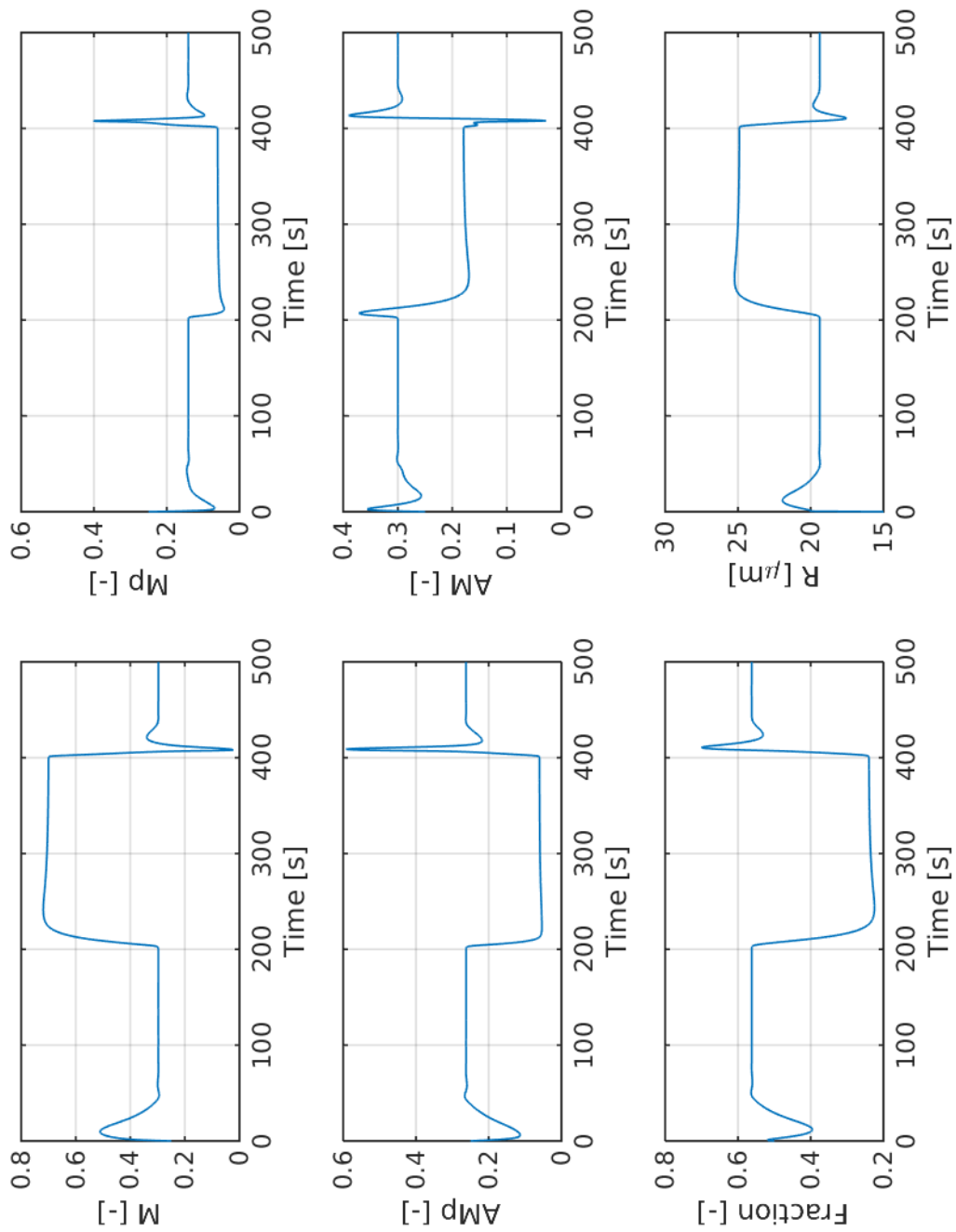


Figure 12: Contraction Model and Radius.

## 5 Equations

Some units need to be corrected in this documentation!

### 5.1 The Neuron and Astrocyte Model

#### Input signals

Neuronal  $K^+$  input signal (-):

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

$$f(t) = 0 \quad (1)$$

For  $t_0 \leq t \leq t_1$ :

$$f(t) = F_{input} \frac{(\alpha + \beta - 1)!}{(\alpha - 1)!(\beta - 1)!} \left( \frac{1 - (t - t_0)}{\Delta t} \right)^{\beta-1} \left( \frac{t - t_0}{\Delta t} \right)^{\alpha-1} \quad (2)$$

For  $t_1 \leq t \leq t_2$ :

$$f(t) = 0 \quad (3)$$

For  $t_2 \leq t \leq t_3$ :

$$f(t) = -F_{input} \quad (4)$$

$t_0$	Start of neuronal pulse	200 s	
$t_1$	End of neuronal pulse	210 s	
$t_2$	Start of back-buffering	230 s	
$t_3$	End of back-buffering	240 s	
$F_{input}$	Amplitude scaling factor	2.5	
$\alpha$	Gamma distribution constant	2	ME <sup>1</sup>
$\beta$	Gamma distribution constant	5	ME
$\Delta t$	Time-scaling factor	10 s	

#### Scaling

AC volume-area ratio (in m):

$$\frac{dR_k}{dt} = L_p(Na_k + K_k + Cl_k + HCO_{3k} - Na_s - K_s - Cl_s - HCO_{3s} + \frac{X_k}{R_k}) \quad (5)$$

SC volume-surface ratio (in m):

$$R_s = R_{tot} - R_k \quad (6)$$

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<sup>1</sup>Model Estimation

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

## Conservation Equations

### Synaptic Cleft

$\text{K}^+$  concentration in the SC (times the SC volume-area ratio  $R_s$ ; in  $\mu\text{M m}$ ):

$$\frac{dN_{K_s}}{dt} = k_C f(t) - \frac{dN_{K_k}}{dt} - J_{BK_k} \quad (7)$$

$\text{Na}^+$  concentration in the SC (times the SC volume-area ratio  $R_s$ ; in  $\mu\text{M m}$ ):

$$\frac{dN_{Na_s}}{dt} = -k_C f(t) - \frac{dN_{Na_k}}{dt} \quad (8)$$

$\text{HCO}_3^-$  concentration in the SC (times the SC volume-area ratio  $R_s$ ; in  $\mu\text{M m}$ ):

$$\frac{dN_{HCO_{3s}}}{dt} = -\frac{dN_{HCO_{3k}}}{dt} \quad (9)$$

$k_C$	Input scaling parameter	$7.35 \times 10^{-5} \text{ } \mu\text{M m s}^{-1}$	[8]
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### Astrocyte

$\text{K}^+$  concentration in the AC (times the AC volume-area ratio  $R_k$ ; in  $\mu\text{M m}$ ):

$$\frac{dN_{K_k}}{dt} = -J_{K_k} + 2J_{NaK_k} + J_{NKCC1_k} + J_{KCC1_k} - J_{BK_k} \quad (10)$$

$\text{Na}^+$  concentration in the AC (times the AC volume-area ratio  $R_k$ ; in  $\mu\text{M m}$ ):

$$\frac{dN_{Na_k}}{dt} = -J_{Na_k} - 3J_{NaK_k} + J_{NKCC1_k} + J_{NBC_k} \quad (11)$$

$\text{HCO}_3^-$  concentration in the AC (times the AC volume-area ratio  $R_k$ ; in  $\mu\text{M m}$ ):

$$\frac{dN_{HCO_{3k}}}{dt} = 2J_{NBC_k} \quad (12)$$

$\text{Cl}^-$  concentration in the AC (times the AC volume-area ratio  $R_k$ ; in  $\mu\text{M m}$ ):

$$\frac{dN_{Cl_k}}{dt} = \frac{dN_{Na_k}}{dt} + \frac{dN_{K_k}}{dt} - \frac{dN_{HCO_{3k}}}{dt} \quad (13)$$

Open probability of the BK channel (non-dim.):

$$\frac{dw_k}{dt} = \phi_w (w_\infty - w_k) \quad (14)$$

## Perivascular Space

K<sup>+</sup> concentration in the PVS (in  $\mu\text{M}$ ):

$$\frac{dK_p}{dt} = \frac{J_{BK_k}}{R_k R_{pa}} + \frac{J_{KIR_i}}{R_{ps}} - R_{decay}(K_p - K_{p,min}); \quad (15)$$

$R_{pa}$	Volume ratio of PVS to AC	$10^{-3}$ [-]	[7]
$R_{ps}$	Volume ratio of PVS to SMC	$10^{-3}$ [-]	[7]
$R_{decay}$	Decay rate	$0.05 \text{ s}^{-1}$	M.E.
$K_{p,min}$	min K <sup>+</sup> concentration	$3 \times 10^3 \mu\text{M}$	M.E.

## Fluxes

K<sup>+</sup> flux (times the AC volume-area ratio  $R_k$ ; in  $\mu\text{M m s}^{-1}$ ):

$$J_{K_k} = \frac{g_{K_k}}{F}(v_k - E_{K_k}) \quad (16)$$

Na<sup>+</sup> flux (times the AC volume-area ratio  $R_k$ ; in  $\mu\text{M m s}^{-1}$ ):

$$J_{Na_k} = \frac{g_{Na_k}}{F}(v_k - E_{Na_k}) \quad (17)$$

Na<sup>+</sup> and HCO<sub>3</sub> flux through the NBC channel (times the AC volume-area ratio  $R_k$ ; in  $\mu\text{M m s}^{-1}$ ):

$$J_{NBC_k} = \frac{g_{NBC_k}}{F}(v_k - E_{NBC_k}) \quad (18)$$

Cl and K<sup>+</sup> flux through the KCC1 channel (times the AC volume-area ratio  $R_k$ ; in  $\mu\text{M m s}^{-1}$ ):

$$J_{KCC1_k} = C_{input} \frac{g_{KCC1_k}}{F} \frac{R_g T}{F} \ln \left( \frac{K_s Cl_s}{K_k Cl_k} \right) \quad (19)$$

Na<sup>+</sup>, K<sup>+</sup> and Cl flux through the NKCC1 channel (times the AC volume-area ratio  $R_k$ ; in  $\mu\text{M m s}^{-1}$ ):

$$J_{NKCC1_k} = C_{input} \frac{g_{NKCC1_k}}{F} \frac{R_g T}{F} \ln \left( \frac{Na_s K_s Cl_s^2}{Na_k K_k Cl_k^2} \right) \quad (20)$$

Flux through the sodium potassium pump (times the AC volume-area ratio  $R_k$ ; in  $\mu\text{M m s}^{-1}$ ):

$$J_{NaK_k} = J_{NaK_{max}} \frac{Na_k^{1.5}}{Na_k^{1.5} + K_{Na_k}^{1.5}} \frac{K_s}{K_s + K_{K_s}} \quad (21)$$

K<sup>+</sup> flux through the BK channel (times the AC volume-area ratio  $R_k$ ; in  $\mu\text{M m s}^{-1}$ ):

$$J_{BK_k} = \frac{g_{BK_k}}{F} w_k (v_k - E_{BK_k}) \quad (22)$$

$F$	Faraday's constant	$9.649 \times 10^4 \text{ C mol}^{-1}$	
$R_g$	Gas constant	$8.315 \text{ J mol}^{-1} \text{ K}^{-1}$	
$T$	Temperature	300 K	
$g_{K_k}$	Specific ion conductance of potassium	$40 \times 10^3 \text{ } \Omega^{-1} \text{ m}^{-2}$	[8]
$g_{Na_k}$	Specific ion conductance of sodium	$1.314 \times 10^3 \text{ } \Omega^{-1} \text{ m}^{-2}$	[8]
$g_{NBC_k}$	Specific ion conductance of the NBC cotransporter	$7.57 \times 10^2 \text{ } \Omega^{-1} \text{ m}^{-2}$	[8]
$g_{KCC1_k}$	Specific ion conductance of the KCC1 cotransporter	$10 \text{ } \Omega^{-1} \text{ m}^{-2}$	[8]
$g_{NKCC1_k}$	Specific ion conductance of the NKCC1 cotransporter	$55.4 \text{ } \Omega^{-1} \text{ m}^{-2}$	[8]
$J_{NaK_{max}}$	Maximum flux through the NaKATPase pump	$1.42 \times 10^{-3} \text{ } \mu\text{Mms}^{-1}$	[8]
$G_{BK_k}$	Specific ion conductance of the BK channel	$4.3 \times 10^3 \text{ pS}$	[2]
$A_{ef,k}$	Membrane area	$3.7 \times 10^{-9}$	[2]
$g_{BK_k}$	Specific ion conductance of the BK channel	$G_{BK_k} \times 10^{-12} / A_{ef,k} = 1.16 \times 10^3 \text{ } \Omega^{-1} \text{ m}^{-2}$	[2]
$C_{input}$	Block function to switch the channel on and off	0 ; 1 [-]	
$K_{Na_k}$	Michaelis-Menten constant	$10^4 \text{ } \mu\text{M}$	
$K_{K_s}$	Michaelis-Menten constant	$1.5 \times 10^3 \text{ } \mu\text{M}$	
$C_{unit}$	Unit converting factor	$10^3$	M.E.

## Additional Equations

### Synaptic Cleft

Cl concentration (times the SC volume-area ratio  $R_s$ ; in  $\mu\text{M m}$ ):

$$N_{Cl_s} = N_{Na_s} + N_{K_s} - N_{HCO_{3_s}} \quad (23)$$

### Astrocyte

Membrane voltage of the AC (V):

$$v_k = \frac{g_{Na_k} E_{Na_k} + g_{K_k} E_{K_k} + g_{Cl_k} E_{Cl_k} + g_{NBC_k} E_{NBC_k} + g_{BK_k} w_k E_{BK_k} - J_{NaK_k} F C_{unit}}{g_{Na_k} + g_{K_k} + g_{Cl_k} + g_{NBC_k} + g_{BK_k} w_k} \quad (24)$$

Nernst potential for the potassium channel (in mV):

$$E_{K_k} = \frac{R_g T}{z_K F} \ln \left( \frac{K_s}{K_k} \right) \quad (25)$$

Nernst potential for the sodium channel (in mV):

$$E_{Na_k} = \frac{R_g T}{z_{Na} F} \ln \left( \frac{Na_s}{Na_k} \right) \quad (26)$$

Nernst potential for the chloride channel (in mV):

$$E_{Cl_k} = \frac{R_g T}{z_{Cl} F} \ln \left( \frac{Cl_s}{Cl_k} \right) \quad (27)$$

Nernst potential for the NBC channel (in mV):

$$E_{NBC_k} = \frac{R_g T}{z_{NBC} F} \ln \left( \frac{Na_s HCO_{3_s}^2}{Na_k HCO_{3_k}^2} \right) \quad (28)$$

Nernst potential for the BK channel (in mV):

$$E_{BK_k} = \frac{R_g T}{z_K F} \ln \left( \frac{K_p}{K_k} \right) \quad (29)$$

Equilibrium state BK-channel (-):

$$w_\infty = 0.5 \left( 1 + \tanh \left( \frac{v_k + v_6}{v_4} \right) \right) \quad (30)$$

Time constant associated with the opening of BK channels (in  $s^{-1}$ ):

$$\phi_w = \psi_w \cosh \left( \frac{v_k + v_6}{2v_4} \right) \quad (31)$$

$gCl_k$	Specific ion conductance of chloride	$0.879 \Omega^{-1}m^{-2}$	[8]
$z_K$	Valence of a potassium ion	1	
$z_{Na}$	Valence of a sodium ion	1	
$z_{Cl}$	Valence of a chloride ion	-1	
$z_{NBC}$	Effective valence of the NBC cotransporter complex	-1	
$v_6$	Voltage associated with the opening of half the population	22 mV	[2]
$v_4$	A measure of the spread of the distribution of the open probability of the BK channel	14.5 mV	[2]
$\psi_w$	A characteristic time for the open probability of the BK channel	$2.664 s^{-1}$	[2]

## 5.2 The Smooth Muscle Cell and Endothelial Cell Model

### Conservation Equations

#### Smooth muscle cell

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

$$\begin{aligned} \frac{d[Ca^{2+}]_i}{dt} = & J_{IP3i} - J_{SR_{uptake_i}} + J_{CICR_i} - J_{extrusion_i} + J_{SR_{leak_i}} \dots \\ & - J_{VOCC_i} + J_{Na/Ca_i} + 0.1 J_{stretch_i} + J_{Ca^{2+}-coupling_i}^{SMC-EC} \end{aligned} \quad (32)$$

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

$$\frac{d[\widehat{Ca}^{2+}]_i}{dt} = J_{SR_{uptake_i}} - J_{CICR_i} - J_{SR_{leak_i}} \quad (33)$$

Membrane potential of the SMC (in mV):

$$\frac{dv_i}{dt} = \gamma_i(-J_{Na/K_i} - J_{Cl_i} - 2J_{VOCc_i} - J_{Na/Ca_i} - J_{K_i} \dots - J_{stretch_i} - J_{KIR_i}) + V_{coupling_i}^{SMC-EC} \quad (34)$$

Open state probability of calcium-activated potassium channels (dim.less):

$$\frac{dw_i}{dt} = \lambda_i (K_{act_i} - w_i) \quad (35)$$

IP<sub>3</sub> concentration om the SMC (in  $\mu$ M):

$$\frac{d[IP_3]_i}{dt} = J_{IP_3-coupling_i}^{SMC-EC} - J_{degrad_i} \quad (36)$$

K<sup>+</sup> concentration in the SMC (in  $\mu$ M):

$$\frac{d[K_i^+]}{dt} = J_{Na/K_i} - J_{KIR_i} - J_{K_i} \quad (37)$$

$\gamma_i$	Change in membrane potential by a scaling factor	1970 mV $\mu$ M <sup>-1</sup>	[5]
$\lambda_i$	Rate constant for opening	45.0 s <sup>-1</sup>	[5]

## Endothelial cell

Cytosolic Ca<sup>2+</sup> concentration in the EC (in  $\mu$ M):

$$\begin{aligned} \frac{d[Ca^{2+}]_j}{dt} = & J_{IP_3_j} - J_{ER_{uptake_j}} + J_{CICR_j} - J_{extrusion_j} \dots \\ & + J_{ER_{leak_j}} + J_{cation_j} + J_{0_j} + J_{stretch_j} - J_{Ca^{2+}-coupling_j}^{SMC-EC} \end{aligned} \quad (38)$$

Ca<sup>2+</sup> concentration in the ER in the EC (in  $\mu$ M):

$$\frac{d[\widehat{Ca}^{2+}]_j}{dt} = J_{ER_{uptake_j}} - J_{CICR_j} - J_{ER_{leak_j}} \quad (39)$$

Membrane potential of the EC (in mV):

$$\frac{dv_j}{dt} = -\frac{1}{C_{m_j}}(J_{K_j} + J_{R_j}) + V_{coupling_j}^{SMC-EC} \quad (40)$$

IP<sub>3</sub> concentration of the EC (in  $\mu$ M):

$$\frac{d[IP_3]_j}{dt} = J_{EC,IP_3} - J_{degrad_j} - J_{IP_3-coupling_j}^{SMC-EC} \quad (41)$$



$C_{m_j}$	Membrane capacitance	25.8 pF	[5]
$J_{PLC}$	PLC / $IP_3$ production rate	0.18 or 0.4 $\mu\text{M s}^{-1}$	[5]
$J_{0_j}$	Constant $Ca^{2+}$ leak term (influx)	0.029 $\mu\text{M s}^{-1}$	[5]

## Fluxes

### Smooth muscle cell

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

$$J_{IP_{3i}} = F_i \frac{[IP_3]_i^2}{K_{ri}^2 + [IP_3]_i^2} \quad (42)$$

$F_i$	Maximal rate of activation-dependent calcium influx	0.23 $\mu\text{M s}^{-1}$	[5]
$K_{ri}$	Half-saturation constant for agonist-dependent calcium entry	1 $\mu\text{M}$	[5]

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

$$J_{SR_{uptake_i}} = B_i \frac{[Ca^{2+}]_i^2}{c_{bi}^2 + [Ca^{2+}]_i^2} \quad (43)$$

$B_i$	SR uptake rate constant	2.025 $\mu\text{M s}^{-1}$	[5]
$c_{bi}$	Half-point of the SR ATPase activation sigmoidal	1.0 $\mu\text{M}$	[5]

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

$$J_{CICR_i} = C_i \frac{[\widehat{Ca}^{2+}]_i^2}{s_{ci}^2 + [\widehat{Ca}^{2+}]_i^2} \frac{[Ca^{2+}]_i^4}{c_{ci}^4 + [Ca^{2+}]_i^4} \quad (44)$$

$C_i$	CICR rate constant	55 $\mu\text{M s}^{-1}$	[5]
$s_{ci}$	Half-point of the CICR $Ca^{2+}$ efflux sigmoidal	2.0 $\mu\text{M}$	[5]
$c_{ci}$	Half-point of the CICR activation sigmoidal	0.9 $\mu\text{M}$	[5]

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

$$J_{extrusion_i} = D_i [Ca^{2+}]_i \left( 1 + \frac{v_i - v_d}{R_{di}} \right) \quad (45)$$

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

$$J_{SR_{leak_i}} = L_i [\widehat{Ca}^{2+}]_i \quad (46)$$

$D_i$	Rate constant for $\text{Ca}^{2+}$ extrusion by the ATPase pump	$0.24 \text{ s}^{-1}$	[5]
$v_d$	Intercept of voltage dependence of extrusion ATPase	-100.0 mV	[5]
$R_{di}$	Slope of voltage dependence of extrusion ATPase.	250.0 mV	[5]
$L_i$	Leak from SR rate constant	$0.025 \text{ s}^{-1}$	[5]

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

$$J_{VOCC_i} = G_{Cai} \frac{v_i - v_{Ca_{1i}}}{1 + \exp(-(v_i - v_{Ca_{2i}}) / R_{Cai})} \quad (47)$$

$G_{Cai}$	Whole-cell conductance for VOCCs	$1.29 \times 10^{-3} \mu\text{M mV}^{-1} \text{s}^{-1}$	[5]
$v_{Ca_{1i}}$	Reversal potential for VOCCs	100.0 mV	[5]
$v_{Ca_{2i}}$	Half-point of the VOCC activation sigmoidal	-24.0 mV	[5]
$R_{Cai}$	Maximum slope of the VOCC activation sigmoidal	8.5 mV	[5]

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

$$J_{\text{Na/Ca}_i} = G_{\text{Na/Ca}_i} \frac{[\text{Ca}^{2+}]_i}{[\text{Ca}^{2+}]_i + c_{\text{Na/Ca}_i}} (v_i - v_{\text{Na/Ca}_i}) \quad (48)$$

$G_{\text{Na/Ca}_i}$	Whole-cell conductance for $\text{Na}^+/\text{Ca}^{2+}$ exchange	$3.16 \times 10^{-3} \mu\text{M mV}^{-1}\text{s}^{-1}$	[5]
$c_{\text{Na/Ca}_i}$	Half-point for activation of $\text{Na}^+/\text{Ca}^{2+}$ exchange by $\text{Ca}^{2+}$	0.5 $\mu\text{M}$	[5]
$v_{\text{Na/Ca}_i}$	Reversal potential for the $\text{Na}^+/\text{Ca}^{2+}$ exchanger	-30.0 mV	[5]

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

$$J_{\text{stretch}_i} = \frac{G_{\text{stretch}}}{1 + \exp\left(-\alpha_{\text{stretch}}\left(\frac{\Delta p R}{h} - \sigma_0\right)\right)} (v_i - E_{\text{SAC}}) \quad (49)$$

$G_{\text{stretch}}$	Whole cell conductance for SACs	$6.1 \times 10^{-3} \mu\text{M mV}^{-1}\text{s}^{-1}$	[5]
$\alpha_{\text{stretch}}$	Slope of stress dependence of the SAC activation sigmoidal	$7.4 \times 10^{-3} \text{mmHg}^{-1}$	[5]
$\Delta p$	Pressure difference	30 mmHg	ME
$\sigma_0$	Half-point of the SAC activation sigmoidal	500 mmHg	[5]
$E_{\text{SAC}}$	Reversal potential for SACs	-18 mV	[5]

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

$$J_{\text{Na/K}_i} = F_{\text{Na/K}_i} \quad (50)$$

$F_{\text{Na/K}_i}$	Rate of the potassium influx by the sodium potassium pump	$4.32 \times 10^{-2} \mu\text{M s}^{-1}$	[5]
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Chloride flux through the chloride channel (in  $\mu\text{M s}^{-1}$ ):

$$J_{\text{Cl}_i} = G_{\text{Cl}_i} (v_i - v_{\text{Cl}_i}) \quad (51)$$

$G_{\text{Cl}_i}$	Whole-cell conductance for $\text{Cl}^-$ current	$1.34 \times 10^{-3} \mu\text{M mV}^{-1}\text{s}^{-1}$	[5]
$v_{\text{Cl}_i}$	Reversal potential for $\text{Cl}^-$ channels.	-25.0 mV	[5]

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

$$J_{\text{K}_i} = G_{\text{K}_i} w_i (v_i - v_{\text{K}_i}) \quad (52)$$

$G_{Ki}$	Whole-cell conductance for $K^+$ efflux.	$4.46 \times 10^{-3} \mu M \text{ mV}^{-1} \text{ s}^{-1}$	[5]
$v_{Ki}$	Nernst potential	-94 mV	[5]
$F_{KIR_i}$	Scaling factor of potassium efflux through the KIR channel	750 mV $\mu M^{-1}$	[2]

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

$$J_{KIR_i} = \frac{F_{KIR_i} g_{KIR_i}}{\gamma_i} (v_i - v_{KIR_i}) \quad (53)$$

IP<sub>3</sub> degradation (in  $\mu M \text{ s}^{-1}$ ):

$$J_{degrad_i} = k_{di} I_i \quad (54)$$

$k_{di}$	Rate constant of IP <sub>3</sub> degradation	0.1 $\text{s}^{-1}$	[5]
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## Endothelial cell

Release of calcium from IP<sub>3</sub>-sensitive stores in the EC (in  $\mu M \text{ s}^{-1}$ ):

$$J_{IP_3j} = F_j \frac{[IP_3]_j^2}{K_{rj}^2 + [IP_3]_j^2} \quad (55)$$

$F_j$	Maximal rate of activation-dependent calcium influx	0.23 $\mu M \text{ s}^{-1}$	[5]
$K_{rj}$	Half-saturation constant for agonist-dependent calcium entry	1 $\mu M$	[5]

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

$$J_{ER_{uptake_j}} = B_j \frac{[Ca^{2+}]_j^2}{c_{bj}^2 + [Ca^{2+}]_j^2} \quad (56)$$

$B_j$	ER uptake rate constant	0.5 $\mu M \text{ s}^{-1}$	[5]
$c_{bj}$	Half-point of the SR ATPase activation sigmoidal	1.0 $\mu M$	[5]

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

$$J_{CICR_j} = C_j \frac{[\widehat{Ca}^{2+}]_j^2}{s_{cj}^2 + [\widehat{Ca}^{2+}]_j^2} \frac{[Ca^{2+}]_j^4}{c_{cj}^4 + [Ca^{2+}]_j^4} \quad (57)$$

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

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

$$J_{extrusion_j} = D_j[Ca^{2+}]_j \quad (58)$$

$D_j$	Rate constant for $\text{Ca}^{2+}$ extrusion by the ATPase pump	$0.24 \text{ s}^{-1}$	[6]
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Calcium flux through the stretch-activated channels in the EC (in  $\mu\text{M s}^{-1}$ ):

$$J_{stretch_j} = \frac{G_{stretch}}{1 + e^{-\alpha_{stretch}(\sigma - \sigma_0)}} (v_j - E_{SAC}) = \frac{G_{stretch}}{1 + e^{-\alpha_{stretch}(\frac{\Delta p R}{h} - \sigma_0)}} (v_j - E_{SAC}) \quad (59)$$

$G_{stretch}$	The whole cell conductance for SACs	$6.1 \times 10^{-3} \mu\text{M mV}^{-1} \text{s}^{-1}$	[5]
$\alpha_{stretch}$	Slope of stress dependence of the SAC activation sigmoidal	$7.4 \times 10^{-3} \text{ mmHg}^{-1}$	[5]
$\Delta p$	Pressure difference	$30 \text{ mmHg}$	ME
$\sigma_0$	Half-point of the SAC activation sigmoidal	$500 \text{ mmHg}$	[5]
$E_{SAC}$	The reversal potential for SACs	$-18 \text{ mV}$	[5]

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

$$J_{ERleak_j} = L_j[\widehat{Ca}^{2+}]_j \quad (60)$$

$L_j$	Rate constant for $\text{Ca}^{2+}$ leak from the ER	$0.025 \text{ s}^{-1}$	[5]
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Calcium influx through nonselective cation channels (in  $\mu\text{M s}^{-1}$ ):

$$J_{cation_j} = G_{cat_j}(E_{Ca_j} - v_j) \frac{1}{2} \left( 1 + \tanh \left( \frac{\log_{10}[Ca^{2+}]_j - m_{3cat_j}}{m_{4cat_j}} \right) \right) \quad (61)$$

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

$$J_{K_j} = G_{tot_j}(v_j - v_{K_j}) (J_{BKCa_j} + J_{SKCa_j}) \quad (62)$$

$G_{catj}$	Whole-cell cation channel conductivity	$6.6 \times 10^{-4} \mu\text{M mV}^{-1}\text{s}^{-1}$	[5]
$E_{Ca_j}$	$\text{Ca}^{2+}$ equilibrium potential	50 mV	[5]
$m_{3catj}$	Model constant	-0.18 $\mu\text{M}$	[5]
$m_{4catj}$	Model constant	0.37 $\mu\text{M}$	[5]
$G_{totj}$	Total potassium channel conductivity.	6927 pS	[5]
$v_{Kj}$	$\text{K}^+$ equilibrium potential	-80.0 mV	[5]

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

$$J_{BK_{Ca_j}} = 0.2 \left( 1 + \tanh \left( \frac{(\log_{10}[Ca^{2+}]_j - c)(v_j - b_j) - a_{1j}}{m_{3bj}(v_j + a_{2j}(\log_{10}[Ca^{2+}]_j - c) - b_j)^2 + m_{4bj}} \right) \right) \quad (63)$$

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

$$J_{SK_{Ca_j}} = 0.3 \left( 1 + \tanh \left( \frac{\log_{10}[Ca^{2+}]_j - m_{3sj}}{m_{4sj}} \right) \right) \quad (64)$$

$c$	Model constant, further explanation see reference	-0.4 $\mu\text{M}$	[5]
$b_j$	Model constant, further explanation see reference	-80.8 mV	[5]
$a_{1j}$	Model constant, further explanation see reference	53.3 $\mu\text{M mV}$	[5]
$a_{2j}$	Model constant, further explanation see reference	53.3 $\text{mV}\mu\text{M}^{-1}$	[5]
$m_{3bj}$	Model constant, further explanation see reference	$1.32 \times 10^{-3} \mu\text{M mV}^{-1}$	[5]
$m_{4bj}$	Model constant, further explanation see reference	0.30 $\mu\text{M mV}$	[5]
$m_{3sj}$	Model constant, further explanation see reference	-0.28 $\mu\text{M}$	[5]
$m_{4sj}$	Model constant, further explanation see reference	0.389 $\mu\text{M}$	[5]

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

$$J_{R_j} = G_{R_j}(v_j - v_{restj}) \quad (65)$$

$G_{R_j}$	Residual current conductivity	955 pS	[5]
$v_{restj}$	Membrane resting potential	-31.1 mV	[5]

$\text{IP}_3$  degradation (in  $\mu\text{M s}^{-1}$ ):

$$J_{degrad_j} = k_{dj}[\text{IP}_3]_j \quad (66)$$

$k_{dj}$	Rate constant of $\text{IP}_3$ degradation	0.1 $\text{s}^{-1}$	[5]
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## Coupling

Heterocellular electrical coupling between SMCs and ECs (in  $\text{mV s}^{-1}$ ):

$$V_{coupling_i}^{SMC-EC} = -G_{coup}(v_i - v_j) \quad (67)$$

Heterocellular  $\text{IP}_3$  coupling between SMCs and ECs (in  $\mu\text{M s}^{-1}$ ):

$$J_{IP_3-coupling_i}^{SMC-EC} = -P_{IP_3}([IP_3]_i - [IP_3]_j) \quad (68)$$

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

$$J_{Ca^{2+}-coupling_i}^{SMC-EC} = -P_{Ca^{2+}}([Ca^{2+}]_i - [Ca^{2+}]_j) \quad (69)$$

$G_{coup}$	Heterocellular electrical coupling coefficient	$0.5 \text{ s}^{-1}$	ME
$P_{IP_3}$	Heterocellular $\text{IP}_3$ coupling coefficient	$0.05 \text{ s}^{-1}$	[5]
$P_{Ca^{2+}}$	Heterocellular $P_{Ca^{2+}}$ coupling coefficient	$0.05 \text{ s}^{-1}$	[5]

## Additional Equations

Equilibrium distribution of open channel states for the voltage and calcium activated potassium channels (dimensionless):

$$K_{act_i} = \frac{([Ca^{2+}]_i + c_{wi})^2}{([Ca^{2+}]_i + c_{wi})^2 + \beta_i \exp(-([v_i - v_{Ca_{3i}}] / R_{Ki}))} \quad (70)$$

Nernst potential of the KIR channel in the SMC (in  $\text{mV}$ ):

$$v_{KIR_i} = z_1 K_p - z_2 \quad (71)$$

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

$$g_{KIR_i} = \exp(z_5 v_i + z_3 K_p - z_4) \quad (72)$$

## 5.3 The Contraction Model

Fraction of free phosphorylated cross-bridges (dimensionless):

$$\frac{d[Mp]}{dt} = K_4[AMp] + K_1[M] - (K_2 + K_3)[Mp] \quad (73)$$

$c_{wi}$	Translation factor for $\text{Ca}^{2+}$ dependence of $\text{K}_{Ca}$ channel activation sigmoidal.	0.0 $\mu\text{M}$	[5]
$\beta_i$	Translation factor for membrane potential dependence of $\text{K}_{Ca}$ channel activation sigmoidal.	0.13 $\mu\text{M}^2$	[5]
$v_{Ca_{3i}}$	Half-point for the $\text{K}_{Ca}$ channel activation sigmoidal.	-27 mV	[5]
$R_{Ki}$	Maximum slope of the $\text{K}_{Ca}$ activation sigmoidal.	12 mV	[5]
$z_1$	Model estimation for membrane voltage KIR channel	$4.5 \times 10^3 \text{ mV} \mu\text{M}^{-1}$	[1]
$z_2$	Model estimation for membrane voltage KIR channel	112 mV	[1]
$z_3$	Model estimation for the KIR channel conductance	$4.2 \times 10^2 \text{ mV}^{-1} \text{s}^{-1}$	[1]
$z_4$	Model estimation for the KIR channel conductance	$12.6 \mu\text{M mV}^{-1} \text{s}^{-1}$	[1]
$z_5$	Model estimation for the KIR channel conductance	$-7.4 \times 10^{-2} \mu\text{M mV}^{-2} \text{s}^{-1}$	[1]

Fraction of attached phosphorylated cross-bridges (dimensionless):

$$\frac{d[AMp]}{dt} = K_3[Mp] + K_6[AM] - (K_4 + K_5)[AMp] \quad (74)$$

Fraction of attached dephosphorylated cross-bridges (dimensionless):

$$\frac{d[AM]}{dt} = K_5[AMp] - (K_7 + K_6)[AM] \quad (75)$$

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

$$[M] = 1 - [AM] - [AMp] - [Mp] \quad (76)$$

Rate constants that represent phosphorylation of M to Mp and of AM to AMp by the active myosin light chain kinase (MLCK), respectively (in  $\text{s}^{-1}$ ):

$$K_1 = K_6 = \gamma_{cross} [Ca^{2+}]_i^{n_{cross}} \quad (77)$$

$K_2$	Rate constant for dephosphorylation (of Mp to M) by myosin light-chain phosphatase (MLCP)	0.5 $\text{s}^{-1}$	[4]
$K_3$	Rate constants representing the attachment/detachment of fast cycling phosphorylated crossbridges	0.4 $\text{s}^{-1}$	[4]
$K_4$	Rate constants representing the attachment/detachment of fast cycling phosphorylated crossbridges	0.1 $\text{s}^{-1}$	[4]
$K_5$	Rate constant for dephosphorylation (of AMp to AM) by myosin light-chain phosphatase (MLCP)	0.5 $\text{s}^{-1}$	[4]
$K_7$	Rate constant for latch-bridge detachment	0.1 $\text{s}^{-1}$	[4]
$\gamma_{cross}$	Sensitivity of the contractile apparatus to calcium	17 $\mu\text{M}^{-3} \text{s}^{-1}$	[6]
$n_{cross}$	Fraction constant of the phosphorylation crossbridge	3 [-]	[6]



## 5.4 The Mechanical Model

Wall thickness of the vessel (in  $\mu\text{m}$ ):

$$h = 0.1R \quad (78)$$

Fraction of attached myosin cross-bridges (dimensionless):

$$F_r = [AM_p] + [AM] \quad (79)$$

Vessel radius (in m):

$$\frac{dR}{dt} = \frac{R_{0_{pas}}}{\eta} \left( \frac{RP_T}{h} - E(F_r) \frac{R - R_0(F_r)}{R_0(F_r)} \right) \quad (80)$$

with:

$$E(F_r) = E_{pas} + F_r (E_{act} - E_{pas}) \quad (81)$$

$$R_0(F_r) = R_{0_{pas}} + F_r(\alpha - 1)R_{0_{pas}} \quad (82)$$

$\eta$	viscosity	$10^4$ Pa s	[5]
$R_{0_{pas}}$	Radius of the vessel when passive and no stress is applied	20 $\mu\text{m}$	ME
$P_T$	Transmural pressure	$4 \times 10^3$ Pa	ME
$E_{pas}$	Young's modulus for the passive vessel	$66 \times 10^3$ Pa	[3]
$E_{act}$	Young's modulus for the active vessel	$233 \times 10^3$ Pa	[3]
$\alpha$	Scaling factor initial radius	0.6	[3]

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