Supplementary Model Details

BrainSignals Revisited:
simplifying a computational model of cerebral physiology
Matthew Caldwell, Tharindi Hapuarachchi, David Highton, Clare Elwell,
Martin Smith, Ilias Tachtsidis

(Model documentation generated by
BCMD module doc_latex.py)
## Contents

1 BrainSignals 7
  1.1 Overview 7
  1.2 Differential Equations 7
  1.3 Algebraic Equations 8
  1.4 Chemical Reactions 8
  1.5 State Variables 8
  1.6 Intermediate Variables 10
  1.7 Parameters 14

2 BSB1 29
  2.1 Overview 29
  2.2 Differential Equations 29
  2.3 Algebraic Equations 30
  2.4 Chemical Reactions 30
  2.5 State Variables 30
  2.6 Intermediate Variables 32
  2.7 Parameters 35

3 BSB2 49
  3.1 Overview 49
  3.2 Differential Equations 49
  3.3 Algebraic Equations 50
  3.4 Chemical Reactions 50
  3.5 State Variables 50
  3.6 Intermediate Variables 52
  3.7 Parameters 55

4 BSB3 69
  4.1 Overview 69
  4.2 Differential Equations 69
  4.3 Algebraic Equations 70
  4.4 Chemical Reactions 70
  4.5 State Variables 70
  4.6 Intermediate Variables 72
  4.7 Parameters 75

5 BSB4 89
  5.1 Overview 89
  5.2 Differential Equations 89
  5.3 Algebraic Equations 90
  5.4 Chemical Reactions 90
  5.5 State Variables 90
  5.6 Intermediate Variables 92
  5.7 Parameters 95

6 BSM0 109
  6.1 Overview 109
  6.2 Differential Equations 109
## Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>6.3</td>
<td>Algebraic Equations</td>
<td>110</td>
</tr>
<tr>
<td>6.4</td>
<td>Chemical Reactions</td>
<td>110</td>
</tr>
<tr>
<td>6.5</td>
<td>State Variables</td>
<td>110</td>
</tr>
<tr>
<td>6.6</td>
<td>Intermediate Variables</td>
<td>112</td>
</tr>
<tr>
<td>6.7</td>
<td>Parameters</td>
<td>114</td>
</tr>
<tr>
<td>7</td>
<td>BSM1</td>
<td>125</td>
</tr>
<tr>
<td>7.1</td>
<td>Overview</td>
<td>125</td>
</tr>
<tr>
<td>7.2</td>
<td>Differential Equations</td>
<td>125</td>
</tr>
<tr>
<td>7.3</td>
<td>Algebraic Equations</td>
<td>126</td>
</tr>
<tr>
<td>7.4</td>
<td>Chemical Reactions</td>
<td>126</td>
</tr>
<tr>
<td>7.5</td>
<td>State Variables</td>
<td>126</td>
</tr>
<tr>
<td>7.6</td>
<td>Intermediate Variables</td>
<td>128</td>
</tr>
<tr>
<td>7.7</td>
<td>Parameters</td>
<td>130</td>
</tr>
<tr>
<td>8</td>
<td>BSM2</td>
<td>141</td>
</tr>
<tr>
<td>8.1</td>
<td>Overview</td>
<td>141</td>
</tr>
<tr>
<td>8.2</td>
<td>Differential Equations</td>
<td>141</td>
</tr>
<tr>
<td>8.3</td>
<td>Algebraic Equations</td>
<td>142</td>
</tr>
<tr>
<td>8.4</td>
<td>Chemical Reactions</td>
<td>142</td>
</tr>
<tr>
<td>8.5</td>
<td>State Variables</td>
<td>142</td>
</tr>
<tr>
<td>8.6</td>
<td>Intermediate Variables</td>
<td>144</td>
</tr>
<tr>
<td>8.7</td>
<td>Parameters</td>
<td>146</td>
</tr>
<tr>
<td>9</td>
<td>BSM3</td>
<td>157</td>
</tr>
<tr>
<td>9.1</td>
<td>Overview</td>
<td>157</td>
</tr>
<tr>
<td>9.2</td>
<td>Differential Equations</td>
<td>157</td>
</tr>
<tr>
<td>9.3</td>
<td>Algebraic Equations</td>
<td>158</td>
</tr>
<tr>
<td>9.4</td>
<td>Chemical Reactions</td>
<td>158</td>
</tr>
<tr>
<td>9.5</td>
<td>State Variables</td>
<td>158</td>
</tr>
<tr>
<td>9.6</td>
<td>Intermediate Variables</td>
<td>160</td>
</tr>
<tr>
<td>9.7</td>
<td>Parameters</td>
<td>162</td>
</tr>
<tr>
<td>10</td>
<td>B1M1</td>
<td>173</td>
</tr>
<tr>
<td>10.1</td>
<td>Overview</td>
<td>173</td>
</tr>
<tr>
<td>10.2</td>
<td>Differential Equations</td>
<td>173</td>
</tr>
<tr>
<td>10.3</td>
<td>Algebraic Equations</td>
<td>174</td>
</tr>
<tr>
<td>10.4</td>
<td>Chemical Reactions</td>
<td>174</td>
</tr>
<tr>
<td>10.5</td>
<td>State Variables</td>
<td>174</td>
</tr>
<tr>
<td>10.6</td>
<td>Intermediate Variables</td>
<td>176</td>
</tr>
<tr>
<td>10.7</td>
<td>Parameters</td>
<td>178</td>
</tr>
<tr>
<td>11</td>
<td>B1M2</td>
<td>187</td>
</tr>
<tr>
<td>11.1</td>
<td>Overview</td>
<td>187</td>
</tr>
<tr>
<td>11.2</td>
<td>Differential Equations</td>
<td>187</td>
</tr>
<tr>
<td>11.3</td>
<td>Algebraic Equations</td>
<td>188</td>
</tr>
<tr>
<td>11.4</td>
<td>Chemical Reactions</td>
<td>188</td>
</tr>
<tr>
<td>11.5</td>
<td>State Variables</td>
<td>188</td>
</tr>
<tr>
<td>11.6</td>
<td>Intermediate Variables</td>
<td>190</td>
</tr>
<tr>
<td>11.7</td>
<td>Parameters</td>
<td>192</td>
</tr>
<tr>
<td>12</td>
<td>B2M1</td>
<td>201</td>
</tr>
<tr>
<td>12.1</td>
<td>Overview</td>
<td>201</td>
</tr>
<tr>
<td>12.2</td>
<td>Differential Equations</td>
<td>201</td>
</tr>
<tr>
<td>12.3</td>
<td>Algebraic Equations</td>
<td>202</td>
</tr>
<tr>
<td>12.4</td>
<td>Chemical Reactions</td>
<td>202</td>
</tr>
<tr>
<td>12.5</td>
<td>State Variables</td>
<td>202</td>
</tr>
</tbody>
</table>
# Contents

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>12.6 Intermediate Variables</td>
<td>204</td>
</tr>
<tr>
<td>12.7 Parameters</td>
<td>206</td>
</tr>
<tr>
<td>13 B2M2</td>
<td>215</td>
</tr>
<tr>
<td>13.1 Overview</td>
<td>215</td>
</tr>
<tr>
<td>13.2 Differential Equations</td>
<td>215</td>
</tr>
<tr>
<td>13.3 Algebraic Equations</td>
<td>216</td>
</tr>
<tr>
<td>13.4 Chemical Reactions</td>
<td>216</td>
</tr>
<tr>
<td>13.5 State Variables</td>
<td>216</td>
</tr>
<tr>
<td>13.6 Intermediate Variables</td>
<td>218</td>
</tr>
<tr>
<td>13.7 Parameters</td>
<td>220</td>
</tr>
</tbody>
</table>
1 BrainSignals

1.1 Overview

The full BrainSignals model, with a refactored implementation.

- 9 differential state variables
- 3 algebraic state variables
- 40 intermediate variables
- 139 parameters
- 4 declared inputs
- 33 default outputs

1.2 Differential Equations

\[
\frac{dC_{u, A, o}}{dt} = 4f_3 - 4f_1 \tag{1.1}
\]

\[
\frac{da_{3, r}}{dt} = 4f_3 - 4f_3 \tag{1.2}
\]

\[
\frac{d\psi}{dt} = \frac{p_3 f_3 + p_1 f_1 + p_3 f_3 - L}{C_{im}} \tag{1.3}
\]

\[
\frac{dH^+}{dt} = \frac{1}{R_{Hi}} L - \frac{p_3}{R_{Hi}} f_3 - \frac{p_1}{R_{Hi}} f_1 - \frac{p_3}{R_{Hi}} f_3 \tag{1.4}
\]

\[
\frac{dO_2}{dt} = \frac{1}{Vol_{mit}} I_{O_2} - f_3 \tag{1.5}
\]

\[
\frac{d\nu_{CO_2}}{dt} = \frac{1}{\tau_{CO_2}} (P_{aCO_2} - \nu_{CO_2}) \tag{1.6}
\]

\[
\frac{d\nu_{O_2}}{dt} = \frac{1}{\tau_{O_2}} (O_{2,c} - \nu_{O_2}) \tag{1.7}
\]

\[
\frac{d\nu_p}{dt} = \frac{1}{\tau_{\nu}} (P_a - \nu_p) \tag{1.8}
\]
\[
\frac{dv_u}{dt} = \frac{1}{\tau_u} (u - v_u)
\] (1.9)

### 1.3 Algebraic Equations

\[
\phi \left( \frac{S_{c,O_2}}{1 - S_{c,O_2}} \right)^{\frac{1}{\tau_u}} - O_{2,c} = 0
\] (1.10)

\[
T_e + T_m - (P_1 - P_{ic}) \ r = 0
\] (1.11)

\[
CBF \ (HbO_{2,a} - HbO_{2,v}) - J_O = 0
\] (1.12)

### 1.4 Chemical Reactions

\[
L \xrightarrow{L} \frac{1}{R_{Hi}} \ H^+
\] (1.13)

\[
\dot{O}_2 \xrightarrow{\text{Vol}_{mit}} \frac{1}{O_2}
\] (1.14)

\[
\frac{p_3}{R_{Hi}} \ H^+ \xrightarrow{f_3} 4 \ Cu_{A,o} + 4 \ a_{3,r}
\] (1.15)

\[
4 \ Cu_{A,o} + \frac{p_1}{R_{Hi}} \ H^+ \xrightarrow{f_1} 
\] (1.16)

\[
O_2 + 4 \ a_{3,r} + \frac{p_3}{R_{Hi}} \ H^+ \xrightarrow{f_3} 
\] (1.17)

### 1.5 State Variables

\[Cu_{A,o}\]
- Implementation Name: \(a\)
- Units: mM
- Initial value: \(Cu_{A,o,i}\)
  - Concentration of oxidised cytochrome c oxidase.

\[a_{3,r}\]
- Implementation Name: \(br\ed\)
- Units: mM
- Initial value: \(a_{3,r,i}\)
  - Concentration of reduced cytochrome \(a_3\).
1.5 State Variables

\( \psi \)
Implementation Name: \( \psi_{n} \)
Units: mV
Initial value: \( \psi_{n} \)
Mitochondrial inner membrane potential. Varies as charge (in the form of protons) is transferred across the membrane capacitance.

\( H^{+} \)
Implementation Name: \( h \)
Units: mM
Initial value: \( H_{n}^{+} \)
Mitochondrial proton concentration.

\( O_{2} \)
Implementation Name: \( O_{2} \)
Units: mM
Initial value: \( O_{2,n} \)
Mitochondrial oxygen concentration.

\( O_{2,c} \)
Implementation Name: \( O_{2,c} \)
Units: mM
Initial value: \( O_{2,c,n} \)
Capillary oxygen concentration.

\( r \)
Implementation Name: \( r \)
Units: cm
Initial value: \( r_{n} \)
Typical blood vessel radius.

\( v_{CO_{2}} \)
Implementation Name: \( v_{CO_{2},c} \)
Units: mmHg
Initial value: \( v_{CO_{2,n}} \)
Filtered carbon dioxide partial pressure.

\( v_{O_{2}} \)
Implementation Name: \( v_{O_{2},c} \)
Units: mM
Initial value: \( v_{O_{2,n}} \)
Filtered capillary oxygen concentration.

\( v_{P_{a}} \)
Implementation Name: \( v_{P_{a},n} \)
Units: mmHg
Initial value: \( v_{P_{a,n}} \)
Filtered arterial blood pressure.

\( v_{u} \)
Implementation Name: \( v_{u,n} \)
Units: dimensionless
Initial value: \( v_{u,n} \)
Filtered demand.

\( HbO_{2,v} \)
Implementation Name: \( HbO_{2,v,n} \)
Units: mM
Initial value: \( HbO_{2,v,n} \)
Venous concentration of oxygen bound to haemoglobin.
1 BrainSignals

1.6 Intermediate Variables

\[ Cu_{A,r} = \text{CCO}_{\text{tot}} - Cu_{A,o} \]
- Implementation Name: a_{red}
- Units: mM
- Initial value: 0
- Concentration of reduced Cu\(_A\).

\[ a_{3,o} = \text{CCO}_{\text{tot}} - a_{3,r} \]
- Implementation Name: b
- Units: mM
- Initial value: 0
- Concentration of oxidised cytochrome a\(_3\).

\[ C_{0,i} = \frac{10^{-pH_m} - 10^{-pH_m - dPH}}{dPH} \]
- Implementation Name: C_{0i}
- Units: dimensionless
- Initial value: 0
- Natural buffering capacity of protons in mitochondria.

\[ CBF = G (P_a - P_v) \]
- Implementation Name: CBF
- Units: ml\_brain ml\_brain s\(^{-1}\)
- Initial value: CBF
- Cerebral blood flow.

\[ \Delta \text{oxCCO} = \Delta \text{oxCCO}_{\text{off}} + 1000 \text{Vol}_{\text{mit}} \left( Cu_{A,o} - Cu_{A,o,n} \right) \]
- Implementation Name: \text{CCO}
- Units: mM
- Initial value: 0
- Cytochrome c oxidase signal measured by NIRS.

\[ CMRO_2 = f_3 \text{Vol}_{\text{mit}} \]
- Implementation Name: CMRO2
- Units: mM s\(^{-1}\)
- Initial value: 0
- Rate of cerebral oxygen metabolism.

\[ \Delta p = \psi + Z \left( pH_m - pH_o \right) \]
- Implementation Name: \text{dp}
- Units: mV
- Initial value: 0
- Proton motive force across the mitochondrial inner membrane.

\[ \eta = R_P \left( \frac{v_P}{v_{P,n}} - 1 \right) + R_O_2 \left( \frac{v_{O_2}}{v_{O_2,n}} - 1 \right) + R_C O_2 \left( 1 - \frac{v_{CO_2}}{v_{CO_2,n}} \right) + R_u \left( 1 - \frac{v_u}{v_{u,n}} \right) \]
- Implementation Name: eta
- Units: dimensionless
- Initial value: 0
- Merged autoregulation stimulus.

\[ f_1 = k_1 Cu_{A,o} - k_{-1} Cu_{A,r} \]
- Implementation Name: f1
- Units: mM s\(^{-1}\)
- Initial value: 0
- Reaction rate for the reduction of Cu\(_A\).

\[ f_2 = k_2 Cu_{A,r} a_{3,o} - k_{-2} Cu_{A,o} a_{3,r} \]
- Implementation Name: f2
1.6 Intermediate Variables

Units: mM s^{-1}
Initial value: 0
Reaction rate for the reduction of a_3.

\[ f_3 = \frac{k_3 O_2 a_3, \exp \left( -c_3 \left( \Delta p - \Delta p_{30} \right) \right)}{1 + \exp \left( -c_3 \left( \Delta p - \Delta p_{30} \right) \right)} \]
Implementation Name: f3
Units: mM s^{-1}
Initial value: 0
Reaction rate for the reduction of O_2.

\[ G = K_G r^4 \]
Implementation Name: G
Units: ml_{blood} ml_{brain}^{-1} mmHg^{-1} s^{-1}
Initial value: 0
Effective conductance of the whole blood flow compartment.

\[ h = \sqrt{r(r + 2r_0 h_0 + h_0 h_0) - r} \]
Implementation Name: h
Units: cm
Initial value: h_n
Thickness of the blood vessel walls.

\[ HbO_2 = (V_a HbO_{2,a} + V_v HbO_{2,v}) \text{ blood}_{hb} \]
Implementation Name: Hb02
Units: uM
Initial value: 0
Oxygenated haemoglobin signal measured by NIRS.

\[ HbT = (V_a + V_v) Hb_{tot} \text{ blood}_{hb} \]
Implementation Name: HbT
Units: uM
Initial value: 0
Total haemoglobin signal measured by NIRS.

\[ HHb = HbT - HbO_2 \]
Implementation Name: HHb
Units: uM
Initial value: 0
Deoxygenated haemoglobin signal measured by NIRS.

\[ J_{O_2} = f_{min} \left( D_{O_2} \left( O_{2,a} - O_2 \right), CBF HbO_{2,a} \right) \]
Implementation Name: J_02
Units: mM s^{-1}
Initial value: 0
Oxygen flux from blood to tissue.

\[ k_1 = k_{1,0} \exp \left( -c_{k_1} \left( \Delta p - \Delta p_n \right) \right) \]
Implementation Name: k1
Units: s^{-1}
Initial value: 0
Forward reaction rate for the reduction of Cu_A.

\[ k_2 = k_{2,n} \exp \left( -c_{k_2} \left( \Delta p - \Delta p_n \right) \right) \]
Implementation Name: k2
Units: s^{-1}
Initial value: 0
Forward reaction rate for the reduction of a_3.

\[ K_{ef} = 10^{\frac{1}{\gamma} \left( \frac{n_e}{n_o} - \delta_1 \right)} \]
Implementation Name: $K_{eq1}$
Units: dimensionless
Initial value: 0
Equilibrium constant for the Cu$_A$ reduction reaction.

$$K_{eq2} = 10^{-\frac{Z}{1}} (\frac{n^2 H}{T^2})$$

Implementation Name: $K_{eq2}$
Units: dimensionless
Initial value: 0
Equilibrium constant for the a$_3$ reduction reaction.

$$k_{-1} = \frac{k_1}{K_{eq1}}$$
Implementation Name: $k_n1$
Units: s$^{-1}$
Initial value: 0
Reverse reaction rate for the reduction of Cu$_A$.

$$k_{-2} = \frac{k_2}{K_{eq2}}$$
Implementation Name: $k_n2$
Units: s$^{-1}$
Initial value: 0
Reverse reaction rate for the reduction of a$_3$.

$L = L_{CV} + L_{lk}$
Implementation Name: $L$
Units: mM s$^{-1}$
Initial value: 0
Rate of proton return to the mitochondrial matrix.

$$L_{CV} = \frac{C_{in} L_{CV, max} (1 - \exp(-\theta))}{1 + r_{CV} \exp(-\theta)}$$
Implementation Name: $L_{CV}$
Units: mM s$^{-1}$
Initial value: 0
Rate at which protons re-enter the mitochondrial matrix due to ADP phosphorylation.

$L_{lk} = k_{unc} L_{lk0} (\exp(\Delta p k_{lk2}) - 1)$
Implementation Name: $L_{lk}$
Units: mM s$^{-1}$
Initial value: 0
Rate at which protons re-enter the mitochondrial matrix via leak channels.

$$\mu = \frac{\mu_{min} + \mu_{max} \exp(\eta)}{1 + \exp(\eta)}$$
Implementation Name: $\mu$
Units: dimensionless
Initial value: 0
Effective strength of the autoregulation response.

$$pH_m = -\log_{10} \left( \frac{[H^+]}{1000} \right)$$
Implementation Name: $pH_m$
Units: dimensionless
Initial value: 0
Mitochondrial pH.

$$r_{buffi} = \frac{C_{buffi}}{C_{0,j}}$$
Intermediate Variables

Implementation Name: \( r_{\text{buffi}} \)
Units: dimensionless
Initial value: 0
Buffering capacity for protons in mitochondria.

\[ R_{Hi} = r_{\text{buffi}} \]
Implementation Name: \( R_{Hi} \)
Units: dimensionless
Initial value: 0
Relative mitochondrial volume for protons, taking into account buffering effect of pH.

\[ S_{c,O_2} = \frac{S_{a,O_2} + S_{v,O_2}}{2} \]
Implementation Name: \( ScO2 \)
Units: dimensionless
Initial value: \( S_{c,O_2,n} \)
Capillary oxygen saturation.

\[ \sigma_e = \sigma_{e,0} \left( \exp \left( \frac{K_e (r - r_0)}{r_0} \right) - 1 \right) - \sigma_{\text{coll}} \]
Implementation Name: \( \text{sigma}_e \)
Units: mm Hg
Initial value: 0
Elastic stress in blood vessel walls.

\[ S_{v,O_2} = \frac{HbO_2,v}{Hb_{\text{tot}}} \]
Implementation Name: \( SvO2 \)
Units: dimensionless
Initial value: \( S_{v,O_2,n} \)
Venous oxygen saturation.

\[ T_{e} = \sigma_e h \]
Implementation Name: \( T_e \)
Units: mm Hg cm
Initial value: 0
Elastic tension in the blood vessel walls.

\[ T_m = T_{\text{max}} \exp \left( \text{pow} \left( \text{fabs} \left( \frac{r - r_m}{r_1 - r_m} \right), n_m \right) \right) \]
Implementation Name: \( T_m \)
Units: mm Hg cm
Initial value: 0
Muscular tension in the blood vessel walls.

\[ T_{\text{max}} = T_{\text{max},0} (1 + k_{\text{aut}} \mu) \]
Implementation Name: \( T_{\text{max}} \)
Units: mm Hg cm
Initial value: 0
Maximal muscular tension in the blood vessel walls.

\[ \theta = k_{CV} (\Delta p + Z \log_{10} (u) - \Delta p_{CV,0}) \]
Implementation Name: \( \theta \)
Units: dimensionless
Initial value: 0
Driving force Complex V.

\[ TOI = \frac{100HbO_2}{HbT} \]
Implementation Name: \( TOI \)
Units: dimensionless
1 BrainSignals

Initial value: 0
Total oxygenation index.

\[ V_{\text{mca}} = CBF \cdot CBFscale \]
Implementation Name: \( V_{\text{mca}} \)
Units: cm s\(^{-1}\)
Initial value: 0
Blood velocity in the middle cerebral artery.

\[ V_a = V_{a,n} \left( \frac{r}{r_n} \right)^2 \]
Implementation Name: \( V_{\text{ol}_\text{art}} \)
Units: dimensionless
Initial value: 0
Relative arterial blood volume.

1.7 Parameters

\( C_{u,a,\text{frac},n} \)
Implementation Name: \( a_{\text{frac},n} \)
Units: dimensionless
Initial value: 0.8
Normal oxidised fraction of \( C_uA \).

\( C_{u,A,\rho,n} \)
Implementation Name: \( a_{\rho,n} \)
Units: mM
Initial value: \( CCO_{\text{tot}} \cdot C_{u,a,\text{frac},n} \)
Normal concentration of oxidised cytochrome c oxidase.

\( C_{u,A,\text{red},n} \)
Implementation Name: \( a_{\text{red},n} \)
Units: mM
Initial value: \( CCO_{\text{tot}} - C_{u,A,\rho,n} \)
Normal concentration of reduced \( CuA \).

\( a_{3,\rho,n} \)
Implementation Name: \( b_{\rho,n} \)
Units: mM
Initial value: \( CCO_{\text{tot}} - a_{3,\text{red},n} \)
Normal concentration of oxidised cytochrome a3.

\( \text{blood}_{\text{hb}} \)
Implementation Name: \( \text{blood}_{\text{hb}} \)
Units: dimensionless
Initial value: 10.00
Factor to convert model haemoglobin concentration to instrumental units. Scales for blood fraction of brain volume, mM to \( \mu M \), and number of binding sites.

\( a_{3,\text{red},n} \)
Implementation Name: \( b_{\text{red},n} \)
Units: mM
Initial value: \[ \frac{f_n}{\gamma_{3,n}} \left[ \frac{1}{1+\exp(-c_3(\Delta p_n-\Delta p_{30}))} \right] \]
Normal concentration of reduced cytochrome a3.
1.7 Parameters

\( c_3 \)
Implementation Name: c3
Units: mV\(^{-1}\)
Initial value: 0.11
Parameter controlling the sensitivity of the reduction of \( a_3 \) to \( \Delta p \).

\( C_{buffi} \)
Implementation Name: C_buffi
Units: dimensionless
Initial value: 0.022
Buffering capacity of protons in mitochondria.

\( C_{im} \)
Implementation Name: C_im
Units: mM mV\(^{-1}\)
Initial value: 0.00675
Capacitance of the mitochondrial inner membrane.

\[ C_{NADH} = \frac{Z}{2} \log_{10} \left( \frac{1}{\frac{NAD}{NADH}} \right) \]
Implementation Name: C_NADH
Units: mV
Initial value: 0
Excess redox potential for NADH at normal demand.

\[ C_{NADH,n} = \frac{Z}{2} \log_{10} \left( \frac{1}{\frac{NAD_n}{NADH_n}} \right) \]
Implementation Name: C_NADH_n
Units: mV
Initial value: 0
Normal value of \( C_{NADH} \).

\( CBF_n \)
Implementation Name: CBFn
Units: ml\(_{\text{blood}}\) ml\(_{\text{brain}}\) s\(^{-1}\)
Initial value: 0.0125
Normal cerebral blood flow.

\( CBFscale \)
Implementation Name: CBFscale
Units: cm
Initial value: 5000
Scale constant relating blood flow to arterial velocity.

\( \Delta oxCCO_{off} \)
Implementation Name: CCO_offset
Units: uM
Initial value: 0
Signal offset for the NIRS CCO measurement.

\( c_{k1} \)
Implementation Name: ck1
Units: mV\(^{-1}\)
Initial value: 0.01
Parameter controlling sensitivity of \( k_1 \) to \( \Delta p \).

\( c_{k2} \)
Implementation Name: ck2
Units: mV\(^{-1}\)
1 BrainSignals

Initial value: 0.02
Parameter controlling sensitivity of $k_2$ to $\Delta p$.

**CMRO$_{2,n}$**
- Implementation Name: CMRO$_{2,n}$
- Units: mM s$^{-1}$
- Initial value: 0.034
- Normal metabolic rate of oxygen consumption.

**CV$_{inh}$**
- Implementation Name: CV$_{inh}$
- Units: dimensionless
- Initial value: 1
- Control parameter representing the action of Complex V inhibitors.

**CCO$_{tot}$**
- Implementation Name: cytox$_{tot}$
- Units: mM
- Initial value: 0
- Concentration of cytochrome c oxidase in mitochondria.

**CCO$_{tis}$**
- Implementation Name: cytox$_{tis}$
- Units: mM
- Initial value: 0.0055
- Concentration of cytochrome c oxidase in tissue.

**D$_{NADH}$**
- Implementation Name: D$_{NADH}$
- Units: dimensionless
- Initial value: 0.01
- Scale parameter for the dependence of NADH redox potential on demand.

**D$_{O_2}$**
- Implementation Name: D$_{O_2}$
- Units: s$^{-1}$
- Initial value: $\frac{I_{O_2,n}}{O_{2,t,n} - O_{2,n}}$
- Diffusion rate for oxygen between capillaries and mitochondria.

**$\Delta p_{3,corr}$**
- Implementation Name: dp$_{3,corr}$
- Units: mV
- Initial value: $-25$
- Difference between $\Delta p_{30}$ and normal $\Delta p$.

$\Delta p_{30} = \Delta p_n + \Delta p_{3,corr}$
- Implementation Name: dp$_{30}$
- Units: mV
- Initial value: 0
- Value of $\Delta p$ at which $a_3$ reduction reaction is maximally sensitive.

**$\Delta p_{CV,0}$**
- Implementation Name: dp$_{CV0}$
- Units: mV
- Initial value: 90
- Value of $\Delta p$ at which $L_{CV}$ is zero under normal demand.

**$\Delta p_n$**
- Implementation Name: dp$_n$
1.7 Parameters

Units: mV
Initial value: $\psi_n + Z \Delta pH_n$
Normal value of $\Delta p$

$dpH$
Implementation Name: dpH
Units: dimensionless
Initial value: 0.001
Parameter in the mitochondrial proton buffering relationship.

$\Delta pH_n$
Implementation Name: dPh_n
Units: dimensionless
Initial value: $pHm,n - pHo,n$
Normal pH difference across the mitochondrial inner membrane.

$\psi_n$
Implementation Name: dpsi_n
Units: mV
Initial value: 145
Normal mitochondrial inner membrane potential.

$E_{1,NADH} = \varepsilon_0(Cu_A) - \varepsilon_0(NADH) + C_{NADH}$
Implementation Name: E1NADH
Units: mV
Initial value: 0
Value of $E_1$ when the reducing substrate is NADH.

$E_{1,NADH,n}$
Implementation Name: E1NADH_n
Units: mV
Initial value: $\varepsilon_0(Cu_A) - \varepsilon_0(NADH) + C_{NADH,n}$
Normal value of $E_{1,NADH}$.

$E_1$
Implementation Name: E_1
Units: mV
Initial value: $E_{1,NADH}$
The energy provided by electron transfer to $Cu_{A,r}$.

$E_{1,n}$
Implementation Name: E_1n
Units: mV
Initial value: $E_{1,NADH,n}$
Normal value of $E_1$.

$E_2$
Implementation Name: E_2
Units: mV
Initial value: $\varepsilon_0(a_3) - \varepsilon_0(Cu_A)$
Energy provided by the transfer of four electrons from $Cu_{A,r}$ to $a_{3,o}$.

$\varepsilon_0(a_3)$
Implementation Name: E_a30
Units: mV
Initial value: 350
Standard redox potential for cytochrome $a_3$.

$\varepsilon_0(Cu_A)$
Implementation Name: E_c0
Units: mV
1 BrainSignals

Initial value: 247
Standard redox potential for Cu_A.

\( E_0(\text{NADH}) \)
Implementation Name: \( E_{\text{N0}} \)
Units: mV
Initial value: \(-320\)
Standard redox potential for NADH.

\( f_n \)
Implementation Name: \( f_{\text{N}} \)
Units: mM s\(^{-1}\)
Initial value: \( \frac{\text{CMRO}_{2,n}}{\text{Vol}_{\text{mit}}} \)
Normal resting value of \( f_1 \) and \( f_2 \).

\( G_n \)
Implementation Name: \( G_{\text{N}} \)
Units: ml_{\text{blood}} ml_{\text{brain}} mmHg\(^{-1}\) s\(^{-1}\)
Initial value: \( P_{a,n} - P_{c,n} \)
Normal blood vessel conductance.

\( h_0 \)
Implementation Name: \( h_{\text{0}} \)
Units: cm
Initial value: 0.003
Thickness of the blood vessel walls at which radius is \( r_0 \).

\( H^+_n \)
Implementation Name: \( h_{\text{N}} \)
Units: mM
Initial value: \( 10^{3-pH_{n,n}} \)
Normal mitochondrial proton concentration.

\( h_n \)
Implementation Name: \( h_{n} \)
Units: cm
Initial value: \( \sqrt{r_n r_n + 2r_0 h_0 + h_0 h_0} - r_n \)
Normal thickness of the blood vessel walls.

\( J_{O_2,n} \)
Implementation Name: \( J_{\text{O2,n}} \)
Units: mM s\(^{-1}\)
Initial value: \( \text{CMRO}_{2,n} \)
Normal oxygen flux from blood to tissue.

\( k_{1,0} \)
Implementation Name: \( k10 \)
Units: s\(^{-1}\)
Initial value: \( \frac{k_{1,n} \text{NADH}}{\text{NADH}_p} \)
Forward reaction rate for the reduction of Cu_A at normal \( \Delta p \).

\( k_{1,n} \)
Implementation Name: \( k_{1,n} \)
Units: s\(^{-1}\)
Initial value: \( \frac{f_n}{C u_{A,o,n} - \frac{1}{k_{1,n}} C u_{A,r,n}} \)
Forward reaction rate for the reduction of Cu_A at normal \( \Delta p \) and NADH.
1.7 Parameters

$k_{2,n}$
Implementation Name: $k_{2,n}$
Units: s$^{-1}$
Initial value: $f_n \frac{C_{u_{A,r,n}} a_{3,o,n}}{K_{eq_{2,n}} C_{u_{A,r,n}} a_{3,r,n}}$
Normal forward reaction rate for the reduction of $a_3$.

$k_3 = \frac{k_{3,0}}{1 + \exp(-c_3 - \Delta p_{30})}$
Implementation Name: $k_3$
Units: s$^{-1}$
Initial value: 0
Forward reaction rate for the reduction of $O_2$.

$k_{3,0}$
Implementation Name: $k_{3,0}$
Units: s$^{-1}$
Initial value: 2.5$E+5$
Apparent second order rate constant for reduction of $O_2$ at zero $\Delta p$.

$k_{au}$
Implementation Name: $k_{au}$
Units: dimensionless
Initial value: 1
Overall functioning of autoregulatory response.

$K_G$
Implementation Name: $K_G$
Units: ml$_{blood}$ ml$^{-1}$ mmHg$^{-1}$ cm$^{-4}$
Initial value: $G_n \frac{\text{pow}(r_n, 4)}{\text{pow}}$
Proportionality constant in Poiseuille relation for conductance.

$k_{lk2}$
Implementation Name: $k_{lk2}$
Units: mV$^{-1}$
Initial value: 0.038
Constant controlling the depending of the leak rate $L_{lk}$ on $\Delta p$.

$K_\sigma$
Implementation Name: $K_\sigma$
Units: dimensionless
Initial value: 10
Parameter controlling the sensitivity of $\sigma_e$ to vessel radius.

$k_{unc}$
Implementation Name: $k_{unc}$
Units: dimensionless
Initial value: 1
Control parameter simulating the effect of adding uncouplers to the system.

$k_{CV} = -\frac{1}{\Delta p_n - \Delta p_{CV,0}} \log \left( \frac{1 - L_{CV,0}}{1 + r_{CV} L_{CV,0}} \right)$
Implementation Name: $k_{CV}$
Units: mV$^{-1}$
Initial value: 0
Parameter controlling the sensitivity of Complex V flux to driving force.

$K_{eq_{1,n}}$
Implementation Name: $K_{eq_{1,n}}$
1 BrainSignals

Units: dimensionless
Initial value: $10^{-\frac{Z(pish_{\text{im}}) - E_{\text{im}})}{Z(pish_{\text{im}}) - E_{\text{im}}}}$

Normal value of the equilibrium constant for the Cu

Implementation Name: $K_{\text{eq2, n}}$
Units: dimensionless
Initial value: $10^{-\frac{Z(pish_{\text{im}}) - E_{\text{im}})}{Z(pish_{\text{im}}) - E_{\text{im}}}}$

Normal value of the equilibrium constant for the a

Implementation Name: $L_{\text{CV0}}$
Units: dimensionless
Initial value: 0.4

Normal Complex V flux as a fraction of maximum possible flux.

$L_{\text{CV, frac}} = 1 - L_{\text{lk, frac}}$
Implementation Name: $L_{\text{CVfrac}}$
Units: dimensionless
Initial value: 0

Normal fraction of proton entry into mitochondria which is due to ADP phosphorylation.

$L_{\text{CV, max}} = \frac{L_{\text{CV, n}}}{L_{\text{CV0}}}$
Implementation Name: $L_{\text{CVmax}}$
Units: mM s$^{-1}$

The maximum rate of proton flow through Complex V.

Implementation Name: $L_{\text{CVn}}$
Units: mM s$^{-1}$
Initia

The resting flow of protons into the matrix through Complex V.

Implementation Name: $L_{\text{lk0}}$
Units: mM s$^{-1}$
Initial value: $L_{\text{lk0}}$

Constant controlling the depending of the leak rate $L_{\text{lk}}$ on $\Delta p$.

Implementation Name: $L_{\text{lk, frac}}$
Units: dimensionless
Initial value: 0.25

Normal fraction of proton entry into mitochondria which is via leak channels.

Implementation Name: $L_{\text{lk, n}}$
Units: mM s$^{-1}$
Initial value: $L_{\text{lk, n}}$

The resting flow of protons into the matrix via leak channels.

Implementation Name: $L_{n}$
Units: mM s$^{-1}$
Initial value: 0

The normal total flow of protons back into mitochondria.
1.7 Parameters

\(\mu_{\text{max}}\)
- Implementation Name: mu_max
- Units: dimensionless
- Initial value: 1
- Upper bound for the transformed stimulus \(\mu\).

\(\mu_{\text{min}}\)
- Implementation Name: mu_min
- Units: dimensionless
- Initial value: \(-1\)
- Lower bound for the transformed stimulus \(\mu\).

\(\mu_n\)
- Implementation Name: mu_n
- Units: dimensionless
- Initial value: 0
- Normal value for the transformed stimulus \(\mu\).

\(n_h\)
- Implementation Name: n_h
- Units: dimensionless
- Initial value: 2.5
- Hill coefficient for oxygen dissociation from haemoglobin.

\(n_m\)
- Implementation Name: n_m
- Units: dimensionless
- Initial value: 1.83
- Exponent in the muscular tension relationship.

\[
NADH = \frac{NAD_{\text{pool}}}{1 + \frac{NAD}{NADH_{\text{n}}}}
\]
- Implementation Name: NADH
- Units: mM
- Initial value: 0
- Concentration of NADH in the mitochondria.

\(NADH_n\)
- Implementation Name: NADHn
- Units: mM
- Initial value: \(\frac{NAD_{\text{pool}}}{1 + \frac{NAD}{NADH_{\text{n}}}}\)
- Normal concentration of NADH in the mitochondria.

\(NAD^{\text{n}} \text{/ NADH}^{\text{n}}\)
- Implementation Name: NADNADHrat
- Units: dimensionless
- Initial value: \(\frac{NAD_{\text{pool}}}{NADH_{\text{n}} \text{ pow}(\mu, 2D_{\text{NADH}})}\)
- NAD/NADH ratio.

\(NAD_{\text{n}} \text{/ NADH}\)
- Implementation Name: NADNADHratn
- Units: dimensionless
- Initial value: 9
- Normal NAD/NADH ratio.

\(NAD_{\text{pool}}\)
- Implementation Name: NADpool
- Units: dimensionless
1 BrainSignals

Initial value: 3
Relative size of the NAD pool, used to estimate normal mitochondrial NADH.

$O_{2,n}$
Implementation Name: 02_n
Units: mM
Initial value: 0.024
Normal mitochondrial oxygen concentration.

$O_{2,c,n}$
Implementation Name: 02c_n
Units: mM
Initial value: $\phi \text{ pow} \left( \frac{S_c,O_{2,n}}{1 - S_c,O_{2,n}} \cdot n_h \right)$
Normal capillary oxygen concentration.

$p_1 = p_{tot} - p_{23}$
Implementation Name: p1
Units: dimensionless
Initial value: 0
Proton cost of the reaction reducing Cu_A.

$p_3$
Implementation Name: p2
Units: dimensionless
Initial value: 4
Proton cost of the reaction reducing a_3.

$p_{23}$
Implementation Name: p23
Units: dimensionless
Initial value: 8
Total protons removed from the mitochondrial matrix by the reductions of a_3 and O_2.

$p_3$
Implementation Name: p3
Units: dimensionless
Initial value: $p_{23} - p_3$
Proton cost of the reaction reducing O_2.

$p_1 = \frac{P_a + P_v}{2}$
Implementation Name: P_1
Units: mm Hg
Initial value: $P_{1,n}$
Average pressure in the blood vessels.

$P_{1,n}$
Implementation Name: P_1n
Units: mm Hg
Initial value: $\frac{P_{a,n} + P_{v,n}}{2}$
Normal value for the average pressure in the blood vessels.

$P_a$
Implementation Name: P_a
Units: mmHg
Initial value: $P_{a,n}$
Mean arterial blood pressure.

$P_{a,n}$
Implementation Name: P_an
1.7 Parameters

Units: mmHg
Initial value: 100
Normal arterial blood pressure.

\[ p_{C1} \]
Implementation Name: \( p_{C1} \)
Units: dimensionless
Initial value: 8
Protons pumped by Complex I.

\[ p_{C3} \]
Implementation Name: \( p_{C3} \)
Units: dimensionless
Initial value: 4
Protons pumped by Complex III.

\[ P_{ic} \]
Implementation Name: \( P_{ic} \)
Units: mm Hg
Initial value: 9.5
Intracranial pressure.

\[ P_{icn} \]
Implementation Name: \( P_{icn} \)
Units: mm Hg
Initial value: 9.5
Normal intracranial pressure.

\[ P_{tot} \]
Implementation Name: \( P_{tot} \)
Units: dimensionless
Initial value: \( P_{tot,NADH} \)
Total protons removed from the mitochondrial matrix by the three modelled electron transport reactions.

\[ P_{tot,NADH} = p_{C1} + p_{C3} + p_{23} \]
Implementation Name: \( P_{tot,NADH} \)
Units: dimensionless
Initial value: 0
Total protons pumped when the reducing agent is NADH.

\[ P_v \]
Implementation Name: \( P_v \)
Units: mmHg
Initial value: \( P_{vn} \)
Venous blood pressure.

\[ P_{vn} \]
Implementation Name: \( P_vn \)
Units: mmHg
Initial value: 4
Normal venous blood pressure.

\[ P_{aCO_2} \]
Implementation Name: \( P_{aCO_2} \)
Units: mmHg
Initial value: \( P_{aCO_2,n} \)
Arterial partial pressure of carbon dioxide.

\[ P_{aCO_2,n} \]
Implementation Name: \( P_{aCO_2n} \)
1 BrainSignals

Units: mmHg
Initial value: 40
Normal arterial partial pressure of carbon dioxide.

\( pH_{in} \)
- Implementation Name: \( pH_{mn} \)
- Units: dimensionless
- Initial value: 7.4
- Normal mitochondrial pH.

\( pH_o \)
- Implementation Name: \( pH_{on} \)
- Units: dimensionless
- Initial value: 7
- Extra-mitochondrial pH.

\( pH_{on} \)
- Implementation Name: \( pH_{on} \)
- Units: dimensionless
- Initial value: 7
- Normal extra-mitochondrial pH.

\( \phi \)
- Implementation Name: \( \phi_{l} \)
- Units: mM
- Initial value: 0.036
- Oxygen concentration at half-maximal saturation.

\( r_0 \)
- Implementation Name: \( r_{0} \)
- Units: cm
- Initial value: 0.0126
- Radius in the elastic tension relationship.

\( R_{CO_2} \)
- Implementation Name: \( R_{autc} \)
- Units: dimensionless
- Initial value: 2.2
- Autoregulatory reactivity to carbon dioxide.

\( R_{O_2} \)
- Implementation Name: \( R_{auto} \)
- Units: dimensionless
- Initial value: 1.5
- Autoregulatory reactivity to oxygen.

\( R_P \)
- Implementation Name: \( R_{autp} \)
- Units: dimensionless
- Initial value: 4
- Autoregulatory reactivity to blood pressure.

\( R_u \)
- Implementation Name: \( R_{autu} \)
- Units: dimensionless
- Initial value: 0.5
- Autoregulatory reactivity to demand.

\( r_{CV} \)
- Implementation Name: \( r_{CV} \)
- Units: dimensionless
1.7 Parameters

Initial value: 5
Parameter controlling the ratio of maximal to minimal rates of oxidative phosphorylation.

$r_m$
Implementation Name: $r_m$
Units: cm
Initial value: 0.027
Vessel radius at which muscular tension is maximal.

$r_n$
Implementation Name: $r_n$
Units: cm
Initial value: 0.0187
Normal blood vessel radius. Normal effective blood vessel radius.

$r_l$
Implementation Name: $r_l$
Units: cm
Initial value: 0.018
Radius in the muscular tension relationship.

$S_{a,O_2,n}$
Implementation Name: $SaO_2_n$
Units: dimensionless
Initial value: 0.96
Normal arterial oxygen saturation.

$S_{a,O_2}$
Implementation Name: $SaO_2$
Units: dimensionless
Initial value: $S_{a,O_2,n}$
Arterial oxygen saturation.

$S_{c,O_2,n}$
Implementation Name: $ScO_2_n$
Units: dimensionless
Initial value: $S_{a,O_2,n} + S_{v,O_2,n}$
Normal capillary oxygen saturation.

$\sigma_{coll}$
Implementation Name: $sigma_coll$
Units: mm Hg
Initial value: 62.79
Pressure at which blood vessels collapse.

$\sigma_{e,0}$
Implementation Name: $sigma_e0$
Units: mm Hg
Initial value: 0.1425
Parameter in the elastic tension relationship.

$\sigma_{e,n}$
Implementation Name: $sigma_en$
Units: mm Hg
Initial value: $\sigma_{e,0} \left( \exp \left( \frac{K_e (r_n - r_0)}{r_0} \right) - 1 \right) - \sigma_{coll}$
Normal elastic stress in blood vessel walls.

$S_{v,O_2,n}$
Implementation Name: $SvO_2_n$
1 BrainSignals

Units: dimensionless
Initial value: \( \frac{HbO_{2,p,N}}{Hb_{tot,N}} \)
Normal venous oxygen saturation.

\( t \)
Implementation Name: \( t \)
Units: s
Initial value: 0
Time over which the system evolves.

\( \tau_{CO_2} \)
Implementation Name: \( t_{c,c} \)
Units: s
Initial value: 5
Filter time constant for stimulus effect of carbon dioxide.

\( T_{r,n} \)
Implementation Name: \( T_{en} \)
Units: mm Hg cm
Initial value: \( \sigma_{r,n} h_n \)
Normal elastic tension in the blood vessel walls.

\( T_{max,0} \)
Implementation Name: \( T_{max0} \)
Units: mm Hg cm
Initial value: \( \frac{T_{max,n}}{1 + k_{aut} \mu_n} \)
Maximal muscular tension under normal regulatory stimulus (\( \mu = \mu_n \)).

\( T_{max,n} \)
Implementation Name: \( T_{maxn} \)
Units: mm Hg cm
Initial value: \( T_{m,n} \exp \left( - \text{pow} (\text{fabs} (r_n-r_{m,m}), n_{m}) \right) \)
Normal maximal muscular tension.

\( T_{m,n} \)
Implementation Name: \( T_{mn} \)
Units: mm Hg cm
Initial value: \( (P_{1,n} - P_{icn}) r_n - T_{r,n} \)
Normal muscular tension in the blood vessel walls.

\( \tau_{O_2} \)
Implementation Name: \( t_{o,o} \)
Units: s
Initial value: 20
Filter time constant for stimulus effect of capillary oxygen.

\( \tau_{p_a} \)
Implementation Name: \( t_{p,p} \)
Units: s
Initial value: 5
Filter time constant for stimulus effect of blood pressure.

\( \tau_{u} \)
Implementation Name: \( t_{u,u} \)
Units: s
Initial value: 0.5
Filter time constant for stimulus effect of demand.
1.7 Parameters

\( \mu \)
Implementation Name: \( \mu \)
Units: dimensionless
Initial value: \( \mu_n \)
Parameter indicating metabolic demand.

\( \mu_n \)
Implementation Name: \( \mu_n \)
Units: dimensionless
Initial value: 1
Normal demand.

\( v_{\text{CO}_2,n} \)
Implementation Name: \( v_{\text{CO}_2,n} \)
Units: mmHg
Initial value: \( P_{\text{CO}_2,n} \)
Normal filtered carbon dioxide partial pressure. Normal filtered carbon dioxide partial pressure.

\( v_{\text{O}_2,n} \)
Implementation Name: \( v_{\text{O}_2,n} \)
Units: mM
Initial value: \( O_{\text{2},n} \)
Normal filtered capillary oxygen concentration. Normal filtered capillary oxygen concentration.

\( v_{\text{P}_a,n} \)
Implementation Name: \( v_{\text{P}_a,n} \)
Units: mmHg
Initial value: \( P_{\text{a,n}} \)
Normal filtered arterial blood pressure. Normal filtered blood pressure.

\( v_{\text{u,n}} \)
Implementation Name: \( v_{\text{u,n}} \)
Units: dimensionless
Initial value: \( u_n \)
Normal filtered demand. Normal filtered demand.

\( V_{\text{Arat}_n} \)
Implementation Name: \( V_{\text{Arat}_n} \)
Units: dimensionless
Initial value: 3
Normal volume ratio of veins to arteries in brain tissue.

\( V_{\text{a,n}} \)
Implementation Name: \( V_{\text{a,n}} \)
Units: dimensionless
Initial value: \( \frac{1}{1 + V_{\text{Arat}_n}} \)
Normal relative arterial blood volume.

\( V_{\text{mit}} \)
Implementation Name: \( V_{\text{mit}} \)
Units: dimensionless
Initial value: 0.067
Fraction of brain tissue volume that is mitochondria.

\( V_v \)
Implementation Name: \( V_v \)
Units: dimensionless
1 BrainSignals

Initial value: \( \frac{V_{\text{Arat}}}{1 + V_{\text{Arat}}} \)
Relative venous blood volume.

\( HbO_{2,a} = Hb_{\text{tot}} S_{a,O_2} \)
Implementation Name: XOa
Units: mM
Initial value: \( HbO_{2,a,n} \)
Arterial concentration of oxygen bound to haemoglobin.

\( HbO_{2,a,n} \)
Implementation Name: XOan
Units: mM
Initial value: \( Hb_{\text{tot,n}} S_{a,O_2,n} \)
Normal arterial concentration of oxygen bound to haemoglobin.

\( HbO_{2,v,n} \)
Implementation Name: XOvn
Units: mM
Initial value: \( \frac{CBF_n HbO_{2,a,n}}{J_{O_2,n}} \)
Normal venous concentration of oxygen bound to haemoglobin.

\( Hb_{\text{tot}} \)
Implementation Name: Xtot
Units: mM
Initial value: 9.1
Total concentration of haemoglobin \( O_2 \) binding sites in blood (4 times haemoglobin concentration).

\( Hb_{\text{tot,n}} \)
Implementation Name: Xtotn
Units: mM
Initial value: 9.1
Normal total concentration of haemoglobin \( O_2 \) binding sites in blood (4 times haemoglobin concentration).

\( Z \)
Implementation Name: Z
Units: mV
Initial value: 59.028
Proportionality constant in calculation of driving forces due to concentration differences.
Defined as \( RT / F \), where \( F \) is Faraday’s constant, \( R \) the ideal gas constant and \( T \) the absolute temperature.
2 BSB1

2.1 Overview

Simplified model in which the blood flow submodel is replaced with variant B1.

- 9 differential state variables
- 3 algebraic state variables
- 35 intermediate variables
- 122 parameters
- 4 declared inputs
- 33 default outputs

2.2 Differential Equations

\[
\frac{dC_{u_{A,\theta}}}{dt} = 4f_3 - 4f_1 \quad (2.1)
\]

\[
\frac{da_{3,\theta}}{dt} = 4f_3 - 4f_2 \quad (2.2)
\]

\[
\frac{d\psi}{dt} = \frac{p_3 f_3 + p_1 f_1 + p_3 f_3 - L}{C_{im}} \quad (2.3)
\]

\[
\frac{dH^+}{dt} = \frac{1}{R_{Hi}} L - \frac{p_3}{R_{Hi}} f_3 - \frac{p_1}{R_{Hi}} f_1 - \frac{p_3}{R_{Hi}} f_3 \quad (2.4)
\]

\[
\frac{dO_2}{dt} = \frac{1}{Vol_{mit}} f_{O_2} - f_3 \quad (2.5)
\]

\[
\frac{dv_{CO_2}}{dt} = \frac{1}{\tau_{CO_2}} (p_{aCO_2} - v_{CO_2}) \quad (2.6)
\]

\[
\frac{dv_{O_2}}{dt} = \frac{1}{\tau_{O_2}} (O_{2,c} - v_{O_2}) \quad (2.7)
\]

\[
\frac{dv_P}{dt} = \frac{1}{\tau_P} (P_a - v_P) \quad (2.8)
\]
\[ \frac{d\nu_u}{dt} = \frac{1}{r_u} (u - \nu_u) \]  \hspace{1cm} (2.9)

### 2.3 Algebraic Equations

\[ \phi \left( \frac{S_c,O_2}{1 - S_c,O_2} \right) \frac{1}{\lambda} - O_{2,c} = 0 \]  \hspace{1cm} (2.10)

\[ \lambda_0 + \frac{\lambda p_a}{P_a} + \lambda \mu \frac{\mu}{P_a} - r = 0 \]  \hspace{1cm} (2.11)

\[ CBF (HbO_{2,a} - HbO_{2,v}) - J_{O_2} = 0 \]  \hspace{1cm} (2.12)

### 2.4 Chemical Reactions

\[ \xrightarrow{L} \frac{1}{R_{Hi}} H^+ \]  \hspace{1cm} (2.13)

\[ \xrightarrow{J_{O_2}} \frac{1}{Vol_{mit}} O_2 \]  \hspace{1cm} (2.14)

\[ \frac{p_3}{R_{Hi}} H^+ \xrightarrow{f_3} 4 Cu_{A,o} + 4 a_{3,r} \]  \hspace{1cm} (2.15)

\[ 4 Cu_{A,o} + \frac{p_1}{R_{Hi}} H^+ \xrightarrow{f_1} \]  \hspace{1cm} (2.16)

\[ O_2 + 4 a_{3,r} + \frac{p_3}{R_{Hi}} H^+ \xrightarrow{f_3} \]  \hspace{1cm} (2.17)

### 2.5 State Variables

- **\( Cu_{A,o} \)**
  - Implementation Name: a
  - Units: mM
  - Initial value: \( Cu_{A,o,n} \)
  - Concentration of oxidised cytochrome c oxidase.

- **\( a_{3,r} \)**
  - Implementation Name: bred
  - Units: mM
  - Initial value: \( a_{3,r,n} \)
  - Concentration of reduced cytochrome a3.
2.5 State Variables

\( \psi \)
Implementation Name: \( \psi_{\text{psa1}} \)
Units: mV
Initial value: \( \psi_n \)
Mitochondrial inner membrane potential. Varies as charge (in the form of protons) is transferred across the membrane capacitance.

\( H^+ \)
Implementation Name: \( H \)
Units: mM
Initial value: \( H^+_{\text{n}} \)
Mitochondrial proton concentration.

\( O_2 \)
Implementation Name: \( 02 \)
Units: mM
Initial value: \( O_2_{\text{n}} \)
Mitochondrial oxygen concentration.

\( O_{2,\text{c}} \)
Implementation Name: \( 02\text{c} \)
Units: mM
Initial value: \( O_{2,\text{c,n}} \)
Capillary oxygen concentration.

\( r \)
Implementation Name: \( r \)
Units: cm
Initial value: \( r_n \)
Typical blood vessel radius.

\( v_{\text{CO}_2} \)
Implementation Name: \( v_{-\text{c}} \)
Units: mmHg
Initial value: \( v_{\text{CO}_2,\text{n}} \)
Filtered carbon dioxide partial pressure.

\( v_{\text{O}_2} \)
Implementation Name: \( v_{-\text{o}} \)
Units: mM
Initial value: \( v_{\text{O}_2,\text{n}} \)
Filtered capillary oxygen concentration.

\( v_{\text{Pa}} \)
Implementation Name: \( v_{-\text{p}} \)
Units: mmHg
Initial value: \( v_{\text{Pa},\text{n}} \)
Filtered arterial blood pressure.

\( v_{\text{u}} \)
Implementation Name: \( v_{-\text{u}} \)
Units: dimensionless
Initial value: \( v_{\text{u,n}} \)
Filtered demand.

\( H\text{bO}_2,\text{v} \)
Implementation Name: \( X0v \)
Units: mM
Initial value: \( H\text{bO}_2,\text{v,n} \)
Venous concentration of oxygen bound to haemoglobin.
2.6 Intermediate Variables

$$Cu_{A,r} = CCO_{tot} - Cu_{A,o}$$
Implementation Name: ared
Units: mM
Initial value: 0
Concentration of reduced Cu$_A$.

$$a_{3,o} = CCO_{tot} - a_{3,r}$$
Implementation Name: b
Units: mM
Initial value: 0
Concentration of oxidised cytochrome a$_3$.

$$C_{0,i} = \frac{10^{-pH_m} - 10^{-pH_m-dpH}}{dpH}$$
Implementation Name: C_{0i}
Units: dimensionless
Initial value: 0
Natural buffering capacity of protons in mitochondria.

$$CBF = G (P_a - P_v)$$
Implementation Name: CBF
Units: ml$^{-1}$blood brain ml$^{-1}$brain s$^{-1}$
Initial value: CBF$_{in}$
Cerebral blood flow.

$$\Delta oxCCO = \Delta oxCCO_{off} + 1000 Vol_{mit} (Cu_{A,o} - Cu_{A,o,n})$$
Implementation Name: C00
Units: mM
Initial value: 0
Cytochrome c oxidase signal measured by NIRS.

$$CMRO_2 = f_3 Vol_{mit}$$
Implementation Name: CMRO2
Units: mM s$^{-1}$
Initial value: 0
Rate of cerebral oxygen metabolism.

$$\Delta p = \psi + Z (pH_m - pH_o)$$
Implementation Name: Dp
Units: mV
Initial value: 0
Proton motive force across the mitochondrial inner membrane.

$$\eta = R_{P_a} \left( \frac{V_{P_a}}{V_{P_a,n}} - 1 \right) + R_{O_2} \left( \frac{V_{O_2}}{V_{O_2,n}} - 1 \right) + R_{CO_2} \left( 1 - \frac{V_{CO_2}}{V_{CO_2,n}} \right) + R_u \left( 1 - \frac{V_u}{V_u,n} \right)$$
Implementation Name: eta
Units: dimensionless
Initial value: 0
Merged autoregulation stimulus.

$$f_1 = k_1 Cu_{A,o} - k_{-1} Cu_{A,r}$$
Implementation Name: f1
Units: mM s$^{-1}$
Initial value: 0
Reaction rate for the reduction of Cu$_A$.

$$f_2 = k_2 Cu_{A,r} a_{3,o} - k_{-2} Cu_{A,o} a_{3,r}$$
Implementation Name: f2
2.6 Intermediate Variables

Units: mM s$^{-1}$
Initial value: 0
Reaction rate for the reduction of $a_3$.

\[ f_3 = \frac{k_3 O_2 a_3 r \exp \left( -c_3 (\Delta p - \Delta p_{30}) \right)}{1 + \exp \left( -c_3 (\Delta p - \Delta p_{30}) \right)} \]

Implementation Name: $f_3$
Units: mM s$^{-1}$
Initial value: 0
Reaction rate for the reduction of $O_2$.

\[ G = K_G r^4 \]

Implementation Name: $G$
Units: ml$^{-1}$ blood$^{-1}$ mmHg$^{-1}$ s$^{-1}$
Initial value: 0
Effective conductance of the whole blood flow compartment.

\[ HbO_2 = (V_a HbO_{2,a} + V_v HbO_{2,v}) \text{ blood}_{hb} \]
Implementation Name: Hb02
Units: uM
Initial value: 0
Oxygenated haemoglobin signal measured by NIRS.

\[ HbT = (V_a + V_v) Hb_{tot} \text{ blood}_{hb} \]
Implementation Name: HbT
Units: uM
Initial value: 0
Total haemoglobin signal measured by NIRS.

\[ HHb = HbT - HbO_2 \]
Implementation Name: HhT
Units: uM
Initial value: 0
Deoxygenated haemoglobin signal measured by NIRS.

\[ J_{O_2} = \text{fmin} \left( D_{O_2} (O_2,c - O_2), CBF HbO_{2,a} \right) \]
Implementation Name: $J_{O2}$
Units: mM s$^{-1}$
Initial value: 0
Oxygen flux from blood to tissue.

\[ k_1 = k_{1,0} \exp \left( -c_{k_1} (\Delta p - \Delta p_{n}) \right) \]
Implementation Name: $k1$
Units: s$^{-1}$
Initial value: 0
Forward reaction rate for the reduction of $Cu_A$.

\[ k_2 = k_{2,n} \exp \left( -c_{k_2} (\Delta p - \Delta p_{n}) \right) \]
Implementation Name: $k2$
Units: s$^{-1}$
Initial value: 0
Forward reaction rate for the reduction of $a_3$.

\[ K_{eq1} = 10^{Z (\frac{\Delta p}{4} - \varepsilon_1)} \]
Implementation Name: $Keq1$
Units: dimensionless
Initial value: 0
Equilibrium constant for the $Cu_A$ reduction reaction.

\[ K_{eq2} = 10^{Z (\frac{\Delta p}{8} - \varepsilon_2)} \]
Implementation Name: $\text{Keq}_2$
Units: dimensionless
Initial value: 0
Equilibrium constant for the $a_3$ reduction reaction.

\[ k_{-1} = \frac{k_1}{K_{eq1}} \]

Implementation Name: $\text{kn1}$
Units: s$^{-1}$
Initial value: 0
Reverse reaction rate for the reduction of $\text{Cu}_A$.

\[ k_{-2} = \frac{k_2}{K_{eq2}} \]

Implementation Name: $\text{kn2}$
Units: s$^{-1}$
Initial value: 0
Reverse reaction rate for the reduction of $a_3$.

\[ L = L_{CV} + L_{lk} \]

Implementation Name: $L$
Units: mM s$^{-1}$
Initial value: 0
Rate of proton return to the mitochondrial matrix.

\[ L_{CV} = \frac{CV_{inh} L_{CV, max} (1 - \exp(-\theta))}{1 + r_{CV} \exp(-\theta)} \]

Implementation Name: $L_{CV}$
Units: mM s$^{-1}$
Initial value: 0
Rate at which protons re-enter the mitochondrial matrix due to ADP phosphorylation.

\[ L_{lk} = k_{unc} L_{lk0} (\exp(\Delta p k_{lk2}) - 1) \]

Implementation Name: $L_{lk}$
Units: mM s$^{-1}$
Initial value: 0
Rate at which protons re-enter the mitochondrial matrix via leak channels.

\[ \mu = \frac{k_{aut} (\exp(\eta) - 1)}{\exp(\eta) + 1} \]

Implementation Name: $\mu$
Units: dimensionless
Initial value: 0
Effective strength of the autoregulation response.

\[ p\text{H}_m = -\log_{10} \left( \frac{H^+}{1000} \right) \]

Implementation Name: $p\text{H}_m$
Units: dimensionless
Initial value: 0
Mitochondrial pH.

\[ r_{buffi} = \frac{C_{buffi}}{C_{0,i}} \]

Implementation Name: $r_{buffi}$
Units: dimensionless
Initial value: 0
Buffering capacity for protons in mitochondria.

\[ R_{Hi} = r_{buffi} \]
### 2.7 Parameters

**Implementation Name:** \( R_{\text{Hi}} \)
- **Units:** dimensionless
- **Initial value:** 0
  Relative mitochondrial volume for protons, taking into account buffering effect of pH.

\[
S_{c,\text{O}_2} = \frac{S_{a,\text{O}_2} + S_{v,\text{O}_2}}{2}
\]

**Implementation Name:** ScO2
- **Units:** dimensionless
- **Initial value:** \( S_{c,\text{O}_2} \)
  Capillary oxygen saturation.

\[
S_{v,\text{O}_2} = \frac{HbO_2}{Hb_{\text{tot}}}
\]

**Implementation Name:** SvO2
- **Units:** dimensionless
- **Initial value:** \( S_{v,\text{O}_2} \)
  Venous oxygen saturation.

\[
\theta = k_{CV} (\Delta p + Z \log_{10} (u) - \Delta p_{CV,0})
\]

**Implementation Name:** theta
- **Units:** dimensionless
- **Initial value:** 0
  Driving force Complex V.

\[
TOI = \frac{100HbO_2}{HbT}
\]

**Implementation Name:** TOI
- **Units:** dimensionless
- **Initial value:** 0
  Total oxygenation index.

\[
V_{mca} = CBF \times CBF_{\text{scale}}
\]

**Implementation Name:** Vmca
- **Units:** cm s\(^{-1}\)
- **Initial value:** 0
  Blood velocity in the middle cerebral artery.

\[
V_a = V_{a,n} \left( \frac{r}{r_n} \right)^2
\]

**Implementation Name:** Vol_art
- **Units:** dimensionless
- **Initial value:** 0
  Relative arterial blood volume.

---

**\( \text{Cu}_{a,\text{frac},n} \)**

- **Implementation Name:** a_frac_n
- **Units:** dimensionless
- **Initial value:** 0.8
  Normal oxidised fraction of Cu_A.

**\( \text{Cu}_{A,o,n} \)**

- **Implementation Name:** a_n
- **Units:** mM
- **Initial value:** \( CCO_{\text{tot}} \times \text{Cu}_{a,\text{frac},n} \)
  Normal concentration of oxidised cytochrome c oxidase.
\( Cu_{A,r,n} \)
- **Implementation Name**: \texttt{ared}_n
- **Units**: mM
- **Initial value**: \( \text{CCO}_{\text{tot}} - Cu_{A,o,n} \)
- Normal concentration of reduced Cu

\( a_{3,o,n} \)
- **Implementation Name**: \texttt{b}_n
- **Units**: mM
- **Initial value**: \( \text{CCO}_{\text{tot}} - a_{3,r,n} \)
- Normal concentration of oxidised cytochrome a

\( \text{blood}_{\text{hb}} \)
- **Implementation Name**: \texttt{blood}_hb
- **Units**: dimensionless
- **Initial value**: 10.00
- Factor to convert model haemoglobin concentration to instrumental units. Scales for blood fraction of brain volume, mM to \( \mu \)M, and number of binding sites.

\( a_{3,r,n} \)
- **Implementation Name**: \texttt{bred}_n
- **Units**: mM
- \[ \frac{f_a}{C_{O_2,n}} \]
- **Initial value**: \( \exp(-c_3(\Delta p_n - \Delta p_{30})) / (1 + \exp(-c_3(\Delta p_n - \Delta p_{30}))) \)
- Normal concentration of reduced cytochrome a3.

\( c_3 \)
- **Implementation Name**: \texttt{c3}
- **Units**: mV\(^{-1}\)
- **Initial value**: 0.11
- Parameter controlling the sensitivity of the reduction of a3 to \( \Delta p \).

\( C_{\text{buffi}} \)
- **Implementation Name**: \texttt{C缓冲}
- **Units**: dimensionless
- **Initial value**: 0.022
- Buffering capacity of protons in mitochondria.

\( C_{\text{im}} \)
- **Implementation Name**: \texttt{C_1m}
- **Units**: mM mV\(^{-1}\)
- **Initial value**: 0.00675
- Capacitance of the mitochondrial inner membrane.

\( C_{\text{NADH}} = \frac{Z}{2} \log_{10} \left( \frac{1}{\text{NAD}} \right) \)
- **Implementation Name**: \texttt{C_NADH}
- **Units**: mV
- **Initial value**: 0
- Excess redox potential for NADH at normal demand.

\( C_{\text{NADH},n} \)
- **Implementation Name**: \texttt{C_NADH_n}
- **Units**: mV
- **Initial value**: \( \frac{Z}{2} \log_{10} \left( \frac{1}{\text{NADH}} \right) \)
- Normal value of \( C_{\text{NADH}} \).
2.7 Parameters

$\text{CBF}_n$
- Implementation Name: $\text{CBF}_n$
- Units: $\text{ml}_{\text{blood}} \text{ ml}_{\text{brain}}^{-1} \text{s}^{-1}$
- Initial value: 0.0125
- Normal cerebral blood flow.

$\text{CBF}_{\text{scale}}$
- Implementation Name: $\text{CBF}_{\text{scale}}$
- Units: cm
- Initial value: 5000
- Scale constant relating blood flow to arterial velocity.

$\Delta \text{oxCCO}_{\text{off}}$
- Implementation Name: $\text{CCO}_{\text{offset}}$
- Units: uM
- Initial value: 0
- Signal offset for the NIRS CCO measurement.

$c_{k_1}$
- Implementation Name: $c_{k_1}$
- Units: mV$^{-1}$
- Initial value: 0.01
- Parameter controlling sensitivity of $k_1$ to $\Delta p$.

$c_{k_2}$
- Implementation Name: $c_{k_2}$
- Units: mV$^{-1}$
- Initial value: 0.02
- Parameter controlling sensitivity of $k_2$ to $\Delta p$.

$\text{CMRO}_{2,n}$
- Implementation Name: $\text{CMRO}_{2,n}$
- Units: mM s$^{-1}$
- Initial value: 0.034
- Normal metabolic rate of oxygen consumption.

$\text{CV}_{\text{inh}}$
- Implementation Name: $\text{CV}_{\text{inh}}$
- Units: dimensionless
- Initial value: 1
- Control parameter representing the action of Complex V inhibitors.

$\text{CCO}_{\text{tot}} = \frac{\text{CCO}_{\text{tis}}}{\text{Vol}_{\text{mit}}}$
- Implementation Name: $\text{cytox}_{\text{tot}}$
- Units: mM
- Initial value: 0
- Concentration of cytochrome c oxidase in mitochondria.

$\text{CCO}_{\text{tis}}$
- Implementation Name: $\text{cytox}_{\text{tot}, \text{tis}}$
- Units: mM
- Initial value: 0.0055
- Concentration of cytochrome c oxidase in tissue.

$D_{\text{NADH}}$
- Implementation Name: $D_{\text{NADH}}$
- Units: dimensionless
- Initial value: 0.01
- Scale parameter for the dependence of NADH redox potential on demand.
\[ D_{O_2} \]
Implementation Name: \texttt{D.02}
Units: s\(^{-1}\)
Initial value: \( \frac{I_{O_2,n}}{O_{2,n} - O_{2,n}} \)
Diffusion rate for oxygen between capillaries and mitochondria.

\[ \Delta p_{3,corr} \]
Implementation Name: \texttt{dp3_corr}
Units: mV
Initial value: -25
Difference between \( \Delta p_{30} \) and normal \( \Delta p \).

\[ \Delta p_{30} = \Delta p_n + \Delta p_{3,corr} \]
Implementation Name: \texttt{dp.30}
Units: mV
Initial value: 0
Value of \( \Delta p \) to which \( a_3 \) reduction reaction is maximally sensitive.

\[ \Delta p_{CV,0} \]
Implementation Name: \texttt{dp_CV0}
Units: mV
Initial value: 90
Value of \( \Delta p \) at which \( L_{CV} \) is zero under normal demand.

\[ \Delta p_n \]
Implementation Name: \texttt{dp_n}
Units: mV
Initial value: \( \psi_n + Z \Delta p_{H_n} \)
Normal value of \( \Delta p \)

\[ dpH \]
Implementation Name: \texttt{dpH}
Units: dimensionless
Initial value: 0.001
Parameter in the mitochondrial proton buffering relationship.

\[ \Delta p_{H_n} \]
Implementation Name: \texttt{dpH_n}
Units: dimensionless
Initial value: \( pH_{m,n} - pH_{o,n} \)
Normal pH difference across the mitochondrial inner membrane.

\[ \psi_n \]
Implementation Name: \texttt{dpsi_n}
Units: mV
Initial value: 145
Normal mitochondrial inner membrane potential.

\[ E_{1,NADH} = E_0(Cu_A) - E_0(NADH) + C_{NADH} \]
Implementation Name: \texttt{E1NADH}
Units: mV
Initial value: 0
Value of \( E_1 \) when the reducing substrate is NADH.

\[ E_{1,NADH,n} \]
Implementation Name: \texttt{E1NADH_n}
Units: mV
Initial value: \( E_0(Cu_A) - E_0(NADH) + C_{NADH,n} \)
Normal value of \( E_{1,NADH} \).
### 2.7 Parameters

**$E_1$**
- **Implementation Name:** $E_{1,1}$
- **Units:** mV
- **Initial value:** $E_{1,NADH}$
  - The energy provided by electron transfer to Cu$_{A,r}$.

**$E_{1,n}$**
- **Implementation Name:** $E_{1,1n}$
- **Units:** mV
- **Initial value:** $E_{1,NADH,n}$
  - Normal value of $E_1$.

**$E_2$**
- **Implementation Name:** $E_{2,2}$
- **Units:** mV
- **Initial value:** $E_{2,NADH}$
  - Energy provided by the transfer of four electrons from Cu$_{A,r}$ to a$_{3,o}$.

**$E_0(a_3)$**
- **Implementation Name:** $E_{0,a30}$
- **Units:** mV
- **Initial value:** 350
  - Standard redox potential for cytochrome a$_3$.

**$E_0(Cu_A)$**
- **Implementation Name:** $E_{0,c0}$
- **Units:** mV
- **Initial value:** 247
  - Standard redox potential for Cu$_A$.

**$E_0(NADH)$**
- **Implementation Name:** $E_{0,N0}$
- **Units:** mV
- **Initial value:** −320
  - Standard redox potential for NADH.

**$f_n$**
- **Implementation Name:** $f_{n,n}$
- **Units:** mM s$^{-1}$
- **Initial value:** $\frac{CMRO_{2,n}}{Vol_{mit}}$
  - Normal resting value of $f_1$ and $f_2$.

**$G_n$**
- **Implementation Name:** $G_{n,n}$
- **Units:** ml$^{-1}$ blood ml$^{-1}$ brain mmHg$^{-1}$ s$^{-1}$
- **Initial value:** $\frac{CBF_n}{P_{a,n} - P_{v,n}}$
  - Normal blood vessel conductance.

**$H^{+}_{n}$**
- **Implementation Name:** $H_{n,n}$
- **Units:** mM
- **Initial value:** $10^{3-pH_{n,n}}$
  - Normal mitochondrial proton concentration.

**$J_{O_2,n}$**
- **Implementation Name:** $J_{O2,n}$
- **Units:** mM s$^{-1}$
- **Initial value:** $CMRO_{2,n}$
  - Normal oxygen flux from blood to tissue.
\[ k_{1,0} \]
Implementation Name: \( k_{10} \)
Units: \( s^{-1} \)
Initial value: \( k_{1,0} \frac{NADH}{NADH_k} \)
Forward reaction rate for the reduction of \( Cu_A \) at normal \( \Delta p \).

\[ k_{1,n} \]
Implementation Name: \( k_{1,n} \)
Units: \( s^{-1} \)
Initial value: \( \frac{f_n}{Cu_{A,o,n} - \frac{1}{K_{eq1,n}} Cu_{A,r,n}} \)
Forward reaction rate for the reduction of \( Cu_A \) at normal \( \Delta p \) and NADH.

\[ k_{2,n} \]
Implementation Name: \( k_{2,n} \)
Units: \( s^{-1} \)
Initial value: \( \frac{f_n}{Cu_{A,r,n} - \frac{1}{K_{eq2,n}} Cu_{A,o,n} a_{3,r,n}} \)
Normal forward reaction rate for the reduction of \( a_3 \).

\[ k_3 = \frac{k_{3,0}}{1 + \exp(-c_3 - \Delta p_{30})} \]
Implementation Name: \( k_3 \)
Units: \( s^{-1} \)
Initial value: 0
Forward reaction rate for the reduction of \( O_2 \).

\[ k_{3,0} \]
Implementation Name: \( k_{30} \)
Units: \( s^{-1} \)
Initial value: \( 2.5E+5 \)
Apparent second order rate constant for reduction of \( O_2 \) at zero \( \Delta p \).

\[ k_{aut} \]
Implementation Name: \( k_{aut} \)
Units: dimensionless
Initial value: 1
Overall functioning of autoregulatory response.

\[ K_G \]
Implementation Name: \( K_G \)
Units: \( ml_{blood} ml_{brain}^{-1} mmHg^{-1} s^{-1} cm^{-4} \)
Initial value: \( G_n pow(r_n/4) \)
Proportionality constant in Poiseuille relation for conductance.

\[ k_{lk2} \]
Implementation Name: \( k_{lk2} \)
Units: \( mV^{-1} \)
Initial value: 0.038
Constant controlling the depending of the leak rate \( L_{lk} \) on \( \Delta p \).

\[ k_{unc} \]
Implementation Name: \( k_{unc} \)
Units: dimensionless
Initial value: 1
Control parameter simulating the effect of adding uncouplers to the system.
$$k_{CV} = \frac{-1}{\Delta p_n - \Delta p_{CV,0}} \log \left( \frac{1 - L_{CV,0}}{1 + r_{CV} L_{CV,0}} \right)$$

Implementation Name: kCV
Units: mV$^{-1}$
Initial value: 0
Parameter controlling the sensitivity of Complex V flux to driving force.

$$K_{eq1,n}$$
Implementation Name: Keq1_n
Units: dimensionless
Initial value: $10^{2.2} \left( \frac{p_{1\Delta p_n}}{p_{1\Delta p_n} - E_{1,n}} \right)$
Normal value of the equilibrium constant for the Cu$_A$ reduction reaction.

$$K_{eq2,n}$$
Implementation Name: Keq2_n
Units: dimensionless
Initial value: $10^{2.2} \left( \frac{p_{3\Delta p_n}}{p_{3\Delta p_n} - E_{2}} \right)$
Normal value of the equilibrium constant for the a$_3$ reduction reaction.

$$L_{CV,0}$$
Implementation Name: L$_{CV0}$
Units: dimensionless
Initial value: 0.4
Normal Complex V flux as a fraction of maximum possible flux.

$$L_{CV,frac} = 1 - L_{lk,frac}$$
Implementation Name: L$_{CVfrac}$
Units: dimensionless
Initial value: 0
Normal fraction of proton entry into mitochondria which is due to ADP phosphorylation.

$$L_{CV,max} = \frac{L_{CV,n}}{L_{CV,0}}$$
Implementation Name: L$_{CVmax}$
Units: mM s$^{-1}$
Initial value: 0
The maximum rate of proton flow through Complex V.

$$L_{CV,n}$$
Implementation Name: L$_{CVn}$
Units: mM s$^{-1}$
Initial value: $L_n L_{CV,frac}$
The resting flow of protons into the matrix through Complex V.

$$L_{lk0}$$
Implementation Name: L$_{lk0}$
Units: mM s$^{-1}$
Initial value: $L_{lk,n} \exp(\Delta p_n k_{l2}) - 1$
Constant controlling the depending of the leak rate $L_{lk}$ on $\Delta p$.

$$L_{lk,frac}$$
Implementation Name: L$_{lkfrac}$
Units: dimensionless
Initial value: 0.25
Normal fraction of proton entry into mitochondria which is via leak channels.

$$L_{lk,n}$$
Implementation Name: L$_{lkn}$
Units: mM s$^{-1}$
Initial value: $L_n L_{lk,frac}$
The resting flow of protons into the matrix via leak channels.

$L_n = P_{tot} f_o$
Implementation Name: $L_n$
Units: mM s\(^{-1}\)
Initial value: 0
The normal total flow of protons back into mitochondria.

$\lambda_0$
Implementation Name: $\lambda_{a0}$
Units: cm
Initial value: 0.02507
Intercept of the fitted linear model for blood vessel radius.

$\lambda_\mu$
Implementation Name: $\lambda_{a\mu}$
Units: cm
Initial value: $-0.0004422$
Fitted linear dependence of blood vessel radius on autoregulatory stimuli.

$\lambda_{Pa}$
Implementation Name: $\lambda_{aPa}$
Units: cm mmHg
Initial value: $-0.6327$
Fitted linear dependence of blood vessel radius on reciprocal of blood pressure.

$\lambda_{Pa,\mu}$
Implementation Name: $\lambda_{aPa,\mu}$
Units: cm mmHg
Initial value: $-0.5286$
Fitted joint dependence of blood vessel radius on autoregulatory stimuli and reciprocal of blood pressure.

$h_h$
Implementation Name: $n_{h}$
Units: dimensionless
Initial value: 2.5
Hill coefficient for oxygen dissociation from haemoglobin.

$NADH = \frac{NAD_{pool}}{1 + \frac{NAD}{NADH}}$
Implementation Name: $NADH$
Units: mM
Initial value: 0
Concentration of NADH in the mitochondria.

$NADH_n$
Implementation Name: $NADHn$
Units: mM
Initial value: $\frac{NAD_{pool}}{1 + \frac{NAD}{NADH_n}}$
Normal concentration of NADH in the mitochondria.

$\frac{NAD}{NADH}$
Implementation Name: $\frac{NAD}{NADH}$
Units: dimensionless
Initial value: $\frac{NAD}{NADH_n} \text{pow}(u, 2D_{NADH})$
NAD/NADH ratio.
2.7 Parameters

\( \frac{NAD}{NADH} \)
Implementation Name: \( \text{NADNADHratn} \)
Units: dimensionless
Initial value: 9
Normal NAD/NADH ratio.

\( NAD_{\text{pool}} \)
Implementation Name: \( \text{NADpool} \)
Units: dimensionless
Initial value: 3
Relative size of the NAD pool, used to estimate normal mitochondrial NADH.

\( O_2, n \)
Implementation Name: \( \text{02_n} \)
Units: mM
Initial value: 0.024
Normal mitochondrial oxygen concentration.

\( O_{2,c, n} \)
Implementation Name: \( \text{02c_n} \)
Units: mM
Initial value: \( \phi \ \text{pow} \left( \frac{S_{c,O_2,n}}{1-S_{c,O_2,n}} \cdot \frac{1}{n_H} \right) \)
Normal capillary oxygen concentration.

\( p_1 = p_{tot} - p_{23} \)
Implementation Name: \( p1 \)
Units: dimensionless
Initial value: 0
Proton cost of the reaction reducing Cu\(_A\).

\( p_3 \)
Implementation Name: \( p2 \)
Units: dimensionless
Initial value: 4
Proton cost of the reaction reducing a\(_3\).

\( p_{23} \)
Implementation Name: \( p23 \)
Units: dimensionless
Initial value: 8
Total protons removed from the mitochondrial matrix by the reductions of a\(_3\) and O\(_2\).

\( p_3 \)
Implementation Name: \( p3 \)
Units: dimensionless
Initial value: \( p_{23} - p_3 \)
Proton cost of the reaction reducing O\(_2\).

\( P_a \)
Implementation Name: \( P_a \)
Units: mmHg
Initial value: \( P_{a,n} \)
Mean arterial blood pressure.

\( P_{a,n} \)
Implementation Name: \( P_{an} \)
Units: mmHg
Initial value: 100
Normal arterial blood pressure.
Implementation Name: $p_{C1}$
Units: dimensionless
Initial value: 8
Protons pumped by Complex I.

Implementation Name: $p_{C3}$
Units: dimensionless
Initial value: 4
Protons pumped by Complex III.

Implementation Name: $p_{tot}$
Units: dimensionless
Initial value: $p_{tot,NADH}$
Total protons removed from the mitochondrial matrix by the three modelled electron transport reactions.

$P_{tot,NADH} = P_{C1} + P_{C3} + P_{23}$

Implementation Name: $P_{tot,NADH}$
Units: dimensionless
Initial value: 0
Total protons pumped when the reducing agent is NADH.

Implementation Name: $P_v$
Units: mmHg
Initial value: $P_v,n$
Venous blood pressure.

Implementation Name: $P_{v,n}$
Units: mmHg
Initial value: 4
Normal venous blood pressure.

Implementation Name: $P_{a,CO_2}$
Units: mmHg
Initial value: $P_{a,CO_2,n}$
Arterial partial pressure of carbon dioxide.

Implementation Name: $P_{a,CO_2,n}$
Units: mmHg
Initial value: 40
Normal arterial partial pressure of carbon dioxide.

Implementation Name: $pH_{mn}$
Units: dimensionless
Initial value: 7.4
Normal mitochondrial pH.

Implementation Name: $pH_o$
Units: dimensionless
Initial value: 7
Extra-mitochondrial pH.
2.7 Parameters

$pH_{o,n}$
Implementation Name: pH\_on
Units: dimensionless
Initial value: 7
Normal extra-mitochondrial pH.

$\phi$
Implementation Name: phi
Units: mM
Initial value: 0.036
Oxygen concentration at half-maximal saturation.

$R_{CO_2}$
Implementation Name: $R_{aut\_c}$
Units: dimensionless
Initial value: 2.2
Autoregulatory reactivity to carbon dioxide.

$R_{O_2}$
Implementation Name: $R_{aut\_o}$
Units: dimensionless
Initial value: 1.5
Autoregulatory reactivity to oxygen.

$R_{Pa}$
Implementation Name: $R_{aut\_p}$
Units: dimensionless
Initial value: 4
Autoregulatory reactivity to blood pressure.

$R_u$
Implementation Name: $R_{aut\_u}$
Units: dimensionless
Initial value: 0.5
Autoregulatory reactivity to demand.

$r_{CV}$
Implementation Name: $r_{CV}$
Units: dimensionless
Initial value: 5
Parameter controlling the ratio of maximal to minimal rates of oxidative phosphorylation.

$r_n$
Implementation Name: $r_{n}$
Units: cm
Initial value: 0.0187
Normal blood vessel radius. Normal effective blood vessel radius.

$S_{a,O_2,n}$
Implementation Name: Sa02\_n
Units: dimensionless
Initial value: 0.96
Normal arterial oxygen saturation.

$S_{a,O_2}$
Implementation Name: Sa02sup
Units: dimensionless
Initial value: $S_{a,O_2,n}$
Arterial oxygen saturation.
$S_{c,O_2,n}$
Implementation Name: $ScO_2,n$
Units: dimensionless
Initial value: $\frac{S_{c,O_2,n} + S_{v,O_2,n}}{2}$
Normal capillary oxygen saturation.

$S_{v,O_2,n}$
Implementation Name: $SvO_2,n$
Units: dimensionless
Initial value: $\frac{HbO_2,v,n}{Hbtot,n}$
Normal venous oxygen saturation.

$t$
Implementation Name: $t$
Units: s
Initial value: 0
Time over which the system evolves.

$\tau_{CO_2}$
Implementation Name: $\tau_c$
Units: s
Initial value: 5
Filter time constant for stimulus effect of carbon dioxide.

$\tau_{O_2}$
Implementation Name: $\tau_o$
Units: s
Initial value: 20
Filter time constant for stimulus effect of capillary oxygen.

$\tau_{Pa}$
Implementation Name: $\tau_p$
Units: s
Initial value: 5
Filter time constant for stimulus effect of blood pressure.

$\tau_{u}$
Implementation Name: $\tau_u$
Units: s
Initial value: 0.5
Filter time constant for stimulus effect of demand.

$u$
Implementation Name: $u$
Units: dimensionless
Initial value: $u_n$
Parameter indicating metabolic demand.

$u_n$
Implementation Name: $u_n$
Units: dimensionless
Initial value: 1
Normal demand.

$\nu_{CO_2,n}$
Implementation Name: $\nu_{cn}$
Units: mmHg
Initial value: $Pa_{CO_2,n}$
2.7 Parameters

Normal filtered carbon dioxide partial pressure. Normal filtered carbon dioxide partial pressure.

\( v_{O_2,n} \)
- Implementation Name: \( v_{\text{on}} \)
- Units: \( \text{mM} \)
- Initial value: \( O_{2,c,n} \)
- Normal filtered capillary oxygen concentration. Normal filtered capillary oxygen concentration.

\( v_{P_a,n} \)
- Implementation Name: \( v_{\text{pn}} \)
- Units: \( \text{mmHg} \)
- Initial value: \( P_a,n \)
- Normal filtered arterial blood pressure. Normal filtered blood pressure.

\( v_{u,n} \)
- Implementation Name: \( v_{\text{un}} \)
- Units: dimensionless
- Initial value: \( u_n \)
- Normal filtered demand. Normal filtered demand.

\( V\text{Arat}_n \)
- Implementation Name: \( V\text{Arat}_n \)
- Units: dimensionless
- Initial value: 3
- Normal volume ratio of veins to arteries in brain tissue.

\( V_a,n \)
- Implementation Name: \( V\text{ol}_{\text{ar}n} \)
- Units: dimensionless
- Initial value: \( \frac{1}{1 + V\text{Arat}_n} \)
- Normal relative arterial blood volume.

\( V\text{ol}_{\text{mit}} \)
- Implementation Name: \( V\text{ol}_{\text{mit}} \)
- Units: dimensionless
- Initial value: 0.067
- Fraction of brain tissue volume that is mitochondria.

\( V_v \)
- Implementation Name: \( V\text{ol}_{\text{ven}} \)
- Units: dimensionless
- Initial value: \( \frac{V\text{Arat}_n}{1 + V\text{Arat}_n} \)
- Relative venous blood volume.

\( HbO_{2,a} = Hb_{\text{tot}} S_a,O_2 \)
- Implementation Name: \( X0a \)
- Units: \( \text{mM} \)
- Initial value: \( HbO_{2,a,n} \)
- Arterial concentration of oxygen bound to haemoglobin.

\( HbO_{2,a,n} \)
- Implementation Name: \( X0a_n \)
- Units: \( \text{mM} \)
- Initial value: \( Hb_{\text{tot},n} S_a,O_2,n \)
- Normal arterial concentration of oxygen bound to haemoglobin.

\( HbO_{2,v,n} \)
- Implementation Name: \( X0v_n \)
Units: mM
Initial value: \( \frac{CBF_n \cdot HbO_{2,n,H} - I_O_{2,n}}{CBF_n} \)
Normal venous concentration of oxygen bound to haemoglobin.

**Hb\text{tot}**
Implementation Name: X\text{tot}
Units: mM
Initial value: 9.1
Total concentration of haemoglobin O\(_2\) binding sites in blood (4 times haemoglobin concentration).

**Hb\text{tot,n}**
Implementation Name: X\text{tot_n}
Units: mM
Initial value: 9.1
Normal total concentration of haemoglobin O\(_2\) binding sites in blood (4 times haemoglobin concentration).

**Z**
Implementation Name: Z
Units: mV
Initial value: 59.028
Proportionality constant in calculation of driving forces due to concentration differences.
Defined as \( RT / F \), where \( F \) is Faraday’s constant, \( R \) the ideal gas constant and \( T \) the absolute temperature.
3 BSB2

3.1 Overview
Simplified model in which the blood flow submodel is replaced with variant B2.
• 9 differential state variables
• 3 algebraic state variables
• 35 intermediate variables
• 121 parameters
• 4 declared inputs
• 33 default outputs

3.2 Differential Equations

\[
\frac{dC_{H_{4}O}}{dt} = 4f_{3} - 4f_{1}
\]  
(3.1)

\[
\frac{da_{3,x}}{dt} = 4f_{3} - 4f_{3}
\]  
(3.2)

\[
\frac{d\psi}{dt} = \frac{p_{3}f_{3} + p_{1}f_{1} + p_{3}f_{3} - L}{C_{im}}
\]  
(3.3)

\[
\frac{dH^{+}}{dt} = \frac{1}{R_{Hi}} L - \frac{p_{3}}{R_{Hi}} f_{3} - \frac{p_{1}}{R_{Hi}} f_{1} - \frac{p_{3}}{R_{Hi}} f_{3}
\]  
(3.4)

\[
\frac{dO_{2}}{dt} = \frac{1}{Vol_{mit}} J_{O_{2}} - f_{3}
\]  
(3.5)

\[
\frac{d\nu_{CO_{2}}}{dt} = \frac{1}{\tau_{CO_{2}}} (P_{aCO_{2}} - \nu_{CO_{2}})
\]  
(3.6)

\[
\frac{d\nu_{O_{2}}}{dt} = \frac{1}{\tau_{O_{2}}} (O_{2,c} - \nu_{O_{2}})
\]  
(3.7)

\[
\frac{d\nu_{P_{a}}}{dt} = \frac{1}{\tau_{P_{a}}} (P_{a} - \nu_{P_{a}})
\]  
(3.8)
\[
\frac{dv_u}{dl} = \frac{1}{\tau_u} (u - v_u)
\]  
\hspace{1cm} (3.9)

### 3.3 Algebraic Equations

\[
\phi \left( \frac{S_{c,O_2}}{1 - S_{c,O_2}} \right) \frac{1}{N} - O_{2,c} = 0
\]  
\hspace{1cm} (3.10)

\[
\lambda_0 + \frac{\lambda_p}{p_a} + \lambda_p \mu - r = 0
\]  
\hspace{1cm} (3.11)

\[
\text{CBF} \ (HbO}_{2,a} - HbO}_{2,o} - I_{O_2} = 0
\]  
\hspace{1cm} (3.12)

### 3.4 Chemical Reactions

\[
\frac{L}{R_{Hi}} \xrightarrow{} H^+ \hspace{1cm} (3.13)
\]

\[
\frac{J_{O_2}}{Vol_{mit}} \xrightarrow{} O_2 \hspace{1cm} (3.14)
\]

\[
\frac{p_3}{R_{Hi}} H^+ \xrightarrow{f_3} 4 \text{Cu}_{A,o} + 4 a_{3,r} \hspace{1cm} (3.15)
\]

\[
4 \text{Cu}_{A,o} + \frac{p_1}{R_{Hi}} H^+ \xrightarrow{f_1} \hspace{1cm} (3.16)
\]

\[
O_2 + 4 a_{3,r} + \frac{p_3}{R_{Hi}} H^+ \xrightarrow{f_3} \hspace{1cm} (3.17)
\]

### 3.5 State Variables

\[
C_{\text{Cu}_{A,o}}
\]
Implementation Name: a
Units: mM
Initial value: \(C_{\text{Cu}_{A,o,n}}\)
Concentration of oxidised cytochrome c oxidase.

\[
a_{3,r}
\]
Implementation Name: brød
Units: mM
Initial value: \(a_{3,r,n}\)
Concentration of reduced cytochrome a_3.
3.5 State Variables

ψ
Implementation Name: Dpsi
Units: mV
Initial value: ψ_n
Mitochondrial inner membrane potential. Varies as charge (in the form of protons) is transferred across the membrane capacitance.

H^+
Implementation Name: H
Units: mM
Initial value: H^+_n
Mitochondrial proton concentration.

O_2
Implementation Name: O2
Units: mM
Initial value: O_{2,n}
Mitochondrial oxygen concentration.

O_{2,c}
Implementation Name: O_{2,c}
Units: mM
Initial value: O_{2,c,n}
Capillary oxygen concentration.

r
Implementation Name: r
Units: cm
Initial value: r_n
Typical blood vessel radius.

v_{CO_2}
Implementation Name: v_{CO_2}
Units: mmHg
Initial value: v_{CO_2,n}
Filtered carbon dioxide partial pressure.

v_{O_2}
Implementation Name: v_{O_2}
Units: mM
Initial value: v_{O_2,n}
Filtered capillary oxygen concentration.

v_{Pa}
Implementation Name: v_{Pa}
Units: mmHg
Initial value: v_{Pa,n}
Filtered arterial blood pressure.

v_{iu}
Implementation Name: v_{iu}
Units: dimensionless
Initial value: v_{iu,n}
Filtered demand.

HbO_{2,c}
Implementation Name: X0v
Units: mM
Initial value: HbO_{2,c,n}
Venous concentration of oxygen bound to haemoglobin.
3.6 Intermediate Variables

\[ \text{Cu}_{A,r} = \text{CCO}_{\text{tot}} - \text{Cu}_{A,o} \]

Implementation Name: ared
Units: mM
Initial value: 0
Concentration of reduced CuA.

\[ a_{3,o} = \text{CCO}_{\text{tot}} - a_{3,r} \]

Implementation Name: b
Units: mM
Initial value: 0
Concentration of oxidised cytochrome a3.

\[ C_{0,i} = \frac{10^{-pH_a} - 10^{-pH_m} - dPH}{dPH} \]

Implementation Name: \( C_{0,i} \)
Units: dimensionless
Initial value: 0
Natural buffering capacity of protons in mitochondria.

\[ \text{CBF} = G (P_a - P_v) \]

Implementation Name: CBF
Units: ml\_blood ml\_brain s\(^{-1}\)
Initial value: CBF\(_n\)
Cerebral blood flow.

\[ \Delta \text{oxCCO} = \Delta \text{oxCCO}_{\text{off}} + 1000 \text{Vol}_{\text{mit}} (\text{Cu}_{A,o} - \text{Cu}_{A,o,n}) \]

Implementation Name: \( \text{CCO} \)
Units: mM
Initial value: 0
Cytochrome c oxidase signal measured by NIRS.

\[ \text{CMRO}_2 = f_3 \text{Vol}_{\text{mit}} \]

Implementation Name: CMRO2
Units: mM s\(^{-1}\)
Initial value: 0
Rate of cerebral oxygen metabolism.

\[ \Delta p = \psi + Z (pH_m - pH_o) \]

Implementation Name: \( \Delta p \)
Units: mV
Initial value: 0
Proton motive force across the mitochondrial inner membrane.

\[ \eta = R_P \left( \frac{\nu_P}{\nu_{P,n}} - 1 \right) + R_O_2 \left( \frac{\nu_{O_2}}{\nu_{O_2,n}} - 1 \right) + R_{CO_2} \left( 1 - \frac{\nu_{CO_2}}{\nu_{CO_2,n}} \right) + R_u \left( 1 - \frac{\nu_u}{\nu_{u,n}} \right) \]

Implementation Name: \( \eta \)
Units: dimensionless
Initial value: 0
Merged autoregulation stimulus.

\[ f_1 = k_1 \text{Cu}_{A,o} - k_{-1} \text{Cu}_{A,r} \]

Implementation Name: \( f_1 \)
Units: mM s\(^{-1}\)
Initial value: 0
Reaction rate for the reduction of CuA.

\[ f_2 = k_2 \text{Cu}_{A,r} a_{3,o} - k_{-2} \text{Cu}_{A,o} a_{3,r} \]

Implementation Name: \( f_2 \)
3.6 Intermediate Variables

Units: mM s$^{-1}$
Initial value: 0
Reaction rate for the reduction of $a_3$.

$$f_3 = \frac{k_3 O_2 a_{3,r} \exp(-c_3 (\Delta p - \Delta p_{30}))}{1 + \exp(-c_3 (\Delta p - \Delta p_{30}))}$$

Implementation Name: $f_3$
Units: mM s$^{-1}$
Initial value: 0
Reaction rate for the reduction of $O_2$.

$$G = K_G t^4$$
Implementation Name: $G$
Units: ml$^{-1}$ brain mmHg$^{-1}$ s$^{-1}$
Initial value: 0
Effective conductance of the whole blood flow compartment.

$$HbO_2 = (V_a HbO_{2,a} + V_v HbO_{2,v}) blood_{hb}$$
Implementation Name: $HbO_2$
Units: uM
Initial value: 0
Oxygenated haemoglobin signal measured by NIRS.

$$HbT = (V_a + V_v) Hb_{tot} blood_{hb}$$
Implementation Name: $HbT$
Units: uM
Initial value: 0
Total haemoglobin signal measured by NIRS.

$$HHb = HbT - HbO_2$$
Implementation Name: $HHb$
Units: uM
Initial value: 0
Deoxygenated haemoglobin signal measured by NIRS.

$$J_{O_2} = f_{min} (D_{O_2} (O_2,c - O_2), CBF HbO_{2,a})$$
Implementation Name: $J_{O2}$
Units: mM s$^{-1}$
Initial value: 0
Oxygen flux from blood to tissue.

$$k_1 = k_{1,0} \exp(-c_{k_1} (\Delta p - \Delta p_n))$$
Implementation Name: $k_1$
Units: s$^{-1}$
Initial value: 0
Forward reaction rate for the reduction of $Cu_A$.

$$k_2 = k_{2,n} \exp(-c_{k_2} (\Delta p - \Delta p_n))$$
Implementation Name: $k_2$
Units: s$^{-1}$
Initial value: 0
Forward reaction rate for the reduction of $a_3$.

$$K_{eq1} = 10^{\frac{1}{2} \left( \frac{\Delta H}{4} - \epsilon_1 \right)}$$
Implementation Name: $K_{eq1}$
Units: dimensionless
Initial value: 0
Equilibrium constant for the $Cu_A$ reduction reaction.

$$K_{eq2} = 10^{\frac{1}{2} \left( \frac{\Delta H}{4} - \epsilon_2 \right)}$$
Implementation Name: $k_{eq2}$
Units: dimensionless
Initial value: 0
Equilibrium constant for the $a_3$ reduction reaction.

$$k_{-1} = \frac{k_1}{K_{eq1}}$$

Implementation Name: $k_{n1}$
Units: $s^{-1}$
Initial value: 0
Reverse reaction rate for the reduction of $Cu_A$.

$$k_{-2} = \frac{k_2}{K_{eq2}}$$

Implementation Name: $k_{n2}$
Units: $s^{-1}$
Initial value: 0
Reverse reaction rate for the reduction of $a_3$.

$$L = L_{CV} + L_{lk}$$

Implementation Name: $L$
Units: mM s$^{-1}$
Initial value: 0
Rate of proton return to the mitochondrial matrix.

$$L_{CV} = \frac{CV_{inh} L_{CV,max} (1 - \exp(-\theta))}{1 + r_{CV} \exp(-\theta)}$$

Implementation Name: $L_{CV}$
Units: mM s$^{-1}$
Initial value: 0
Rate at which protons re-enter the mitochondrial matrix due to ADP phosphorylation.

$$L_{lk} = k_{unc} L_{lk0} (\exp(\Delta p k_{lk2}) - 1)$$

Implementation Name: $L_{lk}$
Units: mM s$^{-1}$
Initial value: 0
Rate at which protons re-enter the mitochondrial matrix via leak channels.

$$\mu = \frac{k_{aut} (\exp(\eta) - 1)}{\exp(\eta) + 1}$$

Implementation Name: $mu$
Units: dimensionless
Initial value: 0
Effective strength of the autoregulation response.

$$pH_m = -\log_{10}\left(\frac{H^+}{1000}\right)$$

Implementation Name: $pH_m$
Units: dimensionless
Initial value: 0
Mitochondrial pH.

$$r_{buffi} = \frac{C_{buffi}}{C_{0,i}}$$

Implementation Name: $r_{buffi}$
Units: dimensionless
Initial value: 0
Buffering capacity for protons in mitochondria.

$$R_{Hi} = r_{buffi}$$
3.7 Parameters

Implementation Name: \( R_{Hi} \)
Units: dimensionless
Initial value: 0
Relative mitochondrial volume for protons, taking into account buffering effect of pH.

\[
S_{c,O_2} = \frac{S_{a,O_2} + S_{v,O_2}}{2}
\]
Implementation Name: Sc02
Units: dimensionless
Initial value: \( S_{c,O_2,n} \)
Capillary oxygen saturation.

\[
S_{v,O_2} = \frac{HbO_2}{Hb_{tot}}
\]
Implementation Name: Sv02
Units: dimensionless
Initial value: \( S_{v,O_2,n} \)
Venous oxygen saturation.

\[\theta = k_{CV} \left( \Delta p + Z \log_{10} (u) - \Delta p_{CV,0} \right)\]
Implementation Name: theta
Units: dimensionless
Initial value: 0
Driving force Complex V.

\[
TOI = \frac{100HbO_2}{HbT}
\]
Implementation Name: TOI
Units: dimensionless
Initial value: 0
Total oxygenation index.

\[
V_{mca} = CBF \times CBF_{scale}
\]
Implementation Name: Vmca
Units: cm s\(^{-1}\)
Initial value: 0
Blood velocity in the middle cerebral artery.

\[
V_a = V_{a,n} \left( \frac{r}{r_n} \right)^2
\]
Implementation Name: V0l_art
Units: dimensionless
Initial value: 0
Relative arterial blood volume.

3.7 Parameters

\( Cu_{a,frac,n} \)
Implementation Name: a_frac_n
Units: dimensionless
Initial value: 0.8
Normal oxidised fraction of Cu\(_A\).

\( CU_{A,o,n} \)
Implementation Name: a_n
Units: mM
Initial value: \( CCO_{tot} \times Cu_{a,frac,n} \)
Normal concentration of oxidised cytochrome c oxidase.
Cu_{A,r,n} 
Implementation Name: ared_n 
Units: mM 
Initial value: \( CCO_{tot} - Cu_{A,o,n} \) 
Normal concentration of reduced Cu_A.

\( a_{3,o,n} \) 
Implementation Name: b_n 
Units: mM 
Initial value: \( CCO_{tot} - a_{3,r,n} \) 
Normal concentration of oxidised cytochrome a_3.

\( \text{blood}_{hb} \) 
Implementation Name: blood_hb 
Units: dimensionless 
Initial value: 10.00 
Factor to convert model haemoglobin concentration to instrumental units. Scales for blood fraction of brain volume, mM to \( \mu \)M, and number of binding sites.

\( a_{3,r,n} \) 
Implementation Name: bred_n 
Units: mM 
\[
\frac{f_a}{O_2} \left( \frac{\exp(-c_3(\Delta p_n - \Delta p_30))}{1+\exp(-c_3(\Delta p_n - \Delta p_30))} \right)
\] 
Initial value: 
Normal concentration of reduced cytochrome a_3.

\( c_3 \) 
Implementation Name: c3 
Units: mV^{-1} 
Initial value: 0.11 
Parameter controlling the sensitivity of the reduction of a_3 to \( \Delta p \).

\( C_{buffer} \) 
Implementation Name: C_buffer 
Units: dimensionless 
Initial value: 0.022 
Buffering capacity of protons in mitochondria.

\( C_{im} \) 
Implementation Name: C_im 
Units: mM mV^{-1} 
Initial value: 0.00675 
Capacitance of the mitochondrial inner membrane.

\[
C_{NADH} = \frac{Z}{2} \log_{10} \left( \frac{1}{\frac{NAD}{NADH}} \right)
\] 
Implementation Name: C_NADH 
Units: mV 
Initial value: 0 
Excess redox potential for NADH at normal demand.

\( C_{NADH,n} \) 
Implementation Name: C_NADH_n 
Units: mV 
Initial value: 
Normal value of \( C_{NADH} \).
3.7 Parameters

**CBFn**
- Implementation Name: CBFn
- Units: ml\_blood ml\_brain s\(^{-1}\)
- Initial value: 0.0125
- Normal cerebral blood flow.

**CBFs**
- Implementation Name: CBFscale
- Units: cm
- Initial value: 5000
- Scale constant relating blood flow to arterial velocity.

**ΔoxCCO\_off**
- Implementation Name: CCO\_offset
- Units: uM
- Initial value: 0
- Signal offset for the NIRS CCO measurement.

**c\_k_1**
- Implementation Name: ck1
- Units: mV\(^{-1}\)
- Initial value: 0.01
- Parameter controlling sensitivity of \(k_1\) to \(Δp\).

**c\_k_2**
- Implementation Name: ck2
- Units: mV\(^{-1}\)
- Initial value: 0.02
- Parameter controlling sensitivity of \(k_2\) to \(Δp\).

**CMRO\_2\_n**
- Implementation Name: CMRO\_2\_n
- Units: mM s\(^{-1}\)
- Initial value: 0.034
- Normal metabolic rate of oxygen consumption.

**CV\_inh**
- Implementation Name: CV\_inh
- Units: dimensionless
- Initial value: 1
- Control parameter representing the action of Complex V inhibitors.

\[
CCO_{tot} = \frac{CCO_{tis}}{Vol_{mit}}
\]
- Implementation Name: cytox\_tot
- Units: mM
- Initial value: 0
- Concentration of cytochrome c oxidase in mitochondria.

**CCO\_tis**
- Implementation Name: cytox\_tot\_tis
- Units: mM
- Initial value: 0.0055
- Concentration of cytochrome c oxidase in tissue.

**D\_NADH**
- Implementation Name: D\_NADH
- Units: dimensionless
- Initial value: 0.01
- Scale parameter for the dependence of NADH redox potential on demand.
$D_{O_2}$
Implementation Name: $d_{0,2}$
Units: s$^{-1}$
Initial value: $\frac{I_{O_2,n}}{O_{2,c,n} - O_{2,n}}$
Diffusion rate for oxygen between capillaries and mitochondria.

$\Delta p_{3,corr}$
Implementation Name: $dp_{3,corr}$
Units: mV
Initial value: $-25$
Difference between $\Delta p_{30}$ and normal $\Delta p$.

$\Delta p_{30} = \Delta p_n + \Delta p_{3,corr}$
Implementation Name: $dp_{30}$
Units: mV
Initial value: 0
Value of $\Delta p$ to which $a_3$ reduction reaction is maximally sensitive.

$\Delta p_{CV,0}$
Implementation Name: $dp_{CV0}$
Units: mV
Initial value: 90
Value of $\Delta p$ at which $L_{CV}$ is zero under normal demand.

$\Delta p_n$
Implementation Name: $dp_n$
Units: mV
Initial value: $\psi_n + Z \Delta pH_n$
Normal value of $\Delta p$

$dpH$
Implementation Name: $dpH$
Units: dimensionless
Initial value: 0.001
Parameter in the mitochondrial proton buffering relationship.

$\Delta pH_n$
Implementation Name: $dpH_n$
Units: dimensionless
Initial value: $pH_{m,n} - pH_{o,n}$
Normal pH difference across the mitochondrial inner membrane.

$\psi_n$
Implementation Name: $dpsi_n$
Units: mV
Initial value: 145
Normal mitochondrial inner membrane potential.

$E_{1,NADH} = E_0(Cu_A) - E_0(NADH) + C_{NADH}$
Implementation Name: $E1NADH$
Units: mV
Initial value: 0
Value of $E_1$ when the reducing substrate is NADH.

$E_{1,NADH,n}$
Implementation Name: $E1NADH_n$
Units: mV
Initial value: $E_0(Cu_A) - E_0(NADH) + C_{NADH,n}$
Normal value of $E_{1,NADH}$. 
3.7 Parameters

$E_1$
- Implementation Name: $E_{1,1}$
- Units: mV
- Initial value: $E_{1,NADH}$
- The energy provided by electron transfer to $Cu_{A,r}$.

$E_{1,n}$
- Implementation Name: $E_{1,1n}$
- Units: mV
- Initial value: $E_{1,NADH,n}$
- Normal value of $E_1$.

$E_2$
- Implementation Name: $E_{2,2}$
- Units: mV
- Initial value: $E_{0}(a_3) - E_0(Cu_A)$
- Energy provided by the transfer of four electrons from $Cu_{A,r}$ to $a_{3,o}$.

$E_0(a_3)$
- Implementation Name: $E_{a3,0}$
- Units: mV
- Initial value: 350
- Standard redox potential for cytochrome $a_3$.

$E_0(Cu_A)$
- Implementation Name: $E_{c0}$
- Units: mV
- Initial value: 247
- Standard redox potential for $Cu_A$.

$E_0(NADH)$
- Implementation Name: $E_{N0}$
- Units: mV
- Initial value: $-320$
- Standard redox potential for NADH.

$f_n$
- Implementation Name: $f_{n,n}$
- Units: mM s$^{-1}$
- Initial value: $CMRO_{2,n}$
- Normal resting value of $f_1$ and $f_2$.

$G_n$
- Implementation Name: $G_{n,n}$
- Units: ml$^{blood} / (ml_{brain} mmHg s^{-1})$
- Initial value: $P_{o,n} - P_{v,n}$
- Normal blood vessel conductance.

$H_{n}^+$
- Implementation Name: $H_{n,n}$
- Units: mM
- Initial value: $10^{3-pH_{n,n}}$
- Normal mitochondrial proton concentration.

$J_{O2,n}$
- Implementation Name: $J_{O2,n}$
- Units: mM s$^{-1}$
- Initial value: $CMRO_{2,n}$
- Normal oxygen flux from blood to tissue.
\[ k_{1,0} \]

Implementation Name: \( k_{10} \)
Units: \( s^{-1} \)
Initial value: \( \frac{k_{1,n} NADH}{NADH_H} \)
Forward reaction rate for the reduction of Cu\(_A\) at normal \( \Delta p \).

\[ k_{1,n} \]

Implementation Name: \( k_{1,n} \)
Units: \( s^{-1} \)
Initial value: \( \frac{f_n}{C_{Cu,A,\rho,n} - \frac{1}{\kappa_{eq,n}} C_{Cu,A,r,n}} \)
Forward reaction rate for the reduction of Cu\(_A\) at normal \( \Delta p \) and NADH.

\[ k_{2,n} \]

Implementation Name: \( k_{2,n} \)
Units: \( s^{-1} \)
Initial value: \( \frac{f_n}{C_{Cu,A,r,n} a_{3,\rho,n} - \frac{1}{\kappa_{eq,n}} C_{Cu,A,\rho,n} a_{3,r,n}} \)
Normal forward reaction rate for the reduction of \( a_3 \).

\[ k_3 = \frac{k_{3,0}}{1 + \exp(-c_3 - \Delta p_{30})} \]

Implementation Name: \( k_3 \)
Units: \( s^{-1} \)
Initial value: 0
Forward reaction rate for the reduction of \( O_2 \).

\[ k_{3,0} \]

Implementation Name: \( k_{30} \)
Units: \( s^{-1} \)
Initial value: \( 2.5E + 5 \)
Apparent second order rate constant for reduction of \( O_2 \) at zero \( \Delta p \).

\[ k_{aut} \]

Implementation Name: \( k_{aut} \)
Units: dimensionless
Initial value: 1
Overall functioning of autoregulatory response.

\[ K_G \]

Implementation Name: \( K_G \)
Units: \( ml_{\text{blood}} ml_{\text{brain}}^{-1} mmHg^{-1} s^{-1} \ cm^{-4} \)
Initial value: \( G_n \ pow(r_n, 4) \)
Proportionality constant in Poiseuille relation for conductance.

\[ k_{lk2} \]

Implementation Name: \( k_{lk2} \)
Units: \( \text{mV}^{-1} \)
Initial value: 0.038
Constant controlling the depending of the leak rate \( L_{lk} \) on \( \Delta p \).

\[ k_{unc} \]

Implementation Name: \( k_{unc} \)
Units: dimensionless
Initial value: 1
Control parameter simulating the effect of adding uncouplers to the system.
3.7 Parameters

\[ k_{CV} = \frac{-1}{\Delta p_n - \Delta p_{CV,0}} \log \left( \frac{1 - L_{CV,0}}{1 + r_{CV} L_{CV,0}} \right) \]

Implementation Name: \( k_{CV} \)
Units: mV\(^{-1}\)
Initial value: 0
Parameter controlling the sensitivity of Complex V flux to driving force.

\[ K_{eq1,n} \]
Implementation Name: \( K_{eq1,n} \)
Units: dimensionless
Initial value: \( 10^{-1} \left( \frac{\Delta p_n}{p_1 \Delta p_n - E_{1,n}} \right) \)
Normal value of the equilibrium constant for the Cu\(_A\) reduction reaction.

\[ K_{eq2,n} \]
Implementation Name: \( K_{eq2,n} \)
Units: dimensionless
Initial value: \( 10^{-1} \left( \frac{\Delta p_n}{p_3 \Delta p_n - E_{2,n}} \right) \)
Normal value of the equilibrium constant for the a\(_3\) reduction reaction.

\[ L_{CV,0} \]
Implementation Name: \( L_{CV,0} \)
Units: dimensionless
Initial value: 0.4
Normal Complex V flux as a fraction of maximum possible flux.

\[ L_{CV,frac} = 1 - L_{lk,frac} \]
Implementation Name: \( L_{CV,frac} \)
Units: dimensionless
Initial value: 0
Normal fraction of proton entry into mitochondria which is due to ADP phosphorylation.

\[ L_{CV,max} = \frac{L_{CV,n}}{L_{CV,0}} \]
Implementation Name: \( L_{CV,max} \)
Units: mM s\(^{-1}\)
Initial value: 0
The maximum rate of proton flow through Complex V.

\[ L_{CV,n} \]
Implementation Name: \( L_{CV,n} \)
Units: mM s\(^{-1}\)
Initial value: \( L_{n} L_{CV,frac} \)
The resting flow of protons into the matrix through Complex V.

\[ L_{lk,0} \]
Implementation Name: \( L_{lk,0} \)
Units: mM s\(^{-1}\)
Initial value: \( \frac{L_{lk,n}}{\exp (\Delta p_n k_{lk2}) - 1} \)
Constant controlling the depending of the leak rate \( L_{lk} \) on \( \Delta p \).

\[ L_{lk,frac} \]
Implementation Name: \( L_{lk,frac} \)
Units: dimensionless
Initial value: 0.25
Normal fraction of proton entry into mitochondria which is via leak channels.

\[ L_{lk,n} \]
Implementation Name: \( L_{lk,n} \)
Units: mM s\(^{-1}\)
Initial value: $L_n L_{lk,frac}$
The resting flow of protons into the matrix via leak channels.

$L_n = p_{tot} f_n$
Implementation Name: $L_n$
Units: mM s$^{-1}$
Initial value: 0
The normal total flow of protons back into mitochondria.

$\lambda_0$
Implementation Name: $1am_0$
Units: cm
Initial value: 0.02327
Intercept of the fitted linear model for blood vessel radius.

$\lambda_\mu$
Implementation Name: $1am_\mu$
Units: cm
Initial value: $-0.006375$
Fitted linear dependence of blood vessel radius on autoregulatory stimuli.

$\lambda_{Pa}$
Implementation Name: $1am_{Pa}$
Units: cm mmHg
Initial value: $-0.4697$
Fitted linear dependence of blood vessel radius on reciprocal of blood pressure.

$n_h$
Implementation Name: $n_h$
Units: dimensionless
Initial value: 2.5
Hill coefficient for oxygen dissociation from haemoglobin.

$NADH = \frac{NAD_{pool}}{1 + \frac{NAD}{NADH}}$
Implementation Name: NADH
Units: mM
Initial value: 0
Concentration of NADH in the mitochondria.

$NADH_n$
Implementation Name: $NADH_n$
Units: mM
Initial value: $\frac{NAD_{pool}}{1 + \frac{NAD}{NADH}}$
Normal concentration of NADH in the mitochondria.

$\frac{NAD}{NADH}$
Implementation Name: $NAD/NADH$
Units: dimensionless
Initial value: $\text{pow}(u, 2D_{NADH})$
NAD/NADH ratio.

$\frac{NAD_n}{NADH_n}$
Implementation Name: $NAD/NADH_n$
Units: dimensionless
Initial value: 9
Normal NAD/NADH ratio.
3.7 Parameters

$NAD_{pool}$
Implementation Name: NADpool
Units: dimensionless
Initial value: 3
Relative size of the NAD pool, used to estimate normal mitochondrial NADH.

$O_{2,n}$
Implementation Name: O2_n
Units: mM
Initial value: 0.024
Normal mitochondrial oxygen concentration.

$O_{2,c,n}$
Implementation Name: O2c_n
Units: mM
Initial value: $\phi^{\text{pow}} \left( \frac{S_{c, O_2, n}}{1 - S_{c, O_2, n}} \right)$
Normal capillary oxygen concentration.

$p_1 = p_{tot} - p_{23}$
Implementation Name: p1
Units: dimensionless
Initial value: 0
Proton cost of the reaction reducing Cu_A.

$p_3$
Implementation Name: p2
Units: dimensionless
Initial value: 4
Proton cost of the reaction reducing a3.

$p_{23}$
Implementation Name: p23
Units: dimensionless
Initial value: 8
Total protons removed from the mitochondrial matrix by the reductions of a3 and O2.

$p_3$
Implementation Name: p3
Units: dimensionless
Initial value: $p_{23} - p_3$
Proton cost of the reaction reducing O2.

$P_a$
Implementation Name: P_a
Units: mmHg
Initial value: $P_{a,n}$
Mean arterial blood pressure.

$P_{a,n}$
Implementation Name: P_an
Units: mmHg
Initial value: 100
Normal arterial blood pressure.

$p_{C1}$
Implementation Name: p_C1
Units: dimensionless
Initial value: 8
Protons pumped by Complex I.
Implementation Name: $p_{C3}$
Units: dimensionless
Initial value: 4
Protons pumped by Complex III.

Implementation Name: $p_{tot}$
Units: dimensionless
Initial value: $p_{tot,NADH}$
Total protons removed from the mitochondrial matrix by the three modelled electron transport reactions.

\[ p_{tot,NADH} = p_{C1} + p_{C3} + p_{23} \]

Implementation Name: $p_{tot,NADH}$
Units: dimensionless
Initial value: 0
Total protons pumped when the reducing agent is NADH.

Implementation Name: $P_v$
Units: mmHg
Initial value: $P_{v,n}$
Venous blood pressure.

Implementation Name: $P_{v,n}$
Units: mmHg
Initial value: 4
Normal venous blood pressure.

Implementation Name: $Pa_{CO_2}$
Units: mmHg
Initial value: $Pa_{CO_2,n}$
Arterial partial pressure of carbon dioxide.

Implementation Name: $Pa_{CO_2,n}$
Units: mmHg
Initial value: 40
Normal arterial partial pressure of carbon dioxide.

Implementation Name: $pH_{mn}$
Units: dimensionless
Initial value: 7.4
Normal mitochondrial pH.

Implementation Name: $pH_o$
Units: dimensionless
Initial value: 7
Extra-mitochondrial pH.

Implementation Name: $pH_{o,n}$
Units: dimensionless
Initial value: 7
Normal extra-mitochondrial pH.
3.7 Parameters

\( \phi \)
Implementation Name: \( \text{phi} \)
Units: mM
Initial value: 0.036
Oxygen concentration at half-maximal saturation.

\( R_{CO_2} \)
Implementation Name: \( R_{\text{aut}c} \)
Units: dimensionless
Initial value: 2.2
Autoregulatory reactivity to carbon dioxide.

\( R_{O_2} \)
Implementation Name: \( R_{\text{auto}} \)
Units: dimensionless
Initial value: 1.5
Autoregulatory reactivity to oxygen.

\( R_P \)
Implementation Name: \( R_{\text{aut}p} \)
Units: dimensionless
Initial value: 4
Autoregulatory reactivity to blood pressure.

\( R_u \)
Implementation Name: \( R_{\text{aut}u} \)
Units: dimensionless
Initial value: 0.5
Autoregulatory reactivity to demand.

\( r_{CV} \)
Implementation Name: \( r_{CV} \)
Units: dimensionless
Initial value: 5
Parameter controlling the ratio of maximal to minimal rates of oxidative phosphorylation.

\( r_n \)
Implementation Name: \( r_n \)
Units: cm
Initial value: 0.0187
Normal blood vessel radius. Normal effective blood vessel radius.

\( S_{a,O_2,n} \)
Implementation Name: \( Sa02_n \)
Units: dimensionless
Initial value: 0.96
Normal arterial oxygen saturation.

\( S_{a,O_2} \)
Implementation Name: \( Sa02\sup \)
Units: dimensionless
Initial value: \( S_{a,O_2,n} \)
Arterial oxygen saturation.

\( S_{c,O_2,n} \)
Implementation Name: \( Sc02_n \)
Units: dimensionless
Initial value: \( \frac{S_{a,O_2,n} + S_{v,O_2,n}}{2} \)
Normal capillary oxygen saturation.
\[ S_{v,O_2,n} \]
Implementation Name: \( S_{vO2,n} \)
Units: dimensionless
Initial value: \( \frac{HbO_{2,v,n}}{Hb_{tot,n}} \)
Normal venous oxygen saturation.

\[ t \]
Implementation Name: \( t \)
Units: s
Initial value: 0
Time over which the system evolves.

\[ \tau_{CO_2} \]
Implementation Name: \( \tau_{c} \)
Units: s
Initial value: 5
Filter time constant for stimulus effect of carbon dioxide.

\[ \tau_{O_2} \]
Implementation Name: \( \tau_{o} \)
Units: s
Initial value: 20
Filter time constant for stimulus effect of capillary oxygen.

\[ \tau_{Pa} \]
Implementation Name: \( \tau_{p} \)
Units: s
Initial value: 5
Filter time constant for stimulus effect of blood pressure.

\[ \tau_{u} \]
Implementation Name: \( \tau_{u} \)
Units: s
Initial value: 0.5
Filter time constant for stimulus effect of demand.

\[ u \]
Implementation Name: \( u \)
Units: dimensionless
Initial value: \( u_n \)
Parameter indicating metabolic demand.

\[ u_n \]
Implementation Name: \( u_n \)
Units: dimensionless
Initial value: 1
Normal demand.

\[ v_{CO_2,n} \]
Implementation Name: \( v_{c,n} \)
Units: mmHg
Initial value: \( P_{aCO_2,n} \)
Normal filtered carbon dioxide partial pressure. Normal filtered carbon dioxide partial pressure.

\[ v_{O_2,n} \]
Implementation Name: \( v_{o,n} \)
Units: mM
Initial value: \( O_{2,c,n} \)
3.7 Parameters

Normal filtered capillary oxygen concentration. Normal filtered capillary oxygen concentration.

\( v_{P_{\alpha,n}} \)
- Implementation Name: \( v_{\alpha \_pn} \)
- Units: mmHg
- Initial value: \( P_{\alpha,n} \)
- Normal filtered arterial blood pressure. Normal filtered blood pressure.

\( v_{u,n} \)
- Implementation Name: \( v_{\_un} \)
- Units: dimensionless
- Initial value: \( u_n \)
- Normal filtered demand. Normal filtered demand.

\( V\text{Arat}_{n} \)
- Implementation Name: \( V\text{Arat}_n \)
- Units: dimensionless
- Initial value: 3
- Normal volume ratio of veins to arteries in brain tissue.

\( V_{\alpha,n} \)
- Implementation Name: \( V_{\alpha \_artn} \)
- Units: dimensionless
- Initial value: \( \frac{1}{1 + V\text{Arat}_{n}} \)
- Normal relative arterial blood volume.

\( V\text{ol}_{\text{mit}} \)
- Implementation Name: \( V\text{ol}_\text{mit} \)
- Units: dimensionless
- Initial value: 0.067
- Fraction of brain tissue volume that is mitochondria.

\( V_{p} \)
- Implementation Name: \( V\text{ol}_\text{ven} \)
- Units: dimensionless
- Initial value: \( \frac{V\text{ol}_{\text{artn}}}{1 + V\text{Arat}_{n}} \)
- Relative venous blood volume.

\( H\text{bO}_2,a = H\text{b}_{\text{tot}} \cdot S_{a,\text{O}_2} \)
- Implementation Name: \( X0a \)
- Units: mM
- Initial value: \( H\text{bO}_2,a,n \)
- Arterial concentration of oxygen bound to haemoglobin.

\( H\text{bO}_2,a,n \)
- Implementation Name: \( X0a_{\_n} \)
- Units: mM
- Initial value: \( H\text{b}_{\text{tot},n} \cdot S_{a,\text{O}_2,n} \)
- Normal arterial concentration of oxygen bound to haemoglobin.

\( H\text{bO}_2,v,n \)
- Implementation Name: \( X0v_{\_n} \)
- Units: mM
- Initial value: \( \frac{C\text{BF}_n \cdot H\text{bO}_2,a,n - J_{\text{O}_2,n}}{C\text{BF}_n} \)
- Normal venous concentration of oxygen bound to haemoglobin.

\( H\text{b}_{\text{tot}} \)
- Implementation Name: \( X\text{tot} \)
Units: mM
Initial value: 9.1
Total concentration of haemoglobin O₂ binding sites in blood (4 times haemoglobin concentration).

Implementation Name: \( X_{\text{tot,n}} \)
Units: mM
Initial value: 9.1
Normal total concentration of haemoglobin O₂ binding sites in blood (4 times haemoglobin concentration).

\( Z \)
Implementation Name: \( Z \)
Units: mV
Initial value: 59.028
Proportionality constant in calculation of driving forces due to concentration differences. Defined as \( RT/F \), where \( F \) is Faraday’s constant, \( R \) the ideal gas constant and \( T \) the absolute temperature.
4 BSB3

4.1 Overview

Simplified model in which the blood flow submodel is replaced with variant B3.

- 9 differential state variables
- 3 algebraic state variables
- 35 intermediate variables
- 120 parameters
- 4 declared inputs
- 33 default outputs

4.2 Differential Equations

\[
\frac{d C_{u_{A,v}}}{dt} = 4f_3 - 4f_1 \tag{4.1}
\]

\[
\frac{d a_{3,r}}{dt} = 4f_3 - 4f_3 \tag{4.2}
\]

\[
\frac{d \psi}{dt} = \frac{p_3 f_3 + p_1 f_1 + p_3 f_3 - L}{C_{im}} \tag{4.3}
\]

\[
\frac{d H^+}{dt} = \frac{1}{R_{Hi}} L - \frac{p_3}{R_{Hi}} f_3 - \frac{p_1}{R_{Hi}} f_1 - \frac{p_3}{R_{Hi}} f_3 \tag{4.4}
\]

\[
\frac{d O_2}{dt} = \frac{1}{Vol_{mit}} J_{O_2} - f_3 \tag{4.5}
\]

\[
\frac{d v_{CO_2}}{dt} = \frac{1}{\tau_{CO_2}} (p_{a_{CO_2}} - v_{CO_2}) \tag{4.6}
\]

\[
\frac{d v_{O_2}}{dt} = \frac{1}{\tau_{O_2}} (O_{2,c} - v_{O_2}) \tag{4.7}
\]

\[
\frac{d v_{P_a}}{dt} = \frac{1}{\tau_{P_a}} (P_a - v_{P_a}) \tag{4.8}
\]
\[
\frac{dv_u}{dt} = \frac{1}{r_u} \left( u - v_u \right)
\]

### 4.3 Algebraic Equations

\[
\phi \left( \frac{S_c O_2}{1 - S_c O_2} \right)^{\frac{1}{n}} - O_{2,c} = 0
\]

\[
\lambda_0 + \lambda_\mu \mu - r = 0
\]

\[
CBF \left( HbO_{2,a} - HbO_{2,v} \right) - J_{O_2} = 0
\]

### 4.4 Chemical Reactions

\[
\xrightarrow{L} \frac{1}{R_{Hi}} H^+
\]

\[
\xrightarrow{J_{O_2}} \frac{1}{Vol_{mit}} O_2
\]

\[
\xrightarrow{p_3} \frac{R_{Hi}}{H^+} \xrightarrow{f_3} 4 \text{Cu}_{A,o} + 4 \text{a}_{3,r}
\]

\[
4 \text{Cu}_{A,o} + \xrightarrow{p_1} \frac{R_{Hi}}{H^+} \xrightarrow{f_1}
\]

\[
O_2 + 4 \text{a}_{3,r} + \xrightarrow{p_3} \frac{R_{Hi}}{H^+} \xrightarrow{f_3}
\]

### 4.5 State Variables

- \(Cu_{A,o}\)
  - Implementation Name: a
  - Units: mM
  - Initial value: \(Cu_{A,o,n}\)
  - Concentration of oxidised cytochrome c oxidase.

- \(a_{3,r}\)
  - Implementation Name: bred
  - Units: mM
  - Initial value: \(a_{3,r,n}\)
  - Concentration of reduced cytochrome a_3.
4.5 State Variables

$\psi$
- Implementation Name: Dpsi
- Units: mV
- Initial value: $\psi_n$
  Mitochondrial inner membrane potential. Varies as charge (in the form of protons) is transferred across the membrane capacitance.

$H^+$
- Implementation Name: H
- Units: mM
- Initial value: $H^+_n$
  Mitochondrial proton concentration.

$O_2$
- Implementation Name: O2
- Units: mM
- Initial value: $O_{2,n}$
  Mitochondrial oxygen concentration.

$O_{2,c}$
- Implementation Name: O2c
- Units: mM
- Initial value: $O_{2,c,n}$
  Capillary oxygen concentration.

$r$
- Implementation Name: r
- Units: cm
- Initial value: $r_n$
  Typical blood vessel radius.

$v_{CO_2}$
- Implementation Name: v_C
- Units: mmHg
- Initial value: $v_{CO_2,n}$
  Filtered carbon dioxide partial pressure.

$v_{O_2}$
- Implementation Name: v_O
- Units: mM
- Initial value: $v_{O_2,n}$
  Filtered capillary oxygen concentration.

$v_{Pa}$
- Implementation Name: v_P
- Units: mmHg
- Initial value: $v_{Pa,n}$
  Filtered arterial blood pressure.

$v_d$
- Implementation Name: v_u
- Units: dimensionless
- Initial value: $v_{u,n}$
  Filtered demand.

$HbO_{2,v}$
- Implementation Name: X0v
- Units: mM
- Initial value: $HbO_{2,v,n}$
  Venous concentration of oxygen bound to haemoglobin.
4.6 Intermediate Variables

\[ \text{Cu}_{A,r} = \text{CCO}_{\text{tot}} - \text{Cu}_{A,o} \]
Implementation Name: \textit{ared}
Units: mM
Initial value: 0
Concentration of reduced Cu\(_A\).

\[ a_{3,o} = \text{CCO}_{\text{tot}} - a_{3,r} \]
Implementation Name: \textit{b}
Units: mM
Initial value: 0
Concentration of oxidised cytochrome a\(_3\).

\[ C_{0,i} = 10^{-pH_m} - 10^{-pH_m - dPH} \frac{dpH}{dpH} \]
Implementation Name: \textit{C0i}
Units: dimensionless
Initial value: 0
Natural buffering capacity of protons in mitochondria.

\[ \text{CBF} = G \left( P_a - P_v \right) \]
Implementation Name: \textit{CBF}
Units: ml\_blood ml\_brain s\(^{-1}\)
Initial value: \( \text{CBF}_{\text{ref}} \)
Cerebral blood flow.

\[ \Delta \text{oxCCO} = \Delta \text{oxCCO}_{\text{off}} + 1000 \text{Vol}_{\text{mit}} \left( \text{Cu}_{A,o} - \text{Cu}_{A,o,n} \right) \]
Implementation Name: \textit{CCCC}
Units: uM
Initial value: 0
Cytochrome c oxidase signal measured by NIRS.

\[ \text{CMRO}_2 = f_3 \text{Vol}_{\text{mit}} \]
Implementation Name: \textit{CMRO2}
Units: mM s\(^{-1}\)
Initial value: 0
Rate of cerebral oxygen metabolism.

\[ \Delta p = \psi + Z \left( pH_m - pH_v \right) \]
Implementation Name: \textit{Dp}
Units: mV
Initial value: 0
Proton motive force across the mitochondrial inner membrane.

\[ \eta = R_p \left( \frac{v_p}{v_p,n} - 1 \right) + R_O_2 \left( \frac{v_O_2}{v_O_2,n} - 1 \right) + R_{CO_2} \left( 1 - \frac{v_{CO_2}}{v_{CO_2,n}} \right) + R_u \left( 1 - \frac{v_u}{v_{u,n}} \right) \]
Implementation Name: \textit{eta}
Units: dimensionless
Initial value: 0
Merged autoregulation stimulus.

\[ f_1 = k_1 \text{Cu}_{A,o} - k_{-1} \text{Cu}_{A,r} \]
Implementation Name: \textit{f1}
Units: mM s\(^{-1}\)
Initial value: 0
Reaction rate for the reduction of Cu\(_A\).

\[ f_3 = k_2 \text{Cu}_{A,r} a_{3,o} - k_{-2} \text{Cu}_{A,o} a_{3,r} \]
Implementation Name: \textit{f2}
4.6 Intermediate Variables

\[ \begin{align*}
\text{Units: mM s}^{-1} \\
\text{Initial value: 0} \\
\text{Reaction rate for the reduction of } a_3.
\end{align*} \]

\[ f_3 = \frac{k_3 O_2 a_{\text{3,r}} \exp \left( -c_3 \left( \Delta p - \Delta p_{\text{30}} \right) \right)}{1 + \exp \left( -c_3 \left( \Delta p - \Delta p_{\text{30}} \right) \right)} \]

Implementation Name: \( f_3 \)

\[ \text{Units: mM s}^{-1} \]

\[ \text{Initial value: 0} \]

\[ \text{Reaction rate for the reduction of O}_2. \]

\[ G = K_G r^4 \]

Implementation Name: \( G \)

\[ \text{Units: ml}_{\text{blood}} \cdot \text{ml}_{\text{brain}}^{-1} \cdot \text{mmHg}^{-1} \cdot \text{s}^{-1} \]

\[ \text{Initial value: 0} \]

Effect of conductance of the whole blood flow compartment.

\[ \text{HbO}_2 = (V_a HbO_{2,a} + V_v HbO_{2,v}) \text{ blood}_{\text{hb}} \]

Implementation Name: \( \text{HbO}_2 \)

\[ \text{Units: } \text{uM} \]

\[ \text{Initial value: 0} \]

Oxygenated haemoglobin signal measured by NIRS.

\[ \text{HbT} = (V_a + V_v) Hb_{\text{tot}} \text{ blood}_{\text{hb}} \]

Implementation Name: \( \text{HbT} \)

\[ \text{Units: } \text{uM} \]

\[ \text{Initial value: 0} \]

Total haemoglobin signal measured by NIRS.

\[ HHb = \text{HbT} - \text{HbO}_2 \]

Implementation Name: \( \text{HHb} \)

\[ \text{Units: } \text{uM} \]

\[ \text{Initial value: 0} \]

Deoxygenated haemoglobin signal measured by NIRS.

\[ J_{O2} = \text{fmin} \left( D_{O2} (O_2,c - O_2), CBF HbO_{2,a} \right) \]

Implementation Name: \( J_{O2} \)

\[ \text{Units: mM s}^{-1} \]

\[ \text{Initial value: 0} \]

Oxygen flux from blood to tissue.

\[ k_1 = k_{1,0} \exp \left( -c_{k_1} \left( \Delta p - \Delta p_{\mu} \right) \right) \]

Implementation Name: \( k_1 \)

\[ \text{Units: s}^{-1} \]

\[ \text{Initial value: 0} \]

Forward reaction rate for the reduction of Cu\(_A\).

\[ k_2 = k_{2,0} \exp \left( -c_{k_2} \left( \Delta p - \Delta p_{\mu} \right) \right) \]

Implementation Name: \( k_2 \)

\[ \text{Units: s}^{-1} \]

\[ \text{Initial value: 0} \]

Forward reaction rate for the reduction of \( a_3 \).

\[ K_{\text{eq}1} = 10^\frac{1}{Z} \left( \frac{\alpha_{\text{h}}}{\Delta E_{\text{h}}} - e_1 \right) \]

Implementation Name: \( K_{\text{eq}1} \)

\[ \text{Units: dimensionless} \]

\[ \text{Initial value: 0} \]

Equilibrium constant for the Cu\(_A\) reduction reaction.

\[ K_{\text{eq}2} = 10^\frac{1}{Z} \left( \frac{\alpha_{\text{h}}}{\Delta E_{\text{h}}} - e_2 \right) \]
Implementation Name: $K_{eq2}$
Units: dimensionless
Initial value: 0
Equilibrium constant for the $a_3$ reduction reaction.

$$k_{-1} = \frac{k_1}{K_{eq1}}$$
Implementation Name: $kn1$
Units: s$^{-1}$
Initial value: 0
Reverse reaction rate for the reduction of $Cu_A$.

$$k_{-2} = \frac{k_2}{K_{eq2}}$$
Implementation Name: $kn2$
Units: s$^{-1}$
Initial value: 0
Reverse reaction rate for the reduction of $a_3$.

$$L = L_{CV} + L_{lk}$$
Implementation Name: L
Units: mM s$^{-1}$
Initial value: 0
Rate of proton return to the mitochondrial matrix.

$$L_{CV} = \frac{CV_{inh} L_{CV,max} (1 - \exp(-\theta))}{1 + r_{CV} \exp(-\theta)}$$
Implementation Name: $L_{CV}$
Units: mM s$^{-1}$
Initial value: 0
Rate at which protons re-enter the mitochondrial matrix due to ADP phosphorylation.

$$L_{lk} = k_{unc} L_{lk0} (\exp(\Delta p k_{lk2}) - 1)$$
Implementation Name: $L_{lk}$
Units: mM s$^{-1}$
Initial value: 0
Rate at which protons re-enter the mitochondrial matrix via leak channels.

$$\mu = \frac{k_{aut} (\exp(\eta) - 1)}{\exp(\eta) + 1}$$
Implementation Name: $mu$
Units: dimensionless
Initial value: 0
Effective strength of the autoregulation response.

$$pH_m = -\log_{10}(\frac{H^+}{1000})$$
Implementation Name: $pH_m$
Units: dimensionless
Initial value: 0
Mitochondrial pH.

$$r_{buffi} = \frac{C_{buffi}}{C_{0,j}}$$
Implementation Name: $r_{buffi}$
Units: dimensionless
Initial value: 0
Buffering capacity for protons in mitochondria.

$$R_{Hi} = r_{buffi}$$
4.7 Parameters

Implementation Name: \text{R}_{\text{Hi}}
Units: dimensionless
Initial value: 0
Relative mitochondrial volume for protons, taking into account buffering effect of pH.

\[ S_{c,\text{O}_2} = \frac{S_{a,\text{O}_2} + S_{v,\text{O}_2}}{2} \]
Implementation Name: Sc02
Units: dimensionless
Initial value: \( S_{c,\text{O}_2} \)
Capillary oxygen saturation.

\[ S_{v,\text{O}_2} = \frac{HbO_{2,v}}{Hb_{\text{tot}}} \]
Implementation Name: Sv02
Units: dimensionless
Initial value: \( S_{v,\text{O}_2} \)
Venous oxygen saturation.

\[ \theta = k_{CV} (\Delta P + Z \log_{10} (u) - \Delta P_{CV,0}) \]
Implementation Name: theta
Units: dimensionless
Initial value: 0
Driving force Complex V.

\[ T0I = \frac{100HbO_2}{HbT} \]
Implementation Name: T0I
Units: dimensionless
Initial value: 0
Total oxygenation index.

\[ V_{mca} = \frac{CBF \cdot CBF_{\text{scale}}}{1} \]
Implementation Name: Vmca
Units: cm s\(^{-1}\)
Initial value: 0
Blood velocity in the middle cerebral artery.

\[ V_a = V_{a,n} \left( \frac{r}{r_n} \right)^2 \]
Implementation Name: Vol_art
Units: dimensionless
Initial value: 0
Relative arterial blood volume.

\[ Cu_{a,\text{frac},n} \]
Implementation Name: a_frac_n
Units: dimensionless
Initial value: 0.8
Normal oxidised fraction of \( Cu_A \).

\[ Cu_{A,\rho,n} \]
Implementation Name: a_n
Units: mM
Initial value: \( CCO_{\text{tot}} Cu_{a,\text{frac},n} \)
Normal concentration of oxidised cytochrome c oxidase.
$Cu_{A,r,n}$
Implementation Name: a\_red\_n
Units: mM
Initial value: $CCO_{\text{tot}} - Cu_{A,o,n}$
Normal concentration of reduced Cu.

$a_{3,o,n}$
Implementation Name: b\_n
Units: mM
Initial value: $CCO_{\text{tot}} - a_{3,r,n}$
Normal concentration of oxidised cytochrome a$_3$.

$blood_{hb}$
Implementation Name: b\_lood\_hb
Units: dimensionless
Initial value: 10.00
Factor to convert model haemoglobin concentration to instrumental units. Scales for blood fraction of brain volume, mM to $\mu$M, and number of binding sites.

$a_{3,r,n}$
Implementation Name: b\_red\_n
Units: mM
Initial value: 
$\frac{f_a}{O_2}$
Normal concentration of reduced cytochrome a$_3$.

$c_3$
Implementation Name: c3
Units: mV$^{-1}$
Initial value: 0.11
Parameter controlling the sensitivity of the reduction of a$_3$ to $\Delta p$.

$C_{buffer}$
Implementation Name: c\_buffer
Units: dimensionless
Initial value: 0.022
Buffering capacity of protons in mitochondria.

$C_{\text{im}}$
Implementation Name: c\_im
Units: mM mV$^{-1}$
Initial value: 0.00675
Capacitance of the mitochondrial inner membrane.

$C_{\text{NADH}} = \frac{Z}{2} \log_{10} \left( \frac{1}{\text{NAD} \text{NADH}} \right)$
Implementation Name: c\_NADH
Units: mV
Initial value: 0
Excess redox potential for NADH at normal demand.

$C_{\text{NADH}_n}$
Implementation Name: c\_NADH\_n
Units: mV
Initial value: $\frac{Z}{2} \log_{10} \left( \frac{1}{\text{NAD}_n \text{NADH}_n} \right)$
Normal value of $C_{\text{NADH}}$. 
4.7 Parameters

$CBF_n$
Implementation Name: $CBF_n$
Units: $ml_{blood} ml_{brain} s^{-1}$
Initial value: 0.0125
Normal cerebral blood flow.

$CBFscale$
Implementation Name: $CBFscale$
Units: cm
Initial value: 5000
Scale constant relating blood flow to arterial velocity.

$\Delta oxCCO_{off}$
Implementation Name: $CCO_{offset}$
Units: uM
Initial value: 0
Signal offset for the NIRS CCO measurement.

$ck_1$
Implementation Name: $ck1$
Units: mV$^{-1}$
Initial value: 0.01
Parameter controlling sensitivity of $k_1$ to $\Delta p$.

$ck_2$
Implementation Name: $ck2$
Units: mV$^{-1}$
Initial value: 0.02
Parameter controlling sensitivity of $k_2$ to $\Delta p$.

$CMRO_{2,n}$
Implementation Name: $CMR2_n$
Units: mM s$^{-1}$
Initial value: 0.034
Normal metabolic rate of oxygen consumption.

$CV_{inh}$
Implementation Name: $CV_{inh}$
Units: dimensionless
Initial value: 1
Control parameter representing the action of Complex V inhibitors.

$CCO_{tot} = \frac{CCO_{tot}}{Vol_{mit}}$
Implementation Name: $cytox_{tot}$
Units: mM
Initial value: 0
Concentration of cytochrome c oxidase in mitochondria.

$CCO_{tis}$
Implementation Name: $cytox_{tot, tis}$
Units: mM
Initial value: 0.0055
Concentration of cytochrome c oxidase in tissue.

$D_{NADH}$
Implementation Name: $D_{NADH}$
Units: dimensionless
Initial value: 0.01
Scale parameter for the dependence of NADH redox potential on demand.
\( D_{O_2} \)
- Implementation Name: \( D_{O_2} \)
- Units: \( s^{-1} \)
- Initial value: \( \frac{I_{O_2,n}}{O_{2,c,n} - O_{2,m,n}} \)
- Diffusion rate for oxygen between capillaries and mitochondria.

\( \Delta p_{3,corr} \)
- Implementation Name: \( \Delta p_{3,corr} \)
- Units: mV
- Initial value: \(-25\)
- Difference between \( \Delta p_{30} \) and normal \( \Delta p \).

\( \Delta p_{30} = \Delta p_n + \Delta p_{3,corr} \)
- Implementation Name: \( \Delta p_{30} \)
- Units: mV
- Initial value: 0
- Value of \( \Delta p \) to which \( a_3 \) reduction reaction is maximally sensitive.

\( \Delta p_{CV,0} \)
- Implementation Name: \( \Delta p_{CV,0} \)
- Units: mV
- Initial value: 90
- Value of \( \Delta p \) at which \( L_{CV} \) is zero under normal demand.

\( \Delta p_n \)
- Implementation Name: \( \Delta p_n \)
- Units: mV
- Initial value: \( \psi_n + Z \Delta pH_n \)
- Normal value of \( \Delta p \)

\( dpH \)
- Implementation Name: \( dpH \)
- Units: dimensionless
- Initial value: 0.001
- Parameter in the mitochondrial proton buffering relationship.

\( \Delta pH_n \)
- Implementation Name: \( \Delta pH_n \)
- Units: dimensionless
- Initial value: \( pH_{m,n} - pH_{o,n} \)
- Normal pH difference across the mitochondrial inner membrane.

\( \psi_n \)
- Implementation Name: \( \psi_n \)
- Units: mV
- Initial value: 145
- Normal mitochondrial inner membrane potential.

\( E_{1,NADH} = E_0(Cu_A) - E_0(NADH) + C_{NADH} \)
- Implementation Name: \( E_{1,NADH} \)
- Units: mV
- Initial value: 0
- Value of \( E_1 \) when the reducing substrate is NADH.

\( E_{1,NADH,n} \)
- Implementation Name: \( E_{1,NADH,n} \)
- Units: mV
- Initial value: \( E_0(Cu_A) - E_0(NADH) + C_{NADH,n} \)
- Normal value of \( E_{1,NADH} \).
4.7 Parameters

\( E_1 \)
- Implementation Name: \( E_{1,1} \)
- Units: mV
- Initial value: \( E_{1,NADH} \)
The energy provided by electron transfer to \( \text{Cu}_{A,r} \).

\( E_{1,n} \)
- Implementation Name: \( E_{1,1n} \)
- Units: mV
- Initial value: \( E_{1,NADH,n} \)
- Normal value of \( E_1 \).

\( E_2 \)
- Implementation Name: \( E_{2,2} \)
- Units: mV
- Initial value: \( E_{1,NADH,n} \)
- Energy provided by the transfer of four electrons from \( \text{Cu}_{A,r} \) to \( a_{3,o} \).

\( \mathcal{E}_0(a_3) \)
- Implementation Name: \( \mathcal{E}_{0,30} \)
- Units: mV
- Initial value: 350
- Standard redox potential for cytochrome \( a_3 \).

\( \mathcal{E}_0(\text{Cu}_A) \)
- Implementation Name: \( \mathcal{E}_{0,c0} \)
- Units: mV
- Initial value: 247
- Standard redox potential for \( \text{Cu}_A \).

\( \mathcal{E}_0(\text{NADH}) \)
- Implementation Name: \( \mathcal{E}_{0,w0} \)
- Units: mV
- Initial value: –320
- Standard redox potential for NADH.

\( f_n \)
- Implementation Name: \( f_{n,n} \)
- Units: mM s\(^{-1}\)
- Initial value: \( \frac{\text{CMRO}_2}{V_{\text{Volmit}}} \)
- Normal resting value of \( f_1 \) and \( f_2 \).

\( G_n \)
- Implementation Name: \( G_{n,n} \)
- Units: ml\(_{\text{blood}}\) ml\(_{\text{brain}}^{-1}\) mmHg\(^{-1}\) s\(^{-1}\)
- Initial value: \( \frac{P_{a,n} - P_{v,n}}{C_{\text{BF}_n}} \)
- Normal blood vessel conductance.

\( H_{n}^+ \)
- Implementation Name: \( H_{n,n} \)
- Units: mM
- Initial value: \( 10^{3-pH_{n,n}} \)
- Normal mitochondrial proton concentration.

\( J_{O_2,n} \)
- Implementation Name: \( J_{02,n} \)
- Units: mM s\(^{-1}\)
- Initial value: \( \text{CMRO}_2 \)
- Normal oxygen flux from blood to tissue.
$k_{1,0}$

Implementation Name: $k10$
Units: $s^{-1}$
Initial value: $k_{1,n} \frac{NADH}{NADH_n}$
Forward reaction rate for the reduction of Cu$_A$ at normal $\Delta p$.

$k_{1,n}$

Implementation Name: $k1_n$
Units: $s^{-1}$
Initial value: $f_n \frac{1}{K_{eq1,n} Cu_{A,r,n}}$
Forward reaction rate for the reduction of Cu$_A$ at normal $\Delta p$ and NADH.

$k_{2,n}$

Implementation Name: $k2_n$
Units: $s^{-1}$
Initial value: $f_n \frac{1}{K_{eq2,n} Cu_{A,o,n} a_{3,r,n}}$
Normal forward reaction rate for the reduction of $a_3$.

$k_3 = \frac{k_{3,0}}{1+\exp\left(-c_3-\Delta p_{30}\right)}$

Implementation Name: $k3$
Units: $s^{-1}$
Initial value: 0
Forward reaction rate for the reduction of O$_2$.

$k_{3,0}$

Implementation Name: $k30$
Units: $s^{-1}$
Initial value: $2.5E+5$
Apparent second order rate constant for reduction of O$_2$ at zero $\Delta p$.

$k_{aut}$

Implementation Name: $k_{aut}$
Units: dimensionless
Initial value: 1
Overall functioning of autoregulatory response.

$K_G$

Implementation Name: $k_G$
Units: $ml_{blood} \cdot ml_{brain}^{-1} \cdot mmHg^{-1} \cdot s^{-1} \cdot cm^{-4}$
Initial value: $G_n \frac{1}{\text{pow} \left( r_n, 4 \right)}$
Proportionality constant in Poiseuille relation for conductance.

$k_{lk2}$

Implementation Name: $k_{lk2}$
Units: $mV^{-1}$
Initial value: 0.038
Constant controlling the depending of the leak rate $L_{lk}$ on $\Delta p$.

$k_{unc}$

Implementation Name: $k_{unc}$
Units: dimensionless
Initial value: 1
Control parameter simulating the effect of adding uncouplers to the system.
4.7 Parameters

\[ k_{CV} = \frac{-1}{\Delta p_n - \Delta p_{CV,0}} \log \left( \frac{1 - L_{CV,0}}{1 + r_{CV} L_{CV,0}} \right) \]

Implementation Name: \( k_{CV} \)
Units: \( \text{mV}^{-1} \)
Initial value: 0
Parameter controlling the sensitivity of Complex V flux to driving force.

\[ K_{eq1,n} \]
Implementation Name: \( K_{eq1,n} \)
Units: dimensionless
Initial value: \( 10^{-1} \left( \frac{1}{P_{\Delta p_n}} - E_{1,n} \right) \)
Normal value of the equilibrium constant for the CuA reduction reaction.

\[ K_{eq2,n} \]
Implementation Name: \( K_{eq2,n} \)
Units: dimensionless
Initial value: \( 10^{-1} \left( \frac{1}{P_{\Delta p_n}} - E_{2} \right) \)
Normal value of the equilibrium constant for the a3 reduction reaction.

\[ L_{CV,0} \]
Implementation Name: \( L_{CV0} \)
Units: dimensionless
Initial value: 0.4
Normal Complex V flux as a fraction of maximum possible flux.

\[ L_{CV,frac} = 1 - L_{lk,frac} \]
Implementation Name: \( L_{CVfrac} \)
Units: dimensionless
Initial value: 0
Normal fraction of proton entry into mitochondria which is due to ADP phosphorylation.

\[ L_{CV,max} = \frac{L_{CV,n}}{L_{CV,0}} \]
Implementation Name: \( L_{CVmax} \)
Units: \( \text{mM s}^{-1} \)
Initial value: 0
The maximum rate of proton flow through Complex V.

\[ L_{CV,n} \]
Implementation Name: \( L_{CVn} \)
Units: \( \text{mM s}^{-1} \)
Initial value: \( L_n L_{CV,frac} \)
The resting flow of protons into the matrix through Complex V.

\[ L_{lk0} \]
Implementation Name: \( L_{lk0} \)
Units: \( \text{mM s}^{-1} \)
Initial value: \( \exp \left( \frac{\Delta p_n k_{lk2}}{L_{lk,n}} - 1 \right) \)
Constant controlling the depending of the leak rate \( L_{lk} \) on \( \Delta p \).

\[ L_{lk,frac} \]
Implementation Name: \( L_{lkfrac} \)
Units: dimensionless
Initial value: 0.25
Normal fraction of proton entry into mitochondria which is via leak channels.

\[ L_{lk,n} \]
Implementation Name: \( L_{lkn} \)
Units: \( \text{mM s}^{-1} \)
Initial value: $L_n L_{lk,frac}$
The resting flow of protons into the matrix via leak channels.

$L_n = p_{tot} f_n$
Implementation Name: $L_n$
Units: mM s$^{-1}$
Initial value: 0
The normal total flow of protons back into mitochondria.

$\lambda_0$
Implementation Name: $\lambda_{am,0}$
Units: cm
Initial value: 0.01856
Intercept of the fitted linear model for blood vessel radius.

$\lambda_\mu$
Implementation Name: $\lambda_{am,\mu}$
Units: cm
Initial value: $-0.003935$
Fitted linear dependence of blood vessel radius on autoregulatory stimuli.

$n_h$
Implementation Name: $n_h$
Units: dimensionless
Initial value: 2.5
Hill coefficient for oxygen dissociation from haemoglobin.

$NADH = \frac{NAD_{pool}}{1 + \frac{NAD}{NADH}}$
Implementation Name: $\text{NADH}$
Units: mM
Initial value: 0
Concentration of NADH in the mitochondria.

$NADH_n$
Implementation Name: $\text{NADH}_n$
Units: mM
Initial value: $\frac{NAD_{pool}}{1 + \frac{NAD}{NADH_n}}$
Normal concentration of NADH in the mitochondria.

$\frac{NAD}{NADH}$
Implementation Name: $\text{NAD/NADH}$
Units: dimensionless
Initial value: $\frac{NAD}{NADH_\mu} \text{pow} (u, 2D_{NADH})$
NAD/NADH ratio.

$\frac{NAD}{NADH_n}$
Implementation Name: $\text{NAD/NADH}_n$
Units: dimensionless
Initial value: 9
Normal NAD/NADH ratio.

$NAD_{pool}$
Implementation Name: $\text{NADpool}$
Units: dimensionless
Initial value: 3
Relative size of the NAD pool, used to estimate normal mitochondrial NADH.
4.7 Parameters

\(O_{2,n}\)
- Implementation Name: O2_n
- Units: mM
- Initial value: 0.024
  Normal mitochondrial oxygen concentration.

\(O_{2,c,n}\)
- Implementation Name: O2c_n
- Units: mM
- Initial value: \(\phi \text{ pow} \left( \frac{S_c,O_{2,n}}{1 - S_c,O_{2,n}} \cdot \frac{1}{h_b} \right)\)
  Normal capillary oxygen concentration.

\(p_1 = p_{tot} - p_{23}\)
- Implementation Name: p1
- Units: dimensionless
- Initial value: 0
  Proton cost of the reaction reducing Cu_A.

\(p_3\)
- Implementation Name: p2
- Units: dimensionless
- Initial value: 4
  Proton cost of the reaction reducing a_3.

\(p_{23}\)
- Implementation Name: p23
- Units: dimensionless
- Initial value: 8
  Total protons removed from the mitochondrial matrix by the reductions of a_3 and O_2.

\(p_3\)
- Implementation Name: p3
- Units: dimensionless
- Initial value: \(p_{23} - p_3\)
  Proton cost of the reaction reducing O_2.

\(P_a\)
- Implementation Name: P_a
- Units: mmHg
- Initial value: \(P_{a,n}\)
  Mean arterial blood pressure.

\(P_{a,n}\)
- Implementation Name: P_an
- Units: mmHg
- Initial value: 100
  Normal arterial blood pressure.

\(P_{C1}\)
- Implementation Name: p_C1
- Units: dimensionless
- Initial value: 8
  Protons pumped by Complex I.

\(P_{C3}\)
- Implementation Name: p_C3
- Units: dimensionless
- Initial value: 4
  Protons pumped by Complex III.
\[ P_{\text{tot}} \]
Implementation Name: \( p_{\text{tot}} \)
Units: dimensionless
Initial value: \( p_{\text{tot}}\text{NADH} \)
Total protons removed from the mitochondrial matrix by the three modelled electron transport reactions.

\[ P_{\text{tot}}\text{NADH} = p_{C_{1}} + p_{C_{3}} + p_{23} \]
Implementation Name: \( p_{\text{tot}}\text{NADH} \)
Units: dimensionless
Initial value: 0
Total protons pumped when the reducing agent is NADH.

\[ P_{\text{v}} \]
Implementation Name: \( P_{\text{v}} \)
Units: mmHg
Initial value: \( P_{\text{v,n}} \)
Venous blood pressure.

\[ P_{\text{v,n}} \]
Implementation Name: \( P_{\text{v,n}} \)
Units: mmHg
Initial value: 4
Normal venous blood pressure.

\[ P_{\text{aCO}_2} \]
Implementation Name: \( P_{\text{aCO}_2} \)
Units: mmHg
Initial value: \( P_{\text{aCO}_2,n} \)
Arterial partial pressure of carbon dioxide.

\[ P_{\text{aCO}_2,n} \]
Implementation Name: \( P_{\text{aCO}_2,n} \)
Units: mmHg
Initial value: 40
Normal arterial partial pressure of carbon dioxide.

\[ P_{\text{Hm,n}} \]
Implementation Name: \( P_{\text{Hm,n}} \)
Units: dimensionless
Initial value: 7.4
Normal mitochondrial pH.

\[ P_{\text{H}} \]
Implementation Name: \( P_{\text{H}} \)
Units: dimensionless
Initial value: 7
Extra-mitochondrial pH.

\[ P_{\text{H,o,n}} \]
Implementation Name: \( P_{\text{H,o,n}} \)
Units: dimensionless
Initial value: 7
Normal extra-mitochondrial pH.

\( \phi \)
Implementation Name: \( \phi \)
Units: mM
Initial value: 0.036
Oxygen concentration at half-maximal saturation.
4.7 Parameters

\( R_{CO_2} \)
- Implementation Name: \( R_{autc} \)
- Units: dimensionless
- Initial value: 2.2
- Autoregulatory reactivity to carbon dioxide.

\( R_{O_2} \)
- Implementation Name: \( R_{auto} \)
- Units: dimensionless
- Initial value: 1.5
- Autoregulatory reactivity to oxygen.

\( R_{Pa} \)
- Implementation Name: \( R_{autp} \)
- Units: dimensionless
- Initial value: 4
- Autoregulatory reactivity to blood pressure.

\( R_u \)
- Implementation Name: \( R_{autu} \)
- Units: dimensionless
- Initial value: 0.5
- Autoregulatory reactivity to demand.

\( r_{CV} \)
- Implementation Name: \( r_{CV} \)
- Units: dimensionless
- Initial value: 5
- Parameter controlling the ratio of maximal to minimal rates of oxidative phosphorylation.

\( r_n \)
- Implementation Name: \( r_n \)
- Units: cm
- Initial value: 0.0187
- Normal blood vessel radius. Normal effective blood vessel radius.

\( S_{a,O_2,n} \)
- Implementation Name: \( SaO2_n \)
- Units: dimensionless
- Initial value: 0.96
- Normal arterial oxygen saturation.

\( S_{a,O_2} \)
- Implementation Name: \( SaO2sup \)
- Units: dimensionless
- Initial value: \( S_{a,O_2,n} \)
- Arterial oxygen saturation.

\( S_{c,O_2,n} \)
- Implementation Name: \( ScO2_n \)
- Units: dimensionless
- Initial value: \( \frac{S_{a,O_2,n} + S_{c,O_2,n}}{2} \)
- Normal capillary oxygen saturation.

\( S_{v,O_2,n} \)
- Implementation Name: \( S_vO2_n \)
- Units: dimensionless
- Initial value: \( \frac{HbO_2,v,n}{HbO_2,tot,n} \)
- Normal venous oxygen saturation.
Implementation Name: $t$
Units: s
Initial value: 0
Time over which the system evolves.

Implementation Name: $\tau_{CO_2}$
Units: s
Initial value: 5
Filter time constant for stimulus effect of carbon dioxide.

Implementation Name: $\tau_{O_2}$
Units: s
Initial value: 20
Filter time constant for stimulus effect of capillary oxygen.

Implementation Name: $\tau_{P_a}$
Units: s
Initial value: 5
Filter time constant for stimulus effect of blood pressure.

Implementation Name: $\tau_u$
Units: s
Initial value: 0.5
Filter time constant for stimulus effect of demand.

Implementation Name: $u$
Units: dimensionless
Initial value: $u_n$
Parameter indicating metabolic demand.

Implementation Name: $u_n$
Units: dimensionless
Initial value: 1
Normal demand.

Implementation Name: $v_{CO_2,n}$
Units: mmHg
Initial value: $P_{tCO_2,n}$
Normal filtered carbon dioxide partial pressure. Normal filtered carbon dioxide partial pressure.

Implementation Name: $v_{O_2,n}$
Units: mM
Initial value: $O_{2,c,n}$
Normal filtered capillary oxygen concentration. Normal filtered capillary oxygen concentration.

Implementation Name: $v_{P_a,n}$
Units: mmHg
Initial value: $P_{a,n}$
4.7 Parameters

Normal filtered arterial blood pressure. Normal filtered blood pressure.

\( v_{u,n} \)
- Implementation Name: \( v_{\_un} \)
- Units: dimensionless
- Initial value: \( u_n \)
- Normal filtered demand. Normal filtered demand.

\( V_{Arat_n} \)
- Implementation Name: \( \text{Varat}_n \)
- Units: dimensionless
- Initial value: 3
- Normal volume ratio of veins to arteries in brain tissue.

\( V_{a,n} \)
- Implementation Name: \( \text{Volart}_n \)
- Units: dimensionless
- Initial value: \( \frac{1}{1 + \text{Varat}_n} \)
- Normal relative arterial blood volume.

\( V_{mit} \)
- Implementation Name: \( \text{Volmit} \)
- Units: dimensionless
- Initial value: 0.067
- Fraction of brain tissue volume that is mitochondria.

\( V_p \)
- Implementation Name: \( \text{Volven} \)
- Units: dimensionless
- Initial value: \( \frac{1}{1 + \text{Varat}_n} \)
- Relative venous blood volume.

\( HbO_{2,a} = Hb_{\text{tot}} S_{a,O_2} \)
- Implementation Name: \( \text{XOa} \)
- Units: mM
- Initial value: \( HbO_{2,a,n} \)
- Arterial concentration of oxygen bound to haemoglobin.

\( HbO_{2,a,n} \)
- Implementation Name: \( \text{XO}_a{}_{\_n} \)
- Units: mM
- Initial value: \( Hb_{\text{tot},n} S_{a,O_2,n} \)
- Normal arterial concentration of oxygen bound to haemoglobin.

\( HbO_{2,v,n} \)
- Implementation Name: \( \text{XO}_v{}_{\_n} \)
- Units: mM
- Initial value: \( \frac{\text{CBF}_n HbO_{2,a,n} - I_{O_2,n}}{\text{CBF}_n} \)
- Normal venous concentration of oxygen bound to haemoglobin.

\( Hb_{\text{tot}} \)
- Implementation Name: \( \text{Xtot} \)
- Units: mM
- Initial value: 9.1
- Total concentration of haemoglobin O\(_2\) binding sites in blood (4 times haemoglobin concentration).

\( Hb_{\text{tot},n} \)
- Implementation Name: \( \text{Xtot}_n \)
Units: mM
Initial value: 9.1
Normal total concentration of haemoglobin O\textsubscript{2} binding sites in blood (4 times haemoglobin concentration).

Z
Implementation Name: Z
Units: mV
Initial value: 59.028
Proportionality constant in calculation of driving forces due to concentration differences. Defined as \( RT/F \), where \( F \) is Faraday’s constant, \( R \) the ideal gas constant and \( T \) the absolute temperature.
5 BSB4

5.1 Overview

Simplified model in which the blood flow submodel is replaced with variant B4.

- 9 differential state variables
- 3 algebraic state variables
- 35 intermediate variables
- 120 parameters
- 4 declared inputs
- 33 default outputs

5.2 Differential Equations

\[ \frac{dC_{4,0}}{dt} = 4f_3 - 4f_1 \]  
(5.1)

\[ \frac{d\alpha_{3,r}}{dt} = 4f_3 - 4f_3 \]  
(5.2)

\[ \frac{d\psi}{dt} = \frac{p_3 f_3 + p_1 f_1 + p_3 f_3 - L}{C_{im}} \]  
(5.3)

\[ \frac{dH^+}{dt} = \frac{1}{R_{Hi}} L - \frac{p_3}{R_{Hi}} f_3 - \frac{p_1}{R_{Hi}} f_1 - \frac{p_3}{R_{Hi}} f_3 \]  
(5.4)

\[ \frac{dO_2}{dt} = \frac{1}{Vol_{mit}} I_{O_2} - f_3 \]  
(5.5)

\[ \frac{dV_{CO_2}}{dt} = \frac{1}{\tau_{CO_2}} (P_{a,CO_2} - v_{CO_2}) \]  
(5.6)

\[ \frac{dV_{O_2}}{dt} = \frac{1}{\tau_{O_2}} (O_{2,c} - v_{O_2}) \]  
(5.7)

\[ \frac{dV_p}{dt} = \frac{1}{\tau_p} (P_a - v_p) \]  
(5.8)
\[ \frac{d\nu_d}{dt} = \frac{1}{\tau_u} (u - \nu_u) \] (5.9)

### 5.3 Algebraic Equations

\[ \phi \left( \frac{S_{c,O_2}}{1 - S_{c,O_2}} \right) \frac{1}{\tau_t} - O_{2,c} = 0 \] (5.10)

\[ \lambda_0 + \frac{\lambda_{p_a}}{P_a} - r = 0 \] (5.11)

\[ \text{CBF} \ (HbO}_{2,a} - HbO}_{2,o}) - IO_2 = 0 \] (5.12)

### 5.4 Chemical Reactions

\[ \xrightarrow{L} \frac{1}{R_{Hi}} \text{H}^+ \] (5.13)

\[ \xrightarrow{J_{O_2}} \frac{1}{Vol_{mit}} \text{O}_2 \] (5.14)

\[ \frac{P_3}{R_{Hi}} \text{H}^+ \xrightarrow{f_3} 4 \text{Cu}_{A,o} + 4 \text{a}_{3,r} \] (5.15)

\[ 4 \text{Cu}_{A,o} + \frac{P_1}{R_{Hi}} \text{H}^+ \xrightarrow{f_1} \] (5.16)

\[ \text{O}_2 + 4 \text{a}_{3,r} + \frac{P_3}{R_{Hi}} \text{H}^+ \xrightarrow{f_3} \] (5.17)

### 5.5 State Variables

\( C_{\text{Cu}_{A,o}} \)

- Implementation Name: a
- Units: mM
- Initial value: \( C_{\text{Cu}_{A,o,n}} \)
  Concentration of oxidised cytochrome c oxidase.

\( \text{a}_{3,r} \)

- Implementation Name: b3rd
- Units: mM
- Initial value: \( \text{a}_{3,r,n} \)
  Concentration of reduced cytochrome a3.
5.5 State Variables

\( \psi \)
Implementation Name: Dpsi
Units: mV
Initial value: \( \psi_n \)
Mitochondrial inner membrane potential. Varies as charge (in the form of protons) is transferred across the membrane capacitance.

\( H^+ \)
Implementation Name: H
Units: mM
Initial value: \( H^+_n \)
Mitochondrial proton concentration.

\( O_2 \)
Implementation Name: 02
Units: mM
Initial value: \( O_{2,n} \)
Mitochondrial oxygen concentration.

\( O_{2,c} \)
Implementation Name: 02c
Units: mM
Initial value: \( O_{2,c,n} \)
Capillary oxygen concentration.

\( r \)
Implementation Name: r
Units: cm
Initial value: \( r_n \)
Typical blood vessel radius.

\( \nu_{CO_2} \)
Implementation Name: \( \nu_{c} \)
Units: mmHg
Initial value: \( \nu_{CO_2,n} \)
Filtered carbon dioxide partial pressure.

\( \nu_{O_2} \)
Implementation Name: \( \nu_{o} \)
Units: mM
Initial value: \( \nu_{O_2,n} \)
Filtered capillary oxygen concentration.

\( \nu_{Pa} \)
Implementation Name: \( \nu_{p} \)
Units: mmHg
Initial value: \( \nu_{Pa,n} \)
Filtered arterial blood pressure.

\( \nu_{u} \)
Implementation Name: \( \nu_{u} \)
Units: dimensionless
Initial value: \( \nu_{u,n} \)
Filtered demand.

\( HbO_{2,v} \)
Implementation Name: \( \chi_{0v} \)
Units: mM
Initial value: \( HbO_{2,v,n} \)
Venous concentration of oxygen bound to haemoglobin.
5.6 Intermediate Variables

\[ Cu_{A,r} = CCO_{tot} - Cu_{A,o} \]
- Implementation Name: ared
- Units: mM
- Initial value: 0
- Concentration of reduced CuA.

\[ a_{3,o} = CCO_{tot} - a_{3,r} \]
- Implementation Name: b
- Units: mM
- Initial value: 0
- Concentration of oxidised cytochrome a3.

\[ C_{0,i} = \frac{10^{-pH_{in}} - 10^{-pH_{in} - dpH}}{dpH} \]
- Implementation Name: C_0i
- Units: dimensionless
- Initial value: 0
- Natural buffering capacity of protons in mitochondria.

\[ CBF = G (P_a - P_v) \]
- Implementation Name: CBF
- Units: ml brain\(^{-1}\) s\(^{-1}\)
- Initial value: CBF\(_{ref}\)
- Cerebral blood flow.

\[ \Delta oxCCO = \Delta oxCCO_{off} + 1000 Vol_{mit} (Cu_{A,o} - Cu_{A,r,n}) \]
- Implementation Name: CCCO
- Units: mM
- Initial value: 0
- Cytochrome c oxidase signal measured by NIRS.

\[ CMRO_2 = f_3 Vol_{mit} \]
- Implementation Name: CMRO2
- Units: mM s\(^{-1}\)
- Initial value: 0
- Rate of cerebral oxygen metabolism.

\[ \Delta p = \psi + Z (pH_m - pH_o) \]
- Implementation Name: Dp
- Units: mV
- Initial value: 0
- Proton motive force across the mitochondrial inner membrane.

\[ \eta = R_P \left( \frac{V_P}{V_{P,o,n}} - 1 \right) + R_{O_2} \left( \frac{V_{O_2}}{V_{O_2,n}} - 1 \right) + R_{CO_2} \left( 1 - \frac{V_{CO_2}}{V_{CO_2,n}} \right) + R_u \left( 1 - \frac{V_u}{V_{u,n}} \right) \]
- Implementation Name: eta
- Units: dimensionless
- Initial value: 0
- Merged autoregulation stimulus.

\[ f_1 = k_1 Cu_{A,o} - k_{-1} Cu_{A,r} \]
- Implementation Name: f1
- Units: mM s\(^{-1}\)
- Initial value: 0
- Reaction rate for the reduction of CuA.

\[ f_3 = k_2 Cu_{A,r} a_{3,o} - k_{-2} Cu_{A,o} a_{3,r} \]
- Implementation Name: f2
5.6 Intermediate Variables

Units: mM s$^{-1}$
Initial value: 0
Reaction rate for the reduction of $a_3$.

\[ f_3 = \frac{k_3 O_2 a_3 r \exp \left( -c_3 (\Delta p - \Delta p_{30}) \right)}{1 + \exp \left( -c_3 (\Delta p - \Delta p_{30}) \right)} \]

Implementation Name: $f_3$
Units: mM s$^{-1}$
Initial value: 0
Reaction rate for the reduction of $O_2$.

\[ G = K_G r^4 \]

Implementation Name: $G$
Units: ml$^{-1}$ blood ml$^{-1}$ brain mmHg$^{-1}$ s$^{-1}$
Initial value: 0
Effective conductance of the whole blood flow compartment.

\[ HbO_2 = (V_a HbO_2_a + V_v HbO_2_v) \text{ blood}_{hb} \]
Implementation Name: Hb02
Units: uM
Initial value: 0
Oxygenated haemoglobin signal measured by NIRS.

\[ HbT = (V_a + V_v) HbTot \text{ blood}_{hb} \]
Implementation Name: HbT
Units: uM
Initial value: 0
Total haemoglobin signal measured by NIRS.

\[ HHb = HbT - HbO_2 \]
Implementation Name: HHb
Units: uM
Initial value: 0
Deoxygenated haemoglobin signal measured by NIRS.

\[ J_{O2} = \text{fmin} \left( D_{O2} (O_{2c} - O_2), CBF HbO_2_a \right) \]
Implementation Name: J_{O2}
Units: mM s$^{-1}$
Initial value: 0
Oxygen flux from blood to tissue.

\[ k_1 = k_{1,0} \exp \left( -c_{k_1} (\Delta p - \Delta p_n) \right) \]
Implementation Name: k1
Units: s$^{-1}$
Initial value: 0
Forward reaction rate for the reduction of $Cu_A$.

\[ k_2 = k_{2,n} \exp \left( -c_{k_2} (\Delta p - \Delta p_n) \right) \]
Implementation Name: k2
Units: s$^{-1}$
Initial value: 0
Forward reaction rate for the reduction of $a_3$.

\[ K_{eq1} = 10^\frac{1}{p} \left( \frac{Hb}{4 - \varepsilon_1} \right) \]
Implementation Name: Keq1
Units: dimensionless
Initial value: 0
Equilibrium constant for the $Cu_A$ reduction reaction.

\[ K_{eq2} = 10^\frac{1}{q} \left( \frac{Hb}{4 - \varepsilon_2} \right) \]
Implementation Name: \( k_{eq2} \)
Units: dimensionless
Initial value: 0
Equilibrium constant for the \( a_3 \) reduction reaction.

\[
k_{-1} = \frac{k_1}{K_{eq1}}
\]

Implementation Name: \( kn1 \)
Units: \( s^{-1} \)
Initial value: 0
Reverse reaction rate for the reduction of \( Cu_A \).

\[
k_{-2} = \frac{k_2}{K_{eq2}}
\]

Implementation Name: \( kn2 \)
Units: \( s^{-1} \)
Initial value: 0
Reverse reaction rate for the reduction of \( a_3 \).

\[
L = L_{CV} + L_{lk}
\]

Implementation Name: \( L \)
Units: mM s\(^{-1} \)
Initial value: 0
Rate of proton return to the mitochondrial matrix.

\[
L_{CV} = \frac{CV_{inh} L_{CV,max} (1 - \exp(-\theta))}{1 + r_{CV} \exp(-\theta)}
\]

Implementation Name: \( L_{CV} \)
Units: mM s\(^{-1} \)
Initial value: 0
Rate at which protons re-enter the mitochondrial matrix due to ADP phosphorylation.

\[
L_{lk} = k_{unc} L_{lk0} (\exp(\Delta p k_{lk2}) - 1)
\]

Implementation Name: \( L_{lk} \)
Units: mM s\(^{-1} \)
Initial value: 0
Rate at which protons re-enter the mitochondrial matrix via leak channels.

\[
\mu = \frac{k_{aut} (\exp(\eta) - 1)}{\exp(\eta) + 1}
\]

Implementation Name: \( \mu \)
Units: dimensionless
Initial value: 0
Effective strength of the autoregulation response.

\[
pH_m = -\log_{10} \left( \frac{H^+}{1000} \right)
\]

Implementation Name: \( pH_m \)
Units: dimensionless
Initial value: 0
Mitochondrial pH.

\[
r_{buffi} = \frac{C_{buffi}}{C_{0i}}
\]

Implementation Name: \( r_{buffi} \)
Units: dimensionless
Initial value: 0
Buffering capacity for protons in mitochondria.

\[
R_{Hi} = r_{buffi}
\]
5.7 Parameters

Implementation Name: \( R_{Hi} \)
Units: dimensionless
Initial value: 0
Relative mitochondrial volume for protons, taking into account buffering effect of pH.

\[
S_{c,O_2} = \frac{S_a,O_2 + S_v,O_2}{2}
\]
Implementation Name: Sc02
Units: dimensionless
Initial value: \( S_{c,O_2,n} \)
Capillary oxygen saturation.

\[
S_{v,O_2} = \frac{HbO_2,v}{HbTot}
\]
Implementation Name: Sv02
Units: dimensionless
Initial value: \( S_{v,O_2,n} \)
Venous oxygen saturation.

\[
\theta = k_{CV} (\Delta p + Z \log_{10} (u) - \Delta p_{CV,0})
\]
Implementation Name: theta
Units: dimensionless
Initial value: 0
Driving force Complex V.

\[
TOI = \frac{100HbO_2}{HbT}
\]
Implementation Name: TOI
Units: dimensionless
Initial value: 0
Total oxygenation index.

\[
V_{mca} = CBF \cdot CBF_{scale}
\]
Implementation Name: Vmca
Units: cm s\(^{-1}\)
Initial value: 0
Blood velocity in the middle cerebral artery.

\[
V_a = V_{a,n} \left( \frac{r}{r_n} \right)^2
\]
Implementation Name: Vol_art
Units: dimensionless
Initial value: 0
Relative arterial blood volume.

5.7 Parameters

\( Cu_{a,frac,n} \)
Implementation Name: a_frac_n
Units: dimensionless
Initial value: 0.8
Normal oxidised fraction of Cu\(_A\).

\( Cu_{A,frac,n} \)
Implementation Name: a_n
Units: mM
Initial value: \( CCO_{tot} Cu_{a,frac,n} \)
Normal concentration of oxidised cytochrome c oxidase.
\[ Cu_{A,r,n} \]
Implementation Name: ared.n
Units: mM
Initial value: \( CCO_{tot} - Cu_{A,o,n} \)
Normal concentration of reduced Cu.

\[ a_{3,o,n} \]
Implementation Name: b_n
Units: mM
Initial value: \( CCO_{tot} - a_{3,r,n} \)
Normal concentration of oxidised cytochrome a3.

\[ blood_{hb} \]
Implementation Name: blood hb
Units: dimensionless
Initial value: 10.00
Factor to convert model haemoglobin concentration to instrumental units. Scales for blood fraction of brain volume, mM to \( \mu \)M, and number of binding sites.

\[ a_{3,r,n} \]
Implementation Name: bred_n
Units: mM
\[
\frac{f_a}{C_{a,n}} \frac{\exp(-c_3(\Delta p_n - \Delta p_30))}{1+\exp(-c_3(\Delta p_n - \Delta p_30))}
\]
Normal concentration of reduced cytochrome a3.

\[ c_3 \]
Implementation Name: c3
Units: mV\(^{-1}\)
Initial value: 0.11
Parameter controlling the sensitivity of the reduction of a3 to \( \Delta p \).

\[ C_{buffi} \]
Implementation Name: C_buffi
Units: dimensionless
Initial value: 0.022
Buffering capacity of protons in mitochondria.

\[ C_{im} \]
Implementation Name: C_im
Units: mM mV\(^{-1}\)
Initial value: 0.00675
Capacitance of the mitochondrial inner membrane.

\[ C_{NADH} = \frac{Z}{2} \log_{10} \left( \frac{1}{NAD/NADH} \right) \]
Implementation Name: C_NADH
Units: mV
Initial value: 0
Excess redox potential for NADH at normal demand.

\[ C_{NADH,n} \]
Implementation Name: C_NADH_n
Units: mV
Initial value: \( \frac{Z}{2} \log_{10} \left( \frac{1}{NAD/NADH} \right) \)
Normal value of \( C_{NADH} \).
5.7 Parameters

\( CBF_n \)
Implementation Name: CBFn
Units: \( \text{ml}_{\text{blood}} \text{ ml}^{-1} \text{s}^{-1} \)
Initial value: 0.0125
Normal cerebral blood flow.

\( CBF_{\text{scale}} \)
Implementation Name: CBFscale
Units: cm
Initial value: 5000
Scale constant relating blood flow to arterial velocity.

\( \Delta oxCCO_{\text{off}} \)
Implementation Name: CCO_offset
Units: uM
Initial value: 0
Signal offset for the NIRS CCO measurement.

\( c_{k_1} \)
Implementation Name: ck1
Units: mV\(^{-1}\)
Initial value: 0.01
Parameter controlling sensitivity of \( k_1 \) to \( \Delta p \).

\( c_{k_2} \)
Implementation Name: ck2
Units: mV\(^{-1}\)
Initial value: 0.02
Parameter controlling sensitivity of \( k_2 \) to \( \Delta p \).

\( CMRO_{2,n} \)
Implementation Name: CMRO2_n
Units: mM s\(^{-1}\)
Initial value: 0.034
Normal metabolic rate of oxygen consumption.

\( CV_{\text{inh}} \)
Implementation Name: CVinh
Units: dimensionless
Initial value: 1
Control parameter representing the action of Complex V inhibitors.

\( CCO_{\text{tot}} = \frac{CCO_{\text{tis}}}{Vol_{\text{mit}}} \)
Implementation Name: cytox_tot
Units: mM
Initial value: 0
Concentration of cytochrome c oxidase in mitochondria.

\( CCO_{\text{tis}} \)
Implementation Name: cytox_tot_tis
Units: mM
Initial value: 0.0055
Concentration of cytochrome c oxidase in tissue.

\( D_{\text{NADH}} \)
Implementation Name: D_NADH
Units: dimensionless
Initial value: 0.01
Scale parameter for the dependence of NADH redox potential on demand.
$D_{O_2}$
Implementation Name: $D_{0.02}$
Units: s$^{-1}$
Initial value: $\frac{I_{O_2,n}}{O_{2,c,n} - O_{2,n}}$
Diffusion rate for oxygen between capillaries and mitochondria.

$\Delta p_{3,corr}$
Implementation Name: $\Delta p_{3,corr}$
Units: mV
Initial value: $-25$
Difference between $\Delta p_{30}$ and normal $\Delta p$.

$\Delta p_{30} = \Delta p_n + \Delta p_{3,corr}$
Implementation Name: $\Delta p_{30}$
Units: mV
Initial value: 0
Value of $\Delta p$ to which $a_3$ reduction reaction is maximally sensitive.

$\Delta p_{CV,0}$
Implementation Name: $\Delta p_{CV0}$
Units: mV
Initial value: 90
Value of $\Delta p$ at which $L_{CV}$ is zero under normal demand.

$\Delta p_n$
Implementation Name: $\Delta p_n$
Units: mV
Initial value: $\psi_n + Z \Delta pH_n$
Normal value of $\Delta p$

$dpH$
Implementation Name: $dpH$
Units: dimensionless
Initial value: 0.001
Parameter in the mitochondrial proton buffering relationship.

$\Delta pH_n$
Implementation Name: $\Delta pH_n$
Units: dimensionless
Initial value: $pH_{n,n} - pH_{o,n}$
Normal pH difference across the mitochondrial inner membrane.

$\psi_n$
Implementation Name: $\psi_n$
Units: mV
Initial value: 145
Normal mitochondrial inner membrane potential.

$E_{1,NADH} = E_0(Cu_A) - E_0(NADH) + \epsilon_{NADH}$
Implementation Name: $E_{1,NADH}$
Units: mV
Initial value: 0
Value of $E_1$ when the reducing substrate is NADH.

$E_{1,NADH,n}$
Implementation Name: $E_{1,NADH,n}$
Units: mV
Initial value: $E_0(Cu_A) - E_0(NADH) + \epsilon_{NADH,n}$
Normal value of $E_{1,NADH}$. 
5.7 Parameters

$E_1$
Implementation Name: $E_{1,1}$
Units: mV
Initial value: $E_{1,NADH}$
The energy provided by electron transfer to $Cu_{A,r}$.

$E_{1,n}$
Implementation Name: $E_{1,1,n}$
Units: mV
Initial value: $E_{1,NADH,n}$
Normal value of $E_1$.

$E_2$
Implementation Name: $E_{2,2}$
Units: mV
Initial value: $E_{2,NADH,n}$
Energy provided by the transfer of four electrons from $Cu_{A,r}$ to $a_{3,0}$.

$\mathcal{E}_0(a_3)$
Implementation Name: $\mathcal{E}_{0,a30}$
Units: mV
Initial value: 350
Standard redox potential for cytochrome $a_3$.

$\mathcal{E}_0(Cu_A)$
Implementation Name: $\mathcal{E}_{0,c0}$
Units: mV
Initial value: 247
Standard redox potential for $Cu_A$.

$\mathcal{E}_0(NADH)$
Implementation Name: $\mathcal{E}_{0,w0}$
Units: mV
Initial value: −320
Standard redox potential for NADH.

$f_n$
Implementation Name: $f_{1,n}$
Units: mM s$^{-1}$
Initial value: $\frac{CMRO_2_{2,n}}{Vol_{mit}}$
Normal resting value of $f_1$ and $f_2$.

$G_n$
Implementation Name: $G_{a,n}$
Units: ml$^{-1}$ blood ml$^{-1}$ brain mmHg$^{-1}$ s$^{-1}$
Initial value: $P_{a,n} - P_{o,n}$
Normal blood vessel conductance.

$H_n^+$
Implementation Name: $H_{1,n}$
Units: mM
Initial value: $10^{3-pH_{m,n}}$
Normal mitochondrial proton concentration.

$JO_{2,n}$
Implementation Name: $J_{02,n}$
Units: mM s$^{-1}$
Initial value: $CMRO_2_{2,n}$
Normal oxygen flux from blood to tissue.
$k_{1,0}$
Implementation Name: k10
Units: $s^{-1}$
Initial value: $k_{1,n} \frac{NADH}{NADH_p}$
Forward reaction rate for the reduction of Cu$_A$ at normal $\Delta p$.

$k_{1,n}$
Implementation Name: k1_n
Units: $s^{-1}$
Initial value: $f_n \frac{Cu_{A,0,n} - \frac{1}{K_{eq,n}} Cu_{A,r,n}}{Cu_{A,0,n} a_{3,0,n} - \frac{1}{K_{eq,n}} Cu_{A,0,n} a_{3,r,n}}$
Forward reaction rate for the reduction of Cu$_A$ at normal $\Delta p$ and NADH.

$k_{2,n}$
Implementation Name: k2_n
Units: $s^{-1}$
Initial value: $f_n \frac{Cu_{A,r,n} a_{3,0,n} - \frac{1}{K_{eq,n}} Cu_{A,0,n} a_{3,r,n}}{Cu_{A,0,n} a_{3,0,n} - \frac{1}{K_{eq,n}} Cu_{A,0,n} a_{3,r,n}}$
Normal forward reaction rate for the reduction of a$_3$.

$k_3 = \frac{k_{3,0}}{1 + \exp(-c_3 - \Delta p_{30})}$
Implementation Name: k3
Units: $s^{-1}$
Initial value: 0
Forward reaction rate for the reduction of O$_2$.

$k_{3,0}$
Implementation Name: k30
Units: $s^{-1}$
Initial value: $2.5E+5$
Apparent second order rate constant for reduction of O$_2$ at zero $\Delta p$.

$k_{aut}$
Implementation Name: k_aut
Units: dimensionless
Initial value: 1
Overall functioning of autoregulatory response.

$K_G$
Implementation Name: k_G
Units: $ml_{blood} ml_{brain} mmHg^{-1} s^{-1} cm^{-4}$
Initial value: $G_n \frac{pow(r_n,4)}{4}$
Proportionality constant in Poiseuille relation for conductance.

$k_{l2}$
Implementation Name: k_l2
Units: $mV^{-1}$
Initial value: 0.038
Constant controlling the depending of the leak rate $L_{lk}$ on $\Delta p$.

$k_{unc}$
Implementation Name: k_unc
Units: dimensionless
Initial value: 1
Control parameter simulating the effect of adding uncouplers to the system.
5.7 Parameters

\[ k_{CV} = \frac{-1}{\Delta p_n - \Delta p_{CV,0}} \log \left( \frac{1 - L_{CV,0}}{1 + r_{CV} L_{CV,0}} \right) \]

Implementation Name: \( k_{CV} \)
Units: mV\(^{-1}\)
Initial value: 0
Parameter controlling the sensitivity of Complex V flux to driving force.

\[ K_{eq1,n} \]
Implementation Name: \( K_{eq1,n} \)
Units: dimensionless
Initial value: \( 10^{-1} \)
Z\((p_1 \Delta p_n^{4} - E_{1,n}) \)
Normal value of the equilibrium constant for the Cu\(\text{A} \) reduction reaction.

\[ K_{eq2,n} \]
Implementation Name: \( K_{eq2,n} \)
Units: dimensionless
Initial value: \( 10^{-1} \)
Z\((p_3 \Delta p_n^{4} - E_{2}) \)
Normal value of the equilibrium constant for the a\(_3 \) reduction reaction.

\[ L_{CV,0} \]
Implementation Name: \( L_{CV0} \)
Units: dimensionless
Initial value: 0.4
Normal Complex V flux as a fraction of maximum possible flux.

\[ L_{CV,frac} = 1 - L_{lk,frac} \]
Implementation Name: \( L_{CVfrac} \)
Units: dimensionless
Initial value: 0
Normal fraction of proton entry into mitochondria which is due to ADP phosphorylation.

\[ L_{CV,max} = \frac{L_{CV,n}}{L_{CV,0}} \]
Implementation Name: \( L_{CVmax} \)
Units: mM s\(^{-1}\)
Initial value: 0
The maximum rate of proton flow through Complex V.

\[ L_{CV,n} \]
Implementation Name: \( L_{CVn} \)
Units: mM s\(^{-1}\)
Initial value: \( L_n L_{CV,frac} \)
The resting flow of protons into the matrix through Complex V.

\[ L_{lk0} \]
Implementation Name: \( L_{lk0} \)
Units: mM s\(^{-1}\)
Initial value: \( \exp(\Delta p_n k_{lk2}) - 1 \)
Constant controlling the depending of the leak rate \( L_{lk} \) on \( \Delta p \).

\[ L_{lk,frac} \]
Implementation Name: \( L_{lkfrac} \)
Units: dimensionless
Initial value: 0.25
Normal fraction of proton entry into mitochondria which is via leak channels.

\[ L_{lk,n} \]
Implementation Name: \( L_{lkn} \)
Units: mM s\(^{-1}\)
Initial value: $L_n L_{lk,frac}$
The resting flow of protons into the matrix via leak channels.

$L_n = \rho \ell f_n$
- Implementation Name: $L_n$
- Units: mM s$^{-1}$
- Initial value: 0
The normal total flow of protons back into mitochondria.

$\lambda_0$
- Implementation Name: $\lambda_{0}$
- Units: cm
- Initial value: 0.01650
Intercept of the fitted linear model for blood vessel radius.

$\lambda_{pa}$
- Implementation Name: $\lambda_{pa}$
- Units: cm mmHg
- Initial value: 0.2483
Fitted linear dependence of blood vessel radius on reciprocal of blood pressure.

$n_h$
- Implementation Name: $n_h$
- Units: dimensionless
- Initial value: 2.5
Hill coefficient for oxygen dissociation from haemoglobin.

$NADH = \frac{NAD_{pool}}{1 + \frac{NAD}{NADH}}$
- Implementation Name: $NADH$
- Units: mM
- Initial value: 0
Concentration of NADH in the mitochondria.

$NADH_n$
- Implementation Name: $NADH_n$
- Units: mM
- Initial value: $\frac{NAD_{pool}}{1 + \frac{NAD}{NADH}}$
Normal concentration of NADH in the mitochondria.

$\frac{NAD}{NADH}$
- Implementation Name: $\frac{NAD}{NADH}$
- Units: dimensionless
- Initial value: $\frac{NAD_{n}}{NADH_{n}}\text{pow} \left( u, 2D_{NADH} \right)$
NAD/NADH ratio.

$\frac{NAD}{NADH}$
- Implementation Name: $\frac{NAD}{NADH}$
- Units: dimensionless
- Initial value: 9
Normal NAD/NADH ratio.

$NAD_{pool}$
- Implementation Name: $NAD_{pool}$
- Units: dimensionless
- Initial value: 3
Relative size of the NAD pool, used to estimate normal mitochondrial NADH.
5.7 Parameters

\( O_{2,n} \)
- Implementation Name: \( O_{2,n} \)
- Units: mM
- Initial value: 0.024
  Normal mitochondrial oxygen concentration.

\( O_{2,c,n} \)
- Implementation Name: \( O_{2c,n} \)
- Units: mM
- Initial value: \( \phi \text{ pow} \left( \frac{S_c, O_{2,n}}{1 - S_c, O_{2,n}} \right) \)
  Normal capillary oxygen concentration.

\( p_1 = p_{\text{tot}} - p_{23} \)
- Implementation Name: \( p_1 \)
- Units: dimensionless
- Initial value: 0
  Proton cost of the reaction reducing Cu.A.

\( p_3 \)
- Implementation Name: \( p_2 \)
- Units: dimensionless
- Initial value: 4
  Proton cost of the reaction reducing a₃.

\( p_{23} \)
- Implementation Name: \( p_{23} \)
- Units: dimensionless
- Initial value: 8
  Total protons removed from the mitochondrial matrix by the reductions of a₃ and \( O_2 \).

\( p_3 \)
- Implementation Name: \( p_3 \)
- Units: dimensionless
- Initial value: \( p_{23} - p_3 \)
  Proton cost of the reaction reducing \( O_2 \).

\( P_a \)
- Implementation Name: \( P_{a,n} \)
- Units: mmHg
- Initial value: \( P_{a,n} \)
  Mean arterial blood pressure.

\( P_{a,n} \)
- Implementation Name: \( P_{a,an} \)
- Units: mmHg
- Initial value: 100
  Normal arterial blood pressure.

\( P_{C1} \)
- Implementation Name: \( p_{C1} \)
- Units: dimensionless
- Initial value: 8
  Protons pumped by Complex I.

\( P_{C3} \)
- Implementation Name: \( p_{C3} \)
- Units: dimensionless
- Initial value: 4
  Protons pumped by Complex III.
\( p_{\text{tot}} \)

**Implementation Name:** \( p_{\text{tot}} \)

**Units:** dimensionless

**Initial value:** \( p_{\text{tot}} \)

Total protons removed from the mitochondrial matrix by the three modelled electron transport reactions.

\[ p_{\text{tot}}, \text{NADH} = p_{\text{1}} + p_{\text{3}} + p_{\text{23}} \]

**Implementation Name:** \( p_{\text{tot}} \text{NADH} \)

**Units:** dimensionless

**Initial value:** 0

Total protons pumped when the reducing agent is NADH.

\( p_v \)

**Implementation Name:** \( p_v \)

**Units:** mmHg

**Initial value:** \( p_v \)

Venous blood pressure.

\( p_{v,n} \)

**Implementation Name:** \( p_{v,n} \)

**Units:** mmHg

**Initial value:** 4

Normal venous blood pressure.

\( P_{a\text{CO}_2} \)

**Implementation Name:** \( P_{a\text{CO}_2} \)

**Units:** mmHg

**Initial value:** \( P_{a\text{CO}_2,n} \)

Arterial partial pressure of carbon dioxide.

\( P_{a\text{CO}_2,n} \)

**Implementation Name:** \( P_{a\text{CO}_2,n} \)

**Units:** mmHg

**Initial value:** 40

Normal arterial partial pressure of carbon dioxide.

\( p_{H_{mn}} \)

**Implementation Name:** \( p_{H_{mn}} \)

**Units:** dimensionless

**Initial value:** 7.4

Normal mitochondrial pH.

\( p_{H_o} \)

**Implementation Name:** \( p_{H_o} \)

**Units:** dimensionless

**Initial value:** 7

Extra-mitochondrial pH.

\( p_{H_{0,n}} \)

**Implementation Name:** \( p_{H_{0,n}} \)

**Units:** dimensionless

**Initial value:** 7

Normal extra-mitochondrial pH.

\( \phi \)

**Implementation Name:** \( \phi \)

**Units:** mM

**Initial value:** 0.036

Oxygen concentration at half-maximal saturation.
5.7 Parameters

$R_{CO_2}$
Implementation Name: $R_{auto}$
Units: dimensionless
Initial value: 2.2
Autoregulatory reactivity to carbon dioxide.

$R_O_2$
Implementation Name: $R_{auto}$
Units: dimensionless
Initial value: 1.5
Autoregulatory reactivity to oxygen.

$R_P_a$
Implementation Name: $R_{autop}$
Units: dimensionless
Initial value: 4
Autoregulatory reactivity to blood pressure.

$R_u$
Implementation Name: $R_{autu}$
Units: dimensionless
Initial value: 0.5
Autoregulatory reactivity to demand.

$r_{CV}$
Implementation Name: $r_{CV}$
Units: dimensionless
Initial value: 5
Parameter controlling the ratio of maximal to minimal rates of oxidative phosphorylation.

$r_m$
Implementation Name: $r_m$
Units: cm
Initial value: 0.0187
Normal blood vessel radius. Normal effective blood vessel radius.

$S_{a,O_2,n}$
Implementation Name: $SaO_2_n$
Units: dimensionless
Initial value: 0.96
Normal arterial oxygen saturation.

$S_{a,O_2}$
Implementation Name: $SaO_2sup$
Units: dimensionless
Initial value: $S_{a,O_2,n}$
Arterial oxygen saturation.

$S_{c,O_2,n}$
Implementation Name: $ScO_2_n$
Units: dimensionless
Initial value: $S_{a,O_2,n} + S_{v,O_2,n}$
2
Normal capillary oxygen saturation.

$S_{v,O_2,n}$
Implementation Name: $SvO_2_n$
Units: dimensionless
Initial value: $\frac{HbO_2, v,n}{Hb_{tot, n}}$
Normal venous oxygen saturation.
Implementation Name: $t$
Units: s
Initial value: 0
Time over which the system evolves.

$\tau_{CO_2}$
Implementation Name: $t_{c}$
Units: s
Initial value: 5
Filter time constant for stimulus effect of carbon dioxide.

$\tau_{O_2}$
Implementation Name: $t_{o}$
Units: s
Initial value: 20
Filter time constant for stimulus effect of capillary oxygen.

$\tau_{P_a}$
Implementation Name: $t_{p}$
Units: s
Initial value: 5
Filter time constant for stimulus effect of blood pressure.

$\tau_{u}$
Implementation Name: $t_{u}$
Units: s
Initial value: 0.5
Filter time constant for stimulus effect of demand.

$u$
Implementation Name: $u$
Units: dimensionless
Initial value: $u_n$
Parameter indicating metabolic demand.

$u_n$
Implementation Name: $u_n$
Units: dimensionless
Initial value: 1
Normal demand.

$\nu_{CO_2,n}$
Implementation Name: $v_{c,n}$
Units: mmHg
Initial value: $P_{a,CO_2,n}$
Normal filtered carbon dioxide partial pressure. Normal filtered carbon dioxide partial pressure.

$\nu_{O_2,n}$
Implementation Name: $v_{o,n}$
Units: mM
Initial value: $O_{2,c,n}$
Normal filtered capillary oxygen concentration. Normal filtered capillary oxygen concentration.

$\nu_{P_a,n}$
Implementation Name: $v_{p,n}$
Units: mmHg
Initial value: $P_{a,n}$
5.7 Parameters

Normal filtered arterial blood pressure. Normal filtered blood pressure.

\( v_{u,n} \)

- Implementation Name: \( v_{\text{un}} \)
- Units: dimensionless
- Initial value: \( u_n \)
- Normal filtered demand. Normal filtered demand.

\( V\text{Arat}_n \)

- Implementation Name: \( V\text{Arat}_\text{n} \)
- Units: dimensionless
- Initial value: 3
- Normal volume ratio of veins to arteries in brain tissue.

\( V_{a,n} \)

- Implementation Name: \( \text{Vol}_{\text{artn}} \)
- Units: dimensionless
- Initial value: \( \frac{1}{1 + V\text{Arat}_n} \)
- Normal relative arterial blood volume.

\( \text{Vol}_{\text{mit}} \)

- Implementation Name: \( \text{Vol}_{\text{mit}} \)
- Units: dimensionless
- Initial value: 0.067
- Fraction of brain tissue volume that is mitochondria.

\( V_p \)

- Implementation Name: \( \text{Vol}_{\text{ven}} \)
- Units: dimensionless
- Initial value: \( \frac{1}{1 + V\text{Arat}_n} \)
- Relative venous blood volume.

\( HbO_{2,a} = Hb_{\text{tot}} S_{a,O_2} \)

- Implementation Name: \( Xo_{a} \)
- Units: mM
- Initial value: \( HbO_{2,a,n} \)
- Arterial concentration of oxygen bound to haemoglobin.

\( HbO_{2,a,n} \)

- Implementation Name: \( Xo_{a,n} \)
- Units: mM
- Initial value: \( Hb_{\text{tot},n} S_{a,O_2,n} \)
- Normal arterial concentration of oxygen bound to haemoglobin.

\( HbO_{2,v,n} \)

- Implementation Name: \( Xo_{v,n} \)
- Units: mM
- Initial value: \( \frac{\text{CBF}_n HbO_{2,a,n} - J_{O_2,n}}{\text{CBF}_n} \)
- Normal venous concentration of oxygen bound to haemoglobin.

\( Hb_{\text{tot}} \)

- Implementation Name: \( X_{\text{tot}} \)
- Units: mM
- Initial value: 9.1
- Total concentration of haemoglobin \( O_2 \) binding sites in blood (4 times haemoglobin concentration).

\( Hb_{\text{tot},n} \)

- Implementation Name: \( X_{\text{tot},n} \)
Units: mM
Initial value: 9.1
Normal total concentration of haemoglobin O₂ binding sites in blood (4 times haemoglobin concentration).

Z
Implementation Name: Z
Units: mV
Initial value: 59.028
Proportionality constant in calculation of driving forces due to concentration differences. Defined as $RT/F$, where $F$ is Faraday’s constant, $R$ the ideal gas constant and $T$ the absolute temperature.
6 BSM0

6.1 Overview

Simplified model in which the metabolic submodel is replaced with variant M0.

- 9 differential state variables
- 3 algebraic state variables
- 27 intermediate variables
- 96 parameters
- 4 declared inputs
- 33 default outputs

6.2 Differential Equations

\[ \frac{dC_{U,A,0}}{dt} = 4f_3 - 4f_1 \]  
(6.1)

\[ \frac{d\alpha_{3,r}}{dt} = 4f_3 - 4f_3 \]  
(6.2)

\[ \frac{d\psi}{dt} = \frac{p_3 f_3 + p_1 f_1 + p_3 f_3 - L}{C_{im}} \]  
(6.3)

\[ \frac{d\nu_{p}}{dt} = \frac{1}{\tau_{p_v}} (P_a - v_P) \]  
(6.8)
\[
\frac{dv_u}{dt} = \frac{1}{\tau_u} (u - v_u)
\]  

(6.9)

### 6.3 Algebraic Equations

\[
\phi \left( \frac{S_{c,O_2}}{1 - S_{c,O_2}} \right) \frac{1}{\tau} - O_{2,c} = 0
\]  

(6.10)

\[T_e + T_m - (P_1 - P_{ic}) \ r = 0\]  

(6.11)

\[CBF \ (HbO_{2,a} - HbO_{2,v}) - J_{O_2} = 0\]  

(6.12)

### 6.4 Chemical Reactions

\[\overset{L}{\rightarrow} \frac{1}{R_{Hi}} \ H^+\]  

(6.13)

\[\overset{j_{O_2}}{\rightarrow} \frac{1}{Vol_{mit}} \ O_2\]  

(6.14)

\[
\frac{p_3}{R_{Hi}} \ H^+ \overset{f_3}{\rightarrow} 4 \ Cu_{A,o} + 4 \ a_{3,r}
\]  

(6.15)

\[4 \ Cu_{A,o} + \frac{p_1}{R_{Hi}} \ H^+ \overset{f_1}{\rightarrow}\]  

(6.16)

\[O_2 + 4 \ a_{3,r} + \frac{p_3}{R_{Hi}} \ H^+ \overset{f_3}{\rightarrow}\]  

(6.17)

### 6.5 State Variables

- **\(Cu_{A,o}\)**
  - Implementation Name: \(a\)
  - Units: mM
  - Initial value: \(Cu_{A,o,n}\)
  - Concentration of oxidised cytochrome c oxidase.

- **\(a_{3,r}\)**
  - Implementation Name: \(br\ ed\)
  - Units: mM
  - Initial value: \(a_{3,r,n}\)
  - Concentration of reduced cytochrome \(a_3\).
6.5 State Variables

\( \psi \)
- Implementation Name: Dpsi
- Units: mV
- Initial value: \( \psi_n \)
  Mitochondrial inner membrane potential. Varies as charge (in the form of protons) is transferred across the membrane capacitance.

\( H^+ \)
- Implementation Name: H
- Units: mM
- Initial value: \( H^+_n \)
  Mitochondrial proton concentration.

\( O_2 \)
- Implementation Name: 02
- Units: mM
- Initial value: \( O_{2,n} \)
  Mitochondrial oxygen concentration.

\( O_{2,c} \)
- Implementation Name: 02c
- Units: mM
- Initial value: \( O_{2,c,n} \)
  Capillary oxygen concentration.

\( r \)
- Implementation Name: r
- Units: cm
- Initial value: \( r_n \)
  Typical blood vessel radius.

\( v_{CO_2} \)
- Implementation Name: v_c
- Units: mmHg
- Initial value: \( v_{CO_2,n} \)
  Filtered carbon dioxide partial pressure.

\( v_{O_2} \)
- Implementation Name: v_o
- Units: mM
- Initial value: \( v_{O_2,n} \)
  Filtered capillary oxygen concentration.

\( v_P \)
- Implementation Name: v_p
- Units: mmHg
- Initial value: \( v_{P,n} \)
  Filtered arterial blood pressure.

\( v_u \)
- Implementation Name: v_u
- Units: dimensionless
- Initial value: \( v_{u,n} \)
  Filtered demand.

\( HbO_{2,v} \)
- Implementation Name: X0v
- Units: mM
- Initial value: \( HbO_{2,v,n} \)
  Venous concentration of oxygen bound to haemoglobin.
6.6 Intermediate Variables

\[ CBF = G \left( P_a - P_v \right) \]
Implementation Name: CBF
Units: \( \text{ml}_{\text{blood}} \text{ ml}^{-1} \text{s}^{-1} \)
Initial value: \( CBF_n \)
Cerebral blood flow.

\[ \Delta \text{oxCCO} = \Delta \text{oxCCO}_{\text{off}} + 1000 \text{Vol}_{\text{mit}} \left( \text{Cu}_{A,0} - \text{Cu}_{A,0,n} \right) \]
Implementation Name: CCO
Units: uM
Initial value: 0
Cytochrome c oxidase signal measured by NIRS.

\[ \text{CMRO}_2 = f_3 \text{Vol}_{\text{mit}} \]
Implementation Name: CMRO2
Units: mM s\(^{-1}\)
Initial value: 0
Rate of cerebral oxygen metabolism.

\[ \Delta p = \psi - Z \left( 4 + \log_{10} (H^+) \right) \]
Implementation Name: \( \Delta p \)
Units: mV
Initial value: 0
Proton motive force across the mitochondrial inner membrane.

\[ \eta = R_P \left( \frac{v_{P_a}}{v_{P_{a,n}}} - 1 \right) + R_{O_2} \left( \frac{v_{O_2}}{v_{O_{2,n}}} - 1 \right) + R_{CO_2} \left( 1 - \frac{v_{CO_2}}{v_{CO_{2,n}}} \right) + R_u \left( 1 - \frac{v_u}{v_{u,n}} \right) \]
Implementation Name: \( \eta \)
Units: dimensionless
Initial value: 0
Merged autoregulation stimulus.

\[ f_1 = \lambda_{f_1} + \lambda_{f_1,a} \log (u) + \lambda_{f_1,P} \Delta p + \lambda_{f_1,a} \log (\text{Cu}_{A,0}) \]
Implementation Name: \( f_1 \)
Units: mM s\(^{-1}\)
Initial value: 0
Reaction rate for the reduction of \( \text{Cu}_{A} \).

\[ f_2 = \lambda_{f_2} + \lambda_{f_2,P} \log (\Delta p) + \lambda_{f_2,a} \log (\text{Cu}_{A,0}) + \lambda_{f_2,b} \log (a_{3,r}) \]
Implementation Name: \( f_2 \)
Units: mM s\(^{-1}\)
Initial value: 0
Reaction rate for the reduction of \( a_3 \).

\[ f_3 = \lambda_{f_3} + \lambda_{f_3,P} \log (\Delta p) + \lambda_{f_3,O} \log (O_2) + \lambda_{f_3,b} \log (a_{3,r}) \]
Implementation Name: \( f_3 \)
Units: mM s\(^{-1}\)
Initial value: 0
Reaction rate for the reduction of \( O_2 \).

\[ G = K_G r^4 \]
Implementation Name: \( G \)
Units: \( \text{ml}_{\text{blood}} \text{ ml}^{-1} \text{mmHg}^{-1} \text{s}^{-1} \)
Initial value: 0
Effective conductance of the whole blood flow compartment.

\[ h = \sqrt{r^2 + 2r_0 h_0 + h_0^2} - r \]
Implementation Name: \( h \)
Units: cm
6.6 Intermediate Variables

Initial value: \( h_n \)
Thickness of the blood vessel walls.

\[
HbO_2 = (V_a HbO_2, a + V_v HbO_2, v) \text{ blood}_{hb}
\]
Implementation Name: \( \text{HbO2} \)
Units: \( \text{uM} \)
Initial value: 0
Oxygenated haemoglobin signal measured by NIRS.

\[
HbT = (V_a + V_v) Hb_{tot} \text{ blood}_{hb}
\]
Implementation Name: \( \text{HbT} \)
Units: \( \text{uM} \)
Initial value: 0
Total haemoglobin signal measured by NIRS.

\[
HHb = HbT - HbO_2
\]
Implementation Name: \( \text{HHb} \)
Units: \( \text{uM} \)
Initial value: 0
Deoxygenated haemoglobin signal measured by NIRS.

\[
J_{O_2} = f_{\text{min}} (D_{O_2} (O_2, c - O_2), CBF HbO_2, a)
\]
Implementation Name: \( J_{O2} \)
Units: \( \text{mM s}^{-1} \)
Initial value: 0
Oxygen flux from blood to tissue.

\[
L = \lambda_L + \lambda_{L,\theta} \theta + \lambda_{L,p} \Delta P
\]
Implementation Name: \( L \)
Units: \( \text{mM s}^{-1} \)
Initial value: 0
Rate of proton return to the mitochondrial matrix.

\[
\mu = \frac{\mu_{\text{min}} + \mu_{\text{max}} \exp(\eta)}{1 + \exp(\eta)}
\]
Implementation Name: \( \mu \)
Units: dimensionless
Initial value: 0
Effective strength of the autoregulation reponse.

\[
R_{Hi} = \frac{R_{Hi,H}}{H^+}
\]
Implementation Name: \( R_{Hi} \)
Units: dimensionless
Initial value: 0
Relative mitochondrial volume for protons, taking into account buffering effect of pH.

\[
S_c,O_2 = \frac{S_a,O_2 + S_v,O_2}{2}
\]
Implementation Name: \( S_cO2 \)
Units: dimensionless
Initial value: \( S_c,O_2,n \)
Capillary oxygen saturation.

\[
\sigma_e = \sigma_{e,0} \left( \exp \left( \frac{K_e (r - r_0)}{r_0} \right) - 1 \right) - \sigma_{coll}
\]
Implementation Name: \( \sigma_{e} \)
Units: \( \text{mm Hg} \)
Initial value: 0
Elastic stress in blood vessel walls.
\[ S_{v,O_2} = \frac{HbO_2,v}{Hb_{tot}} \]

Implementation Name: SvO2
Units: dimensionless
Initial value: \( S_{v,O_2,n} \)
Venous oxygen saturation.

\[ T_e = \sigma_e \cdot h \]

Implementation Name: Te
Units: mm Hg cm
Initial value: 0
Elastic tension in the blood vessel walls.

\[ T_m = T_{max} \exp \left( -\text{pow} \left( \left| \frac{r - r_m}{r_1 - r_m} \right|^n, n_m \right) \right) \]

Implementation Name: Tm
Units: mm Hg cm
Initial value: 0
Muscular tension in the blood vessel walls.

\[ T_{max} = T_{max,0} \left( 1 + k_{aut} \mu \right) \]

Implementation Name: Tmax
Units: mm Hg cm
Initial value: 0
Maximal muscular tension in the blood vessel walls.

\[ \theta = k CV \left( \Delta p + Z \log_{10} (u) - 90 \right) \]

Implementation Name: theta
Units: dimensionless
Initial value: 0
Driving force Complex V.

\[ \text{TOI} = \frac{100HbO_2}{HbT} \]

Implementation Name: TOI
Units: dimensionless
Initial value: 0
Total oxygenation index.

\[ V_{mca} = CBF \cdot CBF_{scale} \]

Implementation Name: Vmca
Units: cm s\(^{-1}\)
Initial value: 0
Blood velocity in the middle cerebral artery.

\[ V_a = V_{a,0} \left( \frac{r}{r_n} \right)^2 \]

Implementation Name: V01_art
Units: dimensionless
Initial value: 0
Relative arterial blood volume.

### 6.7 Parameters

\[ C_{H_A,O_2} \]

Implementation Name: a,n
Units: mM
6.7 Parameters

Initial value: 0.06567
Normal concentration of oxidised cytochrome c oxidase.

\( \text{blood}_{hb} \)
Implementation Name: \( \text{blood}_{hb} \)
Units: dimensionless
Initial value: 10.00
Factor to convert model haemoglobin concentration to instrumental units. Scales for blood fraction of brain volume, mM to \( \mu \text{M} \), and number of binding sites.

\( a_{3r,n} \)
Implementation Name: \( \text{bred}_{n} \)
Units: mM
Initial value: 0.001408
Normal concentration of reduced cytochrome a3.

\( C_{im} \)
Implementation Name: \( C_{im} \)
Units: mM mV\(^{-1}\)
Initial value: 0.00675
Capacitance of the mitochondrial inner membrane.

\( CBF_{n} \)
Implementation Name: \( CBF_{n} \)
Units: \( \text{ml}_{\text{blood}} \text{ ml}_{\text{brain}}^{-1} \text{s}^{-1} \)
Initial value: 0.0125
Normal cerebral blood flow.

\( CBF_{scale} \)
Implementation Name: \( CBF_{scale} \)
Units: cm
Initial value: 5000
Scale constant relating blood flow to arterial velocity.

\( \Delta_{\text{oxCCO}_{off}} \)
Implementation Name: \( \text{CCO}_{\text{offset}} \)
Units: uM
Initial value: 0
Signal offset for the NIRS CCO measurement.

\( \text{CMRO}_{2,n} \)
Implementation Name: \( \text{CMRO}_{2,n} \)
Units: mM \text{s}^-1
Initial value: 0.034
Normal metabolic rate of oxygen consumption.

\( D_{O_{2}} \)
Implementation Name: \( D_{O_{2}} \)
Units: \text{s}^-1
Initial value: \( \frac{\text{I}_{O_{2,n}}}{\text{O}_{2,n} - \text{O}_{2,n}} \)
Diffusion rate for oxygen between capillaries and mitochondria.

\( \psi_{n} \)
Implementation Name: \( \text{psi}_{n} \)
Units: mV
Initial value: 145
Normal mitochondrial inner membrane potential.

\( \lambda_{f_{1}} \)
Implementation Name: \( f_{1,0} \)
Units: mM s\(^{-1}\)

Initial value: 0.1221

Fitted intercept for the linear model for \(f_1\).

\(\lambda_{f_1,a}\)

Implementation Name: \(f_{1.a}\)
Units: mM s\(^{-1}\)
Initial value: 0.1848
Fitted linear dependence of \(f_1\) on logarithm of Cu\(_{A,ox}\).

\(\lambda_{f_1,p}\)

Implementation Name: \(f_{1.p}\)
Units: mM s\(^{-1}\) mV\(^{-1}\)
Initial value: 0.005270
Fitted linear dependence of \(f_1\) on \(\Delta p\).

\(\lambda_{f_1,u}\)

Implementation Name: \(f_{1.u}\)
Units: mM s\(^{-1}\)
Initial value: 0.1087
Fitted linear dependence of \(f_1\) on logarithm of demand.

\(\lambda_{f_2}\)

Implementation Name: \(f_{2.0}\)
Units: mM s\(^{-1}\)
Initial value: 5.432
Fitted intercept for the linear model for \(f_2\).

\(\lambda_{f_2,a}\)

Implementation Name: \(f_{2.a}\)
Units: mM s\(^{-1}\)
Initial value: 1.173
Fitted linear dependence of \(f_2\) on logarithm of Cu\(_{A,ox}\).

\(\lambda_{f_2,b}\)

Implementation Name: \(f_{2,b\text{red}}\)
Units: mM s\(^{-1}\)
Initial value: 0.08545
Fitted linear dependence of \(f_2\) on logarithm of \(a_{3,\text{red}}\).

\(\lambda_{f_2,p}\)

Implementation Name: \(f_{2.p}\)
Units: mM s\(^{-1}\) mV\(^{-1}\)
Initial value: −0.006935
Fitted linear dependence of \(f_2\) on \(\Delta p\).

\(\lambda_{f_3}\)

Implementation Name: \(f_{3.0}\)
Units: mM s\(^{-1}\)
Initial value: 11.69
Fitted intercept for the linear model for \(f_3\).

\(\lambda_{f_3,b}\)

Implementation Name: \(f_{3,b\text{red}}\)
Units: mM s\(^{-1}\)
Initial value: 0.3649
Fitted linear dependence of \(f_3\) on logarithm of \(a_{3,\text{red}}\).

\(\lambda_{f_3,p}\)

Implementation Name: \(f_{3.p}\)
Units: mM s\(^{-1}\) mV\(^{-1}\)
6.7 Parameters

Initial value: $-0.04345$
Fitted linear dependence of $f_3$ on $\Delta p$.

$\lambda_{f_3, O}$
Implementation Name: f3_02
Units: mM s$^{-1}$
Initial value: 0.3923
Fitted linear dependence of $f_3$ on logarithm of $O_2$.

$G_n$
Implementation Name: G_n
Units: ml$\text{blood}$ ml$\text{blood}^{-1}$ mmHg$^{-1}$ s$^{-1}$
Initial value: $\frac{P_{a,n} - P_{c,n}}{CBV_n}$
Normal blood vessel conductance.

$h_0$
Implementation Name: h_0
Units: cm
Initial value: 0.003
Thickness of the blood vessel walls at which radius is $r_0$.

$H^+_n$
Implementation Name: H_n
Units: mM
Initial value: 0.00003981
Normal mitochondrial proton concentration.

$h_n$
Implementation Name: h_n
Units: cm
Initial value: $\sqrt{(r_n r_n + 2r_0 h_0 + h_0 h_0) - r_n}$
Normal thickness of the blood vessel walls.

$J_{O_2,n}$
Implementation Name: J_O2n
Units: mM s$^{-1}$
Initial value: $CMRO_{O_2,n}$
Normal oxygen flux from blood to tissue.

$k_{\text{aut}}$
Implementation Name: k_aut
Units: dimensionless
Initial value: 1
Overall functioning of autoregulatory response.

$K_G$
Implementation Name: K_G
Units: ml$\text{blood}$ ml$\text{brain}^{-1}$ mmHg$^{-1}$ s$^{-1}$ cm$^{-4}$
Initial value: $\frac{G_n}{\text{pow}(r_n, 4)}$
Proportionality constant in Poiseuille relation for conductance.

$K_\sigma$
Implementation Name: K_sigma
Units: dimensionless
Initial value: 10
Parameter controlling the sensitivity of $\sigma_r$ to vessel radius.

$k_{CV}$
Implementation Name: k_{CV}
Units: mV
Initial value: 0.02047339
Factor relating the Complex V driving force to the membrane potential and demand.

\( \lambda_L \)
Implementation Name: L_0
Units: mM s\(^{-1}\)
Initial value: \(-15.339464\)
Fitted intercept for the linear model for \( L \).

\( \lambda_{L,p} \)
Implementation Name: L_dp
Units: mM s\(^{-1}\) mV\(^{-1}\)
Initial value: 0.097097
Fitted linear dependence of \( L \) on \( \Delta p \).

\( \lambda_{L,\theta} \)
Implementation Name: L_th
Units: mM s\(^{-1}\)
Initial value: 5.665904
Fitted linear dependence of \( L \) on \( \theta \).

\( \mu_{max} \)
Implementation Name: mu_max
Units: dimensionless
Initial value: 1
Upper bound for the transformed stimulus \( \mu \).

\( \mu_{min} \)
Implementation Name: mu_min
Units: dimensionless
Initial value: \(-1\)
Lower bound for the transformed stimulus \( \mu \).

\( \mu_n \)
Implementation Name: mu_n
Units: dimensionless
Initial value: 0
Normal value for the transformed stimulus \( \mu \).

\( n_h \)
Implementation Name: n_h
Units: dimensionless
Initial value: 2.5
Hill coefficient for oxygen dissociation from haemoglobin.

\( n_m \)
Implementation Name: n_m
Units: dimensionless
Initial value: 1.83
Exponent in the muscular tension relationship.

\( O_{2,n} \)
Implementation Name: O2_n
Units: mM
Initial value: 0.024
Normal mitochondrial oxygen concentration.

\( O_{2,c,n} \)
Implementation Name: O2c_n
Units: mM
### 6.7 Parameters

Initial value: \( \phi \text{pow} \left( \frac{S_c{\text{O}_2,n}}{1 - S_c{\text{O}_2,n}}, \frac{1}{n_h} \right) \)

Normal capillary oxygen concentration.

**\( P_1 \)**
- Implementation Name: \( p1 \)
- Units: dimensionless
- Initial value: 12
- Proton cost of the reaction reducing \( \text{Cu}_A \).

**\( P_3 \)**
- Implementation Name: \( p2 \)
- Units: dimensionless
- Initial value: 4
- Proton cost of the reaction reducing \( a_3 \).

**\( P_3 \)**
- Implementation Name: \( p3 \)
- Units: dimensionless
- Initial value: 4
- Proton cost of the reaction reducing \( \text{O}_2 \).

\[ P_1 = \frac{P_a + P_v}{2} \]
- Implementation Name: \( P_1 \)
- Units: mm Hg
- Initial value: \( P_{1,n} \)
- Average pressure in the blood vessels.

**\( P_{1,n} \)**
- Implementation Name: \( P_{1,n} \)
- Units: mm Hg
- Initial value: \( \frac{P_{a,n} + P_{v,n}}{2} \)
- Normal value for the average pressure in the blood vessels.

**\( P_a \)**
- Implementation Name: \( P_a \)
- Units: mmHg
- Initial value: \( P_{a,n} \)
- Mean arterial blood pressure.

**\( P_{a,n} \)**
- Implementation Name: \( P_{a,n} \)
- Units: mmHg
- Initial value: 100
- Normal arterial blood pressure.

**\( P_{ic} \)**
- Implementation Name: \( P_{ic} \)
- Units: mm Hg
- Initial value: 9.5
- Intracranial pressure.

**\( P_{icn} \)**
- Implementation Name: \( P_{icn} \)
- Units: mm Hg
- Initial value: 9.5
- Normal intracranial pressure.

**\( P_v \)**
Implementation Name: \( P_{v} \)
Units: mmHg
Initial value: \( P_{v,n} \)
Venous blood pressure.

\( P_{v,n} \)
Implementation Name: \( P_{v,n} \)
Units: mmHg
Initial value: 4
Normal venous blood pressure.

\( P_{aCO_2} \)
Implementation Name: \( P_{a_CO2} \)
Units: mmHg
Initial value: \( P_{aCO_2,n} \)
Arterial partial pressure of carbon dioxide.

\( P_{aCO_2,n} \)
Implementation Name: \( P_{a_CO2,n} \)
Units: mmHg
Initial value: 40
Normal arterial partial pressure of carbon dioxide.

\( \phi \)
Implementation Name: \( \phi_1 \)
Units: mM
Initial value: 0.036
Oxygen concentration at half-maximal saturation.

\( r_0 \)
Implementation Name: \( r_0 \)
Units: cm
Initial value: 0.0126
Radius in the elastic tension relationship.

\( R_{CO_2} \)
Implementation Name: \( R_{aut_c} \)
Units: dimensionless
Initial value: 2.2
Autoregulatory reactivity to carbon dioxide.

\( R_{O_2} \)
Implementation Name: \( R_{auto} \)
Units: dimensionless
Initial value: 1.5
Autoregulatory reactivity to oxygen.

\( R_P \)
Implementation Name: \( R_{aut_p} \)
Units: dimensionless
Initial value: 4
Autoregulatory reactivity to blood pressure.

\( R_H \)
Implementation Name: \( R_{aut_u} \)
Units: dimensionless
Initial value: 0.5
Autoregulatory reactivity to demand.

\( R_{Hi,H} \)
Implementation Name: \( R_{Hi,H} \)
6.7 Parameters

Units: mM
Initial value: 9.565483
Proton buffering factor.

\( r_m \)
Implementation Name: \( r_m \)
Units: cm
Initial value: 0.027
Vessel radius at which muscular tension is maximal.

\( r_n \)
Implementation Name: \( r_n \)
Units: cm
Initial value: 0.0187
Normal blood vessel radius. Normal effective blood vessel radius.

\( r_t \)
Implementation Name: \( r_t \)
Units: cm
Initial value: 0.018
Radius in the muscular tension relationship.

\( S_{a,O_2,n} \)
Implementation Name: \( SaO2_n \)
Units: dimensionless
Initial value: 0.96
Normal arterial oxygen saturation.

\( S_{a,O_2} \)
Implementation Name: \( SaO2_{sup} \)
Units: dimensionless
Initial value: \( S_{a,O_2,n} \)
Arterial oxygen saturation.

\( S_{c,O_2,n} \)
Implementation Name: \( ScO2_n \)
Units: dimensionless
Initial value: \( S_{a,O_2,n} + S_{c,O_2,n} \)
Normal capillary oxygen saturation.

\( \sigma_{coll} \)
Implementation Name: \( sigma_{coll} \)
Units: mm Hg
Initial value: 62.79
Pressure at which blood vessels collapse.

\( \sigma_{e,0} \)
Implementation Name: \( sigma_{e0} \)
Units: mm Hg
Initial value: 0.1425
Parameter in the elastic tension relationship.

\( \sigma_{e,n} \)
Implementation Name: \( sigma_{en} \)
Units: mm Hg
Initial value: \( \sigma_{e,0} \left( \exp \left( \frac{K_e (r_n - r_0)}{r_0} \right) - 1 \right) - \sigma_{coll} \)
Normal elastic stress in blood vessel walls.

\( S_{c,O_2,n} \)
Implementation Name: $SvO_2_{\text{n}}$
Units: dimensionless
Initial value: $\frac{HbO_{2\text{n}}}{Hb_{\text{tot,n}}}$
Normal venous oxygen saturation.

$t$
Implementation Name: $t$
Units: s
Initial value: 0
Time over which the system evolves.

$\tau_{CO_2}$
Implementation Name: $t_{c,c}$
Units: s
Initial value: 5
Filter time constant for stimulus effect of carbon dioxide.

$T_{e,n}$
Implementation Name: $T_{e,n}$
Units: mm Hg cm
Initial value: $c_{e,n} h_n$
Normal elastic tension in the blood vessel walls.

$T_{\text{max,0}}$
Implementation Name: $T_{\text{max,0}}$
Units: mm Hg cm
Initial value: $T_{\text{max,n}} \frac{1 + k_{\text{aut}} \mu_n}{1 + k_{\text{aut}} \mu_n}$
Maximal muscular tension under normal regulatory stimulus ($\mu = \mu_n$).

$T_{\text{max,n}}$
Implementation Name: $T_{\text{max,n}}$
Units: mm Hg cm
Initial value: $T_{\text{m,n}} \exp \left(-\text{pow} \left(\text{fabs} \left(\frac{r_n - r_m}{r_n - r_m}, n_m\right)\right)\right)$
Normal maximal muscular tension.

$T_{\text{m,n}}$
Implementation Name: $T_{\text{m,n}}$
Units: mm Hg cm
Initial value: $(P_{1,n} - P_{\text{icn}}) r_n - T_{r,n}$
Normal muscular tension in the blood vessel walls.

$\tau_{O_2}$
Implementation Name: $t_{o,o}$
Units: s
Initial value: 20
Filter time constant for stimulus effect of capillary oxygen.

$\tau_{P_a}$
Implementation Name: $t_{p,p}$
Units: s
Initial value: 5
Filter time constant for stimulus effect of blood pressure.

$\tau_{u}$
Implementation Name: $t_{u,u}$
Units: s
6.7 Parameters

Initial value: 0.5
Filter time constant for stimulus effect of demand.

\( u \)
Implementation Name: \( u \)
Units: dimensionless
Initial value: \( u_n \)
Parameter indicating metabolic demand.

\( u_n \)
Implementation Name: \( u_n \)
Units: dimensionless
Initial value: 1
Normal demand.

\( v_{CO_2,n} \)
Implementation Name: \( v_{CO_2,n} \)
Units: mmHg
Initial value: \( P_{aCO_2,n} \)
Normal filtered carbon dioxide partial pressure. Normal filtered carbon dioxide partial pressure.

\( v_{O_2,n} \)
Implementation Name: \( v_{O_2,n} \)
Units: mM
Initial value: \( O_{2,c,n} \)
Normal filtered capillary oxygen concentration. Normal filtered capillary oxygen concentration.

\( v_{P,a,n} \)
Implementation Name: \( v_{P,a,n} \)
Units: mmHg
Initial value: \( P_{a,n} \)
Normal filtered arterial blood pressure. Normal filtered blood pressure.

\( v_{u,n} \)
Implementation Name: \( v_{u,n} \)
Units: dimensionless
Initial value: \( u_n \)
Normal filtered demand. Normal filtered demand.

\( V_{Arat,a} \)
Implementation Name: \( V_{Arat,a} \)
Units: dimensionless
Initial value: 3
Normal volume ratio of veins to arteries in brain tissue.

\( V_{a,n} \)
Implementation Name: \( V_{a,n} \)
Units: dimensionless
Initial value: \( \frac{1}{1 + V_{Arat,a}} \)
Normal relative arterial blood volume.

\( Vol_{mit} \)
Implementation Name: \( Vol_{mit} \)
Units: dimensionless
Initial value: 0.067
Fraction of brain tissue volume that is mitochondria.

\( V_v \)
Implementation Name: Vol_ven
Units: dimensionless
Initial value: $\frac{V_{Arat}}{1 + V_{Arat}}$
Relative venous blood volume.

\[ HbO_{2,a} = Hb_{tot} \cdot S_{a,O_2} \]
Implementation Name: X0a
Units: mM
Initial value: $HbO_{2,a,n}$
Arterial concentration of oxygen bound to haemoglobin.

\[ HbO_{2,a,n} \]
Implementation Name: X0a_n
Units: mM
Initial value: $Hb_{tot,n} \cdot S_{a,O_2,n}$
Normal arterial concentration of oxygen bound to haemoglobin.

\[ HbO_{2,v,n} \]
Implementation Name: X0v_n
Units: mM
Initial value: $\frac{CBF_n \cdot HbO_{2,a,n} - J_{O_2,n}}{CBF_n} $
Normal venous concentration of oxygen bound to haemoglobin.

\[ Hb_{tot} \]
Implementation Name: Xtot
Units: mM
Initial value: 9.1
Total concentration of haemoglobin O₂ binding sites in blood (4 times haemoglobin concentration).

\[ Hb_{tot,n} \]
Implementation Name: Xtot_n
Units: mM
Initial value: 9.1
Normal total concentration of haemoglobin O₂ binding sites in blood (4 times haemoglobin concentration).

\[ Z \]
Implementation Name: Z
Units: mV
Initial value: 59.028
Proportionality constant in calculation of driving forces due to concentration differences. Defined as $RT/F$, where $F$ is Faraday’s constant, $R$ the ideal gas constant and $T$ the absolute temperature.
7 BSM1

7.1 Overview

Simplified model in which the metabolic submodel is replaced with variant M1.

- 9 differential state variables
- 3 algebraic state variables
- 27 intermediate variables
- 91 parameters
- 4 declared inputs
- 33 default outputs

7.2 Differential Equations

\[
\frac{dC_{u_{A,e}}}{dt} = 4f_3 - 4f_1 \quad (7.1)
\]

\[
\frac{da_{3,r}}{dt} = 4f_3 - 4f_3 \quad (7.2)
\]

\[
\frac{d\psi}{dt} = \frac{p_3 f_3 + p_1 f_1 + p_3 f_3 - L}{C_{im}} \quad (7.3)
\]

\[
\frac{dH^+}{dt} = \frac{1}{R_{Hi}} L - \frac{p_3}{R_{Hi}} f_3 - \frac{p_1}{R_{Hi}} f_1 - \frac{p_3}{R_{Hi}} f_3 \quad (7.4)
\]

\[
\frac{dO_2}{dt} = \frac{1}{Vol_{mit}} J_{O_2} - f_3 \quad (7.5)
\]

\[
\frac{dv_{CO_2}}{dt} = \frac{1}{\tau_{CO_2}} (P_{aCO_2} - v_{CO_2}) \quad (7.6)
\]

\[
\frac{dv_{O_2}}{dt} = \frac{1}{\tau_{O_2}} (O_{2,c} - v_{O_2}) \quad (7.7)
\]

\[
\frac{dv_{pa}}{dt} = \frac{1}{\tau_{pa}} (P_a - v_{pa}) \quad (7.8)
\]
\[
\frac{dv_u}{dt} = \frac{1}{\tau_u} (u - v_u)
\]  \hspace{1cm} (7.9)

### 7.3 Algebraic Equations

\[
\phi \left( \frac{S_{c,O_2}}{1 - S_{c,O_2}} \right)^\frac{1}{\pi} - O_{2,c} = 0
\]  \hspace{1cm} (7.10)

\[
T_e + T_m - (P_1 - P_{ic}) r = 0
\]  \hspace{1cm} (7.11)

\[
\text{CBF} \ (HbO_{2,a} - HbO_{2,v}) - J_{O_2} = 0
\]  \hspace{1cm} (7.12)

### 7.4 Chemical Reactions

\[
\xrightarrow{L} \frac{1}{R_{Hi}} \ H^+
\]  \hspace{1cm} (7.13)

\[
\xrightarrow{J_{O_2}} \frac{1}{Vol_{mit}} \ O_2
\]  \hspace{1cm} (7.14)

\[
\frac{p_3}{R_{Hi}} \ H^+ \xrightarrow{f_3} 4 \ Cu_{A,o} + 4 \ a_{3,r}
\]  \hspace{1cm} (7.15)

\[
4 \ Cu_{A,o} + \frac{p_1}{R_{Hi}} \ H^+ \xrightarrow{f_1} 4 \ Cu_{A,o}
\]  \hspace{1cm} (7.16)

\[
O_2 + 4 \ a_{3,r} + \frac{p_3}{R_{Hi}} \ H^+ \xrightarrow{f_3} 4 \ a_{3,r}
\]  \hspace{1cm} (7.17)

### 7.5 State Variables

\(Cu_{A,o}\)

- Implementation Name: \(a\)
- Units: mM
- Initial value: \(Cu_{A,o,n}\)
- Concentration of oxidised cytochrome c oxidase.

\(a_{3,r}\)

- Implementation Name: \(bred\)
- Units: mM
- Initial value: \(a_{3,r,n}\)
- Concentration of reduced cytochrome a3.
7.5 State Variables

\[ \psi \]
Implementation Name: Dpsi
Units: mV
Initial value: \( \psi_n \)
Mitochondrial inner membrane potential. Varies as charge (in the form of protons) is transferred across the membrane capacitance.

\[ H^+ \]
Implementation Name: H
Units: mM
Initial value: \( H^+_n \)
Mitochondrial proton concentration.

\[ O_2 \]
Implementation Name: O2
Units: mM
Initial value: \( O_{2,n} \)
Mitochondrial oxygen concentration.

\[ O_{2,c} \]
Implementation Name: O2c
Units: mM
Initial value: \( O_{2,c,n} \)
Capillary oxygen concentration.

\[ r \]
Implementation Name: r
Units: cm
Initial value: \( r_n \)
Typical blood vessel radius.

\[ v_{CO_2} \]
Implementation Name: v_c
Units: mmHg
Initial value: \( v_{CO_2,n} \)
Filtered carbon dioxide partial pressure.

\[ v_{O_2} \]
Implementation Name: v_o
Units: mM
Initial value: \( v_{O_2,n} \)
Filtered capillary oxygen concentration.

\[ v_{Pa} \]
Implementation Name: v_p
Units: mmHg
Initial value: \( v_{Pa,n} \)
Filtered arterial blood pressure.

\[ v_u \]
Implementation Name: v_u
Units: dimensionless
Initial value: \( v_{u,n} \)
Filtered demand.

\[ HbO_{2,v} \]
Implementation Name: XOv
Units: mM
Initial value: \( HbO_{2,v,n} \)
Venous concentration of oxygen bound to haemoglobin.
7.6 Intermediate Variables

\[ CBF = G (P_a - P_v) \]
Implementation Name: CBF
Units: ml_{blood} ml^{-1} brain s^{-1}
Initial value: CBF_{\text{init}}
Cerebral blood flow.

\[ \Delta \text{oxCCO} = \Delta \text{oxCCO}_{\text{off}} + 1000 \text{Vol}_{\text{init}} \ (Cu_{A,o} - Cu_{A,o,n}) \]
Implementation Name: CCO
Units: uM
Initial value: 0
Cytochrome c oxidase signal measured by NIRS.

\[ \text{CMRO}_2 = f_3 \text{Vol}_{\text{init}} \]
Implementation Name: CMRO2
Units: mM s^{-1}
Initial value: 0
Rate of cerebral oxygen metabolism.

\[ \Delta p = \psi - Z \ (4 + \log 10 (H^+)) \]
Implementation Name: \( \Delta p \)
Units: mV
Initial value: 0
Proton motive force across the mitochondrial inner membrane.

\[ \eta = R_p \left( \frac{V_{P_a}}{V_{P_a,n}} - 1 \right) + R_O_2 \left( \frac{V_{O_2}}{V_{O_2,n}} - 1 \right) + R_{CO_2} \left( 1 - \frac{V_{CO_2}}{V_{CO_2,n}} \right) + R_u \left( 1 - \frac{V_u}{V_{u,n}} \right) \]
Implementation Name: \( \eta \)
Units: dimensionless
Initial value: 0
Merged autoregulation stimulus.

\[ f_1 = \lambda_{f_1} + \lambda_{f_1,u} \log (u) + \lambda_{f_1,o} \log (Cu_{A,o}) \]
Implementation Name: \( f_1 \)
Units: mM s^{-1}
Initial value: 0
Reaction rate for the reduction of Cu_{A}.

\[ f_3 = \lambda_{f_3} + \lambda_{f_3,u} \log (a_{3,r}) \]
Implementation Name: \( f_3 \)
Units: mM s^{-1}
Initial value: 0
Reaction rate for the reduction of a_{3}.

\[ f_5 = \lambda_{f_5} + \lambda_{f_5,o} \log (O_2) \]
Implementation Name: \( f_5 \)
Units: mM s^{-1}
Initial value: 0
Reaction rate for the reduction of O_{2}.

\[ G = K_G r^4 \]
Implementation Name: \( G \)
Units: ml_{blood} ml^{-1} brain mmHg^{-1} s^{-1}
Initial value: 0
Effective conductance of the whole blood flow compartment.

\[ h = \sqrt{r r + 2 r_0 h_0 + h_0 h_0} - r \]
Implementation Name: \( h \)
Units: cm
7.6 Intermediate Variables

Initial value: $h_n$
Thickness of the blood vessel walls.

\[ HbO_2 = (V_a HbO_{2,a} + V_v HbO_{2,v}) \text{ blood}_{hb} \]
Implementation Name: $HbO2$
Units: uM
Initial value: 0
Oxygenated haemoglobin signal measured by NIRS.

\[ HbT = (V_a + V_v) HbT_{tot} \text{ blood}_{hb} \]
Implementation Name: $HbT$
Units: uM
Initial value: 0
Total haemoglobin signal measured by NIRS.

\[ HHb = HbT - HbO_2 \]
Implementation Name: $HHb$
Units: uM
Initial value: 0
Deoxygenated haemoglobin signal measured by NIRS.

\[ JO_2 = \text{fmin} \left( D_{O_2} (O_2,c - O_2) \right. \left., CBF HbO_{2,a} \right) \]
Implementation Name: $J_02$
Units: mM s$^{-1}$
Initial value: 0
Oxygen flux from blood to tissue.

\[ L = \lambda_L + \lambda_L \theta + \lambda_L \theta \Delta p \]
Implementation Name: $L$
Units: mM s$^{-1}$
Initial value: 0
Rate of proton return to the mitochondrial matrix.

\[ \mu = \frac{\mu_{\text{min}} + \mu_{\text{max}} \exp(\eta)}{1 + \exp(\eta)} \]
Implementation Name: $mu$
Units: dimensionless
Initial value: 0
Effective strength of the autoregulation response.

\[ R_{Hi} = \frac{R_{Hi,H}}{H^+} \]
Implementation Name: $R_{Hi}$
Units: dimensionless
Initial value: 0
Relative mitochondrial volume for protons, taking into account buffering effect of pH.

\[ S_{c,O2} = \frac{S_{a,O2} + S_{v,O2}}{2} \]
Implementation Name: $S_{c,O2}$
Units: dimensionless
Initial value: $S_{c,O2,n}$
Capillary oxygen saturation.

\[ \sigma_e = \sigma_{e,0} \left( \exp \left( \frac{K_e (r - r_0)}{r_0} \right) - 1 \right) - \sigma_{\text{coll}} \]
Implementation Name: $sigma_e$
Units: mm Hg
Initial value: 0
Elastic stress in blood vessel walls.
$S_{v,O_2} = \frac{HbO_{2,v}}{Hb_{tot}}$

Implementation Name: SvO2
Units: dimensionless
Initial value: $S_{v,O_2,n}$
Venous oxygen saturation.

$T_e = \sigma_e h$
Implementation Name: Te
Units: mm Hg cm
Initial value: 0
Elastic tension in the blood vessel walls.

$T_m = T_{max} \exp \left(-\text{pow} \left(\text{fabs} \left(\frac{r - r_m}{r_l - r_m}\right), n_m\right)\right)$
Implementation Name: Tm
Units: mm Hg cm
Initial value: 0
Muscular tension in the blood vessel walls.

$T_{max} = T_{max,0} \left(1 + k_{aut} \mu\right)$
Implementation Name: Tmax
Units: mm Hg cm
Initial value: 0
Maximal muscular tension in the blood vessel walls.

$\theta = kCV \left(\Delta p + Z \log_{10} (u) - 90\right)$
Implementation Name: theta
Units: dimensionless
Initial value: 0
Driving force Complex V.

$TOI = \frac{100HbO_2}{HbT}$
Implementation Name: TOI
Units: dimensionless
Initial value: 0
Total oxygenation index.

$V_{mca} = CBF \cdot CBF_{scale}$
Implementation Name: Vmca
Units: cm s$^{-1}$
Initial value: 0
Blood velocity in the middle cerebral artery.

$V_a = V_{a,p} \left(\frac{r}{r_n}\right)^2$
Implementation Name: Vol_art
Units: dimensionless
Initial value: 0
Relative arterial blood volume.

### 7.7 Parameters

$Cu_{A,o,n}$
Implementation Name: a_n
Units: mM
7.7 Parameters

Initial value: 0.06567
Normal concentration of oxidised cytochrome c oxidase.

\( \text{blood} \_{\text{hb}} \)
Implementation Name: blood_hb
Units: dimensionless
Initial value: 10.00
Factor to convert model haemoglobin concentration to instrumental units. Scales for blood fraction of brain volume, mM to µM, and number of binding sites.

\( a_{3,r,n} \)
Implementation Name: bred_n
Units: mM
Initial value: 0.001408
Normal concentration of reduced cytochrome a3.

\( C_{\text{im}} \)
Implementation Name: C_im
Units: mM mV\(^{-1}\)
Initial value: 0.00675
Capacitance of the mitochondrial inner membrane.

\( CBF_n \)
Implementation Name: CBFn
Units: ml\(_{\text{blood}}\) ml\(_{\text{brain}}\) s\(^{-1}\)
Initial value: 0.0125
Normal cerebral blood flow.

\( CBFscale \)
Implementation Name: CBFscale
Units: cm
Initial value: 5000
Scale constant relating blood flow to arterial velocity.

\( \Delta oxCCO_{\text{off}} \)
Implementation Name: CCO_offset
Units: uM
Initial value: 0
Signal offset for the NIRS CCO measurement.

\( CMRO_{2,n} \)
Implementation Name: CMRO2_n
Units: mM s\(^{-1}\)
Initial value: 0.034
Normal metabolic rate of oxygen consumption.

\( D_{\text{O}_2} \)
Implementation Name: D_02
Units: s\(^{-1}\)
Initial value: \( \frac{I_{\text{O}_2,n}}{O_{2,r,n} - O_{2,n}} \)
Diffusion rate for oxygen between capillaries and mitochondria.

\( \psi_n \)
Implementation Name: Dpsi_n
Units: mV
Initial value: 145
Normal mitochondrial inner membrane potential.

\( \lambda_{f_1} \)
Implementation Name: f1_0
Units: mM s$^{-1}$
Initial value: 1.490
Fitted intercept for the linear model for $f_1$.

$\lambda_{f_1,a}$
Implementation Name: $f_{1,a}$
Units: mM s$^{-1}$
Initial value: 0.3609
Fitted linear dependence of $f_1$ on logarithm of Cu$_{A,ox}$.

$\lambda_{f_1,u}$
Implementation Name: $f_{1,u}$
Units: mM s$^{-1}$
Initial value: 0.06985
Fitted linear dependence of $f_1$ on logarithm of demand.

$\lambda_{f_2}$
Implementation Name: $f_{2,0}$
Units: mM s$^{-1}$
Initial value: 0.1473
Fitted intercept for the linear model for $f_2$.

$\lambda_{f_2,b}$
Implementation Name: $f_{2,bred}$
Units: mM s$^{-1}$
Initial value: −0.05484
Fitted linear dependence of $f_2$ on logarithm of a$_{3,red}$.

$\lambda_{f_3}$
Implementation Name: $f_{3,0}$
Units: mM s$^{-1}$
Initial value: 0.6324
Fitted intercept for the linear model for $f_3$.

$\lambda_{f_3,O}$
Implementation Name: $f_{3,02}$
Units: mM s$^{-1}$
Initial value: 0.03352
Fitted linear dependence of $f_3$ on logarithm of O$_2$.

$G_n$
Implementation Name: $G_n$
Units: ml$_{blood}$ ml$^{-1}$ brain mmHg$^{-1}$ s$^{-1}$
Initial value: $\frac{P_{a,n} - P_{v,n}}{CBF_n}$
Normal blood vessel conductance.

$h_0$
Implementation Name: $h_0$
Units: cm
Initial value: 0.003
Thickness of the blood vessel walls at which radius is $r_0$.

$H_n^+$
Implementation Name: $h_n$
Units: mM
Initial value: 0.00003981
Normal mitochondrial proton concentration.

$h_n$
Implementation Name: $h_n$
7.7 Parameters

Units: cm
Initial value: \(\sqrt{r_n r_n + 2r_0 h_0 + h_0 h_0} - r_n\)
Normal thickness of the blood vessel walls.

\(J_{O_2,n}\)
Implementation Name: \(J_{O_2n}\)
Units: mM s\(^{-1}\)
Initial value: CMRO\(_2\)\(_n\)
Normal oxygen flux from blood to tissue.

\(k_{aut}\)
Implementation Name: \(k_{aut}\)
Units: dimensionless
Initial value: 1
Overall functioning of autoregulatory response.

\(K_G\)
Implementation Name: \(K_G\)
Units: \(\text{ml}_{\text{blood}} \text{ml}_{\text{brain}}^{-1} \text{mmHg}^{-1} \text{s}^{-1} \text{cm}^{-4}\)
Initial value: \(\frac{G_n}{\text{pow}(r_n, 4)}\)
Proportionality constant in Poiseuille relation for conductance.

\(K_\sigma\)
Implementation Name: \(K_\sigma\)
Units: dimensionless
Initial value: 10
Parameter controlling the sensitivity of \(\sigma_r\) to vessel radius.

\(kCV\)
Implementation Name: \(kCV\)
Units: mV\(^{-1}\)
Initial value: 0.02047339
Factor relating the Complex V driving force to the membrane potential and demand.

\(\lambda_L\)
Implementation Name: \(L_0\)
Units: mM s\(^{-1}\)
Initial value: \(-15.339464\)
Fitted intercept for the linear model for \(L\).

\(\lambda_{L,p}\)
Implementation Name: \(L_Dp\)
Units: mM s\(^{-1}\) mV\(^{-1}\)
Initial value: 0.097097
Fitted linear dependence of \(L\) on \(\Delta p\).

\(\lambda_{L,\theta}\)
Implementation Name: \(L_{th}\)
Units: mM s\(^{-1}\)
Initial value: 5.665904
Fitted linear dependence of \(L\) on \(\theta\).

\(\mu_{max}\)
Implementation Name: \(mu_{max}\)
Units: dimensionless
Initial value: 1
Upper bound for the transformed stimulus \(\mu\).

\(\mu_{min}\)
Implementation Name: \(mu_{min}\)
Units: dimensionless
Initial value: −1
Lower bound for the transformed stimulus $\mu$.

$\mu_n$
Implementation Name: $\mu_n$
Units: dimensionless
Initial value: 0
Normal value for the transformed stimulus $\mu$.

$n_h$
Implementation Name: $n_h$
Units: dimensionless
Initial value: 2.5
Hill coefficient for oxygen dissociation from haemoglobin.

$n_m$
Implementation Name: $n_m$
Units: dimensionless
Initial value: 1.83
Exponent in the muscular tension relationship.

$O_{2,n}$
Implementation Name: $O_{2,n}$
Units: mM
Initial value: 0.024
Normal mitochondrial oxygen concentration.

$O_{2,c,n}$
Implementation Name: $O_{2,c,n}$
Units: mM
Initial value: $\phi \ pow \left( \frac{S_{c,O_2,n}}{1 - S_{c,O_2,n}} \cdot \frac{1}{n_h} \right)$
Normal capillary oxygen concentration.

$p_1$
Implementation Name: $p_1$
Units: dimensionless
Initial value: 12
Proton cost of the reaction reducing Cu$_A$.

$p_3$
Implementation Name: $p_3$
Units: dimensionless
Initial value: 4
Proton cost of the reaction reducing a$_3$.

$p_3$
Implementation Name: $p_3$
Units: dimensionless
Initial value: 4
Proton cost of the reaction reducing O$_2$.

$P_1 = \frac{P_a + P_o}{2}$
Implementation Name: $P_1$
Units: mm Hg
Initial value: $P_{1,n}$
Average pressure in the blood vessels.

$P_{1,n}$
7.7 Parameters

Implementation Name: \( P_{a,n} \)
Units: mm Hg
Initial value: \( \frac{P_{a,n} + P_{v,n}}{2} \)
Normal value for the average pressure in the blood vessels.

\( P_a \)
Implementation Name: \( P_a \)
Units: mmHg
Initial value: \( P_{a,n} \)
Mean arterial blood pressure.

\( P_{a,n} \)
Implementation Name: \( P_{an} \)
Units: mm Hg
Initial value: 100
Normal arterial blood pressure.

\( P_sc \)
Implementation Name: \( P_{sc} \)
Units: mm Hg
Initial value: 9.5
Intracranial pressure.

\( P_{scn} \)
Implementation Name: \( P_{scn} \)
Units: mm Hg
Initial value: 9.5
Normal intracranial pressure.

\( P_v \)
Implementation Name: \( P_v \)
Units: mmHg
Initial value: \( P_{v,n} \)
Venous blood pressure.

\( P_{vn} \)
Implementation Name: \( P_{vn} \)
Units: mmHg
Initial value: 4
Normal venous blood pressure.

\( Pa_{CO_2} \)
Implementation Name: \( Pa_{CO2} \)
Units: mmHg
Initial value: \( Pa_{CO2,n} \)
Arterial partial pressure of carbon dioxide.

\( Pa_{CO_2,n} \)
Implementation Name: \( Pa_{CO2n} \)
Units: mmHg
Initial value: 40
Normal arterial partial pressure of carbon dioxide.

\( \phi \)
Implementation Name: \( \phi \)
Units: mM
Initial value: 0.036
Oxygen concentration at half-maximal saturation.

\( r_0 \)
Implementation Name: $r_0$
Units: cm
Initial value: 0.0126
Radius in the elastic tension relationship.

$R_{CO_2}$
Implementation Name: $R_{autc}$
Units: dimensionless
Initial value: 2.2
Autoregulatory reactivity to carbon dioxide.

$R_{O_2}$
Implementation Name: $R_{auto}$
Units: dimensionless
Initial value: 1.5
Autoregulatory reactivity to oxygen.

$R_{Pa}$
Implementation Name: $R_{autp}$
Units: dimensionless
Initial value: 4
Autoregulatory reactivity to blood pressure.

$R_u$
Implementation Name: $R_{autu}$
Units: dimensionless
Initial value: 0.5
Autoregulatory reactivity to demand.

$R_{Hi,H}$
Implementation Name: $R_{Hi,H}$
Units: mM
Initial value: 9.565483
Proton buffering factor.

$r_m$
Implementation Name: $r_m$
Units: cm
Initial value: 0.027
Vessel radius at which muscular tension is maximal.

$r_n$
Implementation Name: $r_n$
Units: cm
Initial value: 0.0187
Normal blood vessel radius. Normal effective blood vessel radius.

$r_t$
Implementation Name: $r_t$
Units: cm
Initial value: 0.018
Radius in the muscular tension relationship.

$S_{a,O_2,n}$
Implementation Name: $Sa02_n$
Units: dimensionless
Initial value: 0.96
Normal arterial oxygen saturation.

$S_{a,O_2}$
Implementation Name: $Sa02_{sup}$
Units: dimensionless
Initial value: $S_{n,O_2,n}$
Arterial oxygen saturation.

$S_{c,O_2,n}$
Implementation Name: Sc02_n
Units: dimensionless
Initial value: $\frac{S_{a,O_2,n} + S_{c,O_2,n}}{2}$
Normal capillary oxygen saturation.

$\sigma_{coll}$
Implementation Name: sigma_coll
Units: mm Hg
Initial value: 62.79
Pressure at which blood vessels collapse.

$\sigma_{e,0}$
Implementation Name: sigma_e0
Units: mm Hg
Initial value: 0.1425
Parameter in the elastic tension relationship.

$\sigma_{e,n}$
Implementation Name: sigma_en
Units: mm Hg
Initial value: $\sigma_{e,0} \left( \exp \left( \frac{K_e (r_n - r_0)}{r_0} \right) - 1 \right) - \sigma_{coll}$
Normal elastic stress in blood vessel walls.

$S_{v,O_2,n}$
Implementation Name: Sv02_n
Units: dimensionless
Initial value: $\frac{HbO_2,v,n}{Hb_{tot,n}}$
Normal venous oxygen saturation.

$t$
Implementation Name: t
Units: s
Initial value: 0
Time over which the system evolves.

$\tau_{CO_2}$
Implementation Name: $t_{c}$
Units: s
Initial value: 5
Filter time constant for stimulus effect of carbon dioxide.

$T_{r,n}$
Implementation Name: $T_{en}$
Units: mm Hg cm
Initial value: $\sigma_{e,n} \cdot h_n$
Normal elastic tension in the blood vessel walls.

$T_{\text{max},0}$
Implementation Name: $T_{\text{max}0}$
Units: mm Hg cm
Initial value: $\frac{T_{\text{max},n}}{1 + k_{aut} \cdot \mu_n}$
Maximal muscular tension under normal regulatory stimulus ($\mu = \mu_n$).
$T_{\text{max},n}$
Implementation Name: $T_{\text{max}n}$
Units: mm Hg cm
Initial value: $T_{m,n} = \exp\left( -\text{pow}\left( \text{fabs}\left( \frac{r_n-r_m}{r_t-r_m} \right), m \right) \right)$
Normal maximal muscular tension.

$T_{m,n}$
Implementation Name: $T_{\text{mn}}$
Units: mm Hg cm
Initial value: $(P_{1,n} - P_{\text{icn}}) r_n - T_{e,n}$
Normal muscular tension in the blood vessel walls.

$\tau_{O_2}$
Implementation Name: $\tau_{O_2}$
Units: s
Initial value: 20
Filter time constant for stimulus effect of capillary oxygen.

$\tau_{P_a}$
Implementation Name: $\tau_{P_a}$
Units: s
Initial value: 5
Filter time constant for stimulus effect of blood pressure.

$\tau_{u}$
Implementation Name: $\tau_{u}$
Units: s
Initial value: 0.5
Filter time constant for stimulus effect of demand.

$u$
Implementation Name: $u$
Units: dimensionless
Initial value: $u_n$
Parameter indicating metabolic demand.

$u_n$
Implementation Name: $u_n$
Units: dimensionless
Initial value: 1
Normal demand.

$\nu_{CO_2,n}$
Implementation Name: $\nu_{CO_2,n}$
Units: mmHg
Initial value: $P_{\text{icCO_2}}$
Normal filtered carbon dioxide partial pressure. Normal filtered carbon dioxide partial pressure.

$\nu_{O_2,n}$
Implementation Name: $\nu_{O_2,n}$
Units: mM
Initial value: $O_{2,c,n}$
Normal filtered capillary oxygen concentration. Normal filtered capillary oxygen concentration.

$\nu_{P_a,n}$
Implementation Name: $\nu_{P_a,n}$
Units: mmHg
7.7 Parameters

Initial value: $P_{a,n}$
Normal filtered arterial blood pressure. Normal filtered blood pressure.

$v_{u,n}$
- Implementation Name: $v_{un}$
- Units: dimensionless
- Initial value: $u_n$
Normal filtered demand. Normal filtered demand.

$V_{Arat_n}$
- Implementation Name: $V_{Arat_n}$
- Units: dimensionless
- Initial value: 3
Normal volume ratio of veins to arteries in brain tissue.

$V_{a,n}$
- Implementation Name: $Vol_{artn}$
- Units: dimensionless
- Initial value: $\frac{1}{1 + V_{Arat_n}}$
Normal relative arterial blood volume.

$Vol_{mit}$
- Implementation Name: $Vol_{mit}$
- Units: dimensionless
- Initial value: 0.067
Fraction of brain tissue volume that is mitochondria.

$V_{v}$
- Implementation Name: $Vol_{ven}$
- Units: dimensionless
- Initial value: $\frac{1}{1 + V_{Arat_n}}$
Relative venous blood volume.

$HbO_{2,a} = Hb_{tot} \times S_{a,O_2}$
- Implementation Name: $x0a$
- Units: mM
- Initial value: $HbO_{2,a,n}$
Arterial concentration of oxygen bound to haemoglobin.

$HbO_{2,a,n}$
- Implementation Name: $x0a_n$
- Units: mM
- Initial value: $Hb_{tot,n} \times S_{a,O_2,n}$
Normal arterial concentration of oxygen bound to haemoglobin.

$HbO_{2,v,n}$
- Implementation Name: $x0v_n$
- Units: mM
- Initial value: $\frac{CBF_n \times HbO_{2,a,n} - IO_{2,v}}{CBF_n}$
Normal venous concentration of oxygen bound to haemoglobin.

$Hb_{tot}$
- Implementation Name: $x_{tot}$
- Units: mM
- Initial value: 9.1
Total concentration of haemoglobin $O_2$ binding sites in blood (4 times haemoglobin concentration).
7 BSM1

\( H_{b_{tot,n}} \)
- Implementation Name: \( x_{tot,n} \)
- Units: mM
- Initial value: 9.1
  Normal total concentration of haemoglobin O\(_2\) binding sites in blood (4 times haemoglobin concentration).

\( Z \)
- Implementation Name: \( Z \)
- Units: mV
- Initial value: 59.028
  Proportionality constant in calculation of driving forces due to concentration differences.
  Defined as \( RT/F \), where \( F \) is Faraday’s constant, \( R \) the ideal gas constant and \( T \) the absolute temperature.
8 BSM2

8.1 Overview

Simplified model in which the metabolic submodel is replaced with variant M2.

- 9 differential state variables
- 3 algebraic state variables
- 27 intermediate variables
- 90 parameters
- 4 declared inputs
- 33 default outputs

8.2 Differential Equations

\[
\frac{dC_{\text{H}_A,\text{O}}}{dt} = 4f_3 - 4f_1 \tag{8.1}
\]

\[
\frac{da_{3,r}}{dt} = 4f_3 - 4f_3 \tag{8.2}
\]

\[
\frac{d\psi}{dt} = \frac{p_3 f_3 + p_1 f_1 + p_3 f_3 - L}{C_{\text{im}}} \tag{8.3}
\]

\[
\frac{dH^+}{dt} = \frac{1}{R_{\text{Hi}}} L - \frac{p_3}{R_{\text{Hi}}} f_3 - \frac{p_1}{R_{\text{Hi}}} f_1 - \frac{p_3}{R_{\text{Hi}}} f_3 \tag{8.4}
\]

\[
\frac{dO_2}{dt} = \frac{1}{Vol_{\text{mit}}} j_{\text{O}_2} - f_3 \tag{8.5}
\]

\[
\frac{dv_{\text{CO}_2}}{dt} = \frac{1}{\tau_{\text{CO}_2}} (P_a \text{CO}_2 - v_{\text{CO}_2}) \tag{8.6}
\]

\[
\frac{dv_{\text{O}_2}}{dt} = \frac{1}{\tau_{\text{O}_2}} (O_{2,c} - v_{\text{O}_2}) \tag{8.7}
\]

\[
\frac{dv_p}{dt} = \frac{1}{\tau_{p_a}} (P_a - v_{p_a}) \tag{8.8}
\]
\[
\frac{dv_u}{dr} = \frac{1}{\tau_u} (u - v_u)
\]  

**8.3 Algebraic Equations**

\[
\phi \left( \frac{S_{c,O_2}}{1 - S_{c,O_2}} \right)^{\frac{1}{\pi}} - O_{2,c} = 0
\]  

\[
T_c + T_m - (P_1 - P_{ic}) r = 0
\]  

\[
CBF \left( HbO_{2,a} - HbO_{2,v} \right) - J_{O_2} = 0
\]  

**8.4 Chemical Reactions**

\[
\frac{L}{R_{Hi}} \rightarrow 1 H^+
\]  

\[
\frac{J_{O_2}}{Vol_{mit}} \rightarrow \frac{1}{O_2}
\]  

\[
\frac{p_3}{R_{Hi}} \rightarrow H^+ \rightarrow 4 Cu_{A,o} + 4 a_{3,r}
\]  

\[
4 Cu_{A,o} + \frac{P_1}{R_{Hi}} \rightarrow H^+ \rightarrow 4 Cu_{A,o} + 4 a_{3,r}
\]  

**8.5 State Variables**

\[Cu_{A,o}\]
- Implementation Name: a
- Units: mM
- Initial value: \( Cu_{A,o,n} \)
- Concentration of oxidised cytochrome c oxidase.

\[a_{3,r}\]
- Implementation Name: bred
- Units: mM
- Initial value: \( a_{3,r,n} \)
- Concentration of reduced cytochrome \( a_3 \).
8.5 State Variables

\( \psi \)
Implementation Name: \( \delta \psi \)
Units: mV
Initial value: \( \psi_n \)
Mitochondrial inner membrane potential. Varies as charge (in the form of protons) is transferred across the membrane capacitance.

\( H^+ \)
Implementation Name: \( H^+ \)
Units: mM
Initial value: \( H^+_{n} \)
Mitochondrial proton concentration.

\( O_2 \)
Implementation Name: \( O_2 \)
Units: mM
Initial value: \( O_{2,n} \)
Mitochondrial oxygen concentration.

\( O_{2,c} \)
Implementation Name: \( O_{2,c} \)
Units: mM
Initial value: \( O_{2,c,n} \)
Capillary oxygen concentration.

\( r \)
Implementation Name: \( r \)
Units: cm
Initial value: \( r_n \)
Typical blood vessel radius.

\( v_{CO_2} \)
Implementation Name: \( v_{CO_2} \)
Units: mmHg
Initial value: \( v_{CO_2,n} \)
Filtered carbon dioxide partial pressure.

\( v_{O_2} \)
Implementation Name: \( v_{O_2} \)
Units: mM
Initial value: \( v_{O_2,n} \)
Filtered capillary oxygen concentration.

\( v_{Pa} \)
Implementation Name: \( v_{Pa} \)
Units: mmHg
Initial value: \( v_{Pa,n} \)
Filtered arterial blood pressure.

\( v_u \)
Implementation Name: \( v_u \)
Units: dimensionless
Initial value: \( v_{u,n} \)
Filtered demand.

\( HbO_{2,v} \)
Implementation Name: \( X0v \)
Units: mM
Initial value: \( HbO_{2,v,n} \)
Venous concentration of oxygen bound to haemoglobin.
8.6 Intermediate Variables

\[ CBF = G \left( P_a - P_v \right) \]
Implementation Name: CBF
Units: ml\(_{\text{blood}}\) ml\(_{\text{brain}}^{-1}\) s\(^{-1}\)
Initial value: CBF\(_{\text{n}}\)
Cerebral blood flow.

\[ \Delta \text{oxCCO} = \Delta \text{oxCCO}_{\text{off}} + 1000 \text{Vol}_{\text{mit}} \left( C_{\text{UAo}} - C_{\text{UAo,n}} \right) \]
Implementation Name: CCO
Units: uM
Initial value: 0
Cytochrome c oxidase signal measured by NIRS.

\[ \text{CMRO}_2 = f_3 \text{Vol}_{\text{mit}} \]
Implementation Name: CMRO2
Units: mM s\(^{-1}\)
Initial value: 0
Rate of cerebral oxygen metabolism.

\[ \Delta p = \psi - Z \left( 4 + \log_{10}(H^+) \right) \]
Implementation Name: \( \Delta p \)
Units: mV
Initial value: 0
Proton motive force across the mitochondrial inner membrane.

\[ \eta = R_p \left( \frac{v_{p_a}}{v_{p_{a,n}}^x} - 1 \right) + R_{o_2} \left( \frac{v_{O_2}}{v_{O_2,n}^x} - 1 \right) + R_{CO_2} \left( 1 - \frac{v_{CO_2}}{v_{CO_2,n}^x} \right) + R_u \left( 1 - \frac{v_u}{v_{u,n}} \right) \]
Implementation Name: \( \eta \)
Units: dimensionless
Initial value: 0
Merged autoregulation stimulus.

\[ f_1 = \lambda f_1 + \lambda f_{1,a} \log (C_{\text{UAo}}) \]
Implementation Name: \( f_1 \)
Units: mM s\(^{-1}\)
Initial value: 0
Reaction rate for the reduction of \( \text{Cu}_{\text{A}} \).

\[ f_2 = \lambda f_2 + \lambda f_{2,a} \log (a_{3,r}) \]
Implementation Name: \( f_2 \)
Units: mM s\(^{-1}\)
Initial value: 0
Reaction rate for the reduction of \( a_3 \).

\[ f_3 = \lambda f_3 + \lambda f_{3,o} \log (O_2) \]
Implementation Name: \( f_3 \)
Units: mM s\(^{-1}\)
Initial value: 0
Reaction rate for the reduction of \( O_2 \).

\[ G = K_G r^A \]
Implementation Name: \( G \)
Units: ml\(_{\text{blood}}\) ml\(_{\text{brain}}^{-1}\) mmHg\(^{-1}\) s\(^{-1}\)
Initial value: 0
Effective conductance of the whole blood flow compartment.

\[ h = \sqrt{r r + 2 r h_0 + h_0 h_0} - r \]
Implementation Name: \( h \)
Units: cm
Initial value: $h_n$
Thickness of the blood vessel walls.

$HbO_2 = (V_a HbO_2, a + V_v HbO_2, v) \text{ blood}_{hb}$
Implementation Name: HbO2
Units: uM
Initial value: 0
Oxygenated haemoglobin signal measured by NIRS.

$HbT = (V_a + V_v) HbO_2, \text{ blood}_{hb}$
Implementation Name: HbT
Units: uM
Initial value: 0
Total haemoglobin signal measured by NIRS.

$HHb = HbT - HbO_2$
Implementation Name: HHb
Units: uM
Initial value: 0
Deoxygenated haemoglobin signal measured by NIRS.

$J_{O_2} = f_{min} (D_{O_2} (O_2, c - O_2), CBF HbO_2, a)$
Implementation Name: J_O2
Units: mM s$^{-1}$
Initial value: 0
Oxygen flux from blood to tissue.

$L = \lambda_L + \lambda_{l,\theta} \theta + \lambda_{l,\rho} \Delta \rho$
Implementation Name: L
Units: mM s$^{-1}$
Initial value: 0
Rate of proton return to the mitochondrial matrix.

$\mu = \mu_{min} + \mu_{max} \exp (\eta) \over 1 + \exp (\eta)$
Implementation Name: mu
Units: dimensionless
Initial value: 0
Effective strength of the autoregulation response.

$R_{Hi} = \frac{R_{Hi,H}}{H}$
Implementation Name: R_HI
Units: dimensionless
Initial value: 0
Relative mitochondrial volume for protons, taking into account buffering effect of pH.

$S_{c,O_2} = S_{a,O_2} + S_v,O_2,$
Implementation Name: ScO2
Units: dimensionless
Initial value: $S_{c,O_2, n}$
Capillary oxygen saturation.

$\sigma_e = \sigma_{e,0} \left( \exp \left( \frac{K_e (r - r_0)}{r_0} \right) - 1 \right) - \sigma_{coll}$
Implementation Name: sigma_e
Units: mm Hg
Initial value: 0
Elastic stress in blood vessel walls.
\[ S_{v,O_2} = \frac{HbO_2,v}{Hb_{tot}} \]
Implementation Name: SvO2
Units: dimensionless
Initial value: \( S_{v,O_2,n} \)
Venous oxygen saturation.

\[ T_e = \sigma_e h \]
Implementation Name: \( T_e \)
Units: mm Hg cm
Initial value: 0
Elastic tension in the blood vessel walls.

\[ T_m = T_{max} \exp \left( -\text{pow} \left( \left| \frac{r - r_m}{r_1 - r_m} \right|, n_m \right) \right) \]
Implementation Name: \( T_m \)
Units: mm Hg cm
Initial value: 0
Muscular tension in the blood vessel walls.

\[ T_{max} = T_{max,0} (1 + k_{aut} \mu) \]
Implementation Name: \( T_{max} \)
Units: mm Hg cm
Initial value: 0
Maximal muscular tension in the blood vessel walls.

\[ \theta = kCV (\Delta p + Z \log_{10} (u) - 90) \]
Implementation Name: \( \theta \)
Units: dimensionless
Initial value: 0
Driving force Complex V.

\[ TOI = \frac{100HbO_2}{HbT} \]
Implementation Name: \( TOI \)
Units: dimensionless
Initial value: 0
Total oxygenation index.

\[ V_{mca} = CBF \cdot CBF_{scale} \]
Implementation Name: \( V_{mca} \)
Units: cm s\(^{-1}\)
Initial value: 0
Blood velocity in the middle cerebral artery.

\[ V_a = V_{a,n} \left( \frac{r}{r_n} \right)^2 \]
Implementation Name: \( Vol_{art} \)
Units: dimensionless
Initial value: 0
Relative arterial blood volume.

### 8.7 Parameters

\[ C_{H_A,n} \]
Implementation Name: \( a_n \)
Units: mM
8.7 Parameters

Initial value: 0.06567
Normal concentration of oxidised cytochrome c oxidase.

\(\text{blood_{hb}}\)
Implementation Name: blood hb
Units: dimensionless
Initial value: 10.00
Factor to convert model haemoglobin concentration to instrumental units. Scales for blood fraction of brain volume, mM to \(\mu\)M, and number of binding sites.

\(a_{3\tau,n}\)
Implementation Name: bred_n
Units: mM
Initial value: 0.001408
Normal concentration of reduced cytochrome a3.

\(C_{im}\)
Implementation Name: C.im
Units: mM mV\(^{-1}\)
Initial value: 0.00675
Capacitance of the mitochondrial inner membrane.

\(\text{CBF}_n\)
Implementation Name: CBFn
Units: ml
\text{blood} ml\text{brain} s\(^{-1}\)
Initial value: 0.0125
Normal cerebral blood flow.

\(\text{CBFscale}\)
Implementation Name: CBFscale
Units: cm
Initial value: 5000
Scale constant relating blood flow to arterial velocity.

\(\Delta_{oxCCO_{off}}\)
Implementation Name: CCO_offset
Units: uM
Initial value: 0
Signal offset for the NIRS CCO measurement.

\(\text{CMRO}_{2,n}\)
Implementation Name: CMRO2_n
Units: mM s\(^{-1}\)
Initial value: 0.034
Normal metabolic rate of oxygen consumption.

\(D_{O_2}\)
Implementation Name: d_02
Units: s\(^{-1}\)
Initial value: \(\frac{J_{O_2,n}}{O_{2,e,n} - O_{2,n}}\)
Diffusion rate for oxygen between capillaries and mitochondria.

\(\psi_n\)
Implementation Name: dpsi_n
Units: mV
Initial value: 145
Normal mitochondrial inner membrane potential.

\(\lambda_{f_1}\)
Implementation Name: f1_0
Units: mM s$^{-1}$
Initial value: 1.504
Fitted intercept for the linear model for $f_1$.

$\lambda_{f_1,a}$
Implementation Name: $f_{1,a}$
Units: mM s$^{-1}$
Initial value: 0.3658
Fitted linear dependence of $f_1$ on logarithm of Cu$_{A,ox}$.

$\lambda_{f_2}$
Implementation Name: $f_{2,0}$
Units: mM s$^{-1}$
Initial value: 0.1473
Fitted intercept for the linear model for $f_2$.

$\lambda_{f_2,b}$
Implementation Name: $f_{2,bred}$
Units: mM s$^{-1}$
Initial value: $-0.05484$
Fitted linear dependence of $f_2$ on logarithm of $a_{3,red}$.

$\lambda_{f_3}$
Implementation Name: $f_{3,0}$
Units: mM s$^{-1}$
Initial value: 0.6324
Fitted intercept for the linear model for $f_3$.

$\lambda_{f_3,O}$
Implementation Name: $f_{3,02}$
Units: mM s$^{-1}$
Initial value: 0.03352
Fitted linear dependence of $f_3$ on logarithm of O$_2$.

$G_n$
Implementation Name: $G_n$
Units: ml$_{blood}$ ml$_{brain}^{-1}$ mmHg$^{-1}$ s$^{-1}$
Initial value: $CBF_n$
Normal blood vessel conductance.

$h_0$
Implementation Name: $h_{0}$
Units: cm
Initial value: 0.003
Thickness of the blood vessel walls at which radius is $r_0$.

$H_n^+$
Implementation Name: $H_{n,n}$
Units: mM
Initial value: 0.00003981
Normal mitochondrial proton concentration.

$h_n$
Implementation Name: $h_{n}$
Units: cm
Initial value: $\sqrt{(r_n r_n + 2r_0 h_0 + h_0 h_0) - r_n}$
Normal thickness of the blood vessel walls.

$J_{O_2,n}$
Implementation Name: $J_{02,n}$
8.7 Parameters

Units: mM s\(^{-1}\)
Initial value: \(\text{CMRO}_{2,n}\)
Normal oxygen flux from blood to tissue.

\(k_{\text{aut}}\)
Implementation Name: \(k_{\text{aut}}\)
Units: dimensionless
Initial value: 1
Overall functioning of autoregulatory response.

\(K_G\)
Implementation Name: \(K_G\)
Units: \(\text{ml}_{\text{blood}} \text{ ml}_{\text{brain}}^{-1} \text{ mmHg}^{-1} \text{ s}^{-1} \text{ cm}^{-4}\)
Initial value: \(\frac{G_n}{\text{pow} (r_n, 4)}\)
Proportionality constant in Poiseuille relation for conductance.

\(K_\sigma\)
Implementation Name: \(K_\sigma\)
Units: dimensionless
Initial value: 10
Parameter controlling the sensitivity of \(\sigma_e\) to vessel radius.

\(kCV\)
Implementation Name: \(kCV\)
Units: mV\(^{-1}\)
Initial value: 0.02047339
Factor relating the Complex V driving force to the membrane potential and demand.

\(\lambda_L\)
Implementation Name: \(L_0\)
Units: mM s\(^{-1}\)
Initial value: \(-15.339464\)
Fitted intercept for the linear model for \(L\).

\(\lambda_{L,p}\)
Implementation Name: \(L_{\Delta p}\)
Units: mM s\(^{-1}\) mV\(^{-1}\)
Initial value: 0.097097
Fitted linear dependence of \(L\) on \(\Delta p\).

\(\lambda_{L,\theta}\)
Implementation Name: \(L_{\theta}\)
Units: mM s\(^{-1}\)
Initial value: 5.665904
Fitted linear dependence of \(L\) on \(\theta\).

\(\mu_{\text{max}}\)
Implementation Name: \(\mu_{\text{max}}\)
Units: dimensionless
Initial value: 1
Upper bound for the transformed stimulus \(\mu\).

\(\mu_{\text{min}}\)
Implementation Name: \(\mu_{\text{min}}\)
Units: dimensionless
Initial value: \(-1\)
Lower bound for the transformed stimulus \(\mu\).

\(\mu_n\)
Implementation Name: \(\mu_n\)
Units: dimensionless
Initial value: 0
Normal value for the transformed stimulus $\mu$.

$h_{ni}$
Implementation Name: $n_{hi}$
Units: dimensionless
Initial value: 2.5
Hill coefficient for oxygen dissociation from haemoglobin.

$h_{ni}$
Implementation Name: $n_{mi}$
Units: dimensionless
Initial value: 1.83
Exponent in the muscular tension relationship.

$O_{2,ni}$
Implementation Name: $O_{2,ni}$
Units: mM
Initial value: 0.024
Normal mitochondrial oxygen concentration.

$O_{2,c,ni}$
Implementation Name: $O_{2,c,ni}$
Units: mM
Initial value: $\phi \text{ pow} \left( \frac{S_c O_{2,ni}}{1-S_c O_{2,ni}}, \frac{1}{h_{ni}} \right)$
Normal capillary oxygen concentration.

$p_{1i}$
Implementation Name: $p_{1i}$
Units: dimensionless
Initial value: 12
Proton cost of the reaction reducing Cu$_A$.

$p_{3i}$
Implementation Name: $p_{3i}$
Units: dimensionless
Initial value: 4
Proton cost of the reaction reducing a$_3$.

$p_{3i}$
Implementation Name: $p_{3i}$
Units: dimensionless
Initial value: 4
Proton cost of the reaction reducing O$_2$.

$P_{1i} = \frac{P_a + P_o}{2}$
Implementation Name: $P_{1i}$
Units: mm Hg
Initial value: $P_{1,ni}$
Average pressure in the blood vessels.

$P_{1,ni}$
Implementation Name: $P_{1,ni}$
Units: mm Hg
Initial value: $\frac{P_{a,ni} + P_{o,ni}}{2}$
Normal value for the average pressure in the blood vessels.
8.7 Parameters

\( P_a \)
Implementation Name: \( P_{a,n} \)
Units: mmHg
Initial value: \( P_{a,n} \)
Mean arterial blood pressure.

\( P_{a,n} \)
Implementation Name: \( P_{a,n} \)
Units: mmHg
Initial value: 100
Normal arterial blood pressure.

\( P_{ic} \)
Implementation Name: \( P_{i,c} \)
Units: mm Hg
Initial value: 9.5
Intracranial pressure.

\( P_{icn} \)
Implementation Name: \( P_{i,cn} \)
Units: mm Hg
Initial value: 9.5
Normal intracranial pressure.

\( P_v \)
Implementation Name: \( P_{v,n} \)
Units: mmHg
Initial value: \( P_{v,n} \)
Venous blood pressure.

\( P_{v,n} \)
Implementation Name: \( P_{v,n} \)
Units: mmHg
Initial value: 4
Normal venous blood pressure.

\( P_{a\text{CO}_2} \)
Implementation Name: \( P_{a,C02} \)
Units: mmHg
Initial value: \( P_{a,C02,n} \)
Arterial partial pressure of carbon dioxide.

\( P_{a\text{CO}_2,n} \)
Implementation Name: \( P_{a,C02,n} \)
Units: mmHg
Initial value: 40
Normal arterial partial pressure of carbon dioxide.

\( \phi \)
Implementation Name: \( \phi \)
Units: mM
Initial value: 0.036
Oxygen concentration at half-maximal saturation.

\( r_0 \)
Implementation Name: \( r_0 \)
Units: cm
Initial value: 0.0126
Radius in the elastic tension relationship.
\( R_{CO_2} \)
- Implementation Name: \( R_{autc} \)
- Units: dimensionless
- Initial value: 2.2
  Autoregulatory reactivity to carbon dioxide.

\( R_{O_2} \)
- Implementation Name: \( R_{auto} \)
- Units: dimensionless
- Initial value: 1.5
  Autoregulatory reactivity to oxygen.

\( R_{P_a} \)
- Implementation Name: \( R_{autop} \)
- Units: dimensionless
- Initial value: 4
  Autoregulatory reactivity to blood pressure.

\( R_H \)
- Implementation Name: \( R_{autu} \)
- Units: dimensionless
- Initial value: 0.5
  Autoregulatory reactivity to demand.

\( R_{Hi,H} \)
- Implementation Name: \( R_{Hi,H} \)
- Units: mM
- Initial value: 9.565483
  Proton buffering factor.

\( r_m \)
- Implementation Name: \( r_m \)
- Units: cm
- Initial value: 0.027
  Vessel radius at which muscular tension is maximal.

\( r_n \)
- Implementation Name: \( r_n \)
- Units: cm
- Initial value: 0.0187
  Normal blood vessel radius. Normal effective blood vessel radius.

\( r_t \)
- Implementation Name: \( r_t \)
- Units: cm
- Initial value: 0.018
  Radius in the muscular tension relationship.

\( S_{a,O_2,n} \)
- Implementation Name: \( Sa02_n \)
- Units: dimensionless
- Initial value: 0.96
  Normal arterial oxygen saturation.

\( S_{a,O_2} \)
- Implementation Name: \( Sa02sup \)
- Units: dimensionless
- Initial value: \( S_{a,O_2,n} \)
  Arterial oxygen saturation.
8.7 Parameters

\( S_{c,O_2,n} \)
- Implementation Name: \( ScO2_n \)
- Units: dimensionless
- Initial value: \( \frac{S_{c,O_2,n} + S_{v,O_2,n}}{2} \)
- Normal capillary oxygen saturation.

\( \sigma_{coll} \)
- Implementation Name: \( sigma_coll \)
- Units: mm Hg
- Initial value: 62.79
- Pressure at which blood vessels collapse.

\( \sigma_{e,0} \)
- Implementation Name: \( sigma_e0 \)
- Units: mm Hg
- Initial value: 0.1425
- Parameter in the elastic tension relationship.

\( \sigma_{e,n} \)
- Implementation Name: \( sigma_en \)
- Units: mm Hg
- Initial value: \( \sigma_{e,0} \left( \exp \left( \frac{K_{e} \left( r_n - r_0 \right)}{r_0} \right) - 1 \right) - \sigma_{coll} \)
- Normal elastic stress in blood vessel walls.

\( S_{v,O_2,n} \)
- Implementation Name: \( SvO2_n \)
- Units: dimensionless
- Initial value: \( \frac{HbO_2,v,n}{Hb_{tot,n}} \)
- Normal venous oxygen saturation.

\( t \)
- Implementation Name: \( t \)
- Units: s
- Initial value: 0
- Time over which the system evolves.

\( \tau_{CO_2} \)
- Implementation Name: \( t_{-c} \)
- Units: s
- Initial value: 5
- Filter time constant for stimulus effect of carbon dioxide.

\( T_{e,n} \)
- Implementation Name: \( T_{een} \)
- Units: mm Hg cm
- Initial value: \( \sigma_{e,n} h_n \)
- Normal elastic tension in the blood vessel walls.

\( T_{max,0} \)
- Implementation Name: \( T_{max0} \)
- Units: mm Hg cm
- Initial value: \( \frac{T_{max,n}}{1 + k_{aut} h_n} \)
- Maximal muscular tension under normal regulatory stimulus (\( \mu = \mu_n \)).

\( T_{max,n} \)
- Implementation Name: \( T_{maxn} \)
- Units: mm Hg cm
Initial value: \( T_{m,n} = \exp \left( -\text{pow} \left( \text{fabs} \left( \frac{r_n - r_m}{r_t - r_m} \right) , n \right) \right) \)

Normal maximal muscular tension.

\( T_{m,n} \)
Implementation Name: \( T_{\text{mn}} \)
Units: mm Hg cm
Initial value: \( (P_{1,n} - P_{\text{icn}}) r_n - T_{\tau,n} \)
Normal muscular tension in the blood vessel walls.

\( \tau_{O_2} \)
Implementation Name: \( \tau_{\text{o}} \)
Units: s
Initial value: 20
Filter time constant for stimulus effect of capillary oxygen.

\( \tau_{P_a} \)
Implementation Name: \( \tau_{\text{p}} \)
Units: s
Initial value: 5
Filter time constant for stimulus effect of blood pressure.

\( \tau_{u} \)
Implementation Name: \( \tau_{\text{u}} \)
Units: s
Initial value: 0.5
Filter time constant for stimulus effect of demand.

\( u \)
Implementation Name: \( u \)
Units: dimensionless
Initial value: \( u_n \)
Parameter indicating metabolic demand.

\( u_n \)
Implementation Name: \( u_{\text{n}} \)
Units: dimensionless
Initial value: 1
Normal demand.

\( v_{CO_2,n} \)
Implementation Name: \( v_{\text{cn}} \)
Units: mmHg
Initial value: \( P_{aCO_2,n} \)
Normal filtered carbon dioxide partial pressure. Normal filtered carbon dioxide partial pressure.

\( v_{O_2,n} \)
Implementation Name: \( v_{\text{on}} \)
Units: mM
Initial value: \( O_{2,c,n} \)
Normal filtered capillary oxygen concentration. Normal filtered capillary oxygen concentration.

\( v_{P_a,n} \)
Implementation Name: \( v_{\text{pn}} \)
Units: mmHg
Initial value: \( P_{a,n} \)
Normal filtered arterial blood pressure. Normal filtered blood pressure.
8.7 Parameters

\( v_{u,n} \)
Implementation Name: \( v_{un} \)
Units: dimensionless
Initial value: \( u_n \)
Normal filtered demand. Normal filtered demand.

\( VArat_n \)
Implementation Name: \( VArat_n \)
Units: dimensionless
Initial value: 3
Normal volume ratio of veins to arteries in brain tissue.

\( V_{a,n} \)
Implementation Name: \( Vol_{artn} \)
Units: dimensionless
Initial value: \( \frac{1}{1 + VArat_n} \)
Normal relative arterial blood volume.

\( Vol_{mit} \)
Implementation Name: \( Vol_{mit} \)
Units: dimensionless
Initial value: 0.067
Fraction of brain tissue volume that is mitochondria.

\( V_v \)
Implementation Name: \( Vol_{ven} \)
Units: dimensionless
Initial value: \( \frac{1}{1 + VArat_n} \)
Relative venous blood volume.

\( HbO_{2,a} = Hb_{tot} S_a, O_2 \)
Implementation Name: \( XOa \)
Units: mM
Initial value: \( HbO_{2,a,n} \)
Arterial concentration of oxygen bound to haemoglobin.

\( HbO_{2,a,n} \)
Implementation Name: \( XOa_n \)
Units: mM
Initial value: \( Hb_{tot,n} S_a, O_2, n \)
Normal arterial concentration of oxygen bound to haemoglobin.

\( HbO_{2,v,n} \)
Implementation Name: \( XOv_n \)
Units: mM
Initial value: \( \frac{CBF_n HbO_{2,a,n} - J_{O_2,n}}{CBF_n} \)
Normal venous concentration of oxygen bound to haemoglobin.

\( Hb_{tot} \)
Implementation Name: \( Xtot \)
Units: mM
Initial value: 9.1
Total concentration of haemoglobin \( O_2 \) binding sites in blood (4 times haemoglobin concentration).

\( Hb_{tot,n} \)
Implementation Name: \( Xtot_n \)
Units: mM
Initial value: 9.1
Normal total concentration of haemoglobin O₂ binding sites in blood (4 times haemoglobin concentration).

\( Z \)

Implementation Name: \( Z \)
Units: mV
Initial value: 59.028
Proportionality constant in calculation of driving forces due to concentration differences. Defined as \( RT/F \), where \( F \) is Faraday’s constant, \( R \) the ideal gas constant and \( T \) the absolute temperature.
9 BSM3

9.1 Overview

Simplified model in which the metabolic submodel is replaced with variant M3.

- 9 differential state variables
- 3 algebraic state variables
- 25 intermediate variables
- 88 parameters
- 4 declared inputs
- 31 default outputs

9.2 Differential Equations

\[
\frac{dC_{u,A,0}}{dt} = 4f^* - 4f^* \tag{9.1}
\]

\[
\frac{da_{3,r}}{dt} = 4f^* - 4f^* \tag{9.2}
\]

\[
\frac{d\psi}{dt} = \frac{p_3 f^* + p_1 f^* + p_3 f^* - L}{C_{im}} \tag{9.3}
\]

\[
\frac{dH^+}{dt} = \frac{1}{R_{Hi}} L - \frac{p_3}{R_{Hi}} f^* - \frac{p_1}{R_{Hi}} f^* - \frac{p_3}{R_{Hi}} f^* \tag{9.4}
\]

\[
\frac{dO_2}{dt} = \frac{1}{Vol_{mit}} J_{O_2} - f^* \tag{9.5}
\]

\[
\frac{dv_{CO_2}}{dt} = \frac{1}{t_{CO_2}} (p_a_{CO_2} - v_{CO_2}) \tag{9.6}
\]

\[
\frac{dv_{O_2}}{dt} = \frac{1}{t_{O_2}} (O_{2,c} - v_{O_2}) \tag{9.7}
\]

\[
\frac{dv_{P_a}}{dt} = \frac{1}{t_{P_a}} (P_a - v_{P_a}) \tag{9.8}
\]
\[
\frac{dv_u}{dt} = \frac{1}{\tau_u} (u - v_u) \quad (9.9)
\]

### 9.3 Algebraic Equations

\[
\phi \left( \frac{S_{o2}}{1 - S_{c,O2}} \right) \frac{1}{\tau_s} - O_{2,c} = 0 \quad (9.10)
\]

\[
T_e + T_m - (P_1 - P_{\alpha}) = r = 0 \quad (9.11)
\]

\[
CBF (HbO_{2,a} - HbO_{2,v}) - J_{O_2} = 0 \quad (9.12)
\]

### 9.4 Chemical Reactions

\[
\overset{L \rightarrow}{R_{Hi}} \frac{1}{R_{Hi}} H^+ \quad (9.13)
\]

\[
\overset{J_{O_2}}{Vol_{mit}} \frac{1}{Vol_{mit}} O_2 \quad (9.14)
\]

\[
\overset{p_3}{R_{Hi}} H^+ \overset{f^*}{\rightarrow} 4 Cu_{A,0} + 4 a_{3,r} \quad (9.15)
\]

\[
4 Cu_{A,0} + \overset{p_1}{R_{Hi}} H^+ \overset{f^*}{\rightarrow} \quad (9.16)
\]

\[
O_2 + 4 a_{3,r} + \overset{p_3}{R_{Hi}} H^+ \overset{f^*}{\rightarrow} \quad (9.17)
\]

### 9.5 State Variables

- **\( Cu_{A,0} \)**
  - Implementation Name: \( \text{a} \)
  - Units: mM
  - Initial value: \( Cu_{A,0,n} \)
  - Concentration of oxidised cytochrome c oxidase.

- **\( a_{3,r} \)**
  - Implementation Name: \( \text{brzd} \)
  - Units: mM
  - Initial value: \( a_{3,r,n} \)
  - Concentration of reduced cytochrome \( a_3 \).
9.5 State Variables

ψ
Implementation Name: Dpsi
Units: mV
Initial value: $\psi_n$
Mitochondrial inner membrane potential. Varies as charge (in the form of protons) is transferred across the membrane capacitance.

$H^+$
Implementation Name: H
Units: mM
Initial value: $H^+_n$
Mitochondrial proton concentration.

$O_2$
Implementation Name: O2
Units: mM
Initial value: $O_{2,n}$
Mitochondrial oxygen concentration.

$O_{2,c}$
Implementation Name: O2c
Units: mM
Initial value: $O_{2,c,n}$
Capillary oxygen concentration.

$r$
Implementation Name: r
Units: cm
Initial value: $r_n$
Typical blood vessel radius.

$v_{CO_2}$
Implementation Name: v_c
Units: mmHg
Initial value: $v_{CO_2,n}$
Filtered carbon dioxide partial pressure.

$v_{O_2}$
Implementation Name: v_o
Units: mM
Initial value: $v_{O_2,n}$
Filtered capillary oxygen concentration.

$v_{Pa}$
Implementation Name: v_p
Units: mmHg
Initial value: $v_{Pa,n}$
Filtered arterial blood pressure.

$v_u$
Implementation Name: v_u
Units: dimensionless
Initial value: $v_{u,n}$
Filtered demand.

$HbO_{2,c}$
Implementation Name: X0v
Units: mM
Initial value: $HbO_{2,c,n}$
Venous concentration of oxygen bound to haemoglobin.
9.6 Intermediate Variables

\[ CBF = G (P_a - P_v) \]
Implementation Name: CBF
Units: \( \text{ml}_{\text{blood}} \text{ml}_{\text{brain}}^{-1} \text{s}^{-1} \)
Initial value: \( CBF_0 \)
Cerebral blood flow.

\[ \Delta \text{oxCCO} = \Delta \text{oxCCO}_{\text{off}} + 1000 \text{Vol}_{\text{mit}} (\text{Cu}_{A,o} - \text{Cu}_{A,o,n}) \]
Implementation Name: CCO
Units: uM
Initial value: 0
Cytochrome c oxidase signal measured by NIRS.

\[ \text{CMRO}_2 = f^* \text{Vol}_{\text{mit}} \]
Implementation Name: CMRO2
Units: mM s\(^{-1}\)
Initial value: 0
Rate of cerebral oxygen metabolism.

\[ \Delta p = \psi - Z \left(4 + \log_{10}(H^+)\right) \]
Implementation Name: \( \Delta p \)
Units: mV
Initial value: 0
Proton motive force across the mitochondrial inner membrane.

\[ \eta = R_p \left(\frac{V_a}{V_{pa,n}} - 1\right) + R_{O_2} \left(\frac{V_{O_2,n}}{V_{O_2,n}} - 1\right) + R_{\text{CO}_2} \left(1 - \frac{V_{\text{CO}_2,n}}{V_{\text{CO}_2,n}}\right) + R_\eta \left(1 - \frac{V_u}{V_{u,n}}\right) \]
Implementation Name: \( \eta \)
Units: dimensionless
Initial value: 0
Merged autoregulation stimulus.

\[ f^* = \lambda_{f^*} + \lambda_{f^*,p} \Delta p + \lambda_{f^*,G} \log(O_2) + \lambda_{f^*,A} \log(Cu_{A,o}) \]
Implementation Name: \( f^* \)
Units: mM s\(^{-1}\)
Initial value: 0
Shared reaction rate for all three electron transport reactions.

\[ G = K_G r^4 \]
Implementation Name: \( G \)
Units: \( \text{ml}_{\text{blood}} \text{ml}_{\text{brain}}^{-1} \text{mmHg}^{-1} \text{s}^{-1} \)
Initial value: 0
Effective conductance of the whole blood flow compartment.

\[ h = \sqrt{r + 2r_0 h_0 + h_0 - a} \]
Implementation Name: \( h \)
Units: cm
Initial value: \( h_0 \)
Thickness of the blood vessel walls.

\[ \text{HbO}_2 = (V_a \text{HbO}_2,a + V_v \text{HbO}_2,v) \text{blood}_{\text{hb}} \]
Implementation Name: \( \text{HbO}_2 \)
Units: uM
Initial value: 0
Oxygenated haemoglobin signal measured by NIRS.

\[ \text{HbT} = (V_a + V_v) \text{Hb}_\text{tot} \text{blood}_{\text{hb}} \]
Implementation Name: \( \text{HbT} \)
Units: uM
9.6 Intermediate Variables

Initial value: 0
Total haemoglobin signal measured by NIRS.

\[ HHb = HbT - HbO_2 \]
Implementation Name: HHb
Units: uM
Initial value: 0
Deoxygenated haemoglobin signal measured by NIRS.

\[ J_{O_2} = f_{\min} \left( D_{O_2} (O_2, c - O_2) \right), CBF HbO_2, a \]
Implementation Name: J_{O2}
Units: mM s^{-1}
Initial value: 0
Oxygen flux from blood to tissue.

\[ L = \lambda_L + \lambda_{L, \theta} \theta + \lambda_{L, \Delta p} \Delta p \]
Implementation Name: L
Units: mM s^{-1}
Initial value: 0
Rate of proton return to the mitochondrial matrix.

\[ \mu = \frac{\mu_{\min} + \mu_{\max} \exp (\eta)}{1 + \exp (\eta)} \]
Implementation Name: mu
Units: dimensionless
Initial value: 0
Effective strength of the autoregulation response.

\[ R_{Hi} = \frac{R_{Hi,H}}{H} \]
Implementation Name: R_{Hi}
Units: dimensionless
Initial value: 0
Relative mitochondrial volume for protons, taking into account buffering effect of pH.

\[ S_{c,O_2} = \frac{S_{c,O_2}}{2} \]
Implementation Name: ScO2
Units: dimensionless
Initial value: 0
Capillary oxygen saturation.

\[ \sigma_e = \sigma_{e,0} \left( \frac{K_e \left( r - r_0 \right)}{r_0} \right) - 1 - \sigma_{coll} \]
Implementation Name: sigma_e
Units: mm Hg
Initial value: 0
Elastic stress in blood vessel walls.

\[ S_{v,O_2} = \frac{HbO_2}{Hb_{tot}} \]
Implementation Name: SvO2
Units: dimensionless
Initial value: 0
Venous oxygen saturation.

\[ T_e = \sigma_{e, h} \]
Implementation Name: T_e
Units: mm Hg cm
Initial value: 0
Elastic tension in the blood vessel walls.
\[ T_m = T_{\text{max}} \exp \left( -\text{pow} \left( \text{fabs} \left( \frac{r - r_m}{r_1 - r_m} \right), n_m \right) \right) \]

Implementation Name: \( T_m \)
Units: mm Hg cm
Initial value: 0
Muscular tension in the blood vessel walls.

\[ T_{\text{max}} = T_{\text{max},0} \left( 1 + k_{\text{aut}} \mu \right) \]

Implementation Name: \( T_{\text{max}} \)
Units: mm Hg cm
Initial value: 0
Maximal muscular tension in the blood vessel walls.

\[ \theta = kCV (\Delta p + Z \log_{10}(u) - 90) \]

Implementation Name: \( \theta \)
Units: dimensionless
Initial value: 0
Driving force Complex V.

\[ TOI = \frac{100\text{HbO}_2}{\text{HbT}} \]

Implementation Name: \( TOI \)
Units: dimensionless
Initial value: 0
Total oxygenation index.

\[ V_{\text{mca}} = CBF \ CBF_{\text{scale}} \]

Implementation Name: \( V_{\text{mca}} \)
Units: cm s\(^{-1}\)
Initial value: 0
Blood velocity in the middle cerebral artery.

\[ V_a = V_{a,n} \left( \frac{r}{r_n} \right)^2 \]

Implementation Name: \( V_{\text{vol}_\text{art}} \)
Units: dimensionless
Initial value: 0
Relative arterial blood volume.

### 9.7 Parameters

\( C_{u_{A,o,n}} \)
Implementation Name: \( a_n \)
Units: mM
Initial value: 0.06567
Normal concentration of oxidised cytochrome c oxidase.

\( \text{blood}_{\text{hb}} \)
Implementation Name: \( \text{blood}_{\text{hb}} \)
Units: dimensionless
Initial value: 10.00
Factor to convert model haemoglobin concentration to instrumental units. Scales for blood fraction of brain volume, mM to \( \mu M \), and number of binding sites.

\( a_{3,r,n} \)
Implementation Name: \( b_{\text{red}_n} \)
Units: mM
Parameters

\text{Initial value: 0.001408}
Normal concentration of reduced cytochrome a₃.

\text{C_{im}}
Implementation Name: C_{im}
Units: mM mV⁻¹
Initial value: 0.00675
Capacitance of the mitochondrial inner membrane.

\text{CBFₙ}
Implementation Name: CBFₙ
Units: ml_{blood} ml_{brain}⁻¹ s⁻¹
Initial value: 0.0125
Normal cerebral blood flow.

\text{CBFscale}
Implementation Name: CBFscale
Units: cm
Initial value: 5000
Scale constant relating blood flow to arterial velocity.

\Delta \text{oxCCO} \text{off}
Implementation Name: CCO_{offset}
Units: uM
Initial value: 0
Signal offset for the NIRS CCO measurement.

\text{CMRO}₂\text{a,}
Implementation Name: CMRO₂\text{a,}
Units: mM s⁻¹
Initial value: 0.034
Normal metabolic rate of oxygen consumption.

\text{D}_{O₂}
Implementation Name: D_{O₂}
Units: s⁻¹
Initial value: \frac{J_{O₂}}{O_{2,c,n} - O_{2,n}}
Diffusion rate for oxygen between capillaries and mitochondria.

\psi_n
Implementation Name: Dpsi_n
Units: mV
Initial value: 145
Normal mitochondrial inner membrane potential.

\lambda_f\star
Implementation Name: f₃\_0
Units: mM s⁻¹
Initial value: 13.34
Fitted intercept for the linear model for \( f \star \).

\lambda_{f\star,a}
Implementation Name: f₃\_a
Units: mM s⁻¹
Initial value: 1.308
Fitted linear dependence of \( f \star \) on logarithm of CuA,ox.

\lambda_{f\star,O}
Implementation Name: f₃\_02
Units: mM s⁻¹
Initial value: 0.08064
Fitted linear dependence of $f^*$ on logarithm of $O_2$.

$\lambda_{f^*,p}$
Implementation Name: f3_p
Units: mM s$^{-1}$
Initial value: 0.05317
Fitted linear dependence of $f^*$ on $\Delta p$.

$G_n$
Implementation Name: G_n
Units: ml$^{-1}$ ml$^{-1}$ mmHg$^{-1}$ s$^{-1}$
Initial value: \( \frac{P_{p,n} - P_{v,n}}{CBF_n} \)
Normal blood vessel conductance.

$h_0$
Implementation Name: h_0
Units: cm
Initial value: 0.003
Thickness of the blood vessel walls at which radius is $r_0$.

$H^+_n$
Implementation Name: H_n
Units: mM
Initial value: 0.00003981
Normal mitochondrial proton concentration.

$h_n$
Implementation Name: h_n
Units: cm
Initial value: $\sqrt{(r_n r_n + 2r_0 h_0 h_0) - r_n}$
Normal thickness of the blood vessel walls.

$I_{O_2,n}$
Implementation Name: I_O2n
Units: mM s$^{-1}$
Initial value: $CMRO_{2,n}$
Normal oxygen flux from blood to tissue.

$k_{aut}$
Implementation Name: k_aut
Units: dimensionless
Initial value: 1
Overall functioning of autoregulatory response.

$K_G$
Implementation Name: K_G
Units: ml$^{-1}$ ml$^{-1}$ mmHg$^{-1}$ s$^{-1}$ cm$^{-4}$
Initial value: \( \frac{CBF_n}{G_n} \)
Proportionality constant in Poiseuille relation for conductance.

$K_\sigma$
Implementation Name: K_sigma
Units: dimensionless
Initial value: 10
Parameter controlling the sensitivity of $\sigma_\tau$ to vessel radius.

$kCV$
Implementation Name: kCV
9.7 Parameters

Units: mV$^{-1}$
Initial value: 0.02047339
Factor relating the Complex V driving force to the membrane potential and demand.

$\lambda_L$
Implementation Name: L_0
Units: mM s$^{-1}$
Initial value: −15.339464
Fitted intercept for the linear model for $L$.

$\lambda_{L,p}$
Implementation Name: L_Dp
Units: mM s$^{-1}$ mV$^{-1}$
Initial value: 0.097097
Fitted linear dependence of $L$ on $\Delta p$.

$\lambda_{L,\theta}$
Implementation Name: L_th
Units: mM s$^{-1}$
Initial value: 5.665904
Fitted linear dependence of $L$ on $\theta$.

$\mu_{max}$
Implementation Name: mu_max
Units: dimensionless
Initial value: 1
Upper bound for the transformed stimulus $\mu$.

$\mu_{min}$
Implementation Name: mu_min
Units: dimensionless
Initial value: −1
Lower bound for the transformed stimulus $\mu$.

$\mu_n$
Implementation Name: mu_n
Units: dimensionless
Initial value: 0
Normal value for the transformed stimulus $\mu$.

$n_h$
Implementation Name: n_h
Units: dimensionless
Initial value: 2.5
Hill coefficient for oxygen dissociation from haemoglobin.

$n_m$
Implementation Name: n_m
Units: dimensionless
Initial value: 1.83
Exponent in the muscular tension relationship.

$O_{2,n}$
Implementation Name: 02_n
Units: mM
Initial value: 0.024
Normal mitochondrial oxygen concentration.

$O_{2,c,n}$
Implementation Name: 02c_n
Units: mM
Initial value: \( \phi \text{ pow} \left( \frac{S_c O_2, n}{1 - S_c O_2, n} \frac{1}{n_R} \right) \)

Normal capillary oxygen concentration.

\( p_1 \)
- Implementation Name: \( p_1 \)
- Units: dimensionless
- Initial value: 12
- Proton cost of the reaction reducing Cu. 

\( p_3 \)
- Implementation Name: \( p_2 \)
- Units: dimensionless
- Initial value: 4
- Proton cost of the reaction reducing a. 

\( p_3 \)
- Implementation Name: \( p_3 \)
- Units: dimensionless
- Initial value: 4
- Proton cost of the reaction reducing O. 

\[ P_1 = \frac{P_a + P_v}{2} \]
- Implementation Name: \( P_{1_n} \)
- Units: mm Hg
- Initial value: \( P_{1,n} \)
- Average pressure in the blood vessels.

\( P_{1,n} \)
- Implementation Name: \( P_{1,n} \)
- Units: mm Hg
- Initial value: \( P_{a,n} + P_{v,n} \)
- Normal value for the average pressure in the blood vessels.

\( P_a \)
- Implementation Name: \( P_{a_n} \)
- Units: mm Hg
- Initial value: \( P_{a,n} \)
- Mean arterial blood pressure.

\( P_{a,n} \)
- Implementation Name: \( P_{a,n} \)
- Units: mm Hg
- Initial value: 100
- Normal arterial blood pressure.

\( P_{ic} \)
- Implementation Name: \( P_{ic} \)
- Units: mm Hg
- Initial value: 9.5
- Intracranial pressure.

\( P_{icn} \)
- Implementation Name: \( P_{icn} \)
- Units: mm Hg
- Initial value: 9.5
- Normal intracranial pressure.

\( P_v \)
9.7 Parameters

Implementation Name: $P_v$
Units: mmHg
Initial value: $P_{v,n}$
Venous blood pressure.

$P_{v,n}$
Implementation Name: $P_{vn}$
Units: mmHg
Initial value: 4
Normal venous blood pressure.

$Pa_{CO_2}$
Implementation Name: $Pa_{CO2}$
Units: mmHg
Initial value: $Pa_{CO2,n}$
Arterial partial pressure of carbon dioxide.

$Pa_{CO2,n}$
Implementation Name: $Pa_{CO2n}$
Units: mmHg
Initial value: 40
Normal arterial partial pressure of carbon dioxide.

$\phi$
Implementation Name: $\phi_1$
Units: mM
Initial value: 0.036
Oxygen concentration at half-maximal saturation.

$r_0$
Implementation Name: $r_0$
Units: cm
Initial value: 0.0126
Radius in the elastic tension relationship.

$R_{CO_2}$
Implementation Name: $R_{autc}$
Units: dimensionless
Initial value: 2.2
Autoregulatory reactivity to carbon dioxide.

$R_{O_2}$
Implementation Name: $R_{auto}$
Units: dimensionless
Initial value: 1.5
Autoregulatory reactivity to oxygen.

$R_P$
Implementation Name: $R_{autp}$
Units: dimensionless
Initial value: 4
Autoregulatory reactivity to blood pressure.

$R_H$
Implementation Name: $R_{autu}$
Units: dimensionless
Initial value: 0.5
Autoregulatory reactivity to demand.

$R_{HI,H}$
Implementation Name: $R_{HI,H}$
9 BSM3

Units: mM
Initial value: 9.565483
Proton buffering factor.

\( r_m \)
Implementation Name: \( r_m \)
Units: cm
Initial value: 0.027
Vessel radius at which muscular tension is maximal.

\( r_n \)
Implementation Name: \( r_n \)
Units: cm
Initial value: 0.0187
Normal blood vessel radius. Normal effective blood vessel radius.

\( r_t \)
Implementation Name: \( r_t \)
Units: cm
Initial value: 0.018
Radius in the muscular tension relationship.

\( S_{a,O_2,n} \)
Implementation Name: \( SaO2_n \)
Units: dimensionless
Initial value: 0.96
Normal arterial oxygen saturation.

\( S_{a,O_2} \)
Implementation Name: \( SaO2up \)
Units: dimensionless
Initial value: \( S_{a,O_2,n} \)
Arterial oxygen saturation.

\( S_{c,O_2,n} \)
Implementation Name: \( ScO2_n \)
Units: dimensionless
Initial value: \( \frac{S_{a,O_2,n} + S_{c,O_2,n}}{2} \)
Normal capillary oxygen saturation.

\( \sigma_{coll} \)
Implementation Name: \( sigma_coll \)
Units: mm Hg
Initial value: 62.79
Pressure at which blood vessels collapse.

\( \sigma_{e,0} \)
Implementation Name: \( sigma_e0 \)
Units: mm Hg
Initial value: 0.1425
Parameter in the elastic tension relationship.

\( \sigma_{e,n} \)
Implementation Name: \( sigma_en \)
Units: mm Hg
Initial value: \( \sigma_{e,0} \left( \exp \left( \frac{K_e (r_n - r_0)}{r_0} \right) - 1 \right) - \sigma_{coll} \)
Normal elastic stress in blood vessel walls.

\( S_{c,O_2,n} \)
9.7 Parameters

Implementation Name: $SvO_2_n$
Units: dimensionless
Initial value: $\frac{HBO_{2,0,n}}{Hb_{tot,n}}$
Normal venous oxygen saturation.

$t$
Implementation Name: $t$
Units: $s$
Initial value: 0
Time over which the system evolves.

$\tau_{CO_2}$
Implementation Name: $\tau_{c,c}$
Units: $s$
Initial value: 5
Filter time constant for stimulus effect of carbon dioxide.

$T_{\varepsilon,n}$
Implementation Name: $T_{\varepsilon,n}$
Units: mm Hg cm
Initial value: $\sigma_{\varepsilon,n} h_n$
Normal elastic tension in the blood vessel walls.

$T_{\text{max,0}}$
Implementation Name: $T_{\text{max,0}}$
Units: mm Hg cm
Initial value: $\frac{T_{\text{max,n}}}{1 + k_{\text{aut}} \mu_n}$
Maximal muscular tension under normal regulatory stimulus ($\mu = \mu_n$).

$T_{\text{max,n}}$
Implementation Name: $T_{\text{max,n}}$
Units: mm Hg cm
Initial value: $T_{\varepsilon,n} \exp \left( -\text{pow} \left( \text{fabs} \left( \frac{r_n - r_m}{r_n - r_m} \right), n_m \right) \right)$
Normal maximal muscular tension.

$T_{m,n}$
Implementation Name: $T_{m,n}$
Units: mm Hg cm
Initial value: $(P_{1,n} - P_{icn}) r_n - T_{\varepsilon,n}$
Normal muscular tension in the blood vessel walls.

$\tau_{O_2}$
Implementation Name: $\tau_{o,0}$
Units: $s$
Initial value: 20
Filter time constant for stimulus effect of capillary oxygen.

$\tau_{p_a}$
Implementation Name: $\tau_{p_a}$
Units: $s$
Initial value: 5
Filter time constant for stimulus effect of blood pressure.

$\tau_{u}$
Implementation Name: $\tau_{u}$
Units: $s$
Initial value: 0.5
Filter time constant for stimulus effect of demand.

\( u \)
- Implementation Name: \( u \)
- Units: dimensionless
- Initial value: \( u_n \)
- Parameter indicating metabolic demand.

\( u_n \)
- Implementation Name: \( u_n \)
- Units: dimensionless
- Initial value: 1
- Normal demand.

\( v_{CO_2,n} \)
- Implementation Name: \( v_{CO_2,n} \)
- Units: mmHg
- Initial value: \( P_{\text{atm}} \)

\( v_{O_2,n} \)
- Implementation Name: \( v_{O_2,n} \)
- Units: mM
- Initial value: \( O_{2,c,n} \)
- Normal filtered capillary oxygen concentration. Normal filtered capillary oxygen concentration.

\( v_{\text{Pa,n}} \)
- Implementation Name: \( v_{\text{Pa,n}} \)
- Units: mmHg
- Initial value: \( P_{\text{atm}} \)
- Normal filtered arterial blood pressure. Normal filtered blood pressure.

\( v_{\text{un,n}} \)
- Implementation Name: \( v_{\text{un,n}} \)
- Units: dimensionless
- Initial value: \( u_n \)
- Normal filtered demand. Normal filtered demand.

\( V\text{Arat}_n \)
- Implementation Name: \( V\text{Arat}_n \)
- Units: dimensionless
- Initial value: 3
- Normal volume ratio of veins to arteries in brain tissue.

\( V_{\text{art,n}} \)
- Implementation Name: \( V_{\text{art,n}} \)
- Units: dimensionless
- Initial value: \( 1 + V\text{Arat}_n \)
- Normal relative arterial blood volume.

\( V\text{mit} \)
- Implementation Name: \( V\text{mit} \)
- Units: dimensionless
- Initial value: 0.067
- Fraction of brain tissue volume that is mitochondria.

\( V_p \)
9.7 Parameters

Implementation Name: Vol_ven
Units: dimensionless
Initial value: \(\frac{V_{Arat,n}}{1 + V_{Arat,n}}\)
Relative venous blood volume.

\[HbO_{2,a} = Hb_{tot} S_{a,O_2}\]
Implementation Name: X0a
Units: mM
Initial value: \(HbO_{2,a,n}\)
Arterial concentration of oxygen bound to haemoglobin.

\[HbO_{2,a,n}\]
Implementation Name: X0a_n
Units: mM
Initial value: \(Hb_{tot,n} S_{a,O_2,n}\)
Normal arterial concentration of oxygen bound to haemoglobin.

\[HbO_{2,v,n}\]
Implementation Name: X0v_n
Units: mM
Initial value: \(\frac{CBF_n HbO_{2,a,n} - J_{O_2,n}}{CBF_n}\)
Normal venous concentration of oxygen bound to haemoglobin.

\[Hb_{tot}\]
Implementation Name: Xtot
Units: mM
Initial value: 9.1
Total concentration of haemoglobin O\(_2\) binding sites in blood (4 times haemoglobin concentration).

\[Hb_{tot,n}\]
Implementation Name: Xtot_n
Units: mM
Initial value: 9.1
Normal total concentration of haemoglobin O\(_2\) binding sites in blood (4 times haemoglobin concentration).

\[Z\]
Implementation Name: Z
Units: mV
Initial value: 59.028
Proportionality constant in calculation of driving forces due to concentration differences. Defined as \(RT/F\), where \(F\) is Faraday’s constant, \(R\) the ideal gas constant and \(T\) the absolute temperature.
10 B1M1

10.1 Overview

Simplified model combining blood flow variant B1 and metabolic variant M1.

- 9 differential state variables
- 3 algebraic state variables
- 22 intermediate variables
- 74 parameters
- 4 declared inputs
- 33 default outputs

10.2 Differential Equations

\[ \frac{dC_{u,A,o}}{dt} = 4f_3 - 4f_1 \]  
(10.1)

\[ \frac{da_{3,r}}{dt} = 4f_3 - 4f_3 \]  
(10.2)

\[ \frac{d\psi}{dt} = \frac{p_3 f_3 + p_1 f_1 + p_3 f_3 - L}{C_{im}} \]  
(10.3)

\[ \frac{dH^+}{dt} = \frac{1}{R_{Hi}} L - \frac{p_3}{R_{Hi}} f_3 - \frac{p_1}{R_{Hi}} f_1 - \frac{p_3}{R_{Hi}} f_3 \]  
(10.4)

\[ \frac{dO_2}{dt} = \frac{1}{Vol_{mit}} I_{O_2} - f_3 \]  
(10.5)

\[ \frac{dv_{CO_2}}{dt} = \frac{1}{\tau_{CO_2}} (P_{aCO_2} - v_{CO_2}) \]  
(10.6)

\[ \frac{dv_{O_2}}{dt} = \frac{1}{\tau_{O_2}} (O_{2,c} - v_{O_2}) \]  
(10.7)

\[ \frac{dv_{Pa}}{dt} = \frac{1}{\tau_{Pa}} (P_a - v_{Pa}) \]  
(10.8)
\[
\frac{dv_u}{dt} = \frac{1}{\tau_u} (u - v_u)
\]  
(10.9)

### 10.3 Algebraic Equations

\[
\frac{\phi}{S_{c,O_2}} \left(\frac{1}{1 - S_{c, O_2}}\right) = O_{2,c} = 0
\]  
(10.10)

\[
\lambda_0 + \frac{\lambda_{p_a}}{P_a} + \lambda_p \mu + \frac{\lambda_{P_a, \mu}}{P_a} - r = 0
\]  
(10.11)

\[
CBF (HbO_{2,a} - HbO_{2,r}) - I_0 = 0
\]  
(10.12)

### 10.4 Chemical Reactions

\[
\overset{L}{\longrightarrow} \ \frac{1}{R_{Hi}} H^+
\]  
(10.13)

\[
\overset{I_{O_2}}{\longrightarrow} \ \frac{1}{Vol_{mit}} O_2
\]  
(10.14)

\[
\frac{p_3}{R_{Hi}} H^+ \xrightarrow{f_3} 4 Cu_{A,o} + 4 a_{3,r}
\]  
(10.15)

\[
4 Cu_{A,o} + \frac{p_1}{R_{Hi}} H^+ \xrightarrow{f_1} 
\]  
(10.16)

\[
O_2 + 4 a_{3,r} + \frac{p_3}{R_{Hi}} H^+ \xrightarrow{f_3}
\]  
(10.17)

### 10.5 State Variables

- **\(Cu_{A,o}\)**
  - Implementation Name: \(a\)
  - Units: mM
  - Initial value: \(Cu_{A,o,n}\)
  - Concentration of oxidised cytochrome c oxidase.

- **\(a_{3,r}\)**
  - Implementation Name: \(bred\)
  - Units: mM
  - Initial value: \(a_{3,r,n}\)
  - Concentration of reduced cytochrome \(a_3\).
10.5 State Variables

\( \psi \)
Implementation Name: Dpsi
Units: mV
Initial value: \( \psi_n \)
Mitochondrial inner membrane potential. Varies as charge (in the form of protons) is transferred across the membrane capacitance.

\( H^+ \)
Implementation Name: H
Units: mM
Initial value: \( H^+_n \)
Mitochondrial proton concentration.

\( O_2 \)
Implementation Name: 02
Units: mM
Initial value: \( O_{2,n} \)
Mitochondrial oxygen concentration.

\( O_2,c \)
Implementation Name: 02c
Units: mM
Initial value: \( O_{2,c,n} \)
Capillary oxygen concentration.

\( r \)
Implementation Name: r
Units: cm
Initial value: \( r_n \)
Typical blood vessel radius.

\( v_{CO_2} \)
Implementation Name: v_c
Units: mmHg
Initial value: \( v_{CO_2,n} \)
Filtered carbon dioxide partial pressure.

\( v_{O_2} \)
Implementation Name: v_o
Units: mM
Initial value: \( v_{O_2,n} \)
Filtered capillary oxygen concentration.

\( v_{Pa} \)
Implementation Name: v_p
Units: mmHg
Initial value: \( v_{Pa,n} \)
Filtered arterial blood pressure.

\( v_u \)
Implementation Name: v_u
Units: dimensionless
Initial value: \( v_{u,n} \)
Filtered demand.

\( HbO_2,v \)
Implementation Name: XOv
Units: mM
Initial value: \( HbO_{2,v,n} \)
Venous concentration of oxygen bound to haemoglobin.
10.6 Intermediate Variables

\[ CBF = G \left( P_a - P_v \right) \]
Implementation Name: \( CBF \)
Units: \( \text{ml}_{\text{blood}} \text{ml}^{-1} \text{brain} \text{s}^{-1} \)
Initial value: \( \text{CBF}_n \)
Cerebral blood flow.

\[ \Delta \text{oxCCO} = \Delta \text{oxCCO}_{\text{off}} + 1000 \text{Vol}_{\text{mit}} (\text{Cu}_{A,o} - \text{Cu}_{A,o,n}) \]
Implementation Name: \( \text{CCO} \)
Units: \( \text{uM} \)
Initial value: 0
Cytochrome c oxidase signal measured by NIRS.

\[ \text{CMRO}_2 = f_3 \text{Vol}_{\text{mit}} \]
Implementation Name: \( \text{CMRO}_2 \)
Units: \( \text{mM s}^{-1} \)
Initial value: 0
Rate of cerebral oxygen metabolism.

\[ \Delta p = \psi - Z \left( 4 + \log_{10} (H^+) \right) \]
Implementation Name: \( \text{dp} \)
Units: \( \text{mV} \)
Initial value: 0
Proton motive force across the mitochondrial inner membrane.

\[ \eta = R_{P_e} \left( \frac{v_{P_e}}{v_{P_e,n}} - 1 \right) + R_{O_2} \left( \frac{v_{O_2}}{v_{O_2,n}} - 1 \right) + R_{CO_2} \left( 1 - \frac{v_{CO_2}}{v_{CO_2,n}} \right) + R_u \left( 1 - \frac{v}{v_{u,n}} \right) \]
Implementation Name: \( \eta \)
Units: dimensionless
Initial value: 0
Merged autoregulation stimulus.

\[ f_1 = \lambda_{f_1} + \lambda_{f_{1,a}} \log (u) + \lambda_{f_{1,a}} \log (\text{Cu}_{A,o}) \]
Implementation Name: \( f_1 \)
Units: \( \text{mM s}^{-1} \)
Initial value: 0
Reaction rate for the reduction of \( \text{Cu}_A \).

\[ f_3 = \lambda_{f_3} + \lambda_{f_{3,b}} \log (a_{3,f}) \]
Implementation Name: \( f_2 \)
Units: \( \text{mM s}^{-1} \)
Initial value: 0
Reaction rate for the reduction of \( a_3 \).

\[ f_3 = \lambda_{f_3} + \lambda_{f_{3,O}} \log (O_2) \]
Implementation Name: \( f_3 \)
Units: \( \text{mM s}^{-1} \)
Initial value: 0
Reaction rate for the reduction of \( O_2 \).

\[ G = K_G r^A \]
Implementation Name: \( G \)
Units: \( \text{ml}_{\text{blood}} \text{ml}^{-1} \text{brain} \text{mmHg}^{-1} \text{s}^{-1} \)
Initial value: 0
Effective conductance of the whole blood flow compartment.

\[ HbO_2 = (V_a HbO_{2,a} + V_i HbO_{2,i}) \text{ blood}_{hb} \]
Implementation Name: \( \text{Hb02} \)
Units: \( \text{uM} \)
10.6 Intermediate Variables

Initial value: 0
Oxygenated haemoglobin signal measured by NIRS.

\[ HbT = (V_a + V_v) Hb_{tot, blood} \]
Implementation Name: HbT
Units: uM
Initial value: 0
Total haemoglobin signal measured by NIRS.

\[ HHb = HbT - HbO_2 \]
Implementation Name: HHb
Units: uM
Initial value: 0
Deoxygenated haemoglobin signal measured by NIRS.

\[ J_{O_2} = \text{fmin} \left( D_{O_2} (O_2, c - O_2), CBF HbO_2, a \right) \]
Implementation Name: J_{O2}
Units: mM s^{-1}
Initial value: 0
Oxygen flux from blood to tissue.

\[ L = \lambda_L + \lambda_{L, \theta} \theta + \lambda_{L, p} \Delta p \]
Implementation Name: L
Units: mM s^{-1}
Initial value: 0
Rate of proton return to the mitochondrial matrix.

\[ \mu = \frac{k_{aut} (\exp(\eta) - 1)}{\exp(\eta) + 1} \]
Implementation Name: mu
Units: dimensionless
Initial value: 0
Effective strength of the autoregulation response.

\[ R_{Hi} = \frac{R_{Hi, H}}{H^+} \]
Implementation Name: R_{Hi}
Units: dimensionless
Initial value: 0
Relative mitochondrial volume for protons, taking into account buffering effect of pH.

\[ S_{c,O_2} = \frac{S_{a,O_2} + S_{v,O_2}}{2} \]
Implementation Name: ScO2
Units: dimensionless
Initial value: \( S_{c,O_2,n} \)
Capillary oxygen saturation.

\[ S_{v,O_2} = \frac{HbO_2,v}{Hb_{tot}} \]
Implementation Name: SvO2
Units: dimensionless
Initial value: \( S_{v,O_2,n} \)
Venous oxygen saturation.

\[ \theta = kCV (\Delta p + Z \log_{10} (\mu) - 90) \]
Implementation Name: theta
Units: dimensionless
Initial value: 0
Driving force Complex V.
\[ \text{TOI} = \frac{100HbO_2}{HbT} \]

Implementation Name: TOI
Units: dimensionless
Initial value: 0
Total oxygenation index.

\[ V_{mca} = CBF \cdot CBFscale \]
Implementation Name: \( V_{mca} \)
Units: cm \( s^{-1} \)
Initial value: 0
Blood velocity in the middle cerebral artery.

\[ V_a = V_{a,n} \left( \frac{r}{r_n} \right)^2 \]
Implementation Name: \( V_{a,n} \)
Units: dimensionless
Initial value: 0
Relative arterial blood volume.

### 10.7 Parameters

\( C_{u_{a,n}} \)
Implementation Name: \( a_{,n} \)
Units: mM
Initial value: 0.06567
Normal concentration of oxidised cytochrome c oxidase.

\( blood_{hb} \)
Implementation Name: \( blood_{,hb} \)
Units: dimensionless
Initial value: 10.00
Factor to convert model haemoglobin concentration to instrumental units. Scales for blood fraction of brain volume, mM to \( \mu \)M, and number of binding sites.

\( a_{3,r,n} \)
Implementation Name: \( bred_{,n} \)
Units: mM
Initial value: 0.001408
Normal concentration of reduced cytochrome a3.

\( C_{im} \)
Implementation Name: \( c_{,im} \)
Units: mM mV\(^{-1}\)
Initial value: 0.00675
Capacitance of the mitochondrial inner membrane.

\( CBF_n \)
Implementation Name: \( CBFn \)
Units: ml\(^{-1}\) brain\(^{-1}\) ml\(^{-1}\) s\(^{-1}\)
Initial value: 0.0125
Normal cerebral blood flow.

\( CBFscale \)
Implementation Name: \( CBFscale \)
Units: cm
Initial value: 5000
Scale constant relating blood flow to arterial velocity.
10.7 Parameters

\( \Delta_{\text{oxCCO}_\text{off}} \)

Implementation Name: \( \text{CCO\_offset} \)
Units: uM
Initial value: 0
Signal offset for the NIRS CCO measurement.

\( \text{CMRO}_{2,n} \)

Implementation Name: \( \text{CMRO2\_n} \)
Units: mM s\(^{-1}\)
Initial value: 0.034
Normal metabolic rate of oxygen consumption.

\( D_{O_2} \)

Implementation Name: \( D_{0.02} \)
Units: s\(^{-1}\)
Initial value: \( \frac{I_{O_2,a}}{O_{2,r,n} - O_{2,n}} \)
Diffusion rate for oxygen between capillaries and mitochondria.

\( \psi_n \)

Implementation Name: \( \text{Dpsi\_n} \)
Units: mV
Initial value: 145
Normal mitochondrial inner membrane potential.

\( \lambda_{f_1} \)

Implementation Name: \( f1\_0 \)
Units: mM s\(^{-1}\)
Initial value: 1.490
Fitted intercept for the linear model for \( f_1 \).

\( \lambda_{f_{1,a}} \)

Implementation Name: \( f1\_a \)
Units: mM s\(^{-1}\)
Initial value: 0.3609
Fitted linear dependence of \( f_1 \) on logarithm of \( \text{Cu}_{A,rx} \).

\( \lambda_{f_{1,u}} \)

Implementation Name: \( f1\_u \)
Units: mM s\(^{-1}\)
Initial value: 0.06985
Fitted linear dependence of \( f_1 \) on logarithm of demand.

\( \lambda_{f_2} \)

Implementation Name: \( f2\_0 \)
Units: mM s\(^{-1}\)
Initial value: 0.1473
Fitted intercept for the linear model for \( f_2 \).

\( \lambda_{f_{2,b}} \)

Implementation Name: \( f2\_bred \)
Units: mM s\(^{-1}\)
Initial value: -0.05484
Fitted linear dependence of \( f_2 \) on logarithm of \( a_{3,red} \).

\( \lambda_{f_3} \)

Implementation Name: \( f3\_0 \)
Units: mM s\(^{-1}\)
Initial value: 0.6324
Fitted intercept for the linear model for \( f_3 \).
\( \lambda_{f_3,O} \)
Implementation Name: \( f_3,O \)
Units: mM s\(^{-1}\)
Initial value: 0.03352
Fitted linear dependence of \( f_3 \) on logarithm of \( O_2 \).

\( G_n \)
Implementation Name: \( G_n \)
Units: ml\(_{\text{blood}}\) m\(^{-1}\)l\(_{\text{brain}}\) mmHg\(^{-1}\) s\(^{-1}\)
Initial value: \( \frac{P_{o,n} - P_{v,n}}{C_B_{\text{T}_n}} \)
Normal blood vessel conductance.

\( H_n^+ \)
Implementation Name: \( H_n \)
Units: mM
Initial value: 0.00003981
Normal mitochondrial proton concentration.

\( J_{O_2,n} \)
Implementation Name: \( J_{O_2,n} \)
Units: mM s\(^{-1}\)
Initial value: \( \text{CMRO}_2,n \)
Normal oxygen flux from blood to tissue.

\( k_{\text{aut}} \)
Implementation Name: \( k_{\text{aut}} \)
Units: dimensionless
Initial value: 1
Overall functioning of autoregulatory response.

\( K_G \)
Implementation Name: \( K_G \)
Units: ml\(_{\text{blood}}\) m\(^{-1}\)l\(_{\text{brain}}\) mmHg\(^{-1}\) s\(^{-1}\) cm\(^{-4}\)
Initial value: \( \frac{G_n}{\text{pow} (r_n, 4)} \)
Proportionality constant in Poiseuille relation for conductance.

\( k_{\text{CV}} \)
Implementation Name: \( k_{\text{CV}} \)
Units: mV\(^{-1}\)
Initial value: 0.02047339
Factor relating the Complex V driving force to the membrane potential and demand.

\( \lambda_L \)
Implementation Name: \( L_0 \)
Units: mM s\(^{-1}\)
Initial value: \(-15.339464\)
Fitted intercept for the linear model for \( L \).

\( \lambda_{L,p} \)
Implementation Name: \( L_{\Delta p} \)
Units: mM s\(^{-1}\) mV\(^{-1}\)
Initial value: 0.097097
Fitted linear dependence of \( L \) on \( \Delta p \).

\( \lambda_{L,\theta} \)
Implementation Name: \( L_{\theta} \)
Units: mM s\(^{-1}\)
10.7 Parameters

Initial value: 5.665904  
Fitted linear dependence of $L$ on $\theta$.

$\lambda_0$
- Implementation Name: lam0
- Units: cm
- Initial value: 0.02507
- Intercept of the fitted linear model for blood vessel radius.

$\lambda_\mu$
- Implementation Name: lam_mu
- Units: cm
- Initial value: −0.0004422
- Fitted linear dependence of blood vessel radius on autoregulatory stimuli.

$\lambda_{P,a}$
- Implementation Name: lam_p
- Units: cm mmHg
- Initial value: −0.6327
- Fitted linear dependence of blood vessel radius on reciprocal of blood pressure.

$\lambda_{P,a,\mu}$
- Implementation Name: lam_p_mu
- Units: cm mmHg
- Initial value: −0.5286
- Fitted joint dependence of blood vessel radius on autoregulatory stimuli and reciprocal of blood pressure.

$n_h$
- Implementation Name: n_h
- Units: dimensionless
- Initial value: 2.5
- Hill coefficient for oxygen dissociation from haemoglobin.

$O_{2,n}$
- Implementation Name: O2_n
- Units: mM
- Initial value: 0.024
- Normal mitochondrial oxygen concentration.

$O_{2,c,n}$
- Implementation Name: O2c_n
- Units: mM
- Initial value: $\phi$ pow $\left( \frac{S_cO_2,n}{1 - S_cO_2,n} \cdot \frac{1}{n_h} \right)$
- Normal capillary oxygen concentration.

$p_1$
- Implementation Name: p1
- Units: dimensionless
- Initial value: 12
- Proton cost of the reaction reducing $Cu_A$.

$p_3$
- Implementation Name: p2
- Units: dimensionless
- Initial value: 4
- Proton cost of the reaction reducing $a_3$. 

$p_3$
- Implementation Name: p3
Units: dimensionless
Initial value: 4
Proton cost of the reaction reducing $O_2$.

$P_a$
Implementation Name: $P_a$
Units: mmHg
Initial value: $P_{a,n}$
Mean arterial blood pressure.

$P_{a,n}$
Implementation Name: $P_{an}$
Units: mmHg
Initial value: 100
Normal arterial blood pressure.

$P_v$
Implementation Name: $P_v$
Units: mmHg
Initial value: $P_{v,n}$
Venous blood pressure.

$P_{v,n}$
Implementation Name: $P_{vn}$
Units: mmHg
Initial value: 4
Normal venous blood pressure.

$P_{aCO_2}$
Implementation Name: $P_{aCO2}$
Units: mmHg
Initial value: $P_{aCO2,n}$
Arterial partial pressure of carbon dioxide.

$P_{aCO_2,n}$
Implementation Name: $P_{aCO2n}$
Units: mmHg
Initial value: 40
Normal arterial partial pressure of carbon dioxide.

$\phi$
Implementation Name: $\phi$
Units: mM
Initial value: 0.036
Oxygen concentration at half-maximal saturation.

$R_{CO_2}$
Implementation Name: $R_{autc}$
Units: dimensionless
Initial value: 2.2
Autoregulatory reactivity to carbon dioxide.

$R_{O_2}$
Implementation Name: $R_{auto}$
Units: dimensionless
Initial value: 1.5
Autoregulatory reactivity to oxygen.

$R_{Pa}$
Implementation Name: $R_{autop}$
Units: dimensionless
10.7 Parameters

Initial value: 4
Autoregulatory reactivity to blood pressure.

\( R_u \)
- Implementation Name: \( R_{\text{autu}} \)
- Units: dimensionless
- Initial value: 0.5
- Autoregulatory reactivity to demand.

\( R_{\text{Hi, H}} \)
- Implementation Name: \( R_{\text{Hi, H}} \)
- Units: mM
- Initial value: 9.565483
- Proton buffering factor.

\( r_n \)
- Implementation Name: \( r_n \)
- Units: cm
- Initial value: 0.0187
- Normal blood vessel radius. Normal effective blood vessel radius.

\( S_{a, O_2, n} \)
- Implementation Name: \( S_{a02, n} \)
- Units: dimensionless
- Initial value: 0.96
- Normal arterial oxygen saturation.

\( S_{a, O_2} \)
- Implementation Name: \( S_{a02\text{sup}} \)
- Units: dimensionless
- Initial value: \( S_{a, O_2, n} \)
- Arterial oxygen saturation.

\( S_{c, O_2, n} \)
- Implementation Name: \( S_{c02, n} \)
- Units: dimensionless
- Initial value: \( \frac{S_{a, O_2, n} + S_{v, O_2, n}}{2} \)
- Normal capillary oxygen saturation.

\( S_{v, O_2, n} \)
- Implementation Name: \( S_{v02, n} \)
- Units: dimensionless
- Initial value: \( \frac{HbO_2, v, n}{Hb_{tot, n}} \)
- Normal venous oxygen saturation.

\( t \)
- Implementation Name: \( t \)
- Units: s
- Initial value: 0
- Time over which the system evolves.

\( \tau_{\text{CO}_2} \)
- Implementation Name: \( \tau_{\text{c}} \)
- Units: s
- Initial value: 5
- Filter time constant for stimulus effect of carbon dioxide.

\( \tau_{O_2} \)
- Implementation Name: \( \tau_{o} \)
- Units: s
Initial value: 20
Filter time constant for stimulus effect of capillary oxygen.

\( \tau_{P_a} \)
Implementation Name: \( t_{P} \)
Units: s
Initial value: 5
Filter time constant for stimulus effect of blood pressure.

\( \tau_u \)
Implementation Name: \( t_u \)
Units: s
Initial value: 0.5
Filter time constant for stimulus effect of demand.

\( u \)
Implementation Name: \( u \)
Units: dimensionless
Initial value: \( u_n \)
Parameter indicating metabolic demand.

\( u_n \)
Implementation Name: \( u_n \)
Units: dimensionless
Initial value: 1
Normal demand.

\( v_{CO_2,n} \)
Implementation Name: \( v_{CO_2,n} \)
Units: mmHg
Initial value: \( P_{aCO_2,n} \)
Normal filtered carbon dioxide partial pressure. Normal filtered carbon dioxide partial pressure.

\( v_{O_2,n} \)
Implementation Name: \( v_{O_2,n} \)
Units: mM
Initial value: \( O_{2,c,n} \)
Normal filtered capillary oxygen concentration. Normal filtered capillary oxygen concentration.

\( v_{Pa,n} \)
Implementation Name: \( v_{Pa,n} \)
Units: mmHg
Initial value: \( P_{a,n} \)
Normal filtered arterial blood pressure. Normal filtered blood pressure.

\( v_{u,n} \)
Implementation Name: \( v_{u,n} \)
Units: dimensionless
Initial value: \( u_n \)
Normal filtered demand. Normal filtered demand.

\( VArat_n \)
Implementation Name: \( VArat_n \)
Units: dimensionless
Initial value: 3
Normal volume ratio of veins to arteries in brain tissue.

\( V_{o,n} \)
Implementation Name: \( Vol_{artn} \)
10.7 Parameters

Units: dimensionless
Initial value: \frac{1}{1 + VArat_n}
Normal relative arterial blood volume.

\text{Vol}_{mit}
Implementation Name: Vol_{mit}
Units: dimensionless
Initial value: 0.067
Fraction of brain tissue volume that is mitochondria.

\text{V}_v
Implementation Name: Vol_{ven}
Units: dimensionless
Initial value: \frac{VArat_n}{1 + VArat_n}
Relative venous blood volume.

HbO_{2,a,n} = Hb_{tot} S_{a,O_2}
Implementation Name: X0a
Units: mM
Initial value: HbO_{2,a,n}
Arterial concentration of oxygen bound to haemoglobin.

HbO_{2,a,n}
Implementation Name: X0a_n
Units: mM
Initial value: Hb_{tot,n} S_{a,O_2,n}
Normal arterial concentration of oxygen bound to haemoglobin.

HbO_{2,v,n} = \frac{CBF_n HbO_{2,a,n} - J_{O_2,v}}{CBF_n}
Implementation Name: X0v_n
Units: mM
Initial value: \frac{CBF_n HbO_{2,a,n} - J_{O_2,v}}{CBF_n}
Normal venous concentration of oxygen bound to haemoglobin.

Hb_{tot}
Implementation Name: Xtot
Units: mM
Initial value: 9.1
Total concentration of haemoglobin O_2 binding sites in blood (4 times haemoglobin concentration).

Hb_{tot,n}
Implementation Name: Xtot_n
Units: mM
Initial value: 9.1
Normal total concentration of haemoglobin O_2 binding sites in blood (4 times haemoglobin concentration).

Z
Implementation Name: Z
Units: mV
Initial value: 59.028
Proportionality constant in calculation of driving forces due to concentration differences. Defined as RT/F, where F is Faraday’s constant, R the ideal gas constant and T the absolute temperature.
11 B1M2

11.1 Overview

Simplified model combining blood flow variant B1 and metabolic variant M2.

- 9 differential state variables
- 3 algebraic state variables
- 22 intermediate variables
- 73 parameters
- 4 declared inputs
- 33 default outputs

11.2 Differential Equations

\[
\frac{dC_{u, A, o}}{dt} = 4f_3 - 4f_1
\]  
(11.1)

\[
\frac{da_{3,r}}{dt} = 4f_3 - 4f_3
\]  
(11.2)

\[
\frac{d\psi}{dt} = \frac{p_3 f_3 + p_1 f_1 + p_3 f_3 - L}{C_{im}}
\]  
(11.3)

\[
\frac{dH^+}{dt} = \frac{1}{R_{Hi}} L - \frac{p_3}{R_{Hi}} f_3 - \frac{p_1}{R_{Hi}} f_1 - \frac{p_3}{R_{Hi}} f_3
\]  
(11.4)

\[
\frac{dO_2}{dt} = \frac{1}{\text{Vol}_{mit}} j_{O_2} - f_3
\]  
(11.5)

\[
\frac{dv_{CO_2}}{dt} = \frac{1}{\tau_{CO_2}} (p_{aCO_2} - v_{CO_2})
\]  
(11.6)

\[
\frac{dv_{O_2}}{dt} = \frac{1}{\tau_{O_2}} (O_{2,c} - v_{O_2})
\]  
(11.7)

\[
\frac{dv_{P_a}}{dt} = \frac{1}{\tau_{P_a}} (P_a - v_{P_a})
\]  
(11.8)
\[
\frac{dv_u}{dt} = \frac{1}{\tau_u} (u - v_u)
\]  

(11.9)

### 11.3 Algebraic Equations

\[
\phi \left( \frac{S_{c,\text{O}_2}}{1 - S_{c,\text{O}_2}} \right) \frac{1}{\beta} - \text{O}_2 = 0
\]

(11.10)

\[
\lambda_0 + \frac{\lambda_p}{P_a} + \lambda_p \mu + \left( \frac{\lambda_{p_a}}{P_a} \right) - r = 0
\]

(11.11)

\[
\text{CBF} (\text{HbO}_2,\text{a} - \text{HbO}_2,\text{v}) - J_{\text{O}_2} = 0
\]

(11.12)

### 11.4 Chemical Reactions

\[
\xrightarrow{L} \frac{1}{R_{\text{Hi}}} \text{H}^+ 
\]

(11.13)

\[
\xrightarrow{J_{\text{O}_2}} \frac{1}{V_{\text{Volmit}}} \text{O}_2
\]

(11.14)

\[
\frac{p_3}{R_{\text{Hi}}} \text{H}^+ \xrightarrow{f_3} 4 \text{Cu}_{\text{A},\text{o}} + 4 \text{a}_{3,\text{r}}
\]

(11.15)

\[
4 \text{Cu}_{\text{A},\text{o}} + \frac{p_1}{R_{\text{Hi}}} \text{H}^+ \xrightarrow{f_1}
\]

(11.16)

\[
\text{O}_2 + 4 \text{a}_{3,\text{r}} + \frac{p_3}{R_{\text{Hi}}} \text{H}^+ \xrightarrow{f_3}
\]

(11.17)

### 11.5 State Variables

\( \text{Cu}_{\text{A},\text{o}} \)
- Implementation Name: \( \text{a} \)
- Units: mM
- Initial value: \( \text{Cu}_{\text{A},\text{a},\text{n}} \)
- Concentration of oxidised cytochrome c oxidase.

\( \text{a}_{3,\text{r}} \)
- Implementation Name: \( \text{b} \)
- Units: mM
- Initial value: \( \text{a}_{3,\text{r},\text{n}} \)
- Concentration of reduced cytochrome \( \text{a}_3 \).
11.5 State Variables

\( \psi \)
- Implementation Name: Dpsi
- Units: mV
- Initial value: \( \psi_n \)
- Mitochondrial inner membrane potential. Varies as charge (in the form of protons) is transferred across the membrane capacitance.

\( H^+ \)
- Implementation Name: H
- Units: mM
- Initial value: \( H^+_n \)
- Mitochondrial proton concentration.

\( O_2 \)
- Implementation Name: O2
- Units: mM
- Initial value: \( O_{2,n} \)
- Mitochondrial oxygen concentration.

\( O_{2,c} \)
- Implementation Name: O2c
- Units: mM
- Initial value: \( O_{2,c,n} \)
- Capillary oxygen concentration.

\( r \)
- Implementation Name: r
- Units: cm
- Initial value: \( r_n \)
- Typical blood vessel radius.

\( v_{CO_2} \)
- Implementation Name: v_c
- Units: mmHg
- Initial value: \( v_{CO_2,n} \)
- Filtered carbon dioxide partial pressure.

\( v_{O_2} \)
- Implementation Name: v_o
- Units: mM
- Initial value: \( v_{O_2,n} \)
- Filtered capillary oxygen concentration.

\( v_{Pa} \)
- Implementation Name: v_p
- Units: mmHg
- Initial value: \( v_{Pa,n} \)
- Filtered arterial blood pressure.

\( v_u \)
- Implementation Name: v_u
- Units: dimensionless
- Initial value: \( v_{u,n} \)
- Filtered demand.

\( HbO_{2,v} \)
- Implementation Name: X0v
- Units: mM
- Initial value: \( HbO_{2,v,n} \)
- Venous concentration of oxygen bound to haemoglobin.
11.6 Intermediate Variables

\[ CBF = G \left( P_a - P_v \right) \]
Implementation Name: CBF
Units: \( \text{ml}_{\text{blood}} \text{ml}_{\text{brain}}^{-1} \text{s}^{-1} \)
Initial value: \( CBF_n \)
Cerebral blood flow.

\[ \Delta \text{oxCCO} = \Delta \text{oxCCO}_{\text{off}} + 1000 \text{Vol}_{\text{mit}} \left( \text{Cu}_{A,o} - \text{Cu}_{A,n} \right) \]
Implementation Name: CCO
Units: uM
Initial value: 0
Cytochrome c oxidase signal measured by NIRS.

\[ \text{CMRO}_2 = f_3 \text{Vol}_{\text{mit}} \]
Implementation Name: CMRO2
Units: mM s\(^{-1}\)
Initial value: 0
Rate of cerebral oxygen metabolism.

\[ \Delta p = \psi - Z \left( 4 + \log_{10} \left( H^+ \right) \right) \]
Implementation Name: \( \Delta p \)
Units: mV
Initial value: 0
Proton motive force across the mitochondrial inner membrane.

\[ \eta = R_p \left( \frac{v_{p_a}}{v_{p,n}} - 1 \right) + R_{O_2} \left( \frac{v_{O_2}}{v_{O_2,n}} - 1 \right) + R_{CO_2} \left( 1 - \frac{v_{CO_2}}{v_{CO_2,n}} \right) + R_{u} \left( 1 - \frac{v_{u}}{v_{u,n}} \right) \]
Implementation Name: \( \eta \)
Units: dimensionless
Initial value: 0
Merged autoregulation stimulus.

\[ f_1 = \lambda f_1 + \lambda f_{1,a} \log \left( \text{Cu}_{A,o} \right) \]
Implementation Name: \( f_1 \)
Units: mM s\(^{-1}\)
Initial value: 0
Reaction rate for the reduction of \( \text{Cu}_A \).

\[ f_2 = \lambda f_2 + \lambda f_{2,b} \log \left( a_{3,r} \right) \]
Implementation Name: \( f_2 \)
Units: mM s\(^{-1}\)
Initial value: 0
Reaction rate for the reduction of \( a_3 \).

\[ f_3 = \lambda f_3 + \lambda f_{3,O} \log \left( O_2 \right) \]
Implementation Name: \( f_3 \)
Units: mM s\(^{-1}\)
Initial value: 0
Reaction rate for the reduction of \( O_2 \).

\[ G = K_G r^A \]
Implementation Name: \( G \)
Units: \( \text{ml}_{\text{blood}} \text{ml}_{\text{brain}}^{-1} \text{mmHg}^{-1} \text{s}^{-1} \)
Initial value: 0
Effective conductance of the whole blood flow compartment.

\[ HbO_2 = (V_a \text{HbO}_2,a + V_v \text{HbO}_2,v) \text{blood}_{hb} \]
Implementation Name: \( \text{HbO}_2 \)
Units: uM
11.6 Intermediate Variables

Initial value: 0
Oxygenated haemoglobin signal measured by NIRS.

\[ HbT = (V_a + V_v) \text{ Hb}_{tot} \text{blood}_{hb} \]
Implementation Name: \text{HbT}
Units: uM
Initial value: 0
Total haemoglobin signal measured by NIRS.

\[ HHb = HbT - HbO_2 \]
Implementation Name: \text{HHb}
Units: uM
Initial value: 0
Deoxygenated haemoglobin signal measured by NIRS.

\[ J_{O2} = \text{fmin} \left( D_{O2} \left( O_{2c} - O_2 \right) , CBF \text{ HbO}_2 \right) \]
Implementation Name: \text{J}_{02}
Units: mM s\(^{-1}\)
Initial value: 0
Oxygen flux from blood to tissue.

\[ L = \lambda_L + \lambda_L \theta + \lambda_L p \Delta p \]
Implementation Name: \text{L}
Units: mM s\(^{-1}\)
Initial value: 0
Rate of proton return to the mitochondrial matrix.

\[ \mu = \frac{k_{aut} \left( \exp (\eta) - 1 \right)}{\exp (\eta) + 1} \]
Implementation Name: \text{mu}
Units: dimensionless
Initial value: 0
Effective strength of the autoregulation response.

\[ R_{Hi} = \frac{R_{HIH}}{H^+} \]
Implementation Name: \text{R}_{HI}
Units: dimensionless
Initial value: 0
Relative mitochondrial volume for protons, taking into account buffering effect of pH.

\[ S_{c,O2} = \frac{S_{a,O2} + S_{v,O2}}{2} \]
Implementation Name: \text{ScO2}
Units: dimensionless
Initial value: \text{S}_{c,O2,0}
Capillary oxygen saturation.

\[ S_{v,O2} = \frac{HbO_{2,v}}{Hb_{tot}} \]
Implementation Name: \text{SvO2}
Units: dimensionless
Initial value: \text{SvO2,0}
Venous oxygen saturation.

\[ \theta = kCV \left( \Delta p + Z \log10 (\mu) - 90 \right) \]
Implementation Name: \text{theta}
Units: dimensionless
Initial value: 0
Driving force Complex V.
$$T0I = \frac{100HbO_2}{HbT}$$
Implementation Name: T0I
Units: dimensionless
Initial value: 0
Total oxygenation index.

$$V_mca = CBF \times CBFscale$$
Implementation Name: Vmca
Units: cm s$^{-1}$
Initial value: 0
Blood velocity in the middle cerebral artery.

$$V_a = V_{a,n} \left( \frac{r}{r_n} \right)^2$$
Implementation Name: Vol_art
Units: dimensionless
Initial value: 0
Relative arterial blood volume.

### 11.7 Parameters

**$C_{u_{A,o,n}}$**
Implementation Name: a_n
Units: mM
Initial value: 0.06567
Normal concentration of oxidised cytochrome c oxidase.

**blood_hb**
Implementation Name: blood_hb
Units: dimensionless
Initial value: 10.00
Factor to convert model haemoglobin concentration to instrumental units. Scales for blood fraction of brain volume, mM to µM, and number of binding sites.

**$a_{3,r,n}$**
Implementation Name: bred_n
Units: mM
Initial value: 0.001408
Normal concentration of reduced cytochrome a3.

**$C_{im}$**
Implementation Name: c_im
Units: mM mV$^{-1}$
Initial value: 0.00675
Capacitance of the mitochondrial inner membrane.

**$CBF_n$**
Implementation Name: CBFn
Units: ml$^{blood}$ ml$^{-1}brain$ s$^{-1}$
Initial value: 0.0125
Normal cerebral blood flow.

**$CBFscale$**
Implementation Name: CBFscale
Units: cm
Initial value: 5000
Scale constant relating blood flow to arterial velocity.
11.7 Parameters

\( \Delta \text{oxCCO}_{\text{off}} \)
- Implementation Name: \texttt{CCO\_offset}
- Units: \( \mu \text{M} \)
- Initial value: 0
- Signal offset for the NIRS CCO measurement.

\( \text{CMRO}_2 \)
- Implementation Name: \texttt{CMRO2}\_n
- Units: \( \text{mM s}^{-1} \)
- Initial value: 0.034
- Normal metabolic rate of oxygen consumption.

\( D_{O_2} \)
- Implementation Name: \texttt{D\_O2}
- Units: \( s^{-1} \)
- Initial value: \( \frac{J_{O_2,n}}{O_{2,r,n} - O_{2,n}} \)
- Diffusion rate for oxygen between capillaries and mitochondria.

\( \psi_n \)
- Implementation Name: \texttt{Dpsi}\_n
- Units: mV
- Initial value: 145
- Normal mitochondrial inner membrane potential.

\( \lambda f_1 \)
- Implementation Name: \texttt{f1\_0}
- Units: \( \text{mM s}^{-1} \)
- Initial value: 1.504
- Fitted intercept for the linear model for \( f_1 \).

\( \lambda f_{1,a} \)
- Implementation Name: \texttt{f1\_a}
- Units: \( \text{mM s}^{-1} \)
- Initial value: 0.3658
- Fitted linear dependence of \( f_1 \) on logarithm of \( \text{Cu}_{A,\text{ox}} \).

\( \lambda f_2 \)
- Implementation Name: \texttt{f2\_0}
- Units: \( \text{mM s}^{-1} \)
- Initial value: 0.1473
- Fitted intercept for the linear model for \( f_2 \).

\( \lambda f_{2,b} \)
- Implementation Name: \texttt{f2\_bred}
- Units: \( \text{mM s}^{-1} \)
- Initial value: \(-0.05484\)
- Fitted linear dependence of \( f_2 \) on logarithm of \( \text{a}_{3,\text{red}} \).

\( \lambda f_3 \)
- Implementation Name: \texttt{f3\_0}
- Units: \( \text{mM s}^{-1} \)
- Initial value: 0.6324
- Fitted intercept for the linear model for \( f_3 \).

\( \lambda f_{3,0} \)
- Implementation Name: \texttt{f3\_02}
- Units: \( \text{mM s}^{-1} \)
- Initial value: 0.03352
- Fitted linear dependence of \( f_3 \) on logarithm of \( O_2 \).
11 BIM2

\( G_n \)
- Implementation Name: \( G_n \)
- Units: \( \text{ml}_{\text{blood}} \text{ ml}_{\text{brain}}^{-1} \text{ mmHg}^{-1} \text{ s}^{-1} \)
- Initial value: \( \frac{C_{BF_n}}{P_{a,n} - P_{e,n}} \)
- Normal blood vessel conductance.

\( H_{n}^+ \)
- Implementation Name: \( H_{n} \)
- Units: mM
- Initial value: 0.00003981
- Normal mitochondrial proton concentration.

\( J_{O_2,n} \)
- Implementation Name: \( J_{O_2,n} \)
- Units: \( \text{mM s}^{-1} \)
- Initial value: \( \text{CMRO}_{2,n} \)
- Normal oxygen flux from blood to tissue.

\( k_{\text{aut}} \)
- Implementation Name: \( k_{\text{aut}} \)
- Units: dimensionless
- Initial value: 1
- Overall functioning of autoregulatory response.

\( K_G \)
- Implementation Name: \( K_G \)
- Units: \( \text{ml}_{\text{blood}} \text{ ml}_{\text{brain}}^{-1} \text{ mmHg}^{-1} \text{ s}^{-1} \text{ cm}^{-4} \)
- Initial value: \( \text{pow}(r_n, 4) \)
- Proportionality constant in Poiseuille relation for conductance.

\( kCV \)
- Implementation Name: \( kCV \)
- Units: \( \text{mV}^{-1} \)
- Initial value: 0.02047339
- Factor relating the Complex V driving force to the membrane potential and demand.

\( \lambda_L \)
- Implementation Name: \( L_0 \)
- Units: \( \text{mM s}^{-1} \)
- Initial value: -15.339464
- Fitted intercept for the linear model for \( L \).

\( \lambda_{L,p} \)
- Implementation Name: \( L_{dp} \)
- Units: \( \text{mM s}^{-1} \text{ mV}^{-1} \)
- Initial value: 0.097097
- Fitted linear dependence of \( L \) on \( \Delta p \).

\( \lambda_{L,\theta} \)
- Implementation Name: \( L_{d\theta} \)
- Units: \( \text{mM s}^{-1} \)
- Initial value: 5.665904
- Fitted linear dependence of \( L \) on \( \theta \).

\( \lambda_0 \)
- Implementation Name: \( 10_{a_0} \)
- Units: cm
11.7 Parameters

Initial value: 0.02507
Intercept of the fitted linear model for blood vessel radius.

\( \lambda_\mu \)
- Implementation Name: lam\_mu
- Units: cm
- Initial value: −0.0004422
Fitted linear dependence of blood vessel radius on autoregulatory stimuli.

\( \lambda_{P_a} \)
- Implementation Name: lam\_p\_mu
- Units: cm mmHg
- Initial value: −0.6327
Fitted linear dependence of blood vessel radius on reciprocal of blood pressure.

\( \lambda_{P_a,\mu} \)
- Implementation Name: lam\_p\_mu
- Units: cm mmHg
- Initial value: −0.5286
Fitted joint dependence of blood vessel radius on autoregulatory stimuli and reciprocal of blood pressure.

\( n_h \)
- Implementation Name: n\_h
- Units: dimensionless
- Initial value: 2.5
Hill coefficient for oxygen dissociation from haemoglobin.

\( O_{2,n} \)
- Implementation Name: O2\_n
- Units: mM
- Initial value: 0.024
Normal mitochondrial oxygen concentration.

\( O_{2,c,n} \)
- Implementation Name: O2c\_n
- Units: mM
- Initial value: \( \phi \, \text{pow} \left( \frac{S_c \cdot O_{2,n}}{1 - S_c \cdot O_{2,n}}, \frac{1}{n_h} \right) \)
Normal capillary oxygen concentration.

\( p_1 \)
- Implementation Name: p1
- Units: dimensionless
- Initial value: 12
Proton cost of the reaction reducing Cu_A.

\( p_3 \)
- Implementation Name: p2
- Units: dimensionless
- Initial value: 4
Proton cost of the reaction reducing a3.

\( p_3 \)
- Implementation Name: p3
- Units: dimensionless
- Initial value: 4
Proton cost of the reaction reducing O_2.

\( P_a \)
- Implementation Name: P\_a
Units: mmHg
Initial value: $P_{a,n}$
Mean arterial blood pressure.

$P_{a,n}$
Implementation Name: $P_{an}$
Units: mmHg
Initial value: 100
Normal arterial blood pressure.

$P_v$
Implementation Name: $P_{vn}$
Units: mmHg
Initial value: $P_{v,n}$
Venous blood pressure.

$P_{v,n}$
Implementation Name: $P_{vn}$
Units: mmHg
Initial value: 4
Normal venous blood pressure.

$P_{a\text{CO}_2}$
Implementation Name: $Pa_{\text{CO}_2}$
Units: mmHg
Initial value: $Pa_{\text{CO}_2,n}$
Arterial partial pressure of carbon dioxide.

$P_{a\text{CO}_2,n}$
Implementation Name: $Pa_{\text{CO}_2,n}$
Units: mmHg
Initial value: 40
Normal arterial partial pressure of carbon dioxide.

$\phi$
Implementation Name: $\phi_i$
Units: mM
Initial value: 0.036
Oxygen concentration at half-maximal saturation.

$R_{\text{CO}_2}$
Implementation Name: $R_{aut\text{c}}$
Units: dimensionless
Initial value: 2.2
Autoregulatory reactivity to carbon dioxide.

$R_{O_2}$
Implementation Name: $R_{auto}$
Units: dimensionless
Initial value: 1.5
Autoregulatory reactivity to oxygen.

$R_{Pa}$
Implementation Name: $R_{aut\text{p}}$
Units: dimensionless
Initial value: 4
Autoregulatory reactivity to blood pressure.

$R_u$
Implementation Name: $R_{aut\text{u}}$
Units: dimensionless
11.7 Parameters

Initial value: 0.5
Autoregulatory reactivity to demand.

\( R_{H_iH} \)
Implementation Name: \( R_{H_iH} \)
Units: mM
Initial value: 9.565483
Proton buffering factor.

\( r_n \)
Implementation Name: \( r_n \)
Units: cm
Initial value: 0.0187
Normal blood vessel radius. Normal effective blood vessel radius.

\( S_{aO_2,n} \)
Implementation Name: \( S_{aO_2,n} \)
Units: dimensionless
Initial value: 0.96
Normal arterial oxygen saturation.

\( S_{aO_2} \)
Implementation Name: \( S_{aO_2} \)
Units: dimensionless
Initial value: \( S_{aO_2,n} \)
Arterial oxygen saturation.

\( S_{cO_2,n} \)
Implementation Name: \( S_{cO_2,n} \)
Units: dimensionless
Initial value: \( \frac{S_{aO_2,n} + S_{vO_2,n}}{2} \)
Normal capillary oxygen saturation.

\( S_{vO_2,n} \)
Implementation Name: \( S_{vO_2,n} \)
Units: dimensionless
Initial value: \( \frac{HbO_{2,v,n}}{Hb_{tot,n}} \)
Normal venous oxygen saturation.

\( t \)
Implementation Name: \( t \)
Units: s
Initial value: 0
Time over which the system evolves.

\( \tau_{CO_2} \)
Implementation Name: \( \tau_{CO_2} \)
Units: s
Initial value: 5
Filter time constant for stimulus effect of carbon dioxide.

\( \tau_{O_2} \)
Implementation Name: \( \tau_{O_2} \)
Units: s
Initial value: 20
Filter time constant for stimulus effect of capillary oxygen.

\( \tau_{Pa} \)
Implementation Name: \( \tau_{Pa} \)
Units: s
11 BIM2

Initial value: 5
Filter time constant for stimulus effect of blood pressure.

\( \tau_u \)
- Implementation Name: \( t_u \)
- Units: s
- Initial value: 0.5
Filter time constant for stimulus effect of demand.

\( u \)
- Implementation Name: \( u \)
- Units: dimensionless
- Initial value: \( u_n \)
Parameter indicating metabolic demand.

\( u_n \)
- Implementation Name: \( u_n \)
- Units: dimensionless
- Initial value: 1
Normal demand.

\( v_{CO_2,n} \)
- Implementation Name: \( v_{cn} \)
- Units: mmHg
- Initial value: \( P_{aCO_2,n} \)
Normal filtered carbon dioxide partial pressure. Normal filtered carbon dioxide partial pressure.

\( v_{O_2,n} \)
- Implementation Name: \( v_{on} \)
- Units: mM
- Initial value: \( O_{2,c,n} \)
Normal filtered capillary oxygen concentration. Normal filtered capillary oxygen concentration.

\( v_{Pa,n} \)
- Implementation Name: \( v_{pn} \)
- Units: mmHg
- Initial value: \( P_{a,n} \)
Normal filtered arterial blood pressure. Normal filtered blood pressure.

\( v_{un} \)
- Implementation Name: \( v_{un} \)
- Units: dimensionless
- Initial value: \( u_n \)
Normal filtered demand. Normal filtered demand.

\( VArat_n \)
- Implementation Name: \( VArat_n \)
- Units: dimensionless
- Initial value: 3
Normal volume ratio of veins to arteries in brain tissue.

\( V_{a,n} \)
- Implementation Name: \( V_{a,n} \)
- Units: dimensionless
- Initial value: \( \frac{1}{1 + VArat_n} \)
Normal relative arterial blood volume.

\( Volmit \)
11.7 Parameters

Implementation Name: Vol.mit
Units: dimensionless
Initial value: 0.067
Fraction of brain tissue volume that is mitochondria.

Implementation Name: Vol.ven
Units: dimensionless
Initial value: \( \frac{V A r a t_n}{1 + V A r a t_n} \)
Relative venous blood volume.

**HbO\(_2\)a** = \( Hb_{tot} S_{a,O_2} \)
Implementation Name: XOa
Units: mM
Initial value: \( HbO_2,a,n \)
Arterial concentration of oxygen bound to haemoglobin.

**HbO\(_2\)a,n**
Implementation Name: XOa,n
Units: mM
Initial value: \( Hb_{tot,n} S_{a,O_2,n} \)
Normal arterial concentration of oxygen bound to haemoglobin.

**HbO\(_2\)v,n**
Implementation Name: XOv,n
Units: mM
Initial value: \( \frac{CBF_n HbO_2,a,n - I_{O_2,v}}{CBF_n} \)
Normal venous concentration of oxygen bound to haemoglobin.

**Hb\(_{tot}\)**
Implementation Name: Xtot
Units: mM
Initial value: 9.1
Total concentration of haemoglobin O\(_2\) binding sites in blood (4 times haemoglobin concentration).

**Hb\(_{tot,n}\)**
Implementation Name: Xtot,n
Units: mM
Initial value: 9.1
Normal total concentration of haemoglobin O\(_2\) binding sites in blood (4 times haemoglobin concentration).

**Z**
Implementation Name: Z
Units: mV
Initial value: 59.028
Proportionality constant in calculation of driving forces due to concentration differences. Defined as \( RT / F \), where \( F \) is Faraday’s constant, \( R \) the ideal gas constant and \( T \) the absolute temperature.
12 B2M1

12.1 Overview

Simplified model combining blood flow variant B2 and metabolic variant M1.

- 9 differential state variables
- 3 algebraic state variables
- 22 intermediate variables
- 73 parameters
- 4 declared inputs
- 33 default outputs

12.2 Differential Equations

\[
\frac{dC_{u,v}}{dt} = 4f_3 - 4f_1
\]  \hspace{1cm} (12.1)

\[
\frac{da_{3,r}}{dt} = 4f_3 - 4f_3
\]  \hspace{1cm} (12.2)

\[
\frac{d\psi}{dt} = \frac{p_3 f_3 + p_1 f_1 + p_3 f_3 - L}{C_{im}}
\]  \hspace{1cm} (12.3)

\[
\frac{dH^+}{dt} = \frac{1}{R_{Hi}} L - \frac{p_3}{R_{Hi}} f_3 - \frac{p_1}{R_{Hi}} f_1 - \frac{p_3}{R_{Hi}} f_3
\]  \hspace{1cm} (12.4)

\[
\frac{dO_2}{dt} = \frac{1}{Vol_{mit}} J_{O_2} - f_3
\]  \hspace{1cm} (12.5)

\[
\frac{dv_{CO_2}}{dt} = \frac{1}{\tau_{CO_2}} (p_a^{CO_2} - v_{CO_2})
\]  \hspace{1cm} (12.6)

\[
\frac{dv_{O_2}}{dt} = \frac{1}{\tau_{O_2}} (O_{2,c} - v_{O_2})
\]  \hspace{1cm} (12.7)

\[
\frac{dv_p}{dt} = \frac{1}{\tau_{p_v}} (P_a - v_p)
\]  \hspace{1cm} (12.8)
\[
\frac{dv_u}{dt} = \frac{1}{\tau_u} (u - v_u)
\]  
\(12.9\)

### 12.3 Algebraic Equations

\[
\phi \left( \frac{S_{c,O_2}}{1 - S_{c,O_2}} \right) \frac{J_{O_2}}{V_{m,mit}} - O_{2,c} = 0
\]  
\(12.10\)

\[
\lambda_0 + \frac{\lambda_{P_a}}{P_a} + \lambda_{\mu} \mu - r = 0
\]  
\(12.11\)

\[
\text{CBF} \left( HbO_{2,a} - HbO_{2,o} \right) - J_{O_2} = 0
\]  
\(12.12\)

### 12.4 Chemical Reactions

\[
\xrightarrow{L} \frac{1}{R_{Hi}} \text{H}^+
\]  
\(12.13\)

\[
\xrightarrow{J_{O_2}} \frac{1}{V_{m,mit}} \text{O}_2
\]  
\(12.14\)

\[
\frac{p_3}{R_{Hi}} \text{H}^+ \xrightarrow{f_3} 4 \text{Cu}_{A,o} + 4 a_{3,r}
\]  
\(12.15\)

\[
4 \text{Cu}_{A,o} + \frac{p_1}{R_{Hi}} \text{H}^+ \xrightarrow{f_1}
\]  
\(12.16\)

\[
\text{O}_2 + 4 a_{3,r} + \frac{p_3}{R_{Hi}} \text{H}^+ \xrightarrow{f_3}
\]  
\(12.17\)

### 12.5 State Variables

- **\(Cu_{A,o}\):**
  - Implementation Name: \text{a}
  - Units: mM
  - Initial value: \(Cu_{A,o,n}\)
  - Concentration of oxidised cytochrome c oxidase.

- **\(a_{3,r}\):**
  - Implementation Name: br\text{ed}
  - Units: mM
  - Initial value: \(a_{3,r,n}\)
  - Concentration of reduced cytochrome a3.
12.5 State Variables

ψ
Implementation Name: Dpsi
Units: mV
Initial value: \( \psi_n \)
Mitochondrial inner membrane potential. Varies as charge (in the form of protons) is transferred across the membrane capacitance.

\( H^+ \)
Implementation Name: H
Units: mM
Initial value: \( H^+_n \)
Mitochondrial proton concentration.

\( O_2 \)
Implementation Name: 02
Units: mM
Initial value: \( O_{2,n} \)
Mitochondrial oxygen concentration.

\( O_{2,c} \)
Implementation Name: 02c
Units: mM
Initial value: \( O_{2,c,n} \)
Capillary oxygen concentration.

\( r \)
Implementation Name: r
Units: cm
Initial value: \( r_n \)
Typical blood vessel radius.

\( v_{CO_2} \)
Implementation Name: v_c
Units: mmHg
Initial value: \( v_{CO_2,n} \)
Filtered carbon dioxide partial pressure.

\( v_{O_2} \)
Implementation Name: v_o
Units: mM
Initial value: \( v_{O_2,n} \)
Filtered capillary oxygen concentration.

\( v_{Pa} \)
Implementation Name: v_p
Units: mmHg
Initial value: \( v_{Pa,n} \)
Filtered arterial blood pressure.

\( v_{ul} \)
Implementation Name: v_u
Units: dimensionless
Initial value: \( v_{ul,n} \)
Filtered demand.

\( HbO_{2,v} \)
Implementation Name: x0v
Units: mM
Initial value: \( HbO_{2,v,n} \)
Venous concentration of oxygen bound to haemoglobin.
12.6 Intermediate Variables

\( CBF = G \ (P_a - P_v) \)
- Implementation Name: CBF
- Units: \( \text{ml}_{\text{blood}} \text{ ml}^{-1} \text{ s}^{-1} \)
- Initial value: \( \text{CBF}_n \)
- Cerebral blood flow.

\( \Delta \text{oxCCO} = \Delta \text{oxCCO}_{\text{off}} + 1000 \text{Vol}_{\text{mit}} \ (\text{Cu}_{A,o} - \text{Cu}_{A,n}) \)
- Implementation Name: CCO
- Units: uM
- Initial value: 0
- Cytochrome c oxidase signal measured by NIRS.

\( \text{CMRO}_2 = f_3 \text{Vol}_{\text{mit}} \)
- Implementation Name: CMRO2
- Units: mM s\(^{-1}\)
- Initial value: 0
- Rate of cerebral oxygen metabolism.

\( \Delta p = \psi - Z \ (4 + \log_{10} (H^+)) \)
- Implementation Name: \( \Delta p \)
- Units: mV
- Initial value: 0
- Proton motive force across the mitochondrial inner membrane.

\( \eta = R_p \ \left( \frac{v_{P_a}}{v_{P_v,n}} - 1 \right) + R_{O_2} \ \left( \frac{v_{O_2}}{v_{O_2,n}} - 1 \right) + R_{CO_2} \ \left( 1 - \frac{v_{CO_2}}{v_{CO_2,n}} \right) + R_n \ \left( 1 - \frac{v_u}{v_{u,n}} \right) \)
- Implementation Name: \( \eta \)
- Units: dimensionless
- Initial value: 0
- Merged autoregulation stimulus.

\( f_1 = \lambda f_1 + \lambda f_{1,n} \log (u) + \lambda f_{1,\text{a}} \log (\text{Cu}_{A,a}) \)
- Implementation Name: \( f_1 \)
- Units: mM s\(^{-1}\)
- Initial value: 0
- Reaction rate for the reduction of \( \text{Cu}_A \).

\( f_3 = \lambda f_3 + \lambda f_{3,n} \log (a_3) \)
- Implementation Name: \( f_3 \)
- Units: mM s\(^{-1}\)
- Initial value: 0
- Reaction rate for the reduction of \( a_3 \).

\( f_5 = \lambda f_5 + \lambda f_{5,n} \log (O_2) \)
- Implementation Name: \( f_5 \)
- Units: mM s\(^{-1}\)
- Initial value: 0
- Reaction rate for the reduction of \( O_2 \).

\( G = K_G \ r^A \)
- Implementation Name: \( G \)
- Units: \( \text{ml}_{\text{blood}} \text{ ml}^{-1} \text{ brain mmHg}^{-1} \text{ s}^{-1} \)
- Initial value: 0
- Effective conductance of the whole blood flow compartment.

\( \text{HbO}_2 = (V_a \text{HbO}_2,a + V_v \text{HbO}_2,v) \text{ blood}_{\text{hb}} \)
- Implementation Name: \( \text{HbO}_2 \)
- Units: uM
12.6 Intermediate Variables

Initial value: 0
Oxygenated haemoglobin signal measured by NIRS.

\[ HbT = (V_a + V_v) \, Hb_{tot} \, blood_{hb} \]
Implementation Name: HbT
Units: uM
Initial value: 0
Total haemoglobin signal measured by NIRS.

\[ HHb = HbT - HbO_2 \]
Implementation Name: HHb
Units: uM
Initial value: 0
Deoxygenated haemoglobin signal measured by NIRS.

\[ JO_2 = f_{\min} \left( D_{O_2} \left( O_2, c - O_2 \right), CBF \ HbO_2,a \right) \]
Implementation Name: J_02
Units: mM s\(^{-1}\)
Initial value: 0
Oxygen flux from blood to tissue.

\[ L = \lambda_L + \lambda_L,\theta \theta + \lambda_L,\theta \Delta p \]
Implementation Name: L
Units: mM s\(^{-1}\)
Initial value: 0
Rate of proton return to the mitochondrial matrix.

\[ \mu = \frac{k_{aut} \left( \exp(\eta) - 1 \right)}{\exp(\eta) + 1} \]
Implementation Name: mu
Units: dimensionless
Initial value: 0
Effective strength of the autoregulation response.

\[ RHi = \frac{R_{Hi}}{H^+} \]
Implementation Name: R_Hi
Units: dimensionless
Initial value: 0
Relative mitochondrial volume for protons, taking into account buffering effect of pH.

\[ S_{c,O_2} = \frac{S_{a,O_2} + S_{v,O_2}}{2} \]
Implementation Name: Sc02
Units: dimensionless
Initial value: \( S_{c,O_2,n} \)
Capillary oxygen saturation.

\[ S_{v,O_2} = \frac{HbO_2,v}{Hb_{tot}} \]
Implementation Name: Sv02
Units: dimensionless
Initial value: \( S_{v,O_2,n} \)
Venous oxygen saturation.

\[ \theta = kCV \left( \Delta p + Z \log_{10}(u) - 90 \right) \]
Implementation Name: theta
Units: dimensionless
Initial value: 0
Driving force Complex V.
10 \ 0

**TOI** = \frac{100HbO_2}{HbT}

- Implementation Name: TOI
- Units: dimensionless
- Initial value: 0
- Total oxygenation index.

**\text{Vmca} = CBF \ CBFscale**

- Implementation Name: \text{Vmca}
- Units: cm s\(^{-1}\)
- Initial value: 0
- Blood velocity in the middle cerebral artery.

**\text{V}_a = V_{a,n} \left( \frac{r}{r_n} \right)^2**

- Implementation Name: \text{Vol_art}
- Units: dimensionless
- Initial value: 0
- Relative arterial blood volume.

### 12.7 Parameters

- **\text{Cu}_{A,o,n}**
  - Implementation Name: \text{a_n}
  - Units: mM
  - Initial value: 0.06567
  - Normal concentration of oxidised cytochrome c oxidase.

- **\text{blood}_{\text{hb}}**
  - Implementation Name: \text{blood_hb}
  - Units: dimensionless
  - Initial value: 10.00
  - Factor to convert model haemoglobin concentration to instrumental units. Scales for blood fraction of brain volume, mM to \(\mu\)M, and number of binding sites.

- **\text{a}_{3,r,n}**
  - Implementation Name: \text{bred_n}
  - Units: mM
  - Initial value: 0.001408
  - Normal concentration of reduced cytochrome a3.

- **\text{C}_{im}**
  - Implementation Name: \text{c_im}
  - Units: mM mV\(^{-1}\)
  - Initial value: 0.00675
  - Capacitance of the mitochondrial inner membrane.

- **\text{CBF}_n**
  - Implementation Name: \text{CBFn}
  - Units: ml\(_{\text{blood}}\) ml\(_{\text{brain}}\) s\(^{-1}\)
  - Initial value: 0.0125
  - Normal cerebral blood flow.

- **\text{CBFscale}**
  - Implementation Name: \text{CBFscale}
  - Units: cm
  - Initial value: 5000
  - Scale constant relating blood flow to arterial velocity.
12.7 Parameters

**ΔoxCCO**
- Implementation Name: `CCO_offset`
- Units: uM
- Initial value: 0
- Signal offset for the NIRS CCO measurement.

**CMRO_{2,n}**
- Implementation Name: `CMRO2_n`
- Units: mM s\(^{-1}\)
- Initial value: 0.034
- Normal metabolic rate of oxygen consumption.

**D_{O2}**
- Implementation Name: `D02`
- Units: s\(^{-1}\)
- Initial value: \(\frac{J_{O2,n}}{O_{2,r,n} - O_{2,n}}\)
- Diffusion rate for oxygen between capillaries and mitochondria.

**ψ**
- Implementation Name: `Dpsi_n`
- Units: mV
- Initial value: 145
- Normal mitochondrial inner membrane potential.

**λ_{f1}**
- Implementation Name: `f1_0`
- Units: mM s\(^{-1}\)
- Initial value: 1.490
- Fitted intercept for the linear model for \(f_1\).

**λ_{f1,a}**
- Implementation Name: `f1_a`
- Units: mM s\(^{-1}\)
- Initial value: 0.3609
- Fitted linear dependence of \(f_1\) on logarithm of \(Cu_{A,ox}\).

**λ_{f1,u}**
- Implementation Name: `f1_u`
- Units: mM s\(^{-1}\)
- Initial value: 0.06985
- Fitted linear dependence of \(f_1\) on logarithm of demand.

**λ_{f2}**
- Implementation Name: `f2_0`
- Units: mM s\(^{-1}\)
- Initial value: 0.1473
- Fitted intercept for the linear model for \(f_2\).

**λ_{f2,b}**
- Implementation Name: `f2_bred`
- Units: mM s\(^{-1}\)
- Initial value: \(-0.05484\)
- Fitted linear dependence of \(f_2\) on logarithm of \(a_{3,red}\).

**λ_{f3}**
- Implementation Name: `f3_0`
- Units: mM s\(^{-1}\)
- Initial value: 0.6324
- Fitted intercept for the linear model for \(f_3\).
\( \lambda_{f_3,O} \)
Implementation Name: \( f_3,O \)
Units: mM s\(^{-1}\)
Initial value: 0.03352
Fitted linear dependence of \( f_3 \) on logarithm of \( O_2 \).

\( G_n \)
Implementation Name: \( G_n \)
Units: ml\(_{\text{blood}}\) ml\(_{\text{brain}}\) mmHg\(^{-1}\) s\(^{-1}\)
Initial value: \( \frac{P_{\text{a},n} - P_{\text{v},n}}{G_n} \)
Normal blood vessel conductance.

\( H_n^+ \)
Implementation Name: \( H_n \)
Units: mM
Initial value: 0.00003981
Normal mitochondrial proton concentration.

\( J_{O_2,n} \)
Implementation Name: \( J_{O_2,n} \)
Units: mM s\(^{-1}\)
Initial value: \( \text{CMRO}_{2,n} \)
Normal oxygen flux from blood to tissue.

\( k_{\text{aut}} \)
Implementation Name: \( k_{\text{aut}} \)
Units: dimensionless
Initial value: 1
Overall functioning of autoregulatory response.

\( K_G \)
Implementation Name: \( K_G \)
Units: ml\(_{\text{blood}}\) ml\(_{\text{brain}}\) mmHg\(^{-1}\) s\(^{-1}\) cm\(^{-4}\)
Initial value: \( \frac{G_n}{\text{pow}(r_n, 4)} \)
Proportionality constant in Poiseuille relation for conductance.

\( k_{\text{CV}} \)
Implementation Name: \( k_{\text{CV}} \)
Units: mV\(^{-1}\)
Initial value: 0.02047339
Factor relating the Complex V driving force to the membrane potential and demand.

\( \lambda_{L} \)
Implementation Name: \( L_0 \)
Units: mM s\(^{-1}\)
Initial value: \(-15.339464\)
Fitted intercept for the linear model for \( L \).

\( \lambda_{L,p} \)
Implementation Name: \( L_{p} \)
Units: mM s\(^{-1}\) mV\(^{-1}\)
Initial value: 0.097097
Fitted linear dependence of \( L \) on \( \Delta p \).

\( \lambda_{L,\theta} \)
Implementation Name: \( L_{\theta} \)
Units: mM s\(^{-1}\)

208
12.7 Parameters

Initial value: 5.665904
Fitted linear dependence of $L$ on $\theta$.

$\lambda_0$
Implementation Name: lam_0
Units: cm
Initial value: 0.02327
Intercept of the fitted linear model for blood vessel radius.

$\lambda_\mu$
Implementation Name: lam_mu
Units: cm
Initial value: −0.006375
Fitted linear dependence of blood vessel radius on autoregulatory stimuli.

$\lambda_{P_a}$
Implementation Name: lam_pa
Units: cm mmHg
Initial value: −0.4697
Fitted linear dependence of blood vessel radius on reciprocal of blood pressure.

$n_h$
Implementation Name: n_h
Units: dimensionless
Initial value: 2.5
Hill coefficient for oxygen dissociation from haemoglobin.

$O_{2,n}$
Implementation Name: O2_n
Units: mM
Initial value: 0.024
Normal mitochondrial oxygen concentration.

$O_{2,c,n}$
Implementation Name: O2c_n
Units: mM
Initial value: $\phi \text{ pow} \left( \frac{S_c,O_{2,n}}{1 - S_c,O_{2,n}} \frac{1}{n_h} \right)$
Normal capillary oxygen concentration.

$p_1$
Implementation Name: p1
Units: dimensionless
Initial value: 12
Proton cost of the reaction reducing Cu_A.

$p_3$
Implementation Name: p2
Units: dimensionless
Initial value: 4
Proton cost of the reaction reducing a3.

$p_3$
Implementation Name: p3
Units: dimensionless
Initial value: 4
Proton cost of the reaction reducing O2.

$P_a$
Implementation Name: P_a
Units: mmHg
Initial value: $P_{a,n}$
Mean arterial blood pressure.

$P_{a,n}$
Implementation Name: $P_{a,n}$
Units: mmHg
Initial value: 100
Normal arterial blood pressure.

$P_{v}$
Implementation Name: $P_{v}$
Units: mmHg
Initial value: $P_{v,n}$
Venous blood pressure.

$P_{v,n}$
Implementation Name: $P_{v,n}$
Units: mmHg
Initial value: 4
Normal venous blood pressure.

$Pa_{CO_2}$
Implementation Name: $Pa_{CO_2}$
Units: mmHg
Initial value: $Pa_{CO_2,n}$
Arterial partial pressure of carbon dioxide.

$Pa_{CO_2,n}$
Implementation Name: $Pa_{CO_2,n}$
Units: mmHg
Initial value: 40
Normal arterial partial pressure of carbon dioxide.

$\phi$
Implementation Name: $phi$
Units: mM
Initial value: 0.036
Oxygen concentration at half-maximal saturation.

$R_{CO_2}$
Implementation Name: $R_{autc}$
Units: dimensionless
Initial value: 2.2
Autoregulatory reactivity to carbon dioxide.

$R_{O_2}$
Implementation Name: $R_{auto}$
Units: dimensionless
Initial value: 1.5
Autoregulatory reactivity to oxygen.

$R_{Pa}$
Implementation Name: $R_{autp}$
Units: dimensionless
Initial value: 4
Autoregulatory reactivity to blood pressure.

$R_{u}$
Implementation Name: $R_{autu}$
Units: dimensionless
12.7 Parameters

Initial value: 0.5
Autoregulatory reactivity to demand.

\( R_{Hi,H} \)
Implementation Name: \( R_{Hi,H} \)
Units: mM
Initial value: 9.565483
Proton buffering factor.

\( r_n \)
Implementation Name: \( r_n \)
Units: cm
Initial value: 0.0187
Normal blood vessel radius. Normal effective blood vessel radius.

\( S_{a,O_2,n} \)
Implementation Name: \( S_{a,O_2,n} \)
Units: dimensionless
Initial value: 0.96
Normal arterial oxygen saturation.

\( S_{a,O_2} \)
Implementation Name: \( S_{a,O_2}^{sup} \)
Units: dimensionless
Initial value: \( S_{a,O_2,n} \)
Arterial oxygen saturation.

\( S_{c,O_2,n} \)
Implementation Name: \( S_{c,O_2,n} \)
Units: dimensionless
Initial value: \( \frac{2}{2 S_{a,O_2,n} + S_{c,O_2,n}} \)
Normal capillary oxygen saturation.

\( S_{v,O_2,n} \)
Implementation Name: \( S_{v,O_2,n} \)
Units: dimensionless
Initial value: \( \frac{HbO_{2,v,n}}{Hb_{tot,n}} \)
Normal venous oxygen saturation.

\( t \)
Implementation Name: \( t \)
Units: s
Initial value: 0
Time over which the system evolves.

\( \tau_{\text{CO}_2} \)
Implementation Name: \( \tau_{\text{CO}_2} \)
Units: s
Initial value: 5
Filter time constant for stimulus effect of carbon dioxide.

\( \tau_{O_2} \)
Implementation Name: \( \tau_{O_2} \)
Units: s
Initial value: 20
Filter time constant for stimulus effect of capillary oxygen.

\( \tau_{pa} \)
Implementation Name: \( \tau_{pa} \)
Units: s
\( \tau_u \)

Implementation Name: \( t_u \)
Units: s
Initial value: 0.5
Filter time constant for stimulus effect of demand.

\( u \)

Implementation Name: \( u \)
Units: dimensionless
Initial value: \( u_n \)
Parameter indicating metabolic demand.

\( u_n \)

Implementation Name: \( u_n \)
Units: dimensionless
Initial value: 1
Normal demand.

\( v_{CO_2,n} \)

Implementation Name: \( v_{cn} \)
Units: mmHg
Initial value: \( P_{aCO_2,n} \)
Normal filtered carbon dioxide partial pressure. Normal filtered carbon dioxide partial pressure.

\( v_{O_2,n} \)

Implementation Name: \( v_{on} \)
Units: mM
Initial value: \( O_{2,c,n} \)
Normal filtered capillary oxygen concentration. Normal filtered capillary oxygen concentration.

\( v_{P_a,n} \)

Implementation Name: \( v_{pn} \)
Units: mmHg
Initial value: \( P_{a,n} \)
Normal filtered arterial blood pressure. Normal filtered blood pressure.

\( v_{u,n} \)

Implementation Name: \( v_{un} \)
Units: dimensionless
Initial value: \( u_n \)
Normal filtered demand. Normal filtered demand.

\( VArat_n \)

Implementation Name: \( VArat_n \)
Units: dimensionless
Initial value: 3
Normal volume ratio of veins to arteries in brain tissue.

\( V_{a,n} \)

Implementation Name: \( Vol_{artn} \)
Units: dimensionless
Initial value: \( \frac{1}{1 + VArat_n} \)
Normal relative arterial blood volume.

\( Vol_{mit} \)
12.7 Parameters

Implementation Name: \textit{Vol.mit}
Units: dimensionless
Initial value: 0.067
Fraction of brain tissue volume that is mitochondria.

\( V_v \)
Implementation Name: \textit{Vol.ven}
Units: dimensionless
Initial value: \( 1 + V_{Arat_n} \)
Relative venous blood volume.

\( HbO_{2,a,n} = Hb_{tot} S_{a,O_2} \)
Implementation Name: \textit{X0a}
Units: mM
Initial value: HbO\(_{2,a,n}\)
Arterial concentration of oxygen bound to haemoglobin.

\( HbO_{2,v,n} \)
Implementation Name: \textit{X0v_n}
Units: mM
Initial value: \( \frac{\text{CBF}_n HbO_{2,a,n} - I_{O_2,n}}{\text{CBF}_n} \)
Normal venous concentration of oxygen bound to haemoglobin.

\( Hb_{tot} \)
Implementation Name: \textit{Xtot}
Units: mM
Initial value: 9.1
Total concentration of haemoglobin \( O_2 \) binding sites in blood (4 times haemoglobin concentration).

\( Hb_{tot,n} \)
Implementation Name: \textit{Xtot_n}
Units: mM
Initial value: 9.1
Normal total concentration of haemoglobin \( O_2 \) binding sites in blood (4 times haemoglobin concentration).

\( Z \)
Implementation Name: \textit{Z}
Units: mV
Initial value: 59.028
Proportionality constant in calculation of driving forces due to concentration differences. Defined as \( RT / F \), where \( F \) is Faraday's constant, \( R \) the ideal gas constant and \( T \) the absolute temperature.
13 B2M2

13.1 Overview

Simplified model combining blood flow variant B2 and metabolic variant M2.

- 9 differential state variables
- 3 algebraic state variables
- 22 intermediate variables
- 72 parameters
- 4 declared inputs
- 33 default outputs

13.2 Differential Equations

\[
\frac{dC_{u,0}}{dt} = 4f_3 - 4f_1 \quad (13.1)
\]

\[
\frac{da_{3,r}}{dt} = 4f_3 - 4f_3 \quad (13.2)
\]

\[
\frac{d\psi}{dt} = \frac{p_3 f_3 + p_1 f_1 + p_3 f_3 - L}{C_{im}} \quad (13.3)
\]

\[
\frac{dH^+}{dt} = \frac{1}{R_{Hi}} L - \frac{p_3}{R_{Hi}} f_3 - \frac{p_1}{R_{Hi}} f_1 - \frac{p_3}{R_{Hi}} f_3 \quad (13.4)
\]

\[
\frac{dO_2}{dt} = \frac{1}{Vol_{mit}} f_{O_2} - f_3 \quad (13.5)
\]

\[
\frac{dv_{CO_2}}{dt} = \frac{1}{\tau_{CO_2}} (p_{aCO_2} - v_{CO_2}) \quad (13.6)
\]

\[
\frac{dv_{O_2}}{dt} = \frac{1}{\tau_{O_2}} (O_{2,c} - v_{O_2}) \quad (13.7)
\]

\[
\frac{dv_{P_a}}{dt} = \frac{1}{\tau_{P_a}} (P_a - v_{P_a}) \quad (13.8)
\]
\[
\frac{dv_u}{dt} = \frac{1}{\tau_u} (u - v_u)
\]  

(13.9)

13.3 Algebraic Equations

\[
\phi \left( \frac{S_{c,O_2}}{1 - S_{c,O_2}} \right) \frac{1}{h} - O_{2,c} = 0
\]  

(13.10)

\[
\lambda_0 + \frac{\lambda_{p_c}}{P_a} + \lambda_\mu \mu - r = 0
\]  

(13.11)

\[
CBF (HbO_{2,a} - HbO_{2,v}) - J_{O_2} = 0
\]  

(13.12)

13.4 Chemical Reactions

\[
\xrightarrow{L} \frac{1}{R_{Hi}} H^+
\]  

(13.13)

\[
\xrightarrow{J_{O_2}} \frac{1}{Vol_{mit}} O_2
\]  

(13.14)

\[
\xrightarrow{P_3} \frac{H^+}{R_{Hi}} \xrightarrow{f_3} 4 Cu_{A,o} + 4 a_{3,r}
\]  

(13.15)

\[
4 Cu_{A,o} + \xrightarrow{P_1} \frac{H^+}{R_{Hi}} \xrightarrow{f_1} 
\]  

(13.16)

\[
O_2 + 4 a_{3,r} + \xrightarrow{P_3} \frac{H^+}{R_{Hi}} \xrightarrow{f_3} 
\]  

(13.17)

13.5 State Variables

\[Cu_{A,o}\]
- Implementation Name: a
- Units: mM
- Initial value: \[Cu_{A,o,n}\]
- Concentration of oxidised cytochrome c oxidase.

\[a_{3,r}\]
- Implementation Name: bred
- Units: mM
- Initial value: \[a_{3,r,n}\]
- Concentration of reduced cytochrome a3.
13.5 State Variables

\( \psi \)
- Implementation Name: Dpsi
- Units: mV
- Initial value: \(\psi_n\)
- Mitochondrial inner membrane potential. Varies as charge (in the form of protons) is transferred across the membrane capacitance.

\( H^+ \)
- Implementation Name: H
- Units: mM
- Initial value: \(H^+_n\)
- Mitochondrial proton concentration.

\( O_2 \)
- Implementation Name: 02
- Units: mM
- Initial value: \(O_{2,n}\)
- Mitochondrial oxygen concentration.

\( O_{2,c} \)
- Implementation Name: 02c
- Units: mM
- Initial value: \(O_{2,c,n}\)
- Capillary oxygen concentration.

\( r \)
- Implementation Name: r
- Units: cm
- Initial value: \(r_n\)
- Typical blood vessel radius.

\( v_{CO_2} \)
- Implementation Name: v\_c
- Units: mmHg
- Initial value: \(v_{CO_2,n}\)
- Filtered carbon dioxide partial pressure.

\( v_{O_2} \)
- Implementation Name: v\_o
- Units: mM
- Initial value: \(v_{O_2,n}\)
- Filtered capillary oxygen concentration.

\( v_{Pa} \)
- Implementation Name: v\_p
- Units: mmHg
- Initial value: \(v_{Pa,n}\)
- Filtered arterial blood pressure.

\( v_u \)
- Implementation Name: v\_u
- Units: dimensionless
- Initial value: \(v_{u,n}\)
- Filtered demand.

\( HbO_{2,v} \)
- Implementation Name: X0v
- Units: mM
- Initial value: \(HbO_{2,v,n}\)
- Venous concentration of oxygen bound to haemoglobin.
13.6 Intermediate Variables

\[ CBF = G \left( P_a - P_v \right) \]
- Implementation Name: CBF
- Units: \( \text{ml}_{\text{blood}} \text{ ml}^{-1} \text{ brain s}^{-1} \)
- Initial value: \( CBF_n \)
- Cerebral blood flow.

\[ \Delta \text{oxCCO} = \Delta \text{oxCCO}_{\text{off}} + 1000 \text{Vol}_{\text{mit}} \left( \text{Cu}_{A,o} - \text{Cu}_{A,n} \right) \]
- Implementation Name: CCO
- Units: uM
- Initial value: 0
- Cytochrome c oxidase signal measured by NIRS.

\[ \text{CMRO}_2 = f_3 \text{Vol}_{\text{mit}} \]
- Implementation Name: CMR02
- Units: mM s\(^{-1}\)
- Initial value: 0
- Rate of cerebral oxygen metabolism.

\[ \Delta p = \psi - Z \left( 4 + \log_{10} \left( H^+ \right) \right) \]
- Implementation Name: \( \Delta p \)
- Units: mV
- Initial value: 0
- Proton motive force across the mitochondrial inner membrane.

\[ \eta = R_P \left( \frac{v_{Pa}}{v_{Pa,n}} - 1 \right) + R_{O_2} \left( \frac{v_{O_2}}{v_{O_2,n}} - 1 \right) + R_{CO_2} \left( 1 - \frac{v_{CO_2}}{v_{CO_2,n}} \right) + R_{u} \left( 1 - \frac{v_{u}}{v_{u,n}} \right) \]
- Implementation Name: \( \eta \)
- Units: dimensionless
- Initial value: 0
- Merged autoregulation stimulus.

\[ f_1 = \lambda f_1 + \lambda f_{1,a} \log \left( \text{Cu}_{A,o} \right) \]
- Implementation Name: \( f_1 \)
- Units: mM s\(^{-1}\)
- Initial value: 0
- Reaction rate for the reduction of \( \text{Cu}_{A} \).

\[ f_3 = \lambda f_3 + \lambda f_{3,b} \log \left( a_{3,r} \right) \]
- Implementation Name: \( f_3 \)
- Units: mM s\(^{-1}\)
- Initial value: 0
- Reaction rate for the reduction of \( a_3 \).

\[ G = K_G r^A \]
- Implementation Name: \( G \)
- Units: \( \text{ml}_{\text{blood}} \text{ ml}^{-1} \text{ brain mmHg}^{-1} \text{ s}^{-1} \)
- Initial value: 0
- Effective conductance of the whole blood flow compartment.

\[ \text{HbO}_2 = (V_a \text{HbO}_2,a + V_v \text{HbO}_2,v) \text{blood}_{\text{hb}} \]
- Implementation Name: \( \text{Hb02} \)
- Units: uM
13.6 Intermediate Variables

Initial value: 0
Oxygenated haemoglobin signal measured by NIRS.

\[ HbT = (V_a + V_v) Hb_{\text{tot}} \]
Implementation Name: HbT
Units: uM
Initial value: 0
Total haemoglobin signal measured by NIRS.

\[ HHb = HbT - HbO_2 \]
Implementation Name: HHb
Units: uM
Initial value: 0
Deoxygenated haemoglobin signal measured by NIRS.

\[ J_{O_2} = \min \left( D_{O_2} (O_2,c - O_2), CBF HbO_2,a \right) \]
Implementation Name: J_O2
Units: mM s\(^{-1}\)
Initial value: 0
Oxygen flux from blood to tissue.

\[ L = \lambda_L + \lambda_L \theta + \lambda_L \Delta p \]
Implementation Name: L
Units: mM s\(^{-1}\)
Initial value: 0
Rate of proton return to the mitochondrial matrix.

\[ \mu = \frac{k_{\text{aut}} \exp(\eta) - 1}{\exp(\eta) + 1} \]
Implementation Name:\ mu
Units: dimensionless
Initial value: 0
Effective strength of the autoregulation response.

\[ R_{Hi} = \frac{R_{Hi,H}}{H^+} \]
Implementation Name: R_Hi
Units: dimensionless
Initial value: 0
Relative mitochondrial volume for protons, taking into account buffering effect of pH.

\[ S_{c,O_2} = \frac{S_a,O_2 + S_v,O_2}{2} \]
Implementation Name: Sc02
Units: dimensionless
Initial value: \( S_{c,O_2,n} \)
Capillary oxygen saturation.

\[ S_{v,O_2} = \frac{HbO_2,v}{Hb_{\text{tot}}} \]
Implementation Name: Sv02
Units: dimensionless
Initial value: \( S_{v,O_2,n} \)
Venous oxygen saturation.

\[ \theta = kCV (\Delta p + Z \log_{10}(u) - 90) \]
Implementation Name: \theta
Units: dimensionless
Initial value: 0
Driving force Complex V.
\[ \text{TOI} = \frac{100 \text{HbO}_2}{\text{HbT}} \]

Implementation Name: TOI  
Units: dimensionless  
Initial value: 0  
Total oxygenation index.

\[ V_{\text{mca}} = CBF \cdot CBF_{\text{scale}} \]

Implementation Name: \( V_{\text{mca}} \)  
Units: cm s\(^{-1}\)  
Initial value: 0  
Blood velocity in the middle cerebral artery.

\[ V_a = V_{a,n} \left( \frac{r}{r_n} \right)^2 \]

Implementation Name: \( V_{a,\text{art}} \)  
Units: dimensionless  
Initial value: 0  
Relative arterial blood volume.

### 13.7 Parameters

**\( C_{u_{A,o,n}} \)**  
Implementation Name: \( a_{n} \)  
Units: mM  
Initial value: 0.06567  
Normal concentration of oxidised cytochrome c oxidase.

**\( \text{blood}_{hb} \)**  
Implementation Name: \( \text{blood}_{hb} \)  
Units: dimensionless  
Initial value: 10.00  
Factor to convert model haemoglobin concentration to instrumental units. Scales for blood fraction of brain volume, mM to \( \mu \text{M} \), and number of binding sites.

**\( a_{3,r,n} \)**  
Implementation Name: \( \text{bred}_{n} \)  
Units: mM  
Initial value: 0.001408  
Normal concentration of reduced cytochrome a3.

**\( C_{im} \)**  
Implementation Name: \( C_{im} \)  
Units: mM mV\(^{-1}\)  
Initial value: 0.00675  
Capacitance of the mitochondrial inner membrane.

**\( CBF_n \)**  
Implementation Name: \( CBF_n \)  
Units: ml\(_{\text{blood}}\) ml\(_{\text{brain}}\) s\(^{-1}\)  
Initial value: 0.0125  
Normal cerebral blood flow.

**\( CBF_{\text{scale}} \)**  
Implementation Name: \( CBF_{\text{scale}} \)  
Units: cm  
Initial value: 5000  
Scale constant relating blood flow to arterial velocity.
13.7 Parameters

$\Delta oxCCO_{off}$
- Implementation Name: $\text{CCO\_offset}$
- Units: $\mu$M
- Initial value: 0
- Signal offset for the NIRS CCO measurement.

$\text{CMRO}_2,n$
- Implementation Name: $\text{CMRO2\_n}$
- Units: mM s$^{-1}$
- Initial value: 0.034
- Normal metabolic rate of oxygen consumption.

$D_{O_2}$
- Implementation Name: $D_{O_2}$
- Units: s$^{-1}$
- Initial value: $\frac{J_{O_2,n}}{O_{2,c,n} - O_{2,n}}$
- Diffusion rate for oxygen between capillaries and mitochondria.

$\psi_n$
- Implementation Name: $\text{Dpsi\_n}$
- Units: mV
- Initial value: 145
- Normal mitochondrial inner membrane potential.

$\lambda_{f_1}$
- Implementation Name: $f_{1\_0}$
- Units: mM s$^{-1}$
- Initial value: 1.504
- Fitted intercept for the linear model for $f_1$.

$\lambda_{f_1,a}$
- Implementation Name: $f_{1\_a}$
- Units: mM s$^{-1}$
- Initial value: 0.3658
- Fitted linear dependence of $f_1$ on logarithm of $\text{Cu}_{A,\text{ox}}$.

$\lambda_{f_2}$
- Implementation Name: $f_{2\_0}$
- Units: mM s$^{-1}$
- Initial value: 0.1473
- Fitted intercept for the linear model for $f_2$.

$\lambda_{f_2,b}$
- Implementation Name: $f_{2\_b\text{red}}$
- Units: mM s$^{-1}$
- Initial value: $-0.05484$
- Fitted linear dependence of $f_2$ on logarithm of $a_{3,\text{red}}$.

$\lambda_{f_3}$
- Implementation Name: $f_{3\_0}$
- Units: mM s$^{-1}$
- Initial value: 0.6324
- Fitted intercept for the linear model for $f_3$.

$\lambda_{f_3,O}$
- Implementation Name: $f_{3\_O2}$
- Units: mM s$^{-1}$
- Initial value: 0.03352
- Fitted linear dependence of $f_3$ on logarithm of $O_2$. 


**$G_n$**

Implementation Name: $G_n$
Units: $ml_{blood} ml_{brain}^{-1} mmHg^{-1} s^{-1}$
Initial value: $\frac{P_{o,n} - P_{v,n}}{G_n}$
Normal blood vessel conductance.

**$H_n^+$**

Implementation Name: $H_n$
Units: mM
Initial value: 0.00003981
Normal mitochondrial proton concentration.

**$J_{O_2,n}$**

Implementation Name: $J_{O_2,n}$
Units: mM s$^{-1}$
Initial value: $CMRO_{2,n}$
Normal oxygen flux from blood to tissue.

**$k_{aut}$**

Implementation Name: $k_{aut}$
Units: dimensionless
Initial value: 1
Overall functioning of autoregulatory response.

**$K_G$**

Implementation Name: $K_G$
Units: $ml_{blood} ml_{brain}^{-1} mmHg^{-1} s^{-1} cm^{-4}$
Initial value: $G_n^{\text{pow}(r_n, 4)}$
Proportionality constant in Poiseuille relation for conductance.

**$kCV$**

Implementation Name: $kCV$
Units: mV$^{-1}$
Initial value: 0.02047339
Factor relating the Complex V driving force to the membrane potential and demand.

**$\lambda_L$**

Implementation Name: $L_{O_2}$
Units: mM s$^{-1}$
Initial value: $-15.339464$
Fitted intercept for the linear model for $L$.

**$\lambda_{L,p}$**

Implementation Name: $L_{O_2,p}$
Units: mM s$^{-1}$ mV$^{-1}$
Initial value: 0.097097
Fitted linear dependence of $L$ on $\Delta p$.

**$\lambda_{L,\theta}$**

Implementation Name: $L_{O_2,\theta}$
Units: mM s$^{-1}$
Initial value: 5.665904
Fitted linear dependence of $L$ on $\theta$.

**$\lambda_0$**

Implementation Name: $1aa_0$
Units: cm
13.7 Parameters

Initial value: 0.02327
Intercept of the fitted linear model for blood vessel radius.

\( \lambda_{\mu} \)
Implementation Name: lam\_mu
Units: cm
Initial value: −0.006375
Fitted linear dependence of blood vessel radius on autoregulatory stimuli.

\( \lambda_{P} \)
Implementation Name: lam\_p
Units: cm mmHg
Initial value: −0.4697
Fitted linear dependence of blood vessel radius on reciprocal of blood pressure.

\( n_h \)
Implementation Name: n\_h
Units: dimensionless
Initial value: 2.5
Hill coefficient for oxygen dissociation from haemoglobin.

\( O_{2,n} \)
Implementation Name: O2\_n
Units: mM
Initial value: 0.024
Normal mitochondrial oxygen concentration.

\( O_{2,c,n} \)
Implementation Name: O2c\_n
Units: mM
Initial value: \( \phi \) pow \( \left( \frac{S_{c,O_2,n}}{1 - S_{c,O_2,n}}, \frac{1}{n_h} \right) \)
Normal capillary oxygen concentration.

\( p_1 \)
Implementation Name: p1
Units: dimensionless
Initial value: 12
Proton cost of the reaction reducing CuA.

\( p_3 \)
Implementation Name: p2
Units: dimensionless
Initial value: 4
Proton cost of the reaction reducing a3.

\( p_3 \)
Implementation Name: p3
Units: dimensionless
Initial value: 4
Proton cost of the reaction reducing O2.

\( P_a \)
Implementation Name: P\_a
Units: mmHg
Initial value: \( P_{a,n} \)
Mean arterial blood pressure.

\( P_{a,n} \)
Implementation Name: P\_an
Units: mmHg
Initial value: 100
Normal arterial blood pressure.

\[ P_v \]
Implementation Name: \( P_v \)
Units: mmHg
Initial value: \( P_{v,n} \)
Venous blood pressure.

\[ P_{v,n} \]
Implementation Name: \( P_{vn} \)
Units: mmHg
Initial value: 4
Normal venous blood pressure.

\[ P_{aCO_2} \]
Implementation Name: \( Pa_{CO2} \)
Units: mmHg
Initial value: \( P_{aCO2,n} \)
Arterial partial pressure of carbon dioxide.

\[ P_{aCO_2,n} \]
Implementation Name: \( Pa_{CO2n} \)
Units: mmHg
Initial value: 40
Normal arterial partial pressure of carbon dioxide.

\( \phi \)
Implementation Name: \( phi \)
Units: mM
Initial value: 0.036
Oxygen concentration at half-maximal saturation.

\[ R_{CO_2} \]
Implementation Name: \( R_{aut\,c} \)
Units: dimensionless
Initial value: 2.2
Autoregulatory reactivity to carbon dioxide.

\[ R_{O_2} \]
Implementation Name: \( R_{auto} \)
Units: dimensionless
Initial value: 1.5
Autoregulatory reactivity to oxygen.

\[ R_{p_a} \]
Implementation Name: \( R_{aut\,p} \)
Units: dimensionless
Initial value: 4
Autoregulatory reactivity to blood pressure.

\[ R_u \]
Implementation Name: \( R_{aut\,u} \)
Units: dimensionless
Initial value: 0.5
Autoregulatory reactivity to demand.

\[ R_{Hi,H} \]
Implementation Name: \( R_{Hi,H} \)
Units: mM
13.7 Parameters

Initial value: 9.565483
Proton buffering factor.

$r_n$
Implementation Name: $r_{,n}$
Units: cm
Initial value: 0.0187
Normal blood vessel radius. Normal effective blood vessel radius.

$S_{a,O_2,n}$
Implementation Name: $SaO_2_{,n}$
Units: dimensionless
Initial value: 0.96
Normal arterial oxygen saturation.

$S_{a,O_2}$
Implementation Name: $SaO_2_{,n}$
Units: dimensionless
Initial value: $S_{a,O_2,n}$
Arterial oxygen saturation.

$S_{c,O_2,n}$
Implementation Name: $ScO_2_{,n}$
Units: dimensionless
Initial value: $\frac{S_{a,O_2,n} + S_{v,O_2,n}}{2}$
Normal capillary oxygen saturation.

$S_{v,O_2,n}$
Implementation Name: $SvO_2_{,n}$
Units: dimensionless
Initial value: $\frac{HbO_{2,v,n}}{Hb_{tot,n}}$
Normal venous oxygen saturation.

$t$
Implementation Name: $t$
Units: s
Initial value: 0
Time over which the system evolves.

$\tau_{CO_2}$
Implementation Name: $\tau_{,c}$
Units: s
Initial value: 5
Filter time constant for stimulus effect of carbon dioxide.

$\tau_{O_2}$
Implementation Name: $\tau_{,o}$
Units: s
Initial value: 20
Filter time constant for stimulus effect of capillary oxygen.

$\tau_{Pa}$
Implementation Name: $\tau_{,p}$
Units: s
Initial value: 5
Filter time constant for stimulus effect of blood pressure.

$\tau_{tu}$
Implementation Name: $\tau_{,u}$
Units: s
Initial value: 0.5
Filter time constant for stimulus effect of demand.

\( u \)
Implementation Name: u
Units: dimensionless
Initial value: \( u_n \)
Parameter indicating metabolic demand.

\( u_n \)
Implementation Name: u_n
Units: dimensionless
Initial value: 1
Normal demand.

\( v_{CO_2,n} \)
Implementation Name: v_c\_n
Units: mmHg
Initial value: \( P_{aCO_2,n} \)
Normal filtered carbon dioxide partial pressure. Normal filtered carbon dioxide partial pressure.

\( v_{O_2,n} \)
Implementation Name: v_o\_n
Units: mM
Initial value: \( O_2,c,n \)
Normal filtered capillary oxygen concentration. Normal filtered capillary oxygen concentration.

\( v_{P_a,n} \)
Implementation Name: v_p\_n
Units: mmHg
Initial value: \( P_{a,n} \)
Normal filtered arterial blood pressure. Normal filtered blood pressure.

\( v_{u,n} \)
Implementation Name: v_u\_n
Units: dimensionless
Initial value: \( u_n \)
Normal filtered demand. Normal filtered demand.

\( VArat_n \)
Implementation Name: VArat\_n
Units: dimensionless
Initial value: 3
Normal volume ratio of veins to arteries in brain tissue.

\( V_{a,n} \)
Implementation Name: Vol\_artn
Units: dimensionless
Initial value: \( \frac{1}{1 + VArat_n} \)
Normal relative arterial blood volume.

\( Vol_{mit} \)
Implementation Name: Vol\_mit
Units: dimensionless
Initial value: 0.067
Fraction of brain tissue volume that is mitochondria.

\( V_v \)
13.7 Parameters

Implementation Name: Vol_ven
Units: dimensionless
Initial value: \( \frac{\text{Varat}_n}{1 + \text{Varat}_n} \)
Relative venous blood volume.

\[ \text{HbO}_{2,a} = \text{Hb}_{tot} \cdot S_{a,\text{O}_2} \]
Implementation Name: X0a
Units: mM
Initial value: \( \text{HbO}_{2,a,n} \)
Arterial concentration of oxygen bound to haemoglobin.

\[ \text{HbO}_{2,a,n} \]
Implementation Name: X0a_n
Units: mM
Initial value: \( \text{Hb}_{tot,n} \cdot S_{a,\text{O}_2,n} \)
Normal arterial concentration of oxygen bound to haemoglobin.

\[ \text{HbO}_{2,v,n} \]
Implementation Name: X0v_n
Units: mM
Initial value: \( \frac{\text{CBF}_n \cdot \text{HbO}_{2,a,n}}{\text{J}_{O_2,n}} \)
Normal venous concentration of oxygen bound to haemoglobin.

\[ \text{Hb}_{tot} \]
Implementation Name: Xtot
Units: mM
Initial value: 9.1
Total concentration of haemoglobin O\(_2\) binding sites in blood (4 times haemoglobin concentration).

\[ \text{Hb}_{tot,n} \]
Implementation Name: Xtot_n
Units: mM
Initial value: 9.1
Normal total concentration of haemoglobin O\(_2\) binding sites in blood (4 times haemoglobin concentration).

\[ Z \]
Implementation Name: Z
Units: mV
Initial value: 59.028
Proportionality constant in calculation of driving forces due to concentration differences. Defined as \( RT/F \), where \( F \) is Faraday’s constant, \( R \) the ideal gas constant and \( T \) the absolute temperature.