Appendix / Supplementary material

When using the material in this appendix, please cite Lundengård et al. "Mechanistic mathematical modeling tests hypotheses of the neurovascular coupling in fMRI", PLOS Computational, 2016. DOI: 10.1371/journal.pcbi.1004971.

All models have been uploaded to the model archive biomodels.net, where the model and simulation files can be downloaded.

All models and parameter sets have the same name in the appendix as they have in the article. All steady state values were calculated by simulating the model until steady state has been reached (1000s).

1 The metabolic model $M_m$

1.1 $M_{m1}$
The metabolic model $M_{m1}$ assumes that the only mechanism that controls the shape of the BOLD response is that the blood vessels increase the blood flow in response to a lack of oxygen during the stimulus.

1.1.1 States and reactions

| State                      | Interpretation                                      |
|----------------------------|-----------------------------------------------------|
| $d(stimulus)\, dt = 0$     | Stimulus input signal                               |
| $d(oHb)\, dt = v_{1b} - v_{1f} + v_{inO\text{H}b} - v_{outO\text{H}b}$ | Change in oxyhemoglobin level                       |
| $d(dHb)\, dt = v_{1f} - v_{1b} + v_{indO\text{H}b} - v_{outdO\text{H}b}$ | Change in deoxyhemoglobin level                     |
| $d(O_2)\, dt = v_{1f} - v_{1b} - v_{basal} \times \text{proportion}_1 - v_{stim} \times \text{proportion}_2$ | Change in oxygen level                              |
| $d(glucose)\, dt = v_{inG} - v_{outG} - v_{basal} - v_{stim}$ | Change in glucose level                             |
| $d(inputDelay)\, dt = input_1 - v_{ID}$ | Delay state                                         |
| $d(oxygenFbDelay)\, dt = v_{tOOFBD} - v_{OOFBD}$ | Delay state                                         |
| $d(oxygenFbDelay_2)\, dt = v_{OOFBD} - v_{OOFBD_2}$ | Delay state                                         |
| $d(oxygenFbDelay_3)\, dt = v_{tOOFBD_2} - v_{OOFBD_3}$ | Delay state                                         |
| $d(oxygen\, feedback)\, dt = v_{OOFBD_3} - v_{OFBR}$ | Oxygen feedback to the blood flow                   |
### Reaction

| Reaction | Interpretation |
|----------|----------------|
| \( v_1_f = k_1 f \times oHb \) | Rate of releasing oxyhemoglobin into oxygen and deoxyhemoglobin |
| \( v_1_d = k_1 d \times dHb \times O_2 \) | Rate of binding oxygen and deoxyhemoglobin into oxyhemoglobin |
| \( v_{inOHb} = \text{oHb}_{body} \times k_{flow} \) | Oxyhemoglobin influx |
| \( v_{outOHb} = \text{oHb} \times k_{flow} \) | Oxyhemoglobin outflux |
| \( v_{inOHb} = \text{dHb}_{body} \times k_{flow} \) | Deoxyhemoglobin influx |
| \( v_{outOHb} = \text{dHb} \times k_{flow} \) | Deoxyhemoglobin outflux |
| \( v_{inO_2} = O_2_{body} \times k_{flow} \) | Glucose influx |
| \( v_{outO_2} = O_2 \times k_{flow} \) | Glucose outflux |
| \( v_{basal} = k_{basal} \times O_2^{\text{proportion1}} \times \text{glucose} \) | Basal metabolism |
| \( v_{stim} = \text{inputDelay}_5 \times O_2^{\text{proportion2}} \times \text{glucose} \) | Metabolism during stimulation |
| \( v_{inFB} = k_{\text{metabolic}} \times \text{stimulus} \) | Delay state reactions |
| \( v_{ID} = k_{ID} \times \text{inputDelay} \) | Delay state reactions |
| \( v_{O2FB} = O_2_{body} \times \text{glucose} \) | Delay state reactions |
| \( v_{OFBD} = \text{oxygen}_{FBdelay} \times k_{OFBD} \) | Delay state reactions |
| \( v_{OFBD2} = \text{oxygen}_{FBdelay2} \times k_{OFBD2} \) | Delay state reactions |
| \( v_{OFBD3} = \text{oxygen}_{FBdelay3} \times k_{OFBD3} \) | Delay state reactions |
| \( v_{OFB} = \text{oxygenfeedback} \times k_{OFB} \) | Delay state reactions |

### 1.1.2 Variables

| Variable name | Variable unit | Variable value | Interpretation |
|---------------|---------------|----------------|----------------|
| \( k_{flow} \) | 1/s | \( k_{flow} \times O_2 \) \( \text{km} + \text{oxygen feedback} \) | Blood flow |
| \( G_{body} \) | amount | 100 | Glucose in arterial blood |
| \( O_2_{body} \) | amount | 100 | Oxygen in arterial blood |
| \( oHb_{body} \) | amount | 100 | Oxygenated hemoglobin in arterial blood |
| \( dHb_{body} \) | amount | 100 | Deoxygenated hemoglobin in arterial blood |
| \( \hat{y} \) | unitless | \( k_y \times oHb \) \( dHb \) | Output signal |
1.1.3 Parameters and parameter values
Parameters and parameter values for the metabolic feedback model $M_{m1}$ used in Fig. A.

| Parameter name | Parameter unit | Parameter value |
|----------------|----------------|-----------------|
| $k_{1f}$       | 1/s            | 14049.3847      |
| $k_{1b}$       | 1/(amount×s)  | 18645.2545      |
| $k_{basal}$    | 1/(amount×s)  | 0.5064          |
| $k_{flow_{O2}}$ | amount/s      | 3.0207          |
| $k_y$          | unitless       | 12514.7912      |
| $k_{metabolic}$ | 1/s            | 1907.5170       |
| $k_m$          | amount         | 604.8624        |
| proportion1    | oxygen/glucose metabolised | 0.9222 |
| proportion2    | oxygen/glucose metabolised | 0.1632 |
| $k_{ID}$       | 1/s            | 6250.7308       |
| $O_{2Dbody}$   | 1/s            | 29.8642         |
| $k_{O_{FBD}}$  | 1/s            | 5.5231          |
| $k_{O_{FBD2}}$ | 1/s            | 16208.1574      |
| $k_{O_{FBD3}}$ | 1/s            | 16.3427         |
| $k_{O_{FB}}$   | 1/s            | 3189.4025       |

Fig A: Oxygen controls the feedback in the metabolic model $M_{m1}$. Red dots = data mean and SE, blue line = model simulation.
1.2 \( M_{m2} \)

The metabolic model \( M_{m2} \) assumes that the only mechanism that controls the shape of the BOLD response is that the blood vessels increase the blood flow in response to a lack of glucose during the stimulus.

1.2.1 States and reactions

| State                   | Interpretation                        | Steady State value \( p_1 \) | Steady State value \( p_2 \) | Steady State value \( p_3 \) |
|-------------------------|--------------------------------------|------------------------------|------------------------------|-------------------------------|
| \( d(\text{stimulus}) \) \( \frac{dt}{dt} = 0 \) | Stimulus input signal                | 0                            | 0                            | 0                             |
| \( d(oHb) \) \( \frac{dt}{dt} = v_1b - v_1f + v_{inoHb} - v_{outoHb} \) | Change in oxyhemoglobin level       | 107.10                       | 107.10                       | 107.1                         |
| \( d(dHb) \) \( \frac{dt}{dt} = v_1f - v_1b + v_{indHb} - v_{outdHb} \) | Change in deoxyhemoglobin level     | 92.90                        | 92.90                        | 92.9                          |
| \( d(O_2) \) \( \frac{dt}{dt} = v_1f - v_1b - v_{basal} \times \text{proportion}_1 - v_{stim} \times \text{proportion}_2 + v_{ino2} - v_{outo2} \) | Change in oxygen level              | 0.52                         | 0.52                         | 0.52                          |
| \( d(\text{glucose}) \) \( \frac{dt}{dt} = v_{ing} - v_{outg} - v_{basal} - v_{stim} \) | Change in glucose level             | 29.80                        | 29.80                        | 29.8                          |
| \( d(\text{inputDelay}) \) \( \frac{dt}{dt} = \text{input}_1 - v_{ID} \) | Delay state                         | 4.65 \times 10^{-20}        | -1.52 \times 10^{-17}        | -2.08 \times 10^{-18}        |
| \( d(\text{inputDelay}_2) \) \( \frac{dt}{dt} = v_{ID} - v_{ID2} \) | Delay state                         | 4.63 \times 10^{-20}        | -1.51 \times 10^{-17}        | -2.07 \times 10^{-18}        |
| \( d(\text{inputDelay}_3) \) \( \frac{dt}{dt} = v_{ID2} - v_{ID3} \) | Delay state                         | 4.70 \times 10^{-20}        | -1.54 \times 10^{-17}        | -2.1 \times 10^{-18}         |
| \( d(\text{inputDelay}_4) \) \( \frac{dt}{dt} = v_{ID3} - v_{ID4} \) | Delay state                         | 4.59 \times 10^{-20}        | -1.50 \times 10^{-17}        | -2.05 \times 10^{-18}        |
| \( d(\text{inputDelay}_5) \) \( \frac{dt}{dt} = v_{ID4} - v_{ID5} \) | Delay state                         | 1.66 \times 10^{-23}        | -5.41 \times 10^{-21}        | -7.4 \times 10^{-22}         |
| \( d(\text{glucoseFeedback}) \) \( \frac{dt}{dt} = v_{tOGFB} - v_{GFB} \) | Glucose feedback to the blood flow  | 0.16                         | 0.16                         | 0.16                          |
| \( d(\text{glucoseFeedback}) \) \( \frac{dt}{dt} = v_{GFB} - v_{GFB} \) | Glucose feedback to the blood flow  | 0.25                         | 0.25                         | 0.25                          |
### 1.2.2 Variables

| Variable name | Variable unit | Variable value | Interpretation |
|---------------|---------------|----------------|----------------|
| $k_{flow}$    | 1/s           | $k_{flow}t_{glucose}$ | Blood flow |
| $G_{body}$    | amount        | 100             | Glucose in arterial blood |
| $GD_{body}$   | amount        | 100             | Glucose feedback delay |
| $O_{2body}$   | amount        | 100             | Oxygen in arterial blood |
| $oHb_{body}$  | amount        | 100             | Oxygenated hemoglobin in arterial blood |
| $dHb_{body}$  | amount        | 100             | Deoxygenated hemoglobin in arterial blood |
| $\dot{y}$     | unitless      | $k_{y}\times oHb$ | Output signal |

### Reaction

| Reaction | Interpretation |
|----------|----------------|
| $v_{inO2} = oHb_{body} \times k_{flow}$ | Oxyhemoglobin influx |
| $v_{outO2} = oHb_{body} \times k_{flow}$ | Oxyhemoglobin outflux |
| $v_{inDh} = dHb_{body} \times k_{flow}$ | Deoxyhemoglobin influx |
| $v_{outDh} = dHb_{body} \times k_{flow}$ | Deoxyhemoglobin outflux |
| $v_{inG} = G_{body} \times k_{flow}$ | Glucose influx |
| $v_{outG} = G_{body} \times k_{flow}$ | Glucose outflux |
| $v_{inO2} = O_{2body} \times k_{flow}$ | Oxygen influx |
| $v_{outO2} = O_{2} \times k_{flow}$ | Oxygen outflux |
| $v_{basal} = k_{basal} \times O_{2}^{proportion} \times glucose$ | Basal metabolism |
| $v_{stim} = inputDelay_5 \times O_{2}^{proportion} \times glucose \times k_{j2}$ | Metabolism during stimulation |
| $v_{ID} = k_{ID} \times inputDelay$ | Delay state reactions |
| $v_{GFB} = GD_{body} \times glucose$ | Delay state reactions |
| $v_{GFB} = glucose_{FB delay} \times k_{GFB}$ | Delay state reactions |
| $v_{ID2} = inputDelay_2 \times k_{ID2}$ | Delay state reactions |
| $v_{ID3} = inputDelay_3 \times k_{ID3}$ | Delay state reactions |
| $v_{ID4} = inputDelay_4 \times k_{ID4}$ | Delay state reactions |
| $v_{ID5} = inputDelay_5 \times k_{ID5}$ | Delay state reactions |
### Parameters and parameter values

Parameter sets for model $M_{m2}$ used in Fig. 5 B-D. Proportion1 and proportion2 (marked in bold) control the proportion of aerobic and anaerobic metabolism during basal conditions vs. during stimulation.

| Parameter names | Parameter unit | $p_1$  | $p_2$  | $p_3$  |
|-----------------|----------------|--------|--------|--------|
|                 | $(\frac{CMR_{O2}}{CMR_{glu}})_b$ | $(\frac{CMR_{O2}}{CMR_{glu}})_s$ | $(\frac{CMR_{O2}}{CMR_{glu}})_{stim}$ | $(\frac{CMR_{O2}}{CMR_{glu}})_{stim}$ |
| $k_{1f}$        | 1/s            | 627.1792 | 627.1792 | 627.1792 |
| $k_{1b}$        | 1/(amount$\times$s) | 1381.9932 | 1381.9932 | 1381.9932 |
| $k_{basal}$     | 1/(amount$\times$s) | 5.0587 | 5.0587 | 5.0587 |
| $k_{flow_{glucose}}$ | amount/s | 102.6292 | 102.6292 | 102.6292 |
| $k_{Y}$         | unitless/s     | 2905.5532 | 2905.5532 | 2905.5532 |
| $k_{metabolic}$ | 1/s            | 189.3795 | 189.3795 | 189.3795 |
| $k_{m}$         | amount         | 111.8459 | 111.8459 | 111.8459 |
| $k_{2}$         | 1/(amount$^2\times$s) | 11.67404 | 11.67404 | 11.67404 |
| proportion1     | oxygen/glucose metabolised | **1.3159** | **1.3159** | **1.3159** |
| proportion2     | oxygen/glucose metabolised | **1.3159** | 0 | **0.6304** |
| $k_{ID}$        | 1/s            | 0.9575 | 0.9575 | 0.9575 |
| $k_{GFBD}$      | 1/s            | 18641.1377 | 18641.1377 | 18641.1377 |
| $k_{GFB}$       | 1/s            | 11921.2175 | 11921.2175 | 11921.2175 |
| $k_{ID2}$       | 1/s            | 0.9613 | 0.9613 | 0.9613 |
| $k_{ID3}$       | 1/s            | 0.9484 | 0.9484 | 0.9484 |
| $k_{ID4}$       | 1/s            | 0.9703 | 0.9703 | 0.9703 |
| $k_{ID5}$       | 1/s            | 2687.7052 | 2687.7052 | 2687.7052 |
1.3 $M_{m3}$

The metabolic model $M_{m3}$ assumes that the only mechanism that controls the shape of the BOLD response is that the blood vessels increase the blood flow in response to a lack of glucose during the stimulus. The delay states are placed in the glucose feedback, not between stimulus and metabolism.

1.3.1 Interaction graph

![Interaction graph](image)

Fig. B: Interaction graph of the metabolic feedback model $M_{m3}$.
Interaction graphs of the metabolic feedback model and the neurotransmitter feed-forward model.

Whole squares = states, dashed squares = variables (summed from states), whole arrows = transformations, dashed arrows = interactions, green area = astrocyte, blue area = neuron, grey area = blood. All states starting with S and a number are delay states. Stimulus is the input to the model. Gbody, O2body, oHbbody, dHbbody, and PL are variables. Stimulus = input signal. oHb and dHb are oxyhemoglobin and deoxyhemoglobin, respectively.
### 1.3.2 States and reactions

| State                  | Interpretation                                      | Steady State value | Steady State value |
|------------------------|-----------------------------------------------------|--------------------|--------------------|
| \( \frac{d(\text{stimulus})}{dt} = 0 \) | Stimulus input signal                               | 0                  | 0                  |
| \( \frac{d(oHb)}{dt} = v_1b - v_f + v_{inoHb} - v_{outHb} \) | Change in oxyhemoglobin level                       | 1.84               | 16.15              |
| \( \frac{d(dHb)}{dt} = v_1f - v_1b + v_{indHb} - v_{outdHb} \) | Change in deoxyhemoglobin level                     | 18.16              | 3.85               |
| \( \frac{d(O_2)}{dt} = v_f - v_1b - v_{basal} \times \text{proportion}_1 - v_{stim} \times \text{proportion}_2 + v_{ino2} - v_{outo2} \) | Change in oxygen level                              | 0.12               | 0.0018             |
| \( \frac{d(\text{glucose})}{dt} = v_{ing} - v_{outG} - v_{basal} - v_{stim} \) | Change in glucose level                             | 1.41               | 5.60               |
| \( \frac{d(\text{inputDelay})}{dt} = \text{input}_1 - v_{ID} \) | Delay state                                         | \(-2.11 \times 10^{-14}\)  | \(-8.12 \times 10^{-15}\)  |
| \( \frac{d(\text{glucoseFbDelay})}{dt} = v_{togoFBD} - v_{GFBD} \) | Delay states                                       | 0.18               | 3897.12            |
| \( \frac{d(\text{glucoseFbDelay}_2)}{dt} = v_{GFBD} - v_{GFBD2} \) |                                            |                    |                    |
| \( \frac{d(\text{glucoseFbDelay}_3)}{dt} = v_{GFBD2} - v_{GFBD3} \) |                                            |                    |                    |
| \( \frac{d(\text{glucosefeedback})}{dt} = v_{GFBD3} - v_{GFBD} \) |                                            |                    |                    |
| Reaction | Interpretation |
|----------|----------------|
| $v_1_f = k_1 f \times oHb$ | Rate of releasing oxyhemoglobin into oxygen and deoxyhemoglobin |
| $v_1_b = k_1 b \times dHb \times O_2$ | Rate of binding oxygen and deoxyhemoglobin into oxyhemoglobin |
| $v_{inOHb} = oHb_{body} \times k_{flow}$ | Oxyhemoglobin influx |
| $v_{outOHb} = oHb \times k_{flow}$ | Oxyhemoglobin outflux |
| $v_{inDHB} = dHb_{body} \times k_{flow}$ | Deoxyhemoglobin influx |
| $v_{outDHB} = dHb \times k_{flow}$ | Deoxyhemoglobin outflux |
| $v_{inG} = G_{body} \times k_{flow}$ | Glucose influx |
| $v_{outG} = glucose \times k_{flow}$ | Glucose outflux |
| $v_{inO2} = O2_{body} \times k_{flow}$ | Oxygen influx |
| $v_{outO2} = O2 \times k_{flow}$ | Oxygen outflux |
| $v_{basal} = k_{basal} \times O2_{proportion 1} \times glucose$ | Basal metabolism |
| $v_{stim} = inputDelay \times O2_{proportion 2} \times glucose$ | Metabolism during stimulation |
| $input_1 = k_{metabolic} \times stimulus$ | Delay state reactions |
| $v_{ID} = k_{delay} \times input_{delay}$ | Delay state reactions |
| $v_{logFB} = G_{body} \times glucose$ | Delay state reactions |
| $v_{GFB} = glucose_{FBdelay} \times k_{GFB}$ | Delay state reactions |
| $v_{GFB2} = glucose_{FBdelay2} \times k_{GFB2}$ | Delay state reactions |
| $v_{GFB3} = glucose_{FBdelay3} \times k_{GFB3}$ | Delay state reactions |
| $v_{GFB} = glucosefeedback \times k_{GFB}$ | Delay state reactions |

### 1.3.3 Variables

| Variable name | Variable unit | Variable value | Interpretation |
|---------------|---------------|----------------|----------------|
| $k_{flow}$    | 1/s           | $k_{flowglucose}$ over $km + glucosefeedback$ | Blood flow |
| $G_{body}$    | amount        | 100            | Glucose in arterial blood |
| $O2_{body}$   | amount        | 100            | Oxygen in arterial blood |
| $oHb_{body}$  | amount        | 100            | Oxygenated hemoglobin in arterial blood |
| $dHb_{body}$  | amount        | 100            | Deoxygenated hemoglobin in arterial blood |
| $\hat{y}$     | unitless      | $k_y \times oHb$ over $dHb$ | Output signal |
### 1.3.4 Parameters and parameter values

Parameter sets for model M_{m3} used in Fig. 5 G-J.

| Parameter names | Parameter unit | p_4 Only undershoot | p_5 Only initial dip |
|-----------------|----------------|---------------------|----------------------|
| k_{1f}          | 1/s            | 1.3952              | 8.8366               |
| k_{1b}          | 1/(amount×s)   | 0.0011              | 19957.2824           |
| k_{basal}       | 1/(amount×s)   | 174.5880            | 41.8601              |
| k_{flow_glu}    | amount/s       | 2438.7260           | 818.7605             |
| k_y             | unitless       | 297.9752            | 2.7266               |
| k_{metabolic}   | 1/s            | 19943.3114          | 19852.9448           |
| k_m             | amount         | 3.3201              | 0.1918               |
| proportion1     | oxygen/glucose metabolised | 2.1006 | 0.8738 |
| proportion2     | oxygen/glucose metabolised | 0.0011 | 0.1102 |
| k_{ID}          | 1/s            | 7.0830              | 1.4594               |
| GD_{body}       | 1/s            | 2603.4638           | 545.2871             |
| k_{GFBD}        | 1/s            | 19932.2693          | 0.7838               |
| k_{GFBD2}       | 1/s            | 0.6959              | 0.8452               |
| k_{GFBD3}       | 1/s            | 0.6676              | 4916.7131            |
| k_{GFBD}        | 1/s            | 0.4752              | 0.8249               |

Cost: p_4 = 18.02, p_5 = 60.84.
2 The Neurotransmitter model $M_n$

2.1 $M_{n1}$
The neurotransmitter model $M_{n1}$ assumes that the mechanism that controls the shape of the BOLD response is the vessel response to signaling substances released by neurons and astrocytes in response to a stimulus.

2.1.1 Interaction graph

Fig. C: Interaction graph of the neurotransmitter feed-forward model. The neurotransmitter feed-forward hypothesis is described in more detail in Attwell 2010. Whole squares = states, dashed squares = variables (summed from states), whole arrows = transformations, dashed arrows = interactions, green area = astrocyte, blue area = neuron. All states starting with $S$ and a number are delay states. Stimulus is the input to the model. Calcium neuron and calcium Astrocyte = calcium ion ($Ca^{2+}$) level in the cell, NO = nitric oxide, cGMP = cyclic guanosine monophosphate, AA = arachidonic acid, EET = epoxyeicosatrienoic acids, PG = prostaglandins and HETE = hydroxyeicosatetraeonic acid (20-HETE).
## 2.1.2 States and reactions

| State                      | Interpretation                                             | Steady State value |
|----------------------------|------------------------------------------------------------|--------------------|
| $d(\text{Stimulus})/dt$    | Stimulus input signal                                       | 0                  |
| $d(\text{glu})/dt$         | Glutamate release in the synaptic cleft                     | 0                  |
| $d(\text{Ca}_{\text{Astro}})/dt$ | Calcium influx in the astrocyte                            | 1.45               |
| $d(\text{AA})/dt$          | Change in AA level                                          | 768.92             |
| $d(\text{Ca}_{\text{Neuro}})/dt$ | Calcium influx in the neuron                               | 0.78               |
| $d(\text{NO})/dt$          | Change in NO level                                          | 0.72               |
| $d(\text{HETE})/dt$        | HETE effecting the blood vessels                            | 736.81             |
| $d(\text{PG})/dt$          | PG effecting the blood vessels                              | 740.05             |
| $d(\text{EET})/dt$         | EET effecting the blood vessels                             | 722.52             |
| $d(\text{cGMP})/dt$        | cGMP effecting the blood vessels                            | 0.78               |
Reactions

\[ \text{in} = k_1 \times \text{Stimulus} \]
\[ \text{glu}_{\text{Sink}} = \text{glu} \times \text{sink}_{\text{Glu}} \]

*Interpretation*

Stimulus input
Glucose breakdown and reuptake

\[ \text{Glutamate}_A = k_2 \times \text{glu} \]
\[ \text{calcium}_{\text{Astro}1} = C_{\text{a Astro}} \times \text{sink}_A \]
\[ \text{calcium}_{\text{Astro}2} = P L \times C_{\text{a Astro}} \times k_A \]

Calcium influx in the astrocyte
Calcium outflux in the astrocyte
Calcium induced AA

\[ AA_{HETE} = k_5 \times \frac{AA}{(k_m + k_a \times \text{NO})} \]

AA turning into HETE

\[ AA_{PG} = k_6 \times AA \]

AA turning into PG

\[ AA_{EET} = k_7 \times \frac{AA}{(k_m + k_a \times \text{NO})} \]

AA turning into EET

\[ \text{Glutamate}_N = k_3 \times \text{glu} \]
\[ \text{calcium}_{\text{Neuro}1} = C_{\text{a Neuro}} \times \text{sink}_N \]
\[ \text{calcium}_{\text{Neuro}2} = k_10 \times C_{\text{a Neuro}} \]

Calcium influx in the neuron
Calcium outflux in the neuron
Calcium induced NO

\[ NO_{cGMP} = k_{11} \times NO \]
\[ \text{sink}_{\text{NO}} = NO_{\text{sink}} \times NO \]

NO induced cGMP
NO breakdown

\[ v_{1HETE} = k_{12} \times S_{1HETE} \]
\[ v_{2HETE} = k_{13} \times S_{2HETE} \]
\[ v_{3HETE} = k_{14} \times S_{3HETE} \]
\[ HETE_{\text{sink}} = HETE \times \text{sink}_H \]

Delay state reactions
HETE breakdown

\[ v_{1PG} = k_{15} \times S_{1PG} \]
\[ v_{2PG} = k_{16} \times S_{2PG} \]
\[ v_{3PG} = k_{17} \times S_{3PG} \]
\[ PG_{\text{sink}} = PG \times \text{sink}_P \]

Delay state reactions
PG breakdown

\[ v_{1EET} = k_{18} \times S_{1EET} \]
\[ v_{2EET} = k_{19} \times S_{2EET} \]
\[ v_{3EET} = k_{20} \times S_{3EET} \]
\[ EET_{\text{sink}} = EET \times \text{sink}_E \]

Delay state reactions
EET breakdown

\[ v_{1cGMP} = k_{21} \times S_{1cGMP} \]
\[ v_{2cGMP} = k_{22} \times S_{2cGMP} \]
\[ v_{3cGMP} = k_{23} \times S_{3cGMP} \]
\[ cGMP_{\text{sink}} = cGMP \times \text{sink}_c \]

Delay state reactions
cGMP breakdown

### 2.1.3 Variables

| Variable name | Variable unit | Variable value |
|---------------|--------------|----------------|
| Stimulating   | unitless     | \( b_1 \times cGMP + b_2 \times PG + b_3 \times EET \) |
| Inhibiting    | unitless     | \( b_4 \times HETE \) |
| \( \bar{y} \) | unitless     | \( b_1 \times cGMP + b_2 \times PG + b_3 \times EET - b_4 \times HETE \) |
### 2.1.4 Parameters and parameter values
Parameter sets for model M_{\text{n1}} used in Fig. 6A.

| Parameter name | Parameter unit | Parameter Value |
|----------------|----------------|-----------------|
| k_1            | 1/s            | 0.5589          |
| k_2            | 1/s            | 0.053036        |
| k_3            | 1/s            | 3.3634          |
| k_4            | 1/(amount\times s) | 1.6775      |
| k_5            | amount/s       | 0.43467         |
| k_6            | 1/s            | 5.892\times 10^7 |
| k_7            | amount/s       | 1.7891          |
| k_8            | unitless       | 1.0276          |
| k_9            | unitless       | 2.8976          |
| k_{10}         | 1/s            | 1.0993          |
| k_{11}         | 1/s            | 4.8221\times 10^5 |
| k_{12}         | 1/s            | 6.3353\times 10^8 |
| k_{13}         | 1/s            | 0.87781         |
| k_{14}         | 1/s            | 1.0343          |
| k_{15}         | 1/s            | 2.1986          |
| k_{16}         | 1/s            | 0.8836          |
| k_{17}         | 1/s            | 1.2209          |
| k_{18}         | 1/s            | 0.6518          |
| k_{19}         | 1/s            | 0.9190          |
| k_{20}         | 1/s            | 7.5887 \times 10^7 |
| k_{21}         | 1/s            | 2.5067          |
| k_{22}         | 1/s            | 1.7921          |
| k_{23}         | 1/s            | 1.5562\times 10^5 |
| k_{m1}         | amount         | 5.5066\times 10^6 |
| k_{m2}         | amount         | 0.0433          |
| b_1            | 1/amount       | 2.7762          |
| b_2            | 1/amount       | 1.299           |
| b_3            | 1/amount       | 0.8634          |
| b_4            | 1/amount       | 1.0201\times 10^7 |
| Ca_{\text{Abas}} | amount/s     | 3.3823\times 10^7 |
| Ca_{\text{Nbas}} | amount/s     | 1.4943          |
| sink_{\text{Glu}} | 1/s             | 0.5318          |
| sink_{\text{A}}  | 1/s             | 1.3426          |
| sink_{\text{N}}  | 1/s             | 0.9493          |
| sink_{\text{H}}  | 1/s             | 5.7961\times 10^7 |
| sink_{\text{P}}  | 1/s             | 0.9134          |
|     |     |            |
|-----|-----|------------|
| sink_E | 1/s  | 0.7554     |
| sink_c | 1/s  | 6.7692×10^5 |
| NO_{sink} | 1/s  | 1.0735     |
| PL    | amount/s | 945.52    |

Cost: 5.76.

2.2 \( M_{n2} \)

Minimized version of the neurotransmitter model \( M_{n1} \). The main mechanism is the balance between the vasoconstricting and the vasodilating arm of the model structure.

The states, variables and parameters of this model do not have a biological interpretation.

2.2.1 Interaction graph

Fig. D. Interaction graph of the minimized neurotransmitter feed-forward model. Filled grey squares = vasodilation states, checkered grey squares = vasoconstriction states.
2.2.2 Fit to data

Fig E: Fit of the minimal model $M_{n2}$ to data. Red dots = data mean and SE, blue line = model simulation.

2.2.3 States and reactions

| State equation | Steady State values |
|----------------|---------------------|
| $\frac{d(l)}{dt}$ = 0 | 3.86×10^{-21} |
| $\frac{d(S1)}{dt}$ = $I\times k_0 - S1\times k_1$ | -1.88×10^{-14} |
| $\frac{d(S2)}{dt}$ = $S1\times k_1 - S2\times k_2$ | -3.71×10^{-14} |
| $\frac{d(S3)}{dt}$ = $S2\times k_2 - S3\times (k_{3s} + k_{3i})$ | -2.30×10^{-14} |
| $\frac{d(S4)}{dt}$ = $S3\times k_{3s} - S4\times k_{4s}$ | -2.54×10^{-13} |
| $\frac{d(S5)}{dt}$ = $S4\times k_{4s} - S5\times k_{5s}$ | -3.75×10^{-13} |
| $\frac{d(S6)}{dt}$ = $S5\times k_{5s} - S6\times k_{6s}$ | -2.10×10^{-16} |
| $\frac{d(S7)}{dt}$ = $S6\times k_{6s} - S7\times k_{7s}$ | -1.42×10^{-12} |
| $\frac{d(S8)}{dt}$ = $S7\times k_{7s}$ | 0.57 |
| $\frac{d(S1)}{dt}$ = $S3\times k_{3i} - S4\times k_{4i}$ | -4.93×10^{-14} |
| $\frac{d(S5)}{dt}$ = $S4\times k_{4i} - S5\times k_{5i}$ | 2.46×10^{-12} |
| $\frac{d(S6)}{dt}$ = $S5\times k_{5i} - S6\times k_{6i}$ | 5.29×10^{-13} |
| $\frac{d(S7)}{dt}$ = $S6\times k_{6i} - S7\times k_{7i}$ | 6.25×10^{-18} |
| $\frac{d(S8)}{dt}$ = $S7\times k_{7i}$ | 0.43 |
2.2.4 Variables

| Variable name | Variable unit | Variable value |
|---------------|---------------|----------------|
| Stimulating   | unitless      | $S_{5s} + S_{6s} + S_{7s}$ |
| Inhibitory    | unitless      | $S_{5i} + S_{6i} + S_{7i}$ |
| $\hat{y}$     | unitless      | $k_y (S_{5s} - S_{5i} + S_{6s} - S_{6i} + S_{7s} - S_{7i})$ |

2.2.5 Parameters and parameter values

Parameter sets for model $M_{h2}$ used in Fig. D.

| Parameter names | Parameter unit | Parameter values best fit intensity experiment |
|-----------------|----------------|-----------------------------------------------|
| $k_y$           | unitless       | 13467                                         |
| $k_0$           | 1/s            | 0.1034                                        |
| $k_1$           | 1/s            | 0.6245                                        |
| $k_2$           | 1/s            | 0.9430                                        |
| $k_{3s}$        | 1/s            | 1.2261                                        |
| $k_{4s}$        | 1/s            | 0.7059                                        |
| $k_{5s}$        | 1/s            | 1.0579                                        |
| $k_{6s}$        | 1/s            | 1889.7                                        |
| $k_{7s}$        | 1/s            | 0.7730                                        |
| $k_{3i}$        | 1/s            | 0.9163                                        |
| $k_{4i}$        | 1/s            | 1.0627                                        |
| $k_{5i}$        | 1/s            | 0.4454                                        |
| $k_{6i}$        | 1/s            | 2.5427                                        |
| $k_{7i}$        | 1/s            | 0.000021531                                   |

Cost: 29.2.
3 The feed-forward with metabolism model $M_{nm}$

3.1 $M_{nm1}$ Model structure

The combined model $M_{nm1}$ is a merge between the metabolic model $M_{m3}$ and the neurotransmitter model $M_{n1}$. It assumes that the vessel response to signaling substances released by neurons and astrocytes in response to a stimulus controls the blood flow. The metabolism controls the balance of $dHb$ and $oHb$. Therefore, both the metabolism and the intracellular signaling controls the shape of the BOLD response. The metabolism of $O_2$ is the main mechanism behind the intial dip while the blood flow controls the peak and the post-peak undershoot.

3.1.1 Interaction graph

Fig. F: Interaction graph of the combined model $M_{nm1}$. All abbreviations and names as declared above.
### 3.1.2 States and reactions

| State                          | Interpretation                                      | Steady State value p7 | Steady State value p9 |
|-------------------------------|-----------------------------------------------------|-----------------------|-----------------------|
| \(\frac{d(\text{stimulus})}{dt}\) = 0 | Stimulus input signal                               | 0                     | 0                     |
| \(\frac{d(\text{oHb})}{dt} = v_1 - v_{\text{f}} + v_{\text{inO}Hb} - v_{\text{outO}Hb}\) | Change in oxyhemoglobin level                       | 5.54                  | 7.21                  |
| \(\frac{d(Hb)}{dt} = v_{\text{f}} - v_1 + v_{\text{indHb}} - v_{\text{outdHb}}\) | Change in deoxyhemoglobin level                     | 14.45                 | 12.79                 |
| \(\frac{d(O_2)}{dt} = v_{\text{f}} - v_1 - v_{\text{basal}} \times \text{proportion}_1 - v_{\text{stim}} \times \text{proportion}_2 + v_{\text{inO}2} - v_{\text{outO}2}\) | Change in oxygen level                              | 0.8                   | 1.26                  |
| \(\frac{d(\text{glucose})}{dt} = v_{\text{inG}} - v_{\text{outG}} - v_{\text{basal}} - v_{\text{stim}}\) | Change in glucose level                             | 6.85                  | 8.66                  |
| \(\frac{d(\text{inputDelay})}{dt} = \text{input}_1 - v_{\text{ID}}\) | Delay state                                         | 5.54\times10^{-17}  | 7.85\times10^{-18}   |
| \(\frac{d(\text{glu})}{dt} = \text{input}_2 - \text{glu}_{\text{sink}}\) | Glutamate release in the synaptic cleft             | 1.54\times10^{-17}  | 6.08\times10^{-19}   |
| \(\frac{d(Ca_{\text{Astro}})}{dt} = \text{Glutamate}_{A} - \text{calcium}_{\text{Astro}1} + Ca_{\text{bas}}\) | Calcium influx in the astrocyte                     | 8.67                  | 2.15                  |
| \(\frac{d(AA)}{dt} = \text{calcium}_{\text{Astro}2} - (AA_{\text{HETE}} + AA_{\text{PG}} + AA_{\text{EET}})\) | Change in AA level                                  | 1433.15              | 36.56                 |
| \(\frac{d(Ca_{\text{Neuro}})}{dt} = \text{Glutamate}_{N} - \text{calcium}_{\text{Neuro1}} + Ca_{\text{bas}}\) | Calcium influx in the neuron                        | 2885.39              | 2.52                  |
| \(\frac{d(NO)}{dt} = \text{calcium}_{\text{Neuro2}} - \text{sink}_{\text{NO}}\) | Change in NO level                                  | 127.69               | 0.09                  |
| \(\frac{d(HETE)}{dt} = v_{\text{HETE}} - HETE_{\text{sink}}\) | HETE effecting the blood vessels                    | 81.99                 | 38.65                 |
| \(\frac{d(S_{1\text{HETE}})}{dt} = AA_{\text{HETE}} - v_{\text{HETE}}\) | Delay states                                        | 1.084                 | 25.23                 |
| \(\frac{d(S_{2\text{HETE}})}{dt} = v_{\text{HETE}} - v_{\text{HETE}}\) |                                           | 95.37                 | 41.52                 |
| \(\frac{d(S_{3\text{HETE}})}{dt} = v_{\text{HETE}} - v_{\text{HETE}}\) |                                           | 58.49                 | 32.79                 |
| \(\frac{d(\text{PG})}{dt} = v_{\text{PG}} - PG_{\text{sink}}\) | PG effecting the blood vessels                      | 0.06                  | 0.33                  |
| \(\frac{d(S_{1\text{PG}})}{dt} = AA_{\text{PG}} - v_{\text{PG}}\) | Delay states                                        | 2.62                  | 1.77                  |
| \(\frac{d(S_{2\text{PG}})}{dt} = v_{\text{PG}} - v_{\text{PG}}\) |                                           | 0.37                  | 0.39                  |
| \(\frac{d(S_{3\text{PG}})}{dt} = v_{\text{PG}} - v_{\text{PG}}\) |                                           | 0.084                 | 1.49                  |
\[
\begin{align*}
\frac{d(EET)}{dt} &= v^3_{EET} - EET_{sink} \\
\frac{d(S1_{EET})}{dt} &= AA_{EET} - v^1_{EET} \\
\frac{d(S2_{EET})}{dt} &= v^1_{EET} - v^2_{EET} \\
\frac{d(S3_{EET})}{dt} &= v^2_{EET} - v^3_{EET} \\
\end{align*}
\]

EET effecting the blood vessels
Delay states
31.99
39.64
34.05
31.84

\[
\begin{align*}
\frac{d(cGMP)}{dt} &= v^3_{cGMP} - cGMP_{sink} \\
\frac{d(S1_{cGMP})}{dt} &= AA_{cGMP} - v^1_{cGMP} \\
\frac{d(S2_{cGMP})}{dt} &= v^1_{cGMP} - v^2_{cGMP} \\
\frac{d(S3_{cGMP})}{dt} &= v^2_{cGMP} - v^3_{cGMP} \\
\end{align*}
\]

cGMP effecting the blood vessels
Delay states
15.28
2.14
0.47
1.39
0.001
0.01
0.07
0.02
| Reactions         | Interpretation                                                   |
|-------------------|------------------------------------------------------------------|
| \( v_1_f \) = \( k_1 \times oHb \) | Rate of releasing oxyhemoglobin into oxygen and deoxyhemoglobin |
| \( v_1_b \) = \( k_1 \times dHb \times O_2 \) | Rate of binding oxygen and deoxyhemoglobin into oxyhemoglobin |
| \( v_{inoHb} \) = \( oHb_{body} \times k_{flow} \) | Oxyhemoglobin influx                                             |
| \( v_{outHb} \) = \( oHb \times k_{flow} \) | Oxyhemoglobin outflux                                            |
| \( v_{indHb} \) = \( dHb_{body} \times k_{flow} \) | Deoxyhemoglobin influx                                           |
| \( v_{outHb} \) = \( dHb \times k_{flow} \) | Deoxyhemoglobin outflux                                          |
| \( v_{inG} \) = \( G_{body} \times k_{flow} \) | Glucose influx                                                  |
| \( v_{outG} \) = \( glucose \times k_{flow} \) | Glucose outflux                                                 |
| \( v_{inO_2} \) = \( O_2_{body} \times k_{flow} \) | Oxygen influx                                                   |
| \( v_{outO_2} \) = \( O_2 \times k_{flow} \) | Oxygen outflux                                                  |
| \( v_{basal} \) = \( k_{basal} \times O_2^{\text{propportion1} \times \text{glucose}} \) | Basal metabolism                                                |
| \( v_{stim} \) = \( \text{inputDelay} \times O_2^{\text{propportion2} \times \text{glucose}} \) | Metabolism during stimulation                                    |
| \( input_1 \) = \( k_{\text{metabolic}} \times \text{stimulus} \) | Stimulus input to the metabolic module                           |
| \( input_2 \) = \( k_{\text{neurotrans}} \times \text{stimulus} \) | Delay state reaction                                            |
| \( glu_{\text{Sink}} \) = \( \text{sink}_{\text{Glu}} \times \text{glu} \) | Stimulus input to the neurotransmitter module                    |
| \( Glutamate_A \) = \( k_2 \times \text{glu} \) | Glucose breakdown and reuptake                                   |
| \( calcium_{Astro1} \) = \( Ca_{Astro} \times sink_A \) | Calcium influx in the astrocyte                                  |
| \( calcium_{Astro2} \) = \( PL \times Ca_{Astro} \times k_4 \) | Calcium outflux in the astrocyte                                |
| \( AA_{HETE} \) = \( k_5 \times \frac{AA}{(km_1 + k_8 \times NO)} \) | AA turning into HETE                                             |
| \( AA_{PG} \) = \( k_6 \times AA \) | AA turning into PG                                               |
| \( AA_{EET} \) = \( k_7 \times \frac{AA}{(km_2 + k_9 \times NO)} \) | AA turning into EET                                              |
| \( Glutamate_N \) = \( k_3 \times \text{glu} \) | Calcium influx in the neuron                                     |
| \( calcium_{Neuro1} \) = \( Ca_{Neuro} \times sink_N \) | Calcium outflux in the neuron                                   |
| \( calcium_{Neuro2} \) = \( k_{10} \times Ca_{Neuro} \) | Calcium induced NO                                              |
| \( NO_{cGMP} \) = \( k_{11} \times NO \) | NO induced cGMP                                                 |
| \( sink_{NO} \) = \( NO_{sink} \times NO \) | NO breakdown                                                    |
| \( v_{1_{HETE}} \) = \( k_{12} \times S1_{HETE} \) | Delay state reactions                                           |
| \( v_{2_{HETE}} \) = \( k_{13} \times S2_{HETE} \) | HETE breakdown                                                  |
| \( v_{3_{HETE}} \) = \( k_{14} \times S3_{HETE} \) | Delay state reactions                                           |
| \( HETE_{sink} \) = \( HETE \times sink_H \) | HETE breakdown                                                  |
| \( v_{1_{PG}} \) = \( k_{15} \times S1_{PG} \) | Delay state reactions                                           |
| \( v_{2_{PG}} \) = \( k_{16} \times S2_{PG} \) | PG breakdown                                                    |
| \( v_{3_{PG}} \) = \( k_{17} \times S3_{PG} \) | Delay state reactions                                           |
| \( PG_{sink} \) = \( PG \times sink_p \) | Delay state reactions                                           |
| \( v_{1_{EET}} \) = \( k_{18} \times S1_{EET} \) | Delay state reactions                                           |
| \( v_{2_{EET}} \) = \( k_{19} \times S2_{EET} \) | Delay state reactions                                           |
\[ v_3^{EET} = k_{20} \times S_3^{EET} \]
\[ EET_{sink} = EET \times \text{sink}_E \]

\[ v_1^{cGMP} = k_{21} \times S_1^{cGMP} \]
\[ v_2^{cGMP} = k_{22} \times S_2^{cGMP} \]
\[ v_3^{cGMP} = k_{23} \times S_3^{cGMP} \]
\[ cGMP_{sink} = cGMP \times \text{sink}_c \]

3.1.3 Variables

| Variable name | Variable unit | Variable value | Interpretation |
|---------------|---------------|----------------|----------------|
| \(k_{flow}\)  | 1/s           | \(k_{flow_{\text{glucose}}} + \text{stimulating} - \text{inhibiting}\) | Blood flow      |
| \(G_{body}\)  | amount        | 10             | Glucose in arterial blood |
| \(O_{2body}\) | amount        | 10             | Oxygen in arterial blood |
| \(oHb_{body}\)| amount        | 10             | Oxygenated hemoglobin in arterial blood |
| \(dHb_{body}\)| amount        | 10             | Deoxygenated hemoglobin in arterial blood |
| Stimulating   | 1/s           | \(b_1 \times cGMP + b_2 \times PG + b_3 \times \text{EET}\) | Vasodilation    |
| Inhibiting    | 1/s           | \(b_4 \times \text{HETE}\) | Vasoconstriction |
| \(Act\)       | 1/s           | \(b_1 \times cGMP + b_2 \times PG + b_3 \times \text{EET} - b_4 \times \text{HETE}\) | Signal substance effect on blood flow |
| \(\hat{y}\)   | unitless      | \(\frac{k_y \times oHb}{dHb}\) | Output signal   |
### 3.1.4 Parameters and parameter values

Parameter sets for model $M_{nm1}$ used in Fig. 8, Fig. 9 and Fig. 10.

| Parameter names       | Parameter unit     | p7 best opt intensity data | p7 best opt frequency data | p9 best opt intensity data | p9 best opt frequency data |
|-----------------------|--------------------|----------------------------|----------------------------|----------------------------|----------------------------|
| $k_y$                 | amount/s           | 1223.4987                  | 508.4496                   |                            |                            |
| $k_{metabolic}$       | 1/s                | 114.7037                   | 1153.8404                  |                            |                            |
| $k_{neurotrans}$      | 1/s                | 1104.2209                  | 116.0994                   |                            |                            |
| $k_1f$                | 1/s                | 177.3318                   | 1174.2658                  |                            |                            |
| $k_{1b}$              | 1/(amount×s)       | 1122.5565                  | 194.4418                   |                            |                            |
| $k_{basal}$           | 1/(amount×s)       | 91.3332                    | 1381.4508                  |                            |                            |
| $k_{flow_{glucose}}$  | 1/s                | 4.3346                     | 117.9462                   |                            |                            |
| proportion1           | oxygen/glucose metabolised | 2.4188                     | 5.6257                     |                            |                            |
| proportion2           | oxygen/glucose metabolised | 4.5876                     | 2.6729                     |                            |                            |
| sinkinput             | 1/s                | 1.1802                     | 4.6492                     |                            |                            |
| $k_{2}$               | 1/s                | 7.3947                     | 1.1401                     |                            |                            |
| $k_{3}$               | 1/s                | 4.1432                     | 3.7141                     |                            |                            |
| $k_{4}$               | 1/(amount×s)       | 2.0084                     | 4.0534                     |                            |                            |
| $k_{5}$               | amount/s           | 0.8885                     | 2.1437                     |                            |                            |
| $k_{6}$               | 1/s                | 3.5817                     | 0.9628                     |                            |                            |
| $k_{7}$               | amount/s           | 0.3491                     | 3.7232                     |                            |                            |
| $k_{8}$               | unitless           | 1.0228                     | 0.3676                     |                            |                            |
| $k_{9}$               | unitless           | 0.1718                     | 1.0583                     |                            |                            |
| $k_{10}$              | 1/s                | 5.8839                     | 0.1795                     |                            |                            |
| $k_{11}$              | 1/s                | 49.7049                    | 6.1628                     |                            |                            |
| $k_{12}$              | 1/s                | 0.5647                     | 118.5220                   |                            |                            |
| $k_{13}$              | 1/s                | 0.9208                     | 0.6189                     |                            |                            |
| $k_{14}$              | 1/s                | 485.3883                   | 1.0366                     |                            |                            |
| $k_{15}$              | 1/s                | 3481.4269                  | 583.7653                   |                            |                            |
| $k_{16}$              | 1/s                | 15170.2739                 | 1937.3654                  |                            |                            |
| $k_{17}$              | 1/s                | 0.9036                     | 10982.2259                 |                            |                            |
| $k_{18}$              | 1/s                | 1.0520                     | 0.9339                     |                            |                            |
| $k_{19}$              | 1/s                | 1.1249                     | 1.1366                     |                            |                            |
| $k_{20}$              | 1/s                | 350.7833                   | 1.1654                     |                            |                            |
| $k_{21}$              | 1/s                | 1609.9603                  | 592.9449                   |                            |                            |
| $k_{22}$              | 1/s                | 538.4678                   | 1805.0249                  |                            |                            |
| $k_{23}$              | 1/s                | 8.8579                     | 555.2464                   |                            |                            |
| $k_{m1}$              | amount             | 12.7144                    | 9.2642                     |                            |                            |
| $k_{m2}$              | amount             | 7.8886                     | 14.4421                    |                            |                            |
| $Ca_{Abas}$           | amount/s           | 9279.9419                  | 8.2545                     |                            |                            |
| $Ca_{Nbas}$           | amount/s           | 1.5455                     | 9828.1976                  |                            |                            |
| sinkGlu               | 1/s                | 0.9103                     | 1.6419                     |                            |                            |
|        |        |        |        |
|--------|--------|--------|--------|
| sink\(A\) | 1/s    | 3.2162 | 0.8607 |
| sink\(N\) | 1/s    | 0.6568 | 3.4898 |
| sink\(H\) | 1/s    | 19985.5644 | 0.6677 |
| sink\(P\) | 1/s    | 1.1195 | 19830.1832 |
| sink\(E\) | 1/s    | 49.1725 | 1.1691 |
| sink\(c\) | 1/s    | 3.8819 | 54.3174 |
| NO\(\text{sink}\) | 1/s  | 37.9614 | 4.0331 |
| PL | amount | 40.8202 | 38.1518 |
| \(b_1\) | 1/(amount\(\times\)s) | 16.5399 | 40.5355 |
| \(b_2\) | 1/(amount\(\times\)s) | 18.6399 | 20.9122 |
| \(b_3\) | 1/(amount\(\times\)s) | 4.8399 | 19.3131 |
| \(b_4\) | 1/(amount\(\times\)s) | 1223.4987 | 5.0147 |

Cost: \(p7 = 7.17, p9 = 11.24\).

3.1.5 Glucose metabolism in the model \(M\)_{nm1}

![Figure G](image.png)

Figure G: Simulated glucose metabolism in the model \(M\)_{nm1}.  

24
3.2 $M_{nm2}$ Model structure

$M_{nm1}$ is a minimized version of the model structure $M_{nm1}$.

3.2.1 Interaction graph

Fig. H: Interaction graph of the final model structure $M_{nm2}$. The model structure has two modules: the neurotransmitter module, which controls the blood flow, and the metabolic module, which controls the oxygen and glucose metabolism. Whole squares = states, dashed squares = variables (dependent on states), whole arrows = transformations, dashed arrows = interactions, green area = astrocyte, blue area = neuron, grey area = blood. All states starting with "delay" and a number (e.g. delay2) are delay states. Stimulus is the input to the model. Stimulus = input signal. $\text{OHb}$ and $d\text{Hb}$ are oxyhemoglobin and deoxyhemoglobin, respectively. Glu = glucose, Calcium neuron and calcium astrocyte = calcium ion ($Ca^{2+}$) level in the cell, AA = arachidonic acid. All terms starting with k (e.g. k1) are parameters and in most cases represent rate constants. PL is a parameter representing phospholipase A2, which is present in abundance. Gbody, O2body, $\text{OHbbody}$ and $d\text{Hbbody}$, are variables representing the glucose, oxygen and hemoglobin delivered into the area. "Constrict" and "dilate" are states representing the vasoactive substances which control the blood flow.
### 3.2.2 States and reactions

| State                              | Interpretation                                                                 | Steady state value: p8 best opt intensity | Steady state value: p10 best opt frequency |
|------------------------------------|-------------------------------------------------------------------------------|-----------------------------------------|-------------------------------------------|
| $\frac{d(stimulus)}{dt}$ = 0       | Stimulus input signal                                                         | 1                                       | 1                                         |
| $\frac{d(oHb)}{dt}$ = $v_1b - v_1f + v_{inOHB} - v_{outOHB}$ | Change in oxyhemoglobin level                                                 | 3.76                                    | 3.28                                      |
| $\frac{d(dHb)}{dt}$ = $v_1f - v_1b + v_{indHb} - v_{outHb}$ | Change in deoxyhemoglobin level                                               | 16.24                                   | 16.72                                     |
| $\frac{d(O2)}{dt}$ = $v_1f - v_1b - v_{basal} \times proportion_1 - v_{stim} \times proportion_2 + v_{inO} - v_{outO}$ | Change in oxygen level                                                        | 0.77                                    | 0.71                                      |
| $\frac{d(glucose)}{dt}$ = $v_{inG} - v_{outG} - v_{basal} - v_{stim}$ | Change in glucose level                                                       | 8.19                                    | 8.14                                      |
| $\frac{d(inputDelay)}{dt}$ = $input_1 - sink_{input}$ | Delay state                                                                  | $-4.86 \times 10^{-15}$               | $-1.00 \times 10^{-16}$                   |
| $\frac{d(glu)}{dt}$ = $input_2 - glu_{sink}$ | Glutamate release in the synaptic cleft                                       | $-2.53 \times 10^{-17}$               | $-6.09 \times 10^{-19}$                   |
| $\frac{d(Ca_{Astro})}{dt}$ = Glutamate_{Astro} - calcium_{Astro1} + Ca_{bas} | Calcium influx in the astrocyte                                               | 27.71                                   | 10.09                                     |
| $\frac{d(AA)}{dt}$ = calcium_{Astro2} - (AA_{i} + AA_{r}) | Change in AA level                                                           | 386.51                                  | 124.27                                    |
| $\frac{d(constrict)}{dt}$ = delay_{3c} - sink_{c} | Delay states                                                                 | 472.80                                  | 91.66                                     |
| $\frac{d(delay1c)}{dt}$ = AA_{i} - delay_{1c} |                                                                           | 50.49                                   | 10.79                                     |
| $\frac{d(delay2c)}{dt}$ = delay_{1c} - delay_{2c} |                                                                           | 540.77                                  | 150.93                                    |
| $\frac{d(delay3c)}{dt}$ = delay_{2c} - delay_{3c} |                                                                           | 814.2                                   | 179.00                                    |
| $\frac{d(dilate)}{dt}$ = delay_{3d} - sink_{d} | Delay states                                                                 | 210.92                                  | 96.019                                    |
| $\frac{d(delay1d)}{dt}$ = AA_{r} - delay_{1d} |                                                                           | 455.61                                  | 143.60                                    |
| $\frac{d(delay2d)}{dt}$ = delay_{1d} - delay_{2d} |                                                                           | 280.27                                  | 135.65                                    |
| $\frac{d(delay3d)}{dt}$ = delay_{2d} - delay_{3d} |                                                                           | 216.58                                  | 57.206                                    |
| Reactions | Interpretation |
|-----------|----------------|
| $v_1 = k_1 \times oHb$ | Rate of releasing oxyhemoglobin into oxygen and deoxyhemoglobin |
| $v_1 = k_1 \times dHb \times O_2$ | Rate of binding oxygen and deoxyhemoglobin into oxyhemoglobin |
| $v_{inOHb} = oHb_{body} \times k_{flow}$ | Oxyhemoglobin influx |
| $v_{outOHb} = oHb \times k_{flow}$ | Oxyhemoglobin outflux |
| $v_{inDHB} = dHb_{body} \times k_{flow}$ | Deoxyhemoglobin influx |
| $v_{outDHB} = dHb \times k_{flow}$ | Deoxyhemoglobin outflux |
| $v_{inG} = G_{body} \times k_{flow}$ | Glucose influx |
| $v_{outG} = g_{glucose} \times k_{flow}$ | Glucose outflux |
| $v_{inO_2} = O_2_{body} \times k_{flow}$ | Oxygen influx |
| $v_{outO_2} = O_2 \times k_{flow}$ | Oxygen outflux |
| $v_{basal} = k_{basal} \times O_2^{proportion_{1}} \times g_{glucose}$ | Basal metabolism |
| $v_{stim} = inputDelay \times O_2^{proportion_{2}} \times g_{glucose}$ | Metabolism during stimulation |
| input$_1 = k_{metabolic} \times stimulus$ | Stimulus input to the metabolic module |
| input$_2 = k_{neurotransmitter} \times stimulus$ | Stimulus input to the neurotransmitter module |
| glu$_{sink} = glu \times sink_{glu}$ | Glutamate breakdown |
| Glutamate$_A = k_2 \times glu$ | Calcium influx into the cells |
| calcium$_{Astro1} = C_Astrotro \times sink_A$ | Calcium outflux from the cells |
| calcium$_{Astro2} = P_L \times C_Astrotro \times k_4$ | Calcium inducing AA |
| sink$_c = constriict \times sink_{con}$ | Breakdown of vasoconstricting substances |
| sink$_d = dilate \times sink_{Dil}$ | Breakdown of vasodilating substances |
| AA$_1 = k_5 \times AA$ | AA triggering vasoconstricting substances |
| AA$_s = k_7 \times AA$ | AA triggering vasodilating substances |
| delay$_1 = k_{delay1} \times delay1_s$ | Delay states |
| delay$_2 = k_{delay2} \times delay2_s$ | Delay states |
| delay$_3 = k_{delay3} \times delay3_s$ | Delay states |
| delay$_1 = k_{delay1} \times delay1_i$ | Delay states |
| delay$_2 = k_{delay2} \times delay2_i$ | Delay states |
| delay$_3 = k_{delay3} \times delay3_i$ | Delay states |
### 3.2.3 Variables

| Variable name | Variable unit | Variable value | Interpretation |
|---------------|---------------|----------------|----------------|
| $k_{flow}$    | 1/s           | $k_{flow02} + \text{stimulating} - \text{inhibiting}$ | Blood flow |
| $G_{body}$    | amount        | 10             | Glucose in arterial blood |
| $O_{2body}$   | amount        | 10             | Oxygen in arterial blood |
| $oHb_{body}$  | amount        | 10             | Oxygenated hemoglobin in arterial blood |
| $dHb_{body}$  | amount        | 10             | Deoxygenated hemoglobin in arterial blood |
| Stimulating   | 1/s           | $b_1 \times \text{dilate}$ | Vasodilation |
| Inhibiting    | 1/s           | $b_2 \times \text{constrict}$ | Vasoconstriction |
| $\hat{y}$     | unitless      | $\frac{k_y \times oHb}{dHb}$ | Output signal |
3.2.4 Parameters and parameter values
Parameter sets for model $M_{nm1}$ used in Fig. 9 and Fig. 10.

| Parameter names | Parameter unit | $p8$ best opt intensity data | $p10$ best opt frequency data |
|-----------------|----------------|-------------------------------|-------------------------------|
| $k_y$           | unitless       | 3327.7279                     | 3177.2096                     |
| $k_{metabolic}$ | 1/s            | 2425.3854                     | 13592.202                     |
| $k_{neurotrans}$| 1/s            | 140.35                        | 195.9126                      |
| $k_{f}$         | 1/s            | 2289.8029                     | 6996.381                      |
| $k_{b}$         | 1/(amount×s)   | 38.0878                       | 72.7303                       |
| $k_{basal}$     | 1/(amount×s)   | 4751.4719                     | 8097.4782                     |
| $k_{flow_{glucose}}$ | amount/s    | 524.89                        | 1275.8673                     |
| proportion1      | oxygen/gluco| 8.6087                        | 8.5580                        |
| proportion2      | oxygen/gluco| 3.8694                        | 3.8495                        |
| sink_{input}    | 1/s            | 0.6735                        | 4.5253                        |
| $k_{2}$          | 1/s            | 0.4703                        | 0.7295                        |
| $k_{4}$          | 1/(amount×s)   | 0.9977                        | 1.2737                        |
| $k_{5}$          | 1/s            | 0.5446                        | 0.7809                        |
| $k_{7}$          | 1/s            | 0.6699                        | 0.5886                        |
| $C_{A_{bas}}$    | 1/s            | 14.8381                       | 20.5285                       |
| sink_{glu}      | 1/s            | 6.4284                        | 12.5502                       |
| sink_{A}        | 1/s            | 1.4713                        | 0.7409                        |
| sink_{Con}      | 1/s            | 0.7384                        | 0.6384                        |
| sink_{Dil}      | 1/s            | 1.4552                        | 1.0505                        |
| k_{delay1s}     | 1/s            | 0.867                         | 1.0787                        |
| k_{delay2s}     | 1/s            | 0.5797                        | 0.4994                        |
| k_{delay3s}     | 1/s            | 0.6137                        | 0.81178                       |
| k_{delay1i}     | 1/s            | 6.2735                        | 5.9784                        |
| k_{delay2i}     | 1/s            | 0.4484                        | 0.5582                        |
| k_{delay3i}     | 1/s            | 0.3781                        | 0.3707                        |
| PL              | amount         | 15                            | 15                            |
| $b_{1}$         | 1/(amount×s)   | 30.379                        | 41.1749                       |
| $b_{2}$         | 1/(amount×s)   | 13.2335                       | 12.9425                       |

Cost: $p8 = 27.5$ and $p10 = 18.8$