



ISSN: 2744-6204  
Published 21 Dec 2022

# Reproducibility Study for a Computational Model of the Neurovascular Coupling Unit

Sergio Dempsey<sup>1</sup>, Gunnar Cedersund<sup>2</sup>, Maria Engström<sup>3,4</sup>, Gonzalo Maso Talou<sup>1</sup>, and Soroush Safaei<sup>1\*</sup>

<sup>1</sup>Auckland Bioengineering Institute, University of Auckland, New Zealand

<sup>2</sup>Department of Biomedical Engineering, Linköping University, Linköping, Sweden

<sup>3</sup>Department of Health, Medicine and Caring Sciences, Linköping University, Linköping, Sweden

<sup>4</sup>Center for Medical Image Science and Visualization, Linköping University, Linköping, Sweden

## ORIGINAL

### Abstract

The mechanistic model of neurovascular coupling was developed and studied by Sten et al. (2020). This model describes and predicts the arteriolar dilation data of mice under various stimulations while anaesthetised and awake. We reconstructed the model in CellML, using a modular approach for each neuronal pathway, and successfully reproduced the original experiments (see the figures in this article and Sten et al. (2020)). With the success of the result reproduction, the CellML model can now be injected into other OpenCOR workflows to obtain a mechanistic hemodynamic response function of neurovascular coupling arteriolar dilation.

Keywords: CellML; neurovascular coupling; anaesthesia; reproducibility

### Curated Model Implementation

<https://doi.org/10.36903/physiome.21714863>

### Primary Publications

S. Sten, F. Elinder, G. Cedersund, and M. Engström. A quantitative analysis of cell-specific contributions and the role of anesthetics to the neurovascular coupling. *NeuroImage*, 215, 7 2020. ISSN 10959572. doi: 10.1016/j.neuroimage.2020.116827.

## OPEN ACCESS

### Reproducible Model

Edited by

David P. Nickerson

Curated by

Leyla Noroozbabae

\*Corresponding author

soroush.safaei

@auckland.ac.nz

Submitted 14 Sep 2022

Accepted 12 Dec 2022

Citation

Dempsey et al. (2022)

Reproducibility Study for a

Computational Model of the

Neurovascular Coupling

Unit. *Physiome*.

doi: 10.36903/physi-

ome.21714863

## 1 Introduction

Neurovascular coupling (NVC) is the cerebral pathway to modulate blood flow by manipulating local vascular tone (Iadecola, 2017; Schaeffer and Iadecola, 2021). This modulation is required based on the metabolic demand of the tissue, and its impairment can lead to neurodegeneration and cognitive disease (Sweeney et al., 2019; Iadecola and Gottesman, 2019). To prevent this impairment, we need a detailed understanding of the mechanisms of the NVC unit. In line with this goal, researchers have developed mechanistic mathematical models of NVC (Hart et al., 2019; Sten et al., 2020) based on experiment. The mechanistic hemodynamic response functions (HRF) of the models under various stimulations are then tested against *in vivo* experiments. With success, the model is then used to explore other core predictions produced increasing our knowledge of NVC and motivating further study. The model presented in Sten et al. (2020) considers GABAergic interneurons for the first time and is capable of accurately modelling arteriolar dilation data from mice under awake and anaesthetised conditions, as reported by Uhlirova et al. (2016).

Here, we present a CellML version of the model using the system of equations described in Sten et al. (2020) without modifications. Our CellML implementation is modular, allowing future studies to import separate pyramidal (Pyr), GABAergic Nitric Oxide (NO) and GABAergic Neuropeptide

Y (NPY) control. With this model, our objective is to reproduce all steady-state variables that optimise arteriolar dilation results in [Sten et al. \(2020\)](#). We omit the reproduction of confidence intervals generated by Markov Chain Monte Carlo (MCMC) simulations, since the goal is model reproducibility and reusability, not evaluation of model fidelity or sensitivity, as provided in the primary publication ([Sten et al., 2020](#)).

The proposed CellML implementation can be run in OpenCOR<sup>1</sup> and Python software, extending the implementation of the primary publication in MATLAB R2017b. This implementation enables more researchers to access the model.

## 2 Model Description

### 2.1 Primary Publication

The model of [Sten et al. \(2020\)](#) is a mechanistic model of neurovascular coupling that begins with neuronal stimulation and ends with modulation of arterial tone. The model was designed based on the iterative philosophy of systems biology, which allows quantitative experimental data to drive model development and improvement. If a proposed model can capture experimental data and is physiologically sound, then the model is accepted.

At times, an accepted model may be cumbersome due to the number of parameters and the complexity of the system. In these instances, complexity can be reduced if the model is minimised. This is the process of removing parts of the model and re-optimising to the data. This continues until the minimised model can no longer capture the data with confidence ([Lundengård et al., 2016](#)). The model presented in the primary publication is a minimised systems biology model. Interpretations of state variables can be made, but it is important to recognise that potentially multiple processes with similar responses may be lumped into one set of equations.

The model is divided into three sections, neuronal, intracellular, and vascular. In the neuronal section, each type of neuron (pyramidal, GABAergic NO, and GABAergic NPY) can receive stimulation that increases their activity. This activity can activate the other two neurons in the case of pyramidal activation or inhibit activity in the case of GABAergic interneurons. In the respective signalling pathways of neurons, activity stimulates depolarisation and a subsequent increase in calcium that activates the signalling pathway to produce vasodilatory (pyramidal and GABAergic NO pathways) or vasoconstrictive (GABAergic NPY path) factors. These final three outputs are collected and summed with respective weighting coefficients to simulate the response of the vessel. The readers are referred to the primary publication for complete details of the model ([Sten et al., 2020](#)).

The model contains a total of 13 coupled ODEs based on mass-action, or Michaelis-Menten kinetics. The original model was implemented in MATLAB 2017b and used the third-party package AMICI<sup>2</sup> to run the CVODES solver. The model was optimised using MCMC methods provided by the MEIGO<sup>3</sup> and PESTO<sup>4</sup> packages. The scripts to run the original model are provided in the supplementary material of [Sten et al. \(2020\)](#).

### 2.2 CellML Model

The structure of the model is built following recommended CellML best practises (see [Figure 1](#)). This includes modularisation of the pyramidal, GABAergic NO and GABAergic NPY neuronal signalling pathways for best combined prediction or separate use. Best practises also encourage the separation of model mathematics and parameters so that one model can handle various parameter sets. For this model, the parameters simulate different neuronal dynamics. Examples that will impact neuronal dynamics include the type of stimulation, the conditions of the experiment (anaesthesia), and the genetic modulation that manifests itself as coefficient modification. We have achieved these criteria, as well as reduced the number of input parameters by including a

---

<sup>1</sup><https://opencor.ws/>

<sup>2</sup><https://github.com/AMICI-dev/AMICI>

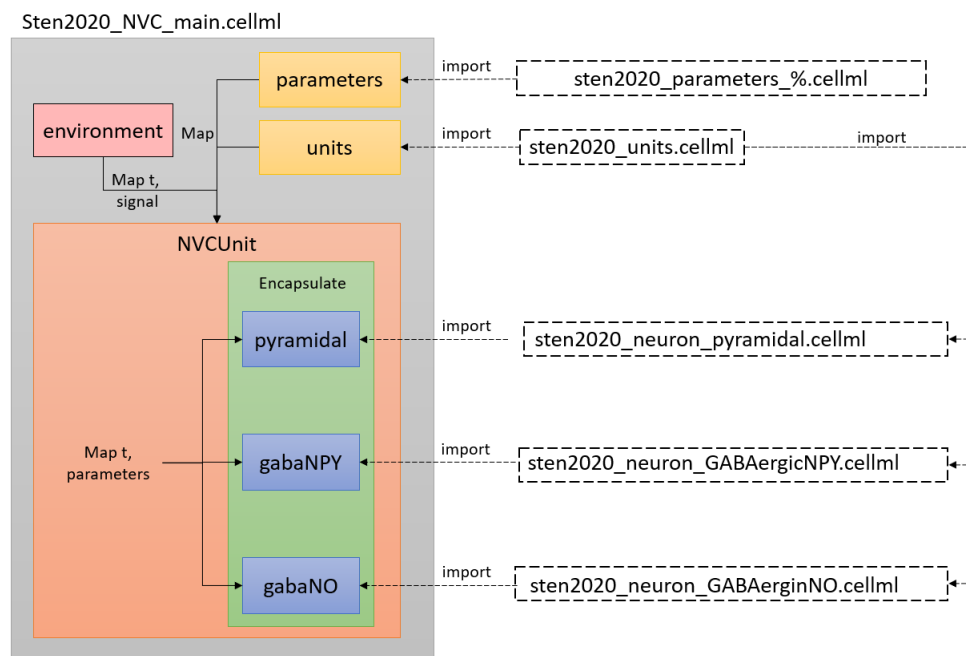
<sup>3</sup>[https://bitbucket.org/jrbanga\\_/meigo64/src/master/](https://bitbucket.org/jrbanga_/meigo64/src/master/)

<sup>4</sup><https://github.com/ICB-DCM/PESTO>

toggle for anaesthesia versus awake conditions in our parameter files. This is a benefit compared to the five separate models required in the primary publication. This simplification also reduces the toll of scripts, allowing users to run different scenarios by only altering the set of parameters. To reproduce all results, only six parameters in the parameters file need to be modified. These six parameters define the start and stop times for stimulation, whether the unit is “awake” or “anaesthetised”, and finally the stimulation scaling constants are discussed in detail in the primary publication.

The CellML model was executed with the optimised rate constants and other parameters tabulated in the supplementary material of the primary publication. These values are rounded from what was optimised in the original code; differences if any, will be discussed in the results. The CellML model is initialised using steady-state values from its own simulation run for 500 seconds and not from the tabulated in the supplementary material. This accounts for any steady-state result errors that may have been caused by rounding. Again, the differences will be discussed in the results.

This model will be used to reproduce Figures 3, 5 and 6 of the primary publication.



**Figure 1.** Arrangement of the model showing the CellML scripts involved. Sten2020\_NVC\_main.cellml imports components from the other scripts and constructs the model through mapping of variables between components.

### 2.3 Clarifications and Modifications

In Figure 3 of the primary publication, the stimulation windows are shown in each graph, but the exact timing of neuronal stimulation is not presented in the manuscript or the supplementary materials. It is presented in the code, which we tabulate here for clarity.

In the reproduction of Figure 5c, the label in  $\Delta v_1 = 1$  is  $V_{\max}$ ; however, the normalisation to reproduce this plot followed Equation 1 below, which means  $1 \equiv V_{\max} - v_1^{\text{SteadyState}}$ .

$$\Delta v_1 = \frac{\frac{V_{\max} NPY(t)}{K_M + NPY(t)} - v_1^{\text{SteadyState}}}{V_{\max} - v_1^{\text{SteadyState}}} \quad (1)$$

$$v_1^{\text{SteadyState}} = \frac{V_{\max} NPY_{\text{SteadyState}}}{K_M + NPY_{\text{SteadyState}}} \quad (2)$$

**Table 1.** Stimulation times to reproduce figures.

Figure # (Primary)	Model Conditions	Stimulation Start Time (sec)	Stimulation Length (sec)
Figure 3	Awake-Sensory Stim	0	1
	Awake-Optogenetic (GABAergic)	0	0.4
	Anesthesia-Sensory	0	2
	Anesthesia-Optogenetic (GABAergic)	0.55	0.45
	Anesthesia-Optogenetic (Pyramidal)	0.9	0.1
Figure 5/6	Awake-Optogenetic (GABAergic)	0	0.4
	Anesthesia-Optogenetic (GABAergic)	0	0.45

Finally, to reproduce the plot data in Figure 6 of the primary publication, the first row of the plots corresponding to the neuronal activity of the NPY and NO pathways is not normalised as suggested in the primary publication. We have changed the title to “Cell Activity”, which is unitless.

### 3 Model Execution

The results were generated using the 2022-05-31 snapshot of OpenCOR (Garny and Hunter, 2015) and MATLAB R2021a to produce the plots (Mat, 2021). The MATLAB code requires software newer than R2019b. The entire code is available at <https://models.physiomeproject.org/workspace/8a2>. To generate results, follow this step-wise procedure for each parameter set named in Table 2.

**Table 2.** Parameter set names

Start Text	Simulation Tag (%%)	End Text
sten2020_parameters_	Fig3A	.cellml
	Fig3B	.cellml
	Fig3C	.cellml
	Fig3D	.cellml
	Fig3E	.cellml
	Fig5and6_Ana	.cellml
	Fig5and6_Awake	.cellml

#### 3.1 Step1: Load parameters

Open `sten2020_NVC_main.cellml` and on line 24 alter the parameter name to any of the tags (%%) in Table 2. All parameter filenames are in the same location as the main function and follow the naming of the figure to be reproduced from the primary publication.

#### 3.2 Step2: Simulation Parameters

The equations were solved using the CVODE solver with a maximum timestep-size equal to 0.01. The model is already initialised in steady state. All run times are 50 seconds with a timestep of 0.01 seconds.

#### 3.3 Step3: Export

When the simulation is complete, export all the data to .csv. Use the default name `sten2020_NVC_main_data.csv` but amend the parameter case (%%) to the end as shown `sten2020_NVC_main_data_%%.csv`. Place each csv file into an <Output CSVs> folder in the workspace. This is filled with the results by default.

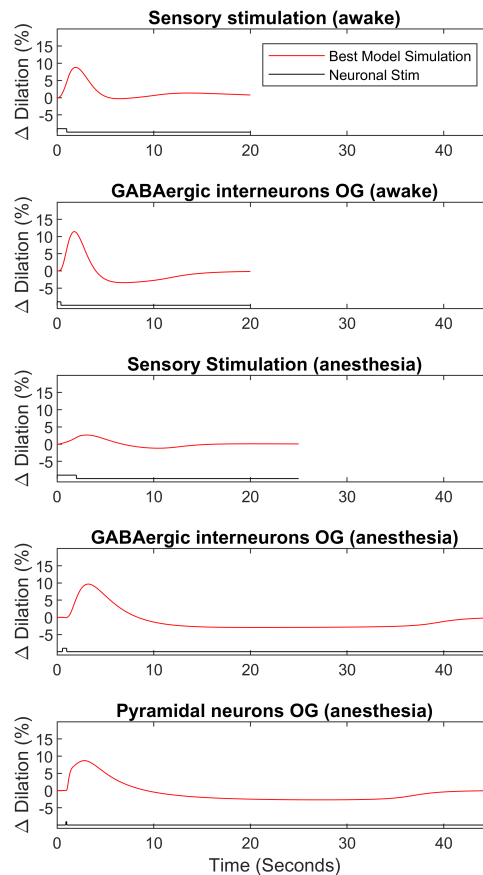
### 3.4 Step4: Generate Plots

To reproduce the figures, run the chosen Matlab function in the folder <MatlabFiles> from within its directory. The name of the script corresponds to the figure it produces; for example, running Figure3.m will produce Figure 3 in the primary publication.

## 4 Model Results

Starting with steady-state values, only 3 values were not identical to those published in the supplementary material of the primary publication. The steady-state values for arachidonic acid, NO, and  $\text{NO}_{\text{vsm}}$  were 6.224, 2944.421, and 352.127 in the CellML model and 6.226, 2944.636, and 352.139 in the primary publication; all differences are less than 0.01%. This led us to conclude that using the rounded numbers was safe to continue with figure reproduction.

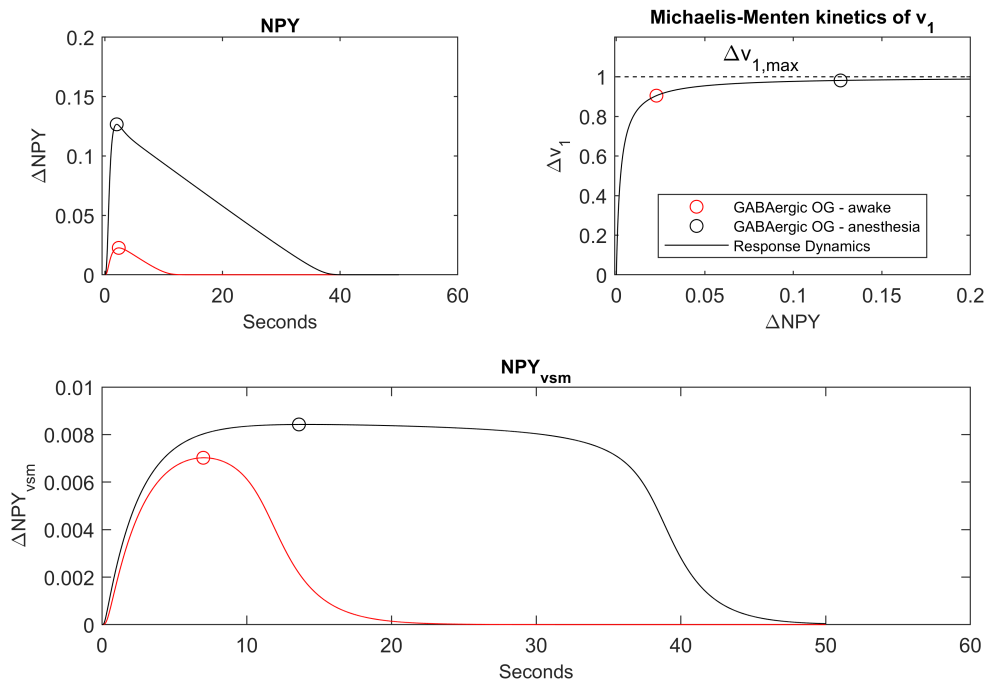
The first figure reproduced is Figure 3 of the primary publication shown in Figure 2. In this figure, the results of arterial dilation are shown for 5 different stimulus cases. The parameters used to produce this graph come from the best-fit parameters in the primary publication. All subplots agree with the primary publication.



**Figure 2.** Best estimated model simulation of arteriolar dilation to sensory or optogenetic stimulation in awake and anesthetised mice. This figure matches the subfigures B-D-F-H-J of Figure 3 in the primary publication and can be reproduced using Figure3.m file.

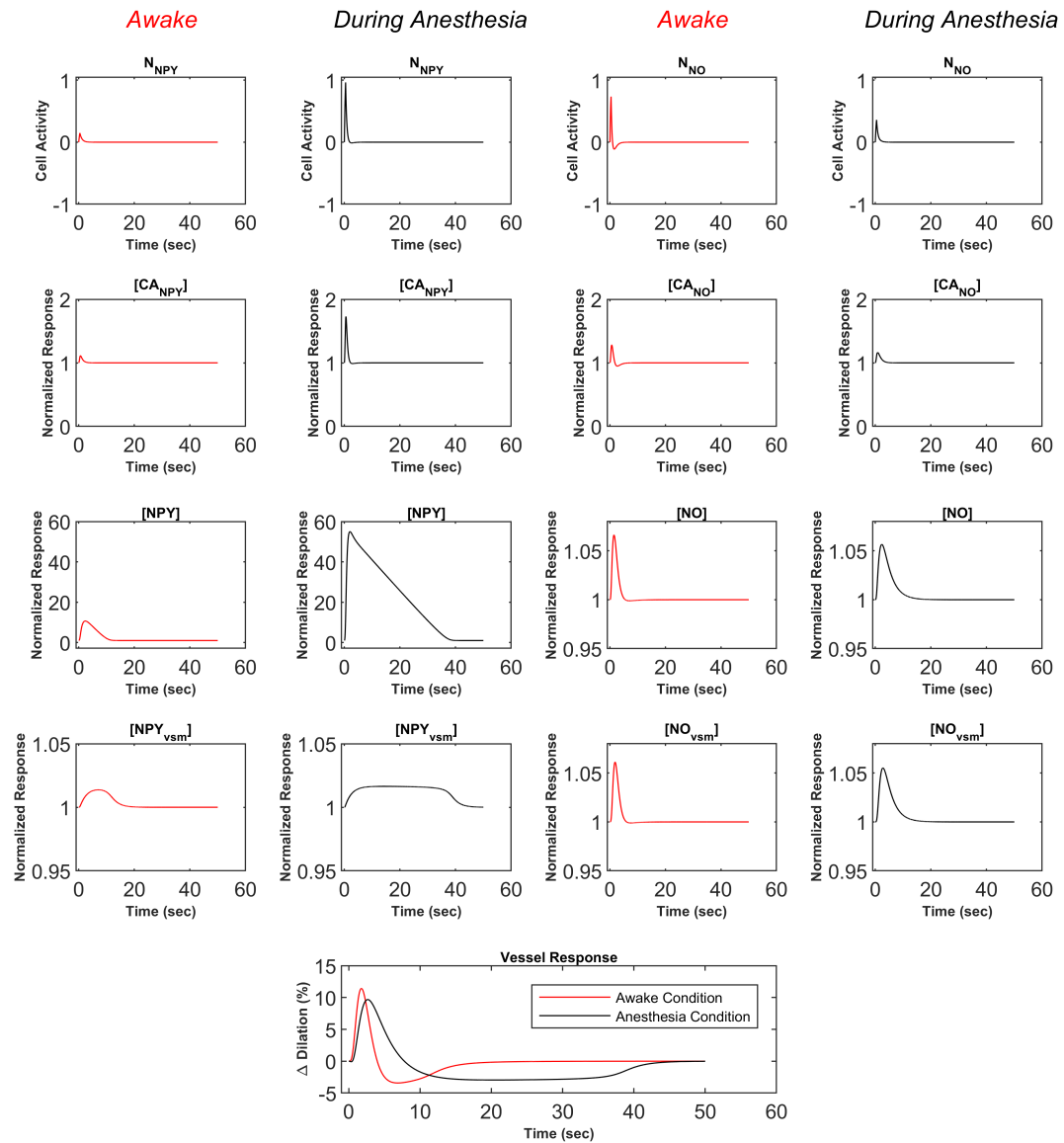
The second figure reproduced is Figure 5 of the primary publication shown in Figure 3. This figure emphasises the impact of using Michaelis-Menten kinetics for the production of NPY in vascular smooth muscle (vsm). All subplots agree with the primary publication.

The last reproduced figure is Figure 6 of the primary publication shown in Figure 4. This figure shows the difference in all state variables of the GABAergic NO and NPY pathways for awake and anaesthetised conditions, highlighting that the prolonged undershoot of the anaesthetic response



**Figure 3.** NPY response from optogenetic stimulation of GABAergic interneurons in awake and anesthetised mice. (top left) Change in NPY from baseline steady state for awake and anesthetised optogenetic GABAergic stimulation. (top right) Change in rate of NPY<sub>vsm</sub> production as a function of NPY produced from baseline showing minor changes in rate for large increases in production in anesthetised vs awake conditions. (bottom) Change in NPY<sub>vsm</sub> over time for anesthetised and awake stimulation. This figure matches the subfigures B-C-D of Figure 5 in the primary publication and can be reproduced using Figure5.m file.

is due to the Michaelis-Menten kinetics of  $\text{NPY}_{\text{vsm}}$ . It also shows the impact of NO and its initial vasodilatory effect. For a complete interpretation and all acronyms, see the primary publication. All sub-plots agree with the primary publication.



**Figure 4.** Complete presentation of the NO and NPY state variables for optogenetic stimulation of GABAergic interneurons in awake (red) and anesthetised (black) mice. This figure matches Figure 6 in the primary publication and can be reproduced using Figure6.m file.

## 5 Discussion

In this paper, we present the CellML version of an NVC model originally developed by Sten et al. (2020) for NVC. Our implementation is modular and can be tuned to many coupling scenarios without the main code modification. Figures illustrating the model predictions from the primary publication were produced without error, and only minor clarifications are made to the titles in the primary publication's figures.

## References

A. Garny and P. J. Hunter. Opencor: a modular and interoperable approach to computational biology. *Frontiers in Physiology*, 6, 2 2015. ISSN 1664-042X. doi: 10.3389/fphys.2015.00026.

- J. L. Hart, P. A. Gremaud, and T. David. Global sensitivity analysis of high-dimensional neuroscience models: An example of neurovascular coupling. *Bulletin of Mathematical Biology*, 81:1805–1828, 6 2019. ISSN 15229602. doi: 10.1007/s11538-019-00578-0.
- C. Iadecola. The neurovascular unit coming of age: A journey through neurovascular coupling in health and disease. *Neuron*, 96:17–42, 9 2017. ISSN 10974199. doi: 10.1016/j.neuron.2017.07.030.
- C. Iadecola and R. F. Gottesman. Neurovascular and cognitive dysfunction in hypertension. *Circulation Research*, 124:1025–1044, 3 2019. ISSN 0009-7330. doi: 10.1161/CIRCRESAHA.118.313260. URL <https://www.ahajournals.org/doi/10.1161/CIRCRESAHA.118.313260>.
- K. Lundengård, G. Cedersund, S. Sten, F. Leong, A. Smedberg, F. Elinder, and M. Engström. Mechanistic mathematical modeling tests hypotheses of the neurovascular coupling in fmri. *PLoS Computational Biology*, 12, 6 2016. ISSN 15537358. doi: 10.1371/journal.pcbi.1004971.
- MATLAB version 9.10.0.1613233 (R2021a)*. The Mathworks, Inc., Natick, Massachusetts, 2021.
- S. Schaeffer and C. Iadecola. Revisiting the neurovascular unit. *Nature Neuroscience*, 24:1198–1209, 9 2021. ISSN 15461726. doi: 10.1038/s41593-021-00904-7.
- S. Sten, F. Elinder, G. Cedersund, and M. Engström. A quantitative analysis of cell-specific contributions and the role of anesthetics to the neurovascular coupling. *NeuroImage*, 215, 7 2020. ISSN 10959572. doi: 10.1016/j.neuroimage.2020.116827.
- M. D. Sweeney, A. Montagne, A. P. Sagare, D. A. Nation, L. S. Schneider, H. C. Chui, M. G. Harrington, J. Pa, M. Law, D. J. J. Wang, R. E. Jacobs, F. N. Doubal, J. Ramirez, S. E. Black, M. Nedergaard, H. Benveniste, M. Dichgans, C. Iadecola, S. Love, P. M. Bath, H. S. Markus, R. A. Salman, S. M. Allan, T. J. Quinn, R. N. Kalaria, D. J. Werring, R. O. Carare, R. M. Touyz, S. C. R. Williams, M. A. Moskowitz, Z. S. Katusic, S. E. Lutz, O. Lazarov, R. D. Minshall, J. Rehman, T. P. Davis, C. L. Wellington, H. M. González, C. Yuan, S. N. Lockhart, T. M. Hughes, C. L. H. Chen, P. Sachdev, J. T. O'Brien, I. Skoog, L. Pantoni, D. R. Gustafson, G. J. Biessels, A. Wallin, E. E. Smith, V. Mok, A. Wong, P. Passmore, F. Barkof, M. Muller, M. M. B. Breteler, G. C. Román, E. Hamel, S. Seshadri, R. F. Gottesman, M. A. Buchem, Z. Arvanitakis, J. A. Schneider, L. R. Drewes, V. Hachinski, C. E. Finch, A. W. Toga, J. M. Wardlaw, and B. V. Zlokovic. Vascular dysfunction—the disregarded partner of alzheimer’s disease. *Alzheimer’s & Dementia*, 15:158–167, 1 2019. ISSN 1552-5260. doi: 10.1016/j.jalz.2018.07.222. URL <https://onlinelibrary.wiley.com/doi/10.1016/j.jalz.2018.07.222>.
- H. Uhlirva, K. Kılıç, P. Tian, M. Thunemann, M. le Desjardins, P. A. Saisan, C. Mateo, Q. Cheng, K. L. Weldy, F. Razoux, M. Vandenberghe, J. A. Cremonesi, C. G. Ferri, K. Nizar, V. B. Sridhar, T. C. Steed, M. Abashin, Y. Fainman, E. Masliah, S. Djurovic, O. A. Andreassen, G. A. Silva, D. A. Boas, D. Kleinfeld, R. B. Buxton, G. T. Einevoll, A. M. Dale, and A. Devor. Cell type specificity of neurovascular coupling in cerebral cortex. *eLife*, 5, 2016. doi: 10.7554/eLife.14315.001.



**Reproducibility report for:** Reproducibility Study for a Computational Model of the Neurovascular Coupling Unit  
**Submitted to:** *Physiome*  
**Manuscript identifier:** S000020

**Curation outcome summary:** Successfully reproduced all the figures presented in this manuscript.

**Box 1: Criteria for repeatability and reproducibility**

**■ Model source code provided:**

■ Source code: a standard procedural language is used (e.g. MATLAB, Python, C)

- There are details/documentation on how the source code was compiled
- There are details on how to run the code in the provided documentation
- The initial conditions are provided for each of the simulations
- Details for creating reported graphical results from the simulation results

■ Source code: a declarative language is used (e.g. SBML, CellML, NeuroML)

- The algorithms used are defined or cited in previous articles
- The algorithm parameters are defined
- Post-processing of the results are described in sufficient detail

**Executable model provided:**

- The model is executable without source (e.g. desktop application, compiled code, online service)
- There are sufficient details to repeat the required simulation experiments

**■ The model is described mathematically in the article(s):**

- Equations representing the biological system
- There are tables or lists of parameter values
- There are tables or lists of initial conditions
- Machine-readable tables of parameter values
- Machine-readable tables of initial conditions

**■ The simulation experiments using the model are described mathematically in the article:**

- Integration algorithms used are defined
- Stochastic algorithms used are defined
- Random number generator algorithms used are defined
- Parameter fitting algorithms are defined
- The paper indicates how the algorithms yield the desired output



### Box 2: Criteria for accessibility

- Model/source code is available at a public repository or researcher's web site
  - Prohibitive license provided
  - Permissive license provided
  - Open-source license provided
- All initial conditions and parameters are provided
- All simulation experiments are fully defined (events listed, collection times and measurements specified, algorithms provided, simulator specified, etc.)

### Box 3: Rules for Credible practice of Modeling and Simulation<sup>a</sup>

<sup>a</sup>Model credibility is assessed using the Interagency Modeling and Analysis Group conformance rubric:  
<https://www.imagwiki.nibib.nih.gov/content/10-simple-rules-conformance-rubric>

- Define context clearly: Extensive
- Use appropriate data: Extensive
- Evaluate within context: Extensive
- List limitations explicitly: Insufficient
- Use version control: Extensive
- Document adequately: Extensive
- Conform to standards: Extensive

### Box 4: Evaluation

- Model and its simulations could be repeated using provided declarative or procedural code
- Model and its simulations could be reproduced

**Summary comments:** Model and source code are available in the associated OMEX archive. This was used in our attempt to reproduce the results presented in the paper. We successfully ran the CellML and Matlab files provided to simulate and reproduce Figure 1 - Figure 3 as presented in this manuscript.



Anand K. Rampadarath<sup>1</sup>, PhD  
Curator at Center for Reproducible Biomedical Modeling

---

<sup>1</sup>Contact: [info@reproduciblebiomodels.org](mailto:info@reproduciblebiomodels.org)