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Reproducibility Study of Computational Modelling of Glucose Uptake by SGLT1 and GLUT2 in the Enterocyte

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ORIGINAL

Abstract

Afshar et al. (2021) generated a computational model of non-isotonic glucose uptake by small intestinal epithelial cells. The model incorporates apical uptake via SGLT1 and GLUT2, basolateral efflux into the blood via GLUT2 and cellular volume changes in response to non-isotonic conditions. The results explain more about the role of apical GLUT2 in intestinal cell glucose absorption. Here, we used the CellML file provided by the model authors, together with SED-ML files and Python scripts, to demonstrate the reproduction of the figures in the original paper by using the associated model.

Keywords: Physiome; CellML; OpenCOR; reproducibility; glucose uptake; water transport; SGLT1; GLUT2; ion channels.

Curated Model Implementation
http://doi.org/10.36903/physiome.21708179

Primary Publications

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1 Introduction

Glucose absorption through epithelial cells in the small intestine is known to be the main source of energy generation in humans and other species. Despite the number of investigations in recent decades (McCance and Madders, 1930; Wertheimer, 1934), the absorption mechanism and transporters involved under different conditions and in different species are still not clear enough and are being debated (Karasov, 2017).

In 2019, Afshar et al. implemented a glucose absorption model in the enterocyte that contains all responsible transporters and was built using the CellML framework. Their model was used to study the role of SGLT1 and apical GLUT2, especially in the presence of a high glucose concentration in the intestinal lumen (Afshar et al., 2019). They later extended their model to a non-isotonic glucose uptake considering water transport and changes in cell volume during the absorption process (Afshar et al., 2021).

A CellML version (Cuellar et al., 2003) of their model can be found in the Physiome Model Repository (Yu et al., 2011). However, the CellML file itself is not sufficient to reproduce all the predictions presented in the primary article. Therefore, some SED-ML files (Waltemath et al., 2011)

and Python scripts were created and used with the aforementioned CellML file to reproduce the main results of Afshar et al. (2021). No modifications were made to the mathematical equations or parameters of the CellML file. All the equations and parameters can be found in the original paper. In the primary article, a validated computational model was proposed. The main goal of this paper is to show that the figures in the primary paper can be reproduced by using the correlated model in the PMR. Here, we introduce a quick instruction to reproduce each figure in the original paper.

2 Model description

The model contains several relevant transporters on either side of the intestinal cell, which has three different compartments (mucosal or intestinal lumen, cell and blood or serosal). The movement of transcellular and paracellular water was based on the osmolarity difference between the two compartments involved, leading to changes in cell volume. Ions and glucose move into and out of the cell through specific transporters. Using the mathematical model, it is possible to predict membrane potentials, intracellular concentrations of glucose and electrolytes (Na^+, K^+, HCO_3^-, Cl^-), and the fluxes of these species. All the equations for ions' fluxes and concentrations are described in the supplementary material in the primary paper.

The model was developed in CellML. Simulations were run until the concentration and fluxes reached steady state. A CellML encoded version of the model is available at https://models.physiomeproject.org/workspace/841. The simulation results presented here were produced using the 2021-10-05 snapshot of OpenCOR (Garny and Hunter, 2015) together with various Python scripts that rely on a SED-ML file to configure (the solver to use, the duration of the simulation, the model parameters to track, etc.) and run a given simulation using the model encoded in CellML. Python scripts are also used to generate figures using Matplotlib (Hunter, 2007). All CellML, SED-ML and Python scripts can be found in https://models.physiomeproject.org/workspace/840.

3 Model results

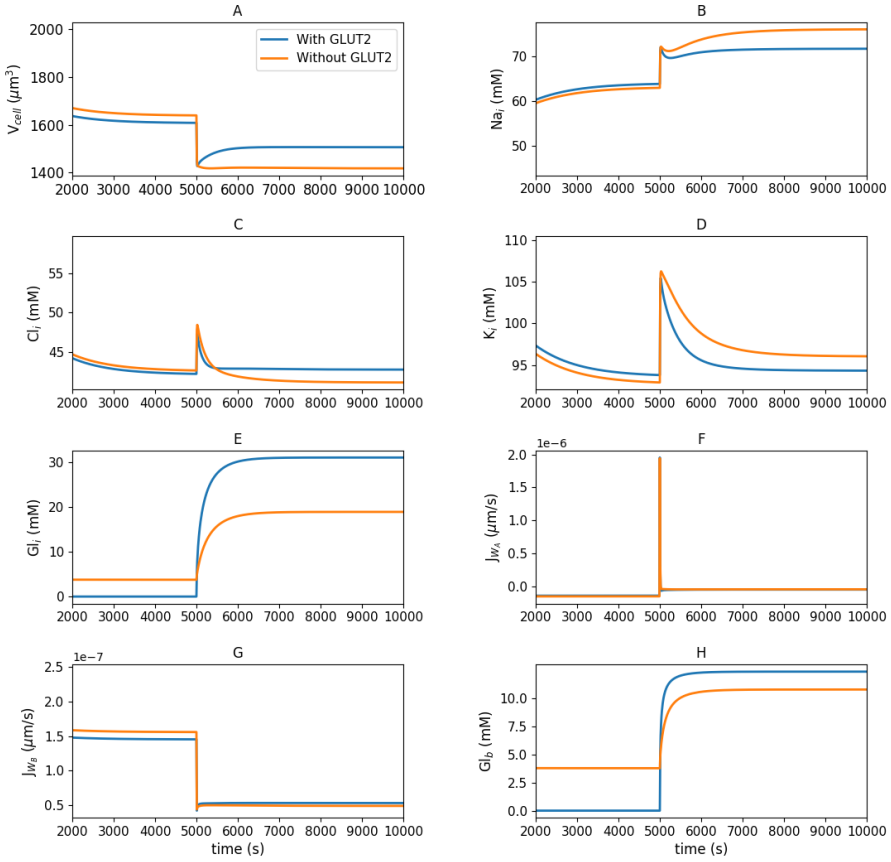

Figure 1. Model behaviour in the absence of luminal glucose ($t < 5,000$ s) and following a step change to 50 mM luminal glucose ($5,000 \leq t < 10,000$ s) of the simulation. (A) cell volume; (B) intracellular concentrations of sodium; (C) chloride; (D) potassium; (E) glucose; (F,G) apical and basolateral water flux; (H) blood glucose. This figure corresponds to Figure 3 in the primary paper and can be reproduced using Figure01.py.

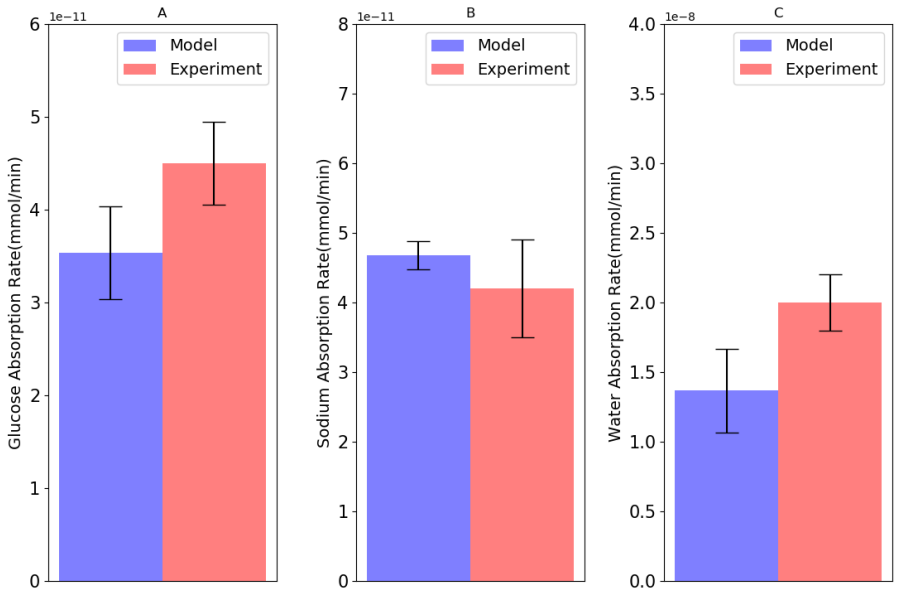

Figure 2. Absorption rates of (A) glucose; (B) sodium; and (C) water through the cell in comparison with intestinal loop data. Error bars in the model represent different values for inlet blood flow. Experimental bars are mean ± SE with 6 tests. This figure corresponds to Figure 4 in the primary paper and can be reproduced using Figure02.py.

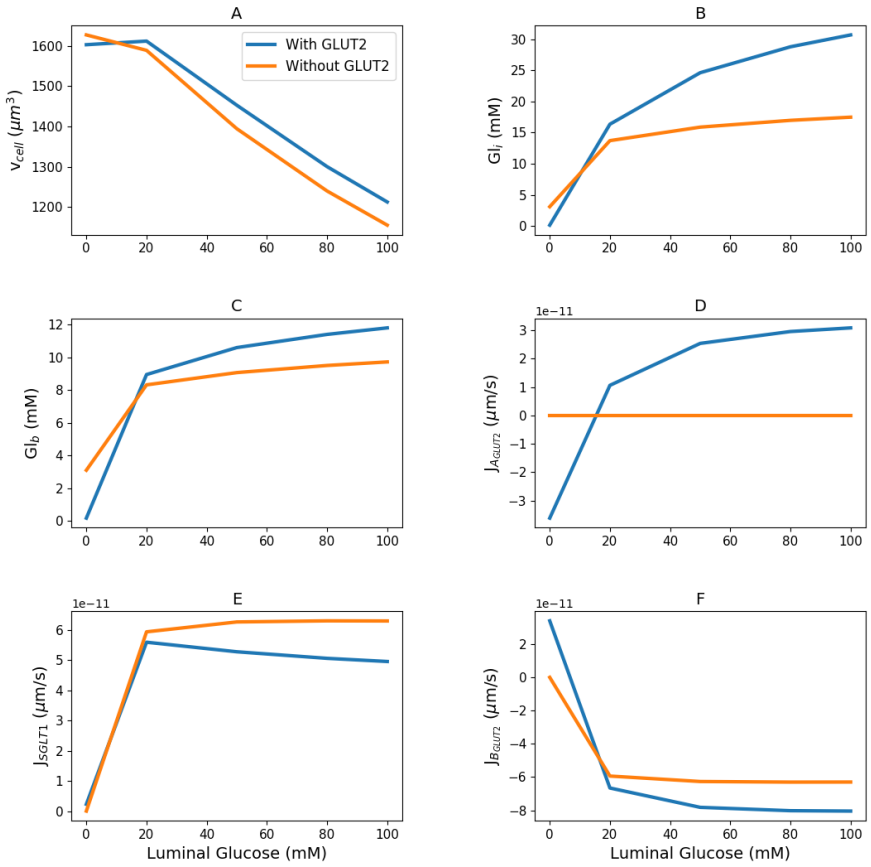

Figure 3. Model response to different luminal glucose concentration. (A) Cell volume; (B) intracellular glucose; (C) blood glucose; (D) apical GLUT2 flux; (E) SGLT1 flux; (F) basolateral GLUT2 flux. The simulation was run under five different luminal glucose concentration (0, 20, 50, 80, and 100 mM). Simulation parameters: number of apical GLUT2 = 10^8, number of basolateral GLUT2 = 2×10^8, number of SGLT1 = 3×10^7, inflow blood glucose = 4 mM, inlet blood flow rate = 10^{-17} m^3/s, and blood volume = 10^{-16} m^3. This figure corresponds to Figure 5 in the primary paper and can be reproduced using Figure03.py.

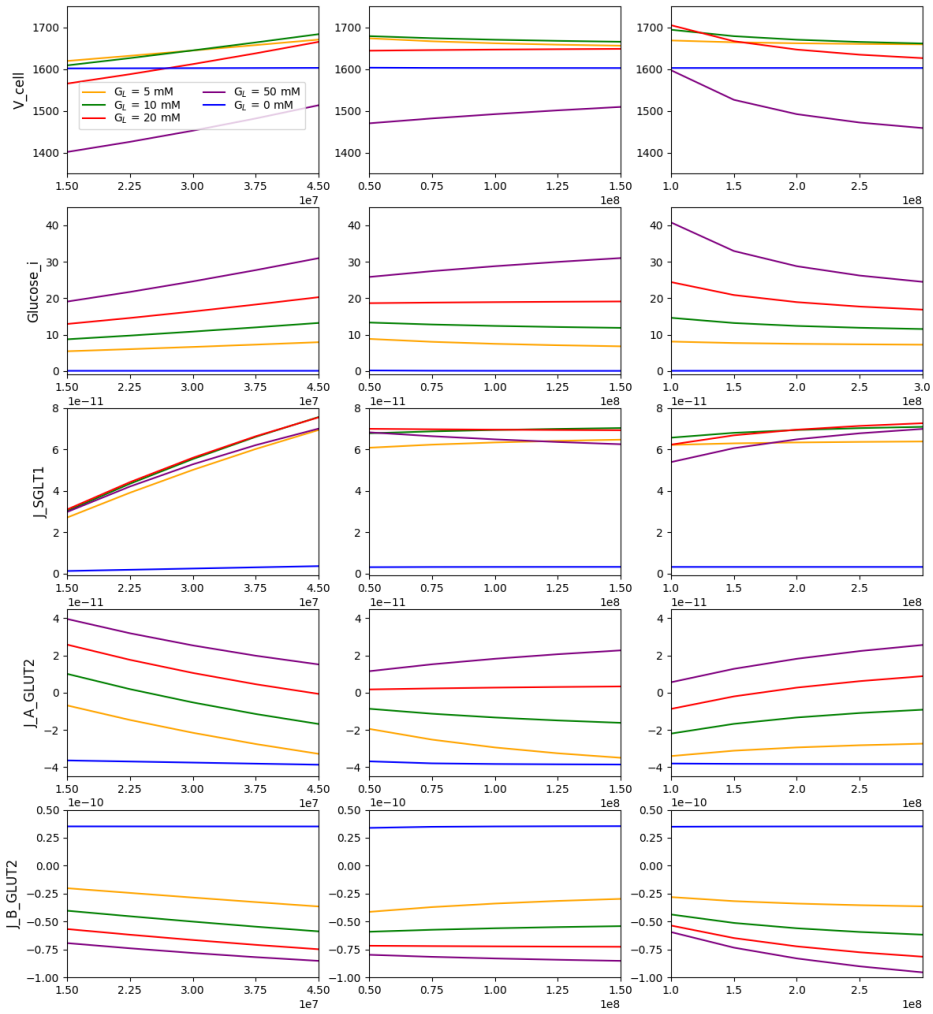

Figure 4. Model response to different transporter densities. (A–C) Cell volume; (D–F) intracellular glucose; (G–I) SGLT1 glucose flux; (J–L) apical GLUT2 flux; (M–O) basolateral GLUT2 flux. In each column, one transporter density is varied while the other two are held constant at the reference value [nSGLT1 = 3×10^7, nGLUT2 (apical) = 10^8, nGLUT2 (basolateral) = 2×10^8]. This figure corresponds to Figure 6 in the primary paper and can be reproduced using Figure04.py.

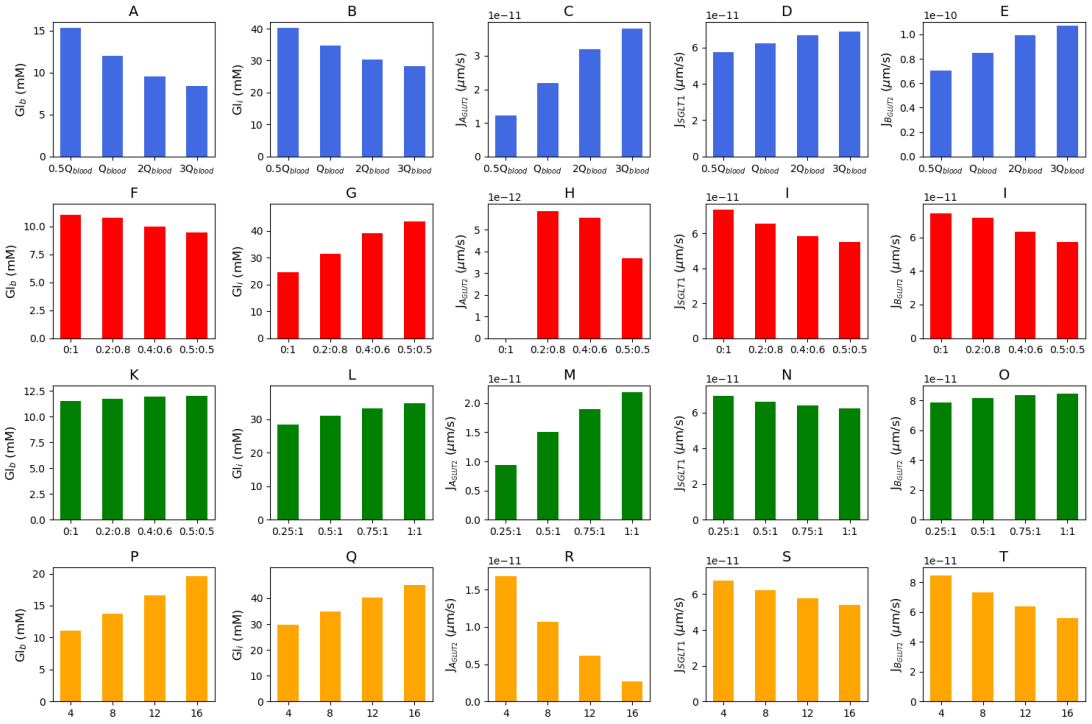

Figure 5. Blood glucose concentration, intracellular glucose concentration, apical GLUT2 flux, SGLT1 flux, and basolateral GLUT2 flux under different conditions. The first row is the model response to different blood flow rates. $Q_{blood} = 10^{-17}$ m^3/s is the baseline value of the blood flow rate (A–E). The second row shows the response to variations in the inlet blood glucose concentration (F–J). Rows three and four consider two different scenarios for GLUT2 translocation to the apical membrane. Row three shows simulations run under the assumption that apical GLUT2 is translocated from basolateral GLUT2. Different ratios between apical and basolateral GLUT2 are considered with the total number fixed (K–O). Row four shows simulations run under the assumption that apical GLUT2 is translocated from intracellular vesicles. The number of basolateral GLUT2 is fixed and labels represent the fraction of total GLUT2 in the apical and basolateral membranes (P-T). This figure corresponds to Figure 7 in the primary paper and can be reproduced using Figure05.py.

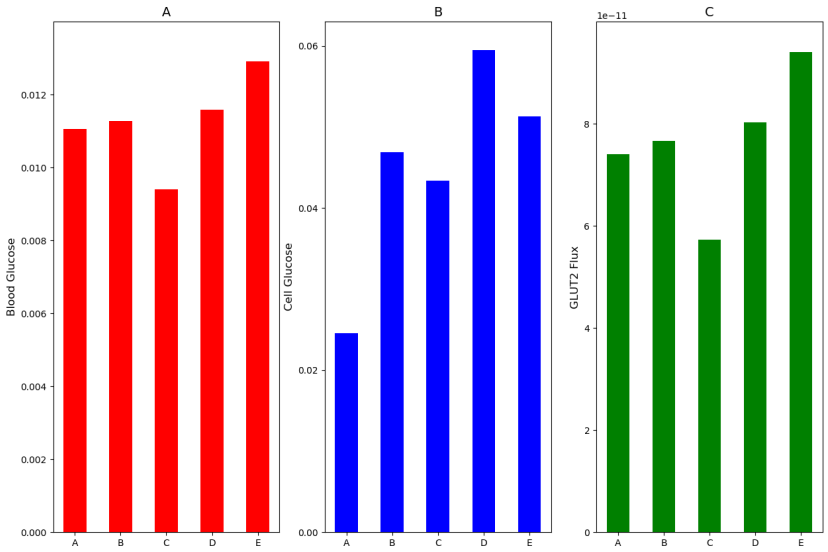

Figure 6. (A) Blood glucose; (B) intracellular glucose; and (C) glucose flux into the blood. Simulation was run under 50 mM stimulus of luminal glucose. Bar A: baseline with no apical GLUT2. Bar B: 50% increase in SGLT1 and apical GLUT2 equal to 0.5 times basolateral GLUT2. Bar C: baseline SGLT1 and apical GLUT2 equal to 1.0 times basolateral GLUT2. Bar D: 100% increase in SGLT1 and apical GLUT2 equal to 0.5 times basolateral GLUT2. Bar E: 100% increase in SGLT1 alone with no apical GLUT2. This figure corresponds to Figure 8 in the primary paper and can be reproduced using Figure06.py.

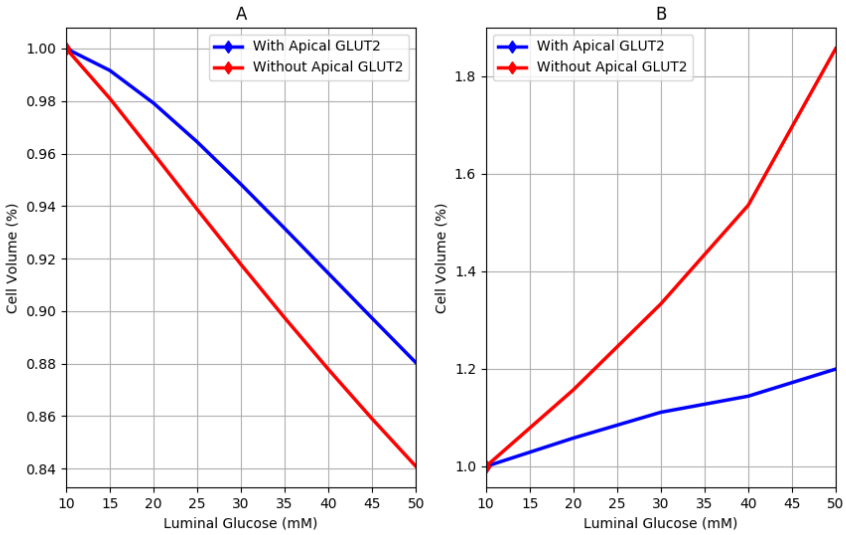

Figure 7. Cell volume behaviour in response to different luminal glucose levels in (A) our model and (B) Naftalin's (2014) model. Values are normalised to baseline values. This figure corresponds to Figure 9 in the primary paper and can be reproduced using Figure07.py.

4 Discussion

In this manuscript, we used the CellML version of the cell model developed by Afshar et al. (2021). Most of the main figures in the primary article were reproducible using the CellML code provided by the authors. Some Python code was required and can be found in https://models.physiomeproject.org/workspace/840.

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Reproducibility report for: Reproducibility Study of Computational Modelling of Glucose Uptake by SGLT1 and GLUT2 in the Enterocyte.
Submitted to: *Physiome*
Manuscript identifier: S000022

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[a]

[a]Model credibility is assessed using the Interagency Modeling and Ananlysis 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: Adequate
- ■ Document adequately: Adequate
- ■ 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 python files provided to reproduce Figure 1 - Figure 7 as presented in this manuscript.

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