**Self-assessment of conformance to the Ten Simple Rules of Credible Practice in Modeling and Simulation in Healthcare**

Biophysical Modelling of Intrinsic Cardiac Nervous System Neuronal Electrophysiology based on Single-cell Transcriptomics

The following self-assessment is based on the rules specified in Erdemir et al. (2020) and the rubric available at: <https://www.imagwiki.nibib.nih.gov/content/10-simple-rules-conformance-rubric>

Date of initial self-assessment: June 08, 2023

**Rule 1: Define context clearly:** Develop and document the subject, purpose, and intended use(s) of the model or simulation.

**Current Conformance Level:** Comprehensive

**Model Context:** Model of the electrophysiological behaviour of minipig right atrial ganglionated plexus (RAGP) principal neurons based on single-neuron transcriptomic data

**Primary goal of the model/tool/database:** The RAGP is a cluster of neurons at the heart that contribute to heart rate control. The primary objective of the modeling study was to connect single-neuron RAGP transcriptomic data to cellular electrophysiology to understand the activity of neurons contributing to heart rate regulation. Single-neuron transcriptomic data from RAGP principal neurons were thresholded to assign the presence or absence of ion channels in each neuron. We selected Hodgkin-Huxley models of these ion channel genes detected by HT-qPCR and inserted them into neuronal models to generate a library of single-neuron parallel conductance models.

**Biological Domain of the Model:** Peripheral nervous system, specifically the intrinsic cardiac nervous system

**Structures of the Model**: RAGP principal neurons and their ion channels

**Spatial Scales Included in the Model:** 10-3 to 10-2 meters (cellular)

**Time Scales Included in the Model:** 0 to 1000 milliseconds

**Other uses for the model (optional):** The cellular model can be upscaled to explore their behaviour as a network in the RAGP ganglia

**Additional comments about the model’s context (optional)**:

**Revision summary:** First version.

**Rule 2: Use contextually appropriate data:** Employ relevant and traceable information in the development or operation of a model or simulation.

**Current Conformance Level:** Extensive

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Data for building the model** | **Published?** | **Private?** | **How is credibility checked?** | **Current Conformance Level** |
| in vitro (primary cells cell, lines, etc.) | Yes | No | The source data is confirmed to meet detailed data requirements for consistency and source description | Extensive |
| ex vivo (excised tissues) | Yes | No | The source data is confirmed to meet detailed data requirements for consistency and source description | Extensive |
| in vivo pre-clinical (lower-level organism or small animal) | N/A | N/A | N/A | N/A |
| in vivo pre-clinical (large animal) | N/A | N/A | N/A | N/A |
| Human subjects/clinical | N/A | N/A | N/A | N/A |

**Revision summary:** First version.

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| --- | --- | --- | --- | --- |
| **Data for validating the model** | **Published?** | **Private?** | **How is credibility checked?** | **Current Conformance Level** |
| in vitro (primary cells cell, lines, etc.) | N/A | N/A | N/A | N/A |
| ex vivo (excised tissues) | Yes | No | The source data is confirmed to meet detailed data requirements for consistency and source description | Extensive |
| in vivo pre-clinical (lower-level organism or small animal) | N/A | N/A | N/A | N/A |
| in vivo pre-clinical (large animal) | N/A | N/A | N/A | N/A |
| Human subjects/clinical | N/A | N/A | N/A | N/A |

**Revision summary:** First version.

**Rule 3: Evaluate within context:** Perform verification, validation, uncertainty quantification, and sensitivity analysis of the model or simulation with respect to the reality of interest and intended use(s) of the model or simulation.

**Current Conformance Level:** Extensive

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| --- | --- | --- | --- | --- |
|  | **Who Does It?** | **When does it happen?** | **How is it done?** | **Current Conformance Level** |
| **Verification** | Developer | During development | Comparison of model output with published animal data | Extensive |
| **Validation** | User performs validation | Can be performed after every new simulation | Can compare model output with animal data | Adequate |
| **Uncertainty Quantification** | User performs uncertainty quantification | Can be performed after every new simulation | User discretion | Adequate |
| **Sensitivity Analysis** | User performs sensitivity analysis | Can be performed after every new simulation | Model simulations are provided for conductance values varied over a ±20% range | Adequate |

**Revision summary:** First version.

**Rule 4: List limitations explicitly:** Provide restrictions, constraints, or qualifications for or on the use of the model or simulation for consideration by the users or customers of a model or simulation.

**Current Conformance Level:** Comprehensive

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| --- | --- | --- | --- |
| **Disclaimer statement (explain key limitations)** | **Who needs to know about this disclaimer?** | **How is this disclaimer shared with that audience?** | **Current Conformance Level** |
| Transcriptomic data is not a direct measure of ion channel density. Ion channel proteins translated from these transcripts could be heteromultimeric or homomultimeric. | Users | Stated explicitly in the main text | Comprehensive |
| Parameters for ion channel models were collected under a variety of experimental conditions | Users | Stated explicitly in the main text | Comprehensive |

**Revision summary:** First version.

**Rule 5:** **Use version control:** Implement a system to trace the time history of modeling and simulation activities including delineation of each contributors’ efforts.

**Current Conformance Level:** Extensive

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| --- | --- | --- | --- |
|  | **Naming Conventions?** | **Repository?** | **Code Review?** |
| **individual modeler** | Yes | Github | Yes |
| **within the lab** | Yes | Github | Yes |
| **collaborators** | Yes | Github | Yes |

**Revision summary:** First version.

**Rule 6:** **Document appropriately:** Maintain up-to-date informative records of all modeling and simulation activities, including simulation code, model mark-up, scope and intended use of modeling and simulation activities, as well as users’ and developers’ guides.

**Current Conformance Level:** Extensive

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|  | **Current Conformance Level** |
| **Code Commented?** | Extensive: comments made in the model file |
| **Scope and intended use described?** | Extensive: described in the main text |
| **User’s Guide** | Extensive: described in the main text and supplemental files |
| **Developer’s Guide?** | Partial: Details of model development in methods of main text |

**Revision summary:** First version.

**Rule 7: Disseminate broadly:** Share all components of modeling and simulation activities, including simulation software, models, simulation scenarios and results.

**Current Conformance Level:** Extensive

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| **Target Audience(s):** | **“Inner Circle”** | **Scientific Community** | **Public** |
| **Simulations** |  |  | Description of simulations stated in the main text. |
| **Models** |  |  | Model files present on GitHub, ModelDB, and Channelpedia. |
| **Software** | The models were tested and executed on the O2S2PARC platform. | Some simulations were run in parallel using SUNY Downstate computing resources. Any high performance computing cluster should be able to run the simulations. | Python and the NEURON and Netpyne libraries were used, which are all publicly available for free. |
| **Results** |  |  | Described in main text. |
| **Implication of Results** |  |  | Described in main text. |

**Revision summary:** First version.

**Rule 8: Get independent reviews**: Have the modeling and simulation activity reviewed by nonpartisan third-party users and developers.

**Current Conformance Level:** Extensive

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| **Reviewer(s) name and affiliation** | Dr. Sujata Patil; Siyan Guo, Joyce Wang |
| When was the review performed | August 28, 2023; April 2023 |
| How was review performed and outcomes of the review? | Members of the research group, not involved in the present study performed the review.  Figures were independently reproduced using the analysis files provided on Github. Current clamp simulations for neuronal-type T54 were reproduced from an earlier draft of this manuscript. |

**Revision summary:** First version.

**Rule 9: Test competing implementations**: Use contrasting modeling and simulation implementation strategies to check the conclusions of different strategies against each other.

**Current Conformance Level:** Adequate

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|  | **Yes or No (briefly summarize)** |
| **Were competing implementations tested?** | Yes, in multiple stages.  Competing implementations of ion channel models from ModelDB and Channelpedia were tested and compared by the first author of the paper during the initial manuscript preparation. |
| **Did this lead to model refinement or improvement?** | Yes, the model was refined and improved whenever inconsistencies with experimental data on RAGP rheobase, input impedance, passive reversal potential and neuron firing rates arose. Specifically, competing ion channel models for a given gene were tested on the basis of their window currents. |

**Revision summary:** First version.

**Rule 10: Conform to standards:** Adopt and promote generally applicable and discipline specific operating procedures, guidelines, and regulations accepted as best practices.

**Current Conformance Level:** Adequate

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|  | **Yes or No (briefly summarize)** |
| **Are there operating procedures, guidelines, or standards for this type of multiscale modeling?** | Yes, as described in the credible practice of modeling and simulation in healthcare: ten rules from a multidisciplinary perspective (Erdemir et al., 2020). |
| **How do your modeling efforts conform?** | Our model is implemented in the widely used python language for computational modeling. The code is commented at critical locations to aid the reader. |

**Revision summary:** First version.

**References:**

Erdemir, A., Mulugeta, L., Ku, J. P., Drach, A., Horner, M., Morrison, T. M., Peng, G., Vadigepalli, R., Lytton, W. W., & Myers, J. G., Jr (2020). Credible practice of modeling and simulation in healthcare: ten rules from a multidisciplinary perspective. Journal of translational medicine, 18(1), 369. <https://doi.org/10.1186/s12967-020-02540-4>