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

Baroreflex adaptation following myocardial infarction in an *in silico* patient cohort

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: August 27, 2024

**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:** Virtual patient cohort model of neural control of cardiovascular behavior following a heart attack (myocardial infarction)

**Primary goal of the model/tool/database:** The primary objective of this computational modeling study was to evaluate the role of neural signals in controlling the dynamic behavior of the heart. We were particularly interested in how these neural signals adapt to compensate for lost heart function after a heart attack. This neural adaptation is thought to help compensate for injury to the heart but contribute to the development of heart failure in the long-term.

Our model builds on a previously developed model of neural control of the heart (Gee *et al.*, 2023). We extended this model by exploring the shift in physiology from before to after a myocardial infarction. Because there is a significant amount of inter-individual heterogeneity in cardiovascular function before a heart attack, we developed a cohort of 59 *in* silico patients that accounts for the range of clinically observed heart function. We then simulated cardiac injury coupled with neural adaptation for each individual in the cohort so that the cohort accounts for the range of heart rates and blood pressures observed in human populations after a heart attack. We then quantified the cardiac function of these patients to assess differences in individuals with better or worse cardiac function. Simulations can be performed to explore different pathways of neural adaptation during and in the hours after a heart attack.

**Biological Domain of the Model:** Cardiovascular system and autonomic control

**Structures of the Model**: Heart, vasculature, brainstem, intrinsic cardiac nervous system

**Spatial Scales Included in the Model:** 10-2 to 10-1 meters

**Time Scales Included in the Model:** 0 to 200 seconds, 0-4 hours

**Other uses for the model (optional):**

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

**Revision summary:**

N/A, 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.) | N/A | N/A | N/A | N/A |
| ex vivo (excised tissues) | N/A | N/A | N/A | N/A |
| in vivo pre-clinical (lower-level organism or small animal) | Yes | No | The source data is confirmed to meet detailed data requirements for consistency and source description | Adequate |
| in vivo pre-clinical (large animal) | N/A | N/A | N/A | N/A |
| Human subjects/clinical | Yes | No | The source data is confirmed to meet detailed data requirements for consistency and source description | Extensive |

**Revision summary:**

N/A, 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) | N/A | N/A | N/A | N/A |
| 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 | Yes | No | The source data is confirmed to meet detailed data requirements for consistency and source description | Extensive |

**Revision summary:**

N/A, 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 and human data | Extensive |
| **Validation** | Lab Member | During development | Model was used to reproduce simulations and figures | Extensive |
| **Uncertainty Quantification** | User performs uncertainty quantification | Can be performed after every new simulation | User discretion | Adequate |
| **Sensitivity Analysis** | Developer or user | Can be performed after every new simulation | PAWN sensitivity analysis (Pianosi and Wagener 2018) | Adequate |

**Revision summary:**

N/A, 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

|  |  |  |  |
| --- | --- | --- | --- |
| **Disclaimer statement (explain key limitations)** | **Who needs to know about this disclaimer?** | **How is this disclaimer shared with that audience?** | **Current Conformance Level** |
| Pre- and post-myocardial infarction data were from separate data sets and the baroreflex sensitivities increase from pre- to post-MI when a decrease would be expected | Users | Stated explicitly in the main text | Comprehensive |
| High-fidelity representation of sympathetic regulation of cardiac function not included | Users | Stated explicitly in the main text | Comprehensive |

**Revision summary:**

N/A, 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** | N/A | N/A | N/A |

**Revision summary:**

N/A, 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

|  |  |
| --- | --- |
|  | **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:**

N/A, 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. |
| **Software** |  | Some simulations were run in parallel using the University of Delaware’s DARWIN computing resources. Any available high performance computing cluster should be able to run the simulations. | MATLAB and Simulink were used, both of which are publicly available for a fee. All figures can be generated using solely MATLAB and Simulink. |
| **Results** |  |  | Described in main text. |
| **Implication of Results** |  |  | Described in main text. |

**Revision summary:**

N/A, 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** | **Alexandra Manchel (Thomas Jefferson University)** |
| When was the review performed | August 29, 2024 |
| How was review performed and outcomes of the review? | A member of the research group, not involved in the present study performed the review.  Model files and tables in the text were cross-checked for consistency.  Simulation results and figures were independently reproduced using the files provided on Github. |

**Revision summary:**

N/A, 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

|  |  |
| --- | --- |
|  | **Yes or No (briefly summarize)** |
| **Were competing implementations tested?** | Yes, in multiple stages.  Competing implementations 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 clinical data. Specifically, parameters describing the heart, baroreceptors, nucleus tractus solitarius, nucleus ambiguus, dorsal motor nucleus of the vagus, and intrinsic cardiac nervous system were varied to simulate a possible patient population. The population was then filtered based on global physiological metrics such as heart rate, mean arterial pressure, and baroreflex sensitivity. |

**Revision summary:**

N/A, 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 MATLAB and Simulink platforms for computational modeling. The code is commented at critical locations to aid the reader. |

**Revision summary:**

N/A, 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.

Pianosi, F., and T. Wagener (2018). Distribution-Based Sensitivity Analysis from a Generic Input-Output Sample. Environmental Modelling & Software 108 (August): 197–207.