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

Dynamic and robust control of the liver homeostatic renewal process: Cell network modeling and analysis

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 self-assessment: August 17, 2022

Model files and documentation: <https://github.com/amanchel/LiverHomeostaticRenewalModel>

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

**Current Conformance Level:** Comprehensive

**Primary goal of the model/tool/database:** The primary objective of the modeling study was to address the molecular and cellular processes controlling liver homeostatic renewal as recent experimental investigations have identified high replication capacity hepatocyte populations as the primary maintainers of liver mass. Therefore, we developed and analyzed a mathematical model describing cellular network interactions underlying liver homeostatic renewal that will enable a quantitative investigation of how different types of feedback control mechanisms influence the dynamics of tissue renewal. We extended our basic model to incorporate putative regulatory interactions and investigated how such interactions may confer robustness on the homeostatic renewal process. Lastly, we extended the model to include feedback control by liver non-parenchymal cells.

**Biological Domain of the Model:** Liver tissue renewal, progenitor cells

**Structures of the Model**: Liver

**Spatial Scales Included in the Model:** cellular (1 to 20 um), tissue (um to cm), systemic/organ (cm to m)

**Time Scales Included in the Model:** 0 to 400 days

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

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

**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

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| --- | --- | --- | --- | --- |
| **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) | 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 | Extensive |
| 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 |

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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.) | Yes | No | the source data is confirmed to meet detailed data requirements for consistency and source description | Extensive |
| 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 | Extensive |
| 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 |

**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 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 every time the model is run for a new scenario | User discretion | Adequate |
| **Sensitivity Analysis** | User performs sensitivity analysis on influential parameters | Can be performed after every new simulation | User discretion | Adequate |

**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:** Extensive

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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** |
| Highly self-renewing hepatocytes, while composed of different subpopulations distributed spatially across the periportal, pericentral, and midlobular regions of liver lobule, can be lumped into a single population of cells with high self-renewal (SRhigh). | Users | Stated explicitly in the supplemental text | Extensive |
| Liver lobules are essentially repeating units. Therefore, simulating renewal of hepatocytes in one lobule is the same as simulating the renewal of hepatocytes in the whole liver. | Users | Stated explicitly in the supplemental text | Extensive |
| Populations of hepatocytes can be grouped into two general phenotypes: SRhigh cells and SRlow cells. Cell-type differences for SRhigh (e.g. oval cells vs. hybrid cells) and SRlow (e.g. binuclear vs. mononuclear) populations can be ignored for the present purposes. | Users | Stated explicitly in the supplemental text | Extensive |
| The transition from an SRhigh to an SRlow cell is irreversible. | Users | Stated explicitly in the supplemental text | Extensive |
| Cell populations can communicate information about the respective population size across a lobule through resource use, physical constraints and associated cues, or biochemical signaling. | Users | Stated explicitly in the supplemental text | Extensive |
| At the tissue scale, the number of functional hepatocytes is so large that the potential stochastic nature of cell proliferation and death can be ignored. | Users | Stated explicitly in the supplemental text | Extensive |
| During homeostatic renewal in the absence of external stimuli, rates of cell proliferation and cell death are equal. | Users | Stated explicitly in the supplemental text | Extensive |
| The process of homeostatic renewal is optimized for robustness to a wide range of stresses rather than for efficient recovery from an individual stress. | Users | Stated explicitly in the supplemental text | Extensive |
| Non-parenchymal cells can sense and maintain a memory of hepatocyte population sizes, through currently unknown mechanisms, and respond instantaneously to such population size changes. | Users | Stated explicitly in the supplemental text | Extensive |

**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** | N/A | Github | Yes |
| **within the lab** | Yes | Yes | Yes |
| **collaborators** | N/A | Github | Yes |

**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 files |
| **Scope and intended use described?** | Extensive: described in the main text and supplemental files |
| **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 |

**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 and supplemental files |
| **Models** |  |  | Model file present in supplementary material and on GitHub. |
| **Software** |  |  | MATLAB and Simulink were used. All of these are publicly available either freely or for a fee. |
| **Results** |  |  | Described in main text |
| **Implication of Results** |  |  | Described in main text |

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

**Current Conformance Level:** Adequate

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| **Reviewer(s) name and affiliation** | **Babita Verma (Thomas Jefferson University)** |
| When was the review performed | 2018 |
| 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 in the supplementary material. |

**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?** | Competing implementations were tested and compared by the first author of the paper. |
| **Did this lead to model refinement or improvement?** | Yes  The model was refined and improved whenever inconsistencies arose. |

**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 platform for computational modeling. The code is commented at critical locations to aid the reader. |

**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