Model Documentation

PBPK/QSP Model of drug X in Y disease

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1 Model Objectives

- Clearly state the scientific question the model is intending to address
  - *What dose level is required to reach the desired level of target engagement?*
- Outline the specific objectives of the model

  a. *Characterize the pharmacokinetics of drug X in preclinical species and human*
  b. *Determine the dose-response relationship for drug X and biomarker Y*
  c. *Perform a clinical trial simulation*

Note: The scientific question and model objectives should be clearly defined and specific. This section should provide the reader with a clear understanding of why the model was developed and what it is intended to accomplish.

2 Data

- Description of the data sources used to develop the model and how they were used. This could include information such as the type of data (e.g., clinical trial data, observational data, etc.), the number of samples, and the population characteristics.
  - *Phase II clincial PK data for Drug X in disease Y was obtained from the literature and is available in supplementary materials as* `data1.csv`*. This dataset has A patients and B samples. Patient demographics are…*
- Information on how the data was obtained, preprocessed, and cleaned before being used for model development.
  - *Missing data was handled by…*
  - *BLQ data was handled by…*
  - *Data was digitzed using the software…*
- Summarizing the data used into a table is recommended. The data table could include additional columns such as sample size, population characteristics, and data handling information. However, it might be best to have this information described in text and only display the summary of the dataset in the table along with the filename and source to reduce the size of the table.

Table 1: Example Data Table

Data	Filename	Source
Phase II clinical PK data for Drug X in disease Y	data1.csv	Reference
In vitro data for Drug X inhibiting biomarker Y	data2.csv	Internal
Phase III clincial PD Data	private	Internal

3 Model Development

- Provide any relevant background information for model development
- Provide the granularity/scope of model development
  - *We used in vitro data to mode the cellular/molecular processes in disease Y tissue*
  - *We linked changes in biomarker Y to clinical endpoint Z*
- Describe the sources of data used to develop the model, literature or experimental data
  - *In vitro data was obtained from in house experiments*
  - *Clincial data was digitized from the literature in {reference}*
- Provide a step-wise description of the model development process, including what software or programming languages were used. Was the model developed new or was a previous model used as a starting point.

Note: The Model Development section should provide a detailed description of how the model was developed, including the methods and data used. The Structure, Parameters, and Assumptions subsections should provide specific information about the model structure, parameter values, and assumptions made during model development. This information should be sufficient for a reader to understand the model, how it was developed, and hopefully enable its reproducibility and usability.

3.1 Structure

- Describe the overall structure of the model, including compartments and pathways
- Provide a diagram or illustration of the model structure
  - *Command to diplay an image:* `![Model Diagram Caption](ModelDiagram.png)`
- Write and explain mathematical equations and algorithms

Write model equations using the following syntax:

$$C(t) = C_0 \cdot e^{-k \cdot t} \tag{1}$$

$$\frac{dC}{dt} = -k \cdot t \tag{2}$$

Note that you can use an online LaTeX editor to help with the equation syntax, such as: LaTeX Editor.

3.2 Parameters

- List and define all model parameters and provide a summary in the table.
- Describe how parameter values were determined and any calculations used.

    1. *Clearance (CL) was obtained from experimental data…*
    2. *Volume of distribution in the central compartment (V1) was obtained from literature*
    3. *Distributional clearance (CLD) was obtained from experimental data…*
    4. *Volume of distribution in the peripheral compartment (V2) was assumed*

- Provide references and sources, such as literature, experimental data, or assumptions.
- Indicate any assumptions or simplifications made in determining parameter values.

Table 2: Example Parameter Table

Parameter	Units	Value	Reference
CL	1.0	L/h	Experiment
V1	5.0	L	Literature
CLD	2.5	L/h	Experiment
V2	20.0	L	Assumed

3.3 Assumptions

- List and explain any assumptions made in the model development, such as simplifications of biological processes or neglect of certain variables
- Describe the impact of these assumptions on the model predictions and overall accuracy
- Explain any uncertainty or variability in the model predictions due to these assumptions
- Outline any major challenges or limitations encountered during model development and how they were addressed
- Describe model assumptions using a table and the recommended columns (Assumption, Justification, Sensitivity Analysis, Uncertainty, and Source)

    - **Assumption**: Describe the assumption in a clear and concise manner.
    - **Justification**: Explain the reasoning behind the assumption. Include relevant research, literature, or expert opinions supporting the assumption.
    - **Sensitivity**: Describe how the assumption affects the model output and how sensitive the model is to changes in the assumption. It could include any sensitivity analysis performed on the model, such as a range of values for the assumption or a list of alternative assumptions that were considered.
    - **Uncertainty**: Describe the level of uncertainty associated with the assumption. This could include any uncertainty analysis that was performed on the assumption, such as a range of possible values or a probability distribution.

– **Source**: This column should cite the sources of the assumptions, such as publications, regulations or expert opinions.

Note: Sensitivity analysis focuses on how changes in an assumption affect the model output, while uncertainty analysis focuses on the level of confidence in the assumption.

Table 3: Example Assumption Table

Assumption	Justification	Sensitivity	Uncertainty	Source
Assumption 1	Justification 1	Sensitivity 1	Uncertainty 1	Source 1
Assumption 2	Justification 2	Sensitivity 2	Uncertainty 2	Source 2

4 Model Validation

- Describe the scope of the model validation and methods/data used to validate the model, such as comparison to experimental data or other models.
  - *The model was validated using clinical data in patients with disease Y. Patients were at this stage of the disease with the following range/distribution of demographics (age, sex, race, etc.). The model was validated for doses ranging between A and B.*
- Indicate any areas where the model may not be suitable for certain applications, such as dose range, species, or disease states.
- Provide any relevant statistical measures, such as R^2 or root mean square error (RMSE)
- Provide any relevant figures or tables to support the validation of the model
- Provide any references or citations for the validation data.
- For models that have extensive validation data from multiple sources, you could consider summarizing this data in a table.

Note: The Model Validation section should provide a clear and thorough assessment of the model's performance and accuracy. This section should include any relevant statistical measures and figures to support the validation, as well as a description of the scope of the validation. The reader should understand the limitations and uncertainties of the model predictions and under what conditions the model is suitable to use.

5 Model Application

- Provide examples of specific applications or case studies where the model has been used or can be used
- Describe the inputs and outputs of the model, and the type of information that can be obtained from the model
- Provide any relevant figures or tables to illustrate the model's predictions or results
- Outline any limitations or considerations for the model's use, such as the range of concentrations or conditions that the model can accurately predict

Note: The Model Application section should provide a clear and comprehensive description of how the model can be used and what kind of information can be obtained from it. This section should include examples of specific applications, inputs and outputs, as well as any limitations or considerations for the model's use. The reader should understand the potential use and the information that can be obtained from the model, and any limitations or future developments of the model. This section provides a comprehensive description of primary and supplementary analyses performed.

6 Model Accessibility and Useability

- Provide information on how the model can be accessed, such as the website or repository where the model can be downloaded.
  - *The model can be obtained from the following GitHub link…*
- Provide any necessary information for running the model, such as the software and version required.
  - *The model was developed in R version X.XX. The primary R packages used were A v1.0, B v2.0, and C v3.0.*
- Describe any licensing or usage restrictions for the model.
- Explain the format of the data inputs required for the model and share any example datasets.
- Explain the format of the data outputs provided by the model.
- Describe any post-processing or data visualization tools that can be used to analyze the model outputs.

Note: Accessibility refers to the ease at which a model can be obtained and setup for use, whereas usability refers to the ease at which the model can be understood and used.

7 References

Example for Adding References

This research is really lame.[1]

References can manually be added by going to Google Scholar. Click the "Cite" icon under the paper of interest. Copy the **BibTex** text and paste it into the bibliography.bib file.

Note that there are alternative methods for adding references to a document, such as citation management tools (Zotero or Mendeley). These tools allow you to easily search for, store, and organize references, and they can automatically generate the BibTeX code for the references.

There are also extensions within VSCode that could be used (e.g., Citation Picker for Zotero). The BibTex `.bib` file can then directly be exported from Zotero after all of the references are added using the Citation Picker.

1. Jones, R. S. Deorphanizing monocarboxylate transporter 6: Evidence of functional roles in lipid metabolism and drug transport. (State University of New York at Buffalo, 2019).

8 Additional Considerations

Certain models could consider the following additional sections if relevant:

8.1 Model Credibility

Describe the model's authors, development team and their qualifications. Provide any relevant publications, presentations or patents that the authors have on the model. Describe any external review that the model has undergone and the outcome of the review.

8.2 Model Maintenance

Describe any ongoing maintenance or updating schedule for the model. Explain any methods for submitting bug reports or suggestions for model improvements. Describe any support or help resources available for users of the model.

8.3 Model Version

This section could include version number of the model, the date of the last update, and a brief summary of any changes that were made in that version. This would allow users to keep track of the different versions of the model and to easily identify which version of the model they are using.

Additionally, providing information on the version history of the model can help users to understand how the model has evolved over time, and to identify which version of the model is most appropriate for their specific needs. This can be particularly important when the model is frequently updated or when different versions of the model are used for different applications.

It's worth noting that versioning and documentation is important for reproducibility, allowing to trace the model's development, testing, and validation, and could be supportive information for regulatory submission of the model.