Qualifying Mechanistic Physiological Models for Use in Pharmaceutical Discovery and Development.

Christina Friedrich* (1), Rada Savic (2), Jim Bosley (1), Rebecca Baillie (1), Ron Beaver (1)
(1) Rosa & Co LLC, San Carlos, CA 94070, (2) Stanford University, Stanford, CA, USA

Drug Development Advisors

Objectives

- **Propose a standard method for qualifying physiological models for use.**

Methods

Mechanistic physiological models are powerful tools that can deliver unique insights and have significant program impact. Their use in drug discovery and development has not reached its full potential in part because there is no standard method for ensuring that a model is fit for purpose.

The goal of physiological modeling is to advance a specific research agenda in a drug discovery and development context. Therefore, the Model Qualification Method should focus on whether the model is as useful in supporting that goal as possible. Physiological models vary dramatically in depth and breadth depending on research context, so the method must be conceptual and customizable rather than prescriptive.

We began by clarifying desiderata of a Model Qualification Method, then employed concepts from statistics, dynamical systems modeling, decision analysis, and related fields to define a Model Qualification Method with the desired properties.

Table1. Desiderata for a Model Qualification Method	
Customizable	Applicable for any research contexts.
Complete	Addresses all aspects of model quality, not just matching data.
Practical	Does not take too long or require unknowable data.
Data-independent	Applies regardless of the type of data available.

Modeling Approaches

Mechanistic Physiological Modeling

Mechanistic ODE-based modeling has long been used in physics and engineering disciplines to study complex systems. Physiological modeling applies these techniques to biological systems. This approach is ideal for addressing drug discovery and development questions related to the mechanistic connections between pathophysiology, therapeutic pathways and outcomes, especially when clinical data are limited. No standard method currently exists for qualifying such models for their intended use, i.e., determining whether they are fit for purpose.

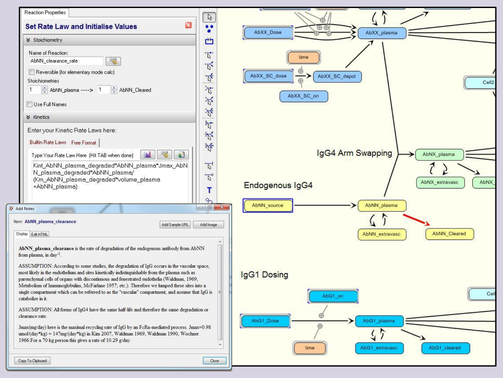


Figure 1. Select components of a physiological model (disguised) investigating antibody dynamics.

Comparison to Statistical Modeling

Statistical models are inferred from data with most model parameters being estimated; the model complexity is determined by the data. Many tools are available to evaluate models internally and externally and to assess goodness of fit. Physiological models, by contrast, are not inferred from any one data set; rather, they start with knowledge and hypotheses of biological processes. Many types of data are used to inform and parameterize the models, but the models are also extremely useful tools for explicitly exploring hypotheses about unknown parts of the biology. Hence, the quality of a physiological model cannot be determined strictly on the basis of comparison to data. Prior attempts at validation strategies failed to account for these qualitative differences between modeling approaches.

Matching relevant existing data is critical, but it is not sufficient for ensuring that a mechanistic physiological model is fit for purpose.

Conclusions

- **A general Model Qualification Method can be defined to ensure that physiological models are fit for purpose.**
- **Statistical methods testing fit to data can be adapted for use with physiological models; however, such statistical testing alone does not ensure model quality.**
- **The Model Qualification Method proposes eight criteria covering:**
  - **Relevance to research context**
  - **Dealing with uncertainty**
  - **Dealing with variability**
  - **Comparison to data**
- **A model that meets all criteria can be used with confidence in drug discovery and development.**

Results: Model Qualification Method

1. Model scope is appropriate for research context

Research context includes several components that should be used to determine relevance, shown in Table 2. All components of the drug discovery and development research context must be considered explicitly in scoping the physiological model. Model scope includes biological components as well as model behaviors and variability and uncertainty explored. Given time and resource constraints, inclusion of extraneous detail can be as detrimental as exclusion of needed components. Relevance to the research context should inform modeling decisions large and small for the duration of the project.

Table 2. Research Context Components
1. Biological system being investigated
2. Key research question or decision
3. Time and resource constraints
4. Data availability

Qualification approach:

If the following questions can be answered in the affirmative, then model scope was appropriate for the research context.

a. Did the modeling work support actionable insights that advanced the research agenda?
b. Was the model constructed in a timely fashion to be useful when decisions had to be made?
c. Were resources applied efficiently?

2. Model represents relevant biological mechanisms

Physiological models must be faithful to known biology and physical laws. This imposes a rich set of constraints.

Qualification approach:

Scientific experts should be able to review the model and confirm that the represented interactions reflect biology. In practice, this should not be left as a testing step at the end; rather, it should be a guiding principle for model construction. A graphical interface (see Figure 2) and annotation capabilities greatly facilitate this process.

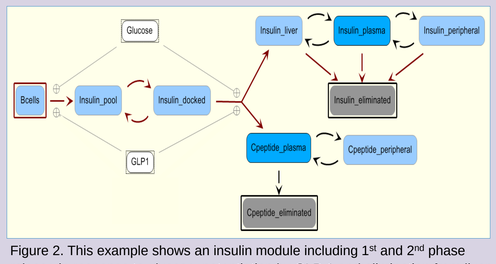


Figure 2. This example shows an insulin module including 1st and 2nd phase release in response to glucose, potentiation by GLP-1 and elimination from liver, plasma, and peripheral tissues. The joint team, including scientific experts, agreed on the representation. Rationale and references were documented.

3. Relevant qualitative uncertainties are assessed

There are often gaps in knowledge about areas of the biology relevant to the research context. Constructing a model brings much-needed rigor to the identification and assessment of knowledge gaps. We use the term *qualitative* uncertainty for knowledge gaps about how biological components interact, while *quantitative* uncertainty concerns the degree or rate of the interaction. Mechanistic physiological models are ideally suited to evaluate the implications of alternative qualitative hypotheses.

Table 3. Possible Qualitative Uncertainty Resolutions	
Document and proceed with agreed-upon most likely hypothesis	Appropriate if impact is localized, distal to the focus of the research, or transient.
Simplify model structure to avoid modeling uncertain area explicitly	Appropriate if possible without compromising the model's ability to address research questions.
Resolve definitively, i.e., eliminate all but one hypothesis through data analysis and/or modeling	May require significant resources, which is warranted if model predictions relevant to the research question are sensitive or likely to be sensitive to the uncertainty.
Maintain multiple hypotheses in model to explore explicitly	Appropriate if model predictions relevant to the research question are sensitive to the uncertainty and if more than one hypothesis satisfies all constraints.

Qualification approach:

Model qualification requires documentation and resolution of qualitative uncertainties. Effort should focus on qualitative uncertainties that are likely to have an impact on the research question, as identified by sensitivity analysis and expert judgment. Table 2 summarizes possible resolutions.

4. Relevant quantitative uncertainties are assessed

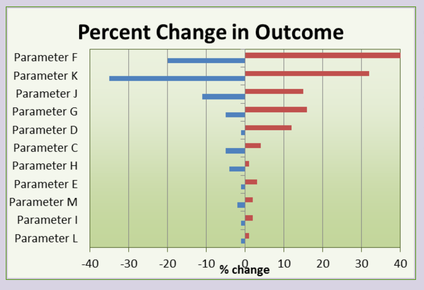


Figure 3. A "tornado diagram" in which parameters are ranked by their impact on model outcomes of interest. This is a classic tool for sensitivity analysis.

Many biological systems of interest for clinical research are very incompletely characterized, leading to often broad ranges of plausible parameter space. The basic tools for dealing with quantitative uncertainty in physiological modeling are sensitivity analysis and virtual patient simulations. Techniques for this are evolving [e.g., 3, 7, 8], but the basic principle is to identify the parameters that have the greatest impact on predictions.

Qualification approach:

Model qualification requires identification of sensitive parameters and model-based exploration of their systemic effects, e.g., via simulations of "virtual patients". Virtual patients may be created by sampling the plausible parameter space for sensitive parameters.

5. Model captures relevant known pathway variabilities

We distinguish known pathway variability from quantitative uncertainty when there are reported data from patients suggesting bounds on the plausible parameter space for an uncertain parameter or rate. For example, the relative degree of insulin secretion vs. insulin resistance in diabetes pathophysiology is an area with known pathway variability. Physiological models can be used to investigate the degree to which known *outcome* variability can be attributed to known pathway variability.

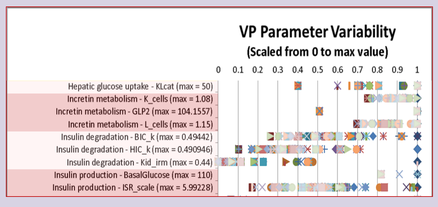


Figure 4. Variability in the parameters governing various biological processes such as hepatic glucose uptake, incretin metabolism, etc. Every marker represents a virtual patient. This variability in parameters translates into variability in total rates that can be checked against data.

Qualification approach:

Sensitive known pathway variabilities should be identified and their impact on model outcomes investigated through the use of virtual patient simulations that draw from the parameter distributions.

6. Relevant clinical variability is reproduced

Clinical variability has obvious implications on many drug development decisions. Analysis of clinical variability in the physiological modeling context strives to illuminate the mechanistic sources of the variability. This can support research objectives such as identifying responder patient types or designing a next-generation compound to have broader efficacy. Clinical variability is reproduced in mechanistic physiological models by creating and simulating a range of virtual patients with diverse parameter values reflecting PK and PD variability, known pathway variability, and uncertainty.

Qualification approach:

The qualification approach depends on the type and amount of data available. Spanning the range of responses or reproducing the distribution of responses may both be appropriate qualification criteria, depending on data and research context. For quantitative matching criteria, see Table 4 in section 8. Figure 5 shows a virtual patient variability example (data disguised).

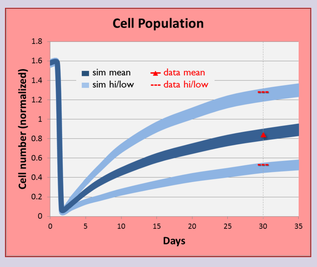


Figure 5. Cell population recovery after treatment compared to data. Simulation ranges are generated by adding noise to uncertainty and/or variability in parameter values.

7. Model results are qualitatively consistent with relevant data and knowledge

Physiological models produce more results than there are clinical data to compare to. Variables can be observed continuously and virtual patients can be subjected to protocols that cannot be ethically done with real patients. This presents extra-ordinary opportunities for model qualification via visual inspection of model results under many conditions. Qualitative testing is also appropriate when the data available are related, but not identical to the scenario of interest, e.g., data for different phenotypes or for related drugs.

Qualification approach:

Qualitative tests must be identified and documented and tested by visual inspection to ensure that expected behaviors are reproduced. See example in Figure 6.

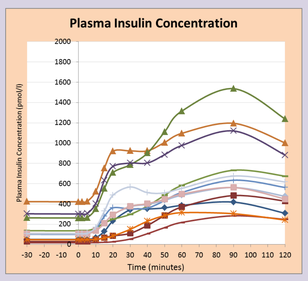


Figure 6. Example of a qualitative check. A selection of virtual patients are visually checked for two-phase insulin secretion as appropriate for disease severity.

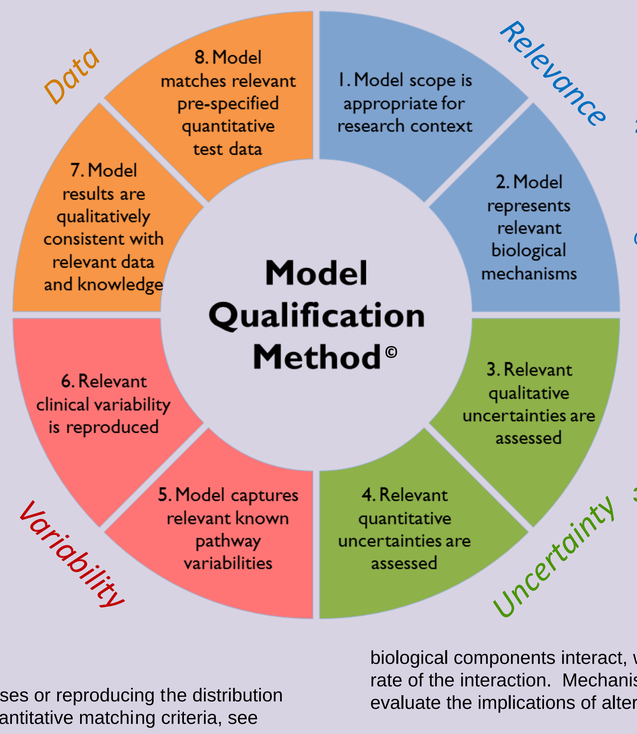
8. Model matches relevant pre-specified quantitative test data

Unlike statistical models, physiological models are not inferred from specific data sets. Hence, the first step toward ensuring that a physiological model is consistent with data is to identify appropriate data sets for quantitative statistical testing. Relevance to the research context (see Table 2) is the primary criterion for test data selection. *Lack of appropriate clinical data for statistical testing does not invalidate the model* – it merely elevates the importance of uncertainty and variability exploration in the model qualification process.

Table 4. Statistical Approaches for Quantitative Test Data	
Data Available	Statistical Test
Summary statistic: Data mean	Test that data mean falls within simulated results with uncertainty and noise added to parameters.
Summary statistic: Data variability measure, e.g., 5th, 95th percentiles	Test that data percentiles fall within simulated results with noise added to variability and uncertainty in parameter values.
Full data set available for comparison	Use simulation-based approaches such as visual predictive check.

Qualification approach:

Quantitative test data should be identified and documented by the joint project team. Statistical methods apply as appropriate given the nature of the available testing data. See Table 4 and Figure 5.



References

1. ADA Consensus Panel, Guidelines for computer modeling of diabetes and its complications. Diabetes Care, 2004. 27(9): p. 2262-5.
2. Beard, D.A., et al., Computational modeling of physiological systems. Physiol Genomics, 2005. 23(1): p. 1-3; discussion 4.
3. Gutenkunst, R.N., et al., Universally sloppy parameter sensitivities in systems biology models. PLoS Comput Biol, 2007. 3(10): p. 1871-78.
4. Holford, N., The Visual Predictive Check - Superiority to Standard Diagnostic (Rorschach) Plots. PAGE 14, 2005: p. Abstract 738.
5. Joyner, M. and B.K. Pedersen, Ten Questions About Systems Biology. J Physiol, 2011.
6. Kumar, N., et al., Applying computational modeling to drug discovery and development. Drug Discov Today, 2006. 11(17-18): p. 806-11.
7. Marino, S., et al., A methodology for performing global uncertainty and sensitivity analysis in systems biology. J Theor Biol, 2008. 254(1): p. 178-96.
8. Weisse, A., et al., Quantifying uncertainty, variability and likelihood for ordinary differential equation models. BMC Systems Biology, 2010. 4(1): p. 144.
9. Wolkenhauer, O., et al., SysBioMed report: advancing systems biology for medical applications. IET Syst Biol, 2009. 3(3): p. 131-6.

Drug Development Advisors

Philadelphia – Boston – Silicon Valley – Seattle

www.rosaandco.com

For more information about this work, please contact:
Christina Friedrich
Rosa & Co LLC
415 643-6534
cfriedrich@rosaandco.com