Considerations for Adapting Previously Built Models for New Quantitative Systems Pharmacology Research

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Introduction

- Using published models is an attractive strategy for quantitative systems pharmacology (QSP) research
- Adapting existing models for new uses can present significant technical and scientific challenges
- Successful adaptation of existing models requires **appropriate expectations**

Objectives

- **Provide guidance** and suggest methodologies for choosing and adapting existing QSP models for new research

Methods

- Publications and websites with mechanistic models of biological pathways are increasingly available
- Technical challenges exist and are often significant
  - Standards are being developed to help (e.g., SBML)
- Rosa has adapted existing proprietary and published models or model components across many therapeutic areas for new research in its PhysioPD™ Platforms
- Adaptation required assessing the existing models for their original research context and their potential fit-for-purpose for the new research application
- Components of the **research context** for a model include:
  1) Key research question(s) or decision(s) to be made
  2) Available data and knowledge
  3) Time and resource constraints
  4) Input from and acceptance by clinical team and management
- Rosa's **Model Qualification Method**[1] (MQM) represents best practices in the construction, qualification, and documentation of QSP models (Figure 1)
- The same standards may be applied to the adaptation of existing models

Figure 1. Rosa's Model Qualification Method[1] (MQM)

Examples

When appropriate, reusing existing models can accelerate project timelines

- FDA review of client drug indicated a perceived inconsistency between HbA1c and plasma glucose change
- Rosa adapted a published model to meet new research needs (Figure 2), simulating clinical trials to understand variability and generate hypotheses to explain the relationships between HbA1c and glucose
- Leveraging an existing model informed client strategy for planned FDA discussions

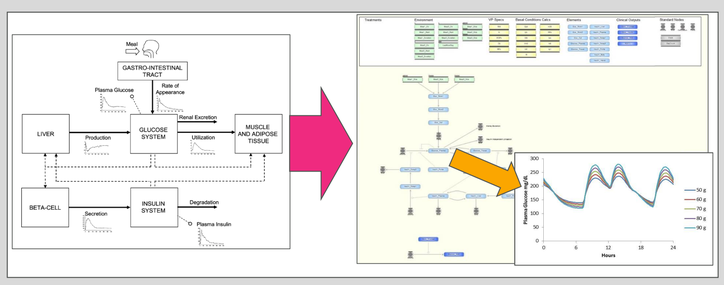

Figure 2. A published model was adapted to meet the research needs

Portions of existing models can be leveraged to construct new models

- Hundreds of models of glucose homeostasis and diabetes have been developed over more than five decades
- Published models have been used to **inform** many of Rosa's diabetes Platforms
  - **Broad models** can be used to guide the design of a **basic architecture** of glucose metabolism
  - **Focused models** can be used to inform specific **submodules**, such as the mathematical representation of two-phase insulin release

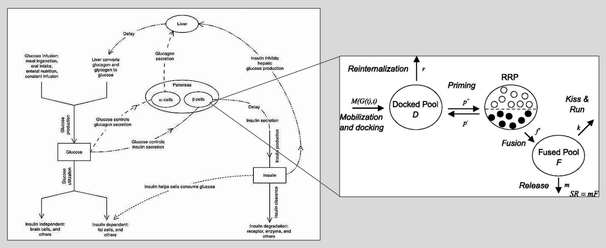

Figure 3. Example models that can inform new model development: Li et al. 2006 (Left) and Pedersen et al. 2010 (Right)

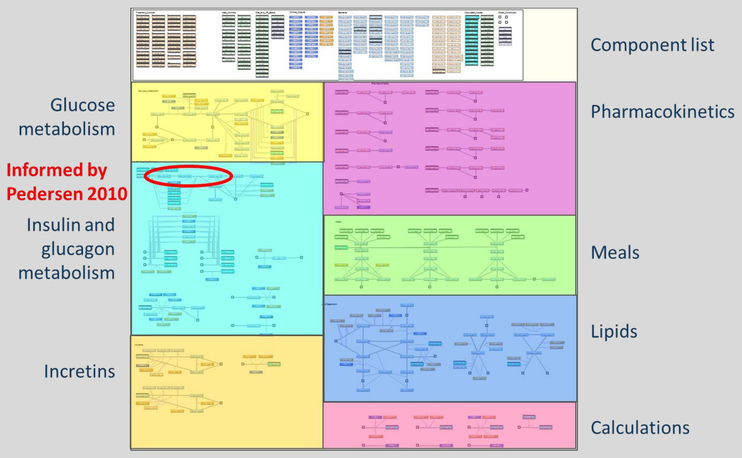

Figure 4. Example type 2 diabetes PhysioPD Platform

Considerations

SCOPE considerations must be assessed with respect to the new research context

- Scope and modeling decisions must be made with the research context in mind
- Necessary detail may depend on the **target** or **timeframe**
- Even if a model appears well-suited, it is advisable to conduct a formal process of answering and documenting the questions below to ensure **understanding and buy-in**
- Management understanding of and confidence in the model is essential for ensuring project **impact**

Criteria	Consideration
Scope	• Does the model represent appropriate biology? • Include necessary biological components and processes? • Appropriate level of biological detail (especially for your target area)? • Represent the appropriate timeframe (e.g., minutes vs. years)? • Represent the phenotype (therapeutic area, severity) of interest? • Is the size and complexity appropriate to the time and resources you can apply? • Is the biology represented appropriately? • Is the embedded biological knowledge current? • Is the original research context clear? • Are assumptions clearly stated? • Are assumption appropriate for the new research context? • Are data and parameter sources appropriate for the new research context?

Which UNCERTAINTIES matter depends on the research context

- There is uncertainty in biology
  - Does a drug target a second pathway? To what extent does the target drive pathophysiology?
- Mechanistic models must make **assumptions** about uncertain pathways
- **Documentation** and assessment of uncertainty provides context for future creation of Virtual Patients (VPs)

- Even if a publication includes a discussion of uncertainties, those uncertainties may not be the most **relevant to the new research context**
- Even if a publication includes an analysis of the impacts of uncertainties, via sensitivity analysis or VPs, results may be different for the new research context
  - Sensitivity analysis is dependent on the outcome, time points, and treatment of interest

Criteria	Consideration
Uncertainty	• Does the publication identify key knowledge gaps and associated assumptions? • Does the publication evaluate the impact of key uncertainties via sensitivity analysis or "what if" scenario testing? • Does the publication include VPs to explore biological uncertainty relevant to the new research context?

It is critical to assess patient VARIABILITY

- Patients may differ in their pathophysiology, clinical presentation, and/or in response to therapy
- VPs should capture aspects of patient variability that is relevant to the new research context
- If VPs relevant for the new research context are not included, they can be added
- Additional considerations are included in the table

Criteria	Consideration
Variability	• Does the publication identify known pathway variability? • Does the publication evaluate the impact of pathway variability via sensitivity analysis or "what if" scenario testing? • Does the publication comment on clinical variability? • Are relevant VPs included? • How do the VPS differ from each other mechanistically? • What clinical phenotype and response to therapy do the VPs represent?

Appropriate qualitative and quantitative testing against DATA should be considered during the model evaluation

- Existing models are often under-tested for the new research context
- Publications often do not fully describe the **testing procedures** or results
- Considerations for evaluating qualitative and quantitative testing are shown below

Criteria	Consideration
Qualitative Testing	• Were relevant experts consulted to assess if model results looked reasonable? • Were relevant sources of information for qualitative testing identified and used, e.g., clinical data from related therapeutic areas, or relevant nonclinical data? • Were "what if" experiments performed to assess model behavior? • Are subsystem behavior tests described, with appropriate data references?
Quantitative Testing	• Were relevant clinical data for the drug of interest used for testing? • Were relevant clinical data for drugs in the same therapeutic area used for testing? • Were multiple disparate types of model perturbations tested and compared to relevant data? • Did the model perform adequately, given the new research context? • Does the model include relevant clinical outcome measures and/or biomarkers? • Is it clear how the outcome measures were derived from the represented biology? • Were population-level outcomes reproduced with appropriate range and distribution of outcomes?

Conclusions

- Adapting existing models for new research is feasible, but drug development teams should do so with appropriate expectations and a high level of care
- Consideration of the original and new research contexts can guide the evaluation of a model's suitability, as well as ensure stakeholder acceptance
- Use of the guidelines helps with the decision making process and to ensure the finished model is fit-for-purpose

References

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