Considerations for Adapting Published Models for PhysioPD™-Style Research

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Title: Considerations for Adapting Published Models for PhysioPD ™ -Style Research

Abstract: The utilization of published models is an attractive strategy for quantitative systems pharmacology research. The process of adapting existing published models for new uses can present significant technical and scientific challenges and should be undertaken with appropriate expectations. In this webinar, we will discuss considerations for choosing and adapting existing models for new research purposes.

Agenda

- Motivation
- Technical Considerations
- Model Scope Evaluation
- Biological Uncertainty and Variability
- Model Testing
- Conclusions

PhysioPD-style published/pre-existing models are becoming more available.

ROSA

- Rosa's PhysioPD™ Research Platforms ("Platforms") are graphical and mathematical models of physiology, disease, and potential or actual drug effects
  - PhysioPD is a type of quantitative systems pharmacology (QSP) modeling
- The Platforms are mechanistic and/or semi-mechanistic representations of interacting biological processes
- Platform and subsystem simulated outcomes are tested against multiple disparate sets of data to ensure robust Platform behavior

- Publications and websites (e.g., www.biomodels.net, http://www.ddmore.eu) with mechanistic representations of biological pathways are increasingly available
- Can published (or otherwise pre-existing) models be utilized for new PhysioPD-style/QSP research?

Motivation for Using Existing Models/Components

- Potential time and cost savings compared to building from scratch
- Build upon others' efforts
- Leverage expert knowledge and solutions to modeling challenges

- Even if one doesn't implement the full model/component, it may still be useful. For example, one might
  - Adapt a portion of the model
  - Use the organized biological knowledge and data

Published Examples and Rosa Case Studies

- Published examples illustrate that mechanistic models can build on prior efforts and evolve, for example:
  - Computational approaches to modeling blood pressure regulation were pioneered by Guyton in the early 1970s[1] and have been continuously updated and adapted
  - A 2013 review[2] traced the genealogy of 100+ models of glucose homeostasis and diabetes developed over the past 50+ years
  - An early osteoclast/osteoblast model[3] is cited in a later model incorporating additional pathways[4], which is cited in later models of osteoporosis[5] and multiple myeloma-induced bone disease[6]

- Rosa routinely draws on our library of previously developed model components
- Two examples from the Rosa practice illustrate reuse of prior published models:
  - Leveraging an entire published model to support discussions with the FDA
  - Leveraging portions of published models to construct a larger research Platform

1. Guyton et al., 1972 (PMID: 4334846)
2. Ajmera et al., 2013 (PMID: 23842097)
3. Komarova et al. 2003 (PMID: 14499354)
4. Lemaire et al. 2005 (PMID: 15234198)
5. Peterson & Riggs, 2012 (PMID: 23835796)
6. Ji et al., 2014 (PMID: 24817420)

Case Study 1: Leveraging an Entire Published Model to Support Client Discussion with the FDA. (1/4)

Preclinical	Phase 1	Phase 2	Phase 3	Phase 4

- Client research challenges:
  - Drug with poorly characterized MOA showed reductions in hemoglobin A1c (HbA1c) and plasma glucose
  - FDA review indicated a perceived inconsistency between HbA1c and average plasma glucose changes with no obvious explanation
- Research approach:
  - Use a mechanistic PhysioPD Research Platform to simulate clinical trial
  - Generate hypotheses to explain observed relationships between HbA1c and glucose
- Research questions were suitable for a published model
  - Focused, high level questions do not require a detailed representation of target mechanisms
  - Conversations with the FDA may benefit if the model was established and peer-reviewed
  - Adapting a published model may help meet a short timeline

Case Study 1: Leveraging an Entire Published Model to Support Client Discussion with the FDA. (2/4)

- The insulin and glucose portion of the Platform had to meet the following criteria:
  - Published model
  - Model accepted by the modeling community and FDA
  - Model evaluated fasting glucose and insulin
  - Model evaluated meal tests
  - Model matched published data for diabetes or healthy individuals
  - Model could be used to evaluate a spectrum of diabetic states

- Rosa reviewed published models and selected the most appropriate one
  - An additional model was selected to translate plasma glucose to predicted HbA1c

Case Study 1: Leveraging an Entire Published Model to Support Client Discussion with the FDA. (3/4)

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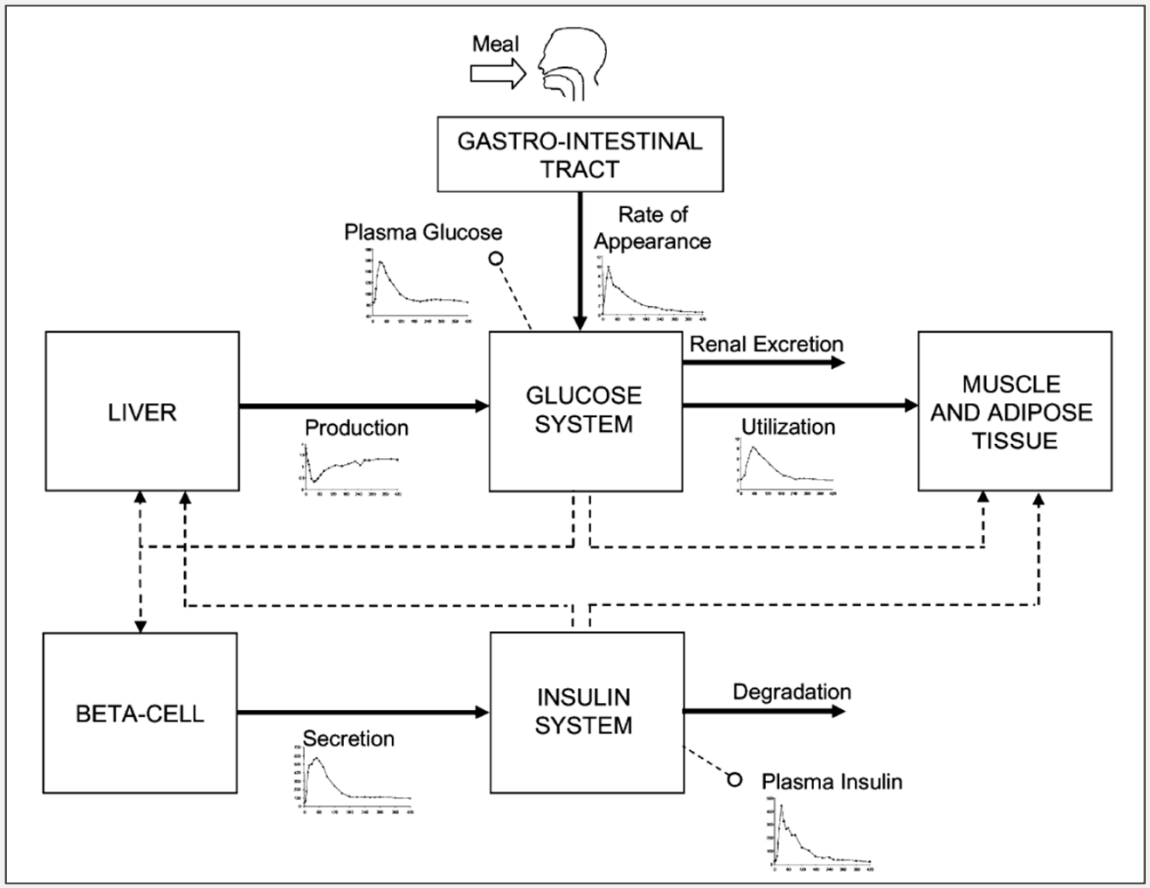
- Rosa adapted the existing model to meet new research needs
  - Adjusted model calibration to match subjects in the clinical trial
  - Developed alternative Virtual Patients (VPs) to explore clinical variability
  - Implemented the therapy of interest
  - Developed a simulation protocol to represent the clinical trial
- Evaluation and adaptation of the existing model facilitated scientific conversations
- PhysioPD research results:
  - Sampling time of fasting plasma glucose likely contributes to a perceived mismatch between HbA1c and glucose
  - Variability in dietary carbohydrate between clinical trial sites may impact observed response
- Program impact:
  - Informed client strategy for planned FDA discussions
  - Recommended strategies for future T2D drug trial design

Case Study 1: Leveraging an Entire Published Model to Support Client Discussion with the FDA. (4/4)

Dalla Man et al., 2007 (PMID: 17926672)



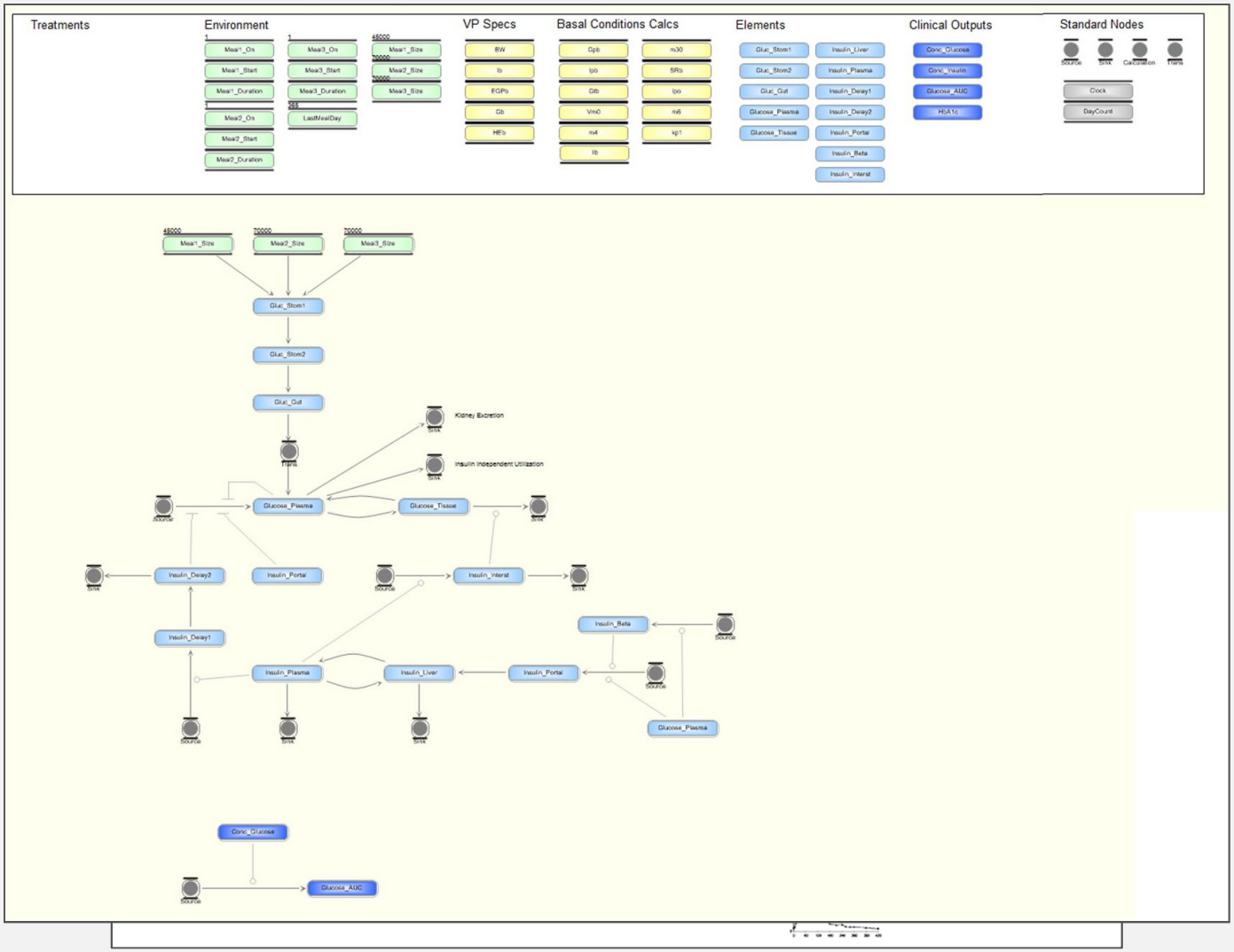
Platform was implemented in JDesigner software (available at https://sourceforge.net/projects/jdesigner/)

Case Study 1: Leveraging an Entire Published Model to Support Client Discussion with the FDA. (4/4)

ROSA

Meals

Glucose & Insulin



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Case Study 1: Leveraging an Entire Published Model to Support Client Discussion with the FDA. (4/4)

ROSA

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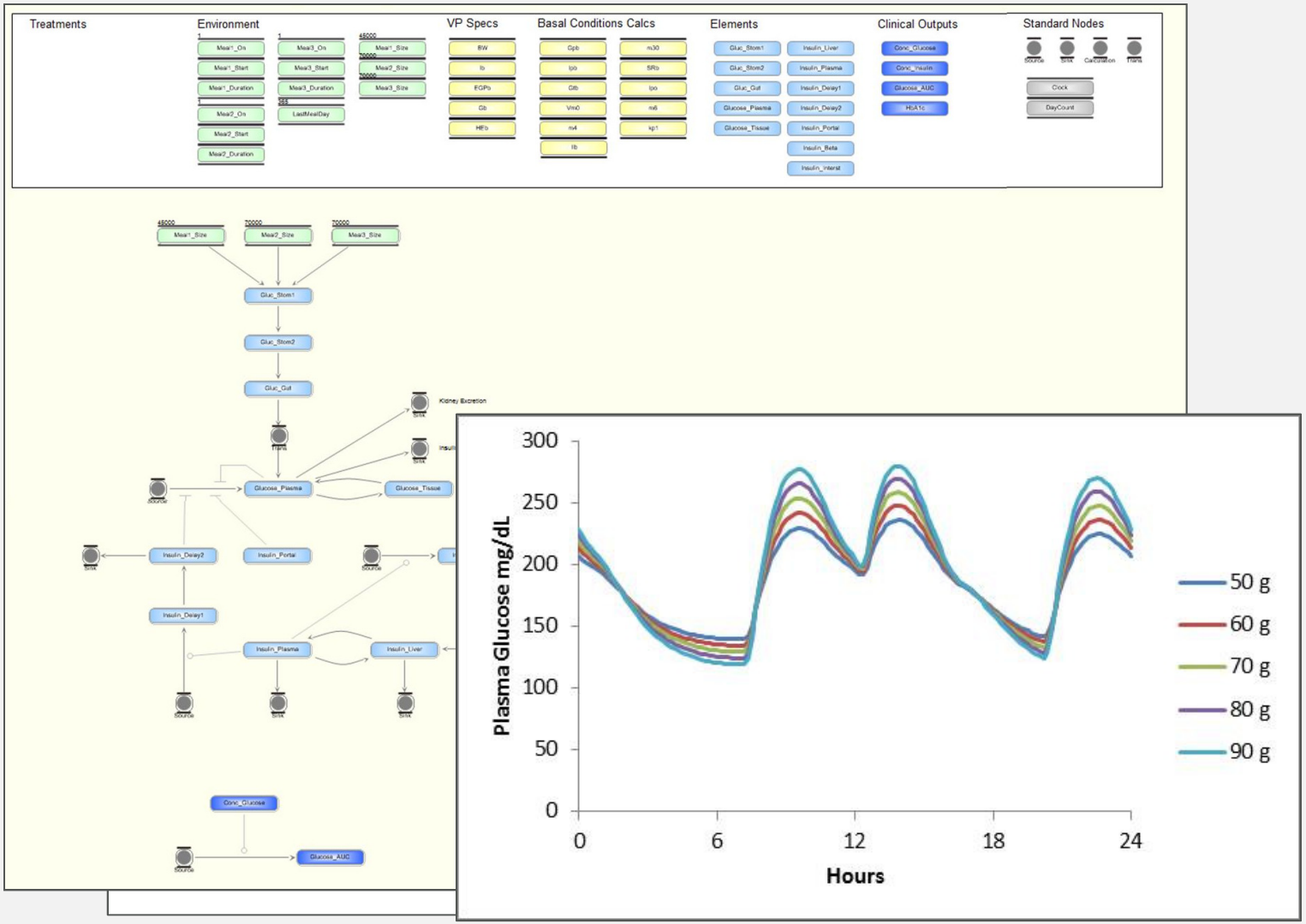
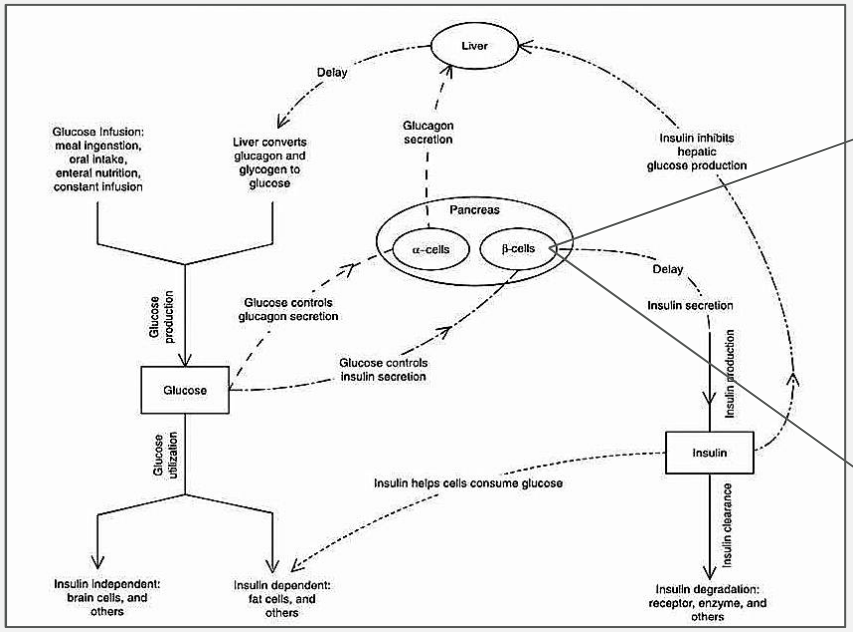


Platform was implemented in JDesigner software (available at https://sourceforge.net/projects/jdesigner/)

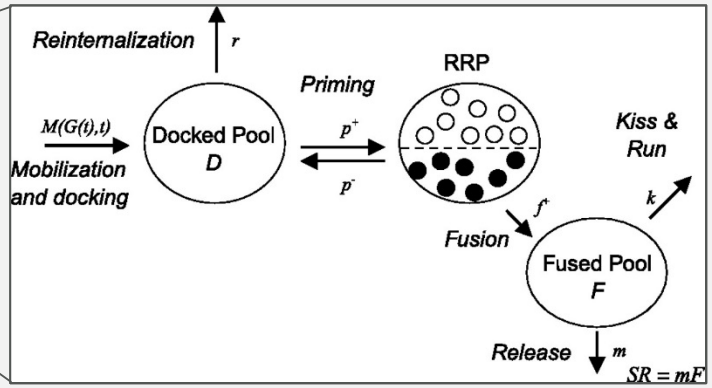
Case Study 2: Leveraging portions of published models (1/3)

- Hundreds of models describing glucose homeostasis and diabetes have been developed over more than five decades[1]
- Published models have been used to inform many of Rosa's diabetes Platforms
  - Broad models such as Li et al., 2006[2] can be used to guide the design of a basic architecture of glucose metabolism
  - Focused models such as Pedersen et al., 2010[3] can be used to inform specific submodules, such as the mathematical representation of two-phase insulin release



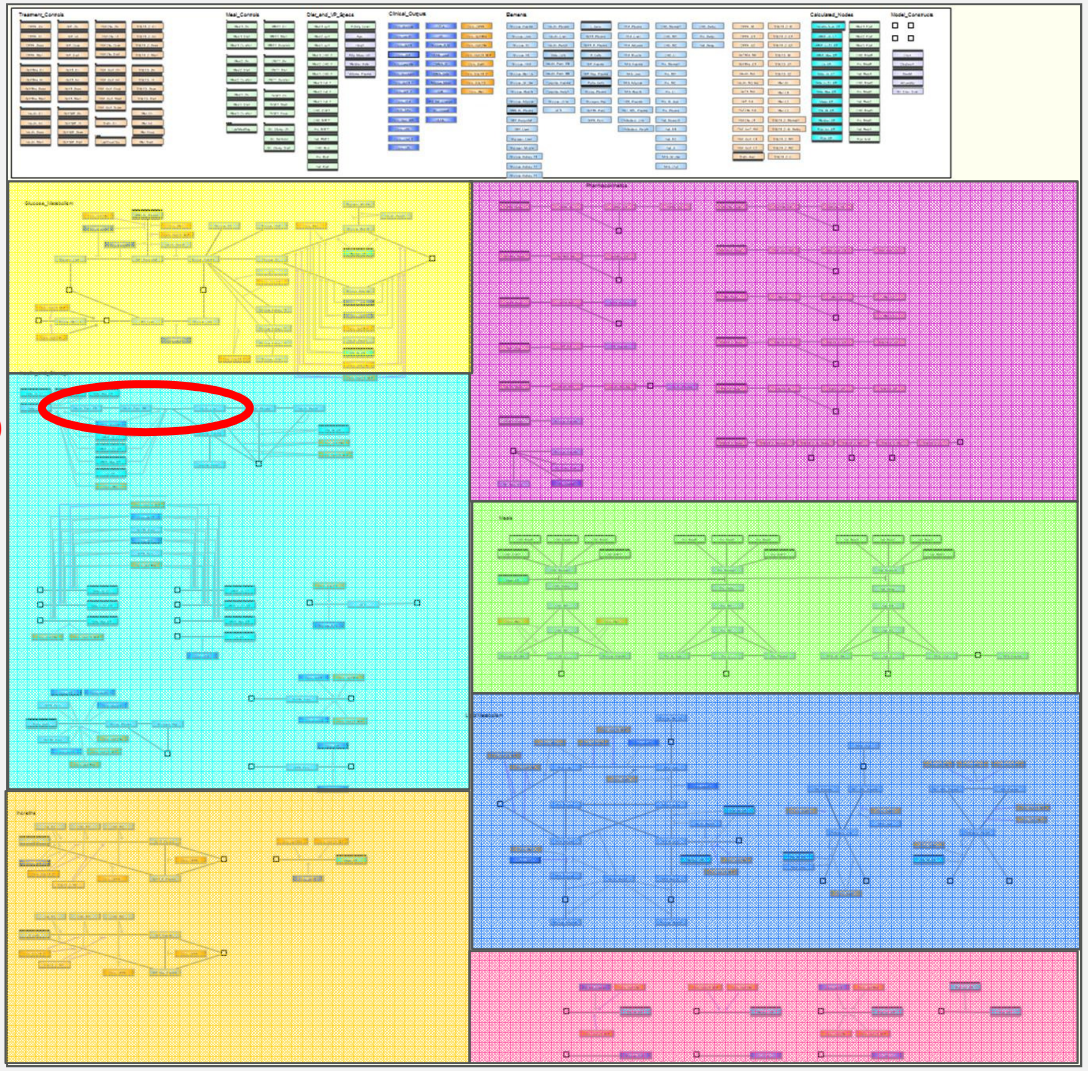
Li et al., 2006

Pedersen et al, 2010



1. Ajmera et al., 2013 (PMID: 23842097)
2. Li et al., 2006 (PMID: 16712872)
3. Pedersen et al, 2010 (PMID: 20009025)

Case Study 2: Leveraging portions of published models (2/3)



Component list

Glucose metabolism

Pharmacokinetics

Informed by Pedersen et al., 2010

Insulin and glucagon metabolism

Meals

Lipids

Incretins

Calculations

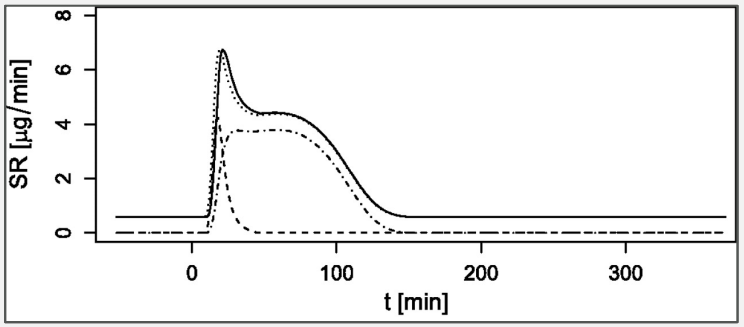
Platform was designed in JDesigner software (available at https://sourceforge.net/projects/jdesigner/)

Case Study 2: Leveraging portions of published models (3/3)

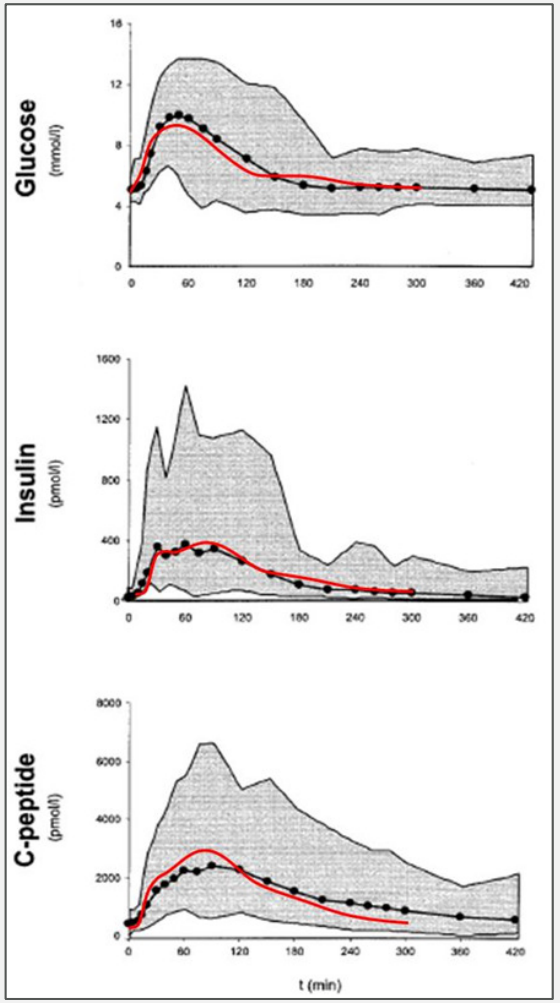
- Previously published efforts contributed to the development of a T2D PhysioPD Research Platform which captured the diverse mechanisms relevant to the client's research questions

- Beta cell mechanisms from Pedersen et al., 2010 informed design of biphasic insulin release, in agreement with data

Simulated insulin secretion rate produced by the mathematical model presented in Pedersen et al., 2010 (PMID: 20009025)



Meal tolerance test in healthy VP (red) as compared with Dalla Man et al., 2005 (PMID: 16249454)



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ROSA

Technical Considerations

- Most of the time, technical issues have to be resolved before a published model will run!

- Example: BioModels.net
  - 627 manually curated models (plus 980 non-curated models)
  - Over 90% of curated models could not be reproduced *

- Common issues *
  - Missing data
  - Incorrect data (wrong units or values)
  - Undefined terms / graph axes
  - Mismatch between text and model
  - Wrong model supplied with paper
  - Only one model supplied but multiple simulations described
  - Software environment no longer available
  - Model no longer available (url points to null)

* Herbert Sauro, “The Importance of Standards in Model Exchange, Reuse and Reproducibility of Simulations”, QSP Congress, 2016

Technical standards are only the first step to ensuring that a model is appropriate for use.

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- Technical challenges are significant
- Standards are being developed to address technical challenges (e.g., SBML)
- Even if a model runs and reproduces published results, care must be taken to evaluate the model's suitability
  - Why was the model built?
  - Under which conditions is the model valid?
  - How was the model qualified?
  - What uncertainties and variabilities were identified during the model development process?
  - Has the impact of these uncertainties or variabilities on model outcomes been evaluated?
- Appropriate models still must be socialized to ensure credibility with stakeholders

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Modeling decisions should be made with the research context in mind.

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Research context components:

- Key research question(s) or decision(s) to be made
- Available data and knowledge
- Time and resource constraints
- Key stakeholders

- Clarity on the research context is essential before building or adapting a model
- Scope and modeling decisions must be appropriate to the research context
- Stakeholders must have confidence that the model is fit-for-purpose

- If a model was previously built, ask:
  - What was the research context?
  - What adaptations are needed to ensure that the model is appropriate for the new research context (i.e., fit for a new purpose)?

Scope considerations must be assessed with respect to the new research context.

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Scope Considerations	Check?
Does the model represent appropriate biology?	☐
Include necessary biological components and processes?	☐
Appropriate level of biological detail (especially for your target areas)?	☐
Does it represent the appropriate timeframe (e.g., minutes vs. years)?	☐
Does it represent the phenotype (e.g. 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 assumptions appropriate for the new research context?	☐
Are data and parameter sources appropriate for the new research context?	☐

Example: Repurpose a Hepatic Metabolism Model?

- A client was interested in modeling hepatic lipid metabolism
- Could a published model be integrated with an existing metabolism model?

- The model comprised the following biological elements:

Liver	Muscle	Adipose	Plasma
Glucose	Glucose	Glucose	Glucose
Glycogen	Glycogen	Free fatty acids	Non-esterified fatty acids
Glucose 6-phosphate	Glucose 6-phosphate	Triglycerides	Endogenous Triglycerides
Pyruvate	Pyruvate	Glycerol	Exogenous Triglycerides
Free fatty acids	Free fatty acids		Insulin
Triglycerides	Triglycerides		
	Notional AMP		

Given the new research context, the existing model would need significant updates to be adapted for use.

ROSA

Scope Consideration	Check?
Does the model represent appropriate biology?	✓
Include necessary biological components and processes?	✓
Appropriate level of biological detail (especially for your target areas)?	No (too detailed)
Does it represent the appropriate timeframe (e.g., minutes vs. years)?	No
Does it represent the phenotype (e.g. therapeutic area, severity) of interest?	No
Is the size and complexity appropriate to the time and resources you can apply?	No
Is the biology represented appropriately?	Not fully assessed
Is the embedded biological knowledge current?	✓
Is the original research context clear?	✓
Are assumptions clearly stated?	✓
Are assumptions appropriate for the new research context?	No
Are data and parameter sources appropriate for the new research context?	Not fully assessed

- Team determined it would be more efficient to build a new Platform, potentially informed by this publication

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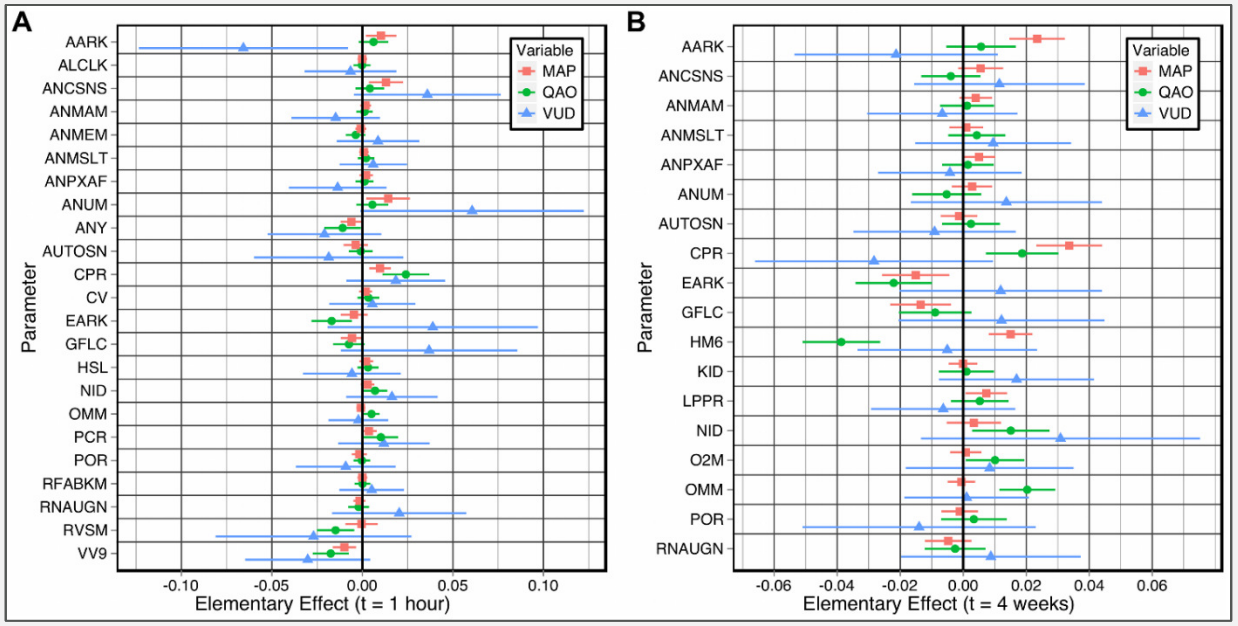
Biological Uncertainty

- There is uncertainty in biology
  - E.g., does the drug target a second pathway? To what extent does the target drive pathophysiology?
- Mechanistic models must make assumptions about uncertain pathways
- Which uncertainty matters most depends on the research context
  - E.g., if you're evaluating a new pathway, you need to evaluate the uncertainty around that new pathway
- Documentation and assessment of uncertainty provides context for future creation of VPs

Uncertainty Considerations	Check?
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 multiple VPs to explore biological uncertainty that is relevant to the new research context?	☐

Some publications address questions about uncertainty using sensitivity analysis and/or VPs.

- E.g., Moss et al., 2012[1] identified the most significant parameters regulating blood pressure, cardiac output, and urine output in the 1992 Guyton model[2] at intermediate and late time points (1 hour and 4 weeks after perturbation)



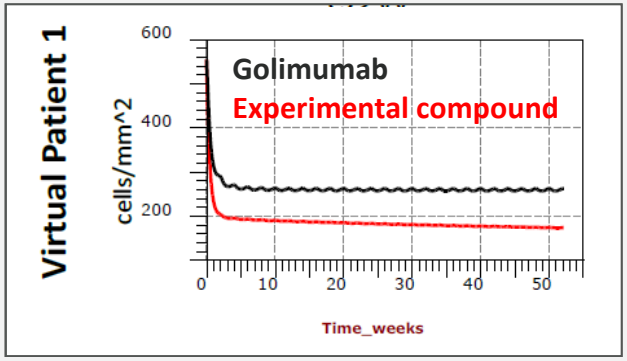
- Parameter sensitivity depends on the outcome, timepoints, and treatment of interest
  - Context matters for evaluating uncertainty

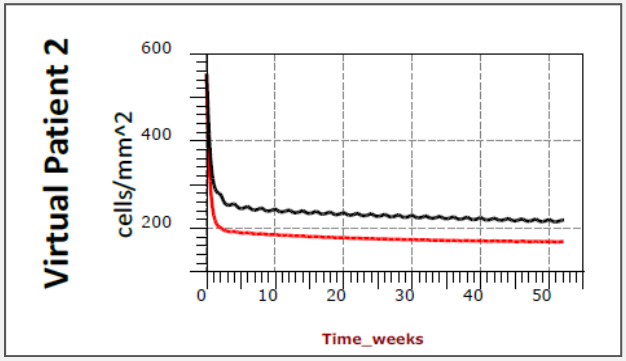
1. Moss et al., 2012 (PMID: 22761561)

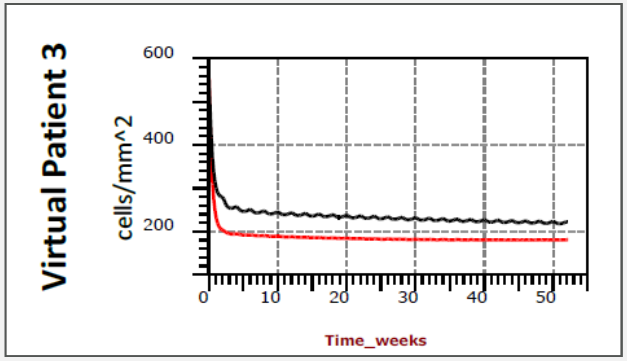
2. Guyton 1992 (PMID 1730451)

In a Rosa Rheumatoid Arthritis PhysioPD Platform, VPs explored the impact of key uncertainties.

	VP1	VP2	VP3
TNF effect on Ang2	No	Yes	Yes
Leaky vessel conversion to normal	No	Yes	Yes
VEGF effect on normal vessels	Yes	Yes	No
Matches steady-state data	Yes	Yes	Yes
Matches Golimumab effect on cell numbers	Yes	Yes	Yes
Golimumab effect on leaky vessels	Reduced growth	Significant decrease	Significant decrease
Golimumab effect on mature vessels	Regression	Stabilization	Increase



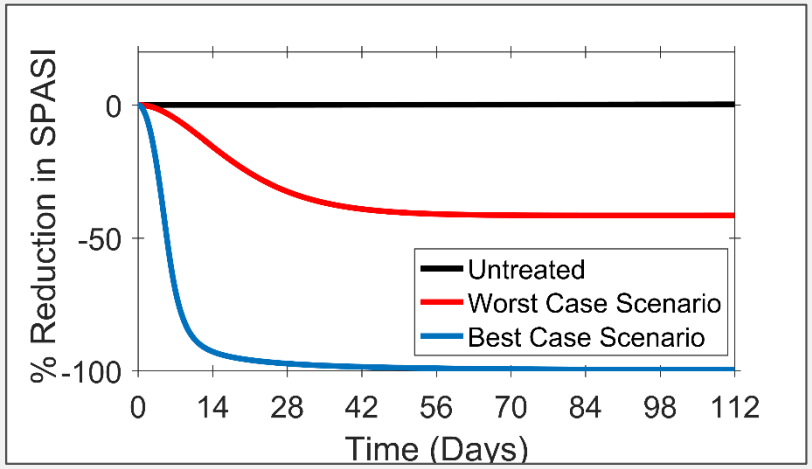


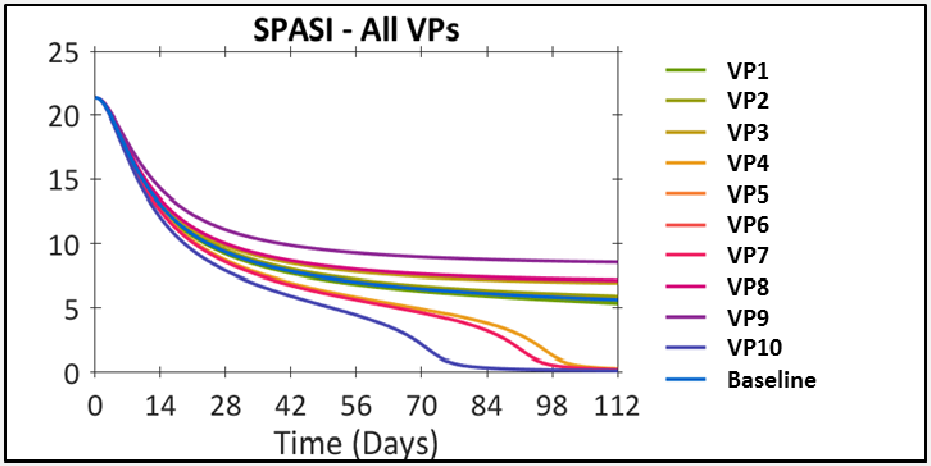


- The research illustrated the impact of different hypotheses on predicted outcomes

In a Rosa Psoriasis PhysioPD Platform, VPs explored the impact of target-related uncertainties.

- Client was developing an inhibitor which targeted specific enzymes
- However, the roles of the individual, similar enzymes were highly uncertain
  - Uncertainties highly specific to this research context
- Two extreme VPs determined the range of possible efficacy (left figure)
- Additional VPs explored the impact of specific uncertainties (right figure)
- This analysis highlighted experiments most critical to de-risk development





Which uncertainty matters depends on the research context.

ROSA

- Even if a publication includes a discussion of uncertainties, those uncertainties may not be the most relevant to the new research context
  - E.g., what about uncertainties related to the new target of interest?

- 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

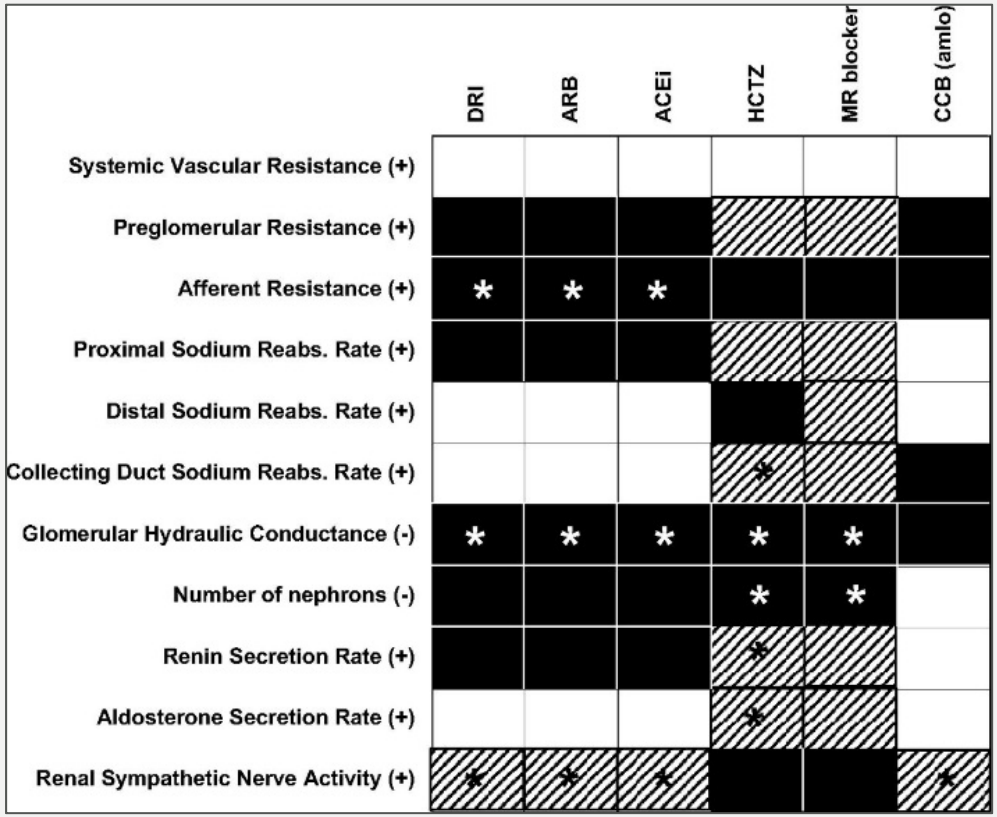
Variability

- Patient heterogeneity is often critical to assess
- Patients may differ in their pathophysiology (mechanistic pathway variability), in their clinical presentation, and/or in their 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

Variability Considerations	Check?
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 multiple relevant VPs included?	☐
If VPs are included, how do they differ from each other mechanistically?	☐
If VPs are included, what clinical phenotype and response to therapy do they represent?	☐

VPs can be used to evaluate the impact of pathophysiological variability.

- For example, Hallow et al., 2014 used VPs to evaluate the impact of underlying hypertension pathology on response to different antihypertensive therapies

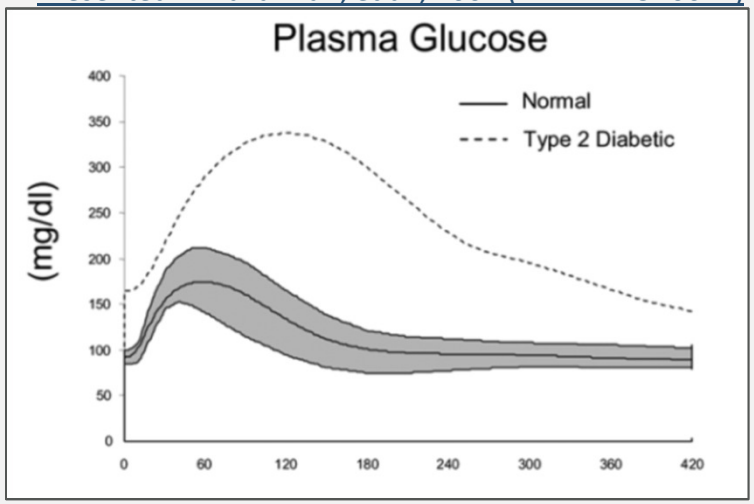


Hallow, et al., 2014 (PMID: 24500431)

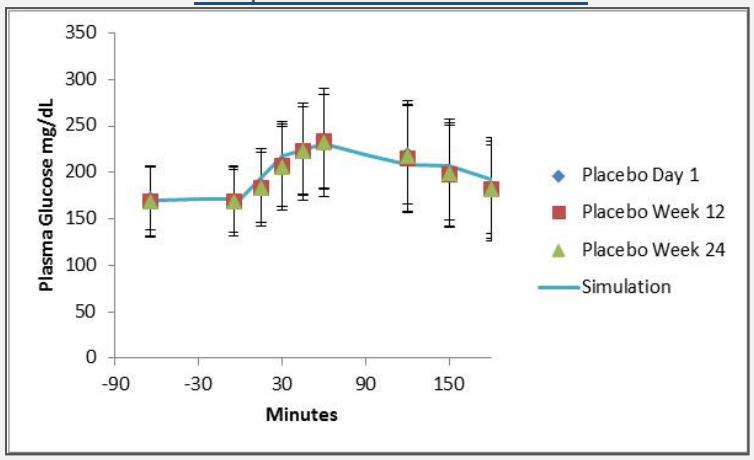
In this example from a Rosa T2D PhysioPD Platform, new VPs were created to match clinical trial subjects.

- A model was adapted from the literature
  - Case Study 1, from earlier in this presentation
- The publication included one diabetic VP (top right figure)
- T2D subjects exhibit significant pathophysiological variability, e.g., in
  - Peripheral insulin resistance
  - Beta cell function
  - Hepatic glucose output
- The published VP was significantly different from many of the subjects in the client's clinical trial data
- Rosa adjusted relevant parameters to create a cohort of VPs with more similar pathophysiology and diabetes severity
- Even if a publication includes VPs, they may not be relevant to the new research context

Simulation of normal and diabetic VPs
Presented in Dalla Man, et al., 2007 (PMID: 17926672)



Simulation of a new diabetic VP, compared to clinical trial data.



In this example from a different Rosa T2D PhysioPD Platform, VPs were explored clinical variability (1/2).

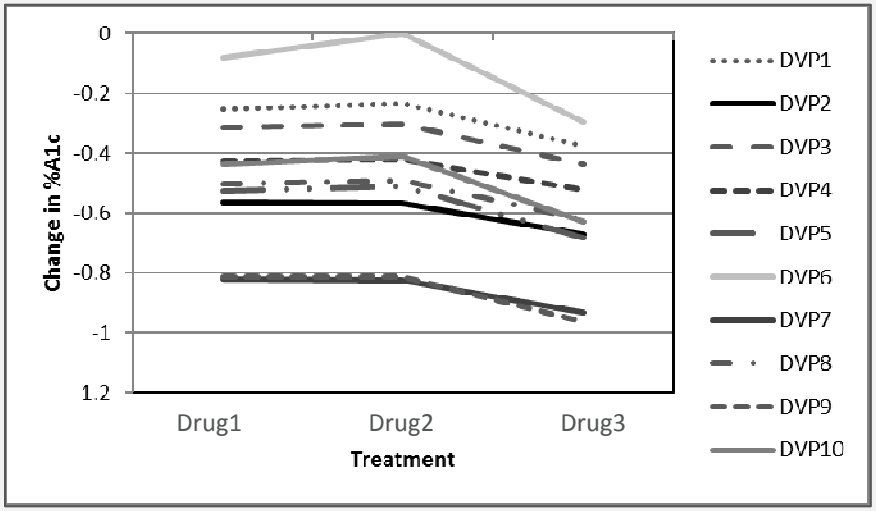
ROSA

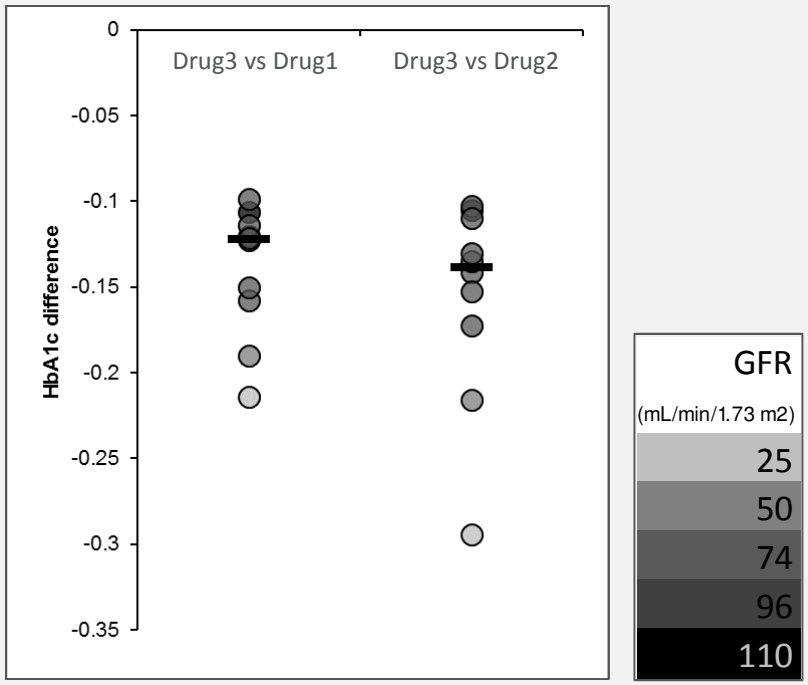
- VPs were created to explore how clinical variability might affect response to a new therapy
- Prototypical VPs were created to explore ranges of diabetes severity and pathophysiology

VP	FPG mg/dL	FPI pM	HbA1c	Peripheral Insulin Resistance	Beta Cell Function	Hepatic Insulin Resistance	GFR mL/min/1.73 m^2
DVP1	126-140	50-75	6.5-8	Moderate	Moderate	Moderate	60-90
DVP2	126-140	>75	7-8	High	Good	High	>100
DVP3	140-160	<50	7-8	Moderate	Poor	Moderate	60-90
DVP4	140-160	50-75	7-8	Moderate	Moderate	High	>90
DVP5	140-160	>75	7-9	High	Good	High	60-90
DVP6	>170	<50	8-10	Moderate	Poor	High	<30
DVP7	>170	<50	8-10	Moderate	Poor	High	>90
DVP8	>170	50-75	8-10	High	Poor	High	60-90
DVP9	>170	<50	8-10	High	Poor	High	60-90
DVP10	>170	<50	8-10	High	Poor	High	40-60

In this example from a different Rosa T2D PhysioPD Platform, VPs explored clinical variability (2/2).

- VPs highlighted the range of expected clinical efficacy, as well as comparison to competitor therapies
- VP variability highlighted specific clinical characteristics that most influence efficacy and competitive differentiation
- If a publication includes VPs, what clinical phenotype and response to therapy do they represent?





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Model Testing

- Existing models are often under-tested for the new research context
- Published models often do not fully describe the testing procedures or results

- Models are constrained by a variety of data types
  - Physical laws and constraints
  - Health and disease physiology
  - Target and drug mechanisms
  - Preclinical pharmacology
  - Marketed therapies
  - Clinical trials for the investigational compound(s)

- Testing should be appropriate for the type of available data
  - Qualitative vs quantitative
  - Subsystem vs whole-system behavior
  - Healthy vs disease physiology

Qualitative and quantitative model testing should be considered.

ROSA

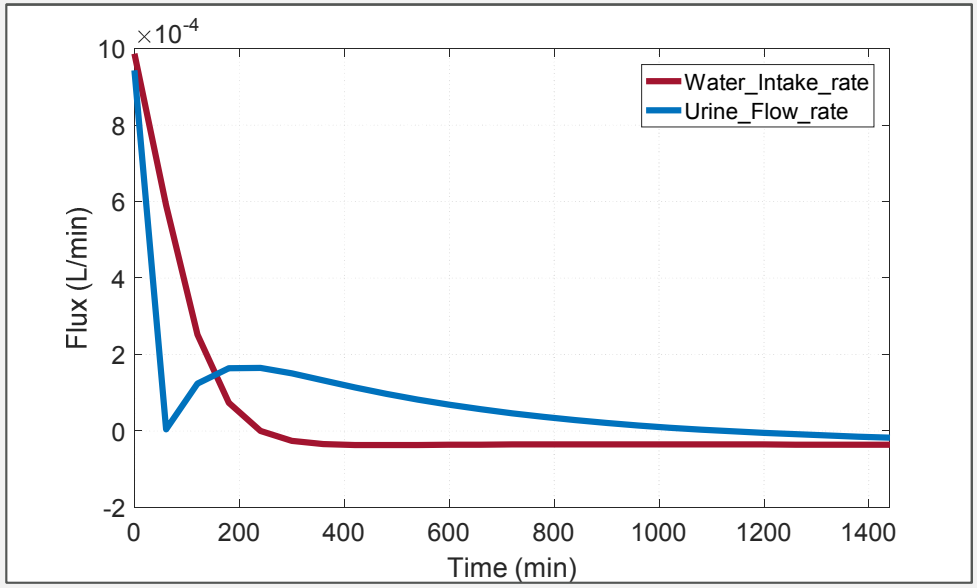
Qualitative Testing Considerations	Check?
Were relevant experts consulted to assess if model results looked reasonable?	☐
Were relevant sources of information for qualitative testing identified and used, e.g., clinical data from related therapeutic areas, or relevant non-clinical data?	☐
Were what-if experiments performed to assess model behavior?	☐
Are subsystem behavior tests described, with appropriate data references?	☐

Quantitative Testing Considerations	Check?
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?	☐

Example: Rosa attempted to apply a published blood pressure model to assess a new drug target.

ROSA

- Published model scope seemed appropriate for the new research context
- Publication focused on different mechanisms, and did not directly test the new target pathway
- Rosa conducted qualitative testing of the new target pathway
  - Inhibiting the target pathway by a reasonable degree resulted in un-physiological responses: negative water consumption and urine output



- Requisite testing depends on the research focus and questions of interest

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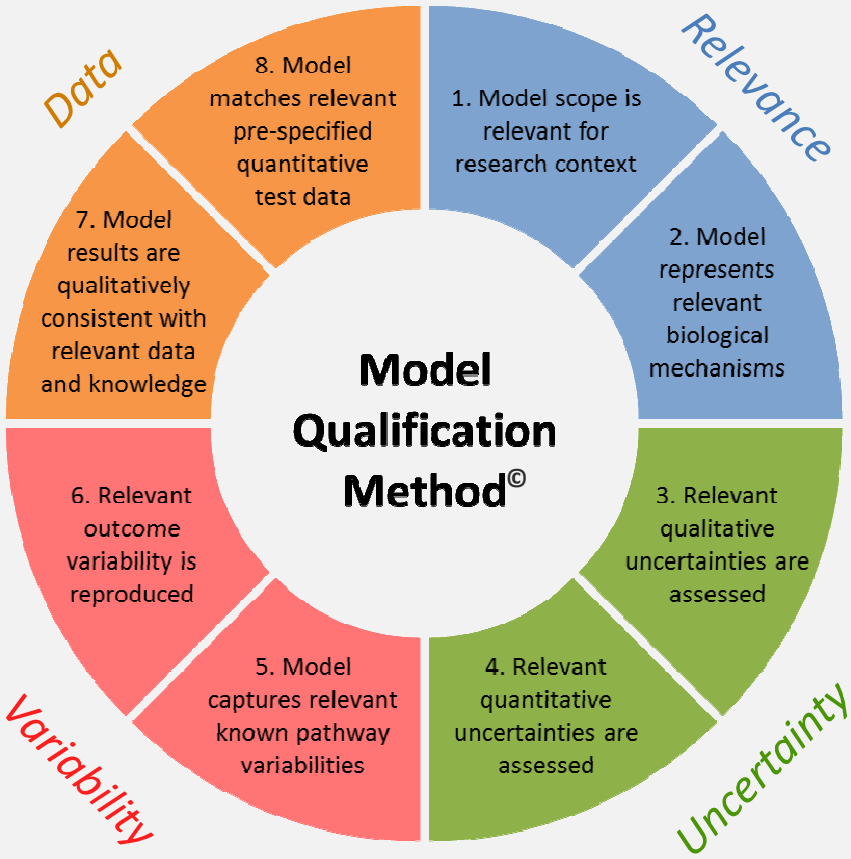
- Conclusions

Rosa's Model Qualification Method (MQM) Best Practices for Construction, Qualification, & Documentation



Ref: Friedrich, CPT Pharmacomet. Syst. Pharm. (2016)

Models must be relevant, correct, and credible to ensure impact.

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- There is more to a model than equations and parameters
- Criteria for assessing if an existing model is fit for a research context should include:
  - Technical considerations
  - Scope
  - Uncertainty and Variability
  - Model Testing
- Stakeholder involvement is crucial for ensuring credibility
- If an existing model does not meet all relevant criteria for the new research context, additional modeling and qualification activities should be expected
- Adapting pre-existing models should be undertaken with appropriate expectations

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Considerations for Adapting Published Models for PhysioPD™-Style Research

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