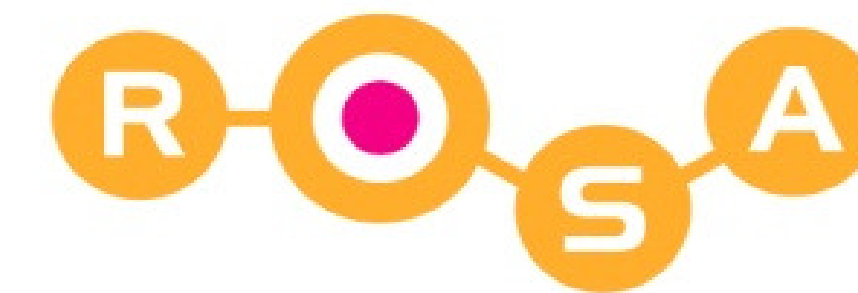


# Modeling Glucose Metabolism in Diabetes



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## Background

The dramatic rise in the incidence of diabetes and associated comorbidities is a major challenge for the medical profession.

- In the US, 20.8 million people have diabetes
- An estimated 6.2 million people have not yet been diagnosed.
- 26% of the US population has impaired fasting glucose.

Development of novel therapeutics and/or use of combinations of novel and existing therapeutics may improve the management of diabetes, particularly for those patients who have poorly-controlled disease with current therapeutics.

Quantitative physiological models being used to support decision-making in pharmaceutical research and development.

Physiological models are built to be

- Internally consistent relative to the laws of mathematics
- Externally consistent relative to pertinent data
  - Clinical trial results
  - Physical laws such as mass conservation.

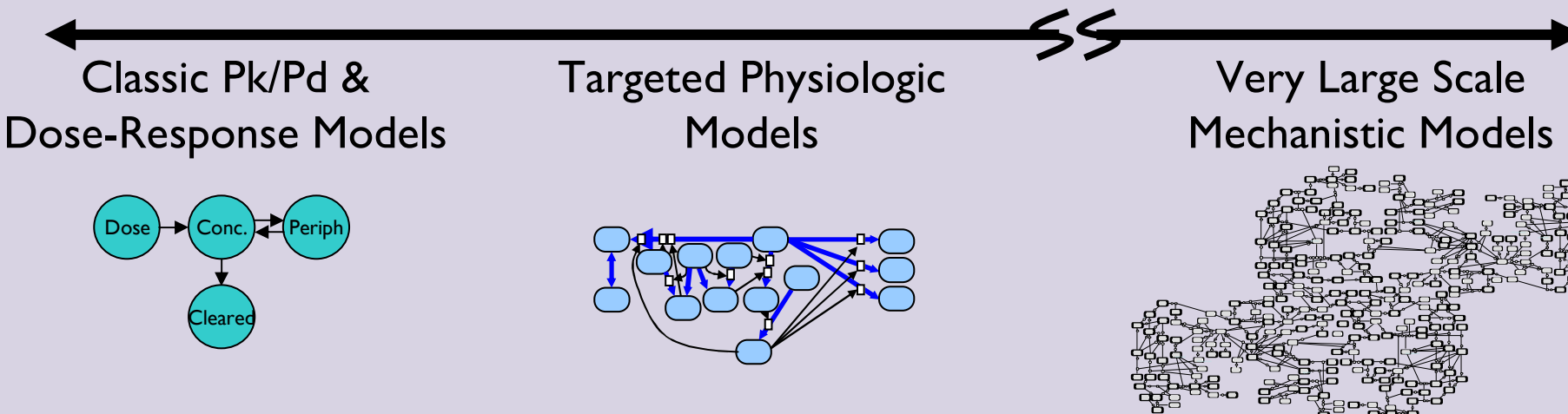
The models

- Vary widely in size
- Have parameters with physiological meaning
- Incorporate large sets of public and proprietary data

The models are used to

- Identify of relevant data gaps
- Explore the viability of a target mechanism,
- Explore the characteristics of lead compounds,
- Test the impact of patient variability on outcomes
- Identify optimal dose and regimen for optimizing patient response.

Different scales of model have different strengths and weaknesses.



- | Classic PK/Pd & Dose-Response Models                                                                                                                                                                               | Targeted Physiologic Models                                                                                                                                                                                                                                     | Very Large Scale Mechanistic Models                                                                                                                                                                                                       |
|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| <ul style="list-style-type: none"><li>• Narrowly targeted</li><li>• Few physiologic insights</li><li>• Require human data</li><li>• Lower cost</li><li>• Statistically rigorous</li><li>• Phenomenologic</li></ul> | <ul style="list-style-type: none"><li>• Decision-focused</li><li>• Mechanistically insightful</li><li>• Exploits nonclinical data</li><li>• Detail &amp; cost focused on decision</li><li>• Useful for trial simulation</li><li>• Not general purpose</li></ul> | <ul style="list-style-type: none"><li>• Broadly applicable</li><li>• Physiologically sound</li><li>• Can use nonhuman data</li><li>• Significant investment</li><li>• Not statistically tractable</li><li>• Difficult to modify</li></ul> |

## Model Development

We developed a simple mathematical model of human glucose metabolism to study the relationship between glucose uptake, glucose release, and insulin production and plasma glucose concentrations. This model was designed to explore several specific decisions in a drug development program.

### Simulation Method

JDesigner (Systems Biology Workbench) was used to generate the graphical and mathematical reaction networks. Documentation for the model was included within and linked to JDesigner. A JDesigner export to MATLAB function was used to generate a MATLAB script with the ordinary differential equations (ODEs) from the JDesigner reaction networks. A wrapper that invoked the JDesigner derived script and parameter sets that defined the virtual diabetic patients was scripted in MATLAB for clinical trial simulation.

### Regulatory Networks

Glucose and insulin regulatory networks were generated on the basis of several models available in the literature. Parameters for these networks were based on values reported in the literature. The physiological networks implemented in this model include:

**Glucose Metabolism** – intestinal absorption, hepatic metabolism, pancreatic metabolism, neural metabolism, peripheral tissue metabolism, kidney secretion.

**Insulin Metabolism** – production, release, metabolism

**Dietary Inputs** – OGTT, MTT

**Drug Pharmacokinetics** – Metformin, Glyburide, SGLT, incretins.

## Purpose

Develop a mathematical model of diabetes that can be qualified for use according to the eight tests of model fitness.

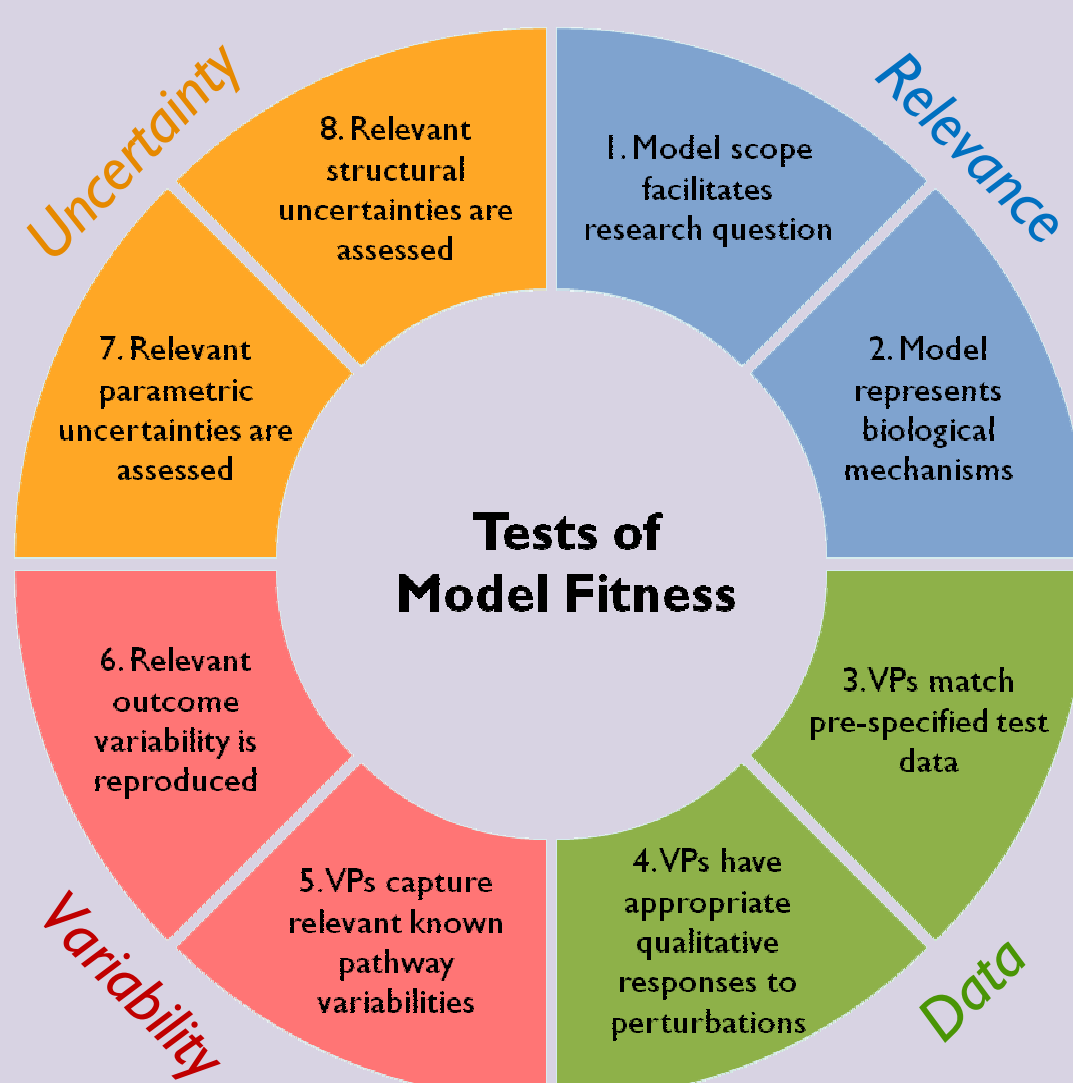
Physiological models can have positive program impact, yet their acceptance has been limited.

One obstacle to wider acceptance is the lack of a formally established methodology for testing the quality of physiological models.

- Current statistical analyses that are used with low-order models are not practical
- Statistical approaches fail to address uncertainty

Diabetes PhysioPD model with examples of tests within each of the main model qualification areas.

## Model Qualification



The eight tests of model fitness as defined by Rosa & Co, LLC. The set of tests represents a framework for qualifying physiological models for use in drug development contexts. When all eight tests are satisfied, research can proceed with confidence.

## Model

Relevance – Model scope must facilitate research question

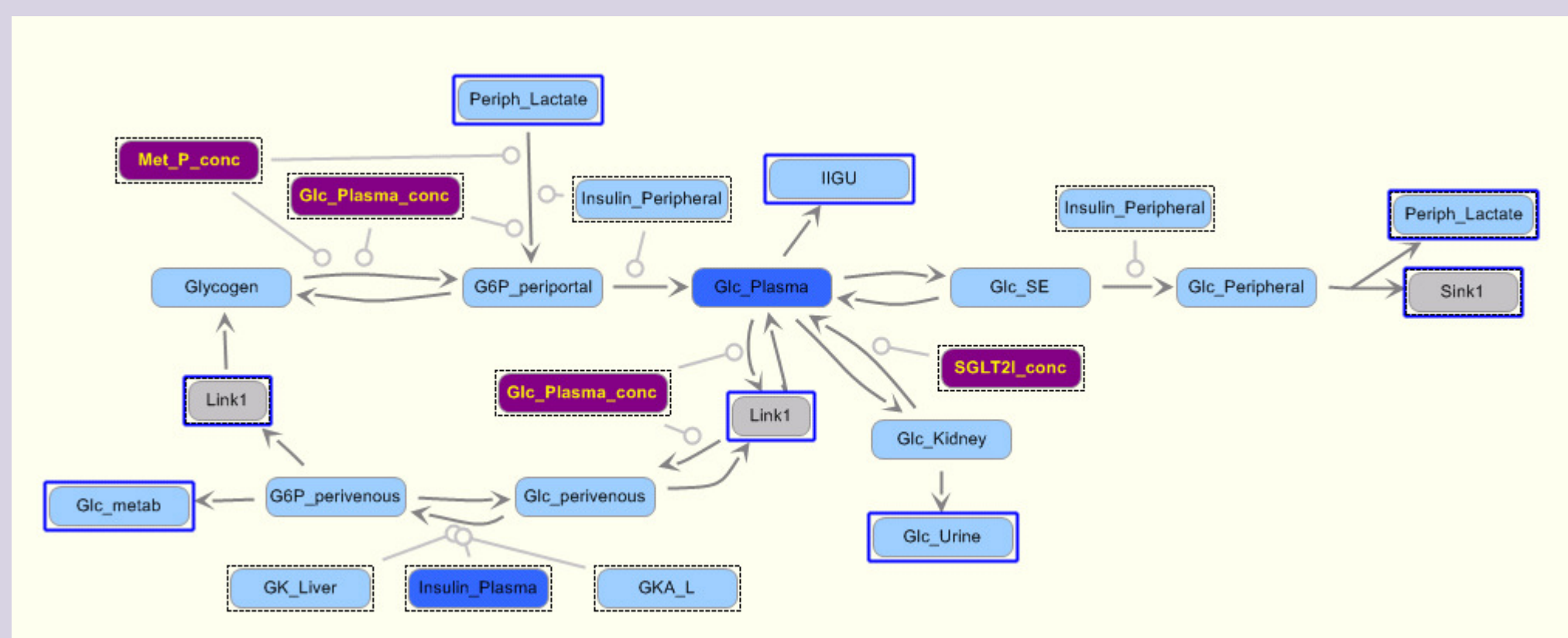
The model must support meaningful investigation of systemic effects of perturbations of interest on outcomes of interest

The model scope included development of a diabetes model focused on a specific mechanism of action (not shown). The mechanism was not in glucose metabolism, however, it could impact hepatic glucose metabolism through alterations in insulin and glucose homeostatis.

The model required glucose metabolism, but did not require either long term function or detailed glucose metabolism.

Therefore, glucose metabolism was modeled at an overall pathway level to meet scoping requirements without adding unnecessary detail. By matching the level of detail to what was needed to address the decision, the model could be developed faster.

The scoping process is critical for defining the decision, model detail, testing criteria, and necessary model quality.

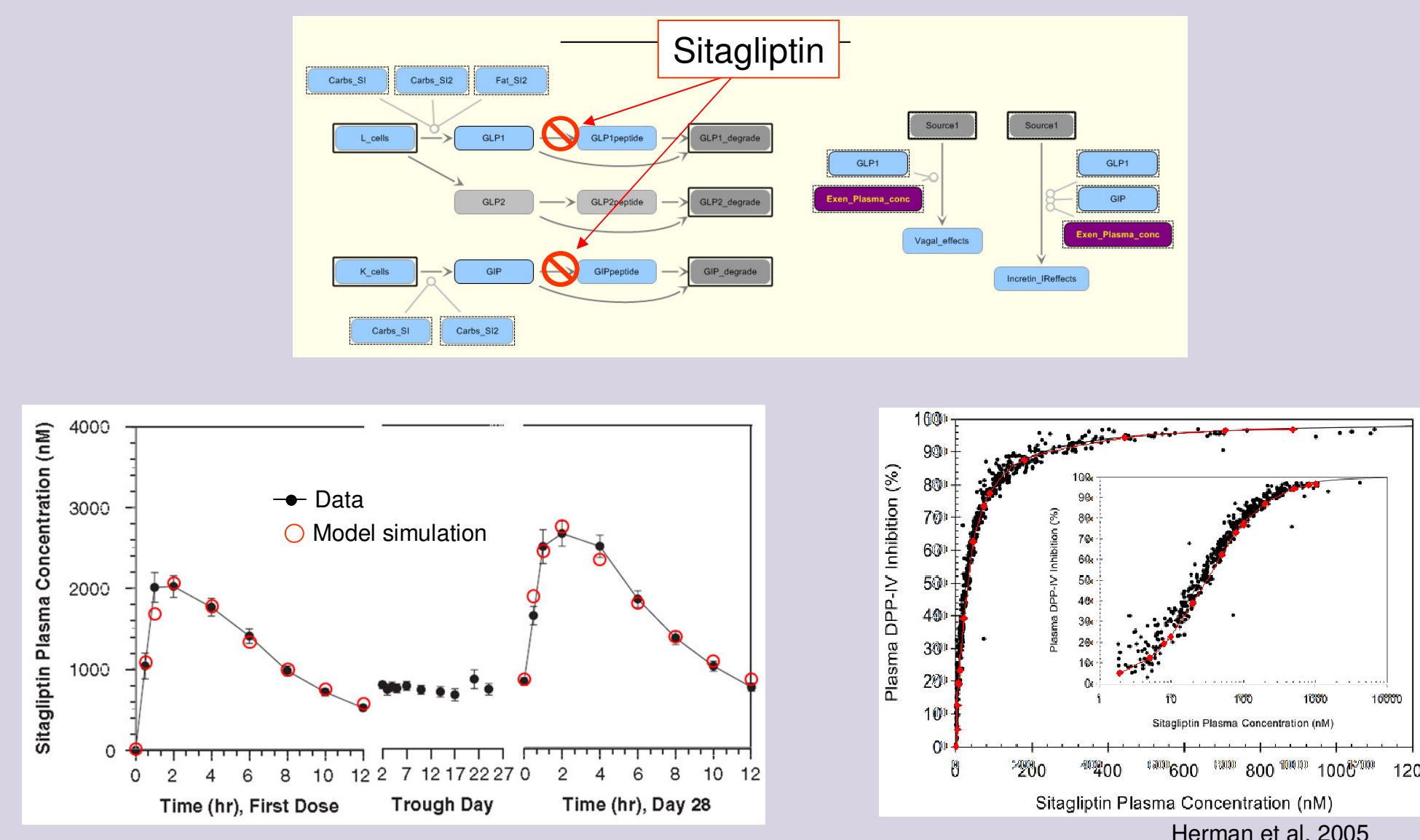


## Conclusions

- Model was developed in collaboration with and used by modeling team for program decisions.
- Initial model development was very rapid
  - Mechanistic detail limited to information needed for decisions
- The model is rapidly modified with new drug classes and targets.
  - Model sections must be requalified with additions

Development of formalized framework for qualifying physiological models will enable these models to gain wider acceptance within the drug development community and federal agencies.

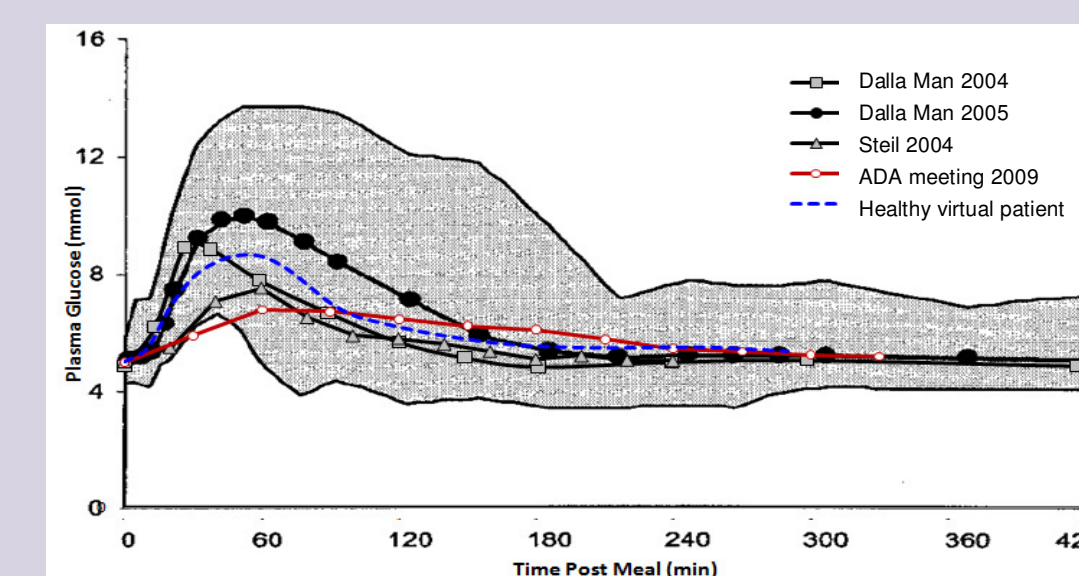
Data – VPs match pre-specified test data



It is critical that the testing data be specified during the scoping process before the model is developed. The test data must reflect outcomes of interest for pathways, organs, and whole body specification.

Including drug pharmacokinetic modeling and drug action within the larger model allowed both component and whole body testing of the model.

Variability – Relevant outcome variability is reproduced

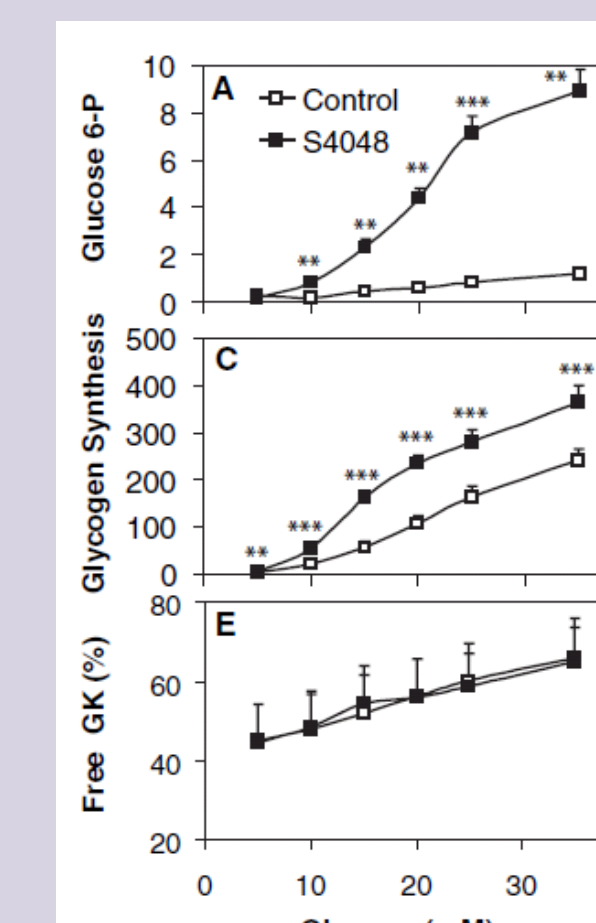


Cohort of virtual patients must span the range of clinical responses (e.g. from 5th to 95th percentile). The appropriate statistical test varies dependent on context. This example shows a median virtual patient compared against test data from four different data sources.

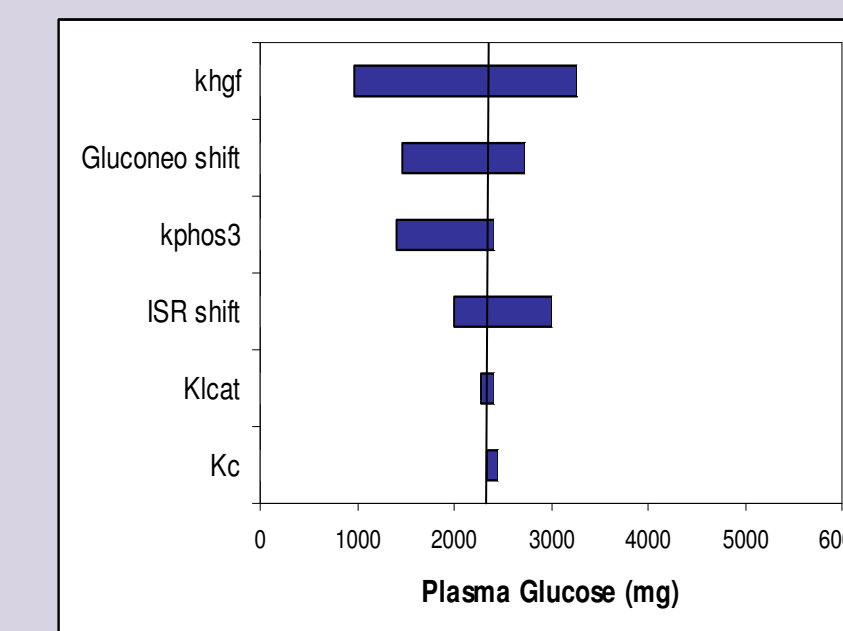
Uncertainty – Relevant parametric uncertainties are assessed

Sensitive uncertainties must be identified and the impact assessed.

Understanding the effect of glucokinase activators requires that glucokinase and its regulation in the liver be included in the model. The exact amount of GK and its intrinsic activity is difficult to measure in human liver. Therefore, in vitro and animal experiments are used to estimate the parameters for this enzyme. This leads to uncertainty as metabolic differences exist between animals and humans, while in vitro experiments lack feedback between multiple cell types and organs. The nature and amount of uncertainty must be documented and, if possible, quantified.



Data from Harndahl 2006 used to build the model.



Sensitivity analysis to explore uncertainty in hepatic glucose parameters. If the outcome of interest is not sensitive to the value of the parameter than the uncertainty around that parameter is decreased.

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