Characterizing postprandial glucose responses in individuals using a computational modelling approach

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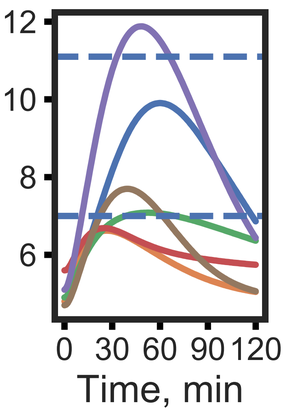
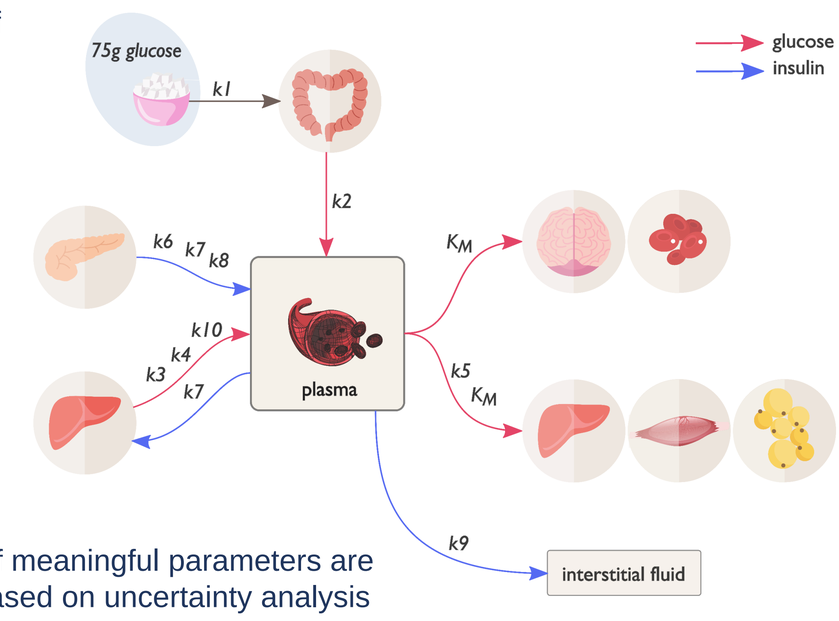
INTRODUCTION



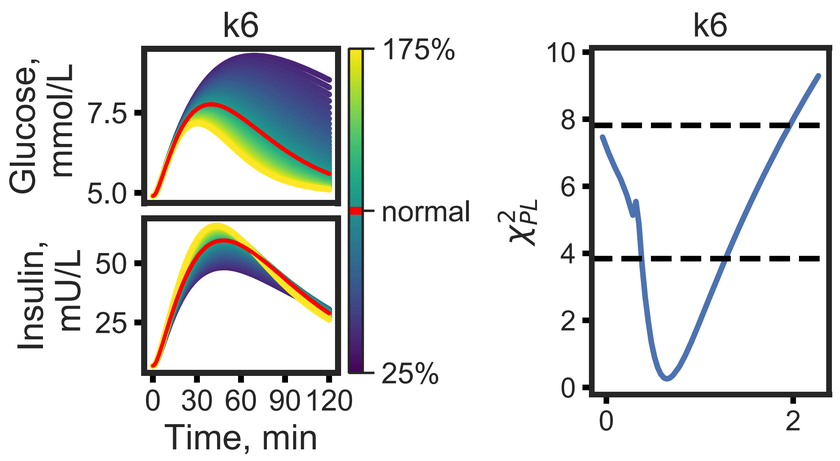
- Single timepoint measures insufficient to characterize glycemic control
- Large variability in the dynamic properties
- Figure: glucose response of individuals to 75g oral glucose bolus

APPROACH

1. Mechanistic model of glucose & insulin dynamics
2. Parameters control the behaviour of mechanisms
3. Personalization via subject specific parameter values

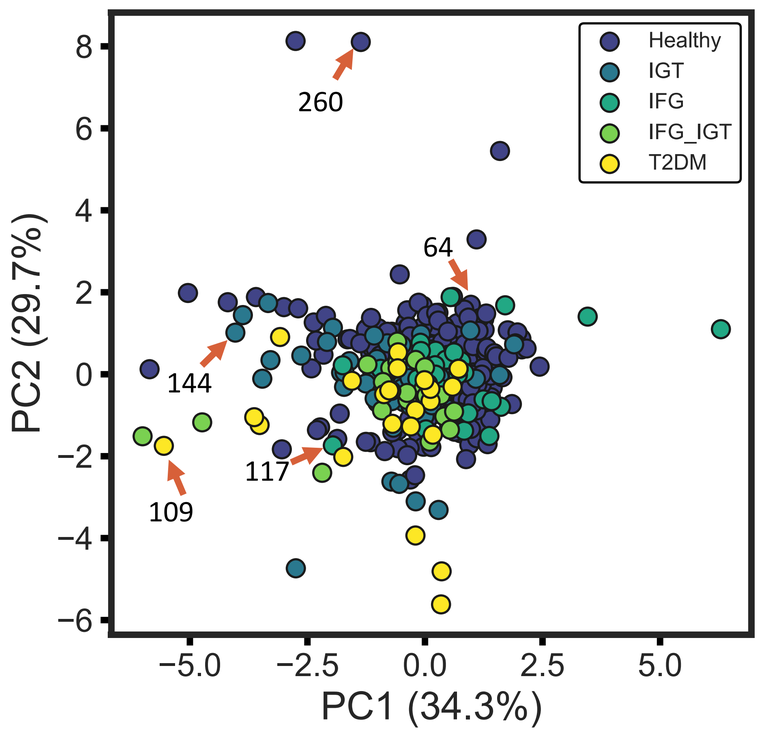


4. A subset of meaningful parameters are selected based on uncertainty analysis
5. The parameters are estimated by fitting the model on participant specific time series data

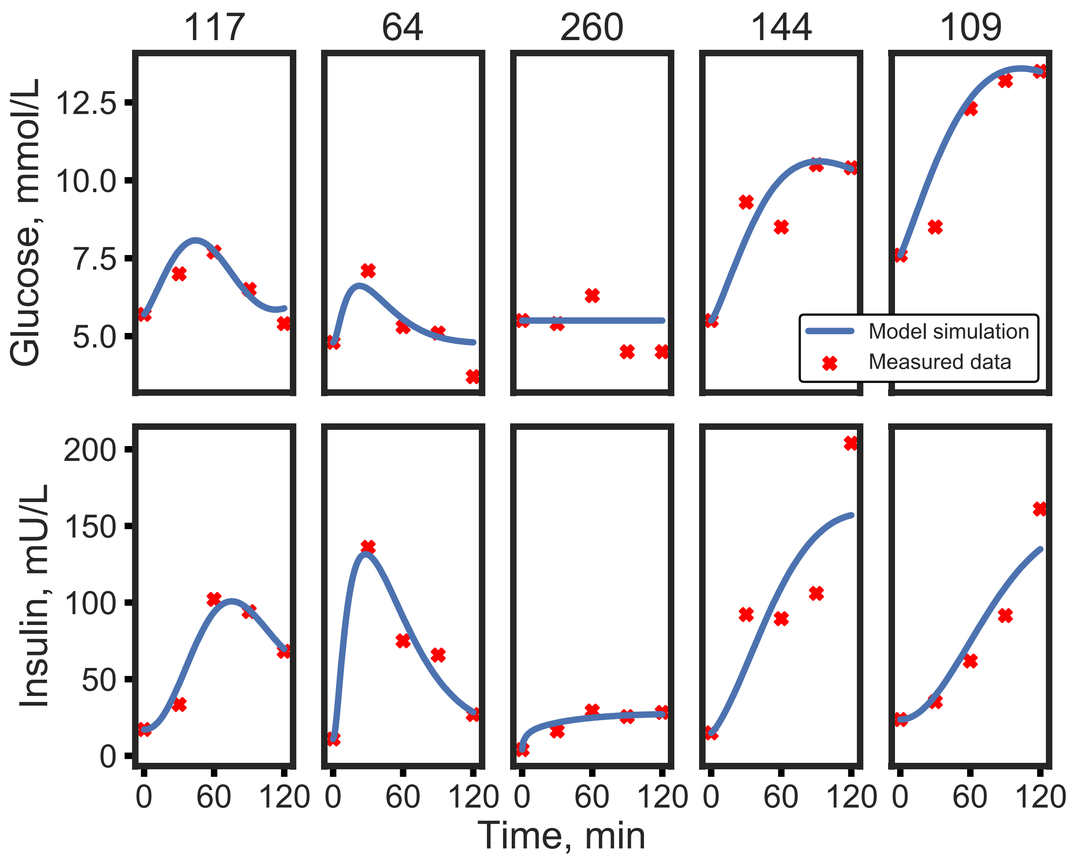


- Figures: schematic of the model (top), example of parameter sensitivity (left), example of parameter identifiability (middle)

RESULTS & DISCUSSION



- A model with 4 parameters was selected for parameter estimation after screening of candidate models
- The personalized models were capable of describing a wide range of responses including healthy, prediabetic and type 2 diabetic but also responses of intermediate states as well



- The personalized models may assist in the understanding of the differences between metabolic states and the trajectories between them
- Figures: Personalized models in the reduced parameter space, colored by classification of diagnosis by the American Diabetes Association criteria (left), examples of personalized model simulations (right)

INTRODUCTION

The evolution from healthy glucose control towards prediabetes and type 2 diabetes occurs continuously over years, characterized by deteriorations in the plasma glucose and insulin concentrations [1]. However, the large heterogeneity in the pathophysiology of type 2 diabetes and individual's glycemic control make it difficult to categorize participants into prevention target groups and necessitates the mechanistic characterization of the glucose and insulin dynamics on a personalized level.

Ordinary differential equation (ODE) based mathematical models have been developed to describe the plasma glucose response in humans to a single dose of glucose [2,3]. These models are mathematical abstractions of the real biological system and they provide quantitative information on the interactions, dynamics and regulation of specific components of the system. Quantifying the response using a modelling approach facilitates the mechanistic understanding of the underlying physiology as well as the development of decision support systems for preventing diabetes.

We aim to characterize an individual's glucose response to an oral glucose tolerance test (OGTT) using a personalized ODE model that describes glucose and insulin dynamics in the postprandial state [4].

APPROACH

Data from the Diogenes [5] dietary intervention study, including a 5 time point OGTT was used in modelling the glucose responses.

In order to estimate participant's glucose and insulin dynamics we fit an ODE based mechanistic model describing glucose and insulin dynamics on the OGTT challenge test data. The model was adapted from [4] to allow personalization by selecting a subset of the parameters to be estimated. The candidate models were then carefully curated for best fitting model while also maintaining certainty (sensitivity and identifiability) in its parameter values. Finally, parameters of the model were estimated on individual's data. The model was implemented in MATLAB 2018b.

RESULTS & DISCUSSION

The screening of candidate models resulted in a model containing four sensitive and identifiable parameters. The model was successfully individualized by fitting it to subject specific time series data. The resulting personalized models were capable of capturing a wide range of glucose and insulin dynamics including normal, prediabetic and type 2 diabetic responses.

The participant's responses can be characterized by their place in the parameter space. This approach also allows observation of the continuous trajectory between healthy to diabetic states, contributing to the mechanistic understanding of changing between states.

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