



Background and Objectives

Type 2 diabetes (T2DM) is a disease exhibiting a gradual worsening of hyperglycemia, on the timescale of years. Studying the critical transitional phase from healthy to diabetic is of interest, but acquiring such data in humans is not practical due to ethical reasons and the long study duration required.

ZSD rats, a strain of rats bred specifically to spontaneously develop metabolic syndrome and type 2 diabetic symptoms [1] has been used in a population model to describe the changes in insulin sensitivity (IS), beta-cell function (BCF) throughout different phases of diabetes and their effects on glucose and insulin.

Methods and Materials

Body weight (WGT), fasting plasma glucose (FPG), and fasting serum insulin (FSI) were collected every 2 weeks for 24 weeks from ZSD rats (n=23) with an ad libitum diet starting from age 7 weeks. During these 24 weeks the rats' insulin sensitivity is decreased as indicated by hyperinsulinemia with normoglycemia. Eventually the rats become overtly diabetic with hypoinsulinemia and hyperglycemia. The weight of the rats increases due to both natural growth and excess growth (Egrowth) owing to the strain's propensity for fat storage and obesity. As the rats become hyperglycemic the weight decreases slightly. A semi-mechanistic model previously developed with human data [2] was adapted to rat data. Baseline IS and BCF were estimated according to the human homeostatic assessment model (HOMA) [3]. Non-linear mixed-effect model estimation was performed with NONMEM 7.3 with first-order interaction.

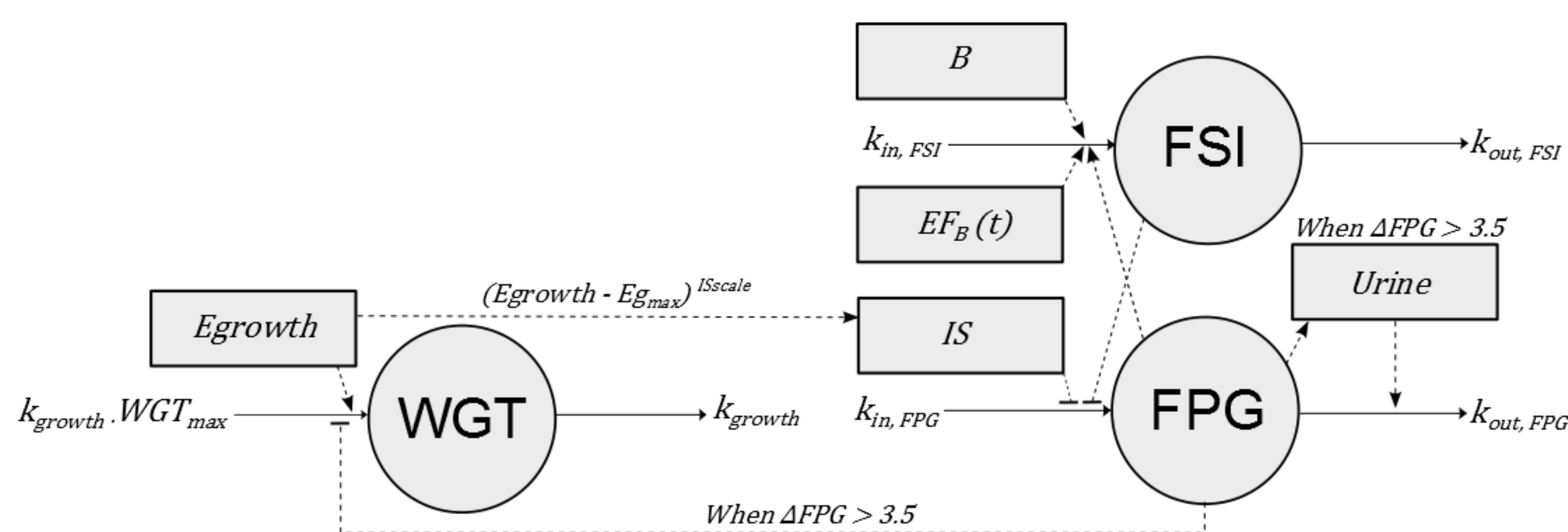


Figure 1. The semi-mechanistic model used to describe diabetes progression in ZSD rats. The model is adapted from a previous semi-mechanistic model developed for humans[2]. WGT change is influenced by the natural growth of rats according to the Brody growth function [4] ($k_{growth} \cdot WGT_{max}$), excess growth (Egrowth) from ZSD strain's natural tendency for obesity, and inhibited when FPG is higher than 3.5 from its baseline. The change in insulin sensitivity (IS) is driven by Egrowth. Beta-cell function (B) is an asymmetrical logistic function which describes the disease progression effect ($EF_B(t)$), estimating the time of beta cell failure. FPG stimulates the production of FSI, while FSI inhibits the formation of FPG. When change in FPG exceeds 3.5 from its baseline, elimination of FPG is accelerated by an exponential function dependent on FPG, resembling increased renal glucose elimination.

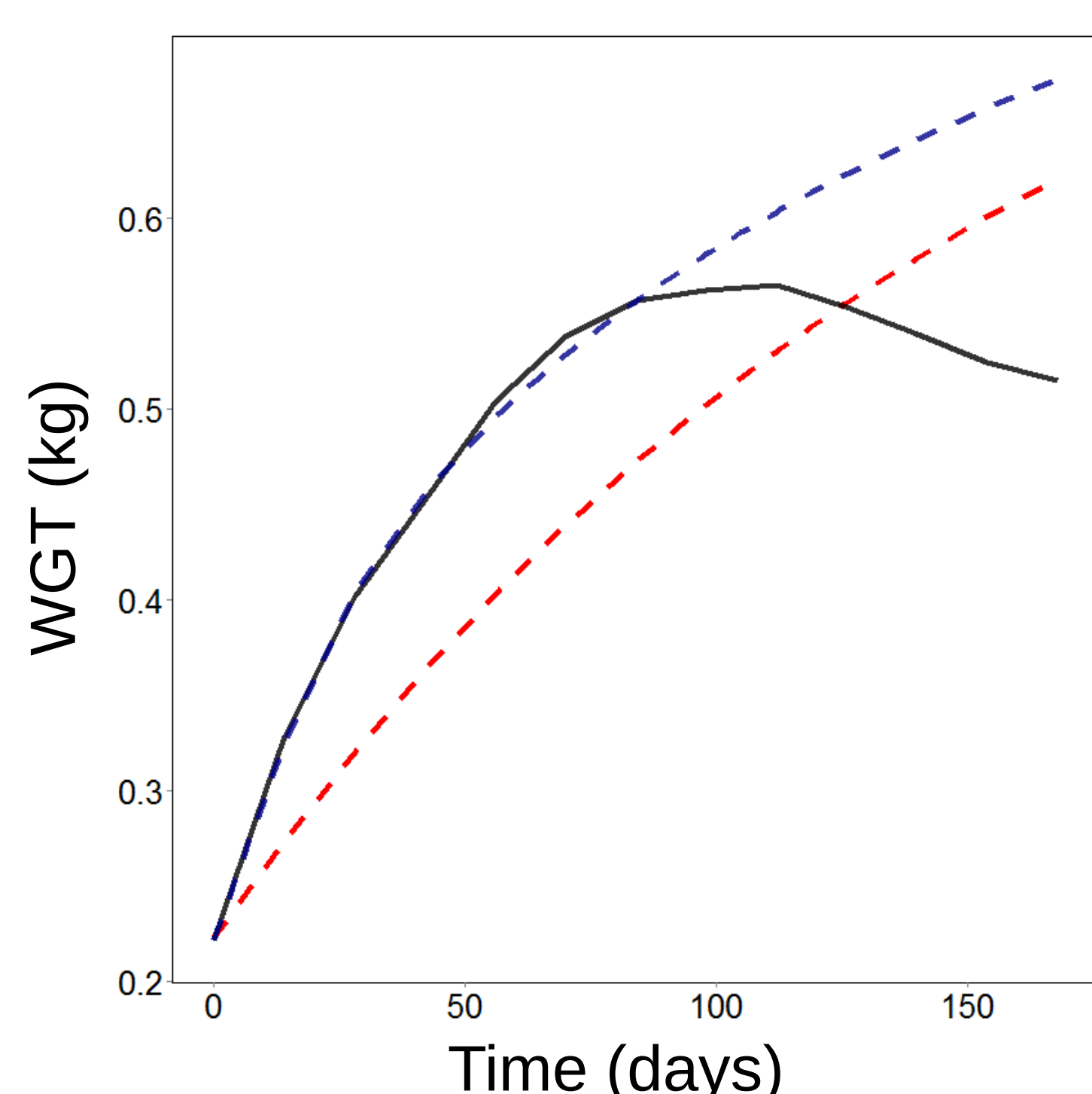


Figure 2. Observed population weight compared to natural growth and excess growth. Black line is the population weight profile, dashed red line is the Brody growth model, and dashed blue line is the Brody growth model with excess growth function (Egrowth). The differential equation for Brody growth model is

$$\frac{dWGT}{dt} = k_{growth} \cdot (WGT_{max} - WGT)$$

with parameters $WGT_{max} = 0.84$ kg, $k = 0.043$, and $WGT(0) = 0.0061$, with start of study at age 7 weeks. The model accounts for the overshoot with Egrowth, and feedback from FPG's effect on weight acts to correctly capture the weight decline towards the end of the study.

Conclusions

- A semi-mechanistic model was successfully developed for a rat population to describe insulin and glucose profiles adequately, transitioning from healthy to an advanced stage of diabetes.
- It is also shown that weight loss can be modeled to mimic "starvation in the midst of plenty" which is a phenomenon related to hypoinsulinemia and hyperglycemia.

Results

Baseline estimated IS and BCF were 41% and 39% of normal humans, respectively. Egrowth was best described with a stimulatory effect with a maximum of 1.8, gradually decreasing to 1. The effect of WGT change on IS can be seen on Figure 3. BCF was described with a non-linear rise until it reached a mean peak at 14 weeks, after which it declined to a negligible level, leading to hypoinsulinemia and hyperglycemia. The FPG-dependent urine effect exerted a 2 to 6-fold increase on the k_{out} of FPG (Figure 3).

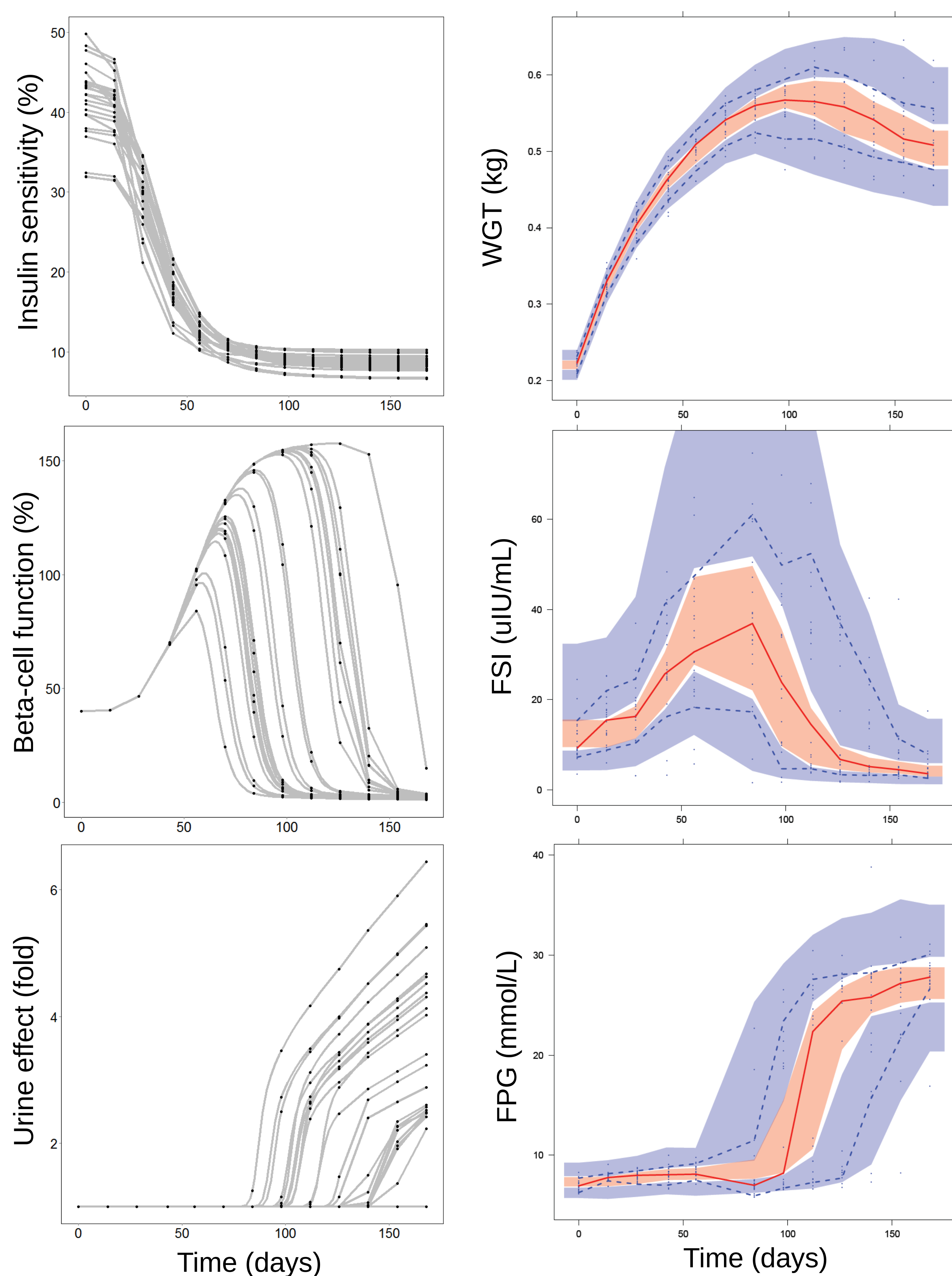


Figure 3. Individual predicted profiles of insulin sensitivity (top panel), beta-cell function (middle panel) and relative renal glucose elimination (bottom panel). Blue dots indicate observations; red lines are the medians of observations; red areas are the 95% confidence intervals (CI) of the median prediction intervals (n=200); blue dotted lines are the 90th and 10th percentile of the observations; blue areas are the 95% CI of the 90th and 10th percentile of the predictions (n=200).

Figure 4. Visual predictive check of WGT (top panel), FSI (middle panel) and FPG (bottom panel). Blue dots indicate observations; red lines are the medians of observations; red areas are the 95% confidence intervals (CI) of the median prediction intervals (n=200); blue dotted lines are the 90th and 10th percentile of the observations; blue areas are the 95% CI of the 90th and 10th percentile of the predictions (n=200).

Acknowledgements

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References

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- [2] Choy S, Kjellsson M, et al. Population Approach Group of Australia & New Zealand. 2013. (Oral presentation).
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- [4] Brody, S. Bioenergetics and Growth. Reinhold Publishing Corporation, New York, 1945.