

Physiologically-based Quantitative Systems Pharmacology Diabetes Platform for Prediction of Treatment Outcomes

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Introduction

Type 2 Diabetes Mellitus (T2DM) is a complex disease that results in the dysregulation of glucose control and elevated glucose levels. The manifestation of T2DM is a long-term process, and different therapies may be required depending on the state of disease progression. Standard medications include metformin, dipeptidyl peptidase 4 (DPP4) inhibitors, sodium–glucose cotransporter 2 (SGLT2) inhibitors, glucagon-like peptide 1 (GLP-1) receptor agonists (RA), thiazolidinediones, and sulfonylureas [1].

Objectives

To develop a physiologically-based (PB) Quantitative Systems Pharmacology (QSP) model of glucose regulation in healthy individuals and T2DM patients for the prediction of treatment outcomes with HbA1c as biomarker.

Methods

The model was developed with the Open Systems Pharmacology Suite (OSPS), version 9 [2]. A previously published model of glucose homeostasis in healthy individuals [3] was coupled with published PBPK and pharmacodynamic (PD) models of the SGLT2i dapagliflozin [4], the DPP4i sitagliptin [5], and a PBPK model of metformin [6]. PD effects of metformin and the GLP-1 RA exenatide have been implemented. A mechanistic model of hemoglobin glycation to describe HbA1c levels was developed and integrated into the PBPK-QSP model. The differences between healthy and T2DM populations were described using data on incretin secretion, insulin response, and oral glucose tolerance tests (OGTT). The HbA1c model has been fitted to 5.6% for healthy individuals.

Results I – The Glucose Homeostasis Model

An outline of the modeled physiology of glucose homeostasis is given in **Figure 1**. The developed platform integrates PBPK models of **glucose**, **insulin**, **glucagon**, **GLP-1** and its **metabolites**, **GIP** and its **metabolite**, and the **feedback loops** on their endogenous production and metabolism processes. Three parameters 1) responsiveness of insulin secretion to glucose changes, 2) insulin action on peripheral glucose uptake, and 3) insulin action on hepatic glucose uptake allow to individualize the model and describe different states of glucose tolerance.

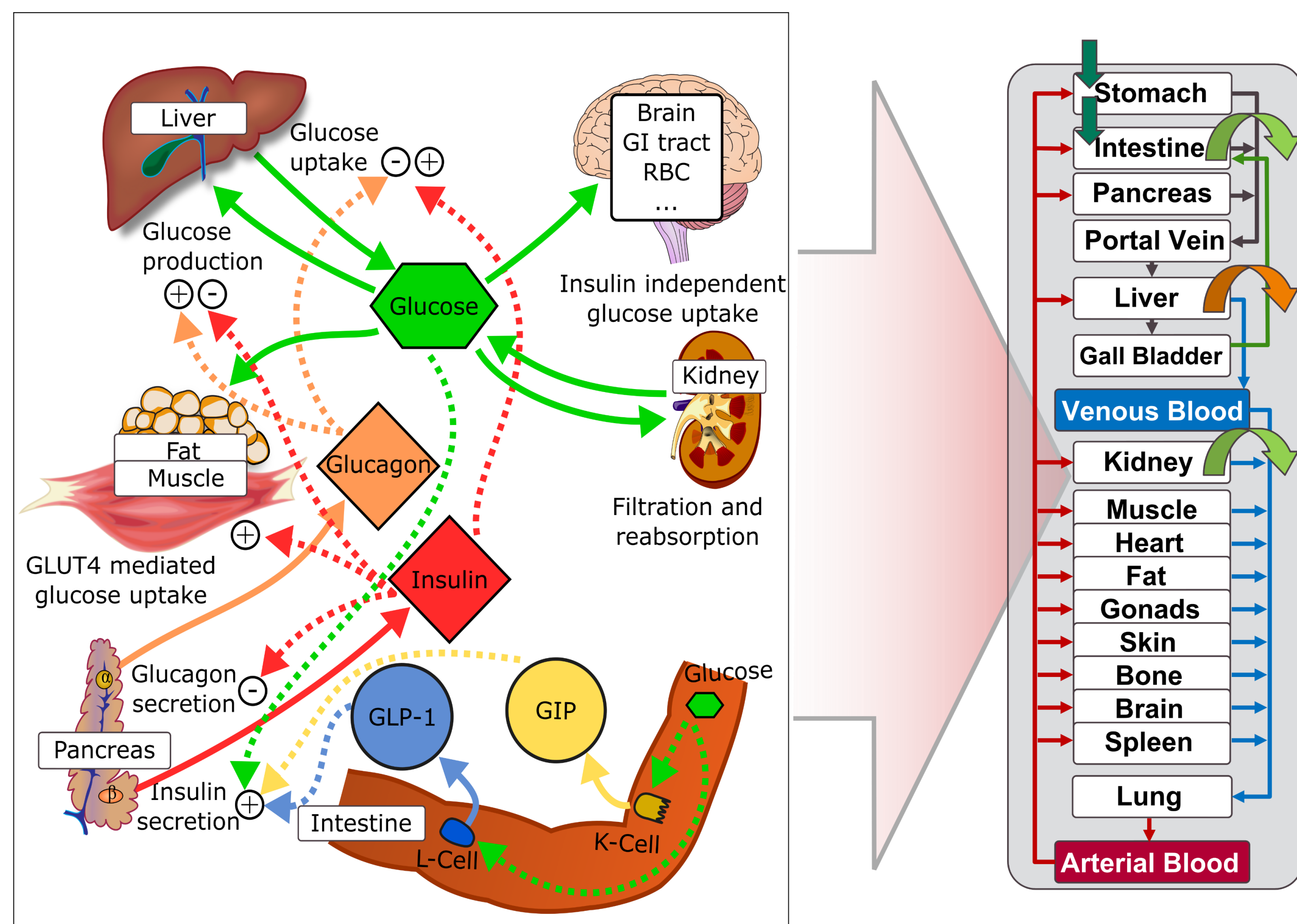


Figure 1: High-level representation of the modeled physiological processes: The platform incorporates PBPK models of glucose, insulin, glucagon, GLP-1, GIP, and c-peptide (not shown). Solid lines represent the most important processes in the relevant organs, dashed lines represent pharmacodynamic (PD) effects. GI: gastrointestinal, RBC: red blood cells, GNG: gluconeogenesis. Not all implemented PD effects are shown.

A mean T2DM population is characterized by an increased expression of the glucose transporters GLUT2 and SGLT2, altered GLP-1 and GIP secretion patterns, reduced insulinotropic effect of GLP-1 and an almost complete loss of insulinotropic effect of GIP. Various states of disease progression are described by model parameters defining insulin and glucose sensitivity. Observed and simulated glucose and insulin concentrations during a 75 g OGTT in two different T2DM states are presented in **Figure 2**.

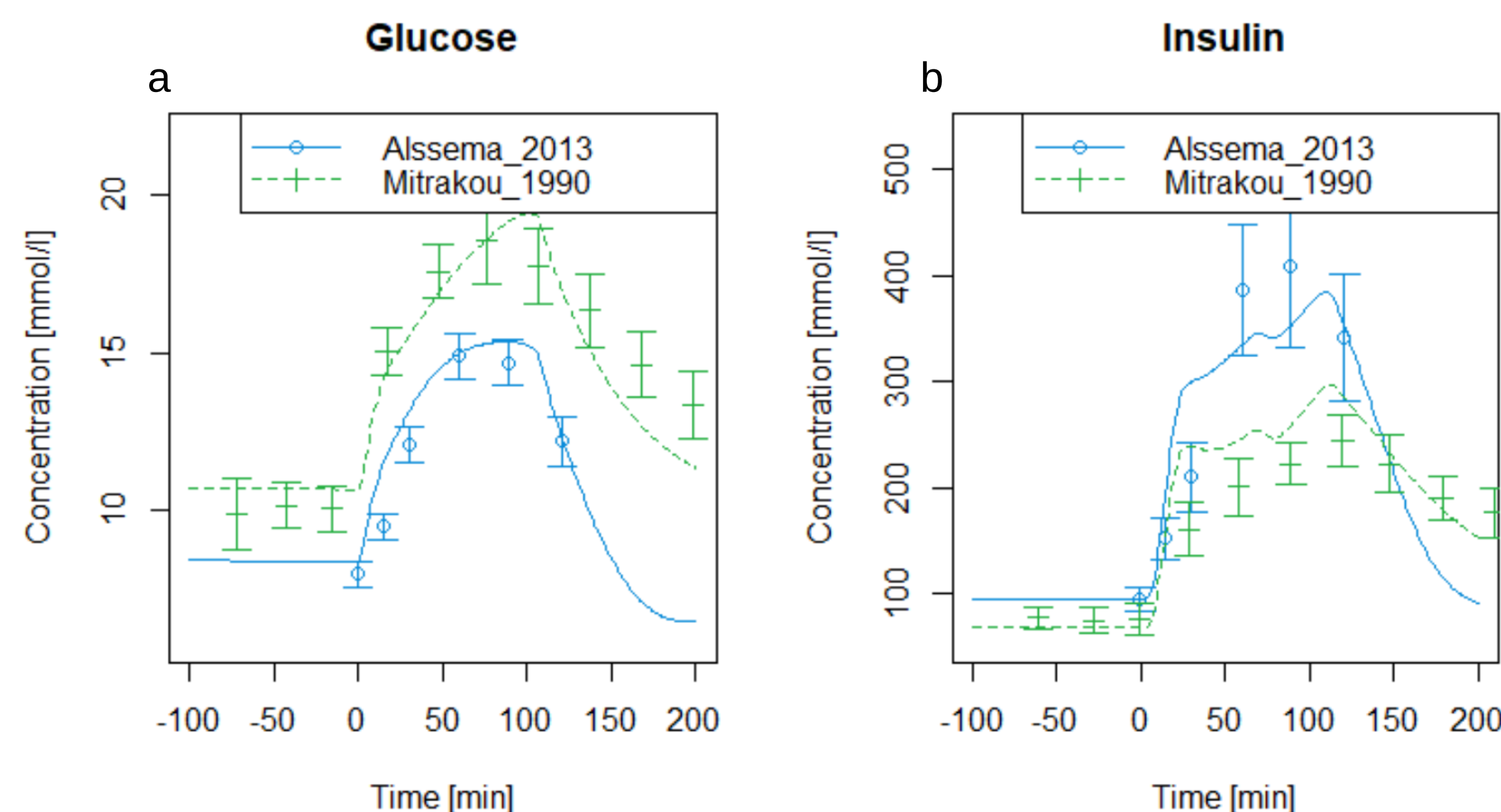


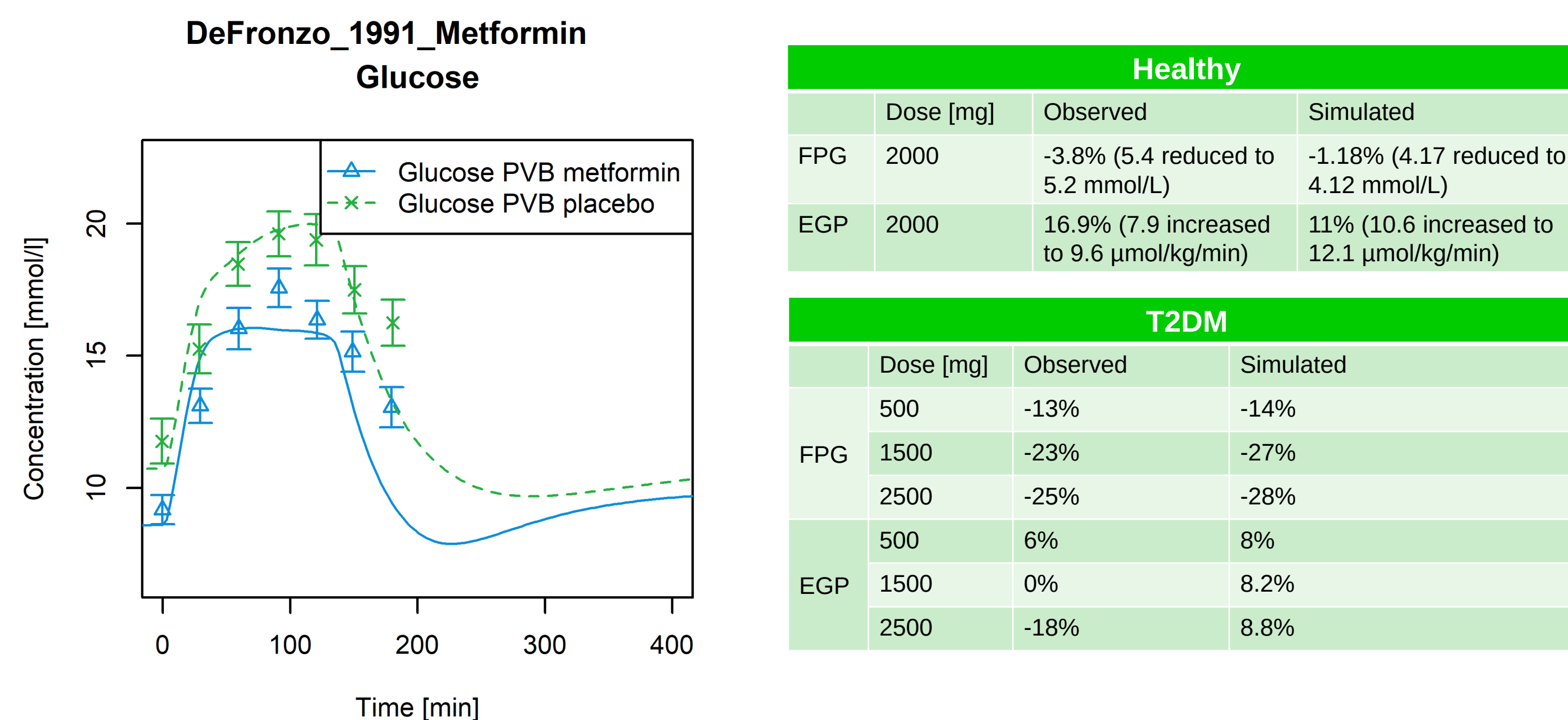
Figure 2: 75 g OGTT in T2DM patients. Observed (symbols $\pm$ SD) and simulated (lines) concentrations of glucose (**Panel a**) and insulin (**Panel b**) in T2DM patients after oral administration of 75 g glucose solution. Data from Alssema et al., 2013 [7] and Mitrakou et al., 1990 [8].

Results II – Medication (Model) Library

The model offers a broad selection of medications for simulation of treatment therapies next to **insulin**. **SGLT2i dapagliflozin** inhibits the reabsorption of renally-filtered glucose by reversibly binding to SGLT2 in the proximal tubule of the kidney and the treatment effect was validated with urinary glucose excretion data in healthy individuals and T2DM patients. **DPP4i sitagliptin** slows down the degradation of GLP-1 and GIP by reversibly binding to the metabolizing enzyme DPP4 and leads to increased insulin production. The effect has been parametrized by fitting to data of percentage inhibition of plasma DPP4 after administration of various doses of sitagliptin.

Metformin decreases hepatic glucose production and restores insulin sensitivity. Comparison of observed and predicted percentage changes in glucose production rates and fasting plasma glucose in healthy individuals and T2DM patients is shown in **Table 1**, glucose concentrations during a 100 g OGTT in T2DM patients in **Figure 4**.

Figure 3 and Table 1: Simulated effect of metformin treatment. **Figure 3:** Plasma glucose concentrations after a 100 g OGTT in T2DM patients without and with metformin treatment (2500 g/day). **Table 1:** Comparison of observed and simulated % changes in fasting plasma glucose (FPG) and endogenous glucose production (EGP) with and without metformin treatment in healthy individuals and T2DM patients. PVB: peripheral venous blood.



Results III – Treatment Predictions

The platform has been applied to predict the **outcomes of different T2DM treatment combinations**. Four scenarios have been simulated, each scenario simulating 3 months with an administration of three meals (total caloric content 2300 kcal) per day. In scenario S1, a virtual male T2DM patient (55 years old, 85 kg body weight) with 10 mmol/l fasting plasma glucose and an HbA1c of 11.52% has been simulated. In scenario S2, the same virtual patient received 500 mg metformin twice daily (total daily dose 1000 mg) and the predicted HbA1c decreased to 8.5%. The addition of 5 mg dapagliflozin daily (S3) did not significantly improve the HbA1c for this patient (8.33%). The addition of 100 mg sitagliptin once daily to the metformin treatment further reduced the HbA1c to 7.45%. The simulated profiles of glucose, insulin, and steady-state HbA1c values are presented in **Figure 4**.

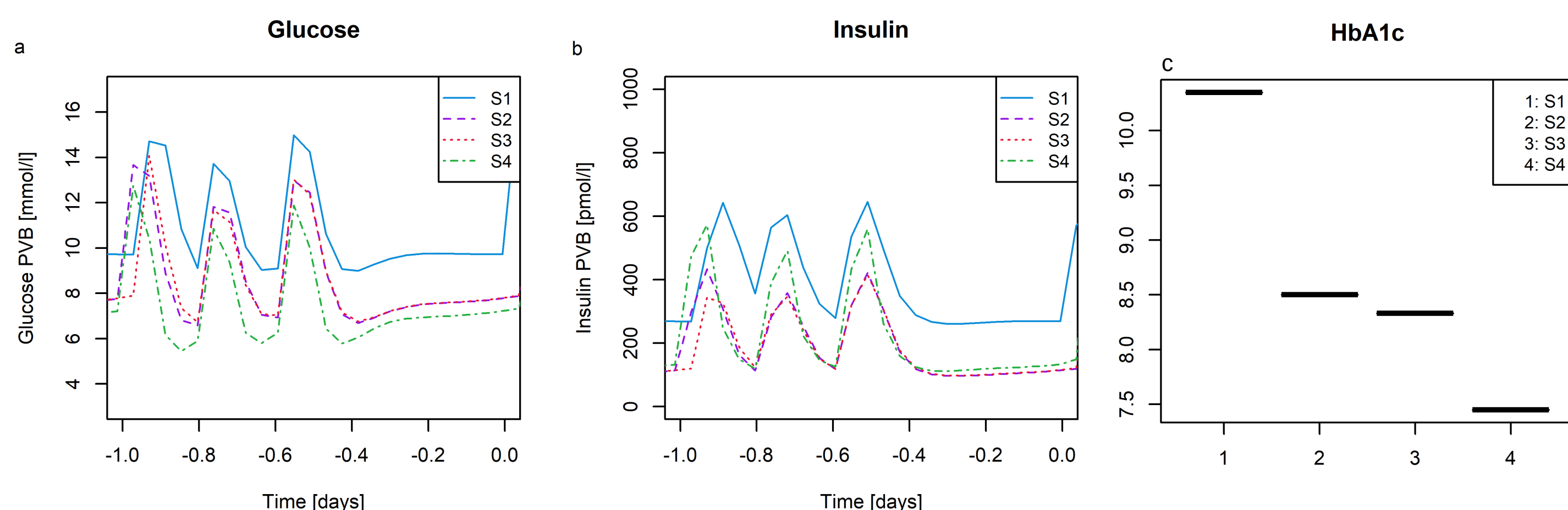


Figure 4: Prediction of T2DM treatment outcomes: The model has been applied to predict the outcomes of 3 months treatment of a virtual T2DM patient on plasma glucose (**Panel a**), plasma insulin (**Panel b**), and HbA1c (**Panel c**). Scenario S1: drug-naïve patient; S2: 500 mg metformin BID; S3: 500 mg metformin BID + 5 mg dapagliflozin QD; S4: 500 mg metformin BID + 100 mg sitagliptin QD. PVB: peripheral venous blood.

Conclusions

We present an integrative PBPK-QSP model for predictions of T2DM treatment combinations of the most commonly used therapies and including a predicted change in HbA1c as a long-term marker. The platform can be a valuable tool for the evaluation of the efficacy of new diabetes treatments and for applications in precision medicine.

The platform allows an early evaluation of the efficacy of newly conceptualized anti-diabetic drugs and the optimization of newly derived treatment combinations. The high mechanistic level of detail of the implemented glucose regulation processes enables the prediction of the efficacy of a new medication from, e.g., *in vitro* measured properties.

Consequently, the platform can be and has been used [9] for optimizing dosing of anti-diabetic drugs and personalized treatment combinations, supporting the choice of the most effective and cost-efficient medication for a specific individual.

References

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