A physiology-based model describing heterogeneity in glucose metabolism

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A physiology-based model describing heterogeneity in glucose metabolism:
the core of the Eindhoven Diabetes Education Simulator (E-DES)

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D) Abbreviations:

• E-DES: Eindhoven Diabetes Educational Simulator

• HbA1c: glycated haemoglobin

• OGTT: Oral glucose tolerance test

E) Key words:

diabetes, education, model, simulator, parameter estimation, heterogeneity

F) Figures and table count:

4 figures, 3 tables
Abstract

Background: Current diabetes education methods are costly, time-consuming and do not actively engage the patient. Here, we describe the development and verification of the physiological model for healthy subjects that forms the basis of the Eindhoven Diabetes Education Simulator (E-DES). E-DES shall provide diabetes patients with an individualized virtual practice environment incorporating the main factors that influence glycaemic control: food, exercise and medication.

Method: The physiological model consists of 5 compartments for which the inflow and outflow of glucose and insulin are calculated using 6 non-linear coupled differential equations and 14 parameters. These parameters are estimated on 12 sets of OGTT data (226 healthy subjects) obtained from literature. The resulting parameter set is verified on 8 separate literature OGTT data sets (229 subjects). The model is considered verified if 95% of the glucose data points lie within an acceptance range of +/-20% of the corresponding model value.

Results: All glucose data points of the verification data sets lie within the predefined acceptance range. Physiological processes represented in the model include insulin resistance and β-cell function. Adjusting the corresponding parameters allows to describe heterogeneity in the data and shows the capabilities of this model for individualization.

Conclusion: We have verified the physiological model of the E-DES for healthy subjects. Heterogeneity of the data has successfully been modelled by adjusting the four parameters describing insulin resistance and β-cell function. Our model will form the basis of a simulator providing individualized education on glucose control.
Introduction

Diabetes is a serious and life-threatening condition, that reduces the quality of life of the patient and is also costly, both in medical costs and in lost work-hours\(^1\). The incidence and severity of the complications of diabetes can considerably be reduced if patients develop a lifestyle that leads to good glycaemic control\(^2,3\). Research has shown that diabetes education can reduce HbA1c over a longer period\(^4,5\), resulting in a lower risk of complications\(^6,7\). Education is therefore a fundamental part of diabetes care. It is currently provided in several one-on-one or group sessions with a physician, diabetes nurse, dietician, or podiatrist. This is time-consuming and costly.

A major part of diabetes education is learning how to adjust insulin injections based on carbohydrate intake, exercise and factors like stress or illness. However, possibilities for the patient to safely practice with this newly acquired knowledge are limited to trying different strategies on his own body. This gives a considerable risk of hypo- or hyperglycaemia.

Electronic educational tools can provide patients with an environment in which they can safely practice with factors influencing glycaemic control, improving HbA1c and other diabetes outcomes\(^8,9\). Two types of electronic environments currently exist: diabetes games (e.g. ‘Time Out’\(^10\), ‘Balance battle’\(^11\), ‘Diabetic Dog’\(^12\)) and mathematical models developed for educational or clinical purposes (e.g. AIDA\(^13\), KADIS\(^14\), GlucoSim\(^15\)). Unfortunately, most games focus on children or young adults and are therefore not suitable for adults. Also, none of the games or models are meant for type-2 patients. Moreover, they generally cannot be individualized to account for the large inter- and intra-patient variability in glucose and insulin responses to meals, resulting from the heterogeneity amongst diabetes patients\(^16,17\).

Our goal is to create an educational simulator, called the Eindhoven Diabetes Education Simulator (E-DES), that can be individualized to account for heterogeneity. The basis of the simulator is a
physiology-based mathematical model that calculates glucose and insulin values during a 24-hour period. The simulator should function for both type-1 and type-2 diabetes patients.

This paper describes the first step in developing E-DES: the development and verification of the mathematical model for healthy subjects. The model is created by adjusting and combining different models from literature. We estimate the parameters for healthy persons based on oral glucose tolerance test (OGTT) data from literature and verify the resulting model parameters on separate literature data sets, testing the capability of our model to describe and predict heterogeneous data.

We aim for an accuracy such that 95% of the glucose data used for verification lie within a range of +/-20% around the results of the model simulation. This range corresponds with the allowed deviation in blood glucose meter measurements as defined in ISO15197:2003, and with the observed glucose variability in healthy patients.

Methods

Model development

The physiological model (shown in Figure 1) consists of four compartments: the gut, the plasma, the interstitial fluid and the subcutaneous tissue. For every compartment we calculate the dynamic in-and outflow of glucose, insulin or both using (coupled) differential equations.

For the gut compartment we only consider glucose balances and assume insulin is not present. The glucose balance in the gut is described in two terms: glucose entering the gut from the stomach, and glucose leaving the gut through uptake by the plasma. For glucose entering the gut we use the gastric emptying model by Elashoff et al. Glucose uptake by the plasma is modeled linearly: the rate of glucose leaving the gut is proportional to the glucose mass in the gut.

For the plasma compartment we calculate both glucose and insulin fluxes. The glucose balance in plasma is modeled using five terms: glucose entering from the gut, glucose entering from
endogenous production in the liver, glucose leaving the plasma through uptake by insulin-independent and by insulin-dependent tissue and organs, and glucose leaving the plasma through renal clearance. The glucose entering from the gut is equal to the glucose uptake by the plasma described in the previous paragraph. The model for endogenous glucose production is derived from Dalla Man et al. \textsuperscript{20}. It consists of a basal production term which is reduced if either the plasma glucose concentration or the interstitial fluid insulin concentration is high. The combined insulin-dependent and insulin-independent glucose uptake follows Michaelis-Menten kinetics and is based on Gottesman et al. \textsuperscript{21} and Dalla Man et al. \textsuperscript{22}. Glucose excretion by the kidneys is modeled using the renal clearance model from Rave et al. \textsuperscript{23} and Lehmann et al. \textsuperscript{24}.

The \textbf{insulin balance in plasma} is composed of five terms: inflow from the pancreas, inflow from both short-acting and long-acting insulin injections, outflow through liver clearance and outflow towards the interstitial fluid. Insulin release by the pancreas is modelled with a proportional-integral-derivative controller similar to the one introduced by Steil et al. \textsuperscript{25}. We added a constant term to model insulin release in the basal state. Short-acting exogenous insulin inflow is equal to the insulin outflow from the subcutaneous compartment. Long-acting exogenous insulin enters the plasma through a time-dependent function, as modelled by Berger et al. \textsuperscript{26}. Insulin clearance by the liver is modelled by a clearance rate proportional to the plasma insulin concentration. Insulin outflow towards the interstitial fluid is modelled by diffusion proportional to the plasma insulin concentration minus the basal concentration.

In the \textbf{interstitial fluid} compartment, we calculate the in- and outflow of insulin. The insulin inflow is equal to the insulin outflow from the plasma. The amount of insulin used by cells is proportional to the interstitial fluid insulin concentration.

In the \textbf{subcutaneous tissue} compartment, insulin enters from short-acting insulin injections, and is taken up by the plasma through two coupled differential equations that create a delay between injection time and uptake, as modelled by Shimoda et al. \textsuperscript{27}.
The model we created can describe the dynamics of the glucose metabolism of healthy persons, diabetes type-1 patients, and diabetes type-2 patients by adjusting the values of the physiological parameters. For instance, for type-1 patients the parameters governing β-cell insulin production will be zero. In the same way the parameter values describing insulin sensitivity will be higher in healthy persons and type-1 patients than in type-2 patients, who generally suffer from insulin resistance. Table 1 shows all model parameters, including the values for healthy persons determined in this paper and an indication of which parameters are adjusted to create every phenotype. The complete model is given in Appendix A.

Data collection

The model parameters for healthy subjects were estimated using OGTT data from literature. For verification, a separate set of OGTT data was used. We performed a search in PubMed using the terms ‘OGTT’, ‘glucose’ and ‘healthy’. A data set was included if it contained more than four measurements in time of both glucose and insulin concentrations and if the included subjects satisfied the following inclusion criteria:

- Normal glucose tolerant: fasting glucose <100mg/dl, peak glucose during OGTT <200mg/dl, 2h glucose during OGTT <140mg/dl

- Normal insulin sensitive: fasting insulin <15μU/ml, peak insulin during OGTT <100μU/ml, 2h insulin during OGTT <50μU/ml

- Normotensive: systolic blood pressure <120mmHg, diastolic blood pressure <80mmHg

- HbA1c <6,5% (48mmol/mol)

- BMI <30kg/m² (<27.5kg/m² for Asian and Pacific populations)
The criteria follow the current guidelines of each respective measurement. They ensure that subjects included in the study were not only normal glucose tolerant, but also did not have any other condition that would influence glucose metabolism, like severe obesity.

OGTT data of tests with either 50 or 75 grams of glucose were included. We obtained 20 data sets adhering to our criteria. These sets were divided in two groups: one for parameter estimation and one for verification. Data sets of 75 grams of glucose and an average time between data points of less than 25 minutes (12 sets, 226 subjects) were used for parameter estimation, which ensures that the data is well spread over the time window, a necessity for model calibration. The remaining data sets (8 sets, 229 subjects) were used for verification. Table 2 (parameter estimation data) and Table 3 (verification data) give the main features of the included data sets.

Parameter estimation and verification

The model was implemented in MATLAB and Optimization Toolbox Release 2010b (The Mathworks Inc, Natick, MA). To solve the coupled differential equations the ode15s solver for stiff systems was used. Parameter estimation was performed based on Maximum Likelihood Estimation principles by optimizing the objective function given in Equation 1 such that the weighted sum of squared residuals (SSR) became smallest. \( N \) represents the number of measurements, \( d_{ij} \) the experimental data of observable \( j \) (either glucose or insulin), \( \sigma_{ij} \) the standard deviation of the experimental data of observable \( j \) and \( y_{ij} \) the corresponding model output as predicted by the current parameter set. For this optimization we used the lsqnonlin algorithm.

\[
SSR = \sum_{j=1}^{m} \sum_{i=1}^{N} \left( \frac{y_{ij} - d_{ij}}{\sigma_{ij}} \right)^2
\]

We optimized the parameters simultaneously on all parameter estimation data sets. To improve the chances of finding the global minimum of the optimization problem we repeated the optimization for 1000 initial parameter sets, which were obtained by performing Latin Hypercube Sampling for
each parameter\textsuperscript{54}. The set with the lowest SSR, calculated on both glucose and insulin data, will be
used as the resulting healthy parameter set.

Verification of our model and healthy parameter set is performed by comparing our model
predictions with the verification data. For each verification data set, simulation is performed using
the glucose and insulin starting values and carbohydrate input of that specific data set. We consider
our model prediction acceptable, and our model verified, if 95\% of the glucose data points lie within
a range of +/-20\% around the corresponding model prediction. This acceptance range corresponds
with the accuracy criteria for blood glucose meters given in ISO15197:2003\textsuperscript{38}. For glucose
concentrations below 75mg/dl the model should not predict higher values, because identifying and
understanding conditions that might lead to hypoglycaemia is important in diabetes education. For
insulin we choose a wider acceptance range of +/-25\%, consistent with the larger variability in insulin
measurements observed in literature\textsuperscript{55}.

Results

First, we estimated the parameter values on the 12 parameter estimation data sets. Figure 2 shows
the different data sets used for parameter estimation (markers), the standard deviation of the data
as reported in the original papers (error bars) and the resulting optimal model prediction (thick solid
line). Both the glucose and insulin data show large variation; in some cases more than 50\%. The
model prediction falls in the middle of the range of data sets and follows the trend of the data sets
well. Table 1 lists the estimated parameter values.

Next, we verified the healthy parameter values on 8 verification data sets. Figure 3A shows the best
predicted case (Ozeki et al.\textsuperscript{47}); for this verification set, all glucose and insulin data points were within
the acceptance range. Figure 3B shows the worst predicted case (Lu et al.\textsuperscript{46}). Here all insulin data
were in range, but one glucose data point was not. However, the difference between model and
data was small. Figure 4 shows the percentage of data points within the acceptance range for each
verification data set. For all verification data sets 100% of the glucose data lie within range, except for the data from Lu, where one data point is just outside range. The percentage of insulin data points within range varies from 100% (Lu et al. 46, Ozeki et al. 47 and Suzuki et al. 49) to 40% (Hashimoto et al. 45).

Lastly, although all verification data sets were described well by our model, we tested if we could individualize the model by fine-tuning only a small set of parameters. The parameters chosen to re-estimate were $k_5$, $k_6$, $k_7$ and $k_8$. These parameters are associated with the insulin resistance and β-cell function of the subject, two processes that largely define the pathophysiology of diabetes type-2. A multi-parametric sensitivity analysis has shown that these parameters are also the most sensitive to change (data available upon request). We re-estimated the four chosen parameters on the individual data sets while keeping all other parameters constant. Figure 4 shows the percentage of glucose and insulin data points within range before and after individualization. The percentage of insulin data points inside the acceptance range is higher after individualization than before for all verification data sets. However, the percentage of glucose data points within range goes down for two studies (Priebe et al. 48, Wachters-Hagedoorn et al. 51).

Discussion

We have shown that our model can predict glucose and insulin profiles for healthy persons. 98.4% of the glucose data points was within range, meaning we achieved our goal of >95% of all glucose data within ±20% of our model predictions. Our model performed less well when predicting insulin profiles. However, we consider the glucose data to be most important for daily practice, since patients can only measure blood glucose and adjust their insulin based on these measurements. Although insulin predictions can provide patients insight, they are of limited clinical importance. Nevertheless, the insulin predictions showed only small deviations from the data. If we look at the worst predicted verification data set more closely (Figure 3B), some of the insulin data points fall
outside the acceptance range, but the trend is described well. Changing only four parameters strongly improved the insulin predictions. This shows that our model is sensitive to its parameters and has possibilities for individualization.

Several other models of the human glucose-insulin system exist. Some are simpler than our model, others more detailed. Analysis of the model accuracy is often limited and usually only the capability of a model to fit the training data is reported. This is partly because data often does not provide sufficient information to constrain all model parameters. We aimed for a limited number of parameters that largely define the dynamic response. Uncertainty analysis via the Profile Likelihood method shows that most of our parameters can be estimated with a finite, relatively small confidence interval (results available upon request). We further analyzed the accuracy of our model by investigating the uncertainty and variability in the predictions for the verification data sets. The model is able to predict the verification sets well, which speaks strongly for the robustness and predictive power of our model.

The main part of our model is based on Dalla Man et al. We reduced the number of differential equations from twelve to six, including two differential equations necessary for the short-acting insulin injection model (not present in the model by Dalla Man). This simplification was possible by reducing food intake to only one differential equation instead of three by using the gastric emptying model by Elashoff et al. We simplified the endogenous glucose production model of Dalla Man by removing the early suppression term, thus removing one more parameter to be fitted. This caused a systematic error of approximately 0.5% on the plasma glucose levels, which we deemed negligible. We made the insulin-independent glucose uptake term dependent on glucose (instead of being constant). This ensured glucose uptake becomes zero if the glucose concentration is zero, preventing a non-physiological situation where the glucose concentration could become negative. The liver insulin and portal vein insulin concentrations were combined into one plasma concentration. We compensated for this by implementing a term that models the removal of insulin by the liver. Our
verification proves that our model, although heavily simplified, is still accurate enough for our purposes. Through this simplification, the model is easier to understand for both patients and physicians and requires less computational resources.

In this paper, we show the capability of our model to predict the outcomes of averaged OGGT data for 455 healthy subjects from 19 publications in literature (data available on request). All included publications described their subjects as ‘healthy’; nevertheless the data are heterogeneous, and the variance in glucose and insulin profiles is quite large Figure 2(Figure 2). Part of the variance in insulin profiles might stem from the fact that insulin immunoassays have not been standardized\textsuperscript{55,61}. But for glucose assays, which are standardized, this cannot explain the large variability observed. We can only conclude that the variance in glucose and insulin profiles is caused by factors that were not measured, for instance by effects of stress, exercise or food taken in the day before.

The dynamic response of insulin and glucose to (complex) meals will show even larger variability. In meals the stomach has to process complex carbohydrates, proteins and fats in liquid and solid form; not only liquid glucose solution. This will slow down the process of glucose uptake considerably, depending on the content and form of the meal\textsuperscript{62}. The parameters estimated from OGGT data will not be able to predict composite meals. In future work we will extend the part of the model concerning food absorption and re-estimate the involved parameters on mixed meal data to resemble postprandial responses in everyday life more closely.

Our next step will be to estimate parameters for patients with diabetes type-1 and type-2. We expect that factors such as age, BMI, total daily insulin dose and duration of diabetes will have a strong correlation with certain parameters in the model. Our aim is to use these correlations to let users adjust the model to their own individual characteristics. As a final step, we will include the model in an attractive user interface, so that it can be used by patients and health care providers for educational purposes.
Conclusion

We have designed a model to predict glucose and insulin profiles over time. The model will be used in a simulator providing individualized education for patients with diabetes. As a first step, we verified our model for healthy subjects. We calculated glucose and insulin predictions for 8 separate data sets and showed that all glucose data points except one were within the acceptance range of +/-20%, thus proving our model verified. By adjusting the parameters influencing insulin resistance and β-cell function we could change the glucose and insulin response, showing the possibilities of our model for individualization including application for type-2 diabetics that have varying levels of insulin resistance and β-cell function.
Funding sources

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Acknowledgements

None.

Disclosures

None.
References


Tables

Table 1: Overview of all model parameters. The parameters have been estimated on OGTT data for healthy subjects; the resulting values for healthy persons are given in the third column. The fourth column shows how some of the parameters need to be adjusted to create the different phenotypes (healthy, diabetes type-1, diabetes type-2).

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Description (units)</th>
<th>Value for a healthy person</th>
<th>Phenotype adjustments</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_1$</td>
<td>Rate constant of glucose appearance in the gut (1/min)</td>
<td>1.45E-02</td>
<td>-</td>
</tr>
<tr>
<td>$k_2$</td>
<td>Rate constant of gut emptying (1/min)</td>
<td>2.76E-01</td>
<td>-</td>
</tr>
<tr>
<td>$k_3$</td>
<td>Rate constant of $\Delta G$ suppression of EGP (1/min)</td>
<td>6.07E-03</td>
<td>0 for type-1</td>
</tr>
<tr>
<td>$k_4$</td>
<td>Rate constant of $\int_{\text{rem}}$ suppression of EGP (1/min)</td>
<td>2.35E-04</td>
<td>0 for type-1</td>
</tr>
<tr>
<td>$k_5$</td>
<td>Rate constant of insulin-dependent glucose uptake (1/min)</td>
<td>9.49E-02</td>
<td>Lower for type-2</td>
</tr>
<tr>
<td>$k_6$</td>
<td>Rate constant of $\Delta G$-dependant insulin production (1/min)</td>
<td>1.93E-01</td>
<td>Lower for type-2</td>
</tr>
<tr>
<td>$k_7$</td>
<td>Rate constant of $\int G$-dependant insulin production (1/min)</td>
<td>1.15E+00</td>
<td>Lower for type-2</td>
</tr>
<tr>
<td>$k_8$</td>
<td>Rate constant of $\int dG/dt$-dependant insulin production (1/min)</td>
<td>7.27E+00</td>
<td>Lower for type-2</td>
</tr>
<tr>
<td>$k_9$</td>
<td>Rate constant of short-acting insulin appearance in plasma (1/min)</td>
<td>0</td>
<td>Only for patients using short-acting insulin</td>
</tr>
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<td>$k_{10}$</td>
<td>Rate constant of short-acting insulin appearance in subcutaneous compartment 1 (1/min)</td>
<td>0</td>
<td>Only for patients using short-acting insulin</td>
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<tr>
<td>$k_{11}$</td>
<td>Rate constant of insulin outflow from plasma to remote compartment (1/min)</td>
<td>3.83E-02</td>
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<tr>
<td>$k_{12}$</td>
<td>Rate constant of remote compartment insulin utilization (1/min)</td>
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<td>-</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Shape factor (no units)</td>
<td>1.34E+00</td>
<td>-</td>
</tr>
<tr>
<td>---</td>
<td>---</td>
<td>---</td>
<td>---</td>
</tr>
<tr>
<td>$K_M$</td>
<td>Michaelis-Menten constant for glucose uptake (mg/dl)</td>
<td>2.36E+02</td>
<td>Higher for type-2</td>
</tr>
</tbody>
</table>
Table 2: Overview of included OGTT data used for parameter estimation. Listed are: the first author and year of publication, if applicable whether we use the male (M) or female (F) data set, the amount of carbohydrates D in grams, the number of glucose (# G) and insulin (# I) data points, the covered time span in minutes, the number of subjects (N), the number of male and female subjects (M/F), the average age plus standard deviation in years, and the average BMI plus standard deviation in kg/m².

<table>
<thead>
<tr>
<th>Author (year of publication)</th>
<th>D [g]</th>
<th># G</th>
<th># I</th>
<th>time span (min)</th>
<th>N</th>
<th>M/F</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderwald et al. (2010, M)</td>
<td>75</td>
<td>10</td>
<td>10</td>
<td>0-180</td>
<td>26</td>
<td>26/0</td>
<td>44.3±1.5</td>
<td>24.7±0.6</td>
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<td>10</td>
<td>10</td>
<td>0-180</td>
<td>48</td>
<td>0/48</td>
<td>44.9±1.3</td>
<td>25.2±0.6</td>
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<tr>
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<td>75</td>
<td>5</td>
<td>5</td>
<td>0-120</td>
<td>10</td>
<td>6/4</td>
<td>25.9±1.6</td>
<td>25.9±1.6</td>
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<tr>
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<td>75</td>
<td>19</td>
<td>19</td>
<td>0-240</td>
<td>6</td>
<td>4/2</td>
<td>45±3</td>
<td>22.5±1.5</td>
</tr>
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<td>Ivović et al. (2012)</td>
<td>75</td>
<td>5</td>
<td>5</td>
<td>0-120</td>
<td>35</td>
<td>5/30</td>
<td>57.57±1.69</td>
<td>26.0±0.6</td>
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<tr>
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<td>75</td>
<td>5</td>
<td>5</td>
<td>0-120</td>
<td>9</td>
<td>9/0</td>
<td>45±4</td>
<td>27±2</td>
</tr>
<tr>
<td>Moore et al. (2000)</td>
<td>75</td>
<td>9</td>
<td>9</td>
<td>0-120</td>
<td>11</td>
<td>5/6</td>
<td>29±2</td>
<td>23.6±0.9</td>
</tr>
<tr>
<td>Nagai et al. (2011)</td>
<td>75</td>
<td>5</td>
<td>5</td>
<td>0-120</td>
<td>30</td>
<td>20/10</td>
<td>24.7±2.3</td>
<td>21.8±3.5</td>
</tr>
<tr>
<td>Numao et al. (2012)</td>
<td>75</td>
<td>7</td>
<td>7</td>
<td>0-120</td>
<td>9</td>
<td>9/0</td>
<td>27±1</td>
<td>21.7±0.6</td>
</tr>
<tr>
<td>Pamidi et al. (2012)</td>
<td>75</td>
<td>5</td>
<td>5</td>
<td>0-120</td>
<td>20</td>
<td>20/0</td>
<td>22.5±0.6</td>
<td>22.6±0.4</td>
</tr>
<tr>
<td>Penesova et al. (2013)</td>
<td>75</td>
<td>9</td>
<td>9</td>
<td>0-120</td>
<td>15</td>
<td>0/15</td>
<td>29.0±5.2</td>
<td>21.6±2.0</td>
</tr>
<tr>
<td>Solomon et al. (2007)</td>
<td>75</td>
<td>5</td>
<td>5</td>
<td>0-120</td>
<td>7</td>
<td>7/0</td>
<td>26±1</td>
<td>24.5±0.3</td>
</tr>
</tbody>
</table>

Table 3: Overview of included OGTT data used for verification. Listed are: the first author and year of publication, if applicable whether we use the male (M) or female (F) data set, the amount of
carbohydrates D in grams, the number of glucose (# G) and insulin (# I) data points, the covered time span in minutes, the number of subjects (N), the number of male and female subjects (M/F), the average age plus standard deviation in years, and the average BMI plus standard deviation in kg/m².

<table>
<thead>
<tr>
<th>Author</th>
<th>D [g]</th>
<th># G</th>
<th># I</th>
<th>time span (min)</th>
<th>N</th>
<th>M/F</th>
<th>Age (years)</th>
<th>BMI (kg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hashimoto et al. (2013) 45</td>
<td>50</td>
<td>6</td>
<td>6</td>
<td>0-360</td>
<td>14</td>
<td>0/14</td>
<td>21.5±0.1</td>
<td>20.0±0.5</td>
</tr>
<tr>
<td>Lu et al. (2009) 46</td>
<td>75</td>
<td>5</td>
<td>5</td>
<td>0-180</td>
<td>133</td>
<td>N/A</td>
<td>45.8±13.8</td>
<td>23.6±3.5</td>
</tr>
<tr>
<td>Ozeki et al. (2007) 47</td>
<td>75</td>
<td>5</td>
<td>5</td>
<td>0-180</td>
<td>11</td>
<td>11/0</td>
<td>41.0±12.0</td>
<td>23.0±4.5</td>
</tr>
<tr>
<td>Priebe et al. (2008) 48</td>
<td>50</td>
<td>17</td>
<td>17</td>
<td>0-360</td>
<td>4</td>
<td>4/0</td>
<td>23.0±1.1</td>
<td>21.4±1.3</td>
</tr>
<tr>
<td>Suzuki et al. (2012) 49</td>
<td>75</td>
<td>4</td>
<td>4</td>
<td>0-120</td>
<td>14</td>
<td>6/8</td>
<td>33.4±11.9</td>
<td>20.7±2.28</td>
</tr>
<tr>
<td>Title et al. (2000) 50</td>
<td>75</td>
<td>5</td>
<td>5</td>
<td>0-240</td>
<td>10</td>
<td>6/4</td>
<td>25.5±3.1</td>
<td>24±3</td>
</tr>
<tr>
<td>Wachters-Hagedoorn et al. (2006) 51</td>
<td>50</td>
<td>17</td>
<td>17</td>
<td>0-360</td>
<td>7</td>
<td>7/0</td>
<td>23.4±1.0</td>
<td>21.6±1.1</td>
</tr>
<tr>
<td>Yamauchi et al. (2008) 52</td>
<td>75</td>
<td>4</td>
<td>4</td>
<td>0-120</td>
<td>36</td>
<td>13/23</td>
<td>24.3±4.7</td>
<td>20.4±1.7</td>
</tr>
</tbody>
</table>
Figure 1: Schematic representation of the model. The grey areas show the four compartments used in the model. Red arrows denote glucose fluxes, blue arrows denote insulin fluxes. The parameters governing the fluxes are written above the arrows.
Figure 2: Parameter estimation data sets (markers and error bars representing mean values and standard deviations, respectively) combined with the optimal model determined by parameter estimation (solid line). The left graph shows the glucose data and model, the right graph shows the insulin data and model.
Figure 3A: Best fitted verification data set. The data from Ozeki et al.\textsuperscript{47} (crosses and error bars) is well predicted by the optimal model (solid line) since all data points lie within the acceptance range (filled area). The left graph shows the glucose data and model + acceptance range, the right graph shows the insulin data and model + acceptance range.

Figure 3B: Worst fitted verification data set. The glucose data from Lu et al.\textsuperscript{46} (crosses and error bars) is well predicted by the optimal model (solid line) since all data points lie within the acceptance range (filled area). However, the insulin data is less well predicted, since 3 data points fall just outside the acceptance range. The left graph shows the glucose data and model + acceptance range, the right graph shows the insulin data and model + acceptance range.
Figure 4: Percentage of data points within the acceptance range, listed per verification data set. The red bars show the percentage of glucose data points within range before (light red) and after (dark red) individualization; the blue bars show the percentage of insulin data points before (light blue) and after (dark blue) individualization.
Appendix A – Full model description

**Glucose in the gut**

\[
\frac{dM_G^{\text{gut}}}{dt} = m_G^{\text{meal}}(D^{\text{meal}}, t) - m_G^{\text{pl}}(M_G^{\text{gut}}(t))
\]

\[
m_G^{\text{meal}}(t) = \sigma_k \tau^{\text{-1}} \exp(-(k_1 t)^\sigma) D^{\text{meal}}
\]

\[
m_G^{\text{pl}}(t) = k_2 M_G^{\text{gut}}(t)
\]

**Glucose in the plasma**

\[
\frac{dG^{\text{pl}}}{dt} = g^{\text{liv}}(G^{\text{pl}}(t), I^{\text{rem}}(t)) + g^{\text{gut}}(M_G^{\text{gut}}(t)) - g^{\text{non-it}}(G^{\text{pl}}(t)) - g^{\text{it}}(G^{\text{pl}}(t), I^{\text{rem}}(t)) - g^{\text{ren}}(G^{\text{pl}}(t))
\]

\[
g^{\text{liv}}(t) = g^{\text{liv}}_b - k_3(G^{\text{pl}}(t) - G^{\text{pl}}_b) - k_4 I^{\text{rem}}(t)
\]

\[
g^{\text{gut}}(t) = \frac{f}{\nu_G M_b} m_G^{\text{pl}}(t) = k_2 \frac{f}{\nu_G M_b} M_G^{\text{gut}}(t)
\]

\[
g^{\text{non-it}}(t) = g^{\text{liv}}_b \left( \frac{K_M + G^{\text{pl}}_b}{G^{\text{pl}}_b} \right) G^{\text{pl}}(t)
\]

\[
g^{\text{it}}(t) = k_5 I^{\text{rem}}(t) \frac{G^{\text{pl}}(t)}{K_M + G^{\text{pl}}(t)}
\]

\[
g^{\text{ren}}(t) = \begin{cases} 
\frac{c_1}{\nu_G M_b}(G^{\text{pl}}(t) - G^{\text{pl}}_{gh}), & \text{if } G^{\text{pl}}(t) > G^{\text{pl}}_{gh} \\
0, & \text{if } G^{\text{pl}}(t) \leq G^{\text{pl}}_{gh}
\end{cases}
\]
Insulin in the plasma
\[
\frac{di_{pl}}{dt} = i^{\text{inc}} \left( G_{\text{pl}}^t(t) \right) + i^{\text{sa}} \left( U_{i}^{\text{sc1}}(t), U_{i}^{\text{sc2}}(t) \right) + i^{\text{la}} \left( U_{i}^{\text{la}}, t \right) - i^{\text{liv}} \left( I_{\text{pl}}^t(t) \right) - i^{\text{rem}} \left( I_{\text{pl}}^t(t) \right)
\]
\[
i^{\text{inc}}(t) = \beta^{-1} \left( k_6 \left( G_{\text{pl}}^t(t) - G_{b}^t \right) + \int_{i_{\text{int}}}^t \left( G_{\text{pl}}^t(t) - G_{b}^t \right) dt + \left( \frac{k_{7}}{\tau_{i}} \right) G_{b}^t + \left( k_8 \tau_d \right) \frac{dG_{\text{pl}}^t}{dt} \right)
\]
\[
i^{\text{sa}}(t) = k_9 \frac{1}{v_i M^b} U_{i}^{\text{sc2}}(t)
\]
\[
\frac{dU_{i}^{\text{sc1}}}{dt} = u^{\text{sa}}(t) - k_{10} U_{i}^{\text{sc1}}(t)
\]
\[
\frac{dU_{i}^{\text{sc2}}}{dt} = k_{10} U_{i}^{\text{sc1}}(t) - k_9 U_{i}^{\text{sc2}}(t)
\]
\[
i^{\text{la}}(t) = \frac{h(t_{0.5})^b t^{b-1}}{(t_{0.5})^b + t^b} v_i M^b U_{i}^{\text{la}}
\]
\[
t_{0.5} = a U_{i}^{\text{la}}(t) + b
\]
\[
i^{\text{liv}}(t) = k_7 \frac{G_{\text{pl}}^t}{\beta \tau_i I_{i}^{\text{pl}}}(I_{\text{pl}}^t(t))
\]
\[
i^{\text{rem}}(t) = k_{11} (I_{\text{pl}}^t(t) - I_{b}^{\text{pl}})
\]

Insulin in the remote compartment
\[
\frac{di_{\text{rem}}}{dt} = i_{\text{pl}}^t (I_{\text{pl}}^t(t)) - i_{\text{il}} (I_{\text{rem}}^t(t))
\]
\[
i_{\text{pl}}^t(t) = i_{\text{rem}}^t (t) = k_{11} (I_{\text{pl}}^t(t) - I_{b}^{\text{pl}})
\]
\[
i_{\text{il}}^t(t) = k_{12} I_{\text{rem}}^t(t)
\]

**Name** | Description | Units | Applicability
--- | --- | --- | ---
**Variables** | | |
\(t\) | Time | min | |
\(M_{G_{\text{gut}}}(t)\) | Glucose mass in the gut | mg | |
\(G_{\text{pl}}^t(t)\) | Plasma glucose concentration | mmol/L | |
\(I_{\text{pl}}^t(t)\) | Plasma insulin concentration | mU/L | |
\(I_{\text{rem}}^t(t)\) | Remote compartment | mU/L | |
<table>
<thead>
<tr>
<th>Component</th>
<th>Description</th>
<th>Unit</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>$U_{i}^{sc1}(t)$</td>
<td>Subcutaneous insulin mass at injection site</td>
<td>U</td>
<td>Only for patients using short-acting insulin</td>
</tr>
<tr>
<td>$U_{i}^{sc2}(t)$</td>
<td>Subcutaneous insulin mass proximal to plasma</td>
<td>U</td>
<td>Only for patients using short-acting insulin</td>
</tr>
<tr>
<td>Input variables</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$D^{meal}$</td>
<td>Food intake</td>
<td>mg</td>
<td></td>
</tr>
<tr>
<td>$M^{b}$</td>
<td>Body mass</td>
<td>kg</td>
<td></td>
</tr>
<tr>
<td>$u^{sa}(t)$</td>
<td>Rate of short-acting insulin injection (for a bolus the injection time is set to 1 minute)</td>
<td>U/min</td>
<td>Only for patients using short-acting insulin</td>
</tr>
<tr>
<td>$U^{la}$</td>
<td>Dose of long-acting insulin injection</td>
<td>U</td>
<td>Only for patients using long-acting insulin</td>
</tr>
<tr>
<td>Fluxes</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>$m_{G}^{meal}(t)$</td>
<td>Glucose mass entering from stomach</td>
<td>mg/min</td>
<td></td>
</tr>
<tr>
<td>$m_{G}^{pl}(t)$</td>
<td>Glucose mass leaving to plasma</td>
<td>mg/min</td>
<td></td>
</tr>
<tr>
<td>$g^{liv}(t)$</td>
<td>Glucose production by the liver (EGP)</td>
<td>mmol/L/min</td>
<td></td>
</tr>
<tr>
<td>$g^{gut}(t)$</td>
<td>Glucose entering from the gut</td>
<td>mmol/L/min</td>
<td></td>
</tr>
<tr>
<td>$g^{non-at}(t)$</td>
<td>Glucose uptake by insulin-independent tissue</td>
<td>mmol/L/min</td>
<td></td>
</tr>
<tr>
<td>$g^{it}(t)$</td>
<td>Glucose uptake by insulin-dependent tissue</td>
<td>mmol/L/min</td>
<td></td>
</tr>
<tr>
<td>$g^{rea}(t)$</td>
<td>Renal glucose elimination</td>
<td>mmol/L/min</td>
<td></td>
</tr>
<tr>
<td>$i^{pnc}(t)$</td>
<td>Pancreas insulin secretion</td>
<td>mU/L/min</td>
<td>Not for patients with diabetes type-1</td>
</tr>
<tr>
<td>$i^{sa}(t)$</td>
<td>Short-acting insulin secretion</td>
<td>mU/L/min</td>
<td>Only for patients using short-acting insulin</td>
</tr>
<tr>
<td>$i^{la}(t)$</td>
<td>Long-acting insulin secretion</td>
<td>mU/L/min</td>
<td>Only for patients using long-acting insulin</td>
</tr>
<tr>
<td>(i_{\text{rem}}(t))</td>
<td>Insulin flowing into remote compartment</td>
<td>mU/L/min</td>
<td></td>
</tr>
<tr>
<td>(i_{\text{liv}}(t))</td>
<td>Insulin uptake by the liver</td>
<td>mU/L/min</td>
<td></td>
</tr>
<tr>
<td>(i_{\text{pl}}(t))</td>
<td>Insulin entering remote compartment from the plasma</td>
<td>mU/L/min</td>
<td></td>
</tr>
<tr>
<td>(i_{\text{it}}(t))</td>
<td>Insulin usage by insulin-dependent tissue</td>
<td>mU/L/min</td>
<td></td>
</tr>
</tbody>
</table>

**Parameters**

<p>| (k_1) | Rate const of glucose appearance in the gut | 1/min |
| (k_2) | Rate const of gut emptying | 1/min |
| (k_3) | Rate const of (\Delta G) suppression of EGP | 1/min | Zero for patients with diabetes type-1 |
| (k_4) | Rate const of (i_{\text{rem}}) suppression of EGP | 1/min | Zero for patients with diabetes type-1 |
| (k_5) | Rate const of insulin-dependent glucose uptake | 1/min |
| (k_6) | Rate const of (\Delta G)-dependant insulin production | 1/min |
| (k_7) | Rate const of (JG)-dependant insulin production | 1/min |
| (k_8) | Rate const of (dG/dt)-dependant insulin production | 1/min |
| (k_9) | Rate const of short-acting insulin appearance in plasma | 1/min | Only for patients using short-acting insulin |
| (k_{10}) | Rate const of short acting insulin appearance in subcutaneous compartment 1 | 1/min | Only for patients using short-acting insulin |
| (k_{11}) | Rate const of insulin outflow from plasma to | 1/min |</p>
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Description</th>
<th>Unit/Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>$k_{12}$</td>
<td>Rate const of remote compartment insulin utilization</td>
<td>1/min</td>
</tr>
<tr>
<td>$\sigma$</td>
<td>Shape factor</td>
<td>-</td>
</tr>
<tr>
<td>$K_M$</td>
<td>Michaelis-Menten constant for glucose uptake</td>
<td>mmol/L</td>
</tr>
<tr>
<td><strong>Constants</strong></td>
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<tr>
<td>$G^p_l$</td>
<td>Basal plasma glucose</td>
<td>mmol/L</td>
</tr>
<tr>
<td>$I^p_l$</td>
<td>Basal plasma insulin</td>
<td>mU/L</td>
</tr>
<tr>
<td>$g^l$</td>
<td>Basal endogenous glucose production</td>
<td>mmol/L/min</td>
</tr>
<tr>
<td>$G_{th}^p$</td>
<td>Renal threshold</td>
<td>mmol/L</td>
</tr>
<tr>
<td>$V^G$</td>
<td>Glucose distribution volume in plasma</td>
<td>L/kg</td>
</tr>
<tr>
<td>$V^l$</td>
<td>Insulin distribution volume in plasma</td>
<td>L/kg</td>
</tr>
<tr>
<td>$\beta$</td>
<td>Unit conversion factor from glucose to insulin</td>
<td>(mmol/L)/(mU/L)</td>
</tr>
<tr>
<td>$f$</td>
<td>Unit conversion factor from mmol to mg glucose</td>
<td>mmol/mg</td>
</tr>
<tr>
<td>$\tau_i$</td>
<td>Integral time const</td>
<td>min</td>
</tr>
<tr>
<td>$t_{int}$</td>
<td>Time constant determining integral window</td>
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</tr>
<tr>
<td>$\tau_d$</td>
<td>Derivative time const</td>
<td>min</td>
</tr>
<tr>
<td>$c_1$</td>
<td>Rate const of glomerular filtration</td>
<td>1/min</td>
</tr>
<tr>
<td>$h$</td>
<td>Time characteristic of absorption</td>
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</tr>
<tr>
<td>$t_{0.5}$</td>
<td>Half-life time of long-acting insulin</td>
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</tr>
<tr>
<td>$a$</td>
<td>Dose shape factor 1</td>
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</tr>
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<td>( b )</td>
<td>Dose shape factor 2</td>
<td>min</td>
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</tbody>
</table>

References


