A comprehensive compartmental model of blood glucose regulation for healthy and type II diabetic subjects

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Abstract

We have expanded a former compartmental model of blood glucose regulation for healthy and type II diabetic subjects. The former model was a detailed physiological model which considered the interactions of three substances, glucose, insulin and glucagon on regulating the blood sugar. The main drawback of the former model was its restriction on the route of glucose entrance to the body which was limited to the intravenous glucose injection. To handle the oral glucose intake, we have added a model of glucose absorption in the gastrointestinal tract to the former model to address the resultant variations of blood glucose concentrations following an oral glucose intake. Another model representing the incretins production in the gastrointestinal tract along with their hormonal effects on boosting pancreatic insulin production is also added to the former model. We have used two sets of clinical data obtained during oral glucose tolerance test and isoglycemic intravenous glucose infusion test from both type II diabetic and healthy subjects to estimate the model parameters and to validate the model results. The estimation of model parameters is accomplished through solving a nonlinear optimization problem. The results show acceptable precision of the estimated model parameters and demonstrate the capability of the model in accurate prediction of the body response during the clinical trials.

Keywords: Type II diabetes mellitus; Compartmental model; Nonlinear optimization; Parameter estimation; Oral glucose tolerance test; Incretins

1. Introduction

Blood glucose homeostasis is maintained in the body by regulatory hormonal effects of insulin and glucagon. Insulin and glucagon hormones are secreted from the beta and alpha cells, respectively, located in the endocrine portion of the pancreas. Insulin enhances absorption of glucose by the liver, muscles and adipose tissues and suppresses endogenous glucose production. On the other hand, glucagon stimulates endogenous glucose production. These hormones act in a complicated feedback mechanism to keep the blood sugar concentration at normal levels. When the blood sugar level is high, pancreas secrets more insulin. Secreted insulin has negative paracrine action on the alpha cells causing inhibition of glucagon secretion. Increased concentration of insulin and decreased concentration of glucagon lead to higher absorption of the blood glucose by body cells and lower endogenous glucose production which collectively decrease the level of blood glucose concentration. When the blood glucose concentration is low, the pancreas secrets more glucagon and less insulin leading to increased endogenous glucose production and lowered absorption of glucose by the body cells which in turn increases the blood glucose concentration [18].

The route of glucose entry into the body plays an important role in maintaining the glucose homeostasis [24]. It is observed that the amount of pancreatic insulin secretion following an oral glucose intake is significantly greater than the corresponding amount in response to the intravenous glucose injection with identical increase in the blood sugar level for both trials [27,45,37,56]. This significant augmentation is due to the secretion of a group of gastrointestinal (GI) hormones called incretins from the walls of the small

intestine following the presence of carbohydrates in the lumen of the duodenum. These hormones stimulate the pancreas to produce more insulin [56,19]. Glucagon-like-peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) gastric hormones are known to be the two main incretins [36,55,54].

Diabetes mellitus is a group of metabolic diseases which causes the deterioration of glucose homeostasis and leads to the high blood sugar levels. Two main forms of diabetes are type I diabetes and type II diabetes. High blood sugar in type I diabetes is due to the partial or complete destruction of the pancreatic beta cells by the immune system which results in lack or insufficiency of insulin production and, in turn, less glucose absorption by the body cells, while type II diabetes is characterized by multiple abnormalities of a number of body organs such as liver, pancreas, muscles and adipose tissues. These abnormalities are:

1- Insulin resistance in the liver, muscles and adipose tissues [28,13,25,46,30,5,35,7,12,6].

2- Glucose resistance in the liver, muscles and adipose tissues [26,47].

3- Reduced or delayed insulin suppression of endogenous glucose production [28,13,25,46,5,7,6,29,17,4,9,8].

4- Impaired first-phase and overall pancreatic insulin production [49,50,61,40,31].

Mathematical modeling of the glucose regulation in the human body has been the topic of many studies since 1961 started with simple linear models proposed by Bolie [11] and Ackerman et al. [1]. More complicated mathematical models with nonlinear equations were proposed later mostly based on the compartmental modeling approach. This approach divides the human body into a number of compartments where each compartment represents an organ or a specific part of the body. Bergman's minimal model [10] was the pioneer of the compartmental models with three compartments.. More detailed models were later proposed by Cobelli and Mari [16], Sorensen [57] and Hovorka et al. [34]. These models considered more compartments to better describe the glucose regulation process in different parts of the body. Several approaches on mathematical modeling of glucose regulations in human body are well reviewed by Makroglou et al. [42], Mari [44], Cedersund and Stralfors [15] and Ajmera et al. [2]. These mathematical models have been widely used in modeling type I diabetes simply by setting the pancreatic insulin production rate to zero [48,51,53,52,14,33,43]. A similar approach can be used to model type II diabetes; however, since multiple abnormalities are associated with type II diabetes, the problem would be much more complicated.

To model type II diabetes based on an existing model of healthy subjects, one approach is to estimate the original model parameters using the patient's clinical data without changing the original model structure [22,60]. We used this approach in our previous study to develop a model for type II diabetes [60]. We chose the Sorensen model [57] as the base model and then estimated the Sorensen model parameters using available clinical data obtained from type II diabetic subjects. The Sorensen model is a detailed

physiological model with sufficient number of compartments which makes it the best choice for type II diabetes mathematical modeling [60], however, lacks some important features. Perhaps, the main drawback of the Sorensen model is its restriction on the route of glucose entrance to the body which is limited to the intravenous injections. On the other hand, availability of the clinical data is very important for the parameter estimation modeling approach whereas many of the available clinical data sets are technically based on oral glucose administration which cannot be handled by the Sorensen mathematical model. In this paper, we have proposed an expansion to the Sorensen model making it capable of handling oral glucose administration. A model of glucose absorption in the GI tract, proposed by Dalla Man et al. [20], is added to the Sorensen model representing the glucose appearance rate in the blood circulation following an oral glucose intake. Another model is also added to the Sorensen model to simulate the release of intestinal incretins following the presence of carbohydrates in the small intestine. The hormonal effects of the incretins on the pancreatic insulin secretion are also considered by modifying the equations calculating the pancreatic insulin release in the Sorensen model. We have used one clinical data set and part of another clinical data set to estimate the parameters of the resultant model through solving a nonlinear optimization problem. Then, the model with new estimated parameters is validated using the remaining part of the clinical data set. The estimation of model parameters and validation of model results have been carried out for both healthy and type II diabetic subjects.

2. Mathematical modeling of the glucose regulation

2.1. The Sorensen model

The Sorensen model is a detailed compartmental model based on a former mathematical model developed by Guyton et al. [32] and modified by Sorensen [57]. The hormonal effects of insulin and glucagon on glucose regulations are considered in the Sorensen model. Variations of glucose, insulin and glucagon concentrations are simulated through three main sub-models. Fig 1 depicts a schematic diagram of the compartmental connections in the insulin sub-model. Each sub-model has individual number of compartments. As Fig 1 shows, insulin sub-model has seven compartments, brain, heat and lungs, liver, pancreas, gut, kidney and periphery. The periphery compartment represents the muscles and adipose tissue cells and the gut compartment comprises the stomach and intestinal system. The glucose sub-model has the same compartments as the insulin sub-model except for the pancreas compartment which is only included in the insulin sub-model. The glucagon sub-model considers the whole body as one compartment. Each compartment can be potentially divided into three well-mixed sub-compartments, capillary space, interstitial fluid space and intracellular fluid space. For each compartment, the blood enters through the capillary space and drained into the veins. The blood solutes may transfer from the capillary space to the interstitial fluid space and from the interstitial fluid space into the interstitial fluid space. Wherever significant transport resistance exists sub-compartments are considered (as that of the periphery compartment in the insulin sub-model. See Fig 1).

The Sorensen model equations comprise mass balance equations over all sub-compartments of each compartment except for the pancreas compartment. Due to the complexities of the pancreatic insulin secretion process, Sorensen has considered a separate model proposed by Landahl and Grodsky [39] for the pancreas compartment. The original Sorensen model equations are available in [60]. The extended model equations including the Sorensen model equations are provided in Appendix A.

2.2. The model of glucose absorption in the GI tract

Several models are proposed in the literature for glucose absorption in the GI tract [20,58,41,21,23,59]. We have chosen a compartmental model proposed by Dalla Man et al. [20] and added it to the Sorensen model to simulate the glucose absorption process in the GI tract following an oral glucose intake. The superiority of this model is proved by Dalla Man et al. [20] over the older models in terms of prediction of ingested glucose appearance rate in blood circulation and higher precision of the estimation of its parameters. Also, since we want to include a model of incretins production (described in the following section) and the Dalla Man et al. model already has a compartment representing the small intestine, it makes the Dalla Man et al. model a better choice for our purpose. The schematic diagram of the Dalla Man et al. model is shown in Fig 2. This model has three compartments, two compartments for the stomach (one for the solid phase and one for the liquid phase) and one compartment for the small intestine. As shown in Fig 2, following the oral glucose intake, glucose enters the stomach in solid form. After the digestion, it turns into the liquid form and then, enters the small intestine and eventually is absorbed to the blood circulation. Fig 3 indicates the connection of the

glucose absorption model with the Sorensen model. As the solid line shows in Fig 3, this model is placed into the gut compartment of the glucose sub-model and is responsible for calculation of the glucose appearance rate into the blood stream following an oral glucose intake. The calculated value of the glucose appearance rate, *Ra*, is inserted in equation (A.4) representing the mass balance over the gut compartment of the glucose sub-model. The Dalla Man et al. model equations comprise mass balance equations over its three compartments and are available in Appendix A.

2.3. The incretins model

We have modified and used a model initially proposed by Alvehag [3] to simulate the release of incretins from the walls of the small intestine following the presence of glucose in the duodenum. Fig 3 indicates the connection of the incretins model with the Sorensen model and the model of glucose absorption in the GI tract. As the solid line in Fig 3 shows, this model is added to the Sorensen model as one sub-model along with the other three main sub-models. Similar to the glucagon sub-model, the incretins sub-model also has one compartment. Its equations comprise two ordinary differential equations; one equation represents the production amount of the incretins following the presence of the glucose in the small intestine and the other one represents the mass balance over the compartment. The equations are available in Appendix A.

Fig 3 shows how the incretins model is connected to the intestine compartment of the glucose absorption model. It also shows its connection to the pancreas compartment of the insulin sub-model. Incretins production starts by the presence of glucose in the small

intestine (equation (A.60)). Produced incretins stimulates the pancreas to increase its insulin production. This effect is represented by including two new terms into two equations of the pancreas model (equations (A.51) and (A.52)).

3. Parameter estimation methodology

3.1. Nonlinear optimization problem

We have used one clinical data set and part of another clinical data set to estimate the model parameters through solving a nonlinear optimization problem. We have employed MATLAB environment to solve the optimization problem. The model parameters are estimated through an iterative optimization algorithm which uses a sequential quadratic programming (SQP) method for solving the constrained optimization problem. In each iteration, the new values of the estimated parameters are used to solve the model equations.

The objective function of the optimization problem is the deviation of model results from the clinical data for both healthy and diabetic subjects as indicated by equation (1):

$$\min_{\Theta} \sum_{i=1}^{n} \left(\left({G_{PC}}_m^i - {G_{PC}}_c^i \right)^2 + \left({I_{PC}}_m^i - {I_{PC}}_c^i \right)^2 + \left(\Psi_m^i - \Psi_c^i \right)^2 \right) \quad (1)$$

where Ψ_m^i is the incretins concentration and ${G_{PC}}_m^i$ and ${I_{PC}}_m^i$ are peripheral glucose and insulin concentrations respectively all obtained at time *i* from the model; Ψ_c^i, ${G_{PC}}_c^i$ and ${I_{PC}}_c^i$ are corresponding clinical measurements; *n* is the size of clinical data set; and Θ is the

vector of model parameters. The best model parameters result in the closest model output to the clinical data

3.2. Selected parameters

Not all model parameters need to be estimated. There is a group of model parameters which are predetermined by a person's physical characteristics such as blood flow rates, capillary space volume, extracellular and intracellular fluid volumes and etc. These model parameters are assumed to be identical for healthy and diabetic subjects with identical weights. Values of these parameters are given for a typical 70 Kg person in Appendix A, Table 1. Another group of model parameters are in equations representing the production and consumption rates of glucose, insulin, glucagon and incretins in different organs. Since functionality of the body organs may differ from one subject to another, these parameters may have different numerical values for any individual. Since the sensitivity of some of these parameters is negligible, not all of these parameters are selected for parameter estimation. The selected model parameters are presented in the following subsections.

3.2.1. The glucose sub-model

From the glucose sub-model, parameters of the glucose metabolic rates and some parameters of the glucose absorption model have been considered for the parameter estimation. As the model equations in Appendix A shows, the glucose metabolic rates in the glucose sub-model has the following general form:

$$r = M^I M^G M^\Gamma r^B \tag{2}$$

where I, G and Γ represent insulin, glucose and glucagon substances respectively, M represents the multiplicative effect of each substance on the glucose metabolic rate and r^B is the metabolic rate at basal condition. The multipliers have the following form:

$$M^C = \frac{(a + b\ tanh[c(C/C^B - d)])}{a + b\ tanh[c(1 - d)]} \tag{3}$$

where C is the concentration of the substance, C^B is the concentration of the substance at basal condition and a, b, c and d are the model parameters. Considering the mathematical representation of M^C given by equation (3), any desirable form of M^C can be obtained by changing the numerical values of c and d. Therefore, to reduce the number of parameters for estimation c and d are selected for the parameter estimation.

The glucose absorption model equations are represented by equations (A.29) to (A.35). The model parameters that have been chosen for parameter estimation are k_{12}, k_{max}, k_{min} and k_{abs}.

3.2.2. The insulin sub-model

From the insulin sub-model, some parameters from the pancreas model have been chosen for parameter estimation. The pancreas model is represented by equations (A.46) to (A.53) from which N_1, N_2, K, γ, α and β are selected for parameter estimation.

The hormonal effects of incretins on the pancreatic insulin production are represented by two terms added to the equations (A.51) and (A.52) in the pancreas model. The related parameters of these two terms (i.e. ξ_1 and ξ_2) are also considered for parameter estimation.

3.2.3. The incretins sub-model

The incretins sub-model is represented by equations (A.60) to (A.63). It has three parameters (i.e. ς, τ_Ψ and $r_{M\Psi C}$) all of which are selected for the parameter estimation.

3.3. Clinical data

The clinical data sets used here are from the clinical trials performed by Knop et al. [38]. Ten type II diabetic subjects (eight men and two women) and ten healthy subjects (eight men and two women) have been selected for the trials. Two different clinical trials are performed on the subjects. In the first trial, a 50 g oral glucose tolerance test (OGTT test) is carried out and 17 blood samples are taken from the subjects during the trial. In the second trial, isoglycemic intravenous glucose infusion test (IIVGIT test) is performed, aimed at copying the plasma glucose profile obtained from the first trial, and 20 blood samples are taken from the subjects. Details about the experiments and the subjects' characteristics are available in [38]. Since the Sorensen model parameters are given for a typical 70 kg individual and the clinical data sets which we are working with are from subjects with different body weights (healthy group: 73±3 kg and diabetic group: 74±4 kg), the concentration of all substances are scaled for a 70 kg body weight using the following equation:

$$C = (C_c - C^B)\frac{W}{70} + C^B \quad (4)$$

where C is the substance concentration, W is the subject's body weight, subscript c refers to the original clinical data and superscript B refers to the basal condition.

The available clinical data sets comprises peripheral glucose, insulin and incretins (GLP-1 plus GIP) concentrations. The data from both trials are used for estimating the model parameters and validating the model results as follows:

From the OGTT test:

- Insulin and incretins concentrations are used to estimate the parameters of the glucose absorption model (i.e. k_{12}, k_{max}, k_{min} and k_{abs}), the parameters of the incretins sub-model (i.e. ς, τ_Ψ and $r_{M\Psi C}$) and the parameters representing the hormonal effects of incretins on the pancreatic insulin production (i.e. ξ_1 and ξ_2).
- Glucose concentrations are used to validate the results of the resultant model with new estimated parameters.

From the IIVGIT test:

- Glucose and insulin concentrations are used to estimate the remaining parameters of the glucose and insulin sub-models.
- Incretins concentrations remain in their basal levels during the IIVGIT test and are not usable for the estimation of model parameters.

3.4. Steady state solution

By adding the model of glucose absorption in the GI tract and the incretins model to the Sorensen model, we have a set of 27 ordinary differential equations (ODE). The initial values for solving the ODEs are calculated by solving the model equations at the steady state condition. The time derivative terms of the ODEs are set to zero and the metabolic rates are assumed to be at their basal rates. For glucose and insulin sub-models, this results in two sets of decoupled algebraic equations - one for the glucose sub-model and one for the insulin sub-model. To solve the resulting sets of algebraic equations, two unknown variables, one for glucose concentration in the glucose sub-model and one for insulin concentration in the insulin sub-model, needed to be set. Since the clinical data includes the measured values of peripheral insulin and glucose concentrations at time zero, these values in the model are set to their measured values for the steady state solution. For glucagon sub-model, since only the normalized value of glucagon concentration is used in the Sorensen model equations, its basal value is arbitrarily chosen for the steady state condition as it does not affect the simulation. For the incretins sub-model, the incretins concentrations are considered to be zero at steady states and all clinical data for the incretins concentrations are subtracted from the measured value of the basal incretins concentration. Since the model inputs are zero at steady state condition and no oral glucose is entering the body, the initial values of all three states of the glucose absorption model are zero.

4. Results and discussion

4.1. Healthy subjects

The parameter estimation results for healthy subjects are shown in Fig 4. Fig 4 indicates variations of the peripheral glucose, insulin and incretins concentrations during the OGTT and IIVGIT tests. The parameter estimation results look acceptable for the overall trends except for the last minutes of the insulin and glucose profiles. This discrepancy is due to the mathematical characteristics of the model. The mathematical solution of the ordinary differential equations ends to the basal concentrations of insulin and glucose (as mentioned in section 3.4 at steady state condition all rates and concentrations are at the basal level), while the experimental glucose and insulin concentrations end to the values a bit below the basal concentrations. It normally takes longer time in which these concentrations return to their basal levels.

Fig 5 indicates the pancreatic insulin secretion rate during both tests. As Fig 4 (b) shows, peripheral insulin concentration following the oral glucose intake is significantly higher than the peripheral insulin concentration following the intravenous glucose injection. Also, as indicated in Fig 5, the amount of pancreatic insulin secretion during the OGTT test is about three times higher with respect to that of IIVGIT test. This is due to the hormonal impact of incretins on the pancreatic insulin production following the oral glucose intake which boosts the insulin production rate by three times compared with the corresponding rate when glucose is administered intravenously.

The model results are validated with the remaining clinical data which is the peripheral glucose concentration during the OGTT test. The validation results are shown in Fig 6. As it is shown, the mathematical model is able to predict the peripheral glucose concentration profile with sufficient accuracy. The model prediction results are a bit off towards the end of the test due to the mathematical characteristics of the model (as explained earlier).

Fig 7 shows the total glucose uptake amount for different parts of the body and Fig 8 indicates the total exogenous and endogenous glucose supplied to the healthy subjects' body. Splanchnic area comprises the digestive system and the liver. The summation of glucose uptake amount from brain, heart and lungs, kidney, and red blood cells are indicated as “other glucose uptake” in Fig 7. This summation is almost constant and independent to the type of trial [57]. All numerical values in Fig 7 and Fig 8 are calculated by integrating the rates up to 140 min. As Figs 4, 5 and 6 show, for both OGTT and IIVGIT tests, the peripheral glucose, insulin and incretins concentrations return to their basal levels approximately in 140 min and variations of the metabolic rates occur within this period. This period is selected to reduce the effects of constant metabolic rates (e.g. the brain glucose uptake rate) on the accuracy of metabolic rates analysis.

According to Fig 7 the splanchnic glucose uptake amount followed by oral glucose intake is significantly higher than when glucose is administered intravenously. Regardless of constant glucose uptake amount by brain, heart and lungs, kidney, and red blood cells, the splanchnic glucose uptake amount accounts for the majority of the blood glucose disposal

during the OGTT test with respect to that of peripheral tissues, while this roll is reversed during the IIVGIT test and the peripheral tissues are the major consumer of the injected glucose. According to Fig 8, during the IIVGIT test, the required amount of infused glucose to copy the blood glucose profile resulted from the OGTT test is approximately half of the glucose amount taken orally for the OGTT test. This is due to the secretion of incretins which push the pancreas to produce more insulin resulting in higher glucose disposal from the blood stream during the OGTT test. These model predictions are all in agreement with the reports by Defronzo [24] for healthy subjects.

4.2. Type II diabetic patients

The parameter estimation results for type II diabetic subjects are shown in Fig 9. Fig 9 shows variations of the peripheral glucose, insulin and incretins concentrations during the OGTT and IIVGIT tests. Similar to the results for healthy subjects, the parameter estimation results look acceptable for the overall trends; however, for the last data points of the insulin profiles the aforementioned mathematical limitation has resulted in the discrepancy.

As Fig 9 shows, in spite of high blood glucose concentration peak in diabetic subjects with respect to that of healthy subjects, the peak of insulin concentration in diabetic subjects is about half of the peak of insulin concentration in healthy subjects. It suggests a high deficiency of the diabetic patients' pancreas in producing required insulin to reduce the blood sugar level. Nevertheless, like healthy subjects, peripheral insulin concentration followed by oral glucose intake is significantly higher than the peripheral insulin

concentration followed by intravenous glucose injection (see Fig 9 (b)). Also, as indicated in Fig 10, the amount of pancreatic insulin secretion during the OGTT test is about two times higher with respect to that of IIVGIT test. This is due to the hormonal impact of incretins on the pancreatic insulin production following the oral glucose intake which boosts the insulin production rate by two times compared with the corresponding rate when glucose is administered intravenously. It suggests that the hormonal effect of incretins in this group of diabetic patients is fairly normal comparing to that of the healthy subjects explained in the previous section.

The model results are validated with the remaining clinical data which is the peripheral glucose concentration during the IIVGIT test. The validation results are shown in Fig 11. As it is shown, although the model prediction results overestimate the blood glucose concentration profile, the overall model prediction is acceptable and the mathematical model is able to predict the peripheral glucose concentration profile with sufficient accuracy.

Fig 12 shows the total glucose uptake amount for different parts of the body and Fig 13 indicates the total exogenous and endogenous glucose supplied to the diabetic subjects' body. All numerical values in Fig 12 and Fig 13 are calculated by integrating the rates up to 240 min.

Unlike healthy subjects, due to the multiple abnormalities of diabetes mellitus, the glucose uptake amounts by different organs of the diabetic group are defected. As Fig 13 shows,

exogenous glucose amounts for IIVGIT and OGTT tests are approximately the same and the route of glucose entrance doesn't affect the glucose disposal from the blood stream. Although the hormonal effects of incretins look fairly normal in stimulating the pancreas to secret more insulin (see Fig 10), however, due to the high insulin resistance in the liver and peripheral tissues, the blood glucose disposal is blunted and almost independent of the route of glucose entrance. Same conclusion is also obtained from the glucose uptake amount by the splanchnic area and peripheral tissues shown in Fig 12. The numerical values of splanchnic glucose uptake rate and peripheral glucose uptake rate are almost identical during the OGTT test and IIVGIT test which means that elevated insulin concentration during OGTT test (compared with that the corresponding rate during IIVGIT test as shown in Fig 9 (b)) is not able to increase the glucose uptake rates which suggests high insulin resistance in the liver and peripheral tissues.

Results also show high glucose resistance in the splanchnic area. During the OGTT test, the glucose concentration present in blood streams of the splanchnic area is higher with respect to the glucose concentration present at peripheral tissues, however, the contribution of the splanchnic area in blood glucose disposal during the OGTT test is not significant compared to the peripheral tissues and also compared to the corresponding amount during the IIVGIT test, while in healthy subjects, the splanchnic area is responsible for the major blood glucose disposal during the OGTT test. These model predictions are all in agreement with the abnormalities associated with diabetic patients reported by Defronzo [24] and categorized in the introduction section.

The numerical values of the estimated parameters are provided in Appendix A (Tables 2, 3, 4 and 5).

5. Conclusion

We presented an expansion accomplished on a former mathematical model proposed by Sorensen for glucose regulations in a healthy human body. The model expansion was accomplished by adding a model of glucose absorption in the GI tract to show the variations of blood glucose concentrations following an oral glucose intake and by adding a model of incretins to account for their hormonal effects on stimulating the pancreatic insulin secretion following oral glucose intake. The parameters of the resultant model were estimated through solving a nonlinear optimization problem and validated using clinical data from both healthy and diabetic subjects. The estimation results had acceptable precision and the validation results showed that the model could predict the body response during the clinical tests reasonably well. Other information obtained from the model was also in agreement with the reports published in the literature. The model parameters can be similarly estimated by the clinical data from other subjects. With the same methodology useful information that provides better understanding of the subjects' medical condition can be obtained from the model.

Appendix A

The following nomenclature is adopted throughout the Sorensen model description:

Model variables in the glucose sub-model

D	Oral glucose amount (mg)
G	Glucose concentration (mg/dl)
M	Multiplier of metabolic rates (dimensionless)
q	Glucose amount in GI tract (mg)
Q	Vascular blood flow rate (dl/min)
r	Metabolic production or consumption rate (mg/min)
Ra	Rate of glucose appearance in the blood stream (mg/min)
T	Transcapillary diffusion time constant (min)
t	time (min)
V	Volume (dl)

Model variables in the insulin sub-model

I	Insulin concentration (mU/l)
M	Multiplier of metabolic rates (dimensionless)
m	Labile insulin mass (U)
P	Potentiator (dimensionless)
Q	Vascular blood flow rate (l/min)
R	Inhibitor (dimensionless)
r	Metabolic production or consumption rate (mU/min)

S Insulin secretion rate (U/min)

T Transcapillary diffusion time constant (min)

t time (min)

V Volume (l)

X Glucose-enhanced excitation factor (dimensionless)

Y Intermediate variable (dimensionless)

Model variables in the glucagon sub-model

Γ Normalized glucagon concentration (dimensionless)

M Multiplier of metabolic rates (dimensionless)

r Metabolic production or consumption rate (dl/min)

V Volume (dl)

t time (min)

Model variables in the incretins sub-model

Ψ Incretins concentration (pmol/l)

r Metabolic production or consumption rate (pmol/min)

V Volume (l)

t time (min)

First superscript

Γ Glucagon

Ψ Incretins

B Basal condition

G Glucose

I Insulin

Second superscript

∞ Final steady state value

Metabolic rate subscripts

BGU Brain glucose uptake

GGU Gut glucose uptake

HGP Hepatic glucose production

HGU Hepatic glucose uptake

$I\Psi R$ Intestinal incretins release

IVG Intravenous glucose injection

IVI Intravenous insulin injection

KGE Kidney glucose excretion

KIC Kidney insulin clearance

LIC Liver insulin clearance

$M\Gamma C$ Metabolic glucagon clearance

$P\Gamma C$ Plasma glucagon clearance

$P\Psi C$ Plasma incretins clearance

PGR Pancreatic glucagon release

PGU Peripheral glucose uptake

PIC Peripheral insulin clearance

PIR Pancreatic insulin release

$RBCU$ Red blood cell glucose uptake

First subscripts

A Hepatic artery

B Brain

G Gut

H Heart and lungs

L Liver

P Periphery

S Stomach

∞ Final steady state value

Second subscripts (if required)

C Capillary space

F Interstitial fluid space

l Liquid

s Solid

A.1. Glucose sub-model

The mass balance equation over each compartment in the glucose sub-model results in following equations:

$$V_{BC}^{G}\frac{dG_{BC}}{dt} = Q_{B}^{G}(G_{H} - G_{BC}) - \frac{V_{BF}^{G}}{T_{B}^{G}}(G_{BC} - G_{BF}) \quad \text{(A.1)}$$

$$V_{BF}^{G}\frac{dG_{BF}}{dt} = \frac{V_{BF}^{G}}{T_{B}^{G}}(G_{BC} - G_{BF}) - r_{BGU} \quad \text{(A.2)}$$

$$V_{H}^{G}\frac{dG_{H}}{dt} = Q_{B}^{G}G_{BC} + Q_{L}^{G}G_{L} + Q_{K}^{G}G_{K} + Q_{P}^{G}G_{PC} - Q_{H}^{G}G_{H} - r_{RBCU} + r_{IVG} \quad \text{(A.3)}$$

$$V_{G}^{G}\frac{dG_{G}}{dt} = Q_{G}^{G}(G_{H} - G_{G}) - r_{GGU} + Ra \quad \text{(A.4)}$$

$$V_{L}^{G}\frac{dG_{L}}{dt} = Q_{A}^{G}G_{H} + Q_{G}^{G}G_{G} - Q_{L}^{G}G_{L} + r_{HGP} - r_{HGU} \quad \text{(A.5)}$$

$$V_{K}^{G}\frac{dG_{K}}{dt} = Q_{K}^{G}(G_{H} - G_{K}) - r_{KGE} \quad \text{(A.6)}$$

$$V_{PC}^{G}\frac{dG_{PC}}{dt} = Q_{P}^{G}(G_{H} - G_{PC}) - \frac{V_{PF}^{G}}{T_{P}^{G}}(G_{PC} - G_{PF}) \quad \text{(A.7)}$$

$$V_{PF}^{G}\frac{dG_{PF}}{dt} = \frac{V_{PF}^{G}}{T_{P}^{G}}(G_{PC} - G_{PF}) - r_{PGU} \quad \text{(A.8)}$$

The metabolic rates for the glucose sub-model are summarized below:

$$r_{BGU} = 70 \tag{A.9}$$

$$r_{RBCU} = 10 \tag{A.10}$$

$$r_{GGU} = 20 \tag{A.11}$$

$$r_{PGU} = M^{I}_{PGU} M^{G}_{PGU}\, r^{B}_{PGU} \tag{A.12}$$

$$r^{B}_{PGU} = 35 \tag{A.13}$$

$$M^{I}_{PGU} = \frac{7.03 + 6.52\, tanh[c(I_{PF}/I^{B}_{PF} - d)]}{7.03 + 6.52\, tanh[c(1-d)]} \tag{A.14}$$

$$M^{G}_{PGU} = G_{PF}/G^{B}_{PF} \tag{A.15}$$

$$r_{HGP} = M^{I}_{HGP} M^{G}_{HGP}\, M^{\Gamma}_{HGP}\, r^{B}_{HGP} \tag{A.16}$$

$$r^{B}_{HGP} = 35 \tag{A.17}$$

$$\frac{d}{dt} M^{I}_{HGP} = 0.04(M^{I\infty}_{HGP} - M^{I}_{HGP}) \tag{A.18}$$

$$M^{I\infty}_{HGP} = \frac{1.21 - 1.14\, tanh[c(I_L/I^{B}_{L} - d)]}{1.21 - 1.14\, tanh[c(1-d)]} \tag{A.19}$$

$$M^{G}_{HGP} = \frac{1.42 - 1.41\, tanh[c(G_L/G^{B}_{L} - d)]}{1.42 - 1.41\, tanh[c(1-d)]} \tag{A.20}$$

$$M_{HGP}^{\Gamma} = 2.7\, tanh[0.39\, \Gamma/\Gamma^B] - f \tag{A.21}$$

$$\frac{d}{dt} f = 0.0154[\left(\frac{2.7\, tanh[0.39\, \Gamma/\Gamma^B] - 1}{2}\right) - f] \tag{A.22}$$

$$r_{HGU} = M_{HGU}^{I} M_{HGU}^{G}\, r_{HGU}^{B} \tag{A.23}$$

$$r_{HGU}^{B} = 20 \tag{A.24}$$

$$\frac{d}{dt} M_{HGU}^{I} = 0.04(M_{HGU}^{I\infty} - M_{HGU}^{I}) \tag{A.25}$$

$$M_{HGU}^{I\infty} = \frac{2.0\, tanh[c(I_L/I_L^B - d)]}{2.0\, tanh[c(1-d)]} \tag{A.26}$$

$$M_{HGU}^{G} = \frac{5.66 + 5.66\, tanh[c(G_L/G_L^B - d)]}{5.66 + 5.66\, tanh[c(1-d)]} \tag{A.27}$$

$$r_{KGE} = 71 + 71\, tanh[0.11(G_K - 460)] \quad 0 \le G_K < 460$$

$$r_{KGE} = -330 + 0.872 G_K \quad G_K \ge 460 \tag{A.28}$$

The model of glucose absorption in the GI tract proposed by Dalla Man et al. [20] is added to the glucose sub-model. The model equations are:

$$\frac{dq_{Ss}}{dt} = -k_{12} q_{Ss} + D\delta(t) \tag{A.29}$$

$$\frac{dq_{Sl}}{dt} = -k_{empt}q_{Sl} + k_{12}q_{Ss} \tag{A.30}$$

$$\frac{dq_{int}}{dt} = -k_{abs}q_{int} + k_{empt}q_{Sl} \tag{A.31}$$

$$k_{empt} = k_{min} + \frac{k_{max} - k_{min}}{2}\{tanh[\varphi_1(q_{Ss} + q_{Sl} - x_1 D)] - tanh[\varphi_2(q_{Ss} + q_{Sl} - x_2 D)] + 2\} \tag{A.32}$$

$$\varphi_1 = \frac{5}{2D(1 - x_1)} \tag{A.33}$$

$$\varphi_2 = \frac{5}{2Dx_2} \tag{A.34}$$

$$Ra = f k_{abs} q_{int} \tag{A.35}$$

where $\delta(t)$ is the impulse function.

A.2. Insulin sub-model

The mass balance equation over the compartments in the insulin sub-model results in following equations:

$$V_B^I \frac{dI_B}{dt} = Q_B^I (I_H - I_B) \tag{A.36}$$

$$V_H^I \frac{dI_H}{dt} = Q_B^I I_B + Q_L^I I_L + Q_K^I I_K + Q_P^I I_{PV} - Q_H^I I_H \tag{A.37}$$

$$V_G^I \frac{dI_G}{dt} = Q_G^I (I_H - I_G) \tag{A.38}$$

$$V_L^I \frac{dI_L}{dt} = Q_A^I I_H + Q_G^I I_G - Q_L^I I_L + r_{PIR} - r_{LIC} + r_{IVI} \tag{A.39}$$

$$V_K^I \frac{dI_K}{dt} = Q_K^I (I_H - I_K) - r_{KIC} \tag{A.40}$$

$$V_{PC}^I \frac{dI_{PC}}{dt} = Q_P^I (I_H - I_{PC}) - \frac{V_{PF}^I}{T_P^I} (I_{PC} - I_{PF}) \tag{A.41}$$

$$V_{PF}^I \frac{dI_{PF}}{dt} = \frac{V_{PF}^I}{T_P^I} (I_{PC} - I_{PF}) - r_{PIC} \tag{A.42}$$

The metabolic rates for the insulin sub-model are summarized below:

$$r_{LIC} = 0.4[Q_A^I I_H + Q_G^I I_G + r_{PIR}] \tag{A.43}$$

$$r_{KIC} = 0.3 Q_K^I I_K \tag{A.44}$$

$$r_{PIC} = \frac{I_{PF}}{[\left(\frac{1 - 0.15}{0.15 Q_P^I}\right) - \frac{20}{V_{PF}^I}]} \tag{A.45}$$

As mentioned, the pancreatic insulin release model used in the Sorensen model has been proposed by Landahl and Grodsky [39]. The graphical representation of Landahl and Grodsky's model is depicted in Fig 14. The aim of Landahl and Grodsky's model is to mimic the biphasic behavior of pancreatic insulin secretion in response to a glucose

stimulus. In this model, a small labile insulin compartment is assumed to exchange insulin with a large storage compartment. The rate at which insulin flows into the labile compartment is regulated by a glucose-stimulated factor, *P*. The rate of insulin secretion, *S*, is dependent on glucose concentration, the amount of labile insulin, *m*, and the difference between the instantaneous level of glucose-enhanced excitation factor, *X*, and its inhibitor, *R*. This functionality provides a mathematical description of the pancreas biphasic response to a glucose stimulus. The first phase insulin release is caused by an instantaneous increase in the glucose-enhanced excitation factor (*X*) followed by a rapid increase in its inhibitor (*R*). The second phase release results from the direct dependence of the insulin secretion rate (*S*) on the glucose stimulus and the gradual increase in the level of the labile compartment filling factor (*P*).

The mass balance equation over each compartment results in:

$$\frac{dm}{dt} = K'm' - Km + \gamma P - S \tag{A.46}$$

$$\frac{dm'}{dt} = Km - K'm' - \gamma P \tag{A.47}$$

It is assumed that the capacity of the storage compartment is large enough and remains at steady state. For a glucose concentration of zero, *P* is set to zero. Therefore, the steady state mass balance equation around the storage compartment is:

$$K'm' = Km_0 \tag{A.48}$$

where m_0 is the labile insulin quantity at a glucose concentration of zero. The rest of the equations for the pancreas model are:

$$\frac{dP}{dt} = \alpha(P_\infty - P) \tag{A.49}$$

$$\frac{dR}{dt} = \beta(X - R) \tag{A.50}$$

$$S = [N_1 Y + N_2(X - R) + \xi_2 \Psi]m \quad X > R$$
$$S = (N_1 Y + \xi_2 \Psi)m \qquad X \leq R \tag{A.51}$$

$$P_\infty = Y = X^{1.11} + \xi_1 \Psi \tag{A.52}$$

$$X = \frac{G_H^{3.27}}{132^{3.27} + 5.93 G_H^{3.02}} \tag{A.53}$$

P_∞ and Y reflect the glucose-induced stimulation effects on the liable compartment filling factor and the insulin secretion rate, respectively.

A.3. Glucagon sub-model

The glucagon sub-model has one mass balance equation over the whole body as follows:

$$V^\Gamma \frac{d\Gamma}{dt} = r_{P\Gamma R} - r_{P\Gamma C} \tag{A.54}$$

The metabolic rates for the glucagon sub-model are summarized below:

$$r_{P\Gamma C} = 9.1\Gamma \tag{A.55}$$

$$r_{P\Gamma R} = M^{G}_{P\Gamma R} M^{I}_{P\Gamma R} r^{B}_{P\Gamma R} \tag{A.56}$$

$$M^{G}_{P\Gamma R} = 1.31 - 0.61 tanh\,[1.06(G_H/G^{B}_{H} - 0.47)] \tag{A.57}$$

$$M^{I}_{P\Gamma R} = 2.93 - 2.09 tanh\,[4.18(I_H/I^{B}_{H} - 0.62)] \tag{A.58}$$

$$r^{B}_{P\Gamma R} = 9.1 \tag{A.59}$$

A.4. Incretins sub-model

Similar to the glucagon sub-model, the incretins model has one compartment. The incretins model equations comprise two ordinary differential equations, one represents the production of the incretins following the presence of the glucose in the small intestine and the other one represents the mass balance over the compartment. The incretins production is calculated from the following differential equation:

$$\frac{d\psi}{dt} = \varsigma k_{empt} q_{Sl} - r_{I\Psi P} \tag{A.60}$$

where ψ is the amount of produced incretins, $k_{empt} q_{Sl}$ is the rate of glucose entrance to the small intestine, $r_{I\Psi P}$ is the rate of incretins absorption into the blood stream, and ς is a constant.

$r_{I\Psi P}$ is calculated from the following equation:

$$r_{I\Psi P} = \frac{\psi}{\tau_{\Psi}} \tag{A.61}$$

where τ_{Ψ} is the time constant of the incretins absorption process into the blood stream. The mass balance equation over the incretins compartment results in:

$$V^{\Psi} \frac{d\Psi}{dt} = r_{I\Psi P} - r_{P\Psi C} \tag{A.62}$$

where V^{Ψ} is the incretins distribution volume, Ψ is the blood incretins concentration and $r_{P\Psi C}$ the rate of plasma incretins clearance which depends on the incretins concentration. The clearance rate is calculated from the following equation:

$$r_{P\Psi C} = r_{M\Psi C}\Psi \tag{A.63}$$

where $r_{M\Psi C}$ is the mean incretins clearance rate and is a constant.

The model constant parameters are summarized in Table 1.

Table 1: The model parameters

$V_{BC}^{G} = 3.5\ dl$	$Q_{B}^{G} = 5.9\ dl/min$	$T_{B}^{G} = 2.1\ min$
$V_{BF}^{G} = 4.5\ dl$	$Q_{H}^{G} = 43.7\ dl/min$	$T_{P}^{G} = 5.0\ min$
$V_{H}^{G} = 13.8\ dl$	$Q_{A}^{G} = 2.5\ dl/min$	$T_{P}^{I} = 20\ min$
$V_{L}^{G} = 25.1\ dl$	$Q_{L}^{G} = 12.6\ dl/min$	$m_0 = 6.33\ U$
$V_{G}^{G} = 11.2\ dl$	$Q_{G}^{G} = 10.1\ dl/min$	$f = 0.9$
$V_{K}^{G} = 6.6\ dl$	$Q_{K}^{G} = 10.1\ dl/min$	$x_1 = 0.82$
$V_{PC}^{G} = 10.4\ dl$	$Q_{P}^{G} = 15.1\ dl/min$	$x_2 = 0.00236$
$V_{PF}^{G} = 67.4\ dl$	$Q_{B}^{I} = 0.45\ l/min$	
$V_{B}^{I} = 0.26\ l$	$Q_{H}^{I} = 3.12\ l/min$	
$V_{H}^{I} = 0.99\ l$	$Q_{A}^{I} = 0.18\ l/min$	
$V_{G}^{I} = 0.94\ l$	$Q_{K}^{I} = 0.72\ l/min$	
$V_{L}^{I} = 1.14\ l$	$Q_{P}^{I} = 1.05\ l/min$	
$V_{K}^{I} = 0.51\ l$	$Q_{G}^{I} = 0.72\ l/min$	
$V_{PC}^{I} = 0.74\ l$	$Q_{L}^{I} = 0.90\ l/min$	
$V_{PF}^{I} = 6.74\ l$		
$V^{\Gamma} = 113.1\ dl$		
$V^{\Psi} = 11.31\ l$		

Table 2: Parameter estimation results for glucose metabolic rates

	Healthy subjects		Diabetic subjects	
	c	*d*	*c*	*d*
M_{PGU}^{I} (equation A.14)	0.15	4.325	0.067	1.126
$M_{HGP}^{I\infty}$ (equation A.19)	0.50	1.20	1.59	0.683
M_{HGP}^{G} (equation A.20)	0.50	0.70	0.62	0.14
$M_{HGU}^{I\infty}$ (equation A.26)	1.147	0.20	1.72	0.023
M_{HGU}^{G} (equation A.27)	2.03	1.99	2.03	1.59

Table 3: Parameter estimation results for glucose absorption model

	Healthy subjects	Diabetic subjects
$k_{12}\,(min^{-1})$	0.1	0.08
$k_{min}\,(min^{-1})$	0.001	0.005
$k_{max}\,(min^{-1})$	0.1	0.05
$k_{abs}\,(min^{-1})$	0.1	0.08

Table 4: Parameter estimation results for insulin sub-model

	Healthy subjects	Diabetic subjects
$\alpha\ (min^{-1})$	0.0482	0.615
$\beta\ (min^{-1})$	0.931	0.931
$K\ (min^{-1})$	0.00794	0.0572
$N_1\ (min^{-1})$	0.0254	0.0499
$N_2\ (min^{-1})$	0.0501	0.00015
$\gamma\ (U/min)$	0.0958	2.366
$\xi_1\ (l/pmol)$	0.0063	0.0026
$\xi_2\ (l/pmol.min)$	0.000093	0.000099

Table 5: Parameter estimation results for incretins sub-model

	Healthy subjects	Diabetic subjects
$\varsigma\ (pmol/mg)$	30.26	29.18
$\tau_\psi\ (min)$	23.46	28.04
$r_{M\Psi C}\ (l/min)$	188.58	174.06

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Figure Caption

Fig 1 Schematic diagram of insulin sub-model. The arrows indicate blood flow directions and the rectangular blocks represent compartments

Fig 2 Schematic diagram of Dalla Man et al. model for glucose absorption in the GI tract

Fig 3 Connections of the incretins model, the glucose absorption model and the Sorensen model. Solid lines represent where models are located and dashed lines represent the direction that models affect each other

Fig 4 Parameter estimation results for healthy subjects. (a) Peripheral glucose concentration during IIVGIT test (model results (–) and clinical data (•), R^2=0.9732); (b) Peripheral insulin concentration during OGTT test (model results (–) and clinical data (•), R^2=0.9667) and IIVGIT test (model results (--), clinical data (×), R^2=0.8790); (c) Peripheral incretins concentration during OGTT test (model results (–) and clinical data (•), R^2=0.9807)

Fig 5 Pancreatic insulin secretion rate for healthy subjects during the OGTT test (–) and IIVGIT test (--)

Fig 6 Peripheral glucose concentration profile for healthy subjects during the OGTT test, model results (–) and clinical data (•), R^2=0.9329

Fig 7 The total glucose uptake amount for different parts of the body of healthy subjects during OGTT and IIVGIT tests

Fig 8 The total exogenous and endogenous glucose supplied to the healthy subjects' body during OGTT and IIVGIT tests

Fig 9 Parameter estimation results for diabetic subjects. (a) Peripheral glucose concentration during IIVGIT test (model results (–) and clinical data (•), R^2=0.9777); (b) Peripheral insulin concentration during OGTT test (model results (–) and clinical data (•), R^2=0.9625) and IIVGIT test (model results (--), clinical data (×), R^2=0.8865); (c) Peripheral incretins concentration during OGTT test (model results (–) and clinical data (•), R^2=0.9806)

Fig 10 Pancreatic insulin secretion rate for diabetic subjects during the OGTT test (–) and IIVGIT test (--)

Fig 11 Peripheral glucose concentration profile for type II diabetic subjects during the OGTT test, model results (–) and clinical data (●), R^2=0.9467

Fig 12 The total glucose uptake amount for different parts of the body of type II diabetic subjects during OGTT and IIVGIT tests

Fig 13 The total exogenous and endogenous glucose supplied to the healthy subjects' body during OGTT and IIVGIT tests

Fig 14 Landahl and Grodsky's model for pancreatic insulin secretion