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Assessment of type II diabetes mellitus using irregularly sampled measurements with missing data

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Abstract Diabetes Mellitus is one of the leading diseases in the developed world. In order to better regulate blood glucose in a diabetic patient, improved modelling of insulin-glucose dynamics is a key factor in the treatment of diabetes mellitus. In the current work, the insulin-glucose dynamics in type II diabetes mellitus can be modelled by using a stochastic nonlinear state-space model. Estimating the parameters of such a model is difficult as only a few blood glucose and insulin measurements per day are available in a non-clinical setting. Therefore, developing a predictive model of the blood glucose of a person with type II diabetes mellitus is important when the glucose and insulin concentrations are only available at irregular intervals. To overcome these difficulties, we resort to online Sequential Monte Carlo (SMC) estimation of states and parameters of the state-space model for type II diabetic patients under various levels of randomly missing clinical data. Our results show that this method is efficient in monitoring and estimating the dynamics of the peripheral glucose, insulin and incretins concentration when 10%, 25% and 50% of the simulated clinical data were randomly removed.

Keywords Type II diabetes mellitus · Online identification · Bayesian framework · SIR particle filtering

1 Introduction

Diabetes mellitus is a serious disorder that can cause death [1]. It occurs when the control of blood glucose levels fails. Glucose is produced in the digestive system by consuming food such as bread, potatoes, rice, pasta and fruit. Blood glucose level is regulated by insulin, a hormone secreted from the islet beta cells of the pancreas. Type I and type II diabetes mellitus are two types of diabetic diseases. About ninety percent of people with diabetes are suffering from type II diabetes [1, 2, 3].

Type II diabetes occurs when the pancreas does not produce enough insulin or the human body cells become resistance against insulin [1]. Insulin resistance happens when the sensitivity of peripheral cells to the metabolic action of insulin is decreased due to genetic factors, environmental factors, obesity, hypertension, dyslipidemias, and/or coronary artery diseases [4]. Exercise and healthy dieting can initially control the blood glucose concentration in type II diabetic patients. However, oral anti-diabetic agent and insulin treatment are required in patients with moderate to severe type II diabetes mellitus. Physicians may provide more appropriate treatments if the etiological factors of patients diabetic conditions are known. [5]. Therefore, diagnosing or detecting the dysfunction of different organs such as the pancreas, liver, muscles and adipose tissues will be very useful for selecting the suitable medications for diabetic patients.

In diabetic patients, the glucose metabolic rates represent the health status of the liver, muscles and adipose tissues. To measure the glucose metabolic rates in the type II diabetic patients, the measurement

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of the glucose and insulin concentrations in different parts of the body are needed. However, clinical measurements of all necessary concentrations deep inside different organs or tissues are just not practical or realistic. Therefore, physicians mostly rely on a few measurements from patients blood and/or capillary glucose measurements at regular or irregular intervals for clinical decisions [5].

Previous studies have shown that important clinical data may be missing owing to different reasons such as inability to record clinical results, infrequent sampling by patients, and illegible hand writing. Lack of complete knowledge about the health status of the diabetic patients poses more problems to physicians in managing type II diabetes while they need time oriented clinical data of past and present status of diabetic patients [6, 7, 8].

Since only a few blood glucose measurements per day are available in a non-clinical setting, developing a predictive model of the blood glucose of a person with type II diabetes mellitus is important. Such a model may provide useful information to diabetic patients of dangerous metabolic conditions, enable physicians to review past therapy, estimate future blood glucose levels, and provide therapy recommendations. It can also be used in the design of a stabilizing control system for blood glucose regulations [9, 10].

Many studies proposed on-line identification of type I diabetes mellitus using neural network modelling approaches [10, 11, 12, 13]. Tresp *et al.* [10] developed a predictive model of the blood glucose of a person with type I diabetes mellitus with partially missing clinical data by using a combination of a nonlinear recurrent neural network and a linear error model. However, developing a nonlinear state-space model for type II diabetes mellitus that can easily deal with missing data has received limited attention. The compartmental minimal modelling (MINMOD) approach for type II diabetes mellitus [14] has been used widely in many studies. Recently, based on the Sorensen model [15], a detailed nonlinear model has been developed by Vahidi *et al.* [16] for the type II diabetic patients. However, none of these approaches considered identification of a type II diabetes model from clinical data, which contain missing data at random intervals.

The goal of this work is to develop a blood glucose predictive model for a type II diabetic patient and the model can be estimated by using patient data collected under normal everyday conditions rather than a well-controlled environment typically done in a clinical facility. Such a model should be able to detect dangerous metabolic states of a patient, and optimize the patient's therapy.

In this study, we use online Bayesian estimation framework to estimate a stochastic nonlinear model for type II diabetes mellitus using clinical data with missing data at random intervals. We adopt the detailed nonlinear model developed by Vahidi *et al.* [16, 17] for type II diabetes since the Vahidi model is a much more detailed model comparing with the MINMOD approach. The Vahidi model is able to effectively model individual abnormalities by characterizing distinct compartments as the faulty organs. To artificially create clinical data sets with missing data at random intervals, we then randomly remove 10%, 25% and 50% of the original available data obtained from the Vahidi model. At the end, glucose, insulin, and incretins concentrations, as well as the parameters of different compartments, are estimated from clinical data with missing data at random intervals. These estimates can then be used to measure the glucose metabolic rates in different organs of the type II diabetic patients.

There is an extensive discussion on estimating the states and the parameters of the nonlinear state-space models from partially missing data using mathematical approaches such as Bayesian filters, Particle filters (PFs), Expectation-Maximization (EM) algorithms, Sequential Importance Resampling (SIR) particle filters [18, 19, 20, 21]. In many studies, Bayesian estimation has been used in metabolism and physiological modelling [22, 23, 24]. Among these methods, we use the SIR based PF proposed by Tulsyan *et al.* [25] for online Bayesian estimation of the states and the parameters of the Vahidi model since it needs less computational cost when a large number of unknown states and parameters must be estimated simultaneously. To do this, a clinical data set, as well as a prior information on the unknown states and parameters of the Vahidi model, are needed. This kind of information can be gathered from physical considerations and population studies.

This paper is organized as follows. In section 2, the mathematical model of type II diabetes mellitus is provided. In sections 3 and 4, a summary description of the SIR filtering algorithm is discussed. The on-line parameters estimation results of the nonlinear type II diabetic model are presented in section 5 when 10%, 25% and 50% of missing clinical data are removed randomly. Then, the application of SIR particle filtering technique in detecting the organ dysfunction of a group of type II diabetic patients under irregularly sampled clinical data is presented.

2 Mathematical modelling of the type II diabetes mellitus

The model of the glucose-insulin interaction in type II diabetic patients used here is based on the Vahidi model [16]. In this model, the concentrations of three substances (*i.e.*, glucose, insulin and glucagon) and

their interactions are described by three main sub-models based on the Sorensen model [15]. Each sub-model is divided into individual numbers of compartments representing specific parts or organs of a human body. The number of compartments is different in each sub-model. As can be seen in Fig. 1, the insulin sub-model has seven compartments: brain, liver, heart and lungs, periphery, gut, kidney, and pancreas. The blocks represent different compartments and the arrows indicate the blood flow directions. The glucose sub-model is similar to the insulin sub-model except that the pancreas compartment is excluded. Since the glucagon concentration is considered to be identical in all parts of the body, only one compartment is used in the glucagon sub-model [26]. In each sub-model, mass balance equations are written for all individual sub-compartments (except for the pancreas, which will be described in more details in Appendix A). The general form of the mass balance equation on each sub-compartment is shown as follows [27]:

$$V \frac{dY}{dt} = Q(Y_{in} - Y_{out}) + r_p - r_c. \quad (2.0.1)$$

where V is the volume of sub-compartments, Y is the concentration of either insulin, glucose, or glucagon, t is time, Q is blood flow rate, and r_p and r_c are metabolic production and consumption rates of the material balance substance, respectively. Since the glucagon sub-model has only one compartment, blood flow rate is set to zero and the glucagon mass balance equation has only the metabolic production and consumption rates. The metabolic rate of different substances takes on the following general form [27]:

$$r = M^I(t, I)M^G(G)M^\Gamma(t, \Gamma)r^B. \quad (2.0.2)$$

where I , G , and Γ represent insulin, glucose, and glucagon substances, respectively. M^i is the i 's multiplier, which represents the regulatory effect of i substance on the metabolic rate, and r^B is the metabolic rate at the basal condition. The general mathematical form of multiplicative effect of each substance is [27]:

$$M^i = A + B \tanh[C(\frac{i}{i^B} - D)]. \quad (2.0.3)$$

where i^B is the concentration of i at basal condition and A , B , C , and D are parameters, which are unknown and should be estimated.

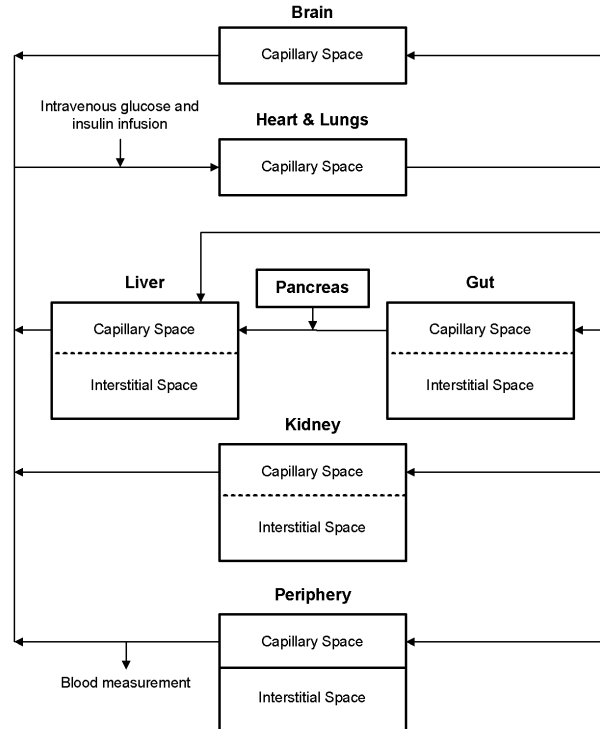


Fig. 1: Schematic diagram of insulin submodel [16]

Later, the Vahidi model was modified to determine the variations of blood glucose concentration resulted from an oral glucose intake by adding a model of gut glucose absorption in the gastrointestinal tract proposed by Dalla Man *et al.* [28, 17]. In addition, the hormonal effects of incretins on boosting pancreatic insulin secretion was included by adding a two compartment model of incretins production in order to simulate the variations of incretins concentrations in blood circulatory system. *Appendix A* contains the details on the complete model equations.

In the Vahidi model, two different clinical tests, oral glucose tolerance test (OGTT) and isoglycemic intravenous glucose infusion test (IIVGIT) performed by Knop *et al.* [29, 30], were used for states and parameters estimation. The clinical data sets are summarized in detail in section 5.1. Estimation of the modified model parameters were carried out by minimizing the deviation of model predictions from the available measurements of peripheral glucose, insulin and incretins concentrations. The deviation of model predictions from the measured clinical data is minimized through the following objective function:

$$\min_{\Theta} \sum_{j=1}^n [(G^j - \hat{G}^j)^2 + (I^j - \hat{I}^j)^2]. \quad (2.0.4)$$

where G^j and I^j are peripheral glucose and insulin concentrations at time j obtained from the model respectively; \hat{G}^j and \hat{I}^j are the corresponding clinical measurements; n is the number of samples in the clinical data set; and Θ is the vector of parameters containing the glucose, insulin, and glucagon metabolic rates [16]. Different parameters of metabolic rates will be obtained after the optimization procedure for each type II diabetic patient since there are different peripheral glucose, insulin and incretins concentrations profile for different patients.

In this study, the estimation of the Vahidi model parameters are carried out by the SIR particle filtering method for data sets that contain randomly deleted simulated data described in the following sections. To do this, the continuous time stochastic nonlinear state-space format of the Vahidi model [17] in equation (2.0.1) is transformed to discrete time format as follows:

$$\hat{y}_t = g(\hat{x}_t, \hat{\theta}_t, u_t), \quad (2.0.5)$$

where g is the measurement dynamic function variables and \hat{y}_t is the vector of concentration of either insulin, glucose, or glucagon at sampling time t (Y in equation (2.0.1)) monitored and recorded by several sensors and measuring devices. These devices record patient's critical variables y_t (output) in response to the test action u_t (input) implemented at some point in time indexed by t . For example, in the intravenous glucose infusion test, insulin concentration measurements as output y_t are recorded at regular intervals against the infused glucose concentration as input u_t . A summary description of this on-line estimation method is provided in the next following sections.

3 Response models

In clinical trials, several sensors and measuring devices were used for monitoring the response of a patient to a clinical test. Let us assume that we have a sequence of time-tagged clinical measurements $y_{1:t} = \{y_1, y_2, \dots, y_t\}$ corresponding to the input action $u_{1:t} = \{u_1, u_2, \dots, u_t\}$, and that we are interested in predicting the response y_{t+1} for some known input action u_{t+1} . Such predictions are valuable to the physician assessing the health of the patient during clinical trials. To solve this problem, we can assume y_{t+1} is independent of $\{u_{1:t}, y_{1:t}\}$, in which case, the prediction of y_{t+1} is impossible. Alternatively, we can assume y_{t+1} depends on the trend recorded in the past data $\{u_{1:t}, y_{1:t}\}$. For the latter assumption— which is true for any causal system— a response model¹ is useful in predicting the response of a patient to a clinical test.

A reliable response model should not only accurately model a patient's physical and biological response to a clinical test, it should also account for the various uncertainties such as modelling and measurement errors. For example, random measurement errors can be modelled by viewing y_t as a random realization of a stochastic process. In this work, we use stochastic state-space models (SSMs) to represent a response model. Mathematically, a SSM can be represented as:

$$x_{t+1} = f(y_t, \theta_t, u_t) + v_t, \quad (3.0.6a)$$

$$y_t = g(x_t, \theta_t, u_t) + w_t, \quad (3.0.6b)$$

¹ A response model is a mathematical model describing the dynamics of the key internal states of a patient in response to a clinical test.

where x_t describes evolution of the internal states of the patient. Physically, x_t models the complete response of a patient subject to a clinical test. Given the states x_t , inputs u_t and model parameters θ_t at time t , the internal states evolve to x_{t+1} . v_t in equation (3.0.6a) is the state noise, which accounts for the unknown and unmeasured variations in the states not captured by the response model. Due to the non-zero random state noise v_t , the states are not precisely known. Equation (3.0.6b) describes how sensor readings y_t relate to the states x_t and parameters θ_t . w_t in equation (3.0.6b) is the noise term, which accounts for the random sensor noise. In clinical trials, measurements of only a few critical states are available at our disposal. This is because the high cost or lack of appropriate sensing technology or devices precludes measurement of all but key internal states. The state-space modelling framework is general, and can be used to represent a wide class of response models, including the type II diabetes mellitus response model given in section 2.

In this paper, we use equation (3.0.6) for real-time estimation of the critical response variables, such as blood glucose, insulin and incretins concentrations during clinical trial of patients with type II diabetes mellitus. Monitoring these variables is critical as it enables the physicians to review past therapy, estimate future blood glucose levels and provide therapy recommendations. To predict the critical variables using equation (3.0.6), the model states and parameters, which are typically unknown for a patient need to be estimated first. Given the state and parameter estimates, the model predictions at t can be computed as:

$$\hat{y}_t = g(\hat{x}_t, \hat{\theta}_t, u_t), \quad (3.0.7)$$

where \hat{y}_t is the response predictions and \hat{x}_t and $\hat{\theta}_t$ are the parameter and state estimates, respectively. Ideally, given an accurate estimate of the states and parameters, the model predictions should match the clinical measurements as closely as possible. Any standard estimation approach involves fitting the model using available clinical measurements; however, data fitting is not straightforward for SSMs because of the following reasons: 1) the states are stochastic, which makes estimation of both states and parameters challenging and 2) the clinical measurements are assumed to be irregularly sampled.

In this paper, we propose the use of Bayesian methods for real-time state and parameter estimation in equation (3.0.6) under irregularly sampled clinical measurements. In the next section, a description of real-time Bayesian estimation is provided.

Remark. There is a much larger appeal to use state-space modelling framework to represent response models. From equation (3.0.7), it is evident that computing the response predictions using a SSM also requires estimation of all the internal states of the patient. Thus, any method designed to compute the response predictions gives away estimation of all the internal states as a side product. This is of immense value to a physician, considering only a handful of the internal states are actually measured.

4 Real-time Bayesian estimation

Our objective is to estimate z_t in real-time using clinical data $\{u_{1:t}; y_{1:t}\}$. Let $z_t = \{x_t, \theta_t\}$ denote an extended vector of unknown states and parameters. It is further assumed that the clinical measurements are recorded at irregular times, such that only a subset of $y_{1:t}$ is available for estimation at t . For notational convenience we dispense with the input u_t in the succeeding discussions; however, the method presented in this paper holds with the inputs included.

In the Bayesian framework, the variables to be estimated are assumed to be random variables. The states are inherently random due to the noise in equation (3.0.6a); and the parameters, which are unknown but non-random are assumed to be random, such that $z_t = \{x_t, \theta_t\}$ is a vector of random variables. To set up the Bayesian estimation, we assume z_0 to be distributed with a prior density $p(z_0|y_{1:0})$. Also, we assume the state and measurement noise are independent and identically distributed (i.i.d) zero mean finite variance Gaussian sequences with the probability density functions (PDF) $p_x(\cdot)$ and $p_y(\cdot)$ known *a priori*.

4.1 Complete clinical data

First we consider the estimation problem using the complete clinical data set. Assuming $y_{1:t}$ to be available, the real-time Bayesian estimation of z_t at t involves computing the posterior density $p(z_t|y_{1:t})$. Here, $p(z_t|y_{1:t})$ is a probabilistic representation of the statistical information available on z_t conditioned on the clinical measurements $y_{1:t}$. Using the Bayes' theorem and Total law of probability, $p(z_t|y_{1:t})$ can be recursively computed in two steps, which are the update and prediction steps as shown below:

Update Step:

$$p(z_t|y_{1:t}) \propto p_y(y_t|z_t)p(z_t|y_{1:t-1}). \quad (4.1.1)$$

Prediction Step:

$$p(z_t|y_{1:t-1}) = \int p_z(z_t|z_{t-1})p(z_{t-1}|y_{1:t-1})dz_t. \quad (4.1.2)$$

In equation (4.1.1), $p_y(y_t|z_t)$ is the measurement noise distribution or the likelihood function indicating how likely it is for z_t to have generated the clinical measurement y_t . $p(z_t|y_{1:t-1})$ is a one-step-ahead prior density representing statistical information on z_t prior to the recorded clinical measurement y_t . The prior density $p(z_t|y_{1:t-1})$ is computed using equation (4.1.2), where $p_z(z_t|z_{t-1})$ is the joint state and parameter noise distribution and $p(z_{t-1}|y_{1:t-1})$ is the posterior distribution at $t-1$.

Starting with $p(z_0|y_{0:1})$, in principle, the recurrence relation between equations (4.1.1) and (4.1.2) provides a complete Bayesian solution to the state and parameter estimation problem under complete clinical data. Finally using $p(z_t|y_{1:t})$, the estimate of \hat{z}_t at t can be computed as the mean of the posterior density, such that the estimate step can be defined as:

$$\hat{z}_t = \int z_t p(z_t|y_{1:t}) dz_t, \quad (4.1.3)$$

where $\hat{z}_t = \{\hat{x}_t, \hat{\theta}_t\}$ is the state and parameter estimation at t . Note that other values, such as the mode or median of $p(z_t|y_{1:t})$ can also be selected as the point estimate.

4.2 Irregular clinical data

From section 4.1, it is evident that if y_t is not measured at t , the posterior density $p(z_t|y_{1:t})$ cannot be computed using equation (4.1.1). In such situations, the estimates at t , in presence of irregular data can be computed by replacing $p(z_t|y_{1:t})$ in equation (4.1.3) using the one-step ahead prior density $p(z_t|y_{1:t-1})$.

Now assuming y_{t+1} to be available at $t+1$, the posterior density for z_{t+1} , given clinical measurements $\{y_{1:t-1}, y_t\}$, *i.e.*, $p(z_{t+1}|y_{1:t-1}, y_{t+1})$ can be computed using the Bayes' theorem and the law of total probability, such that the update step shows that:

$$p(z_{t+1}|y_{1:t-1}, y_{t+1}) \propto p(y_{t+1}|z_{t+1})p(z_{t+1}|y_{1:t-1}). \quad (4.2.1)$$

where $p(z_{t+1}|y_{1:t-1}, y_{t+1})$ is the posterior density for z_{t+1} and $p(z_{t+1}|y_{1:t-1})$ is a two-step ahead prior density computed using the law of total probability, *i.e.*:

$$p(z_{t+1}|y_{1:t-1}) = \int p_z(z_{t+1}|z_t)p(z_t|y_{1:t-1})dz_t. \quad (4.2.2)$$

Substituting equation (4.1.2) into equation (4.2.2) yields the prediction step:

$$p(z_{t+1}|y_{1:t-1}) = \iint p_z(z_{t+1}|z_t)p_z(z_t|z_{t-1})p(z_{t-1}|y_{1:t-1})dz_{t-1}. \quad (4.2.3)$$

Similar to section 4.1, having computed $p(z_{t+1}|y_{1:t-1}, y_{t+1})$, the estimate of z_{t+1} can be computed by replacing the density by $p(z_{t+1}|y_{1:t-1}, y_{t+1})$ in equation (4.1.3). Note that the method proposed in this section is general and can naturally be extended to handle consecutively missing measurements as well.

The Bayesian approach developed in section 4 provides an excellent framework for real-time state and parameter estimation under complete and irregular clinical measurements. Computing the Bayesian solution requires evaluation of the multiple integrals in the prediction and estimation steps. Unfortunately, except for linear systems with Gaussian state and measurement noise, or when the states and parameters take on only finite values, the Bayesian solution cannot be solved exactly with finite computing capabilities.

This paper uses a sequential Monte-Carlo (SMC)-based adaptive sequential-importance-resampling (SIR) filter proposed by Tulsyan *et al.* [25] to numerically approximate the Bayesian solution. In the next section, using SMC method, the estimation results of states and parameters of the state-space model for type II diabetic patients under various levels of randomly missing clinical data are presented.

5 Results and discussion

In this section, the efficiency of the SIR filtering method in handling missing measurements for estimation of the nonlinear stochastic model for type II diabetes mellitus is demonstrated. All the simulations were conducted on a 2.90 GHz CPU with 8 GB RAM Mac using MATLAB 2012b. On-line estimation of states and all the parameters cited in the reference [17] by SIR filtering leads to large memory requirements and computational complexity. To reduce the computation load, only the parameters of type II diabetic subjects that have considerable effects on peripheral glucose, insulin and incretins concentrations were chosen for estimation while keeping all other non-essential model parameters constant.

5.1 Clinical data used for model development

The states and the parameters of the Vahidi model were estimated using two different clinical tests, oral glucose tolerance test (OGTT) and isoglycemic intravenous glucose infusion test (IIVGIT) performed by Knop *et al.* [29, 30]. In the OGTT test, glucose was given to the patient subjects and their blood was sampled afterward to determine how quickly glucagon suppression occurred.

In the OGTT test, 50-grams of water-free glucose was dissolved in 400 millilitres of water over the first 5 minutes of the experiment. The solution was given to 10 patients with type II diabetes mellitus (eight men and two women). Blood was sampled 15, 10 and 0 minutes before, and after the ingestion of glucose at 5, 10, 15, 20, 30, 40, 45, 50, 60, 70, 90, 120, 150, 180 and 240 minutes.

In order to mimic the plasma glucose profile obtained from the OGTT test, the same amount of glucose was injected intravenously to the diabetic subjects in the IIVGIT test. Blood was sampled every 5 minutes [29, 30]. For estimating the states and the parameters of the model in our study, the peripheral glucose, insulin and incretins (GLP-1 plus GIP) concentrations from both tests were used.

5.2 On-line states and parameters estimation results

To apply the SIR particle filtering method, a prior information on the unknown parameters of the Vahidi model from both OGTT and IIVGIT is needed. This information can be obtained from equation (2.0.4) by minimizing the deviation of model predictions from the available clinical measurements of peripheral glucose, insulin and incretins concentrations described in section 5.1.

After the prior information on the unknown parameters obtained, the estimation of the states and parameters of the Vahidi model were estimated using SIR particle filtering method. Firstly, the parameters of the pancreas model were estimated from the isoglycemic intravenous glucose infusion test (IIVGIT) test since no secretion of incretins occurs during the IIVGIT test. In the model parameter estimation, the peripheral insulin concentration in the Vahidi model [17] was considered as a measurement y_k . For implementing the SIR filtering based on the discrepancies between the Vahidi model and the Knop's experimental data, the following parameters were selected:

- The number of particles $N = 5000$
- The sampling time used for discretizing the Vahidi model $\Delta k = 0.4 \text{ min}$
- The maximum states noises $v_k \sim \mathcal{N}(0, 0.001)$
- The measurement noise $w_k \sim \mathcal{N}(0, 0.001)$

A priori information on $\{x_0; \theta\}$ includes the lower (LB) and the upper bound (UB) based on the physiological considerations. Four simulation experiments were carried out to evaluate the effectiveness of our proposed method to identify patient models with incomplete data. In the four experiments, 0%, 10%, 25% and 50% of available data simulated from the Vahidi model were removed randomly. For example, when 10% of data were considered missing, a peripheral insulin concentration at each sampling time was removed from the original data set if a uniformly distributed random variable q in the interval $(0,1)$ is less than 0.1. Similar experiments were done with 25% and 50% missing data [20].

The parameter values after 600 samples from each of these experiments are shown in Table 1. The detailed information about these parameters is available by Vahidi *et al.* [17]. For all the experiments, the parameters converged to the neighbourhood of the original values after a certain number of iterations.

Variations of the peripheral insulin concentrations during the IIVGIT test after 600 samples are shown in Fig. 2a in which, r shows the percentage of missed observations. From the Fig. 2a, the dynamics of peripheral insulin concentration can be estimated reasonably well with physiological responses in all the experiments even when 50% of the simulated clinical data were absent. Fig. 2b presents the goodness of fit between the

Table 1: Parameter estimation results for insulin sub-model after 600 sampling time during IIVGIT test

Parameters [17]	Original Values	Percentage of Missing insulin measurements			
		0%	10%	25%	50%
$\theta_1 : \alpha(\text{min})^{-1}$	0.6152	0.6168	0.5728	0.5803	0.5159
$\theta_2 : \gamma(U/\text{min})$	2.3665	2.3422	2.1860	2.3667	2.5200
$\theta_3 : K(\text{min})^{-1}$	0.0572	0.0565	0.0560	0.0561	0.0544
$\theta_4 : N_1(\text{min})^{-1}$	0.0499	0.0496	0.0519	0.0481	0.0474
$\theta_5 : N_2(\text{min})^{-1}$	0.0001490	0.0001489	0.0001482	0.0001500	0.0001506

estimated output and the measured output performed with MATLAB System Identification Toolbox by using normalized root mean square error (NRMSE) as a cost function. Based on the NRMSE measure, the goodness of fit between the simulated peripheral insulin concentration and the available measurements are more than 80%.

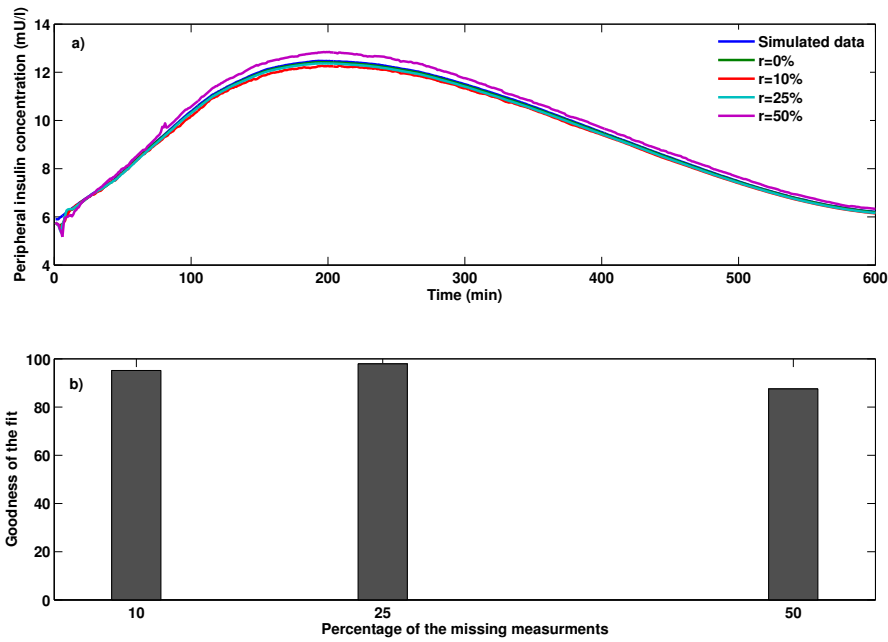


Fig. 2: Peripheral insulin concentration for type II diabetic subjects during the IIVGIT test

Secondly, from the oral glucose tolerance test (OGTT), the peripheral insulin concentration, peripheral glucose concentration and incretins concentrations were considered as measurements y_k for estimation of the rest of the model parameters. These parameters consist of the parameters of the incretins sub-model and those of the glucose sub-model including the parameters of the glucose absorption model and the parameters describing the hormonal effects of incretins on the pancreatic insulin production. For implementing the SIR filtering based on the discrepancies between the Vahidi model and the Knop's experimental data, the following parameters were selected:

- The number of particles $N = 20000$
- The sampling time used for discretizing the Vahidi model $\Delta k = 0.1 \text{ min}$

- The maximum states noises $v_k \sim \mathcal{N}(0, 0.7)$
- The measurement noise $w_k \sim \mathcal{N}(0, 0.7)$

The parameter values after 2400 samples from each of these experiments are shown in Table 2 (see the reference [17] for detailed information about these parameters). In all the experiments, the estimated parameters, except θ_3 and θ_{10} , converged to the neighbourhood of the original values after a certain number of iterations. θ_3 and θ_{10} are not estimated precisely since the sensitivity of the KLD in kernel smoothing algorithm to changes in θ_3 and θ_{10} , is smaller than its variance.

Table 2: Parameter estimation results for insulin sub-model after 2400 sampling time during OGTT test

Parameters [17]	OriginalValues	Percentage of Missing insulin measurements			
		0%	10%	25%	50%
$\theta_1 : c_{PGU}^I$	0.0970	0.0965	0.0965	0.0902	0.1300
$\theta_2 : c_{HGU}^{I\infty}$	3.2606	3.3125	2.9543	2.9625	2.8057
$\theta_3 : c_{HGP}^G$	1.0385	1.0352	1.0885	1.9743	2.0649
$\theta_4 : c_{HGU}^G$	2.03	1.97	1.84	2.23	1.53
$\theta_5 : d_{PGU}^I$	2.752	2.747	2.724	2.897	2.909
$\theta_6 : d_{HGU}^{I\infty}$	0.0031	0.0030	0.0028	0.0030	0.0038
$\theta_7 : d_{HGP}^{I\infty}$	0.3648	0.3676	0.3610	0.3625	0.3667
$\theta_8 : K12(min)^{-1}$	0.0783	0.0796	0.0798	0.0842	0.0616
$\theta_9 : \xi_1(min)^{-1}$	0.000124	0.000125	0.000126	0.000125	0.000141
$\theta_{10} : \xi_2(min)^{-1}$	0.00270	0.00271	0.00280	0.00152	0.00122

Variations of the peripheral glucose, insulin, and incretins concentrations during the OGTT test after 2400 iterations are shown in Figs. 3a-5a. r shows the percentage of missing observations. From the Figs. 3a-5a, the dynamics of peripheral glucose, insulin, and incretins concentration can be estimated reasonably well with physiological responses in all the experiments even when 50% of the clinical data is missing. Figs. 3b-5b present the goodness of fit between the estimated output and the measured output performed with MATLAB System Identification Toolbox by using the normalized root mean square error (NRMSE) as a cost function. From Figs. 3b-5b, the goodness of fit between the simulated peripheral glucose, insulin and incretins concentration and their available measurements were almost 80% in all the experiments except in Fig. 5b when 25% and 50% of peripheral insulin measurements removed randomly. Comparing to Fig. 2b in the IIVGIT test, the peripheral insulin concentration was not estimated precisely in the OGTT test since only the parameters of the incretins sub-model and the parameters of the glucose sub-model were estimated in order to reduce the computational complexity.

The probability density function of the parameter C_{PGU}^I , one of the parameters of the peripheral glucose uptake rate in the insulin sub-model in [27], is reported in Fig. 6. As somewhat expected, the posterior provided by SIR filtering method is concentrated around its original value after about 620 sampling times.

5.3 Application of SIR particle filtering in detection of organ dysfunction in diabetic patients under irregular clinical data

In this section, we will show the application of the adaptive sequential-importance-resampling (SIR) filter in the estimation of the glucose, insulin, and incretins concentrations in different parts of the body under

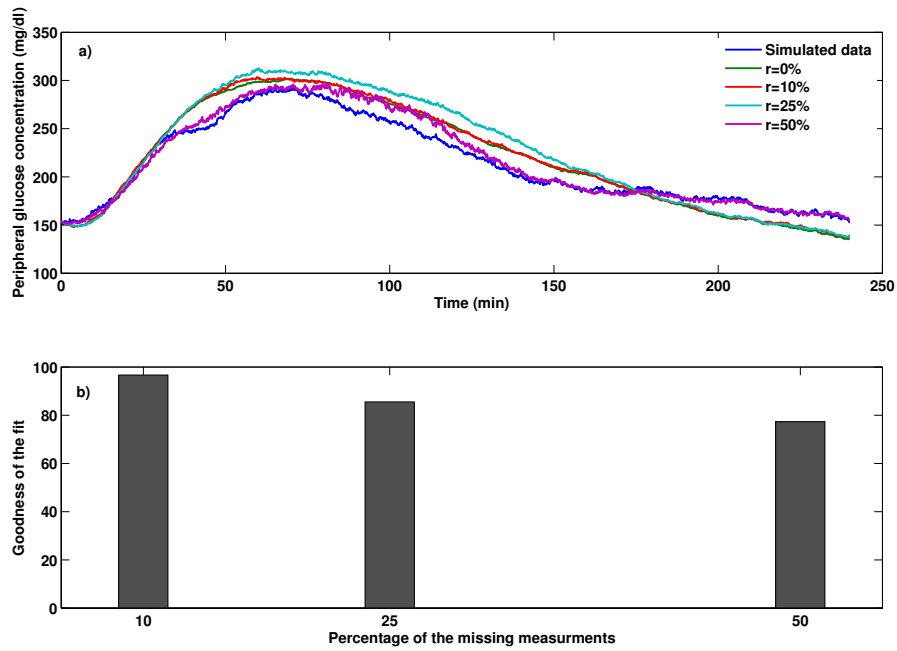


Fig. 3: Peripheral glucose concentration for type II diabetic subjects during the OGTT test

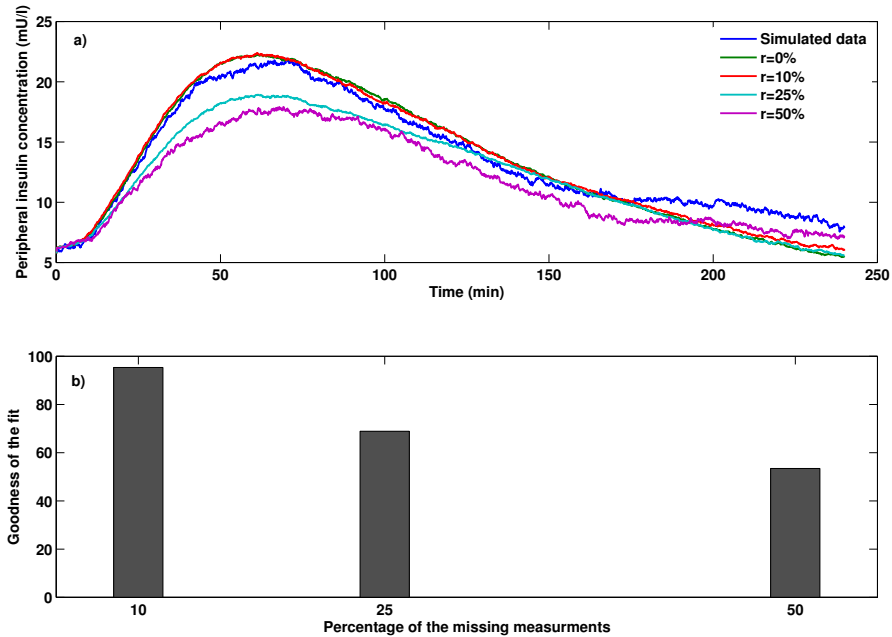


Fig. 4: Peripheral insulin concentration for type II diabetic subjects during the OGTT test

irregularly sampled clinical data. These estimates are used for calculating the glucose metabolic rates in different organs of the type II diabetic patients using irregularly sampled data. Then, by comparing the glucose metabolic rate of each organ in the diabetic patients with the glucose metabolic rate of the same organ in a normal subject, the abnormal functioning of certain organs is detected and identified.

Using the states and parameters of the Vahidi model estimated in the previous section, the glucose metabolic rates in the peripheral tissues and the liver are calculated from equations (2.0.2) and (2.0.3). Figure 7 shows the glucose metabolic rates in peripheral tissues and the liver compared with the healthy subjects. According to Figs. 7a and 7b, the peripheral glucose uptake rate and hepatic glucose uptake rate

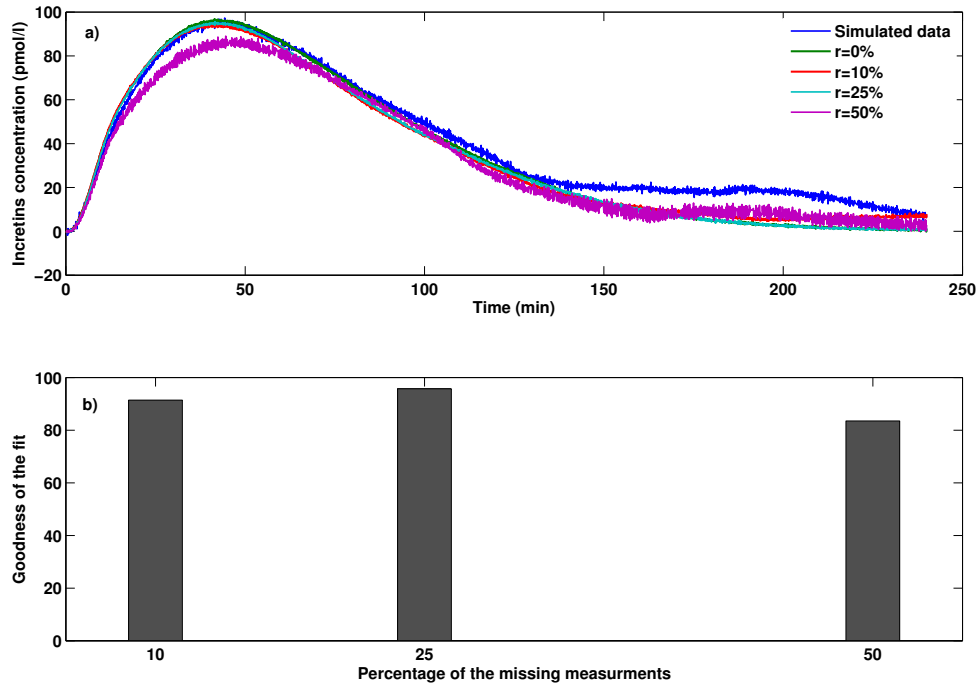


Fig. 5: Incretins concentration for type II diabetic subjects during the OGTT test

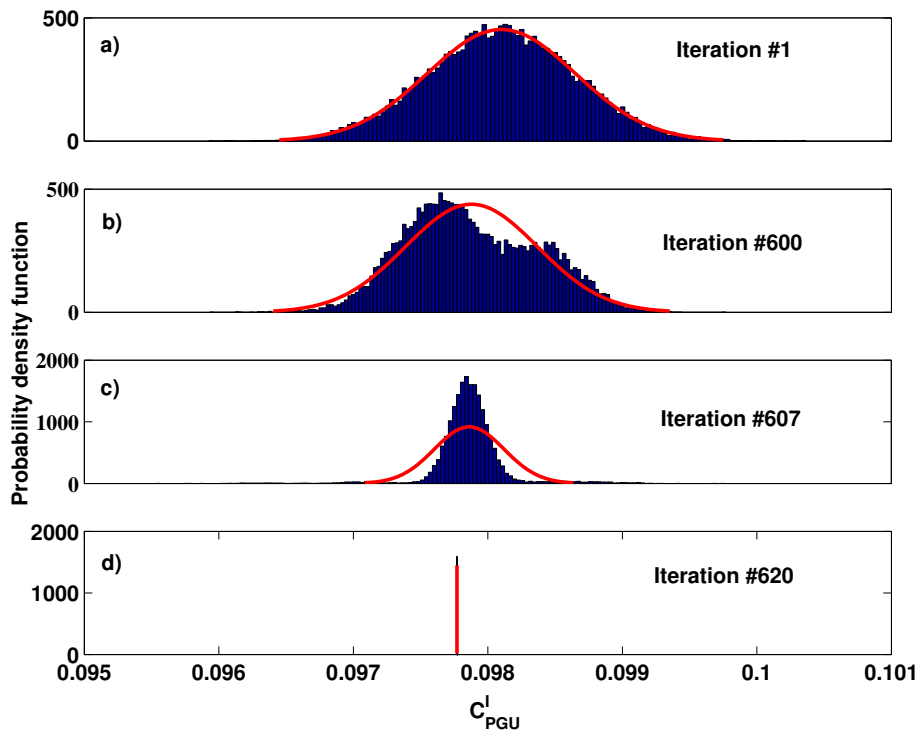


Fig. 6: The probability density function of c_{PGU}^I from Bayesian identification at sampling time number 1, 600, 607 and 620 (area under each curve is unitary). The y -axis quantity is unit-less.

in type II diabetic patients for all experiments are less than the corresponding values in the healthy subjects due to insulin sensitivity in peripheral tissues and dysfunction in the liver of the diabetic patients. Decreased rate of glucose infusion shows that the overall insulin sensitivity of the body is decreased about 54% in diabetic patients. Even under the presence of 50% missing data, the abnormalities of the liver and adipose tissues are detectable, which provides more physiological information to physicians.

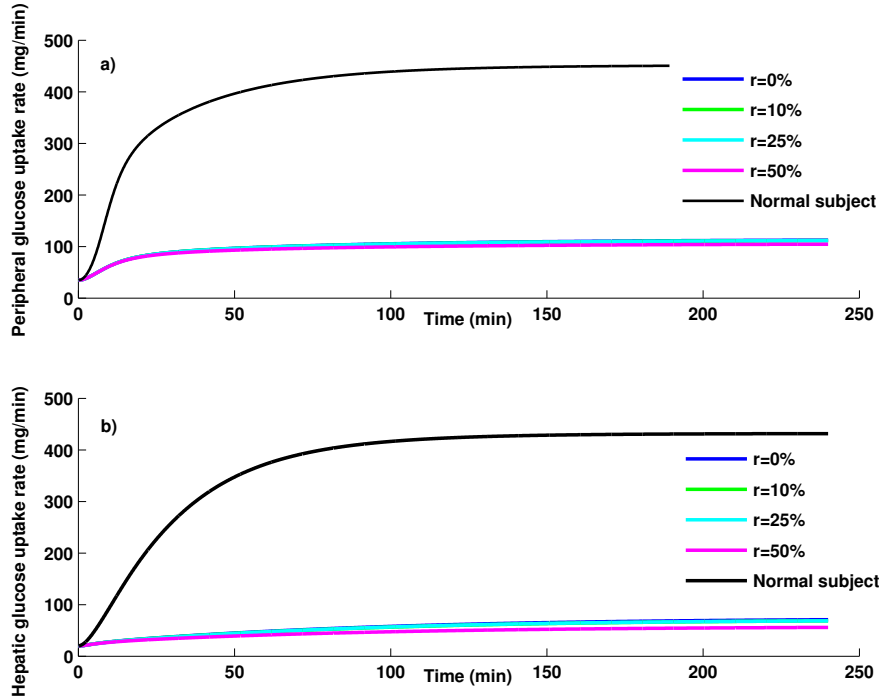


Fig. 7: Variation of different glucose metabolic rates

5.4 Strengths and limitations of the SIR particle filtering in clinical practice

The primary practical advantage of the SIR particle filtering method comparing to the traditional statistical methods is its independence from the degree of nonlinearity of the model unlike extended Kalman filtering [5]. An additional advantage in a clinical practice is that the SIR filtering approach is readily adaptable to sequential updating of information obtained from owner history, clinical examination of diabetic patients, and results of different diagnostic tests [31]. It exhibits good performance even for systems with large process or measurement noise.

Furthermore, the accuracy of the particle filtering method can be improved by increasing the number of particles used in the estimation algorithm. However, particles size over 1000 can be computationally intensive and time consuming [20, 31]. The SIR based PF used in this paper, needs less computational cost when a large number of unknown states and parameters must be estimated simultaneously since the marginal probability distribution of each parameter and state can be obtained from a posteriori probability distribution of the model parameters and states [24].

6 Conclusions

In this study, we have identified the nonlinear states and the parameters of glucose, insulin and incretins sub-model developed by Vahidi et.al [17] for type II diabetes mellitus in the presence of 10%, 25% and 50% of randomly missing clinical observations by employing the Sequential Importance Resampling (SIR) filtering method. The motivation for this study originates from the lack of complete knowledge about the health status of the diabetic patients. In addition, only a few blood glucose measurements per day are

available in a non-clinical setting due to different reasons like unreadable hand writing, inability to record clinical results, and infrequent sampling by patients.

It is shown that by implementing an on-line SIR particle filtering method to the Vahidi model developed for type II diabetes mellitus, we are able to estimate the dynamics of the plasma glucose, insulin and incretins concentration under the presence of maximum 50% available clinical data. In addition, the goodness of fit between the simulated peripheral glucose, insulin and incretins concentration and their available measurements were almost 80% in the most of the experiments. The results of this study can be used to inform type II diabetic patients of their medical conditions, enable physicians to review past therapy, estimate future blood glucose levels, provide therapeutic recommendations and even design a stabilizing control system for blood glucose regulation.

Nomenclature

Model variables in the glucose sub-model

G	Glucose concentration (mg/dl)
M	Multiplier of metabolic rates (dimensionless)
Q	Vascular blood flow rate (dl/min)
r	Metabolic production or consumption rate (mg/min)
T	Transcapillary diffusion time constant (min)
t	ime (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 (dl/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 (dl)
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)
t	time (min)
V	Volume (dl)

Model variables in the incretins sub-model

Ψ	Incretins concentration (pmol/l)
r	Metabolic production or consumption rate (pmol/min)
t	time (min)
V	Volume (dl)

First superscript

Γ	Glucagon
B	Basal condition
G	Glucose
I	Insulin
M	ncretins

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 Ψ R Intestinal incretins release
KGE Kidney glucose excretion
KIC Kidney insulin clearance
LIC Liver insulin clearance
MGC Metabolic glucagon clearance
PGC Plasma glucagon clearance
PGR Pancreatic glucagon release
P Ψ C Plasma incretins clearance
PGU Peripheral glucose uptake
PIC Peripheral insulin clearance
PIR Pancreatic insulin release
RBCU Red blood cell glucose uptake

First superscripts

∞ Final steady state value
A Hepatic artery
B Brain
G Gut
L Liver
P Periphery
S Stomach

Second subscripts (if required)

C Capillary space
F Interstitial fluid space
l Liquid
s Solid

Appendix A

Glucose sub-model

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

$$V_{BC}^G \frac{dG_{BC}}{dt} = Q_B^G (G_H - G_{BC}) - \frac{V_{BF}^G}{T_B^G} (G_{BC} - G_{BF}), \quad (\text{A-1})$$

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

$$V_H^G \frac{dG_H}{dt} = Q_B^G G_{BC} + Q_L^G G_L + Q_K^G G_K + Q_P^G G_{PC} + Q_H^G G_H - r_{BCU}, \quad (\text{A-3})$$

$$V_G^G \frac{dG_G}{dt} = Q_G^G (G_H - G_G) - r_{GGU} + Ra, \quad (\text{A-4})$$

$$V_L^G \frac{dG_L}{dt} = Q_A^G G_H + Q_G^G G_G - Q_L^G G_L + r_{HGP} - r_{HGU}, \quad (\text{A-5})$$

$$V_K^G \frac{dG_K}{dt} = Q_K^G (G_H - G_K) - r_{KGE}, \quad (\text{A-6})$$

$$V_{PC}^G \frac{dG_{PC}}{dt} = Q_P^G (G_H - G_{PC}) - \frac{V_{PF}^G}{T_P^G} (G_{PC} - G_{PF}), \quad (\text{A-7})$$

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

A detailed description about the metabolic rates is available in [15]. The general form of the metabolic production and consumption rates in each organ is as follows:

$$r = M^I M^G M^\Gamma M^B, \quad (\text{A-9})$$

and multipliers have the following general form:

$$M^C = a + b \tanh\left(\frac{C}{CB} - d\right), \quad (\text{A-10})$$

The glucose absorption model that calculates the glucose appearance rate into the blood stream following an oral glucose intake is considered in the gut compartment of the glucose sub-model as follows:

$$\frac{dq_{Ss}}{dt} = -k_{12}q_{Ss} + \delta(t), \quad (\text{A-11})$$

$$\frac{dq_{SI}}{dt} = -k_{empt}q_{Ss} + k_{12}q_{SI}, \quad (\text{A-12})$$

$$\frac{dq_{int}}{dt} = -k_{abs}q_{int} + k_{empt}q_{SI}, \quad (\text{A-13})$$

$$k_{empt} = k_{min} + \frac{k_{max} - k_{min}}{2} \{ \tanh[\varphi_1(q_{Ss} + q_{SI} - x_1D)] - \tanh[\varphi_2(q_{Ss} + q_{SI} - x_2D)] \} + 2, \quad (\text{A-14})$$

$$\varphi_1 = \frac{5}{2D(1 - x_1)}, \quad (\text{A-15})$$

$$\varphi_2 = \frac{5}{2Dx_2}, \quad (\text{A-16})$$

$$Ra = f k_{abs} q_{int}, \quad (\text{A-17})$$

Incretins sub-model

The incretins production is calculated from the following differential equation:

$$\frac{d\psi}{dt} = \varsigma k_{empt} q_{S2} - r_{I\Psi P}, \quad (\text{A-18})$$

$$r_{I\Psi P} = f \frac{\psi}{\tau \psi}, \quad (\text{A-19})$$

The mass balance equation over the incretins compartment results in:

$$\frac{d\psi}{dt} = \varsigma k_{empt} q_{S2} - r_{I\Psi P}, \quad (\text{A-20})$$

$$r_{P\Psi C} = r_{M\Psi C} \psi, \quad (\text{A-21})$$

Insulin sub-model

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

$$V_B^I \frac{dI_B}{dt} = Q_B^I (I_H - I_B), \quad (\text{A-22})$$

$$V_H^I \frac{dI_H}{dt} = Q_B^I I_B + Q_L^I I_L + Q_K^I I_K + Q_P^I I_{PV} - Q_H^I I_H, \quad (\text{A-23})$$

$$V_G^I \frac{dI_G}{dt} = Q_G^I (I_H - I_G), \quad (\text{A-24})$$

$$V_L^I \frac{dI_L}{dt} = Q_A^I I_H + Q_G^I I_G - Q_L^I I_L + r_{PIR} - r_{LIC}, \quad (\text{A-25})$$

$$V_K^I \frac{dI_K}{dt} = Q_K^I (I_H - I_K) - r_{KIC}, \quad (\text{A-26})$$

$$V_{PC}^I \frac{dI_{PC}}{dt} = Q_P^I (I_H - I_{PC}) - \frac{V_{PF}^I}{T_P^I} (I_{PC} - I_{PF}), \quad (\text{A-27})$$

$$V_{PF}^I \frac{dI_{PF}}{dt} = \frac{V_{PF}^I}{T_P^I} (I_{PC} - I_{PF}) - r_{PIC}, \quad (\text{A-28})$$

The pancreas model contains two compartments. The pancreas model equations include mass balance equations over compartments and correlations between variables. The mass balance equation over each compartment results in:

$$\frac{dm}{dt} = K' m_S K m + \gamma P - S, \quad (\text{A-29})$$

$$\frac{dm_S}{dt} = K m - K' m_S - \gamma P, \quad (\text{A-30})$$

The steady state mass balance equation around the storage compartment is:

$$K' m_S = K m_0, \quad (\text{A-31})$$

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

$$\frac{dP}{dt} = \alpha (P_\infty - P), \quad (\text{A-32})$$

$$\frac{dR}{dt} = \beta (X - R), \quad (\text{A-33})$$

$$S = [N_1 Y + N_2 (X - R) + \xi_1 \psi] m \quad x > R, \quad (\text{A-34})$$

$$S = [N_1 Y + \xi_1 \psi] m \quad x \leq R,$$

$$P_\infty = Y = X^{1.11} + \xi_2 \psi, \quad (\text{A-35})$$

$$X = \frac{G_H^{3.27}}{132^{3.27} + 5.93 G_H^{3.02}} \quad (\text{A-36})$$

Glucagon sub-model

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

$$V^\Gamma \frac{d\Gamma}{dt} = r_{PGR} - r_{PGC}, \quad (\text{A-37})$$

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