Application of Modified Watanabe's Approach for Reconstruction of Insulin Secretion Rate During OGTT Under Non-constant Fraction of Hepatic Insulin Extraction

Kiattiyot Juagwon, Yongwimon Lenbury, Andrea De Gaetano, and Pasquale Palumbo

***Abstract*—**In this study, insulin and C-peptide concentration are used to assess the rate of insulin production. First, the data of insulin and C-peptide concentrations during OGTT are generated from an extended combined model (Watanabe *et al*., 1998). Two different patterns of the fraction of hepatic insulin extraction in the extended combined model are utilized to generate the data of insulin and C-peptide concentrations. On the one hand, the fraction is assumed constant. On the other hand, a non-constant fraction is used. Watanabe's approach (Watanabe *et al*., 1998) designed from the extended combined model, assuming constant fractional hepatic extraction, is then used to quantify the rate of insulin production from insulin and C-peptide concentrations generated from the extended combined model with both patterns of fraction of hepatic extraction. It is found that the Watanabe's approach is appropriate for the estimation of the kinetic parameters and the rate of insulin production in the extended combined model only when fractional hepatic extraction is constant. However, Watanabe's approach cannot be relied upon for accurate estimation when the fractional hepatic extraction is not constant. Since there is clinical evidence that the fractional hepatic extraction is not constant during OGTT, the modification of Watanabe's approach is necessary to accommodate variations in the fractional hepatic extraction. The modified approach proposed in this work is able to provide the accurate estimate of the rate of insulin production from the data generated by the extended combined model in the situation where the fractional hepatic extraction is not constant.

***Keywords*—**deconvolution, hepatic extraction, insulin estimation, insulin secretion.

K. Juagwon is with the Department of Mathematics, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok 10400 and the Centre of Excellence in Mathematics, CHE, 328 Si Ayutthaya Road, Bangkok, THAILAND (e-mail: daoke99@hotmail.com).

Y. Lenbury is with the Department of Mathematics, Faculty of Science, Mahidol University, Rama 6 Road, Bangkok and the Centre of Excellence in Mathematics, CHE, 328 Si Ayutthaya Road, Bangkok, Thailand (corresponding author, phone: 662-201-5448; fax: 662-201-5343; e-mail: yongwimon.len@mahidol.ac.th, scylb@yahoo.com).

A. De Gaetano is with the BioMatLab CNR-IASI, Fisiopatologia dello Shock, University Cattolica del SacroCuore, Largo A. Gemelli 8 - 00168 Roma, Italy(e-mail: andrea.degaetano@biomatematica.it).

P. Palumbo is with the BioMatLab CNR-IASI, Fisiopatologia dello Shock, University Cattolica del SacroCuore, Largo A. Gemelli 8 - 00168 Roma, Italy(e-mail: pasquale.palumbo@iasi.cnr.it).

I. Introduction

One cause of type 2 diabetes is the ineffective pancreatic insulin secretion [1]. The ability to identify the rate of insulin release is hence clinically important for the treatment of diabetes mellitus. In order to better control and treat diabetic patients, accurate estimation of endogenous insulin secretion must be available to the physicians to monitor patients with type 2 diabetes. Unfortunately, in practice the direct measurement of pancreatic insulin secretion is not easily accomplished at present [2], [3]. A possible way to identify the amount of insulin production is its estimation by using mathematical modeling approach. To estimate insulin production, more intense study of insulin and C-peptide kinetics models is unavoidable. A model of insulin and C-peptide kinetics, called an extended combined model, was suggested by Watanabe *et al*. [4] in 1998. The extended combined model is a two-compartment model with one-phase clearance for C-peptide kinetics and one-compartment model with two-phase clearance for insulin kinetic. The common assumption among the submodels of insulin kinetics and C-peptide kinetics is that the extended combined model assumes that insulin molecules and C-peptide molecules are produced equimolarly by the pancreas. This means that insulin and C-peptide are produced at the same rate. Another important assumption is that the fraction of hepatic insulin extraction, defined as the proportion of the rate of hepatic insulin extraction during first pass transit of liver to the total rate of pancreatic insulin production, is constant. An alternative approach, based on extended combined model assuming constant fractional hepatic extraction, to estimate the kinetic parameters and rate of pancreatic insulin secretion was then proposed by Watanabe *et al*. [5] in 1998. This approach only needs the data on insulin and C-peptide concentrations to estimate the rate of insulin production and the values of kinetic parameters of insulin and C-peptide control system without the separate experimental method proposed by Eaton *et al*. [6] and Polonsky. *et al*. [7] or experimental protocol concerning the fixed values of the parameters as in [8]. The accuracy of the estimation by using this approach was experimentally examined in vivo in conscious dogs [5]. The known equimolarintraportal insulin and C-peptide infusion is

reconstructed fairly well by the approach. However, there is clinical evidence that the fraction of hepatic insulin extraction is not constant during OGTT [2]. The fraction decreases during high insulin concentration although the total amount of hepatic insulin extraction by the liver increases [2]. One possible way to explain this observation is that a high concentration of insulin in the portal vein causes a decrease in degradation due to receptor down-regulation because most extraction is a receptor-mediated process [9].

Direct assessments of fractional hepatic extraction have been done in the experiments by Brundin [2] and Tura *et al*. [3]. The experiments yielded the rate of hepatic blood flow and measured hepatic venous-arterial difference in insulin and C-peptide concentrations to directly quantify the fractional hepatic extraction during oral glucose administration. Brundin [2] directly measured C-peptide and insulin concentrations in the arterial and hepatic venous blood and estimated the splanchnic (hepatic) plasma flow rate during 375 ml of a 75-g glucose solution ingestion. His work showed that the splanchnic fractional extraction of insulin is not a constant. The splanchnic fractional extraction fell significantly in response to the glucose administration in the oral group [2]. Tura *et al*. [3] also directly determined insulin and C-peptide secretions and their kinetics from C-peptide and insulin concentrations measured in the artery, C-peptide and insulin concentrations measured in the hepatic vein, and hepatic blood flow during an oral glucose tolerance test, and compared them with the secretion and kinetics estimated by using a combined model described in [10] when C-peptide and insulin concentrations are systemically measured. In their original work, the direct-measurement data analysis and the model-based data analysis were done in the following manner. The insulin secretion is determined from C-peptide secretion term in [3]:

$$CPv(t)HBF(t) = CPa(t)HBF(t) + BCS(t)$$

where$CPv(t)$ and $CPa(t)$ are C-peptide concentrations (pmol/l) in the hepatic vein and in the artery, respectively, $HBF(t)$ is the measured hepatic blood flow (l/min), and $BCS(t)$ is β-cell C-peptide secretion rate (pmol/min). The hepatic insulin extraction was expressed as [3]:

$$HIFC(t) = 1 - \{Iv(t)HBF(t) / [Ia(t)HBF(t) + BCS(t)]\}$$

where$HIFC(t)$ is the hepatic insulin fractional extraction (dimensionless), $Iv(t)$ and $Ia(t)$ are insulin concentrations (pmol/l) in the hepatic vein and in the artery, respectively. The mathematical model for Insulin kinetics and C-peptide kinetics used to analyze experimental data is expressed as follows [3].

$$dI(t)/dt = -nI(t) + F \times CPS(t)$$

$$dCP(t)/dt = -k_{01}CP(t) + CPS(t)$$

where$I(t)$ is the measured plasma insulin concentration (pmol/l), n is the systemic insulin fractional clearance (min^{-1}), and $F \times CPS(t)$ is the posthepatic insulin delivery; $(1\text{-}F)$ represents the hepatic insulin fractional extraction (dimensionless). $CP(t)$ is the measured plasma C-peptide concentration (pmol/l), k_{01} is the disappearance constant, which represents the systemic C-peptide fractional clearance (min^{-1}), and $CPS(t)$ is the C-peptide secretion rate estimated by the model (pmol $l^{-1}min^{-1}$). By statistical comparison, values of the parameters from model estimates are not significantly different from the values calculated from experimental data except for the value of hepatic insulin extraction. This may occur because the fraction of hepatic extraction is not constant [3].

Therefore, in this work the approach presented in [4] and [5] is modified so that it can accommodate variations in the fraction of hepatic extraction. The first step in this study begins with the used of the extended combined model [5] to generate the data of insulin and C-peptide concentrations by using the known parameter values and rate of insulin production. The generated data are then added with five levels of random Gaussian error. Next, the Watanabe's approach and its numerical application are re-examined to determine the accuracy of its estimations of kinetic parameters and rate of insulin production on comparing with the known values used to generate the data. In this step, detail of the procedures in the Watanabe's approach and the derivation of analytic solution of extended combined model are also given. In the second step, constant fractional hepatic extraction term in the model of insulin kinetics is replaced by a function of time describing non-constant fractional hepatic extraction. The data of insulin and C-peptide concentrations are then generated with extended combined model assuming non-constant fractional hepatic extraction. To study the efficiency of Watanabe's approach, it is used to identify the kinetic parameters and secretory rate from the generated data of insulin and C-peptide concentrations. The estimated kinetic parameter and secretory rate are then compared with the known values. In the final step, the Watanabe's approach is modified to estimate the rate of insulin production from the insulin and C-peptide concentrations generated by the extended combined model assuming non-constant fractional hepatic extraction. To investigate the accuracy of the estimation, the known values of the rate of insulin production is then compared with the estimated values.

II. Methods

A. The Model and Data Generation

The extended combined model described in [4] and [5] takes into consideration the kinetics of endogenous insulin and C-peptide. These kinetics have the same rate of production because pancreatic insulin and C-peptide are released equimolarly. In the submodel of insulin kinetics, only one compartment of insulin with two phases of insulin clearance is assumed. Depending on the rate of pancreatic insulin release the first phase removal is the hepatic insulin extraction by the liver during the first pass transit and depending on the current insulin concentration, while the second phase removal is the systemic insulin clearance. In [4] and [5], a constant fractional hepatic insulin extraction is assumed throughout the period of interest. In the submodel of C-peptide kinetics, a two-compartment model is applied. In the first C-peptide compartment, the C-peptide clearance depending on the current C-peptide concentration is assumed to occur. The C-peptide clearance in the second C-peptide compartment and hepatic C-peptide extraction by the liver are negligible. Fig. 1 shows the schematic diagram of the extended combined model

and the ordinary differential equations of the extended combined model [4],[5] can be written as

$$\frac{dI(t)}{dt} = -K_I I(t) + \frac{(1-H)R(t)}{V_I} \quad (1)$$

$$\frac{dC_1(t)}{dt} = -K_{01}C_1(t) - K_{21}C_1(t) + K_{12}\frac{V_{C_2}}{V_{C_1}}C_2(t) + \frac{R(t)}{V_{C_1}} \quad (2)$$

$$\frac{dC_2(t)}{dt} = -K_{12}C_2(t) + K_{21}C_1(t)\frac{V_{C_1}}{V_{C_2}} \quad (3)$$

where$I(t)$ is the insulin concentration at time t. $C_1(t)$ and $C_2(t)$ are the C-peptide concentrations in the first compartment and the second compartment, respectively. H denotes the fraction of hepatic insulin extraction by the liver. (1–H) denotes the fraction of insulin transferred into the compartment of insulin after surviving hepatic insulin extraction. $R(t)$ denotes the rate of prehepatic insulin secretion. K_I represents the fractional elimination of insulin in the insulin compartment and K_{01} represents the fractional elimination of C-peptide in the first compartment. K_{12} and K_{21} denote the fractional constants of C-peptide transfer between the first and the second compartments. V_I, V_{C_1} and V_{C_2} are the volume distribution of the insulin compartment, the first C-peptide compartment and the second C-peptide compartment, respectively.

In this study, we have two different sets of data of insulin and C-peptide concentrations. The first set of data is generated by the extended combined model under the assumption of constant hepatic insulin extraction, and the second set of data is generated under the assumption of non-constant hepatic insulin extraction. To generate the data in the first set, the constant shape of the fractional hepatic insulin extraction Hshown in Fig. 2a) is used, and to generate the data in the second set, the shape of the fraction of hepatic insulin extraction reported in [8] is used to derive the function in (4) below (Fig. 2b)) to replace the constant fractional hepatic insulin extraction H in (1).

$$h(t) = a - b(e^{-\beta t} - e^{\gamma t}) \quad (4)$$

That is, the fractional hepatic extraction is represented by this specific function because the plot of this function, shown in Fig 2, can closely mimic the plot of experimentally measured fraction of hepatic extraction reported in Figure 4 in [8].

The rate of insulin production time series and known values of kinetic parameters taken from [1] for the data generation are shown in the figure caption of Fig. 3 and Table 1, respectively.

A total of 60 profiles of insulin and C-peptide concentrations, random Gaussian error with coefficients of 1%, 2%, 3%, 4% and 5% being contained in each set of data, 12 insulin and C-peptide concentration profiles at each level of error. After the data has been generated, the kinetic parameters and secretory rate are estimated by using Watanabe's approach from the first data set and then from the second data set to access the accuracy of parameter identification under conditions of constant and non-constant fractional hepatic insulin extraction, respectively. Next, with the data in the second set our modified Watanabe's approach is applied to estimate the rate of insulin production for comparison with the known values.

B. Parameter Identifications and Numerical Methods

Watanabe's approach described in [4] and [5] to estimate the kinetic parameters and prehepatic insulin secretion can accurately identify the kinetic parameter values and rate of insulin production under the assumption that the fraction of hepatic insulin extraction is constant. This approach does not need any data of exponential decrease in concentration of C-peptide when a bolus of C-peptide is injected [6], [7]. The approach based on the extended combined model has two steps. The first step involves the estimation of kinetic parameters. The estimation of the secretory rate is then determined in the second step. In the first step, (1)-(3), are transformed by the Laplace transforms from the real-domain into the s-domain to obtain the simplified transfer function inthe form

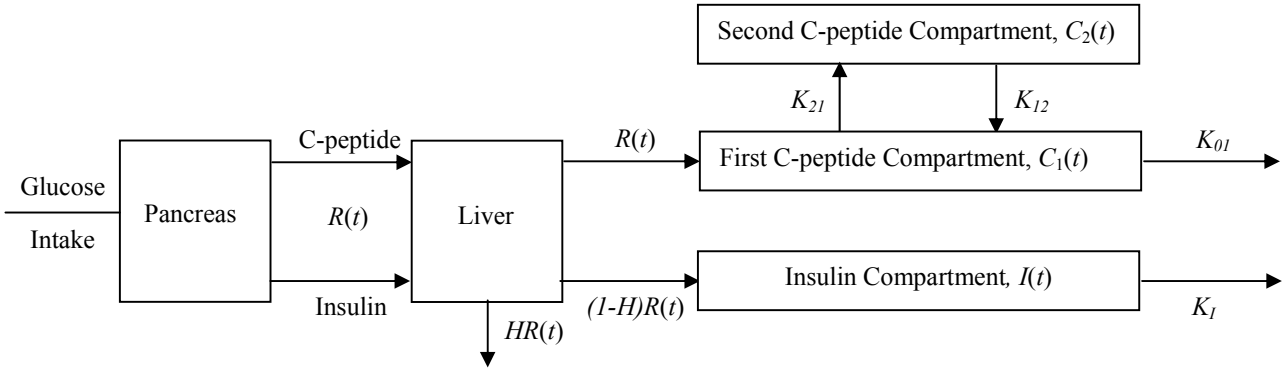

Fig. 1 The diagram of extended combined model. The model consists of two compartments of C-peptide and one compartment of insulin. Insulin and C-peptide are secreted with the same rate $R(t)$ and are transferred into the liver. C-peptide passes the liver without hepatic extraction but insulin is extracted at fraction H. Hence, insulin is delivered into the insulin compartment at the rate $(1-H)R(t)$.

$$\bar{I}(s)=\frac{V_{C_1}}{V_I}(1-H)\frac{(s+\lambda_1)(s+\lambda_2)}{(s+K_I)(s+K_{12})}\bar{C}_1(s) \quad (5)$$

where $\bar{I}$ and $\bar{C}_1$ denote the Laplace transforms of I and C_1, respectively, $\lambda_1\lambda_2 = k_{12}k_{01}$ and $\lambda_1+\lambda_2 = K_{21}+K_{12}+K_{01}$. (Please see [4] and [5] for more detail.) The transfer function of the following system of differential equations has the same expression as the transfer function in (5).

$$\frac{dY_1(t)}{dt}=\frac{1}{1-H}(K_I-\lambda_1)(Y_2(t)+I(t))-\lambda_1 Y_1(t) \quad (6)$$

$$\frac{dY_2(t)}{dt}=(K_{12}-\lambda_2)I(t)-\lambda_2 Y_2(t) \quad (7)$$

with

$$C_1(t)=\frac{V_{C_1}}{V_I}\left[Y_1(t)+\frac{1}{1-H}(Y_2(t)+I(t))\right] \quad (8)$$

or

$$\frac{dZ_1(t)}{dt}=(1-H)(\lambda_1-K_I)(Z_2(t)+C_1(t))-K_I Z_1(t) \quad (9)$$

$$\frac{dZ_2(t)}{dt}=(\lambda_2-K_{12})C_1(t)-K_{12}Z_2(t) \quad (10)$$

with

$$I(t)=\frac{V_{C_1}}{V_I}\left[Z_1(t)+(1-H)(Z_2(t)+C_1(t))\right] \quad (11)$$

where $Y_1(t)$, $Y_2(t)$, $Z_1(t)$ and $Z_2(t)$ are the state variables in the equivalent systems.

Next, the values of the parameters in (1)-(3) are found by estimating the parameters in (6)-(8) and (9)-(11) by using MATLAB function fminsearch when the data of insulin and C-peptide concentrations are given. For (6)-(8), as insulin concentration is assigned to be the input, the kinetic parameters are estimated by fitting the C-peptide concentration, while the estimation of the parameters by using (9)-(11) are done with the C-peptide as the input. Then, the analytic solution of (1)-(3) is given by [5]

$$C_1(t)=\frac{1}{V_{C_1}}\int_0^t R(\tau)\left[\frac{-\lambda_1+K_{12}}{-\lambda_1+\lambda_2}e^{-\lambda_1(t-\tau)}+\frac{-\lambda_2+K_{12}}{\lambda_1-\lambda_2}e^{-\lambda_2(t-\tau)}\right]d\tau \quad (12)$$

and

$$I(t)=\frac{(1-H)}{V_I}\int_0^t R(\tau)e^{-K_I(t-\tau)}d\tau \quad (13)$$

Therefore, in the second step, by substituting the estimated parameter values in (12) and (13), the estimation of the secretory rate $R(t)$ can be found by the deconvolution technique [11].

C. Analytic Solution of Extended Combined Model.

To derive the analytic solution of extended combined model in the form of a convolution integral, the Finger Print method, which has been described by Benet and Turi [12]-[14], is applied. This method provides a fast and comfortable way to transform a Laplace equation back to the function defined on real domain (time domain). The important key is that the method uses the general partial theorem to calculate the inverse Laplace transform with the equation

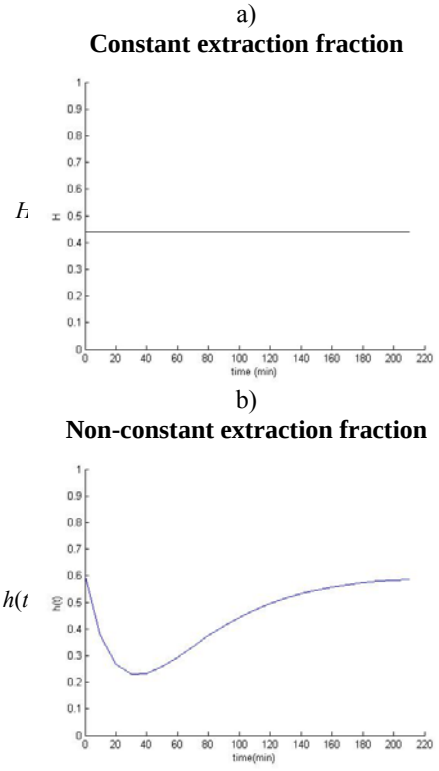

Fig. 2 Graphs of constant fraction of hepatic insulin extraction H and non-constant fraction of hepatic insulin extraction $h(t)$ given in (4). Here, $\alpha = 0.02956$, $\beta = 0.02959$, $a = 0.60$, and $b = 1000$.

$$\mathcal{L}^{-1}\left\{\frac{N(s)}{D(s)}\right\}=\sum_{i=1}^{n}\frac{N(\lambda_i)}{D_1(\lambda_i)}e^{\lambda_i t} \quad (14)$$

Where $\mathcal{L}^{-1}$ is the inverse Laplace operator $N(s)$ and $D(s)$ are the polynomial functions defined on the Laplace-domain. λ_i are the roots of the polynomial function $D(s)$ and n is the number of roots of the polynomial function $D(s)$. $N(\lambda_i)$ is thevalue of the function $N(s)$ at λ_i. $D_1(\lambda_i)$ is the values of function $D(s)$ factored out $(s-\lambda_i)$ at λ_i. (Please see [12] for more detail). The Finger Print method will be used in the process of back transformation of Laplace equations derived from the extended combined model to analytic solution defined on the time domain.

In [5], (1)–(3) are first transformed to Laplace transforms, respectively, as

$$s\bar{I}(s)=-k_I\bar{I}(s)+\frac{1}{V_I}(1-H)\bar{R}(s) \quad (15)$$

$$s\bar{C}_1(s)=-K_{01}\bar{C}_1(s)-K_{21}\bar{C}_1(s)+K_{12}\frac{V_{C_2}}{V_{C_1}}\bar{C}_2(s)+\frac{\bar{R}(s)}{V_{C_1}} \quad (16)$$

$$s\bar{C}_2(s)=-K_{12}\bar{C}_2(s)+K_{21}\frac{V_{C_1}}{V_{C_2}}\bar{C}_1(s) \quad (17)$$

From (15), we have

$$\bar{I}(s)=\frac{(1-H)}{V_I}\frac{1}{s+k_I}\bar{R}(s) \quad (18)$$

By using the Convolution theorem [15] and (14), analytic solution of insulin equation can be written as

$$I(t)=\mathcal{L}^{-1}\left\{\bar{I}(s)\right\}=\frac{(1-H)}{V_I}\mathcal{L}^{-1}\left\{\frac{1}{s+K_I}\bar{R}(s)\right\}$$
$$=\frac{(1-H)}{V_I}\int_0^t e^{-K_I(t-\tau)}R(\tau)d\tau \tag{19}$$

For the C-peptide equations, (17) can be rearranged as

$$\bar{C}_2=\frac{V_{C_1}}{V_{C_2}}\frac{K_{21}}{s+K_{12}}\bar{C}_1(s) \tag{20}$$

Substituting (20) in (16) and rearranging, we have

$$s\bar{C}_1(s)=-K_{01}\bar{C}_1(s)-K_{21}\bar{C}_1(s)+K_{12}\frac{K_{21}}{s+K_{12}}\bar{C}_1(s)+\frac{\bar{R}(s)}{V_{C_1}} \tag{21}$$

which leads to

$$\bar{C}_1(s)=\frac{1}{V_{C_1}}\frac{(s+K_{12})}{s^2+(K_{21}+K_{12}+K_{01})s-K_{12}K_{01}}\bar{R}(s)$$
$$=\frac{1}{V_{C_1}}\frac{(s+K_{12})}{(s+\lambda_1)(s+\lambda_2)}\bar{R}(s) \tag{22}$$

where $\lambda_1+\lambda_2=K_{21}+K_{12}+K_{01}$ and $\lambda_1\lambda_2=k_{12}k_{01}$. By using the Convolution theorem [15] and the Finger-Print method in (14), the inverse Laplace transform of (22) can be expressed as

$$C_1(t)=\frac{1}{V_{C_1}}\int_0^t R(\tau)[\frac{-\lambda_1+K_{12}}{-\lambda_1+\lambda_2}e^{-\lambda_1(t-\tau)}+\frac{-\lambda_2+K_{12}}{\lambda_1-\lambda_2}e^{-\lambda_2(t-\tau)}]d\tau \tag{23}$$

D. Modification of Watanabe's Approach.

To modify the Watanabe's approach, the function $h(t)$ in (4) is used in place of the fractional hepatic extraction H originally appearing in (1) as shown below.

$$\frac{dI(t)}{d\tau}=-K_I I(t)-\frac{(1-h(t))R(t)}{V_I} \tag{24}$$

To derive the analytic solution for the modified equation of insulin, (24) is now expressed as

$$\frac{dI(\tau)}{d\tau}+K_I I(\tau)=\frac{(1-h(\tau))R(\tau)}{V_I} \tag{25}$$

Multiplying both sides by the integrating factor $e^{\int K_I d\tau}$ and integrating from 0 to t, one obtains

$$\int_0^t d(e^{K_I\tau}I(\tau))=\frac{1}{V_I}\int_0^t e^{K_I\tau}(1-h(\tau))R(\tau)d\tau \tag{26}$$

That is,

$$I(t)=I(0)e^{-K_I t}+\frac{1}{V_I}\int_0^t e^{-K_I(t-\tau)}(1-h(\tau))R(\tau)d\tau \tag{27}$$

By assuming that $I(0) = 0$, instead of (19) we then arrive at the new integral expression for $I(t)$ as follow.

$$I(t)=\frac{1}{V_I}\int_0^t e^{-K_I(t-\tau)}\tilde{R}(\tau)d\tau \tag{28}$$

with

$$R(t)=\frac{\tilde{R}(t)}{1-h(t)} \tag{29}$$

Then, by the Convolution theorem [15] and (14), the Laplace transform of the Convolution integral in (28) can be expressed as

$$\bar{I}(s)=\frac{\bar{\tilde{R}}(s)}{V_I(s+k_I)} \tag{30}$$

To derive the auxiliary systems of ordinary differential equations, we begin by dividing (30) by (22), yielding

$$\bar{I}(s)=\frac{V_{C_1}\bar{\tilde{R}}(s)(s+\lambda_1)(s+\lambda_2)}{V_I\bar{R}(s)(s+K_I)(s+K_{12})}\bar{C}_1(s) \tag{31}$$

After the state variables $Z_1(t)$ and $Z_2(t)$ are assumed with $Z_1(0)=0$ and $Z_2(0)=0$, we let

$$\bar{Z}_2(s)+\bar{C}_1(s)=\frac{(s+\lambda_2)}{(s+K_{12})}\bar{C}_1(s) \tag{32}$$

To obtain an auxiliary equation analogous to (10), we rearrange (32) to get

$$\bar{Z}_2(s)=(\frac{(s+\lambda_2)}{(s+K_{12})}-1)\bar{C}_1(s)=\frac{(\lambda_2-K_{12})}{(s+K_{12})}\bar{C}_1(s) \tag{33}$$

That is,

$$s\bar{Z}_2(s)=(\lambda_2-K_{12})\bar{C}_1(s)-K_{12}\bar{Z}_2(s) \tag{34}$$

Thus,

$$\frac{dZ_2(t)}{dt}=(\lambda_2-K_{12})C_1(t)-K_{12}Z_2(t) \tag{35}$$

which is the same as (10).

We next introduce a linearizing approximation as follows. It is well known that if the continuity requirements are satisfied then there exists a $t^*>0$ such that

$$\overline{(1-h)R}(s)=\int_0^\infty(1-h(t))R(t)e^{st}dt=(1-h(t^*))\int_0^\infty R(t)e^{st}dt \tag{36}$$

We propose that its integral mean is a good approximation ofthe function $h(t)$ so that we let

$$1-h^*\approx 1-h_0=\frac{\int_0^{t_{final}}(1-h(\tau))d\tau}{t_{final}} \tag{37}$$

t_{final} being the time at the end of the time period of interest.

We then let

$$\bar{Z}_1(s)+(1-h_0)\overline{(Z_2+C_1)}(s)=\frac{(s+\lambda_1)(s+\lambda_2)}{(s+K_I)(s+K_{12})}(1-h_0)C_1(s) \tag{38}$$

Using (32), (38) becomes

$$\bar{Z}_1(s)=(1-h_0)\overline{(Z_2+C_1)}(s)(\frac{(s+\lambda_1)}{(s+K_I)}-1) \tag{39}$$

or

$$\bar{Z}_1(s)=(1-h_0)\overline{(Z_2+C_1)}(s)\frac{(\lambda_1-K_I)}{(s+K_I)} \tag{40}$$

which leads us to

$$s\bar{Z}_1(s)=(1-h_0)\overline{(Z_2+C_1)}(s)(\lambda_1-K_I)-K_I\bar{Z}_1(s) \tag{41}$$

the inverse of which is

$$\frac{dZ_1(t)}{dt}=(1-h_0)(Z_2(t)+C_1(t))(\lambda_1-K_I)-K_I Z_1(t) \tag{42}$$

which is analogous to (9), with h_0 instead of H.

Using (38) in (31), and using (32) and (36), (31) can be expressed as

$$\bar{I}(s)=\frac{V_{C_1}}{V_I}\cdot\frac{\bar{Z}_1(s)+(1-h_0)\overline{(Z_2+C_1)}(s)}{(1-h_0)\overline{(Z_2+C_1)}(s)}\cdot(1-h_0)\overline{(Z_2+C_1)}(s) \quad (43)$$

or

$$\bar{I}(s)=\frac{V_{C_1}}{V_I}(\bar{Z}_1(s)+(1-h_0)\overline{(Z_2+C_1)}(s)) \quad (44)$$

Therefore, (44) is transformed back to the real-domain as

$$I(t)=\frac{V_{C_1}}{V_I}(Z_1(t)+(1-h_0)(Z_2(t)+C_1(t))) \quad (45)$$

which is analogous to (11), with h_0 instead of H.

Similarly, to find auxiliary equations analogous to (6)–(8), we first express (31) as

$$\bar{C}_1(s)=\frac{V_I\bar{R}(s)(s+K_I)(s+K_{12})}{V_{C_1}\bar{\bar{R}}(s)(s+\lambda_1)(s+\lambda_2)}\bar{I}(s) \quad (46)$$

We then let

$$\bar{Y}_2(s)+\bar{I}(s)=\frac{(s+K_{12})}{(s+\lambda_2)}\bar{I}(s) \quad (47)$$

which yields

$$\bar{Y}_2(s)=(\frac{(s+K_{12})}{(s+\lambda_2)}-1)\bar{I}(s)=\frac{(K_{12}-\lambda_2)}{(s+\lambda_2)}\bar{I}(s) \quad (48)$$

or

$$s\bar{Y}_2(s)=(K_{12}-\lambda_2)\bar{I}(s)-\lambda_2\bar{Y}_2(s) \quad (49)$$

Thus, we obtain

$$\frac{dY_2(t)}{dt}=(K_{12}-\lambda_2)I(t)-\lambda_2Y_2(t) \quad (50)$$

which is the same as (7).

Finally, we let

$$(1-h_0)\bar{Y}_1(s)+\overline{(Y_2+I)}(s)=\frac{(s+K_I)}{(s+\lambda_1)}\overline{(Y_2+I)}(s) \quad (51)$$

That is,

$$\bar{Y}_1(s)=(\frac{(s+K_I)}{(s+\lambda_1)}-1)\frac{\overline{(Y_2+I)}(s)}{1-h_0} \quad (52)$$

which gives

$$\bar{Y}_1(s)=\frac{(K_I-\lambda_1)}{(s+\lambda_1)}\cdot\frac{\overline{(Y_2+I)}(s)}{1-h_0} \quad (53)$$

We then obtain

$$s\bar{Y}_1(s)=(K_I-\lambda_1)\frac{\overline{(Y_2+I)}(s)}{1-h_0}-\lambda_1\bar{Y}_1(s) \quad (54)$$

Equation (54) is thus transformed back to real-domain as

$$\frac{dY_1(t)}{dt}=\frac{1}{(1-h_0)}(K_I-\lambda_1)(Y_2(t)+I(t))-\lambda_1Y_1(t) \quad (55)$$

which is the same as (6), only with $h_0$instead of H.

From (47) and $\frac{(s+K_I)}{(s+\lambda_1)}=\frac{(1-h_0)\bar{Y}_1(s)+\overline{(Y_2+I)}(s)}{\overline{(Y_2+I)}(s)}$ from (51), (46) can be expressed as

$$\bar{C}_1(s)=\frac{V_I}{V_{C_1}}\frac{(1-h_0)\bar{Y}_1(s)+\overline{(Y_2+I)}(s)}{\overline{(Y_2+I)}(s)}\overline{(Y_2+I)}(s)\frac{\bar{R}(s)}{\bar{\bar{R}}(s)} \quad (56)$$

or, on using (36),

$$\bar{C}_1(s)=\frac{V_I}{V_{C_1}}(\bar{Y}_1(s)+\frac{1}{(1-h_0)}(\bar{Y}_2(s)+\bar{I}(s))) \quad (57)$$

Finally, (56) is transformed back to real-domain as

$$C_1(t)=\frac{V_I}{V_{C_1}}(Y_1(t)+\frac{1}{(1-h_0)}(Y_2(t)+I(t))) \quad (58)$$

Thus, in the first step, we use (35), (42), (50), and (55) instead of (6)-(7) and (9)-(10), while (45) is used instead of (11), and (58) instead of (8). Fitting them with the generated data of insulin and C-peptide, we can estimate the kinetic parameters in (1)-(3). In the second step, the estimated K_I from the first step is substituted into (28). The insulin concentration is fitted to the generated data by using the function fminsearch

Table 1. Estimated kinetic parameters (mean ± SE.) of insulin and C-peptide kinetics from Watanabe's approach and the known values used to generate the insulin and C-peptide concentrations by ECM. n = 12.

Parameter	λ_1	λ_2	K_I	K_{12}	$1-H$
Known Value	0.0249	0.1271	0.2000	0.0510	0.5610
With data from ECM assuming constant fraction of hepatic extraction					
0% Error	0.0248	0.1270	0.2002	0.0502	0.5547
1% Error	0.0251 ± 0.0001	0.1270 ± 0.0002	0.2005 ± 0.0005	0.0510 ± 0.0002	0.5583 ± 0.0011
2% Error	0.0251 ± 0.0001	0.1280 ± 0.0002	0.1988 ± 0.0023	0.0515 ± 0.0005	0.5531 ± 0.0046
3% Error	0.0252 ± 0.0001	0.1278 ± 0.0002	0.2008 ± 0.0003	0.0512 ± 0.0001	0.5555 ± 0.0010
4%Error	0.0253 ± 0.0001	0.1283 ± 0.0003	$0.2010+0.0011$	0.0515 ± 0.0001	0.5527 ± 0.0025
5% Error	0.0252 ± 0.0001	0.1288 ± 0.0002	0.2014 ± 0.0006	0.0513 ± 0.0001	0.5520 ± 0.0017
With data from ECM assuming non-constant fraction of hepatic extraction					
0% Error	0.0147	0.2148	0.2216	0.0465	0.5696
1% Error	$0.0146+0.0001$	0.2048 ± 0.0064	0.2173 ± 0.0110	0.0463 ± 0.0018	0.5837 ± 0.0275
2% Error	0.0154 ± 0.0003	0.2039 ± 0.0096	0.1788 ± 0.0125	0.0546 ± 0.0032	0.5408 ± 0.0366
3% Error	0.0152 ± 0.0004	0.1966 ± 0.0087	0.1977 ± 0.0045	0.0489 ± 0.0014	0.5725 ± 0.0252
4% Error	0.0154 ± 0.0004	0.1987 ± 0.0129	0.1870 ± 0.0106	0.0516 ± 0.0033	0.5634 ± 0.0410
5% Error	0.0154 ± 0.0005	0.2035 ± 0.0092	0.1898 ± 0.0154	0.0519 ± 0.0036	0.5334 ± 0.0315

in MATLAB to obtain $\tilde{R}(t)$ via the deconvolution method [11], with which we can determine the secretion rate $R(t)$ from (29).

III. Results

A. Estimation by Watanabe's Approach from the Data Generated with Constant Fractional Hepatic Extraction by Extended Combined Model

Fig. 3 and Table 1 show the ability of the Watanabe's approach to estimate the secretory rate and kinetic parameters, respectively. At all levels of error, the rate of secretion and the kinetic parameters do not differ significantly from the known values. The approach is able to provide accurate estimate of the rate of secretion and the values of kinetic parameters at no error added. The results at 1%, 2%, 3%, 4% and 5% added error imply efficient assessment of insulin secretion by the approach when the fractional hepatic insulin extraction is assumed to be constant.

B. Estimation by Watanabe's Approachfrom the Data Generated with Non-constant Fractional Hepatic Extraction by Extended Combined Model

According to (6)-(11) the estimated kinetic parameters are compared with the known values in Table 1. Based on the deconvolution method when the estimated kinetic parameters are substituted in (12)-(13) with the data generated upon the assumption of non-constant fraction of hepatic insulin extraction, the estimated rate of insulin secretion is compared with the known rate in Fig. 4. We observe that at all levels of error during the first 90 min the mean of estimated secretory rate is markedly higher than the known rate and after the first 90 min the mean of estimated secretory rate is lower than the known rate. This is to be expected, because data have been generated with non-constant fraction of hepatic insulin extraction. Watanabe's approach is therefore not able to provide accurate estimations.

C. Estimation by Modified Watanabe's Approachfrom the Data Generated with Non-constant Fractional Hepatic Extraction by Extended Combined Model

After our modification is made on the model leading us to the new function for the fractional hepatic insulin extraction in (28) together with (29), using the modified auxiliary equations, the estimated averagedrates of secretion are shown in Fig. 5 to fit closely to the known data. In using the data generated with the assumption of non-constant fraction of hepatic extraction by the extended combined model, our modified approach yields accurate estimation of insulin production, indicating that the modified approach is capable of identifying the rate of secretion in an accurate fashion.

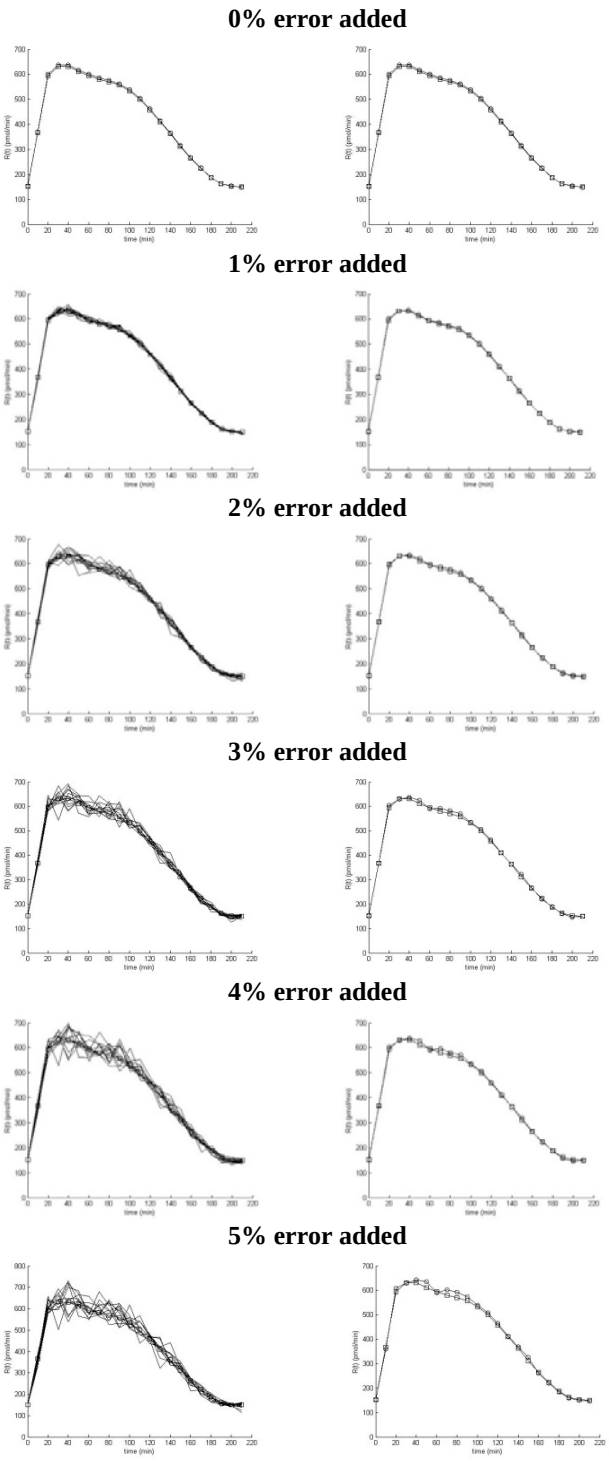

Fig. 3 Estimated secretory rate of insulin using Watanabe's approach with data generated by extended combined model assuming constant fraction of hepatic insulin extraction. Circles indicate the estimated secretory rate and squares denote the known secretory rate (data points taken from [1] by using Datathief program). Left column shows estimated secretory rate for each profile of insulin and C-peptide concentrations and right column shows the mean of estimated secretory rate at 0%, 1%, 2%, 3%, 4% and 5% errors.

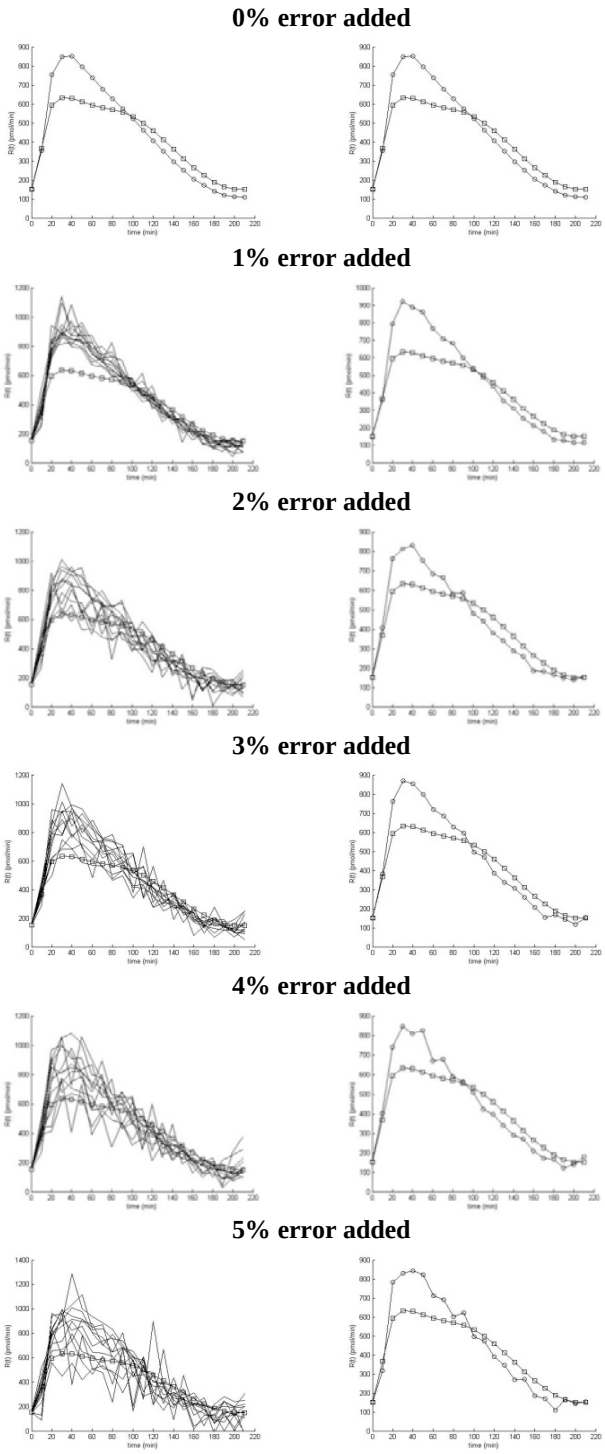

Fig. 4 Estimated secretory rate of insulin using Watanabe's approach with data generated by extended combined model assuming non-constant fraction of hepatic insulin extraction. Circles indicate the estimated secretory rate and squares denote the known secretory rate (data points taken from [1] by using Datathief program). Left column shows estimated secretory rate for each profile of insulin and C-peptide concentrations and right column shows the mean of estimated secretory rate n at 0%, 1%, 2%, 3%, 4%, and 5% errors.

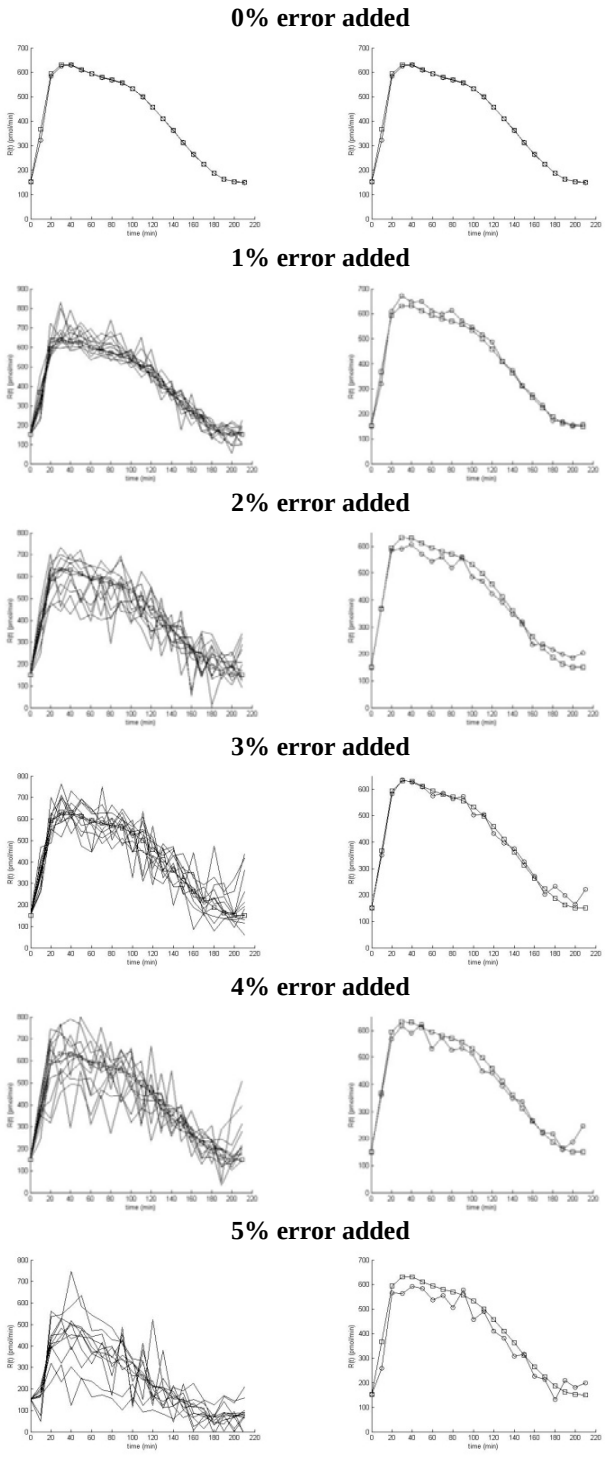

Fig. 5 Estimated secretory rate of insulin using modified Watanabe's approach with data generated by extended combined model assuming non-constant fraction of hepatic insulin extraction. Circles indicate the estimated secretory rate and squares denote the known secretory rate (data points taken from [1] by using Datathief program). Left column shows estimated secretory rate for each profile of insulin and C-peptide concentrations and right column shows the mean of estimated secretory rate at 0%, 1%, 2%, 3%, 4% and 5% errors.

IV. Conclusion

To date, a great deal of effort has gone into diabetes research [16]–[19] and attempts to provide an accurate estimate of the rate of insulin production have been carried out by using the mathematical modeling approach. Many approaches for the reconstruction of pancreatic insulin secretion have been proposed. An approach was suggested in [6] and [7]. Two separate sets of data are required for this classic approach. The exponential decrease in C-peptide concentration during a C-peptide injection is the first data set needed for the estimation of kinetic parameters of C-peptide. The insulin and C-peptide concentrations during a period ofglucose administration are the second data set for the estimation of insulin secretion rate. A more advanced approach was then presented by Watanabe [4], [5]. The dominant character of this approach is that only the data of insulin and C-peptide concentrations during the period of glucose administration are required for the estimation of the rate of secretion. kinetics in the extended combined model.

The algebraic manipulations to factor out the secretory rate $R(t)$ in the extended combined model is the important process in the Watanabe's approach so as to avoid high correlation between the fractional elimination of insulin K_I and the secretion rate $R(t)$ in the equation of insulin

However, clinical evidences [2], [3] indicate that throughout the period of glucose administration the fraction of hepatic extraction is probably not constant. Hence, Watanabe's approach may not be sufficient to estimate the insulin secretion since the approach is based on the assumption that the fraction of hepatic insulin extraction is constant. Therefore, an extension of the approach to also cover reconstruction of insulin production under the assumption of non-constant fraction of hepatic extraction is required.

In this paper, under the assumption of constant fractional hepatic extraction, Watanabe's approach based on the extended combined model has been used to estimate the rate of secretion during OGTT from the data on concentrations of insulin and C-peptide generated by extended combined model in which the fraction of hepatic extraction varies as in (4). The goal was to study the performance of the Watanabe's approach and, as expected, it was not able to provide accurate secretory rate when compared with the known rate since the approach is based on the constant fraction of hepatic insulin extraction assumption. The estimated secretory rates are found to be markedly higher than the known secretory rate during the first 90 min and significantly lower than the known secretory rate after the first 90 min.

When the error pattern of estimation is known, the Watanabe's approach is modified by using (24)-(29) to estimate the rate of secretion with the deconvolution technique. The result indicates that the estimated secretory rate is quite close to the known secretory rate. The key of modification is in the expression for $I(t)$ in (28). Two important inputs are needed for this function, the function $h(t)$ of fraction of hepatic insulin extraction given in (4) and an estimated fractional elimination of insulin K_I determined by Watanabe's approach. The fractional term K_I can be derived by estimation, but known $h(t)$ was taken from curve fitting of (4) to mimic the hepatic extraction curve taken from [8] using the program Datathief.

The mechanism that underlies such variations in the fractional hepatic extraction of insulin is still not completely understood in the present days. However, this work demonstrates that in situations where the pattern of fractional hepatic extraction is known during slow dynamics of glucose administration, the modified approach may be a reliable alternative tool to estimate the insulin secretion.

Acknowledgment

The first author has been supported by the Development and Promotion of Science and Technology Talents Project (DPST), the Office of Commission on Higher Education and, together with the third and the forth authors, BioMatLab CNR-IASI, Italy. The second author is supported by Mahidol University and the Centre of Excellence in Mathematics, CHE, Thailand.

References

[1] L.L. Kjems, E. Christiansen, A. Vølund, R.N. Bergman, S. Madsbad,"Validation of methods for measurement of insulin secretion in humans in vivo,"*Diabetes*, Vol.49, No.4, 2000, pp. 580-588.

[2] T. Brundin,"Splanchnic and extrasplanchnicextraction of insulinfollowingoral and intravenousglucoseloads,"*Clinical Science(London, England: 1979)*, Vol.97, No.4, 1999, pp. 429-436.

[3] A. Tura, B. Ludvik, J.J. Nolan, G. Pacini, K. Thomaseth,"Insulin and C-peptidesecretion and kinetics in humans: direct and model-basedmeasurements during OGTT,"*American Journal of Physiology Endocrinology and Metabolism*, Vol.281, No.5, 2001, pp. 966-974.

[4] R.M. Watanabe, G. M. Steil, R. N. Bergman,"Criticalevaluation of the combinedmodelapproach for estimation of prehepaticinsulinsecretion," *American journal of Physiology*, Vol.274, 1998, pp. 172-183.

[5] R.M. Watanabe, R.N. Bergman,"Accuratemeasurement of endogenousinsulinsecretion does not require separate assessment of C-peptide kinetics,"*Diabetes*, Vol.49, No.3, 2000, pp. 373-382.

[6] P. P. Eaton, R. C. Allen, D. S. Schade, K. M. Erickson, J. Standefer,Prehepaticinsulinproduction in man: kineticanalysis using peripheralconnecting peptidebehaviour, *The Journal of Clinical Endocrinology and Metabolism*, Vol.51, No.3, 1980, pp. 520-528.

[7] K.S. Polonsky, J. Licinio-Paixao, B.D. Given , W. Pugh, P. Rue, J. Galloway, T. Karrison, B. Frank,"Use of biosynthetichumanC-peptide in the measurement of insulin secretionrates in normalvolunteers and type I diabeticpatients,"*The Journal of Clinical Investigation*, Vol.77, No.1, 1986, pp. 98-105.

[8] M. Campioni, G. Toffolo, R. Basu, R.A., Rizz, C. Cobelli,"Minimalmodelassessment of hepaticinsulinextraction during an oraltest from standardinsulinkineticparameters," *American Journal of Physiology Endocrinology and Metabolism*, Vol.297, No.4, 2009, pp. 941-948.

[9] W.C. Duckworth, R.G. Bennett,F.G. Hamel, "Insulin degradation: progress and potential,"*Endocrine Reviews*,Vol.19, No. 1998, pp. 608-624.

[10] K. Thomaseth, A. Kautzky-Willer, B. Ludvik, G. Pacini, "Integratedmathematical model to assess b-cell activity during the oral glucose test,"*American Journal of Physiology Endocrinology and Metabolism*, Vol.270, 1996, pp. 522-531.

[11] M.L. Johnson, J.D. Veldhuis, "Evolution of deconvolution analysis as a hormone pulse detection method,"*Journal ofNeuroscience Methods*, Vol.28, 1995, pp. 1-24.

[12] L.Z. Benet, J.S. Turi, "Use of the general Partial Fraction Theorem for obtaining inverse Laplace transform in pharmacokinetic analysis,"*Journal of Pharmaceutical Sciences*, Vol. 60, 1971, pp. 1593-1594.

[13] L.Z. Benet, "General treatment of linear mammillary models with elimination from any compartment as used in pharmacokinetics," *Journal of Pharmaceutical Sciences*, Vol. 61, 1972, pp. 536-541.

[14] D.W. Bourne. (2010, May 26). Finger Print Method [Online]. http://www.boomer.org/c/p3/c07/c0702.html.

[15] G. Ledder, *Differential equations: a modeling approach*, McGraw-Hill Science/Engineering/Math, 2004, pp. 460-466.

[16] C. Morgovan, S. Ghibu, M.Bota, C. Fleseriu, S. Cosma,"Cost for diabetes mellitus care in Romania and the world in the interval 1998-2007," *Proceedings of the 5th WSEAS International Conference on Economy and Management Transformation (Volume II)*, 2010, pp. 714–719.

[17] E. Supriyanto, W.M. Hafizah, W.W. Yun, M. Jamlos,**"**Ultrasound pancreas segmentation: a new approach towards detection of diabetes mellitus,"*Proceedings of the 15th WSEAS International Conference on Computers,* 2011, pp. 184-188.

[18] C.I. Bondor, D. Matei, A. Mureşan, "OXIDIABASE–software for risk assessment of complications in type 2 diabetes mellitus based on oxidative stress score obtain by Topsis method,"*Proceeding of the International Conferences on Risk Management, Assessment and Mitigation*, 2010, pp. 374-379.

[19] L.G. Cerban, G. Manolea, "Integrated information system for preventing the risk of worsening health condition of people with diabetes, by eating foods with side effects,"*Proceeding of the International Conferences on Risk Management, Assessment and Mitigation*, 2010, pp. 75-77.