Reconstruction of Insulin Secretion under the Effects of Hepatic Extraction during OGTT: A Modelling and Convolution Approach

KIATTIYOT JUAGWON[1,2], YONGWIMON LENBURY*[1,2],
ANDREA DE GAETANO[3], PASQUALE PALUMBO[3]
[1]Department of Mathematics, Faculty of Science, Mahidol University, Bangkok 10400, Thailand;
[2]Centre of Excellence in Mathematics, CHE, 328 Si Ayutthaya Road, Bangkok 10400, Thailand;
[3]BioMatLab CNR-IASI, Fisiopatologia dello Shock University Cattolica del SacroCuore Largo A. Gemelli 8 – 00168 Rome, Italy
*corresponding author: scylb@yahoo.com http://www.sc.mahidol.ac.th/scma/

Abstract: - The reconstruction of insulin secretion rates deriving from insulin and C-peptide concentrations is studied. Two sets of data simulating profiles of insulin and C-peptide concentrations during glucose administration are generated, one of which is generated using an extended combined model (Watanabe et al., 1998) under the assumption of constant fractional hepatic extraction, while the second data set is from assuming non-constant fractional hepatic extraction. A deconvolution approach based on the extended combined model with the constant extraction is then applied to estimate the rate of insulin secretion. The result indicates that variation in the fractional hepatic extraction significantly effects the reconstruction of insulin secretion. When the convolution approach is modified to accommodate the assumption of non-constant fractional hepatic extraction, it can provide more accurate estimates for the rates of insulin production. The modified approach discussed in this paper may thus offer a better option in the attempt to determine an estimation of insulin secretion crucial for the control of diabetes mellitus.

Key-Words: - insulin secretion, insulin estimation, hepatic extraction, deconvolution, C-peptide

1 Introduction

Deeper understanding of insulin kinetics is crucial for the control and treatment of diabetes mellitus. It is clinically important to be able to identify pancreatic secretion of insulin hormone during oral glucose tolerance test (OGTT) because a defect in insulin secretion is characteristic of type 2 diabetes [1]. An accurate estimation of endogenous insulin secretion will allow the physicians to monitor the level of the defect in insulin secretion of β-cells in the pathogenesis of type 2 diabetes in order to better control and treat diabetic patients. An approach based on a two-compartment kinetics model for C-peptide and two-phase clearance of insulin kinetic model for insulin, called an extended combined model (ECM), was proposed by Watanabe et al. [2, 3] to be an alternative approach for the identification of the rate of pancreatic insulin secretion and kinetic parameters. This approach uses the plasma concentrations of insulin and C-peptide sampled from a single experiment protocol to estimate kinetic parameters of insulin and C-peptide control system and to estimate the prehepatic insulin secretion rate without the separate experimental protocol suggested by Eaton et al. [4] and improved by Polonsky et al. [5] or the experimental protocol fixing the values of the parameters [6]. In vivo experiment in conscious dogs was carried out to examine the accuracy of identification [3]. The approach appeared to be able to reconstruct fairly well the known equimolar intraportal infusion of insulin and C-peptide. However, the approach assumes that the fraction of hepatic extraction, defined as the proportion of the amount or rate of insulin clearance during first pass transit of liver to the amount or rate of insulin secretion, is constant. However, there is evidence [7, 8] that the extraction decreases during high concentration of insulin although the total hepatic extraction increases. A possible explanation is that most extraction is a receptor-mediated process and hence high concentration of insulin in the portal vein leads to a reduction in clearance due to receptor down-regulation [9]. By a direct assessment of fractional hepatic extraction, quantified by measured hepatic venous-arterial difference in insulin and C-peptide concentrations and calculated rate of hepatic blood flow, carried out by Brundin [7] and Tura et al. [8], it has been shown that the fraction is not constant during oral glucose administration. Therefore, in this work we modify the approach presented in [2]

ISBN: 978-1-61804-158-6

and [3] so that it is able to accommodate variations in the fractional hepatic extraction.

Thus, the first aim of this study is to re-examine the accuracy of estimations derived by the approach proposed in [2] and its numerical application. The data on concentrations of insulin and C-peptide are generated by the ECM with known parameter values and rate of secretion and the approach is then used to estimate the parameters based on the generated data added with various levels of random Gaussian error.

The second aim is to study the efficiency of the approach when it is applied to estimate the parameters and secretion rate from the data of insulin and C-peptide concentrations generated by ECM with non-constant fractional hepatic extraction term in the kinetic model for insulin.

Finally, we modify the approach to reconstruct the secretory rate when insulin and C-peptide concentrations are given by ECM with non-constant fractional hepatic extraction. To investigate the accuracy of the estimation, the modified approach is used to estimate the rate of secretion from the data, generated by ECM with non-constant fractional hepatic extraction, with different levels of random Gaussian error. Estimated result is then compared with the known values.

2 Methods

2.1 The model and data generation

The extended combined model has been described in [2]. The model takes into consideration the kinetics of endogenous insulin and C-peptide. These components have a common rate of secretion because of pancreatic equimolar release of insulin and C-peptide. For the insulin kinetics, it is assumed that there is only one compartment of insulin and there are two phases of insulin clearance. The first phase removal is the hepatic insulin extraction, depending on the rate of pancreatic insulin release, by the liver during the first pass transit. The second phase removal is systemic insulin clearance, depending on the current insulin concentration. The model assumes that the fractional hepatic insulin extraction is constant throughout the period of interest. For the kinetics of C-peptide, the two-compartment model is applied. The C-peptide clearance is assumed to occur only in the first compartment and hepatic C-peptide degradation in the liver is negligible. The ordinary differential equations in ECM can be written as

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

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

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

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

In this study, there are two different sets of data of insulin and C-peptide concentrations. The data in the first set is generated by ECM under the assumption of constant hepatic extraction and the data in the second set is generated under the assumption of non-constant hepatic extraction. To generate the data in the second set, the shape of the fractional hepatic extraction time course reported in [6] is used to derive the following function to replace the constant fractional hepatic extraction H in Eq. (1)

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

That is, this function has been chosen to represent the fractional hepatic extraction since the graph of this function, shown in Fig. 1, is able to closely mimic the shape of the plot of experimentally measured fractional hepatic extraction reported in Fig. 4 in [6].

The known values of kinetic parameters and rate of secretion time series for the data generation are taken from [1] and shown in Table 1. and the figure caption of Fig. 2, respectively.

Each set of data contains 24 profiles of insulin and C-peptide concentrations added with random Gaussian error with coefficients of 3% and 5%, 12 profiles at 3% error and 12 profiles at 5% error. Once the data has been generated, the Watanabe

ISBN: 978-1-61804-158-6

approach is then used to estimate kinetic parameters and secretory rate from the data in the first set and then in the second set to access the accuracy of parameter identification under conditions of constant and non-constant fractional hepatic extraction, respectively. Next, the modified Watanabe approach is applied with the data in the second set and the estimates are then compared with the known values.

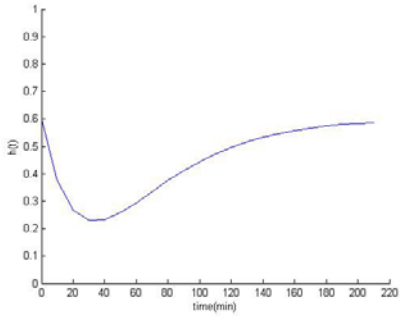

Fig. 1. Graph of $h(t)$ in Eq. (4) representing the fraction of hepatic extraction during OGTT. $\alpha = 0.02956$, $\beta = 0.02959$. $a = 0.60$, $b = 1000$.

2.2 Parameter identifications and numerical methods

Watanabe's approach was described in [2] for the estimation of the kinetic parameters and prehepatic secretion. The approach can accurately estimate the values of parameters and rate of secretion under the assumption of constant fractional hepatic extraction based only on the data of concentrations of insulin and C-peptide during OGTT without any data on exponential decrease in concentration of C-peptide when a bolus of C-peptide is injected [3]. This approach based on ECM has two steps. The first step is the estimation of kinetic parameters and the second step is the estimation of the secretory rate. In the first step, the system of equations, Eq. (1)-(3), are transformed from real-domain into *s*-domain by Laplace transforms leading to the simplified transfer function in the form

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

where $\bar{I}$ and $\bar{C}_1$ are the Laplace transforms of I and C_1, respectively, $\lambda_1+\lambda_2 = K_{21}+K_{12}+K_{01}$ and $\lambda_1\lambda_2 = k_{12}k_{01}$. (Please see ref. [3] for further detail). This transfer function in Eq. (5) is also the transfer function of following system of differential equations.

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

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

with

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

or

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

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

with

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

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

Next, using MATLAB function fminsearch, the values of the parameters in Eq. (6)-(8) or Eq. (9)-(11) are estimated by using the data of insulin and C-peptide concentrations. For Eq. (6)-(8), the parameters are estimated by fitting the C-peptide concentration while insulin concentration is assigned to be the input, while the estimation by using Eq. (9)-(11) is the opposite. Then, the estimated parameters are substituted in the analytic solution of Eq. (1)-(3) given by

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

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

Therefore, the work in the second step is the estimation of the function of secretory rate $R(t)$ by using Eq. (12) and Eq. (13). (Please see ref. [2] for more detail for the derivation of Eq. (12)-(13).)

To modify the Watanabe approach, the fractional hepatic extraction H defined in Eq. (1) is replaced by the function $h(t)$ in Eq. (4), and the secretory rates are calculated by the deconvolution technique [10] as follows. Eq. (1) is now written as

$$\frac{dI(\tau)}{d\tau} + K_I I(\tau) = (1-h(\tau))R(\tau) \qquad (14)$$

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

$$\int_0^t d(e^{K_I\tau} I(\tau)) = \int_0^t e^{K_I\tau}(1-h(\tau))R(\tau)d\tau \quad (15)$$

That is,

$$I(t) = I(0)e^{-K_I t} + \int_0^t e^{-K_I(t-\tau)}(1-h(\tau))R(\tau)d\tau \quad (16)$$

In the case that $I(0) = 0$, we then arrive at the following integral expression for $I(t)$, in place of Eq. (13).

$$I(t) = \int_0^t e^{-K_I(t-\tau)}\tilde{R}(\tau)d\tau \quad (17)$$

with

$$R(t) = \frac{\tilde{R}(t)}{1-h(t)} \quad (18)$$

When the estimated K_I from the first step is substituted, $\tilde{R}(t)$ is estimated by fitting the insulin concentration using function fminsearch in MATLAB. That is, deconvolution allows us to derive the function $\tilde{R}(t)$ at different time t, by which we can calculate the secretion rate $R(t)$ from Eq. (18).

3 Results

3.1 Watanabe approach on data from ECM assuming constant fractional hepatic extraction

The ability of the approach to estimate the kinetic parameters is shown in Table 1. The kinetic parameters and rate of secretion do not differ significantly from the known values for all levels of error. With no error added, the approach is able to provide the correct values of kinetic parameters and rate of secretion.

The results at no error added, at 3%, and 5% added error indicate that the approach provides efficient assessment of insulin secretion when the fractional hepatic extraction is assumed to be constant.

3.2 Watanabe approach on data from ECM assuming non-constant fractional hepatic extraction

The kinetic parameters estimated according to Eq. (6)-(11) are compared with the known values in Table 1, and in Fig. 2 the estimated rate of insulin secretion by the deconvolution method based on Eq. (12)-(13) when the estimated kinetic parameters are substituted is compared with the data generated upon the assumption of non-constant extraction. We observe that the estimated mean of secretory rate is markedly lower than the known rate during the first 90 min and is higher than the known rate after the first 90 min for all levels of error. This is to be expected, since the profiles of insulin concentration have been generated under the assumption of non-constant fraction of hepatic extraction but the processes in the Watanabe approach assume that the fraction is constant, and thus the approach is not able to provide the correct rate of insulin secretion.

3.3 Modified Watanabe approach on data from ECM assuming non-constant fractional hepatic extraction

After modification is made on the expression involving the estimated rate of secretion leading us to the new expression shown in Eq. (17) together with (18), the adjusted rate of secretion is shown in Fig. 3. The result appears to be able to provide accurate rate of secretion from the data generated by the extended combined model under the assumption of non-constant fraction of hepatic extraction.

Table 1. Estimated kinetic parameters (mean ± SE.) of insulin and C-peptide kinetics from Watanabe 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
3% Error	0.0252 ± 0.0001	0.1278 ± 0.0002	0.2008 ± 0.0003	0.0512 ± 0.0001	0.5555 ± 0.0010
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
3% Error	0.0152 ± 0.0004	0.1966 ± 0.0087	0.1977 ± 0.0045	0.0489 ± 0.0014	0.5725 ± 0.0252
5% Error	0.0154 ± 0.0005	0.2035 ± 0.0092	0.1898 ± 0.0154	0.0519 ± 0.0036	0.5334 ± 0.0315

ISBN: 978-1-61804-158-6

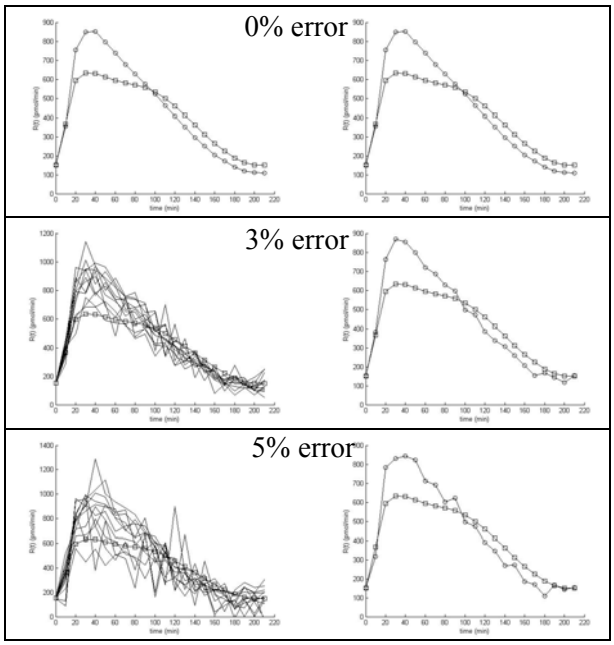

Fig. 2 Estimated rate of insulin secretion from Watanabe approach with data from ECM assuming non-constant fraction of hepatic extraction. Squares represent the known rate of secretion (data points taken from [1] by using Datathief program) and circles indicate the estimated rate of secretion. Left panel shows estimated rate of secretion for each profile of insulin and C-peptide concentrations and right panel shows the mean of estimated rate of secretion at 0%, 3% and 5% errors.

4 Conclusion

To date, many approaches for quantification of pancreatic insulin secretion have been proposed to provide accurate estimate of the rate of insulin production. One of the approaches was suggested in [4] and [5]. This classic approach requires two separate sets of data. The first data set is on the exponential decrease in C-peptide concentration for the estimation of kinetic parameters of C-peptide and the second data set is on insulin and C-peptide concentrations during a period of glucose administration for the estimation of insulin secretion rate. Then, a more advanced approach was proposed by Watanabe [2, 3]. The advantage of this approach is that it needs only the data of insulin and C-peptide concentrations for the identification of kinetic parameters and the rate of secretion during the period of glucose administration. The approach, proposed in [2], uses algebraic manipulations to factor out the insulin secretion rate $R(t)$ in ECM in order to avoid high correlation between the secretion rate $R(t)$ and the fractional elimination of insulin K_I in ECM.

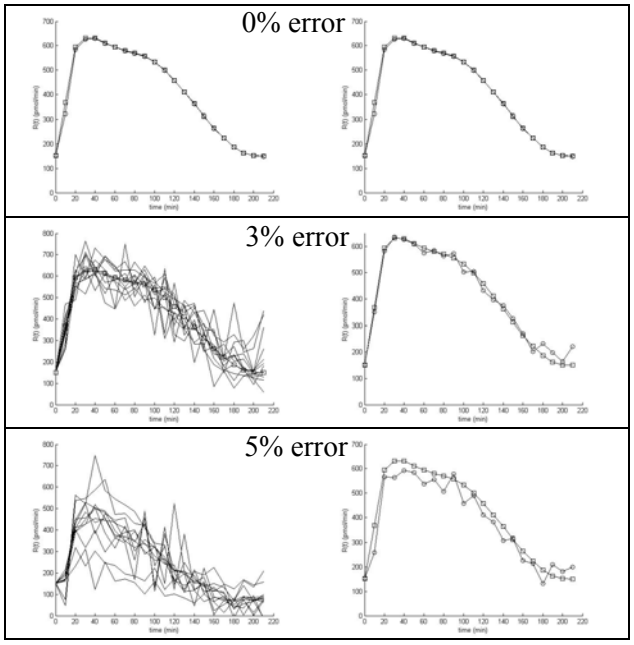

Fig. 3 Estimated rate of insulin secretion from modified Watanabe approach with data from ECM assuming non-constant fraction of hepatic extraction were given. Squares represent the known rate of secretion (data points taken from [1] by using Datathief program) and circles indicate the estimated rate of secretion. Left panel shows estimated rate of secretion for each profile of insulin and C-peptide concentrations and right panel shows the mean of estimated rate of secretion at 0%, 3% and 5% errors.

The results in [2] and [3] indicate that the approach is able to reconstruct insulin production. However, experimental evidences indicate that the fraction of hepatic extraction is probably not constant throughout the period of glucose administration. Hence, Watanabe's approach may not be sufficient for the estimation of insulin production because the approach is based on the assumption of constant fraction of hepatic extraction. Therefore, the approach should be extended to also cover reconstruction of insulin production under the assumption of non-constant fraction of hepatic extraction.

In this work, the approach, based on ECM under the assumption of constant fractional hepatic extraction, has been used to estimate the rate of secretion from the data on insulin and C-peptide concentrations during OGTT, generated by ECM assuming that the fraction of hepatic extraction

ISBN: 978-1-61804-158-6

varies as Eq. (4). The aim was to study the performance of Watanabe approach and, as expected, the approach was not able to provide accurate rate of secretion when compared with the known rate because the approach is based on the constant fraction of hepatic extraction assumption but the data has been generated under the assumption of non-constant fraction. The estimated rate is found to be higher than the known rate during the first 90 min and lower than the known rate after the first 90 min.

When the pattern of error of estimation is known, the Watanabe approach is modified by estimating the rate of secretion using Eq. (14)-(18) by deconvolution. The result indicates that the estimated rate of secretion is quite close to the known rate. The key modification is in the expression for $I(t)$ in Eq. (17). This function requires two important inputs, an estimated fractional elimination of insulin K_I calculated by the Watanabe approach and the function $h(t)$ of fraction of hepatic extraction given in Eq. (4). The term K_I can be derived by estimation, but $h(t)$ was taken from curve fitting of Eq. (4) to the hepatic extraction curve reported in [6].

In the present day, the mechanism that underlies such variations in the fraction of hepatic extraction is still not clearly understood. This work demonstrates that the modified approach may be a reliable alternative tool for the estimation of insulin secretion in the case that the pattern of fractional hepatic extraction during slow dynamics of glucose administration is known.

5 Acknowledgment

The first author has been supported by a scholarship from the Development and Promotion of Science and technology Talents project (DPST) and, together with the third author, the BioMatLab CNR-IASI, Italy. The second author is supported by the Centre of Excellence in Mathematics, CHE, Thailand.

References:

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

[2] T. Brundin, Splanchnic and extrasplanchnic extraction of insulin following oral and intravenous glucose loads, *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-peptide secretion and kinetics in humans: direct and model-based measurements during OGTT, *American Journal of Physiology Endocrinology and Metabolism*, Vol.281, No.5, 2001, pp. 966-974.

[4] 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.

[5] R.M. Watanabe, G.M. Steil, R.N. Bergman, Critical evaluation of the combined model approach for estimation of prehepatic insulin secretion, *American journal of physiology*, Vol.274, 1998, pp. 172-183.

[6] R.M. Watanabe, R.N. Bergman, Accurate measurement of endogenous insulin secretion does not require separate assessment of C-peptide kinetics, *Diabetes*, Vol.49, No.3, 2000, pp. 373-382.

[7] P.P. Eaton, R. C. Allen, D. S. Schade, K. M. Erickson, J. Standefer, Prehepatic insulin production in man: kinetic analysis using peripheral connecting peptide behaviour, *The Journal of clinical endocrinology and metabolism*, Vol.51, No.3, 1980, pp. 520-528.

[8] K.S. Polonsky, J. Licinio-Paixao, B.D. Given , W. Pugh, P. Rue, J. Galloway, T. Karrison, B. Frank, Use of biosynthetic human C-peptide in the measurement of insulin secretion rates in normal volunteers and type I diabetic patients, *The Journal of clinical investigation*, Vol.77, No.1, 1986, pp. 98-105.

[9] M. Campioni, G. Toffolo, R. Basu, R.A. Rizza , C. Cobelli, Minimal model assessment of hepatic insulin extraction during an oral test from standard insulin kinetic parameters, *American Journal of Physiology Endocrinology and Metabolism*, Vol.297, No.4, 2009, pp. 941-948.

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