A mathematical model of the intravenous glucose tolerance test illustrating an \( n \)-order decay rate of plasma insulin in healthy and type 2 diabetic subjects

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Abstract. The most accurate considered method to determine the insulin sensitivity (\( S_I \)) and glucose effectiveness (\( S_G \)), that is the intravenous glucose tolerance test (IVGTT). In this study, the modified minimal model with additions of an \( n \)-order decay rate of plasma insulin function and an insulin infusion rate function is introduced. This modified model enables estimation of two main feature of type 2 diabetes (T2D) diagnostic, that is the index of \( S_I \) and \( S_G \). This paper, the modified model has been used to study four cases published IVGTT data, including normal glucose tolerance (NGT) or healthy subjects and T2D subjects with different types of insulin infusion rates. This modified model study has been shown that in NGT subjects had higher \( S_I \) and \( S_G \) index than T2D subjects. The \( R^2 \) value, the coefficient of determination of between measured and calculated plasma concentrations of these four cases, is above 0.95, which indicates good agreement.

1. Introduction

At this time, many thousands of individuals worldwide have been affected the T2D disease. The population of T2D sufferers is increasing and will keep on to increase rapidly in the future. Much medical research has been performed to prevent this disease and to slow down the number of affected individuals by the disease. Today, mathematical modeling has been applied widely for finding new ideas and for developing incrementally new methods to improve the management and control of T2D sufferers effectively. Someday, this models can become an inspiration of medical and clinical to prevent the number of T2D sufferers worldwide [1, 2].

The model basic idea is how to transform a complex physiological process into simple mathematical equations set and then this model can be appropriately validated to describe a real physiological system and can be used the process of a medical and clinical treatment. The development of a robust, valid and verified model allows its users to further observe, understand and explain a complex physiological system [2].

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Glucose-insulin dynamics models have been widely applied to studying a better understanding of the T2D disease. A valid and verified model may describe some useful information on individuals or groups of subjects through appropriate clinical experiments, such as the rate of glucose disappearance, $S_I$ and $S_G$ index. All parameters of these models that unknown are commonly estimated from a subject experiment data [3, 4].

A simple blood test that usually is used to determine the blood glucose level of an individual cannot be used to diagnose whether they are normal, pre-diabetic or diabetic. Because the test does not directly provide $S_I$ and $S_G$ indexes information for subjects. Therefore, a further IVGTT test is often used to obtain more comprehensive information. An IVGTT procedure is a bolus injection of glucose to increase the glycemic level of an individual followed by frequent blood sampling to obtain some main information when the glucose disappearance in the blood. This test will provide the ability for observing the glucose decrease in the human body system [2].

An IVGTT test is one of the important experimental procedure for estimating the $S_I$ and $S_G$ indexes, since it is relatively easy to measure, and its analysis generates a lot of information. The procedure of IVGTT test is subject will be injected a glucose bolus afterward collecting a set of plasma glucose and insulin samples over a period of 2-3 h. For the T2D subject, it is sometimes necessary to be injected an exogenous insulin infusion due to insufficient endogenous insulin secretion from beta-cell in pancreas although it has been stimulated a glucose injection. The $S_I$ index is one of the main parameters to diagnose T2D subjects. This index will measure how well glucose disappears after insulin is released. The opposite of $S_I$ index is called the insulin resistance ($IR$). The $S_G$ index measures the capability of glucose for suppressing endogenous glucose production. These indexes can be applied for studying and comparing outcomes among groups of different individuals.

For interpreting an IVGTT test, several physiological models have been developed. Mari proposed a circular model and combined it with an IVGTT experimental to describe plasma glucose and insulin profiles for healthy and non-insulin-dependent diabetic (NIDD) subjects [5]. Gaetano and Arino proposed a model of the global physiologic dynamical system, this model showed some numerical results obtained from fitting the dynamical model to plasma glucose and insulin concentrations measured in healthy subjects while undergoing the IVGTT [6].

The purpose of this paper, to develop the minimal model Bergman [7] and also to modify the modified minimal model in previous work [8] for describing how glucose and insulin together control the production and disposal of glucose in the NGT and T2D subjects while undergoing the IVGTT. In the new modified minimal model, the assumption is based on that the insulin decay rate is not always a first-order process and also add a function of the insulin infusion rate in previous literature [9]. The new modified model can be used to estimate two main indices of $S_I$ and $S_G$ indexes.

### 2. Materials and methods

#### 2.1. The intravenous glucose tolerance test without an insulin infusion

For studying case 1 and 2, a case 1 data (Subject 6) and a case 2 data (Subject 7) which will be compared by the present results were obtained from the published literature [6]. A standard IVGTT was applied without an insulin infusion, so a function of insulin infusion rate is presented as follows: $u(t) = 0, \ t \geq 0$ min. When time 0 min, a glucose bolus of 0.33 g/kg body weight was rapidly infused for 3 min. Later blood samples were measured at time intervals: 0, 2, 4, 6, 8, 10, 12, 15, 20, 25, 30, 35, 40, 50, 60, 80, 100, 120, 140, 160 and 180 min.

#### 2.2. The intravenous glucose tolerance test with an insulin infusion

For studying case 3, the averaged IVGTT test data from seven T2D subjects were obtained from the previous literature [5]. In the standard IVGTT test procedure, after the subjects fasting, they will
be measured their basal glucose. Later at 0 min, a 0.3 g/kg body weight glucose bolus was infused immediately. The blood samples will be measured again at time intervals: 2, 3, 4, 5, 6, 8, 10, 15, 20, 25, 30, 40, 60, 80, 100, 120, 140, 160, 180, 210, and 240 min. When time at 20 min in this test, the insulin was infused at a constant rate of 50 mU/kg body weight for 5 min. The insulin infusion rates function is presented as follows: \( u(t) = 50 \text{ (mU/kg body weight)} \) at \( 20 \leq t \leq 25 \text{ min} \).

For studying case 4, an averaged IVGTT test data from eight T2D patients are obtained from the previous literature [10]. In this an IVGTT procedure, a glucose bolus of 200 mg/kg was administrated over 60 seconds at time 0, and then blood samples were measured at time intervals: 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 140, 160, 180, 200, 220, 240, 260, 280, and 300 min. The modified IVGTT procedure was applied to show the response of endogenous insulin secretion in the T2D patients and for reducing the insulin infusion rate to 50% which used usually in the T2D patients. After an injection of the glucose bolus, insulin infusion rates were given: phase 1 (2 to 4 min) 3.5 mU/(kg min); phase 2 (7 to 17 min) 0.5 mU/(kg min); phase 3 (17 to 50 min) 0.25 mU/(kg min). The insulin infusion rate functions are presented as follows:

\[
\begin{align*}
 u(t) = & \begin{cases} 
 3.50 & \text{(mU/kg body weight)} \quad 2 \leq t \leq 4 \text{ min} \\
 0.50 & \text{(mU/kg body weight)} \quad 7 \leq t \leq 17 \text{ min} \\
 0.25 & \text{(mU/kg body weight)} \quad 17 < t \leq 50 \text{ min} \\
 0.10 & \text{(mU/kg body weight)} \quad 50 < t \leq 300 \text{ min} 
\end{cases} 
\end{align*}
\]

2.3. The modified minimal model with the n-order decay rate of plasma insulin rate

In physiological research, the minimal model has been used widely on the metabolism of glucose in the human body and also used in medical and clinical studies for estimating the index of \( S_I \) and \( S_G \). In this study, the minimal model will be modified by an assumption of a decay rate of plasma insulin because of a stimulation by glucose is not always a first-order function. However, this decay rate is an \( n \)-order function. A mathematical model for describing the insulin infusion rate was introduced by Zheng and Zhao [9]. The new modified minimal model in this study will be proposed as follows:

\[
\begin{align*}
 \frac{dG(t)}{dt} &= p_1(G_b - G(t)) - X(t)G(t), & G(t_0) = G_o, \quad (1) \\
 \frac{dX(t)}{dt} &= -p_2X(t) + p_3(I(t) - I_b)^n, & X(t_0) = 0, \quad (2) \\
 \frac{dI(t)}{dt} &= \gamma(G(t) - G_o) - k(I(t) - I_o)^n + \frac{u(t)}{V}, & \text{if, } G(t) > G_o \text{ and } I(t_0) = I_o, \quad (3) \\
 \frac{dI(t)}{dt} &= -k(I(t) - I_o)^n + \frac{u(t)}{V}, & \text{if, } G(t) < G_o \text{ and } I(t_0) = I_o, \quad (4) 
\end{align*}
\]

Parameter, unit, and definition for the new modified minimal model in above are shown in Table 1. The \( S_I \) index was calculated as:

\[
S_I = \frac{p_1}{p_2}. 
\]
The new modified minimal model becomes identical to the modified minimal model [8] when the exogenous insulin infusion rate is set to zero so that the decay rate of the plasma insulin is considered as a first-order process.

**Table 1. Parameter, Unit, and Definition for the New Modified Minimal Model**

| Name   | Unit   | Definition                                                                 |
|--------|--------|-----------------------------------------------------------------------------|
| \(G(t)\) | mg/dl  | the glucose concentration in the plasma compartment at time \(t\)            |
| \(I(t)\) | μU/ml  | the insulin concentration in the plasma compartment at time \(t\)           |
| \(X(t)\) | min\(^{-1}\) | the removal rate of insulin from the interstitial compartment at time \(t\) |
| \(Gb\) | mg/dl  | the basal concentration of glucose                                           |
| \(Ib\) | μU/ml  | the basal concentration of insulin                                           |
| \(G_0\) | mg/dl  | the initial plasma glucose concentration after injection of the glucose bolus|
| \(I_0\) | μU/ml  | the initial plasma insulin concentration after injection of the glucose bolus|
| \(p_1\) | min\(^{-1}\) | the glucose decay rate constant or called the \(S_G\) index                  |
| \(p_2\) | min\(^{-1}\) | the disappearance rate of remote insulin                                    |
| \(p_3\) | (μU/ml) min\(^{-2}\) | the rate at which remote insulin declare increased by plasma insulin         |
| \(k\) | min\(^{-1}\) | the insulin clearance fraction                                               |
| \(γ\) | min\(^{-1}\) | a measure of the secondary pancreatic response to glucose                   |
| \(u(t)\) | (mU/kg) min\(^{-1}\) | the exogenous insulin infusion rate                                           |
| \(V\) | L/kg   | the distribution volume                                                     |
| \(n\) | no unit         | the decay rate of the plasma insulin and the increase rate of the remote insulin |

**2.4. Particle Swarm Optimization parameter estimation techniques**

Particle Swarm Optimization (PSO) is a new method of parameters estimation that is inspired by the behavior of animals, such as birds flock movements. Each animal is considered a particle. A particle in dimensional space has a position and velocity that is encoded as vector coordinates. This position and velocity vector is considered as a condition of the particle in the search space. Each position and velocity in the search space is an alternative estimation that can be evaluated using the new modified minimal model function.

In this research, the parameters of \(p_1, p_2, p_3, k, n,\) and \(γ\) in the new modified minimal model are estimated with IVGTT data using the PSO algorithm. These parameters to determine an index of the \(S_I\) and \(S_G\). Because of the concept effectiveness and simplicity of PSO algorithm cause this algorithm widely be applied in practical problem solving of parameters estimation [11, 12]. The coefficient of determination, \(R^2\), is calculated from parameters estimation. The coefficient of determination between the best-fit curve and the data, \(y_i - \hat{y}_i\), is calculated by the equation as follows:
\[
R^2 = 1 - \frac{\sum_{i=1}^{n} (y_i - \hat{y}_i)^2}{\sum_{i=1}^{n} (y_i - \bar{y})^2},
\]

(6)

where \( y \) is experimental data, \( \hat{y} \) is the prediction of the non-linear least-squares fit and \( \bar{y} \) is the averaged experimental data. The experimental data of the glucose-insulin system of these four cases that obtained from the published literature, including NGT and T2D subjects during the IVGTT test will be estimated their parameters.

3. Results and Discussion

The calculation results of the \( R^2 \) value between experimental data and simulation results of this new model to these four cases is above 0.95. It means that the new modified minimal model was good agreement with the experimental data. The better model could be explained due to occur the increased flexibility of this new model, particularly the assumption of insulin function part which describes the insulin decay rate is not always a first-order process, usually called nonlinearly. Another reason is the insulin injection function can stimulate the insulin secretion from beta-cells in a pancreas which exactly reflects the actual IVGTT test situations.

![Figure 1](image_url)

**Figure 1.** Profiles of plasma glucose and insulin level are produced by the new modified minimal model for NGT human in the case 1, with parameters: \( k = 0.120 \text{ [min}^{-1}] \), \( \gamma = 0.0145 \text{ [min}^{-1}] \), \( G_b = 80 \text{ [mg/dl]} \), \( I_b = 50 \text{ [μU/ml]} \), \( p_2 = 0.075 \text{ [min}^{-1}] \), \( S_I = 5.50 \times 10^{-5} \text{ [μU/ml} \text{ min}^{-1}] \), \( S_G = 0.025 \text{ [min}^{-1}] \), \( u(t) = 0 \), \( n = 0.998 \), \( R^2 \) for glucose = 0.98 and \( R^2 \) for insulin = 0.96.

In case 1 and case 2, this curve profile of the experimental and calculation results of blood glucose concentration and insulin concentration is shown in Figure 1 and 2. In this standard IVGTT, after an injection of glucose bolus occurs the blood glucose rise, so higher glucose concentration than before. Afterward, blood glucose shows an apparent decay immediately to the basal line for 1 h. The insulin concentration also increases due to stimulated by the injected glucose, afterward occur an exponential decay of insulin, and finally a secondary peak appears in case 1 and case 2.

The parameters estimation of \( S_I \) and \( S_G \) index for NGT subjects without an additional insulin infusion shown in Table 2. The precision of the \( S_I \) and \( S_G \) index were compared to the normal range of the \( S_I \) and \( S_G \) index from a previous literature [13]. The parameters estimation was not statistically different from normal ranges of the \( S_I \) and \( S_G \) index. The new modified minimal model provides an
estimation of the $S_I$ and $S_G$ index accurately because these values are in good agreement with previously published values in healthy humans [13].

**Table 2.** Parameters Estimation of The New Modified Minimal Model for Healthy (NGT) Subject without an Insulin Infusion.

| Parameters          | Subject 6 | Subject 7 |
|---------------------|-----------|-----------|
| $G_b$ (mg dl$^{-1}$) | 80        | 90        |
| $I_b$ (μU ml$^{-1}$) | 50        | 30        |
| $S_I$ ((μU/ml min$^{-1}$) | $5.50 \times 10^{-5}$ | $1.75 \times 10^{-4}$ |
| $S_G$ (min$^{-1}$)   | 0.025     | 0.035     |
| $n$                 | 0.998     | 0.925     |
| $R^2$ for glucose   | 0.98      | 0.98      |
| $R^2$ for insulin   | 0.96      | 0.96      |

The approximate normal range pancreatic responsivity of the $S_I$ ($5.0 \times 10^{-5} - 2.2 \times 10^{-3}$ (μU/ml min$^{-1}$)) and $S_G$ (0.0012-0.045 min$^{-1}$) index [13].

In case 3, the study of T2D patients using the new modified minimal model is the same as in the study of case 1 and case 2. A curve profile is shown in Figure 3. The blood glucose takes more than 1.5 h to return to the basal line even though given an insulin infusion for 5 min starting at 20 min. There is a great insulin peak from 20 to 30 min. The present model describes well the actual IVGTT test behavior and achieves the $R^2$ value of plasma glucose is 0.98 and the $R^2$ value of insulin concentration is 0.96.

In case 4, this study about the release rate of insulin from beta-cells in the pancreas by an administration of the exogenous insulin with gradually reduced infusion rates during the IVGTT operation in the T2D patients. Although the exogenous insulin was infused all the time during the IVGTT test, the plasma glucose levels decrease more than 2 h to return to baseline as shown in Figure
4. The calculation results of glucose and insulin concentration are in good agreement. The $R^2$ value for blood glucose is 0.98 and the $R^2$ value of insulin is 0.96.

**Figure 3.** Profiles of plasma glucose and insulin level are produced by modified minimal model with insulin infusion for T2D subject in the case 3, with parameters: $k = 0.109$ [min$^{-1}$], $\gamma = 0.0011$ [min$^{-1}$], $G_b = 138$ [mg/dl], $I_b = 24$ [$\mu$U/ml], $p_2 = 0.088$ [min$^{-1}$], $S_I = 8.5 \times 10^{-7}$ [$\mu$U/ml min$^{-1}$], $S_G = 0.03$ [min$^{-1}$], $u(t) = 50$ (mU/kg body weight) at $20 \leq t \leq 25$ min, $n = 0.980$, $R^2$ for glucose = 0.98 and $R^2$ for insulin = 0.96.

**Figure 4.** Profiles of plasma glucose and insulin level are produced by modified minimal model with insulin infusion for T2D subject in the case 4, with parameters: $k = 0.13$ [min$^{-1}$], $\gamma = 0.0004$ [min$^{-1}$], $G_b = 131$ [mg/dl], $I_b = 20$ [$\mu$U/ml], $p_2 = 0.01$ [min$^{-1}$], $S_I = 4.5 \times 10^{-7}$ [$\mu$U/ml min$^{-1}$], $S_G = 0.0225$ [min$^{-1}$], $u(t) = 3.5$ mU/(kg min) (at 2-4 min); 0.5 mU/(kg min) (at 7-17 min); 0.25 mU/(kg min) (at 17-50 min); 0.1 mU/(kg min) (at 50-300 min), $n = 0.999$, $R^2$ for glucose = 0.98 and $R^2$ for insulin = 0.96.

The parameters estimation of $S_I$ and $S_G$ index for healthy and diabetic subjects with additional insulin infusion shown in Table 3. This study showed that healthy subjects had higher $S_I$ and $S_G$ index than diabetic subjects during an IVGTT, nevertheless, basal glucose was lower in healthy subjects than
diabetic subjects. The parameters estimation was not in the interval from normal ranges of the $S_I$ and $S_G$ index.

Table 3. Parameters Estimation of The New Modified Minimal Model for Diabetic (T2D) Subject with an Insulin Infusion.

| Parameters | Case 3       | Case 4       |
|------------|--------------|--------------|
| $G_0$ (mg dl$^{-1}$) | 138          | 131          |
| $I_0$ (μU ml$^{-1}$) | 24           | 20           |
| $S_I$((μU/ml) min$^{-1}$) | $8.50 \times 10^{-7}$ | $4.5 \times 10^{-7}$ |
| $S_G$ (min$^{-1}$) | 0.03         | 0.0225       |
| $n$          | 0.980        | 0.999        |
| $R^2$ for glucose | 0.98        | 0.98        |
| $R^2$ for insulin | 0.96        | 0.96        |

The approximate normal range pancreatic responsivity of the $S_I$ $(5.0 \times 10^{-5} - 2.2 \times 10^{-3}$ (μU/ml) min$^{-1}$) and $S_G$ $(0.0012 - 0.045$ min$^{-1}$) index [13].

4. Conclusions

The human body is much too complex to model in its entirety so that every model will necessarily require some simplifications and assumptions. The challenges of creating a model of this complex disease are equal by the challenges in designing an appropriate and predictive physiological of the human body. In the disease model, the researcher must make assumptions of physiological of the human body just to analysis which of these variations of tissues are likely to affect the hypothesis of the disease being examined.

The new modified minimal model is used to extend the capabilities of the minimal model to the diagnostic of patients with very low beta-cell sensitivity, including NGT and T2D subjects, by giving an exogenous insulin infusion. This is aiming for improved parameters estimation of $S_I$ and $S_G$, especially for the T2D subject with very low beta-cell sensitivity. An exogenous insulin infusion is applied to extend the range of subjects in which the minimal model can commonly be used, this model is still limited to using data from an IVGTT.

During the IVGTT test, the interaction of glucose-insulin shows a great difference between NGT and T2D patients. Hence, the new modified minimal model with an $n$-order decay rate of plasma insulin function process is proposed for simulating the plasma glucose and insulin profiles, not only for healthy humans but also for type 2 diabetic subjects, especially with the addition of a different insulin infusion rates. The $R^2$ value of between experimental data and calculation results are above average 0.95, this indicates the simulation results are the good agreement. It also indicates that modify the classic minimal model improves the model more flexible.

Acknowledgments

This research was funded by Direktorat Riset dan Pengabdian Masyarakat Direktorat Jenderal Penguatan Riset dan Pengembangan Kementerian Riset, Teknologi dan Pendidikan Tinggi sesuai dengan Perjanjian Pendanaan Penelitian dan Pengabdian kepada Masyarakat Tahun Anggaran 2018 Nomor: 1624/IT3.11/PN/2018 tanggal 21 Februari 2018.

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