Study of Parameters Estimation of the Oral Glucose Tolerance Test Model with The Incretin Effects using Particle Swarm Optimization Algorithm

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Abstract. This study used the coupled ordinary differential equations to model the phenomenon of the results of the oral glucose tolerance test (OGTT). This research has two main challenges, such as (1) implementing the OGTT model with incretin effect and (2) estimating the present model parameters. Both challenges often make calculations difficult. The OGTT equations are formed by the coupled ordinary differential equations to describe the behaviour of the glucose-insulin dynamic system in the body. While the particle swarm optimization (PSO) algorithm is used as a tool to obtain parameter estimates of the ordinary differential equations effectively. This research proves that the PSO algorithm that has been applied to calculate the parameters is a simple and efficient method for the OGTT model with the incretin effect. The PSO algorithm is proven to be accurate, its accuracy is indicated by the $R^2$ value. The $R^2$ value of all simulations proved to be above 90%.

1. Introduction
This study will develop an oral minimal model of glucose and insulin for impaired glucose tolerance (IGT) and type 2 diabetes mellitus (T2DM) based on a physiological model for subjects with normal glucose tolerance (NGT). The original minimal model considered the interaction of glucose and insulin in regulating blood glucose [1]. The present model will develop the original minimal model by adding a function of glucose absorption in the gastrointestinal tract. This model will also include the effects of the incretin hormone on pancreatic insulin secretion followed by oral glucose intake [2, 3]. The parameters of the present model will be estimated. Estimation of the parameters of this modified model was obtained by the PSO algorithm [4, 5], then the results of the estimation of the parameters of this model were validated using available literature data for the subject of NGT, IGT, and T2DM [6]. Estimation of the parameters of this model can be used to calculate the level of incretin effect which is useful for diagnosing prediabetes patients and also for obtaining further information about the patient's medical status.
2. Methods

2.1. Oral glucose tolerance test (OGTT) model

In the OGTT procedure, the patient is given a glucose bolus of 75 g after fasting for 8-10 hours, then a blood sample is drawn before the test, as basal glucose data, and after that, a blood sample is drawn every 30 or 60 minutes for 2 or 3 hours. A two-hour OGTT experiment will allow us to obtain important clinical features. These OGTT data are an important diagnostic tool, and also show the amount of glucose in the bloodstream recorded for two hours after the ingestion of a 75 g glucose bolus. These OGTT data also make it possible to assess a patient's glucose tolerance. Patients were assumed to be an NGT subject if their fasting or basal glucose concentrations were in the range of 80 to 110 mg/dl after two hours of the OGTT test. However, if they had basal glucose values in the range of 100 to 130 mg/dl after fasting, they were an IGT subject. Patients were considered a T2DM subject if the basal glucose value was in the range of 120 to 150 mg/dl after 2 hours of the test.

The present modified model will be developed to fit the oral minimal model and in order to describe the physiological OGTT process [3, 7]. A glucose consumption is usually modelled using a function called glucose absorption rate ($R_a(t)$). This function can be modelled as a linear continuous function but this function obtains accurate results based on complex models. This piecewise continuous function will be used in this study. Although this function requires a number of parameters to describe the appearance of glucose, these existing parameters increase the complexity of the model.

This modified model is based on the glucose compartment of the minimal model for the intravenous glucose tolerance test (IVGTT) which is modified by adding the $R_a(t)$ function so that the following equation:

$$\frac{dG(t)}{dt} = -(p_1 + X(t)G(t)) + p_1G_b + \frac{R_a}{V_G}G(0) = G_b$$

$$\frac{dX(t)}{dt} = -p_2X(t) + p_3(I(t) - I_b), X(0) = 0$$

where $G(t)$ (mg/dl) is a variable that shows the concentration of plasma glucose, $X(t)$ (1/min) is a variable that shows a remote insulin compartment, while $I(t)$ (µU/ml) is a variable that shows the concentration of plasma insulin. $G_b$ (mg/dl) and $I_b$ (µU/ml) are parameters that indicate the concentrations of basal glucose and basal insulin. $V_G$ (L) is a constant indicating the volume distribution of glucose.

The rate function of the absorption of glucose in plasma ($R_a(t)$) (mg/min) can be assumed to be a linear gradual function with $n$ as the sub-domain expressed as follows:

$$R_a(t) = \begin{cases} a_i + \frac{a_i-a_{i-1}}{t_i-t_{i-1}}(t-t_{i-1}), & t_{i-1} \leq t \leq t_i \\ 0, & \text{otherwise} \end{cases}$$

where $t_i, i = 1, ..., n$, is the time of glucose absorption and the initial time is $t_0 = 0$, while the parameter of glucose absorption amplitude is $a_0 = 0$ and $a_i, i = 1, ..., n$, is the parameter to be estimated from the glucose experimental data. $R_a(t)$ is assumed to be equal to the dose fraction of glucose digested and actually absorbed. This fraction is usually estimated to be equal to 86% of the total ingested glucose dose.

2.2. The incretin effect model

The incretin effect represents a unique stimulus of insulin secretion in response to oral glucose ingestion. In this study, the incretin effect will be calculated by the difference in the response to insulin secretion from OGTT in response to oral glucose consumption. The incretin hormone is secreted in the gastrointestinal (GI) tract. Two incretin hormones that have been identified are glucose-
dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1). Incretin hormone is estimated to have contributed about 50%-70% of insulin secretion in NGT subject after consuming glucose orally, whereas this hormone only contributes only 10%-30% in T2DM patients [2]. Because in many clinical studies, the incretin effect can be calculated from the glucose concentration profile during OGTT, this research needs to develop an OGTT model that can be used to calculate the incretin effect from OGTT data.

Physiologically, the incretin hormone is the main stimulus for insulin secretion after the body consumes glucose orally. A model of the incretin effect has been developed to explain glucose-insulin dynamics during OGTT. Although some models still have some limitations, this is due to limited data on incretin hormones, especially those derived from clinical data, these models have included the relationship between incretin hormone, insulin, and the rate of glucose in the GI. A mathematical model of glucose dynamics that includes the effects of the incretin hormone has been introduced by Brubaker and co-authors which has been used to measure the response to oral glucose ingestion of 50 g or 100 g [2]. This model consists of three ordinary differential equations describing the dynamics of plasma glucose, insulin, and the hormone incretin during OGTT. Apart from these three equations, the model also consists of glucose uptake from the GI tract and glucose balance in the liver.

In this study, the glucose absorption function in the GI was modified according to the oral glucose consumption of 75 g [8]. This function represents the transfer of glucose to the duodenum (DuodG (mM/min)). This function also calculates the secretion rate of incretin hormone and the glucose absorption rate into the mesenteric circulation so that it can describe the kinetics of glucose. The equation of this modified model is explained as follows:

\[
Duod_G = \begin{cases} 
0, & t < 5 \text{ min} \\
5.1014 - 0.0304t, & 5 \leq t \leq 166.1 \\
0, & t > 166.1 
\end{cases}
\]

\[
\int_5^{166.1} Duod_G(75\text{g load})dt = 414.27\text{ mM} = 74.58\text{ g}
\]

The equation that describes the concentration of the incretin hormone (Inc (ng/L)) based on the GIP concentration during OGTT follows the following equation:

\[
\frac{dInc(t)}{dt} = \frac{Ra_{inc}}{V} + k_1Duod_G - k_2Inc(t)
\]

\[
Ra_{inc} = k_2VInc_b
\]

where \(V\) (L) is a constant indicating twenty percent of the weight of each subject. \(Ra_{inc}\) (ng/min) is a parameter indicating the basal incretin rate and \(Inc_b\) (ng/L) is a constant indicating the basal incretin concentration determined from the average fasting GIP total of all subjects. Whereas \(k_2\) (min\(^{-1}\)) is a parameter indicating Inc degradation and \(k_1\) (ng/L/mM) is a parameter indicating an increase in rate due to \(Duod_G\). In this study, the estimation of these parameters will be determined by the PSO algorithm.

2.3. The insulin secretion model
In this study, the modified insulin concentration kinetics equation based on the literature from Brubaker and co-authors has several rate parameters [2]. This rate parameters describe the effect of insulin kinetics in the human body. This model equation was also modified with the addition of pancreatic insulin secretion (\(R_i\)) from Seike and co-authors [3]. The modified equation will be used to describe the dynamic insulin secretion (\(R_{i1}\)) and the static insulin secretion (\(R_{i2}\)). The rate of change in insulin plasma concentration can be represented as follows:

\[
\frac{dI(t)}{dt} = k_3G(t) + k_4Inc(t) - k_5I(t) + \beta + R_i
\]
where $k_3$ is a parameter that shows the rate of insulin caused by the second effect of glucose, while $k_4$ is a parameter that shows the insulin secretion caused by the incretin hormone in beta cells and $k_5$ is a parameter that shows the cleansing of insulin from the circulation. The $\beta$ constant is the amount of stimulatory input an inhibiting factor in the $R_{I1}$ beta cells, this indicates the insulin secretion which beta cells can release rapidly in response to increased glucose levels. These equations can be expressed as follows:

$$R_{I1} = R_{I1} + R_{I2}$$  \hspace{1cm} (9)

where $R_{I2}$ is a parameter indicating the sensitivity of dynamic insulin secretion by beta cells while $R_{I2}$ is a parameter indicating insulin secretion in response to incretin stimulation since the increase in glucose levels. The equation can be expressed as:

$$R_{I1} = \begin{cases} 
\frac{dG(t)}{dt} & \text{if } \frac{dG}{dt} > 0 \\
0 & \text{if } \frac{dG}{dt} < 0 
\end{cases}$$  \hspace{1cm} (10)

where $p_{i2}$ is a parameter indicating the sensitivity of dynamic insulin secretion by beta cells while $R_{I2}$ is a parameter indicating insulin secretion in response to incretin stimulation since the increase in glucose levels. The equation can be expressed as:

$$R_{I2} = \begin{cases} 
-\frac{1}{p_{i3}} \left( R_{I2} - Inc \cdot p_{i4} (G(t) - G_b) \right), & G(t) > 0 \\
0, & \text{otherwise} 
\end{cases}$$  \hspace{1cm} (11)

where $p_{i4}$ is a parameter indicating the sensitivity of static insulin secretion by beta cells because the increase in glucose levels and $p_{i3}$ is a parameter that shows a time constant while $Inc$ is a basal incretin.

2.4. The particle swarm optimization (PSO) algorithm

The coupled ordinary differential equations used to construct a fundamental model will face two major challenges, that is the application of the appropriate model and the estimation of the parameters of the selected model. The latter problem often proves difficult or requires computation complexity [9-15]. In this study, the PSO algorithm will be implemented to estimate model parameters, because this method is simple and efficient and can adjust the model and data. This algorithm will show significant effectiveness for calculating the parameter estimates of the OGTT model.

The PSO is an algorithm for estimating the parameters of an equation inspired by the social behaviour of a flock of birds. In general, each bird has a role as a particle. The PSO is a population-based estimation process, the particles are initialized according to a population of random solutions, then grouped into several best solution populations. Each particle in the swarm represents the best candidate solution for the estimation problem, if the solution consists of a set of parameters, then the particles can be a parameter vector.

In the PSO algorithm, each particle will be scattered in the multi-dimensional search space and its position in the search space is ascertained according to its momentum and global memory. Therefore, the particle will take advantage of the best position faced by itself and its neighbours to position itself towards the optimal estimate. At each iteration, the velocity of each particle will be calculated and then the new position of each particle will be calculated using the following equation:

$$v_i(t + 1) = \omega v_i(t) + c_1 r_1 (p_{id} - x_i(t)) + c_2 r_2 (p_{gd} - x_i(t))$$ \hspace{1cm} (12)

$$x_i(t + 1) = x_i(t) + v_i(t + 1)$$ \hspace{1cm} (13)
where \( t \) represents the current step number, \( \omega \) represents the inertia weight, \( c_1 \) and \( c_2 \) represent the acceleration constants, \( r_1 \) and \( r_2 \) represent two random numbers in the range \([0,1]\), \( x(t) \) represents the current position of the particle, \( p_{id} \) represents the best one of the solutions this particle has reached, and \( p_{gd} \) represents the best one of the solutions all the particles have reached. The PSO algorithm will repeat estimations of the update equations above until a stopping criterion if the best solution has been reached. The outline of a present PSO algorithm is as follows:

**Algorithm** Particle Swarm Optimization

```matlab
% The estimated parameters of the OGTT model
glucose_exp_data = load('glucose_data.txt');
incretin_exp_data = load('incretin_data.txt');
isulin_exp_data = load('insulin_data.txt');
uppar = [Gb, Ib, Incb, p1, p2, p3, k1, k2, k3, k4, k5];
lowpar = [Gb, Ib, Incb, p1, p2, p3, k1, k2, k3, k4, k5];
N = maximum of particles;
M = maximum of iteration;
N = zeros(N,11);
V = zeros(N,11);
% Initializing swarm and velocities
for i = 1 : N
    for j = 1 : 11
        X(i,j) = (uppar(j)-lowpar(j)).*rand+lowpar(j);
        V(i,j) = 4*rand;
    end
end
[line, colom] = size(X);
for i = 1 : N
    Gb = X(i,1);
    Ib = X(i,2);
    Incb = X(i,3);
    p1 = X(i,4);
    p2 = X(i,5);
    p3 = X(i,6);
    k1 = X(i,7);
    k2 = X(i,8);
    k3 = X(i,9);
    k4 = X(i,10);
    k5 = X(i,11);
    Xhimel = X; Vhimel = V;
    Xhimel = Xhimel + Vhimel;
    for i = 1 : N
        for j = 1 : 11
            if lowpar(j) <= Xhimel(i,j) && Xhimel(i,j) <= uppar(j)
                X(i,j) = Xhimel(i,j);
            else
                X(i,j) = X(i,j);
            end
        end
    end
    rhomax = 0.9; rhomin = 0.4;
```
% procedure PSO
for it = 1: M
    rho(it) = rhomax - ((rhomax - rhomin)/M)*it;
end
it = 1;
Pbest = X;
fbest = errorG_kuadrat
[minf,idk] = min(errorG_kuadrat);
Gbest = X(idk,:);
M = M 
while it < M
    iteration = it
    r1 = rand; r2 = rand;
    for i =1: line
        Vhimel(i,:) = rho(it).*Vhimel(i,:) + r1.*(Pbest(i,:)
        Xhimel(i,:) = Xhimel(i,:) + Vhimel(i,:);
    end
    for i = 1 : N
        for j = 1:11
            if lowpar(j) <= Xhimel(i,j) && Xhimel(i,j) <= uppar(j)
                X(i,j) = Xhimel(i,j);
            else
                X(i,j) = X(i,j);
            end
        end
    end
    parameter;
    fitness = fitness'.
end

3. Results and Discussion
In this study, the OGTT experimental data is believed to be in accordance with the OGTT model which is composed of coupled ordinary differential equations. This model has initial parameters and values (some known, some unknown) as input and output equations. Then the results of model calculations can be compared with experimental data using a deterministic coefficient ($R^2$), this is necessary to determine the validation value between this model and the OGTT experimental data which is formulated as follows:

$$R^2 = 1 - \frac{X^2}{SST} \times 100\%$$  \hspace{1cm} (14)

where $X^2$ and SST are:

$$X^2 = \sum_{i=1}^{N} (y_{expi} - y_{simi})^2$$  \hspace{1cm} (15)

$$\bar{y} = \sum_{i=1}^{N} (y_{simi} + y_{expi}) / 2N$$  \hspace{1cm} (16)

$$SST = \sum_{i=1}^{N} (y_i - \bar{y})^2$$  \hspace{1cm} (17)
where $y_{\text{exp}}$ is experimental data, $y_{\text{sim}}$ is the simulation results of the OGTT equations and $\bar{y}$ is the averaged data.

One of the advantages of the PSO algorithm, if the vector of unknown inputs to be a position within search space, then the error function selection is the main consideration on the PSO algorithm in order to minimize an error on the model simulation. The deterministic coefficient ($R^2$) on the particle deviations will inclined to decrease larger deviations over smaller ones. The behaviour of an OGTT model is very influenced by parameters, accordingly, it is here that the PSO algorithm is used as model fitting techniques to derive these parameters from data. Their initial and ranges parameters are listed in Table I.

3.1. Normal glucose tolerance (NGT)
The simulation results of the parameter estimation of an OGTT model using PSO for the glucose, incretin and insulin concentration of an NGT Japanese subject are obtained good results as shown by the correlation $R^2$ value. The $R^2$ value results of data fitting are more than 90%. The parameter estimation value for $G_b$ using PSO algorithm is 85 mg/dl, this value shows the $G_b$ range of NGT subject.

![Figure 1. The Simulation Result of Glucose Concentration on Normal Japanese Subject.](image-url)
Figure 2. The Simulation Result of Incretin Concentration on Normal Japanese Subject.

Figure 3. The Simulation Result of Insulin Concentration on Normal Japanese Subject.
Figure 1 also shows the ability of glucose absorption without insulin is good. In the glucose concentration, there is a turbulence of oral glucose, so the glucose level slowly increased until 50 min, then it decreased after 50 min until 180 min and back to a glucose basal level at 300 min. If the insulin sensitivity is high value, then an ability of insulin to accelerate the losing glucose from plasma is good, as shown in Figure 3. The rate of insulin concentration will increase until 60 min, after oral glucose intake to an NGT subject and it will slowly decrease until 300 min. This study also determines the parameter value of the incretin hormone which is represented by $I_{incb}$. The $I_{incb}$ parameter value using the PSO algorithm is 300 ng/dl. The $I_{incb}$ value is more than 200 ng/dl, it is according to a normal subject. This parameter can show that the response of incretin hormone fast, so insulin secretion is also fast, as shown in Figure 2. The rate of incretin concentration increases at interval 0-60 min, after that it slowly decrease after 90 min.

| Estimated parameters | Lower bound | Upper bound |
|----------------------|-------------|-------------|
| $G_b$                | 80.0        | 150.0       |
| $I_b$                | 8.0         | 11.0        |
| $I_{ncb}$            | 100.0       | 300.0       |
| $p_1$                | 0.02        | 0.04        |
| $p_2$                | 0.002       | 0.03        |
| $p_3$                | $10.0 \times 10^{-4}$ | $25.0 \times 10^{-4}$ |
| $k_1$                | 2.5         | 2.6         |
| $k_2$                | 0.01        | 0.02        |
| $k_3$                | 0.01        | 0.04        |
| $k_4$                | 0.002       | 0.005       |
| $k_3$                | 1.2         | 3.0         |

3.2. Impaired glucose tolerance (IGT)
The parameter results of an OGTT model using the PSO algorithm for the glucose, incretin, and insulin concentration of pre-diabetes Japanese subjects show the good result as shown by the correlation $R^2$ value. The value results of fitting data which is represented by $R^2$ value is more than 90%. The parameter value of $G_b$ in this simulation is 117 mg/dl, it is still categorized as pre-diabetes because of an according to the $G_b$ value range for a pre-diabetes subject. It means that this simulation result is quite good to determine the $G_b$ value simulation. This simulation also calculates the parameter value of incretin hormones for pre-diabetes subject using the PSO algorithm, the parameter value is 180 ng/dl. This parameter can represent a pre-diabetes subject since it is less than 200 ng/dl. This parameter will show that response incretin hormones to insulin secretion from beta-cells in the pancreatic is slower than the normal subject, as shown in Figure 5. The rate of incretin concentration increases from 0-120 min, and then it decreases after 150 min.

![Simulation Result of Incretin Concentration on Prediabetes (IGT) Japanese Subject.](image)

**Figure 5.** The Simulation Result of Incretin Concentration on Prediabetes (IGT) Japanese Subject.
3.3. Type 2 diabetes mellitus (T2DM)

Figure 6. The Simulation Result of Insulin Concentration on Prediabetes (IGT) Japanese Subject.

Figure 7. The Simulation Result of Glucose Concentration on Diabetic (T2DM) Japanese Subject.
Figure 8. The Simulation Result of Incretin Concentration on Diabetic (T2DM) Japanese Subject.

Figure 9. The Simulation Result of Insulin Concentration on Diabetic (T2DM) Japanese Subject.
The parameter value for $G_b$ using the PSO algorithm is 140 mg/dl, this value shows a value for the T2DM subject. In this simulation, the $G_b$ value is higher than the pre-diabetes subject. While the value of the incretin hormone parameter is 115 ng/dl, it is less than an incretin hormone normal (200 ng/dl). All values of those parameters can be categorized as a T2DM subject. All parameter estimation can be calculated from fitting Figures 7, 8 and 9.

4. Conclusions
The mathematical model of the present OGTT can be modified with the incretin effect. For calculating the estimation of the parameters of this present model equations are used the PSO algorithm since the PSO is much simpler to implement. The PSO also has the advantage that it does not require the assumption of the initial values of the model parameters and can achieve a high degree of accuracy to estimate the eleven parameters and this accurate result of predictions. It is shown by the $R^2$ value of all simulations have reached above 90%. The PSO algorithm can be applied to give a diabetic feature data from OGTT data that are three features of subjects, such as normal, pre-diabetes, and T2DM.

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