Optimization of Insulin Sensitivity and Glucose Effectiveness Index from an Oral Glucose Tolerance Test Using Modified Oral Minimal Model and Gravitational Search Algorithm

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Abstract

The aim of the study was to develop a combination of the modified oral minimal model (OMM) and gravitational search algorithm (GSA) method for optimization of insulin sensitivity (SI) and glucose effectiveness (SG) index from an oral glucose tolerance test (OGTT). The OGTT was the clinical test used to examine glucose tolerance under exogenous glucose load. The OGTT was defined as a diagnostic criterion of diabetes mellitus. After overnight fasting, the subject receives glucose orally and blood samples are taken frequently sampled over a period of 300 minutes. Then, the modified OMM and GSA method to an OGTT data from 120 subjects showed its ability to provide precise optimization of the SI and SG index. The optimization of SI and SG index using the modified OMM and GSA method shown its applicability to understanding fundamental mechanisms of the OGTT experimental data. It was further assessed using the calculated coefficient of determination, $R^2$, from parameter optimizer and the majority of the parameters, were matched to known experimental data. The averaged $R^2$ value between measured and calculated plasma concentrations is 0.920, which indicates agreement with experimental data. The modified OMM and GSA method appeared a
suitable tool to measure the $S_I$ and $S_G$ index during an oral test applicable in the diabetic medical test.

**Mathematics Subject Classification:** 34K28, 92-08

**Keywords:** Diabetic; Glucose kinetics; Parameter estimation; Rate of appearance of glucose

1 Introduction

In type 2 diabetes mellitus, glucose homeostasis was tightly maintained through the $S_I$ and $S_G$ index. Therefore, finding an accurate method to assess the $S_I$ and $S_G$ index using clinically available data would enhance the quality of diabetic medical care.

The measurement of the $S_I$ and $S_G$ index, which quantifies insulin's ability to control glucose production and utilization, was of primary importance in the assessment of glucose regulatory system efficiency. This index was useful not only for diagnostic purposes but also to evaluate the efficacy of therapy. Quantitative evaluation of this index was usually accomplished with methods involving an intravenous administration of glucose and or insulin, such as the glucose clamp or the intravenous glucose tolerance test (IVGTT) and minimal model (MM) technique [1]. Difficulty in the intravenous administration and high (non-physiological) levels of glycemia and insulinemia achieved during these tests were limitations that need to be resolved. Measurement of the $S_I$ and $S_G$ index of oral tests, such as a meal glucose tolerance test (MGTT) or an oral glucose tolerance test (OGTT), would be better suited to normal life condition. Models for interpretation of data from oral tests, however, enhance the difficult problem of estimating the rate of appearance into plasma, $R_\alpha$, of glucose taken by mouth and absorbed from the gastrointestinal tract [1]. In the present study, a model of the gut was used to describe the conversion into $R_\alpha$ of glucose ingested during an OGTT. This gut model was coupled to the MM of glucose kinetics to set up a suitable tool for estimating $S_I$ and $S_G$ index associated with a rate constant of glucose absorption from the gut. Therefore, it would be highly desirable to have a method able to quantify $S_I$ and $S_G$ index under normal life conditions, e.g., during a meal. Incidentally, an oral test would be more suitable than an intravenous test for use in epidemiological studies involving hundreds, if not thousands, of individuals.

Gravitational search algorithm (GSA) method was a heuristic optimization algorithm which had been gaining interest among the scientific community recently. The GSA is a nature-inspired algorithm which is based on the Newton's law of gravity and the law of motion [2]. The GSA is grouped under the population-based approach and was reported to be more intuitive [3]. The algorithm was intended to improve the performance in the exploration and exploitation capabilities of a population based algorithm, based on gravity rules. However, recently GSA had been criticized for not genuinely based on the law of
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Gravity [4]. The GSA was reported to exclude the distance between masses in its formula, whereas mass and distance were both integral parts of the law of gravity. Despite the criticism, the algorithm was still being explored and accepted by the scientific community.

The purpose of this study was to explore the modified OMM and GSA method in order to determine the reliability of the oral-based index of $S_I$ and $S_G$ from OGTT experimental data, this parameter was also compared with the $S_I$ and $S_G$ index estimated from an OGTT test performed in the normal subjects. The OGTT was a common clinical test used to examine glucose tolerance under exogenous glucose load. This test was conducted in the morning after overnight fasting. At first, a fasting blood sample was taken. Then, the subject receives glucose orally and blood samples were taken again. The sampling schedules depend on the purpose of the test. For instance, glucose concentration at 120 min was defined as a diagnostic criterion of diabetes mellitus, where oral glucose load was applied at time 0 [1]. In this paper, the clinical data from the OGTT experimental from 120 subjects in various stages of glucose tolerance were analyzed to evaluate the optimal accuracy.

2 Materials

This study included 120 subjects enrolled at Tokyo University Hospital in Japan (of Japanese background for at least three generations). The 120 subjects were stratified according to glucose tolerance state (normal glucose tolerance (NGT), impaired glucose tolerance (IGT), or type 2 diabetes mellitus (T2DM), as defined by WHO criteria). Briefly, all subjects received an oral bolus corresponding to 75 g of glucose. Plasma samples were collected at times 0, 10, 20, 30, 60, 90, 120, 150, 180, 240, and 300 minutes for determination of plasma glucose and serum insulin, and were assayed at the Uni-labs laboratory, Copenhagen, Denmark uses validated methods [5].

3 Methods

3.1 Modified Oral Minimal Model

The present model consisted of the modified MM of glucose kinetics [6] coupled with a mono-compartmental description of the conversion of food into the rate of glucose appearance into plasma, $R_a$. The model equations were:

$$\frac{dG(t)}{dt} = -[p_1 + X(t)]G(t) + p_4G_b + \frac{R_a}{V}, \quad G_0 = G_b,$$  \hspace{1cm} (1)

$$\frac{dX(t)}{dt} = -p_3(t) + p_3[I(t) - I_b], \quad X_0 = 0,$$  \hspace{1cm} (2)
where \( R_a(t) \) was the generic expression for the rate of entry of exogenous glucose into the systemic circulation per unit body weight (BW) (milligrams per kg/minute). During the OGTT, \( R_a(t) \) coincides with the impulse injection of a glucose dose (milligrams per kg) and the rate of absorbed glucose.

Variables/parameters of the modified OMM were described: \( G(t) \) was the plasma glucose concentration (milligrams per deciliter (mg/dl)), with \( G_b \) denoting its basal glucose; \( X(t) \) was insulin action (minutes\(^{-1}\)) exerted on glucose disposal from an insulin compartment remote from plasma; \( I(t) \) was the plasma insulin concentration (microunits per ml (μU/ml)), with \( I_b \) denoting its basal insulin; \( V \) was the glucose distribution volume per unit BW (millilitres per kg (ml/kg)). Parameter \( p_1 \) represented the fractional ability of glucose to lower its own concentration in plasma. Parameter \( p_2 \) (minutes\(^{-1}\)) governed the speed of rising and decay of insulin action, and \( p_3 \) (minutes\(^{-2}\) per μU/ml) governed its size.

Insulin was cleared from the plasma compartment at a rate proportional to the amount of insulin in the plasma compartment. The modified OMM for insulin kinetics was given by the ordinary differential equations [6]:

\[
\frac{dI(t)}{dt} = \gamma(G(t) - G_b) - k(I(t) - I_b), \quad I_0 = I_b, \quad \text{if } G(t) > G_b \tag{4}
\]
\[
\frac{dI(t)}{dt} = -k(I(t) - I_b), \quad I_0 = I_b, \quad \text{if } G(t) < G_b. \tag{5}
\]

where \( k \) was the insulin clearance fraction, \( G_b \) was the basal glucose level, and \( \gamma \) was a measure of the secondary pancreatic response to glucose.

The modified OMM parameter's \( p_1, p_2, p_3, \) and \( V \) were estimated by GSA method from glucose data collected during an OGTT data. As was usual, measurements from the first 10 min after glucose was ignored in model identification. The \( S_I \) index, milliliters per kg/minute μU/ml, was calculated as:

\[
S_{I(OGTT)} = \frac{P_3}{P_2} V = S_I V. \tag{6}
\]

The \( S_I \) (OGTT) index was the modified OMM fractional (i.e. per unit volume) index, \( S_I \), multiplied by the glucose distribution volume, \( V \). So defined, \( S_I \) (OGTT) had the same units of the analogous clamp index. Parameter \( p_1 = S_G \) was glucose effectiveness: a measure of the fractional ability of glucose to lower its own concentration in plasma independent of increased insulin.
3.2 Gravitational Search Algorithm

GSA was a novel heuristic optimization method which has been proposed by E. Rashedi and co-worker in 2009 [2]. The basic physical theory which GSA was inspired from being the Newton’s theory that states: Every particle in the universe attract every other particle with a force that was directly proportional to the product of their masses and inversely proportional to the square of the distance between them.

GSA could be considered as a collection of agents (candidate solutions) whose have masses proportional to their value of the fitness function. During generations, all masses attracted each other by the gravitational forces between them. A heavier mass had the bigger attraction force. Therefore, the heavier masses which were probably close to the global optimum attract the other masses proportional to their distances.

The GSA was mathematically modeled as follows. Suppose a system with \( N \) agents. The algorithm starts with randomly placing all agents in the search space. During all epochs, the gravitational forces from agent \( j \) on agent \( i \) at a specific time \( t \) was defined as follows:

\[
F_{ij}^d(t) = G(t) \cdot \left( \frac{M_{pi}(t) \times M_{aj}(t)}{R_{ij}(t)} + \varepsilon \right) \cdot \left(x_i^d(t) - x_j^d(t)\right),
\]

(7)

\( F_{ij}^d(t) \) was the force acting on agent \( i \) from agent \( j \) at \( d^{th} \) dimension and \( i^{th} \) iteration. \( M_{pi} \) and \( M_{aj} \) were the active and passive gravitational masses respectively, while \( M \) was the inertia mass of the \( j^{th} \) agent. \( R_{ij}(t) \) was the Euclidian distance between two agents \( i \) and \( j \) at iteration \( t \). \( G(t) \) was the computed gravitational constant at the same iteration while \( \varepsilon \) was a small constant. The gravitational constant \( G(t) \) was computed at iteration \( t \),

\[
G(t) = G_0 \times \exp\left(-\alpha \times \frac{\text{iter}}{\text{max iter}}\right),
\]

(8)

where \( \alpha \) and \( G_0 \) are descending coefficient and initial value respectively, \( \text{iter} \) was the current iteration, and \( \text{max iter} \) was the maximum number of iterations.

In a problem space with the dimension \( d \), the total force that acts on agent \( i \) is calculated by the following equation:

\[
F_i^d(t) = \sum_{j \neq k, j \neq i} \text{rand}_j \cdot F_{ij}^d(t),
\]

(9)

where \( F_i^d(t) \) was the total force acting on \( i^{th} \) agent calculated and \( \text{rand}_j \) was a random number in the interval [0,1].

According to the law of motion, the acceleration of an agent was proportional to the resultant force and inverse of its mass, so the acceleration of the \( i^{th} \) agents at iteration \( t \) should be calculated as follows:

\[
a_i^d(t) = F_i^d(t)/M_i(t),
\]

(10)
where \( t \) is a specific time and \( M_i \) is the mass of the object \( i \).

Velocity and the position of the agents in the next iteration \((t+1)\) were computed based on the following equations:

\[
v_i^d(t+1) = rand_i \times v_i^d(t) + a_i^d(t),
\]

\[
x_i^d(t+1) = x_i^d(t) + v_i^d(t+1),
\]

where \( rand_i \) was a random number in the interval [0,1].

In GSA, at first, all masses are initialized with random values. Each mass is a candidate solution. After initialization, velocities for all masses are defined using (11). Meanwhile, the gravitational constant, total forces and accelerations are calculated as (8), (9), and (10) respectively. The positions of masses are calculated using (12). Finally, GSA will be stopped by meeting an end criterion. The principle of the GSA was shown in Fig. 1.
The coefficient of determination, $R^2$, was calculated from parameter optimizations. The residuals between the best-fit curve and the data, $y_i - \hat{y}_i$, were used:

$$R^2 = 1 - \frac{\sum_{i=1}^{n} (y_i - \hat{y}_i)^2}{\sum_{i=1}^{n} (y_i - \bar{y})^2},$$

where $y$ was experimental data, $\hat{y}$ was the prediction of the non-linear least-squares fit and $\bar{y}$ was the averaged experimental data.

**4 Results**

To evaluate the performance of GSA, it was applied to the modified OMM function. In this case, the ranges of their search space and their dimensions were the $S_I$ and $S_G$ index. The experimental results are presented in Table 1. The modified OMM and GSA has been proposed that is able to optimize the $S_I$ and $S_G$ index in a given individual from plasma glucose and insulin concentration measured after an oral glucose perturbation, by simultaneously reconstructing also the rate of appearance of the absorbed glucose ($R_a$). The estimated values for plasma glucose showed a significant correlation in the reference's data [5] (see Fig.2, Fig. 3 and Fig. 4). The averaged coefficient of determination, the $R^2$ value between measured and calculated plasma glucose concentrations was 0.920, which indicates good agreement. The measurement accuracy in self-monitoring using blood-glucose meters helps us interpret these results. These meters did not show exactly the same value as that measured in a clinical testing laboratory but were, nevertheless, informative.

To optimize the $S_I$ and $S_G$ index in the OGTT experimental data, the reference values for the model input were extrapolated and interpolated from the observed glucose values. The glucose values at 300 min were assumed to have returned to the baseline levels, based on results reported from 5-h OGTTs. The values at 150-300 min were extrapolated from those at 0, 30, 60, and 120 min using GSA method. For this interpolation, GSA method was also used as one of the interpolation methods. The parameters related to insulin sensitivity were estimated by minimizing the residual sum of squares of the glucose level between the reference and the model.

There are no self-monitoring insulin meters, but the estimation of insulin would be useful. The key finding of this work is the accuracy of extrapolation values at 120 min. Accordingly, it was important to extrapolate values to 300 min. Glucose concentrations during the test do not change biophysically within a period of 50 min, and they hardly change biophysically within a period of 60 min.
after the start of the test. Thus, when values at 0, 30, 60, 100, 120, and 150 min are obtained, it is not difficult to interpolate other data points.

The values at 160 min have large variations in all patients (see Fig. 1, Fig. 2 and Fig. 3). One of the reasons was that the rate of appearance of exogenous glucose in plasma varies greatly at 160 min. Another reason was that insulin-dependent glucose uptake contributes to glucose regulation at 160 min, where the glucose levels did not return to the basal level and insulin secretion was still stimulated. Therefore, if values at 160 min could be reasonably extrapolated from values within 120 min, it means that those models could be used even from values at 0, 30, 60, and 120 min. In this 120-min, some sample protocol was expected to facilitate the model assessment of diabetes in daily practice. The distinguishing feature of the proposed procedure for the reduction of samples was that the original information of clinical data was maintained by the extrapolation. It was reported for non-diabetic subjects that the reproducibility of the model parameters was good between the full sampling and reduced sampling protocols, but it might not be accurate for diabetic patients as well as non-diabetic cases since it loses the informative variation at 160 min.

This research had validated the modified OMM against what could be considered today the state-of-art reference method for optimizing the $S_I$ and $S_G$ index during an OGTT test. In Table 1, the $S_I$ and $S_G$ index of the IGT and T2DM subjects was decreased, whereas the $S_G$ index of the T2DM subjects also was decreased, then the $G_b$ index of the IGT and T2DM subjects was increased.

![Figure 2: Profile of normal glucose tolerance (NGT), the red circle represents experiment data [5], the blue solid lines represent the results of the present model and GSA method. The coefficient of determination was $R^2 = 0.920$.](image)
Figure 3: Profile of impaired glucose tolerance (IGT), the red circle represents experiment data [5], the blue solid lines represent the results of the present model and GSA method. The coefficient of determination was $R^2 = 0.920$.

Figure 4: Profile of type 2 diabetes mellitus (T2DM), the red circle represents experiment data [5], the blue solid lines represent the results of the present model and GSA method. The coefficient of determination was $R^2 = 0.920$. 
This information was provided that the $S_I$ and $S_G$ index measured by the modified OMM and GSA method could be used diagnosis IGT and T2DM subjects. Fig. 1, Fig. 2 and Fig.3 shown that the glucose curves of subjects with NGT, IGT or T2DM were very different, suggesting that the shape included metabolic information not captured by the level of glycemia alone.

Table 1: The $S_I$ and $S_G$ index of OGTT data [5] using the modified OMM and GSA

<table>
<thead>
<tr>
<th></th>
<th>NGT</th>
<th>IGT</th>
<th>T2MD</th>
</tr>
</thead>
<tbody>
<tr>
<td>$S_I$ [ml/kg/min,μU/ml]</td>
<td>$28.21 \times 10^{-4}$</td>
<td>$11.61 \times 10^{-4}$</td>
<td>$1.94 \times 10^{-4}$</td>
</tr>
<tr>
<td>$S_G$ [min$^{-1}$]</td>
<td>0.041</td>
<td>0.034</td>
<td>0.019</td>
</tr>
<tr>
<td>$Gb$ [mg/dl]</td>
<td>81</td>
<td>100</td>
<td>125</td>
</tr>
</tbody>
</table>

5 Discussion

The OGTT was generally considered as more sensitive for the screening of impaired glycemia because it detected changes in postprandial glycemia that tended to precede changes in fasting glucose. The present results noted that a large proportion as the NGT subject screened had a very interesting glucose profile as follows: (i) while the fasting and 120-min plasma glucose concentration was below the IGT and T2DM, the 60-min glucose concentration was in contrast above 150 mg/dl, and (ii) while the fasting and 120-min plasma glucose concentration was below the and T2DM, at 60-min glucose concentration was in contrast strikingly abnormal (250 mg/dl). Conceptually, over 30–60 min after the ingestion of a bolus glucose, not several hours afterward, represented the peak point of metabolic and digestive events and therefore, potentially was a better time to choose for the detection of the earliest signs of metabolic dysfunction. Moreover, in temporal terms at least, what happened in 60-min was bound to affect the 120-min glucose concentration and not vice versa. Obviously, one way to determine the significance of the 60-min glucose concentration would be to study these subjects prospectively to determine the natural history of the glucose abnormality in relation to the development of diabetic complications.

6 Conclusion

The modified OMM and GSA method is a suitable tool to provide optimizer and related precision of the $S_I$ and $S_G$ index for the measurement of blood glucose levels during an OGTT at time points, it may help investigators in the identification of a diabetic diagnostic process which is supposed to vary with age, gender, and pathophysiological states.
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References


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