

# Minimal Modeling of Glucose-Insulin Interactions in the Intravenous Glucose Tolerance Test

<sup>1</sup>Kamariah Noor Binti Ab Kahar, <sup>2</sup>Mustafa Mamat, <sup>1</sup>Zabidin Salleh  
and <sup>2</sup>Zahrahtul Amani binti Zakaria

<sup>1</sup>Department of Mathematics, Universiti Malaysia Terengganu, Malaysia

<sup>2</sup>Faculty of Informatics and Computing, Universiti Sultan Zainal Abidin, Kampus Tembila,  
Terengganu, Malaysia.

Copyright © 2014 Mustafa bin Mamat et al. This is an open access article distributed under the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

## Abstract

The minimal model of glucose and insulin plasma levels is commonly used to analyze the results of glucose tolerance tests in humans. In this paper, a mathematical model for describing the glucose infusion rate was introduced. The minimal model was used to study a few sets of published data including healthy humans and type 2 diabetes. The glucose-insulin system as a dynamic integrated physiological system and generated the real optimized model parameters from the experimental data using the modified minimal model. The averaged  $R^2$  value between measured and calculated plasma concentrations was 0.977, which indicates excellent agreement.

**Keywords:** Minimal model, Intravenous glucose tolerance test, Glucose-insulin system

## INTRODUCTION

Human bodies need to maintain a glucose concentration level in a narrow range (70-110 mg/dl or 3.9-6.04 mmol/l after overnight fast). If one's glucose concentration level is significantly out of the normal range, this person is considered to have a plasma glucose problem: hyperglycemia or hypoglycemia. Diabetes mellitus, or simply, diabetes, is characterized by high blood glucose levels resulted from defects in the glucose-insulin endocrine metabolic regulatory system, in which either the pancreas does not release insulin, or the cells do not properly use insulin to uptake glucose.

Diabetes mellitus has become an epidemic disease in the sense of life style. To diagnose whether or not an individual subject is already a diabetic or has the potential to develop such disease, the so-called metabolic portrait, including the insulin sensitivity index and glucose effectiveness, of the subject needs to be sketched. To this end, several glucose tolerance tests have been developed and applied in clinics and experiments. The fundamental idea of such tests is to examine the response of insulin, called insulin sensitivity, after a large amount of glucose is infused into one's body. A commonly used protocol is the intravenous glucose tolerance test (IVGTT) [1].

Type 2 diabetes (for merely called non-insulin-dependent diabetes mellitus, NIDDM, or adult-onset diabetes), a more widespread metabolic disorder, is primarily characterized by insulin resistance, relative insulin deficiency and hyperglycemia. Some cases of type 2 diabetes also appear to be an autoimmune disease where the immune system attacks the  $\beta$ -cells, decreasing the function of producing insulin, while other type 2 diabetes cases may simply result from excessive body weight that strains the ability of the  $\beta$ -cells to produce sufficient insulin.

In the procedure of IVGTT, overnight fast is required for the subject, and then the subject is given a bolus of glucose infusion intravenously, for example, 0.33 g/kg body weight or 0.5 g/kg body weight of a 50% solution, and is administered into an antecubital vein in approximately 2 min. To observe the metabolic regulation between the glucose and insulin, within the next 180 min, the plasma glucose and serum insulin of the subject are sampled frequently at the time marks 2', 4', 6', 8', 10', 12', 14', 18', 21', 24', 30', 35', 40', 45', 50', 60', 70', 80', 90', 100', 120', 140', 160' and 180'. According to the rich information constituted in the sampled data, appropriate analysis can reveal the metabolic portrait.

One popular approach of the analysis is as follows: (1) formulate or choose a well-formulated kinetic model based on physiology; (2) estimate the parameters of the IVGTT model with experi-

mental data, and then (3) the parameter values are used to obtain physiological information, for example, the insulin sensitivity and glucose effectiveness [2].

The intravenous glucose tolerance test (IVGTT), as an important experimental procedure for the estimation of glucose effectiveness and insulin sensitivity, has been widely used, because it is relatively easy to measure, and its analysis generates a lot of information. The test includes injecting a glucose bolus and then collecting a set of plasma glucose and insulin samples over a period of 3-5 h. For diabetic patients, it is sometimes necessary to have an exogenous insulin infusion because of insufficient endogenous insulin secretion despite stimulation by the glucose injection.

The glucose-insulin system as an integrated dynamic system in physiology, should be described mathematically as a whole. When an integrated dynamic system is split into two interacting sub-systems, and then, the system parameters are optimized by fitting the measured data separately, the generated parameters cannot be thought as optimal ones for the whole system. In the glucose-insulin physiological system both glucose and insulin have feedback effects on each other via pancreatic response and stimulation. It is worth to obtain optimized model parameters from measured plasma glucose and insulin concentrations simultaneously in the time course by using the regression method. This single-step parameter-fitting process could generate a real optimal approximation to the dynamical integrated glucose-insulin system without losing the interaction information implicitly contained in the measured concentration profiles.

The modified minimal-model approach yields estimates of insulin sensitivity ( $S_I$ ) and glucose effectiveness ( $S_G$ ). Insulin sensitivity represents a measure of the dependence of fractional glucose disappearance. The latter term represents a measure of the fractional ability of glucose to lower its own concentration in plasma independent of increased insulin at basal insulin, to normalize its own concentration within the extracellular glucose pool. This normalization occurs after glucose administration and may involve glucose-mediated inhibition of hepatic glucose output and/or accelerated glucose disposition.

### **THE MODIFIED MINIMAL MODEL FROM THE IVGTT**

The dynamic insulin and glucose responses to glucose injection were analyzed as previously described to yield the individual parameters of the minimal model. The modified minimal model,

which we proposed as the simplest representation that can account for the dynamics of glucose during the IVGTT, is described by the following differential equations [3]:

$$\frac{dG(t)}{dt} = p_1(G_b - G(t)) - X(t)G(t), \quad G(t_0) = G_0, \quad (1)$$

$$\frac{dX(t)}{dt} = -p_2X(t) + p_3(I(t) - I_b), \quad X(t_0) = 0, \quad (2)$$

$$\frac{dI(t)}{dt} = \gamma[(G(t) - G_b)]^+ t - k(I(t) - I_b), \quad I(t_0) = I_0, \quad (3)$$

$$R^2 = 1 - \frac{\sum_{i=1}^n (y_i - \hat{y}_i)^2}{\sum_{i=1}^n (y_i - \bar{y}_i)^2}, \quad (4)$$

where  $G(t)$  and  $I(t)$  are glucose and insulin concentrations measured in plasma.  $X(t)$ , insulin action, is proportional to insulin in a compartment remote from plasma, and  $p_1$ ,  $p_2$ , and  $p_3$  are model parameters. Parameter  $p_1$  represents the fractional ability of glucose to lower its own concentration in plasma;  $p_2$  and  $p_3$  are the fractional transfer coefficients of insulin into and out of the remote compartment where it acts to accelerate glucose uptake or decrease glucose production.  $G_0$  is the glucose concentration one would obtain immediately after glucose injection if there were instantaneous mixing of glucose in the extracellular fluid compartment.  $G_b$  and  $I_b$  are the pre-injection values of glucose and insulin. Insulin sensitivity, represented as the insulin sensitivity index,  $S_I$  is calculated as  $p_3/p_2$ . Glucose effectiveness is the ability of glucose, at basal insulin, to normalize its own concentration. This latter parameter is represented as  $S_G$  and is equal to  $p_1$  as defined in equation (1). Where  $\hat{y}$  is the prediction of the least-squares fit. The residuals between the best-fit curve and the data,  $y_i - \hat{y}$ .

Glucose and insulin data [ $G(t)$  and  $I(t)$ ] are submitted to the program modified minimal model, which estimates the model parameters from the real data. This program is based on the nonlinear least-squares estimation method of Marquardt.  $I(t)$  is submitted to the program modified minimal model, which predicts a glucose time course,  $G(t)$ , which fits data  $G(t)$  as

closely as possible in the least-squares sense. In the course of the fitting, the model yields  $X(t)$ , an estimate of  $X(t)$ , as well as estimates of parameters  $p_1$ ,  $p_2$ ,  $p_3$ , and  $G_0$ .  $S_1$  ( $p_3/p_2$ ),  $S_G$  ( $p_1$ ), and the coefficient of determination  $R^2$  are calculated from model parameter estimates.

Fitting the modified minimal model of glucose disappearance to standard IVGTT data yields parameters representing glucose disappearance:  $S_I$  and  $S_G$ . The former term is a measure of the effect of the dynamic insulin response to augment glucose decline; the latter term represents the ability of glucose per se (at basal insulin) to effect its own normalization. Parameter  $S_I$ , varied from  $5.0 \times 10^{-5}$  to  $2.2 \times 10^{-3}$  ( $\mu\text{U/L})^{-1} \text{min}^{-1}$  and  $S_G$  averaged  $1.2 \times 10^{-3}$  to  $4.5 \times 10^{-2} \text{min}^{-1}$ .

To examine the veracity of the  $S_G$  value obtained from analysis of the standard IVGTT, we obtained an independent, direct measure of parameter  $S_G$  from experiments. In accordance with the modified minimal model, the rate constant for the decline in glucose when the dynamic insulin response is suppressed is equal to  $S_G$  ( $S_G = \text{half-time}/0.693$ ).

## RESULTS AND DISCUSSION

In order to exemplify the computation of the proposed stability criteria, we considered sets of parameter values consistent with adaptation to data from actual IVGTT experiments. Simulations were performed by using MATLAB ordinary differential equation solver ode45. Experimental data published in [4]. We obtained these data by manually measuring the data in related figures in [4].

In the original data sets, the time mark  $0'$  is the starting time of the bolus glucose infusion. We further departed from published work in hypothesizing that glycemia increase between the start of infusion to the first observed glycemia point follows an ascending linear ramp. Moreover, in observing that indeed the bolus glucose infusion belongs to the initial condition of the ordinary differential equation model (1)-(3).

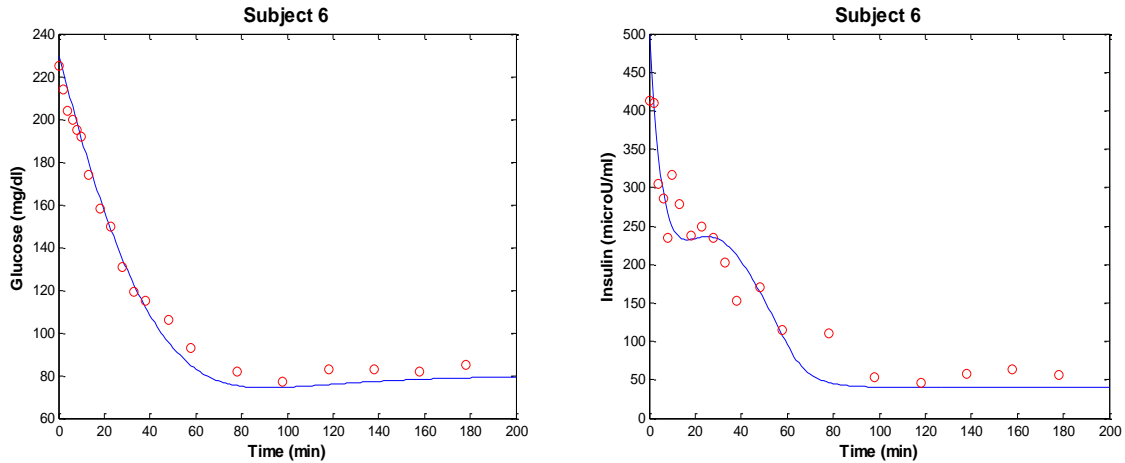


Fig. 1. Profiles of subject 6 in [4] produced by equations (1)-(4) with parameters  $k = 0.12$ ,  $\gamma = 0.015$ ,  $G_b = 80$  [mg.dl<sup>-1</sup>],  $I_b = 40$  [ $\mu$ U/ml],  $p_2 = 0.06$  [min<sup>-1</sup>],  $S_I = 6.5 \times 10^{-4}$  [ $\mu$ U<sup>-1</sup>.ml.min<sup>-1</sup>],  $S_G = 0.025$  [min<sup>-1</sup>],  $I_0 = 230$  [ $\mu$ U/ml] and  $G_0 = 500$  [mg.dl<sup>-1</sup>].

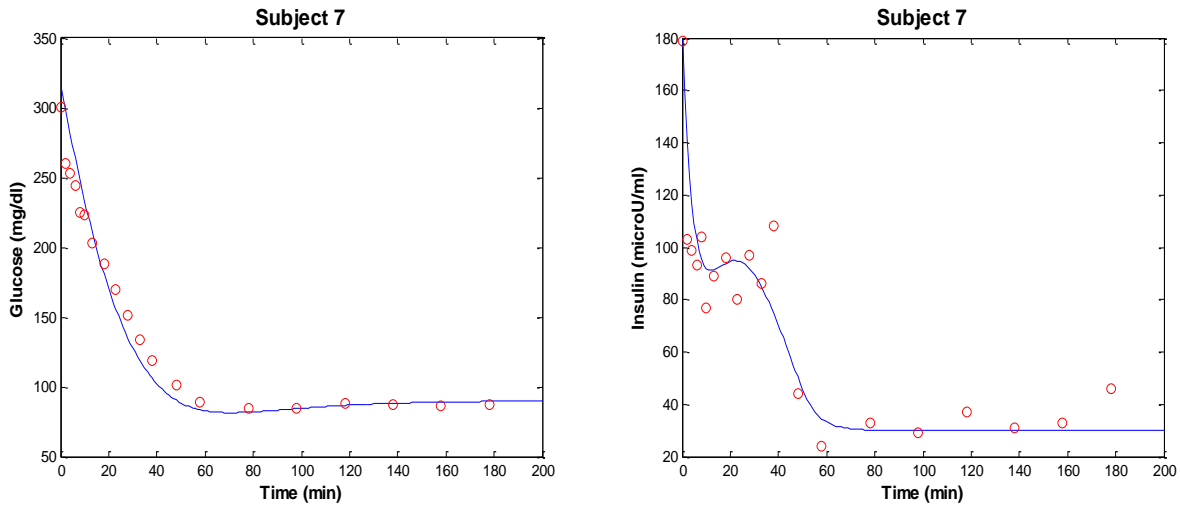


Fig. 2. Profiles of subject 7 in [4] produced by equations (1)-(4) with parameters  $k = 0.16$ ,  $\gamma = 0.0125$ ,  $G_b = 90$  [mg.dl<sup>-1</sup>],  $I_b = 30$  [ $\mu$ U/ml],  $p_2 = 0.06$  [min<sup>-1</sup>],  $S_I = 5.07 \times 10^{-4}$  [ $\mu$ U<sup>-1</sup>.ml.min<sup>-1</sup>],  $S_G = 0.035$  [min<sup>-1</sup>],  $I_0 = 180$  [ $\mu$ U/ml] and  $G_0 = 315$  [mg.dl<sup>-1</sup>].

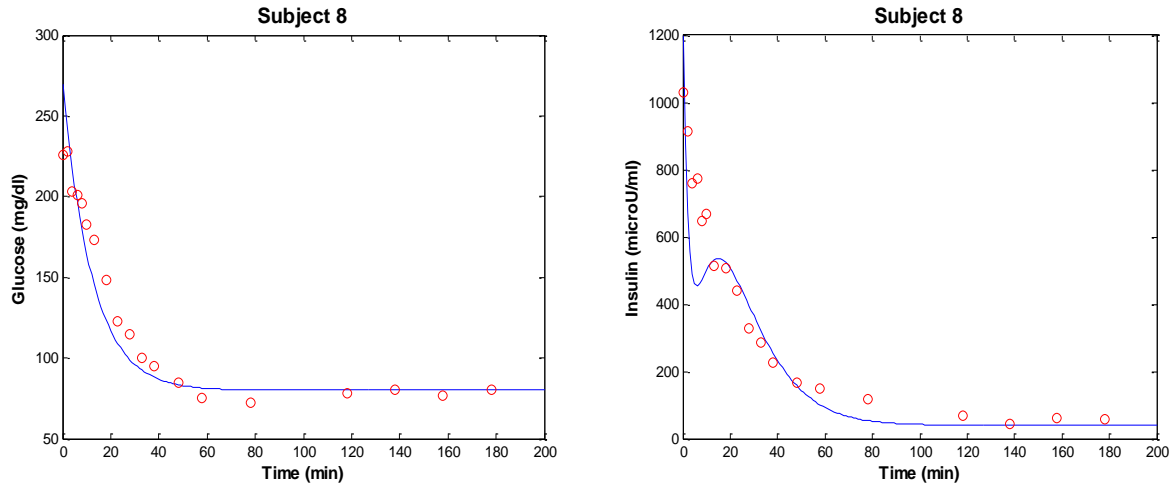


Fig. 3. Profiles of subject 8 in [4] produced by equations (1)-(4) with parameters  $k = 0.35$ ,  $\gamma = 0.18$ ,  $G_b = 80$  [mg.dl<sup>-1</sup>],  $I_b = 40$  [ $\mu$ U/ml],  $p_2 = 0.65$  [min<sup>-1</sup>],  $S_I = 2.5 \times 10^{-4}$  [ $\mu$ U<sup>-1</sup>.ml.min<sup>-1</sup>],  $S_G = 0.08$  [min<sup>-1</sup>],  $I_0 = 300$  [ $\mu$ U/ml] and  $G_0 = 270$  [mg.dl<sup>-1</sup>].

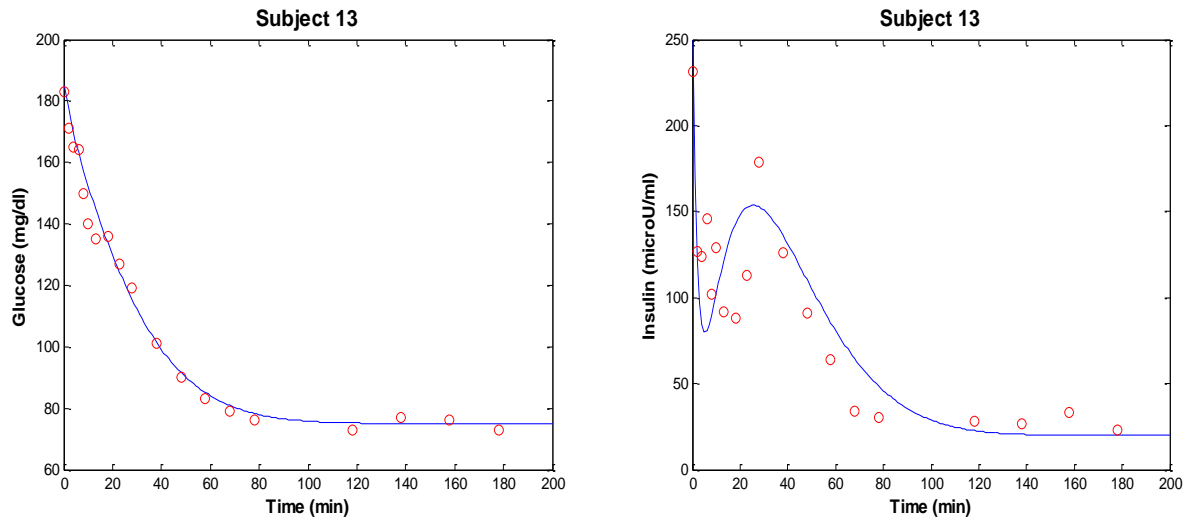


Fig. 4. Profiles of subject 13 in [4] produced by equations (1)-(4) with parameters  $k = 0.45$ ,  $\gamma = 0.027$ ,  $G_b = 75$  [mg.dl<sup>-1</sup>],  $I_b = 20$  [ $\mu$ U/ml],  $p_2 = 0.45$  [min<sup>-1</sup>],  $S_I = 7.5 \times 10^{-3}$  [ $\mu$ U<sup>-1</sup>.ml.min<sup>-1</sup>],  $S_G = 0.026$  [min<sup>-1</sup>],  $I_0 = 250$  [ $\mu$ U/ml] and  $G_0 = 185$  [mg.dl<sup>-1</sup>].

The optimized parameters obtained by fitting the modified minimal model to the experimental data of the five subjects. The averaged  $R^2$  value including glucose and insulin concentrations for these four cases is 0.977; this means that the modified minimal model was excellent. This could be explained by the increased flexibility of the modified minimal model, because of the assumption that the insulin decay rate is not always a first-order process.

In the standard IVGTT, after an injection of glucose bolus, the blood glucose reaches a higher concentration and shows an apparent decay immediately to the basal line in 1 hour. The corresponding insulin concentration stimulated by the injected glucose raises to form a peak, then an approximate exponential decay afterwards, and finally a secondary peak appears.

## CONCLUSIONS

The glucose-insulin time course in IVGTT is a very complex process influenced by many factors. The interaction of glucose-insulin during IVGTT shows a great difference between subjects. The proposed modified minimal model combined with the single-step fitting process can be used to simulate the plasma glucose and insulin profiles subjects. The  $R^2$  value of 0.977 between experimental and calculated time courses indicates the simulation results are excellent. It also indicates that the modification to the classic minimal model improves the model's flexibility. The modifications included an assumption that the decay rate of the plasma insulin is not always a first-order process. The single-step fitting process applied to the modified model generates a set of real optimal model parameters to the glucose-insulin system as a whole dynamic integrated physiological system

## REFERENCES

1. J. Li, M. Wang, A.D. Gaetano, P. Palumbo, S. Panunzi, The range of time delay and the global stability of the equilibrium for an IVGTT model, *Math. Biosci.* **235**, 128-137 (2001).
2. Y. Zheng and M. Zhao, Modified minimal model using a single-step fitting process for the intravenous glucose tolerance test in Type 2 diabetes and healthy humans *Comput. Meth. Prog. Biomed.* **79**, 73-79 (2005).



3. Kamariah Noor Binti Ab Kahar, Modified Minimal Model For Effect Of Exercise On Insulin Sensitivity And Glucose Effectiveness In Type 2 Diabetes And Healthy Human, M.S Thesis, Universiti Malaysia Terengganu, 2013.
4. A.D. Gaetano and O. Arino, Mathematical modeling of the intravenous glucose tolerance test *J. Math. Biol.* **40**, 136-146 (2000).

**Received: February 5, 2014**