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**Improved usability of the Minimal Model of insulin sensitivity based on automated approach  
and Genetic Algorithms for parameter estimation**

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## Abstract

Minimal Model analysis of glucose and insulin data from an intravenous glucose tolerance test is widely used to estimate insulin sensitivity. However, the use of the model often requires intervention by a trained operator, and some problems in the estimation of the model parameters can occur. In this study a new method for Minimal Model analysis, GAMMOD, was developed based on Genetic Algorithms for the estimation of the model parameters. Such algorithm does not require fixing initial values for the parameters (that may lead to unreliable estimates). Our method also implements an automated weighting scheme not requiring manual intervention of the operator, thus improving the usability of the model. We studied a group of 170 women with a history of previous gestational diabetes. Results obtained by GAMMOD were compared to those obtained by a traditional gradient-based algorithm for minimal model analysis, MINMOD. Insulin sensitivity by GAMMOD was  $3.86 \pm 0.19 \cdot 10^{-4} \mu\text{U ml}^{-1} \text{min}^{-1}$  vs.  $4.33 \pm 0.20$  by MINMOD; glucose effectiveness was  $0.0236 \pm 0.0005 \text{min}^{-1}$  vs.  $0.0229 \pm 0.0005$ . The difference in the estimations by the two methods are within the precision expected for such kind of metabolic parameters and are of no clinical relevance. Moreover, both the coefficient of variations of the estimated parameters and the error of fit are generally lower in GAMMOD, despite the fact that it does not require manual intervention. In conclusion the GAMMOD approach for parameter estimation in the Minimal Model provides reliable estimation of the model parameters and improves the usability of the model, thus facilitating its further diffusion and application in a clinical context.

## Introduction

The Minimal Model is widely used to analyze glucose and insulin data from intravenous glucose tolerance tests (IVGTT) for estimating insulin sensitivity in both clinical and epidemiological studies [1-4]. The great part of the strategies for the estimation of the model parameters resort to traditional nonlinear least squares algorithms. However, these algorithms might lead to estimates that are wrong or at least characterized by wide uncertainty [4-6]. As assessed by Godsland and Walton [7], the choice of the strategy for the parameter estimation is a fundamental issue, because it may lead to failure in the convergence to the solution of the equations. Moreover, different initial values of the parameters to be estimated could produce different solutions [8].

The search of a robust method for parameter estimation in Minimal Model analysis led us to select Genetic Algorithms (GAs), which are theoretically and empirically proven to provide a robust search in a complex space [9-11]. GAs are random search algorithms for nonlinear problems based on the rules of natural selection. They do not require fixing an initial value for the model parameters to be estimated.

Another limitation of the Minimal Model is that it often requires the intervention of an experienced operator to produce reliable results [12]. A strategy to limit operator actions would be of great value to improve the usability of the model.

In this study we have developed a new method to estimate the parameters of the Minimal Model in humans, based on Genetic Algorithm approach, GAMMOD. Also, an automated strategy in the model application was developed to reduce the manual intervention by the operator. Our results by GAMMOD were compared to those obtained by the classic MINMOD, the traditional algorithm for Minimal Model analysis [13].

## Methods

### *Subjects and test*

A group of 170 women with a history of previous gestational diabetes (age:  $33.0 \pm 0.4$  years, BMI:  $26.6 \pm 0.4$  kg/m<sup>2</sup>, fasting glucose:  $90.4 \pm 1.3$  mg/dl) was studied 4–6 months after delivery at Department of Internal Medicine III, University of Vienna. All the participants gave written informed consent to the study, which was approved by the local ethics committee.

Gestational diabetes had been diagnosed according to the criteria of the 4<sup>th</sup> Workshop Conference of Gestational Diabetes [14], through a 75 g OGTT. Women with previous ketoacidosis and/or B-cell antibodies were excluded. No woman was still breast feeding at the time of the study. Some of the subjects were already included in previous studies [15].

Lower and upper limits for fasting glucose were 66 and 211 mg/dl, respectively. Thus, all the categories of glucose tolerance were represented in our population.

Frequently-sampled intravenous glucose tolerance test (FSIGT) was performed after 10 to 12-h overnight fasting. Glucose (time 0–0.5 min: 300 mg/kg BW) and then normal insulin (time 20–25 min: 0.03 IU/kg, Humulin R; Eli Lilly, Indianapolis, IN) were infused intravenously. Venous blood samples were taken at timed intervals: at fasting, and at 3, 4, 5, 6, 8, 10, 14, 19, 22, 27, 30, 35, 40, 50, 70, 100, 140, 180 minutes after glucose infusion.

### *Minimal Model*

The Minimal Model, introduced by Bergman and colleagues more than two decades ago [1], is quite well known. We report here a brief description of its two differential equations. The first equation describes the rate of change in glucose concentration following the glucose bolus, while the second describes the rate of change of insulin action from a compartment remote from the plasma:

$$\frac{dG(t)}{dt} = -(S_G + X(t)) \cdot G(t) + S_G \cdot G_b \quad (1)$$

$$G(0) = G_0$$

$$\frac{dX(t)}{dt} = -p_2 \cdot [X(t) - S_I \cdot (I(t) - I_b)] \quad (2)$$

$$X(0) = 0$$

$G(t)$  [mg/dl] is the plasma glucose concentration at time  $t$ ;  $I(t)$  [ $\mu$ U/ml] is the plasma insulin concentration at time  $t$ ;  $G_b$  and  $I_b$  are basal glucose and insulin values;  $X(t)$  [ $\text{min}^{-1}$ ] is insulin action at time  $t$ ;  $S_G$  is the glucose effectiveness [ $\text{min}^{-1}$ ], i.e. the glucose disappearance rate from plasma without any change in dynamic insulin concentration;  $S_I$  represents insulin sensitivity [ $\mu\text{U ml}^{-1} \text{min}^{-1}$ ], which is defined as the ability of insulin to enhance glucose disappearance and inhibit glucose production;  $G_0$  is the value of plasma glucose concentration extrapolated at time zero after glucose injection;  $p_2$  is a parameter related to the dynamics of insulin action. The parameters to be estimated are given by the vector  $\mathbf{P} = [S_G, p_2, S_I, G_0]^T$ .

#### *Parameter estimation through traditional algorithm: MINMOD*

We estimated the unknown parameter vector  $\mathbf{P}$  by using the Minimal Model computer program MINMOD [13], which resorts to traditional weighted nonlinear least squares approach, using particularly the Levenberg-Marquardt algorithm for the minimization procedure. MINMOD also uses a weighting scheme of the glucose data where the weights are equal to the inverse of the variance of the measurement errors. A zero-weighting scheme is used for the early part of the glucose time course, where glucose concentration data may be unreliable since some mixing effects may still be present. It is in charge of the operator to define for each subject's data the time interval where the zero-weighting scheme should be applied. In the MINMOD algorithm the choice of the

initial value of the parameters to be estimated is needed. This task again often requires intervention by the operator.

*Parameter estimation through automated approach based on Genetic Algorithms: GAMMOD*

A weighting scheme not requiring operator intervention was implemented to be applied to the early part of the plasma glucose curve, where some mixing effects can be present. In particular, such scheme was applied over the samples collected in the first 10 minutes of the FSIGT:

(i) the first three samples, considering also the pre-injection sample, are automatically zero-weighted;

(ii) the following samples can be zero-weighted according to the following conditions:

a) if the sample  $G(t_i)$  is lower than  $G(t_{i+1})$ , then  $G(t_i)$  is zero-weighted;

b) if  $(G(t_i) - G(t_{i+1})) > 3 \cdot ((G(t_{i+1}) - G(t_{i+2})))$ , then  $G(t_i)$  is zero-weighted.

Condition b) is based on the hypothesis that plasma glucose should decline rapidly and smoothly in the first minutes after the glucose injection; thus, samples that in this period remain higher or in general much different from the neighbouring samples can be considered unreliable; therefore, they are not weighted in the analysis. However, the number “3” in the condition b) is not based on theoretical reasons but only on our experience in FSIGT analysis.

No weighting scheme was adopted on glucose samples not matching conditions a) and b), and on samples following the 10 minutes interval.

We then applied GAs for the minimization procedure needed to estimate the unknown parameter vector  $\mathbf{P}$ . Genetic Algorithms, firstly introduced by Holland in 1975 [16], are the best-known class of evolutionary algorithms. The evolutionary techniques mimic the principles of natural selection of living entities. They combine elements of direct and stochastic search, and exhibit some advantages over other search methods: in particular, the need of a smaller amount of *a priori* knowledge and, especially, fewer assumptions about the characteristics of the search space. In fact, they do not

require fixing initial values for the estimates, and they usually converge to the global minimum of the error function [17]. In the last years the level of interest in GAs application to engineering problems has grown considerably [11]. Moreover, they have been shown to outperform alternative search techniques on difficult problems involving discontinuous, noisy, high dimensional and multi-modal objective functions [18].

In our study, each possible solution of the minimization procedure was a “chromosome”, which was composed by 4 “genes”, e.g., the four components of the **P** vector. The limits of the parameters to be estimated, defining the borders for the field of existence of the solution, were set according to our experience as follows:  $S_G$  from 0.001 to 0.200  $\text{min}^{-1}$ ;  $p_2$  from 0 to 1  $\text{min}^{-1}$ ;  $S_I$  from 0.01 to  $15 \cdot 10^{-4} \mu\text{U ml}^{-1} \text{min}^{-1}$ ;  $G_0$  from 100 to 600  $\text{mg dl}^{-1}$ .

Overcoming the problem of the possible dependence of the initial values of the parameters [8], the Genetic Algorithm was started with 150 randomly generated chromosomes, and all of them were evaluated. To do that, an appropriate cost function (the so-called “fitness function”) was built up. We considered the standard sum of squares function:

$$\Psi = \sum_{i=1}^N \left( \frac{G_m(t_i) - G_e(t_i)}{G_m(t_i)} \right)^2 \quad (3)$$

$G_m(t_i)$  is the glucose experimental sample at time  $t_i$ , and  $G_e(t_i)$  is the corresponding model estimation, obtained by numerical solution and integration of the equation system 1) and 2);  $N$  is the number of measured samples.

The estimation in each subject’s data of the unknown parameter vector **P** through the minimization of function  $\Psi$  was considered the objective of the GA algorithm. However, as GAs seek to maximize the fitness function, to accomplish the transformation of the minimization problem into a maximization problem the error can be simply subtracted from a large positive constant, as

suggested by Karr et al. [19]. Thus, the goal was to maximize the function  $ff$  defined as  $ff = D - \Psi$ , where  $D$  is a large positive constant parameter.

For each chromosome (i.e. possible solution) the fitness function was evaluated, so that those providing high values of the fitness function were selected. After the evaluation step, two genetic operators were applied for creating new chromosomes from those selected before:

(i) the “cross-over” operator randomly picked up two parents **P1**, **P2** and performed a sort of interpolation between them by generating a random number  $\Omega$  ( $\Omega \in (0, 1)$ ), and creating two children **C1** and **C2** as follows:

$$\mathbf{C1} = \mathbf{P1} \cdot \Omega + \mathbf{P2} \cdot (1-\Omega); \mathbf{C2} = \mathbf{P1} \cdot (1-\Omega) + \mathbf{P2} \cdot \Omega. \quad (4)$$

(ii) the “non-uniform mutation” operator randomly picked up one parent and changed one of its genes (i.e., one of the model parameter) on the basis of a non-uniform probability distribution. This operator searched the space of the solution uniformly at the beginning, and locally as the current generation approached the maximum number of generations.

The new population was formed by the children (derived from the application of the genetic operators) and from some high performance individuals of the old population that were reintroduced by a proper selection function, thus avoiding problems of stagnation [18-20]. The previous evaluation step was repeated on the newly created population, and all the procedure was iterated. To avoid convergence to a local minimum, and to find the minimum number of iterations required for proper convergence (i.e., the number of generations necessary to the desired evolution), a sensitivity study was carried out (data not shown), as in Morbiducci et al. [8]: it was found that a number of 10000 generations was sufficient to obtain an accurate estimation of **P**.

The numerical implementation of the whole method was performed with a proper own code using Matlab<sup>®</sup> (The MathWorks, Inc.)

### *Data analysis*

Statistical comparisons between the model parameters estimated by MINMOD and GAMMOD on each individual were performed by applying Deming regression analysis [21].

Data and results are reported as mean $\pm$ SE unless otherwise designated. Precision of estimates was expressed as the coefficient of variation CV (i.e., fractional SD), calculated from the variance values in the main diagonal of the inverse of the Fisher's information matrix.

### **Results**

Mean glucose and insulin data used in our study and GAMMOD-derived fit are reported in Figure 1. Table 1 summarizes the values of the four model parameters  $S_G$ ,  $p_2$ ,  $S_I$ ,  $G_0$  estimated by GAMMOD approach. The corresponding coefficients of variation are also shown. Only in one case we found extremely high coefficient of variations for  $p_2$  and  $S_I$  (1398 and 138%, respectively). In the same case, however, MINMOD performed even worse (coefficient of variation for  $S_I$  equal to 373%).

To compare the two parameter estimation approaches, we focused on the two most relevant parameters, i.e., insulin sensitivity,  $S_I$ , and glucose effectiveness,  $S_G$  (Table 2): GAMMOD estimated  $S_I$  values were slightly lower than the MINMOD values, and similar results were found for  $S_G$ . However, GAMMOD provided coefficients of variations lower than in MINMOD; in particular that of  $S_I$  was almost half with GAMMOD than with MINMOD.

To investigate the relationship between the estimation of  $S_I$  and  $S_G$  by the two methods, we applied the Deming regression analysis. High values of R were found for both  $S_I$  and  $S_G$ :  $R=0.94$  and  $R=0.86$ , respectively (see Figure 2 and Figure 3). Deming regression also showed that in  $S_I$  the slope of the regression line was virtually coincident with the unit line (slope: 0.971; 95% confidence

interval: from 0.913 to 1.029); therefore, there was no proportional difference in  $S_I$  estimates by the two methods. However, since the intercept of the regression line was different from zero (intercept: -0.345; 95% confidence interval: from -0.563 to -0.127), the two methods slightly differ by a constant amount in  $S_I$  estimates. As regards  $S_G$ , Deming regression showed that there was neither proportional (slope: 1.041; 95% confidence interval: from 0.903 to 1.179) nor constant difference (intercept: -0.0003; 95% confidence interval: from -0.0034 to 0.0028) by the two methods. Bland-Altman test provided similar findings for both  $S_I$  and  $S_G$  (not shown).

In terms of goodness of fit, GAMMOD performed better than MINMOD: the sum of square error averaged over all the study subjects was  $608 \pm 37$  (mg dl<sup>-1</sup>)<sup>2</sup> in MINMOD, and only  $290 \pm 9$  (mg dl<sup>-1</sup>)<sup>2</sup> in GAMMOD.

## Discussion

The Minimal Model is the reference method to estimate insulin sensitivity and glucose effectiveness from IVGTT data. However, the reliability and accuracy of the parameter estimation may strongly depend upon the used numerical approach. Different strategies may yield extremely different parameter estimates and serious numerical problems can occur, such as failure to converge on a solution, or emergence of excessively high coefficient of variations for the estimated values. A traditional algorithm often used in parameter estimation problem is Levenberg-Marquardt, which is the most popular gradient-based method, converging quadratically to the local minimum [22]. This algorithm was used since the beginning in the MINMOD tool for Minimal Model parameter estimation [1, 13].

Apart from this traditional approach other strategies were tested ever since. In particular, Bayesian techniques showed to offer particular advantages in the estimation of insulin sensitivity with the Minimal Model [23-26], thus providing improvements in the model estimation success rate and in

the parameters precision. Recently, Pillonetto et al. [5] developed a Bayesian parameter estimation strategy for the Minimal Model based on Markov chain Monte Carlo approach. Bayesian estimation technique is based on the incorporation of *a priori* knowledge into the estimation process and, as noted by Godsland [27], it could be particularly efficient with the Minimal Model, since the knowledge about insulin sensitivity is notable. However, the Bayesian approach may have some drawbacks, such as the requirement for remodelling an entire population dataset in the presence of any *a posteriori* changes to an individual of the population [24, 27].

A possible alternative is thus represented by the Genetic Algorithms, GAs. In this study, we implemented a new approach for the estimation of Minimal Model parameters based on GAs, with 150 chromosomes in the initial population and 10000 generations. The modest number of parameters to be estimated, together with the specific genetic operators applied (i.e., “cross-over” and “mutation” operators), made consistent the choice adopted for the value of the population size [10].

Beyond the described numerical difficulties in the parameter estimation, another problem exists that limits the usability of Minimal Model in a clinical setting: in several cases the intervention of an operator specifically trained in the model use is necessary to obtain reliable results [12]. In particular, the choice of the weighing scheme for the first glucose samples of the IVGTT may result to be critical. Based on our experience in Minimal Model analysis, we identified an automated weighting scheme procedure that performed well in the majority of cases, thus avoiding manual intervention of the operator. Moreover, improper choices of the initial parameter values may lead in some cases to unreliable solutions. GAs automatically solved this problem, because they do not require fixing initial values for the parameters but only their limits of existence. Our approach based on automated weighting scheme and GAs for numerical parameter estimation was termed GAMMOD. To the best of our knowledge, no other study applied GAs to the Minimal Model analysis.

Results obtained by the GAMMOD approach were compared to those obtained by the traditional MINMOD approach. The two methods provided very similar estimations for both insulin sensitivity and glucose effectiveness. The difference in the estimations by the two methods is within the precision that is expected for such kind of metabolic parameters. Moreover, such differences are probably of no clinical relevance. As regards the insulin sensitivity index (the parameter of major interest), it is worth noting that the differences between the two methods remain almost the same in any interval of physiological relevance. In fact, the  $2.8 \cdot 10^{-4} \mu\text{U ml}^{-1} \text{ min}^{-1}$  value can be assumed as a threshold between impaired and normal insulin sensitivity [15], and in the interval 0–2.8 for  $S_I$  from MINMOD the absolute difference is  $12.2 \pm 1.9 \%$  (55 subjects); in the interval 2.8–6.9, where 6.9 can be assumed as the threshold over which a subject is certainly not insulin resistant [28], the absolute difference is  $11.9 \pm 1.6 \%$  (90 subjects); for values higher than 6.9 the absolute difference is  $12.7 \pm 2.8 \%$  (25 subjects). Therefore, no clinically relevant differences are observed in the whole  $S_I$  range. It must also be noted that some indicators suggest that GAMMOD is performing even better than MINMOD, despite the fact that it does not require manual intervention: in fact, both the coefficient of variations of the estimated parameters and the error of fit are generally lower. Improved goodness of fit was already observed in GAs applied to modeling in glucose metabolism, i.e. a model of insulin secretion and kinetics based on oral glucose tolerance test [8]. The only drawback of GAMMOD compared to MINMOD is the higher computational cost; however, since no real-time results are required, this is not a serious limitation.

In conclusion, we developed a new approach for parameter estimation in the Minimal Model based on automated weighting scheme and Genetic Algorithms. Our approach provided reliable estimation of the model parameters and improved the usability of the model, thus facilitating its further diffusion and application in a clinical setting.

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## Figure captions

Figure 1 – Mean model fit (solid curve) and corresponding 95% confidence interval curves (dotted curves) for glucose concentration over all the subjects. The mean experimental samples for glucose concentration are also reported with the corresponding confidence interval bars. The insert reports mean time course of insulin concentration and corresponding confidence interval bars.

Figure 2 – Comparison of the two methods for the estimation of insulin sensitivity,  $S_I$  [ $10^{-4} \mu\text{U ml}^{-1} \text{min}^{-1}$ ]. The graph displays the scatter diagram, the Deming regression line (solid line) and the identity line (dotted line). The regression equation ( $R=0.94$ ) is also shown.

Figure 3 – Comparison of the two methods for the estimation of glucose effectiveness,  $S_G$  [ $\text{min}^{-1}$ ]. The graph displays the scatter diagram, the Deming regression line (solid line) and the identity line (dotted line). The regression equation ( $R=0.86$ ) is also shown.

## Table legends

### Table 1 – Values for $S_G$ , $p_2$ , $S_I$ , $G_0$ obtained using GAMMOD implementation

Mean values for model parameters estimated according to the GAMMOD approach, together with the minimum and maximum individual values obtained in the investigated population. The precision of estimates, expressed in terms of coefficient of variation, CV (%), is also shown for each parameter estimate.

### Table 2 – Insulin sensitivity and glucose effectiveness from GAMMOD and MINMOD approaches

Mean values of the two most clinically relevant parameters, i.e., insulin sensitivity,  $S_I$ , and glucose effectiveness,  $S_G$ , are reported. Values in square brackets show the mean coefficient of variation (%). The mean value of the percentage differences between individual parameters estimate from GAMMOD and MINMOD are also shown. Results of statistical test for comparison between the two approaches are reported in the Result section.

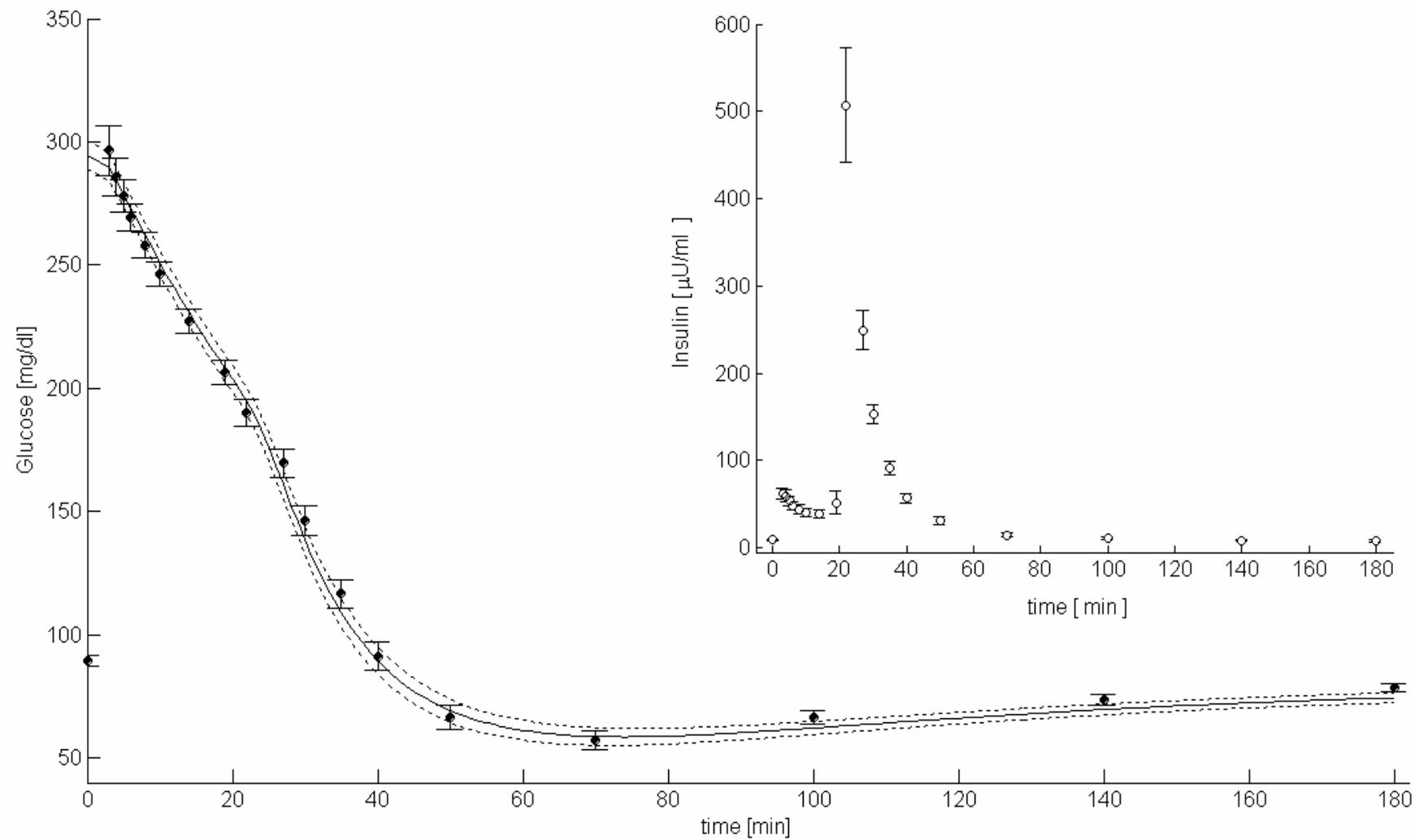


Figure 1

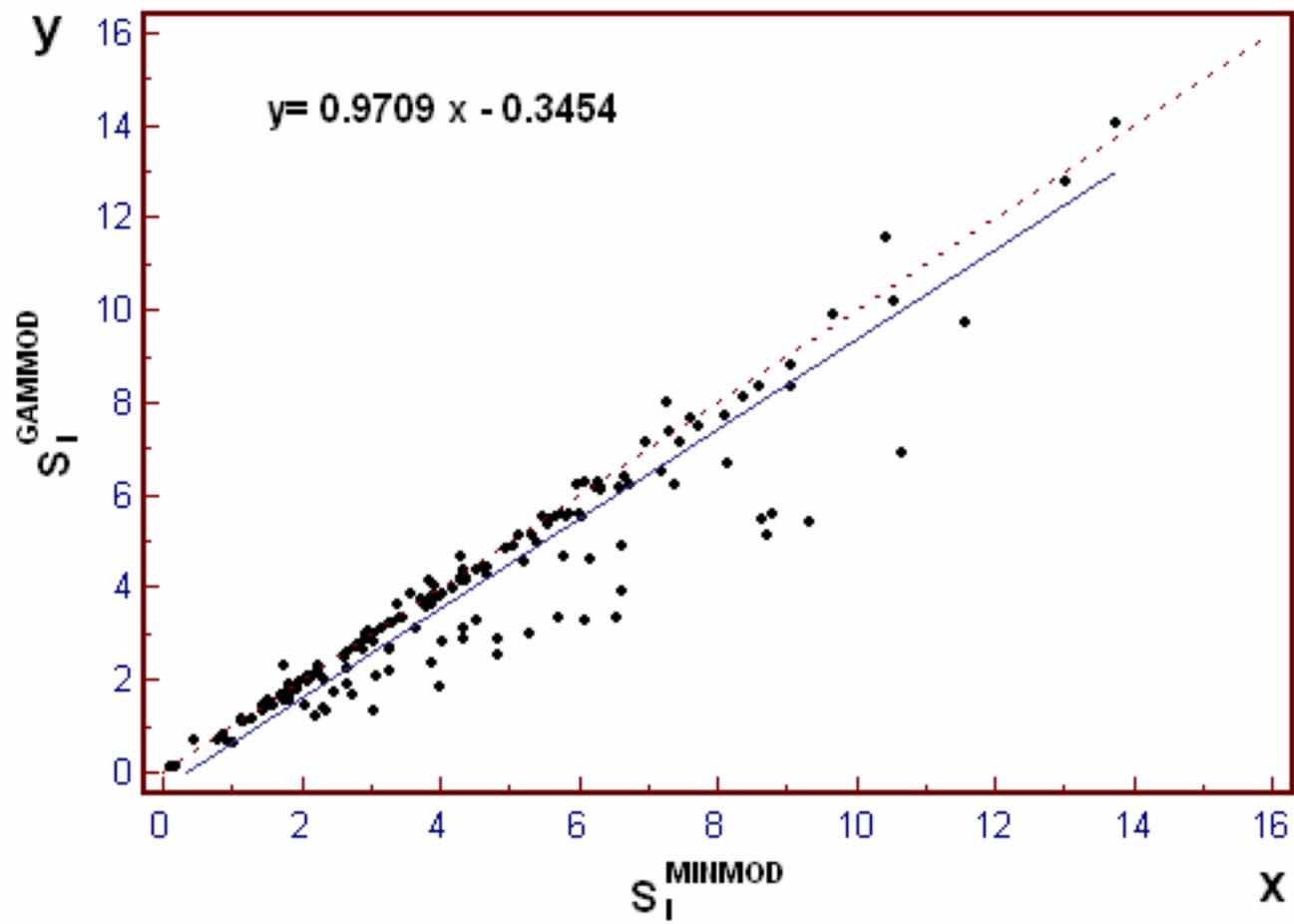


Figure 2

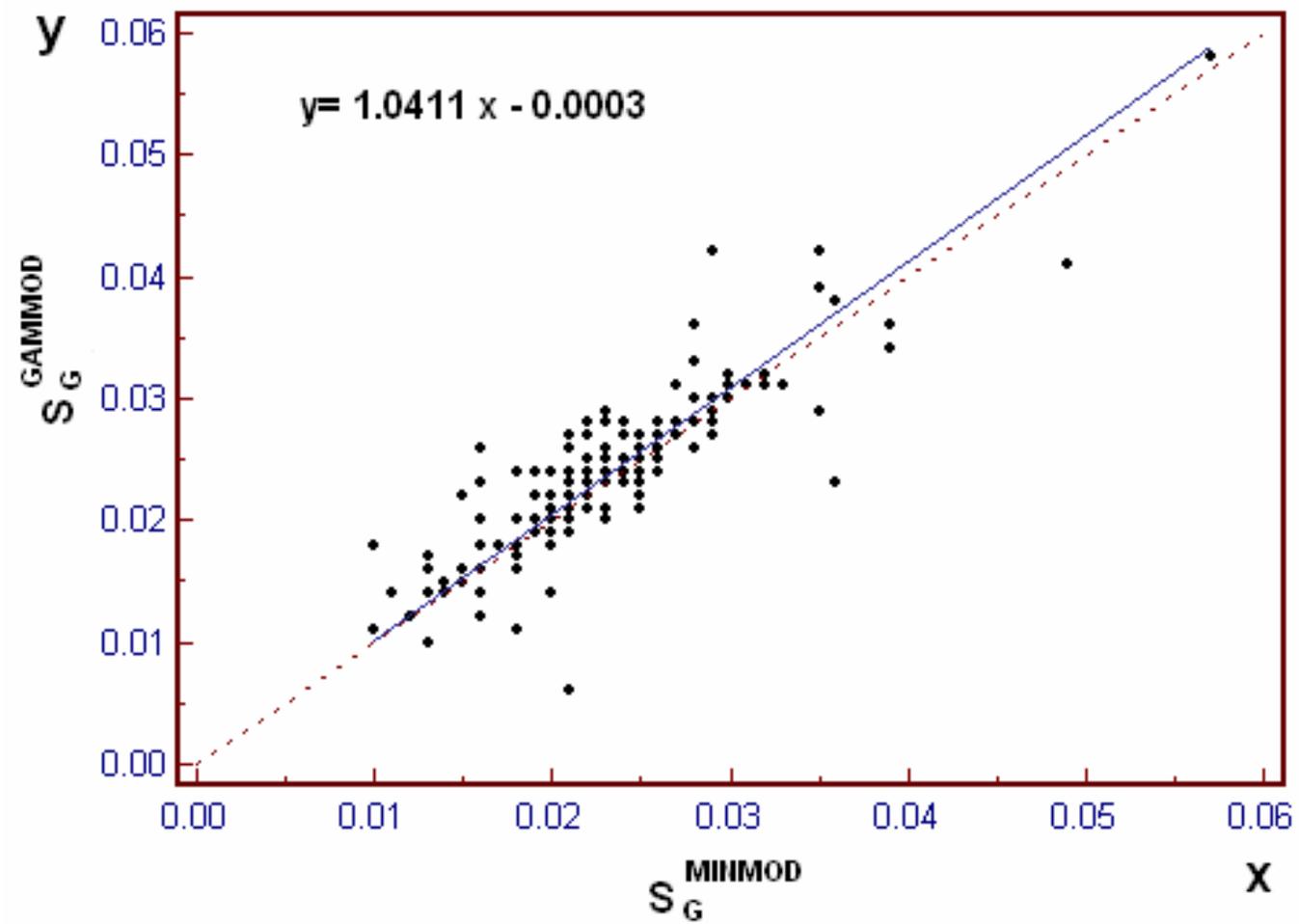


Figure 3

Table 1

<b>GAMMOD</b>	<b>parameter value</b>	<b>parameter value</b>	<b>CV</b>	<b>CV</b>
	<b>mean <math>\pm</math> SE</b>	<b>max/min value</b>	<b>mean <math>\pm</math> SE</b>	<b>max/min value</b>
<b>S<sub>G</sub></b> [min <sup>-1</sup> ]	0.0236 $\pm$ 0.0005	0.0579 / 0.0060	8.5 $\pm$ 0.2	18.4 / 2.0
<b>p<sub>2</sub></b> [min <sup>-1</sup> ]	0.073 $\pm$ 0.008	1.000 / 0.025	61.0 $\pm$ 9.6	1398 / 17
<b>S<sub>I</sub></b> [10 <sup>-4</sup> $\mu$ U ml <sup>-1</sup> min <sup>-1</sup> ]	3.86 $\pm$ 0.19	14.03 / 0.11	9.7 $\pm$ 1.1	137.7 / 1.1
<b>G<sub>0</sub></b> [mg dl <sup>-1</sup> ]	295 $\pm$ 3	456 / 210	0.89 $\pm$ 0.01	1.24 / 0.59

Table 2

	<b>GAMMOD</b>		<b>MINMOD</b>		<b>Absolute difference in S<sub>I</sub></b>	<b>Absolute difference in S<sub>G</sub></b>
	<b>S<sub>I</sub></b> [10 <sup>-4</sup> μU ml <sup>-1</sup> min <sup>-1</sup> ]	<b>S<sub>G</sub></b> [min <sup>-1</sup> ]	<b>S<sub>I</sub></b> [10 <sup>-4</sup> μU ml <sup>-1</sup> min <sup>-1</sup> ]	<b>S<sub>G</sub></b> [min <sup>-1</sup> ]	[%]	[%]
<b>MEAN</b>	3.86 [9.7]	0.0236 [8.5]	4.33 [17.2]	0.0229 [9.0]	12.1	10.3
<b>SE</b>	0.19 [1.1]	0.0005 [0.2]	0.20 [2.4]	0.0005 [0.3]	1.1	1.0