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MODELING IVGTT DATA WITH DELAY-DIFFERENTIAL EQUATIONS

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Abstract

Due to the increasing importance of identifying states of insulin resistance, also due to the increasing prevalence of obesity, a need exists to have a reliable mathematical model representing the glucose/insulin control system. Such a model should be simple enough to allow precise estimation of insulin sensitivity on a single patient in current diabetological research practice, yet should exhibit stable dynamics and reproduce universally accepted physiological behavior. The simple aggregation of the subcomponents of the standard Minimal Model (MM) is not adequate, due to the lack of an equilibrium point, to the prediction of insulin activity tending to infinity, and to its applicability only to single-injection IVGTTs.

A new, discrete Single Delay Model (SDM) of the glucose/insulin control system is proposed, applicable to the IVGTT as well as to multiple injection and infusion schemes, which can be fitted to both glucose and insulin observations simultaneously. The SDM is stable around baseline equilibrium values and has positive bounded solutions at all times. Applying the same definition as for the MM-derived S_I, insulin sensitivity is seen to be directly represented by one of the SDM's free parameters (K_{xgI}). Both SDM and MM are fitted to a sample of 41 IVGTT's from healthy volunteers. Precision of the parameter estimates is generally better with the SDM, in particular, 41 out of 41 subjects show identifiable (CV < 52%) K_{xgI} from the SDM, while 27 out of 41 have identifiable S_I from the MM. K_{xgI} correlates well with the HOMA, while S_I correlates well only when excluding 9 subjects with either very low or very large values of the index. We conclude that the SDM is theoretically sound and practically reliable, and should be considered when characterizing the degree of insulin sensitivity of an individual.

Keywords

Glucose, insulin, dynamical systems, differential equations, delay.

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Introduction

The measurement of insulin sensitivity in humans from a relatively non-invasive test procedure is being felt as a more and more pressing need, heightened in particular by the current increase in the social cost of obesity-related dysmetabolic diseases(1-8). Two experimental procedures are in general use for the estimation of insulin sensitivity in a given subject: the Intra Venous Glucose Tolerance Test (IVGTT), often modeled by means of the so-called Minimal Model (MM) (9,10), and the Euglycemic Hyperinsulinemic Clamp (EHC)(11). The EHC is often considered the golden standard for the determination of insulin resistance. However, the standard IVGTT without Tolbutamide (consisting of injecting I.V. a bolus of glucose and frequently sampling the glucose and insulin plasma concentrations afterwards for a period of about three hours) is simpler to perform, carries no significant associated risk and delivers a potentially richer information content. The difficulty with using the IVGTT is its interpretation, for which it is necessary to apply a mathematical model of the status of the reciprocal negative feedback regulation of glucose and insulin on each other in the studied experimental subject. Due to its relatively simple structure and to its great clinical importance, the glucose/insulin system has been in fact the object of repeated mathematical modeling attempts over the years(12-30). The mere fact that several models have been proposed shows that, notwithstanding their apparent simplicity, mathematical, statistical and physiological considerations have to be carefully integrated when attempting to represent the glucose/insulin system. In modeling the IVGTT, we would require to have a reasonably simple model, with as few parameters to be estimated from data as practicable, and with a qualitative behavior consistent with physiology. Further, the model formulation, while applicable to the standard IVGTT, should lend itself to modeling other often envisaged experimental procedures, like repeated glucose boli, or infusions. Previous work(31,32) had already shown that the assembled Minimal Model equations are not appropriate to this end, due to the absence of an equilibrium, to the possibility of unbounded solutions, to the non-autonomous form allowing only a single initial glucose bolus to be represented. However, even if the Minimal Model has obvious shortcomings, no satisfactory practical replacement has been offered to date.

In the present work, a simple, discrete Single Delay Model (“the discrete SDM”) of the IVGTT is proposed as a mathematically valid and statistically robust alternative to the Minimal Model. The assumptions underlying the new model are discussed, some qualitative properties of its solutions are shown to be consistent with known physiology, and an insulin-sensitivity index is derived from it. The model is fitted onto IVGTT data from 41 healthy

volunteers and fits are compared to those obtained with the Minimal Model as well as with the usual HOMA index of insulin resistance.

Materials and Methods

Experimental protocol

Data from 41 healthy volunteers (19 males and 22 females, anthropometric characteristics reported in Table 1), who had been previously studied in several protocols at the Catholic University Department of Metabolic Diseases were analized. All subjects had negative family and personal histories for Diabetes Mellitus and other endocrine diseases, were on no medications, had no current illness and had maintained a constant body weight for the six months preceding each study. For the three days preceding the study each subject followed a standard composition diet (55% carbohydrate, 30% fat, 15% protein) ad libitum with at least 250g carbohydrates per day. Written informed consent was obtained in all cases; all original study protocols were conducted according to the Declaration of Helsinki and along the guidelines of the institutional review board of the Catholic University School of Medicine, Rome, Italy.

Each study was performed at 8:00 AM, after an overnight fast, with the subject supine in a quiet room with constant temperature of 22-24 °C. Bilateral polyethylene IV cannulas were inserted into antecubital veins. The standard Intra Venous Glucose Tolerance Test (IVGTT) was employed, without using additional Tolbutamide so as to be able to use the recorded data for pancreatic secretion evaluation(9): at time 0 (0') a 33% glucose solution (0.33 g Glucose / kg Body Weight) was rapidly injected (less than 3 minutes) through one arm line. Blood samples (3 ml each, in lithium heparin) were obtained at -30', -15', 0', 2', 4', 6', 8', 10', 12', 15', 20', 25', 30', 35', 40', 50', 60', 80', 100', 120', 140', 160' and 180' through the contralateral arm vein. Each sample was immediately centrifuged and plasma was separated. Plasma glucose was measured by the glucose oxidase method (Beckman Glucose Analyzer II, Beckman Instruments, Fullerton, CA, USA). Plasma insulin was assayed by standard radio immunoassay technique. The plasma levels of glucose and insulin obtained at -30', -15' and 0' were averaged to yield the baseline values referred to 0'.

The discrete Single Delay Model

In the development of the SDM, four two-compartment models, describing the variation in time of plasma glucose and plasma insulin concentrations following an IVGTT, have been considered. For each tested model the glucose equation includes a second-order linear term describing insulin-dependent glucose uptake, which is expressed in net terms since it includes changes in liver glucose delivery and changes in glucose uptake, as well as a zero-order term expressing the net balance between a possible constant, insulin-independent fraction of hepatic glucose output and the essentially constant glucose utilization of the brain and possibly the myocardium.

Variations in plasma insulin concentration depend on the spontaneous decay of insulin and on pancreatic insulin secretion. After the nearly instantaneous first phase insulin secretion, represented in the model by means of the initial condition, a delay term is considered; it represents the pancreatic second phase secretion and formalizes the delay with which the pancreas responds to variations of glucose plasma concentrations. The four models studied differ according to the presence or absence of an insulin-independent glucose elimination rate term ($-K_{xg}\,G$) and according to the presence or absence of an explicit delay in the action of insulin in stimulating tissue glucose uptake ($I(t-\tau_i)$ instead of $I(t)$). The model that does not include either one of these two features was named model A; model B includes the term ($-K_{xg}\,G$); model C uses $I(t-\tau_i)$ instead of $I(t)$; model D includes both (see table 2). Each model was fitted to experimentally observed concentrations and for each of the 41 subjects the Akaike value was computed. Models were compared by performing paired t-tests on the computed Akaike scores. The selected model was model A (the simplest one, including neither insulin-independent glucose elimination nor insulin action delay), whose schematic diagram is represented in Figure 1 and whose equations are reported below:

(1) $$\frac{dG(t)}{dt} = -K_{xgI}\,I(t)\,G(t) + \frac{T_{gh}}{V_g}$$

(1') $$G(t) \equiv G_b \;\forall\; t \in (-\infty, 0)\;,\quad G(0) = G_b + G_\Delta,\quad \text{where}\quad G_\Delta = \frac{D_g}{V_g}$$

(2) $$\frac{dI(t)}{dt} = -K_{xi}\, I(t) + \frac{T_{igmax}}{V_i} \frac{\left(\frac{G(t-\tau_g)}{G^*}\right)^{\gamma}}{1+\left(\frac{G(t-\tau_g)}{G^*}\right)^{\gamma}}$$

(2') $$I(0) = I_b + I_{\Delta G}\, G_{\Delta},$$

where

t	[min] is time;
G(t)	[mM] is the glucose plasma concentration at time t;
G_b	[mM] is the basal (preinjection) plasma glucose concentration;
I(t)	[pM] is the insulin plasma concentration at time t;
I_b	[pM] is the basal (preinjection) insulin plasma concentration;
K_{xgI}	[min^{-1} pM^{-1}] is the net rate of (insulin-dependent) glucose uptake by tissues per pM of plasma insulin concentration;
T_{gh}	[mmol/min/kgBW] is the net balance of the constant fraction of hepatic glucose output (HGO) and insulin-independent zero-order glucose tissue uptake;
V_g	[L/kgBW] is the apparent distribution volume for glucose;
D_g	[mmol/kgBW] is the administered intravenous dose of glucose at time 0;
G_{Δ}	[mM] is the theoretical increase in plasma glucose concentration over basal glucose concentration at time zero, after the instantaneous administration and distribution of the I.V. glucose bolus;
K_{xi}	[min^{-1}] is the apparent first-order disappearance rate constant for insulin;
T_{igmax}	[pmol/min/kgBW] is the maximal rate of second-phase insulin release; at a glycemia equal to G^* there corresponds an insulin secretion equal to $T_{igmax}/2$;
V_i	[L/kgBW] is the apparent distribution volume for insulin;
τ_g	[min] is the apparent delay with which the pancreas changes secondary insulin release in response to varying plasma glucose concentrations;
γ	[#] is the progressivity with which the pancreas reacts to circulating glucose concentrations. If γ were zero, the pancreas would not react to circulating glucose; if γ were 1, the pancreas would respond according to a Michaelis-Menten dynamics, with G^* mM as the glucose concentration of half-maximal insulin secretion; if γ were greater than 1, the pancreas would respond according to a sigmoidal function, more and more sharply increasing as γ grows larger and larger.

$I_{\Delta G}$ [pM/mM] is the first-phase insulin concentration increase per mM increase in glucose concentration at time zero due to the injected bolus.

G^* [mM] is the glycemia at which the insulin secretion rate is half of its maximum;

From the steady state condition it follows that:

$$T_{gh} = K_{xgI}\, I_b\, G_b\, V_g \quad \text{and} \quad T_{ig\,max} = K_{xi}\, I_b\, V_i \left[1+\left(\frac{G_b}{G^*}\right)^{\gamma}\right] \Big/ \left(\frac{G_b}{G^*}\right)^{\gamma}$$

An index of insulin sensitivity may be easily derived from this model by applying the same definition as for the Minimal Model (9), i.e.

$$(3)\ \frac{\partial}{\partial I}\left[-\frac{\partial}{\partial G}\left(\frac{dG}{dt}\right)\right] = \frac{\partial}{\partial I}\left[-\frac{\partial}{\partial G}\left(-K_{xgI}G(t)I(t)+\frac{T_{gh}}{V_g}\right)\right] = K_{xgI}$$

It can be shown that the solutions of the proposed discrete Single-Delay Model for I and G are positive and bounded for all times, and that their time-derivatives are also bounded for all times. Further, the model admits the single (positive-concentration) equilibrium point (G_b, I_b). The system is also asymptotically locally stable around its equilibrium point. Detailed proofs of these statements can be found in Palumbo et al. (33). Parameters G^* and V_i are set respectively to 9 mM and 0.25 L., so that the set of free parameters of the final model to be estimated is therefore $\{V_g, I_\Delta, \tau_g, K_{xgI}, K_{xi}, \gamma\}$.

The Minimal Model

The Model most often used in diabetological research for the interpretation of the IVGTT is the so called “Minimal Model”. The three equations of the original Minimal Model, introduced in the early Eighties, are as follows:

$$(4)\ \frac{dG(t)}{dt} = -\left[b_1 + X(t)\right]G(t) + b_1 G_b, \quad G(0) = b_0$$

$$(5)\ \frac{dX(t)}{dt} = -b_2 X(t) + b_3 (I(t) - I_b), \quad I(0) = I_b$$

$$(6)\ \frac{dI(t)}{dt} = b_4 \left[G(t) - b_5\right]^+ t - b_6 \left[I(t) - I_b\right], \quad I(0) = b_7 + I_b$$

where:

t [min] is time after the glucose bolus;

G(t) [mM] is the blood glucose concentration at time t;

I(t) [pM] is the blood insulin concentration at time t;

$X(t)$ [min^{-1}] is an auxiliary function representing insulin-excitable tissue glucose uptake activity, proportional to insulin concentration in a "distant" compartment;

G_b [mM] is the subject's basal (pre-injection) glycemia;

I_b [pM] is the subject's basal (pre-injection) insulinemia;

b_0 [mM] is the theoretical glycemia at time 0 after the instantaneous glucose bolus;

b_1 [min^{-1}] is the glucose mass action rate constant, i.e. the insulin-independent rate constant of tissue glucose uptake, "glucose effectiveness" ;

b_2 [min^{-1}] is the rate constant expressing the spontaneous decrease of tissue glucose uptake ability

b_3 [min^{-2} pM^{-1}] is the insulin dependent increase in tissue glucose uptake ability, per unit of insulin concentration excess over baseline insulin;

S_I (b_3/b_2) [min^{-1} pM^{-1}] is the insulin sensitivity index and represents the capability of tissue to uptake circulating plasma glucose.

The first part of the model(9), consisting of equations (4) and (5), describes the time-course of glucose plasma concentrations, depending upon insulin concentrations. The second part of the model (10), equation (6), describes the time-course of plasma insulin concentrations, depending on glucose. The proposing Authors employ a "decoupling" estimation procedure (34) whereby the linearly interpolated observed insulin concentrations are used as given input when fitting equations 4 and 5 to glucose observations, and viceversa the linearly interpolated observed glucose concentrations are used as given input when fitting equation 6 to insulin observations. While in later years different versions of the Minimal Model appeared (35,36) the original formulation reported above, and in particular its glucose kinetics part (equations 4 and 5) is most widely employed even in recent research applications (8,37-43).

Statistical Methods

For each subject the four alternative models (A, B, C, D, described in table 2) have been fitted to glucose and insulin plasma concentrations by Generalized Least Squares (GLS, described in Appendix 1) in order to obtain individual regression parameters. All observations on glucose and insulin have been considered in the estimation procedure except for the basal levels. Coefficients of variation for glucose and insulin were estimated with phase 2 of the GLS algorithm, whereas single-subject coefficients of variation for the model parameter estimates were derived from the corresponding variances, obtained from the diagonal elements of the estimated asymptotic variance-covariance matrix of the GLS

estimators. The individual-specific regression parameters were then used for population inference.

For the Minimal Model, fitting was performed by means of a Weigthed Least Squares (WLS) estimation procedure, considering as weigths the inverses of the squares of the expectations and as coefficients of variation 1.5% for glucose and 7% for insulin(9). Observations on glucose before 8 minutes from the bolus injection, as well as observations on insulin before the first peak were disregarded, as suggested by the proposing Authors(9,10). A BFGS quasi-Newton algorithm was used for all optimizations(44). A-posteriori model identifiability was determined by computing the asymptotic coefficient of variation (CV) for the free model parameters: a CV smaller than 52% translates into a standard error of the parameter smaller than 1/1.96 of its corresponding point estimate and into an asymptotic confidence region of the parameter not including zero.

In order to compare the two models under the same statistical estimation scheme, the Minimal Model was also fitted to observed data points using the same GLS algorithm employed for the SDM. Since under this estimation scheme all parameter confidence regions resulted to be as large as, or larger than the corresponding regions obtained by WLS, in the rest of this work only WLS results are considered for the Minimal Model.

RESULTS

Delay Model Selection

Each delay model (A, B, C and D) was fitted on data from each one of the experimental subjects and the Akaike Information Criterion (AIC) was computed. Six paired t-tests were performed (A vs B, A vs C, A vs D, B vs D, C vs D and B vs C). Model A had the lowest average on the individual AIC's. All tests were conducted at a level alpha of 0.05 and resulted significant (A vs B, $P = 0.024$; A vs C, $P = 0.001$; A vs D, $P < 0.001$; C vs D, $P = 0.005$), except for the comparison B vs C and B vs D which resulted non significant ($P = 0.314$ and $P = 0.393$ respectively). The best model under the AIC criterion was therefore model A, which performed significantly better than either model B or C, which were either not inferior to, or better than model D.

Single-Subject Numerical fitting

Table 3 shows the model parameter values obtained for the SDM in the 41 subjects together with the corresponding coefficients of variation derived from the asymptotic results for GLS estimators. All coefficients of variation for all parameters in all subjects resulted to be smaller than 52%, except for parameter τ_G, which was estimated to about zero in 4 subjects, producing therefore a large CV, and for parameter γ, in those 3 subjects for whom it was estimated at a value less than 1. Figure 2 shows the shape of the dynamics of insulin release resulting from the average parameter values estimated on the 41 subjects .

Table 4 shows the model parameter values obtained for the MM; the corresponding standard errors and coefficients of variation were computed, in this case, by applying standard results for weigthed least square estimators, where the coefficients of variation for glucose and insulin were set respectively to 1.5% and 7%.

Table 5 reports the model parameter values for the MM when using the same statistical estimation procedure (GLS) adopted for the SDM.

Figures 3, 4 and 5 portray three typical subjects with both insulin and glucose concentration observations, as well as predicted time courses based on the SDM and the MM. For subjects 13 and 27 (figures 3 and 4) the predicted curves are nearly superimposed. For subject 29 (Figure 5), while the MM curve seems closer to the points than that of the SDM, its predicted insulin concentrations are visibly increasing at the end of the observation period (and will be predicted to increase to extremely high levels within a few hours), instead of tending to the equilibrium value I_b. This behaviour is common to a few subjects (for subjects 23, 26 and 29

most evidently over 180 minutes) and is consistent with the theoretical results demonstrated in De Gaetano and Arino (45).

Figures 6 and 7 report the scatter plots between K_{xgI} and S_I. In the first figure all 41 subjects were considered, whereas in the second one 9 subjects were disregarded: they were those subjects whose indices of insulin-sensitivity S_I were either very small (less than 1.0×10^{-5}) or very large (greater than 1.0×10^{-2}). In all these cases the coefficients of variation of S_I resulted very large, with a single value of 76% and the rest varying between 480% and 70,000%, when constraining the parameters $b_2 \geq 10^{-5}$ and $b_3 \geq 10^{-7}$. In each of these 9 cases, when the b_2 and b_3 parameters were left unconstrained (but greater than zero) the coefficients of variation resulted to be even larger. If these extreme-S_I subjects are not considered, the scatter plot of figure 7 shows a clear positive correlation between K_{xgI} and S_I ($r = 0.85$).

The homeostasis model assessment index, HOMA (computed as the product of the fasting values of glucose, expressed as mg/dL, and insulin, expressed as μU/mL, divided by the constant 22.5) was compared to the estimated S_I and K_{xgI} parameter values. Table 6 reports the correlation results, which are negative since, while S_I and K_{xgI} are indices of insulin-sensitivity, HOMA is an index of insulin resistance. The upper part of the table reports results referred to the whole sample of 41 subjects, while the lower part of the table does not consider the 9 subjects for which the S_I index could not be reliably computed. The correlation between HOMA and K_{xgI} is about the same in the two analyses and is significant in both, whereas the correlation between HOMA and S_I is stronger in the reduced 32-subject sample than over all 41 subjects, and is significant only in the reduced sample.

As an example of single-subject confidence region determination, figure 8 reports the asymptotic 99%, 95%, 90% and 50% confidence regions for the V_G and K_{xgI} parameters from Subject 1.

Sample parameter estimates

Table 7 reports the sample means of the parameter estimates of the SDM as well as their correlation matrix, whereas Table 8 reports the same results for the MM estimated with the standard WLS approach.

It is of interest to note that K_{xgI} and S_I , which measure the same phenomenon, have the same theoretical definition and are computed in the same units, coincide very well in absolute numerical value when the 9 subjects discussed above are not considered ($K_{xgI} = 1.33 \times 10^{-4}$ $min^{-1}pM^{-1}$ vs $S_I = 1.24 \times 10^{-4}$ $min^{-1}pM^{-1}$), whereas differ markedly if the whole sample is considered ($K_{xgI} = 1.41 \times 10^{-4}$ $min^{-1}pM^{-1}$ vs. $S_I = 8.71 \times 10^{-3}$ $min^{-1}pM^{-1}$).

Coefficient of variations for glucose and insulin, when considering the SDM, were estimated by GLS to be respectively 19.8% and 31.6%. (for the MM when adopting the GLS procedure they were estimated to be respectively 17.8% and 31.8%). Although the estimated values are much larger than those reported in literature (9) (1.5% for glucose and 7% for insulin), they reflect both the variability due to measurement error and the variability due to actual oscillation of glucose and insulin concentrations in plasma. While these error estimates are rather large, they may be more realistic, in vivo, than simple estimates of the variance of repeated laboratory measurements on the same solutions.

Discussion

The present work introduces a new model for the interpretation of glucose and insulin concentrations observed during an IVGTT. The model has been compared with the Minimal Model in a sample of "normal" subjects: these subjects' IVGTT's were selected from a larger group of available IVGTT's on the basis of the normality of baseline Glycemia (< 7 mM) and of BMI (< 30Kg/m^2). The new model was chosen on the basis of the Akaike criterion from a group of four different two-compartment models: all models in the group included first-order insulin elimination kinetics, second-order insulin-dependent net glucose tissue uptake, a zero-order net hepatic glucose output and progressively increasing but eventually saturating pancreatic insulin secretion in response to rising glucose concentrations. The final model was chosen because neither the addition of a delay in the insulin action on glucose uptake, nor the addition of a spontaneous, insulin-independent, first-order glucose elimination term appeared to improve model performance.

The delay in the glucose action on pancreatic response, expressed in the discrete SDM by the explicit term τ_g, parallels the non-autonomous t term in the Minimal Model equation for dI/dt (10), which makes pancreatic responsiveness increase as time from the glucose bolus grows. It is on the contrary somewhat surprising that the best model among those studied does not appear to need an explicit delay in insulin dynamics, which had been expressed in the Minimal Model by the 'remote-compartment' insulin activity X (9). Some reports have indirectly substantiated (46,47) an anatomical basis for this delay: it should be kept in mind, however, that an actual delay in the cellular or molecular effect of the hormone is not at all necessary in order to explain the apparent delay in action, as judged by a perceptible decrease in glucose concentrations: in order to explain the observations in the present series, an explicit representation of this mechanism does not seem necessary.

Similarly, another difference with respect to commonly accepted concepts is the lack of a "glucose effectiveness term", i.e. of a first-order, insulin-independent tissue glucose uptake rate term. Except for the fact that it has become customary to see this term included in glucose/insulin models, there appears to be no physiological mechanism to support first-order glucose elimination from plasma, when exception is made of glycemias above the renal threshold and when diffusion into a different compartment is discounted. Tissues in the body (except for brain) do not take up glucose irrespective of insulin, while brain glucose consumption is, under physiological conditions, relatively constant, and is subsumed, for the purposes of the present model, in the net hepatic glucose output term. Again, if such a first-

order mechanism is present, to the effect of fitting the present data series its explicit representation did not seem necessary.

The selected discrete SDM gives apparent fits to the data largely equivalent to those of the Minimal Model (e.g. figures 3, 4, and 5). The sometimes closer adaptation of the MM to the observations depends on the fact that the SDM fits glycemias and insulinemias simultaneously, producing parameter estimates compatible with the integrated feedback loop regulating glucose and insulin. On the other hand, the MM is fitted separately on glycemias and insulinemias: the need of simultaneously fitting the other state variable constrains the SDM, while the MM is not similarly constrained and is therefore freer to adapt to the observations. Further, the SDM has a total of six free parameters, with respect to the eight free parameters of the MM, and this translates into a less flexible, if more stable, model.
It should be noticed that the strategy of fitting one state variable at a time (while assuming the linearly interpolated, noisy observations of the other state variable to provide the true input function) decouples the regulatory system. While the fit is apparently better, the expected feedback effect, of the state variable being fitted onto the other state variable, is disregarded.
It happens thus that the estimated parameters are optimal in predicting the observed glucose assuming the erratic observed insulin as the true value of the insulin concentration, but are far from optimal when the expected glucose determines the expected insulin and is then determined by it in its turn. The separate fitting strategy produces sets of estimated parameters such that the expected time course of glucose using the expected time course of insulin as input may differ markedly from both the actual glucose observations and from the expected glucose obtained using the noisy insulin observations as input. In other words, the separate fitting strategy produces parameter values which do not make model predictions of glucose and insulin consistent with each other.

The possibility to derive an index of insulin-sensitivity is essential to any model which aims at being useful to diabetologists. The application of the same definition of Insulin-Sensitivity-Index to both the SDM and the MM gives rise to two quantities (the K_{xgI} and the S_I) which have the same units of measurement and, over a restricted subject sample, approximately the same average value and a correlation coefficient of 0.85.
One evident difference between the performances of the SDM and the MM over the 41 subjects considered in this series relates to the stability of estimation, in particular with respect to the insulin sensitivity indices (K_{xgI} for the SDM and S_I for the MM). Whereas in

every one of the 41 subjects considered, the estimate of K_{xgI} had a coefficient of variation smaller than 52% (i.e. its 95% asymptotic confidence region excluded the zero), in 14 out of 41 'normal' subjects (about 1/3) the S_I did not result significantly different from zero. Four of these poorly identified S_I's were very small (below 1.E-05), whereas 10 were not small or actually very large: this would contradict the simplistic postulation that only those S_I's are unidentifiable which are too small to be measured, hence correspond to high degrees of insulin resistance. Correlation between the S_I and the K_{xgI} was poor when considering all 41 subjects, rather good when excluding those subjects whose S_I was either very large or very small. Average values of the K_{xgI} and correlation of the K_{xgI} with the HOMA were very similar when using either the full 41-subject sample or the restricted 32-subject sample; average values of S_I varied by two orders of magnitude, and correlation with HOMA dropped, when going from the restricted to the full sample.
Besides the insulin-sensitivity index, also all other model parameters were generally identifiable with the SDM and often not identifiable with the MM, pointing to the fact that the MM appears overparametrized with respect to the information available from the standard IVGTT.

Finally, another difference between the SDM and the MM is that the SDM has been designed for simultaneous fitting to glucose and insulin concentrations and has been proven to have mathematically consistent solutions, admitting the fasting-state equilibrium and converging back to it from the perturbed state. Also, the sigmoidal shape of pancreatic insulin secretion in response to increasing glucose concentrations agrees with plausible physiology. These statistical, mathematical and physiological design features have been shown to translate, when applying the model to available data, into a meaningful, stable estimate of the subject's insulin sensitivity from a standard IVGTT.

Appendix

To obtain subject-specific model parameters and population estimates on the SDM the GLS method was used. GLS is a two-stage method:

(1) at first individual estimates β_i^* for each subject i (i=1,…,41) are obtained;

(2) then the estimates β_i^* are used to construct the population estimates.

When observations are taken at different times from several subjects, it is important to take into account in the modeling procedure two sources of variability: random variation among measurements within a given individual and random variation among individuals. To accommodate these two different variance components a hierarchical statistical model was built:

***Stage 1 (intra-individual variation)*:**

given the model:

$$y_i = f_i(\beta_i) + e_i$$

$$E(e_i|\beta_i) = 0 \quad Cov(e_i|\beta_i) = R(\beta_i, \xi)$$

where $E(y_i) = f_i$ with f_i representing the numerical solution of SDM for subject i, the variability within subject i is expressed by means of the functional form of $R(\beta_i, \xi)$, where the additional intra-individual covariance parameter vector ξ is the same across the individuals. Denotiing with G and I respectively the state variable Glucose and the state variable Insulin, the variance-covariance matrix R in the present application has the structure of a block-diagonal matrix:

$$R_i = \begin{bmatrix} R_G & 0 \\ 0 & R_I \end{bmatrix}$$

where

$$R_i = \begin{bmatrix} \sigma_G^2 f_{iG}^2(\beta_i, t_{i1}) & \dots & 0 \\ \dots & \dots & \dots \\ 0 & \dots & \sigma_I^2 f_{iI}^2(\beta_i, t_{in_{iI}}) \end{bmatrix}.$$

The parameters σ_G^2 and σ_I^2, which have to be estimated, are the squares of the coefficients of variation respectively for glucose and insulin.

Stage 2 (inter-individual variation):

In the second stage of the hierarchical model the variation among individuals (due for example to gender, age, treatment group or simply to biological variability among different individuals), is taken into account by means of a statistical model for the subject structural parameters β_i. In this work the simplest case of a linear model has been considered:

$$\beta_i = \beta + b_i,\ b_i \sim N(0, D)$$

where β is the vector of the fixed effects or the vector of the population parameters, whereas b_i is the vector of the random effects for the i-th individual.

The Standard Two Stage method (STS) proceeds according to the following scheme:

STAGE 1:

(1) In m separate estimation procedures (where m is the total number of subjects), obtain preliminary estimates $\beta_i^{(p)}$ for each individual i, i=1,…,m (m = 41).

(2) Use residuals from these preliminary fits to estimate $\xi = (\sigma_G^2,\ \sigma_I^2)$ minimizing the following function:

$$PL = \sum_{i=1}^{m} \log\left|R_i(\beta_i^{(p)}, \xi)\right| + \left[y_i - f_i(\beta_i^{(p)})\right]^T R_i^{-1}(\beta_i^{(p)}, \xi)\left[y_i - f_i(\beta_i^{(p)})\right]$$

(3) Form estimated weight matrices based on the estimated parameters $\hat{\xi}$ and $\beta_i^{(p)}$:

$$\hat{R}_i(\beta_i^{(p)}, \hat{\xi})$$

(4) Using the estimated weight matrices from step (3), re-estimate the β_i by means of m minimizations: for each individual i, i=1,…m minimize the following quantity

$$[y_i - f_i(\beta_i)]^T R^{-1}(\beta_i^{(p)}, \hat{\xi})[y_i - f_i(\beta_i)].$$

The resulting estimates can be treated as preliminary estimates and it is possible to return to point (2). The algorithm should be iterated at least once and for each individual i the final estimates are denoted with $\beta_{i_{GLS}}$.

STAGE 2:

In this stage it is assumed that the estimates $\beta_{i_{GLS}}$ are treated as they were known. So the population estimates of the vector β and of the variance-covariance matrix D are given by the sample mean and the sample variance-covariance matrix:

$$\hat{\beta} = \frac{1}{m}\sum_{i=1}^{m} \hat{\beta}_{i_{GLS}} \quad \text{and} \quad \hat{D} = \frac{1}{(m-1)}\sum_{i=1}^{m} (\hat{\beta}_{i_{GLS}} - \hat{\beta})^T (\hat{\beta}_{i_{GLS}} - \hat{\beta}) \quad .$$

Table 1: *Antropometric characteristics of the subjects studied.*

Subject	Gb mM	Ib pM	Gender	Age yrs	Height cm	BW kg	BMI Kg/m^2
1	4.39	62.47	M	35	172	72	24.34
2	4.39	51.70	F	28	155	45	18.73
3	4.11	29.37	F	25	162	61	23.24
4	4.44	56.58	M	32	169	68	23.81
5	4.33	47.39	F	26	157	48	19.47
6	5.06	39.20	F	25	155	53	22.06
7	4.89	68.64	F	27	162	65	24.77
8	4.44	53.63	M	28	181	85	25.95
9	4.89	41.07	M	26	175	72	23.51
10	5.00	24.96	M	25	170	66	22.84
11	5.22	82.80	F	32	154	66	27.83
12	4.39	115.10	F	34	158	64	25.64
13	4.11	24.00	M	27	173	82	27.40
14	3.78	15.83	F	44	157	60	24.34
15	3.94	24.00	F	26	160	61	23.83
16	4.11	65.97	F	43	156	61	25.07
17	4.33	14.62	F	38	167	71	25.46
18	4.28	13.80	F	27	156	57	23.42
19	4.17	22.64	F	45	166	76	27.58
20	4.09	98.00	F	39	166	72	26.13
21	4.83	49.98	M	47	176	89	28.73
22	4.15	41.73	F	63	164	59	21.94
23	4.44	35.94	M	57	180	85	26.23
24	4.61	30.28	M	66	165	81	29.75
25	4.94	30.80	M	52	170	70	24.22
26	4.83	29.40	M	42	172	78	26.37
27	4.72	39.90	M	45	170	80	27.68
28	4.56	19.25	M	70	186	81	23.41
29	4.44	26.25	F	55	169	67	23.46
30	4.50	28.70	M	62	169	68	23.81
31	4.67	20.30	M	44	172	70	23.66
32	5.22	37.80	F	72	158	62	24.84
33	5.83	38.40	M	71	180	74	22.84
34	5.33	40.20	F	62	160	62	24.22
35	4.39	24.60	M	71	170	71	24.57
36	4.83	36.00	F	72	158	62	24.84
37	3.89	50.40	M	71	180	73	22.53
38	3.78	39.60	F	62	160	64	25.00
39	3.89	29.40	M	52	160	58	22.66
40	3.99	35.00	F	43	154	52	21.93
41	5.83	26.40	F	65	165	71	26.08

Table 2. *Tested models and relative average Akaike information Criterion (AIC).*

Model	Desciption	Free parameters	Average AIC
A	Without first order plasma glucose elimination (K_{xg}) and without delay on insulin action (τ_I)	V_G, I_Δ, τ_G, K_{xgI}, K_{xi}, γ	385.26
B	With first order plasma glucose elimination (K_{xg}) and without delay on insulin action (τ_I)	V_G, I_Δ, τ_G, K_{xgI}, K_{xi}, γ, K_{xg}	387.89
C	Without first order plasma glucose elimination (Kxg) and with delay on insulin action (τ_I)	V_G, I_Δ, τ_G, K_{xgI}, K_{xi}, γ, K_{xg}, τ_I	388.13
D	With first order plasma glucose elimination (K_{xg}) and with delay on insulin action (τ_I)	V_G, I_Δ, τ_G, K_{xgI}, K_{xi}, γ, K_{xg}, K_{xg}, τ_I	390.35

Table 3: *Subject-specific model parameters obtained with the* SDM.

Subject	V_G	CV	I_Δ	CV	τ_G	CV	K_{xgI}	CV	K_{xi}	CV	γ	CV	T_{igmax}	T_{gh}
1	0.194	13.50	56.98	14.70	23.50	0.12	5.30E-05	15.54	0.059	14.74	2.52	20.69	6.60	0.0028
2	0.104	14.98	38.89	15.10	18.00	0.13	1.83E-04	13.60	0.140	11.13	2.08	15.60	9.87	0.0043
3	0.110	14.54	27.81	14.52	19.00	0.17	2.06E-04	13.52	0.117	11.93	1.77	20.98	4.30	0.0027
4	0.135	15.80	90.91	17.92	60.00	0.66	7.48E-05	13.88	0.075	11.98	0.96	59.21	3.16	0.0025
5	0.120	14.49	47.64	17.37	40.50	0.67	1.06E-04	13.56	0.069	15.99	0.79	94.77	2.28	0.0026
6	0.184	14.65	33.29	16.52	14.22	0.41	1.23E-04	15.90	0.076	13.41	2.35	25.69	3.61	0.0045
7	0.196	14.20	38.38	17.62	11.00	0.40	9.15E-05	15.31	0.053	14.45	2.35	20.84	4.77	0.0060
8	0.099	13.75	42.68	36.40	0.00	2.56E+06	1.30E-04	12.48	0.125	9.42	3.38	11.11	19.96	0.0031
9	0.156	11.86	40.08	13.69	18.50	0.10	7.00E-05	13.45	0.062	11.41	3.46	14.10	5.92	0.0022
10	0.151	13.15	15.10	18.70	8.00	0.13	2.43E-04	14.29	0.140	11.59	2.73	17.32	5.22	0.0046
11	0.132	13.25	38.16	15.45	32.50	0.11	9.85E-05	13.86	0.062	11.90	2.53	15.55	6.40	0.0056
12	0.146	14.21	67.85	38.54	0.00	2.13E+15	6.48E-05	13.93	0.060	12.69	1.76	24.34	7.77	0.0048
13	0.292	13.65	37.82	14.80	13.50	0.06	1.23E-04	16.04	0.096	17.08	3.26	14.99	7.96	0.0035
14	0.129	17.96	31.92	37.25	0.00	5.87E+23	3.43E-04	17.27	0.245	10.06	1.60	27.34	4.87	0.0026
15	0.191	15.77	42.67	36.96	0.00	9.30E+31	2.33E-04	14.30	0.079	10.31	2.10	14.82	3.14	0.0042
16	0.242	15.82	63.18	19.01	20.00	9.65	9.31E-05	18.44	0.063	16.64	0.76	117.08	2.92	0.0061
17	0.196	14.93	35.59	14.98	30.50	0.11	1.44E-04	18.11	0.064	16.54	3.42	16.79	3.08	0.0018
18	0.104	19.06	30.20	35.54	0.50	0.70	4.28E-04	17.04	0.246	9.94	1.58	32.13	3.60	0.0026
19	0.140	12.07	87.75	13.28	13.50	0.19	4.33E-05	11.94	0.058	9.49	3.82	12.15	6.56	0.0006
20	0.190	16.93	89.45	23.49	35.43	34.37	8.18E-05	21.66	0.158	31.08	1.96	24.33	22.04	0.0062
21	0.215	12.88	77.78	12.80	21.50	0.10	5.07E-05	12.92	0.059	10.79	3.90	12.29	8.98	0.0026
22	0.180	11.64	23.42	13.59	23.50	0.22	1.11E-04	12.54	0.039	14.22	1.98	24.68	2.29	0.0035
23	0.140	14.21	46.48	14.62	12.00	0.14	1.41E-04	13.28	0.174	10.07	2.22	17.94	9.06	0.0031
24	0.200	12.40	61.45	13.52	16.50	0.10	5.69E-05	14.13	0.074	11.50	3.46	16.71	6.25	0.0016
25	0.200	11.68	44.69	12.84	28.50	0.08	6.08E-05	13.83	0.061	10.90	3.67	16.93	4.71	0.0019
26	0.191	12.55	48.87	13.78	26.50	0.07	8.07E-05	14.53	0.101	9.83	3.09	18.59	5.77	0.0022

Subject	V_G	CV	I_Δ	CV	τ_G	CV	K_{xgI}	CV	K_{xi}	CV	γ	CV	T_{igmax}	T_{gh}
27	0.103	12.63	64.24	12.37	24.00	0.16	6.32E-05	11.22	0.084	8.89	3.17	13.74	7.27	0.0012
28	0.183	12.20	45.08	12.33	21.00	0.18	8.27E-05	13.24	0.076	10.96	3.65	14.75	4.73	0.0013
29	0.180	11.88	41.48	12.25	28.50	0.08	8.09E-05	13.17	0.066	10.93	3.05	16.99	4.17	0.0017
30	0.199	13.06	53.19	14.18	19.50	0.10	7.85E-05	15.17	0.091	11.16	2.58	23.98	4.54	0.0020
31	0.089	14.91	54.59	14.77	5.50	0.01	2.28E-04	12.16	0.451	10.45	4.15	9.11	37.18	0.0019
32	0.087	12.92	27.42	14.00	18.50	0.15	1.25E-04	12.05	0.090	8.94	2.20	24.33	3.66	0.0021
33	0.168	15.56	18.05	16.96	34.50	0.23	1.64E-04	15.79	0.039	14.47	2.50	27.87	1.49	0.0062
34	0.065	11.39	11.70	15.09	28.50	0.11	2.84E-04	11.39	0.067	10.20	2.32	14.19	2.93	0.0040
35	0.099	13.74	24.69	14.20	11.50	0.07	2.30E-04	11.95	0.117	10.10	2.65	12.50	5.55	0.0025
36	0.106	12.70	20.33	14.09	22.50	0.12	1.59E-04	13.25	0.086	10.31	1.88	24.91	3.27	0.0029
37	0.141	12.90	19.04	15.50	28.00	0.37	1.41E-04	14.66	0.064	14.55	1.20	41.67	3.02	0.0039
38	0.099	12.11	22.82	13.01	18.50	0.12	1.61E-04	11.70	0.068	11.14	1.97	14.30	4.43	0.0024
39	0.106	15.30	23.53	15.14	23.50	0.06	3.07E-04	13.43	0.145	10.30	1.50	20.98	4.81	0.0037
40	0.226	11.76	21.77	17.18	10.50	0.15	1.13E-04	15.28	0.059	15.83	2.47	21.88	4.34	0.0036
41	0.113	13.14	23.32	14.40	22.50	0.21	1.10E-04	13.30	0.051	11.00	3.52	20.06	1.87	0.0019

Table 4: *Subject-specific model parameters for the MM and Insulin Sensitivity index (SI) as obtained from the WLS procedure*

Subject	b_0	CV	b_1	CV	b_2	CV	b_3	CV	b_4	CV	b_5	CV	b_6	CV	b_7	CV	S_I (b_3/b_2)	CV
1	11.38	0.92	0.00010	3177.28	0.06556	22.44	4.03E-06	31.36	0.09684	13.00	4.24	1.77	0.063	9.90	513.73	5.41	6.15E-05	38.57
2	14.45	0.84	0.03204	4.29	0.01048	12.65	2.21E-06	8.00	4.00E-01	8.25	5.05	1.47	0.261	5.74	1048.47	5.83	2.11E-04	14.96
3	13.88	0.80	0.02199	5.20	0.00001	20164.61	9.11E-07	19.35	9.66E-02	13.41	5.26	3.84	0.153	5.37	559.81	5.05	9.11E-02	20164.84
4	12.22	1.15	0.02457	18.07	0.05113	15.93	2.39E-06	22.20	2.77E-04	2974.77	0.00	1.33E+08	0.082	2.90	1341.96	3.49	4.67E-05	27.33
5	13.95	1.07	0.03415	8.60	0.03656	209.02	1.00E-07	434.93	3.44E-02	42.01	4.90	7.23	0.088	5.67	896.32	4.35	2.74E-06	482.55
6	12.37	0.65	0.00010	1544.60	0.07643	9.97	1.14E-05	11.84	1.28E-03	209.93	1.00E-04	8.81E+06	0.037	8.26	258.93	3.99	1.50E-04	15.48
7	12.78	0.92	0.02723	7.21	0.02940	17.56	1.91E-06	18.14	1.37E-01	22.74	4.72	2.60	0.066	14.47	379.98	5.25	6.49E-05	25.24
8	16.31	1.26	0.04284	11.41	0.07448	14.27	8.01E-06	13.94	5.74E-17	Inf	2.31	Inf	0.096	Inf	1307.60	Inf	1.08E-04	19.95
9	16.34	0.75	0.03151	2.54	0.00290	52.15	5.71E-07	10.13	3.54E-01	6.46	4.11	0.42	0.197	7.34	708.79	5.71	1.97E-04	53.13
10	16.15	0.93	0.02840	8.52	0.05833	22.11	1.09E-05	25.13	1.46E-01	8.72	4.65	0.33	0.209	9.79	198.95	6.48	1.87E-04	33.48
11	13.71	0.69	0.00010	3142.81	0.06779	17.72	7.23E-06	21.11	0.17001	14.11	4.78	2.39	0.106	9.74	619.81	5.63	1.07E-04	27.57
12	13.58	0.95	0.03373	6.25	0.03241	12.46	1.50E-06	12.43	4.00E-01	35.08	5.45	8.36	0.074	11.35	1007.60	4.60	4.63E-05	17.60
13	9.59	1.01	0.00811	44.08	0.79241	90.22	7.89E-05	99.59	4.01E-01	8.74	4.35	0.42	0.191	10.10	253.83	6.25	9.96E-05	134.38
14	11.78	0.89	0.02739	7.15	0.00001	71472.70	1.02E-06	72.04	3.13E-02	8.96	3.29	1.28	0.198	3.82	433.39	4.96	1.02E-01	71465.59
15	9.59	0.69	0.01528	10.35	0.08593	8.09	1.91E-05	7.26	3.91E-01	25.53	4.25	0.64	0.105	5.22	493.58	3.79	2.23E-04	10.87
16	9.21	0.68	0.00785	13.65	0.07147	11.43	3.80E-06	13.32	3.21E-02	13.76	2.64	5.50	0.055	4.62	559.74	3.49	5.32E-05	17.55
17	10.80	1.28	0.00635	97.75	0.06373	18.50	7.96E-06	37.45	5.23E-01	10.60	6.12	1.10	0.209	7.07	557.50	5.68	1.25E-04	41.78
18	11.42	1.25	0.02076	25.73	0.02104	28.82	6.79E-06	35.30	2.70E-02	14.78	4.28	4.66	0.224	3.37	559.39	4.91	3.23E-04	45.57
19	13.85	1.01	0.02425	9.34	0.04026	35.08	2.89E-07	67.35	1.08E-04	2538.95	1.00E-04	9.39E+07	0.034	4.56	1032.82	3.08	7.17E-06	75.94
20	10.71	0.76	0.00010	3459.34	0.05667	24.51	5.01E-06	28.92	2.92E-01	14.40	4.06	2.00	0.229	8.41	1120.37	6.16	8.84E-05	37.91
21	11.55	0.76	0.00010	865.25	0.20240	16.52	1.06E-05	17.69	4.56E-01	7.67	4.54	0.94	0.112	7.81	769.63	4.98	5.25E-05	24.20
22	12.24	1.10	0.01040	36.78	0.04197	37.94	4.15E-06	45.57	5.54E-02	13.97	3.71	0.84	0.064	10.62	272.58	5.01	9.89E-05	59.30
23	14.08	0.81	0.02547	4.82	0.00607	48.91	9.99E-07	20.66	4.88E-02	8.83	3.69	1.04	0.098	5.71	415.40	4.67	1.65E-04	53.09
24	13.02	0.74	0.00010	699.34	0.13435	10.41	1.11E-05	11.36	0.00187	159.00	1.00E-04	5.32E+06	0.024	8.74	383.31	3.38	8.29E-05	15.40
25	13.18	0.87	0.00010	771.27	0.30057	24.06	2.21E-05	25.64	1.93E-01	4.86	4.71	0.79	0.180	5.16	688.69	5.24	7.37E-05	35.16
26	14.33	0.88	0.00014	473.20	1.00000	29.13	0.000111	29.51	9.33E-02	4.58	3.64	0.82	0.186	4.27	671.15	5.02	1.11E-04	41.47
27	16.44	0.76	0.02407	3.84	0.00001	23007.84	2.24E-07	19.84	1.83E-01	6.48	4.73	0.95	0.120	4.82	1386.05	4.53	2.24E-02	23007.84
28	13.60	0.96	0.02532	10.14	0.03729	72.28	7.70E-07	96.33	1.69E-01	6.37	4.52	0.16	0.131	6.01	550.06	4.87	2.07E-05	120.43
29	12.35	0.63	0.00010	1213.05	0.06593	10.82	6.41E-06	13.64	5.96E-02	6.66	3.43	0.82	0.094	5.31	504.03	4.41	9.72E-05	17.41

Subject	b_0	CV	b_1	CV	b_2	CV	b_3	CV	b_4	CV	b_5	CV	b_6	CV	b_7	CV	S_I (b_3/b_2)	CV
30	10.56	1.04	0.00010	3173.90	0.01661	30.20	1.90E-06	34.42	3.20E-02	8.45	4.24	1.55	0.070	5.08	423.62	4.07	1.14E-04	45.79
31	15.14	1.12	0.02810	10.99	0.04443	10.04	7.22E-06	11.98	1	9.09	7.30	1.45	0.184	6.20	603.93	4.80	1.63E-04	15.63
32	19.57	0.78	0.02579	3.74	0.00001	35816.97	3.06E-07	33.20	2.56E-02	12.78	5.03	2.11	0.067	5.77	478.06	4.11	3.06E-02	35815.74
33	20.17	0.99	0.06875	1.87	0.00001	20601.18	1.07E-06	15.88	1.50E-01	10.06	5.04	0.64	0.140	9.02	306.24	6.47	1.07E-01	20601.18
34	27.24	0.85	0.05967	1.94	0.01370	11.34	3.39E-06	7.50	2.09E-15	3.93E+13	4.41	4.60E+12	0.037	5.06	248.75	3.57	2.47E-04	13.60
35	14.65	1.07	0.02410	12.08	0.03892	14.17	6.12E-06	16.39	1.95E-01	10.30	4.60	2.31	0.137	7.79	465.94	5.32	1.57E-04	21.66
36	15.39	1.15	0.00030	1173.31	0.03356	10.41	6.36E-06	21.48	5.66E-02	9.98	5.45	2.13	0.122	6.34	428.22	5.16	1.89E-04	23.87
37	14.62	0.90	0.02208	7.42	0.03815	430.69	1.00E-07	812.73	8.33E-02	14.19	5.20	3.25	0.124	8.80	304.30	5.85	2.62E-06	919.79
38	17.28	0.88	0.03127	4.43	0.02260	13.33	2.24E-06	13.42	2.28E-01	10.31	4.23	2.41	0.148	8.46	557.97	5.52	9.90E-05	18.91
39	14.79	0.88	0.03992	4.50	0.02203	530.30	1.00E-07	685.33	1.34E-01	8.58	4.43	2.39	0.273	4.66	649.00	5.62	4.54E-06	866.55
40	11.75	0.85	0.02078	6.75	0.02179	25.10	2.25E-06	20.50	0.15297	8.60	3.42	0.56	0.152	9.30	254.54	5.97	1.03E-04	32.41
41	16.73	0.76	0.00010	2566.12	0.07667	13.06	8.03E-06	19.01	4.40E-16	6.61E+13	3.00	7.56E+12	0.026	4.77	304.62	3.20	1.05E-04	23.06

Table 5: *Subject-specific model parameters for the MM and Insulin Sensitivity index (SI) as obtained from the GLS procedure*

Subject	b_0	CV	b_1	CV	b_2	CV	b_3	CV	b_4	CV	b_5	CV	b_6	CV	b_7	CV	S_I (b_3/b_2)	CV
1	12.10	10.03	1.64E-02	75.58	0.00381	923.96	3.62E-07	261.87	5.52E-02	230.77	4.30	29.39	0.059	167.55	504.87	89.63	9.50E-05	960.35
2	14.42	9.81	3.10E-02	53.60	0.01116	141.72	2.31E-06	93.99	2.74E-01	146.24	5.10	24.11	0.255	94.03	1053.20	97.55	2.07E-04	170.06
3	13.87	9.29	2.17E-02	62.79	0.00000	9.94E+08	9.18E-07	227.38	6.33E-02	226.35	5.34	60.80	0.152	88.74	561.71	84.70	3.87E+02	9.94E+08
4	12.31	13.77	2.57E-02	216.38	0.04846	202.77	2.23E-06	282.05	1.67E-04	50587.15	0.00	2.25E+09	0.082	48.93	1344.60	58.67	4.60E-05	347.37
5	13.41	10.16	2.68E-02	66.61	0.00308	1047.93	4.33E-07	310.62	2.16E-02	688.90	4.98	113.22	0.088	93.78	899.39	73.06	1.41E-04	1092.99
6	12.38	7.62	1.84E-09	9.97E+08	0.07155	116.06	1.08E-05	138.03	7.40E-04	3451.56	0.00	1.45E+08	0.037	135.27	259.96	66.66	1.50E-04	180.34
7	12.78	10.78	2.67E-02	89.40	0.02982	208.09	1.95E-06	217.61	8.16E-02	454.20	5.17	66.23	0.057	251.15	361.00	83.70	6.53E-05	301.10
8	16.76	14.89	4.36E-02	140.42	0.07331	174.27	7.96E-06	171.35	5.86E-17	Inf	2.40	Inf	0.096	Inf	1309.40	Inf	1.09E-04	244.40
9	16.32	8.74	3.12E-02	30.37	0.00326	547.19	5.83E-07	118.43	2.30E-01	119.48	4.12	7.54	0.192	118.97	718.95	94.77	1.79E-04	559.87
10	16.25	10.85	2.87E-02	100.95	0.05684	262.60	1.06E-05	299.29	9.17E-02	164.23	4.65	5.53	0.195	159.65	197.88	106.70	1.87E-04	398.17
11	13.76	8.02	8.22E-09	4.71E+08	0.06555	210.96	6.99E-06	253.81	1.03E-01	249.62	4.83	45.13	0.103	159.53	623.08	93.86	1.07E-04	330.04
12	13.62	10.95	3.44E-02	68.60	0.02843	141.93	1.36E-06	137.25	2.63E-01	602.86	5.70	150.26	0.074	187.72	1015.00	78.19	4.79E-05	197.44
13	9.62	11.91	7.72E-03	540.60	0.72111	954.77	7.29E-05	1060.72	2.57E-01	161.69	4.36	7.09	0.183	164.12	256.51	103.59	1.01E-04	1427.20
14	11.77	10.44	2.72E-02	86.80	0.00000	7.84E+09	1.01E-06	858.15	2.06E-02	154.66	3.30	21.48	0.197	63.13	435.32	83.13	9.36E+02	7.84E+09
15	9.73	8.22	1.69E-02	131.44	0.07885	104.55	1.77E-05	92.75	2.48E-01	521.84	4.34	171.62	0.106	114.42	505.95	73.37	2.24E-04	139.76
16	9.09	7.62	9.71E-03	159.29	0.04657	169.50	2.37E-06	196.51	1.91E-02	231.22	2.65	90.45	0.055	76.91	560.82	58.52	5.09E-05	259.51
17	10.88	15.13	7.05E-03	1128.78	0.06169	242.14	7.58E-06	489.26	3.44E-01	184.87	6.16	18.11	0.201	116.01	556.54	94.86	1.23E-04	545.89
18	11.42	15.07	1.87E-02	394.42	0.02299	353.76	7.59E-06	449.62	1.77E-02	295.58	4.28	113.69	0.222	55.92	561.71	82.43	3.30E-04	572.11
19	13.34	9.14	2.09E-02	53.72	0.00024	11055.48	1.53E-07	229.93	6.25E-05	41299.80	0.00	1.53E+09	0.034	75.30	1033.20	51.58	6.51E-04	11058.17
20	10.28	13.10	1.77E-09	4.57E+09	0.03206	626.16	2.97E-06	672.56	1.96E-01	247.69	4.09	32.84	0.226	138.66	1124.50	103.33	9.25E-05	918.92
21	11.57	8.77	1.08E-11	9.39E+10	0.17208	174.68	9.13E-06	187.71	2.83E-01	136.82	4.58	15.93	0.110	128.79	777.18	82.92	5.30E-05	256.42
22	12.27	12.98	1.04E-02	460.05	0.04161	472.41	4.11E-06	569.59	3.19E-02	240.62	3.72	14.39	0.062	173.99	273.43	83.52	9.88E-05	740.01
23	14.05	9.66	2.47E-02	63.12	0.00744	498.51	1.10E-06	249.95	2.89E-02	155.27	3.68	17.84	0.096	94.84	413.75	77.82	1.48E-04	557.64
24	12.90	8.45	2.67E-13	3.20E+12	0.11327	115.36	9.39E-06	126.71	1.07E-03	2601.16	0.00	8.73E+07	0.024	143.24	383.38	56.55	8.29E-05	171.35
25	13.07	9.96	1.31E-10	7.38E+09	0.20657	230.35	1.52E-05	252.98	1.25E-01	89.45	4.75	15.30	0.176	85.42	686.42	87.41	7.37E-05	342.13
26	14.51	10.68	1.09E-10	7.01E+09	1.00000	449.34	0.0001123	454.12	6.72E-02	85.16	3.84	14.24	0.188	71.50	683.09	84.70	1.12E-04	638.85
27	16.42	8.89	2.38E-02	46.13	0.00000	1.71E+09	2.27E-07	231.80	1.13E-01	114.01	4.76	15.90	0.118	79.98	1383.30	75.65	1.45E+02	1.71E+09
28	13.60	10.87	1.46E-02	201.19	0.21601	339.71	1.10E-05	453.02	1.04E-01	114.36	4.52	2.77	0.128	98.62	554.73	81.24	5.08E-05	566.27
29	12.14	14.00	7.02E-03	751.42	0.02258	674.92	2.05E-06	666.60	3.58E-02	117.05	3.44	13.46	0.092	88.20	502.15	73.46	9.10E-05	948.61

Subject	b_0	CV	b_1	CV	b_2	CV	b_3	CV	b_4	CV	b_5	CV	b_6	CV	b_7	CV	S_I (b_3/b_2)	CV
30	6.40E-05	6.14E+04	0.01664	366.38	1.90E-06	422.27	1.84E-02	148.89	4.25	27.65	0.068	84.63	419.48	67.63	1.14E-04	559.07	6.40E-05	6.14E+04
31	2.82E-02	133.58	0.04403	120.15	7.18E-06	144.71	1.00E+00	124.22	7.44	17.59	0.232	108.72	619.63	86.04	1.63E-04	188.09	2.82E-02	133.58
32	2.56E-02	45.01	0.00000	6.93E+09	2.90E-07	414.61	4.88E-02	246.36	7.11	44.10	0.091	109.61	544.78	76.37	4.55E+02	6.93E+09	2.56E-02	45.01
33	6.48E-02	23.05	0.00000	2.26E+09	1.04E-06	183.75	9.53E-02	178.61	5.03	12.86	0.140	146.13	316.42	108.42	9.83E+02	2.26E+09	6.48E-02	23.05
34	5.70E-02	24.19	0.01531	119.96	3.80E-06	83.19	1.40E-15	1.32E+16	6.17	1.07E+14	0.037	211.24	248.85	57.28	2.48E-04	145.98	5.70E-02	24.19
35	2.35E-02	159.39	0.04007	174.16	6.33E-06	206.38	1.24E-01	190.20	4.78	51.30	0.132	125.19	462.76	87.24	1.58E-04	270.05	2.35E-02	159.39
36	1.02E-03	4.24E+03	0.03254	129.88	6.02E-06	269.12	3.47E-02	175.69	5.49	36.74	0.119	104.82	426.05	86.02	1.85E-04	298.82	1.02E-03	4.24E+03
37	2.23E-02	Inf	0.14341	Inf	3.49E-19	Inf	5.16E-02	243.27	5.23	52.63	0.121	144.25	304.18	97.55	2.43E-18	Inf	2.23E-02	Inf
38	2.99E-02	58.29	0.02410	153.23	2.44E-06	160.04	1.42E-01	185.43	4.31	39.07	0.141	140.71	556.71	92.26	1.01E-04	221.56	2.99E-02	58.29
39	3.98E-02	Inf	0.07513	Inf	1.18E-19	Inf	9.22E-02	149.77	4.46	39.71	0.268	76.20	653.11	93.98	1.57E-18	Inf	3.98E-02	Inf
40	2.06E-02	81.90	0.02199	295.02	2.27E-06	243.62	9.40E-02	154.99	3.42	9.45	0.148	152.59	258.13	99.27	1.03E-04	382.62	2.06E-02	81.90
41	9.17E-11	3.35E+10	0.07294	153.58	7.67E-06	224.79	9.83E-17	Inf	5.69	Inf	0.026	Inf	304.69	Inf	1.05E-04	272.25	9.17E-11	3.35E+10

Table 6: *Correlation between HOMA and the two insulin-sensitivity indices K_{xgI} and S_I*

		K_{xgI}	S_I
HOMA full sample	**Pearson Correlation**	-0.424	-0.131
	Sig. (2-tailed)	0.006	0.415
	N	41	41
		K_{xgI}	S_I
HOMA reduced sample	**Pearson Correlation**	-0.408	-0.374
	Sig. (2-tailed)	0.020	0.035
	N	32	32

Table 7: *Descriptive Statistics of the parameter estimates for the SDM.*

Average parameter estimates						
Parameter	V_G	I_Δ	τ_g	K_{xgI}	k_{xi}	γ
Values	0.154	42.203	19.613	1.41E-04	0.100	2.495
SD	0.050	20.484	12.150	8.70E-05	0.074	0.879
CV (%)	32.43	48.54	61.95	61.89	73.63	35.21
SE	0.008	3.199	1.897	1.36E-05	0.012	0.137
CV (%)	5.06	7.58	9.67	9.66	11.50	5.50
Correlation matrix of the average parameter estimates						
	V_G	I_Δ	τ_g	K_{xgI}	k_{xi}	γ
V_G		0.273	0.036	-0.468	-0.346	0.176
I_Δ			0.209	-0.544	0.025	0.133
t_G				-0.386	-0.394	-0.198
K_{xgI}					0.570	-0.314
k_{xi}						0.068
σ_G^2	0.039	CV_G	19.82%			
σ_I^2	0.099	CV_I	31.55%			

Table 8: *Descriptive Statistics of the parameter estimates from the WLS methods for the MM.*

Average parameter estimates									
Parameter	b_0	b_1	b_2	b_3	b_4	b_5	b_6	b_7	S_I
Values	13.97	0.01936	0.09156	9.28E-06	0.1671	3.99	0.1260	598.02	0.00871
SD	3.272	0.017	0.194	2.05E-05	0.197	1.598	0.067	313.686	0.027
CV (%)	23.42	87.19	211.95	221.32	118.01	40.01	52.95	52.45	306.35
SE	0.511	0.003	0.030	3.21E-06	0.031	0.250	0.010	48.990	0.004
CV (%)	3.66	13.62	33.10	34.56	18.43	6.25	8.27	8.19	47.84

Correlation matrix of the parameter estimates								
	b_0	b_1	b_2	b_3	b_4	b_5	b_6	b_7
b_0		0.650	-0.194	-0.163	-0.145	0.172	-0.124	-0.072
b_1			-0.345	-0.315	0.016	0.188	0.135	0.107
b_2				0.984	0.100	-0.050	0.176	-0.064
b_3					0.105	-0.029	0.202	-0.103
b_4						0.570	0.451	0.116
b_5							0.465	-0.137
b_6								0.115

Figure 1. Schematic representation of the two-compartiment, one-discrete-delay model. V_G and V_I are the distribution volumes respectively for Glucose (G) and Insulin (I). B_G stands for the glucose bolus administered; K_{xgI} is the second-order net elimination rate of glucose; K_{xi} is the first order elimination rate of insulin; T_{gh} is the net difference between glucose production and glucose elimination; T_{igmax} is the maximal rate of second phase insulin release.

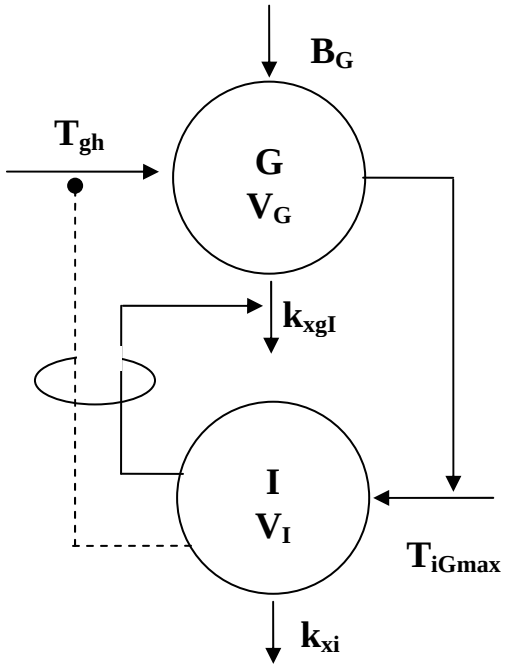


Figure 2. Second-phase pancreatic insulin secretion versus plasma glucose concentrations, as computed from average values of the SDM parameters.

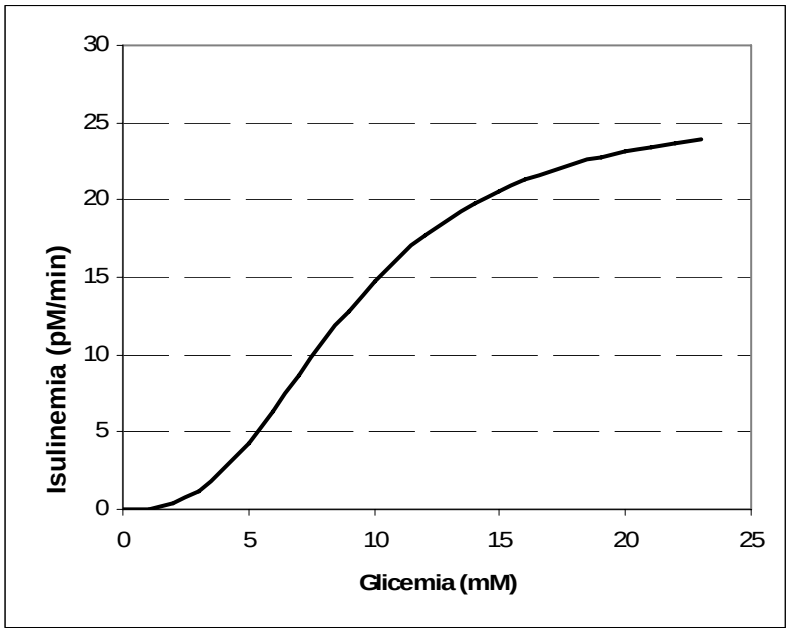


Figure 3. Glucose and Insulin (circles) concentrations versus time together with the predicted time-curves from the SDM (continue lines) and the MM (dotted lines) for subject 13.

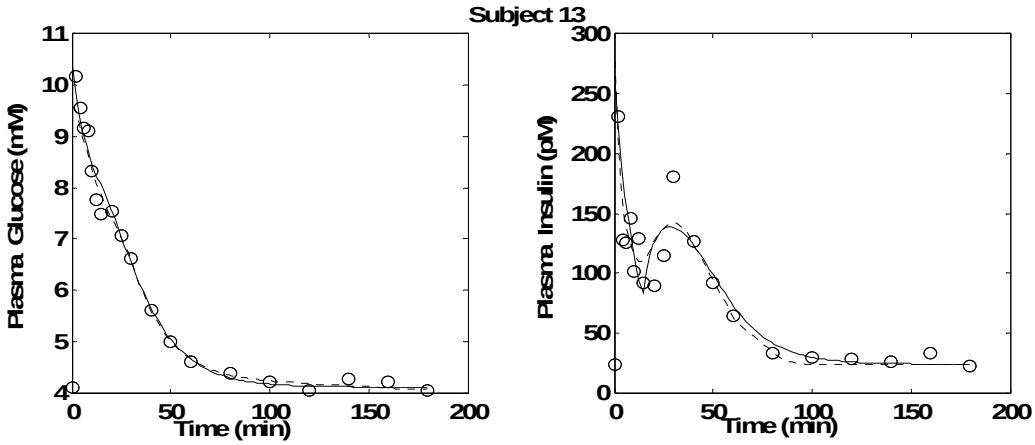


Figure 4. Glucose and Insulin (circles) concentrations versus time together with the predicted time-curves from the SDM (continue lines) and the MM (dotted lines) for subject 27.

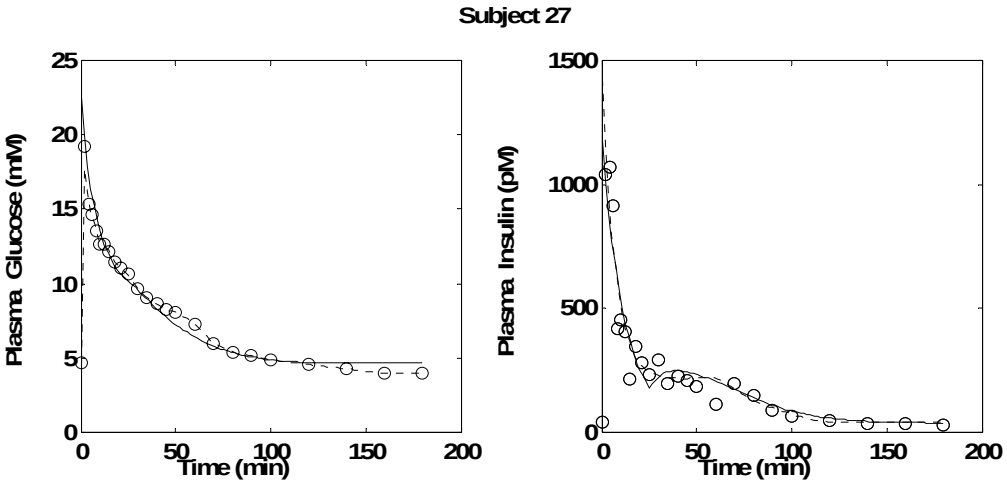


Figure 5. Glucose and Insulin (circles) concentrations versus time together with the predicted time-curves from the SDM (continue lines) and the MM (dotted lines) for subject 29.

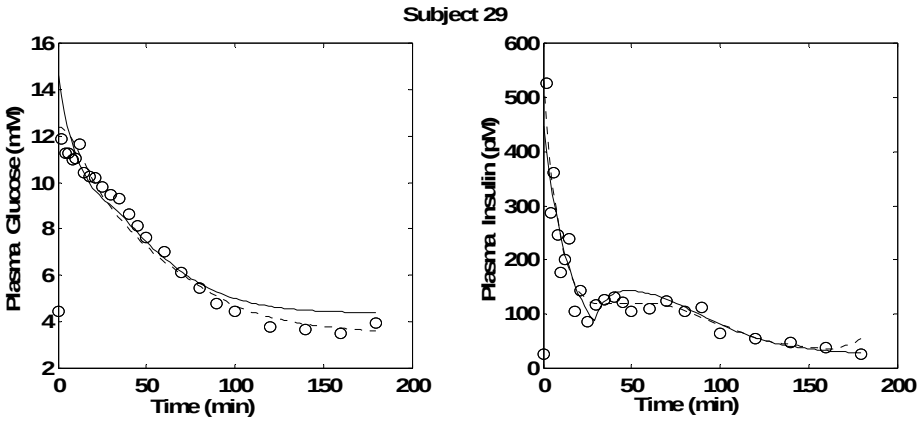


Figure 6. Scatter plot between the Insulin Sensitivity (S_I) derived from MM and the parameter K_{xgI}.

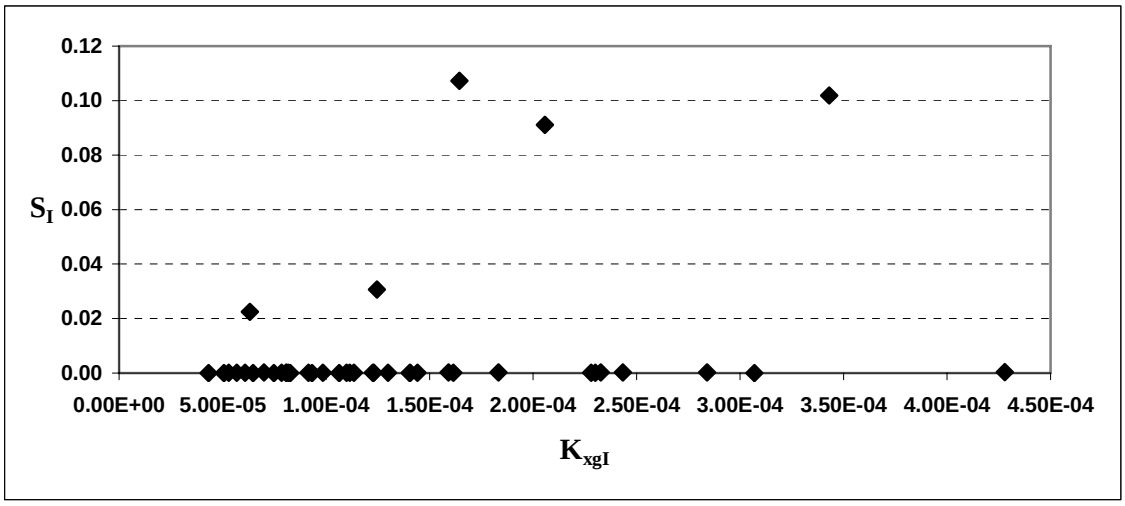


Figure 7. Scatter plot between the Insulin Sensitivity (S_I) derived from MM and the parameter K_{xgI}.

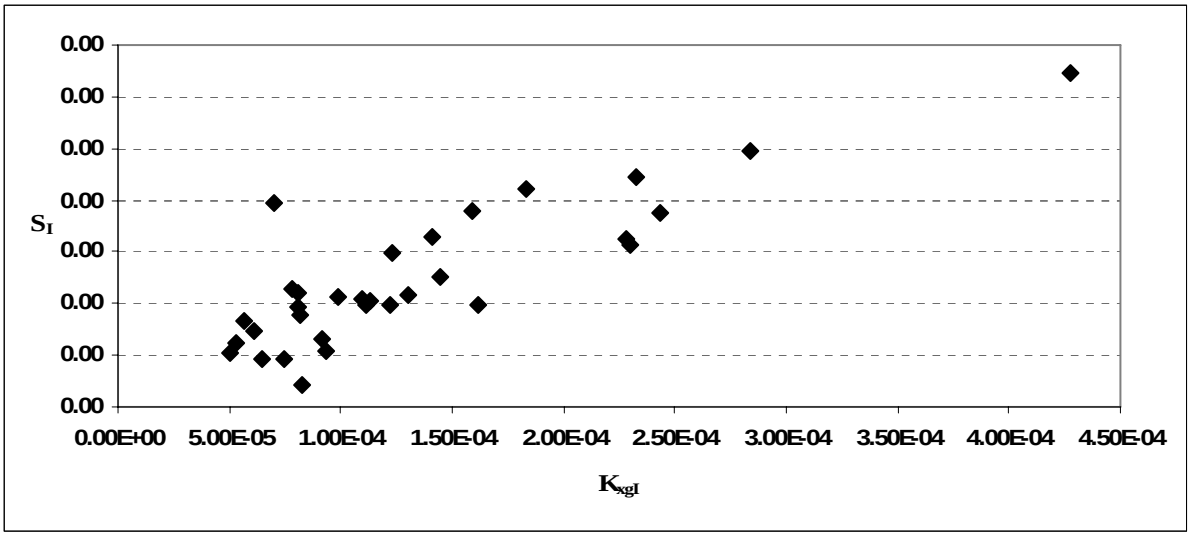
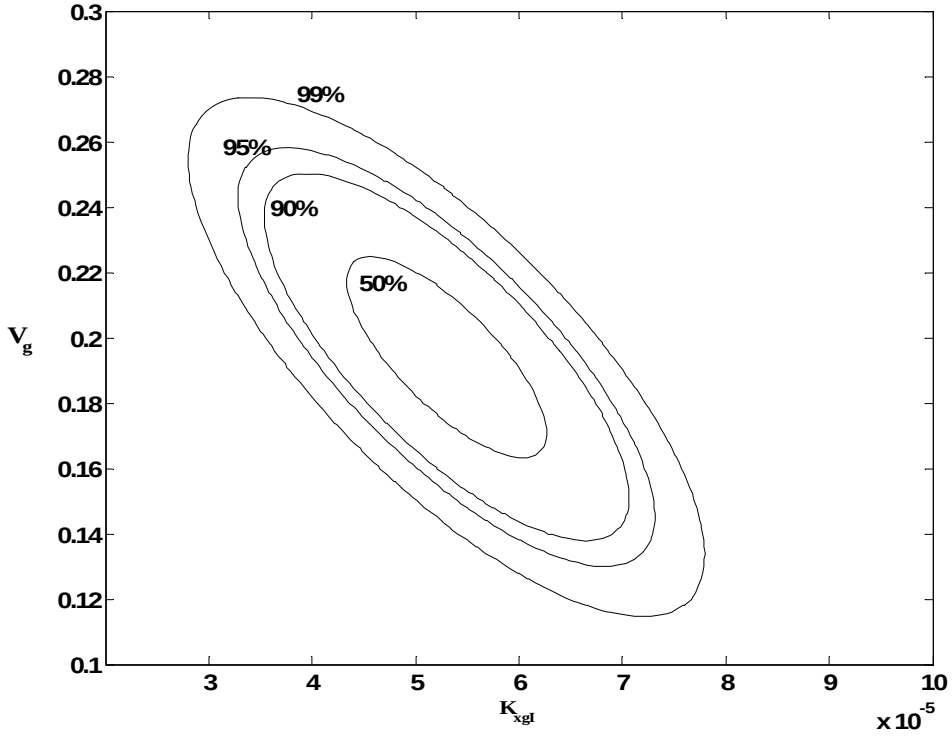


Figure 8. Confidence regions at 99%, 95%, 90% and 50% for the V_G and K_{xgI} parameters from Subject 01.



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