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MINMOD: a computer program to calculate insulin sensitivity and pancreatic responsivity from the frequently sampled intravenous glucose tolerance test

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Insulin sensitivity and pancreatic responsivity are the two main factors controlling glucose tolerance. We have proposed a method for measuring these two factors, using computer analysis of a frequently-sampled intravenous glucose tolerance test (FSIGT). This 'minimal modelling approach' fits two mathematical models with FSIGT glucose and insulin data: one of glucose disappearance and one of insulin kinetics. MINMOD is the computer program which identifies the model parameters for each individual. A nonlinear least squares estimation technique is used, employing a gradient-type of estimation algorithm, and the first derivatives (not known analytically) are computed according to the 'sensitivity approach'. The program yields the parameter estimates and the precision of their estimation. From the model parameters, it is possible to extract four indices: (1) S_G, the ability of glucose per se to enhance its own disappearance at basal insulin, (2) S_I, the tissue insulin sensitivity index, (3) ϕ_1, first phase pancreatic responsivity, and (4) ϕ_2, second phase pancreatic responsitivity. These four characteristic parameters have been shown to represent an integrated metabolic portrait of a single individual.

Mathematical modelling Parameter estimation Least squares Glucose tolerance Insulin sensitivity Diabetes

1. Introduction

Diabetes mellitus and related metabolic disorders are characterized by an inability to dispose of glucose from the blood at normal rates. Although many factors contribute to this defect, two are recognized to play a major role. Gluose disposal depends upon the ability of pancreatic B-cells to secrete insulin in response to glucose stimuli (pancreatic responsivity) and upon the capability of insulin to increase glucose uptake in muscles, liver and adipose tissue (insulin sensitivity). Failure in one or both of these two factors (B-cell impairment and/or insulin resistance) can lead to impaired glucose tolerance, or, if severe, to overt diabetes mellitus [1]. Quantitative knowledge of the two factors should improve classification, prognosis and therapy of the disease.

Several methods have been proposed to assess the relative contributions of B-cell response and insulin sensitivity to glucose tolerance [2–6]. These methods are generally difficult to perform, labor intensive, expensive and not without risk to the patient (cf. [7]). In addition they do not provide simultaneous measurements of insulin sensitivity and pancreatic responsivity, as these methods require suppression of the pancreas. For these reasons we have conceived, developed and experimentally validated a new approach for interpre-

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ting intravenous glucose tolerance data which does provide measures of B-cell function and insulin sensitivity. This method, the 'minimal approach' [8,9], utilizes a digital computer to analyze the plasma glucose and insulin dynamics observed following glucose injection. It yields an in vivo measurement of the relative contributions of the pancreas and insulin-sensitive tissues to glucose disposal. This method has been used in animals [8] and man [10,11] and has been validated in both [12,13]. In this paper we present 'MINMOD', the computer program which analyzes frequently-sampled intravenous glucose tolerance (FSIGT) data and provides the values for the parameters which represent insulin sensitivity (S_I), glucose effectiveness (S_G), and pancreatic responsiveness (first and second phase; ϕ_1 and ϕ_2). These four parameters have been described as representing a comprehensive metabolic portrait of a single individual [10].

2. Background minimal model approach

Our group has been involved in the quantitative assessment of insulin sensitivity for several years [8] and we have gained experience in using several different methods [10,14,15]. The lesson we have learned is that the general tendency is to perform complicated experiments in order to have direct measurements which require only simple mathematical calculations. We believe that the converse method should be preferable. We propose the performing of a simple experiment, the results of which require the use of the computer to be analyzed. These considerations led our group to develop the 'minimal model approach'. From the results of a FSIGT test this tool yields a set of parameters which describe, in quantitative terms, the metabolic status of a single patient. MINMOD is the computer program which provides these parameters.

3. Description of the method

Liver and peripheral tissues, including muscle, are the tissues primarily responsible for the disposition of administered glucose. Utilization processes are controlled by insulin, which enhances glucose uptake. At the same time an increase in glucose concentration augments pancreatic insulin release. The presence of this feedback loop leads to difficulties in interpretation of test results. To overcome this problem, we have decomposed the system into two independent components [16]: (1) the effect of insulin to accelerate glucose uptake and (2) the effect of glucose to enhance insulin secretion. The two subsystems have then been described in mathematical terms by means of two 'minimal' models. In general, minimal modelling indicates a rigorous strategy for selecting models from among a series of rival models of variable complexity. This technique has been successfully applied to the glucose/insulin system in vivo; the rationale and the reasoning which led to the choice of the 'best' models have previously been detailed [8,9]. The two selected models are:

$$\frac{dG}{dt} = -(p_1 + X(t)) \cdot G(t) + p_1 \cdot G_b,$$

$$G(0) = G_0 \tag{1}$$

$$\frac{dX}{dt} = -p_2 \cdot X(t) + p_3 \cdot (I(t) - I_b), \quad X(0) = 0 \tag{2}$$

for glucose disappearance and:

$$\frac{dI}{dt} = -n \cdot I(t) + \gamma \cdot (G(t) - h) \cdot t, \quad I(0) = I_0 \tag{3}$$

for insulin kinetics.

$G(t)$ and $I(t)$ represent the time courses of glucose and insulin in plasma following a rapid glucose injection (usually 0.3 g of glucose per kg body weight); G_b and I_b are basal (preinjection) values; $X(t)$ is the variable which describes the insulin effect on net glucose disappearance and p_1, p_2, p_3, G_0, n, γ, h and I_0 are parameters. Parameter p_1 describes 'glucose effectiveness' S_G, which is the effect of glucose per se, at basal insulin, to normalize the glucose concentration within the extracellular glucose pool [17]. The

ratio between p_3 and p_2 defines S_I, the insulin sensitivity index, which represents the insulin-dependent increase in the net glucose disappearance rate [8]. Parameter n represents fractional insulin clearance [9]. In addition, from the parameters of the model in Eq. 3, it is possible to obtain a quantitative description of the pancreatic sensitivity to any increase in plasma glucose concentration. Since the pancreas typically shows a biphasic reponse when glucose increases rapidly we obtain from the estimated parameters of model 3 two calculated parameters, ϕ_1 and ϕ_2, which describe the sensitivity to glucose of the first and second phase pancreatic responsivity, respectively [9]. They are defined as:

$$\phi_1 = \frac{I_{max} - I_b}{n \cdot (G_0 - G_b)} \tag{4}$$

$$\phi_2 = \gamma \times 10^4 \tag{5}$$

where I_{max} is the computed maximum of first peak insulin release.

4. Description of the program

4.1. General considerations

In Fig. 1 a simplified flow chart of the program is shown. Once discrete glucose and insulin time courses are entered into the computer, the user selects the model to be identified. If the 'glucose disappearance model' (Eqs. 1 and 2) is chosen, insulin data are used as input to the model, and parameters are calculated in order to produce a simulated glucose pattern which fits the measured glucose data. The converse occurs if the 'insulin kinetics model' is identified; in this case glucose is the input and MINMOD searches for the best fit of insulin data.

4.2. Parameter estimation

The program searches for the best set of parameters which allow the minimization of

$$S(\mathbf{P}) = \sum_{i=1}^{N} \frac{1}{\sigma^2(t_i)} (Y(t_i) - f(t_i, \mathbf{P}))^2 \tag{6}$$

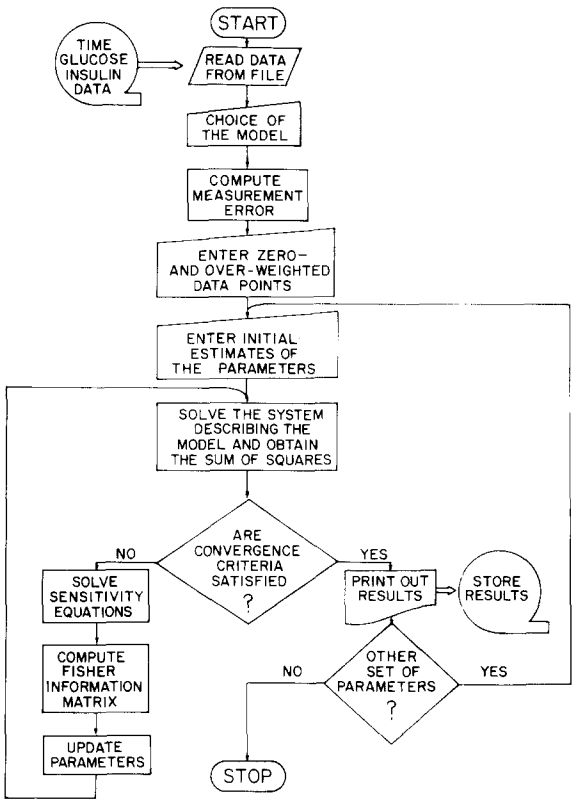


Fig. 1. Simplified flowchart of program MINMOD.

where N is the number of data points, t_i are the discrete times at which FSIGT sampling occurred, Y represents the measured variable to be fitted (glucose if the model 1-2 is identified or insulin if model 3 is identified). Term $f(t_i, \mathbf{P})$ is the model-computed function which fits the data and depends on $\mathbf{P}$, the vector of parameters. For the glucose model (Eqs. 1 and 2):

$$\mathbf{P} = [p_1 \;\; p_2 \;\; p_3 \;\; G_0]^T \tag{7}$$

and for insulin model (Eq. 3):

$$\mathbf{P} = [n \;\; \gamma \;\; h \;\; I_0]^T. \tag{8}$$

$\sigma(t_i)$ is the standard deviation of the measurement error at time t_i.

A nonlinear least squares estimation technique is used [18]. The algorithm selected for this purpose is that of Marquardt [19] which has been

found suitably efficient in parameter estimation of dynamic metabolic models. In particular, the general version of Fletcher [20] has been adapted to the particular situation of the minimal models. This yielded the development of a package of subroutines which is reduced in size in comparison with commercially available software (e.g. [21]). Therefore it has been possible to implement the whole program on microcomputers with limited memory capability.

4.3. Sensitivity equations

The adapted least squares method uses the gradient-type of estimation algorithm which requires the evaluation of the first derivative of the model prediction $f(t, \mathbf{P})$ with respect to every single element of the parameter vector $\mathbf{P}$. Models 1-2 and 3 are not dynamically linear and therefore it is not possible to calculate the exact derivatives since the dependence of $f(t, \mathbf{P})$ on the parameters $\mathbf{P}$ is not known analytically. The program uses the 'sensitivity approach' [18] to calculate the derivatives. In particular, derivatives of Eqs. 1 and 2 are taken with respect to p_1, p_2, p_3, and G_0, and the following system is obtained:

$$\frac{\partial \dot{G}}{\partial p_1} = -(p_1 + X) \cdot \frac{\partial G}{\partial p_1} - (G - G_b), \quad \left.\frac{\partial G}{\partial p_1}\right|_{t=0} = 0 \tag{9a}$$

$$\frac{\partial \dot{G}}{\partial p_2} = -(p_1 + X) \cdot \frac{\partial G}{\partial p_2} - G\frac{\partial X}{\partial p_2}, \quad \left.\frac{\partial G}{\partial p_2}\right|_{t=0} = 0 \tag{9b}$$

$$\frac{\partial \dot{G}}{\partial p_3} = -(p_1 + X) \cdot \frac{\partial G}{\partial p_3} - G\frac{\partial X}{\partial p_3}, \quad \left.\frac{\partial G}{\partial p_3}\right|_{t=0} = 0 \tag{9c}$$

$$\frac{\partial \dot{G}}{\partial G_0} = -(p_1 + X) \cdot \frac{\partial G}{\partial G_0}, \quad \left.\frac{\partial G}{\partial G_0}\right|_{t=0} = 1 \tag{9d}$$

$$\frac{\partial \dot{X}}{\partial p_2} = -p_2 \cdot \frac{\partial X}{\partial p_2} - X, \quad \left.\frac{\partial X}{\partial p_2}\right|_{t=0} = 0 \tag{9e}$$

$$\frac{\partial \dot{X}}{\partial p_3} = -p_2 \cdot \frac{\partial X}{\partial p_3} + (I - I_b), \quad \left.\frac{\partial X}{\partial p_3}\right|_{t=0} = 0 \tag{9f}$$

From Eq. 2 we can derive:

$$\frac{\partial X}{\partial p_1} = \frac{\partial X}{\partial G_0} = 0. \tag{9g}$$

For the insulin kinetics model (Eq. 3) the system of derivatives is the following:

$$\frac{\partial \dot{I}}{\partial n} = -n \cdot \frac{\partial I}{\partial n} - I, \quad \left.\frac{\partial I}{\partial n}\right|_{t=0} = 0 \tag{10a}$$

$$\frac{\partial \dot{I}}{\partial \gamma} = -n \cdot \frac{\partial I}{\partial \gamma} + (G - h) \cdot t, \quad \left.\frac{\partial I}{\partial \gamma}\right|_{t=0} = 0 \tag{10b}$$

$$\frac{\partial \dot{I}}{\partial h} = -n \cdot \frac{\partial I}{\partial h} - \gamma \cdot t, \quad \left.\frac{\partial I}{\partial h}\right|_{t=0} = 0 \tag{10c}$$

$$\frac{\partial \dot{I}}{\partial I_0} = -n \cdot \frac{\partial I}{\partial I_0}, \quad \left.\frac{\partial I}{\partial I_0}\right|_{t=0} = 1 \tag{10d}$$

4.4. Measurement error and weighting scheme

The measurement error is assumed 'white', Gaussian of zero mean, and with a coefficient of variation of 1.5% for glucose data and 7% for insulin data. These values derive from our experience, but can be changed by the user. The rationale and the problems tackled by this approach are detailed in [22]. If the user feels that some measurement lies out of the expected pattern (due to errors in specimen collection, contamination of the test tube, and/or error in the analysis), it is possible to zero-weight that point and the program will ignore it.

The zero-weighting feature is particularly useful for the early part of the glucose pattern. During the first ten minutes after the injection, the pattern of plasma glucose is dominated by extracellular mixing. Because the model assumes a single well-mixed glucose pool, these early data points must not be taken into account for analysis of the glucose model. The program has a built-in weighting scheme which assumes that the mixing phase is complete by the eighth minute after the injec-

tion. In addition, for simulation purposes, the user may wish to have the computed pattern passing through a specific point. In this case it is possible to over-weight that point (1000 fold).

4.5. Initial estimates of the parameters

The program automatically calculates a set of initial estimates of the parameters, $\mathbf{P}_0$. For model 1-2 the initial estimates of p_1 and G_0 are calculated by means of a linear regression of the first five glucose data points which are not zero-weighted. The slope of the regression yields p_1 while the zero-intercept is G_0. The values of p_2 and p_3 are assigned in order to give an initial sensitivity index of 5×10^{-4} min^{-1} $(\mu\text{U ml}^{-1})^{-1}$ (average normal value in humans [10]).

The linear regression is also used to calculate the initial estimates of n and I_0 of model 3. In this case, the insulin data points used are the maximum value of the first peak and the subsequent two data points. The initial γ is 0.0028 min^{-2} $(\mu\text{U ml}^{-1})(\text{mg dl}^{-1})^{-1}$ [10] and the basal glucose value is assigned to h. This rationale for $\mathbf{P}_0$ is based upon our experience from a wide number of identifications carried out in both animals and man. However, a different set of initial estimates may be assigned by the user (see below).

4.6. Solution of differential equations and parameter estimation

For the glucose disappearance model, the system in Eqs. 9 is coupled to Eqs. 1 and 2. For the insulin kinetics model the global system is comprised of Eq. 3 and the system in Eqs. 10. At the kth iteration the global systems are solved for the current set of parameter estimates ($\mathbf{P}_{k-1}$), the time course of $f_k(t_i, \mathbf{P}_{k-1})$ is calculated, and the sum of weighted squares S_k is computed according to Eq. 6. The algorithm which minimizes the sum of weighted squares updates the parameters. This is done in an iterative manner until the final least squares estimate, $\hat{\mathbf{P}}$, is found [20]. The systems of differential equations are solved using a fourth order Runge–Kutta integration algorithm [23]. A fixed step size has been applied and set to 1 min for the glucose model and 0.5 min for the insulin model.

4.7. Analysis of results

In order to assess the adequacy of the computed results, three criteria have been adopted: (1) the goodness of fit, (2) the analysis of the residual errors, and (3) the precision of parameter estimates [18]. The goodness of fit is evaluated by examining the residual sum of squares $S(\hat{\mathbf{P}})$ (from Eq. 6) corresponding to the final parameter estimates $\hat{\mathbf{P}}$. As for the analysis of the residual errors, since there is not a statistically large number of data points, statistical tests (correlation techniques for whiteness and χ^2 for normality) may not be suitable for use. In this case empirical visual methods may be adopted to check whether $[Y(t_i) - f(t_i, \hat{\mathbf{P}})]$ exhibits outliers or systematic deviations. The program output provides at every time the simulated glucose or insulin time course and the deviations from measured values. Assuming that an unbiased, minimum variance estimator is used, the Cramer–Rao theorem can be used and thus the minimum covariance (maximum precision) matrix of the parameter estimates is given by the inverse of the Fisher information matrix.

The program proceeds as follows. At every iteration, the 4×4 Fisher information matrix $\mathbf{J}$ is computed. Its generic element is given by

$$j_{\ell m} = \sum_{i=1}^{N} \frac{1}{\sigma^2(t_i)} \cdot \frac{\partial f(t_i, \mathbf{P})}{\partial p_\ell} \cdot \frac{\partial f(t_i, \mathbf{P})}{\partial p_m} \qquad (11)$$

with $\ell = 1, \ldots, 4$, $m = 1, \ldots, 4$, and p_ℓ, p_m are the generic elements of the vectors given by Eqs. 7 or 8 according to the model which is identified. The derivatives are numerically computed at every iteration, solving systems 9 or 10 for the current set of parameters. The inverse of $\mathbf{J}$ gives a lower bound of the covariance matrix $\mathbf{V}$ of the parameter estimates. Its diagonal element $v_{\ell\ell}$ (p_ℓ) provides the variance of the parameter p_ℓ. If $\hat{p}_\ell$ is the final least squares estimation of p_ℓ, the precision of its estimate can be expressed in terms of: $\hat{p}_\ell \pm \sqrt{v_{\ell\ell}(\hat{p}_\ell)}$ [18]. In the final printout, the program provides a measure of precision for esti-

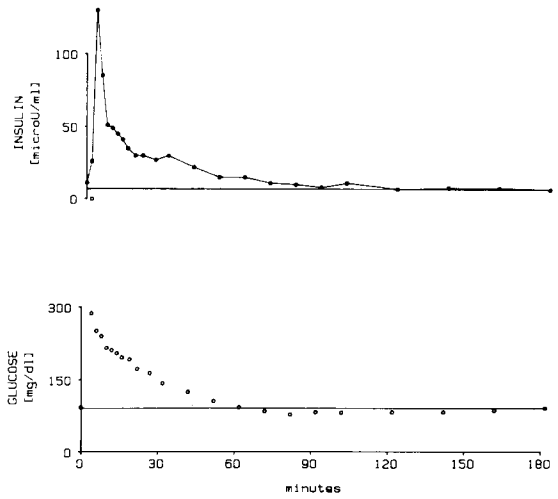
mated parameter* through the coefficient of variation (or fractional standard deviation FSD($\hat{p}_\ell$)) defined as:

$$\mathrm{FSD}(\hat{p}_\ell) = \frac{\sqrt{v_{\ell\ell}(\hat{p}_\ell)}}{\hat{p}_\ell} \times 100 \qquad (12)$$

5. Example run

A typical FSIGT pattern is depicted in Fig. 2. Glucose injection occurred at 0 min (lasting for 30 sec), provoking an initial increment in glucose, followed by a decline. By 1 h glucose is again normalized, and in the subsequent 2 h, a modest undershoot is observed. Hyperglycemia induces an immediate peak in insulin release followed by a decline, and the classical 'second phase' (slower secretion rate) [10]. Glucose and insulin values are stored in a file which is the input to the program (bottom panel of Fig. 2).

After entering the number of desired zero-weight and/or over-weight data points and initial parameter estimates, the program displays the iteration number and the current sum of squares. When the minimum residual square sum has been reached, the result output is printed. In Fig. 3, the printouts of the results are shown for the two minimal models. The program can then be rerun with the same data, with new data, or terminated. In Fig. 4 the continuous line represents the 'best'



Data File : A:NORMAL.DAT

TIME	GLUCOSE	INSULIN
0.0	92.0	11.0
2.0	350.0	26.0
4.0	287.0	130.0
6.0	251.0	85.0
8.0	240.0	51.0
10.0	216.0	49.0
12.0	211.0	45.0
14.0	205.0	41.0
16.0	196.0	35.0
19.0	192.0	30.0
22.0	172.0	30.0
27.0	163.0	27.0
32.0	142.0	30.0
42.0	124.0	22.0
52.0	105.0	15.0
62.0	92.0	15.0
72.0	84.0	11.0
82.0	77.0	10.0
92.0	82.0	8.0
102.0	81.0	11.0
122.0	82.0	7.0
142.0	82.0	8.0
162.0	85.0	8.0
182.0	90.0	7.0

Fig. 2. Time courses of glucose and insulin concentration in plasma during the FSIGT (upper panel). Glucose (0.3 g/kg) was injected at $t = 0$. Insulin data points are linearly connected. Horizontal continuous lines represent the basal levels. The bottom panel shows the data file used as input to the program.

* In the course of the identification process the parameters to be estimated are not subject to any constraints. Although they should be positive by definition (see models Eqs. 1-2 and 3), the program may lead to negative values if these values allow the best fit of the data. This happens if the FSIGT patterns are poorly defined due to sampling errors during the performance of the experiment or to measurement assay errors. Also, negative results may depend upon the choice of the initial parameter estimates. The iterative estimation algorithm can achieve a local minimum; this situation can be identified by a high residual sum of squares, and by a value of 'X' which does not approach zero at 180 min. In such a case, it is advisable to rerun with a different set of initial parameter estimates. This approach must also be used when negative parameters are obtained.

```
---  IDENTIFICATION RESULTS  ---

DATA FILE  :  A:NORMAL.DAT
MODEL : Insulin Sensitivity Model
OPTION :  1
ZERO-WEIGHTED SAMPLES
   1    2    3    4

OVER-WEIGHTED SAMPLES
   5
PARAMETER INITIAL ESTIMATES
      P(1)  =  0.399E-01
      P(2)  =  0.200E-01
      P(3)  =  0.400E-04
      G(0)  =  0.287E+03
```

TIME	OBS.GLU	COMP.GLU	DIFFER	INS.EFFECT	INSULIN
0.0	92.0	287.0	+195.0	0.00E+00	11.0
2.0	350.0	275.1	-74.9	0.20E-03	26.0
4.0	287.0	263.7	-23.3	0.17E-02	130.0
6.0	251.0	251.9	+0.9	0.37E-02	85.0
8.0	240.0	240.2	+0.2	0.48E-02	51.0
10.0	216.0	228.8	+12.8	0.55E-02	49.0
12.0	211.0	218.0	+7.0	0.61E-02	45.0
14.0	205.0	207.7	+2.7	0.66E-02	41.0
16.0	196.0	198.0	+2.0	0.70E-02	35.0
19.0	192.0	184.6	-7.4	0.73E-02	30.0
22.0	172.0	172.4	+0.4	0.76E-02	30.0
27.0	163.0	154.7	-8.3	0.79E-02	27.0
32.0	142.0	140.0	-2.0	0.82E-02	30.0
42.0	124.0	117.5	-6.5	0.85E-02	22.0
52.0	105.0	102.4	-2.6	0.80E-02	15.0
62.0	92.0	92.8	+0.8	0.72E-02	15.0
72.0	84.0	86.8	+2.8	0.64E-02	11.0
82.0	77.0	83.3	+6.3	0.56E-02	10.0
92.0	82.0	81.5	-0.5	0.47E-02	8.0
102.0	81.0	80.7	-0.3	0.41E-02	11.0
122.0	82.0	80.8	-1.2	0.30E-02	7.0
142.0	82.0	82.1	+0.1	0.21E-02	8.0
162.0	85.0	83.6	-1.4	0.15E-02	8.0
182.0	90.0	84.9	-5.1	0.11E-02	7.0

```
   CONVERGENCE ACHIEVED AFTER   9 ITERATIONS

   FINAL SUM OF SQUARE IS  107.9

   FINAL PARAMETER VALUES ( % FSD )

      P(1)  =  0.3082E-01     (   6.6 )
      P(2)  =  0.2093E-01     (  18.2 )
      P(3)  =  0.1062E-04     (  16.3 )
      G(0)  =  0.2870E+03     (   0.9 )

   SENSITIVITY INDEX  =   5.07 E-04    (  33.2 )
```

Fig. 3A. Computer printout of the results of the identification of glucose model (Eqs. 1-2). Option 1 means that the program automatically chooses the weighting scheme and the initial estimates of the parameters. Then, a summary of zero-weighted and over-weighted data points is reported, along with the initial parameter estimates. For every sampling time, the following is shown: the measured glucose (OBS.GLU), the simulated glucose (COMP.GLU), and their difference. Note that the first four points have been zero-weighted; this accounts for the high values of the difference during those times. The heading INS.EFFECT represents variable $X(t)$ of Eq. 2. Insulin (last column) is the measured hormone concentration. Finally, the estimated values of the parameters, along with their fractional deviations, are printed.

fits for both glucose and insulin obtained for this sample case. The insulin sensitivity index (S_I) was 5.07×10^{-4} min^{-1} (μU ml^{-1})$^{-1}$, glucose effectiveness (S_G) was 0.031 min^{-1}, and pancreatic

```
---  IDENTIFICATION RESULTS  ---

DATA FILE  :  A:NORMAL.DAT
MODEL : Pancreatic Secretion Model
OPTION :  1
ZERO-WEIGHTED SAMPLES
   1    2

OVER-WEIGHTED SAMPLES
   3    4    5
PARAMETER INITIAL ESTIMATES
      γ   =  0.257E+00
      g   =  0.100E-02
      h   =  0.920E+02
      I(0)  =  0.351E+03
```

TIME	OBS. INSULIN	COMP. INSULIN	DIFFERENCE	GLUCOSE
0.0	11.0	410.4	+399.4	92.0
2.0	26.0	229.4	+203.4	350.0
4.0	130.0	132.5	+2.5	287.0
6.0	85.0	80.4	-4.6	251.0
8.0	51.0	52.9	+1.9	240.0
10.0	49.0	38.4	-10.6	216.0
12.0	45.0	31.2	-13.8	211.0
14.0	41.0	28.1	-12.9	205.0
16.0	35.0	27.0	-8.0	196.0
19.0	30.0	27.3	-2.7	192.0
22.0	30.0	27.7	-2.3	172.0
27.0	27.0	28.3	+1.3	163.0
32.0	30.0	27.5	-2.5	142.0
42.0	22.0	24.4	+2.4	124.0
52.0	15.0	18.6	+3.6	105.0
62.0	15.0	11.4	-3.6	92.0
72.0	11.0	7.3	-3.7	84.0
82.0	10.0	7.0	-3.0	77.0
92.0	8.0	7.0	-1.0	82.0
102.0	11.0	7.0	-4.0	81.0
122.0	7.0	7.0	+0.0	82.0
142.0	8.0	7.0	-1.0	82.0
162.0	6.0	7.0	-1.0	85.0
182.0	7.0	7.3	+0.3	90.0

```
CONVERGENCE ACHIEVED AFTER   8 ITERATIONS

FINAL SUM OF SQUARE IS  262.8

FINAL PARAMETER VALUES ( % FSD )

      γ   =  0.3000E+00     (   0.9 )
      g   =  0.3343E-02     (   3.4 )
      h   =  0.8950E+02     (   0.4 )
      I(0)  =  0.4034E+03     (   1.4 )
```

Fig. 3B. Computer printout of the results of the identification of the insulin model (Eq. 3). Parameter g represents parameter γ. (For further details see legend to Fig. 3A.)

responsiveness parameters were:

$$\phi_1 = \frac{I_{max} - I_b}{n \cdot (G_0 - G_b)} = \frac{132.5 - 7.3}{0.3(287 - 92)} = 2.14$$

$$\phi_2 = \gamma \times 10^4 = 33$$

The units of ϕ_1 and ϕ_2 are min (μU ml^{-1})(mg dl^{-1})$^{-1}$ and min^{-2} (μU ml^{-1})(mg dl^{-1})$^{-1}$ respectively.

These results show that the subject exhibited normal insulin sensitivity and normal pancreatic responsivity (approximate normal range for S_I: 4.0 to 8.0; for ϕ_1: 2.0 to 4.0; and for ϕ_2: 20 to 35 [10]). A second example is shown in Fig. 5. In this

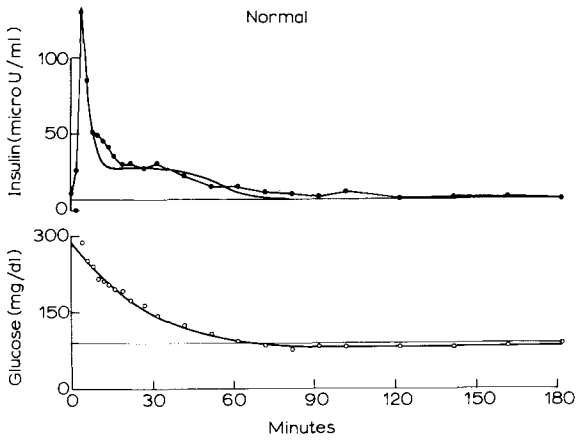


Fig. 4. Model-derived fits from the results shown in Fig. 3.

case the FSIGT has been performed in an elderly subject, and the program yielded results which are in accord with previous findings [24]; i.e. overall glucose tolerance decreases with age due to the inability of pancreatic responsivity to compensate for insulin resistance ($\phi_1 = 1.1$ and $\phi_2 = 18$). The models reveal that pancreatic responsivity parameters and the insulin sensitivity index are lower than the corresponding parameters in the young normal subject.

FINAL SUM OF SQUARE IS 42.8
FINAL PARAMETER VALUES (%FSD)
p(1) = 0.1572E − 01 (6.5)
p(2) = 0.1301E − 01 (35.2)
p(3) = 0.4031E − 05 (31.2)
G(0) = 0.2938E + 03 (0.4)

FINAL SUM OF SQUARE IS 246.5
FINAL PARAMETER VALUES (%FSD)
n = 0.3606E + 00 (1.2)
g = 0.1785E − 02 (4.2)
h = 0.1055E + 03 (1.4)
I(0) = 0.2410E + 03 (1.7)

SENSITIVITY INDEX = 3.10 E-04 (37.2)

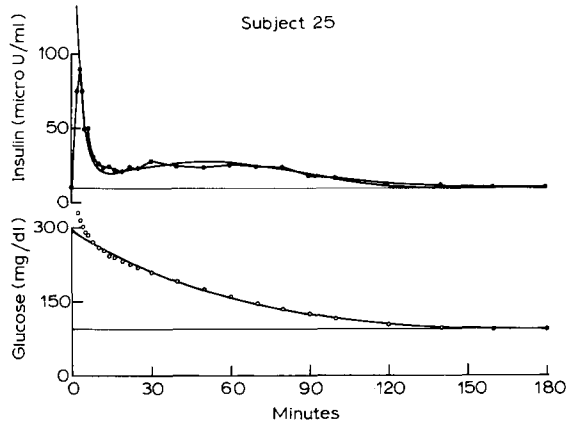


Fig. 5. FSIGT performed in an elderly subject. In the upper panel, the parameters estimated through model identifications are shown.

6. Modified FSIGT

In patients with impaired glucose tolerance (IGT [25]), the insulin response to glucose may be partially or totally suppressed. Of course, without the insulin response, the glucose disappearance model cannot provide an estimate of the metabolic parameters, since there is no input to the model. This limitation can be overcome in nondiabetics by augmenting the insulin response with pharmacologic agents (e.g. tolbutamide). With this pharmacologic augmentation, the dynamic insulin response can be sufficient to achieve an accurate estimate of S_I [13].

As an example, in Fig. 6 we have shown an FSIGT modified with tolbutamide. Glucose was injected as usual at $t = 0$ min; however, in this case, the sulfonylurea tolbutamide (Orinase 300 mg; Upjohn, Kalamazoo, MI) was also injected, but at $t = 20$. Comparing Fig. 6 to Fig. 2 reveals that with tolbutamide there was a substantial secondary insulin peak. As can be seen, the second

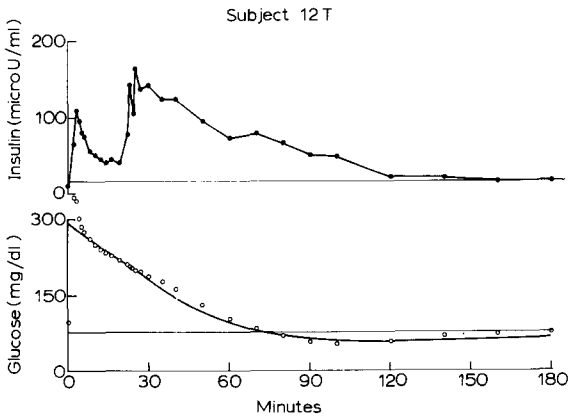


Fig. 6. Modified FSIGT with tolbutamide injection. Glucose is injected at $t = 0$ min as in the standard FSIGT, but also tolbutamide (300 mg) is injected at $t = 20$, provoking a substantial secondary insulin peak. The same program used for the standard FSIGT yielded the fit of glucose data (continuous line) and the following parameters: $S_G = 0.016$ and $S_I = 2.0$ (see text for units).

peak was reflected in an acceleration in the decline of the plasma glucose concentration, as well as a substantial glucose undershoot from $t = 100$ to $t = 145$ min.

The program MINMOD, without modification, was used to analyze the tolbutamide-potentiated FSIGT. As can be seen, the model was able to account for the glucose pattern (given $I(t)$), and good estimates of the model parameters were obtained.

Thus, the program MINMOD is able to calculate S_I and S_G independent of the methodology used to establish the insulin profile. What must be recognized, however, is that when pharmacologic agents are used to elaborate the insulin dynamics, the pancreatic parameters ϕ_1 and ϕ_2 loose their meaning.

7. Future plans

A problem with the current program may arise when the user has to make the right choice of the initial data points to be zero-weighted to avoid the undesired effects of the early mixing phase on the parameter estimates. A study is in progress to automatically detect when the extracellular mixing phase can be considered complete [26]. The findings of this study will allow us to insert into the program a feature for automatic determination of the proper zero-weighting scheme to avoid the confounding influence of the mixing phase on parameter estimation.

Since we are proposing the FSIGT (with the minimal model analysis) as a clinical test, we are aware that a reduction of the number of collected blood samples would improve the impact of the method in clinical practice. A recent study showed that it is possible to optimize the design of the data sampling schedule, i.e. the number and location of the discrete-time points at which blood specimens are collected [27]. Reducing the number of samples withdrawn from a patient, without deteriorating the precision of parameter estimates, will have great potential for improving the cost effectiveness of this clinical test.

8. Software specification

MINMOD is written in standard FORTRAN 77 computer language. This version also includes a separate program for creating data and manipulating data and result files. The program runs on a DIGITAL VAX-750 computer (VMS operating system) or on an IBM PC-XT or PC-AT with the DOS operating system and 8087 microprocessor capability. A slower-running version written in HP-BASIC suitable to run on an HP-9845 computer also exists, but a much longer time is needed by this version for every identification.

9. Conclusions

A computer program for quantitative assessment of factors controlling glucose tolerance in the intact organism has been presented. MINMOD uses the minimal model technique to analyze glucose and insulin data from the intravenous glucose tolerance test. This method is characterized by the estimation of parameters from the identification of two mathematical models: one of glucose disappearance and one of insulin kinetics. From the estimated model parameters it is possible to calculate four metabolic indices (S_I, S_G, ϕ_1 and ϕ_2) which represent an integrated metabolic portrait of a single individual. This approach is less invasive and experimentally simpler than other procedures; therefore it may be very useful in carrying out physiological as well as clinical studies.

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References

[1] G.M. Reaven, Insulin-independent diabetes mellitus: metabolic characteristics, Metab. Clin. 29 (1980) 445–454.

[2] J.B. Halter, R.G. Graf and D. Porte Jr., Potentiation of insulin secretory reponses by plasma glucose levels in man: evidence that hyperglycemia in diabetes compensates for impaired glucose potentiation, J. Clin. Endocrinol. Metab. 48 (1979) 946–954.

[3] E. Cerasi, R. Luft and S. Efendic, Decreased sensitivity of the pancreatic β-cells to glucose in prediabetic and diabetic subjects: a glucose dose–response study, Diabetes 21 (1972) 224–234.

[4] S.-W. Shen, G.M. Reaven and J.W. Farquhar, Comparison of impedance to insulin-mediated uptake in normal and diabetic subjects, J. Clin. Invest. 49 (1970) 2151–2160.

[5] R.A. DeFronzo, J.D. Tobin and R. Andres, Glucose clamp technique: a method for quantifying insulin secretion and resistance, Am. J. Physiol. 273 (1979) E214–E223.

[6] M. Nagulesparan, P.M. Savage, R.H. Unger and P.H. Bennett, A simplified method using somatostatin to assess in vivo insulin resistance over a range of obesity, Diabetes 28 (1979) 1039–1057

[7] R.N. Bergman, D.T. Finegood and M. Ader, Assessment of insulin sensitivity in vivo, Endocrine Rev. 6 (1985) 45–86.

[8] R.N. Bergman, Y.Z. Ider, C.R. Bowden and C. Cobelli, Quantitative estimation of insulin sensitivity, Am. J. Physiol. 236 (1979) E667–E677.

[9] G. Toffolo, R.N. Bergman, D.T. Finegood, C.R. Bowden and C. Cobelli, Quantitative estimation of B-cell sensitivity to glucose in the intact organism; a minimal model of insulin kinetics in the dog, Diabetes 29 (1980) 979–990.

[10] R.N. Bergman, L.S. Phillips and C. Cobelli, Physiologic evaluation of factors controlling glucose tolerance in man, J. Clin. Invest. 68 (1981) 1456–1467.

[11] M. Chen, R.N. Bergman, G. Pacini and D. Porte Jr., Pathogenesis of aging-related glucose intolerance in man: insulin resistance and decreased B-cell function, J. Clin. Endocrinol. Metab. 60 (1985) 13–20.

[12] D.T. Finegood, G. Pacini and R.N. Bergman, The insulin sensitivity index. Correlation in dogs between values determined from the intravenous glucose tolerance test and the euglycemic glucose clamp, Diabetes 33 (1984) 362–368.

[13] J. Beard, R.N. Bergman, K. Ward and D. Porte Jr., Validation by glucose clamp of the IVGTT-derived insulin sensitivity index in man, Clin. Res. 33 (1985) 59A.

[14] G. Pacini, D.T. Finegood and R.N. Bergman, A minimal-model-based glucose clamp yielding insulin sensitivity independent of glycemia, Diabetes 31 (1982) 432–441.

[15] G. Pacini and R.N. Bergman, PACBERG: an adaptive program for controlling the blood sugar, Comp. Prog. Biomed. 16 (1983) 13–20.

[16] R.N. Bergman and C. Cobelli, Minimal modeling, partition analysis and the estimation of insulin sensitivity, Fed. Proc. 39 (1980) 110–115.

[17] M. Ader, G. Pacini, Y. Yang and R.N. Bergman, Importance of glucose per se to intravenous glucose tolerance: comparison of the minimal-model prediction with direct measurements, Diabetes 34 (1985) 1092–1103.

[18] E.R. Carson, C. Cobelli and L. Finkelstein, The mathematical modeling of metabolic and endocrine systems (Wiley, Chichester UK, 1983).

[19] D.W. Marquardt, An algorithm for least-squares estimation of non-linear parameters, J. Soc. Indust. Appl. Math. 11 (1963) 431–441.

[20] R.A. Fletcher, A modified Marquardt subroutine for non-linear least squares, Atomic Energy Research Establishment, Report R AERE-R 6799 (Her Majesty's Stationery Office, London, 1971).

[21] M. Hopper, The Harwell Subroutine Library, Atomic Energy Research Establishment, Report R AERE-R 7477 (Her Majesty's Stationery Office, London 1973).

[22] E.M. Landaw and J.J. DiStefano III, Multiexponential, multicompartmental and noncompartmental modeling. II. data analysis and statistical considerations, Amer. J. Physiol. 246 (1984) R665–R677.

[23] R.L. Burden, J.D. Faires and A.C. Reynolds, Numerical Analysis, 2nd Edn. (Prindle Weber and Schmidt, Boston MA, 1980).

[24] R.I. Fink, O.G. Kolterman, J. Griffin and J.M. Olefsky, Mechanisms of insulin resistance in aging, J. Clin. Invest. 71 (1983) 1523–1535.

[25] National Diabetes Data Group, Classification and diagnosis of diabetes mellitus and other categories of glucose intolerance, Diabetes 28 (1979) 1039–1057.

[26] D.T. Finegood, R. Watanabe and R.N. Bergman, Validation of the estimation of the end of extracellular mixing of injected glucose, Fed. Proc. 43 (1984) 411A.

[27] C. Cobelli, A. Ruggeri, J.J. DiStefano III and E.M. Landaw, Optimal design of multioutput sampling schedules; software and applications to endocrine, metabolic and pharmacokinetic models, IEEE Trans. Biomed. Eng. BME-32 (1985) 249–256.