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MINMOD Millennium: A Computer Program to Calculate Glucose Effectiveness and Insulin Sensitivity From the Frequently Sampled Intravenous Glucose Tolerance Test

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MINMOD Millennium: A Computer Program to Calculate Glucose Effectiveness and Insulin Sensitivity from the Frequently Sampled Intravenous Glucose Tolerance Test

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ABSTRACT

The Bergman Minimal Model enables estimation of two key indices of glucose/insulin dynamics: glucose effectiveness and insulin sensitivity. In this paper we describe MINMOD Millennium, the latest Windows-based version of minimal model software. Extensive beta testing of MINMOD Millennium has shown that it is user-friendly, fully automatic, fast, accurate, reproducible, repeatable, and highly concordant with past versions of MINMOD. It has a simple interface, a comprehensive help system, an input file editor, a file converter, an intelligent processing kernel, and a file exporter. It provides publication-quality charts of glucose and insulin and a table of all minimal model parameters and their error estimates. In contrast to earlier versions of MINMOD and some other minimal model programs, Millennium provides identified estimates of insulin sensitivity and glucose effectiveness for almost every subject.

INTRODUCTION

BERGMAN ET AL.[1] developed a nonlinear "minimal" model to mathematically describe how glucose and insulin together control the production and disposal of glucose in the body. The aforementioned model enables estimation of two key indices of glucose/insulin dynamics: insulin sensitivity (S_I) and glucose effectiveness (S_G). Interest in the minimal model continues to grow, with more than 50 papers being published each year on issues related to the minimal model.[2]

The original "MINMOD" computer program was developed to specifically carry out the necessary calculations to estimate the parameters of the minimal model.[3] Parameter estimates determined using MINMOD software have been shown to be highly concordant with analogous parameters estimated by means of the euglycemic clamp.[4,5] Extant MINMOD software has been used to analyze the data from many

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hundreds of experiments including thousands of patients and has become, in effect, the "industry standard" for analyzing frequently sampled intravenous glucose tolerance test (FSIGT) data.[2]

The parameters of the minimal model are determined using data from either a standard or modified FSIGT. In the standard FSIGT a bolus of glucose (300 mg/kg) is intravenously injected, and blood samples are collected over the 3 h following the glucose injection. In the modified FSIGT 20 min after the glucose injection, insulin (30 mU/kg) is infused.[6] The modified protocol is now almost always used because it allows better estimation of the S_I index.[6] As well as enabling the estimation of S_I and S_G, the minimal model also enables the estimation of a number of other parameters, functions, and indices that are useful for describing the glucose and insulin status of a subject.[1,3,7–12] These include: the basal glucose concentration (G_b); the basal insulin concentration (I_b); a function that describes insulin action in proportion to interstitial insulin [$X(t)$]; a parameter that describes the removal rate of insulin from the interstitial space ($P2$); a parameter that describes the movement of circulating insulin to the interstitial space ($P3$); the acute insulin response to glucose (AIR_g); the disposition index (DI); glucose effectiveness at zero insulin ($GEZI$); insulin-attributable glucose disposal ($IAGD$); and two indices derived from the so-called homeostatic assessment (HOMA) model, HOMA β-cell function and HOMA insulin resistance. The units and typical "normal" values and normal ranges of all of these parameters are shown in Table 1. The mathematical theory and calculations underpinning the minimal model have been discussed previously.[1–3] The Appendix provides an exposition of the minimal model together with the derivation and explanation of the above parameters and indices.

MINMOD1 was written in FORTRAN 77 and designed to run on a DOS platform. While MINMOD 1 was, in most cases, very accurate with respect to parameter estimates, for perhaps in as many as 15% of cases, parameter estimates were not identified. In an attempt to fit these recalcitrant cases, users tended to subjectively "experiment" with the weighting of individual data points, and consequently they sometimes obtained, for specific cases, parameter estimates quite different from those obtained by another user analyzing the same data. In addition, alternative FSIGT protocols were introduced to reduce difficult cases.[6–8]

Improvements were made to the computational algorithms underpinning MINMOD, and versions II and III were released. Some of the computational changes that have been introduced into MINMOD may, prima facie, seem subtle if not trivial, but, nevertheless,

Table 1. Glucose Minimal Model Indices, Their Units, and Typical Normal Values and Normal Ranges

Clinical index			*Typical normal*	
Name	*Abbreviation*	*Unit*	*Value*	*Range*
Glucose effectiveness	S_G	min^{-1}	2.2e-2	(1.2e-3, 4.5e-2)
Insulin sensitivity	S_I	$(mU/L)^{-1}\ min^{-1}$	2.0e-4	(5.0e-5, 2.2e-3)
	$P2$	min^{-1}	5.0e-2	(1.3e-3, 2.0e-1)
	$P3$	$(mU/L)\ min^{-2}$	2.1e-5	(5.4e-7, 8.0e-5)
Basal glucose	G_b	$mg\ dL^{-1}$	84	(65, 103)
Distributed glucose concentration at time 0	G_0	$mg\ dL^{-1}$	200	(150, 400)
Basal insulin	I_b	$mU\ L^{-1}$	10	(1,32)
Acute insulin response to glucose	AIR_g	$mU\ L^{-1}\ min^{-1}$	800	(45, 3700)
Disposition index	DI		8.0e-2	(1.6e-2, 1.0)
Glucose effectiveness at zero insulin	$GEZI$	min^{-1}	1.8e-2	(NA)
Insulin-attributable glucose disposal	$IAGD$	%	10	(0, 90)
β-Cell function	β-Cell function	mU/mM	170	(30, 1,440)
Insulin resistance		$mM\ mU\ L^{-2}$	2.0	(0.4, 8)
Insulin action	X	min^{-1}	0.01	(0, 0.03)
Apparent volume of glucose distribution	V_g	dL	140	(30, 292)

NA, not applicable.

many of these changes significantly improved the ability of MINMOD software to converge on feasible solutions of the minimal model with identified parameter estimates. However, to date, no publications have critically compared the several versions of MINMOD. Furthermore, with the advent of the Windows operating system and the gradual phasing-out of DOS systems, there has been a growing need for a replacement program that would incorporate all of the latest improvements in MINMOD software into a program with standard Windows features. To attempt to satisfy this need we have introduced an entirely new version of MINMOD that incorporates features of Windows, and that is designed to automatically deliver accurate and precise estimates of S_G and S_I. This new version, entitled MINMOD Millennium™, is described herein.

DESIGN CONSIDERATIONS

Before we embarked on the development of MINMOD Millennium, a panel of MINMOD III users was asked to identify design issues they would like to see incorporated into MINMOD Millennium. Although the panel identified over 20 desirable design attributes (see Table 2), they considered the following as most important: be Windows-based, have a simple interface, and be automatic, accurate, repeatable, reproducible, and concordant with prior versions of MINMOD. In order to meet these design considerations we have focused on three main areas: (1) improved automatic estimation of initial values of parameters; (2) an improved baseline correction algorithm; and (3) a highly robust and accurate numerical integrator.

Table 2. Desirable Design Attributes of MINMOD Millennium

- Windows-compatible
- Simple and powerful data editor for data entry and correction
- Consistent and sensible statistical weighting of observations
- Manual data weighting for difficult cases
- Automatic initialization of all estimable parameters
- Automatic and flexible baseline estimation
- Minimal user intervention to produce Minimal Model parameters
- Proven/published estimation and model solution strategies
- Execution time less than 4 s per subject
- Reliable, precise, and efficient
- Accurate, repeatable, and reproducible
- Rigorous testing prior to release
- All Minimal Model determinations and their uncertainties automatically tabulated
- Tabulation of predicted values of glucose and insulin action
- Exportation of results between productivity and statistical packages
- Results concordant with prior versions of MINMOD to better than 90%
- Conservation of prior MINMOD method to simulate interstitial insulin inputs
- Able to process all past MINMOD input files
- A comprehensive help system

MATERIALS AND METHODS

Program development

Optimization of the estimates of the parameters of the minimal model necessitates some sophisticated mathematical procedures.[3] Rather than developing new computer code to carry out these procedures, we chose to utilize in Millennium the new processing kernel in the SAAM (Simulation, Analysis and Modeling) program.[13,14]

The most important part of the development process involved devising an expert system that would enable the program to automatically obtain "best fits" of the minimal model to FSIGT data. The principal features of the expert system were: (a) the automatic estimation of good initial estimates of S_G, G_0, and G_b; (b) the capability to convert Millennium files into files that can be analyzed by the SAAM processing kernel; and (c) the capability to instruct the SAAM processing kernel to progressively adjust the data weighting during the iterative estimation process.

Estimation of initial values of parameters

In order for MINMOD Millennium to optimize the parameters describing the nonlinear differential equations of the minimal model, the program requires initial estimates for each of the adjustable parameters.[3] We considered a number of approaches for obtaining initial es-

timates for parameters S_G, G_0, $P2$, and $P3$. However, after much experimentation, the procedure that we finally chose for our initial estimation of S_G involved a linear regression of log-transformed glucose data between 8 and 20 min, followed by identification of a possible outlier datum. A robust regression was then conducted on the 8–20-min data excluding any identified outlier datum. Our initial estimate of G_0 was then taken as the antilog of the time 0 intercept of this robust regression, and our initial estimation of S_G was taken to be the regression coefficient. We used values of 0.0506 and 0.0000211 as our initial estimates of $P2$ and $P3$, respectively, as these values are consistent with typical values determined for a human population.[15] This is equivalent of having a value of 4.15×10^{-4} as our initial estimate for S_I.

Baseline correction

In the past, minimal model parameter identification was plagued by estimation problems, especially for subjects with inadequate insulin response.[6] For example, failure rates of 4–61% for the fitting procedure for the glucose-only FSIGT data have been reported.[16,17] In these situations, the assignment of an appropriate G_b has been shown to greatly improve the success rate for obtaining identified parameters.[16] In the original MINMOD paper, stationarity was presumed, such that the value of glucose at the end of the test was presumed to be G_b, the pre-injection glucose concentration.[3] In practice, however, the plasma glucose concentration may not return to the exact original pre-injection glucose concentration. Nevertheless, we found it was necessary to address the "changing baseline" phenomenon to produce acceptable results describing the glucose profile.

In MINMOD Millennium, we have addressed this "baseline stationarity" problem by completely automating the procedure for estimating the target "baseline"glucose as follows: (a) If the data file contains a datum at 180 min, and this datum exceeds the pre-injection glucose value, we assign the target glucose to be approached at the end of the test (t = 180 min) to the average of the pre-injection value of glucose and the measured value for glucose at time 180 min. (b) If there is no glucose datum at 180

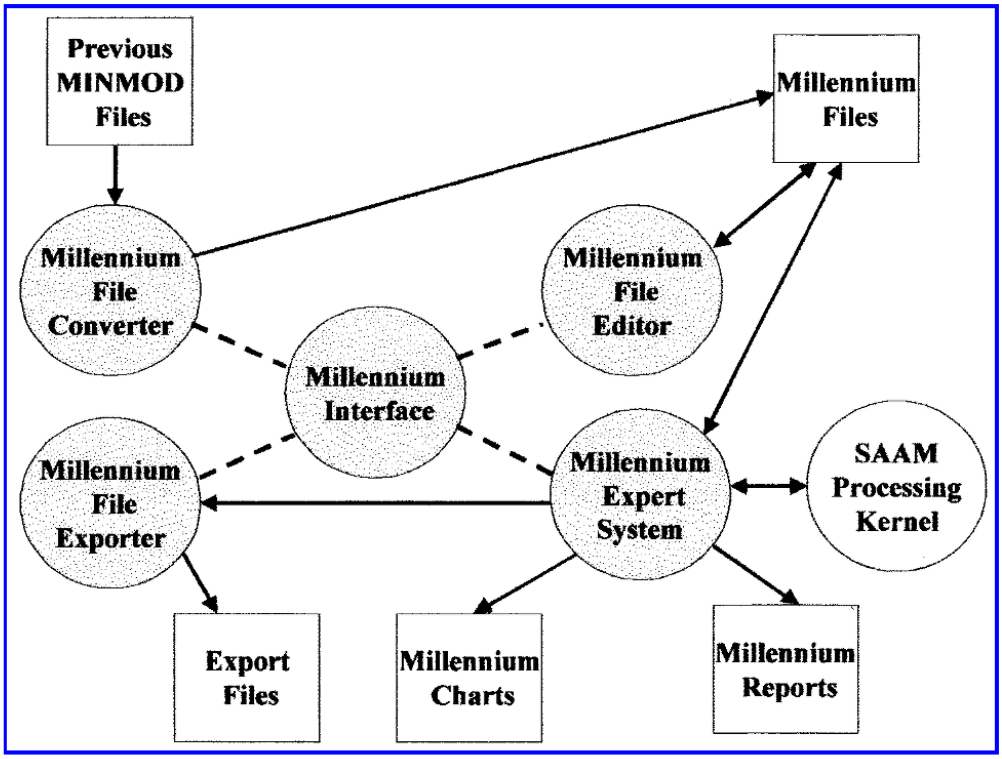


FIG. 1. The structure and functioning of MINMOD Millennium. The gray circles represent the five main parts of MINMOD Millennium, and the dashed lines depict how the interface controls the activities of the other parts. The solid lines represent the pathways for the movement of data through MINMOD Millennium.

min, but data after 180 min and data between 120 and 179 min, then we take the average of the closest datum points on either side of 180 min, and we assign to G_b the average of this value and the pre-injection value of glucose. (c) If we have data with time values greater than 119 min but no data greater than 180 min, then the program assigns the mean of the glucose value of the datum closest to time 180 min and the pre-injection glucose value. (d) If we only have data with time values less than 120 min, then G_b is assigned the pre-injection glucose value.

There are a number of other ways that we might have addressed the issue of changing baseline, and this issue per se has been discussed in detail in the scientific literature.[16] However, we chose as the default option the baseline correction algorithm described above in order to ensure concordance of results obtained from Millennium with results obtained by using previous versions of MINMOD software.

RESULTS

Program description

MINMOD Millennium is written in Visual Basic, designed to run on any PC with a Windows 98 or higher platform, and to have the appearance and general operating features of Windows-based programs. There are five main parts to Millennium: an interface, an input file editor, a file converter, an expert system linked to a SAAM processing kernel, and a file exporter. Figure 1 depicts how the interface controls the other parts of Millennium and how data are handled within Millennium. The Millennium interface has 10 simple elements (Fig. 2). These include the folder Navigator, the file picker, and eight control buttons. Simply put, the Navigator allows you to locate a folder (directory) containing the dataset you want to process. The File Picker allows you to select the actual dataset (file) to process. The Control Buttons allow you to access the help system, to view the "flash screen," to exit Millennium, or

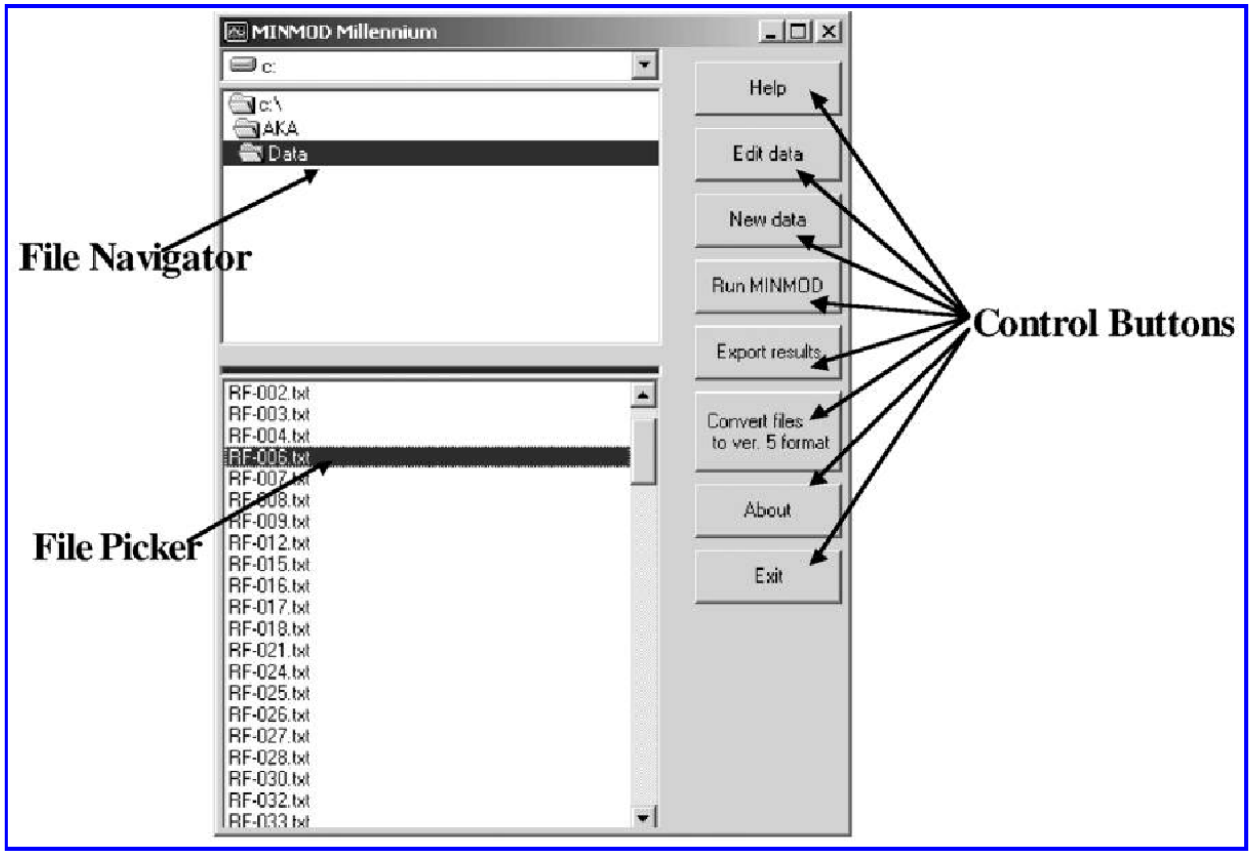
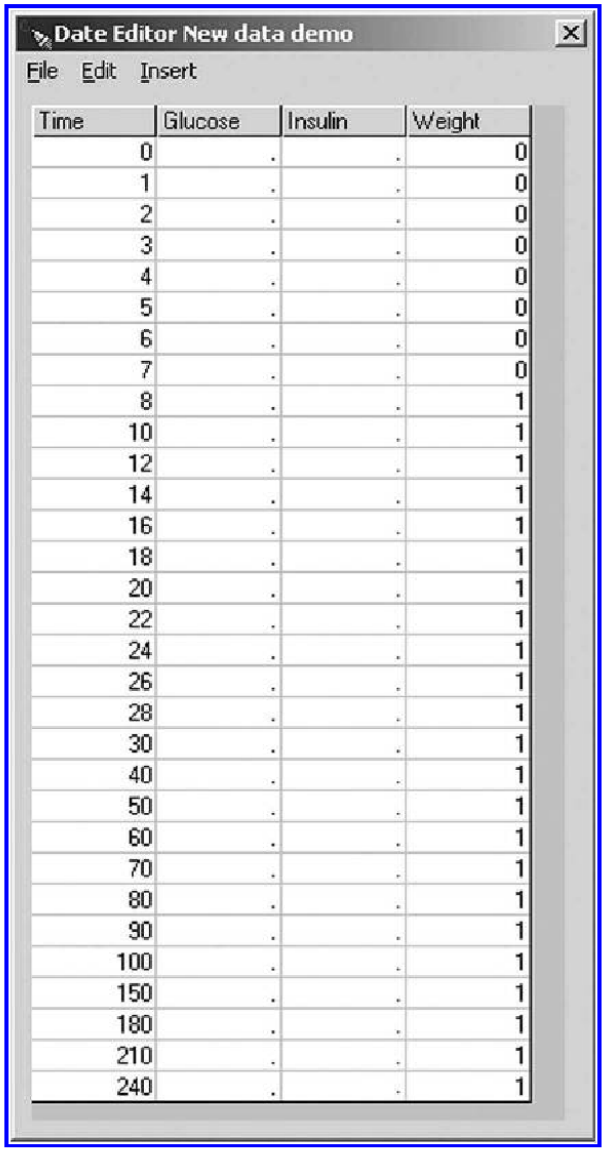


FIG. 2. The MINMOD Millennium interface.

to select what you want to do with (how you want to process) a selected file. The Millennium user simply uses a mouse to click on the appropriate button to perform the selected task or processing step. For example, by clicking on the HELP button, the user is presented with a dropdown menu of the following items: (1) a brief overview of MINMOD Millennium; (2) the purpose of MINMOD Millennium; (3) design criteria for MINMOD Millennium; and (4) instructions for using Millennium. The HELP system is quite comprehensive and self-explanatory.



Time	Glucose	Insulin	Weight
0	.	.	0
1	.	.	0
2	.	.	0
3	.	.	0
4	.	.	0
5	.	.	0
6	.	.	0
7	.	.	0
8	.	.	1
10	.	.	1
12	.	.	1
14	.	.	1
16	.	.	1
18	.	.	1
20	.	.	1
22	.	.	1
24	.	.	1
26	.	.	1
28	.	.	1
30	.	.	1
40	.	.	1
50	.	.	1
60	.	.	1
70	.	.	1
80	.	.	1
90	.	.	1
100	.	.	1
150	.	.	1
180	.	.	1
210	.	.	1
240	.	.	1

FIG. 3. The Millennium file editor. The file editor starts a new file with the default times for a standard FSIGT, and glucose data from the first 7 min are given zero weighting. There are four data columns in the data window: Time, Glucose, Insulin, and Data Weight. The "time" column contains the sampling times for a standard FSIGT protocol, and the data weight column contains the recommended or "default" weighting scheme. The glucose and insulin columns contain "." or periods, which signify missing data. New glucose and insulin data can either be entered directly into this window and the file saved, or data can be copied from an Excel spreadsheet and pasted into the Millennium data editor.

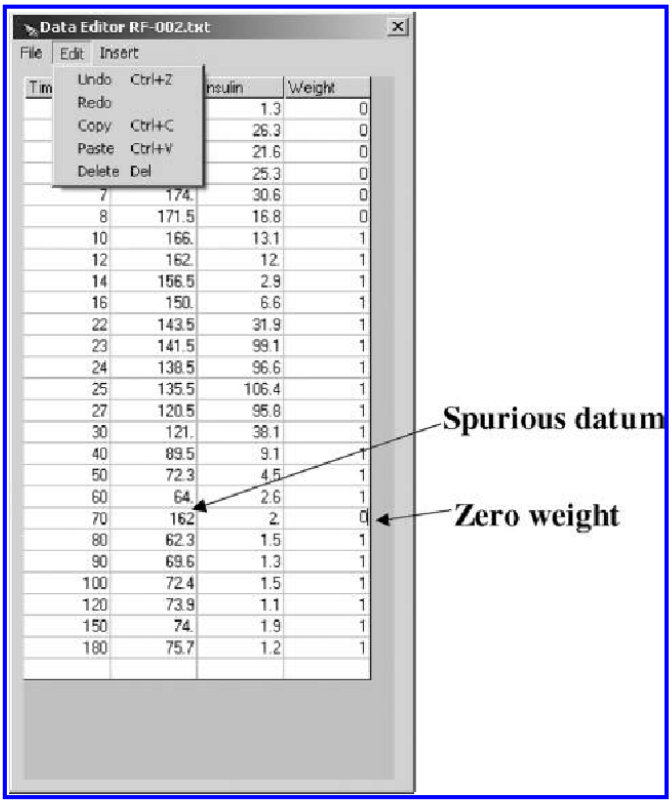
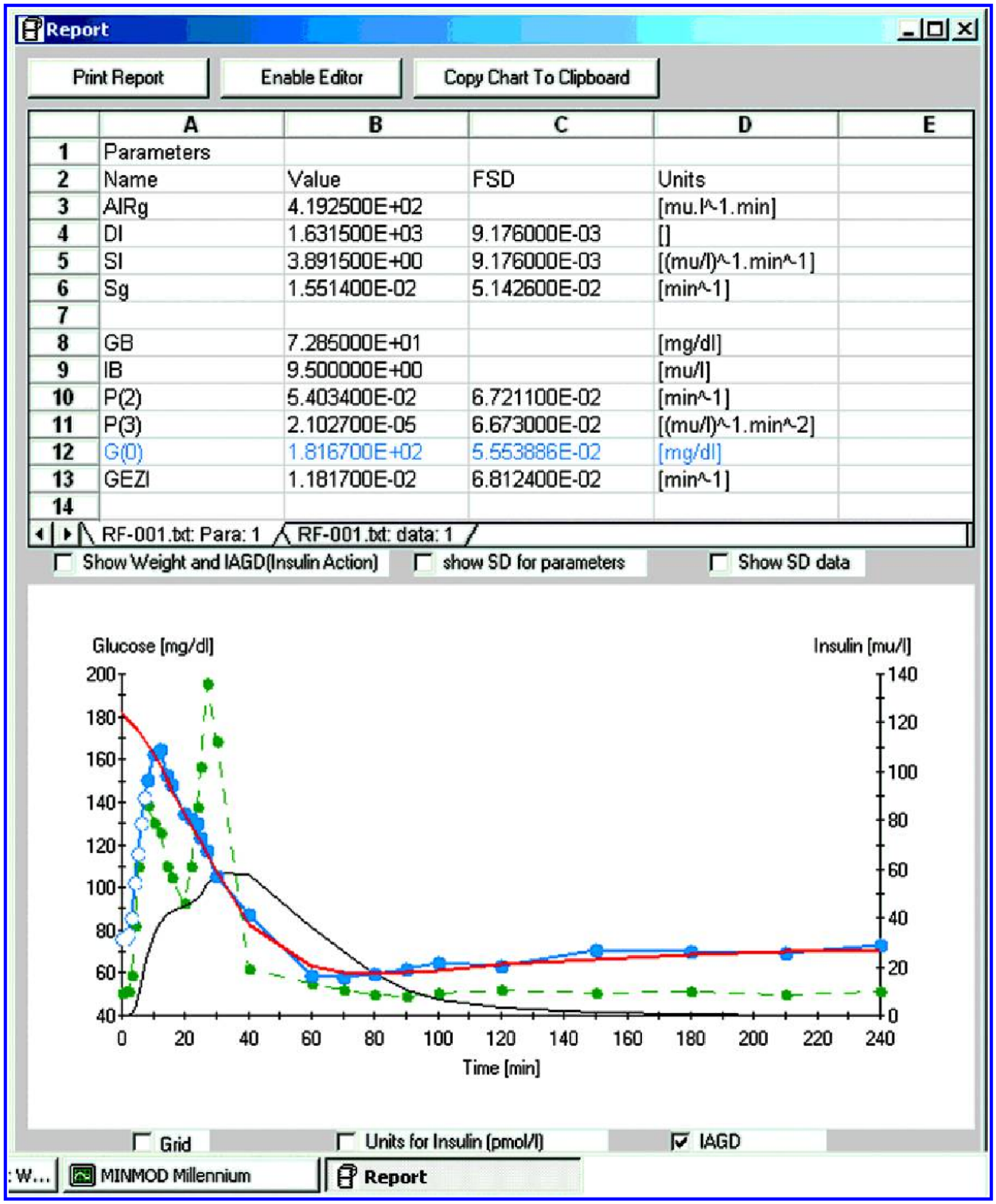


FIG. 4. Editing data. Note that we have activated the "Edit" menu to expose the array of services supported. For example, the user may wish to weight out spurious or unreliable data. To do this, the user changes the "1" weighting to "0" weighting and saves the amended file. The weights are simply factors that scale the proportional influence of each observation in accord with the weight value assigned. For example, if the weight value assigned for a particular observation is "2," then this observation will modify the fit at twice the influence as an identical observation with weight value "1." From the statistical perspective each observation is assigned a constant fractional standard deviation weight, in which the error of an observation is presumed to be proportional to the magnitude of the observation. Weights apply to glucose observations only.

Using MINMOD Millennium

To carry out a processing step, the Millennium user must click on the appropriate button. Note that no processing action can be taken unless one or more files are selected. However, only one processing step at a time is allowed. The five possible processing steps are: (1) editing the data; (2) entering new data; (3) running



	A	B	C	D	E
1	Parameters				
2	Name	Value	FSD	Units	
3	AIRg	4.192500E+02		[mu.l^-1.min]	
4	DI	1.631500E+03	9.176000E-03	[]	
5	SI	3.891500E+00	9.176000E-03	[(mu/l)^-1.min^-1]	
6	Sg	1.551400E-02	5.142600E-02	[min^-1]	
7					
8	GB	7.285000E+01		[mg/dl]	
9	IB	9.500000E+00		[mu/l]	
10	P(2)	5.403400E-02	6.721100E-02	[min^-1]	
11	P(3)	2.102700E-05	6.673000E-02	[(mu/l)^-1.min^-2]	
12	G(0)	1.816700E+02	5.553886E-02	[mg/dl]	
13	GEZI	1.181700E-02	6.812400E-02	[min^-1]	
14					

FIG. 5. Millennium report of minimal model parameters and chart of glucose and insulin data, predicted glucose concentrations, and predicted insulin-attributable glucose disposal (*IAGD*), following a FSIGT. The features of the output parameters window are as follows: All the important parameters estimable from the FSIGT data and the estimates of their uncertainties are summarized. If parameters are not well identified (i.e., their estimated fractional standard deviations are greater than 0.5), then the parameter values and their fractional standard deviations are shown in red. The units of the parameters are provided. Parameters whose values are conditionally estimated (e.g., G_0) are displayed in blue, along with their uncertainties. The following features of the plot are visible: glucose observations, blue dots; unweighted observations, hollow blue dots; fit of minimal model to glucose observations, red line; insulin observations, green dots (joined with a dashed green line); *IAGD*, dark solid line. Discontinuous blue and red lines indicate missing glucose data.

MINMOD; (4) exporting the MINMOD results to a tab-delimited text file; and (5) converting an old MINMOD dataset for processing with MINMOD Millennium.

When a user selects the "New data" button, he/she sees an empty data window as depicted in Figure 3. New glucose and insulin data can be entered directly into the window, and the file is then saved as a Millennium data file with a "txt" file extension. Alternatively, data can be copied from an Excel file and pasted into the Millennium data file. If it is necessary to make changes to the data file, Millennium has a standard Windows-style editing system. The appropriate data file is highlighted, the "edit data" button is selected, and the data appear in a window similar to that shown in Figure 4. Data files that have been produced by previous versions of MINMOD cannot be run directly in Millennium, but must first be converted to a form that can be used by Millennium. This conversion process is easily achieved by highlighting the file(s) that need to be converted, and then selecting the "Convert files to version 5 format" button.

Analysis of data with MINMOD Millennium

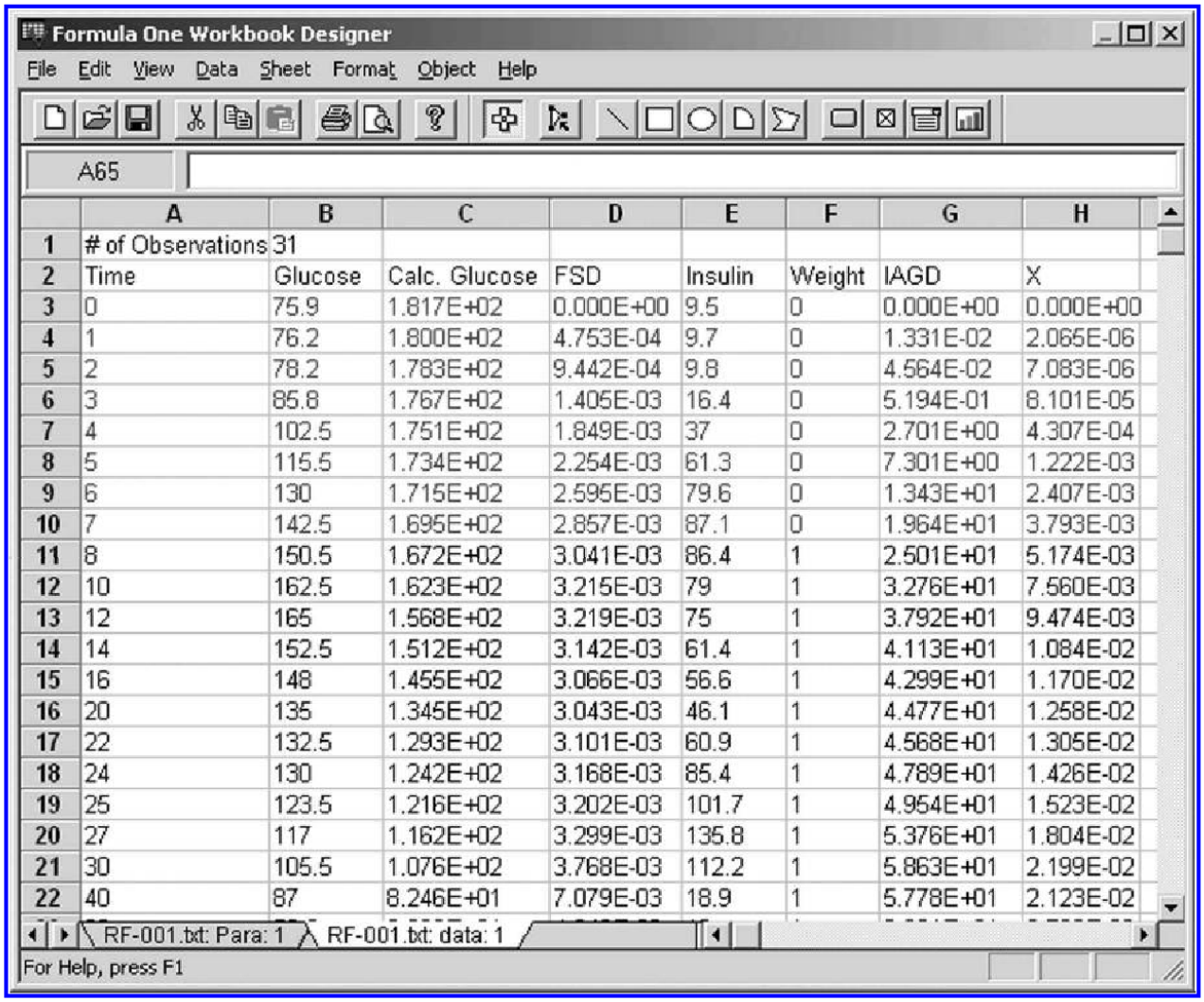
To fit an FSIGT dataset using MINMOD Millennium, the user simply "picks" the file or files to be processed, and invokes the control button "Run MINMOD." With a modern desktop or laptop computer (cycle speed of 1.2 GHz) Millennium provides output in approximately 0.75 s for each dataset. For each dataset analyzed, Millennium produces a report similar to that shown in Figure 5. The parameters window can be directly printed. The results displayed in the parameters window can, by simply clicking on the "Enable editor" button at the top of the parameters window, be loaded into what is known as a designer window (see Fig. 6), and from there, all of the routine spreadsheet services, including exportation, become available. In fact we can accomplish this step using either cut/copy-and-paste operations, or by saving the spreadsheet in the appropriate compatible format.

The plot of the results appears in a plot window accompanying the parameters window (Fig. 5). A grid can be displayed, the units of insulin can be toggled between English and so-called SI units (mU/L vs. pmol/L), and the display of *IAGD* can also be toggled. The symbols, line styles, fonts, and background colors of the plot window can all be changed to the user's preferences. By clicking on the "Copy chart to clipboard" button, the plot window can be copied and then pasted in Word, PowerPoint, or other Windows-based programs.

While clinicians are interested in minimal model parameters of individual subjects, researchers are likely to have a requirement to analyze FSIGT data from multiple subjects in experimental groups or populations. The export facility in Millennium has been specifically designed to facilitate the rapid analysis of FSIGT data from large numbers of subjects. To carry out a minimal model analysis of FSIGT data from multiple subjects, a Millennium user need simply select the relevant files (using the Navigator and File Picker) and then click on the "Export" button. Millennium will respond with a dropdown menu prompting the user to enter the name of a text file in which the results are to be tabulated. Having entered an appropriate file name, Millennium will then produce a tab-delimited "txt" file containing subject identifier, minimal model parameter estimates, and their fractional standard deviations. Statistical or epidemiological analyses can then be performed on these population data using standard statistical packages such as STATA[18] or SAS.[19]

TESTING AND VALIDATION

Data from 131 subjects who had undergone the FSIGT were analyzed by both MINMOD 3 and MINMOD Millennium. Concordance analyses were conducted using the "concord" command in STATA.[18] Figure 7 shows the concordance relationship and concordance statistics for S_G estimated by MINMOD 3 and by MINMOD Millennium, while Figure 8 shows a similar concordance relationship for S_I.[20,21] For this particular population, MINMOD Millennium produced identified estimates (fractional standard deviations less than 0.5) of S_G and S_I for all 131 subjects. In comparison, MINMOD 3 produced identified estimates of S_G and S_I in 125 and 129 subjects, respectively. When the


Formula One Workbook Designer

File Edit View Data Sheet Format Object Help

A65

	A	B	C	D	E	F	G	H
1	# of Observations	31						
2	Time	Glucose	Calc. Glucose	FSD	Insulin	Weight	IAGD	X
3	0	75.9	1.817E+02	0.000E+00	9.5	0	0.000E+00	0.000E+00
4	1	76.2	1.800E+02	4.753E-04	9.7	0	1.331E-02	2.065E-06
5	2	78.2	1.783E+02	9.442E-04	9.8	0	4.564E-02	7.083E-06
6	3	85.8	1.767E+02	1.405E-03	16.4	0	5.194E-01	8.101E-05
7	4	102.5	1.751E+02	1.849E-03	37	0	2.701E+00	4.307E-04
8	5	115.5	1.734E+02	2.254E-03	61.3	0	7.301E+00	1.222E-03
9	6	130	1.715E+02	2.595E-03	79.6	0	1.343E+01	2.407E-03
10	7	142.5	1.695E+02	2.857E-03	87.1	0	1.964E+01	3.793E-03
11	8	150.5	1.672E+02	3.041E-03	86.4	1	2.501E+01	5.174E-03
12	10	162.5	1.623E+02	3.215E-03	79	1	3.276E+01	7.560E-03
13	12	165	1.568E+02	3.219E-03	75	1	3.792E+01	9.474E-03
14	14	152.5	1.512E+02	3.142E-03	61.4	1	4.113E+01	1.084E-02
15	16	148	1.455E+02	3.066E-03	56.6	1	4.299E+01	1.170E-02
16	20	135	1.345E+02	3.043E-03	46.1	1	4.477E+01	1.258E-02
17	22	132.5	1.293E+02	3.101E-03	60.9	1	4.568E+01	1.305E-02
18	24	130	1.242E+02	3.168E-03	85.4	1	4.789E+01	1.426E-02
19	25	123.5	1.216E+02	3.202E-03	101.7	1	4.954E+01	1.523E-02
20	27	117	1.162E+02	3.299E-03	135.8	1	5.376E+01	1.804E-02
21	30	105.5	1.076E+02	3.768E-03	112.2	1	5.863E+01	2.199E-02
22	40	87	8.246E+01	7.079E-03	18.9	1	5.778E+01	2.123E-02

RF-001.txt: Para: 1 RF-001.txt: data: 1

For Help, press F1

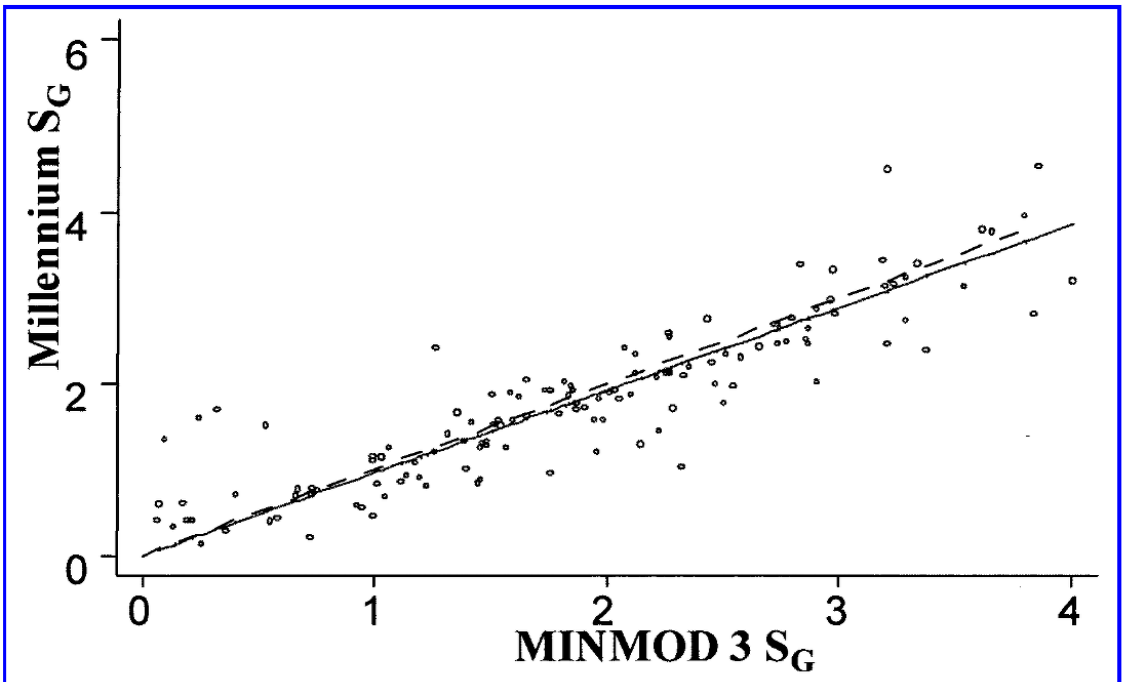
FIG. 6. MINMOD Millennium output spreadsheet.

same user repeatedly analyzed the above data, identical parameter estimates were obtained for the same subjects. Furthermore, identical parameter estimates were also obtained when the same data were analyzed by a different user employing a different computer. The robustness of Millennium is evident from the fact that when it was used to analyze data from 30 subjects that had undergone the original FSIGT protocol (no insulin injection) it was able to produce identified parameters for 29 of the subjects.

In comparison with MINMOD 3, an outstanding attribute of Millennium is the ease and quickness with which it allows the analysis of large numbers of FSIGT cases and the exportation of the results of the analyses to other productivity programs for statistical analysis. Using a Fujitsu (C Series Lifebook) and Millennium, we have analyzed the above 130 FSIGT studies, exported the results to a "txt" file, and then, using STATA, made population estimates of each of the minimal model parameters in less than 4 min! Using MINMOD 3 to do this would have required several hours.

CONCLUSIONS

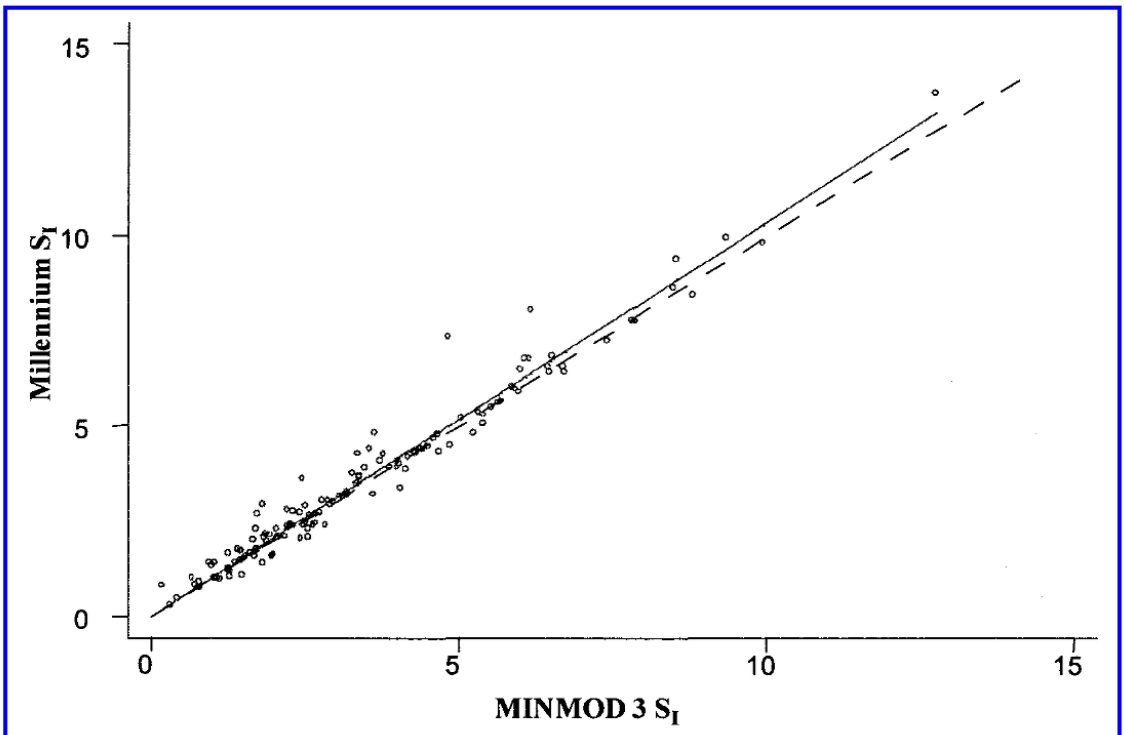
It is a truism that obesity and Type 2 diabetes are reaching epidemic proportions in Westernized populations, including the United States, and rates are increasing alarmingly in developing nations.[22] However, pharmacological and lifestyle approaches to prevention have been demonstrated.[23,24] Recently, it has become possible to predict with some degree of confidence (long before the disease is evident) those




```
. concord msg sg, g(c)

Concordance correlation coefficient (Lin: 1989, 2000)

 rho_c   SE(rho_c)   Obs     [   95% CI   ]     P        CI type
-------------------------------------------------------------------
 0.887     0.019     131     0.851  0.924    0.000    asymptotic
                             0.845  0.919    0.000   z-transform

Pearson's r =  0.890  Pr(r = 0) = 0.000  C_b = rho_c/r =  0.997
Reduced major axis:   Slope =     0.967   Intercept =    -0.008

   Difference (msg - sg)           95% Limits Of Agreement
   Average    Std. Dev.             (Bland & Altman, 1986)
-------------------------------------------------------------------
    -0.070       0.446                -0.944       0.805
```

FIG. 7. A graph showing the high degree of concordance between S_G as determined by MINMOD Millennium and S_G as determined by MINMOD 3. Note that data must overlay the dashed line for perfect concordance. Concordance parameters were obtained by using STATA[18] to analyze the S_G estimates from 131 FSIGT data sets. The concordance correlation coefficient was calculated according to Lin,[20] and the 95% limits of agreement according to Bland and Altman.[21]

subjects likely to develop Type 2 diabetes. It is important to identify those individuals at greatest risk for the disease. A reduced *DI* is predictive of Type 2 diabetes. To accurately estimate *DI* one must assess S_I and AIR_g. This can be done accurately with the present program. MINMOD Millennium is a Windows-based version of minimal model software for the quantitative assessment of the glucose/insulin dynamics of individual subjects. Extensive beta testing of MINMOD Millennium has shown that it is indeed user-friendly, fully automatic, robust, fast, accurate, reproducible, repeatable, and highly concordant with past versions of MINMOD. It has a simple interface, a comprehensive help system, an input file editor, a file converter, an intelligent processing kernel, and a file exporter, and it provides publication-quality charts of glucose and insulin and a table of all minimal model parameters and their error estimates. In contrast to earlier versions of MINMOD and some other minimal model pro-




```
. concord msi si, g(c)

Concordance correlation coefficient (Lin: 1989, 2000)

 rho_c   SE(rho_c)   Obs     [   95% CI   ]     P        CI type
-------------------------------------------------------------------
 0.981     0.003     131     0.974  0.987    0.000   asymptotic
                             0.973  0.986    0.000   z-transform

Pearson's r =  0.983  Pr(r = 0) = 0.000  C_b = rho_c/r =  0.998
Reduced major axis:   Slope =     1.037   Intercept =     0.003

   Difference (msi - si)           95% Limits Of Agreement
   Average    Std. Dev.             (Bland & Altman, 1986)
-------------------------------------------------------------------
     0.129       0.434                  -0.721      0.979
```

FIG. 8. A graph showing the high degree of concordance between S_I as determined by MINMOD Millennium and S_I as determined by MINMOD 3. Note that data must overlay the dashed line for perfect concordance. Concordance parameters were obtained by using STATA[18] to analyze the S_I estimates from 131 FSIGT data sets. The concordance correlation coefficient was calculated according to Lin,[20] and the 95% limits of agreement according to Bland and Altman.[21]

grams, Millennium provides identified estimates of S_I and S_G for almost every subject. It is hoped that the availability of this software may contribute to prevention of diabetes in at-risk individuals.

APPENDIX

Bergman's approach to describe the complex interaction of glucose and insulin involves two differential equations:

$$\frac{dG(t)}{dt} = -G(t) \times [S_G + X(t)] + G_b \times S_G \quad G(0) = G_0 \tag{1}$$

$$\frac{dX(t)}{dt} = -P2 \times X(t) + P3 \times F(t) \quad X(0) = 0 \tag{2}$$

$$F(t) = 0 \text{ if } I(t) \leq I_b, \text{ else } I(t) - I_b$$

$$S_I = P3/P2 \tag{3}$$

where S_G is glucose effectiveness; S_I is insulin sensitivity; $G(t)$ is plasma glucose at time t; G_b is the basal glucose concentration; $I(t)$ is the

plasma insulin concentration at time t; I_b is the basal insulin concentration; $F(t)$ is a function that represents the elevation of plasma insulin above basal insulin; $X(t)$ is insulin action in proportion to interstitial insulin[1,3,9]; $P2$ is a parameter describing the removal rate of insulin from the interstitial space; and $P3$ is a parameter describing the movement of circulating insulin to the interstitial space. The two main indices of the minimal model are S_G and S_I. S_G indicates the capacity of glucose to mediate its own disposal, whereas S_I indicates the net capacity for insulin to promote the disposal of glucose and to inhibit the endogenous production of glucose. In addition to these, a number of other useful indices can be derived from the FSIGT and minimal model. The acute insulin response to glucose (AIR_g) represents the acute insulin response and is defined as the area under the plasma insulin curve between 0 and 10 min:

$$AIR_g = \int_0^{10} [I(t) - I_b]dt \quad (4)$$

The disposition index DI is an overall measure of the ability of the islet cells to secrete insulin normalized to the degree of insulin resistance. DI is the product of AIR_g and S_I:

$$DI = AIR_g \times S_I \quad (5)$$

$GEZI$ (glucose effectiveness at zero insulin), which is an index popularized by Araujo-Vilar et al.,[10] is a measure of S_G that is independent of incremental insulin. It is defined as follows:

$$GEZI = S_G - S_I \times I_b \quad (6)$$

A useful time-varying descriptor is $IAGD$ (insulin-attributable glucose disposal), viz.:

$$IAGD = 100 \times X/(X + S_G) \quad (7)$$

This reflects the instantaneous percentage of glucose disposal attributable to the action of interstitial insulin, as opposed to the action of glucose per se.

V_g (apparent distribution space of glucose) is the extracellular fluid space in which glucose appears to distribute, and is estimated by:

$$V_g = 300 \times BW/G_0 \quad (8)$$

where BW is the body weight in kg.

"HOMA" parameters

Two indices proposed by Mathews et al.[12] from the so-called HOMA model are β-cell function and insulin resistance. These parameters are defined as follows:

$$\text{HOMA } \beta\text{-cell function} = 20 \times I_b/(G_b/18 - 3.5) \quad (9)$$

$$\text{HOMA insulin resistance} = G_b \times I_b/405 \quad (10)$$

Solving the nonlinear differential equations involved in the Bergman glucose minimal model involves some formidable matrix algebra. Furthermore, since glucose and insulin are co-regulating, the relatively strong correlation between plasma glucose and insulin that may occur in some subjects has resulted in some minimal model programs being able to estimate identified parameters in only about 85% of cases.[16] In the original glucose minimal model (Eqs. 2 and 3), Bergman used the actual insulin data (interpolated by straight lines) to represent $I(t)$, thereby uncoupling the glucose model from the insulin model. This wisely obviated the need for the simultaneous determination of the parameters of both the glucose model and the insulin model, and this approach is maintained in MINMOD Millennium.

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