GIM, Simulation Software of Meal Glucose–Insulin Model

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Abstract

Background:
A simulation model of the glucose–insulin system in normal life conditions can be very useful in diabetes research, e.g., testing insulin infusion algorithms and decision support systems and assessing glucose sensor performance and patient and student training. A new meal simulation model has been proposed that incorporates state-of-the-art quantitative knowledge on glucose metabolism and its control by insulin at both organ/tissue and whole-body levels. This article presents the interactive simulation software GIM (glucose insulin model), which implements this model.

Methods:
The model is implemented in MATLAB, version 7.0.1, and is designed with a windows interface that allows the user to easily simulate a 24-hour daily life of a normal, type 2, or type 1 diabetic subject. A Simulink version is also available. Three meals a day are considered. Both open- and closed-loop controls are available for simulating a type 1 diabetic subject.

Results:
Software options are described in detail. Case studies are presented to illustrate the potential of the software, e.g., compare a normal subject vs an insulin-resistant subject or open-loop vs closed-loop insulin infusion in type 1 diabetes treatment.

Conclusions:
User-friendly software that implements a state-of-the-art physiological model of the glucose–insulin system during a meal has been presented. The GIM graphical interface makes its use extremely easy for investigators without specific expertise in modeling.

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Introduction

The ability to simulate the glucose–insulin system in normal life conditions can be very useful in diabetes research. Several simulation models have been proposed in the literature that proved to be useful in tackling various aspects of pathophysiology of diabetes.[1–11] Recently, a new meal simulation model has been proposed.[12] The novelty and strength of this model are that it is based on virtually model-independent measurements of the various glucose and insulin fluxes occurring during a meal.[13,14] In fact, the system is very complex, and only the availability of glucose and insulin fluxes, in addition to their plasma concentrations, has allowed us to minimize structural uncertainties in modeling the various processes. The model consists of 12 nonlinear differential equations, 18 algebraic equations, and 35 parameters. User-friendly simulation software of this model would be of great help, especially for investigators without specific expertise in modeling.

The aim of this article is to present the interactive software GIM (glucose insulin model), implemented in MATLAB version 7.0.1, which allows one to simulate both normal and pathological conditions, e.g., type 2 diabetes and open- and closed-loop insulin infusions in type 1 diabetes. Case studies are only presented to illustrate the potential of the software and do not attempt to address pathophysiological questions or to assess the quality of glucose control by different strategies.

The Model

Normal Subject

The model describing the glucose–insulin control system during a meal is shown in **Figure 1**. This section provides a brief overview of the model while the article by Dalla Man and colleagues[12] should be consulted for a detailed description.

The model is made up of a glucose and insulin subsystem linked by the control of glucose on insulin secretion and by insulin on glucose utilization and endogenous production. The glucose subsystem consists of a two-compartment model of glucose kinetics: insulin-independent utilization
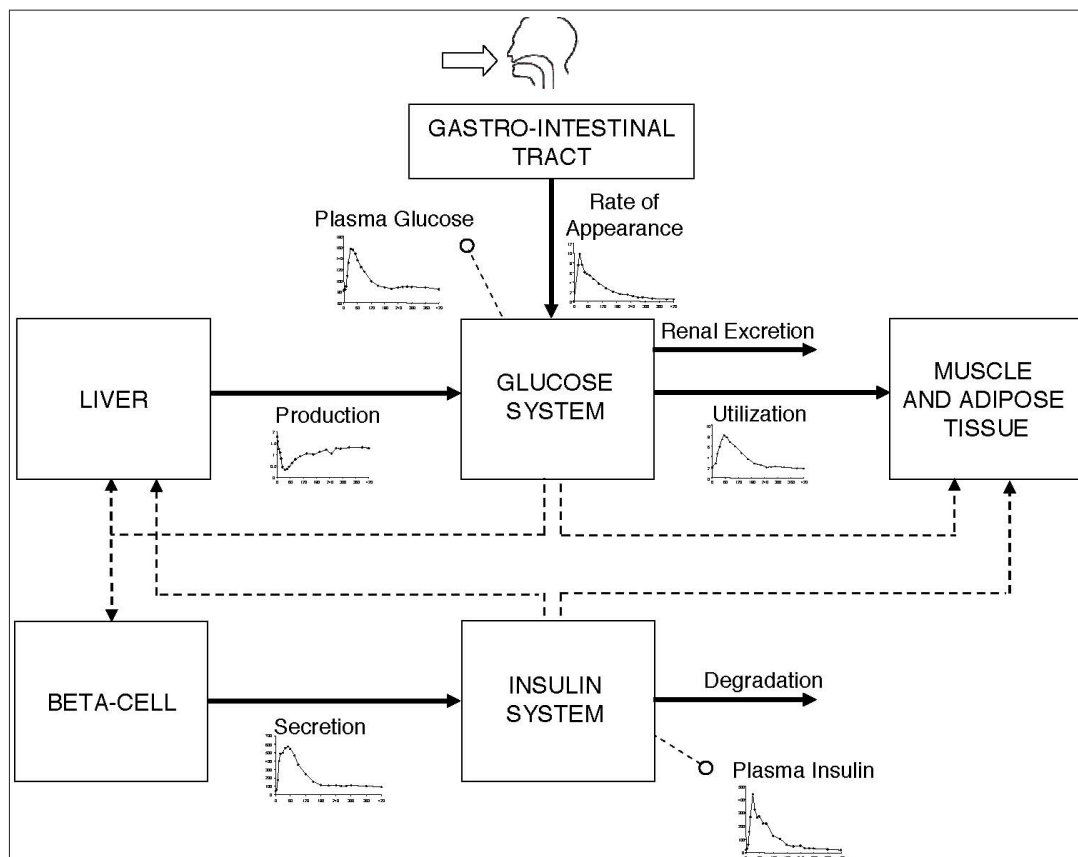

Figure 1. Scheme of the glucose–insulin control system. Continuous lines denote fluxes of material and dashed lines control signals. In addition to plasma glucose and insulin concentration measurements, glucose fluxes (i.e., meal rate of appearance, production, utilization, and renal extraction) and insulin fluxes (i.e., secretion and degradation) are also shown (see text).

occurs in the first compartment, representing plasma and fast equilibrating tissue, while insulin-dependent utilization occurs in a remote compartment, representing peripheral tissues. The insulin subsystem also consists of two compartments, the first representing the liver and the second the plasma. The most important model unit processes are endogenous glucose production, glucose rate of appearance, glucose utilization, and insulin secretion. Suppression of endogenous glucose production is assumed to be linearly dependent on plasma glucose concentration, portal insulin concentration, and a delayed insulin signal. Key parameters are hepatic glucose effectiveness (glucose control on endogenous glucose production suppression) and hepatic insulin sensitivity (insulin control on endogenous glucose production suppression). Glucose intestinal absorption describes the glucose transit through the stomach and intestine by assuming that the stomach is represented by two compartments (one for solid and one for triturated phases), while a single compartment is used to describe the gut; the rate constant of gastric emptying is a nonlinear function of the amount of glucose in the stomach. Glucose utilization during a meal (both insulin independent and dependent) is made up of two components. Insulin-independent utilization in the brain and erythrocytes takes place in the first compartment and is constant, whereas insulin-dependent utilization in muscle and adipose tissue takes place in the remote compartment and depends nonlinearly (Michaelis–Menten) from glucose in the tissues. Beta-cell insulin secretion is described by dynamic and static components. The dynamic component likely represents the release of promptly releasable insulin and is proportional to the rate of increase of glucose concentration through a parameter called dynamic beta-cell responsivity. The static component describes the provision of new insulin to the releasable pool and is proportional to a delayed glucose signal through a parameter called static beta-cell responsivity. All model parameters and GIM values are reported in the article by Dalla Man and co-workers.[12]

Type 2 Diabetes

This model is described in detail elsewhere.[12] Briefly, some derangements of the beta-cell response to glucose, as well as of insulin action on glucose utilization, have been modeled. All GIM parameter values are reported in the article by Dalla Man and colleagues.[12]

Type 1 Diabetes

In order to simulate a type 1 diabetic subject the insulin secretion module is substituted by a subcutaneous insulin infusion module. In order to account for the higher (vs normal) basal glucose, e.g., 180 mg/dl, the software

introduces a higher endogenous glucose production, e.g., 2.4 mg/kg/min (as a result, plasma glucose clearance is lower than normal, e.g., 0.013 dl/kg/min). Because the simulated subject is assumed in good control, all the other parameters are kept at values of the normal subject.[15–17]

Several models of subcutaneous insulin kinetics have been published.[18–20] GIM implements a variation of a model described in Nucci and Cobelli[18] (Dr. A. Vølund, private communication):

$$\begin{cases} \dot{I}_{sc1}(t) = -\left(k_d + k_{a1}\right) \cdot I_{sc1}(t) + IIR(t) & I_{sc1}(0) = I_{sc1ss} \\ \dot{I}_{sc2}(t) = k_d \cdot I_{sc1}(t) - k_{a2} \cdot I_{sc2}(t) & I_{sc2}(0) = I_{sc2ss} \end{cases}, \quad (1)$$

where I_{sc1} is the amount of nonmonomeric insulin in the subcutaneous space, I_{sc2} is the amount of monomeric insulin in the subcutaneous space, $IIR(t)$ (pmol/kg/min) is the exogenous insulin infusion rate, k_d (min^{-1}) is the rate constant of insulin dissociation, and k_{a1} and k_{a2} are the rate constants of nonmonomeric and monomeric insulin absorption, respectively (see **Table 1**).

Table 1.
Parameters of Subcutaneous Insulin Kinetics, Glucose Sensor Delay, and PID Controller

Control	Parameter	Value	Unit
Subcutaneous insulin kinetics	k_d	0.0164	min^{-1}
	k_{a1}	0.0018	min^{-1}
	k_{a2}	0.0182	min^{-1}
Glucose sensor delay	T_d	10	min
PID controller	K_p	0.032	pmol/kg/min per mg/dl
	T_D	66	min
	T_I	450	min

The rate of appearance of insulin in plasma (R_i) is thus

$$R_i(t) = k_{a1} \cdot I_{sc1}(t) + k_{a2} \cdot I_{sc2}(t). \quad (2)$$

Various closed-loop control strategies are available in the literature (for a recent review, see Bequette[21]). Here the simple proportional-integral-derivative (PID) controller proposed in Steil and colleagues[20] to deliver insulin is implemented as an example. As described in Steil *et al.*[20] the PID parameters are assumed to be fixed. The insulin infusion rate (pmol/kg/min) is

$$IIR(t) = PID(t) = Pro(t) + Int(t) + Der(t) \quad (3)$$

with

$$Pro(t) = K_p \cdot \left[G_s(t) - G_{tar} \right] \qquad (4)$$

$$Int(t) = \frac{K_p}{T_I} \int_0^t \left[G_s(\tau) - G_{tar} \right] d\tau \qquad (5)$$

$$Der(t) = K_p \cdot T_D \cdot \frac{dG_s(t)}{dt} \qquad (6)$$

where G_{tar} is the glucose target and $G_s(t)$ is the sensor signal described by

$$\dot{G}_s(t) = -\frac{1}{T_s} \cdot G_s(t) + \frac{1}{T_s} \cdot G(t); \quad G_s(0) = G_b , \qquad (7)$$

where T_s (min) is the physiological delay of the sensor, K_p (pmol/kg/min per mg/dl) is the rate of insulin infusion in response to glucose above basal, T_I (min) is the ratio between proportional and integral release, and T_D (min) is the ratio of derivative to proportional release.

Parameter values of the subcutaneous insulin kinetics model, glucose sensor delay, and PID controller[20] are shown in **Table 1**.

An open-loop control strategy is also possible using the model of subcutaneous insulin kinetics described in Equations (1) and (2) where

$$IIR(t) = \sum_{j=1}^{N_{meal}} D_j^{ins} \cdot \delta(t - t_j) + IIR_b , \qquad (8)$$

where N_{meal} is the number of meals, t_j is the time of meal occurrence, D_j^{ins} is the exogenous insulin dose injected subcutaneously at t_j, and IIR_b is the basal insulin infusion rate.

Finally, it is worth noting that some steady-state constraints in the type1 diabetes model are different than those used in the normal (we refer to Dalla Man et al.[12] for symbol definition). In particular, parameter k_{p1} of glucose production becomes

$$k_{p1} = EGP_b + k_{p2} \cdot G_{pb} + k_{p3} \cdot I_b \qquad (9)$$

as there is no portal insulin signal; the amount of insulin in the liver compartment at basal state is

$$I_{lb} = I_{pb} \cdot \frac{m_2}{m_1 + m_3} \qquad (10)$$

with I_{pb} the amount of insulin in plasma at basal steady state and I_{pb} settable by the user in closed loop while it depends from the IIR_b in open loop:

$$I_{pb} = \frac{IIR_b}{\left(m_2 + m_4 - \dfrac{m_1 \cdot m_2}{m_1 + m_3} \right)} . \qquad (11)$$

Similarly, the basal value of insulin in the subcutaneous compartments, I_{sc1ss} and I_{sc2ss}, depends from I_{pb} in closed loop and from the IIR_b in open loop:

$$I_{sc1ss} = \begin{cases} \dfrac{I_{pb}}{k_d + k_{a1}} \cdot \left(m_2 + m_4 - \dfrac{m_1 \cdot m_2}{m_1 + m_3} \right) & \text{in closed-loop} \\[2ex] \dfrac{IIR_b}{k_d + k_{a1}} & \text{in open-loop} \end{cases} \qquad (12)$$

$$I_{sc2ss} = \frac{k_d}{k_{a2}} \cdot I_{sc1ss} \qquad (13)$$

GIM Software

MATLAB Version

The model described in this article has been implemented in MATLAB, version 7.0.1.

When GIM is run, a dialog box opens and asks the user to select the status of the subject. Three possible options are available: Normal, Type 2 Diabetic, or Type 1 Diabetic subject (**Figure 2**).

When the user clicks on Normal or Type 2 Diabetic an interactive window appears (**Figure 3**). The window is divided into three sections.

1. *Basal*, where basal values of *glucose concentration*, *insulin concentration*, and *glucose production* are set. By clicking on the button CALCULATE, the basal glucose clearance rate is calculated and displayed in the proper square.

2. *Subject*, where the values of *body weight* and main metabolic indices, such as *peripheral* and *hepatic insulin sensitivity* (V_{max} and k_{p3} in model,[12] respectively), *dynamic*, and *static beta-cell responsivity* to glucose (K and β in model,[12] respectively), are entered as a percentage of the normal values[12]; for type 2 diabetic subjects, typical derangements are initially displayed.

3. *Protocol*, where the time of the three meals and the amount of glucose ingested are set.

Once all the fields are set and new values are saved, the simulation starts by clicking on START SIMULATION. Simulation results are presented in a graphic format, i.e., a figure is displayed that shows *glucose* and *insulin*

concentrations, *glucose production*, *glucose utilization*, *meal rate of appearance*, and *insulin secretion* (an example is shown in **Figure 4** and is discussed further in the next section).
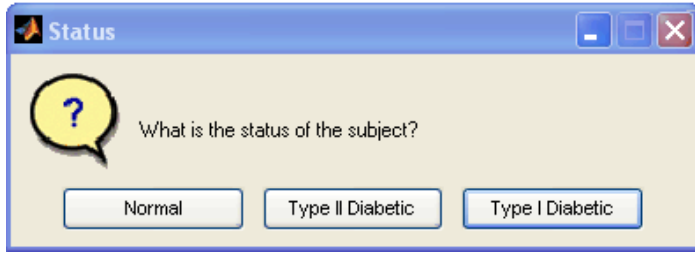

Figure 2. The dialog box allows the user to select the status of the subject: Normal, Type 2 Diabetic, or Type 1 Diabetic.
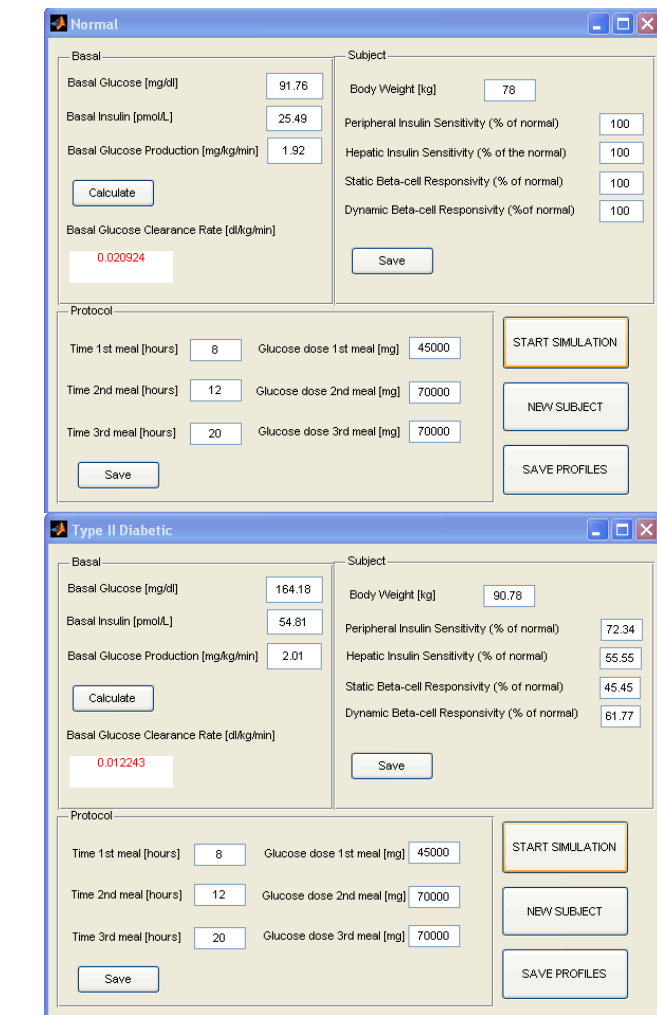

Figure 3. Normal (**top**) and Type 2 Diabetic (**bottom**) windows. Each window is divided into three sections that allow the user to set basal values of glucose concentration, insulin concentration, and glucose production (glucose clearance is calculated and displayed in the proper square); to enter values of body weight and main metabolic indices, such as peripheral and hepatic insulin sensitivity, static, and dynamic beta-cell responsivity to glucose (as percentage of normal values); and to define the time of the three meals and the amount of glucose ingested. The window also shows buttons to start simulation, save the simulated profiles, or run a new subject.

The program also allows the user to save the aforementioned profiles in a .mat file by clicking the button SAVE PROFILES. The interactive window shown in **Figure 5** allows naming the .mat file and placing it in the desired folder. To run a new subject one has simply to click the button NEW SUBJECT.

If the user selects Type 1 Diabetic the interactive windows is a bit different (**Figure 6**): four sections are displayed.

1. *Basal*, which is the same as that described earlier.

2. *Subject*, where the values of body weight and only peripheral and hepatic insulin sensitivity are entered as a percentage of normal values.
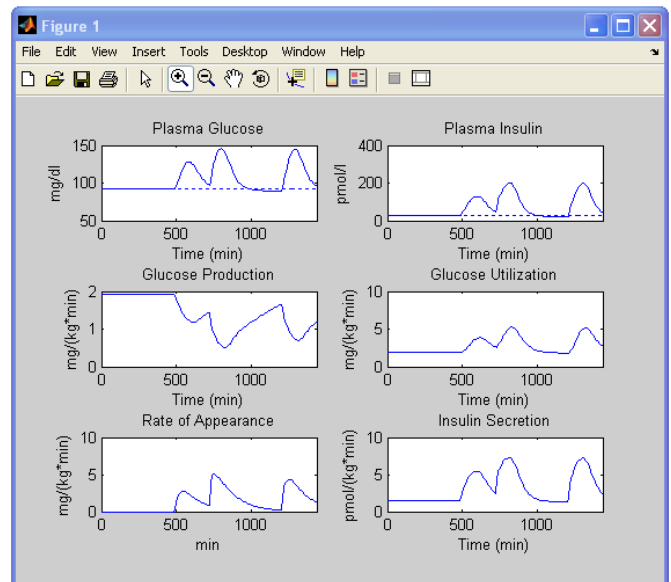

Figure 4. Simulation results of a normal subject. Glucose and insulin concentrations, glucose production, glucose utilization, meal rate of appearance, and insulin secretion rate are obtained with settings of Figure 3 (top).
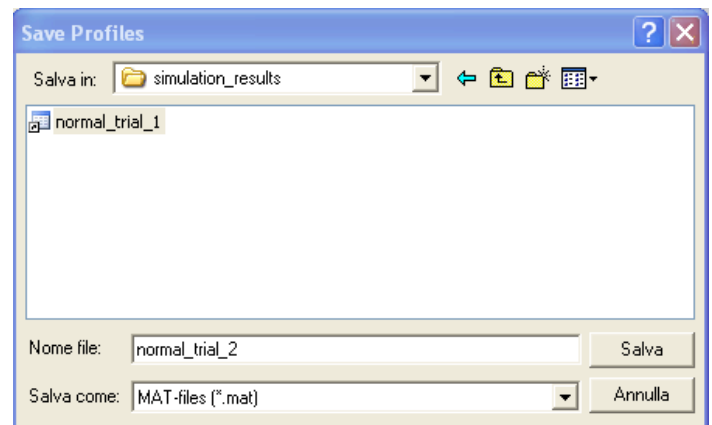

Figure 5. The Save Profiles window allows one to name the .mat file containing the saved solutions and to place it in the desired folder.

3. *Control*, which allows the user to select if the subject is controlled in open loop (**Figure 6**, **left**) or in closed loop with a PID controller (**Figure 6**, **right**). If open loop is selected, the basal insulin infusion rate can be entered [basal insulin concentration is set by (Equation 11)]. If closed loop is selected, the basal insulin concentration can be chosen by the user, which also has to define a glucose target value.

4. *Protocol*, which is the same as that described earlier with the addition that if open loop is selected, one enters the insulin dose injected before each meal.

The program provides default values, which are displayed initially.

Simulink Version

The model was also implemented in Simulink to allow control-oriented investigators to test their closed-loop algorithms easily.

Software

Both Windows and Simulink versions of the software are available by request for academic institutions from the corresponding author.

Case Studies

Three case studies illustrating the potential of the software are now presented.

Normal Subject vs Insulin-Resistant Subject

The goal of this case study is to illustrate the key role of insulin sensitivity in glucose regulation. A normal subject is simulated first. Let us use the default setting of a normal subject (**Figure 3**, **top**): a basal glucose concentration of 91.76 mg/dl; a basal insulin concentration of 25.49 pmol/liter; a basal glucose production of 1.92 mg/kg/min; a body weight of 78 kg; and peripheral insulin sensitivity, hepatic insulin sensitivity, static beta-cell responsivity, and dynamic beta-cell responsivity equal to 100% of the normal; 45 g of glucose is ingested at 8 a.m., 70 g at noon, and 70 g at 8 p.m. The simulation results are shown in **Figure 4**. After the breakfast glucose concentration peaks at around 130 mg/dl, it is still over basal at lunch time. The glucose concentration increases after lunch until around 160 mg/dl and comes back to basal 4 hours later. After dinner the peak is a bit lower than after lunch. These profiles are saved as explained in the previous paragraph. Now, we maintain all settings except for *peripheral* and *hepatic insulin sensitivity*, which are set to 30% of the normal. The program asks which .mat file should be

Figure 6. The Type1 Diabetic window is divided into four sections that allow the user to set basal values of glucose concentration, insulin concentration, and glucose production (glucose clearance is calculated and displayed in the proper square); to enter values of body weight and main metabolic indices, such as peripheral and hepatic insulin sensitivity (as percentage of normal values); to select if the subject is controlled in a open (**left**) or closed loop with a PID controller (**right**); and to define the time of the three meals, the amount of glucose ingested, and, in case of open-loop control, the insulin dose injected before each meal. The window also shows buttons to start simulation, save the simulated profiles, or run a new subject.

used for comparison. By choosing the one just saved, the profiles will be automatically displayed (**Figure 7**, red line) superimposed onto the previous ones (**Figure 7**, blue line). As expected, the glucose concentration is now higher during all meals. Both insulin concentration and secretion rate are higher due to the fact that beta-cell responsivity to glucose is "normal" but the glucose concentration is higher. Glucose utilization is lower, whereas glucose production is more suppressed because of both a higher glucose concentration and a delayed (more than on glucose utilization) insulin action on glucose production.
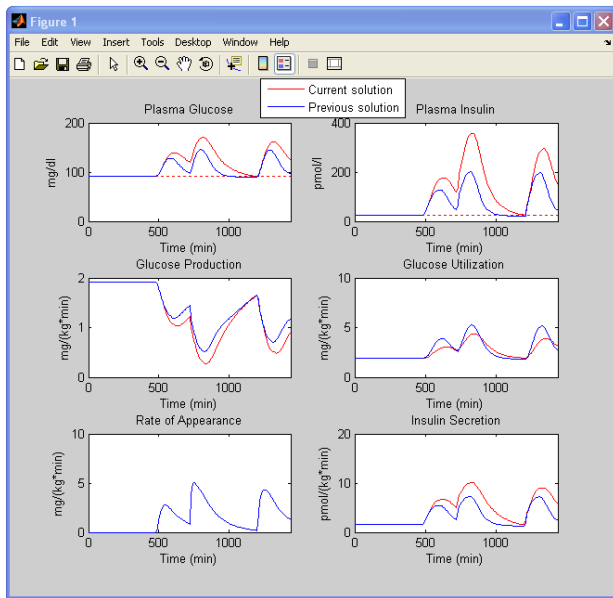

Figure 7. Simulation results of a normal subject vs an insulin-resistant subject. Glucose and insulin concentrations, glucose production, glucose utilization, meal rate of appearance, and insulin secretion rate obtained with settings of Figure 3 (top)(blue line) are superimposed on those obtained with the same setting but 70% lower insulin sensitivity indices (red line).

Open-Loop Controlled Type 1 Diabetic Subject

Let us choose the type 1 diabetic window and use the default settings suggested by the program (**Figure 6**, **left**) and assume that the basal insulin infusion rate is 1 pmol/kg/min. The protocol is 45 g of glucose ingested at 8 a.m. with 3 U of insulin injected, 70 g at noon with 4.5 U of insulin, and 70 g at 8 p.m. with 4.5 U of insulin. The simulation results are shown in **Figure 8** (blue line). One can also predict what happens if the patient forgets to inject insulin before lunch. The program displays the new simulated profiles (**Figure 8**, red line) against the previous ones (**Figure 8**, blue line).

Closed-Loop Controlled Type 1 Diabetic Subject

Let us choose the type 1 diabetic window and use the default settings suggested by the program (**Figure 6**, right)

with the glucose target equal to 130 mg/dl; the protocol is 45 g of glucose ingested at 8 a.m., 70 g at noon, and 70 g at 8 p.m. The simulation results are shown in **Figure 9**.
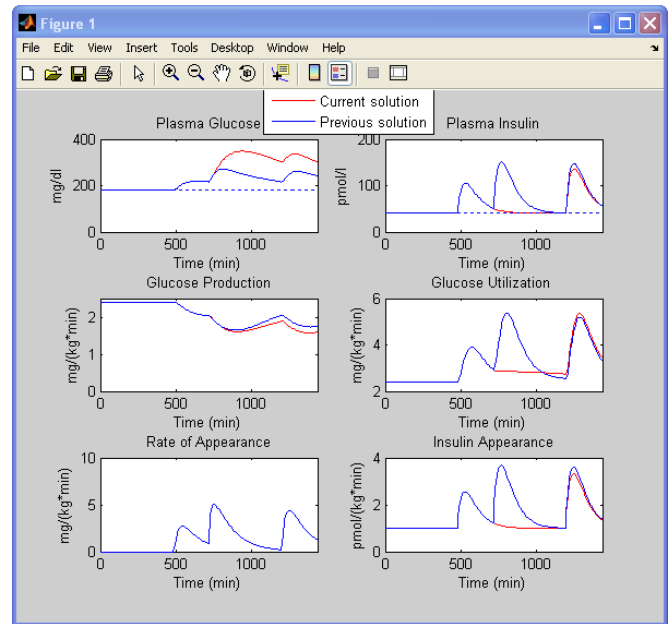

Figure 8. Simulation results of a type 1 diabetic subject controlled in an open loop. Glucose and insulin concentrations, glucose production, glucose utilization, meal rate of appearance, and insulin appearance obtained with settings of Figure 6 (left) (blue line) are superimposed on those obtained in the same subject who forgot to inject insulin before lunch (red line).
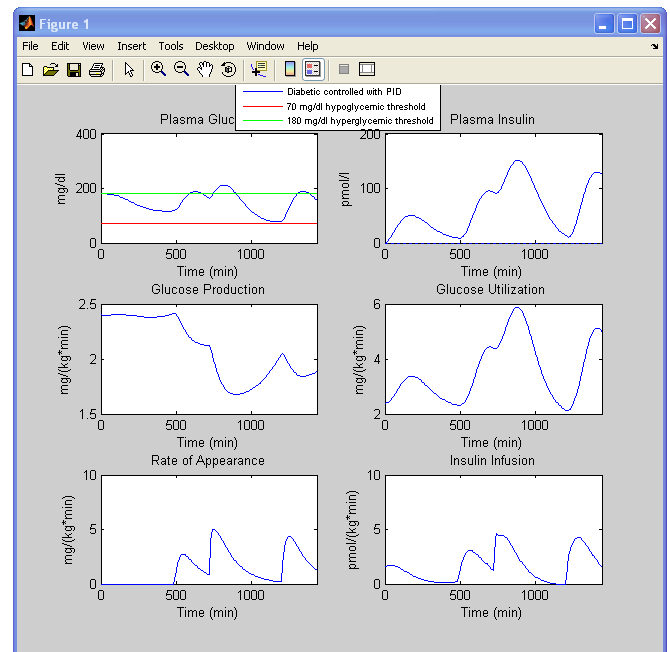

Figure 9. Simulation results of a type 1 diabetic subject controlled in a closed loop with a PID controller. Glucose and insulin concentrations, glucose production, glucose utilization, meal rate of appearance, and insulin infusion are obtained with settings of Figure 6 (right). Hypoglycemia (red) and hyperglycemia (green line) thresholds are also displayed.

Conclusions

The ability to simulate the glucose–insulin system in normal life conditions can be very useful for studying the pathophysiology of diabetes. A new model has been presented that incorporates state- of-the-art physiological knowledge gained at organ/tissue levels.[12] This article presented interactive simulation software, GIM, which implements the aforementioned model. Thanks to its windows interface, its use is extremely easy for investigators without specific expertise in modeling.

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