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SYMPOSIUM

In Silico Preclinical Trials: A Proof of Concept in Closed-Loop Control of Type 1 Diabetes

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Abstract

Arguably, a minimally invasive system using subcutaneous (s.c.) continuous glucose monitoring (CGM) and s.c. insulin delivery via insulin pump would be a most feasible step to closed-loop control in type 1 diabetes mellitus (T1DM). Consequently, diabetes technology is focusing on developing an artificial pancreas using control algorithms to link CGM with s.c. insulin delivery. The future development of the artificial pancreas *will* be greatly accelerated by employing mathematical modeling and computer simulation. Realistic computer simulation is capable of providing invaluable information about the safety and the limitations of closed-loop control algorithms, guiding clinical studies, and out-ruling ineffective control scenarios in a cost-effective manner. Thus computer simulation testing of closed-loop control algorithms is regarded as a prerequisite to clinical trials of the artificial pancreas.

In this paper, we present a system for *in silico* testing of control algorithms that has three principal components: (1) a large cohort of $n = 300$ simulated "subjects" ($n = 100$ adults, 100 adolescents, and 100 children) based on real individuals' data and spanning the observed variability of key metabolic parameters in the general population of people with T1DM; (2) a simulator of CGM sensor errors representative of Freestyle Navigator™, Guardian RT, or Dexcom™ STS™, 7-day sensor; and (3) a simulator of discrete s.c. insulin delivery via OmniPod Insulin Management System or Deltec Cozmo® insulin pump.

The system has been shown to represent adequate glucose fluctuations in T1DM observed during meal challenges, and has been accepted by the Food and Drug Administration as a substitute to animal trials in the preclinical testing of closed-loop control strategies.

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Abbreviations: (BG) blood glucose, (CGM) continuous glucose monitoring, (CHO) carbohydrate, (CVGA) control-variability grid analysis, (FDA) Food and Drug Administration, (i.v.) intravenous, (IDE) investigational device exemption, (JDRF)Juvenile Diabetes Research Foundation, (MPC) model-predictive control, (PID) proportional integral derivative, (s.c.) subcutaneous, (T1DM) type 1 diabetes mellitus

Keywords: computer simulation, diabetes control, modeling

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Introduction

Over thirty years ago, the possibility for external regulation of blood glucose (BG) in people with diabetes has been established by studies using intravenous (i.v.) glucose measurement and i.v. infusion of glucose and insulin. Systems such as the Biostator™ have been introduced and used in hospital settings to maintain normoglycemia by exerting both positive (via glucose or glucagon) and negative (via insulin) control.[1–5] A detailed description of the major early designs, including proportional integral derivative (PID) and model-predictive control (MPC) can be found in the literature.[6–11] More work followed, spanning a broader range of BG control techniques, such as pole placement,[11] adaptive control,[12,13] physiologic modeling,[14] control specific to intensive care units,[15] or linear quadratic Gaussian optimization.[16,17] However, i.v. closed-loop control remains cumbersome and unsuited for outpatient use. An alternative to extracorporeal i.v. control has been presented by implantable i.v.–intraperitoneal systems employing i.v. sampling and intraperitoneal insulin delivery.[18–20] With the advent of minimally invasive subcutaneous (s.c.) continuous glucose monitoring (CGM), increasing academic, industrial, and political effort has been focused on the development of s.c.–s.c. systems, generally using CGM coupled with insulin infusion pump and a control algorithm.[21,22] So far, encouraging pilot results have been reported.[23,24] A recent United States Senate hearing emphasized the artificial pancreas initiative.[25] In September 2006, the Juvenile Diabetes Research Foundation (JDRF) initiated the Artificial Pancreas Project and funded a consortium of university centers to carry closed-loop glucose control research.[26] These centers include Cambridge University, University of Colorado, Sansum Diabetes Research Institute, Stanford University, University of Virginia, and Yale University. In 2007, a group at Boston University joined the JDRF Artificial Pancreas Consortium.

The future development of the artificial pancreas *will* be greatly accelerated by employing mathematical modeling and computer simulation. Numerous precedents from the history of engineering support this assertion. A prime example is the Boeing 777 jetliner, which has been recognized as the first airplane to be 100% digitally designed and assembled in a computer simulation environment. This virtual design has eliminated the need for many costly experiments and accelerated the development process, significantly reducing the time before the final extensive ground and flight testing began. The result has been impressive: the 777s flight deck and passenger cabin received the Design Excellence Award of the Industrial Designers Society—the first time any airplane was recognized by the society.[27]

As with the design of any complex engineering system, realistic computer simulation can provide invaluable information about the safety and limitations of closed-loop control algorithms, can guide and focus the emphasis of clinical studies, and can out-rule ineffective control scenarios in a cost-effective manner prior to human use. In the area of diabetes, accurate computer-simulation prediction of clinical trials has been done by the Archimedes diabetes model;[28,29] a company—Entelos, Inc.—specializes in predictive biosimulation and, in particular, has developed a diabetes simulator. Most existing diabetes simulators, however, are based on population models. As a result, their capabilities are generally limited to prediction of population averages that would be observed during clinical trials. Therefore, for the purposes of artificial pancreas development, a different type of computer simulator is needed—a system that is capable of simulating the glucose–insulin dynamics of a particular person. In other words, a simulator of type 1 diabetes mellitus (T1DM) should be equipped with a cohort of *in silico* "subjects" that spans sufficiently well the observed interperson variability of key metabolic parameters in the general population of people with T1DM. *In silico* subjects are typically created by fitting a metabolic model to data of individuals collected during clinical trials. Various glucose–insulin models[30–32,14] have been developed to serve this purpose, with the first two already used for testing of control scenarios.

The next logical step of *in silico* preclinical trial has been taken. In January 2008, a computer simulator of T1DM developed by our group has been accepted by the Food and Drug Administration (FDA) as a substitute to animal trials for the preclinical testing of control strategies in artificial pancreas studies.[33] Arguably, large-scale simulations would account better for intersubject variability than small-size animal trials and would allow for more extensive testing of the limits and robustness of control algorithms. Thus the simulator was immediately put to its intended use, and in April 2008, an investigational device exemption (IDE) was granted by the FDA for a closed-loop control clinical trial. This IDE was issued solely on the basis of *in silico* testing of the safety and effectiveness of the proposed artificial

pancreas algorithm, an event that sets a precedent for future preclinical studies. Thus the following paradigm has emerged: (i) *in silico* modeling could produce credible preclinical results that could substitute certain animal trials, and (ii) *in silico* testing yields these results in a fraction of the time required for animal trials.

We will now describe the steps enabling the *in silico* development and testing of closed-loop control algorithms. We need to emphasize, however, that good *in silico* performance of a control algorithm does not guarantee *in vivo* performance—it only helps to test extreme situations and the stability of the algorithm and to out-rule inefficient scenarios. Thus computer simulation is only a prerequisite to, but not a substitute for, clinical trials.

Methods

The principal components of a computer simulation environment recreating *in silico* a closed-loop control system are presented in **Figure 1**.

1. A sufficiently large cohort of *in silico* subjects based on real individual data and spanning the observed variability of key parameters in the general population. In this implementation the simulated "cohort" includes $n = 300$ simulated subjects in three age groups: 100 adults, 100 adolescents, and 100 children. **Table 1** presents key demographic and metabolic parameters of these subjects. The carbohydrate (CHO) ratio is calculated as the largest bolus in insulin units per grams of CHO that does not create a drop in plasma glucose lower than 95% of fasting plasma glucose after a meal containing 50 g CHO. The total daily insulin was computed based on a 200 g CHO daily diet, using a basal rate maintaining fasting glucose and the CHO ratio. Insulin sensitivity in the simulator consists of several components such as insulin effect on glucose utilization and insulin effect on glucose production. Insulin effect on glucose utilization is included in **Table 1**.

2. Sensor-specific simulator of sensor errors capable of reproducing the time lag, system and calibration bias, and random noise of s.c. CGM devices: The characteristics of three devices have been implemented: Freestyle Navigator™ (Abbott Diabetes Care, Alameda, CA), Guardian RT (Medtronic, Northridge, CA), and Dexcom™ STS™, 7-day sensor (Dexcom, Inc., San Diego, CA).

3. The model of insulin kinetics in the s.c. space: Because insulin pumps typically deliver discrete insulin subcutaneously, one has to account for the time lag inherent with the insulin transport from s.c. space to plasma. The characteristics of two insulin

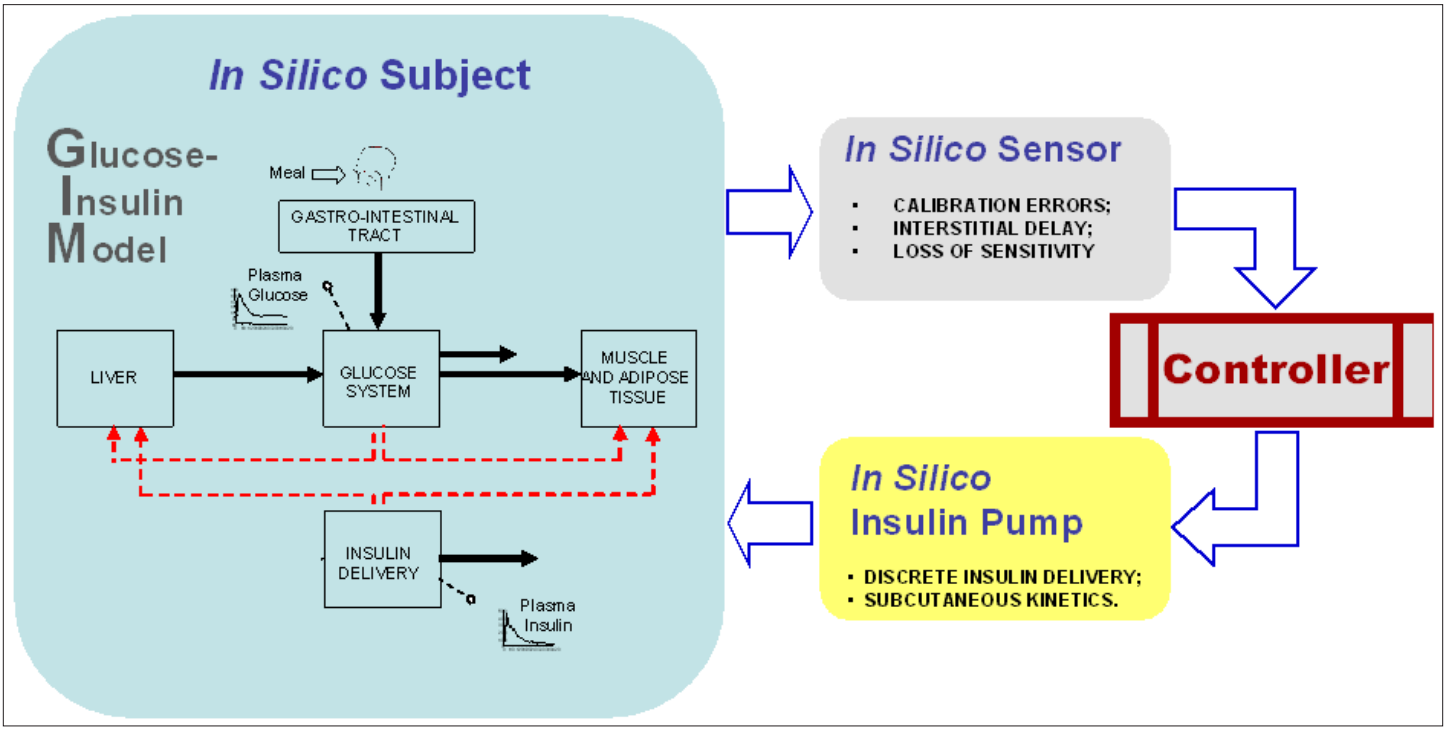

Figure 1. Principal components of computer simulation environment: a model of the glucose–insulin system; a model of sensor error; the controller to be tested; and a model of insulin pump and s.c. insulin kinetics.

Table 1.
Key Demographic and Metabolic Parameters of the *In Silico* Subjects Available in the Simulation Environment[a]

	Adults			Adolescents			Children		
Parameter	Mean (SD)	Min	Max	Mean (SD)	Min	Max	Mean (SD)	Min	Max
Mean Weight (kg) (SD)	79.7 (12.8)	52.3	118.7	54.7 (9.0)	37.0	88.7	39.8 (6.8)	27.6	60.7
Insulin (U/day)	47.2 (15.2)	21.3	98.4	53.1 (18.2)	22.6	141.5	34.6 (9.1)	17.6	56.1
CHO ratio (g/U)	10.5 (3.3)	4.6	21.1	9.3 (2.9)	3.2	19.9	14.0 (3.8)	8.0	25.5
Fasting plasma glucose (mg/dl)	143.4 (9.33)	122.1	167.1	144 (7.8)	124	166.3	142.9 (8.5)	125.5	168.4
Insulin effect on glucose utilization (10^{-2} mg/kg/min per pmol/liter)	3.82 (1.34)	1.08	8.08	3.06 (1.67)	0.95	40.87	12.58 (5.64)	3.61	35.38

[a] SD, standard deviation.

pumps have been implemented: OmniPod Insulin Management System (Insulet Corp., Bedford, MA) and Deltec Cozmo® (Smiths Medical MD, Inc., St. Paul, MN).

In Silico Subjects

The mathematical model providing the base for the *in silico* subjects of the simulation environment has been described in detail in previous publications. Specifically, the previously reported glucose–insulin meal model of Dalla Man and Cobelli[30,31] serves as the foundation for the simulation environment. Briefly, the model assumes that the glucose and insulin subsystems are linked one to each other by the control of insulin on glucose utilization and endogenous production. The glucose subsystem consists of a two-compartment model of glucose kinetics. The insulin subsystem also consists of two compartments, the first representing the liver and the second the plasma. Endogenous glucose production, glucose rate of appearance, and glucose utilization are the most important model unit processes. Suppression of endogenous glucose production is assumed to be linearly dependent on plasma glucose concentration, portal insulin concentration, and a delayed insulin signal. Glucose intestinal absorption describes the glucose transit through the stomach and intestine by assuming the stomach to be represented by two compartments (one for solid and one for liquid phase); a single compartment is used to describe the gut, and the rate constant of gastric emptying is a nonlinear function of the amount of glucose in the stomach. Glucose utilization is the sum of two terms: a constant insulin-independent utilization, which takes place in the first compartment, representing glucose uptake by the brain and erythrocytes, and insulin-dependent utilization, which occurs in a remote compartment, representing peripheral tissues and depending nonlinearly on glucose in the tissues. Renal excretion by the kidney is also taken into account and is assumed to occur if plasma glucose exceeds a certain threshold. The model has 26 free parameters, among which the most important are hepatic and peripheral insulin sensitivity, i.e., the ability of plasma insulin to inhibit endogenous glucose production and enhance glucose disposal, respectively. We should note that, at least in principle, all model parameters, and in particular insulin sensitivity, could vary during the day. However, diurnal variation of model parameters is not yet taken into account in the model due to lack of quantitative knowledge on these phenomena. Once the set of equations defining *in silico* subjects is laid out, *in silico* cohort is created by generating parameter vectors spanning the parameter space observed in T1DM.

In Silico Sensor

In silico sensor is developed on the basis of analysis of sensor errors. In general, CGM provides a detailed time series of consecutive observations upon the underlying process of glucose fluctuations. However, a number of studies have concluded that despite eight years of development, CGM technology continues to face challenges in terms of sensitivity, stability, calibration, and the physiological time lag between blood and interstitial glucose concentration.[34–40] While testing sensor accuracy, these studies have typically generated large amounts of sensor–reference glucose data pairs, thereby allowing the decomposition of sensor errors into errors due to calibration, blood-to-interstitial glucose transfer, and random noise.[41] After generating a random calibration error, the components of sensor error can be modeled as a combination of blood-to-interstitium glucose transport plus a nonwhite noise. The composition of sensor errors is described in detail by Breton and Kovatchev.[42] In some sense, this sensor simulation model provides worst-case scenario sensor errors; we anticipate that the real sensor errors would tend to be smaller during controlled inpatient clinical trials.

In Silico Insulin Pump

In silico insulin pump is used to approximate s.c. insulin delivery, taking into account (i) time and dynamics of insulin transport from s.c. tissue into blood and (ii) discrete insulin infusion corresponding to stepwise basal pump rate and insulin boluses. Several models of s.c. insulin kinetics have been published.[43,44] In the simulation environment, we used the two-compartment model presented in detail by Dalla Man *et al.*,[31] which includes approximation of nonmonomeric and monomeric insulin in the s.c. space.

Software Implementation

In order to create a comprehensive algorithm testing environment, the simulation methods described earlier have been implemented into a computerized simulation platform using Simulink®, which is part of the larger scientific software MATLAB®. **Figure 2** presents the main user interface window of the software, which allows for (1) defining a testing scenario, i.e., a schedule of meals with corresponding CHO amounts; (2) selecting subjects, where specific subgroups (i.e., adults) or specific subjects could be selected or the simulation could be run on the entire cohort; (3) selecting CGM sensor and insulin pump; and (4) selecting a set of outcome metrics.

The set of metrics of glucose control implemented within the simulation environment includes several measures of average glycemia, temporal glucose variability, and associated risks for hypoglycemia and hyperglycemia, which have been shown to be quite sensitive to the effects of various treatments.[45,46] Several graphs are included as well, ranging from glucose traces and individual Poincaré plots of glucose dynamics[45] to control-variability grid analysis (CVGA).[47] **Table 2A** presents the outcome metrics, and **Table 2B** presents the graphs that can be produced for each *in silico* trial.

Table 2.
Key Demographic and Metabolic Parameters of the *In Silico* Subjects Available in the Simulation Environment[a]

A: Numerical Measures of Average Glycemia, Deviations from Target, Variability, and Risk Associated with Extreme Glucose Deviations	
Mean BG	Computed from CGM or BG data for the entire test.
Mean premeal BG	Mean BG restricted to time window 60–0 min premeals.
Mean postmeal BG	Mean BG restricted to time window 60–120 min postmeals.
% time spent within target range of 70–180 mg/dl; below 70 and above 180 mg/dl; and below 50 and above 300 mg/dl	For CGM, this is generally equal to % readings within each of these ranges. For BG measurements that are not equally spaced in time, we suggest calculating the % time within each range via linear interpolation between consecutive glucose readings.
% time within fasting target of 70–145 mg/dl	It is suggested that for overnight control the target range is restricted to 70–145 mg/dl.
Area-under-the-curve per gram CHO	Optional. Computed from the beginning of a meal for 3 h, provided that no other meal occurs during this time.
LBGI	Measure of the frequency and extent of low BG readings.
HBGI	Measure of the frequency and extent of high BG readings.
SD of BG rate of change	A measure of the stability of closed-loop control over time.
B: Glucose Plots and Composite Graphs	
Glucose trace	Traditional plot of frequently sample glucose data.
Aggregated glucose trace	Corresponds to time spent below/within/above a preset target range. Visualizes the crossing of glycemic thresholds.
Density plot	Represents the distribution of glucose values with overlaid % time spent inside/outside target.
Risk trace	Corresponds to LBGI, HBGI, and BGRI. Designed to equalize the size of glucose deviations toward hypo- and hyperglycemia, emphasize large glucose excursions, and suppress fluctuation within target range, thereby highlighting essential variance.
Histogram of BG rate of change	Represents the spread and range of glucose transitions. Related to system stability. Corresponds to SD of BG rate of change.
Poincaré plot	Represents the spread of the system attractors and can be used for detection of cyclic glucose fluctuations (optional).
CVGA	Represents the effectiveness of closed-loop control at a group level. Corresponds to event-based control characteristics.

[a] BGRI, BG risk index; HBGI, high BG index; LBGI, low BG index; SD, standard deviation.

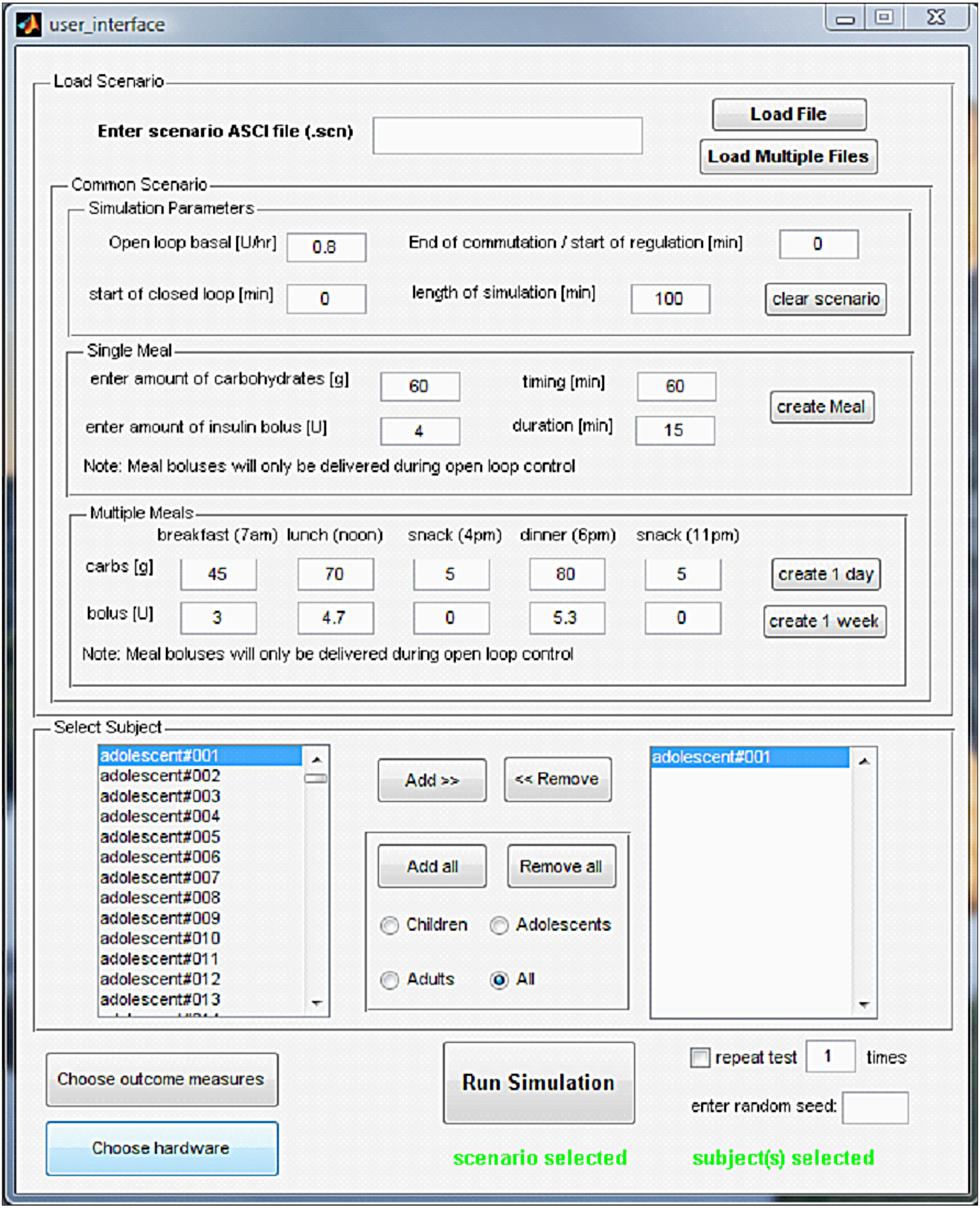

Figure 2. Main user interface window of the simulation software.

Results

In Silico Subjects

To illustrate the use of the simulation environment, we now present several examples of its application. **Figure 3** illustrates the *in silico* testing of a 5-unit premeal insulin bolus followed by ingestion of 75 g CHO. The upper panel of **Figure 3** presents the glycemic reaction of three simulated subjects, while the lower panel presents the simulated plasma insulin concentrations. Both the plasma glucose fluctuations and the plasma insulin concentrations are individual, depending on the metabolic parameters of each simulated subject and are similar to insulin and glucose concentrations measured *in vivo* (see **Figure 1** in Reference 30), which supports the credibility of the simulations.

In general, the validity of the cohort of *in silico* subjects has been tested by several experiments aiming to assess its capability to reflect a variety of clinical situations as closely as possible. These experiments included the following:

1. Reproducing the distribution of insulin correction factors in the T1DM population of children and adults, which guarantees that the variability in the action of insulin administered by control algorithms would accurately reflect the variability in observed insulin action;[32]

2. Reproducing glucose traces in children with T1DM observed in clinical trials performed by the JDRF Continuous Glucose Monitoring Study Group;[48] and

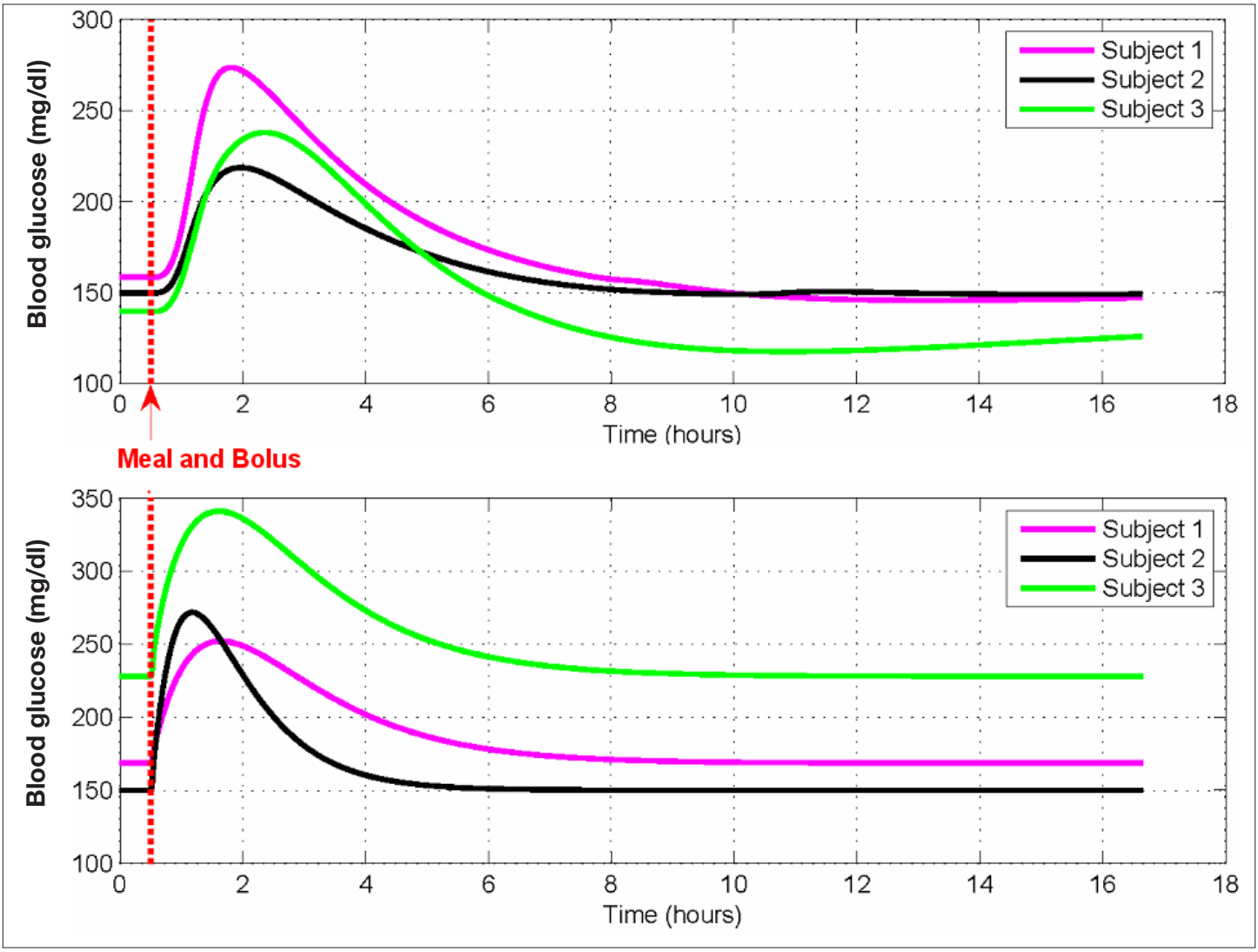

Figure 3. Simulated glucose and insulin traces of three different subjects that received the same amounts of CHO (75 g) and insulin (5 U) at the same time.

3. Reproducing glucose traces of induced moderate hypoglycemia observed in adults in clinical trials at the University of Virginia.

In Silico Sensor

Figure 4 presents the steps of adding an *in silico* sensor, which monitors the glucose fluctuations of an *in silico* subject (**red curve**). First, interstitial glucose delay (**blue curve**) is added using the diffusion model presented in the previous section. Then, autoregressive moving average error is added to account for random errors, resulting in simulated CGM (**green curve**).

To verify the simulation of a CGM device, we conducted multiple experiments generating simulated sensor errors. Then we computed the frequency table of empirical versus simulated distribution of sensor errors using Navigator data sets (56 sensors implanted on 28 patients). The premise behind this verification is that when a sensor simulation is initialized, the corresponding output should be a set of sensor errors with a distribution that is not different from that the error distribution of a real sensor. A Chi-square test showed that we cannot reject the null hypothesis: no significant difference exists between the simulated and the real distribution of sensor errors ($p > .46$). **Table 3** presents the simulated and observed distributions across several bins, covering all possible error values. It is evident that the empirical and simulated error frequencies are indeed very close.

Table 3.
Empirical Versus Simulated Frequency of the Errors of FreeStyle Navigator

Bins	Empirical frequency (%)	Simulated frequency (%)
[-∞,-30] mg/dl	0.5	0.6
[-30,-20] mg/dl	2.9	1.9
[-20,-10] mg/dl	11.4	12.2
[-10,0] mg/dl	34.6	36
[0,10] mg/dl	33.9	30.7
[10,20] mg/dl	11.4	12.4
[20,30] mg/dl	3.5	3.9
[30,∞] mg/dl	1.8	2.2

In Silico Insulin Pump

A major feature of computer simulation is its ability to subject the tested control algorithm to extreme scenarios that cannot be tested *in vivo*. The experiment presented in **Figure 5** simulates an unlikely worst-case scenario taking place during the use of a Deltec Cozmo insulin pump—a complete discharge of the entire pump reservoir at maximum infusion rate. The entire reservoir of the pump contains 300 units of insulin, and the maximum pump rate during a bolus is 150 units/h. We present the results for three *in silico* subjects who, prior to the pump failure, are stable at a glucose level of 110 mg/dl, without recent meal. A subject with very high insulin sensitivity—at the 99th percentile of the cohort of *in silico* subjects—would reach 90 mg/dl after 27.5 min and would reach 70 mg/dl after 37.5 min. For a subject with very low insulin sensitivity (<10th percentile of the cohort of *in silico* subjects), these times would be over 1.5 and 2 h, respectively.

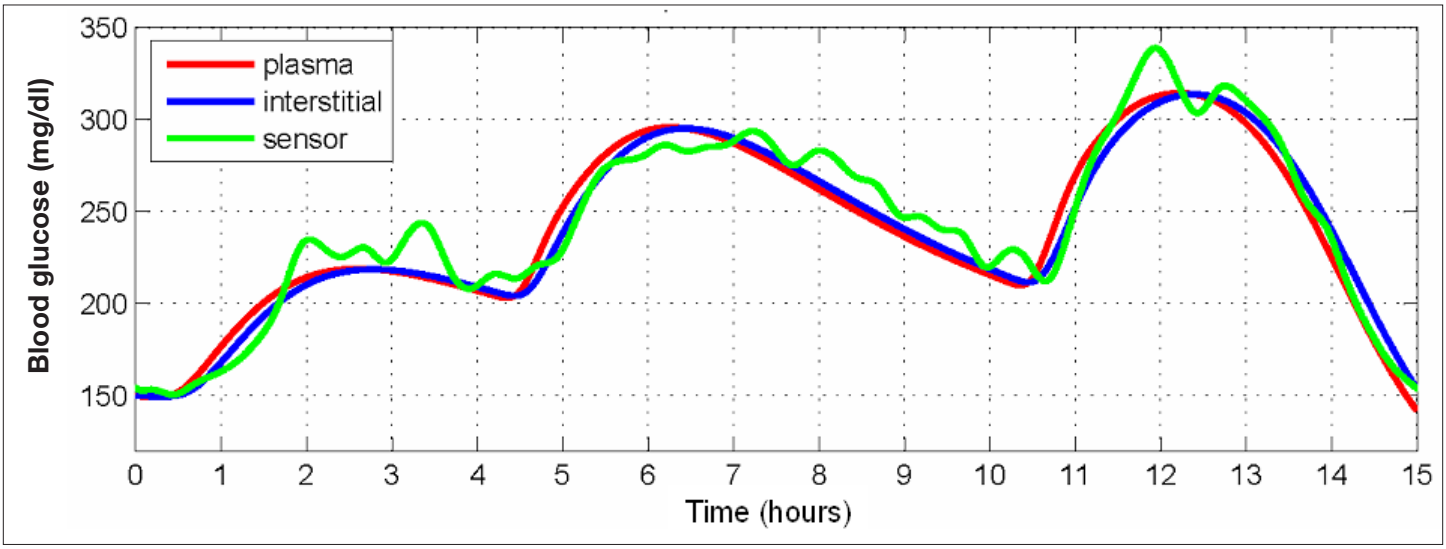

Figure 4. Simulation of CGM errors: example of ideal plasma glucose (**red**), ideal interstitial glucose (**blue**), and noisy interstitial glucose (**green**).

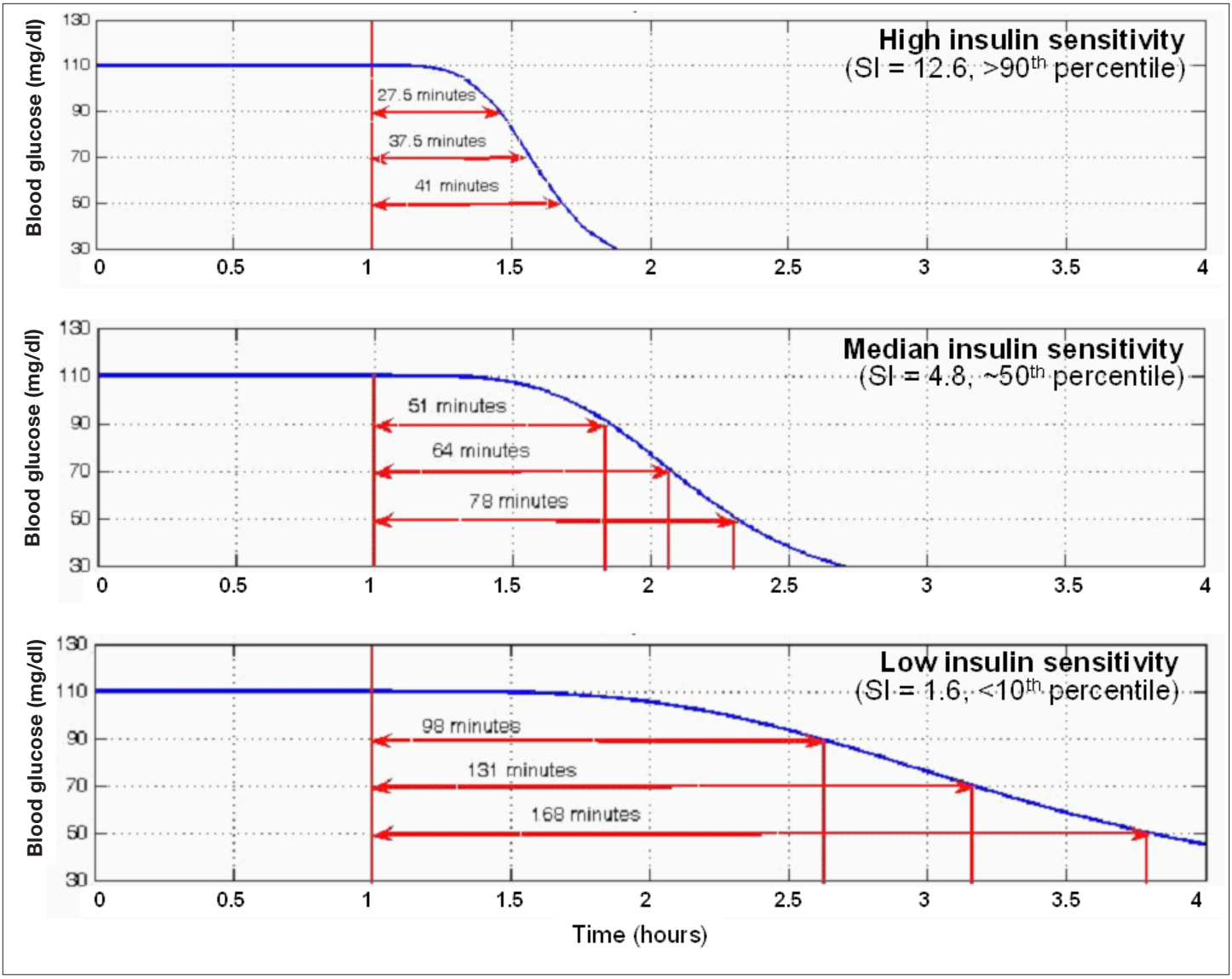

Figure 5. Simulation of extreme insulin pump failure locking the pump at maximum insulin infusion rate in subjects with high (**top**), intermediate (**middle**), and low (**bottom**) insulin sensitivity. SI, International System of Units.

Testing of Closed-Loop Control Algorithms

As stated in the Introduction, testing of the robustness and the limits of closed-loop control algorithms is the primary use of the computer simulation environment. In order to perform such a test, the following steps can be simulated prior to testing:

1. The *in silico* subjects can be screened, and anthropometric data can be recorded as needed for the initialization of the control algorithm; and

2. The *in silico* subjects can be subjected to tests, such as oral glucose tolerance test, which may help deriving additional parameters for the initialization of the control algorithm.

Once these optional steps are completed, *in silico* sensor and insulin pump are applied to the subjects, and then a testing scenario is defined, i.e., a list of the timing and CHO amount of various meals is specified. Here we will illustrate the utility of the simulator for selecting a control algorithm. **Figure 6** presents three identical days of testing of an *in silico* subject with three meals per day.

The green curve represents glucose excursions expected in health. The red curve is the control of a subject with T1DM by a PID control algorithm similar to the control algorithm developed by Steil *et al*.[23] It is evident that PID has the propensity to deliver excessive amount of insulin and induce hypoglycemia a few hours after a

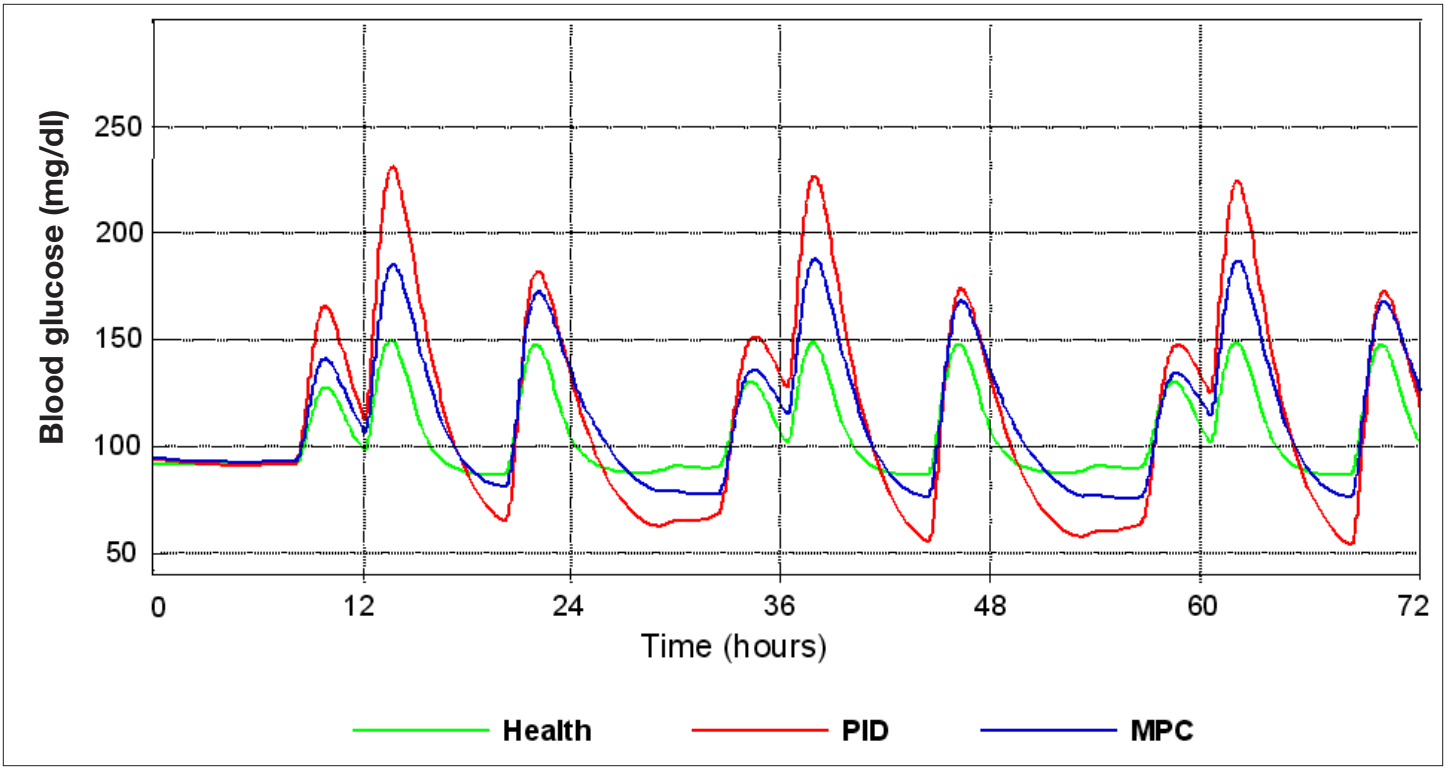

Figure 6. *In silico* comparison of plasma glucose concentration during 72 h in an healthy subject (**green**), a type 1 diabetes subjects controlled with a PID (**red**), and MPC (**blue**) closed-loop control algorithms.

meal–an effect that has been reported also *in vivo*.[23] We do not exclude the possibility that a different tuning of the PID controller would perform better *in silico*—this trace represents only an illustration of the use of the simulation environment for comparison of various control algorithms. The black curve represents the action of a MPC algorithm with meal announcement similar to the reported by Magni *et al*.[49] or Weinzimer *et al*.[50] Due to the preemptive insulin delivery, the postprandial glucose excursions are attenuated and postprandial hypoglycemia is generally avoided.[49]

Conclusions

Continuous glucose monitoring has already proven its utility in optimizing the glycemic control of people with diabetes.[50–54] Based on CGM and insulin delivery, clinical trials of closed-loop control are under way. Comprehensive computer simulation has the potential to greatly accelerate their progress. The principal components of an *in silico* testing environment should include the following: (1) A mathematical model of the human metabolic system that accounts as closely as possible for the dynamics of the glucose–insulin metabolism; (2) An extensive "cohort" of *in silico* "subjects" with widely distributed metabolic parameters that represent well the intersubject variability observed *in vivo*. Such a cohort is the key to successful simulation, as its variability allows for comprehensive testing of the stability and the robustness of closed-loop control; (3) A generator of CGM sensor errors. It is worth noting that sensor errors are typically not random and are poorly represented by white noise. Thus standard techniques based on adding independent identically distributed Gaussian noise to the output of the glucose–insulin model simulation would not produce realistic sensor scenarios. Characteristics, such as degree of dependence between sequential readings, influence of calibration errors, and potential for loss of sensitivity, need to be taken into account; (4) A representation of discrete insulin delivery and a model of s.c. insulin transport, which describes well the significant time delays observed between s.c. insulin injection and the appearance of insulin in plasma; and (5) A final essential component of both *in silico* and *in vivo* trials is a set of outcome measures capable of capturing the variability-reducing effects of the relatively short-term (2–3 days) trials of CGM use or closed-loop control.[45] With these components in place, comprehensive computer-simulation testing of closed-loop control becomes possible, allowing for cost-effective investigation of the performance of control algorithms with various testing scenarios prior to their clinical implementation.

A natural next step of bringing *in silico* experiments to the clinical practice was the use of computer simulation for the preclinical testing of a new type of model-predictive closed-loop control algorithm adapted for s.c. glucose sensing and insulin delivery.[49] This was accomplished in two steps. First, the computer simulation environment presented in this paper was submitted to the FDA with a request for use as a substitute to animal trials in our preclinical closed-loop control experiments. This request was reviewed positively by the agency, and a FDA master file was deposited in January 2008.[33] Second, our request for IDE for a clinical trial of closed-loop control was approved by the FDA in April 2008, based entirely on *in silico* tests. This precedent would allow other investigators to use the route of simulation experiments in support of their FDA submissions. It is premature, however, to claim that the simulator has a FDA approval label—FDA acceptance for certain types of preclinical experiments is a correct description of the current situation. With the accumulation of clinical data supporting the utility and enabling the refinement of the simulation environment, we can envision that *in silico* trials would become a mainstream route for preclinical experimentation.

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