Physical Activity into the Meal Glucose–Insulin Model of Type 1 Diabetes: *In Silico* Studies

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Abstract

Introduction:

A simulation model of a glucose–insulin system accounting for physical activity is needed to reliably simulate normal life conditions, thus accelerating the development of an artificial pancreas. In fact, exercise causes a transient increase of insulin action and may lead to hypoglycemia. However, physical activity is difficult to model. In the past, it was described indirectly as a rise in insulin. Recently, a new parsimonious model of exercise effect on glucose homeostasis has been proposed that links the change in insulin action and glucose effectiveness to heart rate (HR). The aim of this study was to plug this exercise model into our recently proposed large-scale simulation model of glucose metabolism in type 1 diabetes to better describe normal life conditions.

Methods:

The exercise model describes changes in glucose–insulin dynamics in two phases: a rapid on-and-off change in insulin-independent glucose clearance and a rapid-on/slow-off change in insulin sensitivity. Three candidate models of glucose effectiveness and insulin sensitivity as a function of HR have been considered, both during exercise and recovery after exercise. By incorporating these three models into the type 1 diabetes model, we simulated different levels (from mild to moderate) and duration of exercise (15 and 30 minutes), both in steady-state (e.g., during euglycemic–hyperinsulinemic clamp) and in nonsteady state (e.g., after a meal) conditions.

Results:

One candidate exercise model was selected as the most reliable.

Conclusions:

A type 1 diabetes model also describing physical activity is proposed. The model represents a step forward to accurately describe glucose homeostasis in normal life conditions; however, further studies are needed to validate it against data.

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Abbreviations: (bpm) beats per minute, (FDA) Food and Drug Administration, (GLUT-4) glucose transporter-4, (HR) heart rate, (MPC) model predictive control

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Introduction

In healthy subjects, the level of glucose in plasma is tightly controlled by hormones, such as insulin, glucagon, epinephrine, growth hormone, and glucagon-like peptide, which ensure that glycemia remains in a physiological range (~80–150 mg/dl) despite external perturbations, such as meals and physical activity. In particular, insulin is a hormone secreted by pancreatic β cells when plasma glucose increases, which stimulates glucose uptake by insulin-dependent tissues (mainly muscles and adipose tissues) and inhibits hepatic glucose production. Conversely, in type 1 diabetic patients, endogenous insulin secretion is lacking and is usually replaced by exogenous injections/infusions of insulin analogues. This intensive insulin treatment is helpful in maintaining nearly normal levels of glycemia and thus reducing chronic complications markedly; however, it may cause a risk of potentially dangerous severe hypoglycemia, which has been identified as the primary barrier to optimal diabetes management.¹

Thanks to new developments in glucose sensor technology and subcutaneous insulin pumps, recently the research effort has focused on the development of closed loop glycemic control, the so-called artificial pancreas. For instance, recent studies investigated the performances of proportional–integral–derivative^{2,3} and model predictive control (MPC) algorithms,^{4,5} with both *in vivo* and *in silico* trials. The role of *in silico* testing of closed loop glucose control algorithms is of major importance and has been recently recognized also by the Food and Drug Administration (FDA). In fact, in January 2008, a computer simulator of type 1 diabetes developed by our group was accepted by the FDA as a substitute to animal trials for the preclinical testing of control strategies in artificial pancreas studies.⁶ This simulator is based on a model of the glucose–insulin system in the postprandial state.^{7,8} The novelty of this model was that it was validated not only on plasma glucose and insulin concentrations, but also by fitting the major metabolic fluxes (endogenous glucose production, meal rate of appearance, glucose utilization, and insulin secretion) estimated in a model-independent way in a wide population. However, while meal perturbations are satisfactorily taken into account in the model,⁹ a description of the effect of physical activity is lacking. However, adapting insulin delivery during physical activity is difficult and may cause hypoglycemic events. Thus, the inability to describe the effect of physical activity on glucose metabolism is considered one of the major obstacles to the development

of an artificial pancreas usable in normal life conditions. Conversely, the ability to simulate this phenomenon would be of great help in designing control algorithms, especially those based on MPC.

The objective of this study was thus to incorporate in the simulator a model of the exercise effect on insulin-dependent glucose uptake. To do that, since adequate data are not available at the moment, we implemented in the simulator some accepted notions of the effect of exercise on glucose utilization based on published quantitative and qualitative analysis. Exercise has been shown to augment the availability of glucose transporter-4 (GLUT-4), both by translocation to the cell membrane^{10–12} and by increased transcription in muscle cells.^{13,14} These changes have been shown to be associated with an increase in insulin sensitivity and insulin-independent glucose uptake.^{12,15–26} The pathways of exercise-induced translocation and augmented transcription are not entirely elucidated yet, but muscle fibers contractions have been proven to be at the source of these changes.¹⁶

As far as an exercise model is concerned, a description of these cellular events at a macrolevel is not available; in the past, the action of exercise on glucose metabolism has been described indirectly as a rise in insulin.¹⁷ As shown in the literature, the parameters of the minimal model of glucose kinetics can change significantly during and after physical activity.^{23–25} These changes, consequent to the vascular and metabolic adaptations to increased energy utilization and storage described earlier, render the minimal model impossible to use during exercise without a precise description of the amplitude and dynamics of these changes. Moreover, in a closed loop perspective, the timing of exercise is not known, making any real-time use difficult. In a previous publication,²⁴ the authors showed that changes in the minimal model dynamics as a consequence of mild to moderate exercise can be described in two phases: a transient change in insulin-independent glucose clearance and a longer term change in insulin sensitivity, confirming and expanding the work of Derouich and Boutayeb²⁵ with clinical data. A parsimonious exercise model has been proposed that provides a mechanistic description of this phenomenon, aiming to link the change in insulin action and glucose effectiveness to HR.¹⁸

Starting from the latter publication, we proposed and tested three extensions of Breton¹⁸ and included them

into our type 1 diabetes meal model. The reliability of the different descriptions is judged by comparing model predictions during a euglycemic–hyperinsulinemic *in silico* trial, with different intensities and durations of exercise. Having selected the best model, we also show further simulations of glucose profiles during physical activity performed at fasting and 3 hours after a meal.

It has, however, to be emphasized that the current lack of experimental data precludes the possibility to definitively assess model validity at this stage. Thus, further studies are needed to validate and improve the proposed model of physical activity. However, the present study demonstrated the capability of the glucose–insulin simulator to be adapted easily to normal life conditions.

The Meal Glucose–Insulin Model of Type 1 Diabetes at Rest

The model describing the glucose–insulin control system during a meal in type 1 diabetes is shown in **Figure 1**. This section provides a brief overview of the whole model (for details, see Dalla Man and associates^{7,8,19}), while a detailed description of glucose utilization is given due to its relevance in physical activity.

The model is made up of a glucose and an insulin subsystem linked 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. The most important model unit processes are endogenous glucose production, glucose rate of appearance, and glucose utilization. Suppression of endogenous glucose production is assumed to be linearly dependent on plasma glucose concentration, portal insulin concentration, and a remote 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 the solid and one for the triturated phase), 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 is made up of two components: insulin-independent utilization takes place in the first

Figure 1. Scheme of the glucose–insulin system at rest in type 1 diabetes. Solid lines represent glucose and insulin fluxes; dashed lines represent control signals. Physical activity affects insulin-independent glucose utilization.

compartment, is constant, and represents glucose uptake by the brain and erythrocytes (F_{cns}):

$$U_{ii}(t) = F_{cns}, \quad (1)$$

whereas insulin-dependent utilization occurs in the remote compartment, which represents peripheral tissues and depends nonlinearly, i.e., via Michaelis–Menten kinetics, on glucose in tissues^{20,21} (Figure 2):

$$U_{id}(t) = \frac{V_m(X(t)) \cdot G_t(t)}{K_m + G_t(t)}, \quad (2)$$

where G_t (mg/kg) is glucose mass in the remote compartment and V_m is assumed to be linearly dependent on a remote, i.e., interstitial fluid, insulin, X ⁷:

$$V_m(X(t)) = V_{m0} + V_{mx} \cdot X(t), \quad (3)$$

where X (pmol/liter) represents remote insulin described by

$$\dot{X}(t) = -p_{2U} \cdot X(t) + p_{2U}[I(t) - I_b] \quad X(0)=0, \quad (4)$$

where I is plasma insulin, suffix b denotes basal state, and p_{2U} (min^{-1}) is the rate constant of insulin action on peripheral glucose utilization.

Total glucose utilization, U , is thus

$$U(t) = U_{ii}(t) + U_{id}(t). \quad (5)$$

In order to simulate type 1 diabetes subjects, a subcutaneous insulin infusion module was also added to simulate insulin transit from the subcutaneous space to plasma.^{8,19} It is important to note that, at this point in time,

Figure 2. Effect of remote insulin, X , on the relationship between tissue glucose $[G_t(t)]$ and glucose utilization (U_{id}): a rise in X produces an increase in the steady-state value of U_{id} .

this model of glucose–insulin system does not consider diurnal variations of insulin sensitivity (represented here by parameter V_{mx}) or other parameters. This is of course a limitation of the model; however, no data with the depth needed to inform such a model are available to support this hypothesis on possible parameter time courses.

A Model of Physical Activity

We built on a recent parsimonious exercise model that links the change in insulin action and glucose effectiveness to HR.¹⁸ The model assumes that the instantaneous HR correlates well with the duration and intensity of physical activity.²² The following three extensions of the model proposed in Breton¹⁸ have been considered and tested.

Model A

Paralleling Breton,¹⁸ Equation (2) is modified as follows:

$$U_{id}(t) = \frac{V_{m0} \cdot (1 + \beta \cdot Y(t)) + V_{mx} (1 + \alpha \cdot Z(t)) \cdot (X(t) + I_b) - V_{mx} \cdot I_b}{K_m + G_t(t)} \cdot G_t(t), \quad (6)$$

where X follows Equation (4) and Y and Z are given by

$$\dot{Y}(t) = -\frac{1}{T_{HR}} \cdot [Y(t) - (HR(t) - HR_b)] \quad Y(0) = 0 \quad (7)$$

$$\dot{Z}(t) = -\left[\frac{f(Y(t))}{T_m} + \frac{1}{T_{ex}} \right] \cdot Z(t) + f(Y(t)) \quad Z(0) = 0 \quad (8)$$

with

$$f(Y) = \frac{\left(\frac{Y}{a \cdot HR_b} \right)^n}{1 + \left(\frac{Y}{a \cdot HR_b} \right)^n}. \quad (9)$$

In other words, Y is a delayed version of the over-basal HR signal and Z is controlled via a nonlinear differential equation mainly driven by $f(Y)$. Therefore, insulin-independent glucose clearance raises in the few minutes following the onset of exercise as observed in Breton *et al.*²⁴ $f(Y)$ is constructed so that it is negligible until Y reaches a certain fraction of basal HR (controlled by parameter a), corresponding to exercise onset. Thereafter, $f(Y)$ reaches 1 very rapidly (speed is dependent on both a and n) and drives Z upward, in effect mimicking a quick activation of available GLUT-4 transporters (transfer of vesicular GLUT-4 to the membrane) and thus an increase in insulin sensitivity. After exercise, $f(Y)$ resumes negligible values, allowing Z to fall back slowly via a quasi-exponential decay driven by T_{ex} ; this allows the model to follow literature findings

of enhanced insulin sensitivity for up to 22 hours after an exercise bout. In summary, $V_{m0} \cdot \beta \cdot Y$ represents the rapid on-and-off increase in insulin-independent glucose clearance and $V_{mx} \cdot \alpha \cdot Z$ represents the rapid-on/slow-off effect of exercise on insulin sensitivity.

Model B

Alternative models were tested to evaluate the impact of model assumptions on the predicted effect of physical activity on glucose homeostasis. For instance, compared with model A, model B assumes first that the rapid on-and-off change in basal glucose clearance is absent. Then, it also assumes that the rapid-on/slow-off change in insulin sensitivity depends not only on the increase in the steady-state value of the Michaelis–Menten glucose utilization [$V_{mx} \cdot (1 + \alpha \cdot Z)$], but is also due to an enhanced rate of increase of glucose utilization (i.e., K_m is lowered in proportion to insulin action: $K_m \cdot [1 - \gamma \cdot Z \cdot X]$) (Figure 5, bottom):

$$U_{id}(t) = \frac{V_{m0} + V_{mx} \cdot (1 + \alpha \cdot Z(t)) \cdot (X(t) + I_b) - V_{mx} \cdot I_b}{K_m \cdot [1 - \gamma \cdot Z(t) \cdot (X(t) + I_b)]} \cdot G_i(t), \quad (10)$$

where X , Y , and Z follow Equations (4), (7), and (8), respectively.

Model C

Because different levels of exercise (and thus of HR) have the same effect on glucose utilization with model B while the difference is negligible with model A (see Results), we have introduced model C, which assumes that insulin action is increased in proportion to the duration and intensity of exercise, i.e., to the area under the curve of $HR - HR_b$. Insulin-dependent utilization becomes

$$U_{id}(t) = \frac{V_{m0} + V_{mx} \cdot (1 + \beta \cdot Y(t)) + V_{mx} \cdot (1 + \alpha \cdot Z(t) \cdot W(t)) \cdot (X(t) + I_b) - V_{mx} \cdot I_b}{K_m \cdot [1 - \gamma \cdot Z(t) \cdot W(t) \cdot (X(t) + I_b)]} \cdot G_i(t), \quad (11)$$

where X , Y , and Z follow Equations (4), (7), and (8), respectively, and

$$W(t) = \begin{cases} \int_0^t (HR(t) - HR_b) \cdot dt & \text{for } t < t_z \\ 0 & \text{otherwise} \end{cases}, \quad (12)$$

where t_z is the time at which $Z(t)$ comes back to zero (i.e., $t_z = 3 \cdot T_{ex}$). W is thus related to both duration and intensity of exercise (Figure 3). Figure 4 shows the time course of variables Y , Z , and W in response to a square-wave variation of HR. It is worth noting that in real life the heart rate may increase with several patterns, e.g., in a linear fashion; here a step increase in HR is assumed in order to better illustrate model behavior. Figure 5 shows how variables Y , Z , and W influence insulin-dependent glucose utilization.

Model parameters are set to values reported in Breton.¹⁸ They are reported in Table 1.

Figure 3. Change in HR during mild (first and second panels) and moderate (third and fourth panels) exercise (duration of 15 and 30 minutes, respectively). Dashed area represents the variable W , related to both exercise duration and intensity.

Table 1.
Exercise Model Parameters

Parameter	Value	Unit
A	3×10^{-4}	Dimensionless
β	0.01	bpm ⁻¹
γ	1×10^{-7}	Dimensionless
a	0.1	Dimensionless
T_{HR}	5	Minutes
T_{in}	1	Minute
T_{ex}	600	Minutes
n	4	Dimensionless

Figure 4. Time course of variables Y , Z , and W in response to a step increase of HR from basal, HR_b , to maximum, HR_{max} .

Rapid-on&off Change in Basal Glucose Clearance

Rapid-on/Slow-off Change in Insulin Sensitivity

Figure 5. Effect of Y , Z , and W on the relationship between tissue glucose $[G_t(t)]$ and glucose utilization (U_{id}) : a rise in Y produces an increase in the steady-state value of U_{id} , whereas a rise in Z and/or W produces an increase on both U_{id} steady-state values and its speed of rising.

In Silico Experiments

One hundred parameter vectors were generated randomly from the joint parameter distribution, available in the type 1 diabetic population (accepted by the FDA). Each parameter vector corresponds to an *in silico* subject. Thus, 100 type 1 diabetic *in silico* subjects were simulated under several experimental conditions. A constant basal insulin infusion was administered to all subjects to guarantee that basal glucose was maintained in absence of a meal or intravenous perturbation. Basal HR was assumed to be 70 beats per minute (bpm) for all subjects. Each *in silico* subject underwent the following three protocols.

1. Euglycemic–hyperinsulinemic clamp plus exercise: the basal insulin infusion rate was increased by 40% at $t = 60$ minutes; the glucose infusion rate was changed in order to maintain a constant glucose concentration. At $t = 300$ minutes, each subject exercised for 15 and 30 minutes at mild (mild₁₅ and mild₃₀) or moderate (mod₁₅ and mod₃₀) intensity. Mild exercise is defined as physical activity corresponding to an increase of 50% of the basal heart rate ($HR = 1.5 \cdot HR_b$), corresponding

to about 90 bpm; moderate exercise is defined as physical activity corresponding to an increase of 100% of the basal heart rate ($HR = 2 \cdot HR_b$), corresponding to approximately 120 bpm.

2. Exercise only: starting from the basal condition, each subject exercised at $t = 60$ minutes for 15 and 30 minutes at both mild or moderate intensity, $HR = 1.5 \cdot HR_b$ and $HR = 2 \cdot HR_b$, respectively;
3. Meal plus exercise: each subject underwent a meal test containing 85 grams of carbohydrates. The meal was ingested at $t = 30$ minutes. At the same time, an insulin bolus was administered with a fixed carbohydrate to insulin ratio of 15 g/U. Three hours after the meal, each subject exercised for 15 and 30 minutes at both mild and moderate intensity, $HR = 1.5 \cdot HR_b$ and $HR = 2 \cdot HR_b$, respectively.

Results

Comparison of Exercise Models

The reliability of the presented models was assessed by considering model predictions during the euglycemic–hyperinsulinemic clamp (**Figure 6**).

Model B predicts that different levels of exercise (and thus of HR) have the same effect on glucose utilization, whereas this difference is negligible with model A. Conversely, model C predicts a reasonable glucose infusion rate during the euglycemic–hyperinsulinemic clamp. In fact, from the simulations, the increment in insulin action is similar for 15 minutes of moderate exercise and 30 minutes of mild exercise, both higher than the increment due to 15 minutes of mild exercise and lower than the increment due to 30 minutes of moderate exercise. Model C was thus selected as the best among the three presented models.

Figure 6. Glucose infusion rate needed to maintain basal glucose during euglycemic–hyperinsulinemic clamp for different durations and intensities of exercise: model A (**top**), model B (**middle**), and model C (**bottom**) (average of the 100 *in silico* subjects).

In Silico Experiments

Possible experiments, usable to validate the model, or possible scenarios to test closed loop insulin infusion algorithms included physical activity alone or physical activity coupled with a euglycemic–hyperinsulinemic clamp or a meal. Results obtained with model C in 100 *in silico* subjects in the three simulated experiments are described next.

Euglycemic–Hyperinsulinemic Clamp Plus Exercise. The average glucose infusion rate needed to maintain constant glucose during this experiment for different durations and vigorousness of physical activity is shown **Figure 6, bottom**. The area under the glucose infusion rate was $\text{mild}_{15} = 2524 \pm 144$ (mean $\pm$ SE), $\text{mild}_{30} = 2744 \pm 157$, $\text{mod}_{15} = 2741 \pm 157$, and $\text{mod}_{30} = 3176 \pm 183$ mg/kg, and the difference was statistically significant ($p < 0.01$) for all comparisons apart from mild_{30} vs mod_{15} .

Exercise Only. The average glucose concentration for different durations and vigorousness of physical activity is shown in **Figure 7, top**. The suppression of glucose concentration (calculated as the difference between the area under basal glucose and the area under the glucose curve) was $\text{mild}_{15} = 10,428 \pm 903$ (mean $\pm$ SE),

Figure 7. Effect of different durations and intensities of exercise on glucose concentration at fasting (**top**) and during a meal (**bottom**) (average of the 100 *in silico* subjects).

$\text{mild}_{30} = 20,050 \pm 1653$, $\text{mod}_{15} = 19,937 \pm 1646$, and $\text{mod}_{30} = 36,299 \pm 2720$ mg/dl·min, and the difference was statistically significant ($p < 0.01$) for all comparisons apart from mild_{30} vs mod_{15} .

Meal Plus Exercise. The average glucose concentration during this experiment for different durations and vigorousness of physical activity is shown in **Figure 7, bottom**. The area under glucose concentration was $\text{mild}_{15} = 227,011 \pm 3021$ (mean $\pm$ SE), $\text{mild}_{30} = 218,940 \pm 3278$, $\text{mod}_{15} = 218,849 \pm 3279$, and $\text{mod}_{30} = 205,516 \pm 3650$ mg/dl·min, and the difference was statistically significant ($p < 0.01$) for all comparisons apart from mild_{30} vs mod_{15} .

Conclusions

The ability to predict the effect of exercise on glucose disposal in type 1 diabetes could be very helpful, as adaptation of insulin infusion during physical activity is one of the major obstacles to the development of an artificial pancreas working in normal life conditions. The availability of a simulator able to reproduce daily life as much as possible is of great help in testing closed loop control algorithms, especially those based on MPC.^{4,5}

This study incorporated an extension of a parsimonious model of physical activity proposed in Breton¹⁸ into a simulation model of a glucose–insulin system^{7,8,19}. Such a model is based on the idea that HR is a good, and easy to measure, marker of physical activity. Three different models have been considered and tested in simulation. Model A assumes that exercise causes a rapid on-and-off increase in insulin-independent glucose clearance and a rapid-on/slow-off effect on insulin sensitivity. Model B relaxes the assumption that exercise causes a rapid on-and-off increase in insulin-independent glucose clearance. Finally, model C is similar to model A but also assumes that insulin action is increased in proportion to the duration and intensity of exercise, i.e., to the area under the curve of $\text{HR} - \text{HR}_b$.

The quality of the three models was assessed by considering model predictions during euglycemic–hyperinsulinemic clamp simulations (**Figure 6**). Models A and B predict that different levels of exercise (and thus of HR) have basically the same effect on glucose utilization. Conversely, model C predicts a reasonable glucose infusion rate during euglycemic–hyperinsulinemic clamp simulations. In fact, the increment in insulin action is similar for 15 minutes of moderate and 30 minutes of mild exercise, both higher than the increment due to 15 minutes of mild exercise and lower than the increment

due to 30 minutes of moderate exercise. Reasonable time courses are also obtained with model C when simulating glucose profiles during physical activity performed at fasting and 3 hours after a meal (**Figure 7**).

Given the lack of data supporting model assumptions/predictions, it is very difficult at this stage to draw conclusions based on model predictions and comparison. Nonetheless, albeit margins of improvements are present, the proposed model is, to the best of our knowledge, the first attempt to describe in a quantitative way the relationship between physical activity and change in a crucial parameter such as insulin sensitivity. It thus represents a step forward to simulate normal daily life accurately. Moreover, use of a HR signal as an external input makes the model potentially usable for predicting glucose change during physical activity *in vivo* and could be very useful in both testing and developing closed loop control algorithms. However, further studies are needed to validate this model against data; in particular, *in vivo* experiments similar to the *in silico* protocols described in this article are needed, both in normal and in type 1 diabetic subjects.

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Appendix

Model Equations

Glucose Subsystem

$$\begin{cases} \dot{G}_p(t) = EGP(t) + Ra(t) - U_{ii}(t) - E(t) - k_1 \cdot G_p(t) + k_2 \cdot G_i(t) & G_p(0) = G_{pb} \\ \dot{G}_i(t) = -U_{id}(t) + k_1 \cdot G_p(t) - k_2 \cdot G_i(t) & G_i(0) = G_{ib} \\ G(t) = \frac{G_p}{V_G} & G(0) = G_b \end{cases} \quad (A1)$$

Insulin Subsystem

$$\begin{cases} \dot{I}_l(t) = -(m_1 + m_3) \cdot I_l(t) + m_2 I_p(t) & I_l(0) = I_{lb} \\ \dot{I}_p(t) = -(m_2 + m_4) \cdot I_p(t) + m_1 \cdot I_l(t) + R(t) & I_p(0) = I_{pb} \\ I(t) = \frac{I_p}{V_I} & I(0) = I_b \end{cases} \quad (A2)$$

Endogenous Glucose Production

$$EGP(t) = k_{p1} - k_{p2} \cdot G_p(t) - k_{p3} \cdot I_d(t) \quad EGP(0) = EGP_b \quad (A3)$$

$$\begin{cases} \dot{I}_1(t) = -k_i \cdot [I_1(t) - I(t)] & I_1(0) = I_b \\ \dot{I}_d(t) = -k_i \cdot [I_d(t) - I_1(t)] & I_d(0) = I_b \end{cases} \quad (A4)$$

Glucose Rate of Appearance

$$\begin{cases} \dot{Q}_{sto}(t) = Q_{sto1}(t) + Q_{sto2}(t) & Q_{sto}(0) = 0 \\ \dot{Q}_{sto1}(t) = -k_{gri} \cdot Q_{sto1}(t) + D \cdot \delta(t) & Q_{sto1}(0) = 0 \\ \dot{Q}_{sto2}(t) = -k_{empt}(Q_{sto}) \cdot Q_{sto2}(t) + k_{gri} \cdot Q_{sto1}(t) & Q_{sto2}(0) = 0 \\ \dot{Q}_{gut} = -k_{abs} \cdot Q_{gut}(t) + k_{empt}(Q_{sto}) \cdot Q_{sto2}(t) & Q_{gut}(0) = 0 \\ Ra(t) = \frac{f \cdot k_{abs} \cdot Q_{gut}(t)}{BW} & Ra(0) = 0 \end{cases} \quad (A5)$$

Glucose Utilization

$$U(t) = U_{ii}(t) + U_{id}(t) \quad (A6)$$

$$U_{ii}(t) = F_{cns} \quad (A7)$$

$$U_{id}(t) = \frac{V_m(X(t)) \cdot G_i(t)}{K_m(X(t)) + G_i(t)} \quad (A8)$$

$$V_m(X(t)) = V_{m0} + V_{mx} \cdot X(t) \quad (A9)$$

$$K_m(X(t)) = K_{m0} \quad (A10)$$

$$\dot{X}(t) = -p_{2U} \cdot X(t) + p_{2U}[I(t) - I_b] \quad X(0)=0 \quad (A11)$$

Glucose Renal Excretion

$$E(t) = \begin{cases} k_{e1} \cdot [G_p(t) - k_{e2}] & \text{if } G_p(t) > k_{e2} \\ 0 & \text{if } G_p(t) \leq k_{e2} \end{cases} \quad (\text{A12})$$

Subcutaneous Insulin Kinetics

$$\begin{cases} \dot{I}_{sc1}(t) = -(k_d + k_{a1}) \cdot I_{sc1}(t) + IIR(t) \\ \dot{I}_{sc2}(t) = k_d \cdot I_{sc1}(t) - k_{a2} \cdot I_{sc2}(t) \end{cases} \quad \begin{matrix} I_{sc1}(0) = I_{sc1ss} \\ I_{sc2}(0) = I_{sc2ss} \end{matrix} \quad (\text{A13})$$

$$R_i(t) = k_{a1} \cdot I_{sc1}(t) + k_{a2} \cdot I_{sc2}(t) \quad (\text{A14})$$

Steady-State Constraints

$$EGP_b = U_b + E_b \quad (\text{A15})$$

$$k_{p1} = EGP_b + k_{p2} \cdot G_{pb} + k_{p3} \cdot I_b \quad (\text{A16})$$

$$I_{lb} = I_{pb} \cdot \frac{m_2}{m_1 + m_3} \quad (\text{A17})$$

$$I_{pb} = \frac{IIR_b}{\left(m_2 + m_4 - \frac{m_1 \cdot m_2}{m_1 + m_3} \right)} \quad (\text{A18})$$

$$m_3 = \frac{HE_b \cdot m_1}{1 - HE_b} \quad (\text{A19})$$

$$G_{tb} = \frac{F_{cns} - EGP_b + k_1 \cdot G_{pb}}{k_2} \quad (\text{A20})$$

$$V_{m0} = \frac{(EGP_b - F_{cns}) \cdot (K_{m0} + G_{tb})}{G_{tb}} \quad (\text{A21})$$

$$I_{sc1ss} = \frac{IIR_b}{k_d + k_{a1}} \quad (\text{A22})$$

$$I_{sc2ss} = \frac{k_d}{k_{a2}} \cdot I_{sc1ss} \quad (\text{A23})$$

Model Variables (suffix *b* denotes basal state)

G_p (mg/kg) glucose mass in plasma and rapidly equilibrating tissues

G_t (mg/kg) glucose mass in, and in slowly equilibrating tissues

G (mg/dl) plasma glucose concentration

EGP (mg/kg/min) endogenous glucose production

Ra (mg/kg/min) glucose rate of appearance in plasma

E (mg/kg/min) renal excretion

U_{ii} (mg/kg/min) insulin-independent glucose utilization

U_{id} (mg/kg/min) insulin-dependent glucose utilization

I_p (pmol/kg) insulin mass in plasma

I_l (pmol/kg) insulin mass in liver

I (pmol/liter) plasma insulin concentration
 R_i (pmol/kg/min) rate of appearance of insulin in plasma
 I_d (pmol/liter) delayed insulin
 Q_{sto} (mg) amount of glucose in the stomach (solid, Q_{sto1} , and liquid phase, Q_{sto2})
 Q_{gut} (mg) glucose mass in the intestine
 F_{cns} (mg/kg/min) glucose uptake by the brain and erythrocytes
 X (pmol/liter) insulin in the interstitial fluid
 I_{sc1} (pmol/kg) amount of nonmonomeric insulin in the subcutaneous space
 I_{sc2} (pmol/kg) amount of monomeric insulin in the subcutaneous space
 $IIR(t)$ (pmol/kg/min) exogenous insulin infusion rate
 HE (dimensionless) hepatic insulin extraction

Model Parameters

V_G (dl/kg) distribution volume of glucose
 k_1 (min^{-1}) rate parameter of glucose kinetics
 k_2 (min^{-1}) rate parameter of glucose kinetics
 m_1 (min^{-1}) rate parameter of insulin kinetics
 m_2 (min^{-1}) rate parameter of insulin kinetics
 m_3 (min^{-1}) rate parameter of insulin kinetics
 m_4 (min^{-1}) rate parameter of insulin kinetics
 k_{p1} (mg/kg/min) extrapolated EGP at zero glucose and insulin
 k_{p2} (min^{-1}) liver glucose effectiveness
 k_{p3} (mg/kg/min per pmol/liter) parameter governing amplitude of insulin action on the liver
 k_i (min^{-1}) rate parameter accounting for delay between insulin signal and insulin action
 k_{gri} (min^{-1}) rate of grinding
 k_{empt} (min^{-1}) rate constant of gastric emptying, which is a nonlinear function of Q_{sto}
 k_{abs} (min^{-1}) rate constant of intestinal absorption
 f fraction of intestinal absorption that actually appears in plasma
 BW (kg) body weight
 D (mg) amount of ingested glucose
 V_{m0} (mg/kg/min) Michaelis–Menten parameter of glucose utilization at zero insulin action
 K_{m0} (mg/kg) Michaelis–Menten parameter of glucose utilization at zero insulin action
 V_{mx} (mg/kg/min per pmol/liter) disposal of insulin sensitivity
 p_{2U} (min^{-1}) rate constant of insulin action on peripheral glucose utilization
 k_{e1} (min^{-1}) glomerular filtration rate
 k_{e2} (mg/kg) renal threshold of glucose
 k_d (min^{-1}) rate constant of insulin dissociation
 k_{a1} (min^{-1}) rate constant of nonmonomeric insulin absorption
 k_{a2} (min^{-1}) rate constant of monomeric insulin absorption