Meal Simulation Model of the Glucose-Insulin System

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***Abstract*—A simulation model of the glucose-insulin system in the postprandial state can be useful in several circumstances, including testing of glucose sensors, insulin infusion algorithms and decision support systems for diabetes. Here, we present a new simulation model in normal humans that describes the physiological events that occur after a meal, by employing the quantitative knowledge that has become available in recent years. Model parameters were set to fit the mean data of a large normal subject database that underwent a triple tracer meal protocol which provided quasi-model-independent estimates of major glucose and insulin fluxes, e.g., meal rate of appearance, endogenous glucose production, utilization of glucose, insulin secretion. By decomposing the system into subsystems, we have developed parametric models of each subsystem by using a forcing function strategy. Model results are shown in describing both a single meal and normal daily life (breakfast, lunch, dinner) in normal. The same strategy is also applied on a smaller database for extending the model to type 2 diabetes.**

***Index Terms*—Artificial pancreas, diabetes, glucose homeostasis, glucose production, glucose sensors, glucose utilization, insulin infusion system, insulin secretion, kinetics, physiological control.**

I. Introduction

THE availability of a simulation model of the glucose-insulin control system during meals and normal daily life is highly desirable for studying the pathophysiology of diabetes and in particular for the design and evaluation of glucose sensors, insulin infusion algorithms, and decision support systems for treating diabetes, in particular type 1 (insulin dependent). In fact, it may be neither possible, appropriate, convenient, or desirable to perform such evaluation experiments on the diabetic subject, because some experiments cannot be done at all, or are too difficult, too dangerous, or not ethical.

Several simulation models have been proposed and proven to be useful in tackling various aspects of normal physiology and pathophysiology of diabetes [1]–[11]. However, in these last years, new important quantitative knowledge has been gained on glucose metabolism and its control by insulin during a meal both at the organ-tissue and whole-body level, e.g., hepatic glucose production and muscle glucose utilization. This has been generally made be possible by making use of multiple tracer experiments and use of new technologies like NMR and PET (see, e.g., [12]–[16]).

In this paper, we develop a new simulation model of the glucose-insulin system in the normal human capable of describing the physiological events which occur during a standard mixed meal. The scope of this model is different from that of our previous simulation models [3], [4], [10], which were mostly developed for describing a variety of intravenous glucose perturbations, like various infusion patterns and IVGTT. The importance of developing a meal simulator is rather obvious given that oral glucose ingestion is used in everyday meals. However, the oral route is a more difficult situation to model than the intravenous one because one has also to describe the glucose ingestion and absorption processes. A few oral simulation models are available [8], [11]. The major limitations of these models is that they have been validated on plasma concentration measurements only and that their physiology requires to be updated.

The very reason of our new venture is a unique meal data set of 204 normal individuals who underwent a triple tracer meal protocol, thus allowing us to obtain, in a virtually model-independent fashion, the time course of all the relevant glucose and insulin fluxes during a meal [12], [13]. This database has already allowed us to propose and validate a new model of glucose ingestion and absorption [17]. Here, by using this "concentration and flux" portrait, we model the glucose-insulin system by resorting to a subsystem forcing function strategy, which minimizes structural uncertainties in modeling the various unit processes. We develop an average model for the normal subject, but, albeit based on a smaller database, the same strategy is also applied for extending the model to type 2 diabetes.

II. Data Base

A total of 204 normal subjects (age $= 56 \pm 2$ years, body weight $= 78 \pm 1$ kg) received a mixed meal containing 1 ± 0.02 g/kg of glucose [13]. The meal was labeled with ^{13}C-glucose and two additional tracers ([6, 6 $-^2$ H_2]-glucose and [6 $-^3$ H]-glucose) were infused intravenously with the tracer-to-tracee ratio clamp technique, in order to obtain a virtually model-independent estimation of the various glucose fluxes (for details on protocol and measurements we refer to [12]). Fig. 1 shows (mean $\pm$ 1SD) the measured glucose and insulin plasma concentration, glucose rate of appearance, endogenous glucose production and glucose utilization. Also shown is the time course of insulin secretion, which was reconstructed by deconvolution [18]. Indexes of parameter variability in the studied population can be found in [13]. The same type of database was also obtained in 14 type 2 diabetic subjects (age $= 57 \pm 3$ years, body weight $= 91 \pm 5$ kg) (not shown) [19].

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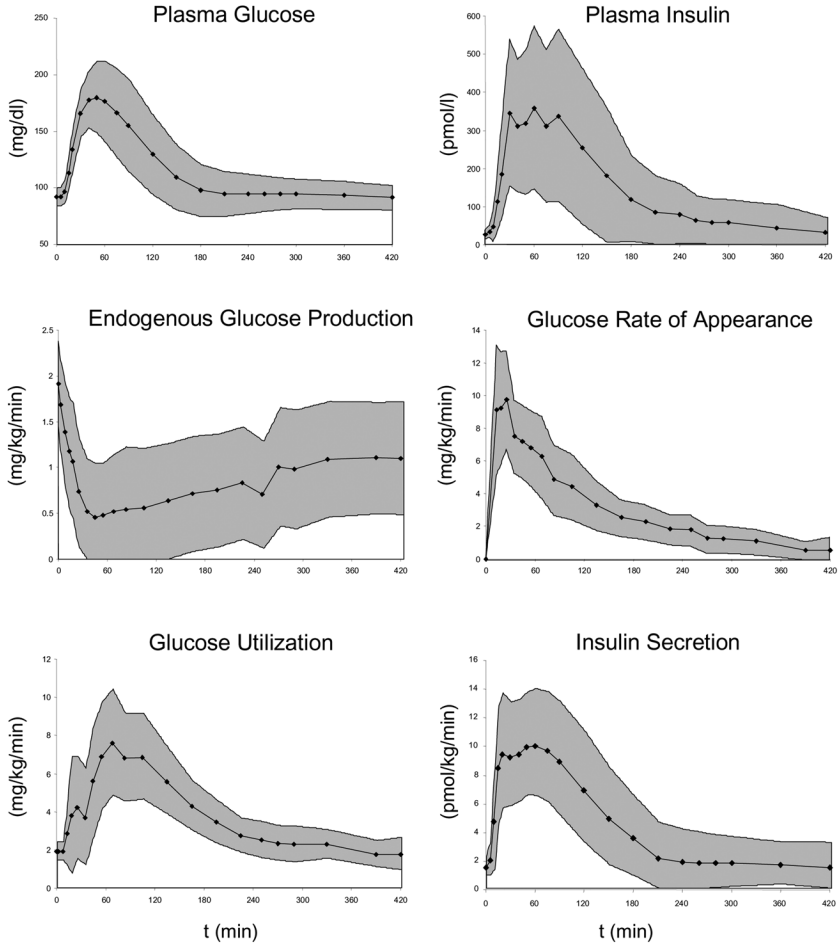

Fig. 1. Mixed meal database (average of 204 normals, gray area represents mean $\pm$ 1SD range). Top panel: glucose (left) and insulin (right) concentrations. Middle panel: endogenous glucose production (left) and glucose rate of appearance (right). Bottom panel: glucose utilization (left) and insulin secretion (right).

III. The Model

A scheme of the glucose-insulin control system which puts in relation the measured plasma concentrations, i.e., glucose G and insulin I and the glucose fluxes, i.e., rate of appearance Ra, production EGP, utilization U, renal extraction E, and insulin fluxes, i.e., secretion S, and degradation D of Fig. 1 is shown in Fig. 2. In other words, given the complexity of the system, the sole availability of plasma glucose and insulin concentrations makes it virtually impossible to build a reliable simulation model, e.g., one can obtain a good description of plasma glucose and insulin concentrations with many different descriptions of Ra, EGP, and U. It is the availability of glucose fluxes that allows a step forward in modeling. In fact, by using a forcing function strategy, one can develop reliable parametric models of each unit process. For instance, to model glucose utilization U, we can postulate a structural model and use as known inputs for its identification glucose production EGP, glucose rate of appearance Ra, and insulin concentration I, and as model output glucose utilization U, and plasma glucose concentration G.

A. Glucose Subsystem

The two compartment model used to describe glucose kinetics [20] is shown in the upper panel of Fig. 3. The model equations are shown in (1) at the bottom of the page, where G_p and G_t (mg/kg) are glucose masses in plasma and rapidly equilibrating tissues, and in slowly equilibrating tissues, respectively, G (mg/dl) plasma glucose concentration; suffix b denotes basal state; EGP is the endogenous glucose production (mg/kg/min); Ra is the glucose rate of appearance in plasma (mg/kg/min); E is renal excretion (mg/kg/min); U_{ii} and U_{id} are the insulin-independent and -dependent glucose utilizations,

$$\begin{cases} \dot{G}_p(t) = EGP(t) + Ra(t) - U_{\mathrm{ii}}(t) - E(t) - k_1 \cdot G_p(t) + k_2 \cdot G_t(t) & G_p(0) = G_{pb} \\ \dot{G}_t(t) = -U_{\mathrm{id}}(t) + k_1 \cdot G_p(t) - k_2 \cdot G_t(t) & G_t(0) = G_{tb} \\ G(t) = \frac{G_p}{V_G} & G(0) = G_b \end{cases} \tag{1}$$

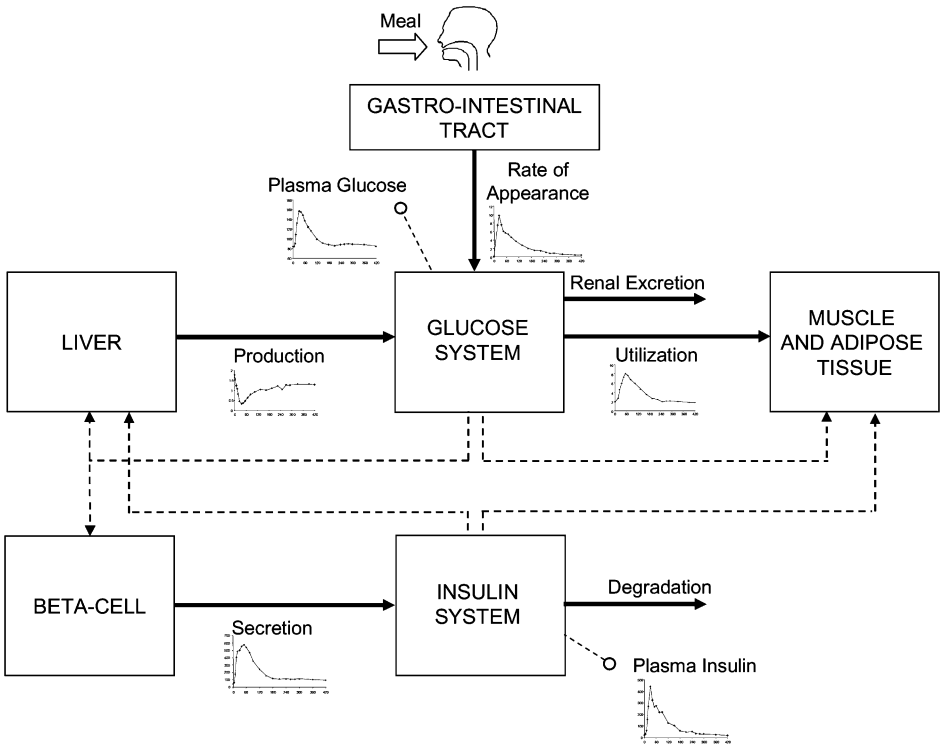

Fig. 2. Scheme of the glucose-insulin control system which puts in relation the measured plasma concentrations, i.e., glucose G, and insulin I, to glucose fluxes, i.e., rate of appearance Ra, production EGP, utilization U, renal extraction E, and insulin fluxes, i.e., secretion S, and degradation D.

respectively (mg/kg/min); V_G is the distribution volume of glucose (dl/kg); and k_1 and $k_2(\min^{-1})$ are the rate parameters.

At basal steady-state endogenous production EGP_b equals glucose disappearance, i.e., the sum of glucose utilization and renal excretion (which is zero in the normal subjects), $U_b + E_b$:

$$EGP_b = U_b + E_b. \tag{2}$$

Parameter values of V_G, k_1, k_2 are reported in Table I (Glucose Kinetics) for both the normal and type 2 diabetic subject.

B. Insulin Subsystem

The two-compartment model used to describe insulin kinetics [21] is shown in the lower panel of Fig. 3. The model equations are shown in (3) at the bottom of the page, where I_p and I_l (pmol/kg) are insulin masses in plasma and in liver, respectively; I (pmol/l) plasma insulin concentration; suffix b denotes basal state; S insulin secretion (pmol/kg/min); V_I distribution volume of insulin (l/kg); and m_1, m_2, and $m_4(\min^{-1})$ rate parameters. Degradation D occurs both in the liver and in the periphery. Peripheral degradation has been assumed linear (m_4). Evidences are available that hepatic extraction of insulin HE, i.e., the insulin flux which leaves the liver irreversibly divided by the total insulin flux leaving the liver, is time varying. Here, following

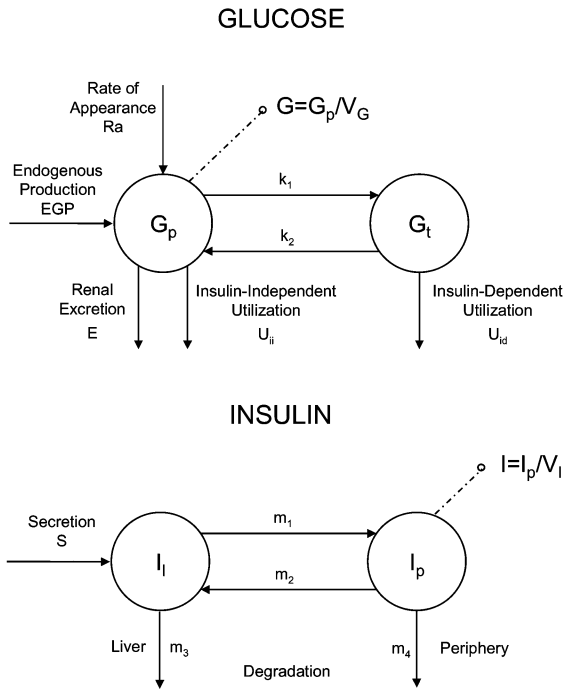

Fig. 3. Scheme of glucose (upper) and insulin (lower panel) subsystems.

$$\begin{cases} \dot{I}_l(t) = -(m_1 + m_3(t)) \cdot I_l(t) + m_2 I_p(t) + S(t) & I_l(0) = I_{lb} \\ \dot{I}_p(t) = -(m_2 + m_4) \cdot I_p(t) + m_1 \cdot I_l(t) & I_p(0) = I_{pb} \\ I(t) = \frac{I_p}{V_I} & I(0) = I_b \end{cases} \tag{3}$$

TABLE I
MODEL PARAMETERS OF THE NORMAL AND TYPE 2 DIABETIC SUBJECT

Process	Parameter	Normal Value	Type 2 Diabetic Value	Unit
Glucose Kinetics	V_G	1.88	1.49	dl/kg
	k_1	0.065	0.042	min^{-1}
	k_2	0.079	0.071	min^{-1}
Insulin Kinetics	V_I	0.05	0.04	l/kg
	m_1	0.190	0.379	min^{-1}
	m_2	0.484	0.673	min^{-1}
	m_4	0.194	0.269	min^{-1}
	m_5	0.0304	0.0526	min ·kg/pmol
	m_6	0.6471	0.8118	dimensionless
	HE_b	0.6	0.6	dimensionless
Rate of Appearance	k_{max}	0.0558	0.0465	min^{-1}
	k_{min}	0.0080	0.0076	min^{-1}
	k_{abs}	0.057	0.023	min^{-1}
	k_{gri}	0.0558	0.0465	min^{-1}
	f	0.90	0.90	dimensionless
	a	0.00013	0.00006	mg^{-1}
	b	0.82	0.68	dimensionless
	c	0.00236	0.00023	mg^{-1}
	d	0.010	0.09	dimensionless
Endogenous Production	k_{p1}	2.70	3.09	mg/kg/min
	k_{p2}	0.0021	0.0007	min^{-1}
	k_{p3}	0.009	0.005	mg/kg/min per pmol/l
	k_{p4}	0.0618	0.0786	mg/kg/min per pmol/kg
	k_i	0.0079	0.0066	min^{-1}
Utilization	F_{cns}	1	1	mg/kg/min
	V_{m0}	2.50	4.65	mg/kg/min
	V_{mx}	0.047	0.034	mg/kg/min per pmol/l
	K_{m0}	225.59	466.21	mg/kg
	p_{2U}	0.0331	0.0840	min^{-1}
Secretion	K	2.30	0.99	pmol/kg per (mg/dl)
	α	0.050	0.013	min^{-1}
	β	0.11	0.05	pmol/kg/mirn per (mg/dl)
	γ	0.5	0.5	min^{-1}
Renal Excretion	k_{e1}	0.0005	0.0007	min^{-1}
	k_{e2}	339	269	mg/kg

recent experiment evidence [22] we link the time course of HE to that of insulin secretion, S:

$$\mathrm{HE}(t) = -m_5 \cdot S(t) + m_6 \quad \mathrm{HE}(0) = \mathrm{HE}_b \tag{4}$$

thus one has

$$m_3(t) = \frac{\mathrm{HE}(t) \cdot m_1}{1 - \mathrm{HE}(t)}. \tag{5}$$

At basal steady state, one has

$$m_6 = m_5 \cdot S_b + \mathrm{HE}_b \tag{6}$$

$$m_3(0) = \frac{\mathrm{HE}_b \cdot m_1}{1 - \mathrm{HE}_b} \tag{7}$$

$$S_b = m_3(0) \cdot I_{lb} + m_4 \cdot I_{pb} = D_b. \tag{8}$$

Moreover, given that the liver is responsible for 60% of insulin clearance in the steady state, one has

$$m_2 = \left(\frac{S_b}{I_{pb}} - \frac{m_4}{1 - \mathrm{HE}_b}\right) \cdot \frac{1 - \mathrm{HE}_b}{\mathrm{HE}_b};$$
$$m_4 = \frac{2}{5} \cdot \frac{S_b}{I_{pb}} \cdot (1 - \mathrm{HE}_b) \tag{9}$$

with S_b and D_b basal secretion and degradation, respectively.

HE_b was fixed to 0.6, and is reported together with V_I, m_1, m_2, m_4, m_5, and m_6 in Table I (Insulin Kinetics) for both the normal and type 2 diabetic subject.

C. Unit Process Models and Identification

The unit processes of glucose and insulin subsystem are shown in Fig. 4. The model for each of them was identified from average data with a forcing function strategy. For sake of space, we present in detail the identification of the endogenous

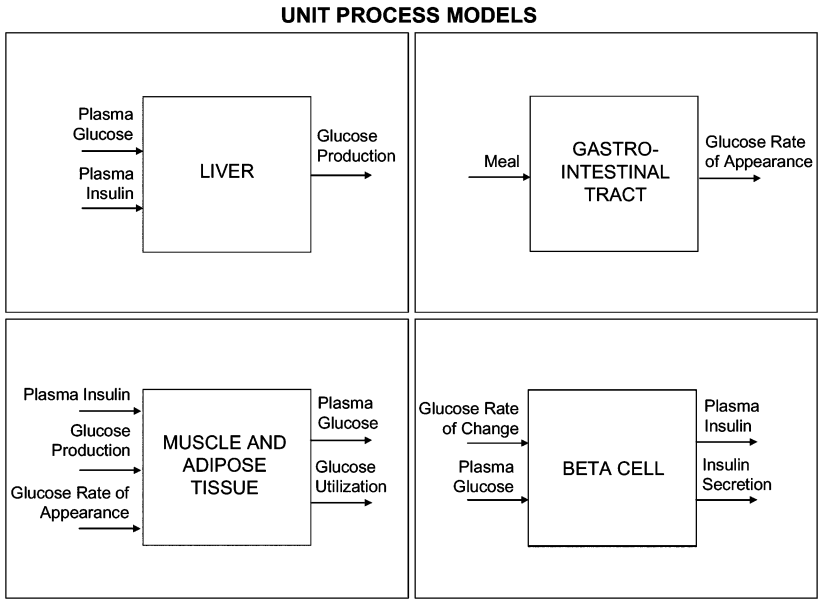

Fig. 4. Unit process models and forcing function strategy: endogenous glucose production (top left panel); glucose rate of appearance (top right panel); glucose utilization (bottom left panel); insulin secretion (bottom right panel). Entering arrows represent forcing function variables, outgoing arrows are model output.

glucose production model; the other unit process models have been identified following a similar strategy.

1) Endogenous Glucose Production: The functional description of EGP in terms of glucose and insulin signals is described in [23]; it comprises a direct glucose signal and both delayed and anticipated insulin signals:

$$\begin{aligned} EGP(t) &= k_{p1} - k_{p2} \cdot G_p(t) - k_{p3} \cdot I_d(t) - k_{p4} \cdot I_{po}(t) \\ EGP(0) &= EGP_b \end{aligned} \tag{10}$$

where I_{po} is the amount of insulin in the portal vein (pmol/kg), I_d (pmol/l) is a delayed insulin signal realized with a chain of two compartments:

$$\begin{cases} \dot{I}_1(t) = -k_i \cdot [I_1(t) - I(t)] & I_1(0) = I_b \\ \dot{I}_d(t) = -k_i \cdot [I_d(t) - I_1(t)] & I_d(0) = I_b \end{cases} \tag{11}$$

k_{p1} (mg/kg/min) is the extrapolated EGP at zero glucose and insulin, $k_{p2}(\min^{-1})$ liver glucose effectiveness, k_{p3} (mg/kg/min per pmol/l) parameter governing amplitude of insulin action on the liver, k_{p4} (mg/kg/Λmin /(pmol/kg)) parameter governing amplitude of portal insulin action on the liver and $k_i(\min^{-1})$ rate parameter accounting for delay between insulin signal and insulin action. EGP is also constrained to be non-negative.

At basal steady state, one has

$$k_{p1} = EGP_b + k_{p2} \cdot G_{pb} + k_{p3} \cdot I_b + k_{p4} \cdot I_{pob}. \tag{12}$$

The model of (10) was identified on mean EGP data with the forcing function strategy (Fig. 4, top left panel): mean insulin, portal insulin and glucose concentrations are the model inputs, assumed to be known without error and EGP is the model output. The measurement error of EGP data was assumed to be independent, with zero mean and unknown constant standard deviation (constant SD assumes relatively more precise values when the signal is higher). The model was numerically identified by nonlinear least-squares [24], [25], as implemented in SAAM II (Simulation Analysis and Modeling software [26]): model fit was satisfactory and parameters were estimated with precision for both the normal and type 2 diabetic subject. They are reported in Table I (Endogenous Glucose Production).

2) Glucose Rate of Appearance: A physiological model of glucose intestinal absorption has been recently developed [17]. Briefly, it 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 triturated phase), while a single compartment is used to describe the gut [see equation (13) at the bottom of the page, where $Q_{\rm sto}$ (mg) is the amount of glucose in the stomach (solid, $Q_{\rm sto1}$ and liquid phase $Q_{\rm sto2}$); $Q_{\rm gut}$ (mg) is the glucose mass in the intestine; $k_{\rm gri}(\min^{-1})$ is

$$\begin{cases} Q_{\rm sto}(t) = Q_{\rm sto1}(t) + Q_{\rm sto2}(t) & Q_{\rm sto}(0) = 0 \\ \dot{Q}_{\rm sto1}(t) = -k_{gri} \cdot Q_{\rm sto1}(t) + D \cdot d(t) & Q_{\rm sto1}(0) = 0 \\ \dot{Q}_{\rm sto2}(t) = -k_{\rm empt}(Q_{\rm sto}) \cdot Q_{\rm sto2}(t) + k_{gri} \cdot Q_{\rm sto1}(t) & Q_{\rm sto2}(0) = 0 \\ \dot{Q}_{\rm gut} = -k_{\rm abs} \cdot Q_{\rm gut}(t) + k_{\rm empt}(Q_{\rm sto}) \cdot Q_{\rm sto2}(t) & Q_{\rm gut}(0) = 0 \\ Ra(t) = \frac{f \cdot k_{\rm abs} \cdot Q_{\rm gut}(t)}{\rm BW} & Ra(0) = 0 \end{cases} \tag{13}$$

the rate of grinding; $k_{\text{empt}}(Q_{\text{sto}})(\text{min}^{-1})$ is the rate constant of gastric emptying, which is a nonlinear function of Q_{sto} [17, eq. 8]) and $k_{\text{abs}}(\text{min}^{-1})$ is the rate constant of intestinal absorption; f is the fraction of intestinal absorption which actually appears in plasma; D (mg) is the amount of ingested glucose; BW (kg) is the body weight; and Ra (mg/kg/min) is the appearance rate of glucose in plasma.

The model of (13) was identified on Ra data with the forcing function strategy (Fig. 4, top right panel). The model fit was good. Parameters k_{gri}, a, and c were fixed following [17], while the remaining parameters were estimated with precision. They are reported in Table I (Glucose Rate of Appearance) for both the normal and type 2 diabetic subject.

3) Glucose Utilization: To describe glucose utilization by body tissues during a meal (both insulin-independent and -dependent), we built on literature results [27]–[30]. We assume that glucose utilization is made up of two components. Insulin-independent utilization takes place in the first compartment, is constant, and represents glucose uptake by the brain and erythrocytes (F_{cns}):

$$U_{\text{ii}}(t) = F_{\text{cns}}. \tag{14}$$

Insulin-dependent utilization takes place in the remote compartment and depends nonlinearly (Michaelis Menten) from glucose in the tissues [29], [30]

$$U_{\text{id}}(t) = \frac{V_m(X(t)) \cdot G_t(t)}{K_m(X(t)) + G_t(t)} \tag{15}$$

where $V_m(X(t))$ and $K_m(X(t))$ are assumed to be linearly dependent from a remote insulin, $X(t)$ [29]:

$$V_m(X(t)) = V_{m0} + V_{mx} \cdot X(t) \tag{16}$$

$$K_m(X(t)) = K_{m0} + K_{mx} \cdot X(t). \tag{17}$$

Note that, when fitting on our data (which show a range of insulin variation narrower than that observed by Yki-Jarvinen *et al.* [29]), K_{mx} collapses to zero so that K_m is no more dependent from X.

X (pmol/L) is insulin in the interstitial fluid described by

$$\dot{X}(t) = -p_{2U} \cdot X(t) + p_{2U}[I(t) - I_b] \quad X(0) = 0 \tag{18}$$

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

Total glucose utilization U is thus

$$U(t) = U_{\text{ii}}(t) + U_{\text{id}}(t). \tag{19}$$

At basal steady state, one has

$$G_{tb} = \frac{F_{\text{cns}} - EGP_b + k_1 \cdot G_{pb}}{k_2} \tag{20}$$

and

$$U_b = EGP_b = F_{\text{cns}} + \frac{V_{m0} \cdot G_{tb}}{K_{m0} + G_{tb}} \tag{21}$$

from which

$$V_{m0} = \frac{(EGP_b - F_{\text{cns}}) \cdot (K_{m0} + G_{tb})}{G_{tb}}. \tag{22}$$

This model and that of (1) were simultaneously identified on U and G data with the forcing function strategy (Fig. 4, bottom left panel). The model fit was good, and parameters were estimated with precision and are reported in Table I (Glucose Utilization) for both the normal and type 2 diabetic subject.

4) Insulin Secretion: The model used to describe pancreatic insulin secretion is that proposed in [31] and [32]. The model equations are

$$S(t) = \gamma \cdot I_{po}(t) \tag{23}$$

$$\dot{I}_{po}(t) = -\gamma \cdot I_{po}(t) + S_{po}(t) \quad I_{po}(0) = I_{pob} \tag{24}$$

$$S_{po}(t) = \begin{cases} Y(t) + K \cdot \dot{G}(t) + S_b & \text{for } \dot{G} > 0 \\ Y(t) + S_b & \text{for } \dot{G} \le 0 \end{cases} \tag{25}$$

and (26), shown at the bottom of the page, where $\gamma(\text{min}^{-1})$ is the transfer rate constant between portal vein and liver, K (pmol/kg per mg/dl) is the pancreatic responsivity to the glucose rate of change, $\alpha(\text{min}^{-1})$ is the delay between glucose signal and insulin secretion, β (pmol/kg/min per mg/dl) is the pancreatic responsivity to glucose, and h (mg/dl) is the threshold level of glucose above which the β-cells initiate to produce new insulin (h has been set to the basal glucose concentration G_b to guarantee system steady state in basal condition).

This model and that of (3) were simultaneously identified on S and I data with the forcing function strategy (Fig. 4, bottom right panel). The model fit was good, and parameters were estimated with precision and are reported in Table I (Insulin Secretion) for both the normal and type 2 diabetic subject.

5) Glucose Renal Excretion: Glucose excretion by the kidney occurs if plasma glucose exceeds a certain threshold and can be modeled by a linear relationship with plasma glucose

$$E(t) = \begin{cases} k_{e1} \cdot [G_p(t) - k_{e2}] & \text{if } G_p(t) > k_{e2} \\ 0 & \text{if } G_p(t) \le k_{e2} \end{cases} \tag{27}$$

where $k_{e1}(\text{min}^{-1})$ is the glomerular filtration rate and k_{e2} (mg/kg) is the renal threshold of glucose. Parameters are reported in Table I (Glucose Renal Excretion).

D. Equations

The complete model is given by (1), (3)–(5), (10)–(11), (13)–(19), (23)–(27), and [17, eq. 8]; Steady state constraints are given in (2), (6)–(9), (12), and (20)–(22); all parameter

$$\dot{Y}(t) = \begin{cases} -\alpha \cdot [Y(t) - \beta \cdot (G(t) - h)] & \text{if } \beta \cdot (G(t) - h) \ge -S_b \\ -\alpha \cdot Y(t) - \alpha \cdot S_b & \text{if } \beta \cdot (G(t) - h) < -S_b; \end{cases} \quad Y(0) = 0 \tag{26}$$

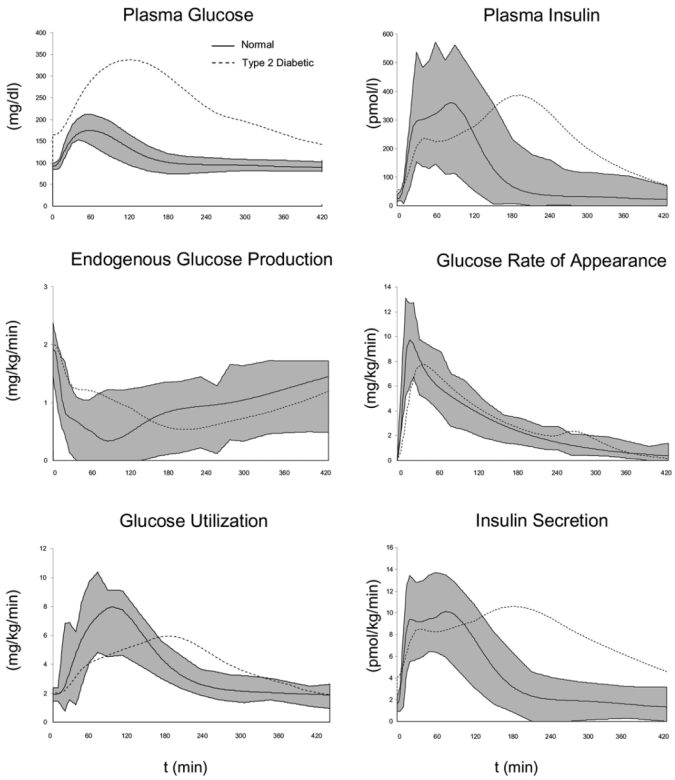

Fig. 5. Meal prediction versus measurement of plasma concentrations and fluxes (Fig. 1) in the normal (continuous) and type 2 diabetic (dashed line) subject.

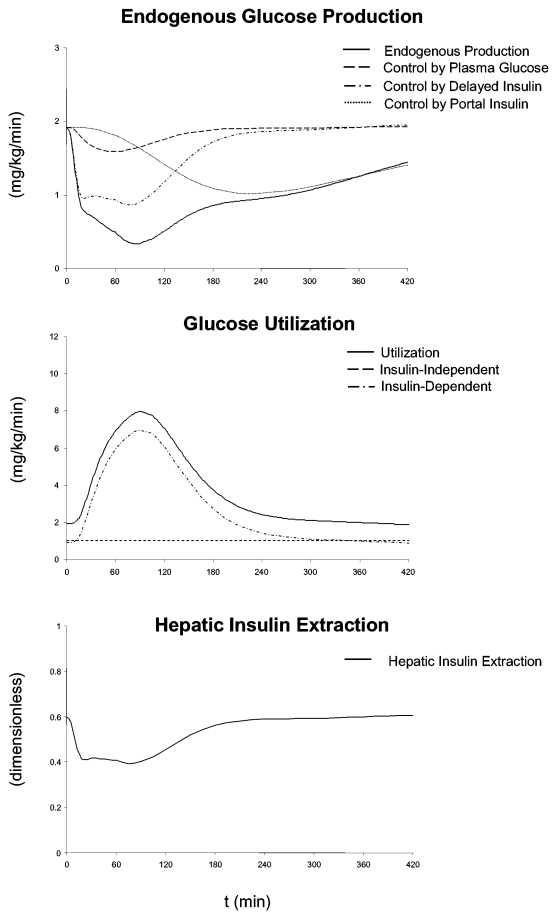

Fig. 6. Upper panel: Meal prediction of EGP (continuous line) and its control by plasma glucose (dashed line), delayed insulin signal (dashed–dotted line), and portal insulin (dotted line). Middle panel: Meal prediction of U (continuous line) and its insulin-independent (dashed line) and -dependent (dashed–dotted line) components. Lower panel: Meal prediction of hepatic insulin extraction.

values are reported in Table I for both the normal and type 2 diabetic subject.

IV. Results

A. Meal in Normal Subject

A normal subject receiving a mixed meal was simulated first using parameters reported in Table I (Normal). Fig. 5 shows the predicted glucose and insulin concentrations and glucose/insulin fluxes (continuous line) against $\pm$1SD confidence limits (gray area, Fig. 1). The model also allows us to predict the effect of the various control signals on glucose production (Fig. 6, upper panel), as well as the insulin-independent and -dependent components of glucose utilization (Fig. 6, middle panel); in addition, hepatic insulin extraction can also be predicted (Fig. 6, lower panel).

B. Meal in Type 2 Diabetic Subject

Albeit on a smaller triple tracer meal database, the model has also been numerically identified in the type 2 diabetic subject. The model structure of the normal subject turned out to be robust and data were fitted well, i.e., the type 2 diabetic subject can be quantitatively described with the same model but with different parameter values (Table I, Type 2 Diabetic). In particular, gut absorption $k_{\rm abs}$ was slower than in normal; parameters quantifying insulin action, both peripheral V_{mx} and hepatic k_{p3}, were lower; hepatic glucose effectiveness k_{p2} was lower and, albeit the maximum utilization by the tissue at basal insulin V_{m0} is higher, it is reached at higher glucose levels K_{m0}; finally both dynamic K and static beta cell responsivity β, as well as rate of response α, were lower. The different parametric portrait reflects in model prediction, i.e., important derangements in both glucose and insulin concentration as well in glucose and insulin fluxes versus normal can be noted (Fig. 5, dashed line).

C. Daily Life in Normal Subject

The model was also employed to simulate a typical day life: 24 h with breakfast at 8 a.m. (45 g), lunch at 12 p.m. (70 g), and dinner at 8 p.m. (70 g). Since insulin sensitivity and beta cell responsivity to glucose are not constant during the day [33], we assumed V_{mx} 25% lower in the evening meal as compared with breakfast and lunch, and β 25% lower both at lunch and evening meals as compared with breakfast. Fig. 7 (continuous line) shows prediction of concentrations and fluxes in the normal subject during the day.

D. Daily Life in Impaired Glucose-Tolerant Subject

Glucose intolerance was also simulated. In particular an impairment in insulin sensitivity (both V_{mx} and k_{p3} halved) was considered both compensated and not by higher beta cell response to glucose. For instance, if parameters V_{mx} and k_{p3} are halved, without a significantly increase in beta cell responsivity,

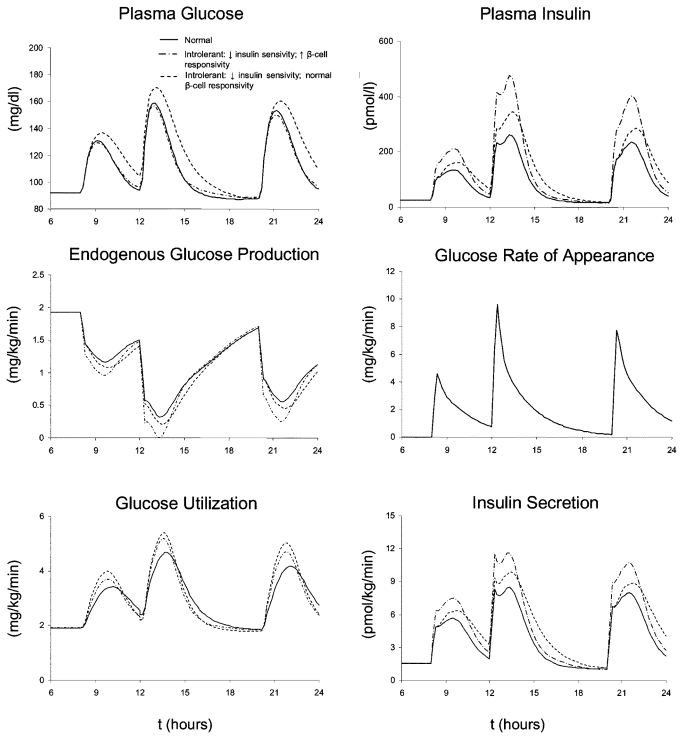

Fig. 7. Whole day simulation of a normal (continuous) and a glucose-intolerant subject (V_{mx} and k_{p3} halved) with (dashed) and without (dashed–dotted line) beta cell responsivity compensation (K and β doubled): model prediction of plasma concentrations and fluxes with breakfast at 8 a.m. (45 g), lunch at 12 p.m. (70 g), and dinner at 8 p.m. (70 g).

glucose concentration peaks higher and returns to basal almost 2 h later than in the normal subject (Fig. 7, dashed line). Conversely, if parameters K and β are both concomitantly doubled, glucose concentration basically does not differ from the normal one, but plasma insulin concentration is doubled (Fig. 7, dashed–dotted line). Finally, if K and β are halved with insulin action being normal, glucose concentration peaks at a higher value and comes back to basal almost 3 h later than in the normal subject, while if V_{mx} and k_{p3} are both concomitantly doubled, glucose concentration is basically normal, but plasma insulin concentration is halved (results not shown).

V. Discussion

A new in silico model of the glucose-insulin regulatory system has been presented. Focusing on quantitating physiological events after a meal is of obvious importance because this route is used in everyday life. The postprandial state has also been intensively investigated in recent years; thus, one can take advantage of all new quantitative knowledge that has became available. The model is made by a number of parsimonious submodels describing the various unit processes that have been identified using a forcing function strategy. This is the major novelty of the proposed model, which is based on virtually model-independent measurements of the various glucose and insulin fluxes occurring during a meal [12], [13]. The glucose-insulin system is, in fact, very complex and the sole availability of plasma glucose and insulin concentrations does not allow us to build a reliable simulation model, since one can obtain a good description of plasma glucose and insulin concentrations with many different descriptions of the underlying fluxes in the system, like meal glucose rate of appearance, hepatic glucose production, and glucose utilization, with structural errors in some unit process models compensating those in others. Conversely, the availability of glucose and insulin fluxes allows us, by using a forcing function strategy, to develop specific reliable parametric models of each unit process.

The model consists of a glucose and insulin subsystem. The glucose system is described by a two-compartment model [20], the first representing glucose mass in plasma and rapidly equilibrating tissues, and the second the slowly equilibrating tissues. Glucose utilization has both an insulin-independent component occurring in plasma and an insulin-dependent component in the second compartment. The insulin-independent utilization is constant and represents glucose uptake by CNS and erythrocytes, while the insulin-dependent utilization is controlled nonlinearly by glucose in the tissue compartment and insulin in the interstitial fluid [27]–[30]. Endogenous glucose production control by glucose and insulin implements recent knowledge [23], in particular it assumes that fast suppression occurs through a portal insulin signal, while slower inhibition by a delayed insulin signal, possibly a surrogate of interstitial fluid/free fatty acids signaling. A new model of glucose transit through the gastro-intestinal tract is used to describe glucose ingestion and absorption [17]; this feature is important because previous simulation models either allowed only intravenous glucose administration [3], [4] or described the process simplistically [8], [11]. The insulin system is described by a two-compartment model [21]. Degradation is assumed to occur linearly in the periphery while liver degradation is assumed to be time-varying in agreement with current knowledge [21]. Insulin secretion is assumed to be dependent on both plasma glucose concentration and its rate of change [31], [32].

In addition to simulating in the normal human a meal (Fig. 5) and daily life (Fig. 7) situations, this last by incorporating variations during the day of insulin sensitivity and beta cell responsivity, the model has been used to describe various glucose intolerance states (Fig. 7), by simulating parametric changes in insulin action (V_{mx}, k_{p3}) and beta cell secretion (K and β). Finally, albeit on a smaller triple tracer meal database, the model has also been numerically identified in the type 2 diabetic subject. The model structure of the normal subject turned out to be robust and data were fitted well, i.e., the type 2 diabetic subject can be quantitatively described with the same model structure but with a different parametric portrait.

As with all models, there are some limitations. The most important is that counteregulatory hormones, such as glucagon, epinephrine, and growth hormone, have not been considered. This will be considered in future model developments. This will be also important for extending the model to type 1 diabetes. Another limitation concerns the glucocentric nature of the model; i.e., the role of other fuel substrates like free fatty acids and their interaction with glucose and insulin is not considered. Finally, when modeling daily life, it would be important to include diurnal variation of parameters. Some quantitative knowledge on insulin sensitivity and beta cell responsivity behavior during the three meals is available [33] and has been included, but it would

certainly be desirable to improve this description as well as include more circadian parametric variations. Finally, the model is a "mean" model, and it will be important to further exploit the information content of our database by also accounting for the intersubject variability.

In conclusion, we have proposed a physiologically based model of the glucose-insulin system during meals. The modeling strategy is novel and has taken advantage of a unique meal data set both in normal and type 2 diabetes in which not only plasma concentrations but also relevant glucose and insulin fluxes during a meal were available. The model should prove valuable as simulator in several situations dealing with the pathophysiology of diabetes.

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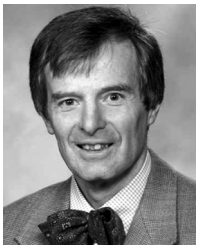

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