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Mixed Meal Simulation Model of Glucose-Insulin System

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Abstract— **A simulation model of the glucose-insulin system in the postprandial state can be useful for studying the pathophysiology of diabetes. Here we present a new simulation model which describes the physiological events which occur after a meal, by employing the quantitative knowledge which has become available in recent years. Model parameters were set to fit data of 204 normal subjects which underwent a triple tracer meal protocol which provided quasi model-independent estimates of major glucose and insulin fluxes. Model results are shown in describing normal daily life (breakfast, lunch, dinner) both in normal and pathophysiological situations. The potential of the model for studying type 1 diabetes is illustrated by simulating both open- and closed-loop insulin infusion strategies.**

I. INTRODUCTION

The availability of a simulation model of the glucose-insulin control system during normal daily life is highly desirable for studying the pathophysiology of diabetes, *e.g.* for the design and evaluation of glucose sensors, insulin infusion algorithms and decision support systems. Several simulation models have been proposed [1-4]. However, new important quantitative knowledge has been recently gained on glucose metabolism and its control by insulin both at the organ-tissue and whole-body level [5-7].

In this paper we develop a new mixed meal simulation model of the glucose-insulin system in the normal human. The oral route is a more difficult situation to model than the intravenous one because one also has to describe the glucose absorption process. A few oral simulation models are available [2,3], but their major limitation is that they have been validated on plasma concentration measurements only. Here we exploit an unique data set of 204 normals who underwent a triple tracer meal protocol which allowed us to obtain virtually model-independent glucose and insulin fluxes [5]. This data base has already allowed us to propose and validate a new model of glucose absorption by the gut [8]. Here we model the glucose-insulin system by resorting to a sub-system forcing function strategy which minimizes structural uncertainties in the various unit process models. We develop the model for the normal subject but the same strategy is also applied to a smaller data base to model the type 2 diabetic subject. We show the potential of the model as a simulator in several glucose intolerance states as well as in open- and closed-loop control of diabetes.

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II. DATA BASE

204 normal subjects received a triple tracer mixed meal containing 1± 0.02 g/kg of glucose, which provides a virtually model-independent estimation of the various glucose fluxes by employing the tracer-to-tracee ratio clamp technique [5]. The same experiment was also performed in 14 type 2 diabetic subjects (unpublished data).

III. GLUCOSE AND INSULIN SYSTEMS

A. Glucose Subsystem

The two compartment model was used to describe glucose kinetics [9]:

$$\begin{cases} \dot{G}_p(t) = EGP(t) + Ra(t) - U_g(t) - E(t) \\ \qquad\qquad - k_1 \cdot G_p(t) + k_2 \cdot G_t(t) & G_p(0) = G_{pb} \\ \dot{G}_t(t) = -U_i(t) + k_1 \cdot G_p(t) - k_2 \cdot G_t(t) & G_t(0) = G_{tb} \\ G(t) = \dfrac{G_p}{V_G} & G(0) = G_b \end{cases} \quad (1)$$

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 endogenous glucose production (mg/kg/min), Ra glucose rate of appearance in plasma (mg/kg/min), E renal excretion (mg/kg/min), U_g and U_i insulin-independent and dependent glucose utilizations (mg/kg/min), V_G glucose distribution volume (dl/kg), and k_1 and k_2 (min^{-1}) rate parameters.

B. Insulin Subsystem

The two compartment model is used to describe insulin kinetics [10]:

$$\begin{cases} \dot{I}_l(t) = -(m_1 + m_3(t)) \cdot I_l(t) + m_2 I_p(t) + S(t) & I_l(0) = I_{lb} \\ \dot{I}_p(t) = -(m_2 + m_4) \cdot I_p(t) + m_1 \cdot I_l(t) & I_p(0) = I_{pb} \\ I(t) = \dfrac{I_p}{V_I} & I(0) = I_b \end{cases} \quad (2)$$

where I_p and I_l (pmol/kg) are insulin masses in plasma and in liver, respectively, I (pmol/l) plasma insulin concentration, S insulin secretion (pmol/kg/min),V_I insulin distribution volume (l/kg), m_1, m_2, m_4 (min^{-1}) rate parameters. Here we

assume a linear peripheral degradation (m_4), while hepatic extraction is:

$$HE(t) = -m_5 \cdot S(t) + m_6 \qquad HE(0) = HE_b \tag{3}$$

$$m_3(t) = \frac{HE(t) \cdot m_1}{1 - HE(t)} \tag{4}$$

IV. Unit Process Models & Identification

The unit process models of each subsystem were identified with a forcing function strategy. For sake of space we present the identification of the endogenous glucose production model; the other unit process models have been identified following a similar strategy.

A. Endogenous Glucose Production

The functional description of EGP [11] comprises a direct glucose signal and both delayed and anticipated insulin signals [12]:

$$\begin{aligned} &EGP(t) = k_{p1} - k_{p2} \cdot G_p(t) - k_{p3} \cdot I_d(t) - k_{p4} \cdot I_{po}(t) \\ &EGP(0) = EGP_b \end{aligned} \tag{5}$$

where I_{po} is the amount of insulin in the portal vein (pmol), I_d (pmol/l) a delayed insulin signal realized with a chain of two compartments with rate parameters k_i (min^{-1}), k_{p1} (mg/kg/min) the extrapolated EGP at zero glucose and insulin, k_{p2} (min^{-1}) liver glucose effectiveness, k_{p3} (mg/kg/min per pmol/l) and k_{p4} (mg/kg/min/pmol) parameters governing amplitude of delayed and portal insulin action, respectively. The model of eq. 5 was identified on EGP data assuming portal insulin, plasma insulin and glucose concentrations as the model inputs, known without error and EGP as the model output, measurement error independent, gaussian, with zero mean and unknown constant standard deviation. The model was numerically identified by nonlinear least squares [13]. Model fit was satisfactory.

B. Glucose Rate of Appearance

A physiological model of glucose intestinal absorption has been recently developed [8]:

$$\begin{cases} Q_{sto}(t) = Q_{sto1}(t) + Q_{sto2}(t) & Q_{sto}(0) = 0 \\ \dot{Q}_{sto1}(t) = -k_{gri} \cdot Q_{sto1}(t) + D \cdot \delta(t) & Q_{sto1}(0) = 0 \\ \dot{Q}_{sto2}(t) = -k_{empt}(Q_{sto}) \cdot Q_{sto2}(t) + k_{gri} \cdot Q_{sto1}(t) & Q_{sto2}(0) = 0 \\ \dot{Q}_{gut} = -k_{abs} \cdot Q_{gut}(t) + k_{empt}(Q_{sto}) \cdot Q_{sto2}(t) & Q_{gut}(0) = 0 \\ Ra(t) = \dfrac{f \cdot k_{abs} \cdot Q_{gut}(t)}{BW} & Ra(0) = 0 \end{cases} \tag{6}$$

where Q_{sto} (mg) is amount of glucose in the stomach (solid, Q_{sto1}, and liquid phase, Q_{sto2}), Q_{gut} (mg) glucose in the intestine, k_{gri} (min^{-1}) rate of grinding, $k_{empt}(Q_{sto})$ (min^{-1}) rate constant of gastric emptying which is a nonlinear function of Q_{sto} (see [8] for details) and k_{abs} (min^{-1}) rate constant of intestinal absorption, f fraction of intestinal absorption which appears in plasma, D (mg) amount of ingested glucose, BW (kg) body weight.

C. Glucose Utilization

Glucose utilizations by body tissues (both insulin-independent U_g and –dependent U_i) were described by [9]:

$$U_g(t) = [2 \cdot \frac{PCR_b}{V_G} - S_G - (\frac{PCR_b}{V_G} - S_G) \cdot \frac{G_p(t)}{G_{pb}}] \cdot G_p(t) \tag{7}$$

$$U_i(t) = K_i(t) \cdot G_t(t) = X(t) \cdot G_t(t) \tag{8}$$

where PCR_b (dl/kg/min) is basal plasma clearance rate, S_G (min^{-1}) fractional glucose effectiveness and X (min^{-1}) insulin action described by:

$$\dot{X}(t) = -p_2 \cdot [X(t) - S_I \cdot I(t)] + p_2 \cdot [X_b - S_I \cdot I_b]; \quad X(0) = X_b \tag{9}$$

where I is plasma insulin, p_2 (min^{-1}) rate constant of insulin action and S_I (min^{-1} per pmol/l) insulin sensitivity.

D. Insulin Secretion

The model used to describe pancreatic insulin secretion is that proposed in [14]. The model equations are:

$$S(t) = \gamma \cdot I_{po}(t) \tag{10}$$

$$\dot{I}_{po}(t) = -\gamma \cdot I_{po}(t) + S_{po}(t) \qquad I_{po}(0) = I_{pob} \tag{11}$$

$$S_{po}(t) = \begin{cases} Y(t) + K \cdot \dot{G}(t) + S_b & \text{for } \dot{G} > 0 \\ Y(t) + S_b & \text{for } \dot{G} \le 0 \end{cases} \tag{12}$$

and

$$\dot{Y}(t) = \begin{cases} -\alpha \cdot [Y(t) - \beta \cdot (G(t) - h)] & \text{if } G(t) \ge h \\ -\alpha \cdot Y(t) & \text{if } G(t) < h \end{cases}; \quad Y(0) = 0 \tag{13}$$

where γ (min^{-1}) is the transfer rate constant between portal vein and liver, K (10^{-1} pmol·l /kg/mg) pancreatic responsivity to glucose rate of change, α (min^{-1}) delay between glucose and insulin secretion, β (10^{-1} pmol·l/kg/mg/min) pancreatic responsivity to glucose, and h (mg/dl) (set to G_b) threshold level of glucose above which the β-cells initiate to secrete insulin.

E. 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:

$$E(t) = \begin{cases} k_{e1} \cdot [G_p(t) - k_{e2}] & \text{if } G_p(t) > k_{e2} \\ 0 & \text{if } G_p(t) \le k_{e2} \end{cases} \tag{14}$$

where k_{e1} (min^{-1}) is glomerular filtration rate and k_{e2}

(mg/kg) renal threshold of glucose.

V. Simulation Results

A. Meal

The single meal for the normal subject was simulated first. Figure 1 shows the predicted glucose and insulin concentrations and glucose/insulin fluxes (continuous line) against ±1SD confidence limits (grey area). Then, a type 2 diabetic subject was simulated (dashed line). Important derangements in both glucose and insulin concentration as well in glucose and insulin fluxes of the type 2 diabetic can be noted

B. Daily Life

The model was also employed to simulate a typical day life: 24h with breakfast at 8 am (45 g), lunch at 12 (70 g) and dinner at 8 pm (70 g). S_I was assumed to be 25% lower in the third meal as compared with breakfast and lunch, while β was assumed be a 25% lower in both second and third meals [15]. Figure 2 shows predicted concentrations and fluxes in the normal subject during the day. Moreover glucose intolerant subjects can be also simulated by opportunely adjusting insuling sensitivtiy and β-cell responsivity parameters (not shown).

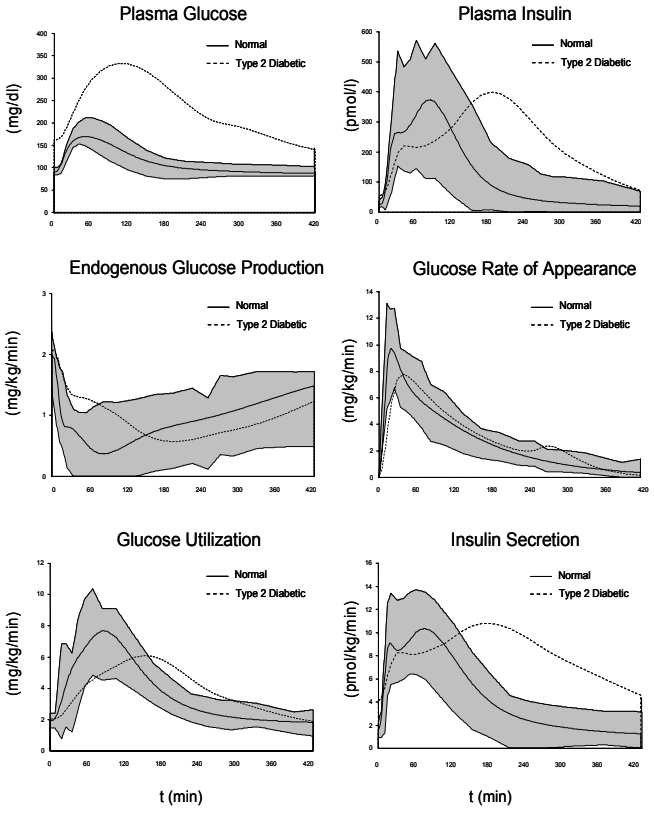

Figure 1: Single meal predictions vs. measurement of plasma concentrations and fluxes in the normal (continuous lines) and type 2 diabetic (dashed lines) subject. Grey area represents mean±1SD range in the normal.

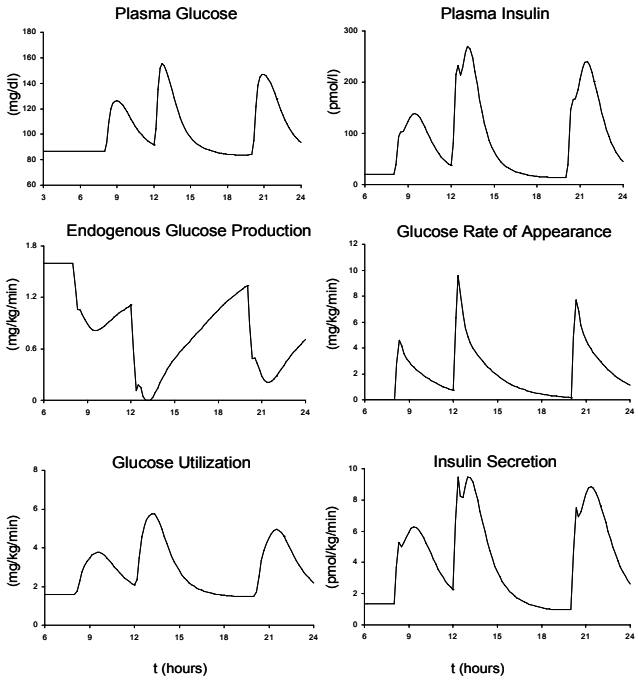

Figure 2: Day simulation of a normal subject.

C. Closed- and Open-Loop Controlled Type 1 Diabetic Subject

The model has also been used to simulate a type 1 diabetic subject both receiving exogenous insulin in a closed-loop scheme (a PID controller recently proposed in [16], Figure 3, solid line) or controlled in open-loop with subcutaneous insulin injections.

In the last case we have used the model of subcutaneous insulin kinetics based on a logistic equation of insulin absorption [17]. Simulation results with breakfast at 8 am (45 g of glucose, 2 U of fast insulin), lunch at 12 (70 g, 5 U of fast insulin) and dinner at 8 pm (70 g, 5 U of fast insulin) are shown in Figure 3 (dashed line).

VI. Discussion

A new simulation model of glucose-insulin regulatory system capable of describing the physiological events occurring after a meal has been presented. The postprandial state is of obvious importance because this route is used in everyday meals and has also been intensively investigated in recent years thus one can take advantage of all new quantitative knowledge which has became available. The model is made by a number of parsimonious sub-models describing the various unit processes which have been identified using a forcing function strategy. This is the major novelty of the proposed model which takes advantage of the availability of the virtually model-independent measurements of the glucose and insulin fluxes, occurring during a meal [5]. The glucose-insulin system, in fact, is very complex and the sole availability of plasma glucose and insulin concentrations does not allow 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. The model was numerically identified in normal subject (Figure 1) but it has also been used to describe various glucose intolerance states, by simulating parametric changes in insulin action and β-cell secretion (not shown). Albeit on a smaller triple tracer meal data base, the model has been also numerically identified in the type 2 diabetic subject (Figure 1). 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 parametric portrait: in particular gut absorption rate, insulin sensitivity, glucose effectiveness and both dynamic and static β-cell responsivity were lower in the diabetic than in the normal subject. A type 1 diabetic subject was also simulated by removing the insulin secretion portion while leaving the other parameters set at the same values of the normal subject (Figure 3). A model of subcutaneous insulin absorption [17] was used to simulate a common open-loop insulin therapy, i.e. a dose of fast insulin (analogue) is given in correspondence of the meals. A closed-loop scheme of insulin delivery was also tested by using as a controller a PID [16]. As with all models there are some limitations, the most important is that counteregulatory hormones, such as glucagon, epinephrine, growth hormone, have not been considered. This will be considered in next model development since important quantitative knowledge on the role of the counteregulatory hormones, particularly glucagon, during meals both in normal and diabetes is being gained.

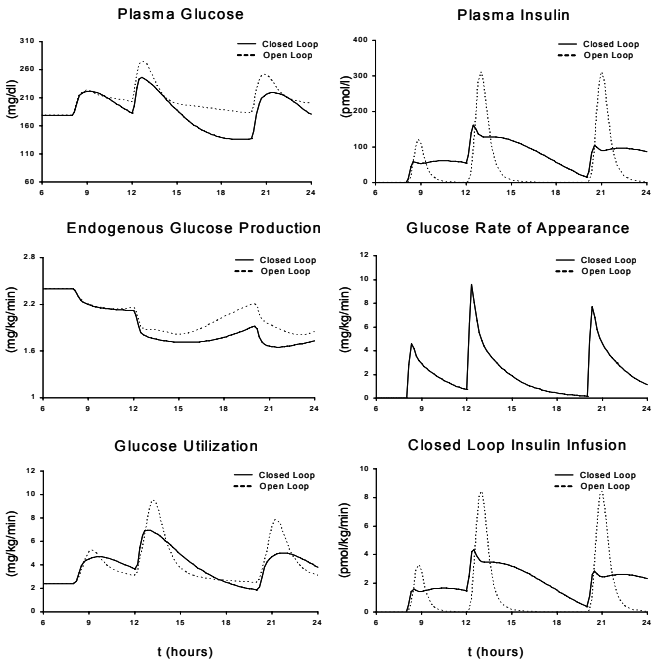

Figure 3: Day simulation of a type 1 diabetic subject controlled in closed-loop (solid line) and open-loop (dashed line).

VII. Conclusion

In this study 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 containing model-independent glucose and insulin fluxes both in normal and type 2 diabetes. The model should prove valuable as a simulator in several situations dealing with the pathophysiology of diabetes.

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