

MODELING THE INTRA-VENOUS GLUCOSE TOLERANCE
TEST: A GLOBAL STUDY FOR A
SINGLE-DISTRIBUTED-DELAY MODEL

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ABSTRACT. The Intra Venous Glucose Tolerance Test (IVGTT) is a simple and established experimental procedure in which a challenge bolus of glucose is administered intra-venously and plasma glucose and insulin concentrations are then frequently sampled. The modeling of the measured concentrations has the goal of providing information on the state of the subject's glucose/insulin control system: an open problem is to construct a model representing simultaneously the entire control system with a physiologically believable qualitative behavior. A previously published single-distributed-delay differential model was shown to have desirable properties (positivity, boundedness, global stability of solutions) under the hypothesis of a specific, square-wave delay integral kernel. The present work extends the previous results to a family of models incorporating a generic non-negative, square integrable normalized kernel. Every model in this family describes the rate of glucose concentration variation as due to both insulin-dependent and insulin-independent net glucose tissue uptake, as well as to constant liver glucose production. The rate of variation of plasma insulin concentration depends on insulin catabolism and on pancreatic insulin secretion. Pancreatic insulin secretion at time t is assumed to depend on the earlier effects of glucose concentrations, up to time t (distributed delay). We consider a non-negative, square integrable normalized weight function ω on $R^+ = [0, \infty)$ as the fraction of maximal pancreatic insulin secretion at a given glucose concentration. No change in local asymptotic stability is introduced by the time delay. Considering an appropriate Lyapunov functional, it is found that the system is globally asymptotically stable if the average time delay has a parameter-dependent upper bound. An example of good model fit to experimental data is shown using a specific delay kernel.

1. Introduction. The homeostasis of glucose, involving the secretion of its controlling hormone insulin by the pancreas, has been the object of several mathematical models over the past thirty years ([1]-[13]). One of the goals of this modeling

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effort is the measurement of the degree to which a given subject is able to accommodate a load of glucose, by means of an increase in peripheral tissue glucose uptake driven by an increase in the plasma concentration of insulin. The lack or insufficiency of this normal mechanism is termed "insulin resistance" and has an increasingly recognized importance in the pathogenesis of conditions like diabetes, obesity, and cardiovascular disease ([14]-[16]).

The Intra Venous Glucose Tolerance Test (IVGTT) is an experimental procedure in which a subject at rest is administered a bolus amount of glucose by injection into an arm vein, and the subject's plasma glucose and insulin concentrations are then measured repeatedly over a period of time, customarily three hours. The procedure is easy to perform, minimally invasive, and yields a rich data set.

For the analysis of the data obtained with an IVGTT, a recently published delay differential model [17] has been shown to allow simultaneous estimation of both insulin secretion and glucose uptake parameters, to have positive, bounded solutions, and to be globally asymptotically stable around the pre-injection equilibrium plasma glucose and insulin concentrations.

While the fact that such regular behavior can be proven for a specific model is of interest, it is on the other hand conceivable that this specific model may not be considered appropriate under all circumstances. For example, the diabetologist may reasonably believe that the pancreas does not exhibit an all- or-none response, of either zero or constant magnitude, to past glucose concentrations. On the other hand, the data recorded from different subjects may be best approximated numerically using kernels of different shape.

It was felt that these concerns could be best addressed not by assessing the behavior of a different specific model, but by investigating the qualitative properties shared by any model in a possibly wide family. In this way, the choice of which specific model to use could be left to the researcher in the field, based upon theoretical or numerical grounds.

A generic weight function ω is therefore introduced in the delay integral kernel for the pancreatic response to glucose, in place of the previously used specific rectangular weighting function (constant over a finite interval, zero otherwise).

The analytical demonstration of an appropriate qualitative behavior for this generic model, under mild requirements for ω , is the departure point for the subsequent experimental and numerical determination of an optimal shape for ω . This shape should best represent the pancreatic sensitivity to circulating glucose in a single subject or, in the average, over a class of similar subjects. Under mild assumptions, this optimal ω found for each subject would in every case give rise to solutions with desirable global qualitative properties.

2. Methods. The family of dynamic models to be studied is:

$$\frac{dG(t)}{dt} = -b_1G(t) - b_4I(t)G(t) + b_7, \quad G(t) \equiv G_b, \forall t \in (-\infty, 0), G(0) = G_b + b_0, \quad (1)$$

$$\frac{dI(t)}{dt} = -b_2I(t) + b_6 \int_0^\infty \omega(s)G(t-s)ds, \quad I(0) = I_b + b_3b_0, \quad (2)$$

where:

t [min] is time;

G [mg/dl] is the glucose plasma concentration;

G_b [mg/dl] is the basal (preinjection) plasma glucose concentration;

$I[\mu IU/ml]$ is the insulin plasma concentration;

$I_b[\mu IU/ml]$ is the basal (pre-injection) insulin plasma concentration;

b_0 [mg/dl] is the theoretical increase in plasma concentration over basal glucose concentration at time zero after instantaneous administration and redistribution of the I.V. glucose bolus;

$b_1[min^{-1}]$ is the spontaneous glucose first order disappearance rate constant;

$b_2[min^{-1}]$ is the apparent first-order disappearance rate constant for insulin;

$b_3[(\mu IU/ml)/(mg/dl)]$ is the first-phase insulin concentration increase per (mg/dl) increase in the concentration of glucose at time zero due to the injected bolus;

$b_4[min^{-1}(\mu IU/ml)^{-1}]$ is the constant amount of insulin-dependent glucose disappearance rate constant per $(\mu IU/ml)$ of plasma insulin concentration;

$b_6[min^{-1}(\mu IU/ml)/(mg/dl)]$ is the constant amount of second-phase insulin release rate per (mg/dl) of average plasma glucose concentration per unit time;

$b_7[(mg/dl)min^{-1}]$ is the constant increase in plasma glucose concentration due to constant baseline liver glucose release.

For ease of comparison with the previous model [17], the same parameter names have been maintained. The rectangular interval width b_5 relative to the previous model's integral kernel has therefore disappeared from the present formulation.

The weight function $\omega(s)$ is assumed to be a non-negative square integrable function on $R^+ = [0, \infty)$ such that $\int_0^\infty \omega(s)ds = 1$, $\int_0^\infty s\omega(s)ds = \tau < +\infty$, where τ represents the average time delay.

Each model in the above family describes glucose concentration changes in plasma as depending from spontaneous, insulin-independent net glucose tissue uptake, from insulin-dependent net glucose tissue uptake and from constant baseline liver glucose production. The term *net glucose uptake* indicates that changes in tissue glucose uptake and in liver glucose delivery are considered together.

Insulin plasma concentration changes are considered to depend from a spontaneous constant-rate decay, due to insulin catabolism, and from pancreatic insulin secretion. The delay term refers to the pancreatic secretion of insulin: effective pancreatic secretion (after the liver first-pass effect) is considered up to time t .

If V_G [ml/kgBW] is the volume of distribution of glucose, H [kg] the body weight of the experimental subject and D_G [mg] is the dose of injected glucose, then $b_0 = \frac{D_G}{V_G H}$, and the model may be expressed in terms of V_G instead of in terms of b_0 .

The model's free parameters are only five (b_0 through b_4). In fact, assuming the subject is at equilibrium at $(G^* = G_b, I^* = I_b)$ for a sufficiently long time ($t \rightarrow +\infty$), then

$$0 = -b_1 G_b - b_4 I_b G_b + b_7 \text{ and } 0 = -b_2 I_b + b_6 G_b \text{ together imply}$$

$$b_7 = b_1 G_b + b_4 I_b G_b, \quad b_6 = b_2 \frac{I_b}{G_b}.$$

To these five free parameters, the number of free parameters necessary for the specification of ω (hence for the passage from the generic family to the specific model) must be added. For instance, if one were to take ω as a normalized difference of exponentials, $\omega(s) = \frac{\alpha\beta}{\beta-\alpha}(e^{-\alpha s} - e^{-\beta s})$, with $\alpha > \beta$, then two more parameters would be necessary for a complete description of the time courses of glucose and insulin in a given subject.

Some Preliminaries. Let us consider $x(t) = (x_1(t), x_2(t)) \in \Omega$, where $\Omega = \{(x_1, x_2) \in R^{+2}\}$, the vector of concentrations at time t . Unless differently specified, choose a norm for $x \in R^2$ as $\|x\| = \max\{|x_1|, |x_2|\}$. $x_t = (x_1(t+s), x_2(t+s))$, $s \in$

$(-\infty, 0]$ is the continuous vector function mapping $(-\infty, 0] \rightarrow R^2$. A vector norm for x_t is then defined as: $\|x_t\| = \sup_{\theta \in (-\infty, 0]} |x(t + \theta)|$.

Initial conditions for (1-2) are $x_1(s) = \phi_1(s), x_2(s) = \phi_2(s), s \in (-\infty, 0]$, where $\phi = (\phi_1, \phi_2)$ is a bounded continuous, non-negative function on $(-\infty, 0]$.

According to Kuang [19] and adopting the same nomenclature as Beretta and Takeuchi [20],[21], denote $C((-\infty, 0], R^2)$, the Banach space of continuous functions mapping the interval $(-\infty, 0]$ into R^2 with topology of uniform convergence; i.e., $\phi \in C((-\infty, 0], R^2)$, with the norm $\|\phi\| = \sup_{\theta \in (-\infty, 0]} |\phi|$. If r is a real positive constant, let B_r be the open ball centered at 0, with radius r and $\phi(0) > 0$; ϕ being a given function on B_r . The system (1-2) with the given initial conditions can then be written as the initial value problem for the autonomous Retarded Functional Differential Equations (RFDE) $\dot{x} = f(x_t), t \in R^+, x_0 = \phi(s), s \in (-\infty, 0]$, where $\phi : (-\infty, 0] \rightarrow R^2, x_t = x(t + s)$.

Here we will be concerned with the stability properties of (1-2) with the initial value $\phi \in B_r, t = 0$. Owing to the biological meaning of (1-2), consider only the interior equilibrium; in the following, center (1-2) on the equilibrium by the change of variables such that $\phi \in B_r, at t = 0$.

It is easy to check that f is locally Lipschitzian [22], i.e., there exists $M_1 > 0$ such that $\|f(\psi_1) - f(\psi_2)\| \leq M_1 \|\psi_1 - \psi_2\|, \forall \psi_1, \psi_2 \in B_r$. This property ensures the local existence, uniqueness and continuous dependence on $\phi \in B_r$ of the solution (1-2) for all $t \in [t_0, t_0 + \epsilon)$.

Secondly, if there exists $t^* \in [t_0, t_0 + \epsilon)$ such that $x(t^*) = 0$, then $f(t^*) \geq 0$, which implies that $\phi \in B_r$ is a vector function with positive components, then the solution $x(t)$ will remain positive for all $t \in [0, \epsilon)$. In particular $\phi(0) = (G(0), I(0)) \in \Omega, \forall t \in [0, \epsilon)$, then $x(t) = (G(t), I(t)) \in \Omega, \forall t \in [0, \epsilon)$.

Thirdly, positive invariance of Ω implies boundedness of the solution of (1-2) for all $t \in [0, \epsilon)$. This leads to continuity of the solutions of (1-2) together with their properties of uniqueness and continuous dependence on the initial condition up to $\epsilon = \infty$, that is for all $t \in [0, \infty)$ [20], [23].

Before discussing the stability of the system, let us suppose that $f(0) = 0, \forall t \in (0, \infty)$, which ensures that the equation (1-2) admits the solution $x(t) = 0$. Denote with $\gamma_j(m), m \geq 0$, a class of scalar continuous, non-decreasing functions such that $\gamma_j(0) = 0, \gamma_j(m) > 0$ for $m > 0$ and $\lim_{m \rightarrow +\infty} \gamma_j(m) = +\infty$. Also denote with $(x(t), \bullet)$, for $t \geq 0$, the space of continuous bounded function $x_t \in (-\infty, t] \rightarrow R^2$, with $\|x_t\| = \sup_{s \in (-\infty, 0]} |x(t + s)|$ and $|\bullet|$ any norm on R^2 . The symbol $X_r(t)$ denotes the set of functions x_t with $\|x_t\| \leq r$. The following theorem due to Burton [23] applies:

THEOREM 2.1. *Let $V(x_t)$ be a continuous scalar functional, which is locally Lipschitzian in x_t for $x_t \in X_r(t)$ for some $r > 0$ and for all $t \geq 0$. The following propositions hold:*

1. *If $V(x_t) \geq \gamma_1(|x(t)|), V(0) = 0, \dot{V}(x_t) \leq 0$, for $t \geq 0$, then $x = 0$ is stable.*
2. *If, in addition to (a), $\dot{V}(x_t) \leq \gamma_2(|x(t)|)$, then $x = 0$ is uniformly stable.*
3. *Suppose that (a) holds and there exists $M_2 > 0$ such that $x \in X_r(t), t_0 < t < +\infty$ implies that $|f(x_t)| \leq M_2$ and $\dot{V}(x_t) \leq -\gamma_3(|x(t)|)$ then $x = 0$ is asymptotically stable.*

Since our system represents an autonomous RFDE, $X_r(t)$ coincides with B_r for all $t \geq 0$ with, in our case, $t_0 = 0$ as initial time.

3. Results.

3.1. Stability of the dynamic model. It can be shown that the any model in the generic family (1, 2) admits one and only one equilibrium point with positive concentrations, (G_b, I_b) . The proof of the following propositions can be obtained in a similar way as in De Gaetano and Arino [17], see also Weijiu [18].

PROPOSITION 3.1. *The solutions $\{G(t), I(t)\}$ are positive and bounded.*

PROPOSITION 3.2. *The time derivatives of the solutions are bounded.*

In the following, we try to show that any solution to the original system converges to (G_b, I_b) and that the system is stable, indeed asymptotically stable.

3.1.1. Local stability analysis. Consider the linearized system around the interior equilibrium (G^*, I^*) by substituting $u_1(t) = G(t) - G^*$, $u_2(t) = I(t) - I^*$, in Eqs.(1-2), obtaining

$$\frac{du_1}{dt} = -(b_1 + b_4 I^*)u_1 + b_4 G^* u_2, \quad (3)$$

$$\frac{du_2}{dt} = -b_2 u_2 + b_6 \int_0^\infty \omega(s) u_1(t-s) ds. \quad (4)$$

The corresponding characteristic equation is

$$\Delta(\lambda) := \lambda^2 + (A + b_2)\lambda + b_2 A + b_4 b_6 G^* W(\lambda) = 0,$$

where $A = b_1 + b_4 I^*$, and $W(\lambda) = \int_0^\infty e^{-\lambda s} \omega(s) ds$ denotes the Laplace transform of $\omega(s)$.

Since all parameters are positive and the Laplace transform involved in the characteristic equation is positive, the real roots are negative. Secondly, it is observed that $\lambda = 0$ cannot be a root of the characteristic equation since $b_2 A + b_4 b_6 G^* W(0) = b_2 A + b_4 b_6 \neq 0$.

So the only possibility for instability is through a Hopf bifurcation: we have to check [24] whether there exists a real $\mu > 0$, so that $\lambda = i\mu$ is a root of $\Delta(\lambda) = 0$, writing as usual $i = \sqrt{-1}$. Substituting $\lambda = i\mu$ in $\Delta(\lambda) = 0$, we have

$$-\mu^2 + i(A + b_2)\mu + b_2 A + b_4 b_6 G^* W(i\mu) = 0.$$

Hence,

$$W(i\mu) = \frac{\mu^2 - b_2 A - i(A + b_2)\mu}{b_4 b_6 G^*}.$$

Since $|W(i\mu)| \leq \int_0^\infty \omega(s) |e^{-i\mu s}| ds = 1$, it is necessary that $|W(i\mu)| \leq 1$.

Let

$$R(\mu) = \frac{(\mu^2 - b_2 A)^2 + \mu^2 (A + b_2)^2}{(b_4 b_6 G^*)^2}$$

and

$$R(0) = \frac{(b_2 A)^2}{(b_4 b_6 G^*)^2} = \frac{(b_1 b_2 + b_4 b_6 G^*)^2}{(b_4 b_6 G^*)^2} > 1.$$

Also

$$\frac{dR(\mu)}{d\mu} = \frac{4\mu(\mu^2 - b_2 A) + 2\mu(A + b_2)^2}{(b_4 b_6 G^*)^2} = \frac{2\mu(2\mu^2 + b_2^2 + A^2)}{(b_4 b_6 G^*)^2} \geq 0.$$

This shows that $R(\mu)$ is an increasing function of μ and $R(0) > 1$; it follows that $R(\mu) > 1$ for all $\mu \geq 0$. Thus $|W(i\mu)| > 1, \forall \mu \geq 0$. But $|W(i\mu)| < 1$, for every $\mu > 0$. Hence there is no possibility of stability switching. So the system is always locally asymptotically stable.

3.1.2. *Global stability properties around the interior equilibrium.* Before proceeding with the demonstration of global stability, we rearrange the system by substituting $x_1 = \frac{G-G^*}{G^*}$ and $x_2 = \frac{I-I^*}{I^*}$. We may therefore write

$$\frac{dx_1}{dt} = -b_1x_1 - b_4I^*x_2 - b_4I^*x_1(x_2 + 1), \quad (5)$$

$$\frac{dx_2}{dt} = -b_2x_2 + b_6 \int_0^\infty \omega(s)x_1(t-s)ds. \quad (6)$$

Consider the Lyapunov functional

$$\begin{aligned} V(x_t) = & \beta_1x_1^2 + \beta_2x_2^2 + V_0^2(x_t) + \beta_3 \int_0^\infty \omega(s) \int_{t-s}^t x_1^2(v)dvds \\ & + \beta_4 \int_0^\infty \omega(s) \int_{t-s}^t dt_1 \int_{t_1}^t x_1^2(v)dvds, \end{aligned}$$

where, $V_0(x_t) = x_2 + a \int_0^\infty \omega(s) \int_{t-s}^t x_1(v)dvds$, $\beta_j > 0, j = 1, \dots, 4$, and a is an arbitrary constant.

We observe that $V(x_t) \geq \beta(|x|)$, where $\beta = \min(\beta_1, \beta_2)$ and $\beta(|x|)$ is an increasing function of $|x|$. So, $\beta(|x|) \rightarrow +\infty$, as $|x| \rightarrow +\infty$. Next we note that

$$\begin{aligned} \frac{d}{dt}(\beta_1x_1^2) &= 2\beta_1[-b_1x_1^2 - b_4I^*x_1x_2 - b_4I^*x_1^2(x_2 + 1)], \\ \frac{d}{dt}(\beta_2x_2^2) &\leq \beta_2[(b_6 - 2b_2)x_2^2 + b_6 \int_0^\infty \omega(s)x_1^2(t-s)ds], \end{aligned}$$

and

$$\frac{d}{dt}(V_0^2) = 2V_0[-b_2x_2 + ax_1 + b_2 \int_0^\infty \omega(s)x_1(t-s)ds - a \int_0^\infty \omega(s)x_1(t-s)ds].$$

Choose $a = b_2$, then

$$\begin{aligned} \frac{d}{dt}(V_0^2) = 2V_0b_2(x_1 - x_2) \leq & [2b_2x_1x_2 + b_2\tau x_1^2 + (b_2^2\tau - 2b_2)x_2^2 \\ & + 2b_2^2 \int_0^\infty \omega(s) \int_{t-s}^t x_1^2(v)dvds], \end{aligned}$$

$$\frac{d}{dt}(\beta_3 \int_0^\infty \omega(s) \int_{t-s}^t x_1^2(v)dvds) = \beta_3[x_1^2 - \int_0^\infty \omega(s)x_1^2(t-s)ds],$$

$$\frac{d}{dt}(\beta_4 \int_0^\infty \omega(s) \int_{t-s}^t dt_1 \int_{t_1}^t x_1^2(v)dvds) = \beta_4[\tau x_1^2 - \int_0^\infty \omega(s) \int_{t-s}^t x_1^2(v)dvds].$$

Adding all above inequalities and choosing $\beta_3 = (2b_2 - b_6)\beta_2, \beta_4 = 2b_2^2$, we may write

$$\begin{aligned} \frac{d}{dt}(V(x_t)) \leq & -[2\beta_1b_1 - \beta_3 - (b_2^2 + \beta_4)\tau]x_1^2 + 2(b_2 - \beta_1b_4)x_1x_2 \\ & - [\beta_2b_2 + 2b_2 - b_2^2\tau]x_2^2 - 2\beta_1b_4I^*x_1^2(x_2 + 1). \end{aligned}$$

Again, $x_2 + 1 = \frac{I}{I^*} \geq 0$, and if we choose $\beta_1 = \frac{b_2}{b_4}$, then

$$\frac{d}{dt}(V(x_t)) \leq -[2b_1\frac{b_2}{b_4} - \beta_2b_2 - 3b_2^2\tau]x_1^2 - [\beta_2b_2 + 2b_2 - b_2^2\tau]x_2^2.$$

Note that the coefficients of x_1^2 and x_2^2 are negative for sufficiently small $0 < \beta_2 < \frac{2b_1}{b_4}$. So the choice of such a $\beta_2 > 0$ ensures that there exists some $\gamma = \gamma(\beta_2, \tau) > 0$, such that $\frac{d}{dt}(V(x_t)) \leq -\gamma(x_1^2 + x_2^2)$, provided that $2b_1\frac{b_2}{b_4} - \beta_2b_2 - 3b_2^2\tau > 0$, i.e., $\tau < \frac{1}{3b_2}(\frac{2b_1}{b_4} - \beta_2)$ and that $\beta_2b_2 + 2b_2 - b_2^2\tau > 0$, i.e., $\tau < \frac{1}{b_2}(2 + \beta_2)$.

It is therefore sufficient to choose $\tau < \min[\frac{1}{b_2}(2 + \beta_2), \frac{1}{3b_2}(\frac{2b_1}{b_4} - \beta_2)]$ to have negativity of the derivative of the considered Lyapunov functional. *Theorem 2* then follows immediately:

TABLE 1. OLS parameter estimates for the model (1), (2), (7) . Parameters are denoted as free to vary in the fitting, fixed (baseline Glycemia and Insulinemia values) or computed (from equilibrium conditions).

b_0	free	159.74
b_1	free	0.018063
b_2	free	0.041342
b_3	free	2.8274
b_4	free	1e-005
α	free	0.1022
G_b	fixed	79
I_b	fixed	62.5
b_6	computed	0.032707
b_7	computed	1.4763

THEOREM 3.1. *If the average time delay $\tau < \min[\frac{1}{b_2}(2 + \beta_2), \frac{1}{3b_2}(\frac{2b_1}{b_4} - \beta_2)]$, then the system (1-2) is globally asymptotically stable.*

Proof. It can be easily checked that above-mentioned Lyapunov functional satisfies all the conditions of Theorem(2.1). This completes the proof. \square

3.2. Numerical integration and estimation. By way of example, one model of the family, obtained by specifying the delay kernel as a second-order gamma function, has been fitted by Ordinary Least Squares (OLS) to experimental time-concentration data obtained on a normal volunteer. The model equations used are therefore (1), (2) above and (7) below:

$$\omega(s) = \alpha^2 s e^{-\alpha s}. \quad (7)$$

The point parameter estimates are shown in Table 1, the fitted Glucose and Insulin data together with the model prediction, are shown in Figure 1, and the shape of the (optimal) delay kernel, depending on the estimated parameter α , is shown in Figure 2. The average delay obtained from (7) with the estimated value for α is 19.6 minutes. For any $\beta_2 \in (0, 800]$, the stability criterion given by Theorem (3.1) is greater than 50 minutes, hence larger than the average delay; the system is therefore globally asymptotically stable.

4. Discussion. The model in the present work goes one step further, with respect to the already published model with square-wave delay kernel [17], towards providing a tool which the diabetologist may consider useful in the experimental evaluation of the homeostatic control of glycemia.

The physiologic meaning of the delay kernel reflects the sensitivity of the pancreas to the concentration of glucose in circulating plasma: the pancreas will output insulin, at a given time t , at a rate proportional to the suitably weighted average of the past plasma glucose concentrations, which is related to the glucose concentration in interstitial fluid to which the pancreatic β -cells have been exposed in the past. Even assuming instantaneous equilibration of arterial glucose concentrations with pancreatic interstitial fluid, the chain of events leading from the increased glucose signalling on membrane receptors, to the resulting secretion of active insulin from the β -cells, takes time. The interactions among different steps of a complex

biochemical and cellular transport chain within the pancreatic cell make the hypothesis of a single discrete delay less plausible than that of a distributed delay, where the concentrations of glucose at different times in the past have different relevance to the present insulin secretion rate.

The first approach to a workable model had been simply to hypothesize that glucose concentrations were uniformly effective throughout an interval of time up to the present. This primitive hypothesis could have been substituted with any one of possibly several more refined hypotheses, each specifying a functional form of the delay kernel on the basis of physiological knowledge or experimental results in a patient or in a (homogeneous) class of patients. The choice of a better model could then have been followed by the analytic demonstration of its qualitative properties.

The approach followed in the present work is somewhat similar to that followed by Li, Kuang and Li [25] who also postulated a generic class of models for the glucose-insulin system. In fact, the family considered in the present work is a sub-family of that considered by these Authors. In both cases, the original concern is that of improving on the assumptions previously made. Further, by specifying two instances of models in their extended family, these Authors are able to address issues like local stability switches in the linearized system, for changes in the delay parameter.

The goal of the present work, on the other hand, is to guarantee qualitative properties for the entire (albeit smaller) family, without further specification of the kernel ω , subject only to mild integrability conditions.

The demonstration of local and global asymptotic stability of the models incorporating such a generic ω paves the way to the experimental determination of its shape, knowing that it can reach back to minus infinity and that any reasonable shape is admissible without prejudice to the model's asymptotic behavior. It is to be expected that different patient populations will show a different shape of the kernel function: normal individuals, with a prompt and appropriate insulin response to hyperglycemic stimuli will likely have a promptly rising, promptly falling ω curve; NIDDM (Non Insulin Dependent Diabetes Mellitus) subjects, with a sustained insulin response to moderately hyperglycemic stimuli, will probably have persistently elevated ω for long times in the past; IDDM (Insulin Dependent Diabetes Mellitus) subjects, with poor or absent pancreatic response to circulating glucose, will in all likelihood have a small ω over a long time. Suitable parametrization of ω may then offer the possibility of differentiating between patient populations by means of experimental parameter identification.

This approach to the numerical quantification of the homeostasis of the glucose-insulin system from the mathematical modeling of the IVGTT has the advantage of explicitly representing the two arms of the whole system together (insulin sensitivity of tissues and pancreatic sensitivity to circulating glucose), allowing the eventual simultaneous fitting of glucose and insulin concentration data.

While the number of parameters with respect to the previous model appears to be reduced by one, in order to demonstrate qualitative properties the kernel ω has in fact not been represented at all in a functional form with respect to elapsed time: its representation could be done in several fashions compatible with the general notion of an increasing then decreasing pancreatic sensitivity to glucose at progressively increasing times in the past. The initial increase would depend on the necessity to activate intracellular mechanisms, the subsequent decrease to a declining effect of past glucose stimuli on present pancreatic performance. A difference of exponentials

or a 2nd degree gamma-function would both be compatible with this general shape. In particular, the gamma-function approach $\omega(s) = \alpha^2 s e^{-\alpha s}$ could introduce a single new parameter α , without undue a-posteriori identification difficulties.

Even the present formulation has some evident limits from the physiological point of view. On one hand, it would be necessary to assemble a single formulation which could account for more than one type of experimental procedure. The IVGTT, the Euglycemic Hyperinsulinemic Clamp (EHC) and the Oral Glucose Tolerance Test (OGTT), at least, should be described within a single coherent framework. On the other hand, a better model should also describe the delayed action of insulin to increase tissue glucose uptake. Finally, the kinetics of insulin could be better followed by simultaneously accounting for C-peptide concentrations in plasma.

The need exists, furthermore, to extend the results obtained in the laboratory to the real-life conditions of the diabetic patient, in order to address the pressing need to reliably predict the time course of plasma glucose concentrations as a function of food intake, physical exercise and therapy.

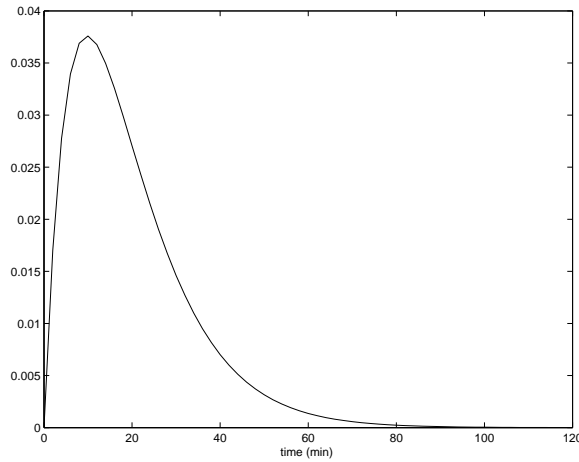


Figure 1

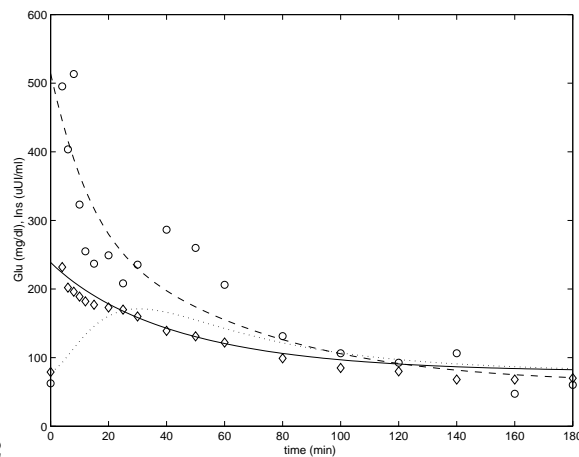


Figure 2

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