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Article *in* Journal of Mathematical Biology · March 2000

DOI: 10.1007/s002850050007 · Source: PubMed

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Journal of Mathematical Biology

Mathematical modelling of the intravenous glucose tolerance test

Andrea De Gaetano[1,⋆], **Ovide Arino**[2]

[1]CNR, Centro Fisiopatologia Shock, Università Cattolica del Sacro Cuore, Largo A. Gemelli, 8, 00168 Roma, Italy. e-mail: biomath@tin.it
[2]Laboratoire de Mathématiques Appliquées, UPRES A 5033 IPRA, Pau, France

Received: 22 June 1998 / Revised version: 24 February 1999

Abstract. Several attempts at building a satisfactory model of the glucose-insulin system are recorded in the literature. The minimal model, which is the model currently mostly used in physiological research on the metabolism of glucose, was proposed in the early eighties for the interpretation of the glucose and insulin plasma concentrations following the intravenous glucose tolerance test. It is composed of two parts: the first consists of two differential equations and describes the glucose plasma concentration time-course treating insulin plasma concentration as a known forcing function; the second consists of a single equation and describes the time course of plasma insulin concentration treating glucose plasma concentration as a known forcing function. The two parts are to be separately estimated on the available data. In order to study glucose-insulin homeostasis as a single dynamical system, a unified model would be desirable. To this end, the simple coupling of the original two parts of the minimal model is not appropriate, since it can be shown that, for commonly observed combinations of parameter values, the coupled model would not admit an equilibrium and the concentration of active insulin in the "distant" compartment would be predicted to increase without bounds. For comparison, a simple delay-differential model is introduced, is demonstrated to be globally asymptotically stable around a unique equilibrium point corresponding to the pre-bolus conditions, and is shown to have positive and bounded solutions for all times. The results of fitting the delay-differential model to experimental data from ten healthy

⋆ Corresponding author.

volunteers are also shown. It is concluded that a global unified model is both theoretically desirable and practically usable, and that any such model ought to undergo formal analysis to establish its appropriateness and to exclude conflicts with accepted physiological notions.

Key words: Glucose – Insulin – Dynamical systems – Differential equations – Delay

1. Introduction

Since the sixties, the homeostasis of glucose, involving the secretion of its controlling hormone insulin by the pancreas, has been the object of several mathematical models [1, 3, 6, 12, 14, 16, 17, 23, 26, 27, 29]. With the increased emphasis on derangements of the sensitivity of tissues to insulin in diverse pathological conditions like diabetes, obesity, and cardiovascular disease [8, 9, 11], the quantitation of insulin sensitivity from a relatively non-invasive test procedure has acquired greater importance in physiological research.

Of the two experimental procedures currently in use for the estimation of insulin sensitivity in a subject, the intra venous glucose tolerance test (IVGTT) has appeal, over the euglycemic hyperinsulinemic clamp [10], because of its ease of execution, especially in its unmodified form (without additional Tolbutamide injection [30]), and because of the richness of the information its analysis yields. The test consists of injecting I.V. a bolus of glucose and frequently sampling the glucose and insulin plasma concentrations afterwards, for a period of about three hours.

The physiological model which has been mostly used in the interpretation of the IVGTT, since its publication in the early eighties, is generally known as the "Minimal Model" [2, 28]: it is described below (Eqs. 1–3). The model, as originally proposed by the authors, is to be regarded as composed of two separate parts. The first part [2] uses Equations (1) and (2) to describe the time course of plasma glucose concentration, accounting for the dynamics of glucose uptake dependent on and independent of circulating insulin; for this first part, plasma insulin concentration is to be regarded as a known forcing function. The second part [28] consists of Equation (3) and describes the time course of plasma insulin concentration, accounting for the dynamics of pancreatic insulin release in response to the glucose stimulus; for this second part plasma glucose concentration is to be

regarded as a known forcing function. The proposing authors specifically stated [19] that the model parameter fitting has to be conducted in two steps: first, using the recorded insulin concentration as input data in order to derive the parameters in the first two equations, then using the recorded glucose as input data to derive the parameters in the third equation.

However, the glucose-insulin system is an integrated physiologic dynamical system and we would like to be able to describe it as a whole, this unified description being also conducive to a single-step parameter fitting process.

We first offer a formal study of the dynamical system obtained by coupling the two parts of the minimal model. By doing so, this coupled model will be shown to present some difficulties in describing mathematically the glucose-insulin system from a unified point of view. We want to underscore that by so doing we depart from the explicitly stated objectives of the model's proponents: no criticism is therefore implied regarding its fulfilling its original goals and regarding its practical usefulness; indeed, our group uses the minimal model in the routine evaluation of insulin sensitivity in clinical patients [5], and we have introduced improved statistical techniques to make the determination of its coefficients (notably those of its first part, relative to glucose dynamics) more efficient [7].

We then introduce a different global dynamical model of the glucose-insulin system and discuss its stability properties. We also show some numerical results obtained from fitting this dynamical model to plasma glucose and insulin concentrations measured on healthy volunteers undergoing the IVGTT.

2. Materials and methods

2.1. Patient sample

Ten healthy volunteers (5 males and 5 females, anthropometric characteristics reported in Table 1) participated in the study. All subjects had negative family and personal histories for diabetes mellitus and other endocrine diseases, were on no medications, had no current illness and had maintained a constant body weight for the six months preceding the study. For the three days preceding the study each subject followed a standard composition diet (55% carbohydrate, 30% fat, 15% protein) ad libitum with at least 250g carbohydrates per day.

Each study was performed at 8:00 AM, after an overnight fast, with the subject supine in a quiet room with constant temperature of

22–24 °C. Bilateral polyethylene IV cannulas were inserted into antecubital veins. The standard Intra Venous Glucose Tolerance Test (IVGTT) was employed, without using additional Tolbutamide so as to be able to use the recorded data for pancreatic secretion evaluation: at time 0 (0′) a 33% glucose solution (0.33 g Glucose/kg body weight) was rapidly injected (less than 3 minutes) through one arm line. Blood samples (3 ml each, in lithium heparin) were obtained at $-30'$, $-15'$, $0'$, $2'$, $4'$, $6'$, $8'$, $10'$, $12'$, $15'$, $20'$, $25'$, $30'$, $35'$, $40'$, $50'$, $60'$, $80'$, $100'$, $120'$, $140'$, $160'$ and $180'$ through the contralateral arm vein. Each sample was immediately centrifuged and plasma was separated. Plasma glucose was measured by the glucose oxidase method (Beckman Glucose Analyzer II, Beckman Instruments, Fullerton, CA, USA). Plasma insulin was assayed by standard radio immunoassay technique. The plasma levels of glucose and insulin obtained at $-30'$, $-15'$ and $0'$ were averaged to yield the baseline values referred to $0'$.

2.2. Minimal model

As we have seen, the physiologic experiment consists in injecting into the bloodstream of the experimental subject a bolus of glucose, thus inducing an (impulsive) increase in the plasma glucose concentration $G(t)$ and a corresponding increase of the plasma concentration of insulin $I(t)$, secreted by the pancreas. These concentrations are measured during a three-hour time interval beginning at injection, after which time interval it is found that the perturbed concentrations $G(t)$ and $I(t)$ have essentially returned to normal. In order to describe the time course of these concentrations, the minimal model of the glucose-insulin kinetics has been proposed.

We will use the standard formulation of the minimal model, renaming some parameters for ease of notation:

$$\frac{dG(t)}{dt} = -[p_1 + X(t)]\,G(t) + p_1 G_b, \qquad G(0) = p_0 \tag{1}$$

$$\frac{dX(t)}{dt} = -p_2 X(t) + p_3[I(t) - I_b], \qquad X(0) = 0 \tag{2}$$

$$\frac{dI(t)}{dt} = p_4[G(t) - p_5]^+ t - p_6[I(t) - I_b], \qquad I(0) = p_7 + I_b \tag{3}$$

where

$G(t)$ [mg/dl] is the blood glucose concentration at time t [min];
$I(t)$ [μUI/ml] is the blood insulin concentration;

$X(t)$ [min^{-1}] is an auxiliary function representing insulin-excitable tissue glucose uptake activity, proportional to insulin concentration in a "distant" compartment;
G_b [mg/dl] is the subject's baseline glycemia;
I_b [μUI/ml] is the subject's baseline insulinemia;
p_0 [mg/dl] is the theoretical glycemia at time 0 after the instantaneous glucose bolus;
p_1 [min^{-1}] is the glucose "mass action" rate constant, i.e. the insulin-independent rate constant of tissue glucose uptake, "glucose effectiveness";
p_2 [min^{-1}] is the rate constant expressing the spontaneous decrease of tissue glucose uptake ability;
p_3 [min^{-2} $(\mu\text{UI/ml})^{-1}$] is the insulin-dependent increase in tissue glucose uptake ability, per unit of insulin concentration excess over baseline insulin;
p_4 [$(\mu\text{UI/ml})\ (\text{mg/dl})^{-1}\,\text{min}^{-1}$] is the rate of pancreatic release of insulin after the bolus, per minute and per mg/dl of glucose concentration above the "target" glycemia;
p_5 [mg/dl] is the pancreatic "target glycemia";
p_6 [min^{-1}] is the first order decay rate constant for Insulin in plasma;
p_7 [μUI/ml] is the theoretical plasma insulin concentration at time 0, above basal insulinemia, immediately after the glucose bolus.

In Eq. (3), only the positive part of the term $[G(t) - p_5]$ is taken, i.e. when $G(t)$ is greater than p_5 the value is taken to be $[G(t) - p_5]$, otherwise the value is zero. Also in Eq. (3), the multiplication by t is introduced by the authors to express, as a first approximation, the hypothesis that the effect of circulating hyperglycemia on the rate of pancreatic secretion of insulin is proportional both to the hyperglycemia attained and to the time elapsed from the glucose stimulus [28]. Multiplying by t in this way introduces the necessity of establishing an origin for time, effectively binding this model to the IVGTT experimental procedure.

Parameters p_0, p_1, p_4, p_5, p_6 and p_7 are usually referred to in the literature as G_0, S_G, γ, h, n and I_0 respectively, while the insulin sensitivity index S_I is computed as p_3/p_2.

2.3. Dynamical model

In order to overcome the difficulties of the coupled minimal model, another model for the glucose-insulin system is proposed. The

physiological hypotheses underlying Eq. (1) in the minimal model above have been retained, i.e. that disappearance of glucose from plasma may be described as a first-order process, of rate partly dependent on insulin concentration and partly independent of it. However, it was desired not to introduce non-observable state variables if possible, to represent delay explicitly when a delay is apparent, and to avoid a non-autonomous form of the equation, difficult to justify from a physiological point of view and likely to contribute to model instability. The questionable physiological assumption that the pancreas is able to linearly increase its rate of insulin secretion with time, and the related necessity of establishing an initial time point with respect to which all biochemical events take place, are both avoided in the proposed formulation. In this way an attempt is made to formulate a model embodying the underlying physiological mechanism, without associating it by necessity to the IVGTT experiment. The dynamical model of the glucose-insulin system to be studied is therefore:

$$\frac{dG(t)}{dt} = -b_1 G(t) - b_4 I(t) G(t) + b_7,$$

$$G(t) \equiv G_b \; \forall t \in [-b_5, 0), \qquad G(0) = G_b + b_0 \tag{4}$$

$$\frac{dI(t)}{dt} = -b_2 I(t) + \frac{b_6}{b_5} \int_{t-b_5}^{t} G(s)\, ds, \qquad I(0) = I_b + b_3 b_0, \tag{5}$$

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 [pM] is the insulin plasma concentration;
I_b [pM] is the basal (preinjection) 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 [pM/(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 [$\text{min}^{-1}\,\text{pM}^{-1}$] is the constant amount of insulin-dependent glucose disappearance rate constant per pM of plasma insulin concentration;

b_5 [min] is the length of the past period whose plasma glucose concentrations influence the current pancreatic insulin secretion;
b_6 [$\min^{-1}$ pM/(mg/dl)] is the constant amount of second-phase insulin release rate per (mg/dl) of average plasma glucose concentration throughout the previous b_5 minutes;
b_7 [(mg/dl) $\min^{-1}$] is the constant increase in plasma glucose concentration due to constant baseline liver glucose release.

The above model describes glucose concentration changes in blood as depending on spontaneous, insulin-independent net glucose tissue uptake, on insulin-dependent net glucose tissue uptake and on 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 on a spontaneous constant-rate decay, due to insulin catabolism, and on pancreatic insulin secretion. The delay term refers to the pancreatic secretion of insulin: effective pancreatic secretion (after the liver first-pass effect) at time t is considered to be proportional to the average value of glucose concentration in the b_5 minutes preceding time t.

Due to the delay, as initial conditions for the problem we have to specify not only the level of glucose at time zero, but also its value at times from $-b_5$ to 0.

If V_G [ml/kgBW] is the volume of distribution of glucose, W [kg] the weight of the experimental subject and D_G [mg] is the dose of injected glucose, then $b_0 = D_G/(V_G W)$, and the model may be expressed in terms of V_G instead terms of b_0.

The term $(1/b_5)$ in front of the integral in Eq. (5) has been introduced so as to make the integral equal one for constant unit glucose concentration, thus making b_6, pancreatic responsiveness, independent of b_5, the time period of pancreatic sensitivity to plasma glucose concentrations.

The free parameters are only six (b_0 through b_5). In fact, assuming the subject is at equilibrium at (G_b, I_b) for a sufficiently long time ($> b_5$) prior to the administration of the bolus, then

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

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

For model fitting, observations have been weighted according to the usual IVGTT scheme [19]: glucose observations before 8 minutes have been given a weight of zero (assuming glucose bolus distribution

to be complete by 8 minutes), and insulin observations before the first insulin peak (usually at 2 or 4 minutes) have also been given a weight of zero. No points have been overweighted (i.e. all points have weight either zero or one). Parameter values were obtained by weighted least squares using a quasi-Newton minimization algorithm [22].

3. Results

The proofs of all the statements contained in this section are reported in the Appendix.

I. Formal study of the minimal model

Recall that in the minimal model p_5 is the target glycemia which the pancreatic secretion of insulin attempts to attain (i.e. above which the pancreas is assumed to secrete the glycemia-lowering hormone insulin), whereas G_b is the measured baseline glycemia, which results from the equilibrium between the pancreatic action to lower glycemia down to p_5 and the endogenous (liver) glucose production which tends to raise glycemia. In general, G_b may be greater than p_5, and this is in fact the case in [19] where the program to estimate the parameters of the minimal model is described: in the reported series $G_b = 92$ mg/dl, $p_5 = 89.5$ mg/dl.

Proposition I.1 refers to the case in which glycemia $G(t)$ returns to basal G_b after the metabolization of the glucose bolus.

Proposition I.1. *Suppose* $G_b > p_5$, $\limsup_{t\to\infty} G(t) > p_5$. *Then* $\limsup_{t\to\infty} X(t) = \infty$.

Proposition I.2 refers to the case in which glycemia tends to drop below the pancreatic target level p_5:

Proposition I.2. *Suppose* $\limsup_{t\to\infty} G(t) < p_5$; *then* $G_b \leqq p_5$.

Remark I.3. Proposition I.1 shows the model to exhibit a pathologic behavior if $\limsup_{t\to\infty} G(t) > p_5$. Proposition I.2 shows that if $\limsup_{t\to\infty} G(t) < p_5$, then necessarily $G_b \leqq p_5$, contrary to what observed. The two propositions above leave open the possibility that the upper limit of glycemia, as t increases, exactly equals p_5. The analysis of this boundary case is not easy: however, either one of the two above cases would be produced for arbitrarily small changes in the p_5 parameter. In fact, more can be proven, i.e.:

Proposition I.4. *For any value $p_5 < G_b$ the system does not admit an equilibrium.*

The above fact may be stated in another way:

Proposition I.5. *If the subject is considered to be at steady state before the glucose bolus, then G_b must be lesser than or equal to p_5.*

The above objections to the qualitative behavior of the system (1, 2, 3) would indicate as a possible solution the imposition that the parameter p_5 exactly equal the experimentally observed quantity G_b. This empirical operation, which would actually change the model to a different one, finds little justification. In fact, p_5 is the unknown but true value of a model parameter, while G_b is a measured quantity equal to the sum of the true unknown value of the pre-injection equilibrium state plus some (observation) error. In any case, it is interesting to note that, in the case where $p_5 = G_b$, the possible solutions, which start out at a greater value than G_b (due to the bolus injection of glucose) are forced to pass below the G_b level before they can converge to G_b, and once they pass below this value, they can never cross it again to become greater than G_b. In other words, it is not possible for a solution to converge to G_b from above or to oscillate in any way (damped or otherwise) around G_b.

Proposition I.6. *Let $p_3 > 0$, $p_5 = G_b$, $G(0) > G_b$. Assume $G(t)$, $X(t)$ bounded. Then there exists $T > 0$ such that $G(t) > G_b$ for all $t < T$, $G(T) = G_b$, and $G(t) < G_b$ for all $t > T$.*

A brief discussion of the properties of the minimal model in case $G_b < p_5$ follows the proof of Proposition I.6 in the Appendix.

II. Stability of the dynamical model

It can be shown that the dynamical model admits one and only one equilibrium point with positive concentrations, (G_b, I_b).

Proposition II.3. *The solutions $\{G(t), I(t)\}$ are positive and bounded.*

Proposition II.4. *The time derivatives of the solutions are bounded.*

It can be finally shown that any solution to the original system converges to (G_b, I_b) and thus this state is asymptotically stable.

III. Numerical fitting of the dynamical model

The parameter estimates obtained for each subject by fitting the dynamical model to the experimental data are reported in Table 1, which also shows the sample mean, sample standard deviation, sample standard error and coefficient of variation for each parameter. The corresponding sample correlation matrix is reported in Table 2.

It has to be noted that the parameter b_5 was evaluated in every experimental subject as an integer value, since the resolution of the estimate of delay (in minutes) depends on the smallest increment in time used in the evaluation of the integral, in this case one minute.

The fitting was good to excellent for all subjects: the R-squared computed from the simple (unweighted) deviance lying between 0.862 and 0.990.

Figures 1, 2 and 3 report the observed and predicted time courses for three prototypical subjects: one (Fig. 1) showing an apparently exponential decay of insulin after its primary peak, one (Fig. 2) presenting no secondary insulin peak but a clear non-exponential decay of insulin towards the basal value, and finally one (Fig. 3) showing a well-defined secondary insulin peak.

We notice in passing that while the minimal model was originally described using μUI/ml as the units for Insulin concentration, our laboratory provides insulin concentrations in pM (pico moles/Liter): 1 μUI/ml being equal to 7.00 pM.

4. Discussion

The IVGTT is a reasonably simple experiment yielding a potentially very rich data set, and, in the applications, parameters referring both to tissue glucose uptake and to pancreatic responsiveness are of interest [4, 20, 21].

From a dynamical point of view, the pancreas and tissues form an integrated system with feedback regulations and it would seem desirable to have a model explicitly representing the whole system, which could be fitted in a single pass to both glucose and insulin data, rather than splitting the model into two subsystems and fitting separately each one. In fact, for a model fitting simultaneously the two arms of the control mechanism, the error variance would be a more appropriate expression of the effective applicability of the assumptions underlying both subsystems to the experimental situation. In other words, by fitting simultaneously the two parts, we observe the coherent fitting of the entire dynamical model to the entire set of observations. By

Table 1. Dynamical model results: anthropometric characteristics and dynamical model parameter values found for each experimental subject, together with their sample mean, standard deviation, standard error and coefficient of variation. BW is body weight, LBM is lean body mass, FBM is fat mass, bas. gluc. is basal blood glucose, bas. insul. is basal plasma insulin, R^2 is the (unweighted data) coefficient of determination.

Subject	Sex	Age (years)	Height (cm)	BW (kg)	LBM (kg)	FM (kg)	bas. gluc. (mg/dl)	bas. insul. (pM)	b_0 (mg/dl)	b_1 (min^{-1})	b_2 (min^{-1})	b_3 pM/(mg/dl)	b_4 (min^{-1}) pM^{-1}	b_5 (min)	b_6 min^{-1} pM/(mg/dl)	b_7 (mg/dl) min^{-1}	R^2
1	m	35	172	72	56	16	69	71.3	170	0.0226	0.0437	2.57	3.80E-08	20	0.045	1.56	0.865
2	f	28	155	45	36.2	8.8	79	51.7	241	0.0509	0.2062	3.55	1.29E-07	14	0.135	4.02	0.955
3	f	25	162	61	48.4	12.6	74	29.4	208	0.0309	0.1817	2.96	6.99E-07	12	0.072	2.29	0.931
4	m	32	169	68	53.5	14.5	80	56.6	355	0.0084	0.1039	4.25	7.55E-05	8	0.073	1.01	0.985
5	m	23	179	65	55	10	74	45	216	0.0273	0.0275	2.77	1.10E-07	5	0.017	2.02	0.869
6	f	27	162	65	44.5	20.5	88	68.6	209	0.0002	0.0422	1.64	1.09E-04	23	0.033	0.68	0.953
7	m	25	170	66	53	13	87	37.9	311	0.0001	0.2196	0.64	3.73E-04	23	0.096	1.24	0.957
8	f	34	158	64	42.4	21.6	78	55.8	217	0.0565	0.0438	4.39	5.70E-06	19	0.031	4.43	0.99
9	m	42	172	78	61.2	16.8	70	43.8	156	0.0135	0.2972	5.92	3.51E-08	11	0.186	0.94	0.93
10	f	55	169	67	47.4	19.6	67	37.7	184	0.0159	0.0965	2.51	8.72E-08	14	0.054	1.07	0.862
Mean		32.6	166.8	65.1	49.8	15.3	76.6	49.8	226.7	0.0226	0.1262	3.12	5.64E-05	14.9	0.074	1.93	0.93
s.d.		9.8	7.3	8.5	7.4	4.4	7.2	13.6	62.1	0.0194	0.0938	1.49	1.18E-04	6.2	0.052	1.31	0.048
s.e.		3.1	2.3	2.7	2.3	1.4	2.3	4.3	19.6	0.0061	0.0297	0.47	3.73E-05	2	0.017	0.41	0.015
c.v. (%)		9.5	1.4	4.1	4.7	9	3	8.6	8.7	27.1	23.5	15.1	66.1	13.1	22.4	21.5	1.6

Table 2. Dynamical model: matrix of sample partial correlation coefficients between the free parameters.

	b_0	b_1	b_2	b_3	b_4	b_5
b_0	1.000					
b_1	− 0.233	1.000				
b_2	0.044	− 0.110	1.000			
b_3	− 0.213	0.398	0.290	1.000		
b_4	0.594	− 0.571	0.237	− 0.628	1.000	
b_5	− 0.062	− 0.168	− 0.081	− 0.532	0.519	1.000

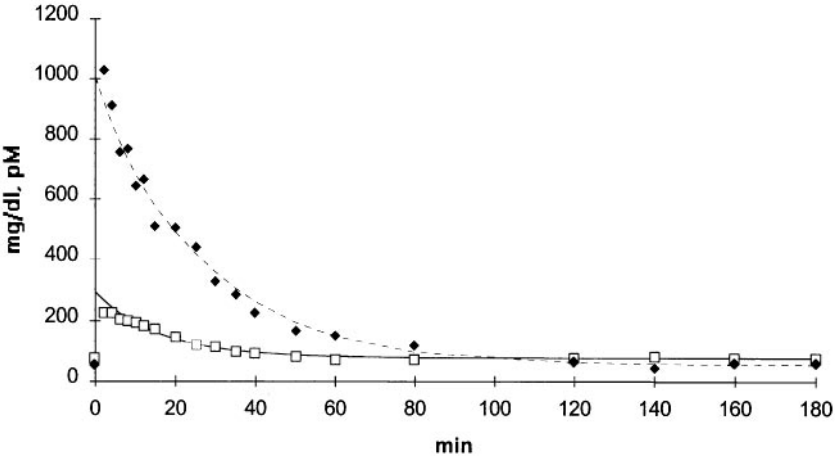

Fig. 1. Blood glucose (data: blank squares; model: continuous line) and plasma insulin (data: solid diamonds; model: dashed line) time courses for subject 8. Both glucose and insulin decays seem grossly exponential.

splitting the two subsystems we may estimate coefficients for one segment, by optimally fitting the relative data, which are not the ones which would generate an optimal approximation to the whole data set if the interaction between the two subsystems were allowed. The end result is that by splitting the system we obtain an impression of success because our error looks smaller, but we are in fact omitting an internal coherency check. Consequently, we may assert that the (global) system works in some way (i.e. with some parameters) which may be different from the best approximation to the real one. It may indeed happen (like in finding a value for b_5 smaller than the value for G_b) that the global system cannot work at all with the estimated parameter values.

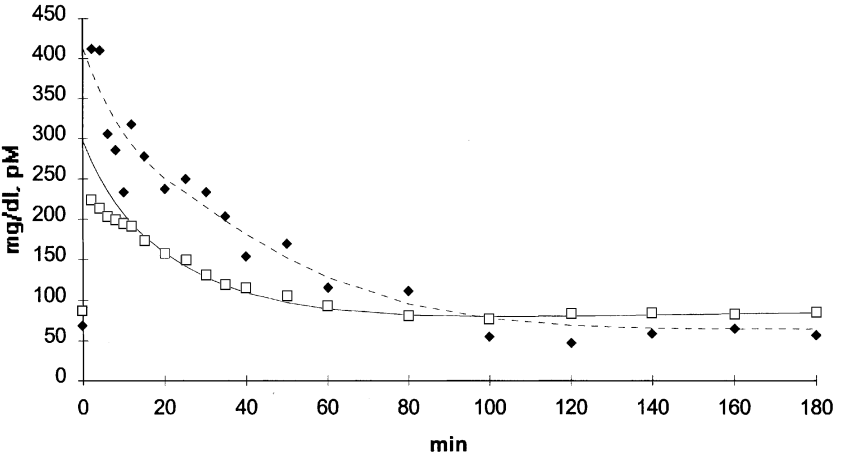

Fig. 2. Blood glucose (data: blank squares; model: continuous line) and plasma insulin (data: solid diamonds; model: dashed line) time courses for subject 6. While glucose seems grossly exponentially decaying, the insulin time course shows appreciable changes in decay rate, but no secondary peak.

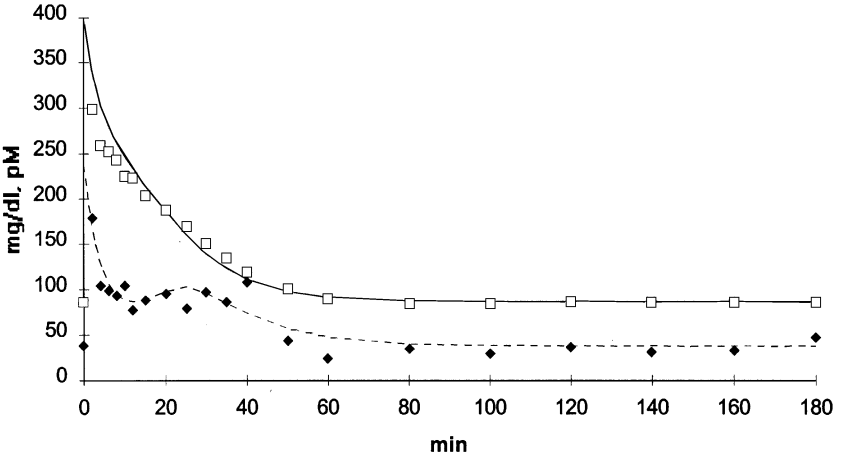

Fig. 3. Blood glucose (data: blank squares; model: continuous line) and plasma insulin (data: solid diamonds; model: dashed line) time courses for subject 7. To an evident secondary peak in insulin plasma concentration, there corresponds a parallel variation in blood glucose decay rate.

In the applied use of the minimal model, the feeling that the most important piece of information is the S_I index may lead physicians to fit only the first part of the minimal model (Eqs. 1, 2), disregarding the second part (Eq. 3), using insulin as the "fixed" input data [18]: using the minimal model in this way avoids formal problems due to

feedback, but it fails to provide information on the pancreatic response to circulating glucose, information which is implicitly contained in the available measured insulin concentration curve. It is to be noted that insufficient interaction between insulin and glucose levels (e.g. in the case of NIDDM or obese patients) makes estimation of the minimal model parameters impossible in a certain number of cases. Taking into account the absolute levels of glucose and insulin reached during the experiment may help: an insulin resistant subject being defined as one whose insulin levels are maintained higher than normal for comparable glucose levels. It seems, in fact, that NIDDM subjects have a higher insulin response, and a more prolonged one, as if the stimulus represented by glucose were higher in them than in normals. Following this line of thought it would seem that it is the second part of the minimal model (Eq. 3) that probably best discriminates this behavior, as if insulin sensitivity were only part of the picture, pancreatic responsiveness being the other part: in other words, estimation of the parameters of (Eq. 3) or of an equivalent formulation of glucose effect on insulin seems needed as well.

Once the necessity of a single global dynamical model of the insulin-glucose system is appreciated, the first likely candidate model to be studied is the one obtained by coupling the three Minimal Model equations (Eqs. 1–3). In the present work, a formal study of the qualitative behavior of this model has been conducted, and three basic results have been proved. The first result (Propositions I.1 and I.2) says that under the stated set of model definitions, allowing baseline glycemia to be greater than pancreatic target glycemia, the model equations give rise to unbounded solutions except, at best, for a boundary case (any small perturbation from which would reinstate the unbounded solutions). The second result (Propositions I.4 and I.5) says that the defining equations as proposed impose that baseline glycemia be smaller than or at most equal to pancreatic target glycemia, otherwise no equilibrium solution can be obtained. The third result (Proposition I.6) poses a qualitative limit to the behavior of the solutions in the case that b_5 is exactly equal to G_b, that is, in this case there cannot be any solutions where glycemia progressively decreases towards the target equilibrium value. If it is considered that, at steady state, basal levels of insulin are observed and that therefore pancreatic activity continues (i.e. the true pancreatic set-point seems in reality to be lower than baseline glycemia), then the physiologic likelihood of the model seems to be somewhat diminished by these results.

If, on one hand, the original minimal model was actually designed to cope just with the three hours after the administration of the glucose

bolus, making infinite-time asymptotic behavior somewhat less important, on the other hand the definition itself of the Insulin Sensitivity index S_I is strictly valid only at infinite time. Moreover, the steady state conditions which the present aggregated model has difficulties with are not only those established many hours after the administration of the glucose bolus, but also those prevailing a few minutes before such administration.

In addition, if the current pancreas model is retained, its nonautonomous form, requiring a definite starting time, makes its application difficult to any experimental set-up different from a theoretically instantaneous IV bolus glucose injection. For all of these reasons, it seems that the system that we could obtain by piecing together the available components of the minimal model should be changed.

It must be noted that the minimal model incorporates some basic ideas that should be kept under consideration in any further work. First of all, the action of the pancreas on peripheral tissue utilization of glucose is not immediate. In the minimal model this delay has been represented as the progressive accumulation of the active hormone in an intermediate compartment (X), and while other formalizations may be preferred, the idea itself is important and should be retained. Secondarily, a delay is also introduced, via the nonautonomous term t in the third equation, on the actual insulin incretion. That a delay is present is apparent from the classically biphasic shape of the insulin concentration curve after a glucose bolus: while first-phase insulin response occurs immediately (indicating the availability of readily released hormone), second-phase insulin response appears over several tens of minutes, indicating either the slow release of the hormone from previously stored reserves (different from those responsible for first-phase insulin release) or the necessity of de-novo synthesis. The form chosen to represent this delay is the reason of many of the analytic difficulties of the aggregated model, and even from a physiologic point of view this simplification, requiring the pancreas to secrete second-phase insulin with linearly increasing response to the glucose stimulus as time progresses, can be improved. However, while it is easy to improve on the description of the pancreatic response to glucose, it is difficult to do so without introducing additional parameters. In fact, the most obvious alternative would be to model pancreatic response as a nonlinear curve with respect to time, attaining asymptotically a maximum of responsiveness for long times. This curve needs, unfortunately, two parameters to be described (the maximum responsiveness to the unit glucose stimulus and the time to half-maximum responsiveness), instead of the single slope parameter in the minimal model. Since the

experiment on which the parameters are estimated consists only of about twenty points for glucose and twenty for insulin, estimating nine parameters instead of eight is a major experimental cost which we would like to avoid, if possible. In fact, if at all possible, we would like to reduce the number of parameters needed to model the experiment to a smaller number than eight.

One possible form of a dynamical model for the glucose-insulin system is that described by Equations (4) and (5). It depends on six free parameters overall and may exhibit a secondary insulin peak. The model admits only one equilibrium point, which represents the resting, basal glucose and insulin values for the subject. The stability of the model around this equilibrium point is assured, and numerical evaluation of its parameters presents no problems, with small coefficients of variation and good overall fitting to the experimental observations. Solutions to this model are positive and bounded.

While no claims are made that the dynamical model presented may be more than a working approximation to a structure which diabetologists and physiologists might consider acceptable, its very existence underscores two basic concepts which we believe ought to be taken into account by any future improved models. First of all, the whole self-regulatory system of insulin and glucose (at least) should be simultaneously considered and can actually be modelled to yield a reasonably close approximation to actual data. Second, the dynamic properties of any suggested model ought to be formally investigated in order to subject to closer scrutiny and meaningful numerical estimation those models which are known structurally to possess desirable overall characteristics, like stability, or positivity of solutions, or boundedness of solutions and the like.

Appendix: Proofs

I. Formal study of the minimal model

We would like to establish some basic results first:

Proposition I.0.

i) $\liminf_{t\to\infty} I(t) \geqq I_b$;

ii) $\liminf_{t\to\infty} X(t) \geqq 0$;

iii) $\limsup_{t\to\infty} G(t) \leqq G_b$.

If, furthermore, $I(0) > I_b$, *then*
iv) $I(t) > I_b \forall\ t \geqq 0$;
v) $X(t) \geqq 0\ \forall\ t \geqq 0$;
vi) *if* $G(T) < G_b$ *for some* $T > 0$, *then* $G(t) < G_b\ \forall\ t > T$.

Proof. These results are easily obtained by standard arguments on differential inequalities, and the proof is skipped.

Proposition I.1. *Suppose* $G_b > p_5$, $\limsup_{t\to\infty} G(t) > p_5$. *Then* $\limsup_{t\to\infty} X(t) = \infty$.

Proof. If $X \to \infty$ there is nothing to show. Let us suppose then that $\liminf_{t\to\infty} X(t)$ finite.

Solve Eq. (3) to obtain

$$I(t) - I_b = p_7 e^{-p_6 t} + p_4 \int_0^t e^{-p_6(t-u)} [G(u) - p_5]^+ u du;$$

solving Eq. (2) and substituting we get

$$X(t) = \int_0^t e^{-p_2(t-u)} p_3 [I(u) - I_b]\, du,$$

or

$$X(t) = p_3 p_7 e^{-p_2 t} \int_0^t e^{(p_2 - p_6)u}\, du + p_3 p_4 \int_0^t e^{-p_2(t-u)} \left(\int_0^u e^{-p_6(u-s)} [G(s) - p_5]^+ s ds \right) du.$$

Now, we have two possible cases, $p_2 = p_6$, or $p_2 \neq p_6$.

Introduce the auxiliary function z, defined as

$$z(t) = \int_0^t e^{(p_2 - p_6)u}\, du = \begin{cases} t, & \text{if } p_2 = p_6 \\ \dfrac{e^{(p_2 - p_6)t} - 1}{p_2 - p_6}, & \text{if } p_2 \neq p_6 \end{cases}$$

and, changing the order of integration in the double integral at right hand-side above we obtain

$$X(t) = p_3 p_7 e^{-p_2 t} z(t) + p_3 p_4 \int_0^t e^{-p_2(t-s)} z(t-s) [G(s) - p_5]^+ s ds.$$

Now, since $X(t) + p_1 > 0$ for all sufficiently large t, the derivative of G is bounded superiorly, and under the assumptions made, $\exists \{t_n\} \subset \mathbb{R}$, $t_n \to \infty$, $h > 0$, $T > 0 \ni \forall n \in \mathbb{N}$, $G(s) \geqq p_5 + h$ for $t_n \leqq s \leqq t_n + T$.

For $t_n \leqq s \leqq t_n + T$, both the first term and the factors of the integrand above are positive quantities. Now, $z(t) \geqq 1$, and we get

$$X(t_n + T) \geqq p_3 p_4 t_n h \int_{t_n}^{t_n + T} e^{-p_2(t_n + T - s)}\, ds,$$

$$X(t_n + T) \geqq p_3 p_4 t_n h \int_{-T}^{0} e^{p_2 s}\, ds$$

and

$$X(t_n + T) \to \infty, \quad \text{as } n \to \infty.$$

Proposition I.2. *Suppose* $\limsup_{t \to \infty} G(t) < p_5$; *then* $G_b \leqq p_5$.

Proof. Suppose $G_b > p_5$. By Eq. (3),

$$\limsup_{t \to \infty} G(t) < p_5 \Rightarrow \frac{dI(t)}{dt} = -p_6[I(t) - I_b] \Rightarrow I(t) \to I_b$$

$$\Rightarrow X(t) \to 0 \Rightarrow G(t) \to G_b\text{: contradiction.}$$

Proposition I.4. *For any value* $p_5 < G_b$ *the system does not admit an equilibrium.*

Proof. Letting $dG/dt = dX/dt = dI/dt = 0$ we can easily see that the only possible equilibrium state is $(G_b, 0, I_b)$. We claim that for $p_5 < G_b$ this is not an equilibrium state, hence that there is no equilibrium. If there were an equilibrium at $(G_b, 0, I_b)$, Eq. (3) would give

$dI/dt = p_4(G_b - p_5) > 0$, a contradiction.

Proposition I.5. *If the subject is considered to be at steady state before the glucose bolus, then* G_b *must be lesser than or equal to* p_5.

Proof. Suppose we consider the subject's glucose-insulin system in the steady state condition preceding the glucose bolus. Then all derivatives in Equations (1), (2) and (3) are zero, $t = 0^-$, i.e. can be considered arbitrarily small preceding the bolus, and $X = 0$ from the initial condition of Eq. (2). It follows from Eq. (2) that $I(0^-) = I_b$ and from Eq. (1) that $G(0^-) = G_b$, as expected. Therefore Eq. (3) would imply that $G_b \leqq p_5$.

Proposition I.6. *Let* $p_3 > 0$, $p_5 = G_b$, $G(0) > G_b$. *Assume* $I(0) > I_b$. *Then* $\exists\ T > 0 \ni G(t) > G_b\ \forall t < T$, $G(T) = G_b$, *and* $G(t) < G_b\ \forall\, t > T$.

Proof. We will first establish the fact that $G(t) \to G_b$ as $t \to \infty$. This is clear if $G(T) < G_b$ for some T, since if $G(t) < G_b$ after some time, eventually $I(t) \to I_b$ and $X(t) \to 0$, so that $G(t) \to G_b$. However, assuming $G(t) > G_b \ \forall \ t > 0$, since from proposition (I.0) $\limsup_{t \to \infty} G(t) \leqq G_b$, then $\lim_{t \to \infty} G(t) = G_b$.

Suppose now that $G(t) > G_b \ \forall \ t > 0$: we want to show that we reach a contradiction, in which case the theorem is proved.

Let us study again the above integral. Since $\int_0^t X(s)G(s)\,ds$ is bounded (following from Eq. (1) by formal integration and using $\int_0^t X(s)G(s)\,ds < G(0) - G(t) \leqq (G(0) - G_b)\,e^{-p_1 t}$), then

$$G_b \int_0^t X(s)\,ds \leqq \int_0^t X(s)G(s)\,ds < +\infty,$$

which means that

$$\int_0^t X(s)\,ds < +\infty.$$

Integrating Eq. (2) we obtain

$$X(t) = X(t) - X(0) = -p_2 \int_0^t X(s)\,ds + p_3 \int_0^t (I(s) - I_b)\,ds \Rightarrow$$

$$X(t) + p_2 \int_0^t X(s)\,ds = p_3 \int_0^t (I(s) - I_b)\,ds,$$

but $I(t) \geqq I_b$, and therefore the integral on the right is positive. Now, $\liminf_{t \to \infty} X(t) = 0$, otherwise X would integrate to infinity, so $\exists \{t_n\} \to +\infty \ni X(t_n) \to 0$ and

$$X(t_n) + p_2 \int_0^{t_n} X(s)\,ds = p_3 \int_0^{t_n} (I(s) - I_b)\,ds,$$

and as $t_n \to \infty$ we have

$$0 + p_2 \int_0^{\infty} X(s)\,ds = p_3 \int_0^{\infty} (I(s) - I_b)\,ds,$$

so that the integral on the right is finite since that on the left is finite. Moreover, letting $t \to \infty$ in the equation

$$X(t) + p_2 \int_0^t X(s)\,ds = p_3 \int_0^t (I(s) - I_b)ds,$$

we have that $X(t) \to 0$ (not only its lim inf does).

We notice in passing that the same result is obtained if p_1 is replaced with a function that tends to zero as t goes to infinity. In the present case, since p_1 is independent of t, $G(t) \to G_b$ at least exponentially:

$$\frac{dG}{dt} \leqq -p_1(G(t) - G_b) \Rightarrow G(t) - G_b \leqq \mathrm{e}^{-p_1 t}(G(0) - G_b),$$

so that with $G(t) > G_b \forall\, t$, $G(t) \to G_b$ at least exponentially. This means that $p_4(G(t)\text{-}G_b)^+ t = p_4(G(t)\text{-}G_b)t$ also goes to zero exponentially, so that from Eq. (3) we may write

$$\frac{dI}{dt} \leqq -p_6[I(t) - I_b] + \delta(t), \quad \text{with } 0 \leqq \delta(t) \leqq C\,\mathrm{e}^{-kt},\ 0 < k < p_1.$$

This differential inequality of course implies that $[I(t) - I_b] \to 0$ at least exponentially as $t \to \infty$.

With the same reasoning, letting X be majored by a function which decreases exponentially we deduce that $X(t) \to 0$ exponentially as $t \to \infty$.

Now, we will try to estimate more closely the rates of convergence of the three functions G, X and I, to evidence a contradiction. For the following of the present proof it is clearer to switch to the notation $u(t) = G(t) - G_b$, and $v(t) = I(t) - I_b$. Notice that in the context of the present proof $u(t) > 0 \forall\, t$; we rewrite therefore the model equations as

$$\frac{du}{dt} = -p_1 u - Xu - XG_b$$

$$\frac{dX}{dt} = -p_2 X + p_3 v$$

$$\frac{dv}{dt} = -p_6 v + tu$$

We integrate the three equations between t and ∞ (knowing that they decrease to zero at least exponentially and are therefore integrable). Integrating, remembering that $u(\infty) = X(\infty) = v(\infty) = 0$, and changing all signs we obtain:

$$u(t) = p_1 \int_t^\infty u(s)\,ds + \int_t^\infty X(s)\,u(s)\,ds + G_b \int_t^\infty X(s)\,ds$$

$$X(t) = p_2 \int_t^\infty X(s)\,ds - p_3 \int_t^\infty v(s)\,ds$$

$$v(t) = p_6 \int_t^\infty v(s)\,ds + \int_t^\infty su(s)\,ds$$

We deduce some relations: from the second model equation we have

$$p_2 \int_t^\infty X(s)\,ds = X(t) + p_3 \int_t^\infty v(s)\,ds,$$

and since all terms on the right-hand side are positive,

$$\int_t^\infty X(s)\,ds \geqq \frac{p_3}{p_2} \int_t^\infty v(s)\,ds.$$

Similarly, from the third equation we get

$$p_6 \int_t^\infty v(s)\,ds \geqq \int_t^\infty su(s)\,ds,$$

but since $s \geqq t$, $su(s) \geqq t\,u(s)$, so

$$\int_t^\infty v(s)\,ds \geqq \frac{t}{p_6} \int_t^\infty u(s)\,ds,$$

and incorporating the inequality above,

$$\int_t^\infty X(s)\,ds \geqq \frac{p_3}{p_2} \frac{t}{p_6} \int_t^\infty u(s)\,ds.$$

From the first integrated model equation we get

$$u(t) \geqq p_1 \int_t^\infty u(s)\,ds + G_b \int_t^\infty X(s)\,ds,$$

and replacing for the integral of X

$$u(t) \geqq \left(p_1 + \frac{p_3}{p_2} \frac{t}{p_6} G_b \right) \int_t^\infty u(s)\,ds.$$

Now let

$$w(t) = \int_t^\infty u(s)\,ds, \qquad a = \frac{p_3 G_b}{p_2 p_6}.$$

We may rewrite the last inequality as

$$\frac{dw}{dt} \leqq -(p_1 + at)w(t) \quad \text{or} \quad \frac{w'(t)}{w(t)} \leqq -(p_1 + at),$$

and integrating we obtain

$$\log\frac{w(t)}{w(0)} \leqq -\int_0^t [p_1 + as]\,ds \quad \text{or} \quad \log\frac{w(t)}{w(0)} \leqq -\left(p_1 t + a\frac{t^2}{2}\right),$$

that is

$$w(t) \leqq w(0)\,\mathrm{e}^{-\left(p_1 t + a\frac{t^2}{2}\right)},$$

which means that $w(t) \to 0$ faster than exponentially, or

$$\int_t^\infty u(s)\,ds \leqq C\mathrm{e}^{-p_1 t - \frac{a}{2}t^2} \Rightarrow \int_t^{2t} u(s)\,ds \leqq C\mathrm{e}^{-p_1 t - \frac{a}{2}t^2}.$$

But u is a decreasing function (for sufficiently large t), hence

$$tu(2t) \leqq \int_t^{2t} u(s)\,ds,$$

and therefore

$$u(2t) \leqq \frac{1}{t} C\mathrm{e}^{-p_1 t - \frac{a}{2}t^2}.$$

Calling $r = 2t$, $h = a/2$, and taking $t > 1$ we can write $u(r) \leqq C_1\,\mathrm{e}^{-hr^2}$, so that we can see u decreases faster than exponentially. Therefore, since

$$u(t) \geqq G_b \int_t^\infty X(s)\,ds,$$

we have that

$$u(t) \geqq G_b \frac{p_3}{p_2} \int_t^\infty v(s)\,ds,$$

so that

$$\int_t^\infty v(s)\,ds \to 0$$

faster than exponential, i.e.,

$$\int_t^\infty v(s)ds \leqq C_2\,\mathrm{e}^{-ht^2}.$$

On the other hand,

$$\frac{dv}{dt} \geqq -p_6 v(t) \Rightarrow v(t) \geqq \mathrm{e}^{-p_6 t} v(0) \Rightarrow \int_t^\infty v(s)\,ds \geqq \frac{v(0)}{b_6} \mathrm{e}^{-p_6 t}.$$

Therefore

$$C_3 \mathrm{e}^{-p_6 t} \leqq \int_t^\infty v(s)\,ds \leqq C_2 \mathrm{e}^{-ht^2}:$$

contradiction.
Therefore it is not possible that $G(t)$ remains above G_b for all times, and at a finite time the solution passes below G_b.

For completeness we also consider the case when $G_b < p_5$. We notice that ($G = G_b$, $X = 0$, $I = I_b$) is an equilibrium point. If we start from any initial data ($G(0)$, 0, $I(0)$), we see that

$$\frac{dI}{dt} \geqq -p_6(I(t) - I_b) \Rightarrow \liminf_{t \to +\infty} (I(t)) \geqq I_b \Rightarrow \liminf_{t \to +\infty} X(t) \geqq 0;$$

$$\frac{dG}{dt} \leqq -[p_1 - \varepsilon]\, G(t) + p_1 G_b; \quad t \geqq T \Rightarrow \limsup_{t \to +\infty} G(t) \leqq G_b.$$

We conclude that there exists a T' such that

$$t \geq T' \Rightarrow G(t) \leqq G_b + \varepsilon < p_5 \Rightarrow \frac{dI}{dt} = -p_6(I(t) - I_b), \quad t \geqq T'$$

which implies that $I(t) \to I_b$, $X(t) \to 0$, $G(t) \to G_b$. In this case, therefore, the behavior of the model is as expected. Further, we remark that we may have both $G(t) > G_b \; \forall\, t$, and $G(t) < G_b$ for some time, depending on the relative magnitude of the coefficients, $p_1 > \min(p_2, p_6)$ with $p_3 > 0$ being a sufficient condition for $G(T) = G_b$ for some T. Notice that a secondary insulin peak can only occur when $G(t) > p_5$.

It is interesting to evaluate whether there exist time limits to the occurrence of the secondary insulin peak. Indeed, the peak may only occur when the second derivative of insulin is negative and its first derivative is zero. Considering that $G(t) > p_5 > G_b$, we may write

$$\begin{aligned}
\frac{d^2 I}{dt^2} &= -p_6 \frac{dI}{dt} + p_4[G(t) - G_b] + p_4 t \frac{dG}{dt} \\
&= p_4[1 - p_1 t]\,[G(t) - G_b] - p_4 t\, X(t)\, G(t) \\
&= -t[p_1 p_4 (G(t) - G_b) + p_4 X(t) G(t)] + p_4[G(t) - G_b]
\end{aligned}$$

So, requiring the second derivative to be negative, we have that the time to the secondary peak, call it t_2, must satisfy the relation

$$t_2 > \frac{[G(t_2) - G_b]}{p_1[G(t_2) - G_b] + X(t_2)G(t_2)} \geqq \frac{1}{p_1 + X(t_2)}.$$

From the second model equation, using the differential inequality with initial data 0, we have that

$$X(t_2) \leqq \max_{0 \leqq t \leqq t_2} \frac{p_3}{p_2}[I(s) - I_b],$$

and since G is exponentially decreasing, we can only have a finite number of peaks. As far as the second one is concerned,

$$X(t_2) \leqq \frac{p_3}{p_2} \max(I(0) - I_b, I(t_2) - I_b),$$

and

$$t_2 \geqq \frac{1}{p_1 + \frac{p_3}{p_2} \max(I(0) - I_b, I(t_2) - I_b)}.$$

But from the third model equation we get, for $0 \leqq t \leqq t_2$,

$$\frac{dI}{dt} - p_6[I(t) - I_b] + p_4[G(0) - G_b]\, t_2,$$

since $G(t)$ is decreasing, and therefore

$$I(t) - I_b \leqq \max\left[I(0) - I_b, \frac{p_4[G(0) - G_b]\, t_2}{p_6} \right],$$

so that

$$t_2 \geqq \frac{1}{p_1 + \frac{p_3}{p_2} \max\left(I(0) - I_b, \frac{p_4[G(0) - G_b]\, t_2}{p_6} \right)},$$

which can be rewritten as

$$t_2 \geqq \min\left(\left[p_1 + \frac{p_3}{p_2}(I(0) - I_b) \right]^{-1}, \left[p_1 + \frac{p_3}{p_2} \frac{p_4[G(0) - G_b]\, t_2}{p_6} \right]^{-1} \right).$$

Solving explicitly for t in the second lower bound, we obtain

$$\frac{p_3 p_4}{p_2 p_6}[G(0) - G_b]\, t_2^2 + p_1 t_2 - 1 \geqq 0.$$

Of the two roots, one is negative and is not applicable, hence

$$t_2 \geqq \frac{-p_1p_2p_6 + \sqrt{p_1^2p_2^2p_6^2 + 4p_2p_3p_4p_6[G(0) - G_b]}}{2p_3p_4[G(0) - G_b]},$$

and we can finally write that the time t_2 to the second peak must satisfy

$$t_2 \geqq \min\left[\left(p_1 + \frac{p_3}{p_2}(I(0) - I_b)\right)^{-1}, \frac{-p_1p_2p_6 + \sqrt{p_1^2p_2^2p_6^2 + 4p_2p_3p_4p_6[G(0) - G_b]}}{2p_3p_4[G(0) - G_b]}\right].$$

II. Stability of the dynamical model

For notational convenience we rewrite the model as:

(M1)

II.1) $$\frac{dG}{dt} = -b_1G(t) - b_4I(t)G(t) + b_7,$$

$$G(t) \equiv G_b \ \forall t \in [-b_5, 0), \quad G(0) = G_b + b_0,$$

II.2) $$\frac{dI}{dt} = -b_2I(t) + \frac{b_6}{b_5}\int_{-b_5}^{0} G(t+s)\,ds, \quad I(0) = I_b + b_3b_0.$$

The initial conditions translate physiologically into the requirement that the subject be at his/her (presumably equilibrium) state (G_b, I_b) for at least b_5 minutes prior to (and excluding) the bolus injection of the glucose load. From this equilibrium state, the concentrations of glucose and insulin are supposed to jump instantaneously to new values determined by the amount of glucose administered and by the corresponding first-phase pancreatic secretion of insulin.

Since we are dealing with a delayed differential equation, the state of the system is properly defined by the present concentration of insulin $I(t)$, together with all present and past concentrations of glucose from time $(t - b_5)$ to the present time t. The past concentrations of glucose may be regarded as given by a piecewise continuous function γ from the specified time interval $[-b_5, 0]$ into the set of admissible glucose values (the positive reals). We will employ the usual notation in the domain of delay-differential equations [13], writing $G_t(s) = G(t + s)$ with $-b_5 \leqq s \leqq 0$.

At equilibrium,

$$\phi^* = (G^*, I^*)^T, \qquad 0 = -b_1 G^* - b_4 G^* I^* + b_7,$$
$$0 = -b_2 I^* + b_6 G^*.$$

We had assumed that (since the subject is assumed at equilibrium before perturbation)

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

therefore

$$\begin{cases} b_4 \dfrac{I_b}{G_b} G^{*2} + b_1 G^* - (b_1 G_b + b_4 G_b I_b) = 0 \\ I^* = I_b \dfrac{G^*}{G_b} \end{cases}$$

and since we require $G^* \geqq 0$, then $\begin{cases} G^* = G_b \\ I^* = I_b \end{cases}$.

There is then only one equilibrium point with positive concentrations, $\phi^* = (G_b, I_b)$.

In order to show stability of the system around the equilibrium point, we can follow one of two approaches: linearize the system around the equilibrium point and study the real parts of the eigenvalues of the resulting linear system [13,15], or show convergence to the equilibrium for every solution by majoring and minoring at infinity. While the first approach is the more usual one, it leads, in our case, to a condition for stability in terms of the parameters on which it is not easy to improve. We will instead demonstrate stability for any set of parameter values following the second approach.

We need to establish beforehand boundedness of the solutions.

Proposition II.3. *The solutions* $\{G(t), I(t)\}$ of M1 *are positive and bounded.*

Proof. By inspection of Eq. (II.2), since G_b, I_b and all b's are positive, $I(t)$ is positive for all times. Hence, by Eq. (II.1), $G(t)$ is positive; further, it cannot exceed $\max(G_b + b_0, b_7/b_1)$. Hence G is bounded. Substituting the bound for G in the integral in Eq. (II.2), we can see that $I(t)$ cannot exceed $\max(I_b + b_0 b_3, b_6 b_7/(b_2 b_1))$, and is bounded.

Proposition II.4. *The time derivatives of the solutions are bounded.*

Proof. Obvious from Proposition II.3 and the form of the derivatives in Equations (4) and (5).

A key idea is the following:

Proposition II.5. *Any sequence of points in phase space along a solution of* M1 *admits a convergent subsequence.*

Proof. May show precompactness coordinate-wise.

For $I(t)$ it is enough to consider that the values of the sequence are reals in a bounded set (by Proposition II.3), close the set with $\{0\}$ and the bound, and use the Heine-Borel property of $\mathbb{R}$.

For G_t: the values of the sequence are functions in C^1 and Propositions II.3 and II.4 imply that the sequence is bounded as a subset of C^1 (since both the norm of the function and the norm of its derivative are bounded). Therefore the conditions of the Arzela-Ascoli theorem hold [24] and the sequence is precompact.

Corollary II.6. *The ω-limit set of the system* M1 *is not empty.*

Definition II.7. *Pick a solution $F(t) = \{G(t), I(t)\}$ of* M1, *and from it a converging subsequence. Denote as $F_0 = \{\eta, \varphi\}$ the point of convergence. Let $F^*(t) = \{G^*(t), I^*(t)\}$ be the solution of M1 starting from the initial condition $F_0 = \{\eta, \varphi\}$.*

We remark that since F_0 is in the ω-limit set, which is positively invariant [25], the solution $F^*(t)$ is defined for every positive real t and F^* can be estended as a solution for negative real t so that F_t^* is in the ω-limit set for every t. Also, we will refer to the result on the approximation of the solutions to the limit solution (Saperstone IV,4) (25) as:

Lemma II.8. *There exists a sequence $\{T_n\} \to \infty \ni G(t + T_n) \to G^*(t)$, $I(t + T_n) \to I^*(t)$ as $T_n \to \infty$.*

Now we have assembled all the necessary machinery and we proceed to prove stability.

Proposition II.9. $\limsup_{t\to\infty} G(t) \leqq b_7/b_1$. *Moreover, if for some $t_0 \geqq 0$ $G(t_0) \leqq b_7/b_1$, then $G(t) < b_7/b_1 \; \forall t > t_0$.*

Proof. Majoring the solution for G we have

$$\frac{dG(t)}{dt} \leqq -b_1 G(t) + b_7 \Rightarrow G(t) \leqq \mathrm{e}^{-b_1 t} G(0) + b_7 \int_0^t \mathrm{e}^{-b_1(t-s)}\, ds$$

$$= \mathrm{e}^{-b_1 t} G(0) + \frac{b_7}{b_1}(1 - \mathrm{e}^{-b_1 t}),$$

so that

$$\limsup_{t\to\infty} G(t) \leqq \frac{b_7}{b_1}.$$

Similarly, applying this inequality for $t > t_0$, the second statement follows.

We note in particular that if $G(0) \leqq b_7/b_1$, $G(t) < b_7/b_1 \; \forall t > 0$.

Corollary II.10. $G^*(t) \leqq \dfrac{b_7}{b_1} \; \forall t.$

Proof. Immediate by Proposition II.9 and Lemma II.8.

Having thus obtained a majoring bound for G^*, for every couple (G^*, I^*) in the ω-limit set, we use it to obtain a majoring bound for I^*:

Let $x = \dfrac{b_6 b_7}{b_1 b_2}$.

Proposition II.11. *$I^*(t) \leqq x$. Moreover, if for some $t_0 \geqq 0 / I(t_0) \leqq x$ and*

$$G(t_0) \leqq \frac{b_7}{b_1}, \quad \textit{then } I(t) < x \;\; \forall t > t_0.$$

Proof.

$$\frac{dI^*}{dt} = -b_2 I^*(t) + \frac{b_6}{b_5} \int_{-b_5}^{t} G^*(s)\, ds \leqq -b_2 I^*(t) + \frac{b_6}{b_5}\left(b_5 \frac{b_7}{b_1}\right) \forall t \in \mathbb{R}.$$

Therefore, for arbitrary $t_0 \leqq t$, knowing that I^* is bounded,

$$I^*(t) \leqq \mathrm{e}^{-b_2(t-t_0)} I^*(t_0) + \int_{t_0}^{t} \mathrm{e}^{-b_2(t-s)} \frac{b_6 b_7}{b_1}\, ds,$$

or

$$I^*(t) \leqq \mathrm{e}^{-b_2(t-t_0)} I^*(t_0) + x(1 - \mathrm{e}^{-b_2(t-t_0)}).$$

Now let $t_0 \to -\infty$ to obtain the first result. For the second statement, use the maxima given in the inequality

$$I(t) \leqq \mathrm{e}^{-b_2(t-t_0)} I(t_0) + x(1 - \mathrm{e}^{-b_2(t-t_0)})$$

obtained in the same way.

A majoring bound on I^* for each (G^*, I^*) in the ω-limit set allows us to derive a minoring bound on G^*:

Proposition II.12. *$G^*(t) \geqq \dfrac{b_7}{b_1 + b_4 x}$. Moreover, if for some $t_0 \geqq 0$ and for all $t > t_0$,*

$$G(t_0) \geqq \frac{b_7}{b_1 + b_4 x} \quad \textit{and} \quad I(t) \leqq x,$$

then $G(t) > \dfrac{b_7}{b_1 + b_4 x} \quad \forall t > t_0.$

Proof.

$$\frac{dG^*}{dt} = -b_1 G^*(t) - b_4 G^*(t) I^*(t) + b_7$$

$$\geqq -b_1 G^*(t) - b_4 x G^*(t) + b_7 \quad \forall t \in \mathbb{R}.$$

Knowing that G^* is bounded, and by the same reasoning as for Proposition II.11, the first statement follows. The second statement follows similarly to II.10 and II.11.

Having minored G^* we can now minor I^*. Let $\sigma = \dfrac{b_1 b_7}{b_1^2 b_2 + b_4 b_6 b_7}$.

Proposition II.13. *$I^*(t) \geqq \sigma$. Moreover, if for some $t_0 \geqq 0$*

$$I(t_0) \geqq b_6 \sigma \quad \textit{and} \quad G(t_0) \geqq b_2 \sigma$$

then

$$I(t) > b_6 \sigma \quad \forall\, t > t_0.$$

Proof.

$$\frac{dI^*}{dt} = -b_2 I^*(t) + \frac{b_6}{b_5} \int_{t-b_5}^{t} G^*(s)\, ds$$

$$\Rightarrow \frac{dI^*}{dt} \geqq -b_2 I^*(t) + \frac{b_6}{b_5} b_5 b_2 \sigma$$

and as for II.11 and for II.12, the stated inequality follows. The second statement follows in the same fashion as II.11.

Having a lower bound for I^*, we can find an upper bound for G^*. Let $\gamma = \dfrac{b_7}{b_1 + b_4 b_6 \sigma}$.

Proposition II.14. *$G^*(t) \leqq \gamma$. Moreover, if for some $t_0 \leqq 0$ and*

$$\forall\, t > t_0 \quad G(t_0) \leqq \gamma \quad \textit{and} \quad I(t) > b_6 \sigma, \quad \textit{then } G(t) < \gamma \quad \forall\, t > t_0.$$

Proof. $dG^*/dt = -b_1 G^*(t) - b_4 I^*(t) G^*(t) + b_7 \leqq -(b_1 + b_4 b_6 \sigma) G^*(t) + b_7$, and as for II.11, the first statement follows. The statement follows in the same fashion as II.12.

At this point, we can see the regularity of the general process: if G^* is bounded above by some α, then I^* is bounded above by α/b_2,

then G^* is bounded below by $b_7/(b_1 + b_4\alpha/b_2)$, then I^* is bounded below by $b_7/(b_2(b_1 + b_4\alpha/b_2))$, then G^* is bounded above by $b_7/(b_1 + b_4 b_7/(b_2(b_1 + b_4\alpha/b_2)))$, and so on. Similarly, if G_0 is bounded above by some α, and $I(0)$ is bounded.

We can build two sequences, m_j and M_j, made up of the successive lower and upper bounds to G^*.

Proposition II.15. *Let* $\{m_j\}$, $\{M_j\}$ *be the sequences respectively of lower and upper bounds to* $G^*(t)$ *obtained by repeated application of Propositions II.*11 *through II.*14, *with* $M_0 = b_7/b_1$, $m_0 = b_7/(b_1 + b_4 b_6 b_7/(b_1 b_2))$. *Then*

i) $M_{j+1} = h(M_j)$, $m_{j+1} = h(m_j)$, with $h(x) = \dfrac{b_7}{b_1 + \dfrac{b_4 b_7}{b_1 b_2 + b_4 x}}$;

ii) *h is monotonically increasing in x*;

iii) $h(M_{j+1}) \leqq h(M_j)$, $h(m_{j+1}) \geqq h(m_j)$;

iv) $\{M_j\}$, $\{m_j\}$ *are bounded.*

Proof.

i) by direct computation;

ii) obvious by inspection;

iii) obvious because of (ii) and since $M_1 < M_0$ and $m_1 > m_0$ by direct computation;

iv) since h monotonically increasing and $M_0 > m_0$, then $M_j > m_j \, \forall j$ by induction. From this fact and from iii, all terms in the two sequences $\{M_j\}$ and $\{m_j\}$ are bounded by M_0 above and by m_0 below.

Now we have two monotonic sequences on R which are bounded, hence converge. A point of convergence for any one of the two sequences must be a fixed point of h, and we study therefore the number of fixed points of h.

Proposition II.16. *h has only one positive fixed point.*

Proof. Let x be a fixed point of h. Then $x = h(x)$ or

$$x = \frac{b_7}{b_1 + \dfrac{b_4 b_7}{b_1 b_2 + b_4 x}} \Rightarrow b_1 b_4 x^2 + b_1^2 b_2 x - b_1 b_2 b_7 = 0.$$

Keeping in mind that all coefficients are positive, the discriminant is positive hence all roots are real; one root is negative, the other positive. Hence the proposition.

Since h only has one positive fixed point, and since both $\{M_j\}$ and $\{m_j\}$ converge to a fixed point of h, then there must be only one value to which both $\{M_j\}$ and $\{m_j\}$ converge, hence they converge to the same value. Since G^* is bounded by the two sequences, it follows that G^* is constant, and all possible points in the ω-limit set share the same constant G_t component. Inserting this one value for $G^*(t)$ in the original system, we obtain only one possible value for I^*. We conclude that the ω-limit set consists exactly of one point. Since the equilibrium point (G_b, I_b) belongs to the ω-limit set, it must be its only point. Therefore, any solution to the original system converges to (G_b, I_b).

Now, in order to demonstrate stability we need that solutions for G and I remain within respective arbitrary intervals $[G_{\min}, G_{\max}]$, $[I_{\min}, I_{\max}]$, when starting from within suitable intervals contained in them. But for each couple of intervals $[G_{\min}, G_{\max}]$, $[I_{\min}, I_{\max}]$, we can find a couple of subintervals

$$[m_j, M_j], \left[\frac{b_6}{b_2}m_j, \frac{b_6}{b_2}M_j\right]$$

for some j such that

$$m_j > G_{\min}, \quad M_j < G_{\max}, \quad \frac{b_6}{b_2}m_j > I_{\min}, \quad \frac{b_6}{b_2}M_j < I_{\max},$$

by repeated applications of statements II.11 through II.14, knowing that the two sequences $\{M_j\}$ and $\{m_j\}$ converge to the same point. Once $G(t_0) \in [m_j, M_j]$ and $I(t_0) \in [\frac{b_6}{b_2}m_j, \frac{b_6}{b_2}M_j]$, the solution remains within those intervals for every $t > t_0$, again because of Propositions II.11–II.14. Hence the system is stable and, because of global convergence, asymptotically stable.

Acknowledgements. Thanks go to Prof. A.V. Greco and to Dr. G. Mingrone (Division of Metabolic Diseases, Università Cattolica, Rome) for having kindly provided the experimental data. The authors wish to thank Prof. Karl Hadeler and an anonymous referee of the Journal of Mathematical Biology for the very thorough and valuable review of the first draft of the manuscript.

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