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Control oriented model of insulin and glucose dynamics in type 1 diabetics

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Abstract The aim of the study was to realize a mathematical model of insulin–glucose relationship in type I diabetes and test its effectiveness for the design of control algorithms in external artificial pancreas. A new mathematical model, divided into glucose and insulin sub-models, was developed from the so-called “minimal model”. The key feature is the representation of insulin sensitivity so as to permit the personalisation of the parameters. Real-time applications are based on an insulin standardised model. Clinical data were used to estimate model parameters. Root mean square error between simulated and real blood glucose profiles (G_{rms}) was used to evaluate system efficacy. Results from parameter estimation and insulin standardisation showed a good capability of the model to identify individual characteristics. Simulation results with a G_{rms} 1.30 mmol/l in the worst case testified the capacity of the model to accurately represent glucose–insulin relationship in type 1 diabetes allowing self tuning in real time.

Keywords Physiological model · External artificial pancreas · Type 1 diabetes · Insulin replacement · Feedback control

1 Introduction

The insulin therapy optimisation for type 1 diabetic patients can significantly improve their quality of life and life expectancy [29]. Therefore, since the early 1970s,

an external device capable of tuning insulin infusion to blood glucose changes was the objective of many studies [1, 21]. Research in this field has always been model-based and has moved from the development of the structure of a model of glucose and insulin dynamics stepping towards model parameter estimation and model personalisation to each single patient's requirements. The models thus represented a platform for the development of insulin control strategies [2] and a tool for their preliminary testing. The Biostator [7] is probably the most important example of bedside extracorporeal artificial pancreas which was developed almost 30 years ago and is still used for research purposes [13, 19, 20]. Its control algorithms were based on intravenous glucose sampling and intravenous insulin infusion. The shift towards the subcutaneous route is still in progress [10, 11, 17, 22, 25, 33, 31], because whilst subcutaneous insulin infusion pumps and rapid acting insulin analogues are a well established reality, stable and reliable subcutaneous glucose sensors that can finely and safely detect blood glucose oscillations and drive insulin feedback are not yet available [6]. In fact, the subcutaneous sensors obtainable from the market [14] have many limitations that are not compatible with the strict requirements of control algorithms. In this context, the study of our mathematical model aimed at realising the basis for a future external wearable artificial pancreas intended as a closed loop system using the subcutaneous route. Model structure and parameter estimation were tailored towards the further development of control algorithms capable of maintaining euglycaemia in type 1 diabetics, adjusting the insulin dose in real time by continuous subcutaneous insulin infusion (CSII). The main objective was the production of a reliable model representing a “virtual patient” that may allow the assessment of different control strategies. But on the other hand, it was clear that the main key to producing an effective insulin infusion control is the capability of the model to represent the single patient (personalisation) following real time changes of the patient's physiological responses.

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Consequently the structure of the model and its estimated parameters must meet the time requirements imposed by this primary real time personalisation task.

The aim of the present study was the realisation of a model complex enough to give a close representation of glucose metabolism pathways but none the less capable of real time parameter estimation in order to achieve fine tuning of safe insulin infusion. The model has been developed on the basis of the so-called *minimal model* (MM), proposed for healthy subjects by R.N. Bergman and C. Cobelli in the late 1970s [5, 8], which is characterized by a bi-linear description of the insulin-dependent glucose metabolism. The model has been modified to represent type 1 diabetic patients under continuous insulin infusion and external inputs such as meals and glucose boles. Its parameters have been estimated and its accuracy validated by simulations run on data collected during a clinical experiment.

2 Materials and methods

2.1 Mathematical model

The feedback control must face the changes in patient sensitivity to exogenous insulin, which occur both daily (the well-known circadian variation of insulin sensitivity) and in the long term. The controller must meet the requirements of *self-tuning*, i.e. its parameters must change as a function of the specific patient response. The key for tuning the controller parameters resides in the model of insulin and glucose dynamics and kinetics included in the controller. Moreover, the same insulin–glucose model represents a tool for investigating a feasible structure of the controller itself, and the dependence of its parameters on the main features of insulin dynamics and insulin-dependent glucose metabolism.

In order to be used as the kernel of the self-tuning controller, the model must fulfil the main requirement of on-line identification on the basis of easily and promptly measurable biological quantities. Two biological variables of interest are easily accessible during the patient's normal life: blood glucose and plasma insulin concentrations. Whilst glucose concentration is easily measured by precise and stable—even if not yet available for implantation—electrochemical sensors, evaluation of

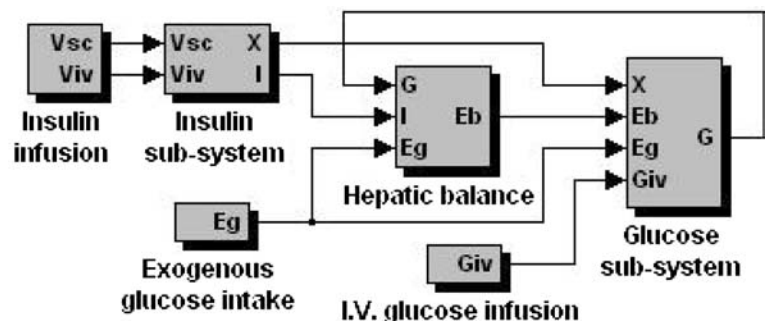
insulin concentration at present requires lengthy laboratory analyses that make it useless for feedback control. Therefore, control action must be performed on the basis of glucose values only, whilst the whole insulin dynamics, from its administration site to the sites of glucose metabolism, hepatic release, etc. must be represented by a model that standardises individual behaviour.

Another important issue is the time required for model identification, because it affects promptness and accuracy of the control action. It increases almost exponentially with the number of estimated parameters which, consequently, should be minimized. On the contrary, a negligible time expenditure, is needed for microprocessor units (even implanted) to perform the large number of algebraic and logical operations required by a fairly complex model. Therefore, the model structure should be as refined as possible, to accurately reproduce the biological process in spite of the reduced number of parameters characterizing the patient's individual response. An adequate set of experimental data is then required to test model accurateness.

The MM describes the glucose metabolism as proportional to the product of glucose and insulin concentrations, thus depending on only one coefficient of “insulin sensitivity” subjected to estimation. MM has been developed and tested on healthy subjects, whose insulin is released by pancreas depending on the actual blood glucose concentration. MM was modified to represent insulin-dependent diabetic patients mainly substituting pancreatic release of endogenous insulin with exogenous insulin administration. Renal clearance, a glucose homeostasis feature peculiar in type 1 diabetes, was included in the glucose balance. The need to simulate food assumption and consequently hepatic balance, led to the introduction of corresponding submodels.

The complete model block diagram (Fig. 1) shows the two main subsystems representing, as in the MM, insulin and glucose dynamics. The insulin block receives the externally administrated insulin, and generates the insulin concentrations acting at the interstitial and hepatic levels. The glucose block receives the glucose contribution from food ingestion, and includes liver uptake and release, insulin-independent metabolism and renal clearance. Moreover, a second interstitial compartment was integrated into the description of glucose

Fig. 1 Simulink model



metabolism following Regitting et al. [23], where insulin-dependent glucose metabolism is still represented by a bi-linear term, as in the MM. A third algebraic block was then added, representing liver glucose uptake and release and connected to the representation of food assumption.

Model equations are described below. Their variables are listed in Table 1, and parameter meaning and values in Table 2.

2.1.1 Insulin sub-model

The original MM of insulin kinetics includes a *plasma compartment* (Eq. 1) and a *remote* one (Eq. 2). We chose to maintain the inherited presence of a “black box” compartment such as the remote one because it gives the opportunity of taking into account some complex phenomena that cause a reduction of the amount of glucose available without increasing the modelling burden. This is the case of the synthesis of proteoglycans which has a diffused biological impact [27, 30, 34] and is responsible for the rate of endothelial glucose uptake. We decided to put this process in the remote “black box” area and to consider the global rate of glucose somehow metabolized while avoiding detailed investigation. The present insulin sub-model is obtained from MM by suppressing therein the input of endogenous insulin, and including the external inputs V_{iv} ($\mu\text{U}/\text{h}$) of exogenous insulin directly administrated in vein and S ($\mu\text{U}/\text{h}$) of insulin coming from subcutaneous administration:

$$\frac{dI}{dt} = \frac{1}{T_{xi}}(-I + K_i(V_{iv} + S)), \quad (1)$$

$$\frac{dX}{dt} = \frac{1}{T_m}(-X + I), \quad (2)$$

where I ($\mu\text{U}/\text{ml}$) is the plasma insulin concentration and X ($\mu\text{U}/\text{ml}$) the equivalent concentration in the remote compartment: only I is measurable. V_{iv} is the rate of appearance in plasma of insulin administrated by continuous infusion or by boles.

The input S , i.e. the rate of appearance in plasma of insulin coming from subcutaneous administration, is generated by a third equation, which has been added to the previous ones to describe a *subcutaneous compartment*:

$$\frac{dS}{dt} = \frac{1}{T_i}(-S + V_{sc}), \quad (3)$$

where V_{sc} ($\mu\text{U}/\text{h}$) is the rate of subcutaneous administration (infusion or bolus) and S ($\mu\text{U}/\text{h}$) the release rate to plasma compartment. Therefore, two insulin inputs are available, subcutaneous V_{sc} and intravenous V_{iv} .

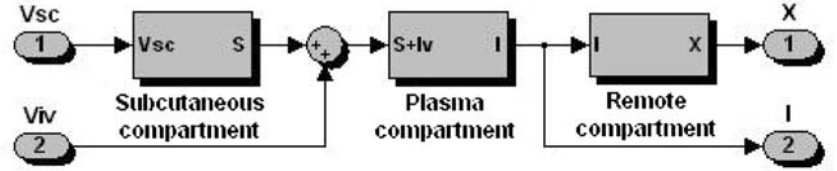
T_{xi} (h), T_m (h) and T_i (h) are time constants related to insulin diffusion through the three compartments. The constant T_i of diffusion in the subcutaneous compartment is not identifiable because the variable X (the equivalent insulin concentration in the remote compartment, $\mu\text{U}/\text{ml}$) is not measurable; it has a value (Table 2) obtained from literature and depending on the insulin type [15, 16, 18]. The constants of diffusion in the plasma and remote compartments, T_{xi} and T_m (whose reciprocals are both dominant poles of the insulin sub-model), as well as the gain constant K_i (ml/h), which is related to the plasma distribution volume, are estimated to determine the insulin model. The whole model is shown in Fig. 2.

Table 1 List of variables

Symbol	Dimensions	Type	Meaning
t	h		Time
V_{iv}	$\mu\text{U}/\text{h}$	Input	Rate of insulin intravenous infusion
V_{sc}	$\mu\text{U}/\text{h}$	Input	Rate of insulin subcutaneous infusion
S	$\mu\text{U}/\text{h}$	State	Insulin flow from the subcutaneous to the plasma compartment
I	$\mu\text{U}/\text{ml}$	State	Plasma insulin concentration
X	$\mu\text{U}/\text{ml}$	State	Equivalent insulin concentration in the remote compartment
G	mmol/l	State, output	Blood glucose concentration
Y	mmol/l	State, alt. output	Glucose concentration in the interstitial compartment
G_{iv}	mmol/h	Input	Rate of intravenous glucose infusion
E_g	mmol/h	State	Rate of exogenous glucose input in blood (intestinal absorption)
E_b	mmol/h	Internal	Rate of endogenous glucose input in blood (hepatic balance)
P_{circ}	–	Internal	Coefficient of the circadian variation of insulin sensitivity
E_r	mmol/h	Internal	Rate of renal glucose clearance
E_m	mmol/h	Internal	Auxiliary variable in the renal clearance description
R_i	mmol/h	Input	Rate of carbohydrate ingestion during meals
A_g	mmol/h	State	Rate of glucose appearance in blood from sugar
A_s	mmol/h	State	Rate of glucose appearance in blood from fast absorption starch (starch100)
A_m	mmol/h	State	Rate of glucose appearance in blood from slow absorption starch (mixed meal)
Q_r	mmol/h	Internal	Rate of hepatic glucose release
Q_c	mmol/h	Internal	Rate of hepatic glucose uptake
E_{rel}	mmol/h	Internal	Auxiliary variable in the hepatic release description
Q_g	mmol/h	Internal	Auxiliary variable in the hepatic uptake description

Table 2 List of parameters

Symbol	Dimensions	Value	Meaning
K_i	ml/h	Estimated	Constant related to the plasma insulin distribution volume
T_{xi}	h	Estimated	Time constant of insulin diffusion in the plasma compartment
T_m	h	Estimated	Time constant of insulin diffusion in the remote compartment
T_i	h	Case dependent	Time constant of insulin diffusion in the subcutaneous compartment (insulin-dependent: regular insulin 1.52, lispro 0.152)
T_{yg}	h	0.194	Time constant of glucose diffusion from blood to interstitial compartment
T_{gy}	h	0.194	Time constant of glucose diffusion from interstitial to blood compartment
K_{is}	ml/ μ U/min	Estimated	Sensitivity coefficient in the insulin-dependent glucose metabolism
V_g	l	9.91	Distribution volume of the blood glucose compartment
K_{yg}	–	0.952	Rate between the distribution volumes of interstitial and blood compartments
t_{ini}	h	Case dependent	Starting time of the experiment
P_c	–	Estimated	Phase of the circadian rhythm
A_c	–	Estimated	Relative amplitude of circadian rhythm
M_c	h	Computed	Time of minimum insulin sensitivity
F_s	–	Case dependent	Starch fraction in the total meal carbohydrate amount
F_m	–	Case dependent	Fraction of mixed meal in the starch absorption model
I_0	μ U/ml	Estimated	Initial value of plasma insulin in the infusion suppression phase
Ins	μ U/ml	Estimated	Root-mean-square error of plasma insulin estimation during the infusion suppression phase
I_{rms}	μ U/ml	Estimated	Root-mean-square error of plasma insulin estimation in the whole experiment
G_{rms}	mmol/l	Estimated	Root-mean-square error of blood glucose estimation in the whole experiment

Fig. 2 Insulin sub-system

2.1.2 Glucose sub-model

The original MM includes only one *blood glucose compartment*. One more *interstitial compartment* was added here, following Regittig et al. [23], where insulin-dependent glucose metabolism takes place according to the bi-linear rule of MM. Five more terms have been inserted in the blood compartment equation (Eq. 4), to refine the overall description: a constant M_i (h) describing the insulin-independent metabolism; two input variables E_g (mmol/h) and E_b (mmol/h), whose generation will be described in the following sections, accounting for the glucose contributions, respectively, from ingested food and from hepatic release; the external input G_{iv} (mmol/h), from intravenous glucose administration (as in intravenous glucose tolerance tests, IVGTT), and, finally, the glucose subtraction E_r (mmol/h) by renal clearance. Therefore, the equations are:

$$\frac{dG}{dt} = -\frac{G}{T_{yg}} + \frac{Y}{T_{gy}} + \frac{1}{V_g} (-M_i + E_g + E_b + G_{iv}) - E_r, \quad (4)$$

$$\frac{dY}{dt} = K_{yg} \left(\frac{G}{T_{yg}} - \frac{Y}{T_{gy}} \right) - K_{is} P_{circ} X Y. \quad (5)$$

G (mmol/h) and Y (mmol/l) are glucose concentrations, both measurable depending on the glucose sensor type and location. The term $G/T_{yg} - Y/T_{gy}$ describes the

exchanges between compartments; the values of V_g (distribution volume of blood glucose compartment, 9.91 l), K_{yg} (rate between the distribution volume 0.952), T_{yg} (=0.194 h) and T_{gy} (=0.194 h) are obtained by a best-fit of the experimental responses of Regittig et al. [23]. The insulin sensitivity coefficient K_{is} (ml/ μ U/h), in Eq. 5, rules the glucose metabolism according to a bi-linear law which, as already stated, is the main assumption of MM. The non-dimensional coefficient P_{circ} allows the description of circadian sensitivity variation, assumed to be sinusoidal:

$$P_{circ} = 1 + A_c \sin \left(\frac{\pi t}{12} + P_c \right). \quad (6)$$

The values of K_{is} and, if necessary, of the amplitude A_c and phase P_c of the circadian rhythm are estimated, and characterize the model of the individual subject. It should be borne in mind that the amplitude A_c has some meaning only if the set of experimental values covers a reasonable length of time, i.e. it includes the times of minimum and maximum sensitivity; in that case, it is bound to 1 as K_{is} cannot become negative; moreover, no circadian variation should be computed if the model is inserted in a self-tuning controller, where K_{is} is evaluated on-line at a frequency much higher than the circadian rhythm: in that case $P_{circ} = 1$. After computing P_c , also the time of minimum insulin sensitivity can be determined off-line:

$$M_c = \left(t_{\text{ini}} + 24 \left(\frac{P_c}{2\pi} - \frac{1}{4} \right) \right)_{\text{mod}24}, \quad (7)$$

where t_{ini} (h) is the starting time of the experiment.

The renal clearance in hyperglycemic conditions is described by a non-linear feedback loop:

$$E_m = 0.117(0.87 + \tanh(0.0045(G - 175)),$$

$$E_r = \begin{cases} E_m & \text{if } E_m \geq 0 \\ 0 & \text{else} \end{cases}. \quad (8)$$

Numerical coefficients have been chosen so as to reproduce the well-known mean course of renal clearance [26]. The whole model is shown in Fig.3.

2.1.3 Food intake

The variable E_g (mmol/h), describing glucose input from meals, is obtained by processing a time dependent input representing the rate of food intake. According to Arleth et al. [3, 4], gut absorption is split in three terms, each one corresponding to a class of carbohydrates with different absorption rates: sugar A_g (mmol/h), fast absorption starch A_s (mmol/h), and slow absorption starch A_m (mmol/h), as derived from mixed meals, where the presence of different nutrients slows down the absorption of carbohydrates:

$$E_g = A_g + A_s + A_m, \quad (9)$$

where A_g , A_s and A_m are obtained by filtering the ingestion rate R_i by appropriate transfer functions, which were obtained by numerical fitting of the results of Arleth et al. [3]:

$$A_g(s) = (1 - F_s) \frac{16.6}{(s + 1.44)(s + 135)} R_i(s), \quad (10)$$

$$A_s(s) = F_s(1 - F_m) \frac{467}{(s + 1.61)(s + 7.20)(s + 7.18)} R_i(s), \quad (11)$$

$$A_m(s) = F_s F_m \frac{75.1}{(s + 0.466)(s + 5.54)(s + 5.86)(s + 6.43)} R_i(s) \quad (12)$$

where F_s is the fraction of starch (and, therefore, $1 - F_s$ the fraction of sugar) and F_m is the fraction of mixed meal in the total amount of starch. An oral glucose tolerance test (OGTT) is easily represented by a meal of pure sugar, i.e. by putting $F_s = 0$.

2.1.4 Hepatic balance

The need to handle food input also requires the representation of liver uptake and release, which play a considerable role in post-prandial glucose homeostasis. A non linear block describes the hepatic balance taking into account glycogenosynthesis, glycogen storage and hepatic release due to glycogenolysis [9, 12, 24] and gluconeogenesis [32], as depending on blood glucose, plasma insulin and gut absorption rate:

$$E_b = Q_r - Q_c, \quad (13)$$

where Q_r (mmol/h) describes the glucose release:

$$Q_r = \begin{cases} E_{\text{rel}} = 840/I - 10 \\ 52.6 & \text{if } E_{\text{rel}} > 52.6 \\ E_{\text{rel}} & \text{if } 52.6 \geq E_{\text{rel}} \geq 0 \\ 0 & \text{else} \end{cases} \quad (14)$$

and Q_c (mmol/h) the uptake:

$$Q_g = \begin{cases} 3.64G - 15 & \text{if } 3.64G - 15 \geq 14 \\ 14 & \text{else} \end{cases} \quad (15)$$

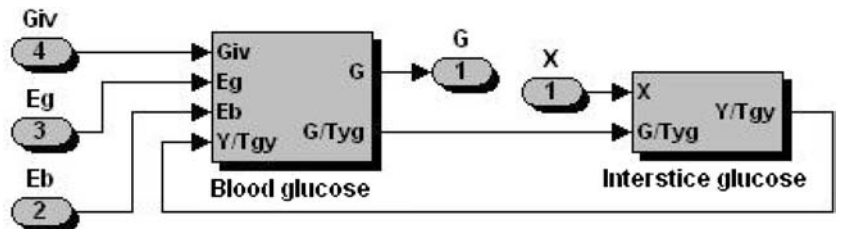
$$Q_c = 0.25E_g + Q_g.$$

The equation structure, and coefficient values, have been obtained by fitting several average responses reported in [9, 12, 24, 32].

2.2 Clinical data set

Parameters T_{xi} , T_m (time constants of insulin diffusion in plasma and remote compartments), K_i (constant related to plasma insulin distribution volume, ml/h), K_{is} (sensitivity coefficient in the insulin-dependent glucose metabolism, ml/ μ U/min) and P_c (phase of circadian rhythm) were estimated on the basis of data collected during a 10 h clinical trial on six type 1 diabetic patients (identified according to the WHO criteria) on continuous subcutaneous insulin infusion therapy (CSII) with lispro insulin. All patients had a diabetes history of at least 5 years, were C-peptide negative, and were treated with CSII for at least 6 months before the study. The study was conducted in the outpatient metabolic research unit of the Department of Internal Medicine (DIMI) of Perugia University (Perugia, Italy). Patients arrived at the Hospital at 7:30 a.m. after an overnight fast; during the following 30 min the insulin infusion rate was kept constant. The experiment included two

Fig. 3 Glucose sub-system



phases, lasting 4 and 6 h, respectively: an *infusion suppression* phase, used for estimation of T_{xi} (time constant of insulin diffusion in plasma compartment, h), and a *recovery* phase. The remaining parameters have been estimated on the whole 10 h trial. At 8:00 a.m., starting time of the suppression phase, the CSII was interrupted; at noon it was re-established, a s.c. bolus was administered according to the level of metabolic deterioration and a standard meal (40 g of carbohydrates) was given. The bolus was followed by the reprise of the usual basal insulin infusion. Insulin infusion rate was changed every 30 min during the recovery phase; blood glucose samples were collected every 30 min, plasma insulin every hour. The study ended at 6.00 p.m. after 6 h of recovery.

2.3 Estimation procedure

2.3.1 Insulin sub-model

In order to estimate T_{xi} (time constants of insulin diffusion in remote compartment, h), an explicit model has been deduced from the implicit one of Eqs. 1 and 2. During the suppression phase, the insulin subsystem is not fed by any input, and, therefore, the output of the plasma insulin block evolves in free response bi-exponentially with the time constants T_i of the subcutaneous compartment ($T_i = 0.152$ h for lispro insulin) and T_{xi} of the plasma compartment. If, as in our case, the infusion rate has been kept constant for at least 15 min before stopping, plasma insulin is given thereafter by:

$$I = I_0 \left(\left(1 + \frac{T_i}{T_{xi}} \right) \exp \left(-\frac{t}{T_{xi}} \right) - \frac{T_i}{T_{xi}} \exp \left(-\frac{t}{T_i} \right) \right), \quad (16)$$

where I_0 is the initial value, which is also estimated. Estimation was performed by minimizing the RMS error Err between computed and experimental values.

The constant K_i , which does not appear in Eq. 16, was then determined by minimizing the RMS error, I_{rms} , between computed and experimental plasma insulin values, on the whole experiment time. Finally, the third time constant T_m of insulin sub-model was estimated, together with the main parameter K_{is} of the glucose sub-model, by minimizing the glucose RMS error, G_{rms} .

2.3.2 Glucose sub-model

The insulin sensitivity coefficient of glucose metabolism K_{is} (ml/ μ U/min), and the circadian variation parameters, A_c and M_c were computed (together with the remaining time constant T_m of the insulin sub-model) on the 10 h glucose response of the model, equipped with the previously computed values of T_{xi} and K_i . Estimated and experimental glucose profiles were compared to assess the quality of estimation, the RMS error G_{rms} between real data and simulated blood glucose values was chosen as quality index.

The model was programmed in Matlab 6 language and Simulink 3 graphic toolbox and simulated on personal computers. All values were estimated by a simplex algorithm (Matlab *Fminsearch* function), which has also been used for the best-fit of literature data on glucose exchanges between compartments, renal clearance, gut absorption and hepatic balance.

3 Results

3.1 Parameter estimation

Three different methods were considered to estimate the unknown model parameters:

1. All parameters were estimated patient by patient, their mean values were then computed (Table 3);
2. A unique value of T_{xi} , (time constant of insulin diffusion in plasma compartment, h), was evaluated for the whole group of patients on the set of the 6 \times 5 insulin values during the suppression phase; then K_i (constant related to the plasma insulin distribution volume, ml/h) and all the remaining parameters were estimated for each individual patient;
3. After evaluating T_{xi} and K_i as in (2), the remaining individual parameters were computed by using the mean value $K_i = 0.0101$ ml/h in place of its individual values (Table 4). Two ways were tested for evaluating T_{xi} in cases (2) and (3): estimating individual values for each patient, as in case (1), and computing the mean $T_{xi} = 3.96$ h of the 6 estimated values; or directly computing $T_{xi} = 1.81$ h on the whole set of 30 experimental values, after normalizing each individual data series with respect to its mean. The second way was preferred as it produced a lower mean value of the root mean square error I_{rms} between experimental and simulated plasma insulin profiles (4.15 ± 1.17 μ U/ml, mean \pm SD, vs. 4.72 ± 1.24 μ U/ml) while estimating K_i , with equal values of the root mean square error G_{rms} between measured and simulated blood glucose profiles.

Method (1), i.e. individual estimation of all parameters, was implemented only for comparison with the remaining ones, as it requires evaluation of insulin concentration case by case and, therefore, is useless for on-line application; moreover, it produces the highest RMS error in the estimation of the glucose parameters ($G_{rms} = 1.03$ mmol/l). Both methods (2) and (3) produced the same glucose error, $G_{rms} = 0.88$ mmol/l, and the third one was preferred as it does not involve case-by-case computation of K_i from the insulin values. Tables 3 and 4 also include phase P_c of circadian rhythm and time M_c of minimum C_s off-line computed by Eq. 7.

3.2 Standard insulin model

As seen above, standard values of T_{xi} (time constant of insulin diffusion in plasma compartment, h) and K_i

Table 3 Parameter estimation case by case

Case	T_{xi}	Err	K_i	I_{rms}	T_m	K_{is}	P_c	M_c	G_{rms}
1	0.43	0.010	0.0047	7.27	0.025	0.0781	4.95	7.08	1.10
2	3.93	0.064	0.0123	2.48	0.696	0.0206	4.92	7.20	1.29
3	3.04	0.084	0.0120	1.80	0.612	0.0360	5.72	5.15	0.90
4	1.41	0.239	0.0125	3.59	1.976	0.0357	5.34	5.60	0.83
5	12.99	0.161	0.0179	3.88	0.231	0.0541	4.90	7.78	1.30
6	1.97	0.070	0.0194	4.05	2.427	0.0242	5.45	5.17	0.41
Mean	3.96	0.105	0.0131	3.85	0.995	0.0426		6.33	1.03
SD	4.59	0.082	0.0052	1.89	0.977	0.0214		1.16	0.34

Table 4 Parameter estimation with fixed T_{xi} and K_i

Case	$T_{xi}=1.81$		$K_i=0.0101$				
	K_i	I_{rms}	T_m	K_{is}	P_c	M_c	G_{rms}
1	0.0046	3.41	1.06	0.0653	4.73	7.92	0.61
2	0.0095	4.11	0.71	0.0237	4.82	7.57	1.28
3	0.0102	2.50	0.61	0.0423	5.80	4.85	0.80
4	0.0097	4.78	2.87	0.0436	5.24	5.97	0.83
5	0.0074	5.92	2.10	0.0659	4.80	8.16	1.17
6	0.0190	4.16	7.37	0.0236	5.42	5.30	0.59
Mean	0.0101	4.15	2.45	0.0441		5.30	0.88
SD	0.0048	1.17	2.56	0.0188		2.80	0.29

(constant related to the plasma insulin distribution volume, ml/h) are required for on-line use of the model, while T_m (time constant of insulin diffusion in remote compartment, h) could be estimated, together with K_{is} (sensitivity coefficient ml/ μ U/min), on the glucose response. Nevertheless, using the mean value $T_m=2.45$ h resulting from Table 4 reduces the burden of on-line computation of two parameters on the basis of the measurement of glucose only, and avoids its loss of accuracy. Therefore, a *standard model* of insulin kinetics has been characterized by the estimated T_{xi} and the mean values of K_i and T_m , i.e. $T_{xi}=1.81$ h, $K_i=0.0101$ ml/h, $T_m=2.45$ h. Such values were used to compute once again the parameters of the glucose sub-model: they are listed in Table 5; the mean insulin sensitivity is $K_{is}=0.0481$ ml/ μ U/h. Parameters of circadian variation have also been computed: Table 5 lists, as Tables 3 and 4, phase P_c as well as the time of minimum insulin sensitivity. Tables 3, 4 and 5 do not list the estimated values of the amplitude A_c as they are meaningless, because the times of minimum and maximum insulin sensitivity are outside the experimental interval (sometimes A_c was larger than 1). Figure 4 shows the glucose courses, compared with the simulated responses, of two cases, no.1 with the lowest G_{rms} (0.66 mmol/l) and no.2 with the highest one (1.33 mmol/l).

4 Discussion and conclusions

The present study proposes a mathematical model of insulin and glucose metabolism in type I diabetes which is, first of all, a very easy-to-handle tool, with person-

alization facilities that allow a quick estimation of its parameters (K_{is} and, if necessary, M_c and A_c) based only on the blood glucose response of the individual patient. The Simulink structure increases the user-friendliness of the model without affecting the computer performance over time.

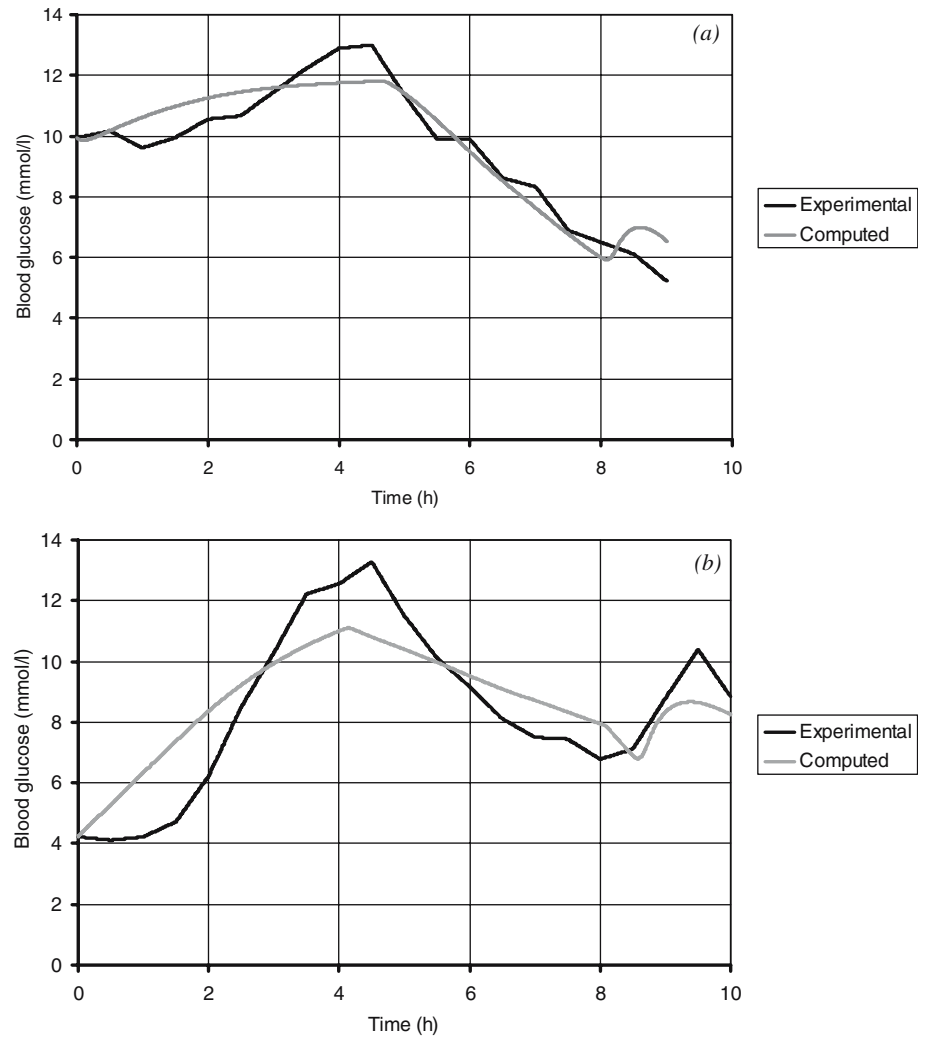
Estimation results The graphs of Fig. 4 show that the model, equipped with the standard insulin parameters, seem capable of producing a satisfactory approximation even in the worst case, where the RMS error G_{rms} between measured and simulated blood glucose profiles is 1.33 mmol/l.

Standard insulin model Comparison between Tables 3 and 5 show that the use of the standard insulin model does not appreciably affect the accuracy of representation, as measured by glucose RMS error G_{rms} : the use of the standard value of T_m , time constant of insulin diffusion in remote insulin compartment, in place of its value estimated case by case, slightly reduces the accuracy ($G_{rms}=0.94$ vs 0.91 mmol/l). The individual values of the insulin sensitivity are rather different, but their mean values are almost indistinguishable ($K_{is}=0.0481 \pm 0.0189$ vs 0.0441 ± 0.0188 ml/ μ U/min, mean \pm SD). The same is valid even for case (1) ($K_{is}=0.0426 \pm 0.0214$ ml/ μ U/min). Therefore, the standard insulin model that makes possible the on-line tuning of the model can be assumed as a mean representation of the insulin kinetics, robust enough to be used for different subjects. As a consequence, it can be adopted for developing self-adaptive control algorithms based on on-line model tuning. This inference is also

Table 5 Parameter estimation, standard insulin model

Case	$T_{xi}=1.81, K_i=0.0101, T_m=2.45$			
	K_{is}	P_c	M_c	G_{rms}
1	0.0706	4.88	7.37	0.66
2	0.0263	4.88	7.37	1.33
3	0.0397	5.68	5.31	1.01
4	0.0395	5.29	5.81	0.84
5	0.0725	4.72	8.48	1.15
6	0.0401	5.40	5.37	0.66
Mean	0.0481		6.62	0.94
SD	0.0189		1.31	0.27

Fig. 4 Time courses of blood glucose. *Solid line* experimental; *dashed* simulated. **a** Case no. 1, $G_{rms} = 0.66$ mmol/l; **b** case no. 2, $G_{rms} = 1.33$ mmol/l



supported by the fact that the mean value of T_m is indistinguishable from the corresponding parameter of MM (1.52 h). In other words, the diffusion through compartments of exogenous insulin in diabetics looks quite similar to that of endogenous insulin in healthy subjects.

Circadian rhythm The values of M_c , time of minimum insulin sensitivity, cannot be assumed as being quantitative evaluations of patients' circadian rhythm, as the experiment time covers only the ascending segment of the sinusoid of Eq. 6; but their mean values, all situated around 6 a.m., are in accordance with the well-known dawn phenomenon [28]. Anyway, they indicate at least a general increase of sensitivity with time, which is more relevant during the first part of the experiment, in accordance with the physiological knowledge.

Virtual patient The set of Eqs. 1, 2, 3, 4, 5 (with $P_{circ} = 1$) and 8, 9, 10, 11, 12, 13, 14 and 15, once equipped with the standard insulin coefficients of

Table 4, and the mean K_{is} value of Table 5, fully characterizes a "virtual patient", which is a useful tool for first approximation theoretical studies on the structure of a feedback controller. Moreover, variation ranges of the controller parameters can be argued to depend on the range of K_{is} values. The control algorithm could be designed on such a virtual patient resulting from the average values of the estimated parameters for the cluster of patients. This operation will represent a further error filter. Introducing the standard values of insulin model also improves the estimation quality by filtering insulin measurement noise.

Closed loop system A closed loop external artificial pancreas would basically constitute: (1) a glucose sensor, (2) a micro-controller equipped with a mathematical algorithm able to control insulin infusion as a function of the measured glucose values, and (3) an insulin infusion pump. At present two major obstacles impair the realization of a fully automated artificial pancreas usable in daily life: implanted sensors cannot yet be considered sufficiently reliable for securing the quality of

continuous glucose monitoring required to close the loop, and studies on control algorithms are still in progress towards satisfactory results. This mathematical model was conceived with the global aim of making a step towards the realization of a closed loop artificial pancreas. From this general purpose spring two immediate and connected objectives. The model must support studies for the development of control algorithms and must be a tool for their testing, either by simulation or during clinical trials. The capability of the model to be effective in the development of control algorithms is related to its accuracy in representing a diabetic subject. The results in terms of the main accuracy index (G_{rms}) seem to ensure a suitable closeness between real and simulated data but it has to be said that only successive studies on algorithms will finally testify that this range provides the adequate accuracy of diabetes pathophysiology representation and the filtering of measurement artefacts.

Conclusion At the state of the art of the present study we can conclude that a useful tool has been developed for the purpose of further simulation studies on glucose feedback control algorithms. The model is an adequate representation of diabetic subjects. Technical characteristics of the model ensure that it can be used during a clinical trial on real patients, where the model can work on-line as a virtual interface, representing a particular patient, towards other devices. The model of a virtual patient then gives the possibility of testing control algorithms before applying them to people, improving the expectations and reducing the risk of experimental activities on real patients.

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