MP Modeling of Glucose-Insulin Interactions in the Intravenous Glucose Tolerance Test

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Summary. The Intra Venous Glucose Tolerance Test (IVGTT) is an experimental procedure in which a challenge bolus of glucose is administered intra-venously and plasma glucose and insulin concentrations are then frequently sampled. An open problem is to construct a model representing simultaneously the entire control system. In the last three decades, several models appeared in the literature. One of the mostly used one is known as the *minimal model*, which has been challenged by the *dynamical model*. However, both the models have not escape from criticisms and drawbacks. In this paper we apply Metabolic P systems theory for developing new physiologically based models of the glucose-insulin system which can be applied to the Intra Venous Glucose Tolerance Test. We considered ten data-sets obtained from literature and for each of them we found an MP model which fits the data and explains the regulations of the dynamics. Finally, further analysis are planned in order to define common patterns which explain, in general, the action of the glucose-insulin control system.

1 Introduction

Glucose is the primary source of energy for body's cells. It is transported from the intestines or liver to body cells via the bloodstream, and is absorbed by the cells with the intervention of the hormone *insulin* produced by the pancreas. Blood glucose concentration is a function of the rate of glucose which enters the bloodstream, the glucose appearance, balanced by the rate of glucose which is removed from the circulation, the glucose disappearance. Normally, in mammals this concentration is tightly regulated as a part of metabolic homeostasis. Indeed, although several exogenous factors, like food intake and physical exercise, affect the blood glucose concentration level, the pancreatic endocrine hormones insulin and glucagon[1] keep this level in the range $70-110$ mg/dl. When the blood glucose concentration level is high, the pancreatic $\beta-$cells release insulin which lowers that concentration by

[1] Others gluco-regulatory hormones are: amylin, GLP-1, glucose-dependent insulinotropic peptide, epinephrine, cortisol, and growth hormone.

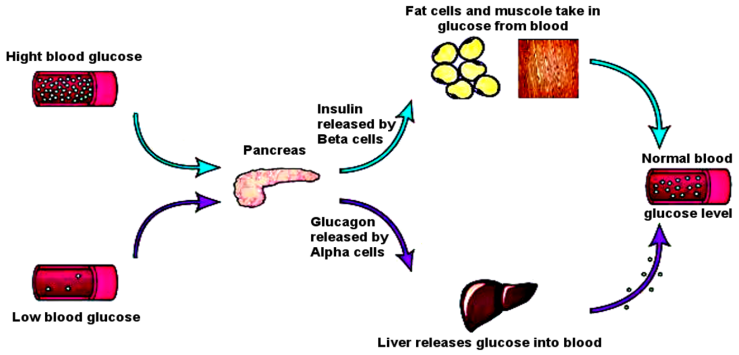


Fig. 1. The glucose homeostasis.

inducing the uptake of the excess glucose by the liver and other cells and by inhibiting hepatic glucose production. On the contrary, when the glucose level is low, the pancreatic $\alpha-$cells release glucagon that results in increasing the blood glucose level by acting on liver cells and causing them to release glucose into the blood[2] (see Figure 1).

If the plasma glucose concentration level is constantly out of the usual range, then we are in presence of blood glucose problems. In particular, when this level is constantly higher than the range upper bound (which is referred to as *hyperglycemia*), we are in presence of *Diabetes*: a dreadfully severe and pervasive illness which concerns a good number of structures in the body. Diabetes is classified into two main categories known as *type I* and *type II*, respectively. Type I diabetes is an illness concerning the pancreas during which the body demolishes its individual β-cells and the pancreas is no longer capable of making insulin. By means of no insulin to stir glucose within the body units, glucose assembles in the bloodstream and the concentrations rise. This category is most widespread among citizens below 30 and frequently appears in early days. The crest beginning is 12-14 years of period. Insulin injections are necessary for the residue of the victims' life. Luckily, Type I Diabetes results in $5-10\%$ of all categories of diabetes [30]. In quick disparity, Type II diabetes asserts the remaining 90%. It typically begins at the age of 35 or older and is particularly widespread in the aged. This type of diabetes may include an amalgamation of troubles. The pancreas is at rest capable to compose insulin, however regularly it does not compose sufficient or/and the units are not capable to utilize the insulin. Contrasting type I diabetes, insulin injections are not at all times essential, since the body is capable of at rest making a little insulin. Every now and then oral prescriptions, habitual work outs and high-quality nourishment are capable to controlling the elevated glucose heights. However, in both the types of diabetes, the illness can lead to several complications like retinopathy, nephropathy, peripheral neuropathy and blindness [6].

[2] We refer the reader to [24] for a deeper description of the processes that underlies the glucose-insulin system.

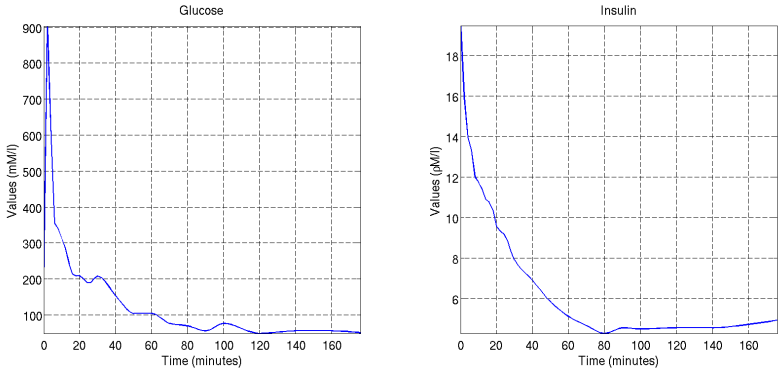


Fig. 2. Plots of a IVGTT data-set starting from the time of the glucose injection. The glucose dynamics is given on the left, while the insulin dynamics is given on the right.

While different regulatory interactions in the pathogenesis of this disease remain to be clarified [9] the number of diabetic patients is increasing [33]. This motivates researches to study the glucose-insulin endocrine regulatory system. In particular, the glucose-insulin system has been the object of repeated, mathematical modelling attempts. The majority of the proposed models were devoted to the study of the glucose-insulin dynamics by considering experimental data obtained by *intravenous glucose tolerance test*, shortly *IVGTT*, and the *oral glucose tolerance test*, shortly *OGTT*. In these models, the insulin-glucose system is assumed to be composed of two linked subsystems modelling the insulin action and the glucose kinetics, respectively. Since the action of insulin is delayed with respect to plasma glucose, the subsystems of insulin action typically includes a delay.

However, considering the limits of the existing mathematical models, a need exists to have reliable mathematical models representing the glucose-insulin system. The mere fact that several models have been proposed [4, 14, 23] shows that mathematical and physiological considerations have to be carefully integrated when attempting to represent the glucose-insulin regulatory mechanism. In particular, in order to model the IGVTT, a reasonably simple model is required. It has to have a few parameters to be estimated and has to have dynamics consistent with physiology and experimental data. Further, the model formulation, while applicable to model the IGVTT, should be logically and easily extensible to model other envisaged experimental procedures.

2 The intravenous glucose tolerance test

The *intravenous glucose tolerance test* focuses on the metabolism of glucose in a period of 3 hours starting from the infusion of a bolus of glucose at time $t = 0$. It is based on the assumption that, in a healthy person, the glucose concentration decreases exponentially with time following the loading dose (see Figure 2). It

has been recommended as a method to asses the use of insulin in order to identify subjects which may be diabetics [26]. This test makes use of an interaction between clearance of insulin from β-cells and the actions of insulin to accelerate glucose disappearance and to inhibit endogenous glucose production.

The IVGTT starts by rapidly, less that 3 minutes, inject into the blood stream of a subject a 33% glucose solution (i.e. $0.33g/Kg$) in order to induce an impulsive increase of the plasma concentrations of glucose and insulin. These concentrations are measured, by taking blood samples, during a period of three hours beginning at injection. The samples are then analysed for glucose and insulin context. In fact, in a healthy person, after this time interval the glucose and insulin plasma concentrations return normal (i.e. they return to their basal levels). Differently, this does not happen in a sick person.

Qualitatively, the plasma glucose level starts at a peak due to the injection, drops to a minimum which is below the basal glucose level, and then gradually returns to the basal level. At the same time, the plasma insulin concentration rapidly rises to a peak which follows the injection, drops to a lower level which is still above the basal insulin level, rises again to a lesser peak, and then gradually drops to the basal level. Depending to the state of the patient, there can be wide variations from this response. The glucose concentration may not drop below the basal level, the first peak of insulin level may have different amplitude, there may be no secondary peak in insulin concentration, or there may be more than two peaks in insulin.

3 Mathematical models of the intravenous glucose tolerance test

A variety of mathematical models, statistical methods and algorithms have been proposed to understand different aspects of diabetes. In this section we briefly review the two mathematical models which had the most important impact in diabetology for modelling the intravenous glucose tolerance test. They have been useful to assess physiological parameters and to study the glucose-insulin interactions. However, they have not escape from criticism and drawbacks.

Although several others models have been proposed [2], the real start of modeling glucose-insulin dynamics is due to the *minimal model* developed in [3, 32]. It has been characterized as the simplest model which is able to describe the glucose metabolism reasonably well by using the smallest set of identifiable and meaningful parameters [3, 27]. Several versions based on the minimal model have been proposed, and the reader can find further information on them in [2, 7]. The minimal model has been formulated by using the following system of differential equations:

$$\begin{aligned}\frac{dG(t)}{dt} &= -\left(p_1 + X(t)\right) G(t) + p_1 G_b \\ \frac{dX(t)}{dt} &= -p_2 X(t) + p_3 \left(I(t) - I_b\right) \\ \frac{dI(t)}{dt} &= p_4 \left(G(t) - p_5\right) t - p_6 \left(I(t) - I_b\right)\end{aligned} \tag{1}$$

where $G(t)$ $[mg/dl]$ and $I(t)$ $[\mu UI/ml]$ are plasma glucose and insulin concentration at time t $[min]$, respectively. $X(t)$ $[min^{-1}]$ is an auxiliary function which models the time delay of the insulin consumption on glucose. G_b and I_b are the subject baseline blood glucose and insulin concentration, while p_i, for $i = 1, 2, \ldots, 6$, are the model's parameters (we refer the reader to [3, 32] for all the details connected to these parameters). The first two equations of (1) represent the glucose disappearance subsystem, while the third one describes the insulin kinetic subsystem. In the second subsystem, the following rule is applied:

$$\left(G(t) - p_5\right) = \begin{cases} \left(G(t) - p_5\right) & \text{if } \; G(t) > p_5 \\ 0 & \text{if } \; G(t) \leq p_5 \end{cases} \tag{2}$$

while the multiplication by t is introduced to approximate the hypothesis that the effect of circulating hyperglicemia on the rate of pancreatic secretion of insulin is proportional both to the attained hyperglicemia and to the time delay from the glucose injection [32].

Although (1) is very useful in physiology research, it has some dynamical and mathematical drawbacks. First, some results produced by this model are not realistic [10]. Second, the glucose-insulin regulatory mechanism is an integrated dynamical system having feedback regulations, while the minimal model is composed of two subsystems. The parameters of these two subsystems are to be separately fitted from the available data, but by following this approach an internal coherency check is omitted. Last, the artificial non-observable variable $X(t)$ is introduced to model the delay in the action of insulin.

To overcome these drawbacks the *dynamical model* has been proposed in [10]:

$$\begin{aligned}\frac{dG(t)}{dt} &= -b_1 G(t) - b_4 I(t) G(t) + b_7 \\ G(t) &\equiv G_b \quad \forall t \in [-b_5, 0) \\ \frac{dI(t)}{dt} &= -b_2 I(t) + \frac{b_6}{b_5} \int_{t-b_5}^{t} G(s) ds.\end{aligned} \tag{3}$$

It is a delay integro-differential equation model which is a more realistic representation of the glucose-insulin dynamics which follows an IVGTT. Although it retains the physiological hypotheses underlying the first equation of (1), non-observable state variables are not introduced. Moreover, the physiological assumption underlying the third equation of (1), that pancreas is able to linearly increase its rate of insulin production with respect to the time, is not taken into account. The dynamical model assumes that the glucose concentration depend *i)* on insulin-independent

net glucose tissue uptake, *ii)* on spontaneous disappearance and *iii)* on constant liver glucose production. The insulin concentration, instead, is assumed to depend *i)* on a spontaneous constant-rate decay, which is due to the insulin catabolism, and *ii)* on pancreatic secretion. In particular, the insulin secretion at time t is assumed to be proportional to the average value in the b_5 minutes which precede t, where b_5 is assumed to lie in a range from 5 to 30.

The term $\frac{b_6}{b_5}\int_{t-b_5}^{t} G(s)ds$ represents the *decaying memory kernel* [8], which is introduced to model the time delay. The physiologic meaning of the delay kernel reflects the pancreas' sensitivity to the blood glucose concentration. At a given time t, the pancreas will produce insulin at a rate proportional to the suitably weighted average of the plasma glucose concentrations in the past.

The dynamical model allows simultaneous estimation of both insulin secretion and glucose uptake parameters. However, it is conceivable that the dynamical model may not be considerable appropriate under all circumstance [25]. This is due to the fact that the IVGTT data related to several subjects could be best fitted by using different delay kernels. Therefore, an extension of (3) is proposed in [25], where a generic weight function ω is introduced in the delay integral kernel modeling the pancreatic response to glucose level. In this way, the second equation of (3) becomes:

$$\frac{dI(t)}{dt} = -b_2 I(t) + b_6 \int_0^{\infty} \omega(s) G(t-s) ds \tag{4}$$

where $\omega(s)$ is assumed to be a non-negative square integrable function on $\mathbb{R}^+ = [0, \infty)$, such that $\int_0^{\infty} \omega(s)ds = 1$ and $\int_0^{\infty} s \cdot \omega(s)ds$ is equal to the average time delay. The idea is that different patients populations show different shapes of the kernel function ω, and then suitable parametrization of such a function could offer the possibility to differentiate between patient populations by means of experimental parameter identification.

Despite the models (3) and (4) solve the drawbacks of the minimal model, they made some assumptions that may not be realistic. The main restriction regards the way used to introduce the delay, for which the justification is only based on a subjective assumption. This limit implies the study of others ways to consider the time delay. To this end, an alternative approach to incorporate the time delay is analyzed in [13], where the authors propose a model which includes (3) and (4) as special cases. In this model, the delay is modelled by using a Michaelis-Menten form, and the effective secretion of insulin at time t is assumed to be regulated by the concentrations of glucose in the b_5 minutes which precede time t instead of the average amount in that period.

4 MP modelling

An important problem of systems biology is the mathematical definition of a dynamical system which explains the observed behaviour of a phenomenon by increasing what is already known about it. An important line of research of biological modelling is aimed at defining new classes of discrete models avoiding some

limitations of classical continuous models based on ordinary differential equations (ODEs). In fact, very often, the evaluation of the kinetic reaction rates is problematic because it may require measurements hardly accessible in living organisms. Moreover, these measurements dramatically alter the context of the investigated processes. In contrast to ODEs, *Metabolic P systems* (MP systems) [18, 16, 17, 15], based on Păun's P systems [28], were introduced for modelling *metabolic systems*.

In MP systems no single instantaneous kinetics are addressed, but rather the variation of the whole system under investigation is considered, at discrete time points, separated by a specified macroscopic interval τ. The dynamics is given along a sequence of steps and, at each step, it is governed by partitioning the matter among reactions which transform it. Metabolic P systems proved to be promising in many contexts and their applicability was tested in many situations where differential models are prohibitive due to the unavailability or the unreliability of the kinetic rates [15, 21, 19, 20, 22, 5].

A Metabolic P system is essentially a multiset grammar where multiset transformations are regulated by functions. Namely, a rule like $a + b \to c$ means that a number u of molecules of kind a and u of kind b are replaced by u molecules of type c. The value of u is the *flux* of the rule application. Assume to consider a system at some time steps $i = 0, 1, 2, \ldots, t$, and consider a substance x that is produced by rules r_1, r_3 and is consumed by rule r_2. If $u_1[i], u_2[i], u_3[i]$ are the fluxes of the rules r_1, r_2, r_3 respectively, in the passage from step i to step $i + 1$, then the variation of substance x is given by:

$$x[i + 1] - x[i] = u_1[i] - u_2[i] + u_3[i].$$

In an MP system it is assumed that in any state the flux of each rule is provided by a function, called *regulator*. Substances, reactions, and regulators (plus parameters which are variables different from substances occurring as arguments of regulators) specify a discrete dynamics at steps indexed in the set $\mathbb{N}$ of natural numbers. Moreover, a *temporal interval* τ, a conventional *mole size* ν, and substances masses are considered, which specify the time and population (discrete) granularities respectively. They are *scale factors* that do not enter directly in the definition of the dynamics of a system, but are essential for interpreting it at a specific physical level of mass and time granularity.

Here we apply an algorithm, called *Log-Gain Stoichiometric Stepwise Regression* (LGSS) [19], to define new MP models which describe the glucose-insulin dynamics in the IVGTT. LGSS represents the most recent solution, in terms of MP systems, of the inverse dynamics problem, that is, of the identification of (discrete) mathematical models exhibiting an observed dynamics and satisfying all the constraints required by the specific knowledge about the modelled phenomenon. The LGSS algorithm combines and extends the log-gain principles developed in the MP system theory [17, 15] with the classical method of Stepwise Regression [12], which is a statistical regression technique based on Least Squares Approximation and a statistical F-test [11]. The method can be correctly applied independently

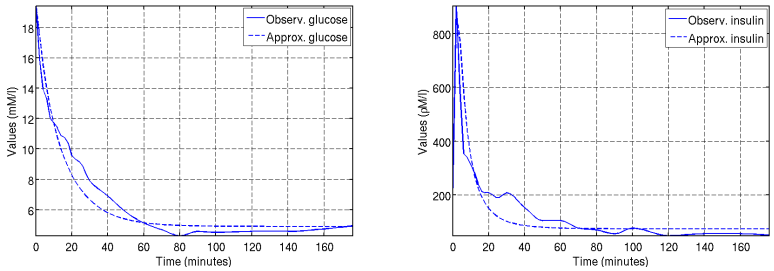


Fig. 3. The dynamics calculated by means of the MP grammar given in Table 1.

from any knowledge about reaction rate kinetics, and can provide, with respect to differential models, different and even simpler mathematical formulations.

The first MP grammar we give is the one of Table 1 which models the dynamics depicted in Figure 2. The model is given by 2 substances (G for the blood glucose level and I for the level of insulin) and 4 rules, the first two related to glucose and the others related to insulin: *i)* r_1: constant release of glucose in the blood, *ii)* r_2: glucose disappearance due to a term which represents the normal decay of glucose (depending on G) and to a term which indicate the action of insulin (depending on both G and I), *iii)* r_3: release of insulin by the pancreas which depends on the blood glucose level, and *iv)* r_4: normal decay of insulin.

The MP grammar is defined for a value of τ of two minutes[3] (which gives the length of the time interval between two consecutive computed step) and allows the calculation of the curves depicted in Figure 3. The dynamics is quite close to the data-set we started from. In fact, the multiple coefficients of determination R^2_G and R^2_I, calculated to estimate the goodness of the approximation for glucose and insulin [1], are equal to 0.94 and 0.87 respectively[4]. The usage of the term G^3 in φ_3, against the possibility of choosing monomials of G with lower degree, expresses the high sensitivity of the pancreas $\beta-$cells for the blood glucose level when they release insulin.

[3] In order to maintain the models as accurate as possible, we adopt here a time unit τ of two minutes because it is the minimal time granularity used in the data-sets we considered.

[4] The coefficient value ranges from 1, when the regression model perfectly fits the data, to 0 according to the goodness of the model fit.

$r_1 : \emptyset \to G$	$\varphi_1 = 0.6$
$r_2 : G \to \emptyset$	$\varphi_2 = 0.12G + 1.6 \cdot 10^{-6} G^2 I$
$r_3 : \emptyset \to I$	$\varphi_3 = 49.9 + 0.1G^3$
$r_4 : I \to \emptyset$	$\varphi_4 = 0.84I$

Table 1. The MP grammar which models the dynamics given in Figure 2 ($\tau = 2$ min).

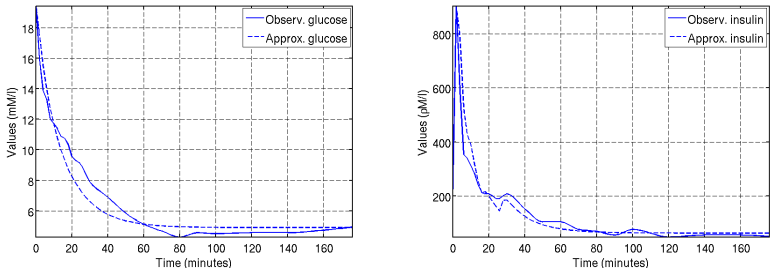


Fig. 4. The dynamics calculated by means of the MP grammar given in Table 2.

The formula of each regulator has been calculated by means of LGSS which selects suitable linear combinations starting from a given set of possible basic functions, called regressors, associated to each rule. Due to the biological meaning given to each reaction, in our analysis we forced: *i)* φ_1 to be a constant, *ii)* φ_2 to be a linear combination of monomials of G and I, *iii)* φ_3 to be a linear combination of monomials of G, and *iv)* φ_4 to depend on I. These assumptions, however, do not take into account the time delays which occur in the insulin release reducing the precision of the models. If we consider the dynamics of Figure 3, for example, the simulation fails to describe the insulin peak which occurs between the 20th and the 40th minute. This missing peak is quite small and for this reason our approximation seems to be enough precise, but if we try to define new MP grammars for other data-sets related to the IVGTT, we reach very soon situations in which the missing peaks are very high causing a dramatical lost of precision.

In the differential models introduced in Section 3, the delay of the insulin release is approached by adding artificial substances or by considering a delay integral kernel. Here, instead, we solve the problem by assuming that φ_3 is given by a linear combinations of monomial of G and of its memories. This permits to point out in a more natural and detailed way the different delays which act in the insulin production. If we indicate by $G^t = (G[i]|0 \leq i \leq t)$ the vector containing the time-series of glucose in a given data-set, we define the time-series G^t_{-m} related to the memory of glucose shifted m steps after as the vector

$$G^t_{-m} = (\underbrace{G_b, G_b, \ldots, G_b}_{m \ \ times}, G[0], G[1], \ldots, G[t-m])$$

where G_b is the basal value of the blood glucose level[5]. Memories are very simple to be managed in MP systems and increase a lot the approximation power of the models as showed in [21], where memories have been applied in the context of periodical function approximation.

The extension of the MP grammar of Table 1 which considers glucose memories is given in Table 2, while the new calculated dynamics is depicted in Figure 4.

[5] Since during the IVGTT the glucose level gradually returns to its basal level, here we assume G_b to be equal to the last value of the considered glucose time-series.

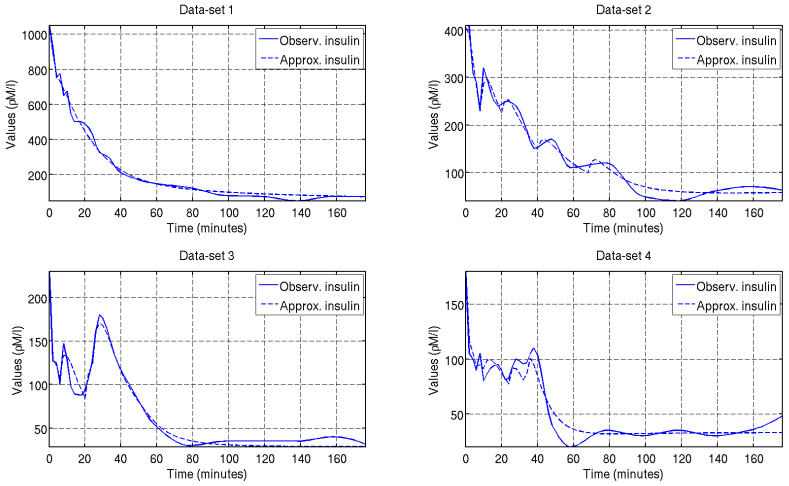
The new model provides a better data fitting for the insulin curve. The multiple coefficient of determination for the insulin is increased from 0.87 to 0.95. Moreover φ_3 gives now an idea of the different phases which act in the blood release of insulin by pointing out their strength (given by the degree of the selected monomials) and their delay (given by the delay of the selected memories).

In our analysis we considered ten different data-sets published in literature and obtained by applying the intravenous glucose tolerance test to ten healthy patients. All subjects have negative family histories for diabetes and other endocrine diseases. During the test, the patients were on no medications and had no current illness. Each test has been performed during the morning after an overnight fast, and for the three days preceding the test each subject followed a diet composed of 55% carbohydrates, 30% fats, and 15% proteins. The curves of the considered data-sets are very different form each other, especially the curve related to the insulin dynamics which exhibits values and peaks of different height and at different delays. In all the cases, however, we found MP models which provide good data fitting (the average of the calculated multiple coefficients of determination for all the models is greater than 0.95 for both glucose and insulin). In Table 3 we provide the regulators related to four of the considered data-sets, and the plotting of the corresponding calculated dynamics for the insulin. The depicted dynamics exhibit examples of all the different scenarios we observed concerning the insulin release in our data-sets. We can have situations where the insulin curve exhibits many peaks which model the different release phases, or we can have dynamics without significant peaks but that are in any case modelled by a delayed insulin secretion (this is the case of data-set 1).

The total number of monomials used to define φ_3 can be changed by acting on the thresholds used by LGSS during the computing of its statistical tests. The models provided here have been defined trying to balance their simplicity with their power of approximation. Each model provides a sort of picture of the metabolism of the subject which have been analysed.

$r_1 : \emptyset \to G$	$\varphi_1 = 0.6$
$r_2 : G \to \emptyset$	$\varphi_2 = 0.12G + 1.6 \cdot 10^{-6} G^2 I$
$r_3 : \emptyset \to I$	$\varphi_3 = 1.5 \cdot 10^{-5} G^6 + 0.25 G^2_{-6} + 0.17 G^2_{-8}$ $+2.65 G_{-16} + 3.6 G_{-26}$
$r_4 : I \to \emptyset$	$\varphi_4 = 0.65 I$

Table 2. The MP grammar which models the dynamics given in Figure 2 ($\tau = 2$ min) enriched with the usage of glucose memories (subscripts give the delay in minutes of each memory).



Data-set	Regulators
1	$\varphi_1 = 0.011$ $\varphi_2 = 6.6 \cdot 10^{-5} GI$ $\varphi_3 = 0.5 G^2_{-4}$ $\varphi_4 = 0.16 I$
2	$\varphi_1 = 0.056$ $\varphi_2 = 5.2 \cdot 10^{-4} I + 8.1 \cdot 10^{-5} GI$ $\varphi_3 = 3.76 \cdot 10^{-6} G^7 + 0.74 G^2_{-8} + 0.02 G^3_{-20} + 0.21 G^2_{-40} + 10^{-4} G^5_{-68}$ $\varphi_4 = 0.49 I$
3	$\varphi_1 = 0.12$ $\varphi_2 = 0.02 G + 1.9 \cdot 10^{-4} GI$ $\varphi_3 = 0.04 G^3_{-2} + 3.3 \cdot 10^{-5} G^6_{-6} + 0.44 G^2_{-20} + 0.04 G^3_{-24}$ $\varphi_4 = 0.5 I$
4	$\varphi_1 = 0.11$ $\varphi_2 = 6.2 \cdot 10^{-4} GI$ $\varphi_3 = 0.1 G^2_{-2} + 0.9 G_{-6} + 1.07 G_{-10} + 2.4 \cdot 10^{-4} G^4_{-24}$ $+5.4 \cdot 10^{-7} G^6_{-32} + 5.3 \cdot 10^{-8} G^7_{-34}$ $\varphi_4 = 0.4 I$

Table 3. MP regulation and the calculated insulin dynamics related to four of the considered data-sets ($\tau = 2$ min).

5 Conclusions and ongoing work

The main goal of this work was to study the possible application of MP systems as an alternative to model the intravenous glucose tolerance test. In Section 2 we briefly described the test, while Section 3 reviewed two mathematical models which had the most important impacts in diabetology and analysed their limits and drawbacks. In Section 4 we proposed the use of Metabolic P systems to model

the IVGTT data-sets by combining some principles of MP systems with statistical techniques to obtain MP models of IVGTT. Our preliminary results and analysis suggest that glucose-insulin metabolism needs a careful evaluation which makes evident different aspects related to different subjects. MP models seem to provide comprehensive tools for discovering personalized glucose-insulin dynamics. Further analysis should permit to characterize the differentiation between subjects by considering physiological parameters such as the height, the weight, the work, the sport activity, and so on. Despite these differences, we are working in order to point out common features in the regulation governing the release of insulin. Our regression approach allows us a quantitative analysis which could highlight results which have been only theorized during the development of the differential models.

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