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

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ABSTRACT

The Intravenous Glucose Tolerance Test is an experimental procedure used to study the glucose-insulin endocrine regulatory system. An open problem is to construct a model representing simultaneously the entire regulative mechanism. In the past three decades, several models have appeared, but they have not escaped criticisms and drawbacks. In this paper, the authors apply the Metabolic P systems theory for developing new physiologically based models of the glucose-insulin system, which can be applied to the IVGTT. Ten datasets obtained from literature were considered and an MP model was found for each, which fits the data and explains the regulations of the dynamics. Finally, each model is analysed to define a common pattern which explains, in general, the action of the glucose-insulin control system.

Keywords: Biomathematical Discrete Modelling, Diabetes, Intravenous Glucose Tolerance Test, Metabolic P Systems, Personalized Glucose-Insulin Dynamics

1. INTRODUCTION

Glucose is the primary source of energy for body 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 glucagon1 keep this level in the range 70 – 110 mg/dl. When the blood glucose concentration level is high, the pancreatic β–cells release insulin which lowers that concentration by 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 α–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 (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, 5−10% of all categories of diabetes, results from autoimmune destruction of β-cells and the pancreas is no longer capable of making insulin. Therefore, daily insulin injections are necessary. Diabetes of type II refers to the remaining 90% and occurs when the pancreas produces insulin but cells fail to use it properly. In both the types of diabetes, the illness can lead to several complications like retinopathy, nephropathy, peripheral neuropathy and blindness. 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 the 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.

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 (Figure 2). It has been recommended as a method to assess the use of insulin in order to identify subjects which may be diabetics (National Diabetes Data Group, 1979). 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 (Boutayeb & Chetouani, 2006; Makroglou, Li, & Kuang, 2006; Mari, 2002) 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 IVGTT, 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 IVGTT, should be
logically and easily extensible to model other envisaged experimental procedures.

2. 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 escaped from criticism and drawbacks.

Although several other models have been proposed (Bergman, Finegood, & Ader, 1985), the real start of modelling glucose-insulin dynamics is due to the minimal model developed in Bergman, Ider, Bowden, and Cobelli (1979) and Toffolo, Bergman, Finegood, Bowden, and Cobelli (1980). 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 (Bergman et al., 1979; Pacini & Bergman, 1986). Several versions based on the minimal model have been proposed, and the reader can find further information on them in Bergman et al. (1985) and Cobelli and Mari (1983). The minimal model has been formulated by using the following system of differential equations:

\[ \frac{dG(t)}{dt} = -\left( p_1 + X(t) \right) G(t) + p_1 G_b \]
\[ \frac{dX(t)}{dt} = -p_2 X(t) + p_3 \left( I(t) - I_b \right) \]
\[ \frac{dI(t)}{dt} = p_4 \left( G(t) - p_5 \right) t - p_6 \left( I(t) - I_b \right) \]

where \( G(t) [\text{mg/dl}] \) and \( I(t) [\mu\text{U/ml}] \) are plasma glucose and insulin concentrations at time \( t [\text{min}] \), respectively, and \( (G(t) - p_5) \) is assumed to be 0 when \( G(t) < p_5 \). \( X(t) [\text{min}^{-1}] \) 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 concentrations, while \( p_i \), for \( i = 1, 2, \ldots, 6 \), are the model parameters (we refer the reader to Bergman et al., 1979; Toffolo et al., 1980 for all the details connected to these parameters).

Although (1) is very useful in physiology research, it is based on some oversimplified mathematical representations. In fact, the artificial unobservable variable \( X(t) \) is introduced to model the delay in the action of insulin. Therefore the dynamical model has been proposed in Gaetano and Arino (2000):
\[
\frac{dG(t)}{dt} = -b_1 G(t) - b_4 I(t)G(t) + b_7
\]
\[
G(t) \equiv G_b \quad \forall t \in [-b_5, 0)
\]
\[
\frac{dI(t)}{dt} = -b_2 I(t) + \frac{b_6}{b_5} \int_{t-b_5}^{t} G(s)ds.
\]

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 depends 1) on insulin-independent net glucose tissue uptake, 2) on spontaneous disappearance and 3) on constant liver glucose production. The insulin concentration, instead, is assumed to depend 1) on a spontaneous constant-rate decay, which is due to the insulin catabolism, and 2) 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 integral term in (2) represents the *decaying memory kernel* (Cushing, 1977), 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 circumstances (Mukhopadhyay, Gaetano, & Arino, 2004). 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 (2) is proposed in Mukhopadhyay et al. (2004), where a generic delay kernel \( \omega(s) \) is introduced in the delay integral kernel modeling the pancreatic response to glucose level. In this way, the second equation of (2) becomes:

\[
\frac{dI(t)}{dt} = -b_2 I(t) + b_6 \int_{0}^{\infty} \omega(s)G(t-s)ds
\]

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 patient populations show different shapes of the kernel function \( \omega \), and then suitable parametrization of such a function could offer the possibility to differentiate between patient populations by means of experimental parameter identification.

An alternative approach for dealing with time delay is analysed in Li, Kuang, and Li (2001), where the authors propose a model which includes (2) and (3) 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.

### 3. 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 re-search 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 liv...
ing organisms. Moreover, these measurements dramatically alter the context of the investigated processes. In contrast to ODEs, Metabolic P systems (MP systems) (Manca, Bianco, & Fontana, 2005; Manca, 2010a, 2009, 2010b), based on Păun’s P systems (Păun, 2002), 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 $\tau$. 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 (Manca, 2010b; Manca & Marchetti, 2010a, 2010b, 2011; Manca, Pagliarini, & Zorzan, 2009; Castellini, Franco, & Pagliarini, 2011).

A Metabolic P system (Manca, 2010a) is essentially a multiset grammar where multiset transformations are regulated by functions. Namely, a rule like $a + b \rightarrow c$ 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 $i + 1$, $i \in \mathbb{N}$, the set of natural numbers, 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 $r_i$ is provided by a state function $\varphi_j$ called regulator of the rule. Substances, reactions, and regulators (plus parameters which are variables different from substances occurring as arguments of regulators) specify the following discrete dynamics ($x[i] | i \in \mathbb{N}$) for any substance $x$, starting from the given value $x[0]$, called EMA (Equational Metabolic Algorithm):

$$x[i + 1] = x[i] + \sum_{j=1}^{m} \alpha_j u_j[i]$$

where $m$ is the number of rules and $\alpha_j$ are the coefficients of fluxes acting on substance $x$. Moreover, a temporal interval $\tau$, a conventional mole size $\nu$, 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. In the following the MP dynamics we will present are computed in MATLAB by applying the EMA formula given in (4).

Here we apply an algorithm, called Log-Gain Stoichiometric Stepwise Regression (LGSS) (Manca & Marchetti, 2011), 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 (Manca, 2009, 2010b) with the classical method of Stepwise Regression (Hocking, 1976), which is a statistical regression technique based on Least Squares Approximation and a statistical F-test (Draper & Smith, 1981). The logic of this algorithm is quite complex because it combines several features for a systematic search procedure in suitable parameter spaces. We refer to the cited paper for details and motivations and to textbooks of statistics (Aczel & Sounderpandian, 2006) for the main statistical concepts (correlation and multiple coefficient of determination) on which our model evaluations are based.

The first MP grammar we give is the one of Table 1 which models the dynamics depicted in
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: 1) \( r_1 : G \rightarrow \emptyset \), constant release of glucose in the blood, 2) \( r_2 : G \rightarrow I \), 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), 3) \( r_3 : \emptyset \rightarrow I \), release of insulin by the pancreas which depends on the blood glucose level, and iv) \( r_4 : I \rightarrow \emptyset \), normal decay of insulin.

The MP grammar is defined for a value of \( \tau \) of two minutes\(^3\) (which gives the length of the time interval between two consecutive computed steps) and allows the calculation of the curves depicted in Figure 2. The dynamics is quite close to the data-set we started from. In fact, the multiple coefficients approximation for glucose and insulin (Aczel & Sounderpondian, 2006), are equal to 0.94 and 0.87 respectively\(^4\). The usage of the term \( G_3 \) in \( \phi_3 \), 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.

The formula of each regulator has been calculated by means of LGSS which selects suitable linear combinations starting from a set of possible basic functions, called regressors, associated to each rule (constants, I, G, \( I^1 \), \( G^2 \), \( GI \), \( I^3 \), \( G^2 I \) and \( GI^2 \)) satisfying some natural constraints due to the biological meaning of the variables. However, the MP grammar given in Table 1 does not take into account the time delays which occur in the insulin release and this reduces the precision of the model. In fact, if we consider the dynamics of Figure 2, 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 dramatic loss of precision.

In the differential models introduced in Section 2, 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 \( \phi_3 \) is given by linear combinations of monomials of G and of its “memories”. This permits pointing 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 \( G_{-m}^t \) related to the memory of glucose shifted \( m \) steps after as the vector

\[
G_{-m}^t = (G_0, G_1, \ldots, G_m, G[0], G[1], \ldots, G[t - m])
\]

where \( G_0 \) 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 Manca and Marchetti (2010b), where memories have been applied in the context of periodical function approximation.

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

<table>
<thead>
<tr>
<th>Rule ( r_i )</th>
<th>Function ( \phi_i )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( r_1 : G \rightarrow \emptyset )</td>
<td>( \phi_1 = 0.6 )</td>
</tr>
<tr>
<td>( r_2 : G \rightarrow I )</td>
<td>( \phi_2 = 0.12G + 1.6 \cdot 10^{-4}G^2I )</td>
</tr>
<tr>
<td>( r_3 : \emptyset \rightarrow I )</td>
<td>( \phi_3 = 49.9 + 0.1GI )</td>
</tr>
<tr>
<td>( r_4 : I \rightarrow \emptyset )</td>
<td>( \phi_4 = 0.84I )</td>
</tr>
</tbody>
</table>
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 3. 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 $\varphi_3$ 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 from 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

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

**Table 2. The MP grammar which models the dynamics given in Figure 3 ($\tau = 2$ min) enriched with the usage of glucose memories (subscripts give the delay in minutes of each memory)**

**Figure 3. The dynamics calculated by means of the MP grammar given in Table 2**
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 $\varphi_t$ 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. This is reflected in the form of the regu-

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

<table>
<thead>
<tr>
<th>Data-set</th>
<th>Regulators</th>
</tr>
</thead>
</table>
| 1        | $\varphi_1 = 0.011$  
           | $\varphi_2 = 6.6 \cdot 10^{-5} GI$  
           | $\varphi_3 = 0.5G_{24}^2$  
           | $\varphi_4 = 0.16I$ |
| 2        | $\varphi_1 = 0.056$  
           | $\varphi_2 = 5.2 \cdot 10^{-4} I + 8.1 \cdot 10^{-5} GI$  
           | $\varphi_3 = 3.76 \cdot 10^{-6} G^7 + 0.74G_{23}^2 + 0.02G_{-20}^3 + 0.21G_{-40}^2 + 10^{-4} G_{-68}^5$  
           | $\varphi_4 = 0.49I$ |
| 3        | $\varphi_1 = 0.12$  
           | $\varphi_2 = 0.02G + 1.9 \cdot 10^{-4} GI$  
           | $\varphi_3 = 0.04G_{-2}^3 + 3.3 \cdot 10^{-3} G_{-3}^6 + 0.44G_{-20}^2 + 0.04G_{-24}^3$  
           | $\varphi_4 = 0.5I$ |
| 4        | $\varphi_1 = 0.11$  
           | $\varphi_2 = 6.2 \cdot 10^{-4} GI$  
           | $\varphi_3 = 0.1G_{-2}^2 + 0.9G_{-6} + 1.07G_{-10} + 2.4 \cdot 10^{-4} G_{-24}^4 + 5.4 \cdot 10^{-7} G_{-32}^5 + 5.3 \cdot 10^{-8} G_{-34}^7$  
           | $\varphi_4 = 0.4I$ |
lators which is different in each model. The form of \( \varphi_3 \) changes according to the different pancreatic response to the increasing of the blood glucose level which we found to be different for each person. This confirms experimentally the idea introduced in the analysis of the dynamical model (Mukhopadhyay et al., 2004) regarding the different forms of the kernel function \( \omega \) in (3). By analysing the correlations between the \( \varphi_3 \) regulators, we observed that some of them are uncorrelated while others exhibit common behaviours. This could be an experimental evidence that patients can be differentiated by considering the behaviour of \( \varphi_3 \), as suggested in Mukhopadhyay et al. (2004) where is indicated the possibility of differentiating between patient populations by considering the form and the parameters of the kernel function.

Even if we found differences in the regulation governing the release of insulin, it is possible to recognize a common pattern. The topmost chart of Figure 4 provides the total number of models which use, in \( \varphi_3 \), a memory with delay given in the x-axis. Here a common logic in the usage of memories becomes evident. Moreover we distinguish two peaks in the first ten minutes which agree with literature. In vivo, insulin secretion is biphasic with a first phase burst in insulin secretion occurring within the first ten minutes and a second phase that is long some hours (Gerich, 2002). The two peaks we observe perfectly fit with the first phase of insulin secretion and recall the first and the second pancreatic peaks introduced in the analysis of the minimal model (Bergman et al., 1979; Toffolo et al., 1980). The strength of the peaks is emphasized by the chart on the bottom of Figure 4 where the memory usage is weighted with respect to the degree of the corresponding monomials used in \( \varphi_3 \). Here we can see that the first peak is twice the second one and that the release of insulin follows an oscillatory pattern according to experimental results, as reported in Gilon, Ravier, Jonas, and Henquin (2002).

4. CONCLUSIONS AND ONGOING WORK

The main goal of this work was to study the possible application of MP systems as an alterna-

Figure 4. Bar charts which give the total number of MP models that use a memory with delay given in the x-axis. In the chart on the bottom the number of models is weighted by considering the degree of the corresponding monomials used in the models.
tive to model the intravenous glucose tolerance test. After having briefly described the test, in Section 2 we reviewed two mathematical models which had the most important impacts in diabetology and we analysed their limits and drawbacks. In Section 3 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 MP models seem to provide comprehensive tools for discovering personalized glucose-insulin dynamics. In fact, our regression approach allows us a quantitative analysis which could highlight results which have been only theorized during the development of the differential models. 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.

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ENDNOTES

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

2 We refer the reader to Martini (2008) for a deeper description of the processes that underlies the glucose-insulin system.

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

4 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.

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Luca Marchetti, graduated in Computer Science, is now PhD student in Computer Science under the guide of Vincenzo Manca and works as research associate at the "Computational BioMedical Center" (CBMC) of the University of Verona. His research interests are mainly focused on Systems Biology, Natural Computing and, more specifically, on the developing of new techniques for modelling in silico natural phenomena by means of Metabolic P systems (MP systems). In the last year he defined, in collaboration with his mentor Vincenzo Manca, the Log-Gain Stoichiometric Stepwise regression algorithm (LGSS) which represents the most recent solution, in terms of MP systems, of the inverse dynamics problem, that is, the problem of identifying (discrete) mathematical models exhibiting an observed dynamics and satisfying all the constraints required by the specific knowledge about the modelled phenomenon. He is co-author of scientific papers published in journals, volumes, and conference proceedings.

Roberto Pagliarini graduated in Computer Science and earned his PhD in Computer Science at the University of Verona, where he is currently a post-doc research associate. He visited for eight mounts the Bioinformatic Group at the Cranfield University (UK). His research interests focus on Systems Biology, Natural Computing, and modelling of natural phenomena by means of Membrane Computing. In particular he investigates the possibility of obtaining efficient and systematic methods for defining membrane models from experimental data of given processes. Along this direction, he collaborated with the biochemistry and vegetal physiology group at Biotechnological Department of Verona University, in order to investigate computational models for crucial events related to photosynthetic organisms. Moreover, he is studying the possibility of inferring causality networks among species by developing and integrating specific statistical indexes. He is co-author of scientific papers published in journals, volumes, and conference proceedings.