A NEW GLUCOSE REGULATION SYSTEM MODEL
Carlos E. Valero, Gustavo Sanchez
Department of Processes and Systems, Simón Bolívar University
Caracas Venezuela
cevalero@usb.ve; gsanchez@usb.ve

ABSTRACT
The aim of this work was to develop a new mathematical model describing the human glucose regulation system, as an important step in order to design more efficient Diabetes Mellitus treatments. The model was developed in Scilab, which is a free software, in order to make it freely testable. According to measured error indexes, the new model fits better real clinical data and is more simple than others previously proposed.

KEY WORDS
Diabetes, glucose model, mathematical and biological models.

1. Introduction

Diabetes Mellitus (DM) is a metabolic disease in which a person has constantly high blood sugar level. It is estimated that the number of diabetes patients worldwide will reach 380 million by 2025 [1]

The glucose regulation system has different mechanisms to keep the body in homeostasis, ie, to maintain normal blood glucose (80mg/dl - 100mg/dL). When blood glucose falls below 80mg/dl, the islets of Langerhans located in the pancreas, measured the activity and release of glucagon proportionally by alpha cells; while increasing the production of this hormone and decreases production and release of insulin from beta cells. Moreover, thanks to the release of glucagon, promotes the phosphorylation of glycogen and gluconeogenesis, therefore glucose levels rise. In the second case (as higher blood glucose 100mg/dL), beta cells increase the release of insulin and insulin production, while alpha cells antagonistically reducing both the production and the release of glucagon. Also in the liver glycogen synthesis promoted by insulin, as well as insulin-dependent tissues absorb glucose from the blood, as does the nervous system in both cases (high or low blood glucose) and is also known as independent insulin tissue. And so decreases the glycemic of a subject. A simplified scheme of this system can be seen in Figure 1.

There are two main types of DM. Type 1 results from a condition in which cells fail to use insulin properly, previously referred to as Non Insulin-Dependent Diabetes Mellitus (NIDDM).

2 results from a condition in which cells fail to use insulin properly, previously referred to as Non Insulin-Dependent Diabetes Mellitus (NIDDM).

The aim of the work described in this paper was to develop a mathematical model describing the glucose regulatory system, as an important step in order to design more efficient DM treatments.

Since 1970, many models have been developed to better understand this system. One of the most cited is the so-called “minimal model” [2] widely used in physiological research to estimate Glucose Effectiveness (SG) and Insulin Sensitivity (SI) from intravenous glucose tolerance tests [3]. This minimal model is described by only three variables, three non-linear differential equations and eight parameters.

After this seminal work, the focus has been put on improving the minimal model by adding or modifying different terms, in order to better fit measured data and explain observed phenomena.

As an example, consider small-amplitude insulin pulses that occur every 10-15 min in monkeys, dogs, and humans. These small rapid oscillations are superimposed on slower larger amplitude oscillations that occur approximately every 120 min. In [4] the authors try to determine whether these slow oscillations could reflect the dynamic properties of the insulin-glucose regulation or whether it is necessary to postulate the existence of an ultradian pancreatic pacemaker to account for their occurrence. A mathematical model of the two major negative feedback loops between insulin and glucose production was developed.

In [5] proposed a simplified model based on the interactions between the liver and pancreas through the hormones insulin / glucagon on phosphorylation and glycogen synthesis in the liver. This model is corroborated by the authors' using clinical data taking by [6].

In this paper a new model is proposed, developed in Scilab(Xcos), which better fits real clinical data and is better describe the real system, trying explain the
production y release of insulin inside of islets of langerhans.

The organisation of the paper is as follows: Section 2 contains the description of the proposed model. Numerical results and discussion are presented in Section 3. Finally, conclusions are drawn in Section 4.

2. Mathematical model

The glucose regulation model proposed in this paper is depicted in figure 1. It could be split in four sub-systems which will be described next.

2.1 Insulin production

Beta cells are those responsible for the production and release of insulin by the islets of Langerhans located in the pancreas. This rate of production and release, is directly dependent on blood glucose levels. Insulin release of this microsystem is the inflow of it into the plasma, while the production will relate to the amount of the protein in vesicles within the cell. On other hand, the maximum rate of insulin production and release is strictly dependent limitations assembly having beta cells (size and resources, generally). For that reason, this model was based on a logistic model of population, where the growth rate or production as well as to decrease or release of insulin is regulated by blood glucose concentrations.

From this hypothesis is developed the following equations:

\[
\frac{dI_i(t)}{dt} = K_1(g)I_i(t) - K_2(g)I_i(t) - K_3I_i^2(t)
\]

where:

\(I_i\) ≡ Insulin Concentration in the set of beta cell, locate in Islets of Langerhans

\(g\) ≡ Blood Glucose concentration

\(K_1, K_2\) ≡ Insulin production and releasing rates, with

\[
K_j(g) = \frac{Rm_j}{1 + b_1j e^{(a_2j(c_j - g))}} \quad \text{for} \quad j = 1, 2
\]

\(Rm_j\) ≡ Max. production and releasing rates

\(a_2j, b_1j\) ≡ Growing rates

\(c_1\) ≡ Glucose reference value
To the best of our knowledge equation (1), in that exact form, has not been previously proposed. This section of the model has been modeled by authors such as [2], [5], [7], using the model of [8] which is determined by the structure of $K_j(g)$, which in itself alone can not describe the internal mechanism in the production and release of insulin out of the bloodstream.

2.2 Insulin and glucagon transition subsystem

To account for the transition delay between plasma insulin and remote cellular insulin the following model will be used:

$$\frac{ds_j^p}{dt} = -k_{j,1} s_j^p (t - t_0) - k_{j,2} s_j^p (t - t_1) + u_j$$  \hspace{1cm} \text{for } j = 1, 2 \hspace{1cm} (3)$$

$$u_1(g) = \frac{Gm}{1 + b_1 e^{(a_1 (g - 1000))}}$$  \hspace{1cm} (4)$$

$$u_2(t, g) = K_2(g) l_t (t)$$  \hspace{1cm} (5)$$

where

$s_j^p \equiv \text{Glucagon concentration in plasma}$

$s_j^i \equiv \text{Insulin concentration in plasma}$

$k_{j,1} \equiv \text{Transitional rate constants}$

$k_{j,2} \equiv \text{Degradation rate constants}$

$u_j \equiv \text{Glucagon and insulin infusion rates}$

$Gm \equiv \text{Max. glucagon infusion rate}$

$a_1, b_1 \equiv \text{Growing rates}$

Note that in equation (3) index $j = 1$ stands for glucagon and $j = 2$ stands for insulin. In this sub-system $t_0, t_1$ are new time constants introduced in this work to account for the biological delay observed in the insulin and glucagon transition sub-system. This model is a modification of [5] and [4]. Furthermore, one approximation of [9].

2.3 Insulin and glucagon receptor subsystem

Considering the insulin and glucagon receptor as a closed subsystem (the synthesis equals the degradation) we have the following equations:

$$\frac{ds_j}{dt} = -k_{j,1} s_j (R_j^0 - r_j) - k_{j,2} s_j + \frac{k_{j,1}^p s_j^p V_p}{V}$$  \hspace{1cm} (6)$$

$$\frac{dr_j}{dt} = k_{j,1}^r s_j^r (R_j^0 - r_j) - k_{j,2}^r r_j$$  \hspace{1cm} (7)$$

where

$s_1, s_2 \equiv \text{intracellular glucagon and insulin}$

$r_1, r_2 \equiv \text{glucagon and insulin-bound receptors}$

$R_j^0, R_j^r \equiv \text{the total concentrations of receptors}$

$k_{j,1}^r, k_{j,2}^r \equiv \text{association rates for glucagon and insulin to bind their receptors}$

$k_{j,2}^r, k_{j,2}^r \equiv \text{degradation rates for glucagon and insulin}$

$k_{j,1}^r, k_{j,2}^r \equiv \text{inactivation rates}$

$V_p \equiv \text{plasma insulin volume}$

$V \equiv \text{cellular insulin volume}$

2.4 Glucose production and utilization subsystem

Again following reference [7] it is assumed plasma glucose has two sources: endogenous hepatic glucose and exogenous glucose taken from food. The Michaelis–Menten equation will be used to model the conversion between glucose and glycogen. This results in the following equations:

$$\frac{dg_1}{dt} = \frac{k_1 r_2}{1 + k_2 r_1 K_m^g + g} V_{max}^g + g$$

$$\frac{V_{max}^g g_1}{K_m^g + g} - f_1(g) - f_2(g) f_3(s_2) + \frac{g}{g_{in}} \hspace{1cm} (10)$$

$$\frac{dg}{dt} = \frac{k_1 r_2}{1 + k_2 r_1 K_m^g + g} V_{max}^g + g$$

$$\frac{V_{max}^g g_1}{K_m^g + g} - f_1(g) - f_2(g) f_3(s_2) + \frac{g}{g_{in}} \hspace{1cm} (11)$$

$$\frac{dg}{dt} = \frac{1 - e^{-\frac{g}{C_2}}}{C_2} \hspace{1cm} (12)$$

$$f_3(s_2) = U_0 + \frac{(U_m - U_0) S_2 \beta}{1 + \left(\frac{S_2}{C_4}\right)^\beta} \hspace{1cm} (13)$$

where

$g_1 \equiv \text{Glycogen concentration}$

$V_{max}^{gs}, V_{max}^{gp} \equiv \text{max velocity of glycogen phosphorylase and glycogen synthase}$
$K_m^{G_s}, K_m^{GP}$ \equiv$ Michaelis–Menten constants

$G_{in}$ \equiv exogenous glucose input rate from food

$U_b, C_2, C_3, U_d, U_m, C_a,$ and $\beta \equiv$ are all positive constants

3. Numerical results and discussion

In this section the results of simulations based on the proposed model will be presented. The package SCILAB (Xcos) was used in order to generate a model which could be freely tested.

The results will be compared both against real clinical data [6] and again results obtained by [5]. Three different error indexes will be used: RMSE (Root Mean Square Error), MAE (Mean Absolute Error) and NMAE (Normalized Mean Error), given by:

$$RMSE = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (x_i - x_{obs})^2}$$  \hspace{1cm} (13)

$$MAE = \frac{1}{N} \sum_{i=1}^{N} |x_i - x_{obs}|$$  \hspace{1cm} (14)

$$NMAE = \frac{\sum_{i=1}^{N} |x_i - x_{obs}|}{x_{obs}}$$  \hspace{1cm} (15)

where

$x_i \equiv$ Data generated by simulation

$x_{obs} \equiv$ Real clinical data

To calculate the numerical solution of this model, we need to find so many parameters, but in the most of cases, we used de values of [5]. However, for the first subsystem (insulin production); we estimate the values with the physiological data found in [10]. We used the variation of some parameters and we used those where the MAE is lower. And that result in: $K_5 = 119.2/87.5$, $Rm_1 = 120$, $Rm_2 = 0.8$, $a_{21} = 1/350$, $a_{22} = 1/800$, $G_1 = 1900$, $G_2 = 1800$, $b_1 = 0.6$ and finally $b_{13} = 0.6$. So too, are made variations of the delays in the model and discuss the results, and we got the $t_0 = 1/50$, $t_1 = 6$, however. We can watch the variation in the figure 4.

Tables 1 and 2 present values and a brief description of each model parameter (35 in total). They were all taken from reference [5].
Figure 3 presents the dynamics of blood glucose obtained by three different sources: the proposed new model (in black), the model [5] proposed by Liu et al (2008) in green and real clinical data in red. It is possible to appreciate that the new model fits better real data, starting from time 140s.

This observation is confirmed by computation of error indexes, as shown in Table 3 (for glucose signal) and 4 (for insulin signal). Note the new model achieves better values than reference [5].

4. Conclusion

In this paper a new glucose regulation system model was proposed which fits better real data when compared to another well-known model previously proposed. This is probably due to an improvement in the biological approach of the new model: e.g the hypothesis related to internal insulin production through a time dependent logistic model and new delays included in equation (4) to account for the biological delay observed in the insulin and glucagon transition sub-system. This approach could be extended to glucagon modelling to improve the simulated response.

References


