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Blood Glucose Control Using Differential Equations Systems for Patients with Diabetes Type 1

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Abstract
Diabetes has become a real pandemic of this century, with an increasing prevalence and incidence in all countries, be them poor, developing or prosperous. Medium and long term epidemiological estimations are disturbing due to the alarming increase of the diabetic population which, in 2030, is estimated to reach 360 million people. In Romania, the incidence of diabetes is 11.6% among adult population between 20 and 79 years old and 3% in case of children aged 0 to14 years. The mathematical model presented refers mainly to the dynamic of glucose and insulin. The analysis was made on both healthy subjects and on various types of patients diagnosed with diabetes. The data used in this study were collected from subjects diagnosed with type 1 diabetes, using the FreeStyle Libre glycemic sensor. We took into consideration the daily glycemic means during a period of 15 days to observe the variability of glucose in the blood in relation to the quantity of insulin administered. The entry data, based on which the statistical study was performed, were collected from diabetic patients. They adapted their insulin doses depending on the physical activity and the food quantity. The graphic representations showed that insulin absorption is a complex process influenced by many factors, including the type of insulin, the injected volume, concentration, place of injection and blood flow in the tissues.

Keywords: Glucose;Insulin;Differential Systems;Diabets

Introduction
Type 1 diabetes is currently considered an autoimmune condition of multifactor etiology, caused by the interaction of several genetic and environment factors whose consequence is the progressive destruction of beta-pancreatic cells and finally the absolute endogenous deficit. Although now the transmission of a genetic predisposition for type 1 diabetes is generally accepted, it hasn't proved to be, in Mendelian terms, neither dominant nor recessive (Bergman: 2002). It is assumed that it is conditioned by a genetic combination (probably the localization in the HLA complex) with a high penetrant that influences other loci on other chromosomes, with an additive effect.
Type 1 diabetes sets in under the age of 40, with an "incidence peak" during puberty. It was assessed however that almost 1 of 10 patients, with diabetes setting in after the age of 65, have type 1 diabetes and that almost 1 of 5 diabetics with clinical features of type 2 diabetes have the immunological markers of type 1 diabetes, the autoimmune process of beta cellular distraction being slower, however (Kalergis: 2005).
The debut symptomatology of type 1 diabetes may include muscular cramps, constipation, sight disorders as well as cutaneous-mucous candidiases and pyoderma. Glycemia and glycosuria usually have clearly higher values and the presence of evident ketonuria confirms, most of the times, the diagnosis of type 1 diabetes (Sundell & Knuuti: 2003).
Considering the rising incidence of the disease, the high mortality generated but especially the serious deterioration of the patient's well-being in the medium and advanced stages, as well as the social and familial impact, the state leaders at a European and world level declared diabetes as a condition with a major impact, a constitutive part in the evaluation and quantification of the national standard of life quality and granted major financial and human resources for the research of the pathogenic mechanisms of the disease, for the quantification

of the risk factors and proper stage identification of the disease – all these for the purpose of developing and improving adequate therapeutic approaches (Nucci &, Cobelli: 2000).

The target of the antidiabetic treatment is to maintain the glycemia values as close as possible to the normal, to reduce the development of cardiovascular, retina and peripheral nervous system complications. Glucose is continuously and practically irreversible combined with hemoglobin along the lifecycle of erythrocytes (120 days); therefore, the level of glycosylate hemoglobin is in proportion to the mean level of plasmatic glucose during the last 6-12 weeks. The risk of nephropathy and diabetic retinopathy increases following an improper metabolic control.

Materials and methods

This paper introduces a new approach with regard to the regulation of the glucose level in patients with diabetes. The model takes into consideration all the plasmatic concentration of glucose, the concentration of generalized insulin and the plasmatic concentration of insulin. The mathematical model shown refers, mainly, to the dynamic of glucose and insulin (Boutayeb & Chetouani: 2006). Most models are based on the glucose-insulin distribution to explain the interaction between the two. The mathematical model presented in the pages below is used for the diagnosis of diabetes, a condition characterized by a very high concentration of glucose in the blood. In this test, a high dose of glucose is administered to the patient, who ate overnight. In the 3-5 hours several measurements of the glucose concentration in the blood are made.

The purpose of this test was to obtain differentiating criteria of healthy individuals from pre-diabetic and incipient diabetics from several blood samples during the glucose tolerance test (Makroglou $ Kuang: 2006). The model represented by a system of two differential equations is a gross model and only takes into account the concentrations of glucose $x(t)$ in the blood and of net hormonal concentration $y(t)$. Analytically, the model is described by the following system:

$$\begin{cases} \dfrac{dX}{dt} = -\alpha_1 X - \alpha_2 Y + at + b \\ \dfrac{dY}{dt} = \alpha_3 X - \alpha_4 Y \end{cases} \quad (1)$$

where $\alpha_i, i = \overline{1,4}, a, b$ are real positive constants, with the notations $X(t) = x(t) - x_0, Y(t) = y(t) - y_0$. (2)

It was considered that the unknown X and Y have the initial values x_0, y_0 calculated when the starving patient arrives at the hospital. It is noticed that if: $X(t) \geq 0, Y(t) = 0$, then the concentration of glucose will decrease by being processed by the tissues and by depositing the excess in the liver, as glycogen. If $X(t) > 0$, the endocrine glands secrete hormones that tend to rise the value of $Y(t)$. This model can be used only for the diagnosis of incipient diabetes and sometimes there results a minimum correspondence of data 3-5 hours after the ingestion of glucose (Landersdorfer & Jusko: 2008). The analysis was made on both healthy subjects and on various types of patients diagnosed with diabetes. Glucose was administered to the patients and then the plasmatic concentration of the glucose was studies, as well as the variation of the generalized insulin in the patients' bodies. The data used in this study were collected from 35 subjects diagnosed with type 1diabetes, using the FreeStyle Libre glycemia sensor (figure 1). The sensor is represented by a round disk of 5 mm thickness and 35 mm in diameter, approximately the size of a quarter dollar (Derouich & Boutayeb: 2002). The sensor is applied on the skin by means of a manual applicator and is valid for 14 days. During the 14 days of use, the sensor allows scanning by means of a hand-held device which sends the data on. When we scan the sensor we find out not only the value of the glycemia at that particular moment, as in the case of an ordinary glucometer, but also the tendency of the glycemia to go up or down. The data supplied by the FreeStyle Libre glycemia sensor are similar to those offered by the continuous glycemic monitoring, as long as you make sure you are scanned at minimum 8 hours intervals (Lam et all: 2012).

Fig. 1: Sensor for blood glucose monitoring

Fig. 2 : Blood glucose monitoring device

Results & Discussion

For the continuation of the study the daily mean glycemia values will be considered, for a period of 15 days, to be able to see the blood glucose variability in relation to the quantity of insulin administered.

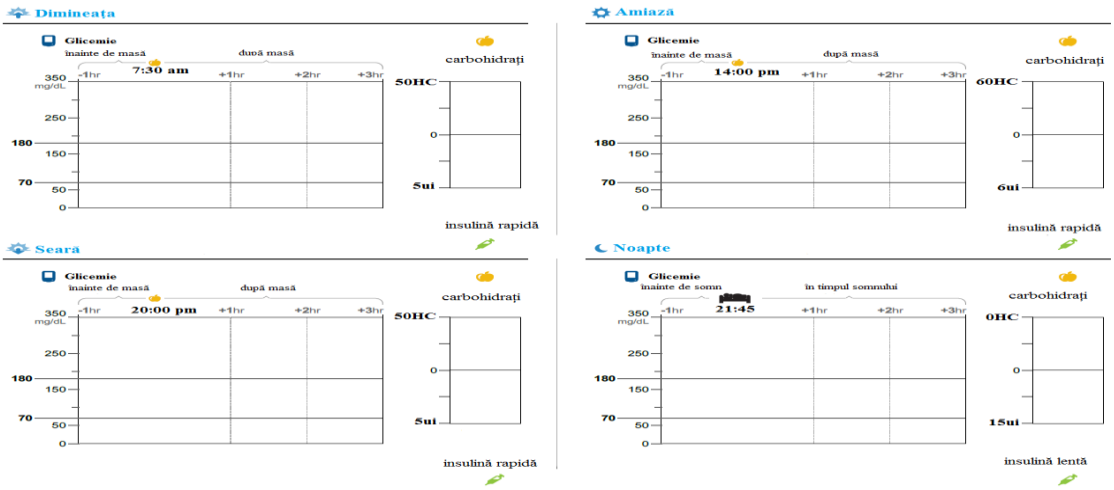

Fig. 3: Scheme of treatment (morning – upper left, noon – upper right, evening – lower-left, night – lower right)

Figure 3 shows the daily relation between carbohydrates and subcutaneously injected insulin. Prior to every meal, the patient injects various quantities of insulin, depending on the carbohydrates they consume, aiming at keeping a balance and constant values of the glycemia, similar to a healthy individual with a normal pancreas. Taking into account this treatment scheme, for a period of 24h it is noticed that the patient manages to obtain a mean value of the glycemia equal to 154 mg/dL, a value that slightly exceeds the normal limits interval of the glucose in the blood, namely 120 mg/dL. Exactly the same method is used by the glycemia continuous monitoring systems. Generally, glycemia at the level of the interstitial liquid is similar to the glycemia at the blood level, but there may be certain differences. The differences shouldn't be very high, but they can become significant especially when it comes to low glycemic values. That is why it is recommended to run several glycemia tests during the day to test the accuracy of the values and especially to test glycemia by means of the glucometer if you notice symptoms of hypoglycemia.

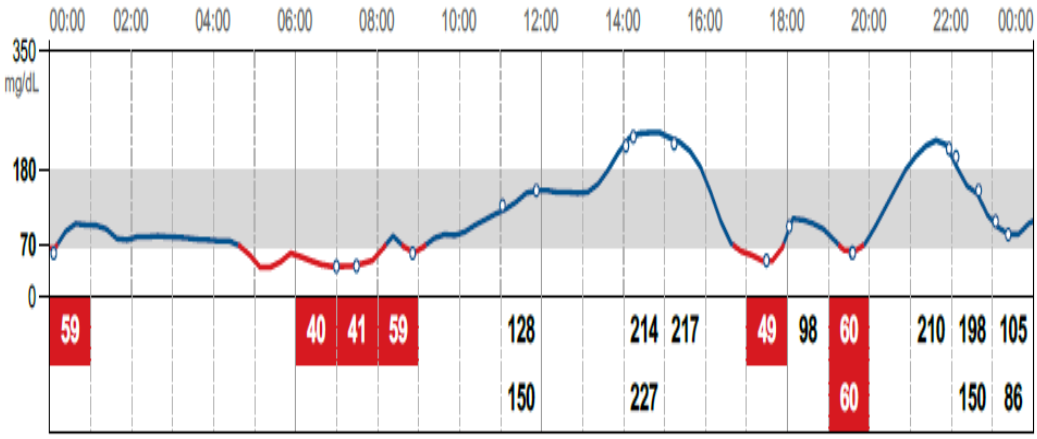

Fig. 4: Glycemic monitoring equilibrium 24 hours

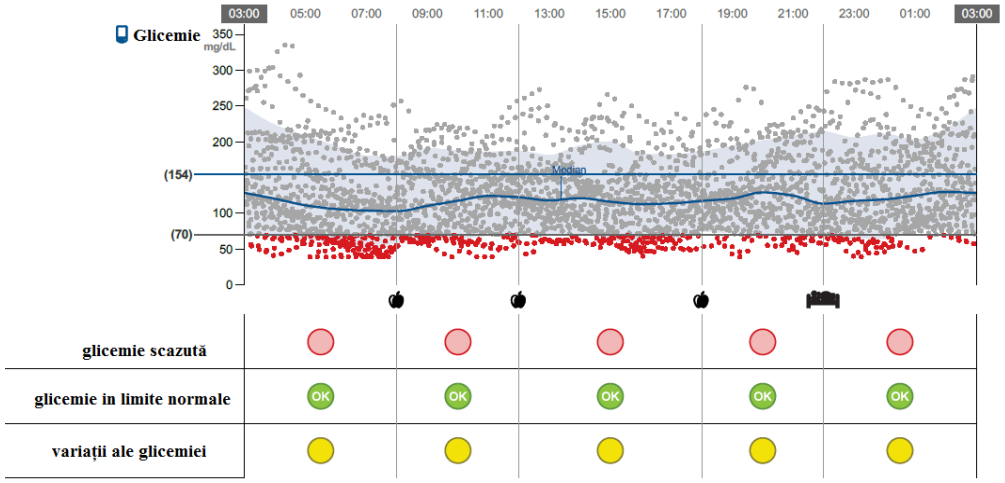

Fig. 5: Glycemic balance, monitoring 24 hours

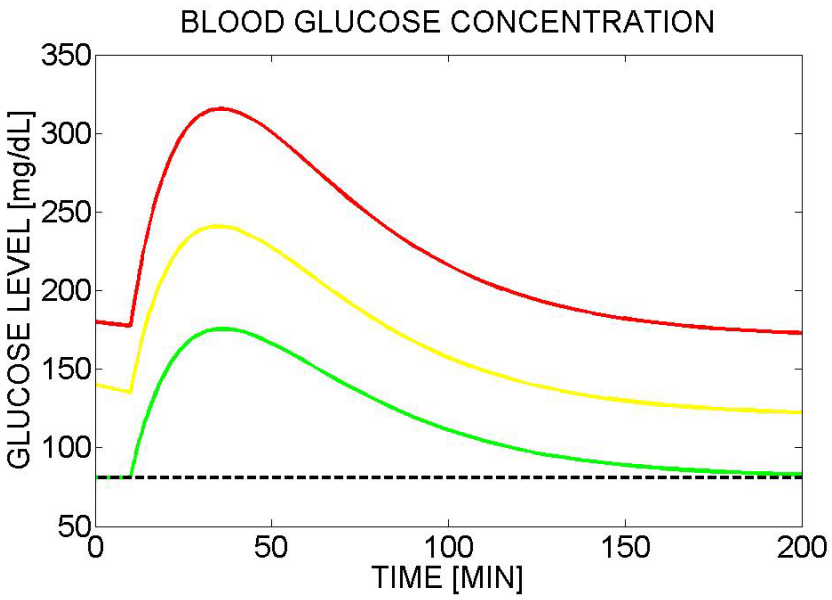

Fig. 6: Matlab simulations of data obtained with the sensor

For blood glucose monitoring (Green graph: Normal glucose tolerance, Yellow graph: Pre-Diabetes. Red graph: Diabetes)

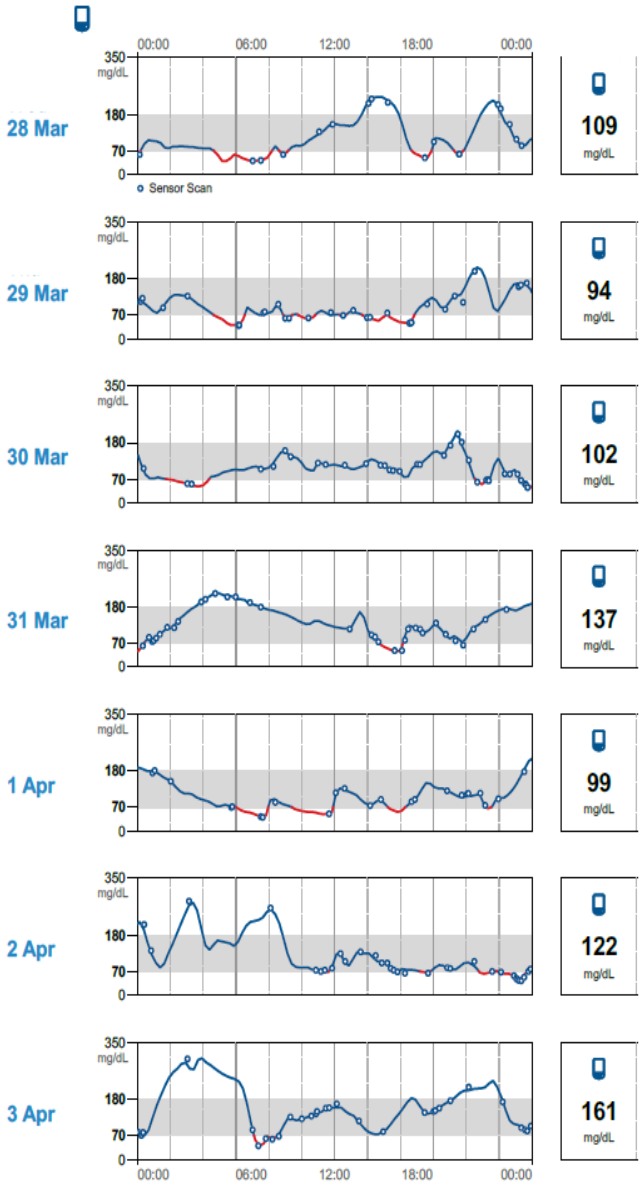

Fig. 7: The blood glucose variability relative to the amount of insulin administered in the first week

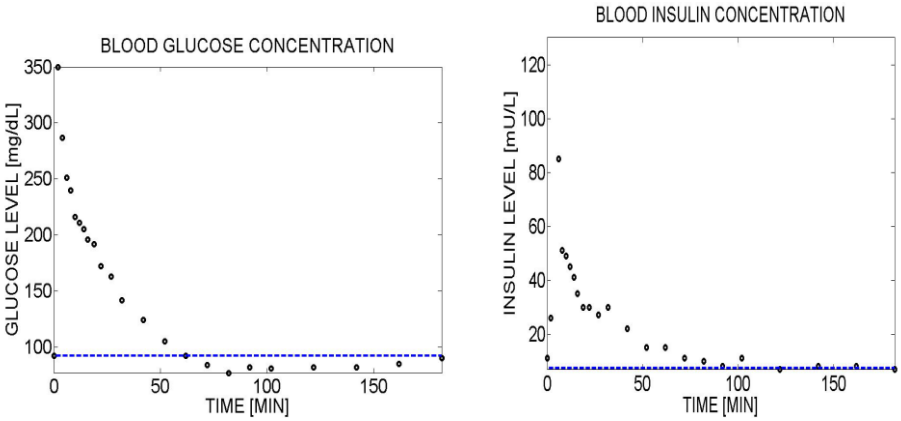

Fig. 8: Graphical representations of the measured data used to estimate parameters of differential system

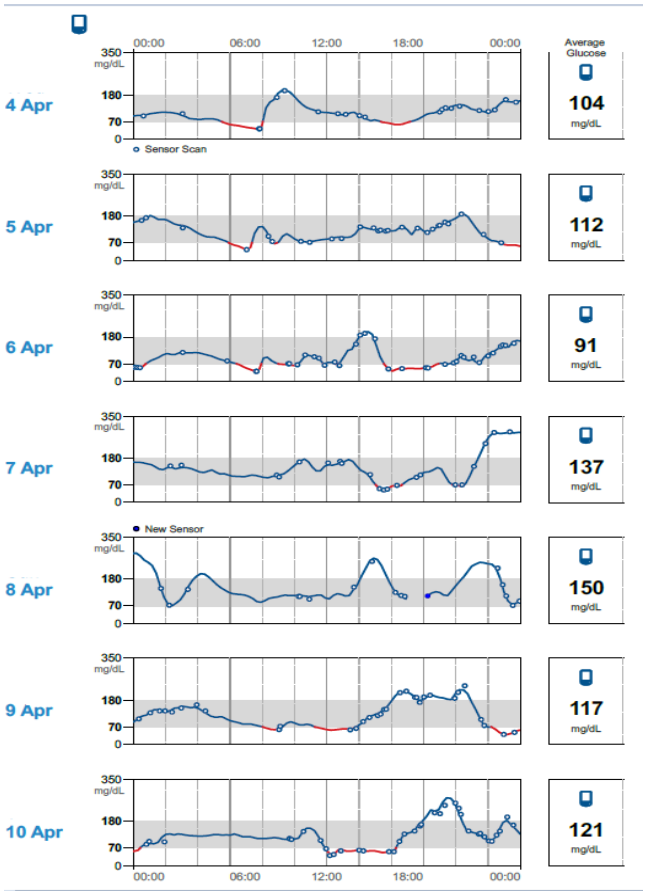

Fig. 9: The blood glucose variability relative to the amount of insulin administered in the second week

Conclusions

In this article we presented a mathematical model that describes the glucose – insulin system in the blood. This model is derived from Bergman's minimal model, which is mainly used to design the glucose-insulin system. Taking into account the complexity of the condition, its major social and familial impact as well as the fascinating technical and scientific evolution in the last years, we decided to approach a theme related to this pathology. The estimation of the glucose quantity in the blood flow, after intestinal absorption and the total insulin quantity in the blood flow following the subcutaneous injection of slow and fast action analogies are the entry variables, by means of which this study was conducted. The entry data the statistical study was based on were collected from diabetic patients who followed the day to day routine. They adapted their insulin doses depending on the physical activity and the food quantity. The patients were monitored by means of a glycemia sensor, recording all the glycemic values for a period of 15 days. The collection and processing of data raise technical problems, since structurally a part of the system parameters are either not available or cannot be converted into measurable units. From what we presented, it results that the design and simulation off the glucose-insulin system follows the modern tendency of knowledge integration, being in them the result of an interdisciplinary research.

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