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THE MATHEMATICAL MODEL OF GLUCOSE DYNAMICS IN BLOOD OVER 24-HOUR PERIOD

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Abstract: The article is concerned with the problem of controlling the glucose concentration in blood with minimal application of invasive measuring. The mathematical model of digestion of recepted glucose, which depends on the volume of consumed carbohydrates (instantaneous, fast, slow) has been developed. The mathematical model is built for long-term observations with the use of specially organized experiments. The blood glucose level depends on the intensity of the effect of insulin, that is why the model of insulin dynamics has been developed either. The accumulated insulin is presented as combination of the insulin produced by the body and the insulin coming from injections. The Levenberg-Marquardt method is used to identify the blood glucose dynamics.

Key words: nonautonomous model, glucose dynamics, diabetes mellitus, identification, distribution model.

1. Introduction

Diabetes mellitus is ranking the third most widespread and dangerous disease in the world, which is associated with the change of environmental factors, as well as genetic and demographic characteristics of the human body, and concentration of its risk factors in populations (e.g. obesity, hypertension, high incidence of cardiovascular diseases, lipid metabolism disorders, etc.). This leads to early disability of patients with diabetes, due to the presence of complications of the disease. Pancreas is responsible for the glucose level in a human body: it produces hormones of insulin and glucagon, which allow increasing or decreasing the glucose concentration in blood. However, the patients with diabetes mellitus suffer from pancreas malfunction in combination with the decreased susceptibility to insulin. It results in oscillation of glucose in blood and, particularly, occurring the cases of hyperglycemia (high glucose concentration) and hypoglycemia (low concentration).

Controlling the glucose concentration in blood is crucial for the analysis of the state of patients with diabetes mellitus. Ingestion is one of the important factors that influence glucose levels. The empiric selection of a nutrition mode contains the risks of exceeding the maximum or minimum allowable glucose concentration in blood. Those risks can be considerably reduced with the use of mathematical model of glucose level in blood, which considers individual peculiarities. The existing mathematical models are phenomenological ones and don't provide the possibility to conduct identification based on the observation results of a specific patient. Therefore, the development of mathematical model of glucose dynamics during the digestion process of a concrete patient is an urgent problem.

The majority of plasma models of the blood glucose dynamics were built on data provided by the intravenous glucose tolerance test (IGTT): the models of Bergman, Roy, Cobelli, Hovorka and others were built on this principle [1–5]. During this test a patient receives one glucose injection on the empty stomach. Blood insulin levels are measured before the injection, and again at specific intervals after the injection. The timing may vary, but the main point of the test is to measure glucose dynamics. Usually the test takes about 3 hours with a 10-minute measurement interval. The IGTT shows increased glucose levels for the patients with diabetes mellitus, while the standard for normal tolerance is a return to the initial glucose level in blood. However, diabetes mellitus is not the only cause of the low glucose tolerance index. Liver malfunctions, obesity, medications and infections may also cause such results of the IGTT [6]. Thus, IGTT-based models cannot describe the glucose dynamicsr during the day, since a patient eats throughout the day. And since it is necessary to take into account the digestion process, the oral way of receiving glucose is a more intricate problem for simulation of glucose dynamics.

Breton's model allows estimating the glucose dynamics in blood under the influence of physical activities [7]. It considers one-time glucose injections only.

Recently, the method of glucose concentration control by an insulin pump was intensely used [8–10]. However, the insulin pump has a few drawbacks. Its frequent usage reduces the pancreas hormone-productive function, which results in its non-operability; there is a risk that a patient would not be provided with a necessary insulin dose because of operational or other device failures. So the question, that remains pressing, is that the patients should control the glucose concentration in their blood by themselves considering their nutrition.

The receipt of glucose from outside of the human body plays an important role in controlling its levels in blood. The quantitative estimation of the glucose received with a meal and the peculiarities of its digestion have an obvious importance, since nutrition process takes place every day.

The numerical experiment of the glucose concentration in blood, that depends on the volume and contents of nutrition during the active twenty-four hour period can be conducted with the help of math models. Identification will allow us to adapt the constructed model to the features of an individual organism.

2. Mathematical model of glucose level during twenty-four-hours period

An individual consumes carbohydrates with each meal containing starch or sugar. Carbohydrates decompose into glucose and other components and are integrated into blood through the intestine walls during the digestion process. Cells consume glucose that enters them with blood circulation, converting it into energy. However, glucose needs a special hormone, namely insulin, in order to penetrate into the cell. The level of glucose in blood rises after having a meal. Glucose is turned into energy by the cell with the help of insulin hormone, thus the level of blood sugar is reduced. If insulin is either under-produced, or does not provide penetration of glucose into the cell, the level of glucose in blood starts rising [11].

The main purpose of the diabetes mellitus treatment is the maintenance of glucose level in blood as close to normal as possible. Unfortunately, an individual is practically not capable of feeling the changes of glucose levels between 4 and 10 millimole per litre [11]. This is a treachery of diabetes mellitus, because high level of glucose in blood unavoidably leads to the complications of a disease (obesity, hypertension, high rate of cardiovascular diseases, disorders of lipid metabolism, stroke, heart attack, diabetic retinopathy, nephropathy, diabetic microangiopathy in ischemic limb). Only regular and frequent self-control of glucose in blood allows to avoid the deterioration in the patient's condition.

The development of a mathematical model allowing to estimate the general volume of glucose which comes in depending on the volume and the components of the daily nutrition scheme is advisable in this case.

The Breton model is taken as a prototype for the concept [5]:

$$\frac{d}{dt}G(t) = -p_1(G(t)-G_b)^+ + p_2G_m(t) - \\ - X(t)\cdot G(t) - b\cdot Y(t)\cdot G(t); \quad (1)$$

$$\frac{d}{dt}X(t) = -p_3X(t) + S_i p_3(g(t)G(t) - I_b); \quad (2)$$

$$\frac{d}{dt}Y(t) = -\frac{1}{t_{HR}}Y(t) + \frac{1}{t_{HR}}dH(t); \quad (3)$$

$$(G(t)-G_b)^+ = \begin{cases} G(t)-G_b, & G(t)-G_b \geq 0 \\ 0, & G(t)-G_b \leq 0 \end{cases}$$

The first equation of the model describes the blood glucose dynamics, where $G(t)$, *mmol/l* is the current glucose level in blood plasma; G_b, *mmol/l* is the initial glucose level in blood plasma; p_1, *1/min* is a coefficient that accounts for decrease of the glucose level; p_2 is a coefficient that accounts for increase of the glucose level as a result of nutrition; $G_m(t)$, *mmol/(l·min)* is the time-dependence of the change in glucose level due to receipt of nutrition during twenty-four hour period; $X(t)$, *U/(l·min)* is a change in remote insulin level in the course of time; the insulin is measured in units that can be recalculated in *ml* in such a way: *1 ml=100 U*; β is a coefficient that takes into account short changes of cardiac rhythm as a result of physical activity, $Y(t)$, *1/min* is a filtered differential cardiac rhythm that indends to mimic the increase in the energy expenditure due to physical activity.

The second equation of the model describes the insulin dynamics, where p_3, *1/min* is a coefficient that characterizes insulin behavior and its activity; S_i, *1/min* is a coefficient that describes patient's sensitiveness to insulin, $g(t)$, *U/mmol* is the intensity of insulin production; I_b, *U/l* is an initial level of insulin.

The third equation of the model represents filtered differential cardiac rhythm that imitates the increase of energy expenditure due to physical activity, where dH is a difference between the cardiac rhythm after the physical activity and its initial value; t_{HR}, *min* is a time constant that accounts for reaction of cardiac rhythm to the energy expenditure.

In order to simplify the model on the initial stage we eliminate the influence of physical activities. Also we eliminate the influence of intramuscular insulin on the glucose concentration in order to take into account only the observable values. Thus, the equations (2) and (3) are eliminated and the components that include remote insulin dynamics $X(t)$ and differential cardiac rhythm $Y(t)$ are removed from the first differential equation. So the model has been reduced to the following form:

$$\frac{\mathrm{d}}{\mathrm{dt}}\mathrm{G(t)} = -\mathrm{p_1G(t)} - \mathrm{G_b})^+ + \mathrm{p_2G_m(t)}. \quad (4)$$

The observation of the blood glucose dynamics and the glucose dosage during the food consumption shows disparity of volume of the consumed glucose and its concentration in blood. It has provided for the introduction of a hypothesis about considering the influence of the type of consumed glucose on its concentration in blood. Since it is common to divide carbohydrates into instantaneous, fast and slow, we differentiate the variables that represent the volume of glucose received with a meal accordingly: $G_{m1}(t)$ is a change in glucose level due to instantaneous carbohydrates; $G_{m2}(t)$ is a change in glucose level due to fast carbohydrates; $G_{m3}(t)$ is a change in glucose level due to slow carbohydrates. It

leads to the modification of the differential equation (1). As a result, we obtain the following model of the glucose dynamics over twenty-four hours:

$$\frac{d}{dt}G(t) = -p_1(G(t)-G_b)^+ + p_2(G_{m1}(t)+ \\ +G_{m2}(t)+G_{m3}(t)). \quad (5)$$

However, such a model doesn't set apart the influence of the insulin hormone on the digestion of glucose. The concentration of insulin has a crucial importance for the patients with diabetes. The malfunction of every metabolism type occurs due to the lack of insulin in the body. Therefore, the insulin level must be included in the model, taking into account that the intensity of the hormone impact is not permanent, but decreases substantially after reaching a certain barrier. We show the cumulative insulin dynamics being present in a patient's organism as a combination of the dynamics of insulin $I(t)$, *U/(l·min)* produced by the organism (i.e. human insulin) and insulin $N(t)$, *U/(l·min)* coming from injections (i.e. insulin analogue). We take also into account that, due to the complexity of measuring insulin concentration, it is assessed by the means of mathematical modeling on the basis of its impact on glucose concentration. Thus, the equation (5) is transformed as follows:

$$\frac{d}{dt}G(t) = -p_1(G(t)-G_b)^+ + \sum_{l=1}^{L}\sum_{i=1}^{3} p_2 G_{mi}(t,t_l) - \\ -g_1\frac{I(t)G(t)}{p_4+G(t)} - g_2\sum_{k=1}^{K}\frac{N_k(t)G(t)}{p_4+G(t)}, \quad (6)$$

where p_4, *mmol/l* is a coefficient that is used to describe nonlinear time-dependence of insulin; g_1, *mmol/U* is a coefficient that describes glucose absorption by the help of human insulin; g_2, *mmol/U* is a coefficient that describes glucose absorption by the help of insulin analogue; L is the number of nutrition receipts; t_l, *min* is the time of l-th nutrition receipt; K is the number of insulin injections.

We represent the dynamics of the human insulin with a differential equation. This equation considers insulin production affected by glucose exceeding its base level and certain intensity of insulin disintegration caused by insulin exceeding its own base level

$$\frac{d}{dt}I(t) = p_5(G(t)-G_b)^+ - p_6(I(t)-I_b), \quad (7)$$

where p_5, *U/(mmol·min)* is a constant that characterizes the rate of production of human insulin; p_6, *1/min* is a constant that accounts for insulin disintegration.

The obtained model contains some time-distributed values, which are difficult to observe, such as the digestion of consumed glucose and insulin coming from injections.

3. Development of expressions for time-dependences of consumed glucose and insulin analogue concentrations

The problem of building up the function describing time-dependence of consumed glucose and insulin analogue concentrations rises up due to the fact that it is relatively easy to determine the volumes of consumed carbohydrates and insulin, however these factors don't operate instantly. The time-dependence of the indicated factors can be developed on the basis of time-dependences of glucose and insulin levels after single glucose injection [3]. The analysis of such depencences allows us to approximate them with a simple and general parabolic function [12]. It is known that the meal digestion process is completed during a certain time t_z. The change in the glucose concentration in blood due to nutrition receipt has to reach its maximum by that point of time and then it starts going down. This phenomenon is modelled by a simple parabolic dependence with the use of exponential function:

$$G_{m,i}(t,t_l) = (a_i - b_i(t-t_l-0.5t_{zi})^{2a_i})e^{-b_i(t-t)}\cdot \\ \cdot q(t-t_l)q(t_l+t_{zi}-t), \quad (8)$$

where $G_{mi}(t,t_l)$ is glucose dynamics (i.e. a change in glucose level) as a result of consumption of the i-th type carbohydrates at the moment t_l; a_i, *mmol/(l·min)* is the maximal value of glucose dynamics; a_i, b_i, *mmol/(l·min²)*, b_i, *min*$^{-1}$ are model coefficients; t_{zi} is the duration of the i-th type carbohydrates digestion; $q(\cdot)$ is Heaviside step function.

Meanwhile, the total volume of digested carbohydrates must coincide with the volume of their consumption

$$\int_t^{\infty}\sum_{l=1}^{L} G_{m,i}(t,t_l)dt = G^*_{m,i}, \quad (9)$$

where $t = \min(t_l)$ is the moment of the first meal receipt; $G^*_{m,i}$ is the total volume of the consumed i-th type carbohydrates.

The parameters a_i, b_i are set empirically and b_i, a_i are determined by the following expressions:

$$b_i = \frac{G^*_{m,i}}{\int_0^{t_{zi}}((0.5t_{zi})^{2a_i} - (t-0.5t_{zi})^{2a_i})dt}; \quad (10)$$

$$a_i = b_i(0.5t_{z_i})^{2a_i}. \quad (11)$$

The offered model of glucose dynamics due to consumed carbohydrates has provided the acceptable accuracy of modelling the blood glucose dynamics during two meals. For longer observation periods it is necessary to increase the simulation accuracy for the glucose dynamics from carbohydrates. This can be

achieved by using specially-organized experiments. The analysis of the results of such experiments proved the necessity of using piecewise cubic Hermite polynomials $H(t,\vec{T},\overrightarrow{W})$ which minimize the function fluctuation between the nodes of interpolation. Here $(\vec{T},\overrightarrow{W})$ represents some collection of temporary nodes and corresponding values of the interpolated function:

$$G_{m,i}^{H}(t,t_l) = G_{m.i}^{*} g_{m.i}(t,t_l) \qquad (12)$$

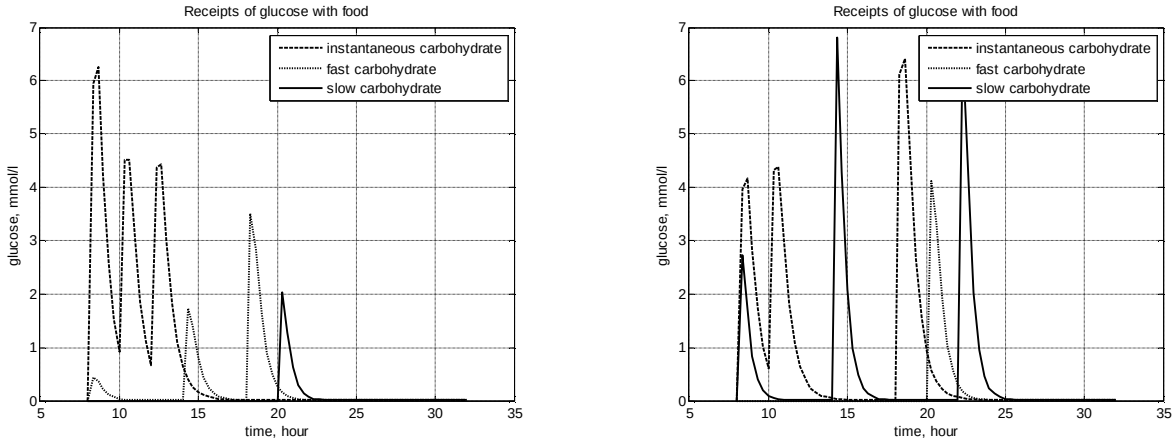
$$g_{m,i}(t,t_l) = H_{m,i}(t-t_l,\overrightarrow{T_i},\overrightarrow{W_i}) \qquad (13)$$

where $G_{m,i}^{*}$ is the volume of glucose consumed with the i-th type carbohydrates at the moment t_l and calculated using the calorie calculator; $g_{m,i}(t,t_l)$, min^{-1} is the profile of glucose dynamics in consequence of the i-th type carbohydrates at the point of time t_l.

The parameters of the Hermite polynomials are set on the basis of interpolation of the experimental observations of glucose levels after consumption of the i-th type carbohydrates.

We observed a patient with diabetes mellitus for two days in order to investigate the efficiency of the proposed models.

Thus, the Fig.1a) represents the distribution of consumed glucose during the first twenty-four hours and Fig.1b) does the same during the second day.



a) *b)*

Fig. 1. Distribution of glucose receipt:a) during the first twenty-four hours; b) during the second twenty-four hours.

We don't observe the dynamics of insulin in domestic environment. However, the coefficient of glucose disintegration intensity is significantly lower in comparison with the insulin effect. For the patients with type 2 diabetes, the effect of insulin analogue is significantly more intensive than that of human insulin. The change in insulin analogue level is proportional to glucose redundance, that is why the dynamics of insulin analogue is proportional to the dynamics of glucose in blood.

Thus, the distribution of insulin analogue is determined by the distribution of glucose in blood:

$$N(t,t_l) = N_t^{*} H_N(t_l - t,\overrightarrow{T_N},\overrightarrow{W_N}) \qquad (14)$$

The reduction of the glucose concentration in blood corresponds to the reduction of the concentration of insulin analogue. Therefore, we determine the coefficients of the polynomial H_N from the task of interpolation of glucose values after the last meal; the insulin injection is administered 30 min before the meal.

The distributions of insulin are identical during the first and the second day, since an identical dose of insulin is used at the same point of time.

Fig. 2 shows the simulated distribution of insulin analogue that was administered at 8 am and 6 pm with dosages of 16 and 20 units.

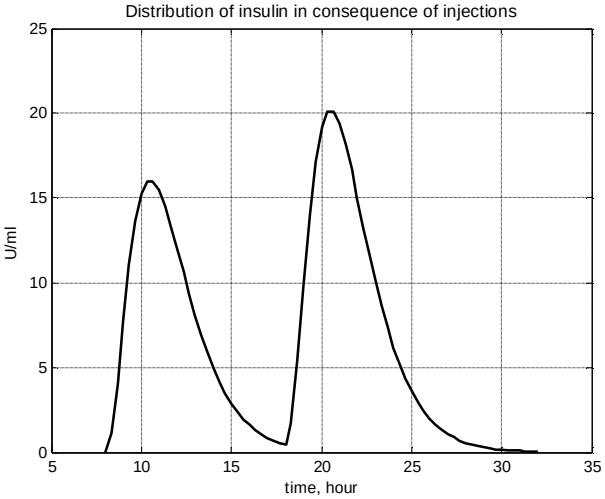


Fig. 2. Distribution of insulin.

In order to estimate the dynamics of glucose during next twenty-four hours, it is necessary to conduct model identification during the first twenty-four hours. Such prognosis allowi us to control the level of glucose and avoid injuring the patient with the frequent skin pricking. Fig. 3 represents the diagram of model identification during the first twenty-four hours.

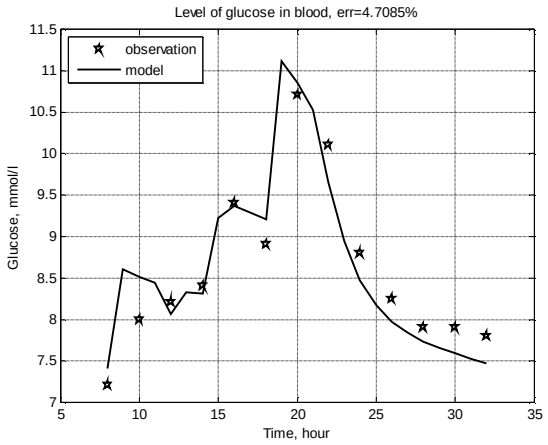


Fig. 3. Identification of the model during the first twenty-four hours.

The error of identification for the model (6) is 4,7085 % for the first day. It is necessary to predict the dynamics of glucose during the second day on the basis of the model's coefficients which we got as a result of identification during the first twenty-four hours in order to verify the efficiency of our identification. Satisfactory precision of forecast will allow simulation of the glucose level dynamics without numerous traumatic empiric measurements. The dynamics' prediction is shown in Fig. 4.

The acceptable level of relative error (8,0045 %) allows using the developed model for the prediction of glucose level dynamics of a patient on the basis of measured volume and character of the meals and the volumes of insulin injections.

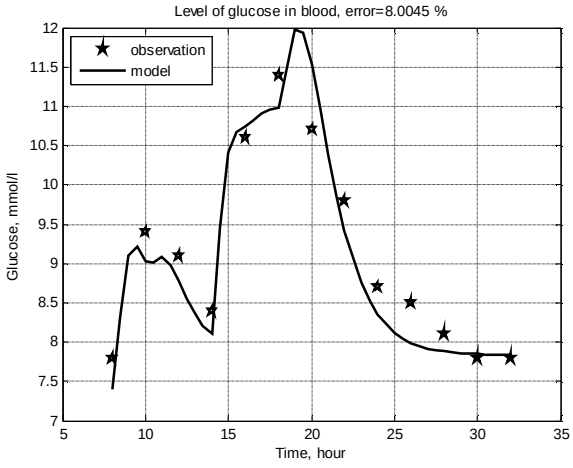


Fig. 4. Prediction of glycemia dynamics during the second twenty-four hours.

4. Conclusion

The models of glucose dynamics in the process of food consumption that depends on the volume of the consumed carbohydrates (instantaneous, fast, slow) are first offered in this article. Models are based on the data from long-term observations. The majority of scientists use short-term models. Particularly Begman, Cobelli, Hovorka, D.Roy apply one-time glucose injection and monitor its dynamics for 3 hours.

However, it is difficult to prognose the glucose level in blood as a result of such observations. It is due to the fact that the simulation problem for dynamics of glucose received orally is very complicated, since it is necessary to consider frequent reception of glucose and the processes of its assimilation. The model of distribution of glucose intake to blood during the given process is offered on the base of the Breton model. For the long-term periods the exactness of carbohydrates distribution is presented with the use of specially-organized experiments.

The glucose dynamics also depends on the insulin dynamics. Consequently, the insulin dynamics must be included into the model. The intensity of the insulin activity in blood is estimated by the means of mathematical modeling of its effect on the glucose concentration in blood. The cumulative insulin is presented as combination of human insulin and insulin analogue.

The Levenberg-Marquardt method is used for identification of the offered models. The identification of the model is conducted on the basis of experimental data during first 24 hours with an error of 4.7085%. The glucose dynamics is predicted for the next twenty-four hours on the basis of the identified model. The error of the prediction is of 8.0045 % which confirms prognosis properties of the offered model.

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МАТЕМАТИЧНА МОДЕЛЬ КОНЦЕНТРАЦІЇ ГЛЮКОЗИ В КРОВІ ПРОТЯГОМ ДОБИ

Юлія Чайківська, Роман Пасічник,
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У цій статті розглянуто проблему контролю концентрації глюкози в крові із мінімізацією застосування інвазивних вимірювань. Розроблено математичну модель розподілу поступлення глюкози, що залежить від обсягу спожитих вуглеводів (миттєві, швидкі, повільні). Математичну модель побудовано для довготривалих спостережень із використанням спеціально-організованих експериментів. Рівень глюкози в крові залежить від інтенсивності дії гормону інсуліну, тому побудовано модель динаміки інсуліну. Сукупний інсулін представлено як поєднання інсуліну, що виробляється організмом та інсуліну, що поступає з ін'єкцій. Для ідентифікації динаміки глюкози в крові використано метод Левенберга – Маквардта.

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