Medical and Biological Cybernetics

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HIERARCHICAL SIMULATION. ALGORITHM FOR PREDICTION OF GLYCEMIC PROFILE FOR DIABETES

Introduction. *Diabetes mellitus, a common chronic disease, requires lifelong treatment and, like any chronic disease, requires regular monitoring and self-control at home. Revolutionary changes in glycemic control in diabetic therapy have occurred thanks to the development of sensors for continuous glucose monitoring (CGM), which can, almost continuously, measure the concentration of glucose in the subcutaneous tissue. The most common barriers to CGM use are related to high device costs and lack of insurance coverage for their purchase, alleged sensor inaccuracy, anxiety, which is associated with*

dislike of wearing the device. Thus, sensors are good but expensive, not affordable for everybody and could be uncomfortable. Therefore, the constant search for alternative solutions remains an important challenge.

The purpose of the paper is to show the possibility of using hierarchical modeling technology to develop and study glycemic profile prediction algorithm as, to some extent, alternative to continuous monitoring sensors in a context of limited irregular measurements.

Results. The program-algorithmic structure for realization of the concept of hierarchical simulation is developed. The possibility of conducting research on models of varying complexity is shown. An algorithm for insulin-glucose tolerance test was synthesized. A procedure for predicting the daily glycemic profile by analytical formulas has been developed, which provides an opportunity to assess the trend of glycemic dynamics as an addition to the irregular glucose measurements with a glucometer. A simulation study, the result of which is the visualization of glycemic profile in a context of expected food intake schedule and compensating insulin doses obtained by the analytical algorithm, was conducted.

Conclusions. The proposed hierarchical modeling technology, based on the use of mathematical models of varying complexity, allows to conduct a complex of simulation studies to correct glycemia in diabetes at the preclinical and pre-ambulatory stages. During the simulation of forecasting procedure, configuration discrepancies of the glycemic profile obtained from different models were detected, but they are within the margin of error and reproduce the main trend in the dynamics of glycemia during meals and insulin injections. The calculated bolus doses of insulin are almost identical to those used by insulin-dependent patients. The simplicity of calculations using analytical formulas can be a prerequisite for the implementation of the algorithm in a special-purpose portable autonomous devices or in applications for Android OS.

Keywords: digital medicine, hierarchical simulation, glycemic control system, identification algorithms control, forecasting, simulation preclinical trials.

INTRODUCTION

Diabetes mellitus (DM) is a chronic disease that manifests in a persistent elevation in blood glucose level caused by absolute or relative deficiency of insulin, a hormone that stimulates glucose transport from the blood stream into cells, providing the body with the main energy resource.

The problem of diabetes is becoming increasingly important due to the ever-growing number of patients in all countries and on every continent. To date, the number of patients on the planet is more than 180 million people, the current number of which, according to WHO estimates, will almost double by 2045 [1]. Currently, this disease is a global medico-social problem. This is not only because of progressive increase in the number of patients with diabetes, but also because of the extremely high risk of complications that lead to loss of working capacity, disability and mortality in this group of patients. Consequently, at present, the main focus of diabetic patient treatment is the development of methods and programs aimed at risk reduction of micro- and macrovascular complications of the disease [2].

Diabetes mellitus, as a chronic disease, requires lifelong treatment. The goal of treatment is "disease compensation", i.e. achievement of glycemic indicators that are close to normal values, since glycemic indicators that go beyond certain limits cause complications. This remains one of the main tasks to prevent their appearance and progression.

Diabetes, like any other chronic condition, requires regular monitoring and self-control at home. Unconditionally, it is very important to measure blood glucose level regularly — the main indicator that describes the state of

carbohydrate metabolism and the diabetic status of an organism. To address this issue, the modern industry produces affordable glucometers, using of which the patient can take measurements, if necessary, few times a day, that contributes to a better quality of glycemic self-control.

Despite the various etiologies of the existing types of diabetes and the peculiarities of the course, their therapy pursues a common goal — the normalization of glycemia, the elimination of symptoms associated with high blood glucose level, the reduction of risks of hypoglycemia and the prevention of complications.

One of the methods of treatment for diabetes with endogenous insulin deficiency is intensive hormone therapy based on repeated daily injections, which include one or two long-acting hormone injections per day to create a basal concentration of glucose in the blood (fasting glucose level is an indicator for this) and additional fast-acting hormone injections before each meal in an amount that depends on glucose component.

To avoid complications, it is very important to choose an adequate insulin dose, consistent with the carbohydrate component in the food. Insufficient insulin dose can lead to hyperglycemia. And if this happens regularly, it could cause severe vascular complications such as retinopathy, nephropathy, neurological damage and diabetic foot syndrom. They are the cause of disability and increased mortality. On the other hand, an overdose of insulin can cause hypoglycemia which leads to loss of consciousness and if it is not compensated immediately, even to death. As a result, diabetics should monitor glucose concentration during the day and adjust insulin therapy accordingly.

An insulin pump is used to improve injection therapy in modern diabetic practice. This is medical device that injects fast-acting insulin into abdominal subcutaneous tissue during the day at a constant rate to ensure glucose levels in the permissible background range. Additional insulin doses are injected before meal to ensure its utilization. Many papers, for example [3], outline the effectiveness of insulin pump usage, which, compared with injection therapy, improves glycemic control.

But despite continuous improvement of insulin administration methods, all patients on insulin therapy should conduct self-control of blood glucose (SCBG), which is an integral part of effective therapy. For many patients, this will require testing 6–10 times a day. Glycemic control in diabetic therapy has been revolutionized by the development of sensors for continuous glucose monitoring (CGM), which can measure glucose concentration in the subcutaneous tissue almost continuously (eg. Every 5 minutes) [4, 5]. The results of studies on the use of these devices provided in a review paper [6]. The result of their use in combination with intensive insulin therapy regimens is a decrease in HbA1c levels and the frequency of hypoglycemic events [7, 8]. However, the CGM sensors usage remains limited for a large segment of the population with diabetes, mainly for patients with type 1 diabetes [9]. More recent data show that even in highly developed countries only 17 % – 25 % of patients use CGM [10, 11]. The use of CGM is even less widespread among patients with type 2 diabetes [12–14]. The most common barriers to CGM use were related to high device costs and lack of insurance coverage for their purchase [15, 16]. The most common reasons for stopping CGM use were cost, anxiety, alleged sensor inaccuracy, and dislike of

wearing the devices. Thus, sensors are good but expensive, not affordable for everybody and could be uncomfortable. Therefore, the constant search for alternative solutions remains an important challenge for researchers.

Diabetes is a complex metabolic disease that requires involvement of specialists from many related disciplines: pathophysiologists, pharmacologists, technicians etc. In modern society, the technology of mathematical modeling is practically an essential component that accompanies almost all branches of activity. State-of-the-art information technologies that are based on mathematical modeling can be an effective auxiliary decision support tool in many segments of endocrinology at various stages of diagnostic processes and diabetes treatment. A person with diabetes has to perform many routine calculations forming a diet that is aligned with physical activity and therapeutic measures. Daily glycemic profile of the patient is an indicator of the adequacy of interactions of therapeutic measures and harmonization of dietary exposure and vigorous activity. There is a large segment of users who are not able regularly use continuous glycemic monitoring devices (CGM).

The purpose of the paper is to show the possibility of using hierarchical modeling technology to develop and study glycemic profile prediction algorithm in a context of limited irregular measurements.

EVOLUTION OF MODELLING

Currently, a large number of mathematical models are known. Information about them can be found in review publications [17–21], devoted to the study of various aspects of glycemic regulation, the dysfunction of which is the cause of diabetes mellitus.

In case of an advanced system of models, it is advisable to structure their set according to the principle of hierarchy, the basis of which is a different level of abstraction during the imitation of functional features of investigated system. In this paper, for the synthesis of the algorithm and evaluation of its effectiveness hierarchical modeling technology was used, which envisages the usage of models of varying complexity from the most complex systems of nonlinear differential equations, that with some degree of approximation try to recreate systematicity, complexity and functionality of real physiological regulation to the simplest minimal models used in autonomous technical devices [22].

The evolution of study of dynamic properties of the physiological system of glycemic regulation using mathematical modeling methods began with an analysis of the interaction of insulin-glucose bonds and has now moved on to a large-scale simulation studies *in silico*, which are reported [19–23] and which enable to conduct a number of different studies of the functioning of the system at the preclinical stage, including engineering tests of glycemic control devices by using closed-loop artificial pancreas.

Minimal models. Methodological analysis and examples of the use of minimal modeling approach conducted in [24, 25, 26]. The key requirements for minimal models are that they must have a minimum number of parameters that must be identified by a single dynamic response under a limited number of system measurements and at the same time satisfy the purpose for which it was created — to reproduce the basic intended functionality of the system regulation. Further developed class of this type of models is based on classic Bolie model, 1961 [27]. This is a system of differential equations that has 2 compartments and

describes the linear nature of glucose-insulin interaction in the zero-order approximation. Various modifications and examples of its use are provided in papers [28–31]. The general view of this type of model can be written in the system of equations:

$$\frac{dx}{dt} = a_{11} F_1(x,y) + a_{12} F_2(x,y) + G_u$$

$$\frac{dy}{dt} = a_{21} F_3(x,y) + a_{22} F_4(x,y) + I_u,$$

where x, y — blood glucose and insulin concentrations, $F_i(x,y)$ — delivery rate and utilization rate of glucose and insulin as a result of metabolic transformations resulting from homeostatic regulation, G_u, I_u — the rates of external influence of factors that increase or decrease the level of glycemia (it can be glucose in a food or injections / infusions of insulin).

There is a known methodology for constructing models based on the criterion of dynamic equilibrium of glucose and insulin flows in the body as in an open system [32–33]. A model of this type was developed by Russian scientists Novoseltsev V.N., Orkina E.L., Kuchkarov Z.A. etc. and described in [24].

An example of the most minimal model, that in its structure has only one glucose compartment, is a physiologically adequate mathematical model of glycemic regulation, developed by Ukrainian scientists, in the form of a first-order differential equation with a delayed argument, which makes it possible to reproduce the dynamics of the glycemic curve under various external influences quite accurately. The structure of the model has allowed the authors to conduct a series of studies taking into account the peculiarities of glucose absorption from the intestinal lumen, improve the detection of latent forms of diabetes mellitus and simulate the calculated optimal regimen of insulin therapy for an automated dispenser [34–35].

Maximal models. Mathematical modeling technology is constantly being improved by creation of new tools and methods available for biomedical modeling. Furthermore, the demand for theoretical simulation studies of various hypotheses verification of functioning of carbohydrate metabolism regulation system and also for quantitative assessment of elements interconnection in a complex biological systems is not decreasing. This led to the creation of computational structures that facilitate comprehensive analysis of theoretical ideas about holistic biological system functioning [36].

The basis of these computational complexes are mathematical models with advanced link architecture, that describe in more detail the set of physiological mechanisms of glicemia metabolic regulation. They represent the systems of high-dimensional differential equations with many nonlinearities and unknown parameters, which illustrate (even if only hypothetically) a wide range of possible interactions in a real physiological system. Such models enable the creation of various modeling scenarios with which it is possible to conduct analysis of the effectiveness of various treatment strategies without spending resources on real research.

It should be noted that the identification of such models is a complex issue, which is analyzed and discussed in [37, 19, 25]. The problem of identification of these models is reduced through the use of real functional dependencies obtained in a special physiological experimental studies that are included in a complex simulation model by separate modules [38]. Partially, the solution to the problem of identification and complex models was proposed by Novoseltsev V.N. back to 1991 [21]. This approach consists in the fact that a minimal parametric structure is allocated in a complex model, that permits an identification computational procedure according to the available data of specific measurements. The last part of the unknown parameters is verified based on fundamental functional dependencies known in physiology and a priori personal information about a particular patient. It should be noted that the problem of complicated identification of such models is also reflected in forecasting since these models reproduce the population tendency of the dynamic properties of a real physiological processes. However, the role of such mathematical objects, which have accumulated many years of knowledge about functioning of the regulatory system, encoded in mathematical structures and parameters, which are used in the educational process as textbooks is difficult to overestimate [39, 40].

Such models enable stimulation of different scenarios of occurrence, course and treatment of the disease, followed by assessment of treatment measures by using possibility, unprecedented in clinical practice, of repeatedly renewing clinical situations. Complex of models equipped with a specialized interface is a kind of "virtual clinic" which includes the subsystems "virtual diagnostics" and "virtual therapy".

This entire arsenal of tools can be a clear illustration of the treatment process in teaching, can serve as a guide for classroom training on the one hand, on the other — allows medical students to be active participants in many stages of the treatment process, to offer and to check using virtual objects — models — their options of condition assessment, therapeutic effects, recommendations. Undoubtedly, the main form of accumulating practical experience is a clinical practice under the guidance of a teacher. However, the effectiveness of this form of training can be significantly improved with the involvement of new computer technologies.

Simulation studies on complex models are provided in publications [38–40]. They are used when it is difficult and risky to conduct studies of the effectiveness of therapeutic measures in a real conditions or they require valuable costs. In this case, simulation studies on complex models perform the function of preclinical trials. In foreign papers these studies are published under the term "*in silico*". In silico research has become especially relevant in the study of the effectiveness of not only feedback control algorithms directly, but also their technical implementation with all their problematic attributes related to the accuracy of measurements, testing the accuracy of algorithms to ensure infusion of insulin into the body etc.

For example, in paper [41], the model for such studies consists of 13 differential equations, has 35 parameters and is able to simulate the personal variability of the main metabolic parameters of the regulatory system, which is observed in type 1 diabetes, in virtual space. The feasibility of using this approach is confirmed by the fact that the FDA [45–47] has adopted simulation tests in silico with a global model as a necessary step in replacing preclinical

animal trials before authorized permission for clinical trials directly on humans. Such large-scale studies are also reported in [48–54] publications.

ALGORITHM SYNTHESIS

The synthesis of the algorithm was performed directly on the model of minimum complexity MINIMODEL, which can be used to obtain analytical solutions of the problem. The model of greater complexity MIDIMODEL is used to compare numerical solutions with analytically obtained formulas and then these variants of algorithms are tested on a more complex model MAXIMODEL, which simulates a real object.

The main technological stages of using mathematical modeling to obtain information tools for visualization of glycemic profile and the possibilities for its correction:

1 stage — mathematical structure for problem solutions on analytical formulas;

2 stage — development of an insulin-glucose tolerance test for *identification* of parameters;

3 stage — obtaining analytical solutions of identification tasks, prediction and optimization of the compensating insulin dose within the limitations;

4 stage — formation of a common fundamental structure and software implementation of the algorithm simulation studies using hierarchical simulation technology.

Model for analytical solutions. A simple mathematical model is proposed, which provides the identification of unknown parameters by analytical formulas and with limited number of blood sugar measurements, which allow to estimate the dose of insulin for utilization of the amount of carbohydrates taken with food while preventing glycemia to exceed the specified range:

$$\frac{dI}{dt} = -k(y - y_n) - \lambda I + b_2 G(t), \quad y(0) = y_0$$

$$\frac{dI}{dt} = -b_1 I, \quad I(0) = I_0,$$

$$G(t) = \begin{cases} G_0, 2\tau \leq t < \vartheta \\ 0, t < \vartheta \end{cases}$$

(1)

where y – current blood glucose level (mg %), y_0 — initial glucose level, y_n — fasting glucose level, I_0 — insulin dose before meal, $I(t)$ — insulin, which is absorbed into the blood from the site of subcutaneous injection, G_0 — the rate of carbohydrate absorption from the gastrointestinal tract into the bloodstream, k, λ, b_1, b_2 — coefficients of dimension and proportionality, 2τ — the moment of the beginning of food intake, ϑ — duration of absorption of carbohydrates taken with food into the blood.

Identification. Insulin-glucose tolerance test. The identification of personal characteristics of the dynamics of glycemia is based on the data of insulin-glucose tolerance test. The detailed measurement of glucose on the background of injected insulin before meals, in which the amount of

carbohydrate component is known, may serve as this test. The fasting blood sugar test is taken — y_n (0). For example, a patient is injected subcutaneously with insulin in the amount of Io units in the morning (for us it is $t = 0$). Before the first meal it is necessary to perform a second measurement y_1 (τ) through τ (min.) and at the time of eating a third measurement y_2 (2τ). The last measurement in the test a while after eating — y_3 ($2\tau + \theta$). It is desirable to choose the length of the interval θ so that the process of absorption of carbohydrates received with food almost ended. This is necessary in order to assess the magnitude of the maximum rise of glycemia level in the background of food intake. The carbohydrate content in the test breakfast should be regulated. The parameter b_1, which characterizes the type of insulin — its dynamic properties, is introduced. The rate of absorption of carbohydrates from the gastrointestinal tract — G_0 is defined by physiological data, this is an average of 1 g / kg / h, the amount of insulin injected subcutaneously before breakfast, I_0 — the amount of insulin before a meal, Dg — the amount of carbohydrates in the breakfast, τ — discreteness of measurements (min), value of $2\tau + \theta$ — time of the maximum (min). The unknown parameters k , b_2 i λ that need to be found in the identification process characterize the user's individual sensitivity to the procedure. The structure of the test study is shown schematically in Fig. 1.

The procedure for calculating the unknown parameters is following.

Let's we write the solution of equation (1) on the background of insulin action:

$$y - y_n = \frac{\lambda b_1 I_0}{k - b_1} \left[\exp(-kt) - \exp(-b_1 t) \right].$$

(2)

Substituting the values of glucose measurements at times τ and 2τ: y_1 (τ) and y_2 (2τ) in this equation, the following system is obtained:

$$y_1 - y_n = \frac{\lambda b_1 I_0}{k - b_1} \left[\exp(-k\tau) - \exp(-b_1 \tau) \right]$$

$$y_2 - y_n = \frac{\lambda b_1 I_0}{k - b_1} \left[\exp(-2k\tau) - \exp(-2b_1 \tau) \right] \cdot$$

(3)

Substituting the values of glucose measurements at times τ and 2τ: y_1 (τ) and y_2 (2τ) in this equation, the following system is obtained:

$$k = -1/\tau * \ln \left[\frac{y_2 - y_n}{y_1 - y_n} - \exp(-b_1 \tau) \right],$$

(4)

$$\lambda = \frac{(k - b_1)(y_2 - y_n)}{b_1 I_0 \left[\exp(-2k\tau) - \exp(-2b_1 \tau) \right]},.$$
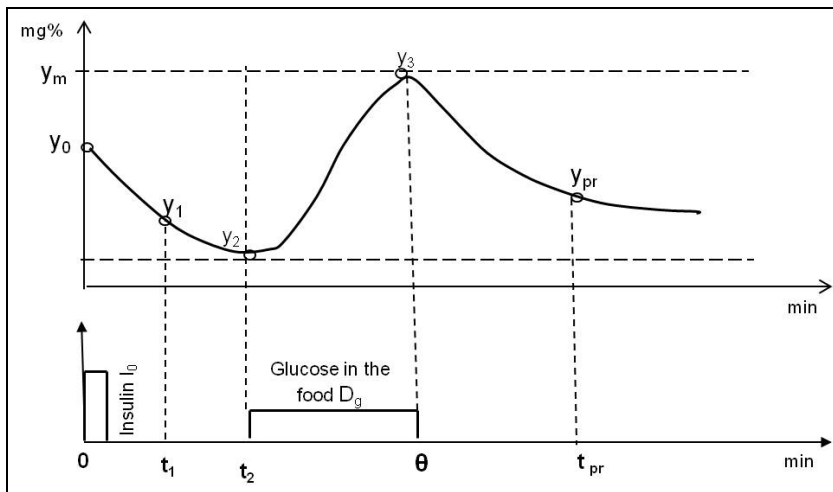
(5)

Fig. 1. The structure of the test study

Formulas for calculating unknown parameters k i λ are obtained by solving the above mentioned system.

To find the unknown parameter b_2 we use the solution of equation (2) on the background of absorption of carbohydrates from the gastrointestinal tract:

$$y - y_n = \frac{\lambda b_1 I_0}{k - b_1} \left[\exp(-kt) - \exp(-b_1 t)\right] + \frac{b_2 G_0}{k} \left[1 - \exp(-k(t - 2\tau))\right], \quad t > 2\tau. \tag{6}$$

Using the measurements of glucose at the point of the expected maximum– y_3 ($2\tau + \theta$), formula for calculating the coefficient b_2 is obtained:

$$b_2 = k * \left[y_3 - y_n - \frac{\lambda b_1 I_0}{k - b_1} \left[\exp\left(-k(2\tau + \vartheta)\right) - \exp\left(-b_1(2\tau + \vartheta)\right)\right] \right] /$$
$$G_0 \left[1 - \exp(-k\vartheta)\right]. \tag{7}$$

These parameters are used in the calculation of the predicted glycemic curve at given glucose loads. It should be noted, that their identification can be carried out not in a special test study, but in the context of normal breakfast, in which the amount of carbohydrate component in food is known.

Control problem. In determining the control problem under the conditions of standard injectable insulin therapy, it is necessary to take into account that the main task is to choose insulin dose that would facilitate the absorption of food nesessary to compansate energy consumption, for adequate vital activity of a particular patient and which whould ensure glycemic variability in the acceptable limits. The entire control process is divided into as many cycles as number of meals and insulin injections expected. One cycle from the moment of the initial injection to the next one is divided into three intervals. The first interval $[0, \tau_i]$ — the period of time from the start of injection to the food intake, the second interval $[\tau_i, \theta_i]$ — duration of assimilation of i-th food

intake, the third interval — $[\theta_i, \tau_{i+1}]$ — the duration of time between assimilation of food intake and subsequent food intake, or by injection of insulin depending on the intended regulation.

The solution of equations at these three intervals has the form:

$$y - y_n = (y_0 - y_n)\exp(-kt) + \frac{\lambda b_1 I_0}{k - b_1}(\exp(-kt) - \exp(-b_1 t)),$$

$$0 \le t \le \tau_i, \tag{8}$$

$$y - y_n = (y_0 - y_n)\exp(-kt) + \frac{\lambda b_1 I_0}{k - b_1}(\exp(-kt) - \exp(-b_1 t)) +$$

$$\frac{b_2 G_0}{k}(1 - \exp(-k(t - \tau_i))), \quad \tau_i < t \le \vartheta_i, \tag{9}$$

$$y - y_n = (y_0 - y_n)\exp(-kt) + \frac{\lambda b_1 I_0}{k - b_1}(\exp(-kt) - \exp(-b_1 t)) -$$

$$\frac{b_2 G_0}{k}(\exp(-k(t - \tau_i)) - \exp(-k(t - \vartheta_i))), \quad \vartheta_i < t \le \tau_{i+1}. \tag{10}$$

To obtain the formula for calculating insulin dose I_0 in injection before meal, in order to prevent glycemia level from going beyound the acceptable limits on the background of food assimilation, the solution of an equation on the food assimilation interval (9) is used, according to which:

$$I_0 = \frac{k - b_1}{\gamma b_1} * \frac{A(y_0 - y_n) + B * b_2 G_0 / k - (y_m - y_n)}{C - A}, \tag{11}$$

where $A = \exp(-k(\tau + D/G_0)); \qquad B = 1 - \exp(-k * D/G_0);$

$C = \exp(-b_1(\tau + D/G_0)); y_m$ — the upper limit of control range,

According to the described algorithm on the basis of the previous insulin-glucose testing, it is possible to obtain a daily prediction of the glycemic profile, taking into account the expected diet and insulin therapy. The input data is the fasting glucose concentration and glucose concentration before meal, its carbohydrate component, the upper limit of glucose level, the time interval over which after insulin injection it is necessary to take food. As a result, the predicted value and insulin dose are calculated.

It should be noted, that extremely complex processes that occur in the body with impaired carbohydrate regulation can not be accurately described by formal mathematical procedures, especially linear ones. The patient's sensitivity to insulin can vary over fairly short periods of time due to the influence of various external unforeseen factors that are difficult to take into account, such as quantitative and qualitative food composition, variety of physical activity, emotional component, other random disturbances that undoubtedly affect the glycemic variability, which couldn't be accurately considered using irregular measurements, even with the help of more detailed models. Actually, long-term forecasting for the whole day can reflect only a fundamental trend in the

dynamics of glycemia on the background of planned treatment and food regimens. In the presence of a glucometer, the correction of bolus dose before meal according to the described algorithm can be carried out not based on predicted glycemia level, but using real measurements. However, the algorithm allows to take into account the carbohydrate component, the level of glucose before eating and the limitations of maximum rise on the background of food intake that cannot be exceeded.

At the same time, if glycemic value predicted by the algorithm lies within the margin of error of the received from glucometer usage, the correction does not occur. If the obtained value is out of the acceptable range, finding the solution to the task continues with the new obtained initial value. Therefore, it is advisable to provide additional correction of insulin doses before meals by attracting discrete feedback from glucose measurements using glucometer. In this case, it can be used to prevent hypoglycemia in calculation of the predicted glycemic value during insulin injection before the next meal, when the effect of the previous meal is already over, and the previous insulin still continues to fulfill its function.

Thus, the synthesis of program perturbation control is implemented when the carbohydrate component in the food is taken into account, with discrete feedback connection by including in the algorithm the predicted glycemia value by the model or measurements by glucometer. The tight control by which the compensating insulin dose is calculated on condition that raising of glycemia to the upper limit is limited, can be somewhat mitigated by a higher assignment of the upper acceptable limit, which occurs at a lower dose values.

SOFTWARE IMPLEMENTATION

The developed algorithm for identifying the parameters of model equations and calculating the insulin dose, that compensates the amount of carbohydrates in the food, is implemented programmatically in Matlab environment. The central role in the program is taken by the module which implements an algorithm for selecting doses of insulin injections before meals and calculating the daily dynamics of blood sugar levels. This algorithm is based on dividing the entire daily interval into a sequence of food intake cycles. Under the food intake cycle, within the framework of this formalism, is taken to be a set of processes proceeding from one insulin injection to another. The algorithm includes procedures for calculating the required insulin dose, calculating the insulin dynamics between the moment of insulin injection and the beginning of food intake, calculating the glycemia dynamics during the intake of carbohydrates from the gastrointestinal tract into the bloodstream, and calculating the glycemia dynamics after the end of glucose intake from the gastrointestinal tract, calculating the predicted value at the time of the next injection and continues as many times as number of meals expected.

Simulation study of the algorithm was performed on models of different complexity: 1) on the *model*, that has *analytical solutions* — one compartment — MINIMODEL, that imitates glucose dynamics, regimen of meals and control actions of insulin 2) on the *two-compartment model* — MIDIMODEL, that includes insulin-glucose interconnections, 3) on the *complex model* — MAXMODEL, which simulates a *virtual patient*. This is a model of the type [38], adapted for use in our conditions. In

this model, the glucose balance in the body is realized through the insulin regulation subsystem and the counterinsular subsystem. It has seven differential equations, 15 nonlinear functional dependencies of sigmoidal type and more than 40 parameters. The structure of the model consists of insulin-dependent and non-insulin-dependent tissues, synthesis and secretion of insulin in the pancreas, insulin dynamics in the liver, in the intercellular fluid, dynamics of glucagon are simulated.
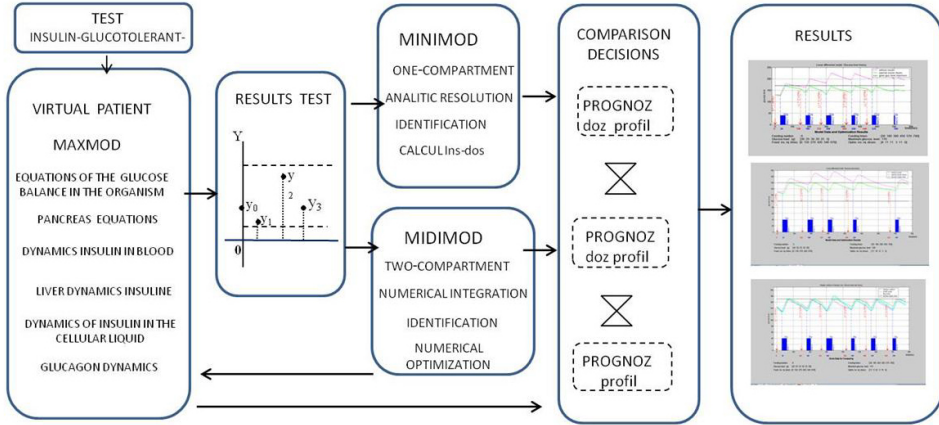

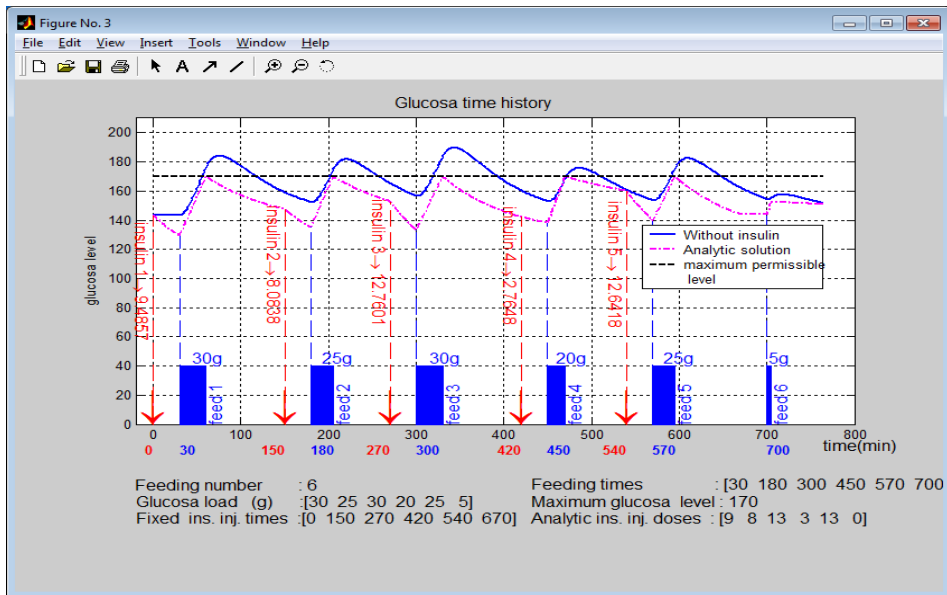**Fig. 2.** The structure of the simulation study

Fig. 3. Predicted glycemic profile obtained using the analytical solution of the control problem
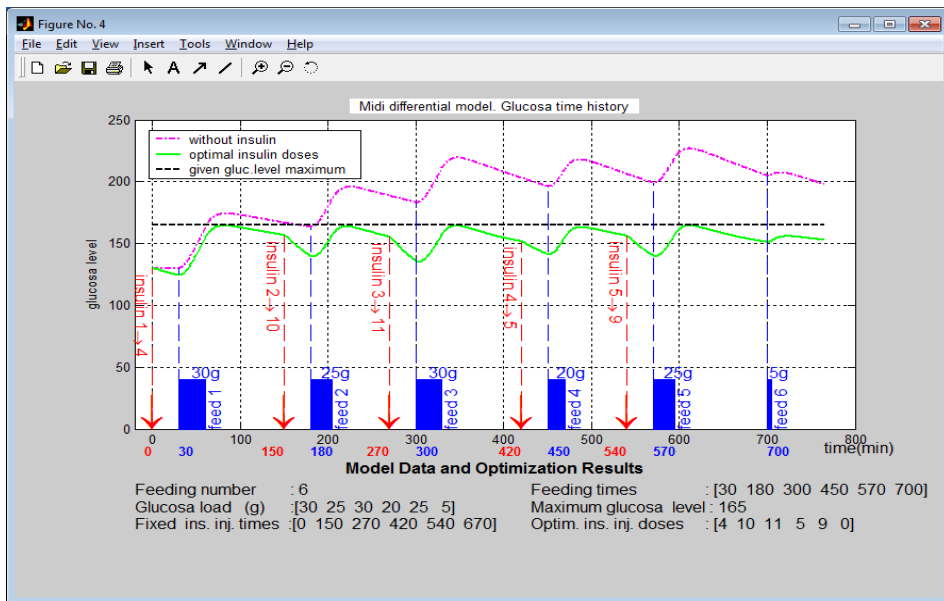
Fig. 4. Predicted glycemic profile (controlled / uncontrolled) obtained using a numerical algorithm for solving the control problem using two-compartment Midimodel

Software interface provides user-friendly navigation in terms of developed technology, in particular, model selection on which the appropriate stage of the work is currently being performed, analytical solution of the problem, numerical integration, identification, forecasting, graphic visualization.

The process of simulation research took place as follows. First, test insulin-glucose load was applied to the virtual patient model, key test points of measurement were applied to the MINIMOD and MIDIMOD models, by which their parameters were identified. Then their solutions with identical scheme of food intake per day were compared with compensating insulin doses calculated according to the appropriate algorithm on condition.

Figure 3 illustrates the glycemic profile forecast obtained by *analytical formulas*, in which six meals with compensating injections of insulin are planned.

Numerical algorithm. To simulate the process of glycemia correction in a model that takes into account glucose-insulin bonds, for which the analytical solution is problematic, the search for the optimal insulin dose was performed using a numerical algorithm by multiple integration of the corresponding equations. The optimal dose is the one at which the maximum level of glycemia reaches the upper permissible limit set by the user. The corresponding graphical illustration of the glycemia dynamics is shown (Fig. 4).

The simulation study of the algorithm obtained by the analytical solution was performed on models of different complexity. The optimal insulin doses obtained by this algorithm were applied to a model that simulates only glucose-insulin bonds and to a model that has a significant number of nonlinearities in its structure and simulates a real object — a virtual patient. The corresponding glycemic profile at different values of the upper permissible limit and various amount of carbohydrate components in the food are shown (Fig. 5 a,b), where
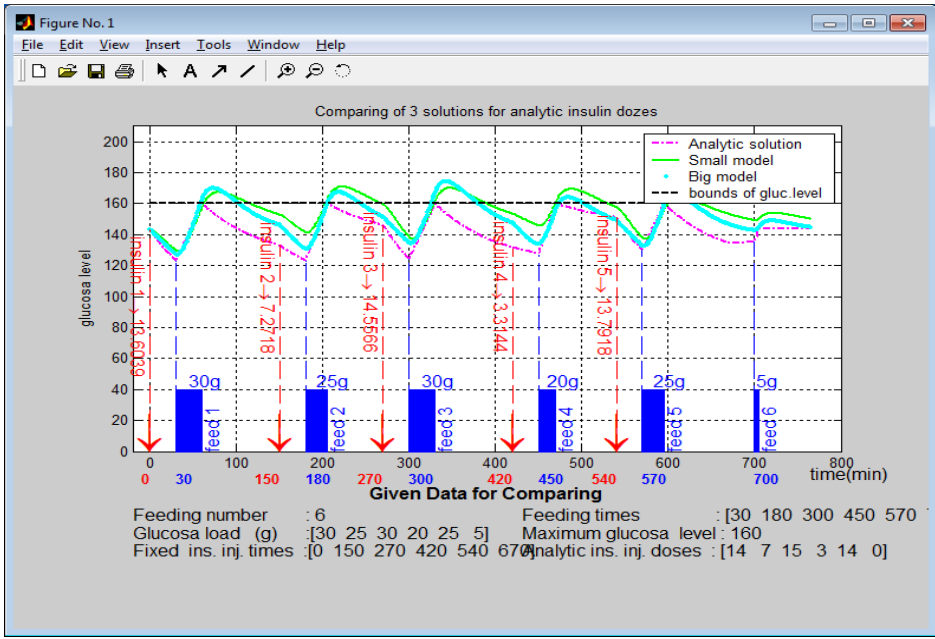
a)
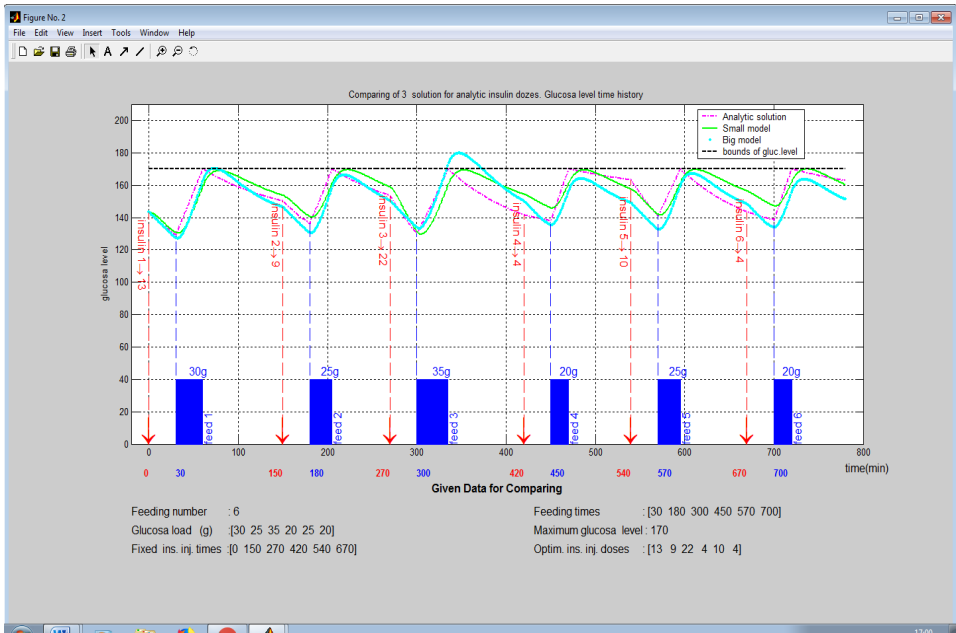
b)

Fig. 5, *a, b.* Glycemic profiles obtained on models of varying complexity

solid curve — the solution using a complex model with a large number of nonlinearities Maxmod, dashed curve — a model that simulates only the glucose-insulin interaction — Midimod, dash-dotted curve — analytical solution of the problem — Minimod.

Small discrepancies in the solutions of the forecasting problem obtained on at MAXMOD (virtual patient) model and MIDIMOD, an approximation model reproducing glucose-insulin bonds, indicate that it reproduces dynamic properties, even in the zeroth approximation. The profile obtained by analytical formulas differs more significantly, especially on the decline of the glycemic curve. But, in the key points, highs and lows, these discrepancies are not significant and are within measurement errors. This expected result can be considered a disadvantage, but it is compensated by a fairly simple computational procedure for obtaining compensatory doses of insulin, which are virtually indistinguishable from those used by insulin-dependent patients.

CONCLUSIONS

The proposed hierarchical modeling technology, based on the use of mathematical models of varying complexity, allows to conduct a complex of simulation studies to correct glycemia in diabetes at the preclinical and pre-ambulatory stages. During the simulation of forecasting procedure, configuration discrepancies of the glycemic profile obtained from different models were detected, but they are within the margin of error and reproduce the main trend in the dynamics of glycemia during meals and insulin injections. The calculated bolus doses of insulin are almost identical to those used by insulin-dependent patients. The simplicity of calculations using analytical formulas can be a prerequisite for the implementation of the algorithm in special-purpose portable autonomous devices, or in applications for Android OS.

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ІЄРАРХІЧНЕ ІМІТАЦІЙНЕ МОДЕЛЮВАННЯ. АЛГОРИТМ ПРОГНОЗУВАННЯ ГЛІКЕМІЧНОГО ПРОФІЛЮ У РАЗІ ДІАБЕТУ

Вступ. Цукровий діабет (розповсюджене хронічне захворювання) потребує пожиттєвого лікування і як будь-яке хронічне захворювання вимагає регулярного контролю і самоконтролю у домашніх умовах. Революційні зрушення у контролюванні глікемії у діабетичній терапії відбулися завдяки розроблення давачів безперервного моніторингу глюкози крові (БМГК), які можуть майже безперервно вимірювати концентрацію глюкози у підшкірній клітковині. Найпоширеніші перешкоди на шляху використання БМГК є пов'язаними з високими витратами на пристрої і відсутністю страхового полісу на їх закупівлю, передбачувана неточність давача і втома пацієнта від тривоги, яка пов'язана з неприязню до носіння пристроїв. Отже, давачі — це добре, але вони є дорогими, незручними і не всім доступними. Тож важливим завданням залишається постійний пошук альтернативних рішень.

Мета роботи — показати можливість використання технології ієрархічного моделювання для розроблення і дослідження алгоритму прогнозування глікемічного профілю як, певною мірою, альтернативи давачам неперервного контролю за умови обмежених нерегулярних вимірювань.

Результати. Розроблено програмно-алгоритмічну структуру для реалізації концепції ієрархічного моделювання. Показано можливість проведення досліджень на моделях різної складності. Синтезовано алгоритм інсуліно-глюкозо-толерантного тесту. Розроблено процедуру прогнозування добового глікемічного профілю за аналітичними формулами, яка надає можливість оцінити тенденцію динаміки глікемії як доповнення до нерегулярних вимірювань глюкози глюкометром. Проведено імітаційне дослідження, результатом якого є візуалізація глікемічного профілю на тлі передбачуваного регламенту прийому їжі і отриманих за аналітичним алгоритмом компенсувальних доз інсуліну.

Висновки. Запропонована технологія ієрархічного моделювання, яка базується на використанні різних за складністю математичних моделей, дає змогу проводити комплекс імітаційних досліджень корекції глікемії у разі діабету на доклінічному і доамбулаторному етапах. Внаслідок імітації процедури прогнозування виявлено розбіжності конфігурації глікемічного профілю, отриманого за різними моделями. Цей очікуваний результат компенсується за рахунок досить простої обчислювальної процедури отримання компенсувальних доз інсуліну, які практично не відрізняються від тих, що застосовують інсулінозалежні пацієнти. Простота обчислень за аналітичними формулами може бути передумовою для реалізації алгоритму в портативних автономних пристроях спеціального призначення або у смартзастосунках під ОС Андроїд.

Ключові слова: *цифрова медицина, ієрархічне моделювання, система регуляції глікемії, алгоритми ідентифікації, прогнозування, керування, імітаційні доклінічні випробування.*