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MODELING OF PANCREAS-LIVER INTERACTION UNDER CONTROLED HEMODYNAMICS

Autonomous software (AS) was created to simulate the dynamics of the glucose-insulin-glycogen-glucagon relationship in a healthy person. Our AS is based on a quantitative mathematical model consisting of three components: a model describing the pancreas-liver and the pancreas-skeletal muscles relationships; a model describing blood circulation in the branched cardiovascular system, taking into account neurohumoral regulators of cardiac function, vascular tone and total blood volume; and a model describing blood filtration in the renal glomeruli and tubular reabsorption. A glucose tolerance test (GTT) was also programmed. Test simulations demonstrated adequate model responses. The program is integrated into a specialized computer simulator (SCS). It allows studying mechanisms that, depending on the dynamics of exogenous and endogenous physicochemical variables, dynamically form multidimensional health landscape of biometric indicators. The effect of extreme blood flow increase on the dynamics of the main variables of the model was also simulated without additional carbohydrate intake. AS is created in C#, and can be delivered as an Exe-module for IBM-compatible computers. Medical students can be additional users of the AP as an additional didactic tool. The AS ensures the preservation of all simulation data for future reviews and publications. The AS can be used by future endocrinologists in their training. Physiologists interested in the integrative physiology of cellular life support are recommended to use the SCS.
Keywords: glucose homeostasis, physiological systems, mathematical model, visualization, students

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МОДЕЛЮВАННЯ ВЗАЄМОДІЇ ПІДШЛУНКОВОЇ ЗАЛОЗИ ТА ПЕЧІНКИ В УМОВАХ КОНТРОЛЬОВАНОЇ ГЕМОДИНАМІКИ

Автономне програмне забезпечення (АПЗ) створено для моделювання динаміки взаємозв'язку ендогенних агентів глюкоза-інсулін-глікоген-глюкагон у здорової людини. АПЗ базується на кількісній математичній моделі, що складається з трьох компонентів: моделі, що описує взаємозв'язок підшлункова залоза-печінка; моделі, що описує кровообіг у розгалуженій серцево-судинній системі, враховуючи нейрогуморальні регулятори серцевої функції, судинного тонусу та загального об'єму крові; та моделі, що описує фільтрацію крові в ниркових клубочках та канальцеву реабсорбцію. Також було запрограмовано тест на толерантність до глюкози (ГТТ). Тестові симуляції продемонстрували адекватні реакції моделі. Програма інтегрована у спеціалізований комп'ютерний симулятор (СКС). Він дозволяє вивчати механізми, які, залежно від динаміки екзогенних та ендогенних фізико-хімічних змінних, динамічно формують багатовимірній ландшафт здоров'я у просторі біометричних показників. Вплив екстремального збільшення кровообігу на динаміку основних змінних моделі також було змодельовано без додаткового притока вуглеводів. АПЗ — це автономне програмне забезпечення на C#, що постачається як Exe-модуль для IBM-сумісних комп'ютерів. Студенти-медики можуть користуватися АПЗ як додатковим дидактичним засобом. АПЗ, що забезпечує збереження всіх даних моделювання для майбутніх розглядів та публікацій, може бути використане ендокринологами у дослідженнях. Фізіологам, які цікавляться інтегративною фізіологією клітинного життєзабезпечення, рекомендується використовувати СКС.
Ключові слова: гомеостаз глюкози, фізіологічні системи, математична модель, візуалізація, студенти

Introduction

Irregular intake of carbohydrates can create energy problems in human sensitive cells like neurons, kidney cells, hepatocytes, and myocytes. Special mechanisms smoothing out the flow of glucose into the blood and providing glucose homeostasis evolved. Important roles in glucose homeostasis play the pancreas producing insulin, hepatocytes, and myocytes that

transform the exec amount of blood glucose into liver and muscle glycogen. However, namely the liver, accumulating up to 120 g glycogen and capable of its reverse transformation to blood glucose when its concentration essentially drops, is the main organ dynamically reacting to blood glucose lack. Normally, the urine does not contain essential concentration of glucose. At the same time, the mechanism responsible for blood glucose homeostasis has of limited power. Therefore, even under physiological conditions, extreme glucose intakes lead to elevated concentrations of glucose in the urine which finally removes serious volumes of glucose. In endocrinology, special glucose tolerance test (GTT) is applied to assess the efficiency of mechanisms providing glucose homeostasis [1].

The main product of the pancreas is the hormone insulin. It performs two functions: first, it promotes the entry of glucose into the cell; second, it activates the transformation of excess glucose into glycogen and its accumulation in the liver and muscles. An additional product of the pancreas is the hormone glucagon. Its production is activated when there is not enough glucose in the blood.

It is under such conditions that the reverse transformation of glycogen into glucose occurs in hepatocytes. Glucagon enhances the action of the heart pump and affects blood pressure. Therefore, we model these physiological processes, since they are an important link in the energy supply of cell metabolism.

The model of glucose homeostasis

Various models have been proposed for an in-depth study of the glucose homeostasis mechanism and its possible disturbances (for examples, [2-8]). The models [5,6] help understand the mechanisms of type 2 diabetes by demonstrating how disruptions at the cellular level lead to impaired glucose regulation throughout the body.

The model we proposed describes dynamic interactions of blood glucose ($G(t)$), insulin ($I(t)$), liver glycogen ($g_L(t)$), muscle glycogen ($g_M(t)$), and glucagon ($g_G(t)$) depending on velocities of glucose incomes ($v_{G+}(t)$) and consumption ($v_{G-}(t)$). The model takes into account that in certain cells (hepatocytes, fats, and skeletal myocytes) glucose consumption is associated with insulin concentration while other specialized cells directly consume glucose.

$$T_G \frac{dG(t)}{dt} = G(t) + \alpha \cdot I(t) - \beta \cdot W(t), \quad (1)$$

In (1), T_G is the time constant of glucose dynamics, $W(t)$ - presents the power of general biological work, coefficient $\alpha \neq 0$ only for hepatocytes, fats, and skeletal myocytes. Virtually, by altering the value of coefficient β, the user can simulate nuances of glucose consumption dynamics in chosen cell types.

The dynamics of insulin is described by following differential equation:

$$T_I \frac{dI(t)}{dt} = \gamma \cdot G(t) - \chi \cdot I(t), \quad (2)$$

In (2), γ and χ are approximation constants.

Special mechanism providing blood glucose homeostasis is modeled using the differential equation describing excess glucose transformation into $g_L(t)$ and $g_M(t)$, and reverse transformation of $g_L(t)$ to $G(t)$.

$$T_{gL} \frac{dg_L(t)}{dt} = \begin{cases} k_G^g \cdot (G(t) - G_{cr}) - g_L(t), & G(t) \geq G_{cr} \\ 0, & G(t) < G_{cr} \end{cases}, \quad (3)$$

$$T_{gM} \frac{dg_M(t)}{dt} = k_G^{g_M} \cdot (G(t) - G_{cr} - g_M(t)) - g_M(t), \quad (4)$$

$$G(t) \geq G_{cr}; g_M(t) < g_M^{\max}$$

In (4), T_{gM}, $k_G^{g_M}$, and $g_M^{\max}$ are approximation constants.

The next equation describes the dynamics of glucagon:

$$T_{gG} \frac{dg_G(t)}{dt} = \begin{cases} \delta \cdot (G(t) - G_{cr}) - g_G(t) - g_u, & G(t) > G_{cr} \\ \delta \cdot (G_{cr} - G(t)) - g_G(t), & G(t) \leq G_{cr} \end{cases}, \quad (5)$$

In (5), T_{gG}, δ, and g_u are approximation constants.

So, the equation system (1)-(5) describes the dynamics of the glucose-insulin-glycogen-glucagon relationships in a healthy individual.

Autonomic software (AS) was created for the numerical solution of this system of equations on a computer. The primary user of this program was intended to be a

specialist (endocrinologist), so a problem-oriented, user-friendly interface (UI) was developed. In parallel, a simulator was developed that reproduces the integrative responses of human internal organs to a wide range of endogenous and exogenous dynamic factors [9,10]. They are subdivided into eight clusters. The appearance of a special screen form that allows the user to operate with the simulation results is shown in Figure 1. The user can arbitrarily generate the desired set of characteristics for graphical visualization. Initially, these characteristics are grouped by related features into eight clusters on the left side of the window. On the right side of the window are two sub-windows where the variables to be analyzed are collected. These sub-windows allow the model's input and output variables to be separated. By opening each cluster one by one, the user selects a variable in it and moves it to one of the sub-windows on the right side. This quickly generates a set of analyzed variables in the form of graphs.

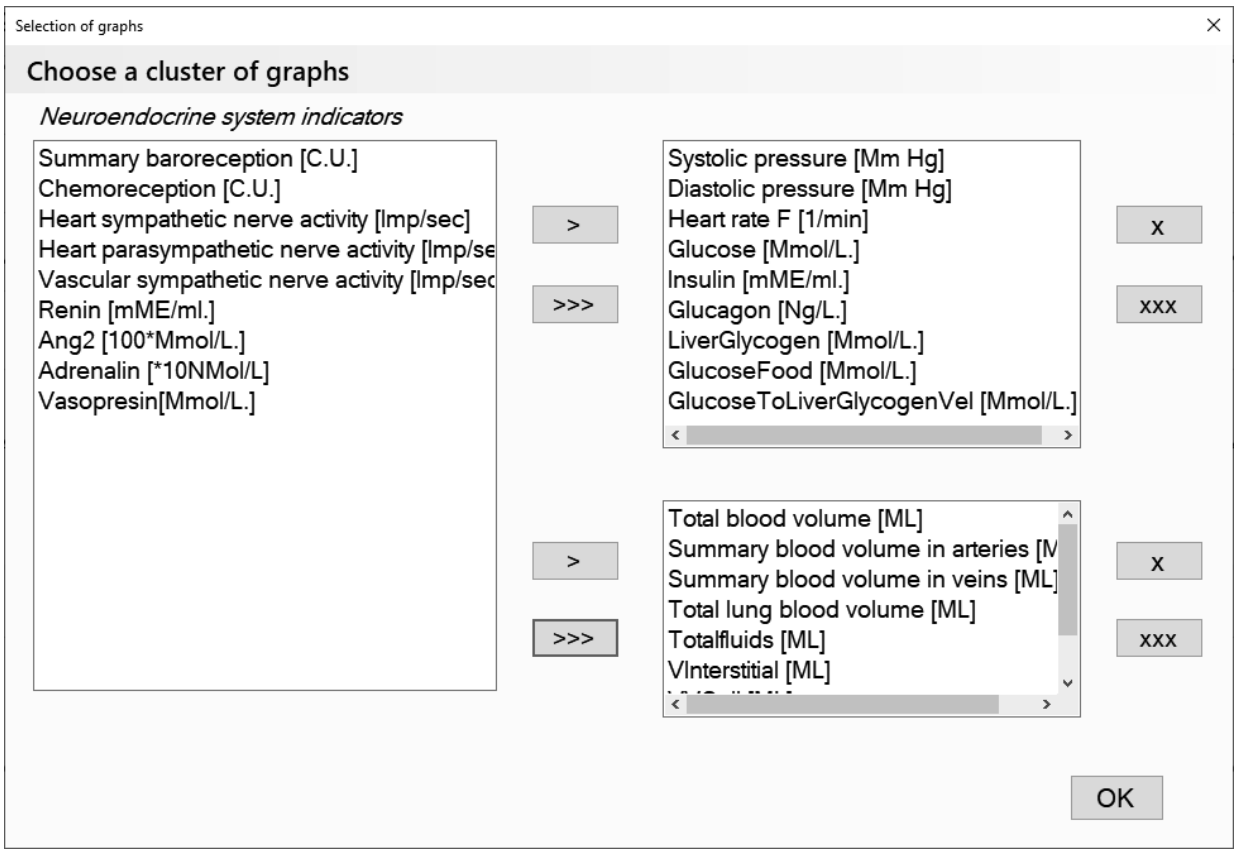

Fig. 1. The screen form of UI for actualizing sets of input-output variables

In particular, our complex model that also describes the overall circulation includes special equations concerning hemodynamic effects of glucagon through its dilating influence on coronary arteries and increase of coronary circulation. The latter effect elevates the myocardium power. Besides, assistant equations describing velocities of glucose incomes $v_{G+}(t)$ and consumption $v_{G-}(t)$ create an opportunity to simulate different scenarios of glucose dynamics depending on given $v_{G+}(t)$ and $v_{G-}(t)$.

Naturally, current rates of glucose incomes $v_{G+}(t)$ and consumption $v_{G-}(t)$ are unpredictable variables. Our software provides with special options to simulate both these variables using a list of analytical functions and screen forms for modifying values of coefficients. Two examples below illustrate this modification by actualizing values of constants $v(0), \eta_1, \eta_2, \eta_3, \varphi, and\, v_2$.

$$v_{G+}(t) = \begin{cases} v(0) + \eta_1 \cdot t, & v_{G+}(t) \le v_1 \\ v(0) - \eta_2 \cdot t, & v_{G+}(t) \ge v_2 \end{cases},$$

$$v_{G+}(t) = v(0) + \eta_3 \cdot \sin(\varphi \cdot t), \quad 0 < (t) \le t_1.$$

In contrast, $v_{G-}(t)$ depends on organs' activities generally correlating with regional blood flows. Therefore, the equation describing this dependency looks like (6):

$$\frac{dv_{G-}}{dt} = a_1 \cdot q_b(t) + a_2 \cdot q_h(t) + a_3 \cdot q_k(t) \cdot (1 + a_4 \cdot q_{kr}(t)) + a_5 \cdot I \cdot (c \cdot q_h(t) + a_6 \cdot q_{lm}(t)), \quad (6)$$

Here, $q_b(t)$ is the summary brain flow, $q_h(t)$ is the coronary blood flow, $q_k(t)$ is the kidney glomeruli blood flow, $q_{kr}(t)$ reabsorption fraction, $q_h(t)$ and $q_{lm}(t)$ represent blood flows in insulin-depended organs, while $a_1 - a_6$ are approximation constants.

$$\frac{dv_L}{dt} = \partial \cdot C_L(t) + a_{11} \cdot W(t) \cdot I(t) \cdot (c \cdot q_h(t) + a_{12} \cdot q_{lm}(t)) + a_{13} \cdot q_h(t) + a_{14} \cdot q_k(t) \cdot (1 + a_{15} \cdot q_{kr}(t)) + a_{16} \cdot I(t) \cdot (c \cdot q_h(t) + a_{17} \cdot q_{lm}(t)), \quad (7)$$

In (7), ∂, a_{11} - a_{17}, and c are approximation constants.

Food glucose velocity $v_{FG+}(t)$ is proportional to the volume F_{G+} of glucose intake, so $v_{FG+}(t) = k_g \cdot F_{G+} / t$, where k_g characterizes the average intensity of glucose entry from the gastrointestinal tract into the blood.

Glucagon altering the lumen of coronary arteries modulates their resistance $R_C(t)$ relatively to initial value of $R_C(0)$ characteristic for basal coronary flow $q_C(0)$:

$$R_C(t) = R_C(0) \cdot (1 - \varpi_6 \cdot q_C(0) / q_C(t)), \quad (6)$$

This elevates the ventricle contractility $k(t)$

$$k(t) = k(0) + \varpi_4 \cdot (q_C(t) - q_C(0)). \quad (7)$$

In (6) and (7), $\varpi_4, \varpi_6, and\ k(0)$ are constants.

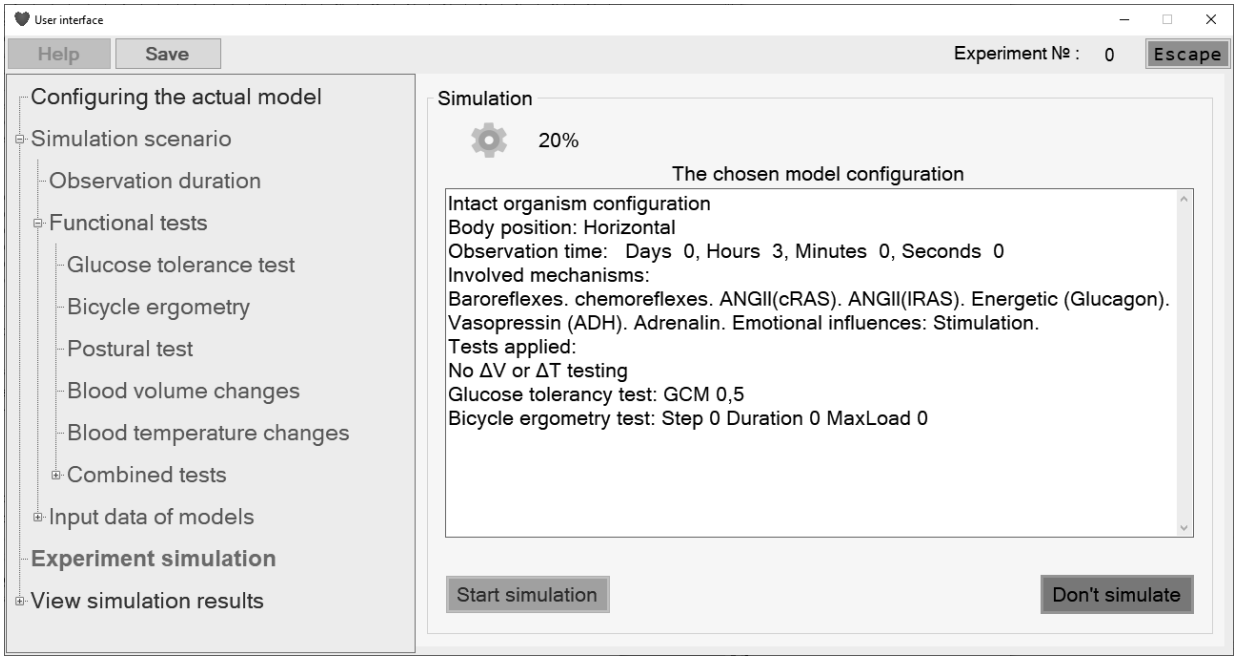

Fig. 2. The screen-form indicating a part of options for configuring the actual model and constructing the simulation scenario (left) and information concerning the chosen model configuration (right)

Examples of simulations

Our simulator has two versions: AS and extended simulator (ES). The latter includes models of the functionally integrated internal organs that optimize cell life support (see [9,10]).

Simulations presented further are addressed both to programmers and experts modeling human physiology. At the same time, the reader's belief in the simulator depends in no small part on the adequacy of the simulations.

ES can simulate effects caused by other organs and physiological systems. Therefore, before to consider simulations provided AS, it is useful to look at Figure 3. It presents main hemodynamic characteristics simulated ES. They show that transient processes in the system resolve quickly: a steady-state circulation regime is observed for almost the entire ten-minute exposure period. This guarantees that the dynamics of all variables in the glucose homeostasis model provided by AS are determined by the dynamics of variables specific to the glucose homeostasis model. Naturally, if the characteristics of the coupled models change, the dynamics of the glucose homeostasis model variables will also change.

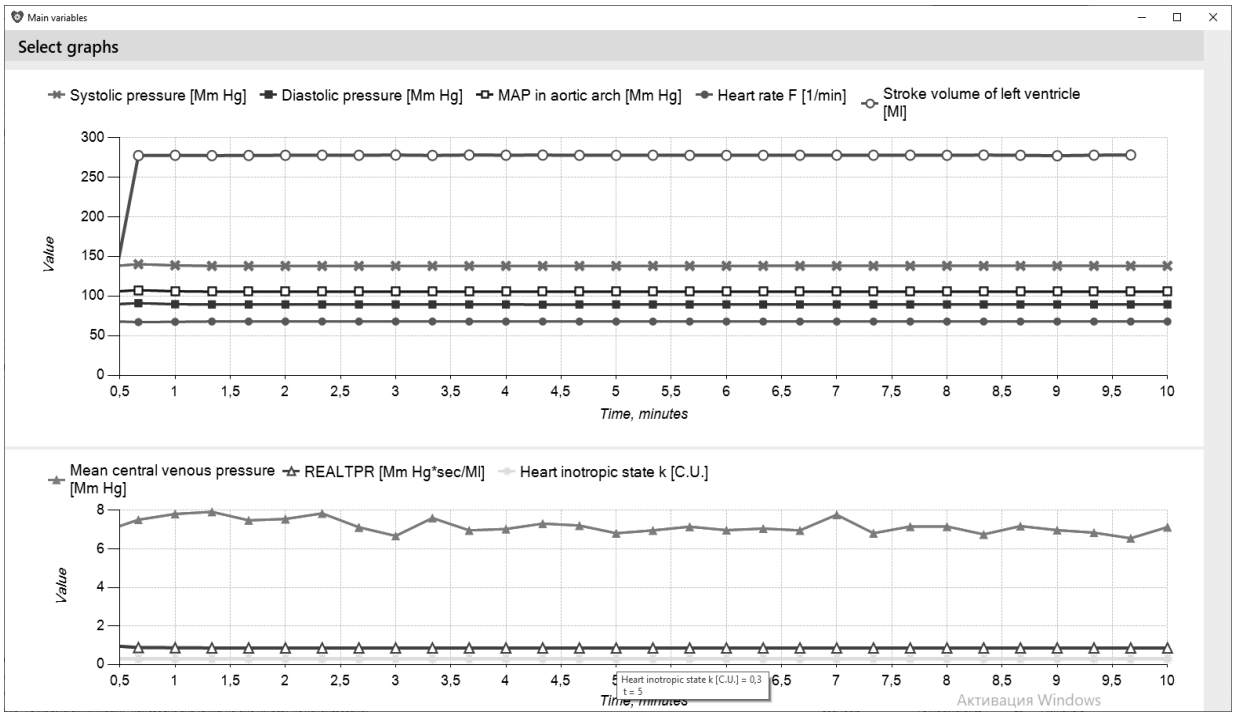

Fig. 3. Hemodynamics in control simulation

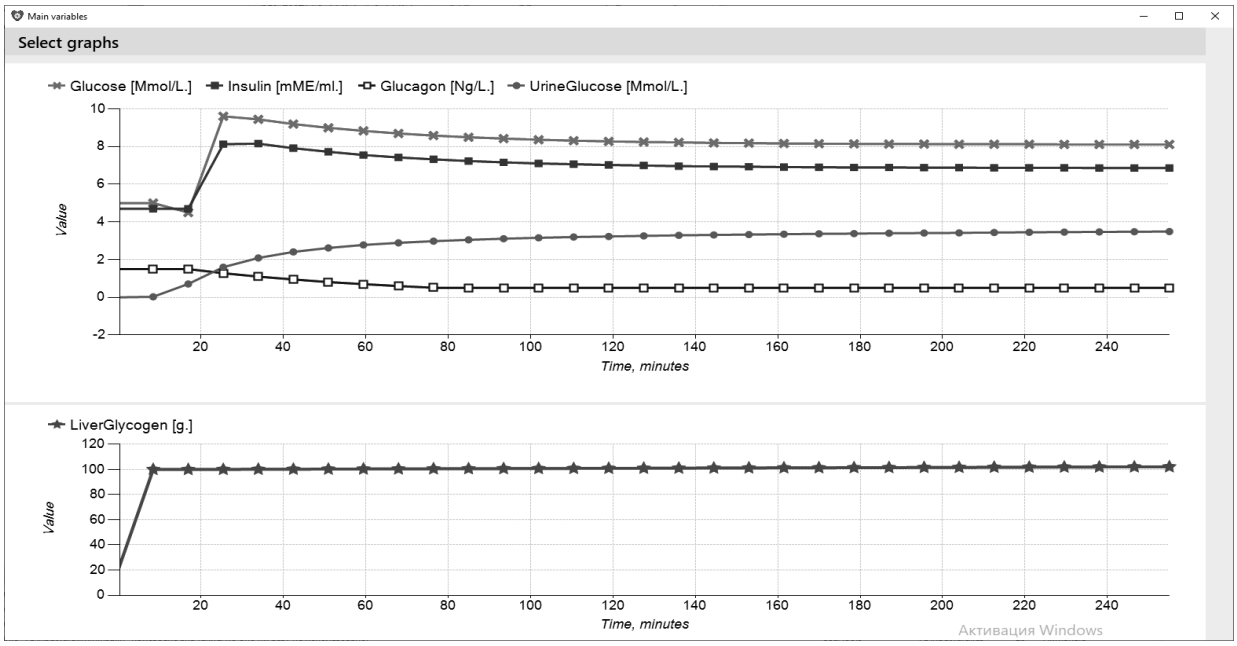

Fig. 4. Simulated dynamics of glucose, insulin, glucagon, and urine glucose (upper curves) and liver glycogen (bottom) in a healthy person model under stable glucose production (0.07 mmol/min) and consumption (0.05 mmol. /min) rates for 4.15 hours real time exposure

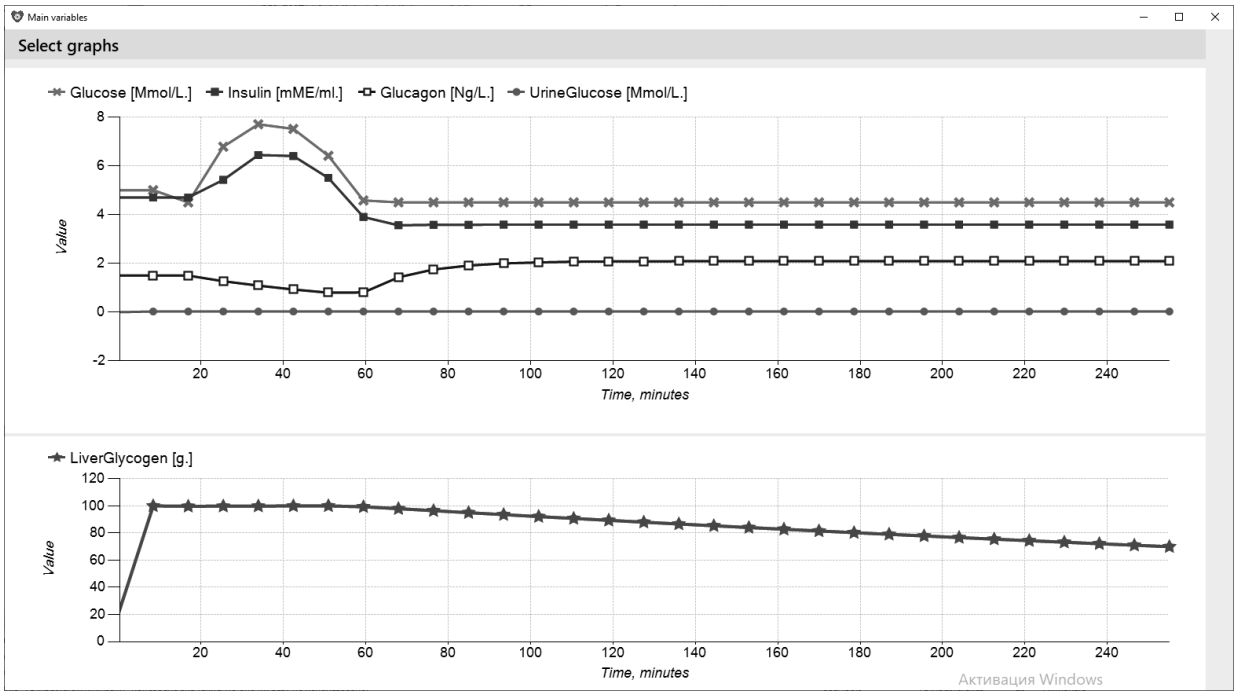

Fig. 5. Simulated dynamics of glucose, insulin, glucagon, and urine glucose (upper curves) and liver glycogen (bottom curve) in a healthy person model under stable glucose production (0.07 mmol/min) and consumption (0.075 mmol. /min) rates for 4.15 hours real time exposure

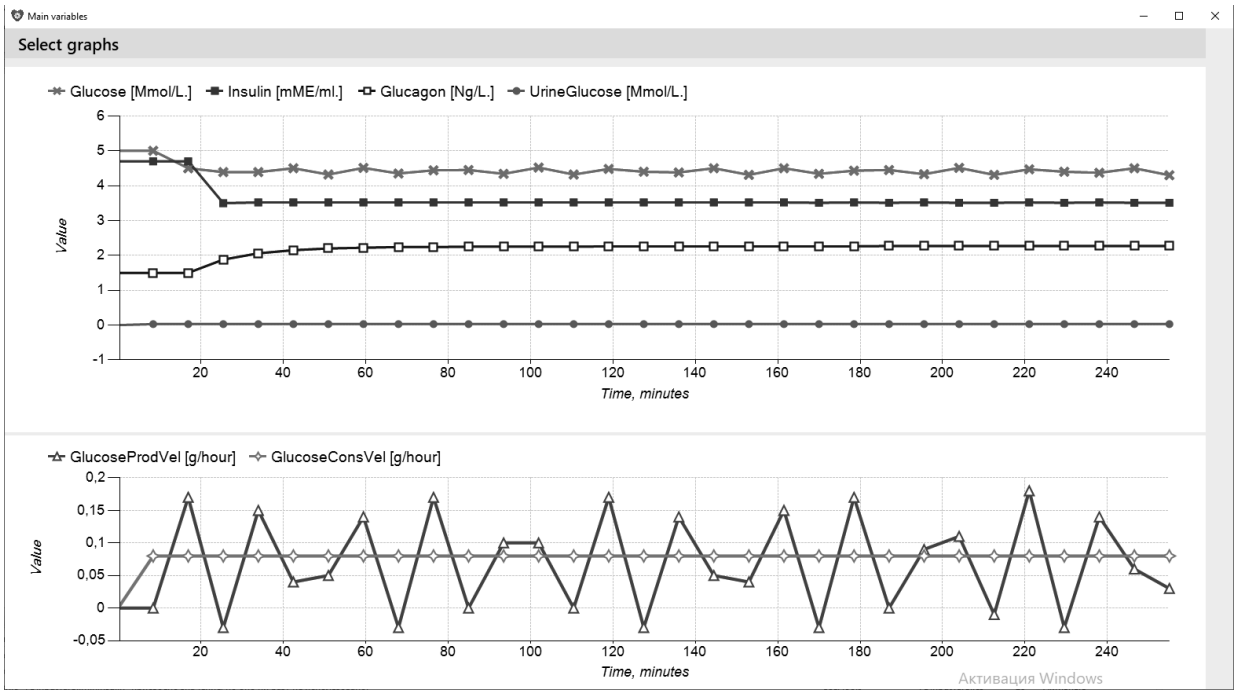

Fig. 6. Simulated dynamics of glucose, insulin, glucagon, and urine glucose (upper curves) and liver glycogen (bottom curve) in a healthy person model under periodic changes in the rate of glucose production according to a sinusoidal law and stable consumption (0.075 mmol. /min) rate for 4.15 hours real time exposure

Figures 3-6 demonstrate that our simulator is mainly adequate at least in the time intervals considered. This gives us the opportunity to simulate specific medical GTT-test.

Simulating glucose tolerance test - GTT

Pictures 7 and 8 illustrate simulations of standard GTT for different healthy persons and persons diseased with type 1 diabetes.

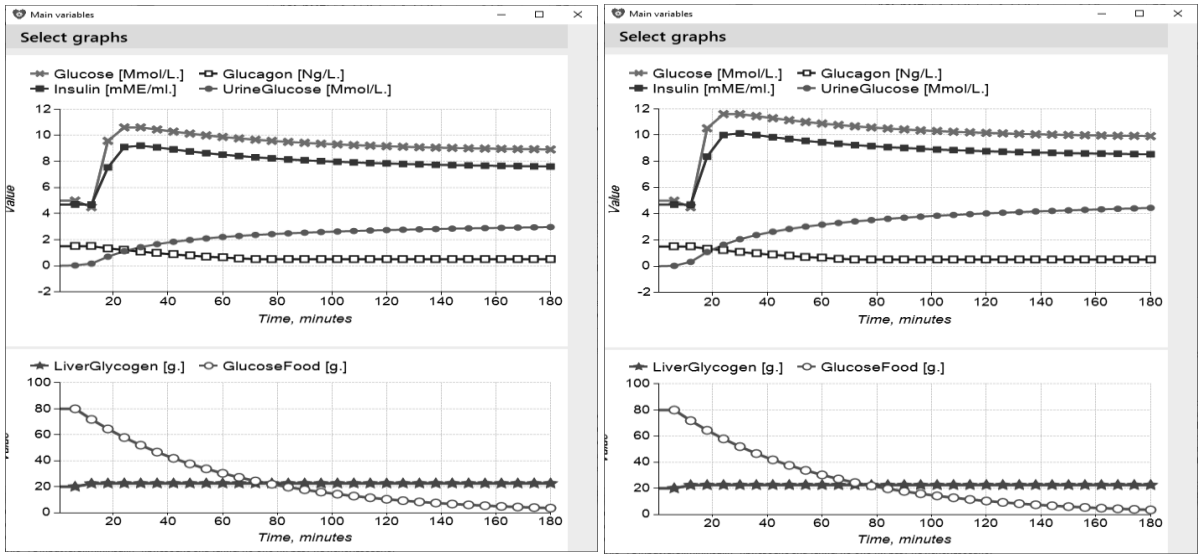

Fig. 7. Two simulated GTT (glucose tolerance tests) on models of the same healthy person. The left picture displays dynamics of glucose, insulin, glucagon, and urine glucose (upper curves) and liver glycogen and test glucose income (bottom curve) under stable glucose consumption rate of 0.06 mmol. /min but for glucose production rate of 0.085 mmol. /min. The right picture displays these same curves for the case of 0.095 mmol. /min glucose production rate and stable consumption rate of 0.06 mmol. /min.

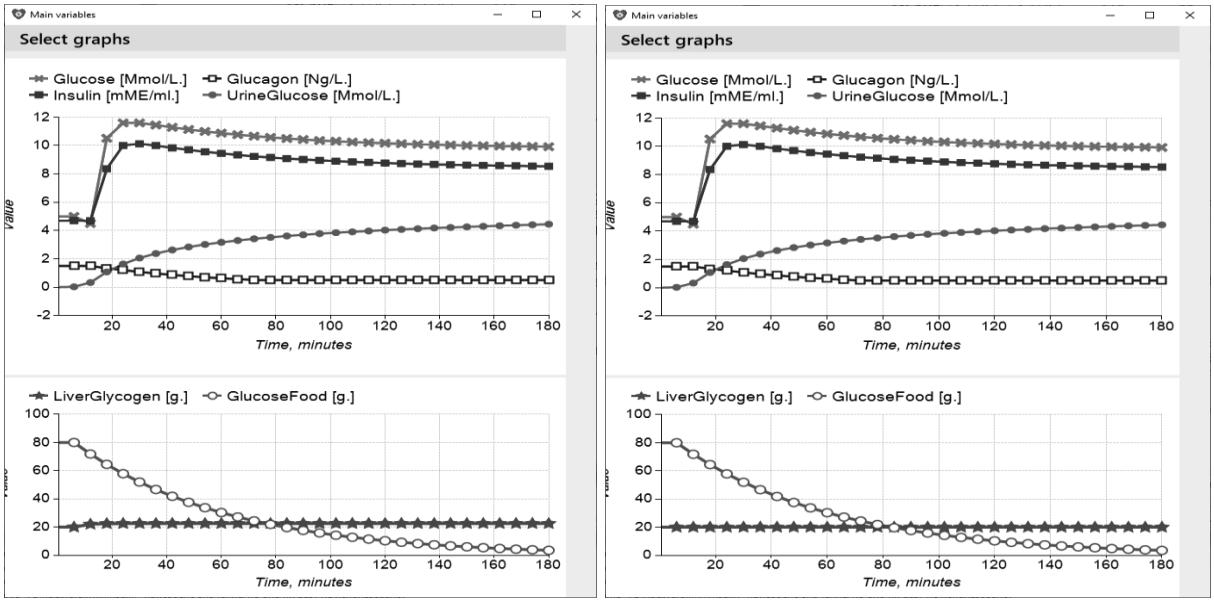

Fig. 8. Two simulated GTT (glucose tolerance tests) on models of persons having problems with glucose homeostasis. The left picture displays dynamics of glucose, insulin, glucagon, and urine glucose (upper curves) and liver glycogen and test glucose income (bottom curve) under stable glucose consumption rate of 0.06 mmol. /min. but for glucose production rate of 0.085 mmol. /min but with two-times weak homeostasis while the right picture displays these same curves for the uncontrolled blood glucose.

The graphs in the last figure should be compared with those on the left side of Figure 7. The most significant difference is evident when comparing the dynamics of urine glucose: as blood glucose homeostasis weakens, the amount of glucose in the urine increases. Under providing of real GTT, this is an objective indicator for the diagnosis of type 1 diabetes.

Discussion

In a real organism, most of biological variables are also influenced by other endogenous factors not accounted for in our model or in simulations demonstrated. Therefore, the proposed model is limited in its simulation capabilities. At the same time, an analysis of available clinical data shows that our model is generally adequate. This conclusion is also true during comparison of simulation results provided by our model with similar models by other authors (e.g., [1-7]), Moreover, our model offers a number of new possibilities for theoretical research aimed at understanding of fundamental physiological mechanisms and practical consideration of their nuances. For example, the inclusion of a muscle-mediated mechanism of glycogen storage, control of excess urinary glucose excretion, and the ability to model different pathways that deplete liver glycogen make our model a useful tool capable of providing insight into the uncontrolled underlying mechanisms that drive individual differences during GTT.

When performing a glucose tolerance test, the physician has no information on the levels of residual glycogen in the liver or muscles. The rate of accumulation of one of these products influences the rate of accumulation of the other. However, we were unable to find quantitative data on these residual products in the literature, and therefore cannot confirm the accuracy of the modeled rate dynamics. However, we note that incorporation of this model into an extended model describing the interaction of human internal organs has provided the first tool for theoretically studying the role of neuroendocrine modulators in glucose homeostasis.

To improve the effectiveness of our simulator, we plan to model the effects of lactate, adrenaline, and fat concentrations. In particular, it is well known that under low insulin, the body breaks down fats, creating ketone bodies (acetoacetate and β-hydroxybutyrate) for energy. Blood ketones normally less than 0.6 mmol/L, under Type 1 diabetes can elevate up to danger level of 3 mmol/L with symptoms extreme thirst, frequent urination, nausea, vomiting, abdominal pain, and fruity-smelling breath, requiring emergence care. As our complex model describes cardiovascular and kidney-urinary systems, its proper advancement could make the simulator usable for deeper study of pathological scenarios too.

Conclusion

A quantitative mathematical model of human glucose homeostasis has been developed. The model is implemented as a C# program. The program can function both as a standalone executable module and as part of a newly proposed integrated program that simulates the fundamental physiological patterns of the dynamic interactions of human internal organs. The program can serve as an additional didactic tool for visualization of the glucose-insulin-glycogen-glucagon dynamic relationships in a healthy individual.

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