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A structural model of glucose regulation for building prognostic algorithms for controlling insulin therapy

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Abstract
This work discusses the physiological processes influencing the dynamics of blood glucose concentration in patients with diabetes mellitus and approaches to mathematical modeling of blood glucose metabolism are proposed to build predictive models as required for automating insulin therapy. Insulin-dependent and non-insulin-dependent processes occurring in the liver, kidneys, and other organs and tissues, the hormones regulating these processes, and enzymes modulating the rates of these processes are considered. A unified scheme is presented which systematizes the interaction of these substances in various processes with indications of localizations.

Introduction

Insulin therapy is the main approach to compensating for type 1 diabetes mellitus (DM), and has the objective of maintaining glycemia within normal range. Many studies have addressed a variety of methods of administering insulin to patients, including studies using intraperitoneal administration of insulin [1]. However, currently the most common method of insulin therapy in patients with diabetes is subcutaneous insulin infusion, as this method ensures higher safety levels due to the lower invasiveness of the procedure as compared with other methods.

A key current direction in progressing the management of diabetes is the development of new technologies and devices for optimal control of blood glucose (BG) levels in patients; in particular, many studies have sought to create automatic personalized wearable systems for adaptive administration to patients in terms of both basal insulin in continuous mode to maintain BG concentrations in the normal range and insulin boluses for timely stabilization of sudden changes in BG dynamics occurring due to external influences on patients' bodies [2]. Implementation of a system providing automatic insulin therapy requires, first, development of an algorithm for controlling insulin administration modes to patients based on prediction of the patient's state of glycemia. A key component of an insulin pump control system is a mathematical model of glucose metabolism, which, working from data from patients and predicted changes in BG dynamics, calculates the optimal parameters of insulin boluses for infusion.

Correlation of the calculated insulin doses to be administered to the patient in the ongoing state is ensured by the adequacy of the pump control algorithm. This correlation can be achieved by constructing a mathematical model providing for the most physiological description of the glucose regulation system in type 1 DM and, thus, allowing quantitative assessment of the dynamics of the metabolic system and analysis of all possible scenarios for the processes of synthesis, storage, and breakdown of BG. The physiological approach to mathematical modeling primarily involves mapping the system under consideration, i.e., creating a graphical representation of the structure and interaction of metabolic pathways in the body's subsystems.

The work presented here generalizes data on glucose metabolism, and includes the description of the principles of the processes of carbohydrate metabolism, their localizations, and their hormonal regulation factors, with the aim of creating a comprehensive mathematical model of blood glucose regulation in patients with type 1 DM, which will in turn ensure timely responding on the part of the automated insulin therapy system to predicted rises in BG to above-normal levels.

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The challenge of mathematical modeling of the glucose regulation system

The blood glucose regulation system is a multi-level system. Many studies seeking to describe its behavior using mathematical tools have been published. Creation of a comprehensive mathematical model of blood glucose dynamics is still an urgent task in the development of automated insulin therapy systems, as many models, despite the completeness of the description of some metabolic processes, have gaps in their inclusion of other, equally important, processes of carbohydrate metabolism.

One of the best known and complete mathematical models is that of BG regulation developed at the University of Padova [3–6]. This model provides quite accurate descriptions of the absorption of glucose into the blood when a patient ingests food and the regulatory effect of glucagon on changes in blood glucose levels. At the same time, this model does not take account of the apparent influences of the key processes of glucose regulation—glycogenesis, glycogenolysis, and gluconeogenesis—on glucose concentrations in various compartments, which does not correspond to real human physiology and makes it difficult to refine and study the model.

Use of models of this type in insulin pump therapy requires a description of the processes of the interactions between the human body and the technical insulin dosing system. The process of the distribution of insulin after subcutaneous administration to a patient is represented in a number of models both by multicompartmental systems and by differential equations with delay. One basic models is that of Cragen et al. [7], with two compartments describing two-stage insulin absorption by first-order kinetics. Similarly, the insulin system is described in the nonlinear model of Govorka et al. [8, 9]. In addition, the Govorka model describes in detail the effect of subcutaneously administered insulin on glucose kinetics. However, this model addresses control of glucose concentrations in patients with type 1 diabetes mellitus only in conditions of fasting, such that assessment of blood glucose dynamics is incomplete. Subcutaneous administration of insulin is also provided for in the model of glucose-insulin metabolism in type 1 diabetes described in [10, 11]; a distinctive feature of this model is a new approach to modeling carbohydrate digestion and the absorption system: the authors suggested that the glycemic index of foods and carbohydrate availability should be considered as factors influencing the rate of glucose absorption. This approach allows more accurate descriptions of the effects of patients' carbohydrate intake on postprandial blood glucose levels to be obtained. Despite the fact that this model reflects the patient's post-prandial condition with considerable accuracy, the overall system of equations does not provide such an adequate level of output parameter accuracy, because of the simplified approach to modeling the kinetics of the glucose-insulin system and the absorption of subcutaneously administered insulin.

Despite the large number of existing models, there is still a need for an integrated approach to mathematical modeling of the glucose regulation system in patients with type 1 diabetes mellitus, which involves consideration of the physiology of human metabolism and taking into account all factors influencing the blood glucose level.

Physiology of glucose metabolism and methods of mathematical glucose metabolism description

Glucose metabolism is a complex system made up of the processes of synthesis, breakdown, and conversion of substances, the organs, and tissues in which these processes occur, and the enzymes and hormones regulating the rate and direction of the reactions of carbohydrate exchange.

The key external influence on glucose metabolism is a person's food intake. Ingested carbohydrate-containing foods move through the esophagus into the stomach and then enter the intestine, where pancreatic enzymes and enzymes secreted by intestinal microbiota further degrade carbohydrates into glucose or other monosaccharides, which are actively transported through intestinal epithelial cells into lymph and blood vessels. This process is well modeled by a three-compartment model [3] with first-order kinetics and a rate coefficient of glucose transfer from the stomach to the intestine with a nonlinear dependence on the quantity of food remaining in the stomach.

Glucose is distributed from the plasma to organs and tissues depending on their energy needs, a process using special carrier proteins. The best-known type of glucose transporters is the GLUT family, which includes several isoforms, each with its own specific expression pattern in particular organs and tissues. In turn, the needs of different tissues and the nature of their glucose consumption may vary depending on their physiological functions and the conditions obtaining in the body. Glucose uptake by insulin-dependent tissues is mediated by the action of the transporter protein GLUT-2 in the liver and the insulin-sensitive transporter GLUT-4 in muscle and adipose tissues [12, 13]. Muscle tissue uses glucose to produce energy during physical activity, while adipose tissue cells convert glucose into fat for long-term energy storage. Glucose consumption by insulin-dependent tissues is represented in [4] by a nonlinear dependence on glucose in tissues using the Michaelis-Menten equation, where the maximum rate of glucose utilization in insulin-dependent tissues is not constant but has a linear relation with insulin in the intercellular space, with

a shift corresponding to the maximum rate of the reaction in the absence of insulin.

Insulin-independent glucose uptake is characterized by distinctive mechanisms of glucose uptake that do not require stimulation by insulin. Glucose transport into central nervous system tissues, particularly into the cells of the brain—an extremely energy-consuming organ—is mediated by GLUT-1 transporter protein [14]. Insulin-independent glucose consumption is currently poorly described in the literature and is assumed by many models to be constant, though glucose transport into insulin-independent tissues is also known to obey Michaelis-Menten kinetics, which expresses a nonlinear dependence of the rate of the process [15, 16].

The kidneys are also insulin-independent glucose-consuming organs. They play a key role in regulating blood glucose levels by means of reabsorption. In the case of diabetes mellitus, where the body produces excess quantities of glucose, as shown in [17], excess glucose not used to nourish cells is converted into fructose via the polyol pathway. This process occurs in all body tissues but is most intense in the muscles and liver, because of their large numbers of mitochondria. In addition, when there is excess glucose in the blood, the kidneys release glucose into the urine (glycosuria). The renal glucose excretion subsystem is described in [4] in terms of a conditional function expressing a linear dependence on BG content. This model is not strictly correct because there is a basal level of glucose excretion, though in general terms it approximates the process quite accurately.

The liver is an important organ in maintaining glycemia: unlike other organs, which are primarily glucose consumers, the liver acts as a regulator of glycemic control. This is because the liver contains the enzyme glucokinase, which catalyzes the formation of the central metabolite glucose-6-phosphate, a compound whose formation is involved in most metabolic pathways. Glucokinase is an isoform of the hexokinases present in all organs and promoting the oxidation of glucose to glucose-6-phosphate. Glucokinase is noted in [13, 18] to be a sensor of BG levels involved in the process of activation of the secretion of regulatory hormones by the pancreas.

All key metabolic processes affecting the BG level occur in the liver. The first stage of glucose metabolism is glycolysis, which is the process of decomposition of glucose into two pyruvic acid molecules [19], which can then be utilized in aerobic metabolism in the Krebs cycle, where it is oxidized to acetyl-CoA and then "burned" or directed to glucose synthesis in the process of gluconeogenesis if the body needs to provide cells with energy in situations of stress. An alternative pathway for glucose oxidation is the pentose phosphate pathway, which is a series of biochemical reactions oxidizing glucose-6-phosphate with formation of reduced NADP coenzyme [20]. The current state of the body, i.e., the needs of the cell at any given moment, and the oxidized NADP content in the cytosol determine the next stage of glucose-6-phosphate transformation and ensure switching of glucose metabolism between glycolysis and the pentose phosphate pathway [20]. A mathematical description of the pentose phosphate pathway is currently not provided in the literature, though the role of this process in glucose homeostasis is large because of the influence of its reaction products on the activity of glycolytic enzymes.

However, after eating a meal, especially one rich in carbohydrates, some proportion of glucose not immediately required by the body for metabolism accumulates in the liver and muscles in the form of the polysaccharide glycogen during glycogenesis [21], this compound serving as a reserve source of glucose and energy. When hypoglycemia occurs and there is no supply of glucose from food for some long period of time, the process reversing glycogenesis, i.e., glycogenolysis, is activated and liver glycogen is broken down into glucose [22]. As the mutually alternating operation of these processes is based on reciprocal switching of the activity of the enzymes glycogen synthase and glycogen phosphorylase, which depends directly on the regulatory actions of insulin and glucagon, changes in the levels of enzyme activity can be represented as four first-order differential equations expressing alternating changes in enzyme activity, which in turn set the direction of glycogen dynamics in the liver. Changes in glycogen content in the liver are determined by the difference in the rates of glycogen accumulation and the reverse process—breakdown back to glucose—and this can be expressed using Michaelis-Menten equations for enzyme kinetics.

When glycogen stored in the liver is depleted in conditions of prolonged fasting, alternative energy sources are activated in the human body, predominantly the gluconeogenesis pathway forming glucose from non-carbohydrate sources [23]. The mechanism of gluconeogenesis includes a cascade of enzyme reactions occurring in different cellular compartments. Mathematical expression of series of sequential biochemical reactions during gluconeogenesis produces systems consisting of large numbers of differential nonlinear equations describing the rates of formation of substances in each reaction; this makes the final model complicated and difficult to solve numerically. As only the final reaction product is significant for modeling, this problem can be solved by reducing the number of reactions simulated by approximating the rate curve for the synthesis of substances, ultimately reducing the system to a set of two differential equations describing the dynamics of

glucose formation in two compartments: mitochondrial and cytosolic:

$$\frac{d\,E_1\,(t)}{dt} = k_{r1} \cdot p_l\,(t) - k_{r2} \cdot E_1\,(t)\,; \tag{1}$$

$$\frac{d\,E_n\,(t)}{dt} = k_{r2} \cdot E_1\,(t) - v_{\text{gng}}, \tag{2}$$

where E_1 and E_n are intermediate products of gluconeogenesis reactions in the mitochondrial and cytosolic compartments respectively, p_l is the pyruvate content in the liver; k_{r1} and k_{r2} are rate constants, and v_{gng} is the rate of gluconeogenesis.

Like the processes of glycogenesis and glycogenolysis, gluconeogenesis is controlled by the actions of certain enzymes. In particular, the synthesis of glucose from pyruvate, whose hepatic dynamics are described by Eq. 3, is controlled by the switching of the enzyme pyruvate carboxylase between active and inactive phases depending on the current state of the body, which can be expressed by two first-order differential equations, Eqs. 4 and 5, taking the regulatory effects of insulin and glucagon into account:

$$\frac{d\,p_l\,(t)}{dt} = U_{id} - k_{r1} \cdot p_l\,(t) - k_{Kc} \cdot p_l\,(t)\,. \tag{3}$$

In Eq. 3, the change in the liver pyruvate content p_l is determined by the rate of glucose consumption by insulin-dependent tissues U_{id} and the total rate of consumption of pyruvate for glucose synthesis and energy production in the tricarboxylic acid cycle (Krebs cycle).

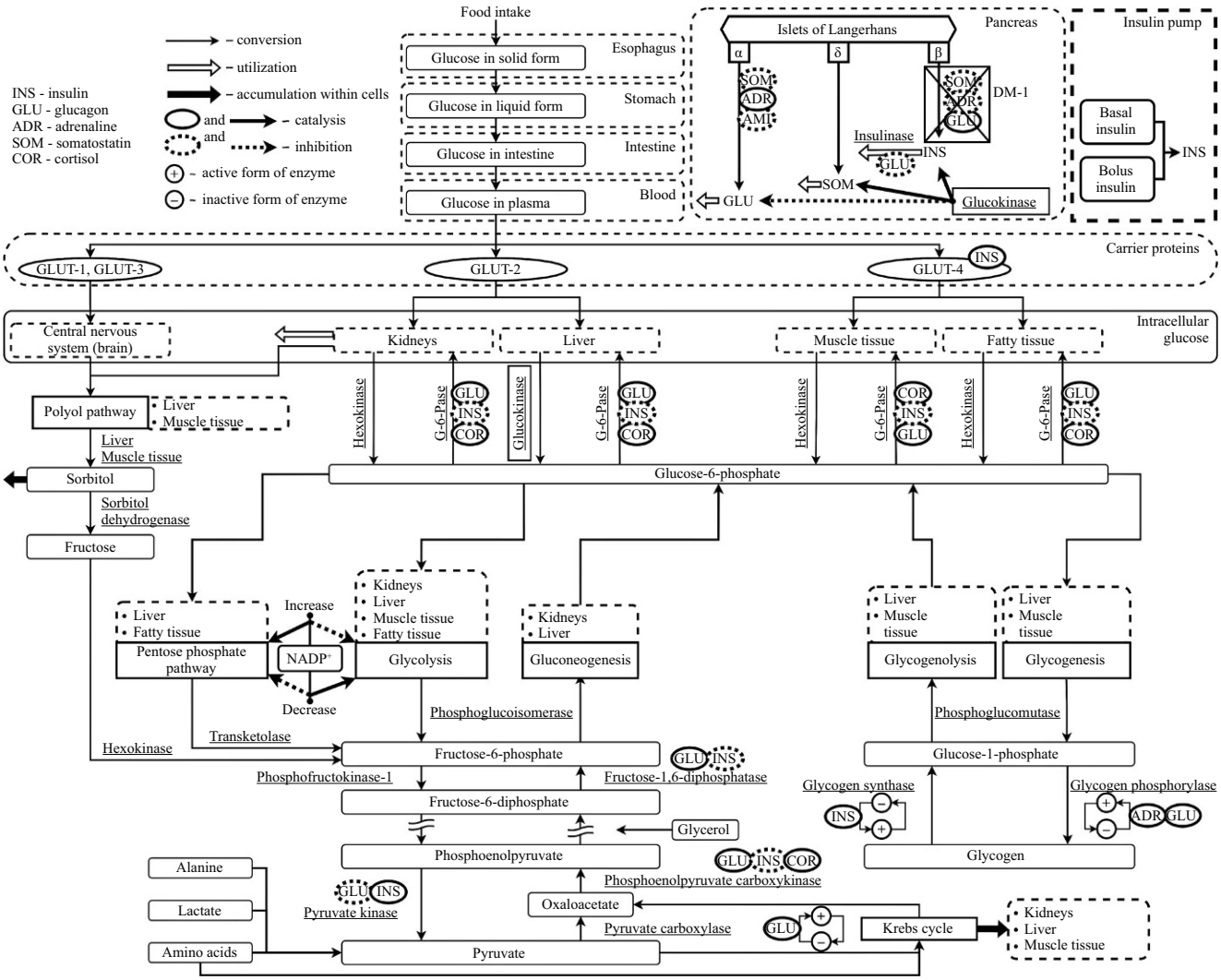

Fig. 1 Schematic showing glucose metabolism (see text for explanation)

The mathematical interpretation of changes in enzyme activity is represented by the following equations:

$$\frac{d\,P_c^a\,(t)}{dt} = k_{h1} \cdot H_p\,(t) \cdot P_c^n\,(t) - k_{h2} \cdot I_l\,(t) \cdot P_c^a\,(t)\,; \quad (4)$$

$$\frac{d\,P_c^n\,(t)}{dt} = k_{h2} \cdot I_l\,(t) \cdot P_c^a\,(t) - k_{h1} \cdot H_p\,(t) \cdot P_c^n\,(t)\,, \quad (5)$$

where P_c^a and P_c^n are the active and inactive phases of pyruvate carboxylase respectively, H_p is the plasma glucagon concentration; k_{h1} and k_{h2} are rate constants.

The interconnected operation of metabolic processes comes from the fact that they are regulated by hormones. Blood glucose levels are controlled primarily by the actions of three hormones: insulin, glucagon, and cortisol [15, 21]. Insulin and glucagon are produced by β- and α-cells in islets of Langerhans in the pancreas respectively, and have regulatory functions operating in opposite directions; cortisol is secreted by the adrenal cortex and has actions similar to those of glucagon. Insulin lowers blood glucose levels by increasing the glucose absorption by body cells; it also stimulates the conversion of excess glucose into glycogen and reduces glucose production in the liver. Glucagon and cortisol help increase plasma glucose concentrations by stimulating glycogenolysis and gluconeogenesis. In addition, cortisol also reduces the ability of body cells to utilize glucose as an energy source by stimulating fatty acid consumption.

Systematized data on the above processes supporting glucose metabolism are presented in Fig. 1.

This illustration presents the key metabolic processes and their locations, along with factors catalyzing and inhibiting substance synthesis and breakdown. The map of glucose metabolism includes descriptions of hormone secretion and degradation, the regulatory effects of hormones and enzymes on the course of processes determined by the operation of transport proteins involved in glucose consumption, and metabolic processes including the polyol pathway, the pentose phosphate pathway, glycolysis, gluconeogenesis, glycogenolysis, glycogenesis, and the Krebs cycle. Due to the reversibility of most of the reactions involved in glycolysis and gluconeogenesis, the scheme omits the chain of reversible transformations of fructose-1,6-diphosphate and phosphoenolpyruvate, including the formation of 2-phosphoglycerate, 3-phosphoglycerate, 1,3-diphosphoglycerate, glyceraldehyde-3-phosphate, and dihydroxyacetone phosphate, only the irreversible reactions characteristic of these processes being reflected.

Conclusions

Automation of insulin therapy for patients with type 1 diabetes mellitus is an actively developing area of biomedical engineering. One promising approach to constructing algorithms for the automatic control of automated insulin therapy systems consists of developing the most complete and physiologically based predictive mathematical models, these requiring descriptions of all significant processes affecting the dynamics of blood glucose concentration.

The present work examines the most important processes occurring in the liver, kidneys, muscles, and other body tissues. A number of processes, such as the distribution of subcutaneously administered insulin, the absorption of glucose from ingested food, and the renal excretion of glucose, are either well studied or have good mathematical descriptions. At the same time, some processes do not as yet have a generally accepted mathematical description. This primarily relates to gluconeogenesis and insulin-independent glucose consumption. The processes forming the gluconeogenic pathway are known and can be described by enzyme kinetics equations. At the same time, in order to reduce the number of calculations employing a method for approximating cascades of sequential reactions using two equations is proposed. This scheme of glucose metabolism includes all relevant key processes, the hormones and enzymes involved in them, as well as their locations. It can be used to build more complete mathematical models which provide the basis for predicting a wider range of situations and making longer-term forecasts, which in turn will help improve the efficiency of automated insulin therapy.

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