UDC 572. 511:61+004.94
DOI: 10.15587/1729-4061.2018.141451

DEVELOPMENT OF AN APPROACH TO MATHEMATICAL DESCRIPTION OF IMBALANCE IN METHABOLIC PROCESSES FOR ITS APPLICATION IN THE MEDICAL DIAGNOSTIC INFORMATION SYSTEM

В роботі розглянуто проблему діагностики метаболічного синдрому, пов'язаного з порушенням вуглеводного та ліпідного обміну. Запропоновано новий підхід до визначення порушень балансу обмінних процесів, який базується на поєднані моделей проточного культиватора та Лотки-Вольтерры. Використання моделі проточного культиватора забезпечує можливість об'єктивної оцінки початкових умов поведінки системи, в якості якої виступає організм людини, і дозволяє узгодити в часі основні параметри моделі. Визначені початкові умови для моделювання обмінних процесів із використанням моделі Лотки-Вольтерры. Використання даних умов дозволяє визначити стійкість обмінних процесів з урахуванням індивідуальних значень окружності талії, окружності стегон, ваги, частоти серцевих скорочень, віку, систолічного і діастолічного артеріального тиску, розрахункового значення Харріса-Бенедикта.

Перехресна перевірка на можливий розвиток метаболічних процесів у людей з нормальним і порушеним обміном речовин показала, що розроблений підхід може бути використаний в медичних установах для ранньої діагностики метаболічних порушень. Для визначення балансу обмінних процесів, які характерні для людей без і з метаболічними порушеннями, були проаналізовані ретроспективні дані дослідження ста п'ятдесяти п'яти молодих людей, які спостерігалися протягом декількох років в Харківській міській клінічній лікарні № 11 (Україна).

Запропонований підхід є основою математичного забезпечення для інформаційної медичної діагностичної системи визначення порушень балансу обмінних процесів, що розробляється. Використання такої системи в подальшому дозволить детально дослідити вплив різних гендерних, територіальних та вікових характеристик на збалансованість метаболічних процесів в організмі людини

Ключові слова: проточний культиватор, модель Лотки-Вольтерри, метаболічний синдром, баланс, підхід, депонування енергії, витрати енергії

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1. Introduction

Metabolic syndrome (MS) is a complex of pathological conditions the medico-social significance of which puts it in the category of crucial problems of the 21st century. It occurs in every fourth middle-aged patient. Prevalence of both MS in general and its comorbid conditions (obesity, arterial hypertension, insulin resistance, type 2 diabetes mellitus) is ever growing from year to year [1, 2].

Currently, these "diseases of civilization" acquire a pandemic character affecting most civilized countries on every continent. According to the WHO information, prevalence of obesity averages 30 % of the world cases and reaches up to 50 % in highly developed countries. Scientists predict that the number of people suffering from obesity will reach about 300 million by 2025. In Ukraine, prevalence of overweight is 33 % for men and 27 % for women [3, 4]. The growing number of children with overweight and obesity is a warning fact [5, 6].

According to [7], 10 % of women and 15 % of men have MS as a disease associated with metabolic disorders in absence of carbohydrate metabolism violations, 42 and 64 % at increased fasting melitemia and/or impaired tolerance to glucose and 78 and 84 % at diabetes mellitus, respectively. Therefore, the metabolic rate is an indicator of early MS development.

Metabolic disorders within the MS framework are asymptomatic for a long time, often beginning to form in juvenile and preadult age, long before the clinical manifestation of hypertension, atherosclerotic vascular lesions, type 2 diabetes which determines heterogeneity of clinical manifestations at various stages of this pathology development [8].

Available data indicate urgency and need for early diagnosis of both MS and obesity for timely prevention and treatment of these disorders.

Improvement of existing approaches to diagnosing metabolic disorders, including application of new mathematical models and methods, is an important step in timely MS risk identification.

The use of advanced approaches and application of a modern mathematical apparatus for increasing efficiency of MS diagnostics and improving quality of therapist's work a priori require automation of this process. Creation of an information system for diagnosis of metabolic disorders will make it possible to identify them at an early stage of development and will be a simple and at the same time highly effective means of both informational and medical decision support.

2. Literature review and problem statement

Correlation analysis is widely used in anthropology and medicine with construction of regression scales and normative tables [9, 10]. In the simplest case, it uses the following data: length and weight of the body, circumference of chest, waist, hips, etc. This method allows doctors to identify physical development violations and construct the profile of person's physical development. Its disadvantage is that when the number of features increases, the calculation process and especially data analysis become much more complicated. Also, shortcomings include the lack of consideration of indicators of metabolic processes which enable determination of imbalance of metabolic processes at early stages of disease development.

For objective comparison of morphological and functional characteristics of organs and systems of people with various physical data, the method of indices is used. The indices express ratios of individual somatometric features with the aid of a priori mathematical formulas. The most common is the body-mass index (BMI) which is used to determine the body weight (reduced or high) and obesity which is the basis for assessing physical development of a child's growing body or physical condition of an adult. It is calculated by the formula:

BMI (kg/m^2)=body weight (kg)/height (m^2).

It should be noted that BMI has an important prognostic value for characterization of cardiovascular diseases [3]. However, this index is only aimed at classifying the people with obesity without the possibility of predicting the course of metabolic processes in the human body and does not ensure early diagnosis of metabolic disorders.

There is also a method of mean-square deviations with subsequent construction of tables, nomograms or morphograms (graphs) of an individual or group profile [9]. Disadvantage of this method consists in a complexity of taking into account the necessary calculation parameters and the intricate experimentation procedure.

In the current literature, there are data on the use of various approaches to forecasting development of obesity and its consequences on the basis of methods of mathematical statistics [11]. In particular, the application of methods of multivariate analysis of retrospective data has made it possible to develop a method for predicting the risk of abdominal syndrome [12].

The regression analysis is often used to predict a person's condition. For example, a logistic model of predicting development of metabolic syndrome in a juvenile age is known. The separating function (p) whose coefficients were estimated by the Rosenbrock method contains average systolic and diastolic arterial pressure, triglycerides, glucose and uric acid level. If $p<0.5$, then the probability of metabolic syndrome is more than 50 %. If $p>0.5$, the likelihood of developing a metabolic syndrome is small or the metabolic imbalance will be regressive [13]. Disadvantage of the model consists in age limitations as well as the specificity that manifests itself in comorbidity of metabolic abnormalities and as a consequence, small applicability of the models obtained for each case of concomitant diseases.

A chemostat model is used in biology. It allows one to describe mathematically the adaptive system under certain environmental conditions and, if necessary, calculate its productivity. A mathematical model based on a flow chemostat of Michaelis-Menten type describes coexistence of two species of microorganism populations [14]. The obtained results enable control of the processes of production of useful biomass and obtaining of various final products. A steady-state process was studied when the input nutrient substrate flow is constant or periodic. All stationary states of such a system were determined. Production processes are controlled by varying amplitude and frequency of oscillations of the substrate concentration at the chemostat inlet.

A modified chemostat model is known. It includes diffusion, chemotaxis and nonlocal competitive losses. The system of equations includes random parameters to take into account the impact of external environment of ecosystem on population. The three dynamic regimes proposed depend on the values of the system parameters: transition from the initial state to spatially homogeneous stationary state, spatially inhomogeneous distribution of the population concentration and elimination of the population concentration [15].

There are dot models of dynamics of biomasses of main phytoplankton species. For example, four variants of describing dynamics of the phytoplankton community biomass in an aquatic ecosystem were proposed. There is a continuum set of positive equilibrium solutions in closed models and there is a finite set of isolated nonnegative equilibrium solutions in open models for flow systems. Stability of equilibrium solutions was proved for models without taking into account intracellular content of substance. This can be done under certain restrictions [16] for the models taking into account the intracellular nutrient content.

Dynamic models are often used to predict and evaluate the object states. One of such most common and well-studied models is the Lotka-Volterra model. This model was used to describe interaction of cognitive and/or emotional modes of brain [17] as well as modeling of infectious diseases [18].

The Lotka-Volterra models are also used to describe metabolic processes. A mathematical model of diabetes mellitus and the process of metabolism in the human body is known [19]. This model allows one to describe variation of sugar and insulin levels in the body of a patient with diabetes mellitus for injection and non-injection methods of treatment.

Definition of metabolic abnormalities is a difficult task requiring automation of the process by creating medical information systems (IS) that are able to perform all necessary actions to diagnose these disorders.

A calculator of basic metabolism [20] which uses such indicators as age, height, gender and weight was widely used to calculate the metabolic rate.

A calculator of basic metabolism [21] is also known which calculates the metabolic rate with the use of such parameters as age, height, level of physical activity, gender, breastfeeding and weight. Disadvantage of these calculators is their specificity and narrow directedness.

An automated system for diagnostics and selection of individual pharmacotherapy of arterial hypertension is known [22]. This system based on data of age, height, weight, blood pressure, heart rate and pulse metering data enables calculation of a number of informative features (body-mass index, vegetative pulse rhythm indicator, vegetative index and true sinus rhythm). The system is aimed at determining the degree and stage of arterial hypertension and the risk of stroke or myocardial infarction and selection of drugs for hypertension treatment. Disadvantage of the system is its orientation only to patients with arterial hypertension.

A program implementation of the model for calculating the level of sugar and insulin which involves determining of the coefficients of metabolic model in the human body using a number of characteristic features was proposed in [19]. These features characterize binding of glucose to insulin, the degree of insulin dissolution and absorption as well as the degree of absorption of glucose which enters the body with food. This program drawback consists in its specificity since it is aimed at assessing insulin and blood sugar levels for people with diabetes of type I and II.

Also, medical information systems are known that use various mathematical apparatuses to automate the process of detecting metabolic disorders in the presence of other concomitant diseases. Such diseases include, e.g. diseases of the cardiovascular system [23], other disorders of metabolism [24] and adaptive mechanisms of the human body [25]. There are results of the use of mathematical models and methods that describe compensatory mechanisms of the body for making a diagnostic decision in the fields of anesthesiology [26], ophthalmology [27], psychiatry [28] and ecology [29]. The main disadvantages of the systems examined are their specificity, narrow orientation and the lack of ability to determine imbalance of the metabolic occurring in the processes of obesity formation.

The issue of early diagnosis of the metabolic syndrome associated with a metabolic disorder that requires development of a specialized approach that predicts the course of metabolic processes in the human body for early diagnosis and prevention of complications of the pathology in question remains unsolved.

3. The aim and objectives of the study

The study objective was to develop an approach to mathematical description of imbalance of metabolic processes in a course of metabolic syndrome formation. This will improve quality of analysis of medical information using the obtained model as an element of the decision support system being the part of a medical diagnostic information system for determining metabolic disorders in the human body.

To achieve this objective, it was necessary to solve the following tasks:

– to choose and justify structure of a mathematical model that adequately describes balance of metabolic processes and initial conditions for imbalance modeling;

– to suggest an algorithm for using a mathematical model to determine balance of metabolic processes in the human body;

– to implement numerically the model and propose a diagram of interaction between the modules of the medical diagnostic information system in which the developed mathematical model is a part of the decision support system.

4. Choice and justification of the structure of mathematical description and determination of initial conditions for modeling

The main concept of the developed approach is the combined use of two mathematical models, namely, the flow cultivator and the Lotka-Volterra models.

The flow cultivator model is used to calculate the system's performance and allows one to present adaptive systems for modeling the processes occurring in them. A particular case of such systems is the human body and its compartments. The process of flow cultivation of self-replicating elements under the action of some constant nutrient medium flow D is represented by formula (1). It is this ratio that ensures equilibrium state in the generative host environment.

Thus, the dynamic system representing the organism can be written as a set of constant flow D of the nutrient medium working with a certain efficiency coefficient, α, and producing some product of activity, u. Taking into account the fact that the considered system can be located in another medium, μ, the equation describing speed of the occurring processes, y_0, in the mediate medium can take the form [30]:

$$\frac{dy_0(t)}{dt} = D(y_{00} - y_0(t)) - \alpha\mu u(t), \quad (1)$$

where $\mu = \frac{\mu_m \cdot y_0}{k_y + y_0}$ is the rate of use of the results of the input information flow; μ_m is the biomass assimilation rate reflecting activity of object-medium relations; y_0 is the substrate concentration at the input reflecting a stationary random process or a course of processing and assimilation; k_y is the saturation constant; y_{00} is the objectively existing concentration of information in the incoming flow; $(y_{00}-y_0)$ is the difference in speed of processing and assimilation in the system; α is the efficiency of use of the obtained information; u is the product of useful activity.

Since not all formations can have time to be assimilated under the influence of certain factors, it is necessary to take into account the rate of their elimination. The equation describing the rate of formation of adequate forms of stereotyped behavior of the system has the form:

$$\frac{du(t)}{dt}=\mu u(t)-Du(t), \tag{2}$$

where $Du(t)$ is the number of incomplete adequate responses practically not participating in ensuring the final result of adequate reactions [30].

Then, in accordance with (1), the equation for calculating the nutrient medium flow rate is:

$$D=\mu_m\cdot\left(1-\sqrt{\frac{y_0}{k_y+y_0}}\right). \tag{3}$$

The produced useful product of the organism can be defined as:

$$u(t)=\frac{1}{\alpha}\left[\left(k_y+y_0(t)\right)-\sqrt{y_0\left(k_y+y_0(t)\right)}\right]. \tag{4}$$

In order to determine initial conditions of interaction of two competing systems (in our case, deposition and consumption of energy) in the human body, productivity of the flow system can be determined as:

$$W=D\cdot u(t). \tag{5}$$

Or, in accordance with (3) and (4):

$$W=\frac{\mu_m}{\alpha}\cdot\left(\sqrt{k_y+y_0(t)}-\sqrt{k_y}\right)^2. \tag{6}$$

The human body can be represented as an energy request on the one hand and the request satisfaction on the other hand. Thus, to determine imbalance of metabolic processes in formation of MS and obesity as its consequence, it is necessary to take into account the factors responsible for accumulation of energy and for its consumption.

Then, in accordance with this assumption, two equations can be formed:

– to calculate the system's productivity in terms of energy deposition

$$w_1=\frac{\mu_{m1}}{\alpha_1}\cdot\left(\sqrt{k_{y1}+y_{01}}-\sqrt{k_{y1}}\right)^2, \tag{7}$$

where μ_{m1} is the indicator characterizing biomass assimilation and reflecting the waist circumference, α_1 is the indicator characterizing the heart rate, k_{y1} is the indicator characterizing the process of energy deposition (saturation) and reflecting the patient's weight, y_{01} is the indicator characterizing the biomass processing and assimilation and reflecting the patient thigh circumference;

– to calculate the system's productivity in terms of energy consumption

$$w_2=\frac{\mu_{m2}}{\alpha_2}\cdot\left(\sqrt{k_{y2}+y_{02}}-\sqrt{k_{y2}}\right)^2, \tag{8}$$

where μ_{m2} is the indicator characterizing biomass assimilation and reflecting the basal metabolism, α_2 is the indicator characterizing systolic blood pressure, k_{y2} is the indicator characterizing the process of energy consumption and reflecting diastolic blood pressure of the patient, y_{02} is the indicator characterizing the process of processing and assimilation and reflecting the patient's age.

Age is an important indicator for assessing metabolic processes in the human body. It is included in the well-known formulas for calculating basal metabolism [20, 21]. The most intensive metabolic processes occur in childhood which is associated with growth, formation of organs and systems, the great motor activity of the child and then in the puberty age. With termination of growth and further with the years, slowdown in the rate of metabolic processes takes place which is most pronounced in the elderly and senile age. Low metabolic rate and predominance of biomass deposition over energy consumption often result in obesity.

In order to take into account interaction of productivity of the systems of energy deposition, w_1, and consumption, w_2, and determination of the balance ratios in these communities (the systems of energy deposition and consumption are meant by communities), it is suggested to use the model of interaction of these communities in rendition of Volterra and Timofeev-Resovsky [31]. The model takes the form:

$$\begin{cases}\dfrac{dW_1(t)}{dt}=\varepsilon W_1(t)-\beta W_1(t)W_2(t),\\ \dfrac{dW_2(t)}{dt}=\gamma W_1(t)W_2(t)-\delta W_2(t),\end{cases} \tag{9}$$

where $W_1(t)$ is the indicator characterizing productivity of the body system responsible for ability to energy deposition; $W_2(t)$ is the indicator characterizing productivity of the body system which is responsible for the ability to energy consumption; ε is the an indicator characterizing the increase in population of "victims" (biomass assimilation) and reflecting the amount of triglycerides; β is the model coefficient; γ is the indicator characterizing reduction in the number of "victims" and correlating with the amount of total cholesterol; δ is the indicator characterizing increase in the number of "predators" and reflecting the amount of glucose.

As initial conditions for solution of the system (9), it is proposed to use the obtained productivity of the flow systems responsible for energy deposition and consumption, respectively:

$$W_1(0)=w_1,\quad W_2(0)=w_2. \tag{10}$$

Let us take the coefficient β equal to 1.618 since a substantial part of the studies on harmony in living nature use Fibonacci numbers for a formal description. This "golden section" approach is very common in studies of the human heart [32], beauty of the human face [33], facial recognition [34], step harmony [35] and as a biological marker of sarcopenia [36].

Asymptotic behavior of solution of the system (9), (10) determined in the phase trajectories of the approximate solution in Mathcad is the basis for diagnosis of the patient's condition and prognosis. There are 5 types of phase portraits and asymptotic behavior.

According to the basic concept [31], the phase trajectory of the system in the form of an ellipse (Fig. 1) corresponds to the steady-state development of processes. Solution of the system (9), (10) is assumed to be dimensionless, so coordinate axes in Fig. 1 and the following figures are dimensionless axes of the Cartesian coordinate system W_1, W_2.

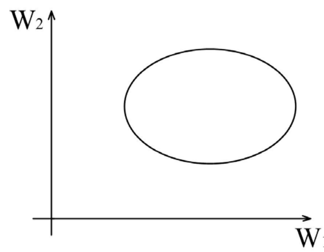
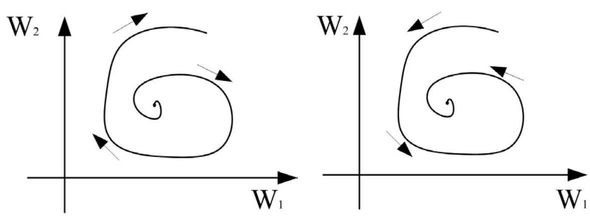


Fig. 1. Phase trajectory of the classical Lotka-Volterra system characteristic of the balanced processes

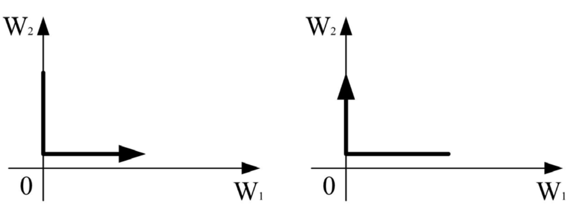
Violation of balance of the processes leads to formation of spiral trajectories (Fig. 2, *a, b*) which means superiority of one process over another.



a *b*

Fig. 2. Phase trajectory of the Lotka-Volterra system in imbalance: superiority of the first process over the second one (*a*); superiority of the second process over the first one (*b*)

Analysis of stability of the Lotka-Volterra system carried out in [37–39] allows us to conclude that with unrestricted competition and strong interferences, the system becomes absolutely unstable and an unlimited concentration of resources occurs in it which can result in phase trajectories presented in Fig. 3.



a *b*

Fig. 3. Phase trajectories of the Lotka-Volterra system in case of a pronounced predominance of one process over another: predominance of the process of consumption over the process of deposition (*a*); preponderance of the process of deposition over the process of consumption (*b*)

The trajectory behavior is analyzed individually for each patient. Asymptotic behavior of the approximate solution is the basis for diagnosis.

5. The algorithm of using a mathematical model to determine the balance of metabolic processes in the human body

To determine imbalance of metabolic processes on the basis of the proposed mathematical model, it is expedient to implement the following algorithm.

1. Information acquisition including questioning, examination and conducting clinical and laboratory studies.

2. Determination of the patient's normal indicators and normalization coefficients.

3. Calculation of initial values for the equation responsible for energy deposition. According to works [40] and [2], waist and thigh circumference, heart rate and weight can be chosen as the indicators reflecting satisfaction (deposition of energy).

To calculate indicators μ_{m1}, y_{01}, k_{y1}, α_1 of equation (7), it is necessary to use formulas (11):

$$\begin{cases} \mu_{m1} = K_{1\mu} + B_{1\mu} \cdot X_1, \\ y_{01} = K_{1y} + B_{1y} \cdot X_2, \\ k_{y1} = K_{1k} + B_{1k} \cdot X_3, \\ \alpha_1 = K_{1\alpha} + B_{1\alpha} \cdot X_4, \end{cases} \qquad (11)$$

where X_1 is the waist circumference (cm); X_2 is the hip circumference (cm); X_3 is the weight (kg); X_4 is the heart rate (bpm); $K_{1\mu}$, $B_{1\mu}$, K_{1y}, B_{1y}, K_{1k}, B_{1k}, $K_{1\alpha}$, $B_{1\alpha}$ are the normalization coefficients.

The general formula for calculating the normalization coefficients K_{ij} and B_{ij} is:

$$\mathrm{K}_{ij} = \frac{\left(a_{ij} \cdot \left(d_{ij} - c_{ij}\right) - c_{ij} \cdot \left(b_{ij} - a_{ij}\right)\right)}{d_{ij} - c_{ij}}, \qquad (12)$$

$$B_{ij} = \frac{b_{ij} - a_{ij}}{d_{ij} - c_{ij}}, \qquad (13)$$

where a_{ij} is the lower value of the range of the μ, *y*, *k*, α parameters of approximate solution of equations (7) and (8) with the help of the Newton's method and the system of equations (9), (10) with the help of Runge-Kutta method of the fourth order for the ε, δ, γ; parameters; b_{ij} is the upper value of the range of the μ, *y*, *k*, α parameters of approximate solution of equations (7) and (8) with the help of Newton's method and equations (9), (10) using the fourth-order Runge-Kutta method for the ε, δ, γ; parameters; c_{ij} is the initial value of the norm range for the selected indicator on the basis of generally accepted medical norms; d_{ij} is the final value of the norm range for the selected indicator on the basis of generally accepted medical norms [42–44]; i=1,2; $j \in \{\mu, y, k, \alpha, \varepsilon, \delta, \gamma\}$.

4. Calculation of initial values for the equation responsible for energy consumption. It is shown in work [36] that the processes of energy demand (consumption) are characterized by such indicators as basal metabolism, systolic arterial pressure, diastolic arterial pressure and age. To calculate μ_{m2}, y_{02}, k_{y2}, α_2 parameters of equation (8), the following formula is used:

$$\begin{cases} \mu_{m2} = K_{2\mu} + B_{2\mu} \cdot X_5, \\ y_{02} = K_{2y} + B_{2y} \cdot X_6, \\ k_{y2} = K_{2k} + B_{2k} \cdot X_7, \\ \alpha_2 = K_{2\alpha} + B_{2\alpha} \cdot X_8, \end{cases} \qquad (14)$$

where X_5 is the value of basal metabolism (Harris-Benedict equation) (kcal); X_6 is the value of age (years); X_7 is the value of diastolic blood pressure (mmHg); X_8 is the value of systolic blood pressure (mmHg); $K_{2\mu}$, $B_{2\mu}$, K_{2y}, B_{2y}, K_{2k}, B_{2k}, $K_{2\alpha}$, $B_{2\alpha}$ are the normalization coefficients.

The normalization coefficients of the system of equations (14) are calculated according to (12) and (13).

5. Calculation of the ε, δ, γ coefficients and construction of the phase trajectory.

It was shown in [5, 35, 36] that metabolic processes in the body mainly reflect such indicators as triglycerides, glucose and total cholesterol. Initial conditions for equation (9) are the values w_1 and w_2 calculated according to formulas (7) and (8), respectively.

The ε, δ, γ coefficients are calculated according to (15):

$$\begin{cases} \varepsilon = K_\varepsilon + B_\varepsilon \cdot X_9, \\ \delta = K_\delta + B_\delta \cdot X_{10}, \\ \gamma = K_\gamma + B_\gamma \cdot X_{11}, \end{cases} \qquad (15)$$

where X_9 is the value of triglycerides in the blood (mmol/l); X_{10} is the value of glucose in blood (mmol/l); X_{11} is the value of total cholesterol in blood (mmol/l); K_ε, B_ε, K_δ, B_δ, K_γ, B_γ are the normalization coefficients.

The normalization coefficients of the system of equations (15) are calculated according to (12) and (13).

The results obtained make it possible to construct a phase trajectory reflecting individual features of the course of metabolic processes in the human body.

6. Numerical implementation of the model and justification of the scheme of interaction of modules in the medical diagnostic information system

Numerical simulation was performed according to the algorithm proposed above. Let us consider the simulation process using the following examples.

Patient 1: a 75-year-old man, with no obesity, underwent clinical and laboratory examinations at Kharkiv municipal hospital No. 11, The patient's parameters for the system of hemostat equations describing energy deposition in the body (weight, waist and thigh circumference, heart rate) are given in Table 1.

Basal metabolism was calculated according to the Harris-Benedict formula.

Table 1

Initial data of patient 1

Indicator	Value
Weight, kg	60
Waist circumference, cm	79
Thigh circumference, cm	98
Heart rate, bpm	88
Age, years	75
Basal metabolism, kcal	1193.47
Systolic pressure, Hg mm	200
Diastolic pressure, Hg mm	100
Glucose, mmol/l	3
Total cholesterol, mmol/l	5.2
Triglycerides, mmol/l	1.15

The patient 1 parameters were compared with the norms fixed by the protocols of the Ministry of Health of Ukraine and international medical recommendations [41–43]. The range of normal values of the parameters important for the processes of energy deposition and consumption are given in Table 2.

Table 2

The range of normal values for the patient 1

Indicator	Minimum of the normal range (c)	Maximum of the normal range (d)
Weight, kg	55	71
Waist circumference, cm	60	94
Thigh circumference, cm	98	104
Heart rate, bpm	60	90
Age, years	60	70
Basal metabolism, kcal	1240	1300
Systolic pressure, Hg mm	100	130
Diastolic pressure, Hg mm	60	85
Glucose, mmol/l	4.6	6.4
Total cholesterol, mmol/l	3.73	6.86
Triglycerides, mmol/l	0.62	2.96

The examined patient had the following indicators within the normal values: weight, waist circumference, thigh circumference, heart rate, total cholesterol, triglycerides. Deviations from the normal levels of systolic and diastolic pressure, glucose and the value of the basal metabolism were observed.

Calculation of the K_{ij} and B_{ij}, coefficients according to formulas (12) and (13) was made on the basis of c_{ij} and d_{ij} values obtained with taking into account conventional medical norms [41–43] as well as the values obtained on the basis of individual patient data. The values of the K_{ij} and B_{ij} coefficients for patient 1 are given in Table 3.

Table 3

Patient 1 data for calculation of the body's ability to deposit energy

Indicator	a_{ij}	b_{ij}	c_{ij}	d_{ij}	K_{ij}	B_{ij}
Waist circumference	30.67	100	60	94	–91.677	2.0391
Heart rate	0.1	0.604	60	90	–0.907	0.0168
Weight	0.1	0.257	55	71	–0.441	0.0098
Thigh circumference	1.9907	2	98	104	1.8388	0.0016

Performance of the system in terms of energy deposition, w_1, calculated based on the μ_{m1}, y_{01}, k_{y1}, α_1 values according to formula (11) was as follows: μ_{m1}=64,41, y_{01}=1,99, k_{y1}=0,149, α_1=0.57.

Thus, the system's performance in terms of energy deposition was w_1=141.15.

Similarly, the system's performance in terms of energy consumption, w_2, was calculated. The values of the K_{ij} and B_{ij}, coefficients calculated from formulas (12) and (13) are given in Table 4.

The system's productivity in terms of energy consumption, w_2. was calculated based on the μ_{m2}, y_{02}, k_{y2}, α_2 values according to formula (14): μ_{m2}=2,69, y_{02}=23,89, k_{y2}=0,25, α_2=2,84.

The system's productivity in terms of energy consumption, w_2=18.43.

The balance of metabolic processes was determined on the basis of indicators of the content (or level indicators) of triglycerides, glucose and total blood cholesterol.

The K_{ij} and B_{ij} coefficients calculated according to formulas (12) and (13) are given in Table 5.

Table 4

Patient 1 data for calculating the body's capacity for energy consumption

Indicator	a_{ij}	b_{ij}	c_{ij}	d_{ij}	K_{ij}	B_{ij}
Basal metabolism	9.619	18.549	1240	1300	–174.945	0.1488
Systolic pressure	0.1	0.9231	100	130	–2.644	0.0274
Diastolic pressure	0.1	0.1946	60	85	–0.127	0.0038
Age	10.122	19.298	60	70	–44.934	0.9176

Table 5

Patient 1 data for calculating the balance of metabolic processes

Indicator	a_{ij}	b_{ij}	c_{ij}	d_{ij}	K_{ij}	B_{ij}
Triglycerides	8.99	33.71	0.62	2.96	2.44	10.56
Glucose	0.5	3.99	4.6	6.4	12.91	–1.94
Total cholesterol	0.1	0.78	3.73	6.86	–0.71	0.22

Using the values of the K_{ij} and B_{ij} coefficients calculated according to formula (15) and given in Table 5, the values of ε, δ, γ were calculated: ε=14.58, δ=7.09, γ=0.41.

To determine the balance of metabolic processes, a system of differential equations was formed:

$$\begin{cases} \dfrac{dW_1}{dt} = 14{,}58 * W_1 - 1{,}618 * W_1 * W_2, \\ \dfrac{dW_2}{dt} = 0{,}41 * W_1 * W_2 - 7{,}09 * W_2. \end{cases}$$

Using the MathCAD package, an approximate solution of the system of differential equations was found. When the calculated values of initial conditions $W_1(0)$=141.15 and $W_2(0)$=18.43 were substituted, the phase trajectory of the system was obtained (Fig. 4).

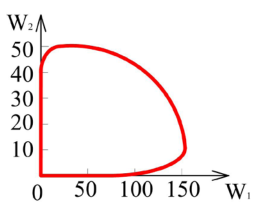


Fig. 4. The phase trajectory of the system corresponding to the patient 1

Thus, according to Fig. 4, the metabolic processes in patient 1 were balanced and after a while, the patient's condition should not change which was confirmed by the records in the outpatient card.

Changing the initial conditions to $W_1(0)$=1 and $W_2(0)$=92, the phase trajectory of the system was obtained (Fig. 5).

When the initial conditions ($W_1(0)$=1 and $W_2(0)$=92) changed, then according to Fig. 5, the system became unstable which indicates imbalance of metabolic processes. Thus, the choice of arbitrary values as initial conditions can lead to an incorrect prediction.

The initial data of the three other patients and the calculations results are presented in Tables 6, 7.

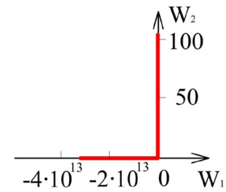


Fig. 5. The phase trajectory of the system corresponding to patient 1 for $W_1(0)$=1 and $W_2(0)$=92

Table 6

Initial data of patients 2-4

Indicator \ Patient No.	No. 2	No. 3	No. 4
Gender	F	M	F
Age, years	57	76	45
Initial state	Normal	Stage1	Stage 3
Waist circumference, cm	90	104	150
Thigh circumference, cm	102	111	138
Heart rate, bpm	60	84	90
Weight, kg	67	104	138
Diastolic pressure, Hg mm	90	90	115
Systolic pressure, Hg mm	160	160	190
Triglycerides, mmol/l	1.2	1.02	3
Glucose, mmol/l	4.4	5.2	4.35
Total cholesterol, mmol/l	4.7	2.3	5.62
Condition when revisited	Weight loss	Stage 2	Stage 1

Table 7

Model parameters for patients 2-4

Patient No.	$W_1(0)$	$W_2(0)$	ε	δ	γ
2	1374.4	119.028	15.117	2.171	0.153
3	275.83	756.83	18.68	2.8	–0.21
4	380.12	365.492	43.597	2.247	0.491

The results of simulation are shown in Fig. 6–8.

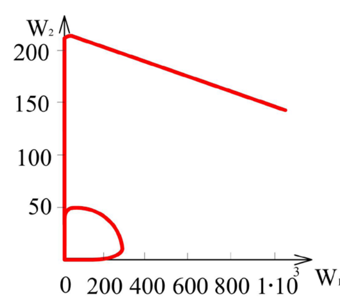


Fig. 6. Phase trajectory of the system corresponding to patient 2

According to the initial data, at the initially normal body weight, weight loss was found after a while in patient 2 with further weight stabilization which corresponded to an inward spiraling of the phase trajectory (a globally stable system).

A process of further increase in body weight was observed in patient 3 with transition from the first to the second stage of obesity. This was reflected in the phase trajectory shown in Fig. 7 where energy deposition is seen which asymptotically tends to infinity (a globally unstable system).

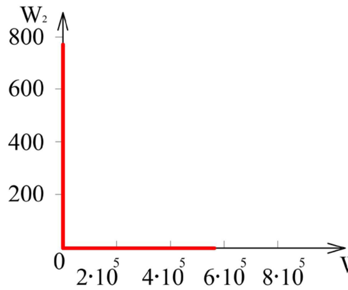


Fig. 7. Phase trajectory of the system corresponding to the patient 3

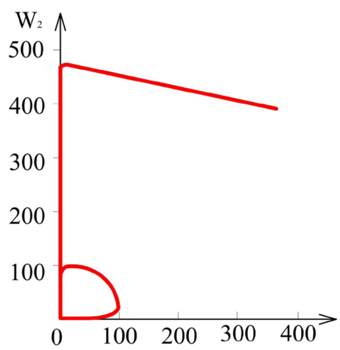


Fig. 8. Phase trajectory of the system corresponding to the patient 4

Weight loss was observed in patient 4 earlier having obesity of the third stage and transition to the first stage of obesity with further weight stabilization. The spiral of the phase trajectory in Fig. 8 is curled inwards.

The results of condition assessment for patients 2–4 were confirmed by the records in their outpatient cards. The control examination revealed changes in some laboratory parameters in patients. A high glucose level (5.2 mmol/l) in blood was found in patient 3 in the fasting state which indicates that there was no carbohydrate metabolism compensation. Patient 4 had an elevated level of total cholesterol (5.62 mmol/l), i. e. lipid metabolism disorder was observed which is dangerous because of formation and progression of arteriosclerosis of the vessels. The changes revealed allowed the doctor to correct diagnosis and prescribe the appropriate treatment.

Indicators were within the normal range in patient 2. This patient did not need therapy correction.

On a second visit, a stable state was found in patient No. 2 who was in a satisfactory condition, with normal heart rate and blood pressure and no changes in laboratory data.

There was also an improvement in the patient 4 condition on the basis of the patient's subjective sensations and objective data: normalization of blood pressure and the blood lipid profile.

The patient No. 3 has shown a slight condition worsening associated with weight gain (up to 114 kg) and an increase in glucose level (up to 8.2 mmol/l).

Similarly, data of the remaining 151 patients were examined. Calculations showed that the simulation results adequately describe the metabolic processes occurring in the human body.

Thus, the results of numerical simulation have shown that the proposed approach can be used to predict metabolic disturbances in the human body. The model that was obtained adequately described these processes and the results of prediction depended on the choice of initial conditions of integrating the Lotka-Volterra system of differential equations (SDE).

The proposed approach was used as the basis for the information system operation to detect imbalance of metabolic processes. Development and implementation of such a system in medical institutions will improve quality of early MS diagnosis in patients of diverse age groups.

The medical diagnostic information system for determining disturbances in the metabolic processes of the human body consists of four subsystems (Fig. 9).

The block of calculation of the initial value for the equation responsible for energy deposition is intended to obtain the coefficients of linear approximation of the deposition hemostat parameters as well as the deposition chemostat coefficients. The block for calculating the initial value for the equation responsible for energy consumption is intended to obtain coefficients of linear approximation of the flow chemostat parameters and the flow chemostat coefficients.

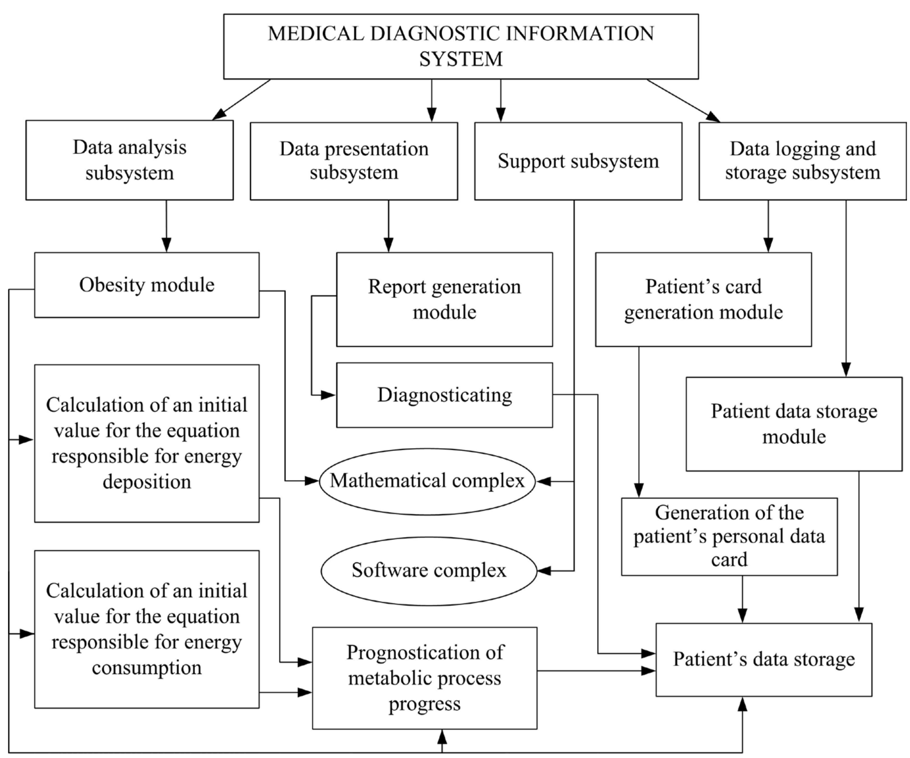


Fig. 9. Structural diagram of the medical diagnostic information system

The block for predicting the course of metabolic processes in the human body is intended to obtain coefficients of linear approximation of parameters of the Lotka-Volterra model as well as the coefficients of the Lotka-Volterra equations system that describe behavior of the organism of a given patient and obtain numerical solution of the Lotka-Volterra equation system for MS prediction. The patient card generation module is designed to create an individual patient card and the conclusion generation module generates a conclusion about the state of metabolic processes in the human body.

Development of an information system for detection of metabolic disorders in the human body will be carried out in a Microsoft Visual Studio environment in C# language for the Microsoft.NET Framework 4.0 based on the principles of object-oriented programming for use in Windows 7 operating system. MySQL was chosen as the database control system. The database should contain complete information on diagnostic studies, general patient information as well as the results of their processing and analysis.

The system software will be represented by a set of programs and program documents intended for debugging, functioning and verifying the system's operability. The software will be developed on the basis of mathematical support including mathematical models and algorithms presented in the work. As the most effective algorithm for protecting information, the symmetrical encryption algorithm of DSTU 7624:2014 was chosen which has allowed us to provide high level of attack resistance, confidentiality and data integrity. Technical support of the information system for determining disturbances in the metabolic processes of the human body must satisfy the following requirements. RAM: at least 4 GB, disk space: at least 100 GB, processor: at least 64 bits, processor clock speed: no less than 1 GHz, video adapter: integrated in the processor, peripherals: keyboard, monitor, mouse.

7. Discussion of the results obtained in using the proposed approach to determining the balance of metabolic processes

The proposed approach allows one to consider the process of depositing and consuming energy as a set of necessary and interrelated elements including waist and thigh circumference, weight, heart rate (the system productivity in terms of energy deposition, w_1); basal metabolism, age, systolic and diastolic pressures (the system productivity in terms of energy consumption, w_2); triglycerides; glucose; total cholesterol.

The use of the flow cultivator model enables an objective assessment of initial conditions of the system behavior and timing of the main parameters of deposition and consumption of energy. That is, in this situation, we can talk about consistency of input values of clinic-laboratory and clinic-instrumental indicators with integral output characteristics describing internal state of the human body. Such a decision has become possible due to the numerical description of integral indicators characterizing productivity of the energy consumption and deposition systems based on the formula for converting medical quantities into coefficients of corresponding equations. Calculation of these coefficients represents the applied value of the proposed approach. Namely, these coefficients represent dependences of the initial and final values of the range of solution of the system of equations (9) on the initial and final values of the normative range for corresponding medical indicators.

However, use of natural values of indicators as initial values of the Lotka-Volterra model is impossible because they have different dimensions and units of measurement.

When comparing the proposed approach with the approach to MS determination based on binary logistic regression [13], the results presented in Table 9 were obtained.

Table 9

Results of probation of the proposed approach

Subject of investigation	Group	Total number of cases, n_1	The number of erroneous cases, n_2	Se, %	Sp, %
Determination of imbalance of metabolic processes based on Lotka-Volterra and flow cultivator models	With normal metabolism	66	4	95.34	89.85
	With metabolism disturbances of various degree of intensity	89	7		
Determination of metabolic disturbance based on binary logistic regression	With normal metabolism	66	15	93.97	84.72
	With metabolism disturbances of various degree of intensity	89	21		

Note: Se: sensitivity; Sp: specificity

Cross-check for the possible development of metabolic processes in people with normal and disturbed metabolism processes has shown that the developed approach can be used in medical institutions for early diagnosis of metabolic disorders. Accuracy of determining violations of the balance of metabolic processes was 92.9 %.

Higher accuracy is achieved by taking into account integral parameters w_1 and w_2 characterizing the processes of deposition and consumption of energy as well as the indicators of lipid and carbohydrate metabolism.

It should be noted that the body weight loss observed in dynamics corresponded to the graphic representation of the energy consumption growth and the body weight gain corresponded to the graphic representation of the energy deposition growth. These conditions were also confirmed by standard studies of lipid and carbohydrate metabolism.

Besides, advantage of the proposed approach consists in leveling-off the influence of the patient age characteristics which makes it possible to assess the possibility of disturbance of metabolic processes for various age groups.

However, given that the calculation of the predictive characteristics involves statistical norms, subjective errors associated with borderline situations are possible which may lead to a distortion of the diagnostic results.

This study further development can include the following:

– detailed analysis of influence of various age and gender characteristics on the type and form of graphic representation of the change in energy consumption as well as territorial and constitutional groups with the aim of developing a single integral criterion for estimating the balance of metabolic processes;

– study of the influence of statistical characteristics of the model coefficients on the resulting prognosis of the patient's condition;

– transformation of the Lotka-Volterra model by reducing it to an equivalent system depending on two effective parameters and a mathematical analysis of this system for the purpose of classifying the phase portraits determining the patient's diagnosis [44].

8. Conclusions

1. Dynamics of the processes of energy deposition and consumption was described in the form of a system of differential equations of the Lotka-Volterra type depending on the initial conditions. Parameters of the Lotka-Volterra model (ε, δ, γ) and initial conditions (w_1, w_2) are calculated proceeding from the patient's initial data such as weight, waist and thigh circumference, heart rate, basal metabolism, age, systolic and diastolic blood pressure, triglycerides, glucose and total cholesterol.

2. An algorithm was proposed for using a mathematical model to determine the balance of metabolic processes in the human body. The model parameters were determined according to the patient's individual data, an approximate solution of the Lotka-Volterra system and the asymptotic behavior of the orbit of the given system was made which serves as a classifying attribute for assigning the patient to a corresponding group. Five types of phase portraits have been revealed: for balanced metabolic processes (in the form of an ellipse in Fig. 1), for imbalance, in the form of superiority of one process over another and vice versa (the second and third phase trajectories in Fig. 2, *a*, *b*) and degeneracy of the previous two states (Fig. 3, *a, b*).

3. A structural diagram of the information system that will perform the following main functions based on the developed model and algorithm was proposed: determination of productivity of the systems energy deposition and consumption, obtaining a prognosis of the course of metabolic processes in the human body.

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