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Mathematical modeling of metabolic and hormonal regulation: risk assessment of environmental and radiation influence on various links of endocrine system

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Abstract

Advanced modeling method for health risk assessment has been elaborated. It is based on catastrophes, bifurcation, and chaos theories. The human organism has been examined as a developing system with dissipative structure, near an unstable steady state far from equilibrium in bifurcation zone, where any fluctuation leads to an unpredictable feature. The possibility of chaotic oscillations (Lorenz attractor) in an energy conversion system has been shown. The high susceptibility to initial conditions is a common feature of all chaotic systems and causing impossibility to predict patient's health and a treatment effectiveness. The 4-dimensional typology of the organism network as a self-reproducing, self-organizing entity, has been proposed. A nonlinear mathematical model of neuro-immune-endocrine network has been elaborated. It makes possible to investigate interrelations between various control mechanisms of metabolic and hormonal regulation, radiation, and stress impacts on thyroid system, mechanisms of various endocrine diseases formation. The following tasks have been examined: 1) comparative analysis of endocrine system regulation for some types of thyroid system pathology (such as hypo- and hyperthyroidism, T3- and T4-thyreotoxicoses); 2) optimum control of thyroid system restoration; 3) ranking of radiation influence on various links of thyroid system. The method of casual search has been chosen as an optimization method. The performed system data analysis made

it possible to reveal the most probable sequence of metabolic and hormonal changes leading to a thyroid pathology occurrence.

1 Introduction

An organism in contrast with a machine is a self-reproducing, self-organizing whole. According to [1], the term "self-organization" as a definition of the nature of live organisms has been proposed by Immanuel Kant. The main contradiction of the current medicine appears to be the fact that it attempts to treat not a patient but some organism subsystems, whereas an illness is a consequence of structural changes on molecular and subcellular levels. It is getting developed based on various algorithms, simultaneously affecting different subsystems and organs. Even in those cases where a performed therapy provides with a positive effect, there is no guarantee that it is not achieved due to reduced functionality of some other organs. The side effects of such therapy can intensify de-synchronization of various regulatory mechanisms, break a balance of various controlling systems, and cause a vicious circle of pathological disturbances.

It will be possible to move from the medicine of "consequences" to the medicine of "reasons" and to work out adequate tactics of patient's treatment, only if we take into account individual features of an organism as a whole.

The direction of the therapy should become 1) a support and stimulation of the organism protective functions, upraising its adaptiveness and balancing individual controlling systems and their communication; 2) an achievement of maximum positive effect of used medicines with a minimum side effect on other subsystems of the organism; 3) a development of a combined therapy optimal dynamics to ensure positive changes in reserve abilities of the organism as a whole.

Mathematical modeling becomes an important auxiliary tool to solve these problems. It upraises considerably efficiency of system analysis of contradictory experimental data, transforming it into new understanding, based on integrated parameters of environmental and radiation effect on an organism as a whole and its individual systems. Better approximation of radiation and other environmental factors impact on the organism can be achieved using such an approach.

Computer technologies are to be used as learning tools to teach a physician to treat an organism as a whole in opposite to a specific illness, to see an integrated picture of interconnected organism's systems, to predict con-

sequences of stress impact, to individualize the treatment process (choice of an optimal treatment strategy).

The objective of this article is to develop a mathematical model investigating a role of the neuro-immune-endocrine network (NIEN) connected metabolic and hormonal mechanisms control under stress reaction and risk assessment of an environmental and radiation influence on various NIEN parts. The developed model will be used to manage the problem of thyroid function restoration control under some types of the thyroid system (TS) pathology...

> "We are but whirlpools in a river of ever-flowing water.
> We are not stuff that abides, but patterns that perpetuate themselves."
> **Norbert Wiener**, *The Human Use of Human Beings*, p.96 (1950).

2 The mathematical model of health risk assessment

A human organism (HO) can be considered as an open, non-Hamiltonian, non-linear, dissipative, potential, self-reproducing, self-organizing system with networking elements, near an unstable steady state far from equilibrium, in bifurcation zone where any fluctuation leads to an unpredictable future [2]. A disturbance in some network node may lead to catastrophic consequences in the whole network. The effects of a disturbance could impact areas far from the initial source due to existing longer-term links and a great extent of cause and effect in HO. Health risks are those insidious risks emerging slowly but surely over time. Any environmental impact increases possibility of the case where some fluctuation can cascade into a disease with unpredictable health consequences..

The high initial conditions susceptibility is a common feature of such systems and it makes it impossible to predict patient's health or a treatment effectiveness. Traditional methods to predict a system development are not enough efficient. There is a "growing recognition that risk management should not be based on the assumption of linear cause and effect", as noted in [3, p.387]. Such entities are usually examined using recent theories of nonlinear systems, synergetics, chaos, and bifurcation.

Let us propose that organism satisfies all the requirements of potential system and can be described by some potential function $U(X)$ of variable X. This function has some steady states; some of them are stable, others – unstable. The transformations of system from one steady state to another,

or transformation of a character of a steady state (for instance, from stable to unstable) are functions of control parameters **A** . These parameters control both a movement of system's current position upon surface U, and transformations of the surface itself.

Let X be a level of health. To make it simple, it is possible to put forward following suppositions. Potential function $U(X,\boldsymbol{A})$ has three stable steady states (Fig. 1). The first one (X_1) characterizes normal condition. The level of health in this state is maximal. The second one (X_2) characterizes premorbidal or pre-pathological state with a medium level of health (the reserves of the organism and its adaptiveness are lowering, but yet not across the critical level which separates normal functioning and an illness. The third one (X_3) characterizes disease.

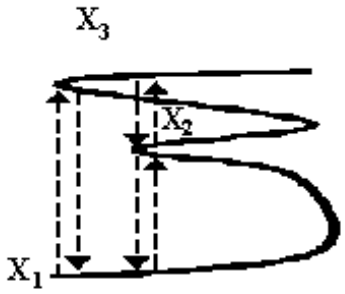

Figure 1: Transformation between various steady states.

The risk estimation of sudden and unexpected transformation from one steady state to another may be performed using the theory of catastrophes allowing the calculation of bifurcation values, curves, and surfaces of control parameters. The risk is estimated as an extent of a control parameter approaching these bifurcation values characterizing system's transition from one steady state (norm) to another (catastrophe) [4]. The main advantage of this approach is a determination of risk as a function of dynamic variables of the investigated system. It also allows to identify the weakest link of the system under examination and the areas in need of an improvement.

So, the set of values of the potential function $U(X,\boldsymbol{A})$ control parameters and their deviations from bifurcation surfaces may be utilized for risk matrix determination to calculate probabilities of transformations between various steady-states of physiological system. Thus, the potential function $U(X,\boldsymbol{A})$ determines the level of health. One of the catastrophes' theory universal

deformations can be used to define $U(X,\boldsymbol{A})$ depending on the number of control parameters.

Let us introduce some postulates that we use as a basis to develop the model.

1. A state of an organism is considered as complex interrelationship in a "square of health" (SH), which is determined by a state of NIEN regulation, cellular, and physiological adaptiveness, mental sphere, and a genomic pre-history. A set of health threats, including environmental and radiation impact, has a potential to destroy an intricate balance existing within the SH by altering the above-mentioned factors. The balance disturbance within the SH is a most formidable health threat to be prevented, as it leads to a transition from norm to diseases.

2. To examine a health environmental impact problem we have chosen a 4-dimensional typology. The transformations of health are defined by one of the universal deformations of catastrophes' theory – a "butterfly":

$$-\partial U(X,A)/\partial X = X^5 + A_1X^3 + A_2X^2 + A_3X + A_4, \qquad (1)$$

where A_i (i=1,4) are control parameters, characterizing various aspects of the organism's functioning (i=1 – index of NIEN regulation, determined by hormones levels, energetic substrates, sub-populations of lymphocytes, etc.; i=2 – index of cellular and physiological adaptiveness to environmental impacts, determined by the balance between energy synthesis and consumption processes, reserve possibilities to extreme loads, etc.; i=3 – index of mental health, determined by psychical and psychological peculiarities of the organism; i=4 – index of genomic pre-history, determined by genetic inclinations of the organism).

3. Now, based on the works dealing with methods of catastrophes' theory, the following algorithm of risk assessment can be proposed [4]:

- Collecting of information characterizing the above-mentioned indices input from contemporary databases.
- Determination of indices characterizing appropriate group of parameters calculation by means of developed mathematical models using inputted data.
- Calculation of the bifurcation parameters values at which the number of system states is changing.
- Estimation of restoration possibilities of each considered systems by the remoteness of the parameter characterizing appropriate index from its bifurcation value.

According to Prigogine's theory, dissipative structures can not only maintain themselves in a stable state far from equilibrium but may even evolve. When the flow of energy and matter through them increases, they may go through new instabilities and transform themselves into new structures with increased complexity. That is why organism (as pointed by F. Capra), can be considered as a giant web of life, which consists of fractal networks where any network contains another one. And a node of the network being zoomed is getting transformed into a new network [1].

Under more detailed investigation, parameters A_i also may be examined as n-dimensional functions $\boldsymbol{A}_i(F_j)$ (j=1,n), that are arguments of some potential functions U_{Ai}. Variables F_j describe each index in more detail. Such iterative process leads to the next sublevel of bifurcation sets, determined by

$$dA_i/dt = -\,\partial U_{A_i}/\partial A_i,$$
$$A_i^M + B_{i1}A_i^{M-2} + \ldots + B_{i(M-3)}A_i^2 + B_{i(M-2)}A_i + B_{i(M-1)} = 0. \qquad (2)$$

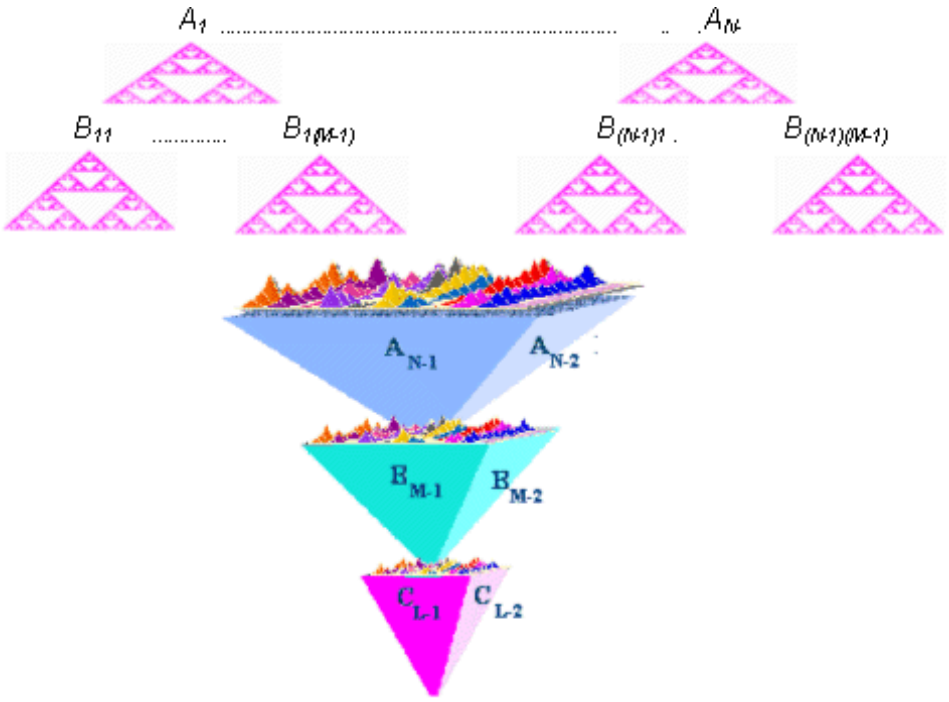

Figure 2: Fractal pyramid of bifurcation sets

So, a peculiar "fractal pyramid" of bifurcation sets can be constructed; by using this pyramid a hierarchical risk matrix of system transformation from one health sublevel to another can be determined. In Fig. 2 projections of "fractal pyramid" on the surfaces $A_{N-1}A_{N-2}$, $B_{M-1}B_{M-2}$, $C_{L-1}C_{L-2}$ are presented.

For instance, the state of NIEN regulation can be determined on the basis of integrated indices of hormone system status (B_{11}), energetic status of cells (B_{12}), immune system status (B_{13}), blood system status (B_{14}), characterizing endocrine, energetic, immune and blood systems, respectively. A mathematical method of risk assessment of pathological and pre-pathological state arising was developed using these indices, which characterize a degree of functional disturbances [5].

Shifts in the organism's functional systems change the parameters B_{1j} (i=1,4). Those may cause transfers from norm to pre-pathology or to pathology. Bifurcation values of these parameters can be calculated by means of proposed mathematical methods. Reaching such critical values abruptly increases the probability of a transfer from one functional state to another. Thus, for a given organism's state, it is possible to determine ranges of functional parameter values corresponding to the states of norm, pre-pathology and pathology. The examples of such indices calculation for NIEN and cellular and physiological adaptiveness are presented in the subsequent chapters.

3 Chaotic oscillations in a system of energy exchange

The analysis of an energy exchange shows that while such dissipative structures as an organism receive their energy from outside, the instabilities and jumps to such new forms of organization as a disease appear to be a result of fluctuations amplified by positive feedback loops [1,2].

Let us examine these feedback loops more deeply to investigate possible mechanisms of chaotic behavior developing in the energy conversion system.

Based on experimental investigation of cellular energy exchange [6], the following postulates can be proposed:

1. Oxidative phosphorilation in mitochondria plays a central role in the energy supply of various cellular functions: active ion transport, proliferation, muscle contraction, protein synthesis, etc.

2. An organism has some demand on activities of various physiological systems, cellular, and subcellular networks.

3. Some part of the cell energy is getting consumed for internal cellular functions; another part is used for external functions, determined by the organism demand.

4. The demand depends on various factors: current states of physiological systems, loads, environmental impacts, hormonal pool, efficacy of control mechanisms, etc. Let $b_{1i}(t)$ denote a current demand on activity of i-th control system normalized to the energy synthesis unit (mitochondrion) - Y_i.

5. The current state of i-th control system is characterized by a level of its external function which determines its supply to the organism demand. The supply may correspond to the demand or may not. Let $b_{2i}(t)$ denote a level of supply normalized to the unit of i-th control system's function (a contractility for muscle, a rate filtration for a kidney, etc) X_i. According to the proposed designations, $b_{1i}(t)Y_i$ and $b_{2i}(t)X_i$ characterize total demand on activity of i-th system and total supply on fulfillment of external function determined by possibilities of mitochondria, correspondingly.

6. Let the rate of supply change be proportional to the prevalence of organism demand over supply. Then we have the following equation for a dynamics of external function

$$dX_i/dt = a_{1i}(t)[b_{1i}(t)Y_i - b_{2i}(t)X_i],$$

where $a_{1i}(t)$ is a parameter characterizing adaptive possibilities.

7. Some cellular mechanisms exist that modify intracellular structures and involve new mitochondria in energy synthesis under prevalence of demand (biosynthesis, redistribution of ion and energy currents, etc.). Let us assume that the higher X_i is the greater is a number of mitochondria Y_i involved in the process. Let $c_{1i}(t)$ be a demand on an increasing of number of mitochondria normalized to X_i unit, and $c_{2i}(t)$ be a share of Y_i involved in X_i maintenance. Thus, $c_{1i}(t)X_i$ and $c_{2i}(t)Y_i$ characterize total demand and supply on mitochondria correspondingly.

8. Let the rate of mitochondria change be proportional to a prevalence of energy demand over supply. Then we have the following equation for a dynamics of mitochondria involved in energy synthesis

$$dY_i/dt = a_{2i}(t)[c_{1i}(t)X_i - c_{2i}(t)Y_i], \tag{3}$$

where $a_{2i}(t)$ is similar to $a_{1i}(t)$.

9. The fact that an increase of Y_i is limited by various biological factors (for instance, by a competition for substrates) is not taken into account in

(3). Moreover, some part of Y_i is involved in cellular internal functions. This part is proportional to X_i (which adds to an existing demand to i-th system structures). It is also proportional to the level of pathological disturbances Z_i developing in cellular structures and demanding additional energy for their elimination. Consequently, the equation (3) is to be transformed into

$$dY_i/dt = a_{2i}(t)[c_{1i}(t)X_i - c_{2i}(t)Y_i - c_{3i}(t)X_iZ_i], \tag{4}$$

where c_{3i}(t) is a demand on Y_i caused by a maintenance of cellular internal functions and normalized to units of external function and disturbances that are being developed in the cell.

10. The rise of disturbances is proportional to the load level on the structures maintaining external function X_i. It depends on $X_{i,}$ and the number of Y_i involved in the energy synthesis. We also propose the existence of some control (adaptive) mechanisms**,** which eliminate some part of disturbances under some restrictions. These mechanisms are getting activated under appearance and accumulation of disturbances. Let d_{1i}(t) and d_{2i}(t) be the constants of proportionality. Thus, the rate of disturbances will be described by the equation

$$dZ_i/dt = [d_{1i}(t)X_iY_i - d_{2i}(t)Z_i]. \tag{5}$$

Let us examine one isolated cell that has one external function. Let all model coefficients be constant. Introduce the following designations

$t = t^*/(a_2c_2)$, $\sigma = (a_1b_2)/(a_2c_2)$, $r = (b_1c_1)/(b_2c_2)$, $b = d_2/(a_2c_2)$,
$x = d_1X(c_3/d_1)^{1/2}/(a_2c_2)$, $y = d_1b_1Y(c_3/d_1)^{1/2}/(b_2a_2c_2)$,
$z = (b_1c_3Z)/(b_2a_2c_2)$.

In this case equations (3-5) become

$$dx/dt^* = \sigma(y - x),\ dy/dt^* = rx - y - xz,\ dz/dt^* = xy - bz. \tag{6}$$

According to Lorenz [7], sustained chaotic behaviour arises in this model as shown at Fig. 3.

Thus, relationships between cellular external function, cellular energy, and cellular disturbances may be described by the Lorenz model of Metastable chaos. A transition, from stability to instability of energetic flows, could be analogous to the transition from a laminar to turbulent flow.

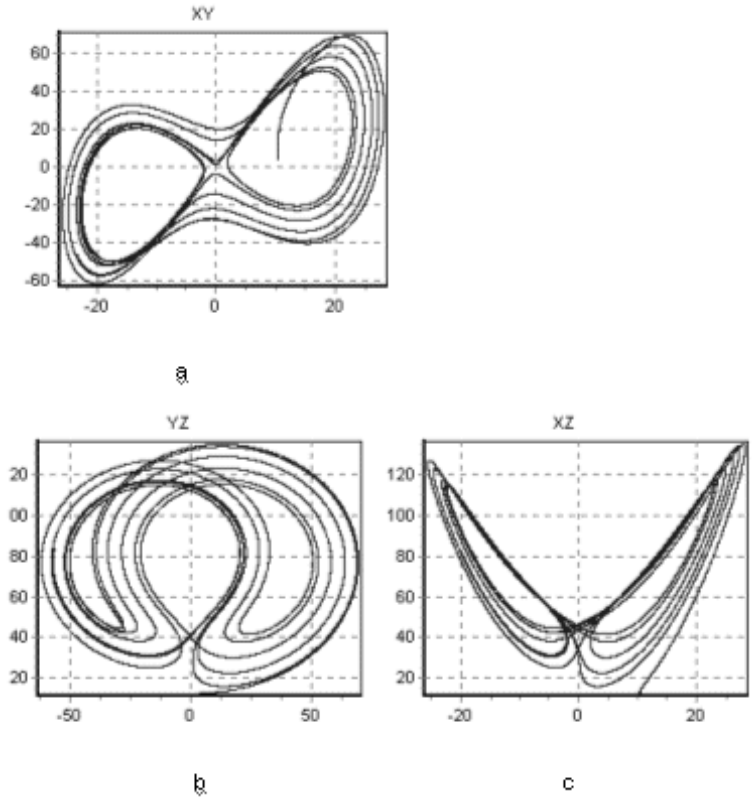

Figure 3: Projection of the Lorenz attractor: a - XY, b - YZ, c - XZ

4 Comparative analysis of neuro-immune-endocrine regulation during some types of thyroid system pathology

Analysis of experimental data concerning various aspects of radiation negative influence on human organism unambiguously testifies that one of its most appreciable consequences is a harsh spike of the diseases dealing with thyroid system (TS) function disturbances. These sorts of diseases are progressing during all after-Chernobyl period [7].

Despite the intensive research carried out lately, there is no uniform vision of the exact TS links and regulatory mechanisms which are the main targets for radioactive iodine. What are the chains of events which are get-

ting realized with the greatest probability under a radiation action? Which links are primary targets of radiation action, and which ones are just of a secondary, or compensatory character? Without the answers to these questions it is impossible to develop an effective prevention under radiation action on a human organism.

So, detailed analysis of TS control mechanisms appears to be one of the most actual problems in modern endocrinology. A weakening of the TS function triggers a consequent sequence of hormone and metabolic violations, resulting in the development of various pathological processes. Thus, it is also essential to determine an effective therapy strategy which would lead to a synchronization of various regulatory mechanisms activities and optimization of the usage of specific medicines, normalizing levels of thyroid hormones (TH) during different types of TS pathology.

Cyclic nucleotides (CN), cell membrane system (the activity of calcium and sodium pumps), corticothropin-releasing factor (CRF), corticothropin (ACTH), thyrothropin-thyrostimulating hormone (TTH), thyrothropin-releasing-factor (TRF), triiodothyronine (T3), thyroxin (T4), interleukin-1, arachidonic acid (AA), catecholamines (CC), glucocorticoids (GC), and a number of other hormones and metabolic factors play an important role in the control of NIEN [8–10].

Interleukin (IL-1) appears to be one of the most important links between immune and endocrine system. It is being produced not only by cells participating in myelo- and lymphopoesis (monocytes, macrophages, neutrophyle granulocytes, B-lymphocytes, natural killers, and so on), but also by the cells of central and peripheral nervous systems (brain neurons, peripheral neurones and others). IL-1 activates hypothalamus-hypophysis-adrenocortical system; it stimulates synthesis of CRF and somatostatin, causes alterations in noradrenergetic neurones' activity. A high level of IL-1 leads to GC and ACTH levels growth in blood and inhibits TTH synthesis. This inhibition consequently causes drop of TTH, T_3 and T_4 levels. GC also causes an inhibition of IL-1 synthesis.

Block-scheme of radiation impact on NIEN is presented at Fig. 4.

Shvitra's TS model based on non-linear equations with a delay [11], has been modified introducing some terms to take into account impacts of metabolic and stress factors (including radiation) on NIEN [12]

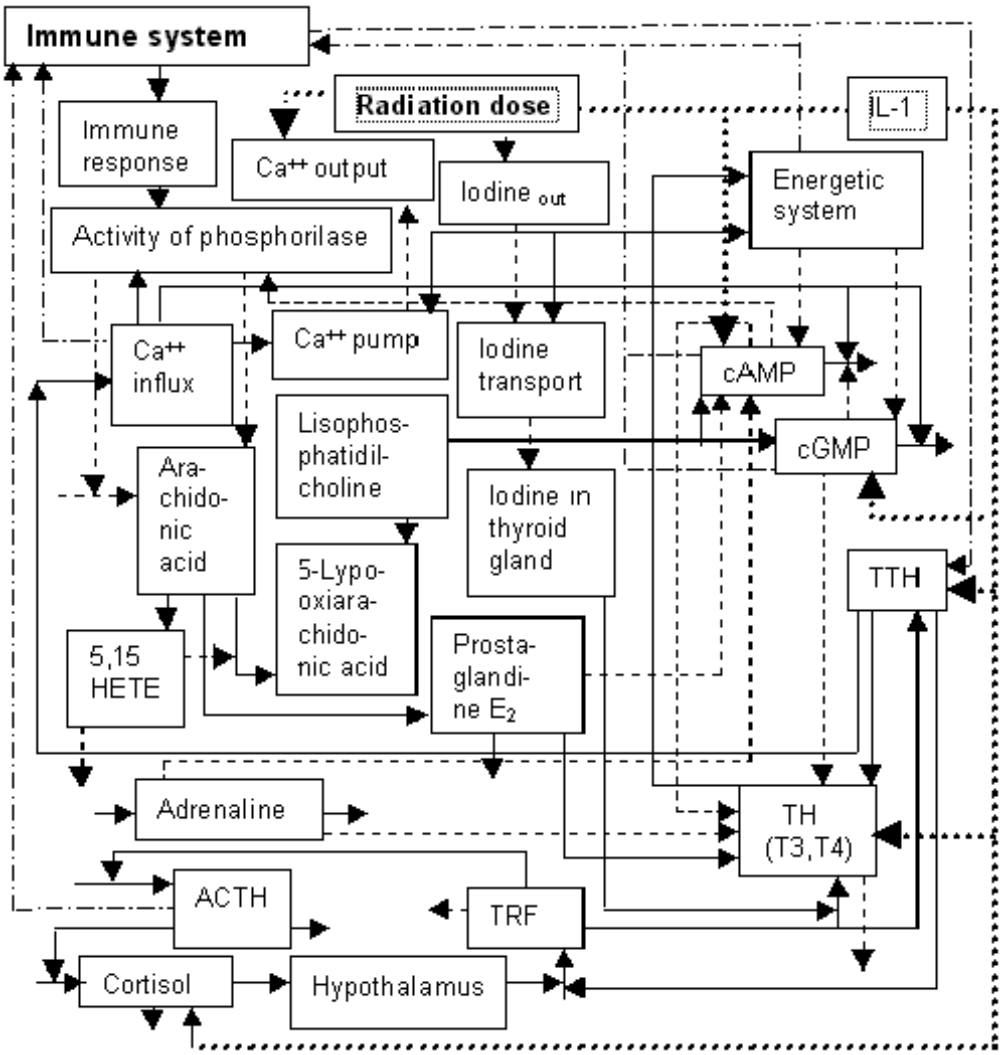

Figure 4: Block-scheme of NIEN. Solid and dashed lines are used for hormonal control of TS, dash-and-dot line - for interrelation between immune and endocrine systems, and dotted line - for radiation impact on NIEN.

$$
\begin{aligned}
dT_1/dt = \; & \alpha_1\{\beta_1+\beta_2 Ah(t)[\delta_1+IL1(t)]+\delta_2 IL1(t)-\delta_3 S(t)\} \\
& \{1+a_1[1-T_3(t)/K_3]+a_2[1-T_4(t)/K_4]-d_1 T_1(t-h_1)/K_1\}T_1(t), \\
dT_2/dt = \; & \alpha_2\{[\gamma_1+\gamma_2 A(t)+a_2+a_3-\delta_4 GH(t)-\delta_5 D_N(t)-\delta_6 IL1(t)-\delta_7 C(t)-\delta_8 E_S(t)] \\
& d_2 T_1(t)/K_1-a_3 T_3(t)/K_3-a_2 T_4(t)/K_4-d_3 T_2(t-h_2)/K_2\}T_2(t), \\
dT_3/dt = \; & \alpha_3\{\beta_3[\gamma_3+\gamma_4\nu_1+\gamma_5 Pr(t)]d_4 T_2(t)/K_2+ \\
& [1-\beta_3]T_4(t)/K_4-d_5 T_3(t-h_3)/K_3\}T_3\ (t), \\
dT_4/dt = \; & \alpha_4\{\ [\gamma_6+\gamma_7\nu_2+\gamma_8 Pr(t)]d_6 T_2(t)/K_2-d_7 T_4(t-h_4)/K_4\}T_4, \\
dCa/dt = \; & c_1[\ c_2+c_3 T_2(t)][1-\exp(-\alpha_5 t)]\ \exp(-\alpha_6 t)\ -\ P_{ca}(t)\{E(t)/[b_1+E(t)]\}, \\
\nu_1 = \; & [k_1+G(t)][k_2-A(t)][k_3+Lp(t)][k_4+I(t)]E(t)/[b_2+E(t)], \\
\nu_2 = \; & [k_5+G(t)][k_6-A(t)][k_7+Lp(t)][k_8+I(t)]E(t)/[b_3+E(t)],
\end{aligned}
\tag{7}
$$

where Ca(t) - ions of calcium, T_i (t) ($i=\overline{1,4}$) - concentrations of the thyroid system components, namely: respectively, TRF- (i=1), TTH (i =2), triiodothyronine, (i=3), thyroxin in blood serum (i=4); h_i ($i=\overline{1,4}$) - delays describing, respectively, mean lifetime of each thyroid system components; K_i ($i=\overline{1,4}$) – respectively, their mean values; $a_i(i=\overline{1,3})$, $b_i(i=\overline{1,3})$, $c_j(j=\overline{1,3})$, d_i ($i=\overline{1,7}$), k_m ($l=\overline{1,8}$), $\alpha_n(m=\overline{1,6})$, β_i ($j=\overline{1,3}$), $\delta_m(s=\overline{1,8})$, γ_m ($n=\overline{1,8}$) - model parameters.

Functions E(t) - energy substrates, Pr(t) - prostaglandines, G(t) - cGMP, A(t) - cAMP, Lp(t) - 5-lipo-oxiarachidonic acids, P_{ca}(t) –calcium pump, I(t) - iodine ion level in thyroid gland; Ah(t) - hypothalamus activity; C(t) - cortisol; D_N (t) – dopamine, IL1(t) - interleukin-1; GH(t) - growth hormone, S(t) – somatostatin, E_S(t) - estrogens can be defined based on the mathematical model [8].

A software for NIEN analysis at some types of TS pathologies (hypo- and hyperthyroidism, T3 - and T4 -thyreotoxicoses) has been developed; it has been used to assess the role of metabolic and thyroid components in a NIEN disturbances development process.

TH dynamics for norm, hypothyroidism, and hyperthyroidism, obtained in a model experiment, is shown at Fig. 5.

The frequency of T3 and T4 oscillations and their amplitudes increase during hyperthyroidism according to the model. The opposite results were obtained in the case of hypothyroidism.

TH changes under T3- and T4-thyreotoxicosis have been also investigated. T3-thyreotoxicosis causes an increase of T3 and a frequency of its oscillations, but decrease of TTH. The oscillations of T4 practically do not vary on amplitude, but vary on a phase. T4-thyreotoxicosis causes an essential increase of the level of T4 and a frequency of its oscillations. A frequency

of T3 oscillations also considerably increases, but their amplitude does not vary so intensely. A level of TTH decreases to a lesser degree than during T3-thyreotoxicosis.

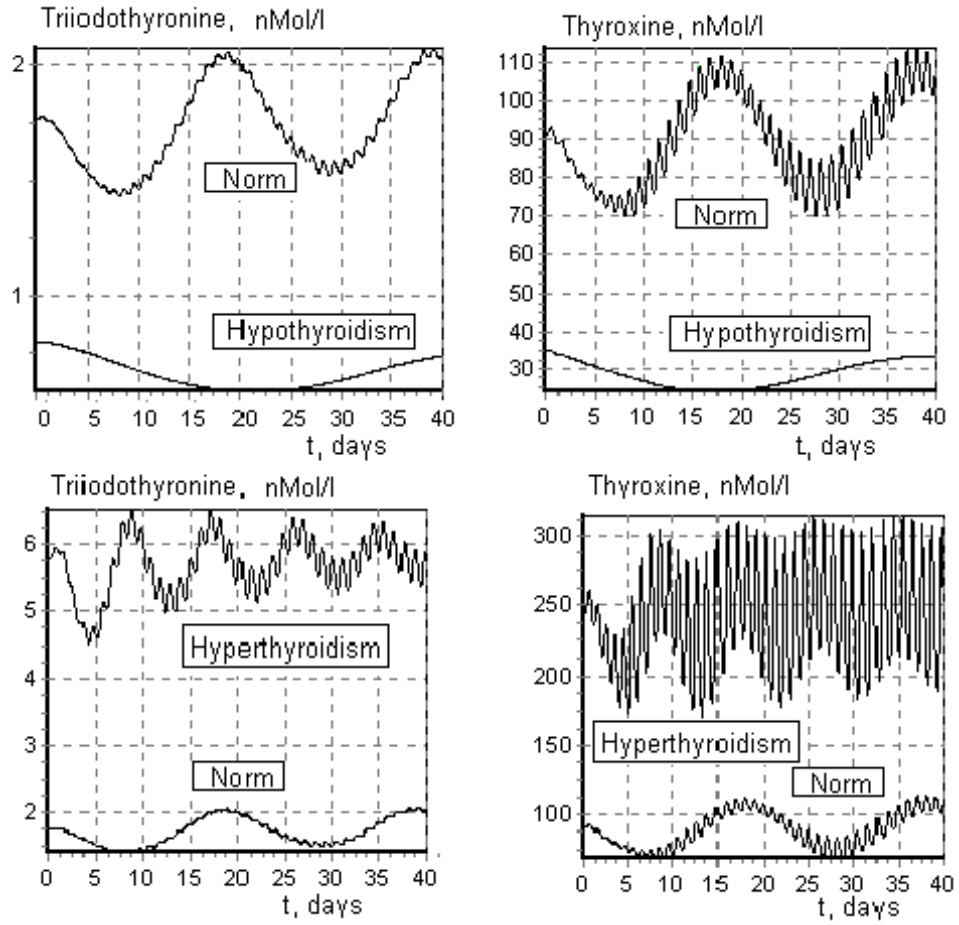

Figure 5: Modeling of TH's dynamics.

Average values of metabolic factors in the interval of modeling are presented at Fig. 6.

Basing on the model we can conclude that hyperthyroidism, T3-, and T4-thyreotoxicosis are not linked to essential changes in metabolic factors dynamics. On the contrary, hypothyroidism is a unique disease (from the above list), which is linked with an amplification of Ca^{++} influx, intensifi-

cation of cell metabolism, and essential changes of metabolic factors. First of all, those are CN and AA.

Our research results in the following ranking of thyroid pathologies by the role of metabolic impacts in NIEC disturbances: T4-thyreotoxicosis (minimal impact), T3-thyreotoxicosis and hyperthyroidism (medium), hypothyroidism (maximal). Thus, the following schemes of development of pathological processes may be considered.

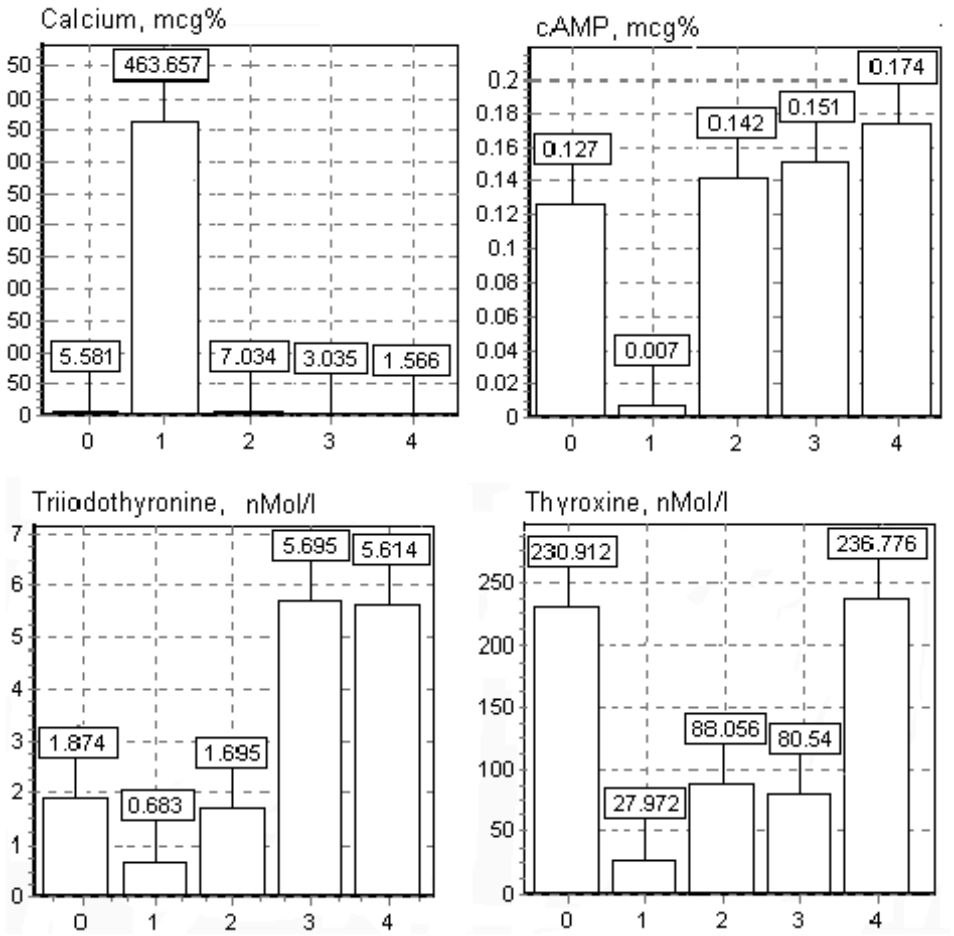

Figure 6: The comparative analysis of metabolic changes during thyroid diseases: 0 - T4- thyreotoxicosis, 1 - hypothyroidism, 2 - norm, 3 - T3-thyreotoxicosis, 4 - hyperthyroidism.

1. A primary disturbance of TS regulation is getting transferred to a level of metabolic regulation due to the changes in Ca^{++} influx intensity and energy synthesis. During hypothyroidism it results in essential misbalance between the processes of synthesis and energy consumption in a cell. Some existing experimental observations corroborate this assumption: 1) inhibition of energy synthesis due to a decrease of T3 and T4; 2) activation of energy consumption linked to the increase of Ca^{++} input in cells because of the increased TTH.

2. The energy disbalance causes metabolic shifts, for instance cAMP and prostaglandines level changes. Probably, they have compensatory character to limit negative changes in TH ratio.

5 Optimal control of the thyroid system restoration

The task of optimal control of TS restoration has been defined as follows: mathematical model of TH synthesis, control parameters U_i (i=1 – activators of oxidative phosphorylation, i=2 activators of Ca^{++} transport, i=3 – Iodine ions, i=4 – intensity of Ca^{++}-pump work, i=5 – inhibition of hypothalamus activity by cortisol) and their minimum and maximum values, accordingly U_{imin}, U_{imax} have been given. Control effects and phase trajectories minimizing functional F_j on an interval $(0,T_k)$ are to be found.

$$F_j(U_1,U_2,U_3,U_4,U_5) = \sqrt{\sum_{k=1}^{3}(\gamma_{ik}\sum_{l=1}^{n}(x_{ik}(t_l)-x_{Hk}(t_l))^2)},$$

where n – number of points in which the values x_{jk} were fixed (x_{j1} - TTH, x_{j2} - T3, x_{j3} - T4); j - index of disease (1 - hypothyroidism, 2 – hyperthyroidism, 3 - T3-thyreotoxicosis, 4 - T4- thyreotoxicosis); x_{Hk} - values of TH levels appropriate to norm; γ_{jk} - weight coefficients introduced to equalize a contribution of each addend to the objective function, with the limitations $U_i \in [U_{imin},U_{imax}]$. The method of casual search has been selected as an optimization method.

To define an efficiency of TS normalization, the quality of optimization has been introduced as an index (QO), showing in how many times the deviation of each TH from norm has been reduced in a result of control. The indices QO are defined as

$$QO(x_{jk}) = |I(x_{Hk}) - I(x_{jk})|/|I(x_{Hk}) - I(x_{OptHjk})|.$$

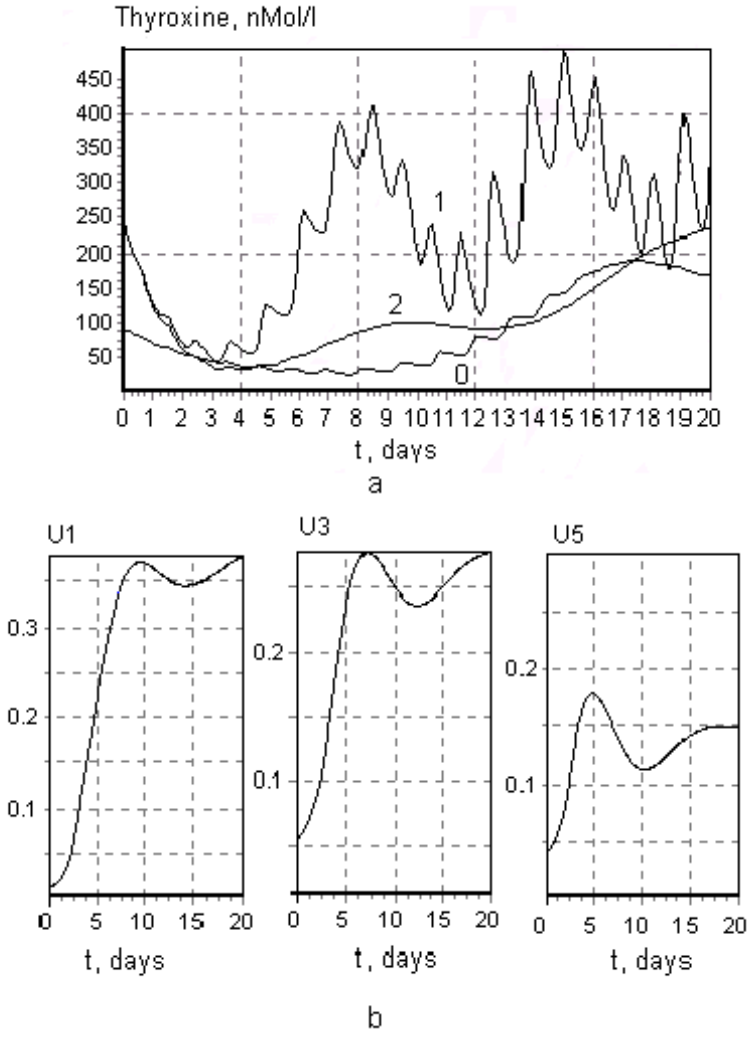

Figure 7: Some results of optimal control task solution: a) dynamics of thyroxine (0 – norm, 1 - T4- thyreotoxicosis, 2- optimization); b) dynamics of controls.

The following denotations of k-th hormone indices have been accepted:

$$I_{X_{Hk}} = \int_0^T x_{Hk} dt, \quad I_{X_{jk}} = \int_0^T x_{jk} dt, \quad I_{OptX_{jk}} = \int_0^T x_{jk}(U_i) dt.$$

They determine total amount of k-th hormone in the time interval [0, T] in norm, at disease j, and at presence of control effects U_i. The model experiments were carried out. Their objective was normalization of TH levels at the above mentioned diseases. The modeling results obtained at controls U_i (i=1,5) have allowed us to rank the efficiency of control process under above diseases (Fig. 7).

Following are QO consequences in the descending order.

1. *Hypothyroidism.* In this case essential increase of T3 and T4 levels is possible, as well as some decrease of TTH level. QO indices for the above hormones are, respectively, 24.9942, 2.52003, and 3.23769.

2. *T4-thyreotoxicosis.* Some decrease of T3 and T4 levels and some increase of TTH level are possible. QO indices are, respectively, 18.948, 1.26746, and 2.17923.

3. *Hyperthyroidism.* Small decrease of T3 and T4 levels and small increase of TTH level are possible. QO indices are, respectively, 1.55966, 1.72004, and 1.15142.

4. *T3-thyreotoxicosis.* The decrease of T3 and T4 and rise of TTH levels are insignificant. QO indices are, respectively, 1.07491, 1.04857, and 1.62824.

Disease		U_1	U_2	U_3	U_4	U_5
Hyper-thiro-idism	NE	1	1	1	1	1
	TI	0-6,6-20	0-8,8-20	0-7,7-20	0-5,5-20	0-6,6-20
	TC	↓↑	↓↑	↓↑	↓↑	↑↓
T3-thy-reoto-xicosis	NE	1	1	2	1	1
	TI	0-12,12-20	0-6,6-20	0-4,4-12, 12-20	0-5,5-20	0-8,8-20
	TC	↓↑	↑↓	↑↓↑	↓↑	↑↓
T4-thy-reoto-xicosis	NE	1	1	1	1	1
	TI	0-10,10-20	0-8,8-20	0-14,14-20	0-6,6-20	0-8,8-20
	TC	↑↓	↓↑	↑↓	↓↑	↑↓
Hypo-thyro-idism	NE	1	2	2	1	1
	TI	0-8,8-20	0-5,5-10, 10-20	0-7,7-18, 18-20	0-10,10-20	0-7,7-20
	TC	↑↓	↓↑↓	↑↓↑	↑↓	↑↓

Table 1: Changes of controls under restoration of thyroid gland (NE – extremum number, TI - time interval (hours), TC - type of changes: ↓- decrease, ↑ - increase).

Table 1 shows the critical time points of controls U_i (i=1,5) where they change the direction of their variation.

The increase of control parameters number essentially improves the quality of the optimization. It is possible to rank controls on their contribution in TS normalization. For instance, control U_5 addition essentially improves QO indices in the case of T3 normalization under hypothyroidism. Apparently, it has been caused by the decrease of hypothalamus inhibition by cortisol (increase of the parameter U_5). On the contrary, control U_4 addition doesn't improve QO significantly. Indeed, the decrease of Ca^{++}-pump intensity (increase of the parameter U_4) doesn't make such a direct contribution to TS normalization. In this case there is a growth of Ca^{++} level in the cell. It can render not specifically directed effects depending on the balance of various cell intermediates. Thus, the performed numerical research shows that TS restoration is a complicated problem. It is necessary to change the vector of control parameters' variations several times in the considered time period, i.e. essentially change the therapy used.

6 Radiation impact investigation on thyroid system

The radiation impact on an organism has a large variety of possible targets. This complexity makes it difficult to estimate correctly contribution of various changes in forming pathological processes evoked by the radiation.

The key moment in forming TS disturbances is a dependency of CN system (cAMP and cGMP) on an irradiation doze level [10]. cAMP action prevails at small irradiation dozes. It stimulates a TTH synthesis and restricts a TH synthesis. cGMP action prevails at high irradiation dozes, resulting in an opposite effect. What can be a reason for such a discrepancy?

It is possible to assume the following probable reasons:

1. Free radicals' accumulation at high irradiation dozes; it causes the decrease of a prostaglandin's synthesis rate, in spite of the increased level of Ca^{++} and weakening one of adenylatcyclase activation mechanisms.

2. Exhaustion of the adrenergic system also causes the decrease of an adenylatcyclase activity.

3. Allosteric regulation of phosphodiesterase activity by a high level of cGMP; calcium accumulation in the cell at high irradiation dozes also causes the rise of cGMP level. High level of cGMP increases the activity of phosphodiesterase causes acute drop of cAMP level, which can not be compensated by a stimulation of the adenylatcyclase activity due to prostaglandines.

The model (7) has been utilized to investigate possible mechanisms of pathology forming caused by a radiation action on the organism. We took into account that an increase of the exposure doze (D) varies the rates of TH synthesis and destruction, as well as the intensity of Ca^{++} ions fluxes through cellular membrane in both directions (see Fig. 4). Based on these data, let us introduce the functions to define a dependence of some model parameters on a radiation doze: d_j=d_j(D), (j=1,7), b_1=b_1(D), $\beta_2 = \beta_2$(D), $\gamma_2 = \gamma_2$(D). These functions have been determined based on the parameter identification problem solution using the method of causal search.

The mathematical problem statement has been formulated as follows:

Let $\boldsymbol{X}_i = (x_i(D_1),\ldots x_i(D_n))$, ($i$=1,3) be a sample of experimental data, where X_1 - TTH, X_2 - T3, X_3 - T4, $x_i(D_n)$ is a level of i-th hormone in the middle of n-th intervals of exposed doses.

Let the mathematical model be given as

$$dx/dt \ = F(t, x, U_1(D)\ldots U_m(D)),$$

where $\boldsymbol{x}(t)$ – vector of model variables, $\boldsymbol{U}_m(D)$ – vectors of model coefficients depending on the dose.

It is required to find vectors $\boldsymbol{U}_m(D)$ on the interval (t_0, t_n) to minimize the functional

$$I = \{\sum_{i=1}^{3} G_i \sum_{j=1}^{n} [x_i(D_j) - \overline{x_i(D_j)}]\}^{1/2},$$

where $x_i(D_j)$ and $\overline{x_i(D_j)}$ are the model and sample levels of i-th hormone under the exposed dose from j-th interval, G_i-.weight coefficients.

Hormones (nmole/l)	Data type	Norm	Exposed doze		
			1-2 Gy	2-4 Gy	10 Gy
T4	ED	91.34±5.05	85.20±7.36	128.24±7.97	157.21±10.01
	MR	92.48	91.78	127.61	148.24
T3	ED	1.77±0.15	1.76±0.25	1.57±0.36	3.09±0.23
	MR	1.77	1.75	1.56	2.48
TTH	ED	1.91±0.20	2.09±0.32	1.86±0.32	1.52±0.12
	MR	1.91	2.10	1.87	1.79

Table 2: Irradiation doze impact on thyroid hormones level

Table 2 shows a comparison of model results (MR) and experimental data (ED) obtained during an inspection of persons injured as a result of the Chernobyl accident.

Fig. 8 shows the total amount of TH versus the irradiation doze.

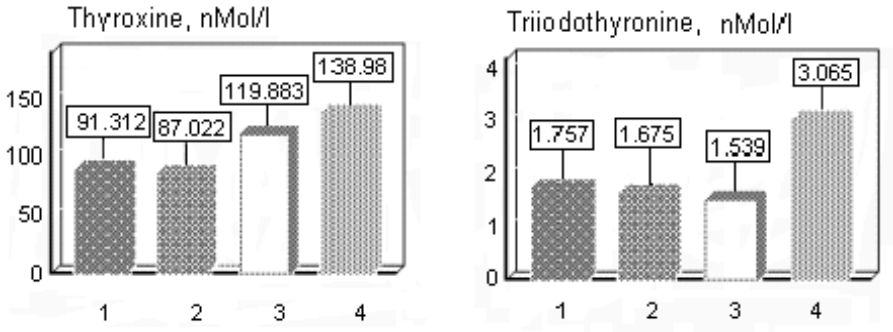

Figure 8: Model research of radiation impact on a total level of TH (columns show average values of hormones during time of modeling experiment:
1 - D = 0, 2 - D = 1.5 Gy, 3 - D = 3.0 Gy, 4 - D = 8.0 Gy).

The results of a performed model research made it possible to rank sensitivity of different TS regulation links to radiation action. At the dose of 0-2 Gy, the most influenced by radiation impact are the processes of TH synthesis, TTH, and TRF destruction, as well as Ca^{++}-pump. At the doze of 2-4 Gy, the radiation also affects a Ca^{++} influx. At the doses of 4-10 Gy, the radiation also affects a destruction of T3 and T4. It has been known that various cellular processes which were considered as targets of a radiation action, are controlled by the CN system. Besides, it has been shown that a dysfunction of the CN system manifests in early periods after irradiation and can precede changes in other systems. All these facts raise the question whether postradiation changes in the CN system are the mechanism triggering disturbances in other systems. In this case the disturbances are caused rather by metabolic modifications in cells connected with the changes of the CN ratio, than by a direct effect of free radicals formed by irradiation and other products of radiolysis (at least, on the early stages). Thus, the research of a CN role in formation of post-radiation disturbances is one of the central problems of modern radiobiology. The increasing number of publications makes the conclusion that these research can shed light on the mechanisms forming radial affection and permit a development of complex

therapeutic schemes of the individualized therapy, as well as new methods for estimation of its efficiency and health risk.

7 Conclusion

The program complex has been developed to analyze a research of TH control during some types of TS pathology. The distinct feature of this complex is a possibility to get an approximation of the real sequence of the events developing in the organism as a whole under the action of radiation and others stress factors, on the basis on some integrated parameters of environmental impact on the organism as a whole and on its separate control systems. The research made it possible to rank various links of TS by their sensibility to a radiation impact and determine the following most probable sequence of their changes: radiation action → change in the NIEN system → change of ACTH and cortisol levels → change of TTH level → change of Ca^{++} input → change in the CN system → change in TH synthesis → disturbances in metabolism of Ca^{++} ions.

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