Integrated Approach To System Researches Of Complex Problems Of Medicine And Biology

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ABSTRACT

In this paper one approach to the use of the System Sciences is described. As the result of this effort an effective instrument for practical needs and scientific researches was created. The instrument itself is the computer system that implements a mathematical model of the respiratory system of the human body. To build the system methods of systems analysis, mathematical modeling, medical science, biology, physiology and information sciences were successfully integrated. Optimal control theory was used to realize the mechanisms of self-organization in the model. Only development of the mathematical model is shown in this paper; the computer system architecture and the description of the methods of numerical calculations implemented in software are omitted.

Keywords: system science**,** aggregate, mathematical modeling, functional respiratory system, pharmacological correction

1. SELF-ORGANIZATION OF THE FUNCTIONAL RESPIRATORY SYSTEM AND THE AGGREGATIVE PRINCIPLE OF SYSTEM BUILDING

The respiratory system of the human organism is one of the most complex systems of biological nature. To build a model of it many different approaches were used. All of them were chosen in accordance with the task of the research and resources available. To build the model described in this paper the authors aimed to create a computer-based system that could:

- calculate gas conditions in different parts of the human body with the adequate level of resulting data accuracy;
- allow to make prognosis of efficiency of self-regulating mechanisms for defined extreme conditions for significant amount of time;
- allow to simulate influence of regulating mechanisms on the respiratory system if changes of internal parameters happen (medical treatment);
- allow to simulate influence of combined external and internal regulating mechanisms on the respiratory system if changes of external parameters take place (hypoxia, hyperbaria);
- be self-adaptive;
- work in real-time regime.

Considering all these requirements we worked out the hybrid approach with the use of the theory of aggregative systems.

Let us say a few words about aggregates and their role in computer system creation. We consider an aggregate as a certain information transformer. Suppose that T is a set of elements of time, X, Y, U - sets of input, output and control signals relatively, and Z is a set of states of the aggregate. Then the aggregate is considered as an object that is defined by sets T, X, Y, U, Z and operators H and G. Operators H and G are named operators of transitions and outputs of the aggregate. They are realizations of the functions of the state z(t) and output signals y(t). The scheme of the aggregate is given on Figure 1.

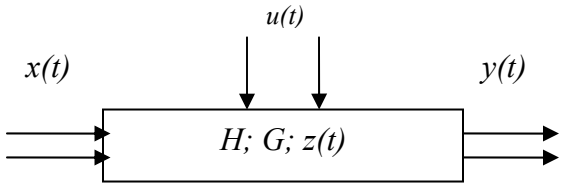

Figure 1. The structural scheme of the aggregate

Thus, the computer system that imitates the activity of the respiratory system is build as an aggregative system. It allowed building of the model with multi-level

controls. This fact is especially important because the respiratory system itself realizes the mechanisms of self-organization on different levels of own functionality.

Depending on the ways operators H, G, sets X, Y, T, and Z were defined various methods and technologies were used. Three large groups of aggregates were used to design the imitation system. First group consisted of aggregates that represented hardware platform (first of all we consider complex medical devices interacting with the human body). Second group related aggregates composed software platform. The structure of these two groups varied depending on the designated assignment of the system. The third group of aggregates created a design platform for the core of the system – the model of the respiratory function of the respiratory system.

Development of the model of the respiratory function went through four stages.

On the first stage, the aggregates were defined. Here are the main groups of the aggregates: respiratory paths, body tissues, blood vessels, blood components, respiratory gases.

On the second stage the methods of realization of the aggregates and building of elements of control were done. The concept of the theory of aggregates allowed using the methods of pure and applied mathematics. It was decided to use methods of the theory of differential equations, the methods of mathematical programming, the theory of optimal control, the methods of numerical calculations.

The chosen methods were realized on the third stage. The gas states (Z) of the aggregates (respiratory paths, body tissues, blood vessels) were presented by differential equations. To realize the control system we used the theory of optimal control. The operators H and G were implemented in the optimum criteria.

On the fourth stage, the task of creation of the unified imitation model was fulfilled.

We have to note again, that the respiratory system is a self-organized system. Consequently, characteristics of its elements and their associations depend on internal or external conditions. That is why the authors assumed that the aggregative system had to have variable structure. To realize it the model was supposed to have two subsystems depending upon one another. Functional destination of the first system was to control the structure and changing the attributes of the second (controlled) system. Each of the systems combined closely related elements (aggregates).

Let us give the general description of the model functioning. The aggregate of the system with variable structure was considered defined if were defined: set Z; operator of transition H from one state to another on the interval [0, T]; exit operator G; the scheme S of relations of aggregate with other aggregates of the system. In addition, each aggregate was considered connected to the control system and being receiving control signals. The process of functioning of the aggregate A of the controlled system consisted of relocations inside the area Z. The control system had two control units – program unit Up and synthesis unit Us. Both units consisted of related aggregates. Unit Us was designed to examine the conditions of aggregates of controlled system, to select the regimes of functioning, and define structure S depending on the results of examination and the task of the system. The task could be defined in unit Up or came from outside. Unit Up also selects the program of actions to realize the task. Up works out controls u(t). The process is repeated as a new task comes.

The basic model of the respiratory system considers 7 different body tissues: brain, heart, liver, kidney, skeleton muscles, skin tissue and the tissue that represents all other. With the use of the described approach to the whole system creation we can easily divide the listed tissues into smaller pieces or locate new ones. It depends on the task of calculations or the kind of pathology simulated.

2. THE MATHEMATICAL MODEL OF FUNCTIONAL RESPIRATORY SYSTEM AND ITS ANALYSIS

The third stage of the model development had two the most important phases. The first one was creation of the system of differential equations that described the process of transport and exchange of mass of respiratory gases on the respiratory cycle (the inhale phase, the exhale phase and the pause). The problem of control of this system was formulated and solved on the second phase.

The controlled system is a system of nonlinear differential equations [1]. The variables of the equations

are partial pressure of oxygen (P^{O_2}), carbon dioxide (P^{CO_2}) and nitrogen (P^{N_2}) in respiratory paths and alveoli, and tension of these gases in blood and tissues of an organism. The independent variable is time that consists of respiratory cycles.

It was proven that:

1. The solution of the system of differential equations:
   - exists and is unique in all area of the definition of the system variables;
   - is non-negative and limited from above.
2. A stationary (periodical) solution of the dynamic system is the only one and Lyapunov stable.

The model considers the main function of the respiratory system as regulation (self-organization) of the delivery of oxygen and removal of carbon dioxide from the organism.

This regulation should happen in proper time and be effective. The task of regulation is fulfilled by the control system and is formulated as a task of optimal control of the disturbed dynamic (controlled) system. The control parameters are:

- lungs ventilation ($\dot{V}$);
- blood flows ($\dot{Q}_i$) in tissues;
- system blood flow ($\dot{Q} = \dot{Q}_1 + ... + \dot{Q}_m$).

The criterion of optimality is the functional

$$I = \int_{\tau_0}^{T_c} [\rho_1 \sum_{t_i} \lambda_{t_i} (G_{t_i}^{O_2} - q_{t_i}^{O_2})^2 + \rho_2 \sum_{t_i} \lambda_{t_i} (G_{t_i}^{CO_2} - q_{t_i}^{CO_2})^2 + \rho_3 \sum_{t_i} \lambda_{t_i} (G_{t_i}^{N_2})^2] d\tau \quad , i = \overline{1,m} \tag{1}$$

If $\varepsilon_i^{O_2} > 0$, $\varepsilon_i^{CO_2} > 0$, $\varepsilon_i^{N_2} > 0$, $q_{t_i}^{O_2}(\xi), i = \overline{1,m}$ represent the velocity of consumption of oxygen, and $q_{t_i}^{CO_2}(\xi), i = \overline{1,m}$ represents the velocity of producing of carbon dioxide, then the task of control is formulated as:

find $\dot{V}$ >= 0 and $\dot{Q}_i$ >= 0 that transfer the disturbed system into the attraction area of the steady state M(τ):

$$\begin{cases} \dfrac{\int_{\tau_0}^{\tau_0+\tau} q_{t_i}^{O_2}(\xi) d\xi - \varepsilon_i^{O_2}}{D_{t_i}^{O_2} S_{t_i}} \le \int_{\tau_0}^{\tau_0+\tau} \left(P_{ct_i}^{O_2}(\xi) - P_{t_i}^{O_2}(\xi)\right) d\xi \le \dfrac{\int_{\tau_0}^{\tau_0+\tau} q_{t_i}^{O_2}(\xi) d\xi + \varepsilon_i^{O_2}}{D_{t_i}^{O_2} S_{t_i}} \\ \dfrac{\int_{\tau_0}^{\tau_0+\tau} q_{t_i}^{CO_2}(\xi) d\xi - \varepsilon_i^{CO_2}}{D_{t_i}^{CO_2} S_{t_i}} \le \int_{\tau_0}^{\tau_0+\tau} \left(P_{ct_i}^{CO_2}(\xi) - P_{t_i}^{CO_2}(\xi)\right) d\xi \le \dfrac{\int_{\tau_0}^{\tau_0+\tau} q_{t_i}^{CO_2}(\xi) d\xi + \varepsilon_i^{CO_2}}{D_{t_i}^{CO_2} S_{t_i}} \\ -\varepsilon_i^{N_2} \le \int_{\tau_0}^{\tau_0+\tau} \left(P_{ct_i}^{N_2}(\xi) - P_{t_i}^{N_2}(\xi)\right) d\xi \le \varepsilon_i^{N_2} \end{cases} \tag{2}$$

In (1) – (2) λ_{t_i} reflect influence of the structural-morphological peculiarities of the tissue on autoregulation. $\rho_k, k = 1,2,3$ - are coefficients of sensitivity of a certain organism to hypoxia, hypercapnia and degree of the accumulation of nitrogen, $D_{t_i}^j$ - are the coefficients of transparency of gases through the membrane, which separates blood and the tissue; S_{t_i} , $i = \overline{1,m}$ – is the area of surface of mass exchange

Adequacy of the model to the processes described is shown by mathematical analysis of the solutions of the system of differential equations and the control task.

The system described above represents a system that interacts with environment and compensates external and internal disturbances.

External disturbances are:

- changes in gas pressure;
- changes in gas compounds and quality of gas mixture;
- internal disturbances that may be caused by artificial heart activity, and the heart diseases (ischemia, atherosclerosis).

To study the behavior of the solutions of this system was critical for the creation of the imitation model. That was why the authors provided a thorough analysis of the system and found that:

- there is an optimal control in the class of continuous $0 \le \dot{V}(\tau) \le \overline{V}$, $0 \le \dot{Q}(\tau) \le \overline{Q}$ that minimizes the criterion (1) and transfers the disturbed controlled system [1] into M(τ) in a limited amount of time
- the optimal control is unique.

3. IMITATION MODEL OF THE FUNCTIONAL RESPIRATORY SYSTEM

Structurally the imitation system includes several levels of program modules.

The lowest level of the system (Figure 2) reflects the process of operation of the controlled part of the model. The parts of it are presented as aggregates connected by flows of information of the values of partial pressures of gases, levels of saturation of oxyhemoglobin and carbohemoglobin, mioglobin, concentration of the medicine, and many others.

The middle level of the imitation system reflects the process of operation of the modules that provide selection of optimal parameters (Up). The data received from the aggregates of the system are processed (unit Us) and then the optimal ventilation ($\dot{V}$), blood flows ($\dot{Q}_i$) in tissues, and system blood flow ($\dot{Q} = \dot{Q}_1 + ... + \dot{Q}_m$) are selected (unit Up).

The upper level of the system includes the program modules of imitation of changes in system activity. Some of them are disturbances in intensity of oxidative processes, imitation of ischemia and its medical treatment, changes of environment. The imitation of the process of operation of the controlled system is provided by the program module, which realizes the algorithms of numerical integration of the controlled system.

In the middle and upper levels we included mechanisms of evaluation of states of the controlled system, resources of control and decision making.

As major input data system considers parameters which illustrate air components, consumption of oxygen, human weight, the masses of selected organs and tissues, concentration of haemoglobin, concentration of enzyme carbonic anhydrase, level of ischemia, respiratory volume, and many others. Some of these parameters are defined by simple measurements, some by medical examination.

4. HYPOXIC STATES IN CASE OF ISCHEMIA HEART DISEASE AND THEIR PHARMACOLOGICAL CORRECTION

To study the influence of ischemia disease on hypoxic states [2] of the organism the model is modified – the heart is presented by four-chamber system with bringing and leading round arteries to each of the chambers. Then the equations for the tension of oxygen in the blood of tissue of the heart capillaries, tissue liquid of the heart, and concentration of the medicine with which ischemia cured is presented by the following equations:

$$\frac{dp_{jct_2}^{O_2}}{d\tau} = \frac{1}{\left(V_{jct_2} + \int_{\tau_0}^{\tau}\left(\underline{Q}_{jt_2}(\xi) - \overline{Q}_j(\xi)\right)d\xi\right)}\left(\alpha_1 + \gamma Hb\frac{\partial \eta_{jct_2}}{\partial p_{jct_2}^{O_2}}\right)\times$$

$$\left(\alpha_1 \overline{Q}_{jt_2} p_{ja}^{O_2} - \alpha_1 \underline{Q}_{jt_2} p_{jct_2}^{O_2} + \gamma Hb \underline{Q}_{jt_2}\eta_{aj}\right. \qquad (3)$$

$$\left. - \gamma Hb \overline{Q}_{jt_2}\eta_{ct_2} - G_{jt_2}^{O_2}\right)$$

$$\frac{dp_{jt_2}^{O_2}}{d\tau} = \frac{1}{\alpha_{1jt_2} V_{jt_2}}\left(G_{jt_2}^{O_2} - q_{jt_2}^{O_2} - \gamma_{Mb} MbV_{jt_2}\frac{d\eta_{jMb_2}}{d\tau}\right)$$

$$\alpha_f V_{jct_2}\frac{dc_{fct_2}}{d\tau} = \alpha_f Q_{jt_2} c_{fa} - G_{jft_2} - \alpha_f Q_{jt_2} c_{fct_2}$$

$$\alpha_{ft_2} V_{jt_2}\frac{dc_{ft_2}}{d\tau} = G_{jft_2}$$

j = 1, 2, 3, 4.

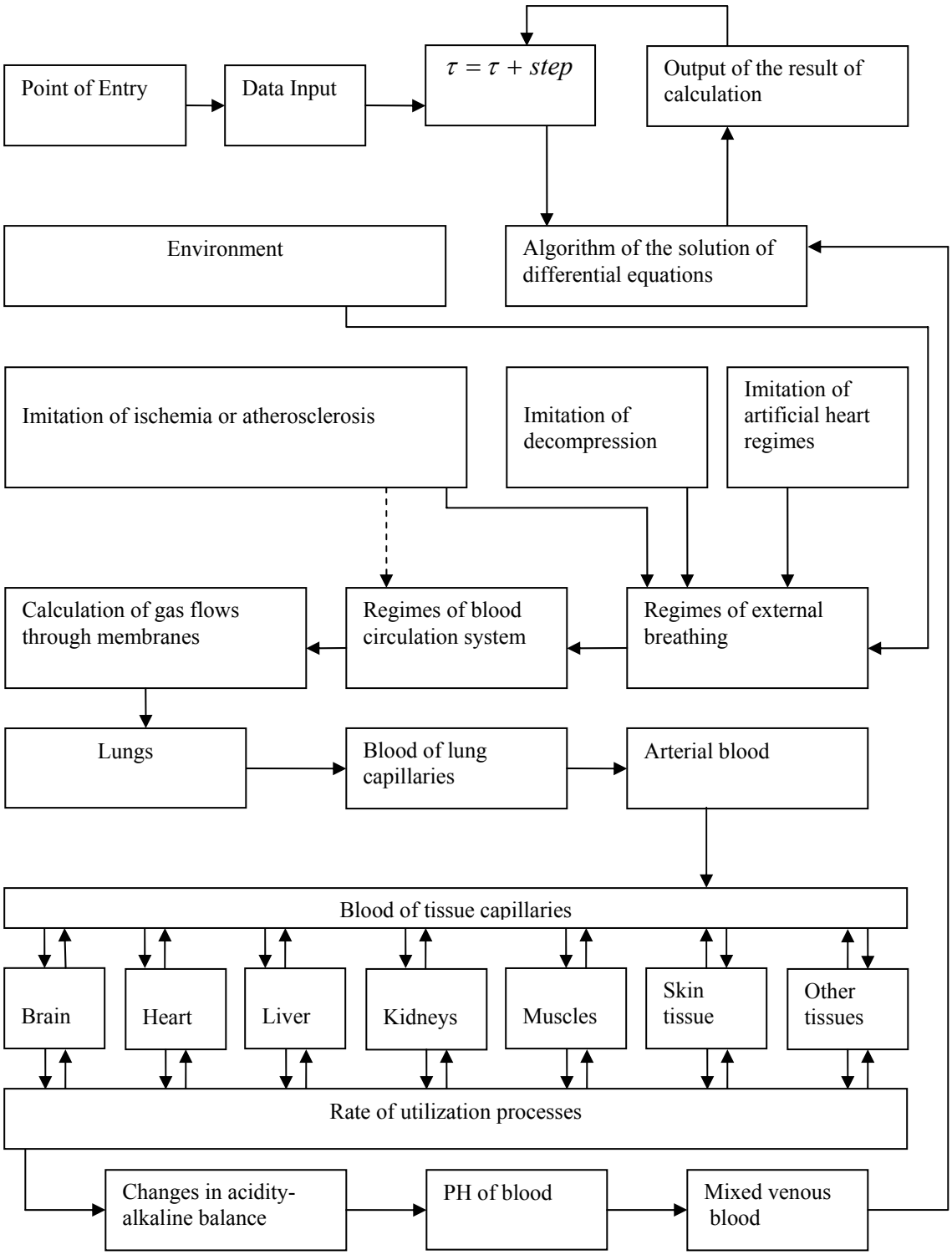

Figure 2. The structure of the imitation system

Index j shows the number of compartment of the myocardium, index 2 is the index of myocardium itself, $\underline{Q}_{jt_2}$, $\overline{Q}_{jt_2}$ are the values of coming in and going out volumetric blood flows in compartment j, α are coefficients of dissolubility of gases in blood, α_{t_2} are the coefficients of dissolubility of gases in heart tissue liquid, γ is the Hufner's coefficient, Hb is the amount of haemoglobin in blood, V_{jct_2}, Vj_{t_2} are the volumes of the blood of the tissue of the compartment j and the liquid of the tissue the compartment j of respectively.

Other variables are described in [1] and [2]

The equations that describe the transport of pharmacological preparations are entered into the model. The equations depend on a way of its injection into the system and the character of its influence on smooth vascular muscles of capillaries.

The model allows investigating features of a gas portrait in separate structures of the heart and the organism if ischemia is developed by insufficient blood supply and atherosclerosis.

Depending on a doze of a pharmacological preparation and its influence on a tone of smooth vascular muscles of vessels, the model allows to provide optimal pharmacological correction.

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