

Mathematical Methodes of Biological System Models Synthesis from the Medical Data

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Abstract— Biological systems are complex. Very often practical experts that work with the them don't have enough mathematical skill for building correct models of such systems. Authors suggest an approach to automatic synthesis of biological system models on the basis of experimental data. For solving this problem it is suggested to use multilevel relative finite state operational automata. The algorithm for automata synthesis is described. Results of solving real life problems show advantages of the suggested approach.

Key words— biological systems; system analysis; methods of synthesis

I. INTRODUCTION

Investigations of multiple properties of biological systems have shown to scientists and practical experts the necessity of developing systematic approaches to analysis and assessment of the functional conditions of biological systems and estimation of their changing state. In the considered case a system can be defined as a totality of elements which are organized without fixed criteria of association and ordering. The systematic approach in biology and medicine domains can be defined through features of the systems [1, 2].

This article is based on the systematic approach to biological systems modelling which is proposed in the monograph of A. M. Lushnov and coauthors [3]. In the medical domain adaptive mechanisms of human body can be observed in many functional systems: leykotsitarny, biochemical, electrolytic and others. Analysis of changes in physiological systems is primarily focused on estimation of the coherence of internal interaction of biological systems elements, that shows the self-organization of the elements.

Main objective of the study of the self-organizing systems is assessment of their functional state in general and control

them taking into account external and internal influencing factors. Nowadays methods of mathematical statistics, multivariate data analysis are usually used for solving problems of systems analysis. In practice the systematic approach to biological systems study is rarely used. Therefore, the task of implementation of the systematic approach to the analysis of the state of physiological systems of healthy people and patients with pathologies in practice of health care is relevant.

II. MODELS AND METHODS OF BIOLOGICAL SYSTEMS INVESTIGATION

Researchers suggest different types of indicators for assessment of the functional state of an organism: physiological, medical, single, complex, temporal, etc. The most part of them is applicable for static estimation of separate parameters. But there are almost no results of the researchers in the field of dynamic modelling of these parameters and there are no publications about building complex models of biological systems in dynamic. The most significant results in this domain are received during the multi parameter simulation directed to assessment of the functional state of an organism. The received statistical models and methods used for their creation can form a basis for automation of processes of biological systems modelling.

From the point of view of automatic modelling one can define the following specific features of biological systems.

The first special feature is that analysis and assessment of the biological system state is to be based on comparing current values of the parameters and values that were observed earlier. Modern approaches assume comparison of current parameters values with reference values.

The second special feature is that it is necessary to evaluate the coherence of different variations between parameters in the context of general system state. If observed variations show disorder in functioning of a system, then the dynamic of this mismatch is to be analyzed.

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For implementation of the models with the given features, the existing computer models of biological systems do not always have enough capabilities [4, 5]. As a rule, common biological system models are based on regression, qualitative and simulation models. The main disadvantages of such models are high computational complexity and low level of agility.

In [6] the analysis and estimation of known approaches to complex object modelling is given. A new approach to complex object modelling is suggested. It assumes usage of automata models for object description. The models are generated from object parameters. In order to use this approach for building biological systems models it is necessary to modify the proposed models taking into account specific features of biological systems.

III. THE PROBLEM OF BIOLOGICAL SYSTEMS MODELS SYNTHESIS ON THE BASE OF RESULTS OF FRAGMENTARY EXAMINATION OF HUMAN ORGANISM

Let the system B is observed in the time period $\Delta T = [t_s, \dots, t_r]$, where t_s – a moment of observation starting and t_r – a moment of time after which no new information about the system was received. Initial state of the system B_s is unknown. Observation assumes that periodically separate parameters of the system are measured. Processes of parameters measurement are managed. As a result the set of observations $Z = \{Z_s, \dots, Z_r\}$ is obtained, where Z_i – are results of observations of the set of parameters at i -th moment of time.

The point of interest is assessment of the current system state taking into account earlier observed variations in the system state and prediction of the expected system state for time interval $[t_{r+1}, \dots, t_{r+k}]$. Assessment must be based on available data about system parameters variations $\Delta \hat{B} : M_r = \{\hat{B}_r | \Delta \hat{B}_{r-1}, \dots, \Delta \hat{B}_{r-j}, Z\}$.

For complex system state evaluation, it is necessary to define the functionals that reflect changes of dependences between parameters. In general functionals can be defined as $F = \text{func}(\Delta p)$, where $p = \{p_i\}$, $p_i \in P$, P – the set of all measured parameters. Of particular interest are stable consistent dependences defined on the set of functionals. Stability in time is characterized by duration of the interval of time on which the dependence is observed $S = \{\Delta t_{s-k} : F(t_s) \& \dots \& F(t_k) = 1\}$. Consistency is defined on the base of physical properties of parameters. In particular, it is taken into account that step-function changes are not in nature of biological systems parameters. In this regard the consistency is measured by computation of smoothness of the parameters values curve: $L = \{\Delta t_{j-k} : \text{curv}(\Delta F(t_{i,j})) < \varepsilon\}$.

IV. MODELLING OF BIOLOGICAL SYSTEMS ON THE BASIS OF RELATIVELY FINITE OPERATIONAL AUTOMATA

The usage of hierarchical relatively finite operational automata [7] allows build hierarchical models of objects on the base of the results of measurements of parameters.

The structure of automata model reflects the structure of real world biological systems. The bottom level contains information about parameters, higher levels – about subsystems. The set of the admissible states of the analyzed systems are defined in terms of changes in comparison with previous states. Transitions between states are carried out on the base of calculated values of functionals. Admissible sets of transitional functions and output data are limited by functionals, that can be calculated using available data.

The hierarchical automatic model is defined as a sequence of interdependent automata machines of different levels:

$$DOKA^0 \Leftrightarrow DOKA^1 \Leftrightarrow \dots \Leftrightarrow DOKA^i \Leftrightarrow \dots \Leftrightarrow DOKA^r.$$

Let us consider a model of the i -th level on the r -th step. In general such model is described as

$$OKA_r = \{d_{ar}, d_{br}, d_{cr}, F_r^b, F_r^c, DA(\bar{d}_{br-1}), DB(\bar{d}_{br-1}), DC(\bar{d}_{br-1}), FB(\bar{d}_{br-1}), FC(\bar{d}_{br-1})\},$$

where \bar{d}_{ar} – is a vector of input data; \bar{d}_{br} – is a vector of internal state parameters; \bar{d}_{cr} – is a vector of output parameters; F_r^b – is a function of transitions between automata internal states; F_r^c – is a function of outputs. States \bar{d}_{br} , \bar{d}_{cr} , \bar{d}_{ar} and functions F_r^b , F_r^c , which describe automata at the r -th moment of time must satisfy the following conditions: $\bar{d}_{ar} \in DA(\bar{d}_{br-1})$, $\bar{d}_{br} \in DB(\bar{d}_{br-1})$, $\bar{d}_{cr} \in DC(\bar{d}_{br-1})$, $F_r^b \in FB(\bar{d}_{br-1})$, $F_r^c \in FC(\bar{d}_{br-1})$.

According to these conditions, for each parameter of the automata model the set of admissible values is defined relatively to the previous $r-1$ step.

Taking into account specific features of biological systems the automata model can be defined as $OKA_r = \Delta T_r OKA_{r-1}$, where ΔT_r – operator, which reflects changes in a system state on interval $[r-1, r]$.

Considering n – multiple iteration of operators one can systemically trace the changes of the system state starting from some moment of time t_s : $OKA_r = \Delta T_r \dots \Delta T_1 OKA_0$.

As both internal states, and output data describe changes of the system state, there is no need to separate sets of admissible values DB and DC . It is possible to define the set $DBC = DB = DC$. The dependence of these sets on the previous step remains, i.e. $DBC(b_{r-1})$.

The sets of admissible functions of internal transitions and outputs are also similar $FBC = FB = FC$. As the set

FBC depends on the functionals, it can be defined as $FBC(F(b_{r-1}))$.

The offered model of biological systems on the basis of the relatively finite operational automata is a completely tunable model. For its reconfiguration it is enough to redefine the set of the calculated functionals or the set of the considered states of the systems.

V. . THE RECOMMENDED METHODS FOR COMPLEX ASSESSMENT OF BIOLOGICAL SYSTEMS

In the field of the theoretical medicine one can observe a steady tendency to reduce numerous facts and empirical rules to few or even a single law. For this the principle of optimality is often used.

The biological sense of such models lie in calculation of the maximum of correlation links in the normal system state and in estimation of the degree of links misbalance in the case when dysfunctions takes place. Sometimes it is reasonable to perform the transformations that allow choose optimum subsets of features and to give systematical estimation for each object of the multidimensional sample using the criteria function [8, 9].

Other systemic statistical method of studying states of a functional system for a sample (an array of multidimensional data) is based on definition of an optimizing aggregated estimation which is considered as a functional. In this, the thresholds of importance of links are defined and the set of objects is split into non-intersecting classes which, for example, can correspond to the sets of physiological parameters. [3, 9, 10, 11].

In addition to the listed above methods, other methods also can be used, in particular, the method based on estimation of the functionals of the system using correlation matrix [11], the method for building logical decision rules [12], etc.

VI. RESULTS OF SIMULATION

Automata models of biological systems were synthesized on the base of data on the system of peripheral blood (a leukogram, erythrocytes, a hemoglobin) and the system of an acid-base condition of blood – an acid-base equilibrium (ABC-ABE). Total number of the analyzed parameters made several tens of parameters.

The sample data were generated from 4074 protocols of mainly cardiosurgical interventions, ABC-ABE (21951 cases), hematological analyzes of leukocyte peripheral blood (24397 cases) – leukograms (LG) of patients with cardiopathology treated in Almazov National Medical Research Centre.

For the above indicators of patients (ABC-ABE, LG), functionals [11] and criteria functions [9] were constructed in dynamics according to the mentioned methods (Fig. 1–3).

The example of dynamic systemic assessment (functional) of an acid-base condition (ABC-ABE) and LG before, in time, and after surgery on the example of tests of blue blood of cardiac patients is given in Table 1, in Fig. 1, 2.

TABLE 1. DYNAMICS OF THE ABC-ABE FUNCTIONAL OF VENOUS BLOOD BEFORE, IN TIME AND AFTER SURGERY

Days	Sample size	Functional of ABC-ABE	Threshold of importance of communications of ABC-ABE	Number of classes of splitting parameters of ABC-ABE
-14	28	13.31	0.42	9
-7	39	26.71	0.27	4
-3	129	12.32	0.36	9
0 - surgery	2908	13.98	0.35	8
1	4128	12.95	0.34	9
2	1460	12.22	0.38	9
3	847	10.23	0.47	11
4	535	13.22	0.37	8
5	340	11.71	0.42	9
6	193	11.08	0.46	10
9	215	14.12	0.35	8
14	322	12.17	0.43	9

Visual representation of the considered parameters is shown in Fig. 1. As seen in Fig. 1 the dynamics of the functional of ABC-ABE gives an idea of the set of metabolic changes in acid-base exchange of the patients.

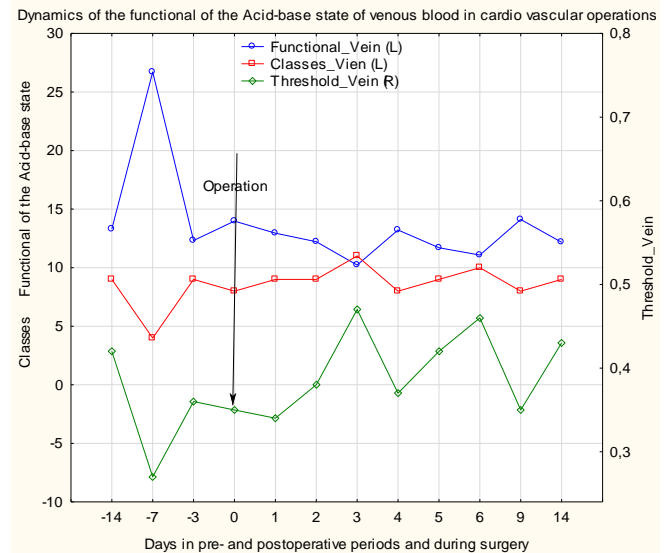


Fig. 1. Dynamics of a functional of ABC-ABE, thresholds of importance of links and classes of splitting parameters of blue blood of patients before, in time and after surgery

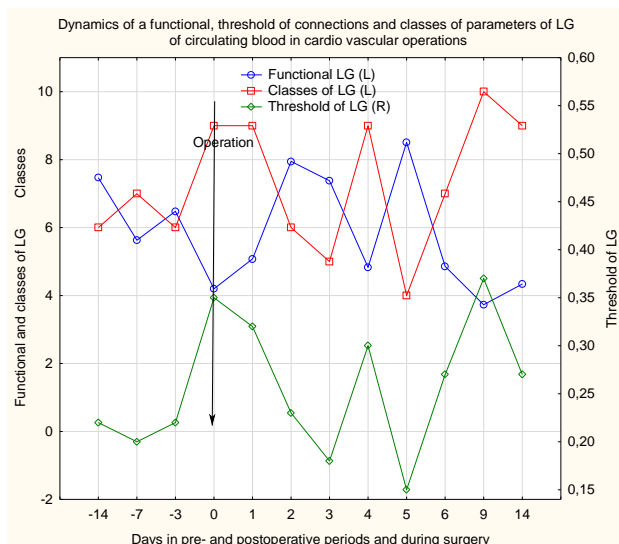


Fig. 2. Dynamics of a functional of LG, classes of splitting and thresholds of importance of links for patients before, in time and after surgery

The above graphs of the systemic indicators of ABC-ABE and LG show changes in peripheral blood and in ABC-ABE during the treatment of the patients, allow reduce the dimensionality of the feature space to facilitate the evaluation of a large number of parameters by the physician, to describe the process in a compact manner.

Another example is given for the ABC-ABE system of arterial blood of 65 cardiosurgical patients. The blood fetuses were performed 6 times during the treatment of the patients. The size of the total sample was 390 observations. Further, for each patient, the criteria function (CF) was calculated in dynamics. Fig. 3 shows the dynamics for CF of the ABC-ABE of the patient D. The dynamics for CF of the ABC-ABE of this patient, as well as of other patients, indicates the individual type of response of ABC-ABE indicators. Therefore, the CF of the ABC-ABE can allow in the future identify the types of responses of individuals to external and internal impacts.

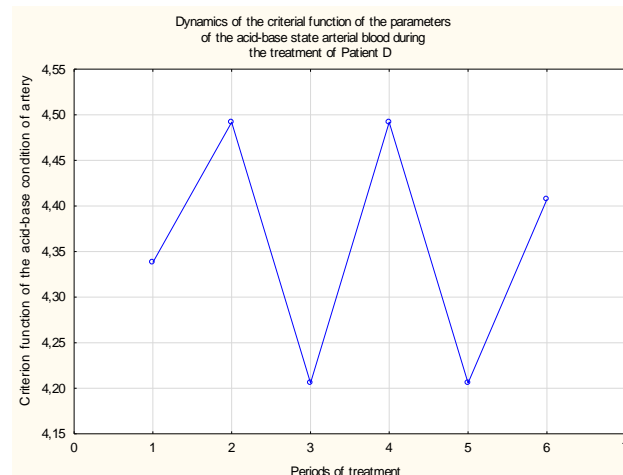


Fig. 3. Dynamics of CF of ABC-ABE of the patient D

The received results of the pilot research allow make a conclusion on a possibility of usage of the proposed automata models for biological systems modelling.

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