PROGNOSTICATION OF EFFICIENCY OF MEDICAL AND PROPHYLACTIC MEASURES AT DIFFERENT HOMOEOSTASIS VIOLATION OF HUMAN ORGANISM BY MARKOV PROCESSES THEORY

Boris Samura, Anatoly Povoroznuk, Olga Kozina, Elena Visotskaja,
Elena Chernykh, Nikolay Shukin, Andrei Porvan

Abstract: This article is devoted to the questions of prognostication of efficiency medical and prophylactic measures at renewal of the broken equilibrium of human organism by vegetable medications. The methods of modeling of different processes are considered in the article from position of systems analysis. There was chosen Markov processes theory for description of renewal of the broken homoeostasis process, which rotined high correlation between clinical supervisions and forecast process.

Keywords: casual process, Markov chains, medical and prophylactic measures, MAIS, MFPS.

ACM Classification Keywords: I.6 Simulation and modeling, I.6.3 Applications; J.3 Life and medical sciences – Medical information systems

Introduction

For today increased interest of doctors is concentrated in the alternative methods of human treatment and, especially, by phitotherapy. It is method of human organism treatment by medications of phitomaterials, which can be used as independent or additional type of treatment and prophylaxis of different diseases and rehabilitation of patients with the chronic diseases. A new coil in development of this type of treatment demanded the revision of attitude toward it, and development of modern methods of lead through and estimation of it efficiency. Phitotherapy foresees setting of medical plants, allowing individualizing the process of treatment taking into account classification of illnesses, their etiologic nosotropic essence, and to receives most and on possibility fast clinical effect with the minimum sides' actions, that is not always arrived at the use of synthetic medicinal preparations.

One of important stages of prophylaxis and treatment of different diseases is the ground of application expedience of one or another type of therapy. As result, the research directed on the exposure of degree of influencing of medications of vegetable origin on a time of the broken renewal of human organism homoeostasis is great scientific and practical interest.

Set the problem and analysis of existent works

In connection with introduction of mathematic and computer technologies to human knowledge field the last years interest of doctors increased by the different mathematical methods, approaches and estimation facilities of the human organism state at the different methods of therapy, in particular estimations of change of the human organism state at treatment by phito-medications (PHM) [Самура, 2003]. Application of mathematical methods and facilities allows to the specialist to obtain complete information about processes what is going on in the human organism and in good time to produces correction of the appointed treatment.

Problem related to estimation of process of renewal of the broken equilibrium of human organism continues to remain actual, because the effective methods of its decision not are found thus far. Presently a systems research receives wide distribution in not only biology and medicine but also pharmacology. Efficiency of the appointed treatment in a great deal depends on quality of application of systems approach, not having an alternative in the conditions of scientific prognostication and medically-practical activity in the new problem situation related to the phitotherapeutic method of complex individual renewal of the broken equilibrium of human organism.

One of main instruments of system analysis of any explored process is its mathematical modelling. In obedience to the base classification of methods of modelling of the systems and processes, offered by F.E. Temnikov, select two classes:

- methods and models directed on activating of intuition and experience of specialists (MAIS);
- methods and models of formalization presentation of the systems (MFPS).

Such division of methods is in accordance with the basic idea of systems analysis, which consists of combination in models and methods of formal and informal presentations, that helps in the choice of methods of formalization and analysis of problem situation [Волкова, 1993, Славиц, 1989].

Therefore, MAIS imply verbal description of problem situation at which no necessity is in proof of the explored process. In the turn of MFPS allow to transform verbal description in formal one. This process is important component part of decision-making process.

The methods of formalization presentation of the systems can be divided to four classes:

- analytical methods;
- methods of discrete mathematics;
- statistical methods;
- methods of graphic presentation.

Graphic presentation is the comfortable mean of research of structures and processes in the complex systems (for example, human organism), and mean of organization of human and hardware co-operation. For description of different processes, this class of methods is used by the directed count of the states or network graph. However much application of these methods at estimation of the organism state, by virtue of the specificity, does not allow considering feedbacks and cyclic processes arising up in a process treatment of human.

The methods of discrete mathematics make theoretical basis of development of simulation and informative and searching languages and include set-theoretic, logical, linguistic and semiotics methods and models. A set-theoretic method are based on the concepts of great number, relations of great numbers and continuum and is used as summarizing a language at comparison of mathematics and other disciplines. The common state of organism, described by these methods, can be represented by the aggregate of great numbers and subsets of heterogeneous chambers with the arbitrarily entered elements and relations. However, introduction of arbitrary relations results in that in formalization description of the organism state can will be revealed an insoluble contradiction that does not allow operating by the received set-theoretic model the same way, as with classic analytical or statistical correlations, guarantying authenticity of the got results. The methods of mathematical linguistics and semiotics are a comfortable vehicle for formalization of decisions in tasks with a great initial vagueness and are one of constituents of construction of the complex systems of decision-making. However applying these methods it is necessary to have because of, that at complication of formal model by the rules of arbitrary grammar and semiotics it is hardness enough to guarantee authenticity of the got results, and

explanation of the got results not always carries objective character. The methods of mathematical logic are used at research of the systems of different nature, in which character of interrelations between elements not is clear and their analytical presentation is not possible, and statistical researches did not result in the exposure of statistical conformities to the law. However needed it is to have because of, that description of the systems by the methods of mathematical logic implies the use of logical base statutory Boolean algebra. In also time semantic possibility of logical methods is strictly limited, and the use of multiple-valued a logician appears enough by labour intensive procedure and requires the special proofs of authenticity of the received results [Гилл, 1985].

The widest distribution was got by analytical methods. These methods allow adequately representing the explored process by the determined values or dependences. These methods are widely used in the optimizations tasks of planning and analysis of the different systems in biology and medicine. However, the use of these methods requires the obvious pointing of all connections between components and goals of the system as analytical dependence.

The human organism is the open system which different external factors influence on. The processes what is going on in an organism carry probabilistic character partly. That is why it is possible to assume that the change of homoeostasis of organism also will carry probabilistic character. As result application of all higher described classes of methods and models for adequate description of homoeostasis change process as a result of complex therapy vegetable medications are not possible.

Application of the known methods of the statistical programming allows investigating the processes of the studied system without the exposure of the clear determined conformities to the law. It is explained to those, that at application of statistical presentations the process of raising of task is partly replaced by statistical researches or expert estimations, the result of which with the certain share of probability influences on the conduct of all system on the whole.

At the modelling of the complex system, a few models are usually used from a number the varieties mentioned above. Any system can be represented by different ways, which differ from each other on complication and working out in detail. In such situations for the generalized description of work of the modelling process it can be applied the imitation modelling.

All simulations models are models as the so-called black box. It means that it provide delivery of output signal of the system, if an entrance signal acts on its influencing subsystems. Therefore, for the receipt of necessary results it is necessary to carry out driving away of simulations models.

A simulation model is the special programmatic complex, which allows imitating activity of some complex object and reflects the great number of parameters subject to time-history and space.

On the stage of research and analysis of the systems at construction and realization of different models, the method of statistical design of Monte Carlo, which is based on the use of casual values, is widely used. Essence of method of statistical modelling is taken by construction for the process of functioning of the explored system of some modelling algorithm imitating the conduct and co-operation of elements of the system taking into account accidental influences and influences of external environment. The series of particular values of the sought after values or functions statistical treatment of which allows to receives information about the conduct of the real object or process in the arbitrary moment of time turn out as a result of statistical design of the system. However, for achievement of sufficient statistical stability of the system and reliable exactness of description of the explored process plenty of experiments of the system are needed. In addition, the use of method of Monte Carlo allows

building a «fictitious» model only, not having connection with an object or process of design. Markov models, in-use for the analysis and synthesis of calculable structures, which can be considered as stochastic systems without the consequences, allow taking into account this failing [Панкратова, 2005].

Basic material and research results

Markov chain models are a natural approach to take when modeling the transitions of patients between discrete health states over time, for example, the progression over stages of a disease. There is a distinction between discrete-time Markov chains, whereby we consider transitions to occur at fixed points in time and we work with transition probabilities, and continuous time Markov chains, whereby transitions can occur at any point in time and we work with transition rates. The use of discrete-time Markov chain models in medical decision applications dates back to the work of others have championed the use of continuous-time Markov chain models based on stochastic trees and have pointed out the mathematical convenience and simplicity of these models as long as the same rates are applied over a full lifetime. A discrete- time model can approximate a continuous-time Markov model by defining a cycle length of interest (for example, yearly or 6-month intervals). The advantage of the forward equations approach is that transition rates, rather than transition probabilities, form a common basis for combining information from different studies.

The disadvantage of Markov models is that departure from the simple assumptions of stationary, first-order Markov chains while, conceptually possible, makes for disproportionate degrees of difficulty in analysis and computation. Moreover, like all other succession models, the validation of Markov models depends on predictions of system behavior over time, is therefore frequently difficult, and may even be impossible, for long periods [Медик, 2007, Токмачев, 2003] .

Renewal of the broken equilibrium of organism of human with the help PHM it is possible to represent as casual process of transition from one state in other, at which each of the states describes the degree of violations passing in an organism.

However, there is some system of E, describing the process of renewal of the broken equilibrium of organism, which in the process of functioning can adopt the different states $E_i, i = \overline{1,K}$ with probabilities $P_i(t)$.

It is known that the human organism state in the moment of time can be classified on the degree of disease as: $E1$ as the conditionally healthy; $E2$ as the initial changes; $E3$ as the easy degree; $E4$ as the middle degree; $E5$ as the heavy degree; $E6$ as the extremely heavy degree; $E7$ as the fatal outcome.

For research of influencing of synthetic and phitotherapeutic preparations on the renewal process of the broken equilibrium of human organism 150 patients were inspected. Coming statistical data from the vectors of apriory probabilities of finding were received in i^{th} state of organism of patient – $P_i(0)$.

$$P_1(0) = [0.985; 0.015; 0.00; 0.00; 0.00; 0.00; 0.00];$$

$$P_2(0) = [0.03; 0.955; 0.015; 0.00; 0.00; 0.00; 0.00];$$

$$P_3(0) = [0.00; 0.03; 0.94; 0.03; 0.00; 0.00; 0.00];$$

$$P_4(0) = [0.00; 0.00; 0.015; 0.97; 0.15; 0.00; 0.00];$$

$$P_5(0) = [0.00; 0.00; 0.00; 0.045; 0.955; 0.00; 0.00];$$

$$P_6(0) = [0.00; 0.00; 0.00; 0.00; 0.015; 0.985; 0.000];$$

$$P_7(0) = [0.00; 0.00; 0.00; 0.00; 0.00; 0.00; 1.00].$$

A finite Markov chain is a process with a finite number of states in which the probability of being in a particular state at step (i+1) depends only on the state occupied at step i.

The dynamic supervision after patients included the clinical, laboratory-biochemical and bacteriologic examinations. After rising of diagnosis and determination of values of the initial states setting of treatment was conducted. Controls examinations were conducted during a semi year first time per a month.

At every the instant the system can is in one of seven states. Except for the initial state of the system (in the initial moment of the time t=0), being in which a patient appealed to the doctor, known also one step transition

$P_{mn} = P\{E_i = E_n | E_{i-1} = E_m\}$, m, n =1..7 (see fig.1), where one step is equal to the interval between the moments of conducting of control researches. Consequently, the random process of state transition of the organism $E_i = E(t)$ is the homogeneous Markovian chain.

$$P_{ij}^{(1)} = \begin{vmatrix} 1.00 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 \\ 0.93 & 0.06 & 0.01 & 0.00 & 0.00 & 0.00 & 0.00 \\ 0.00 & 0.90 & 0.07 & 0.03 & 0.00 & 0.00 & 0.00 \\ 0.00 & 0.00 & 0.83 & 0.14 & 0.03 & 0.00 & 0.00 \\ 0.00 & 0.00 & 0.00 & 0.80 & 0.13 & 0.07 & 0.00 \\ 0.00 & 0.00 & 0.00 & 0.00 & 0.67 & 0.32 & 0.01 \\ 0.00 & 0.00 & 0.00 & 0.00 & 0.00 & 0.00 & 1.00 \end{vmatrix}$$

Fig. 1 Matrix of transitional probabilities from one state in other for the explored group

Transition probabilities from one state in other can be presented in the following as (fig. 2):

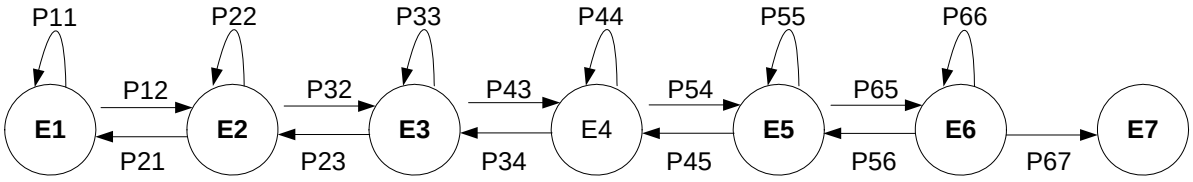

Fig. 2 Marked graph of the states for the model

We will take on to every no zeroing element of the transitions probabilities matrix during one-step P_{mn} the random variable T_{nm} with the function of distributing F_{nm} ($t_{nm} \le t$). For the examined system the random variable T_{nm} is discrete delay time of patient in a state of E_n, on condition that following state will be E_m. In other words, a patient remains in a state E_n in the flow time T_{nm}, before his state will be replaced on E_m. After the E_m state achievement «instantly» (in accordance with matrix of transitional probabilities), a next state E_k is selected. Since the E_k state is chosen delay time in E_k T_{kl} relies equal with function of probabilities distribution $F_{kl}(t)$. This process can proceed long time, choosing an each time independent next state and delay time.

It ensues from the resulted determination, that if to ignore random character of delay time and to take interest only transition moment, a process $E(t)$ will be a Markov's homogeneous chain (or embedded chain).

However at the account of stay of process $E(t)$ in the different states during the random intervals of time will not satisfy to equalization Markov (if not all times are up diffused exponentially). Consequently, a process is Markov's process only in the transition moments. The said justifies the name of «semi -Markov process» or «semi-Markov chain».

At the given initial state the further conduct of semi-Markov process fully concerns by the matrix of transitional probabilities $\{P_{ij}(t)\}$, i, j = 1..7, and matrix of functions of probabilities distributions $\{F_{ij}(t)\}$. We will assume that in some moment of time, taken as a start (t_0=0), the system is in a state of E_i. Let the following state is chosen (with probability of P_{ij}) the state of E_j. Then by theorems of product and adding probabilities, we find the absolute function of distributing of complete delay time in a state E_i

$$F_i(t) = P(t_i < t) = \sum_{i=1}^{7} P_{ij}^{(1)} \cdot F_{ij}(t), \quad j=1..7 \tag{1}$$

Middle value of absolute delay time T_i in state E_i equal

$$T_i = \sum_{j=1}^{7} P_{ij}^{(1)} \cdot \overline{T_{ij}} \tag{2}$$

We will pass now to the decision of main task arising up at the analysis of semi-Markov processes, i.e. to the calculation of probabilities of the states. Let $C_{ij}(t)$ is conditional probability at which in the time moment t system is in a state of E_j, if in the time moment t_0=0 it was in a state of E_i. Probability of $C_{ij}(t)$ can be named interval-transitional probability. The system, starting from the initial state of E_i, can get in the state of E_i in the time moment equal t by different ways. Firstly, if $E_i = E_j$, it can stay in state E_i during all interval t or, going out from the state E_i at least once, it all the same goes back into the state $E_j = E_i$ till the time t. Secondly, the system can get in the arbitrary state of E_j, occupying in the time moment τ some transient state of E_k. Probabilities of these two mutually eliminating possibilities must be added:

$$C_{ij}(t) = \delta_{ij} \cdot \left(1 - \sum_{j=1}^{7} P_{ij}^{(1)} \cdot F_{ij}(t)\right) + \sum_{k=1}^{7} P_{ij}^{(1)} \cdot \sum_{t=0}^{t} F_{ik}(\tau) \cdot C_{kj}(t-\tau), \; 1 \le i, j \le 7, \tag{3}$$

where δ_{ij} – Kronecker's symbol, δ_{ij} = 1 at $i = j$ and δ_{ij} = 0 at $i \neq j$.

The first member on the right in equation (3) takes into account probability of event $E_i = E_j$, because $(1 - \sum_{j=1}^{7} P_{ij}^{(1)} \cdot F_{ij}(t))$ is probability at which the system will not leave the state E_i during interval time t. The second member in (3) presents probability of sequence of events, while the system accomplishes transition from E_i to E_k (it can be even in itself) to moment τ and then passes from the state of E_k to the state of E_i for remaining time of t-τ. Probabilities of every possible transition are added on all transient states of E_k, in which transitions are possible from the initial state of E_i, and are summing on various times of transitionτ of τ between 0 and t.

System of linear integral equations (3) is basis. It gives expression of interval-transitional probabilities by main characteristics of semi-Markov process. Nevertheless, to get the analytical decision of this system not simply. Some simplification gives application of method of Laplace's transformation.

For simplification of calculations according (3) and when probabilities distributions of random processes $F_{ij}(t)$ for every state E_i unknown, we will ignore random character of delay time in every state and to take interest only transition moments. In other words, let assume that we have Markov's homogeneous chain for which probability of staying in the state E_k, in the moment of time of ($t + \Delta t$) will concern by the formula of complete probability:

$$P_K(t + \Delta t) = P_1(t) \cdot P_{1K} + P_2(t) \cdot P_{2K} + \ldots + P_K(t) \cdot P_{KK} + \ldots + P_n(t) \cdot P_{nK}. \tag{4}$$

with condition that $\sum_{i=1}^{7} P_i = 1$. According to (4) with given vectors of apriory probabilities of staying in every states $P_i(0)$ and one-step transition matrix $P_{ij}^{(1)}$ we we received sets of state probabilities during first 12 months.

In tabl.1 shown that if patient first time come to doctor with middle degree of disease (i.e. E_4 state exist at t=0 with probability $P_4(t=0)=0.75$) then on 3step or after 3 months probability of state E_1 will equal 0.653 to contrary with probability of state E_4 which will equal 0.029. Thus in tabl.1 we analyze number of step at which probability of state E_1 – the conditionally healthy – higher than any other probabilities as dependence on initial vectors P_i (0). For all initial vectors P_i (0) in all next steps after steps marked into tabl.1, probability of state E_1 is increase and probabilities of others states are decrease.

The Markov chain on fig.1 is absorbing because it has two absorbing states, and from every state it is possible to go to absorbing states. As known, in a finite number of steps the chain will enter an absorbing state and then stay in that state. Also, the long-term trend depends on the initial state – changing the initial state can change the final result. This property of our analyzed system is reflected into tabl.1 and in common distinguishes absorbing Markov chain from regular Markov chains, where the result is independent of the initial state.

Table 1. Probabilities of states E_i for different initial vectors P_i (t=0)

Step, t	$P_1(t)$	$P_2(t)$	$P_3(t)$	$P_4(t)$	$P_5(t)$	$P_6(t)$	$P_7(t)$
0	0.985	0.015	0.000	0.000	0.000	0.000	0.000
1	0.999	0.001	0.000	0.000	0.000	0.000	0.000
0	0.030	0.955	0.015	0.000	0.000	0.000	0.000
2	0.993	0.006	0.001	0.000	0.000	0.000	0.000
0	0.000	0.030	0.940	0.030	0.000	0.000	0.000
2	0.816	0.133	0.042	0.008	0.001	0.000	0.000
0	0.000	0.000	0.140	0.750	0.110	0.000	0.000
3	0.653	0.223	0.084	0.029	0.008	0.003	0.000
0	0.000	0.000	0.000	0.045	0.955	0.000	0.000
4	0.571	0.232	0.117	0.053	0.019	0.007	0.001
0	0.000	0.000	0.000	0.000	0.015	0.985	0.000
6	0.644	0.174	0.093	0.048	0.018	0.008	0.016

To obtain information about the time to absorption in an absorbing Markov chain, we first calculate the fundamental matrix B_m for our patients from one-step transition matrix $P_{ij}^{(1)}$ [Гармоткина, 2005]. Let I_1 represent the 1×1 identity matrix in the upper left corner of $P_{ij}^{(1)}$; let O represent the matrix of zeros in the upper right; the R represent the matrix in the lower left; and let Q represent the matrix in the lower right. Using these symbols, $P_{ij}^{(1)}$ can be written as

$$P_{ij}^{(1)} = \begin{bmatrix} I_1 & O \\ R & Q \end{bmatrix}.$$

The fundamental matrix for the absorbing Markov chain is matrix B, where

$$B = \left(I_n - Q\right)^{-1}. \tag{5}$$

Here I_n is the $n \times n$ identity matrix corresponding in size to matrix Q, so that the difference I_n-Q exist. For our Markov chain transition matrix $P_{ij}^{(1)}$ can be rewritten in follow view:

$$P_{ij}^{(1)} = \left[\begin{array}{cc|ccccc} 1 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 1 & 0 & 0 & 0 & 0 & 0 \\ \hline 0 & 0.93 & 0.07 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0.90 & 0.07 & 0.03 & 0 & 0 \\ 0 & 0 & 0 & 0.83 & 0.14 & 0.03 & 0 \\ 0 & 0 & 0 & 0 & 0.80 & 0.13 & 0.07 \\ 0 & 0.01 & 0 & 0 & 0 & 0.67 & 0.32 \end{array}\right]$$

Thus, our fundamental matrix will be

$$B = \begin{bmatrix} 1.075 & 0 & 0 & 0 & 0 \\ 1.075 & 1.111 & 0.040 & 0.002 & 0.000 \\ 1.075 & 1.111 & 1.245 & 0.047 & 0.005 \\ 1.073 & 1.109 & 1.243 & 1.295 & 0.133 \\ 1.058 & 1.093 & 1.225 & 1.276 & 1.602 \end{bmatrix}$$

Let our Markov chain currently in state i. The expected number of times that the chain visits state j at this time is 1 for i and 0 for all other states. The expected number of times that the chain visit state j at next step is given by element in row I, column j of the transition matrix Q. The expected number of times the chain visits state j two steps from now is given by corresponding entry in matrix Q^2. The expected number of visits in all steps is given by $I_n+Q^2+Q^3+Q^4+\ldots$ To find out whether this infinite sum is the same as $(I_n - Q)^{-1}$, multiply the sum by $(I_n - Q)$:

$$(I + Q + Q^2 + Q^3 + \cdots) \cdot (I - Q) = I + Q + Q^2 + Q^3 + \cdots - Q - Q^2 - Q^3 + \cdots = I,$$

which verifies our results.

It can be shown that

$$P_{ij}^{(k)} = \left[\begin{array}{c|c} I_n & O \\ \hline \left(I + Q + Q^2 + \cdots + Q^{k-1}\right) \cdot R & Q^k \end{array}\right],$$

where I_n is the $n \times n$ identity matrix. As $k \to \infty$, $Q^k \to O_n$, the $m \times m$ zero matrix, and

$$P_{ij}^{(k)} = \left[\begin{array}{c|c} I_m & O \\ \hline B \cdot R & O_n \end{array}\right],$$

so BR gives the probabilities that if the system was originally in a non-absorbing state, it ends up in one of absorbing states.

The entry b_{ij} of B gives the expected number of times that the process is in the transient state E_j if it is started in the transient state E_i.

The total number of steps expected before absorption equals the total number of visits which expected to make to all the non-absorbing states. This is the sum of all the entries in the i^{th} row of B. For our fundamental matrix the total number of steps expected before absorption (means state E_1) show in tabl.2.

Table 2. The total number of steps expected before absorption for different start state

Start state	E_2	E_3	E_4	E_5	E_6
№ steps	1.075	2.223	3.483	4.855	6.254

Comparing of data from tabl.1 and tabl.2 show aproximally same results.

Conclusion

Theory of the Markov processes allows numeral to describe the behavior of the complex system, namely influence of phito-medications facilities on human organism. Thus, it is possible to get a prognosis on duration of stay of patient on all selected states of medically diagnostic cycle depending on prevalence's. The numerical results of mathematical modeling with the use of simplification through assumption that analyzed process can be described via embedded Markov chain, shows high correlation to clinical observations. However, mathematically will be more correctly to use theory of semi-Markov processes in our case. As shown, semi-Markov processes theory cannot give finite analytical results. But if clinicians will give distributions of probabilities of delay time in every state during the treatment it may be to use simulation to receive numerical results of probabilities that patient will be on the state in any time.

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Authors' Information

Boris Samura – doctor of pharmaceutical sciences, professor, honoured worker of scitech Ukraine, academician of ANTK of Ukraine, Head of Pharmacotherapy Department of National University of Pharmacy, Darwin street, 8/10, Kharkov, 61002, Ukraine

Anatoly Povoroznuk – PhD, professor of Computers and Programing Department of National Technical University 'KPI', Frunze street, 21, Kharkov, 61002, Ukraine

Olga Kozina – PhD, lecturer of Computers and Programing Department of National Technical University 'KPI', Frunze street, 21, Kharkov, 61002, Ukraine; okaraban@rambler.ru

Elena Visotskaja – PhD, lecturer of Biomedical Electronic Devices and Systems Department of Kharkov National University of Radio Electronics, Lenina Av., 14, Kharkov, 61166, Ukraine; e-mail: diagnost@kture.kharkov.ua

Elena Chernykh – PhD, lecturer of Computers and Programing Department of National Technical University 'KPI', Frunze street, 21, Kharkov, 61002, Ukraine

Nikolay Shukin – probationer is a researcher of Biomedical Electronic Devices and Systems Department of Kharkov National University of Radio Electronics, Lenina Av., 14, Kharkov, 61166, Ukraine

Andrei Porvan – engineer of Biomedical Electronic Devices and Systems Department of Kharkov National University of Radio Electronics, Lenina Av., 14, Kharkov, 61166, Ukraine; e-mail: borman_d@mail.ru