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SYSTEMS ANALYSIS OF SOME BIO-MEDICAL PROBLEMS RELATED TO MEDICAL TREATMENT MANAGEMENT

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Abstract

A systems approach to the investigation of bio-medical problems related to treatment of certain types of diseases is discussed in this article. Problems of determining admissible and optimal management with criteria designed for both rapidly and slowly developing diseases are described here. Examples are given of analyzing problems in the management of two typical diseases.

A considerable number of current bio-medical problems are both difficult and complicated. Special techniques outside "traditional" medicine have been widely used for investigating these problems. One approach combines medical, biological, and physio-chemical methods of investigating living objects with control theory apparatus. Two groups of problems of special interest in applying control theory methods are 1) those in which a living object is considered as a large number of interrelated physiological systems with uncertain and changeable mutual links, and 2) those where the living object is an element of a complex system. The first type of problem would include individual medical examination and treatment of the most widespread diseases such as cardiovascular and oncological diseases. An example of the second type of problem is the organization of health centers and mass treatment, both in normal conditions and in emergencies such as epidemics.

The conceptual framework of systems analysis [1] contains an approach to studying actual bio-medical problems using the entire arsenal of existing techniques aimed at investigating living objects and of mathematical methods of control theory. Problems of living sub-systems management, specifically with the goals of medical treatment, have already been investigated by many authors [2,4]. However, the problem of managing the state of the living object as a whole, or as a part of a more complex system in the process of medical treatment, meets with considerable difficulties because of the extreme complexity of these objects.

A new stage of the research on this problem based on the systems approach has now become a reality through the successful application of control theory methods, mathematical modelling, and the use of computers in biology and medicine [5,7]. A complex living object is treated as a set of interacting elements, or sub-systems; this approach permits deeper insight into the structure, the functioning mechanisms, and mutual links of the sub-systems of living objects. This is the antithesis of the methods based on the idea of the so-called "black box." Though the mathematical tools of systems analysis have not as yet been completely shaped, the systems approach to living objects will probably use the control theory methods developed to work with incomplete data [8,9] and with state space [10].

The system approach to bio-medical problems (hereafter we shall refer to them as medical treatment problems) involves several consecutive stages:

1) description of the living object as a "whole" by estimating observability of pathological processes in the object at different stages of the disease;

2) formulation of the management goals resulting in an efficient application of control theory methods;

3) determination of feasible management classes which also include optimal management and estimation of its effectiveness. Such management will be referred to as "tactics of treatment" and consist of systems of rules a) for testing the state of the object (the schedule of examinations and the degree of details), and b) for applying specific treatments; and

4) classification and evaluation of the various stages of diseases and the possibilities of influencing the pathological processes at these stages, with regard to their limited observability.

In most cases the difficulties of obtaining a sufficient amount of information about the living objects make the problem of medical treatment stochastic, i.e. all previous stages must be in terms of stochastic concepts. The following characteristics of treatment given may be sufficient to provide such information:

1) probability P of achieving goals related to the treatment of one patient as well as of a contingent of patients; and

2) average expenditures Z connected with treatment.

Depending on the disease, the goals of treatment can be formulated on the basis of given characteristics following conditional functionals:

$$\max P \quad \text{subject to } Z \leq Z^* \tag{1}$$

or

$$\min Z \quad \text{subject to } P \leq P^* \quad . \tag{2}$$

Maximization or minimization of P or Z is carried out on a set of feasible tactics of treatment. Sensitivity of functionals (1) and (2) to the variations of tactics is important. Their practical application to the concrete tasks requires preliminary classification of diseases. This can be done differently, however, using control theory methods favoring classification based on the rate of disease progression.

Let us divide diseases into two classes: rapidly developing diseases (RDD) and slowly developing diseases (SDD). The most characteristic feature of the RDD is late diagnosis, i.e. diagnosis while the disease is in full progress and most of the organs have pathological variations [4]. In the SDD, in contrast, diagnosis is early.

If we conventionally limit ourselves with a one-step scheme of making a diagnosis and selecting a tactic of treatment, and assume that P = 0 when the diagnosis is wrong, then

$$P = P^i(t) = r(t)\, q^i(t) \quad , \qquad i = 1,\ldots,n, \tag{3}$$

where $r(t)$ is the probability of making a correct diagnosis by the time t, and $q^i(t)$ is a conditional probability of curing the patient with the right diagnosis using the i-treatment tactic from the moment t; $r(t)$ is almost always an increasing function of time t which is counted from the very beginning of a disease. The trivial relativity $r(0) = 0$, $q^i(t) \to 0$ with $t \to \infty$, $r(t) \leq 1$, $q^i(t) \leq t$ leads to the conclusion that $p^i(t)$ has a maximum with respect to t (see Fig. 1).

The index * refers to feasible values of respective variables.

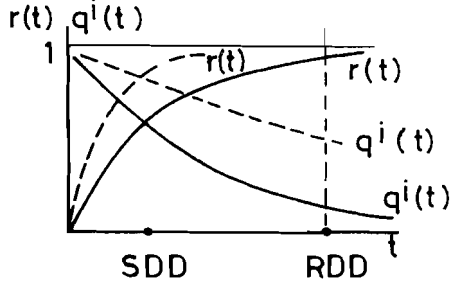

Figure 1. The probability of the correct diagnosis $q^i(t)$, and the conditional probability of successful patient cure r(t) if the diagnosis is correct. (Solid lines correspond to RDD's, the dotted lines to SDD's. The dots on the t axis roughly represent the moments of making the diagnosis.)

The average expenditure Z has two components--the diagnostic expenditures $Z_D(t)$ and the treatment expenditures $Z_1{}^i(t)$.

$$Z = Z_D(t) + Z_1{}^i(t) \quad ,$$

where t is the moment of fixing a diagnosis. For the RDD, $q^i(t) \leq 1$ for all i because of the late diagnosis. For the same reason $P^i(t) \leq 1$, and the problem of choosing the most "economic" treatment tactic after diagnosis practically vanishes. It is reasonable to assume that $Z_{RDD} = Z_D(t) + C$, where C is a constant and $Z_D(t)$ is a decreasing function of t (the later the diagnosis is made, the "easier" it can be done). The criterion for estimating the performance of treatment in cases of RDD can be given by (1), i.e. it can be represented as $\max P^i(t)$.

The chronic diseases which are usually recognized early but continue over a long period of time (sometimes an entire lifetime) are examples of SDD and represent a great interest for systems analysis. Successful treatment of SDD means making the patient as comfortable as possible [5]. In this

case we can assume that $r(t) \simeq 1$, that there exist treatment tactics in which $q^i(t) \simeq 1$, and hence $P^i(t) \simeq 1$. Where there are several such tactics, the small differences in $P^i(t)$ cannot serve as the basis of choosing the concrete strategy, which makes sufficiently accurate determination of $P^i(t)$ rather difficult. Average expenses for SDD treatment are less dependent on the expense of making a diagnosis, i.e. $Z_{SDD}(t) \simeq Z_1{}^i(t)$. In this case criterion (2) seems appropriate:

$$\min_i Z_1(t) \quad .$$

Let us consider two illustrative examples.

1. Systems Analysis of Rapidly Developing Disease

The oncological disease (OD) is a complex dynamic process involving most systems of the organism. Consideration of the interactions of the systems during treatment should take into account the probabilistic character of the processes within those systems and their interrelationships. In the example given, we shall assume that the reactions of the organism's systems to the treatment are random and thus account for *a priori* unknown individual differences among organisms. Specific treatments restricted to a one-time chemical therapy using the drug, sarcolyzin, of carcinoma type K-755 tumour implanted into animals will be considered. The diagnostics (i.e. the type of the r(t) function) will not be detailed. The differences among treatment tactics depend on the dosage given at the moment t; $\max P^i(t)$ serves as the criterion. This example mainly illustrates the existence of optimal treatment tactics depending on t. The model used in this example was designed by a joint group of scientists from the Institute of Control Science (A.M. Petrovsky, E.L. Orkina, M.P. Sakharov) and from the Institute of Experimental and Clinical Ontology (Z.P. Sofjina, M.F. Merkulov); calculations were done by computers.

At present, there exist numerous mathematical models simulating processes of malignant tumour growth. Those related to the cells' population level are of great interest and show that, in spite of the differences among the OD forms, the development of the respective processes of malignant growth over time may be described in the same way [4].

The model used in the example implies the following assumptions. First, the development of the cancer can be represented by a well-known Skipper's model [11]; the state of the organism as a whole, as well as the normally developing tissue,

can be conventionally represented by the amount of leukocytes. This value alone will define the limiting doses of medicines. The organism is supposed to have a specific anit-cancer immunity which prevents malignant growth and which changes depending upon the state of the organism itself and the size of the tumour.

The model also implies that the tumour's cells may belong to three different kinds of populations: A) the population which includes growth and division, B) the population which includes those cells still capable of further division, but whose growth has "slowed down," and C) the population of dead cells.

The sizes of those populations are represented in the model by the variables Y_1, Y_2, and Y_3, respectively, connected by the following equations:

$$\dot{Y}_1 = Y_1 \frac{1}{T_G}(2K_A - 1) + Y_2K_{BA} - Y_1K_C - IK_{i1}\sqrt{Y_1} \quad , \quad (4)$$

$$\dot{Y}_2 = Y_1 \frac{1}{T} 2(1 - K_A) - Y_2K_{BA} - Y_2K_C - IK_{i2}\sqrt{Y_2} \quad , \quad (5)$$

$$\dot{Y}_3 = (Y_1 + Y_2)\ K_C - Y_3 \frac{1}{T_C} \quad . \quad (6)$$

A number of cells of population A, which are divided over the unit of time, are proportional to the magnitude of the population and inversely proportional to the time of generation T_G (the cycle of time of nucleic division).

The cells formed after division can either re-enter population A or be transferred to population B. The probability of getting the cell into population A is the most important characteristic of the tumour's growth rate. In the model it is represented by the coefficient K_A. The probability of the cell re-entering population B is $I - K_A$, respectively.

The cells of population B can transfer into population A at the rate K_{BA}. For a young tumour of small size, K_{BA} is initially rather high, but decreases with the growth of populations A and B. When population A decreases--for example, through surgery or chemotherapy--K_{BA} increases drastically.

The parameters included in K_A and K_{BA} are given as the initial data and characterize the rate of growth of a concrete tumour. They are chosen so as to provide an accurate match between the simulated growth curve and the experimental curve,

as well between simulated and experimental proliferative pools (the relative part of the tumour cells being divided).

The rate of cell transfer from populations A and B into population C is represented by the same coefficient K_C. The dead cells of the organism gradually disseminate with the time constant T_C.

The variable I in equations (4) and (5) characterizes the value of anti-cancer immunity of the organism, and the coefficients K_{i1} and K_{i2} represent the degree of its influence on the cells of populations A and B.

The state of the organism as a whole as well as its normal tissue are conventionally defined by the amount of leukocytes, Y_6, and the mass of blood-creating tissue, Y_5. The latter variables are related as

$$\dot{Y}_5 = Y_5 \frac{1}{T_N} (2\alpha - 1) - Y_1 K_O \quad , \tag{7}$$

$$\dot{Y}_6 = Y_5 \frac{1}{T_N} 2\beta - Y_6 \frac{1}{T_M} \quad . \tag{8}$$

The leukocyte generating mechanism used in this model is the same as in any cell's regenerating population [12]. After division, the blood-creating cell can either join the population of blood-creating cells with the probability α, or differentiate and become a leukocyte again with the probability $\beta = 1 - \alpha$. The number of cells divided over the unit of time is directly proportional to the mass of blood-creating tissue, and inversely proportional to the time generation T_N for the cells of a given type. The model implies that the coefficient β depends on the mass of blood-creating tissue. If part of the blood-creating tissue is destroyed, the probability of converting the cell into a leukocyte decreases, and a great number of cells, upon division, repeat the same process; the result is blood regeneration. The second term of the equation (8) represents the dying-off process of the leukocytes; T_M is a time constant of the process.

An assumption adopted in the model holds that as the tumour grows, the mass of blood-creating tissue in the organism decreases. The coefficient K_O is initially given and represents the degree of tumour influence on the mass of the blood-creating tissue. The probability of organism destruction caused by the effect on the blood-creating system is continuously calculated in the model. This probability takes into account the decrement of the leukocyte level, as well as the time of this level.

It is known that the organism immunity level depends on the amount of cell production in the lymphatic glands, in the thyroid gland, and in the blood-creating tissues. As the number of leukocytes decreases, the non-specific immunity of the organism (i.e. immunity towards different diseases) is reduced, further increasing the probability of organism destruction. The equation describing the state of a specific anti-cancer immunity is represented as

$$I = R_I D_N \left[1 - Y_7 K_M\right] \quad , \tag{9}$$

where:

D_N = the ratio of the blood-creating tissue mass (at the given moment) to its normal value;

R_I = the immunity index;

R_{I_O} = the initial value of the index; and

Y_7 = an auxiliary variable representing the leukocyte level of the organism.

Equation (9) thus describes the gradual slowing down process of immunological activity resulting from a low leukocyte level over a long period of time. The coefficient K_M as well as the coefficients K_{i1} and K_{i2} in equations (4) and (5) are given as the initial data; the coefficient K_D in equation (10) is given in the same way.

Let us assume that the immunity level rises in proportion to the amount of the destroyed cancer cells D_R, after the anti-tumour drug is injected into the organism:

$$R_I = R_{I_O} + D_R K_D \quad . \tag{10}$$

This drug simultaneously affects the blood-creating system, and consequently the immunity drops significantly.

Let us consider the influence of the cytoxitic drug on both the tumour cells and the blood-creating system. Some authors [13] suggest that most of the cytoxitic substances, particularly of the sarcolyzin type, disseminate rapidly in the organism--within several minutes. Since this dissemination time is of a lesser magnitude than the time constants in equations (4-10), the model implies instantaneous action of the drug on the tumour cells and tissues. The malignant

cells destroyed by the sarcolyzin lose their ability to divide and dissociate. The relative amount of the surviving cells of the populations A, B, and the blood-creating tissue exponentially depends on the dose of sarcolyzin D_s multiplied by the sensitivity coefficient of the respective population to the given medicine.

The result of treatment depends 1) on the tumour sensitivity to the drug, 2) on the state of the blood-creating and immunity systems at the time of administration, and 3) on the character of development of subsequent processes.

Large doses of sarcolyzin can kill almost all the malignant cells. However, they may also destroy the blood-creating system to such an extent that the organism may not have enough protection for supressing the surviving cells. By destroying the appropriate number of malignant cells, a smaller dosage causes less damage to the organism, whose protection mechanisms can efficiently affect the surviving cells.

Such considerations lead to the hopeful conclusion that optimal doses of the drug do exist. To our knowledge, the problem of finding the optimal treatment tactic (dosage of the drug) has not yet been set forth. By assuming a specific distribution of sensitivity to the drug in a stochastic formulation, one may obtain the probability of successful OD cure (full dissociation of the tumour) as a function of t under the optimal $q^i(t)$--see Fig. 2*. The curves in Figure 2 testify to the existence of optimal treatment tactics and accord with the well-known fact of the decrease of treatment effectiveness due to the lack of prompt diagnosis.

2. Systems Analysis of Slowly Developing Disease

The treatment of the slowly developing, or chronic, disease is a long-lasting process of interactions between patient (or a contingent of patients) and a doctor (or a medical institution). This process involves several interchanging stages of clinical and dispensary treatment [5].

We shall consider a dispensary stage only where the problem of stabilization of the "comfort" state of the patient is being solved. The interaction between a doctor and a patient in this case has been reduced to a series of patient examinations for testing the patient's state and for correcting the treatment tactics if necessary (including more careful examination and treatment in clinics). Interactions between a doctor and a patient are characterized by the frequency F of the patient's visits to a dispensary. The date T_s of the succeeding visit is a random number which is determined a) by the doctor at the moment T_{s-1}, corresponding to the previous exami-

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*The sensitivity distribution shown in Fig. 2 is random as no sufficient experimental data are yet available.

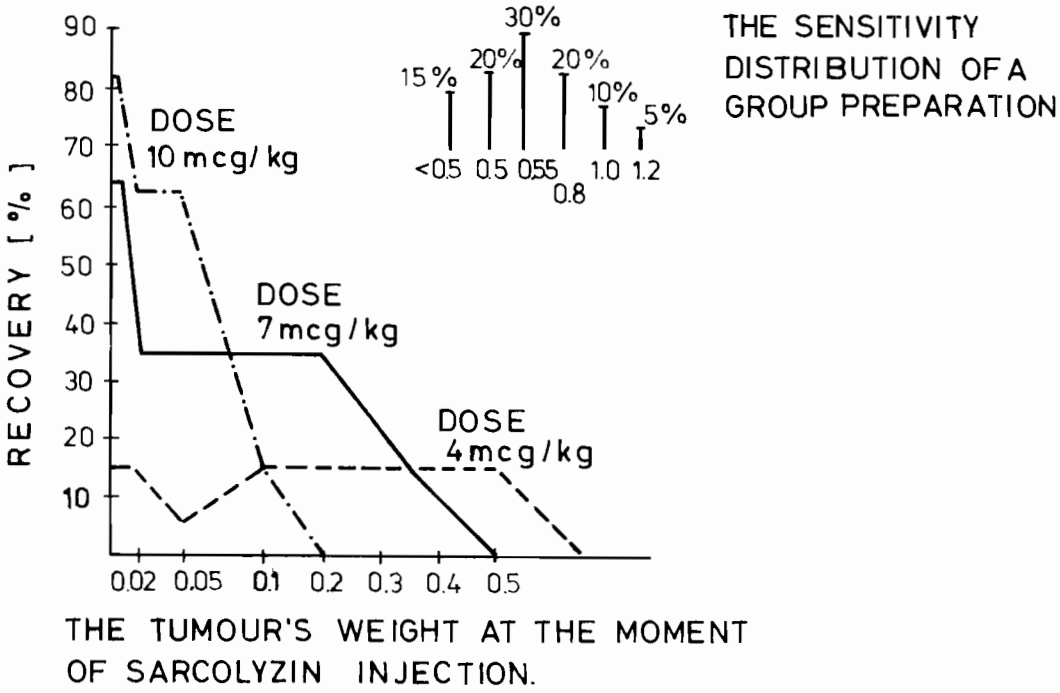

Figure 2. Recovery of a group of mice after one injection of sarcolyzin (recovery represented as a function of tumour weight).

nation of the patient, and b) by subjective reasons (e.g. a change in the patient's feelings). We write

$$T_s = \int [\eta_{s-1}(S),\ \xi_s] \quad , \tag{11}$$

where $\eta_{s-1}(S)$ is a prognosis of the patient's state by the T_sth moment, defined at the moment T_{s-1}; ξ_s is a random number which represents the patient's state (for example, $\xi_s = 0$, when the patient is in a "normal" state); and $\xi_s = I$, when the change for the worse is noticeable.

We may require that

$$\delta_s = T_s - T_{s-1} \leq \Delta_{s-1} \quad , \tag{12}$$

where Δ_{s-1} is the maximal admissible interval between two

successive visits to dispensary as given, for example, by the rules for preventive examinations.

We shall consider $\eta_{s-1}(s)$ as a functional of the preceding observations $X_{s-1},\ldots,X_{s-k}$ of the patient's state at the moments $T_{s-1},\ldots,T_{s-k}$:

$$\eta_{s-1}(s) = \phi(X_{s-1},\ldots,X_{s-k}) \quad , \tag{13}$$

where k is a memory time of the prognosis.

The practical use of the relations (13) and (14) should be based on the mathematical models of the SDD or on subjective medical estimates. Thus, slowly developing diseases can be divided into two classes: 1) those for which mathematical prognostic models can be built (e.g. slowly developing hypertension diseases), and 2) those which cannot be described by a prognostic model (e.g. forms of hypertension diseases with crisis phenomena). Improving the prognostic methods of the SDD may maximize the sequences of η_s for the patients with SDD's of the first type. This allows the doctor to pay more attention to patients with the SDD for which mathematical prognostic models cannot be elaborated.

Consider the hypertension disease (HD) of the second stage, with a slow development. We shall restrict ourselves to the problem of predicting the patient's state by two characteristics of the arterial pressure (AP): systolic pressure (SAP) and diastolic pressure (DAP). Difficulty in describing the development of the HD with consideration for each patient's peculiarities led us to assume that AP depends on time as a polynomial function

$$AP = C_{0,s-1} + C_{1,s-1}t + \cdots + \varepsilon_t \quad , \tag{14}$$

where t is being counted from the moment T_{s-1}, and $C_{r,s-1}$ are the coefficients of the polynomial approximation. The AP are the functionals similar to one given by (13); ε_t is a random component representing non-observable factors.

A doctor should determine the possibility for using the mathematical prognosis on an individual basis; when this problem is solved positively, T_s is computed by using (11-13). The experience with practical testing of the algorithms given by (14) with patients having the HD of the second stage proved to be sufficient in many cases.

A retrospective test (14) based on the 10-year history of the DAP and the CAP of a typical patient with the HD of the second stage (100 doctor's visits) may serve as an example. The calculations of $C_{0's-1}$ and $C_{1's-1}$ and the variances $D_{0's-1}$ and $D_{1's-1}$ were made by the standard methods. At the moments T_{s-1}, the confidence intervals were defined where an actual sample of the AP should presumably have been found with a high probability. The intersection of limits of these intervals with the levels of the maximal permissible deviations of the AP ($\mp$ 15 mm of mercury in the given example) define T_s. To assess feasibility of a given method for selection of T_s, a frequency of an actual sample of the AP which is outside the borders of admissible deviations may be used as a criterion. The results of the retrospective analysis for the given sample are as follows:

The number of calculated CAP points is 22; the number of DAP points is 24, i.e. approximately 4 times less than the number of visits. The frequency of the prognostic intervals where AP deviations stay in the admissible range of $\mp$ 15 mm of mercury, is equal to 0.89 for the DAP and to 0.84 for the CAP. Note that the maximal memory time of the prognosis did not exceed 180 days, the limit value having been closely observed in approximately 50% of the cases.

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