A Method of Analyzing of the "Dose-Effect" Dependence in Multifactor Medico-Biological Experiments

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A conceptual-logical and mathematical approximation model has been created for the organism's response to external factors. The mathematical model of the "dose-effect" dependence for the combined effect of several factors is constructed using the basic equation of the Volterra mathematical theory of the struggle for existence.

Key Words: *dose; biological effect; mathematical model; multifactor experiment*

The methodology of quantitative analysis of the interaction between bioobjects and environmental factors is acquiring a key role in ecology. The diversity of response mechanisms of the organism's systems to the action of external factors and the multiplicity of indexes studied hamper the search for the most common regularities inherent in the effect on any level considered. The method proposed is based on the extrapolation of known biological theoretical postulates to the conceptual-logical and mathematical model of the organism's response to several external factors of increasing intensity.

The organism is a complicated system of specialized interacting systems (subsystems). Depending on the type and strength of the acting force, the response changes occurring in certain systems and organs exhibit qualitative features and a magnitude determined by the characteristics of the external factors. Still, although the reactions are so diverse, the "dose-effect" dynamics shows some common regularities.

1. Any reaction used to assess an effect as well as the indexes characterizing this reaction (namely ingredients of the organism's internal medium, electrophysiological parameters, and so on) are in equilibrium due to the harmony between the systems of the top and bottom level before the beginning of the external action. There-

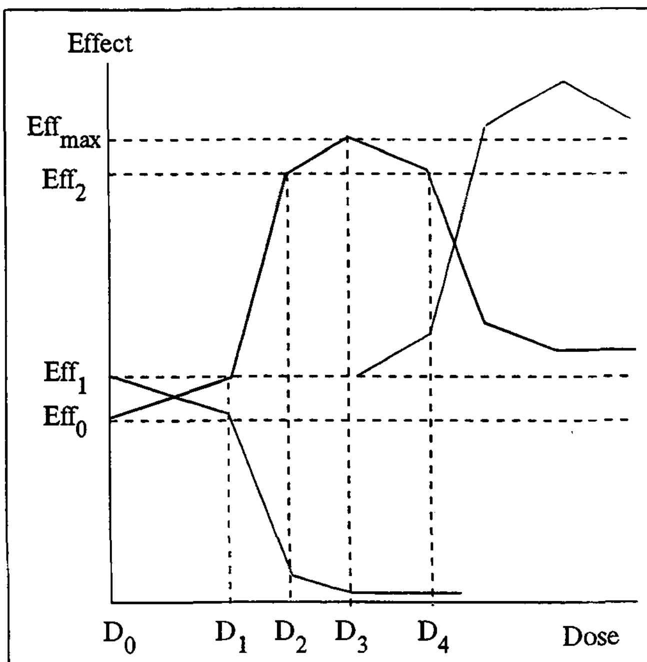

Fig. 1. Theoretical graphic two-dimensional model of the "dose-effect" dependence. Plots of the "dose-effect" dependence are given for different hierarchical levels of systems.

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fore, there is some basic level corresponding to a zero biological effect no matter what the qualitative peculiarities of the index being studied (Eff_o, Fig. 1).

2. First and foremost, adaptation, accommodation, and compensation of damaged functions represent the variation of biological reaction rates [6]. The effect increases at an uneven rate depending on the parameters of the acting factor as well as on the hierarchical level of the index in question among the organism's systems. If the parameters of the factor are close to zero, the rate of change of the biological indexes will be minimal. Mechanisms of the bottom levels operating in the given range of doses (D_o-D_1) prevent the destabilization of the system of the level studied. Exhaustion of the compensatory possibilities of the bottom level results in an explosive activation of the reactions under investigation, which manifests itself in a spasmodic change of the rate of increment of the biological effect. The effect continues to mount in the dose interval D_1-D_2 at a constant rate and reaches the Eff_2 value corresponding to the D_2 dose. If the dose exceeds the D_2 value, the rate of increase of the effect will decrease, and when the dose is equal to D_3 the effect reaches its maximum (Eff_{max}).

3. Although the potentials for compensatory hyperplasia of the structures are extremely high, they are still not boundless and, sooner or later, the capacity of the organism to reproduce more and more new structures is exhausted and decompensation sets in [6]. Consequently, any index characterizing the state of the organism or one of its systems cannot change indefinitely and always has a limit.

4. The next postulated proposition includes a fragment of the known model of the reaction of the organism's systems to external agents [3], namely a lowering of the index of system (subsystem) activity on a specific level after the attainment of the maximum due to the exhaustion of compensatory possibilities. The leading function in the maintenance of homeostasis is transferred from a lower-level system to a higher-level system in the D_3-D_4 interval.

Thus, a graphic two-dimensional model of the change of the biological effect as a function of the intensity of a factor's action is created based on known theoretical premises and represents a conceptual-logical model.

The best approximation of the dose-effect dependence in toxicometry, including the assessment of integral indexes (Mahalanobis distance) is considered to be the logistic function [2,4,5]

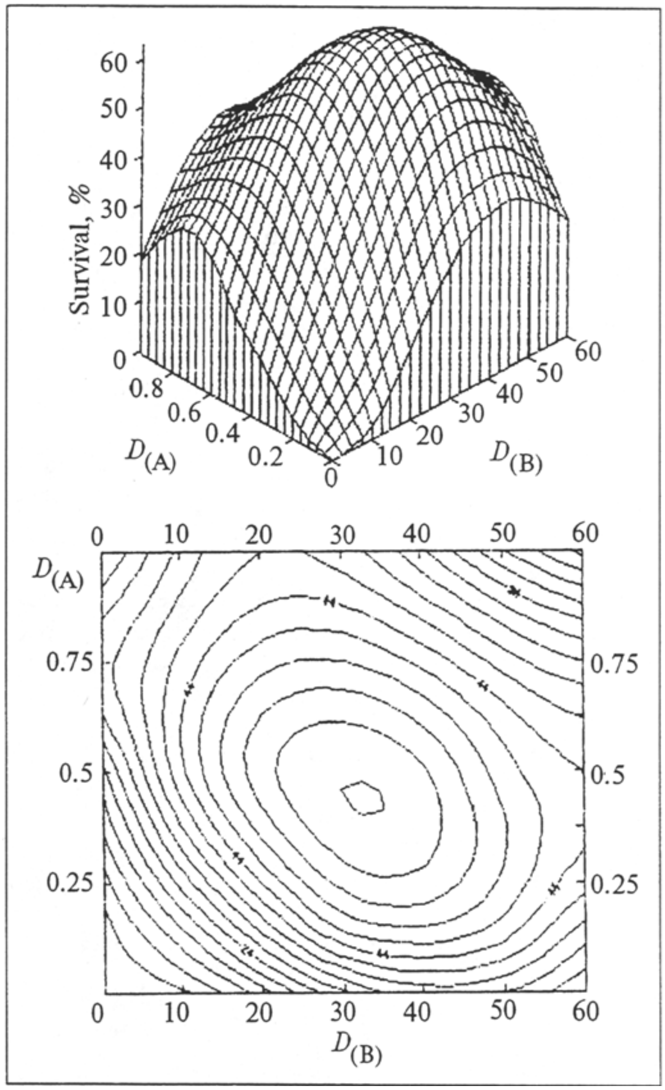

Fig. 2. Three-dimensional plot and topogram of the dependence between the survival rate and doses of two antidotes. D(A) and D(B) denote doses of antidotes A and B in conventional units.

$$Y = \frac{a_1}{1 + \exp(a_2 + a_3 x)}, \qquad (1),$$

where $a_1...a_3$ are regression coefficients.

It is evident that this function describes the part of the conceptual-logical model for the argument values D_o-D_3.

Isoeffective dose combinations of different environmental factors are sought in medico-biological experiments. The dependence between the doses of two factors is most comprehensively described by the power function

$$Y = c_1 x^{c_2}, \qquad (2),$$

where c_1 and c_2 are regression coefficients.

If coefficient c_2 is positive, the factors are synergists. When c_2 is negative, the factors exert an opposite action on the effect assessed. A classic example of factor antagonism approximated by a power function with $c_2=-1$ is Haber's formula.

A mathematical model for multidimensional matrixes is created by transforming the basic differential equation of Volterra's theory [1] to accommodate the above propositions:

$$\sum_{k=1}^{n} A_k(x)\frac{\delta U}{\delta x_k} = B(x)U(U_0 - U) \qquad (3)$$

where $x = (x_1 ... dx_n)$ are factors affecting the process; n is the number of factors; U is the reaction of the bioobject to the change of x factors; U_0 is the maximal value of the U reaction; B(x) are identified functions.

Solving this equation yields a mathematical expression for the multidimensional "dose..dose-effect" model and gives rise to the functional dependence:

$$\begin{aligned} U(x) &= \frac{U_0}{1 + e^{V(x)}} \\ U(x) &= a_0 + \sum_{k=1}^{n} a_k x_k + \sum_{k=1}^{n} b_k x_k^2 + \\ &\sum_{k=1}^{\frac{n(n-1)}{2}} c_k x_{k1} x_{k2} + \mathrm{d}\ \ln\Big(\sum_{k=1}^{n} e_k x_k^{sk} + \sum_{k=1}^{\frac{n(n-1)}{2}} h_k\, x_{k1}^{S_{k1}} x_{k2}^{S_{k2}}\Big) \end{aligned} \qquad (4)$$

where $k_1<k_2$, $k_1=1$, ..., $n-1$, $k_2=2$, ..., n $d\times S_k<-1$, $e_k>0$, $h_k>0$

The mathematical model of the "dose-effect" dependence is realized in the specially created Biokinetik software package which is part of the Robot-Vychislitel' (Computer-Robot) system. The software is designed for applied problems of statistical and imitation modeling, as well as the nonlinear-parametric identification of multidimensional mathematical models of biological processes based on experimental data.

The data on the survival of white mice subjected to a toxic substance in an experiment to determine the optimal correlation of two antidote components are used as an example of the Biokinetik software's possibilities. The "dose-dose-effect" dependence is described in this case by the equation

$$Eff = \frac{100}{1 + \exp(0.3 - 3.7x - 0.7y + 4.5x^2 + 3.0xy + 2.3y^2 - 21\ln(x + 1.3y + 2.5xy)}, \qquad (5)$$

where *Eff* denotes the survival in % and x is the dose of antidote (component) "A" and y the dose of antidote "B" in conventional units.

The use of the comprehensive mathematical model as well as of the three-dimensional plot and topogram (Fig. 2) constructed according to the results of the calculations facilitate the search for the optimal combination of antidote doses. In addition, the model obtained may have a certain prognostic value not only for the interpolation, but also for the extrapolation of experimental data.

The following positive aspects emerged from the first stage of the new method of analysis of the "dose-effect" dependence.

1. The construction of models based on general theoretical concepts enables transfer to multidimensional modeling.
2. The informativeness of data analysis and the reliability of conclusions are enhanced.
3. The degree of influence of information "noise" on the results of the experiment decreases.
4. The probability of discovering the regularities determining the peculiarities of the processes studied increases.

Thus, the sequence of modeling of biological processes according to the scheme conceptual-logical - theoretical mathematical - biological (experimental) - comprehensive mathematical model offers a number of advantages over the trivial scheme: biological (experimental) - statistical model. The proposed method may find application in different branches of experimental biology, medicine, and ecology.

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