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The Theory of Chain Growth and Inhibition of Biological Populations by Chemical Agents

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In this work, the model of the development of biological populations based on the general concepts of the cyclic development of individuals is considered. The simplest cycle of the individual development comprises the birth, growth due to substrate absorption, and multiplication. Being presented via quasi-chemical reactions, such a cycle is identical to the unit of branched chain reactions discovered by Semenov *et al.* 70 years ago [1,2]. Therefore, the development of both intact populations and populations exposed to chemical toxicants can be quantitatively described in terms of the theory of chain reactions. In this work, the ecotoxicological equation of population development was obtained based on this approach. The validity of this equation was previously demonstrated by the example of cell culture data obtained by Ershov *et al.* [3-5].

The dynamics of development of biological populations can be formally described by different empirical equations. For various biological species, the Verhulst logistic dependence [6,7] is the most general:

$$N(t) = (p/a) / (1 + (p/a/N_0 - 1) \exp(-pt)), \quad (1)$$

where $N(t)$ is the current population size at instant t , N_0 is the initial population size at $t = 0$, p is the multiplication factor (chain propagation), and a is the autoinhibition factor.

The Verhulst function is widely used. One of the reasons for this popularity is, in addition to its generality, the obviousness of the differential law of the propagation kinetics:

$$dN/dt = pN - aN^2, \quad N = N_0 \text{ at } t=0. \quad (2)$$

Here, kinetic coefficients p and a are the same as in equation (1).

Formula (1) is a partial integral of differential equation (2).

Equation (2) is undoubtedly identical to the corresponding Semenov equation that describes the kinetics of the N active sites in a branched chain reaction with a square-law termination at the zero initiation rate [2]. However, the principle of the processes is different.

To reveal it requires constructing a comprehensive model of biological development.

The necessity of constructing a comprehensive model based on a more detailed growth mechanism is also caused by a certain inconsistency between theoretical equation (1) and experimental data. The Verhulst model contains two parameters, p and a . Additionally the theoretical equation includes the initial population size N_0 .

In the initial region of the exponential growth, the experimental population size and that calculated by equation (1) often differs considerably. The difference can amount to several orders of magnitude. However, in the time interval of growth inhibition, the theoretical curve fits the experimental data.

As an example, the figure shows the growth curves of the *Saccharomyces cerevisiae* yeast cells in a wort as a culture medium at different concentrations of nickel(H) sulfate [3]. These curves are evidence for the toxic action of nickel(H) ions. Increasing the toxicant concentration leads to a decrease in the exponential growth rate [parameter p in equation (1)] and the maximum yeast population size [parameter a in equation (1)] at the same initial yeast population size $N_0 = 100$ cell/ml.

Similar data were obtained in [3-6] when studying the toxic action of pure silver(I), copper(H), chromium(I), chromium(VI), and magnesium(H) salts and their combinations.

At the Ni(H) concentrations lower than 10 (mmol/l, the toxicant action is not observed at the level of the method sensitivity (cytotoxicity); in a concentration range of 0.1-1.0 mmol/l, the toxicant exhibits the cyto-static effect. At concentrations more than 2 mmol/l, Ni(D) ions have a cytotoxic action on yeast.

In no instances does equation (1) describe the yeast population growth over the whole time interval from inoculation to attaining the maximum value.

The inflection point in curve 1 also differs considerably from the experimental point.

This discrepancy was observed in many other cases [6,7]. Evidently, the mathematical model of growth (2) is a very rough approximation. It may be used for rough

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estimations, e.g., when classifying population development [8,9].

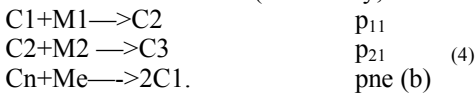
To construct a more adequate model requires a comprehensive description of the development and multiplication of species based on biochemical concepts [10-12].

The necessary condition for the population growth of a certain biological species is the availability of the set of nutrients (substrates)

$$M_s = (M_{S1}, M_{S2}, \dots, M_{Se}) \quad (3)$$

where M_s is the vector of the (M_i, M_s) substrate set for species S .

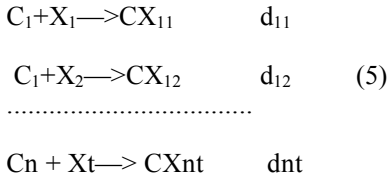
Absorbing the substrates, a population develops. This development can be described by a set of successive pseudochemical reactions (for brevity, index s is omitted):



Here, C_1 is the newborn individual, which absorbs substrate M_1 to convert into C_2 . Individual C_2 absorbs M_2 and converts into C_3 , etc. The whole chain of the development from the newborn C_1 individual to the mature individual C_n , which forms two new C_1 individuals (birth), is described in this fashion.

The set of thermodynamic constants (p_{11}, pne) determines the kinetic growth vector.

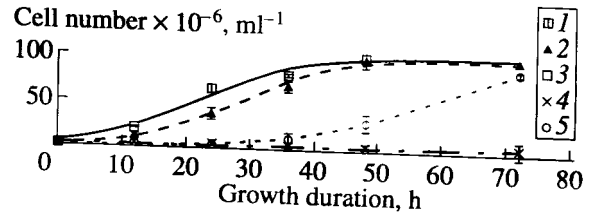
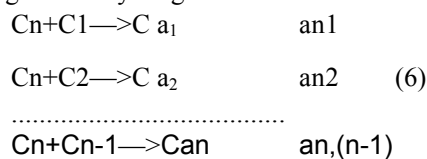
Toxicants X , can influence the growth at any stage. This action is described in a similar way:



Here, (X_1, X_t) is the vector of toxicants, and (d_{11}, d_{nt}, \dots) is the corresponding kinetic vector of toxic action.

The total number of reactions (5) is great and determined from the number of combinations of different cell stages and toxicants.

Additionally, one should take into account autoinhibition processes, when the mature individuals C_n inhibit the growth of young individuals:



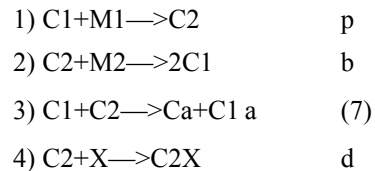
Theoretical curves and experimental points [4] of the yeast growth in the wort in the absence and under the action of various concentrations of nickel(II) sulfate (mol/l): (1) 0.00, (2) 5.00×10^{-4} (3) 8.00×10^{-4} , (4) 1.00×10^{-3} , and (5) 2.00×10^{-3}

The set of these interactions is described by the kinetic vector of autoinhibition $(a_{n1}, a_{n(n-1)})$. Sexual multiplication can be described in a similar way.

The set of pseudochemical equations (4)-(6) is conventionally described by a set of differential kinetic equations with kinetic coefficients [10, 13, 14]. The resulting system is of high order. Its qualitative analysis is rather complicated; however, the numerical solution of such systems is possible.

The system can be reduced to the second-order system by means of different approximations [14]. Such a system bears sufficient information and makes it possible to give a qualitative, and sometimes, quantitative description of the development of different populations. This system may also be used for solving some economical problems.

Let us consider the reduced system of pseudochemical reactions that gives a more adequate description of the biological development chain:



The designations are the same as in systems (4)-(6), but the indices are omitted for brevity. C_1 and C_2 are the mature and young cells, respectively; C_a is the cell in anabiosis; C_2X is the cell poisoned with toxicant X , M_1 and M_2 are the substrates.

Under the assumption that the amounts of substrates M_1 and M_2 and toxicant X are constant, the kinetics of the chain growth and inhibition of population C_1 is described by the set of two differential equations:

$$1) \frac{dc_1}{dt} = -pc_1 + 2bc_2; \quad (8.1)$$

$$2) \frac{dc_2}{dt} = pc_1 - bc_2 - dx_2 - ac_1c_2. \quad (8.2)$$

Here, c_2 and c_1 are the concentrations of the mature and young cells; x is the content of the toxicant; a, b, d , and p are the kinetic coefficients of autoinhibition, birth (branching), death, and propagation of the population chain.

Coefficients p and b include constant amounts of substrates M1 and M2.

As a rule, equation (8.2) describes faster changes than equation (8.1). For C2 (intermediate product), a quasi-stationary approximation is applicable. In terms of this approximation, set of equations (8) is reduced to one equation

$$dc_1/dt = pc_1(K_1 - c_1)/(k_2 + c_1) \quad (9)$$

Here, the following notations are used:

$$K_1 = b/a - xd/a \quad (10)$$

$$K_2 = b/a + xd/a \quad (11)$$

If toxicant X is absent, the following equality is valid:

$$K_1 = K_2 = b/a = K \quad (12)$$

where K is the maximum population size or the capacity of a biosystem in the absence of the toxic action. The particular solution of equation (9) is

$$c_1^{-1}(K_1 - c_1)^{(1+K_1/K_2)} = A \exp(-tpK_1/K_2) \quad (13)$$

where A equals the left part of the equation when d equals its initial value of $C_1(0)$ at $t = 0$.

Equation (13) describes the kinetics of the C_i population propagation in the presence of toxicant X and can be called the ecotoxicological equation of population development.

According to definitions (10)-(12), the following inequalities are valid:

$$K_1 > K_2 \quad (1 + K_1/K_2) < 2. \quad (14)$$

Therefore, the kinetic curves of population development can be explicitly obtained only in particular cases.

In the absence of toxicant X ($x = 0$), we obtain the equation of the intact population development

$$c_1^{-1}(K_1 - c_1)^2 = A_0 \exp(-tp) \quad (15)$$

where $A_0 = A$ at $K_1/K_2 = 1$.

Given the amount of the toxicant $xc = b/d$, the population does not grow and occurs at the initial level with $c_1(t) = c_1(0)$.

The value $xc = b/d$ corresponds to the critical amount of the toxicant (growth inhibition).

At $x = b/d$, the population does not propagate. For cell cultures, this corresponds to the cytostatic action.

At $x > b/d$, the population dies. For cell cultures, this corresponds to the cytocide action.

If x increases from 0 to $K = b/d$, the biosystem capacity $K_1 = K_2 - xd/a$ decreases from K to 0.

According to equation (13), the inhibited growth constant is determined by the equality

$$px = pK_1/K_2 = (pb - xd)/(b + xd). \quad (16)$$

Equation (16) indicates that increasing the inhibitor content x leads to a decrease in the px value, although positive, from the intact value p to zero at $x = x_c = b/d$. A further increase in x leads to negative p values. This is accompanied by a decrease in population size from the initial $c(0)$ value to 0.

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