

# Model of Chain Growth and Inhibition of Biological Populations by Chemical Agents

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The proposed model of development of a biological population is based on the elementary cycle of individual development which is presented as a system of quasichemical reactions. The system includes elimination of an individual upon interaction with a toxic agent. Analytical solution of the system of kinetic equations describing the dynamics of the model is presented. The solution can be used for quantitative evaluation of the effects of toxic compounds on a population and in epidemiological studies. The model adequately describes the effect of heavy metals on a population of yeast cells.

**Key Words:** growth curve; population; heavy metals; ecology

Here we describe a model describing the development of biological population. The model is based on the general concept of individual cyclic development. The adequacy of such a model has been demonstrated on cell cultures [3,5,7].

The simplest cycle of individual development includes birth, growth as a result of substrate consumption, and reproduction. Interpreted with a system of quasichemical reactions, this cycle proves to be identical to a component of branched chain reactions discovered by N. N. Semenov in the 1920s [6,8]. Thus, on the basis of the chain reaction theory the development not only of intact population but also of those affected by toxic agents can be characterized quantitatively.

Formally, the dynamics of developing biological population can be described using various empirical equations. The growth of populations has been generally described with Verhulst's equation [1].

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

where  $N(t)$  is the number of individuals in a population at time  $t$ ,  $N_0$  is the initial number of the popula-

tion at time  $t=0$ ,  $p$  is the reproduction factor (chain growth), and  $a$  is the autoinhibition factor.

The obviousness of the differential growth kinetics is one of the reason for the "popularity" of equation (1). Indeed:

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

where the coefficients  $p$  and  $a$  are the same as in equation (1), which is a partial integral of equation (2).

There are no doubts over the identity of equation (2) and Semenov's equation describing the kinetics of active centers  $N$  in a branched chain reaction with quadratic chain condition at the initiation rate equal to zero [6]. However, the essence of processes is different. To clarify it, an appropriate model of biological development is necessary, because there is a discrepancy between theoretical curves based on equation (1) and experimental data.

The Verhulst model contains two parameters:  $p$  and  $a$ . In addition, it also includes the initial number of individuals in the population ( $N_0$ ). A discrepancy between experimental data and calculations based on equation (1) often occurs at the initial growth segment of the curve. The difference sometimes reaches several orders of magnitude. At the same time, there is good correlation between experimental and theoretical values at the slow growth phase.

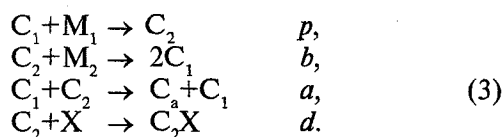
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The aforesaid can be exemplified by the data on the growth of the yeasts *Saccharomyces cerevisiae* in wort depending on the concentration of nickel (II) sulfate [5]. These data demonstrate toxicity of  $\text{Ni}^{2+}$  toward the cells. As the concentration of  $\text{Ni}^{2+}$  increases, the rate of exponential growth (parameter  $p$  in equation 1) and the maximum number of individuals in the population (parameter  $a$ ) decrease at the same initial number of cells in the population ( $N_0=100$  cells/ml). Similar data were obtained in the investigation of toxicity of Ag (I), Cu (II), Cr (I), Cr (VI), Mg (II) and their combinations [3,5,7]. At concentrations lower than 10  $\mu\text{mol/liter}$   $\text{Ni}^{2+}$  had no appreciable effect on the cells, while at 0.1-1 mmol/liter it exhibited cytostatic activity. At concentrations higher 2 mmol/liter Ni (II) produces cytotoxic effect. In all cases (1) it was impossible to describe the yeast population growth within the entire observation period (from growth initiation till reaching the maximum level). The point of inflection on theoretical curve (1) differs considerably from experimental values.

Such a discrepancy occurs in many other cases [1,4]. Obviously, mathematical model (2) is very approximate. It can be used for rough calculations, for example, in the classification of populational development [2].

In order to obtain a more adequate model, the development and reproduction of an organism should be presented in more detail based on biochemical concepts.

Let us consider a system of quasichemical equations providing a more concrete description of the development of a biological chain.



where  $C_1$  and  $C_2$  are adult and young cells;  $C_a$  is the anabiotic cell;  $C_2X$  is the cell poisoned with the toxicant X, and  $M_1$  and  $M_2$  are the substrates.

Assuming that the amounts of substrate  $M_1$ ,  $M_2$ , and toxicant X are constant, the kinetics of chain growth and inhibition of the population is described by a system of two differential equations:

$$dc_1/dt = -pc_1 + 2bc_2 \quad (4.1)$$

$$dc_2/dt = pc_1 - bc_2 - dxc_2 - ac_1c_2 \quad (4.2)$$

where  $c_1$  and  $c_2$  are the amounts of adult and young cells, respectively;  $x$  is the amount of toxicant;  $a$ ,  $b$ ,  $d$ , and  $p$  are kinetic coefficient of autoinhibition, birth (branching), death, and growth of the population chain. The coefficients  $p$  and  $b$  include constant amounts of substrates  $M_1$  and  $M_2$ .

Generally, equation (4.2) is "rapid" in comparison with equation (4.1) (for instance, mitotic cells exist for a relatively short time period and quickly divide). Therefore, quasistationary approximations can be applied to  $C_2$ . In this approximation the system (4) can be written as one equation:

$$dc_1/dt = pc_1(K_1 - c_1)/(K_2 + c_1). \quad (5)$$

where:

$$K_1 = b/a - xd/a, \quad (6)$$

$$K_2 = b/a + xd/a. \quad (7)$$

If the amount of toxicant X is equal to zero,

$$K_1 = K_2 = K = b/a, \quad (8)$$

where  $K$  is the maximum number of individuals in the population or the capacity of intact biological system.

Quotient solution of equation (5) is as follows:

$$c_1^{-1}(K - c_1)^{(1+K_1/K_2)} = A \exp(-tpK_1/K_2), \quad (9)$$

where  $A$  is equal to the left part of the equation, when at  $t=0$   $c_1$  is equal to its initial value  $c_1(0)$ .

Equation (9) describes the growth kinetics of  $C_1$  population in the presence of toxic agent X and can be referred to as *ecotoxicological equation for populational development*.

According to equations (6-9), there is the following inequity:

$$K_1 \geq K_2; (1 + K_1/K_2) \leq 2. \quad (10)$$

Consequently, explicit kinetic curves for the growth of a population can be obtained only for special cases.

The following equation describing the development of intact population is obtained in the absence of toxic agent ( $x=0$ ).

$$c_1^{-1}(K - c_1)^2 = A_0 \exp(-pt), \quad (11)$$

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

If the amount of toxic agent reaches the level equal to  $x_c = b/d$ , the population does not grow and remains at the initial level  $c_1(t) = c_1(0)$ .

The  $x_c = b/d$  value is the *critical* amount of toxic agent (growth inhibitor), i.e., at  $x = b/d$  the population does not grow (the agent produces a *cytostatic* effect). At  $x > b/d$  the cells die, i.e., bactericidal *cytotoxic* effect is observed. If  $x$  increases from 0 to  $K = b/d$ , the capacity of the biosystem ( $K = K - xd/a$ ) drops from the maximum value  $K$  to zero.

According to equation (9), the constant of growth inhibition is determined by the following equity:

$$p_x = pK_1/K_2 = (pb - xd)/(b + xd). \quad (12)$$

According to equity (12), as the inhibitor concentration  $x$  increases, the  $p_x$  value remains positive

and declines from the "intact" value  $p$  to zero at  $x=x_c=b/d$ . Further increase in  $x$  turns  $p$  negative. The number of individuals in the population drops from the initial value of  $c(0)$  to zero.

Thus, we have developed an *ecotoxicological equation* describing the *growth of a population*.

## REFERENCES

1. A. D. Bazykin, *Mathematical Biophysics of Interacting Populations* [in Russian], Moscow (1985).
  2. Yu. A. Ershov, *Thermodynamics of Quasiequilibria in Biological Systems* [in Russian], Moscow (1983).
  3. Yu. A. Ershov, N. B. Esmenskaya, and T. V. Pleteneva, *Khim. Farm. Zh.*, No. 11, 6-7 (1995).
  4. Yu. A. Ershov and M. N. Mashkomborov, *Kinetics and Thermodynamics of Biochemical and Physiological Processes* [in Russian], Moscow (1990).
  5. Yu. A. Ershov, T. V. Pleteneva, and T. K. Slonskaya, *Byull. Eksp. Biol. Med.*, **123**, No. 5, 594-600 (1997).
  6. N. N. Semenov, *Chain Reactions* [in Russian], Moscow (1986).
  7. T. K. Slonskaya, "Combined effects of inorganic compounds (drug models) on the eukaryotic cell," Author's Synopsis of PhD Dissertation [in Russian], Moscow (1996).
  8. A. E. Shilov, *Review on Scientific Activities of N. N. Semenov* [in Russian], Moscow (1990).
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