

MODELLING OF REGULATION MECHANISMS OF LIVING SYSTEMS

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Received March 26, 2003

ABSTRACT. One of the possible approaches for quantitative study of a regulatory mechanism of living systems is considered. The equations of a state of regulation system are constructed taking into account a cooperation of processes, presence of a combined feedback and a temporary relations in a regulation loop. Results of the qualitative analysis of equations and their model systems have shown existence of following functioning regimes: rest, stable functional state, periodic and irregular fluctuations. In some cases the "black hole" effect - solutions collapse to a trivial attractor is observed. The application of results of model investigations for analysis of some biological problems shows, according to our opinion, that the proposed method can be used for quantitative study of a mechanism of living systems at the norm and anomalies.

Introduction. Development of cybernetic approaches in study of living systems [1-5] are providing the rapid growth of investigations on modelling of living systems control mechanisms. The basis of evolution modelling on PC; the theory of molecular-genetic systems control; the modelling methods of intracellular processes regulation mechanisms, the cellular functions and the cellular communities [2- 5, 6-10] were designed. The mathematical models of living systems are intended for the quantitative analysis of elements set behavior (a complex macromolecules), functioning in some special environment and capable to react to the certain external influences. This fact had let [11,12] to formulating the notions *or* (operators-regulators) - elements of regulation system capable to the perception and production of certain nature signals and *asta* (active system with time average) - a signal medium of regulation system in which an activity of an interconnected elements is realized on the basis of feedback with some average time h (time, passed from a moment of forming the signals till a moment of their (or their products) influences to the elements activity) [11]. The complex *or* together with *asta* is constituted of a regulation system - *orasta*. The geometry of such regulation systems is dynamical, in which notion of immovable point loses a sense [12]. The time unit of the *orasta* is h . In a nature cases of separate existence *or* and *asta* are observed. The viruses are an examples of *or* without *asta*, but the ripe nuclear-free erythrocytes are *asta* without *or*.

The main equations. Let us have *orasta* with n elements. The activity equations of *or* for given regulation system, constructing on the basis of generalising the B. Goodvin's approaches at modelling of regulation mechanisms of intracellular processes [4,7], ideas of V.A. Ratner and M. Eigen at modelling of mechanisms of macromolecules evolutions [5,13,14] taking into account co-operation of considered processes, temporary relations and presence of multifunction feedback in *asta* [11 -12] have following form

2000 *Mathematics Subject Classification.* 34K35, 34K60.

Key words and phrases. regulatory mechanisms, living systems, functional-differential equations, qualitative study, microorganisms, cancer.

$$(1) \quad \frac{dx_i(t)}{dt} = A_i^n(x(t-h)) \exp\left(-\sum_{k=1}^n \delta_{ik} x_k(t-h_{ik})\right) - b_i x_i(t)$$

with

$$A_i^n(x(t-h)) = \gamma_{io} + \sum_{j=1}^n \left(\sum_{k_1, \dots, k_j=1}^n \gamma_{ik_1 \dots k_j} \prod_{m=1}^j x_{k_m}(t-h_{ik_m}) \right),$$

where $x_i(t)$ are a values, which characterizes an amount of signals of i^{th} or at the time moment t ; h_{ik} are a temporary distance from k^{th} or till i^{th} or (in common cases they are continuous functions); h is maximum amongst h_{ik} ; γ_{io} are parameters of *asta's* signal formation; $\gamma_{ik_1 \dots k_j}$, δ_{ik} , b_i are constant; $i, j, k_j = 1, 2, \dots, n$.

Vector $M_c(C_1, \dots, C_n)$, which elements values are calculated by formulas

$$(2) \quad C_i = \int_0^\infty \dots \int_0^\infty A_i^n(S) \exp\left(-\sum_{j=1}^n \delta_{ij} S_j\right) dS_1 \dots dS_n - 1$$

is called "measure of regulation system evolution" and defines possible variants of system development, since its value selects areas of their possible behavior on the parametric portrait of (1) in the cases of concrete regulation systems. On the other hand, M_c expresses interrelation of regulation system with the external medium, as far as its value is defined by given concrete values of coefficients of equation (1) [12]. In the case when $M_c = 0$ the system is in "equilibrium" with the external medium. The equations (1) from class of function-differential equations and, at the giving of continues functions on the initial temporary segment of length h , its continues decision can be received by the method of consequent integrating [15]. At the realization of given method using PC there appears a problem of decision building using given discrete values of variables, which is actual at the quantitative description of biological processes by function-differential equations at presence only discrete experimental data too. Given problem for determined class of linear function-differential equations is solvable and designed method of decision building [15] can be used for the quantitative analysis of decision behavior of the equation (1).

The equations of most simplest regulation system. Let us consider simplified (by scaling, by suggestions of signal formation absence in the medium and presence of general time of the feedback which is the time unit of *orasta*: $h_{ij} = h$; $i, j = 1, 2, \dots, n$) equations of most simplest (assotiative, mutual-conjugate and self-conjugate) regulation systems.

In the case of assotiative regulation systems for the operation of i^{th} or it is necessary a total activity of *or* group. We have

$$A_i^n(x(t-h)) = \sum_{j=1}^n a_{ij} x_j(t-h) \quad a_{ij} \geq 0 \quad (i, j = 1, 2, \dots, n)$$

and for the quantitative study of assotiative *orasta* functioning, the equations are equitable

$$(3) \quad \frac{\theta_i dx_i(t)}{h dt} = \sum_{j=1}^n a_{ij} x_j(t-1) \exp\left(-\sum_{k=1}^n x_k(t-1)\right) - x_i(t).$$

where θ_i, a_{ij} ($i, j = 1, 2, \dots, n$) are defined by means of coefficients values of the equation (1). For the elements of M_c vector we have

$$C_i = \sum_{j=1}^n a_{ij} - 1; \quad i = 1, 2, \dots, n.$$

The functioning of mutual-conjugate regulation systems requires presence of product of all *or*. We have

$$A_i^n(x(t-h)) = a_i \prod_{j=1}^n x_j(t-h);$$

$$(4) \quad \frac{\theta_i}{h} \frac{dx_i(t)}{dt} = a_i \prod_{j=1}^n x_j(t-h) \exp(-\sum_{k=1}^n x_k(t-h)) - x_i(t);$$

$$C_i = a_i - 1; \quad i = 1, 2, \dots, n.$$

In the case of the equilibrium with the external medium we have that $a_i = 1$ ($i = 1, 2, \dots, n$).

In some cases for the functioning of *or* regulation system it is necessary n signals same one *or* (n in this case may associate with the Hill's coefficient). Let this *or* be j^{th} *or*. Then functioning of all *or* identically occurs and

$$(5) \quad \frac{\theta_i}{h} \frac{dx_i(t)}{dt} = a_i x_j^n(t-1) \exp(-\sum_{k=1}^n x_k(t-1)) - x_i(t);$$

$$C_i = a_i \int_0^\infty S_j^n \exp(-\sum_{k=1}^n S_k) dS_1 \dots dS_n - 1, \quad i = 1, 2, \dots, n.$$

We can consider a limit case for one *or*. Then we have the self-conjugate regulation system, functioning of which is described by following equation

$$(6) \quad \frac{\theta}{h} \frac{dx(\tau)}{d\tau} = ax^n(\tau-1)e^{-nx(\tau-1)} - x(\tau); \quad C = a \int_0^\infty S^n e^{-nS} dS - 1.$$

In the case of equilibrium with the external medium we have equation

$$(7) \quad \frac{\theta}{h} \frac{dx(t)}{dt} = \frac{n^n}{(n-1)!} x(t-1)e^{-nx(t-1)} - x(t),$$

which under sufficiently greater conjugates, on the basis of Stirling's formula [12], can be written as

$$(8) \quad \frac{\theta}{h} \frac{dx(t)}{dt} = \sqrt{\frac{n}{2\pi}} x^n(t-1)e^{n(1-x(t-1))} - x(t), \quad n \gg 1.$$

Here $x(t)$ is a value, which characterizes an amount of *or* signal; θ is constant, characterizing average time of signals existence; h is average time of feedback; n is a degree of self-conjugation [11,12].

The qualitative study. Usually mathematical models include the quantitative description of functioning of modelled object or phenomena on the basis of the mathematical equations. However, the equations are not mathematical model. The necessary part of mathematical modelling of regulation systems is definition the most general properties of solutions behavior of considered equations - the qualitative study of appropriated equations [12]. The analysis results of solutions nature of the equations (8), on the basis of qualitative study methods of function-differential equations [11,12,16] have shown presence of their solutions in the first quadrant of phase space under the non-negative values of parameters and initial conditions; instability of infinite points; possibility of existence of trivial and nontrivial steady states. Solutions behavior in the field of nontrivial steady states, which is the functional active state of regulation system have following regimes: steady stationary regime, Poincare type limit cycles and complex fluctuations [11,12,17]. Let us consider some main laws of functioning of regulation mechanisms (regulatorika [11]) of self-conjugate systems on the basis of qualitative analysis of the equations (8).

If we accept that the signals, developed *or* and existed under the average θ time units in the case of normal regulatorika should "live" till realization of feedback loop (i.e. $\theta = h$), then in this case instead of the equation (8) we get following equation

$$(9) \quad \frac{dx(t)}{dt} = \sqrt{\frac{n}{2\pi}} x^n(t-1) e^{n(1-x(t-1))} - x(t), \quad n \gg 1,$$

which does not contain constants except of self-conjugate values. If $\theta > h$, then signal (product of *or* activity) can participate in *orasta* regulation more then once (since the signal is living longer in comparison with a time, required for realization of feedback loop). This case can be named as strong regulatorika. Naturally that the case when $\theta < h$ can be named as mild regulatorika. At the very mild regulatorika ($\theta \ll h$) for preliminary qualitative analysis of the considered regulation systems we have [11,12]

$$(10) \quad x(t) = \sqrt{\frac{n}{2\pi}} x^n(t-1) e^{n(1-x(t-1))}, \quad n \gg 1,$$

and its discrete analog

$$(11) \quad x_{k+1} = \sqrt{\frac{n}{2\pi}} x_k^n e^{n(1-x_k)}, \quad n \gg 1,$$

where X_k is a value, expressing quantity of signals, produced *or* on k^{th} step of *orasta* activity. Step value in this case corresponds to a time required for realization of feedback loop in considered *orasta* (time unit of *orasta*).

Existence condition of stationary modes of functioning (nontrivial steady state in the first quadrant of phase space) for considered systems is expressed as

$$(12) \quad P = \sqrt{\frac{n}{2\pi}} (1 - 1/n)^{n-1} \geq 1.$$

Under $P < 1$ there is only trivial steady state. Nontrivial steady state appears when $P = 1$ in the point $C = (n-1)/n$ by means of hard excitement. Growth of value P leads to bifurcation of steady state C to two nontrivial steady states ($A, B; A < B$), gradually moved from the point C on two sides. Calculations on PC show (taking into account the accepted approach and on basis of Stirling's formula for greater n [12]) that nontrivial steady state of self-conjugate regulation systems appeared under $n \geq 6$ and as the n increases, at first they moved from point C , further they come together with each other, remaining in the different parties from C .

Let us consider stability of the steady state under $n \geq 6$. It is obvious the stability of trivial steady state. Using a Lyapunov's method, by linearizations of (8) near nontrivial steady state ξ , we have the characteristic equation

$$(\theta\lambda + h)e^\lambda + hn(1 - \xi) = 0.$$

Negativity of real part of roots of given transcendental equation can be researched based on the Hayse's criterion [16,17]

$$(13) \quad \begin{aligned} h + \theta &> 0; \\ (1 + n(\xi - 1)) &< 0; \\ hn(\xi - 1) &< \theta\mu \sin\mu - h\cos\mu, \end{aligned}$$

where μ is the root of equation

$$\theta\mu = -htg\mu, \quad 0 < h < \theta\pi.$$

The first condition of (13) for considered equations is always executed, but second is reduced to $x > (n - 1)/n$ and is executed for B only. Consequently, steady state A is unstable and functionally active area of considered regulation system is a actions sphere of an attractor B . For B the third condition of (13), in the case of the normal regulatorika, is reduced to $\xi < 2.24/n + 1$, which is executed not always. Concrete calculations show that for $6 \leq n \leq 8$ we have stability of B , but for $n > 8$ the B is unstable. The stability loss is accompanied by appearance of fluctuations around B . For the case of system with very mild regulatorika we get a condition for stability B as inequality $\xi < 1 + 1/n$. Calculations show that already for $n \geq 9$ it is not executed, i.e. under $n \geq 9$ stability of steady state in the point B is violated. Results of the qualitative research of solutions (11) in the field of unstability have shown existence of complex behavior diapason of considered models of self-conjugate regulation systems. Aside from periodic regimes of functioning, it is possible irregular fluctuations and effect of "black hole" [12]. The "black hole" effect is concluded in arising of the destructive changes in a modelled system and is expressed loss of fluctuations - solutions collapse to the trivial steady state. The calculations using PC by means of calculations of Lyapunov's value, informational and high dimensionality of solutions, buildings of Lameray diagrams (11), show existence of irregular fluctuations under $n \geq 9$ and coming the "black hole" effect under $n > 12$. Consequently, stabile self-conjugate regulation system with very mild regulatorika, which is in the equilibrium with the external medium, can exist under $6 \leq n \leq 12$ only.

The results applications. The method of quantitative study of regulation mechanisms of living system was applied for solution of some physician-biological problems with corresponding specialists [17-21]. Let us consider results of the model study of growing mechanisms of microorganisms [17] and cancer origin [19]. Regularities of cells growing of chlorella were considered in the first case for solving the problem of optimization of their growing [17]. Using a considered approach has shown that ontogeny of chlorella (growing of young cell (before maternal) \rightarrow division-crushing \rightarrow leaving the young cells of chlorella to the external medium) is accompanied by increasing of self-conjugation of cell's population at the division. Achievement of self-conjugation (amounts of cells) of threshold value (12) lead to the effect of "black hole", i.e. to the system dissociation, that we may observe at experiments after 4-5th multiple divisions [17]. In the second case the analysis of origin mechanisms of cancer was conducted. It was considered hypothesis on control of the early embryonic development by means of products (m-RNA) genetic Autonomous Development System (ADS). ADS functions in step of "lamp brushes" of oogenesis for forming of a necessary amount of corresponding m-RNA (and keeping in the form of informosome). They are used, after the fertization, for ensuring of fetus an autonomous development from the maternal organism before including own genome (usually before gastrula [20]). The results of model studies based on the considered equations of living systems regulatorika [19] have shown that ADS can consist of several blocks (initiations, formation of m-RNA and repression) and is hardly blocked after oogenesis. Activation of ADS, on the basis of internal and external reasons, brings to the appearance of consequent volleys of genetic information ADS and development of autonomous cells, which can give birth of malignant growing [19,21]. The products of initiation block, appearing before the autonomous development, can be used for early finding of the activation ADS, but products of repression block - for the suppression of functional ADS [19,21]. The results of model researches can be used for early diagnostics, treatment and prophylaxis of cancer [19-21].

Summary. Modelling of living system regulatorika taking into account the processes cooperation, presence of temporary relations and multifunction feedback leads to the system functional-differential equations. The results of the qualitative analysis shows presence of steady state regimes and functionally active states, unstability of infinite points and that the

solutions are in the first quadrant of phase space under positive values of initial conditions and parameters. Behavior study for self-conjugate regulation systems based on their discrete equations (11) have shown possibility existence of irregular fluctuations and destructive changes in regulation systems - effect of "black hole". "Black hole" limits a number of possible variants of stable self-conjugate regulation systems. In the balance conditions with the external medium the self-conjugate regulation system with very mild regulatorika have seven variants of stable existence, when degree of self-conjugate regulation is increasing from six up to twelve. More high conjugations can exist by organizing of hierarchical regulation systems (as it is observed in real conditions). Using the given approaches for model study of regulation systems for the analysis of development mechanisms of microorganisms [17,18] and cancerous tumors [19-21] have shown its acceptability for the quantitative study of biosystem regulation mechanisms. This research was partially supported by FFR AS RUZ 40-96 and 61-00 grants.

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