REGULATION MECHANISMS OF LIVING SYSTEMS

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Received February 27, 2006

Abstract. Using a regulatorika (functioning of regulatory mechanisms) methodology for dynamical systems, the equations for studying living systems based on the functional-differential, functional and discrete equations have been developed. From results of the qualitative analysis of model systems for equations follows, that the functional state can have a varied nature: stable state, stable limit cycle, deterministic chaos and break-down of solutions to the trivial attractor ("black hole" effect). It is shown that there are only seven stable systems, which are in the balance with an external medium. Control problems for regulatorika systems in areas of dynamical chaos and "black hole" effect are considered.

1 Introduction. The beginning of the second half of last century has seen the development of cybernetics, computers design and technology and a great scientific attraction, especially after World War II, towards biology, in areas reach of urgent problems demanding solutions. Wiener's research on cybernetics, defined as a science on control and communication in the animal and the machine, and the book Schrödinger about perspective ways of quantitative research in living beings gave rise to a sort of revolution in biology. Fundamental results after the World War II are: the discovery of DNA structure, the definition of regulation mechanisms for intercellular processes (the operon theory) and the "end-product inhibition" effect. The scientific atmosphere has been so much invaded by cybernetics ideas, that for instance the work by Jacob-Monod, on genes regulation mechanisms for bacteria, is full of terms such as gene-operator, gene-regulator, RNA information, activator and repressor.

Pioneers in the model researches of a cellular regulatory mechanisms, based on the operon theory, have been Goodwin and Sendov who formulated the ordinary differential equations to model intercellular processes regulation [1, 2].

In the decade 1970-1980 a joint group of mathematicians and molecular biologists was established under the leadership of Sendov and Tsanev. It resulted in development of mathematical and computer models for regulation mechanisms of embryonic cells, epithelial cells and cellular functions (mitosis, differentiation and ageing) for the regularities analysis during early development and cancer [2, 3]. During the successive 10 years, the basic direction for the quantitative analysis of regularities for the regulatory mechanisms functioning (regulatorika) in cellular processes led to a more detailed account of regulation object, i.e. the functioning of the intracellular medium and its mutual relations with the environment. The well-known works by Eigen [4] on modeling "information box" containing an interconnected activity of biologically active ensemble, Ratner's research on "sysers" [5], White's work on "auto-genes" [6] and Prigogine, Nicolis and others investigations on Eigen type models and on brusselator functioning pertain to this area [7]. Researches on quantitative analysis of Belousov-Jabotinskey reaction [7], excitation regularities in the cardiac tissues [8] and the

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

Key words and phrases. Living systems, regulatory mechanisms, differential-delay equations, chaos, "black hole", control.

development of the theory of dynamical systems (Kolmogorov, Arnold, Moser) had lead to focus a special attention to regulation mechanisms. During quantitative research on regulatory mechanisms for intracellular processes it has been understood that it is important to take into account the time relations in a feedback system, the cooperative character of the biological processes and the "end-product inhibition" effect. Development of this line of investigations [9, 10, 11, 12] has led to progress in real quantitative description of mechanisms acting in real biological processes and has offered the opportunity for understanding the normal regulation of living systems as well as its anomalies.

2 Functional-differential equations in regulation mechanisms of living systems. One of the possible methods for the quantitative analysis of living system regulation mechanisms is based on the functional-differential equations **orasta**[12].

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

with

$$\Lambda_i^n(X(t-h)) = a_{i0} + \sum_{j=1}^{n} \left(\sum_{k_1,\dots,k_j=1}^{n} a_{ik_1,\dots,k_j} \prod_{m=l}^{j} x_{k_m}(t-h_{ik_m}) \right),$$

where $x_i(t)$ are the value describing i-th signal quantity in orasta at time t; h_{ik} is the time interval necessary for activity change of i-th elements under influence upon k-th elements activity; a_{i0}, $a_{ik_1,\dots,k_j}$, b_i are the velocity parameters of i-th signal formation in medium orasta, by elements orasta and i-th signal decay, accordingly; δ_{ik} is the repression parameter of i-th elements by activity products of k-th elements, $i, j, k_j = 1, 2, \dots, n$.

In the case when

$$M_c = \int_0^\infty \dots \int_0^\infty \Lambda_i^n(S) \exp\left(-\sum_{j=1}^{n} \delta_{ik} S_j\right) dS_1 \dots dS_n - 1 = 0 \tag{2}$$

the system is in "equilibrium" with the external environment. Equations (1) have been constructed as a generalization of the approaches by Goodwin, Smith, Ratner, Eigen [1, 13, 5, 4].

3 Basic equations. One of the basic elementary regulatorika equation is

$$\frac{\theta}{h}\frac{dX(t)}{dt} = \sqrt{n/2\pi} X^n(t-1) e^{n(1-X(t-1))} - X(t), \tag{3}$$

where $X(t)$ is the value describing a signal quantity in the regulatorika system; a is the resource parameter; θ is the average "life" time of signals; h is the time necessary for a feedback realization; n is the self-conjugate degree. If $\theta << h$, for the qualitative analysis we have the following model system:

$$X(t) = \sqrt{n/2\pi} X^n(t-1) e^{n(1-X(t-1))} \tag{4}$$

and its discrete analogue

$$X_{k+1} = \sqrt{n/2\pi} X_k^n e^{n(1-X_k)}; k = 0, 1, \dots; n >> 1, \tag{5}$$

where X_k represents the number of signals, synthesized by **or** on a k-th step of **orasta** activity. Also, for heuristic purposes we use the following discrete equation:

$$X_{k+1} = pX_k^n e^{-X_k}; k, n = 0, 1, ..., \tag{6}$$

where p is the resource parameter. Possible ways for transition from (3) to (4), (5) are considered in [14, 12].

4 The qualitative study. The analysis of solutions character for (3)-(6) shows that solutions are in the first quadrant of the phase space at non-negative values of parameters and initial conditions; indefinite points are unstable; there are trivial and positive equilibrium points.

The trivial equilibrium point exists always. The existence condition for positive equilibrium points has the form (Figure 1):

$$\sqrt{n/2\pi}(1 - 1/n)^{n-1}e \geq 1. \tag{7}$$

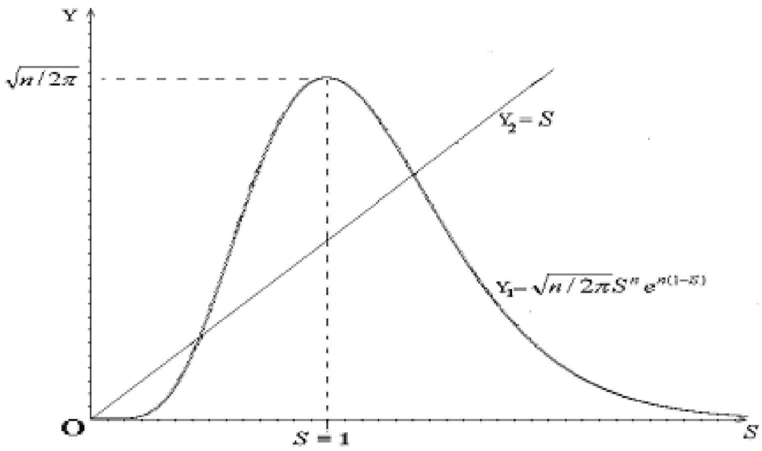


Figure 1: Existence positive equilibrium points (3)-(5).

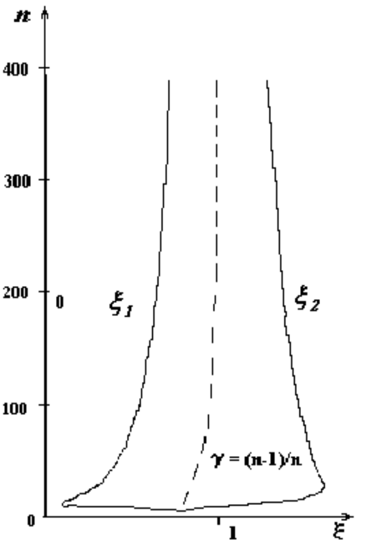
If condition (7) does not hold, only the trivial equilibria exist. Positive equilibrium points arise at $\gamma = (n-1)/n$, by rigid excitation, if condition (7) is satisfied. Increase of n ($n > 5$) leads to equilibria bifurcation into two positive equilibrium points ξ_1, ξ_2 (we consider only integer n). Calculations show (taking into account the accepted approximation, based on Sterling formulae, namely $\left(ne^{-1}\right)^n/(n-1)! \sim \sqrt{n/2\pi}$, when n is large) that for increasing n the positive equilibrium points first move away from γ, and then approach each other, though remaining on opposite sides with respect to γ (Figure 2; a).

Let us consider equilibria stability at $n \geq 6$. It is clear that the trivial equilibria are stable. Since we consider only discrete values for n, it can be assumed that all equilibrium points are isolated (Figures 1, 2).

Linearizing (5) near equilibria $\xi > 0$ we get

$$\frac{\theta}{h}\frac{dZ(t)}{dt} = n(1-\xi)Z(t-1) - Z(t); h > 0$$

with the characteristic equation



a

n	ξ_1	ξ_2	$L(\xi_2)$
6	0.7197	0.9637	-1.3945
7	0.6989	1.0379	-1.3265
8	0.6937	1.0859	-0.3747
9	0.6936	1.1184	-0.1614
10	0.6955	1.1416	-0.1113
11	0.6987	1.1585	+0.3794
12	0.7020	1.1714	+0.6806

b

Figure 2: Quantitative characteristics for dynamics of the self-conjugated regulatorika systems (on the basis of (3)-(5)); **a** shows the dynamics of the positive equilibrium points, **b** the values of positive equilibrium points and Lyapunov's parameter ($L(\xi_2)$) for the stable regulatorika systems.

$$(\theta\lambda + h)e^{\lambda} + hn(\xi - 1) = 0. \tag{8}$$

Negativity conditions for real part of roots of the transcendental equation (8) can be investigated using Hayse criterion [15]:

$$\begin{gathered} h + \theta > 0; \\ 1 + n(\xi - 1) > 0; \\ hn(\xi - 1) < \theta\mu \sin\mu - h\cos\mu, \end{gathered} \tag{9}$$

where μ is a root of the equation $\theta\mu = -htg\mu$; $0 < \mu < \pi$.

The first condition in (9) for considered equations is always satisfied, the second condition has the form $\xi > (n-1)/n$ and holds only for equilibria ξ_2. It follows that equilibria ξ_1 is unstable and basin for ξ_2 attractor is functionally active area for considered regulatory system. For ξ_2 the third condition (9) is reduced to $\xi_2 < 2.24/n + 1$ in the case of normal regulatorika (θ=h). We see from the table (Figure 2, b) that this condition is not always satisfied.

The calculations show that for $6 \le n \le 8$ equilibrium ξ_2 is stable, and if $n > 8$ equilibrium ξ_2 is unstable. Loss of the stability is accompanied by occurrence of oscillations (Poincare type limit cycles) around equilibria ξ_2 .

Results of the qualitative researches of the (5)-(6) solutions in the field of instability, by using methods of qualitative analysis of equations and computer calculation, show that there exists a complex behavior of the considered model of the self-conjugated regulatory systems (Figure 3). In Figure 3, region A is the area of rest (there exists only trivial attractor), B is the area of stationary state (non-trivial attractor is stable), C is the area of regular oscillations (Poincare type limit cycles), D is the area of irregular oscillations (deterministic chaos), E is the area of oscillations failure. Besides periodic states of functioning, there are irregular oscillations (area D) and a "black hole" effect ("E" area). This effect means that destructive changes exist in the model system and that there is oscillations failure [15] solutions movement to trivial equilibria. The analysis of solution behavior for the considered regulatorika equations has shown its presence, in area D, in the form of small regions with regular solutions (Figure 3, 4).

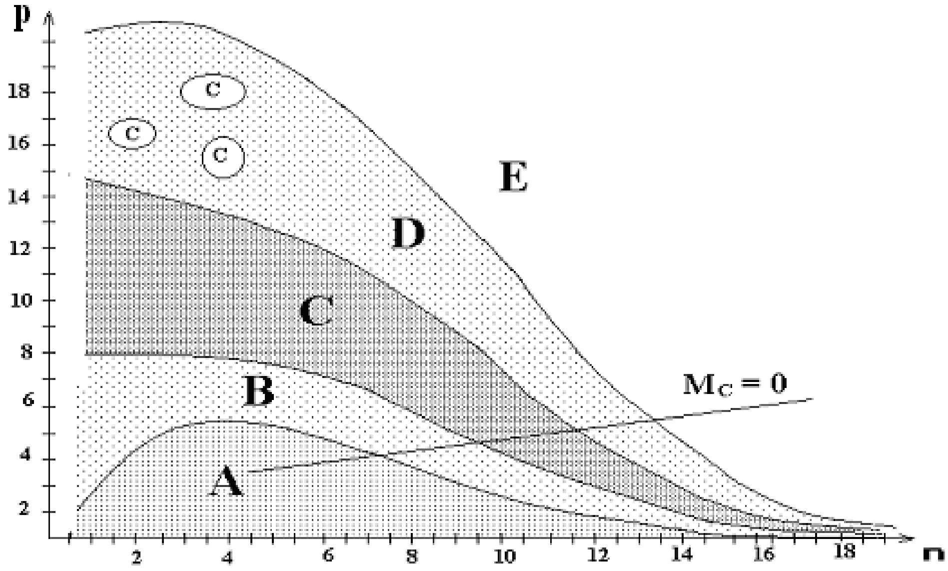


Figure 3: The scheme for parametrical portrait of (6).

Researches based on the Lamerey diagrams construction, calculations of Lyapunov parameter, Hausdorff and high dimensions for (5) solutions, show existence of irregular oscillations if $n \geq 9$ and "black hole" effect if $n > 12$. Hence, the stable self-conjugated regulatorika systems, which are in balance with medium, can exist only if $6 \leq n \leq 12$. This explains the hierarchical organization of the natural regulatorika systems (consequently of the living system, too) and evolution progressiveness. We can view the self-conjugate degree n as the development criterion for living systems during evolution.

5 Control of living systems in anomalies areas. Using the considered approach we performed (based on the equations (1),(3)-(5)) quantitative analysis of the regulation mechanisms of genes [11, 12], cells, cellular communities [10] and heart tissue [14]. Let us consider the application of the obtained results to the control of living systems in areas of dynamical diseases.

Usually areas D and E (Figure 3) can be identified with areas of dynamical diseases in living systems [15]. Existence of the small areas with regular oscillations (r-windows) in area C (deterministic chaos) allows temporarily to solve the problem by entering the system to the nearest r-window to take out the system from area D. It follows that a construction of a path for moving out the system from irregularity area into area C by using r-windows series (Figure 5) is effective.

The transit of destructive changes in the "black hole" area complicates the problems of control of the system behavior. Indeed, it is required the estimation of the time during

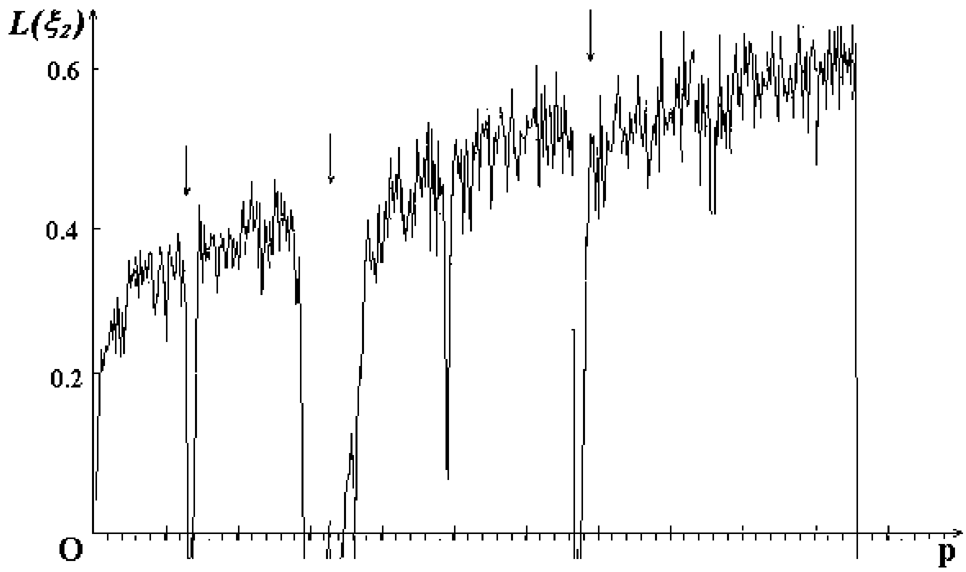


Figure 4: The graph for dynamics of Lyapunov parameter ($L(\xi_2)$) in the field of dynamic chaos (arrows specify small areas with regular solutions).

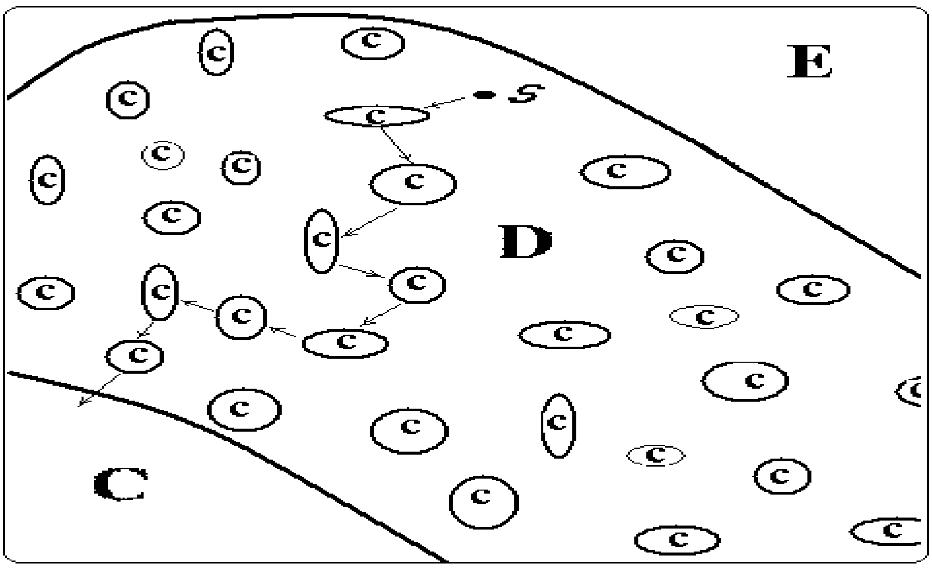


Figure 5: A possible path for moving out the system from area of the deterministic chaos into area of self-oscillations (S is initial position).

which the system is in the functional attractor basin and development of the effective (on time) ways for moving out the systems to area of the deterministic chaos and then to area of the regular oscillations. Some researches on the problem have shown the existence of a paradoxical control with an initial short worsening of the system state (the system turns into "black hole") and the further transfer of the system to the area of the regular oscillations.

The analysis of questions of controlling by the dynamic systems the molecular-genetic, cellular and organism levels and applying the effects of the Pontryagin maximum principle lead to take note of the necessities of "the principle of not worsening of the state" in the dynamic system during the process of control. The performance of this principle requires the evaluation of the system state dynamic close by the norm area and the small areas with regular oscillations (Figure 3, small C in D).

Another principle is related to the limited level of the common possible pressure on the living system during external controlling influences in the field of anomalies. The control must be "sparing" with the minimally possible level of the pressure. The acceptance in the capacity of the pressure value of an irregularity level (H) of the dynamical system conditions is natural in the field of anomalies. H can be calculated on the base of Kolmogorov entropy or Lyapunov number. "The principle of the minimal pressure" can be reached by minimization of $H(t)$ during control:

$$H(t) = \int_{t_0}^{t} K(x(\theta), u(\theta)) d\theta,$$

where $K(x(\theta), u(\theta))$ is Kolmogorov entropy at concrete values for functions of state $x(\theta)$ and control $u(\theta)$ at the time moment θ, t_0 is the initial time of control $t \geq t_0$.

An intensive scientific researches in the field of the genetic, cellular engineering and biotechnology require use of the "principle of ecological purity of control". Observance of this principle assumes that the dynamic system is in a given class of systems during control. Formalization of this principle depends on an organization level of the considered system and in conservation claim the quantity of basic elements, systems of functional and temporal mutual relations.

6 Acknowledgements. This research was partially supported by FPFI AS RUz (grants No. 41-98, No. 61-00), ZST RUz (grant No. F-1.3.1).

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