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MATHEMATICAL AND NUMERICAL MODELS OF TWO ASYMMETRIC GENE NETWORKS

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Abstract. We construct and study mathematical models of two gene networks: a circular gene network of molecular repressilator, and a natural gene network which does not have circular structure. For the first model, we consider discretization of phase portrait of corresponding nonlinear dynamical system and find conditions of existence of an oscillating trajectory (cycle) in this phase portrait. The second model describes the central regulatory circuit of one gene network which acts on early stage of the fruit fly *Drosophila melanogaster* mechanoreceptors morphogenesis. For both models we give biological interpretations of our numerical simulations and give a short description of software elaborated specially for these experiments.

Keywords: nonlinear dynamical systems, cycles, phase portraits, gene networks models, hyperbolic equilibrium points, Grobman-Hartman theorem, Brouwer fixed point theorem, numerical analysis.

1. Introduction

Development and functioning of living organisms are controlled by gene networks, i.e., by complexes of structural components of genome (genes) related by processes of auto- and transregulation not only by corresponding primary products of these genes (mRNAs and proteins) but also by different signal molecules, metabolites, energetic components etc. Nowadays, considerable Big Data are collected from

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experiments based on various methods of modern molecular and cell biology, as well as on bioinformatic analysis of experimental results (in genomics, transcriptomics, proteomics, metabolomics etc). Formalized description, sistematization, and analysis of gene networks with the help of mathematical and numerical modeling allow to understand mechanisms of functioning of these systems and to predict their behavior in different conditions. On the other hand, this mathematical approach gives possibility to construct artificial analogues of these natural systems in order to use them in various applications: in bioengineering and biotechnologies, in particular, in construction of highly effective producers biosensors, etc. [1]–[8].

So, the main aim of our work is elaboration of mathematical tools which allow to give full description of phase portraits of nonlinear dynamical systems of kinetic type and, on the other hand, can be used in planning of numerical experiments with analogous dynamical systems which appear in modeling of natural gene networks.

In the section 2, we consider a hypothetical model of one asymmetric molecular repressilator, and we obtain there sufficient conditions of existence of a cycle in the phase portrait of corresponding asymmetric dynamical system. Some simplified, dimensionless and symmetric versions of such dynamical systems were studied in [11, 13].

In the section 3, we construct a nonlinear dynamical system which describes functioning of the Central Regulatory Circuit (CRC) of the gene network supporting the early stages of drosophila mechanoreceptors development. As in the section 2, we study here the equilibrium points of this system, and

1. we show that there are no oscillations in this model;
2. we find conditions of uniqueness of its equilibrium point;
3. we have realized numerical experiments with this model.

2. Molecular repressilator

In this section we study phase portraits of nonlinear dynamical systems which model functioning of gene networks described by circular schemes of the following type:

$$\dots \to p_{n,s_n} \multimap m_1 \to p_{1,1} \to \dots \to p_{1,s_1} \multimap m_2 \to p_{2,1} \to \dots$$

$$\dots \to p_{2,s_2} \multimap m_3 \to p_{3,1} \to \dots \to p_{3,s_3} \multimap \dots \tag{1}$$

Here, the symbol $\multimap$ denotes negative feedbacks in the gene network, and the symbol $\to$ corresponds to positive feedbacks, see [9, 10]. The letters m_j denote the mRNAs contained in this gene network, and the symbols $p_{j,s}$ denote proteins which appear on intermediate stages of the circular gene network functioning. Some very particular cases of this scheme for

$$n = 3, \quad s_1 = s_2 = s_3 = 1; \tag{2}$$

were studied in [11]–[15]. In contrast with these publications, we consider here much more asymmetric circular gene network model represented by the following nonlinear dynamical system with $n = 3$, $s_1 = 3$, $s_2 = 2$, $s_3 = 1$.

$$\frac{dx_1}{dt} = -k_1 x_1 + f_1(x_9); \quad \frac{dx_2}{dt} = \mu_2 x_1 - k_2 x_2; \quad \frac{dx_3}{dt} = \mu_3 x_2 - k_3 x_3;$$

$$\frac{dx_4}{dt} = \mu_4 x_3 - k_4 x_4; \quad \frac{dx_5}{dt} = -k_5 x_5 + f_5(x_4); \quad \frac{dx_6}{dt} = \mu_6 x_5 - k_6 x_6; \tag{3}$$

$$\frac{dx_7}{dt} = \mu_7 x_6 - k_7 x_7;\ \ \frac{dx_8}{dt} = -k_8 x_8 + f_8(x_7);\ \ \frac{dx_9}{dt} = \mu_9 x_8 - k_9 x_9.$$

Here, the variables x_1, x_5, x_8 denote, respectively, concentrations of the mRNAs m_1, m_5, m_8, the other variables x_ℓ denote concentrations of the proteins $p_{j,s}$ in the scheme (1); smooth monotonically decreasing function f_1, f_5, f_8 describe negative feedbacks; equations 2, 3, 4, 6, 7 and 9, which do not contain the functions f_1, f_5, f_8, correspond to positive feedbacks in the gene network; positive coefficients μ_j, k_ℓ characterize kinetics of its processes, $\ell = 1, \ldots, 9$, $j \neq 1, 5, 8$.

If the condition (2) is satisfied, i.e., in the case of just one intermediate stage (the protein p_j) between any two consecutive mRNAs m_j and m_{j+1} in the circular gene network, corresponding dynamical system has dimension 6. In a very particular case $\mu_1 = \mu_2 = \mu_3$, $k_1 = k_2 = k_3$, $f_1(w) = f_2(w) = f_3(w) = \alpha \cdot (1+w^m)^{-1} + \alpha_0$; which is symmetric with respect to cyclic permutations of pair of the components (m_j, p_j): $(m_1, p_1) \to (m_2, p_2) \to (m_3, p_3) \to (m_1, p_1)$, such dynamical system was introduced in [11] for description of oscillations in simplest molecular repressilator of the type (1) composed by 3 proteins and corresponding 3 mRNAs in the cell *Escherichia coli*. Later, this symmetric dynamical system was studied in numerous publications, see, for example [13]. Analogous asymmetric dynamical systems corresponding to more complicated circular gene networks, including higher-dimensional cases, were studied in [15, 17, 16].

Let $A_j := \frac{f_j(0)}{k_j}$, if $j = 1, 5, 8$; $A_j := \frac{\mu_j}{k_j} A_{j-1}$, if $j \neq 1, 5, 8$; and $Q^9 := \prod_{j=1}^{j=9} [0, A_j] \subset \mathbb{R}^9_+$.

Denote by X nine-dimensional vector-function with coordinates $x_1(t), \ldots, x_9(t)$. The next lemma follows from analysis of signs of coordinates of the vector dX/dt at the points of faces of the parallelepiped Q^9, as it was done in [15, 17], for some other dynamical systems of the type (1).

Lemma 1. *Q^9 is positively invariant domain of the system* (3).

This means that trajectories of the points of Q^9 do not leave it when t grows.

Lemma 2. *The system* (3) *has exactly one equilibrium point $S_0 \in Q^9$.*

The proof follows from solution of system of 9 equations $dX/dt = 0$ which have the form $k_j x_j = f_j(x_{j-1})$, or $k_s x_s = \mu_s x_{s-1}$, where $j = 1, 2, 3$, and $s = 2, 3, 4, 6, 7, 9$. This system reduces to just one equation:

$$k_1 x_1 = f_1\left(\frac{\mu_9}{k_9 k_8} f_8\left(\frac{\mu_7 \mu_6}{k_7 k_6 k_5} f_5\left(\frac{\mu_4 \mu_3 \mu_2}{k_4 k_3 k_2} x_1\right)\right)\right).$$

The left-hand side of this equation grows monotonically with the variable x_1, and the right-hand side is composition of three monotonically decreasing functions of x_1 and decreases monotonicaly as well. Thus, this equation has a unique solution x_1^0. The other coordinates of the equilibrium point are defined by $k_2 x_2^0 = \mu_2 x_1^0$ etc. The lemma is proved.

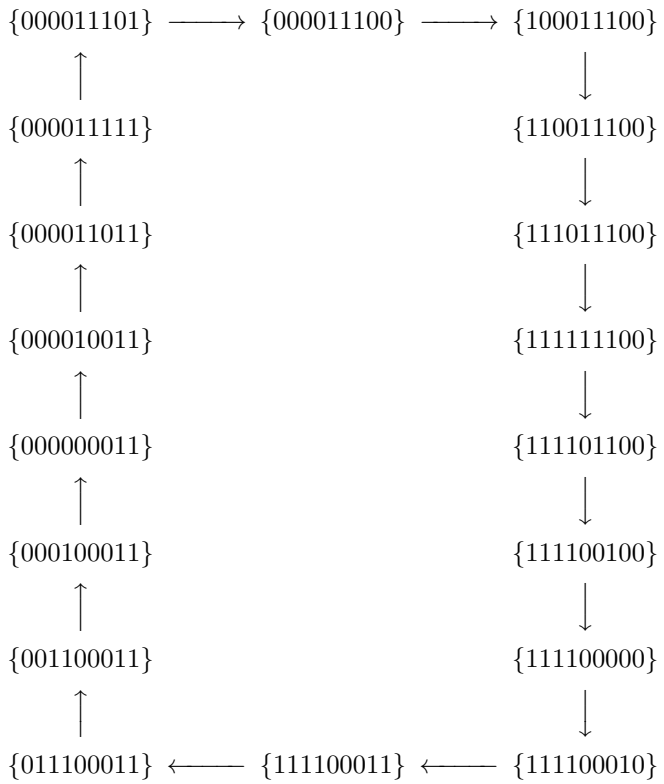
Let $(x_1^0; x_2^0; x_3^0; x_4^0; x_5^0; x_6^0; x_7^0; x_8^0; x_9^0)$ be coordinates of the point S_0. Consider decomposition of the domain Q^9 by hyperplanes $x_j = x_j^0$, $j = 1, 2, \ldots 9$. We obtain 512 smaller parallelepipeds (blocks) which we shall denote by binary multi-indices $\{\varepsilon_1, \ldots \varepsilon_9\}$ as follows: $\varepsilon_j = 0$, if $x_j \leq x_j^0$ for all points of this block, and $\varepsilon_j = 1$, if $x_j \geq x_j^0$ for all its points.

Lemma 3. *For any pair E_1, E_2 of adjacent blocks of this decomposition, trajectories of all points of their common 8-dimensional face $F = E_1 \cap E_2$ either pass from E_1 to E_2 ($E_1 \Rightarrow E_2$), or pass from E_2 to E_1 ($E_2 \Rightarrow E_1$).*

Let the face F be contained if the hyperplane $x_j = x_j^0$. The proof follows from analysis of signs of dx_j/dt at the points of this face, as in the previous two Lemmas.

We say that the *valency of the block* $E = \{\varepsilon_1, \dots \varepsilon_9\}$ equals r, if it has exactly r adjacent blocks E_a such that $E \Rightarrow E_a$.

(4)



The cyclic diagram (4) contains all the blocks with valency 1, and its arrows show all possible transitions of trajectories of the system (3) from one block to another. Let W be the union of the blocks contained in this diagram. Its interior is homeomorthic to the torus $S^1 \times B^8$. As it was done in the Lemmas 1 and 3 above, one can verify that W is positively invariant domain of the system (3). At the same time, the points which do not belong to W can enter W when $t \to +\infty$, see the Fig. 1.

Consider the linearization matrix of the system (3) at the point S_0:

$$M_0 = \begin{pmatrix} -k_1 & 0 & 0 & 0 & 0 & 0 & 0 & 0 & -q_1 \\ \mu_2 & -k_2 & 0 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & \mu_3 & -k_3 & 0 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & \mu_4 & -k_4 & 0 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & -q_5 & -k_5 & 0 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & \mu_6 & -k_6 & 0 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & \mu_7 & -k_7 & 0 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & -q_8 & -k_8 & 0 \\ 0 & 0 & 0 & 0 & 0 & 0 & 0 & \mu_9 & -k_9 \end{pmatrix}$$

Here $-q_j = \frac{df_j}{dp_{j-1}}$ for $j = 1, 5, 8$. The characteristic polynomial of the matrix M_0 has the form:

$$P(\lambda) = \prod_{j=1}^{j=9}(k_j + \lambda) + b^9, \quad \text{where} \quad b^9 := \prod\nolimits_{j=1,5,8} q_j \cdot \prod\nolimits_{j\neq 1,5,8} \mu_j.$$

Recall that equilibrium point of a dynamical system is called hyperbolic if the eigenvalues of corresponding linearization matrix do have positive and negative real parts and do not have zero real parts.

Lemma 4. *For sufficiently large values of the parameter b, the equilibrium point S_0 is hyperbolic, and the polynomial $P(\lambda)$ has four complex roots with positive real part, one negative root and four roots with negative real parts.*

Proof. Let $z := \dfrac{\lambda}{b}$. For fixed values of the parameters k_j and sufficiently large values of b, the roots of the polynomial

$$P_b(z) = \frac{1}{b^9}P(\lambda) = \prod\nolimits_{j=1}^{j=9}\left(\frac{k_j}{b} + z\right) + 1,$$

can be done arbitrary close to the corresponding roots of the polynomial $P_0(z) = z^9 + 1$ which obviously has four roots with positive real parts. □

In terms of [18], similar configurations of eigenvalues of linearization matrices is called dichotomy of the spectrum with respect to the imaginary axis.

Theorem 1. *If S_0 is hyperbolic point of the dynamical system* (3)*, then the invariant domain W contains at least one cycle of this system, and this cycle travels from block to block according to the diagram* (4)*.*

Proof. It follows from the Grobman-Hartman theorem (see [19]) that after some smooth change of variables, the nonlinear dynamical system (3) is linearized in a small neighborhood U of the equilibrium point S_0. Hence, the behavior of trajectories of the system (3) near this point is completely determined by signs of real parts of its linearization matrix at the point S_0.

Now, the proof of our theorem follows from the Brouwer's fixed point theorem (see, for example [20]) which was used in proofs of existence of cycles in various cases of dynamical systems analogous to (3) as in [15, 17, 21], see also references therein.

Denote by $F = \mathcal{E}_1 \cap \mathcal{E}_2$ common face of two adjacent blocks in the diagram (4), and let $U \approx D^4 \times D^5$ be sufficiently small open neighborhood of the equilibrium point S_0. Here D^5 is 5-dimensional open disk parallel to plane corresponding to

eigenvalues of the matrix M_0 with negative real parts, see Lemma 4; similarly, we denote by D^4 the 4-dimensional ball parallel to the plane constructed by the eigenvalues of M_0 with positive real parts.

Consider compact set $\widehat{F} = F \setminus (F \cap U)$ which is homeomorphic to 8-dimensional cube. Trajectories of all its points returns to this compact after 18 steps along the arrows of the diagram (4). The Brouwer's fixed point theorem implies that the compact set $\widehat{F}$ contains at least one point X_1 such that its trajectory returns to X_1 after these 18 steps. Thus, the trajectory of this point X_1 is a cycle. $\square$

Remark 1. *Similarly, all statements of this section can be extended to the cases of arbitrary odd n and any nonnegative integers $s_1, \dots, s_n$.*

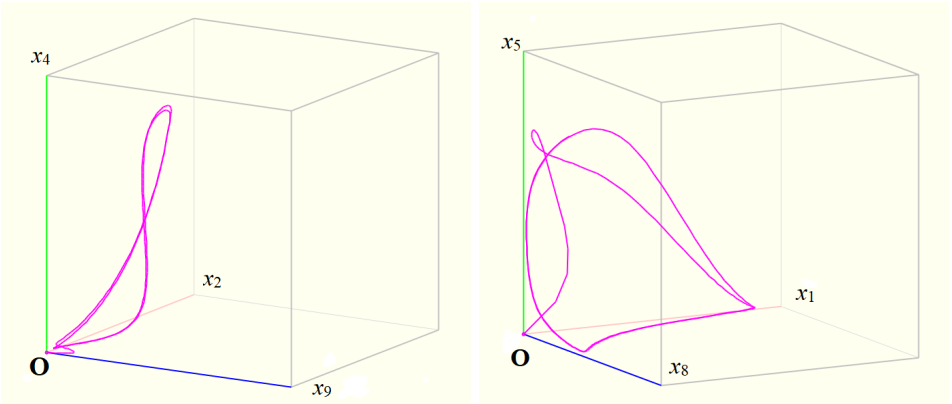


Рис. 1. Projections of a trajectory of 9-dimensional system (3) onto coordinates planes x_2, x_4, x_9 (left), and x_1, x_5, x_8 (right).

Using the software STEP created under the guidance of S.I.Fadeev in Sobolev institute of mathematics, we have accomplished several series of numerical experiments. Some of their results are shown on the Fig. 1 and Fig. 2. The Fig. 1 shows projections of a trajectory and that of corresponding limit cycle of the system (3) onto coordinate plane x_2, x_4, x_9 (left) and x_1, x_5, x_8 (right) for the following values of parameters: $k_1 = 1.1,\ k_2 = 1.2,\ k_3 = 1.3,\ k_4 = 1.4,\ k_5 = 1.5,\ k_6 = 1.6,$

$k_7 = 1.7,\ k_8 = 1.8,\ k_9 = 1.9;$

$\mu_2 = 1.15,\ \mu_3 = 1.25,\ \mu_4 = 1.35,\ \mu_6 = 1.55,\ \mu_7 = 1.65,\ \mu_9 = 1.85;$

$f_1(x_9) = 30 \cdot \exp(-3x_9),\ f_5(x_4) = 40 \cdot (1 + x_4^2)^{-1},\ f_8(x_7) = 30 \cdot \exp(-4x_7).$

The Fig. 2 corresponds to the values $k_1 = k_2 = k_3 = k_4 = \mu_2 = \mu_3 = \mu_4 = 0.8$; the other parameters k_i and μ_i, $i \geq 5$, equal 0.6. The functions f_1, f_2, f_3 are same as for the Fig. 1. The initial points of these trajectories are chosen near the origin, this corresponds to the usual assumption on initial stages of the circular gene networks functioning. The colors of the graphs $x_j(t)$, corner of the Fig. 2.

Numerical experiments with the system (3) for other initial data $x_j(0)$ and for other values of parameters of this system have shown similar behavior of trajectories of the system and similar shapes of its cycle. These numerical results generate a conjecture on uniqueness and stability of the cycle mentioned in the Theorem 1. In one particular case, this conjecture was proved, see [14].

One can see here that after some $t > 0$ the graphs of the functions $x_1(t)$, $x_2(t)$, $x_3(t)$, $x_4(t)$ are "congruent with good precision" with respect to shifts along the

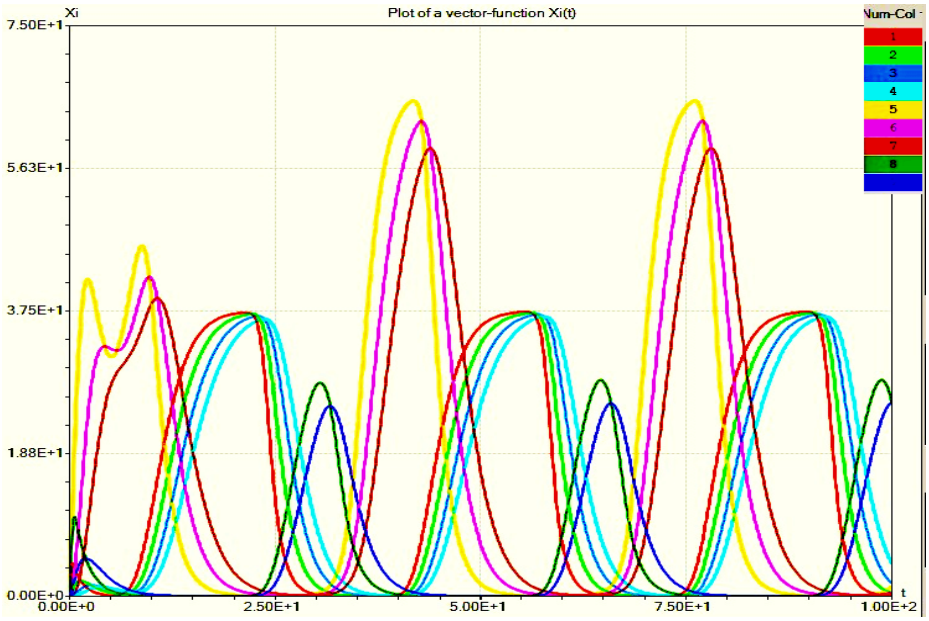


Рис. 2. Graphs of the functions $x_j(t)$.

axis t. Similarly look the graphs of the functions $x_5(t)$, $x_6(t)$, $x_7(t)$. Two graphs $x_8(t)$ and $x_9(t)$ "repeat" each other as well. Similar phenomena appear in modeling of multistage biochemical precesses, cf. [26].

Analogous results concerning sequences of almost congruent graphs were obtained for other values of parameters and other functions in the dynamical system (3). Recall that in our considerations $x_1(t)$ is concentration of the mRNA m_1, and $x_2(t)$, $x_3(t)$, $x_4(t)$ are concentrations of the "intermediate" proteins $p_{1,1}$, $p_{1,2}$, $p_{1,3}$, respectively; $x_5(t)$ is concentration of the mRNA m_2, and $x_6(t)$, $x_7(t)$ are concentrations of the proteins $p_{2,1}$, $p_{2,2}$; $x_8(t)$, $x_9(t)$ are concentrations of the mRNA m_3 and, respectively, that of the protein $p_{3,1}$, between m_3 and m_1, see (1).

Similar numerical experiments were realized for other dynamical systems constructed by this scheme (see [15, 17, 24] where we used the package STEP and software elaborated on the basis of the language R specially for studies of these gene networks models, see also the next sections. This software is described in https://maxim-kazantsev.shinyapps.io/ElowitzLeibler/ some results of numerical experiments are presented there as well.

3. Central regulatory circuit of gene network controlling morphogenesis of *Drosophila melanogaster* mechanoreceptors

Alongside with gene networks regulating cyclic processes, there are networks supporting acyclic processes which ensure reaching a stable finite state by a system under control. Morphogenesis of drosophila mechanoreceptors is an example of such an acyclic process. Corresponding gene network constructed on the basis of experimental data contains about 400 objects [25]. The key component of this

network is the Central Regulatory Circuit (CRC) which controls the amount of proteins Achaete-Scute (AS-C) in the mechanoreceptor precursol cell (Fig. 3).

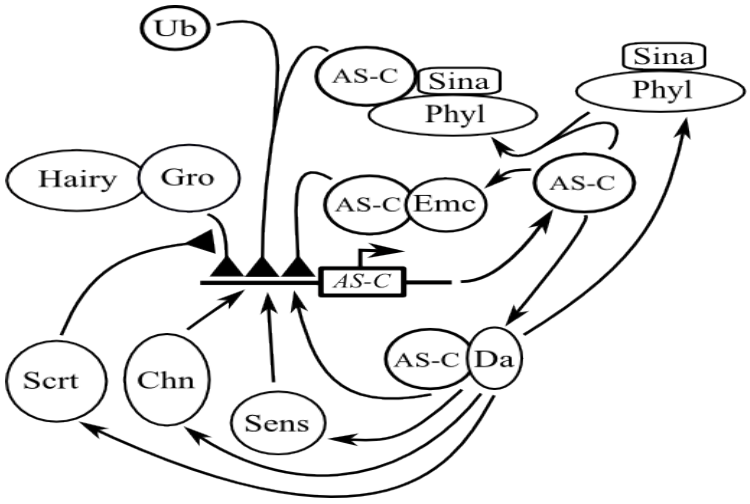


Рис. 3. Central regulatory circuit of the gene network of *D.melanogaster* sensor organs morphogenesis

The proteins containing in CRC and their concentrations are denoted here and below as follows: Acaete-Scute (AS-C), $x(t)$; Hairy, $y(t)$; Senseless (SENS), $z(t)$; Scratch (SCRT), $u(t)$; Charlatan (CHN), $w(t)$; Phyllopod (PHYL), $p(t)$; Daughterless (DA), D; Extramacrochaete (EMC), E; Groucho (GRO), G; Seven in one (SINA), S; and Ubiquitin (UB), U. As in the previous section, the arrows $\to$ denote here the positive feedbacks, and the symbols $\dashv$ correspond to the negative feedbacks.

It is well-known that the protein PHYL appears in the cell in 10-12 hours after the proteins AS-C, thus the CRC functioning can be described by a system of delay differential equations which is composed on the basis of the scheme depicted on the Fig. 3 following general methodology of construction of such models described in [9, 26, 27].

Since concentrations of 5 proteins DA, EMC, GRO, SINA and UB are almost constant in the processes under consideration, we assume that the parameters D, E, G, S, U do not depend on time. For the remaining 6 proteins, dependence of their concentrations on t is represented by the following system of differential equations where the first and the last equations which describe concentrations of AS-C and PHYL contain functions with delayed arguments:

$$\frac{dx}{dt} = \frac{\sigma_1(D\cdot x)+\sigma_3(z)+\sigma_5(w)}{(1+G\cdot y)(1+E\cdot x)} - k_1(1+p(t-\Delta t)US)x;$$

$$\frac{dy}{dt} = \frac{C}{d1+u} - k_2 y; \quad \frac{dz}{dt} = s_3(D\cdot x) - k_3 z; \quad \frac{du}{dt} = s_4(D\cdot x) - k_4 u; \tag{5}$$

$$\frac{dw}{dt} = s_5(D\cdot x) - k_5 w; \quad \frac{dp}{dt} = \frac{s_6(D\cdot x)h(t-\Delta t)(t-\Delta t)^2}{1+(t-\Delta t)^2} - k_6 p.$$

Here $h(t)$ is the Heaviside function which describes decomposition of the process to two stages with the delay $\Delta t = 12$ mentioned above, the positive coefficients k_1, k_2, k_3, k_4, k_5, k_6 characterize degradations of the corresponding proteins. The positive summand in the second equation of the system (5) describes the negative feedback SCRT —◀ Hairy, Fig. 3. The sigmoid functions $\sigma_j > 0$, $j = 1, 3, 5$ and $s_i > 0$, $i = 3, 4, 5, 6$ describe positive feedbacks on the Fig. 3 and have the form

$$\sigma_j(q) = \frac{d_j q^2}{1+q^2}; \quad s_i(q) = \frac{a_i \exp(\frac{q-b_i}{c_i})}{1+\exp(\frac{q-b_i}{c_i})},$$

(see [9, 10]), here a_i, b_i, c_i, d_j are positive constants. Some more simple versions of this model, without delay differential equations were considered in [10, 28], where detailed analysis of phase portraits of corresponding dynamical systems was given.

It is worthy to note that as in [21], we use step-functions $h(t-\Delta t)$ in the following sense: for $t < 12$ we have $h(t-\Delta t) \equiv 0$; then for $t = 12$, we take the values $x(12)$, $y(12)$, $\dots p(12)$ as the initial data for the Cauchy problem of the system (5) for $t \geq 12$. Actually, the function $h(t-\Delta t)\cdot(t-\Delta t)^2$ is continuous at the point $t = \Delta t$.

The Fig. 4 shows one of our numerical results of CRC modeling with the following values of parameters and initial data which were chosen according to the experimental data ([22, 23]) on character of dynamics of the proteins considered in our model:

$G = 1.41$; $E = 1.48$; $D = 2.05$; $U = 1.99$; $S = 5.6$.

$C = 1$; $n = 2$; $k_1 = 1$; $k_2 = 1$; $k_3 = 0.32$; $k_4 = 1$; $k_5 = 1$; $k_6 = 0.17$.

$a_3 = 3.61$; $b_3 = 4.96$; $c_3 = 1.35$; $a_4 = 4.43$; $b_4 = 6.09$; $c_4 = 1.66$; $a_5 = 8.09$; $b_5 = 11.13$; $c_5 = 3.03$; $a_6 = 2.67$; $b_6 = 3.67$; $c_6 = 1$; $d_1 = 7.46$; $d_3 = 2.77$; $d_5 = 1.24$.

$x(0) = 0.25$; $y(0) = 1.08$; $z_(0) = 0.5$; $u(0) = 0$; $w(0) = 0.07$; $p(0) = 0$.

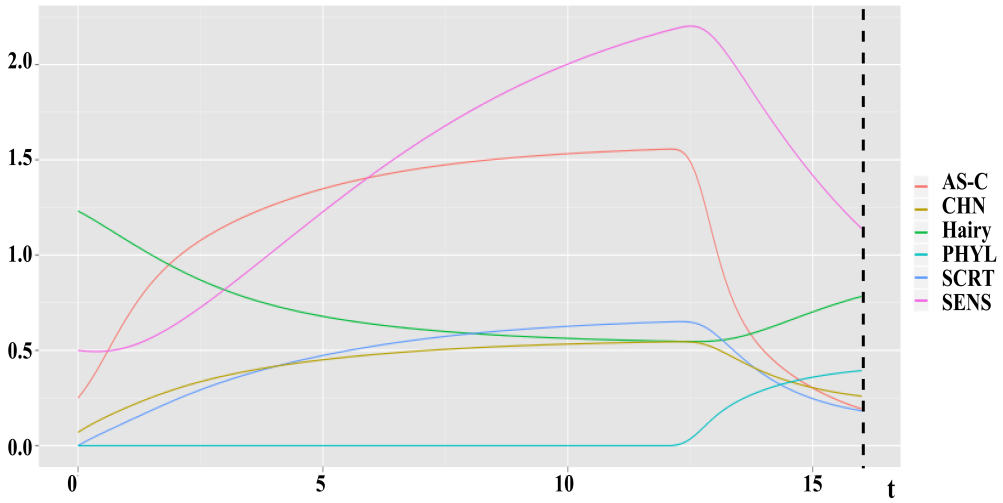


Рис. 4. Graphs of the functions $x(t)$, $y(t)$, $z(t)$, $u(t)$, $w(t)$, $p(t)$

The dashed vertical line shows the moment of the cell division, the colors of the graphs are indicated in the right part of the Fig. 4.

4. Software

We have elaborated a special software for numerical analysis of dynamical systems which simulate the processes described in the previous sections. The soft is based on the language R, see [29] and https://www.r-project.org/ which was used earlier in numerical modeling of some other biological systems with the help of delay differential equations, [24, 30]. This INTERNET source contains various tools of visualization of results of the numerical experiments. The elaborated software is realized as a Shiny-application of the language R (http://shiny.rstudio.com/), the numerical results are available at

https://maxim-kazantsev.shinyapps.io/AS-C/

https://maxim-kazantsev.shinyapps.io/as-c_with_delays/.

This application is based on "client-server" approach. Here, the client part is represented by the web-page were one can fill in the values of parameters of the dynamical system in order to obtain the numerical results and corresponding graphs. The server part of this software is the script on the language R which produces all required calculations. In our numerical experiments with the dynamical systems, considered as gene networks models of the CRC functioning, we used the numerical method *dede* of the package *deSolve* of the language R. This high-productive method uses Hermitian cubic interpolation for calculations of functions with delayed arguments, see [31].

5. Conclusions

In the first section (see Theorem 1 and Remark 1), we have considered one generalization of molecular repressilator model described in pioneering work by Elowitz and Leibler [11], where the repressilator composed by just 3 mRNAs and 3 proteins of the *E. coli* was presented. It should be emphasized that this was the origin of new perspective direction of synthetic biology, intensively developing now [2].

This model was verified experimentally and numerically and confirmed possibility of construction of artificial oscillating systems. There are many analogous oscillating gene networks which control cellular cycles, and important physiological parameters (such as cardiac activity, respiration, insulin secretion, circadian rhythms etc) in living organisms, The mechanisms of their functioning is studied on their artificial analogues, see [4, 32, 33].

In our previous publications [28] we have considered a dynamical system analogous to (5) as a model of the same CRC functioning (Fig. 3) neglecting the delay arguments phenomena: in the first and in the last equations it was written t instead of $(t - \Delta t)$. In that more simple case, we have described parameters of the system compatible with experimental data that guarantee uniqueness and stability of the equilibrium point of that system. These conditions imply uniqueness and stability of the equilibrium point of the system (5) as well. In numerical experiments described in this paper the parameters satisfied these conditions.

The main conclusion from the analysis of our model of CRC functioning and corresponding numerical experiments is the following: for all values of parameters of this model the trajectories of corresponding dynamical system are bounded and do not have oscillations. This also corresponds to the biological data, (http://www.sdbonline.org/sites/fly/aimain/1aahome.htm).

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