MATHEMATICAL AND NUMERICAL MODELING OF GENE NETWORK FUNCTIONING [1]

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Abstract. We find conditions of existence of stable cycles in some models of gene networks regulated by negative feedbacks and by simple combinations of negative and positive feedbacks. Special algorithms and programs for numerical simulations of these results are elaborated as well.

Introduction. Questions of existence of periodic trajectories in natural gene networks and in their mathematical models play an important role in the theory of the gene networks [6, 7]. Similar questions appear in various domains of pure and applied mathematics, and even in the case of 2-dimensional dynamical systems very famous problems, such as the Center-Focus problem, are still open.

Some sufficient conditions of existence of cycles and corresponding stability questions for odd-dimensional nonlinear dynamical systems of chemical kinetics were studied in our previous publications [1, 2, 3, 4] where these systems were considered as models of gene networks functioning.

The behavior of trajectories of these systems in even-dimensional dynamical systems of this type, or in presence of positive feedbacks in corresponding gene networks, is much more complicated. Usually, such systems have several stationary points and cycles. Some of these points and cycles are stable, and boundaries between the basins of these attractors contain unstable stationary points and/or cycles. Description of the phase portraits of these systems, visualization of these boundaries and detection of these unstable cycles are hard problems both in pure and in numerical mathematics.

At first, we study here simple gene networks models, where the regulation is realized by the negative feedbacks only. In this rather simple case, we have detected in our numerical experiments non-uniqueness of limit cycles. Then we consider some models of gene networks regulated by combinations of negative and positive feedbacks. More complicated gene networks models can be interpreted as combinations of these "elementary" models, see [1, 2, 7].

1. Gene networks models with negative feedbacks. We start with consideration of odd-dimensional nonlinear dynamical system of chemical kinet-

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ics in dimensionless form:

$$\begin{cases} \dfrac{dx_1}{dt} = f_1(x_{2k+1}) - x_1; \\ \dfrac{dx_2}{dt} = f_2(x_1) - x_2; \\ \quad \dots \quad \dots \\ \dfrac{dx_{2k}}{dt} = f_{2k}(x_{2k-1}) - x_{2k}; \\ \dfrac{dx_{2k+1}}{dt} = f_{2k+1}(x_{2k}) - x_{2k+1}. \end{cases} \tag{1}$$

Here f_i are positive monotone decreasing functions defined for $x_i \geq 0$. These variables denote concentrations of substances in gene networks. We assume also that $f_i(x_{i-1}) \to 0$ for $x_{i-1} \to \infty$, $i = 1, 2, \dots 2k+1$, and that if $i = 1$ then $x_{i-1} = x_{2k+1}$. Sometimes we express the system (1) in the vector form $\dfrac{d\mathbf{X}}{dt} = \mathbf{V}(\mathbf{X})$. As above, the coordinates of the vector $\mathbf{X}$ are $x_1, \dots, x_{2k+1}$, and we call the vector $\mathbf{V}(\mathbf{X})$ the velocity vector field of the system (1).

According to the standard biological interpretations, see [7, 8, 9], the monotone decreasing of these functions simulates negative feedbacks in gene network, and the monotone increasing here corresponds to positive feedbacks.

The summand $f_i(x_{i-1})$ in the i-th equation describes the relation between the rate of synthesis of substance " x_i " and the concentration of the substance " x_{i-1}". The negative terms in these equations correspond to the natural process of degradation of biological molecules. In applications, these negative feedbacks are described by the Hill's functions $f(w) = \dfrac{a}{1+w^n}$, where $a, n > 0$. And the Glass-Mackey functions $\Lambda(w) = \dfrac{a \cdot w}{1+w^n}$, the logistic functions $\Lambda(w) = a \cdot w \cdot (b-w)$, and other unimodal functions describe variable feedbacks, which are positive below some threshold value of concentration of the regulating substance, and are negative for larger values of these concentrations. Some gene networks models with this type of regulation are considered below.

Proposition 1. *The dynamical system* (1) *has exactly one stationary point.*

The proof follows directly from any attempt to find the stationary point from the system of equations $\dfrac{d\mathbf{X}}{dt} = \mathbf{V}(\mathbf{X}) = 0$, and from the simple observation that any composition of odd monotonically decreasing functions is again monotonically decreasing function, see [4, 7] for details. Denote this stationary point by M^*, its radius-vector by $\mathbf{X}^* = (x_1^*, x_2^*, \dots, x_{2k}^*, x_{2k+1}^*)$, and the maximal values $f_i(0)$ of the functions $f_i(x_{i-1})$ by B_i.

It is easy to verify that all trajectories of the vector field $\mathbf{V}(\mathbf{X})$ eventually enter the parallelepiped $Q = [0, B_1] \times [0, B_2] \dots \times [0, B_{2k}] \times [0, B_{2k+1}]$ and never leave it. Hence, Q is an invariant domain of the dynamical system (1).

Now we consider the partition of Q by $2k+1$ hyperplanes $\{x_i = x_i^*\}$ containing the stationary point $M^* \in Q$ and parallel to the coordinate hyperplanes.

This gives us a collection of 2^{2k+1} smaller parallelepipeds which can be enumerated by binary indices: $\{\varepsilon_1\varepsilon_2\varepsilon_3\ldots\varepsilon_{2k+1}\} :=$

$$\left\{\mathbf{X} \in Q \mid x_1 \gtrless_{\varepsilon_1} x_1^*,\, x_2 \gtrless_{\varepsilon_2} x_2^*,\, x_3 \gtrless_{\varepsilon_2} x_3^*,\, \ldots,\, x_{2k+1} \gtrless_{\varepsilon_{2k+1}} x_{2k+1}^*, \right\}.$$

Here $\mathbf{X} = (x_1, x_2, x_3, \ldots, x_{2k+1})$, and $\varepsilon_1,\, \varepsilon_2,\, \varepsilon_3,\, \ldots\, \varepsilon_{2k+1} \in \{0,1\}$. All the relations here are defined as follows: the symbol $\gtrless_0$ means $\leq$, and the symbol $\gtrless_1$ means $\geq$. The faces of these parallelepipeds are contained either in ∂Q, or in the interior of Q in the intersection $\{x_i = x_i^*\} \cap int(Q)$. Analysis of the velocities $\{f_i(x_{i-1}) - x_i\}$ at the points of the interior faces implies the following

Proposition 2. *If* $x_{i-1} < x_{i-1}^*$ *then* $\dot{x}_i\Big|_{x_i = x_i^*} > 0$. *Hence all trajectories starting in* $\{..\varepsilon_{i-2}00\varepsilon_{i+1}..\}$ *enter the adjacent parallelepiped* $\{..\varepsilon_{i-2}01\varepsilon_{i+1}..\}$.

Conversely, if $x_{i-1} > x_{i-1}^*$ *then* $\dot{x}_i\Big|_{x_i = x_i^*} < 0$, *hence all trajectories starting in the domain* $\{..\varepsilon_{i-2}11\varepsilon_{i+1}..\}$, *enter the adjacent parallelepiped* $\{..\varepsilon_{i-2}10\varepsilon_{i+1}..\}$.

In both cases, the index changes on the i-th place only.

Just for brevity, we use the notations for some of these parallelepipeds:

$Q_{0,2m+1} = \{0101\ldots00\ldots01\}$, the first of two zeros in "00" stands on the place number $2m+1$;

$Q_{0,2m} = \{1010\ldots00\ldots0\}$, the first of two zeros in "00" stands on the place number $2m$;

$Q_{1,2m+1} = \{1010\ldots11\ldots0\}$, the first of the "11" stands on the place number $2m+1$;

$Q_{1,2m} = \{0101\ldots11\ldots01\}$, the first of the "11" stands on the $2m$-th place.

The intersection $\Pi = Q_{1,2k+1} \cap Q_{0,1}$ is contained in the hyperplane $x_1 = x_1^*$. It follows from the previous proposition that the trajectories of all points of all other faces of $Q_{1,2k+1}$ enter inside $Q_{1,2k+1}$, and the trajectories of all points of Π pass from $Q_{1,2k+1}$ to $Q_{0,1}$. So, we obtain the diagram

$$Q_{1,2k+1} \to Q_{0,1} \to Q_{1,2} \to Q_{0,3} \to \ldots \to Q_{1,2k-1} \to Q_{0,2k} \to \ldots. \tag{2}$$

All trajectories of the system (1) pass through the common face of two adjacent parallelepipeds "along" the arrows, and, from $Q_{0,2k}$ to $Q_{1,2k+1}$. Hence, the union $\mathcal{Q}_{4k+2}$ of all these $4k+2$ parallelepipeds is an invariant non-convex domain of the dynamical system (1), and it contains all possible cycles of (1).

Actually, each of these parallelepipeds $Q_{\varepsilon,j}$, where $j = 1, 2, \ldots 2k+1$ and $\varepsilon \in \{0,1\}$, can be reduced to corresponding triangle prism $P_{\varepsilon,j} \subset Q_{\varepsilon,j}$ so that the union $\mathcal{P}_{4k+2}$ of these $4k+2$ prisms remains an invariant domain of the system (1). All arguments below can be reproduced for this smaller domain $\mathcal{P}_{4k+2}$ as well.

2. Existence of cycles and stability questions. Below, we denote as usual by $[x]$ the integer part of a real number x. The linearization of the system

(1) near its stationary point M^* has the form

$$\frac{d\mathbf{X}}{dt} = \begin{pmatrix} -1 & 0 & \dots & 0 & f_1'(x_{2k+1}^*) \\ f_2'(x_1^*) & -1 & \dots & 0 & 0 \\ 0 & f_3'(x_2^*) & \dots & 0 & 0 \\ \dots & \dots & \dots & \dots & \dots \\ 0 & 0 & \dots & f_{2k+1}'(x_{2k}^*) & -1 \end{pmatrix} (\mathbf{X} - \mathbf{X}^*). \qquad (3)$$

Let $f_1'(x_{2k+1}^*) \cdot f_2'(x_1^*) \cdot f_3'(x_2^*) \dots f_{2k+1}'(x_{2k}^*) = -a^{2k+1}, \qquad a > 0.$

The eigenvalues of this linearization satisfy the equation

$$(-1-\lambda)^{2k+1} - a^{2k+1} = 0,$$

and one of them is real: $\lambda_1 = -1 - a < 0$. It corresponds to the eigenvector $+e_1$ with positive coordinates. All other eigenvalues here are complex:

$\mathbb{R}e\lambda_{2,3} := \mathbb{R}e\lambda_2 = \mathbb{R}e\lambda_3 = -a \cdot \cos\frac{2\pi}{2k+1} - 1 < 0,$

$\dots$

$\mathbb{R}e\lambda_{2k,2k+1} := \mathbb{R}e\lambda_{2k} = \mathbb{R}e\lambda_{2k+1} = +a \cdot \cos\frac{\pi}{2k+1} - 1.$

Here $\lambda_1 < \mathbb{R}e\lambda_{2,3} < \mathbb{R}e\lambda_{4,5} < \mathbb{R}e\lambda_{2k,2k+1}$.

If $\mathbb{R}e\lambda_{2k,\,2k+1} < 0$ then the point M^* is stable.

The stationary point M^* is called **hyperbolic** if $\mathbb{R}e\lambda_{2k,2k+1} > 0$, and there are no imaginary eigenvalues in the linearization of the dynamical system at this point, i.e., none of these $\mathbb{R}e\lambda_{2s,2s+1}$ vanishes. Let M^* be hyperbolic. Denote by $2m$ the total amount of the eigenvalues λ_j with positive real parts, so

$$\text{if} \quad a \cdot \sin\frac{\pi \cdot \left(4\left[\frac{k}{2}\right] - 2k + 3\right)}{2(2k+1)} > 1, \quad \text{then} \quad m = \left[\frac{k+1}{2}\right]. \qquad (4)$$

Since the eigenvectors $\pm e_1$ of the linearization (3) show the directions from the point to the parallelepipeds $\{00\dots00\}$ and $\{11\dots11\}$, we can cut off the invariant domain $\mathcal{Q}_{4k+2}$ a small cylindric neighborhood $U = B^{2m} \times I^{2k+1-2m}$ of the point M^*. Same operation can be done with the invariant domain $\mathcal{P}_{4k+2}$. Here the plane containing a small ball B^{2m} corresponds to the eigenvalues λ_j with positive real parts, and the plane containing small parallelepiped $I^{2k+1-2m}$ corresponds to λ_1 and to other eigenvalues with negative real parts. Hence, the reduced domains $\mathcal{Q}'_{4k+2} = \mathcal{Q}_{4k+2} \setminus U$ and $\mathcal{P}'_{4k+2} = \mathcal{P}_{4k+2} \setminus U$ are invariant for the system (1) as well. According to the well-known "torus principle", we obtain the theorem:

Theorem 1. *If the stationary point M^* of the system* (1) *is hyperbolic then the invariant domain $\mathcal{P}'_{4k+2}$ contains at least one cycle of this system.*

Note that "torus principle" and the topological fixed point theorem do not imply stability or uniqueness of the cycle in this situation. However, in some cases this uniqueness and stability near the stationary points can be derived from the Andronov-Hopf bifurcation theorem.

As it was shown in [6], for each cycle of the system (1) its projection along any vector with positive coordinates does not have self-intersections. So, in visualization of such cycles of high-dimensional dynamical systems, it is convenient sometimes to consider projection of the trajectories along the vector e_1 or other vectors with positive coefficients.

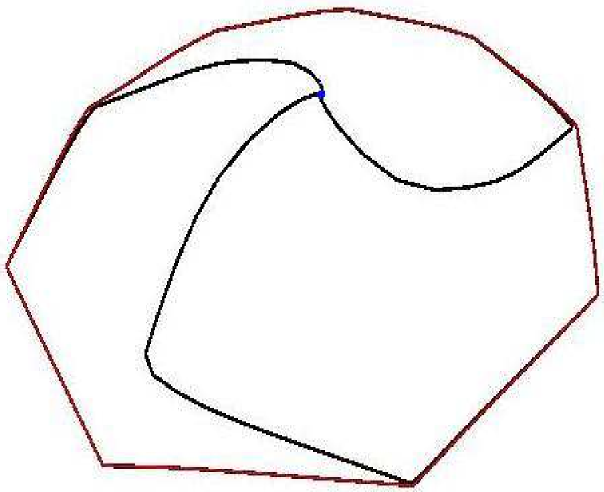

Figure 1: Projection of trajectories of 9-D system (5) onto 3-D plane $P_{1,8,9}$.

The figures 1, 2 show orthogonal projections of three trajectories of symmetric dynamical system of the type (1) in the case $k = 4$, onto 3-dimensional planes $P_{1,8,9}$ and $P_{1,6,7}$ corresponding to the eigenvalues λ_1 , λ_8, λ_9 and, respectively, λ_1 , λ_6, λ_7 of the linearization (3). In the similar way we define 2-dimensional planes $P_{8,9}$ and $P_{6,7}$ etc. The real eigenvalue $\lambda_1 < 0$ corresponds to the vertical direction on the figure 2, and

$$f_i(w) = \frac{130}{1 + w^n}, \quad \text{for all } \ i, \quad \mathbf{X}^* = (2, 2, 2, 2, 2, 2, 2, 2, 2) \in \mathbb{R}^9_+. \tag{5}$$

Here $n = 6$, and all these trajectories start "near" the 2-dimensional plane $P_{8,9}$ in a small neighborhood of the stationary point M^* . Projection of the cycle of the dynamical system on the figure 1 is the "9-gone", and on the figure 2 this cycle projects onto the curvilinear triangle at the bottom. The projection of the point M^* is in the center of the figure 1, and on the top of the figure 2.

Some results on stability of cycles in the phase portraits of the nonlinear dynamical systems of the type (1) can be obtained with the help of theorems of Russell Smith, see [10].

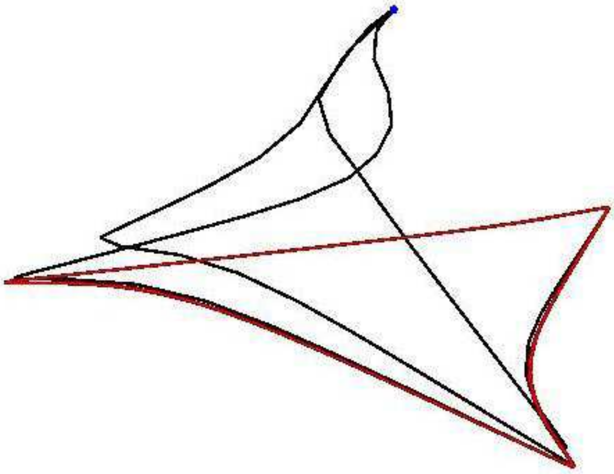

Figure 2: Projections of same trajectories onto 3-D plane $P_{1,6,7}$.

Theorem 2, ([4]). *If the conditions of the theorem* 1 *are satisfied and for some* $\eta > 0$ *and for all* i, $1 \le i \le 2k+1$, *the inequalities*

$$-\eta \cdot \Big(1+\sin\frac{2\pi}{2k+1}\cdot\sin\frac{\pi}{2k+1}\Big) < f_i'(x_{i-1}) < -\eta \cdot \Big(1-\sin\frac{2\pi}{2k+1}\cdot\sin\frac{\pi}{2k+1}\Big),$$

hold in the invariant domain $\mathcal{P}'_{4k+2}$ *then this domain* $\mathcal{P}'_{4k+2}$ *contains a stable cycle of the system* (1).

It is well-known (see [5]), that any nonlinear dynamical system is topologically equivalent to its linearization in **some small** neighborhood W of its **hyperbolic** stationary point. Consider linearization of symmetric dynamical system of the type (5). If the exponent n is sufficiently large, see (4), then

$$\mathbb{R}e\lambda_{4,\,5} \;<\; 0 \;<\; \mathbb{R}e\lambda_{6,\,7} \;<\; \mathbb{R}e\lambda_{8,\,9},$$

and hence, the 2-dimensional planes $P_{8,9}$ and $P_{6,7}$ are covered by unwinding trajectories of this linear dynamical system. Hence, the neighborhood W contains two invariant 2-dimensional manifolds of the system (5), which are covered by unwinding trajectories of this nonlinear dynamical system.

We have demonstrated in our numerical experiments, that in contrast with the figures 1 and 2, trajectories of the system (5) with starting points, say $M_{8,9}$ and $M_{6,7}$, "near" these two planes $P_{8,9}$ and $P_{6,7}$, respectively, have different limit cycles, as it is shown on the figure 3. The small curvilinear triangle here (it is red, as on the figure 2) is the projection of the limit cycle of the trajectory with starting point $M_{8,9}$, and the large (blue) triangle is that of the trajectory with starting point $M_{6,7}$. Both these triangles seem to be homothetic on this

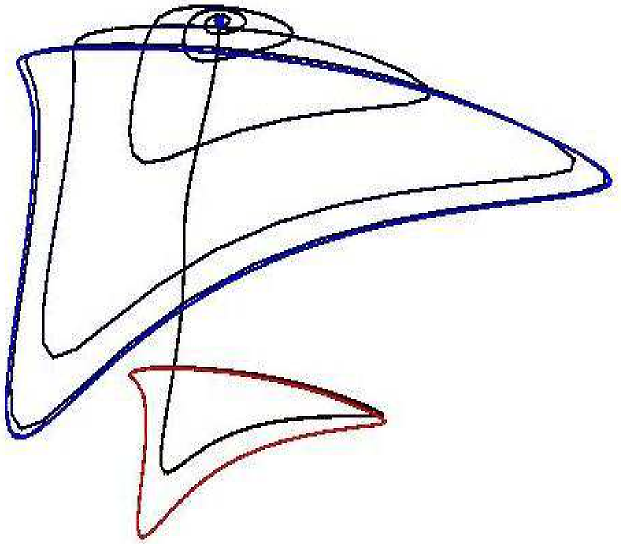

Figure 3: Projections of two cycles of the same system onto 3-D plane $P_{1,6,7}$.

picture, though the shapes of corresponding cycles in the ambient space $\mathbb{R}^9$ are quite different. The projection of the stationary point M^* is seen here on the top of the figure.

Note that near the point M^* the 2-dimensional plane $P_{8,9}$ is contained in the domain $\mathcal{P}_{4k+2}$, and the plane $P_{6,7}$ intersects $\mathcal{P}_{4k+2}$ just by one point, M^*.

Similar non-uniqueness of the cycles should be detected in higher-dimensional (and in asymmetric) analogues of the system (1). It seems to the authors that there are as many different cycles, as pairs of complex conjugate eigenvalues $\lambda_{2j},\ \lambda_{2j+1}$ of the linearization (3), such that $\mathbb{R}e\lambda_{2j,2j+1} > 0$. So, for sufficient large values of n, there should be two different cycles in the phase portrait of the system (5) (or (1)) in the cases $2k+1=7,\ 2k+1=9$. For $2k+1=11$, $2k+1=13$ there are three cycles etc., see (4). But, at the present time we do not have any proof of this hypothesis. All difficulties here happen outside of W.

3. More complicated gene networks models. The same approach can be used in considerations of models of gene networks with more complicated collections of feedbacks. We assume here that all the functions f_i are strictly monotonically decreasing, and each function Λ_j is unimodal and describes a combination of the negative and positive feedbacks, as above. Some particular 3-dimensional cases of such gene networks models were studied in [1].

Consider for example the dynamical system :

$$\begin{cases} \dfrac{dx_1}{dt} = f_1(x_l) - x_1, \\ \qquad \dots \quad \dots \\ \dfrac{dx_m}{dt} = f_m(x_{m-1}) - x_m, \\ \dfrac{dx_{m+1}}{dt} = \Lambda_{m+1}(x_m) - x_{m+1}, \\ \qquad \dots \quad \dots \\ \dfrac{dx_l}{dt} = \Lambda_l(x_{l-1}) - x_l. \end{cases} \tag{6}$$

in the case $l = 6$, $m = 5$. As in the proofs of the proposition 1 and the theorem 1, we find the stationary points. Let $\Psi(x_6) := f_5(f_4(f_3(f_2(f_1(x_6)))))$. Since this function strictly monotonically decreases, its inverse function Ψ^{-1} is well-defined. The stationary points $X^* = (x_1^*, x_2^*, x_3^*, x_4^*, x_5^*, x_6^*)$ of the system (6) are determined from the equation

$$\Lambda_6(\Psi(x_6^*)) = x_6^*,$$

and from $x_1^* = f_1^*(x_6^*),\ x_2^* = f_2^*(x_1^*)\ x_3^* = f_3^*(x_2^*),\ x_4^* = f_4^*(x_3^*),\ x_5^* = f_5^*(x_4^*)$. Let x_5^M be the maximum point of the unimodal function $\Lambda_6(x_5)$. If

$$\Psi^{-1}(x_5^M) < \Lambda(x_5^M), \tag{7}$$

then the system (6) has exactly one stationary point X^{*I} such that $x_5^{*I} < x_5^M$. In some applications this condition (7) is not satisfied, and we have here two more stationary points X^{*II} and X^{*III} such that $x_5^{*II} > x_5^M$ and $x_5^{*III} > x_5^M$. The behavior of trajectories of the system (6) near these two points is much more simple than near the point X^{*I}.

The derivatives of the functions f_i are negative, and we have the inequality $d\Lambda_6/dx_5 > 0$ near the point X^{*I}, so the linearization of the system (6) at this point has the following eigenvalues $\lambda_{3,4} = -1 \pm i \cdot a$, and
$\lambda_{1,2,5,6} = -1 + a \cdot [\pm \frac{\sqrt{3}}{2} \pm i \cdot \frac{1}{2}]$, where

$$a^6 = -\frac{df_1}{dx_6} \cdot \frac{df_2}{dx_1} \cdot \frac{df_3}{dx_2} \cdot \frac{df_4}{dx_3} \cdot \frac{df_5}{dx_4} \cdot \frac{d\Lambda_6}{dx_5}.$$

As above, all derivatives here are calculated at the stationary point X^{*I}. Thus, we can construct its invariant neighborhood

$$Q = [x_1^-, x_1^+] \times [x_2^-, x_2^+] \times [x_3^-, x_3^+] \times [x_4^-, x_4^5] \times [x_5^-, x_5^+] \times [x_6^-, x_6^+].$$

Its boundaries are determined as follows: x_6^- and x_6^+ are the proximate to x_6^{*I} solutions of the equation $\Lambda_6(\Psi(\Lambda_6(\Psi(x_6)))) = x_6$, i.e., $x_6^* \in [x_6^-, x_6^+]$. In the same way we define other segments $I_j = [x_j^-, x_j^+]$. So, $x_1^- = \min\limits_{x_6 \in I_6} f_1(x_6)$;

$x_1^+ = \max\limits_{x_6 \in I_6} f_1(x_6)$; $x_2^- = \min\limits_{x_1 \in I_1} f_2(x_1)$, $x_2^+ = \max\limits_{x_1 \in I_1} f_2(x_1)$; etc.

As in the proof of the theorem 1, we decompose the invariant neighborhood Q by the hyperplanes parallel to the coordinate ones and containing the stationary point X^{*I}. In this domain Q the unimodal function Λ_6 satisfies the conditions:

If $\mathbf{X} \in Q$ then $\Lambda_5(x_5) < x_6^{*I}$ for $x_5 < x_5^{*I}$ and $\Lambda_5(x_5) > x_6^{*I}$ for $x_5 > x_5^{*I}$. Hence, the trajectories transition rules from one small parallelepiped in this decomposition to another remain almost the same, as in the proposition 2. The direction of this transition changes to the opposite one at the points of the hyperplane $x_5 = x_5^{*I}$ only. So, we get a diagram, analogous to (2):

$$\begin{tikzcd}
\{101010\} \arrow[r] & \{101011\} \arrow[r] & \{001011\} \arrow[r] & \{011011\} \arrow[r] & \{010011\} \arrow[d] \\
\{101000\} \arrow[u] & & & & \{010111\} \arrow[d] \\
\{101100\} \arrow[u] & \{100100\} \arrow[l] & \{110100\} \arrow[l] & \{010100\} \arrow[l] & \{010101\} \arrow[l]
\end{tikzcd}$$

The union $Q_{(12)}$ of these 12 parallelepipeds is an invariant domain of (6).

Theorem 3. *If* $a \cdot \cos\frac{\pi}{6} > 1$*, and the condition* (7) *is satisfied then the 6-dimensional dynamical system* (6) $(l = 6, m = 5)$ *has a cycle in* $Q_{(12)}$.

This theorem is proved exactly as the theorem 1. The figure 4 shows projections of three trajectories of the system (6) onto 3-D plane corresponding to the eigenvalues λ_1, λ_2 and λ_6. These trajectories start near the stationary point and tend to the limit cycle. Here

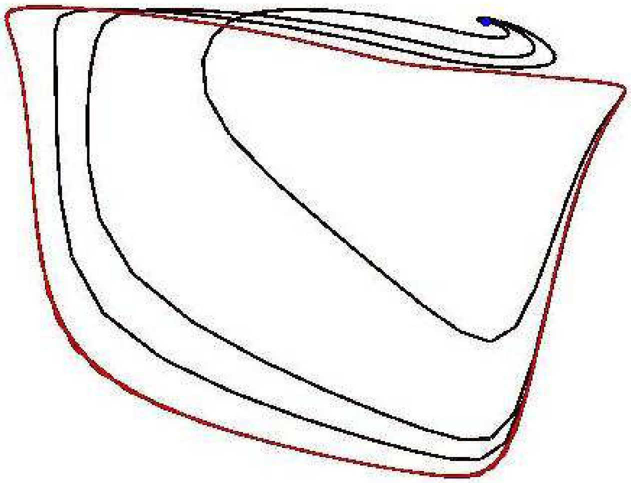

Figure 4: Projections of trajectories of the system (6) onto 3-D plane $P_{1,2,6}$.

$$f_1(x_6) = \frac{7}{1 + x_6^3}; \quad f_2(x_1) = \frac{7}{1 + x_1^3}; \quad f_3(x_2) = \frac{8}{1 + x_2^3};$$

$$f_4(x_3) = \frac{12}{1+x_3^3}; \quad f_5(x_4) = \frac{11}{1+x_4^3}; \quad \Lambda_6(x_5) = \frac{18x_5}{1+x_5^2}.$$

Similar results can be obtained for other dynamical systems of the type (6) using the same approach. In particular, we can make there any permutation of the equations. An analogue of the theorem 2 can be obtained for the dynamical systems of the type (6) as well.

All numerical experiments and figures in the present paper were realized by the Program **GeneNetworkModeller** composed by A.A.Akinshin.

References

[1] Gaidov Yu.A., Golubyatnikov V.P., Likhoshvai V.A. On some nonlinear dynamical systems modeling asymmetric gene networks models. Part 2. (Russian), *Bull. Novosibirsk State University*, 2007, v. 10, N. 1, p. 18 – 28.

[2] Golubyatnikov V.P.,Likhoshvai V.A., Fadeev S.I., Ratushny A.V., Matushkin Yu.G., Kolchanov N.A. Mathematical and Computing modeling of genetic networks. *Proc. 6-th Internat. conf. "Human and Computers"*, University of Aizu, Japan, 2003. p. 200 – 205.

[3] Golubyatnikov V.P. V.A.Likhoshvai, A.V.Ratushny Existence of Closed Trajectories in 3-D Gene Networks. *The journal of three dimensional images 3D Forum*, Japan, 2004, v. 18, N. 4, p. 96 – 101.

[4] Golubyatnikov V.P., Golubyatnikov I.V. On periodic trajectories of nonlinear dynamical systems of a special type. (Russian) *Herald of Novosibirsk state university*, 2010, v. 10, N. 3, p. 3 – 16.

[5] Hartman Ph. Ordinary differential equations. New York, 1964.

[6] Hirsch M.W. Systems of differential equations which are competetive or cooperative. I: limit sets. *SIAM Journal Math.Anal.*, 1982, v. 13, N. 2, p. 167 – 179.

[7] Computational systems biology, Eds. Kolchanov N.A., Goncharov S.S. Novosibirsk, SB RAS, 2008, 667 pp.

[8] Mackey M.C., Glass L. Oscillation and chaos in physiological control systems. *Science*, 1977, v.15, N 2, p. 287 – 289.

[9] Murray J.D. Mathematical biology. 1. An introduction. 3-d Edition. NY, Springer-Verlag, 2002.

[10] Smith R.A. Orbital Stability for Ordinary Differential Equations. *Journ. of Differential Equations.* 1987. v. 69. P. 265 – 287.