

## Existence and stability of closed cycles in nonlinear dynamical systems of kinetic type

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### 1. Introduction

The main goal of this work is to give mathematical explanation of some of numerical experiments with periodic trajectories and other stationary regimes in gene networks models, see [1 – 7]. These experiments were performed in collaboration of Sobolev Institute of Mathematics and Institute of Cytology and Genetics of SB RAS. Inverse problems of determination of regulatory mechanisms of the gene networks and the parameters of corresponding nonlinear dynamical systems from behavior of their trajectories and from other qualitative properties of their phase portraits naturally appear in this gene networks modeling in quite different situations.

One of the most significant properties of all these gene networks models is multistability. So, we are interested in estimates of possible number of the stationary points of corresponding dynamical systems and, especially, in estimates of the number of their limit cycles and description of behavior of other their trajectories because the natural biological processes occur usually in a periodic manner (circadian rhythm, mitotic oscillations, cell cycle engine etc). This is very important from the viewpoint of the gene networks and molecular parallel computing design for the needs of biotechnology, pharmacogenetics, gene therapy [8] and, particularly, for construction of the “biological computers”, which constitute the principal tool of all these practical applications.

### 2. Mathematical models.

a. We consider here the following 3-dimensional nonlinear dynamical systems as kinetic models of the gene networks regulation with negative feedbacks

$$\dot{x} = \Phi_1(z, x), \quad \dot{y} = \Phi_2(x, y), \quad \dot{z} = \Phi_3(y, z). \quad (1)$$

Here  $\Phi_i$  are sufficiently smooth and monotonically decreasing with respect to both their arguments so, that  $x \equiv x_1, y \equiv x_2, z \equiv x_3 \in [0, \infty)$ . We assume that  $\Phi_i(x_{i-1}, 0) > 0$  and  $\frac{\partial \Phi_i}{\partial x_i}(x_{i-1}, x_i) \leq \delta_i < 0$ . Here and below, for  $i = 1, x_{i-1} \equiv x_3$ . As usual, the biochemical variables  $\mathbf{X}(t) = \{x(t), y(t), z(t)\}$  denote the concentrations of the components in the gene network and have nonnegative values. For all nonlinear dynamical systems here and below we shall use sometimes their vector form  $\dot{\mathbf{X}} = \Phi(\mathbf{X})$ .

Similar dynamical systems can be studied in higher dimensional spaces, see [3,6,7,10]. The system (1) and each of its odd-dimensional analogues has a unique stationary point  $M_*$ ,  $\Phi(M_*) = 0$ . One can verify that its topological index, i.e. the index of the vector field  $\Phi$  at this point, equals  $-1$ .

b. Another wide class of the gene networks models which we continue to study here contains combinations of positive and negative feedbacks in the gene networks regulation. These combinations of different feedbacks appear in various natural and artificial gene networks, see for example [5,6,8,9]. As it was noted in [8], the absence of the positive feedbacks makes the functioning of a gene networks much more stable. One important

and typical example of these models with different feedbacks is described by the Glass-Mackey dynamical system ([9]):

$$\dot{x} = \frac{\alpha z}{1 + z^\gamma} - x, \quad \dot{y} = \frac{\alpha x}{1 + x^\gamma} - y, \quad \dot{z} = \frac{\alpha y}{1 + y^\gamma} - z. \quad (2)$$

Here  $\alpha > 0$ ,  $\gamma > 1$ . Let  $g(w) := \frac{\alpha w}{1 + w^\gamma}$ . As in [3], just for simplicity of exposition, we restrict here our description of the Glass-Mackey system to the case symmetric with respect to cyclic permutation of the variables  $x \rightarrow y \rightarrow z \rightarrow x$ . Actually, we can extend our considerations to the dynamical systems of this type with other uni-modal right-hand sides and to asymmetric dynamical systems, see [3,4]. So, in all formulas containing  $g(w)$  below, we shall keep in mind more general cases as well.

Numerical experiments with these systems have shown that for sufficient large values of  $\alpha$  and  $\gamma$  they have four limit cycles, see [3]. One of them  $C_\Delta$  turns around the diagonal  $\Delta = \{x = y = z\}$  of the positive octant, three other cycles  $C_x$ ,  $C_y$  and  $C_z$  are located near the axes  $Ox$ ,  $Oy$  and  $Oz$  respectively and turn around stationary points with topological index  $-1$ . We shall give here mathematical explanation of these experimental observations.

### 3. Existence of cycles.

**a.** First, we describe the asymmetric gene networks models with negative feedbacks. Let  $\alpha_i = \Phi_i(0,0)$  be the maximal value of the function  $\Phi_i$  in the dynamical system (1). All its trajectories eventually enter some parallelepiped  $\Pi = [\varepsilon_1, D_1] \times [\varepsilon_2, D_2] \times [\varepsilon_3, D_3]$ . Hence,  $\Pi$  is a positively invariant domain of the system (1). Here, one can start with the most simple estimates  $\varepsilon_i = 0$  and  $D_i = \alpha_i/\delta_i$ . The best values of  $\varepsilon_i$  and  $D_i$  satisfy the equations

$$\Phi_i(D_{i-1}, \varepsilon_i) = 0, \quad \Phi_i(\varepsilon_{i-1}, D_i) = 0, \quad i = 1, 2, 3; \quad \text{for } i = 1, \quad i - 1 := 3.$$

Consider the planes parallel to the coordinate planes and containing the stationary point  $M_* = (x_*, y_*, z_*)$  of the system (1). They compose the subdivision  $\Pi = \bigcup Q_{abc}$ , where

$$Q_{abc} = \{x \in \Pi \mid x \geq_a x_*, y \geq_b y_*, z \geq_c z_*\},$$

$a, b, c \in \{0, 1\}$ , the symbol  $\geq_0$  denotes  $\leq$ , and  $\geq_1$  denotes  $\geq$ . Direct calculations show that the parallelepipeds  $Q_{000}$  and  $Q_{111}$  can be excluded from the invariant domain. The union of remaining 6 parallelepipeds  $\tilde{\Pi} \subset \Pi$  is again a positively invariant domain of the system (1). Denote their common faces as follows:  $F_{001} = Q_{001} \cap Q_{011}$ ,  $F_{011} = Q_{011} \cap Q_{010}$ ,  $F_{010} = Q_{010} \cap Q_{110}$  etc. The shifts along the trajectories of the system (1) define a sequence of smooth mappings

$$\dots \rightarrow F_{001} \rightarrow F_{011} \rightarrow F_{010} \rightarrow F_{110} \rightarrow F_{100} \rightarrow F_{101} \rightarrow F_{001} \rightarrow \dots \quad (3)$$

Similar diagram was constructed in [10] for quite different class of dynamical systems which describe genetic regulatory mechanisms.

The characteristic equation of linearization of the system (1) in a neighborhood of the point  $M_*$  has one negative eigenvalue  $\lambda_1 < 0$  corresponding to an eigenvector  $e_1$  with positive coordinates. Let  $\lambda_2, \lambda_3$  be its other eigenvalues. In the case  $\text{Re}\lambda_2, \text{Re}\lambda_3 < 0$ , the point  $M_*$  is stable and attracts all trajectories of this system.

Let  $\text{Re}\lambda_2, \text{Re}\lambda_3 > 0$ . In this case the stationary point  $M_*$  is unstable. Since the vectors  $\pm e_1$  are directed from  $M_*$  into  $Q_{000}$  or  $Q_{111}$ , the invariant domain of our system can be reduced to a smaller domain  $(\tilde{\Pi} \setminus U)$  where  $U$  is some neighborhood of the point  $M_*$ . Consider the intersection  $F' = (\tilde{\Pi} \setminus U) \cap F_{001}$  and composition  $\varphi_6$  of 6 consecutive shifts  $\varphi_6 : F_{001} \rightarrow F_{001}$  in (3) which maps the compact contractible set  $F'$  into itself  $\varphi_6 : F' \rightarrow F'$ . The well-known torus principle and Brouwer's fixed point theorem imply existence of at least one point  $M_0 \in F'$  such that  $\varphi_6(M_0) = M_0$ . So, trajectory of this point is a closed cycle, and we have proved

**Theorem 1.** *If  $\text{Re}\lambda_2, \text{Re}\lambda_3 > 0$ , then the dynamical system (1) has at least one periodic trajectory in the invariant domain.*

If  $\Phi_i(u, w) = f_i(u) - w$ , then this invariant domain  $\tilde{\Pi}$  can be reduced to the union of 6 trihedral prisms  $P_{abc} \subset Q_{abc}$ ,  $1 \leq a + b + c \leq 2$  spanned on the intersections listed in the sequence (3). Each of these prisms  $P_{abc}$  is obtained by excising from  $Q_{abc}$  along one of its diagonal planes and contains the point  $M_*$ , see [4]. Further reductions of this invariant domain can be realized as well.

**b.** We describe now the gene networks models of the Glass-Mackey type. Let  $\alpha$  and  $\gamma$  in the dynamical system (2) be sufficiently large. Consider the graph of the uni-modal function  $u = g(w)$  on the plane  $Owu$  and the graphs of its iterations  $u = g^{(2)}(w) = g(g(w))$  and  $u = g^{(3)}(w) = g(g(g(w)))$ . Denote by  $a$  the maximal value of  $g(w)$  for all positive  $w$  and let  $g(w_M) = a$ . Now, denote by  $w_2, w_6$  ( $w_2 < w_6$ ) all possible solutions of the equation  $g(w) = w_M$ . So  $g^{(2)}(w_2) = g^{(2)}(w_6) = a$ . Let  $w_1 < w_3 < w_5 < w_7$  be all possible solutions of the equation  $g^{(2)}(w) = w_M$ , or  $g^{(3)}(w) = a$ .

All stationary points of the system (2) and dynamical systems with similar uni-modal right-hand sides can be determined from the intersections of the diagonal line  $u = w$  with the graph of the iteration  $u = g^{(3)}(w)$ . Let  $0 < s_1 < s_2 < s_3 < s_4 < s_5 < s_6 < s_7$  be the  $w$ -coordinates of these consecutive intersections and denote by  $M_0, M_1, M_2, M_3, M_4, M_5, M_6, M_7$  corresponding stationary points ( $\Phi(M_i) = 0$ ), here  $M_0$  is the origin. It is not difficult to see that

$$g(a) < w_1 < s_1 < w_2 < s_2 < w_3 < s_3 < w_M < s_4 < w_5 < s_5 < w_6 < s_6 < w_7 < s_7 < a.$$

Simple analysis of linearizations of the systems of the type (2) in the neighborhoods of all these points  $M_i$ ,  $i = 0, \dots, 7$ , shows that the topological index of the vector field  $\Phi$  at the points  $M_1, M_3, M_5, M_7$  which correspond to the intersections of the line  $u = w$  with four descending parts of the graph of  $u = g^{(3)}(w)$  equals  $-1$ .

It follows from the estimates of the coordinates  $s_i$  that the point  $M_5$  is contained in the diagonal  $\Delta$ , all its coordinates satisfy the equation  $s_5 = g(s_5)$ . Other stationary points  $M_2, M_4, M_6$  which correspond to the intersections of the line  $u = w$  with the ascending parts of the graph of  $u = g^{(3)}(w)$  are located outside of  $\Delta$  and have topological index  $+1$ , so the total index of the vector field  $\Phi(\mathbf{X})$  on the boundary of the domain which is obtained from the parallelepiped  $0 \leq x, y, z \leq a$  by cutting off some small neighborhood of the origin equals  $-1$ .

Let  $w_8$  be the unique solution of the equation  $g(w_8) = w_7$  on the interval  $(0, w_M)$ . Consider the parallelepipeds

$$\Pi_z : \quad g(a) \leq x \leq w_2, \quad w_8 \leq y \leq w_M, \quad w_7 \leq z \leq a;$$

$$\Pi_x : \quad g(a) \leq y \leq w_2, \quad w_8 \leq z \leq w_M, \quad w_7 \leq x \leq a;$$

$$\Pi_y : \quad g(a) \leq z \leq w_2, \quad w_8 \leq x \leq w_M, \quad w_7 \leq y \leq a.$$

One can verify that  $M_1 \in \Pi_z$ ,  $M_3 \in \Pi_y$ ,  $M_7 \in \Pi_x$  and that all these parallelepipeds are invariant domains of the system (2).

**Theorem 2.** *If the parameters  $\alpha$  and  $\gamma$  are sufficiently large and if linearization of the system (2) in one of its stationary points  $M_1, M_3, M_7$  has one negative eigenvalue and two complex eigenvalues with positive real parts, then the dynamical system (2) has at least one periodic trajectory in each of three parallelepipeds  $\Pi_x, \Pi_y, \Pi_z$ .*

Restrictions of the phase portrait of the system (2) on these polyhedral domains are symmetric each other with respect to the cyclic permutations of the variables, so the cycles  $C_z \subset \Pi_z$ ,  $C_y \subset \Pi_y$ ,  $C_x \subset \Pi_x$  map each to other by rotations around  $\Delta$  by the angles  $120^\circ$  and  $240^\circ$ .

Same considerations can be realized for other dynamical systems of the type (2) with other similar uni-modal right-hand sides. Some sufficient condition for existence of the cycle  $C_\Delta$  in these systems were described in [3].

#### 4. Andronov-Hopf bifurcation.

Brouwer's fixed point theorem does not guarantee uniqueness and stability of the cycles in the theorems 1 and 2. Simple numerical experiments, see for example [2,5], show that the trajectories of the systems of

the types (1) and (2) do not approach to the limit cycles monotonically, so, their stability can not be proved with the help of elementary estimates. In some particular cases, for small positive values of  $\text{Re}\lambda_2, \text{Re}\lambda_3$ , uniqueness and stability of this cycle in a small neighborhood of the stationary point  $M_*$  can be obtained by methods of the well-known Andronov-Hopf bifurcation theory. An explicit formula for the first Lyapunov parameter  $\nu_1$  was obtained in [7] for the gene networks models with negative feedbacks, i.e. for symmetric dynamical systems (1) with the right-hand sides of the type

$$\Phi_1(z, x) = f(z) - x; \quad \Phi_2(x, y) = f(x) - y; \quad \Phi_3(y, z) = f(y) - z. \quad (4)$$

The case particularly interesting for biologists  $f(w) = \frac{\alpha}{1 + w^\gamma}$  was studied there, and the domain of parameters corresponding to  $\nu_1 < 0$  was described. This inequality implies stability the bifurcation cycle in the system (1), (4), see also [1,2]. In the case of asymmetric dynamical system (1), (4) of the general type the explicit analytic expression for  $\nu_1$  becomes too cumbersome, but it is easily used in the analysis of the numerical experiments.

Similar results on existence of periodic trajectories, their bifurcations and stability of the bifurcation cycles can be obtained for other odd-dimensional asymmetric dynamical systems of the types (2), (4) and for more complicated right-hand sides of these systems as well, see for example [3 – 5]. The even-dimensional dynamical systems of these types have usually several stationary points, so their analysis and description of corresponding separatrix surfaces are more complicated, as one could see in the studies of the Glass-Mackey gene networks models in the previous section.

### 5. Stability of cycles.

Following R.A.Smith [11], consider the vector form of the dynamical system (1) as a model of gene networks with negative feedbacks

$$\frac{d\mathbf{X}}{dt} = A \cdot \mathbf{X} + \Psi(\mathbf{X}), \quad (5)$$

where

$$A = \begin{pmatrix} -1 & 0 & -4\eta \\ -4\eta & -1 & 0 \\ 0 & -4\eta & -1 \end{pmatrix}, \quad \Psi(\mathbf{X}) = \begin{pmatrix} 4\eta \cdot z + f_1(z) \\ 4\eta \cdot x + f_2(x) \\ 4\eta \cdot y + f_3(y) \end{pmatrix}.$$

Here  $\eta$  is a positive constant and the functions  $f_i$  are monotonically decreasing as above.

One of the eigenvalues of the constant matrix  $A$  equals  $(-1 - 4\eta)$  and corresponds to the diagonal eigenvector  $e_1 = (1, 1, 1)$ . The real parts of its other two complex eigenvalues equal  $(-1 + 2\eta)$ . Let  $\nu$  be a real number such that  $-4\eta < \nu < 2\eta$  and let  $E$  be the unit  $3 \times 3$  matrix. Consider the transfer matrix  $\chi(i\omega - 1 + \nu) := ((i\omega - 1 + \nu)E - A)^{-1}$ , its norm  $|\chi(i\omega - 1 + \nu)|$ , and let

$$\mu(\nu) = \sup |\chi(i\omega - 1 + \nu)| \quad \text{for} \quad -\infty < \omega < \infty.$$

Now let  $\nu = -\eta$ . Direct and very long calculations show that  $\mu(-\eta) = \frac{1}{3\eta}$ . Denote by  $\Psi'_X$  the Jacobi matrix of the vector function  $\Psi(\mathbf{X})$ , let  $|\Psi'_X| = \max_i \sup_X |4\eta + f'_{i+1}(x_i)|$ ,  $i = 1, 2, 3$  be its norm.

It was shown in [11], that the condition  $|\Psi'_X| < (\mu(\nu))^{-1}$  is sufficient for stability of a periodic trajectory in the system (5), and it was indicated there that this estimate is not best possible! Anyway, using our estimates of the norm of the transfer matrix we obtain

**Theorem 3.** *If the system (5) satisfy the conditions of the theorem 1, and for all points  $M(x, y, z)$  in the invariant domain the following estimate is valid*

$$-7\eta < f'_{i+1}(x_i) < -\eta, \quad i = 1, 2, 3,$$

*then this system (5) has at least one periodic trajectory which is orbitally stable in the invariant domain.*

More narrow stability estimate for dynamical systems of a similar type symmetric with respect to the cyclic permutations of the variables ( $f_1 = f_2 = f_3$ ) was obtained in [12] in the case  $\nu = 0$  which is not so hard from the analytical viewpoint. After all calculations of the norm of the transfer matrix  $\chi(i\omega - 1 + \nu)$  it becomes clear that the value  $\nu = -\eta$  mentioned above gives the maximal width of the stability estimate in the theorem 3 in the frame of the approach proposed by R.A.Smith.

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