ASYMMETRIC MODELS OF THE GENE NETWORKS

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SUMMARY

Motivation: Detection of closed trajectories in particular dynamical systems is a hard mathematical problem. We considered it in our previous publications in the case of symmetric dynamical systems as models of the gene networks. It is necessary now to study the general asymmetric gene networks because natural biological processes occur usually in a periodic manner (end-product repression of mRNA synthesis, circadian rhythm, mitotic oscillations, cell cycle engine etc) and do not have any symmetries.

Results: We extend our previous investigations to a much more wide class of the gene network models which are not assumed to be symmetric. We prove existence of periodic trajectories of corresponding dynamical systems. Description of the Andronov-Hopf bifurcation in these models is given as well.

INTRODUCTION

Our main aim is to give a rigorous mathematical explanation of some numerical experiments concerning the limit-cycle oscillations of the gene networks with negative feedbacks described in Likhoshvai et al. (2001) and Golubyatnikov et al. (2006a, b). In these publications, the right-hand sides of corresponding differential equations were represented by the Hill’s functions $F(\bar{x})/G(\bar{x})$ where the variables $\bar{x}$ denote the concentrations of the components, $F$ and $G$ are polynomials with positive coefficients. Most of results obtained there concerned symmetric gene network models. Now, we study more general and more complicated right-hand sides of the equations.

MODEL

We continue our studies (Golubyatnikov et al., 2005, 2006a) of special dynamical systems as models of the gene networks regulated by negative feedback control loop on the stages of initiation of the mRNA and/or protein synthesis. Consider 3-dimensional nonlinear dynamical system of a general type:

$$\frac{dx_1}{dt} = f_1(x_1) - x_1; \quad \frac{dx_2}{dt} = f_2(x_2) - x_2; \quad \frac{dx_3}{dt} = f_3(x_3) - x_3. \quad (1)$$
Here the functions \( f_1(x_1), f_2(x_2), f_3(x_3) : [0, \infty) \to (0, \infty) \) are assumed to be smooth and monotonically decreasing so that \( f_1(u) \to 0 \), as \( u \to \infty \). This system has exactly one stationary point \( M = (x_1^*, x_2^*, x_3^*) \) in the positive octant. Linearization of (1) near its stationary point is described by the matrix

\[
A = \begin{pmatrix}
-1 & 0 & -p_1 \\
-p_2 & -1 & 0 \\
0 & -p_3 & -1
\end{pmatrix}, \quad -p_i = \frac{df_i}{dx_{(i-1)}}(x_{(i-1)})^r.
\]

We assume here and in the sequel that \( x_{(i-1)} = x_3 \) for \( i=1 \) and denote by \( P \) the product \( p_1 p_2 p_3 \). One of eigenvalues of this matrix \( A \) is negative, \( \lambda_1 = -1 - \sqrt[3]{P} \) and corresponds to an eigenvector \( e_1 \) with positive coordinates. Other its eigenvalues are complex,

\[
2 \text{Re} \lambda_2 = 2 \text{Re} \lambda_3 = \sqrt{3} \sqrt[3]{P} - 2, \quad 2 \text{Im} \lambda_{2,3} = \pm \sqrt{3} \sqrt[3]{P}.
\]

Let \( Q = [0, f_1(0)] \times [0, f_2(0)] \times [0, f_3(0)] \). One can verify that this parallelepiped is positively invariant with respect to trajectories of the system (1). Following (Hastings et al., 1977), where quite different types of dynamical systems were studied, consider subdivision \( Q = \bigcup S_{ij} \) \( i, j, k = 0,1 \). Here the parallelepipeds \( S_{ijk} \) are defined as:

\[
S_{000} = \{ x_1 \leq x_1^*; x_2 \leq x_2^*; 0 \leq x_3 \leq x_3^* \}, \\
S_{100} = \{ x_1 \leq x_1^*; 0 \leq x_2 \leq x_2^*; 0 \leq x_3 \leq x_3^* \}, \\
S_{101} = \{ x_1 \leq f_1(0); 0 \leq x_2 \leq x_2^*; 0 \leq x_3 \leq x_3^* \},
\]

etc.

Subscript 0 on the \( m \)-th place means that \( S_{ij} \) borders on the face \( x_m = 0 \) of \( Q \) and subscript 1 on this place means that \( S_{ij} \) borders on the face \( x_m = f_1(0) \) of \( Q \). Note that the vectors \( \pm e_1 \) show the directions from \( M \) into the parallelepipeds \( S_{000} \) and \( S_{111} \).

**RESULTS AND DISCUSSION**

1. Denote by \( F \) the face \( x_2 = x_2^* \) of the parallelepiped \( S_{011} \). Direct calculations show that trajectories of all points of its face \( x_3 = x_3^* \) enter the parallelepiped \( S_{010} \) and that trajectories of all other faces of \( S_{011} \) enter \( S_{011} \). Now, consider the parallelepiped \( S_{010} \). As above, for all points of its face \( x_1 = x_1^* \), their trajectories enter the parallelepiped \( S_{110} \) and trajectories of the points of all other faces of \( S_{010} \) enter \( S_{010} \). After six steps of these shifts along these trajectories \( S_{011} \to S_{010} \to S_{110} \to S_{100} \to S_{101} \to S_{001} \to S_{011} \) we see that trajectories of all points of \( F \subseteq S_{001} \) enter \( S_{011} \) and trajectories of all points of other faces of \( S_{001} \) enter \( S_{011} \), so we get a continuous mapping \( \varphi : F \to F \), \( F = S_{011} \cap S_{001} \).

Let \( S_6 \) be the union of all these 6 parallelepipeds above. If \( P > 8 \), then \( \text{Re} \lambda_{2,3} > 0 \) and the stationary point \( M \) has a small open neighborhood \( U \) such that all points in \( U \cap S_6 \) are moved off \( M \) during the shifts along the trajectories of (1).
Let \( F' = F \setminus (F \cap U) \).

This compact contractible set is homeomorphic to disc. Now, \( \varphi \) maps \( F' \) into \( F' \), and the fixed point theorem implies existence of at least one point \( M_0 \) in \( F' \) such that \( \varphi(M_0) = M_0 \).

Clearly, the trajectory of this point \( M_0 \) is a closed cycle and we get

**Theorem**  If \( P > 8 \), then the system (1) has at least one periodic trajectory.

2. Denote by \( W(\bar{x}) \) vector field with coordinates \( f_1(x_1), f_2(x_1), f_3(x_1) \), so
\[
\frac{d\bar{x}}{dt} = W(\bar{x}) - \bar{x}
\]
is the vector form of the system (1). Since \( \text{div}(W(\bar{x}) - \bar{x}) = -3 \), the volume of any bounded domain in \( \mathbb{R}^3 \) decreases during the shifts along the trajectories exponentially: \( V(t) = V_0 \cdot e^{-3t} \). Note, that the fixed point theorem and this exponential decreasing do not imply immediately stability or uniqueness of the cycle in our theorem. Nevertheless, numerical experiments with the systems of the type (1) show these stability and uniqueness:

The Fig. 1 demonstrates trajectories convergent to this cycle in the cases of

\[
\begin{align*}
f_1'(z) &= \frac{6}{1 + z^2}; & f_2'(x) &= \frac{3}{1 + x}; & f_3'(y) &= 7e^{-5y}, \quad \text{(left)}; \\
f_1'(z) &= \frac{6}{1 + z^2}; & f_2'(x) &= \frac{3}{1 + x}; & f_3'(y) &= \frac{7}{1 + y^3}, \quad \text{(right)}. 
\end{align*}
\]

The big black points in the centers of the pictures indicate positions of the stationary points of these systems. Similar behavior of trajectories was observed in other numerical experiments with the system (1) and in natural gene networks (Elowitz, Leibner, 2000).

3. Let \( \alpha \) be a real parameter. Consider the dynamical system

\[
\begin{align*}
\frac{dx}{dt} &= f_1(x, \alpha) - x_1; \\
\frac{dy}{dt} &= f_2(x, \alpha) - x_2; \\
\frac{dz}{dt} &= f_3(x, \alpha) - x_3.
\end{align*}
\]

**Figure 1.** Closed cycles of the system (1).
We assume that for all values of $\alpha$ the functions $f_i$ are smooth and monotonically decreasing as in the case of (1). Let $\alpha = \alpha_0$ corresponds to $P = P(\alpha_0) = 8$, this is equivalent to $\text{Re} \lambda_{2,3} = 0$. As in (Golubyatnikov et al., 2006; Volokitin, 2004), the bifurcation theorem implies that if $D_0 \equiv \frac{dP}{d\alpha}(\alpha_0) \neq 0$, and $(\alpha - \alpha_0) \cdot D_0$ is positive and sufficiently small, then the system (2) has a bifurcation cycle in a neighborhood of the point $M_* = M_*(\alpha)$.

4. Analogous results on periodic trajectories and their bifurcations can be obtained for more general type of dynamical systems

$$\frac{dx_1}{dt} = f_1(x_1) - g(x_1)$$
$$\frac{dx_2}{dt} = f_2(x_1) - g(x_2)$$
$$\frac{dx_3}{dt} = f_3(x_2) - g(x_3),$$

where the functions $f_i$ are as above and the function $g$ is monotonically increasing.

Similar considerations can be done for other odd-dimensional asymmetric gene network models with the help of sequences $\varphi$ of the shifts much more complicated than in (Hastings et al., 1977). Biological significance of these mathematical studies and their direct relations to negative feedback oscillations in natural gene networks is discussed in (Elowitz, Leibner, 2000; Likhoshvai et al., 2001).

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