GENE NETWORK MODELS
WITH DIFFERENT TYPES OF REGULATION

Golubyatnikov V.P.*, Gaidov Yu.A.2, Kleshchev A.G.1, Volokitin E.P.1
1 Institute of Mathematics, SB RAS, Novosibirsk, 630090, Russia; 2 Novosibirsk State University, Novosibirsk, 630090, Russia
* Corresponding author: e-mail: glbtm.math.nsc.ru

Key words: dynamical system, negative feedback, transcriptional regulation, post-transcriptional regulation, periodic trajectory, fixed point theorem, Andronov-Hopf bifurcation

SUMMARY

Motivation: Determination of periodic trajectories and stationary regimes in gene network models with various types of regulation of their functioning, investigation of their properties are fundamental and challenging problems of bioinformatics.

Results: We prove existence of closed trajectories and describe their bifurcations for a wide class of asymmetric gene network models where the regulation of each of their element is controlled by the post-transcriptional mechanism. These results can be generalized to the case of the gene networks of mixed types, where this regulation is effected either at the stages of initiation of mRNA and proteins synthesis or at the stages of their degradation.

INTRODUCTION

We consider nonlinear dynamical systems as models of gene networks with negative feedbacks which are realized at the stages of degradation of protein synthesis, i.e. are described by the post-transcriptional regulation mechanism. Our previous publications (Golubyatnikov et al., 2005, 2006a) were devoted to the investigations of much more restricted classes of these models, in particular all corresponding dynamical systems were assumed to be symmetric and to have a very special type. Here we continue our studies in a more wide class of gene network models.

IMPLEMENTATIONS AND RESULTS

1. We start with consideration of 3-dimensional nonlinear dynamical system of a general type:

\[
\begin{align*}
\frac{dx_1}{dt} &= \alpha_1 - x_1 \cdot g_1(x_1) \\
\frac{dx_2}{dt} &= \alpha_2 - x_2 \cdot g_2(x_2) \\
\frac{dx_3}{dt} &= \alpha_3 - x_3 \cdot g_3(x_3)
\end{align*}
\]

(1)

Here \( \alpha_j > 0, x_j \geq 0, j = 1, 2, 3 \) and the functions \( g_1(x), g_2(x), g_3(x) : [0, \infty) \to [1, \infty) \) are smooth and monotonically increasing so that \( g_i(0) = 1 \) for all \( i = 1, 2, 3 \). It follows from the monotone behavior of these functions that the system (1) has exactly one stationary point \( M^* = (x_1^*, x_2^*, x_3^*) \) in the positive octant. Linearization of this system near its stationary point is described by the matrix with six strictly negative coefficients
Here and in the sequel, we mean that $x_{i+1} = x_i$ for $I = 1$. Let $P$ be the product $p_i p_2 p_3$. Since the characteristic polynomial of $A$ has the form $(\lambda + s_1) (\lambda + s_2) (\lambda + s_3) + P = 0$, one of the eigenvalues $\lambda_i$ of this matrix $A$ is negative and corresponds to an eigenvector $e_i$ with positive coordinates. The well-known Routh-Hurwitz criterion gives necessary and sufficient conditions for positivity of the real parts of two other eigenvalues:

$$\text{Re}\lambda_2 = \text{Re}\lambda_3 > 0 \text{ if and only if}$$

$$\left( s_1 + s_2 + s_3 \right) \left( s_1 s_2^2 + s_1 s_3^2 + s_2 s_3^2 \right) - s_1 s_2 s_3 - P < 0. \quad (2)$$

Let $Q = [0, \alpha_x] \times [0, \alpha_y] \times [0, \alpha_z]$. This parallelepiped is positively invariant with respect to trajectories of the system (1). As in (Hastings et al., 1977), where quite different types of dynamical systems were studied, consider subdivision $Q = \bigcup S_{ijk}$. Here the parallelepipeds $S_{ijk}$, $i,j,k = 0$ or 1, are defined as:

$$S_{000} = \{0 \leq x_1 \leq x_2^*; 0 \leq x_2 \leq x_3^*; 0 \leq x_3 \leq \alpha_3^* \},$$

$$S_{100} = \{x_2^* \leq x_1 \leq \alpha_1^*; 0 \leq x_2 \leq x_3^*; \alpha_3 \leq x_3 \leq \alpha_3 \} \text{ etc.}$$

The subscript 0 on the $m$-th place means that $S_{ijk}$ borders on the face $x_m = 0$ of $Q$, subscript 1 on this place means that $S_{ijk}$ borders on the face $x_m = \alpha_m$ of $Q$ and the vectors $\pm e_i$ show the directions from the point $M$ into the parallelepipeds $S_{000}$ and $S_{111}$.

Now, our arguments in this paragraph will follow almost literally (Golubyatnikov et al., 2006a). The shifts $S_{011} \rightarrow S_{010} \rightarrow S_{110} \rightarrow S_{100} \rightarrow S_{101} \rightarrow S_{001} \rightarrow S_{011}$ along trajectories of the system (1) determine a continuous mapping $\varphi : F \rightarrow F$ of the rectangle $F = S_{011} \cap S_{001}$. If the inequality (2) is satisfied, then the fixed point theorem implies existence of at least one point $M_0$ in $F' = F \setminus (F \cap U)$ such that $\varphi(M_0) = M_0$. Here $U$ is some small open neighborhood of the point $M_0$. So, the trajectory of this point $M_0$ is a closed cycle and we obtain

**Theorem.** If the condition (2) is satisfied, then the system (1) has at least one periodic trajectory.

2. Let $(\alpha_1 - x_1 \cdot g_1(x_1); \alpha_2 - x_2 \cdot g_2(x_1); \alpha_3 - x_3 \cdot g_3(x_2))$ be the coordinates of vector field $G(x)$. Hence, $\frac{d\mathbf{x}}{dt} = G(x)$ is the vector form of the system (1). We see that $\text{div}(G(x)) \leq -3$, so, the volume of any bounded domain in $\mathbb{R}^3$ decreases during the shifts along the trajectories exponentially: $V(t) < V_0 \cdot e^{-3t}$. Again, the fixed point theorem and this decreasing do not imply immediately stability or uniqueness of the cycle in our

\[ A = \begin{pmatrix} -s_1 & 0 & -p_1 \\ -p_2 & -s_1 & 0 \\ 0 & -p_3 & -s_2 \end{pmatrix}, \quad p_i = x_i^* \cdot \frac{dg_i}{dx_{(i-1)^*}}(x_{(i-1)^*}), \quad s_i = g_i(x_{(i-1)^*}). \]
Part 4

Theorem, though numerical experiments with this system and with more complicated systems show that this cycle is stable and unique, as in (Golubyatnikov et al., 2006a, b) and below.

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

\[
\frac{dx}{dt} = \alpha_1(\mu) - x_1 g_1(x_1, \mu); \quad \frac{dx}{dt} = \alpha_2(\mu) - x_2 g_2(x_1, \mu); \quad \frac{dx}{dt} = \alpha_3(\mu) - x_3 g_3(x_1, \mu).
\]

(3)

We assume that for all values of \( \mu \) the functions \( g_i \) are smooth and monotonically increasing as in the case of (1). Let \( \mu = \mu_0 \) corresponds to \( \Re \lambda_{2,3} = 0 \). As in our previous considerations (Volokitin, Treskov, 2005; Golubyatnikov et al., 2006a), the Hopf bifurcation theorem, see for example (Kuznetzov, 1995), implies that if \((\mu - \mu_0) \frac{dP}{d\mu}(\mu_0)\) is positive and sufficiently small, then the system (3) has a bifurcation cycle in a neighborhood of the point \( M_\ast = M_\ast(\mu) \). In the case of symmetric gene networks of special type, we have obtained the stability conditions of these bifurcation cycles based on the formula for Lyapunov parameter \( \nu_1 \). Similar explicit formulae can be derived for the asymmetric system (3) as well, but in this case the analytical expression of \( \nu_1 \) is too cumbersome and can be used only in the numerical experiments.

4. Using exactly the same arguments, analogous results on periodic trajectories and their bifurcations can be obtained for the gene networks of mixed types, where some of the equations have the form (1) and other equations describe regulation on the stages of the genes expression activation, i.e., have the form \( \frac{dx_i}{dt} = f_i(x_{i-1}) - x_i \). Here, the functions \( f_i \) are monotonically decreasing as in (Golubyatnikov et al., 2006b).

The left and the right parts of the Fig. 1 show (respectively) trajectories convergent to the bifurcation cycles in dynamical systems

\[
\frac{dx}{dt} = \alpha_1 - x; \quad \frac{dy}{dt} = \frac{9}{1+x^2} - y; \quad \frac{dz}{dt} = \alpha_3 - z(1+y^3); \quad \alpha_1 = 8.02, \quad \alpha_3 = 2.88,
\]

\[
\frac{dx}{dt} = \alpha_1 - x(1+z^3); \quad \frac{dy}{dt} = \frac{9}{1+x^2} - y; \quad \frac{dz}{dt} = \alpha_3 - z(1+y^3); \quad \alpha_1 = 6.15, \quad \alpha_3 = 2.4.
\]

The black “eyes” on the pictures indicate positions of the stationary points of these systems.

Figure 1. Andronov-Hopf bifurcations in gene networks models of mixed types.
DISCUSSION

Separation of regular and chaotic domains in the spaces of parameters is an actual problem of the gene network modeling. In some higher-dimensional symmetric gene network models, we have already discovered appearance of chaotic behavior of trajectories (Golubyatnikov et al., 2005). Similar behavior of trajectories was observed in natural gene networks functioning (Gardner et al., 2000), and in other numerical experiments with the systems considered above and in (Golubyatnikov et al., 2006b). So, one of our current tasks is to determine conditions of regular behavior of these trajectories and to study questions of stability and uniqueness of the cycles discovered in the dynamical systems considered above, bifurcations of these cycles and their higher-dimensional analogues.

ACKNOWLEDGEMENTS

The work was supported by leading scientific schools grant No. 8526.2006.1 of President of Russian Federation and by interdisciplinary integration grants 24 and 46 of SB RAS. The authors are indebted to V.A. Churkin for discussions.

REFERENCES