Examples of periodic biological oscillators: transition to a six-dimensional system

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Abstract: We study a genetic model (including gene regulatory networks) consisting of a system of several ordinary differential equations. This system contains a number of parameters and depends on the regulatory matrix that describes the interactions in this multicomponent network. The question of the attracting sets of this system, which depending on the parameters and elements of the regulatory matrix, isconsidered. The consideration is mainly geometric, which makes it possible to identify and classify possible network interactions. The system of differential equations contains a sigmoidal function, which allows taking into account the peculiarities of the network response to external influences. As a sigmoidal function, a logistic function is chosen, which is convenient for computer analysis. The question of constructing attractors in a system of arbitrary dimension is considered by constructing a block regulatory matrix, the blocks of which correspond to systems of lower dimension and have been studied earlier. The method is demonstrated with an example of a three-dimensional system, which is used to construct a system of dimensions twice as large. The presentation is provided with illustrations obtained as a result of computer calculations, and allowing, without going into details, to understand the formulation of the issue and ways to solve the problems that arise in this case.

Key-Words: gene regulatory network, attractors, logistic function, numerical analysis

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1 Introduction

The dynamics of gene regulatory networks can be described by a system of ordinary differential equations in the form

$$\begin{cases} x'_1 = \dfrac{1}{1 + e^{-\mu_1(w_{11}x_1 + w_{12}x_2 + \cdots + w_{1n}x_n - \theta_1)}} - x_1, \\ \cdots \\ x'_n = \dfrac{1}{1 + e^{-\mu_n(w_{n1}x_1 + w_{n2}x_2 + \cdots + w_{nn}x_n - \theta_n)}} - x_n, \end{cases} \quad (1)$$

where$x_i$corresponds to the expression of the protein by the i-th element of the system,μ_i and $\theta_i$are parametershaving biological meaning. Interaction between network elements (classified as activation, inhibition or no influence) is described by the regulatory matrix

$$W = \begin{pmatrix} w_{11} & \cdots & w_{1n} \\ \cdots & \cdots & \cdots \\ w_{n1} & \cdots & w_{nn} \end{pmatrix}, (2)$$

where the positivity (negativity) of the element w_{ij} means the activation (inhibition) of the i-th gene by the j-th gene.Zero value means no influence. The combined result of these

interactions forms the network response to changes in the external environment.
Among these reactions, periodic reactions are distinguished, which are often caused by periodic processes in the environment. These periodic reactions are formed by bio-oscillators. Our goal is to give examples of bio-oscillators in mathematical models of gene networks. These examples are reflections of specific types of network interactions. These specific types correspond to certain regulatory matrices. The system of differential equations describing the gene network has an infinite set of solutions, which correspond to trajectories in the space of variables x. We are especially interested in the case of periodic attractors that arise from stable periodic solutions of the system.
It should be noted that the system (1) is also used in modeling processes of various natures. One of its earliest appearances in the literature is an article by Wilson and Cowan, which describes the behavior of groups of neurons.[15] In the future, the system repeatedly appeared as an element of dynamic models of gene networks.[1], [2], [3], [10], [11], [14]. This system was also used to build the optimal topology of telecommunication networks.[9]In this case, the behavior of gene networks was taken as a model. The literature on issues related to the modeling of complex networks such as gene networks and/or telecommunications has hundreds of articles and continues to grow. Fairly complete lists of articles can be found in the reviews [8], [12], [13], [4]. The works [1], [7], [16] are devoted to qualitative and/or numerical analysis of systems of type (1). Periodic solutions and related issues were considered in [6], [7]. Applications in medicine of system (1) are the subject of works [5], [14].

2 Three-dimensional system

Consider the three-dimensional system (1) with regulatory matrix

$$W = \begin{pmatrix} k & 0 & -1 \\ -1 & k & 0 \\ 0 & -1 & k \end{pmatrix}. (3)$$

This matrix contains the inhibitory cycle

$$W = \begin{pmatrix} 0 & 0 & -1 \\ -1 & 0 & 0 \\ 0 & -1 & 0 \end{pmatrix} (4)$$

and auto-activation

$$W = \begin{pmatrix} k & 0 & 0 \\ 0 & k & 0 \\ 0 & 0 & k \end{pmatrix}. (5)$$

For values k from the interval$(0.36; 2)$ the three-dimensional system is

$$\begin{cases} x_1 = \frac{1}{1+e^{-\mu_1(\mathrm{k}x_1 - x_3 - \theta_1)}}, \\ x_2 = \frac{1}{1+e^{-\mu_2(-x_1 + \mathrm{k}x_2 - \theta_2)}}, \\ x_3 = \frac{1}{1+e^{-\mu_3(-x_2 + \mathrm{k}x_3 - \theta_3)}}. \end{cases} (6)$$

It has a periodic solution that attracts the other solutions. Figure 1 and Figure 2 show the periodic solutions of the system (6) for $k = 1$ and $k = 0.5$.The values of other parameters are as follows$\mu_i = 5$; $\theta_i = \frac{k-1}{2}$.

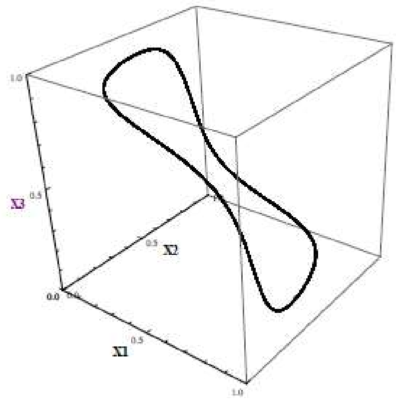

Figure 1. Periodic solutions, $k = 1$.

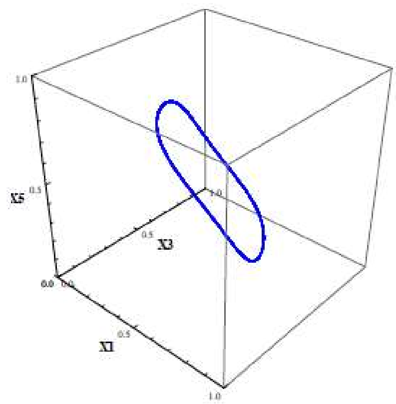

Figure 2. Periodic solutions, $k = 0.5$.

The specified three-dimensional periodic solution arises as a result of a three-dimensional Andronov-Hopf bifurcation. For small values of

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k, the attractor of the system (6) exists in the form of a single critical point of the type of stable focus and attraction in the remaining dimension. As k increases, the point type changes to an unstable focus. The result is a three-dimensional limit cycle.

3Six-dimensional system

Consider the $\mathbf{6} \times \mathbf{6}$ regulatory matrix

$$W = \begin{pmatrix} k & 0 & -1 & 0 & 0 & 0 \\ -1 & k & 0 & 0 & 0 & 0 \\ 0 & -1 & k & 0 & 0 & 0 \\ 0 & 0 & 0 & k & 0 & -1 \\ 0 & 0 & 0 & -1 & k & 0 \\ 0 & 0 & 0 & 0 & 1 & k \end{pmatrix}, \quad (7)$$

where the 3D diagonal blocks correspond to the matrix (3).

Let $k = 1$.The system (7) has an attractor as a periodic solution generated by the three-dimensional periodic solution shown in the Figure 1.The projections of this periodic attractor onto three-dimensional subspaces are shown in Figure 3, Figure 4 and Figure 5.

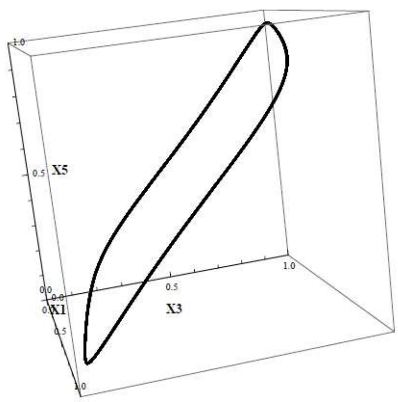

Figure 3. The projection of the attractor on (x_1, x_3, x_5)

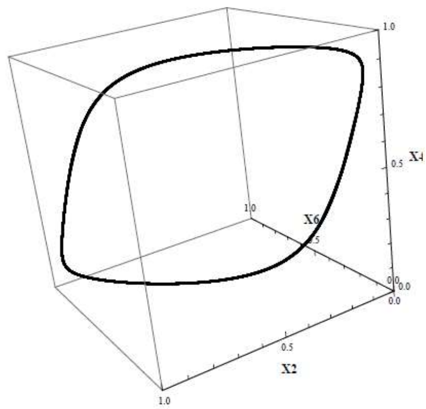

Figure 4. The projection of the attractor on (x_2, x_4, x_6)

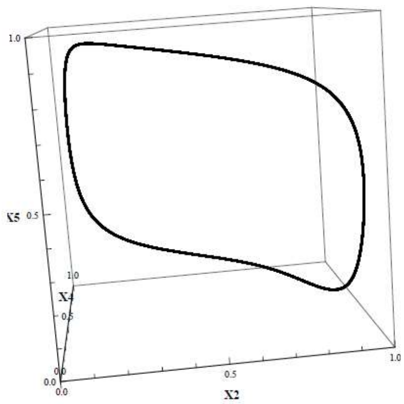

Figure 5. The projection of the attractor on (x_2, x_4, x_5)

Consider the $\mathbf{6} \times \mathbf{6}$ regulatory matrix

$$W = \begin{pmatrix} k_1 & 0 & -1 & 0 & 0 & 0 \\ -1 & k_1 & 0 & 0 & 0 & 0 \\ 0 & -1 & k_1 & 0 & 0 & 0 \\ 0 & 0 & 0 & k_2 & 0 & -1 \\ 0 & 0 & 0 & -1 & k_2 & 0 \\ 0 & 0 & 0 & 0 & 1 & k_2 \end{pmatrix}, (8)$$

where $k_1 = 1$ and $k_2 = 0.5$. The system (8) has an attractor generated by two periodic solutions shown in the Figure 1 and Figure 2. The projections of this periodic attractor onto three-dimensional subspaces are shown in Figure 6, Figure 7 and Figure 8.

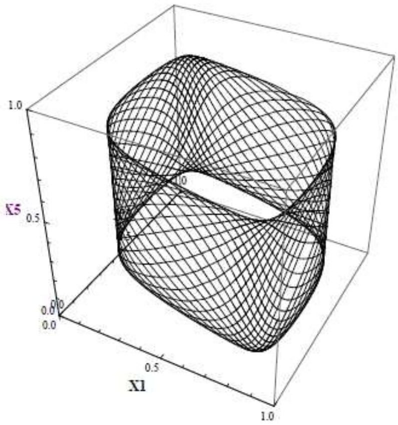

Figure 6. The projection of the attractor on (x_1, x_3, x_5)

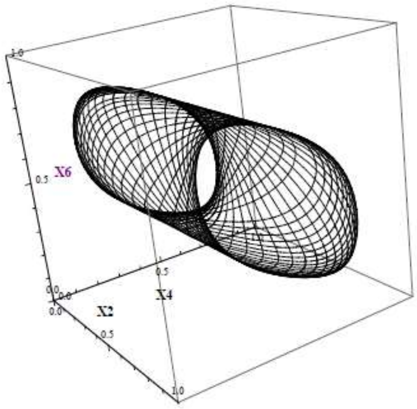

Figure 7. The projection of the attractor on (x_2, x_4, x_6)

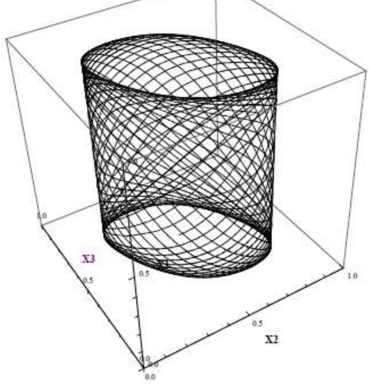

Figure 8. The projection of the attractor on (x_2, x_4, x_5)

The projections of this attractor (black) are repeatedly shown in figures 9, 10, 11 together with the solution (red), which starts close to the attractor and has the initial conditions

$$x_1(0) = 0;\ x_2(0) = 0.4;\ x_3(0) = 0.1;$$
$$x_4(0) = 0.2;\ x_5(0) = 0.1;\ x_6(0) = 0.1.$$

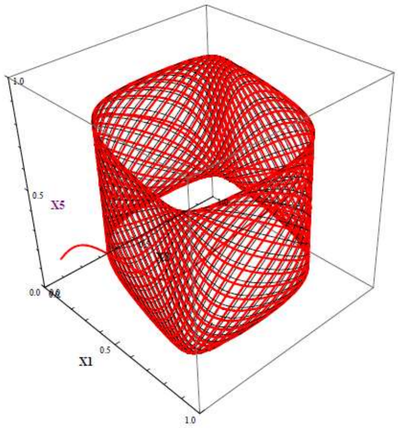

Figure 9. The projection of the attractor on (x_1, x_3, x_5)

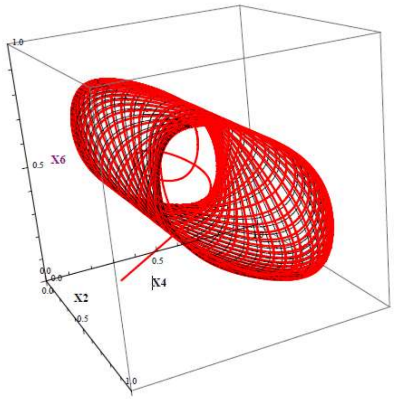

Figure 10. The projection of the attractor on (x_2, x_4, x_6)

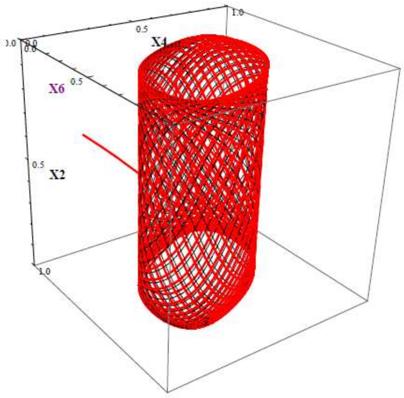

Figure 11. The projection of the attractor on (x_2, x_4, x_5)

Further study of attractors and solutions can be carried out using the perturbation of the regulatory matrix W.
Consider the matrix

$$W = \begin{pmatrix} k_1 & 0 & -1 & 0 & 0 & m \\ -1 & k_1 & 0 & 0 & 0 & 0 \\ 0 & -1 & k_1 & 0 & 0 & 0 \\ 0 & 0 & 0 & k_2 & 0 & -1 \\ 0 & 0 & 0 & -1 & k_2 & 0 \\ -m & 0 & 0 & 0 & 1 & k_2 \end{pmatrix}, (9)$$

which differs from the previous matrix (8) only by the presence of non-zero elements (m and $-m$) at the end points of the secondary diagonal. Numerical experiments gave the following results. At small values of m, a picture similar to that shown in Figure 6, Figure 7, and Figure 8 is preserved, which corresponds to the ideas about the structural stability of systems encountered in the theory of gene networks. With a further increase in $m(to\ m < 0.5)$, the form of threedimensional projections, while remaining regular, changes significantly. A further increase in m leads to an increase in the irregularity and chaotic behavior of the solutions.

4 Conclusions

For systems (1) used in the mathematical modeling of gene networks, it is true: 1) There is an invariant set in the phase space: the vector field defined by the system is directed inside this set. This follows from the properties of sigmoidal functions used in systems (1); 2) There is always an equilibrium (critical point). There may be several critical points, but apart from degenerate cases, a finite number only; 3) An attractor in the system (1) can have the form of several stable equilibria (critical points); 4) An attractor can exist in the form of an attracting closed trajectory (limit cycle); 5) The system of type (1) of any dimension can be constructed with attractors of different types. In particular, for any dimension, a system of the form (1) can be constructed with a periodic attractor; 6) Constructing such a system, block-type regulatory matrices are used. In this case, the blocks correspond to systems of lower dimension with attractors installed in them; 7) By perturbation of such matrices, it is possible obtain and study systems with chaotic behavior of solutions.

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