Mathematical Modeling of Four-dimensional Genetic Regulatory Networks Using a Logistic Function

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Abstract: Mathematical modeling is a universal tool for the study of complex systems. In this paper formulas for characteristic numbers of critical points for the systems of order four (4D) are considered. We show how an unstable focus-focus can appear in a four-dimensional system. Projections of 4D trajectories on two-dimensional and three-dimensional subspaces are shown. In the considered four-dimensional system the logistic function is used. The research aims to investigate the four-dimensional system, find critical points of the system, calculate the characteristic numbers, and calculate Lyapunov exponents.

Key-Words: mathematical modeling, nullclines, Lyapunov exponents, periodic solutions, linearized system, critical points

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1 Introduction

Every natural science consists of three parts: empirical, theoretical, and mathematical. The empirical part contains factual information obtained in experiments and observations. The theoretical part develops theoretical concepts. The mathematical part constructs mathematical models that serve to test the basic theoretical concepts provide methods for the primary processing of experimental data so that they can be compared with the results of the models, and develops methods for planning an experiment in such a way that, with a small expenditure of effort, it is possible to obtain sufficiently reliable data from experiments, [1]. Mathematical models are routinely used in the physical and engineering sciences to help understand complex systems and optimize industrial processes. There are numerous examples of the fruitful application of mathematical principles to problems in cell and molecular biology, and recent years have seen increasing interest in applying quantitative techniques to problems in biotechnology, [3]. The main problem in the mathematical modeling of a dynamic system is to develop a model and then to determine dependencies and coefficients in the equations used in developing the model, [7]. To quote the statistician Dr. George E. P. Box (1919-2013): “Essentially, all models are wrong, but some are useful, [8].” Gene regulatory networks are structurally represented by spatially located objects, consisting of occurring and hundreds of elements of different natures and complexity. The most important property of the gene regulatory networks is the ability to change the state in response to changes in the conditions of the external and internal environment, [2]. A variety of approaches have been used to model the gene regulatory networks: Graph method, differential, statistical equations, and more.

Consider the matrix

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

The graph with the regulatory matrix (1) is considered in Figure 1.

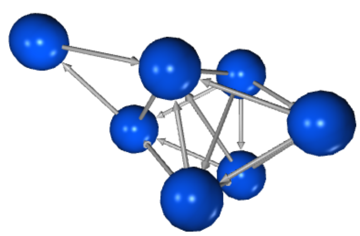

Figure 1: The graph with the regulatory matrix (1).

2 Four-dimensional systems

We consider systems of ordinary differential equations of the form

$$\begin{cases} \dfrac{dx_1}{dt} = \\ \dfrac{1}{1+e^{-\mu_1(w_{11}x_1+w_{12}x_2+w_{13}x_3+w_{14}x_4-\theta_1)}} - v_1x_1, \\ \dfrac{dx_2}{dt} = \\ \dfrac{1}{1+e^{-\mu_2(w_{21}x_1+w_{22}x_2+w_{23}x_3+w_{24}x_4-\theta_2)}} - v_2x_2, \\ \dfrac{dx_3}{dt} = \\ \dfrac{1}{1+e^{-\mu_3(w_{31}x_1+w_{32}x_2+w_{33}x_3+w_{34}x_4-\theta_2)}} - v_3x_3, \\ \dfrac{dx_4}{dt} = \\ \dfrac{1}{1+e^{-\mu_4(w_{41}x_1+w_{42}x_2+w_{43}x_3+w_{44}x_4-\theta_4)}} - v_4x_4. \end{cases} \quad (2)$$

Such systems arise in the theory of complex networks, such as genetic networks, [4], [5], [6],[7], [9], telecommunications networks, [10], neuronal networks, [11], and more.
The greater the number of equations in the system, the closer the model is to a realistic gene regulatory network. But even the three-dimensional system contains many parameters, which makes the study not trivial. In this paper, we consider the four-dimensional system. This system consists of 24 parameters.
The system (2) consists of four equations that define the nullclines. The nullclines are given by

$$\begin{cases} v_1x_1 = \dfrac{1}{1+e^{-\mu_1(w_{11}x_1+w_{12}x_2+w_{13}x_3+w_{14}x_4-\theta_1)}}, \\ v_2x_2 = \dfrac{1}{1+e^{-\mu_2(w_{21}x_1+w_{22}x_2+w_{23}x_3+w_{24}x_4-\theta_2)}}, \\ v_3x_3 = \dfrac{1}{1+e^{-\mu_3(w_{31}x_1+w_{32}x_2+w_{33}x_3+w_{34}x_4-\theta_2)}}, \\ v_4x_4 = \dfrac{1}{1+e^{-\mu_4(w_{41}x_1+w_{42}x_2+w_{43}x_3+w_{44}x_4-\theta_4)}}. \end{cases} \quad (3)$$

Critical points are solutions of the system (3).

2.1 Linearized system

The linearized system for critical point $(x_1^*, x_2^*, x_3^*, x_4^*)$ is

$$\begin{cases} u_1' = -v_1u_1 + \mu_1w_{11}g_1u_1 + \mu_1w_{12}g_1u_2 + \\ \mu_1w_{13}g_1u_3 + \mu_1w_{14}g_1u_4, \\ u_2' = -v_2u_2 + \mu_2w_{21}g_2u_1 + \mu_2w_{22}g_2u_2 + \\ \mu_2w_{23}g_2u_3 + \mu_2w_{24}g_2u_4, \\ u_3' = -v_3u_3 + \mu_3w_{31}g_3u_1 + \mu_3w_{32}g_3u_2 + \\ \mu_3w_{33}g_3u_3 + \mu_3w_{34}g_3u_4, \\ u_4' = -v_4u_4 + \mu_4w_{41}g_4u_1 + \mu_4w_{42}g_4u_2 + \\ \mu_4w_{34}g_4u_3 + \mu_4w_{44}g_4u_4, \end{cases}$$

where

$$g_1 = \frac{e^{-\mu_1(w_{11}x_1^*+w_{12}x_2^*+w_{13}x_3^*+w_{14}x_4^*-\theta_1)}}{[1+e^{-\mu_1(w_{11}x_1^*+w_{12}x_2^*+w_{13}x_3^*+w_{14}x_4^*-\theta_1)}]^2},$$

$$g_2 = \frac{e^{-\mu_2(w_{21}x_1^*+w_{22}x_2^*+w_{23}x_3^*+w_{24}x_4^*-\theta_2)}}{[1+e^{-\mu_2(w_{21}x_1^*+w_{22}x_2^*+w_{23}x_3^*+w_{24}x_4^*-\theta_2)}]^2},$$

$$g_3 = \frac{e^{-\mu_3(w_{31}x_1^*+w_{32}x_2^*+w_{33}x_3^*+w_{34}x_4^*-\theta_3)}}{[1+e^{-\mu_3(w_{31}x_1^*+w_{32}x_2^*+w_{33}x_3^*+w_{34}x_4^*-\theta_3)}]^2},$$

$$g_4 = \frac{e^{-\mu_4(w_{41}x_1^*+w_{42}x_2^*+w_{43}x_3^*+w_{44}x_4^*-\theta_4)}}{[1+e^{-\mu_4(w_{41}x_1^*+w_{42}x_2^*+w_{43}x_3^*+w_{44}x_4^*-\theta_4)}]^2}.$$

Properties of a critical point $(x_1^*, x_2^*, x_3^*, x_4^*)$ are described by the four numbers (they are called the characteristic numbers) $\lambda_1; \lambda_2; \lambda_3; \lambda_4$ which can be found from the chracteristic equation, [9].
The characteristic equation is

$$\lambda^4 + A\lambda^3 + B\lambda^2 + M\lambda + L = 0, \qquad (4)$$

where

$$A = (v_1+v_2+v_3+v_4) - g_1w_{11}\mu_1 - g_2w_{22}\mu_2 - g_3w_{33}\mu_3 - g_4\mu_4w_{44},$$

$$\begin{aligned}B = {} & v_3v_4 - g_1v_3w_{11}\mu_1 - g_1v_4w_{11}\mu_1 - \\ & g_2v_3w_{22}\mu_2 - g_2v_4w_{22}\mu_2 - g_1g_2w_{21}w_{12}\mu_1\mu_2 + \\ & g_1g_2w_{11}w_{22}\mu_1\mu_2 - g_3v_4w_{33}\mu_3 - \\ & g_1g_3w_{31}w_{13}\mu_1\mu_3 + g_1g_3w_{11}w_{33}\mu_1\mu_3 - \\ & g_2g_3w_{32}w_{23}\mu_2\mu_3 + g_2g_3w_{22}w_{33}\mu_2\mu_3 - \\ & g_1g_4w_{41}\mu_1\mu_4w_{14} - g_2g_4w_{42}\mu_2\mu_4w_{24} - \\ & g_3g_4w_{43}\mu_3\mu_4w_{34} - g_4v_3\mu_4w_{44} + \\ & g_1g_4w_{11}\mu_1\mu_4w_{44} + g_2g_4w_{22}\mu_2\mu_4w_{44} + \\ & g_3g_4w_{33}\mu_3\mu_4w_{44} + \\ & v_2(v_3+v_4-g_1w_{11}\mu_1-g_3w_{33}\mu_3-g_4\mu_4w_{44}) + \\ & v_1(v_2+v_3+v_4-g_2w_{22}\mu_2-g_3w_{33}\mu_3-g_4\mu_4w_{44}),\end{aligned}$$

$$\begin{aligned}M = {} & -g_1v_3v_4w_{11}\mu_1 - g_2v_3v_4w_{22}\mu_2 - \\ & g_1g_2v_3w_{21}w_{12}\mu_1\mu_2 - g_1g_2v_4w_{21}w_{12}\mu_1\mu_2 + \\ & g_1g_2v_3w_{11}w_{22}\mu_1\mu_2 + g_1g_2v_4w_{11}w_{22}\mu_1\mu_2 - \\ & g_1g_3v_4w_{31}w_{13}\mu_1\mu_3 + g_1g_3v_4w_{11}w_{33}\mu_1\mu_3 - \\ & g_2g_3v_4w_{32}w_{23}\mu_2\mu_3 + g_2g_3v_4w_{22}w_{33}\mu_2\mu_3 + \\ & g_1g_2g_3w_{31}w_{22}w_{13}\mu_1\mu_2\mu_3 - \\ & g_1g_2g_3w_{21}w_{32}w_{13}\mu_1\mu_2\mu_3 - \\ & g_1g_2g_3w_{31}w_{12}w_{23}\mu_1\mu_2\mu_3 + \\ & g_1g_2g_3w_{11}w_{32}w_{23}\mu_1\mu_2\mu_3 + \\ & g_1g_2g_3w_{21}w_{12}w_{33}\mu_1\mu_2\mu_3 - \\ & g_1g_2g_3w_{11}w_{22}w_{33}\mu_1\mu_2\mu_3 - \\ & g_1g_4v_3w_{41}\mu_1\mu_4w_{14} + \\ & g_1g_2g_4w_{41}w_{22}\mu_1\mu_2\mu_4w_{14} - \\ & g_1g_2g_4w_{21}w_{42}\mu_1\mu_2\mu_4w_{14} + \\ & g_1g_3g_4w_{41}w_{33}\mu_1\mu_3\mu_4w_{14} - \\ & g_1g_3g_4w_{31}w_{43}\mu_1\mu_3\mu_4w_{14} - \\ & g_2g_4v_3w_{42}\mu_2\mu_4w_{24} - \\ & g_1g_2g_4w_{41}w_{12}\mu_1\mu_2\mu_4w_{24} + \\ & g_1g_2g_4w_{11}w_{42}\mu_1\mu_2\mu_4w_{24} + \\ & g_2g_3g_4w_{42}w_{33}\mu_2\mu_3\mu_4w_{24} - g_2g_3g_4w_{32}w_{43}\mu_2\mu_3\mu_4w_{24} - \\ & g_1g_3g_4w_{41}w_{13}\mu_1\mu_3\mu_4w_{34} + g_1g_3g_4w_{11}w_{43}\mu_1\mu_3\mu_4w_{34} - \\ & g_2g_3g_4w_{42}w_{23}\mu_2\mu_3\mu_4w_{34} + g_2g_3g_4w_{22}w_{43}\mu_2\mu_3\mu_4w_{34} + \\ & g_1g_4v_3w_{11}\mu_1\mu_4w_{44} + g_2g_4v_3w_{22}\mu_2\mu_4w_{44} + \\ & g_1g_2g_4w_{21}w_{12}\mu_1\mu_2\mu_4w_{44} - g_1g_2g_4w_{11}w_{22}\mu_1\mu_2\mu_4w_{44} + \\ & g_1g_3g_4w_{31}w_{13}\mu_1\mu_3\mu_4w_{44} - g_1g_3g_4w_{11}w_{33}\mu_1\mu_3\mu_4w_{44} + \\ & g_2g_3g_4w_{32}w_{23}\mu_2\mu_3\mu_4w_{44} - g_2g_3g_4w_{22}w_{33}\mu_2\mu_3\mu_4w_{44} + \\ & v_1(v_3v_4 - g_2v_3w_{22}\mu_2 - g_2v_4w_{22}\mu_2 - g_3v_4w_{33}\mu_3 - \\ & g_2g_3w_{32}w_{23}\mu_2\mu_3 + g_2g_3w_{22}w_{33}\mu_2\mu_3 - \\ & g_2g_4w_{42}\mu_2\mu_4w_{24} - \\ & g_3g_4w_{43}\mu_3\mu_4w_{34} - g_4v_3\mu_4w_{44} + \\ & g_2g_4w_{22}\mu_2\mu_4w_{44} + \\ & g_3g_4w_{33}\mu_3\mu_4w_{44} + \\ & v_2(v_3 + v_4 - g_3w_{33}\mu_3 - g_4\mu_4w_{44})) + \\ & v_2(v_3(v_4 - g_1w_{11}\mu_1 - g_4\mu_4w_{44}) - \\ & g_1\mu_1(v_4w_{11} + g_3w_{31}w_{13}\mu_3 - \\ & g_3w_{11}w_{33}\mu_3 + g_4w_{41}\mu_4w_{14} - g_4w_{11}\mu_4w_{44}) - \\ & g_3\mu_3(v_4w_{33} + g_4w_{43}\mu_4w_{34} - g_4w_{33}\mu_4w_{44})),\end{aligned}$$

$$\begin{aligned}L = {} & v_1(v_2(v_3(v_4 - g_4\mu_4w_{44}) - \\ & g_3\mu_3(v_4w_{33} + g_4w_{43}\mu_4w_{34} - g_4w_{33}\mu_4w_{44})) -\end{aligned}$$

$$g_2\mu_2(v_3(v_4w_{22}+g_4\mu_4(w_{42}w_{24}-w_{22}w_{44}))+ g_3\mu_3(v_4(w_{32}w_{23}-w_{22}w_{33})+ g_4\mu_4(-w_{42}w_{33}w_{24}+w_{32}w_{43}w_{24}+w_{42} w_{23}w_{34}-w_{22}w_{43}w_{34}-w_{32}w_{23}w_{44}+w_{22}w_{33}w_{44}))))- g_1\mu_1(v_2(v_3(v_4w_{11}+g_4\mu_4(w_{41}w_{14}-w_{11}w_{44}))+ g_3\mu_3(v_4(w_{31}w_{13}-w_{11}w_{33})+ g_4\mu_4(-w_{41}w_{33}w_{14}+w_{31}w_{43}w_{14}+w_{41}w_{13}w_{34}- w_{11}w_{43}w_{34}-w_{31}w_{13}w_{44}+w_{11}w_{33}\ w_{44})))+ g_2\mu_2(v_3(v_4(w_{21}w_{12}-w_{11}w_{22})+ g_4\mu_4(-w_{41}w_{22}w_{14}+w_{21}w_{42}\ w_{14}+w_{41}w_{12}w_{24}- w_{11}w_{42}w_{24}-\ w_{21}w_{12}w_{44}+w_{11}w_{22}w_{44}))+ g_3\mu_3(v_4(-w_{31}w_{22}w_{13}+w_{21}\ w_{32}w_{13}+w_{31}w_{12}w_{23}- w_{11}\ w_{32}w_{23}-w_{21}w_{12}w_{33}+w_{11}\ w_{22}w_{33})+ g_4\mu_4(-w_{21}w_{42}w_{33}w_{14}+w_{21}w_{32}w_{43}w_{14}+ w_{11}w_{42}w_{33}w_{24}-w_{11}w_{32}w_{43}w_{24}+ w_{21}w_{42}w_{13}w_{34}-w_{11}w_{42}w_{23}w_{34}- w_{21}w_{12}w_{43}w_{34}+w_{11}w_{22}w_{43}w_{34}+ w_{41}(-w_{32}w_{23}w_{14}+w_{22}w_{33}w_{14}+w_{32}w_{13}w_{24}- w_{12}w_{33}w_{24}-w_{22}w_{13}w_{34}+w_{12}w_{23}w_{34})- w_{21}w_{32}w_{13}w_{44}+w_{11}w_{32}w_{23}w_{44}+ w_{21}\ w_{12}w_{33}w_{44}-w_{11}w_{22}w_{33}w_{44}+ w_{31}(w_{42}w_{23}w_{14}-w_{22}w_{43}w_{14}-w_{42}w_{13}w_{24}+ w_{12}w_{43}w_{24}+w_{22}w_{13}w_{44}-w_{12}w_{23}w_{44}))))).$$

Such formulas are considered in paper [16].

2.2 Logistic function

The logistic function or logistic curve $f(z) = \dfrac{1}{1+e^{-\mu(z-\theta)}}$ [7]. The sigmoid logistic function was introduced in a series of three papers by Pierre Francois Verhulst between 1838 and 1847, who devised it as a model of population growth by adjusting the exponential growth model. The sigmoid function has the the characteristic properties:

1. monotonically increasing from zero to unity;
2. possessing a unique inflection point, [12].

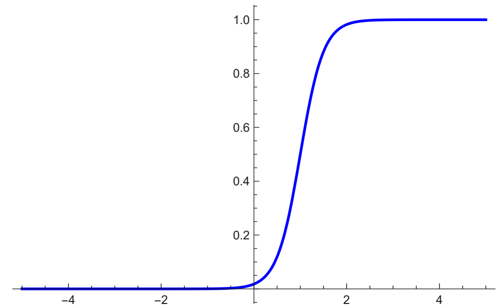

Figure 2: The sigmoid logistic function.

2.3 Critical points

The four-dimensional system has 4 eigenvalues.

- **4D node**. All eigenvalues are real and have the same sign. The node is stable (unstable) when the eigenvalues are negative (positive).
- **4D star**. All eigenvalues are equal. The 4D star is stable (unstable) when the eigenvalues are negative (positive).
- **Saddle**. All eigenvalues are real and at least one of them is positive and at least one is negative. Saddles are always unstable.
- **Focus – Node**. It has two real eigenvalues and a pair of complex-conjugate eigenvalues, and all eigenvalues have real parts of the same sign. The critical point is stable (unstable) when the sign is negative (positive).
- **Node – Focus**. It has two real negative eigenvalues and a pair of complex-conjugate eigenvalues with positive real part. The critical point is unstable.
- **Saddle – Focus**. Two real eigenvalues have different signs and complex-conjugate eigenvalues with positive or negative real part. The critical point is unstable.
- **Focus – Focus**. Two pairs of complex-conjugate eigenvalues. The

critical point is stable when the signs of real parts are negative. The critical point is unstable when there is at least one positive real part.

3 Materials and methods

Our consideration is geometrical. The main intent is to use the 2D and 3D projections of the 4D trajectories on different subspaces, to construct the graphs of solutions for understanding and managing the system. Visualizations where possible, are provided. The dynamics of Lyapunov exponents are shown. Computations are performed using Wolfram Mathematics, [12]. In the article for Lyapunov exponents calculation the package "lce.m for Mathematica" was used, [13]. Another Wolfram Mathematica program Lynch-DSAM.nb was also used to check the correctness of Lyapunov exponents calculation, [14], [15].

3.1 The example of four-dimensional system

Consider the system (2) with the regulatory matrix

$$W = \begin{pmatrix} 1 & 2 & 2 & 0 \\ -2 & 1 & 0 & 0 \\ -2 & 0 & 0.7 & 2 \\ 0 & 0 & -2 & 1 \end{pmatrix} \tag{5}$$

and $\mu_1 = \mu_3 = \mu_4 = 5$, $\mu_2 = 15$, $v_1 = v_2 = v_3 = v_4 = 1$. In paper [9] θ_i, where $i = 1, 2, 3, 4$ are calculated as

$$\begin{cases} \theta_1 = \dfrac{w_{11} + w_{12} + w_{13} + w_{14}}{2}, \\ \theta_2 = \dfrac{w_{21} + w_{22} + w_{23} + w_{24}}{2}, \\ \theta_3 = \dfrac{w_{31} + w_{32} + w_{33} + w_{34}}{2}, \\ \theta_4 = \dfrac{w_{41} + w_{42} + w_{43} + w_{44}}{2}. \end{cases}$$

$\theta_1 = 2.5$, $\theta_2 = -0.5$, $\theta_3 = 0.35$, $\theta_4 = -0.5$.

The initial conditions are

$$x_1(0) = 0.2;\ x_2(0) = 0.15;$$

$$x_3(0) = 0.3;\ x_4(0) = 0.35. \tag{6}$$

The critical point is $(0.5; 0.5; 0.5; 0.5)$. The characteristic equation for the critical point is (4), where $A = -3.125, B = 32.2813, M = -39.8359$ and $L = 125.174$. Solving the equation we have $\lambda_{1,2} = 0.606091 \pm 2.15656i$ and $\lambda_{3,4} = 0.956409 \pm 4.90201i$. The type of the critical point is unstable focus-focus. The projection of 4D trajectories on two-dimensional subspace (x_1, x_2) is in the figure below.

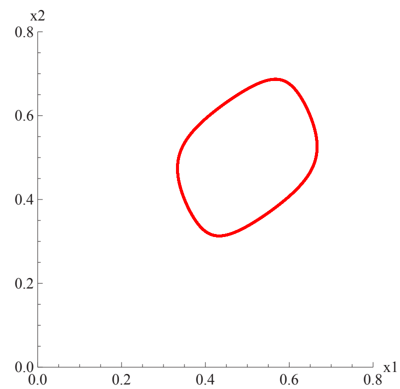

Figure 3: The projection of 4D trajectories to 2D subspace (x_1, x_2).

The graphs of periodic solutions $(x_1(t), x_2(t), x_3(t), x_4(t))$, the graphs of periodic solutions $(x_1(t), x_4(t))$ and the graphs of periodic solutions $(x_1(t), x_4(t))$ of the system (2) with the regulatory matrix (5) are shown in Figure 4, Figure 5 and Figure 6.

The projection of 4D trajectories to 3D subspace (x_1, x_2, x_4) is shown in Figure 7.

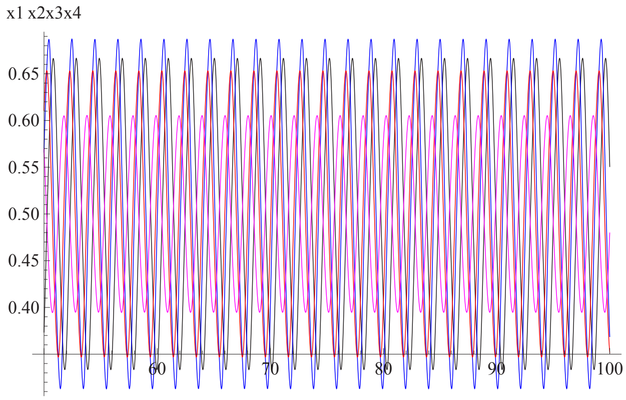

Figure 4: The graphs of periodic solutions $(x_1(t), x_2(t), x_3(t), x_4(t))$ of the system (2) with the regulatory matrix (5).

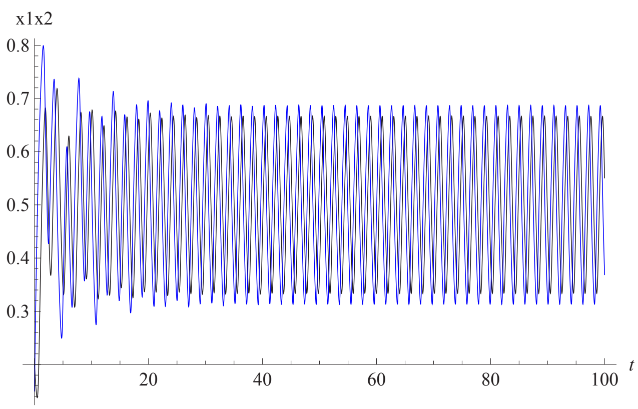

Figure 5: The graphs of periodic solutions $(x_1(t), x_2(t))$ of the system (2) with the regulatory matrix (5).

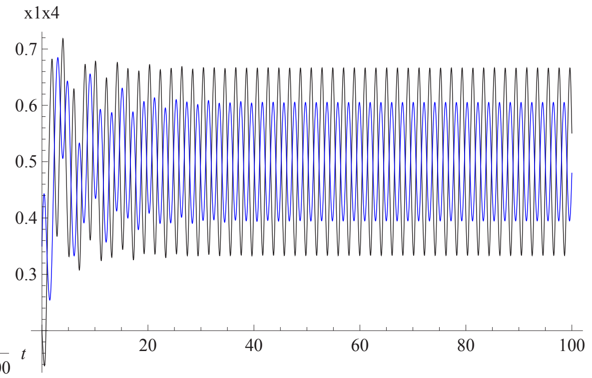

Figure 6: The graphs of periodic solutions $(x_1(t), x_4(t))$ of the system (2) with the regulatory matrix (5).

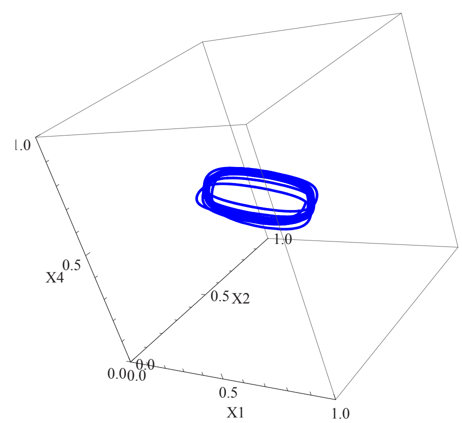

Figure 7: The projection of 4D trajectories to 3D subspace (x_1, x_2, x_4).

The dynamics of Lyapunov exponents are shown in Figure 8. Lyapunov exponents are $LE_1 = 0.001, LE_2 = -0.124, LE_3 = -0.127, LE_4 = -0.639$ it means $(0, -, -, -)$. The system (2) with the regulatory matrix (5) has periodic solutions.

4 Conclusions

In this paper, we concern with mathematical models of genetic networks. We have considered the four-dimensional system. Such a system has four characteristic numbers which can be found from the characteristic equation. Formulas for the characteristic equation coefficients (A, B, M, L) are considered. The projections of 4D trajectories to 2D subspace and 3D subspace are considered using the software Mathematica Wolfram. Also, the graphs of periodic solutions of the system (2) with the regulatory matrix (5) are considered using the same software. As we see the attractor can exist in the form of an attracting closed trajectory (limit cycle). In the future, we can perturbation the regulatory matrix coefficients to have other types of solutions for the system (2), for example, chaotic solutions.

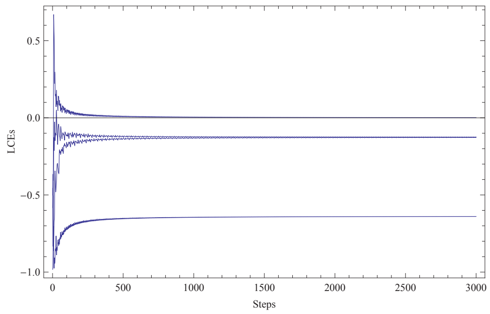

Figure 8: $LE_1 = 0.001, LE_2 = -0.124, LE_3 = -0.127, LE_4 = -0.639$.

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