On modelling of genetic regulatory networks

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Abstract: We consider a mathematical model of genetic regulatory networks (GRN). This model consists of a nonlinear system of ordinary differential equations. The vector of solutions $X(t)$ is interpreted as a current state of a network for a given value of time t. Evolution of a network and future states depend heavily on attractors of a system of ODE. We discuss this issue for low dimensional networks and show how the results can be applied for the study of large size networks. Examples and visualizations are provided.

Key-Words: Mathematical modelling, genetic regulatory networks, differential equations, attractors

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1 Introduction

Gene regulatory networks (GRN in short) exist in any cell of any living organism. GRN are responsible for morphogenesis, regulation of reactions to changes in the environment, and management of functioning of any kind. GRN can be imagined as a discrete object, consisting of elements (genes), that generally are in continuous interaction with others elements. This interaction can be roughly classified and modelled. One can speak about activation, inhibition, or no interaction. As a result of this interaction, the entire network can work effectively and rapidly.

It is to be mentioned, that there were attempts to borrow principles of self-organization of GRN to other areas, for instance, to telecommunication networks [1], [2] and for the design of artificial ones. To study GRN, experimental data are used extensively in combination with some theoretical means. In this paper, we will focus on mathematical models formulated in terms of differential equations. Differential equation models, if adequately selected, can predict future states of a described phenomenon, based on the given structure and rules in a model and information about the current state (or previous states). The efficacy of mathematical models in different areas is repeatedly confirmed. In the last decades mathematical methods of study of GRN are developed extensively. The interested reader can consult the review [3], [4], [5], [6] and others, concerning complex biological networks [7], [8], [9].

Due to difficulties in directly studying GRN, mathematical models are used. To describe the evolution of GRN, dynamical models, formulated as systems of ordinary differential equations (ODE), are used. Systems of ODE can be studied by traditional methods of mathematical analysis. Solutions are treated as curves in phase space of the corresponding dimensionality, which is equal to the number of elements (genes) in GRN. Trajectories can tend to some geometrical objects in phase space, which are called attractors. To understand the principles of GRN, one has to study first attractors in the respective mathematical model.

We are motivated by the work [10], where the authors provide an example of realistic GRN. This GRN is treated in the conditions of "large granular lymphocyte leukaemia associated with blood cancer". In this model, the cancerous states are identified with "undesired" attractors. The current state of GRN is described by the vector $X(t) = (x_1(t), \dots, x_n(t))$, where t is interpreted as time. As a disease progresses, this vector tends to a "wrong" attractor. The goal of the controllability problem is to redirect the trajectory $X(t)$ to a "normal" attractor, which in real life terms means to develop a cure.

In this paper, we describe the mathematical model of a four-dimensional GRN and consider the possibilities of control and management of this GRN. If the current system state, that is, the vector $X(t)$ is in the basin of attraction of

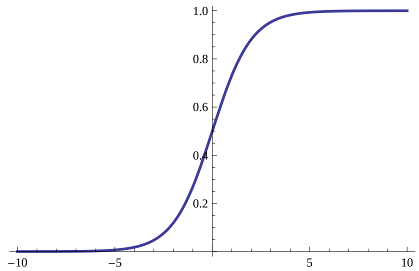

Figure 1: Sigmoidal function

an "undesired" attractor, the system (which corresponds to a living organism) will tend to an "undesired" attractor with possibly negative consequences. The problem is, using adjustable parameters, to redirect the vector $X(t)$ from an "undesired" attractor to a normal one. Mathematically (in a model) this can be sometimes done by skillfully tuning the system. More discussion on this subject can be found in [10]. In the system considered in [10], the dimensionality of the system is not too large (60 nodes, of which three nodes only were attractive). The sigmoidal function is presented in Figure 1.

2 Problem Formulation

Our model is formulated in terms of the system of ODE of the form

$$\begin{cases} x_1' = \frac{1}{1+e^{-\mu_1(w_{11}x_1+w_{12}x_2+\ldots+w_{1n}x_n-\theta_1)}} - x_1, \\ x_2' = \frac{1}{1+e^{-\mu_2(w_{21}x_1+w_{22}x_2+\ldots+w_{2n}x_n-\theta_2)}} - x_2, \\ \ldots \\ x_n' = \frac{1}{1+e^{-\mu_n(w_{n1}x_1+w_{n2}x_2+\ldots+w_{nn}x_n-\theta_n)}} - x_n, \end{cases} \quad (1)$$

This system contains the function $f(z)$, where the argument z is substituted by formations like $-\mu_1(w_{11}x_1 + w_{12}x_2 + w_{13}x_3 - \theta_1)$. The function $f(z)$ may be any sigmoidal function, which is supposed to be strictly monotone with $f(-\infty) = 0$ and $f(+\infty) = 1$. We use the function $f(z) = \frac{1}{1+e^{-z}}$.

The regulatory matrix contains information about relation between elements of a network (any element can be positive, negative, or zero, meaning activation, inhibition, or no relation).

$$W = \begin{pmatrix} w_{11} & w_{12} & \ldots & w_{1n} \\ w_{21} & w_{22} & \ldots & w_{2n} \\ \ldots & & & \\ w_{n1} & w_{n2} & \ldots & w_{nn} \end{pmatrix}. \quad (2)$$

The so called equilibria (or, alternatively, critical points) can be found from the system

$$\begin{cases} x_1 = \dfrac{1}{1+e^{-\mu_1(w_{11}x_1+w_{12}x_2+\ldots+w_{1n}x_n-\theta_1)}}, \\ x_2 = \dfrac{1}{1+e^{-\mu_2(w_{21}x_1+w_{22}x_2+\ldots+w_{2n}x_n-\theta_2)}}, \\ \ldots \\ x_n = \dfrac{1}{1+e^{-\mu_n(w_{n1}x_1+w_{n2}x_2+\ldots+w_{nn}x_n-\theta_n)}}, \end{cases} \quad (3)$$

Stable equilibria, that is, equilibria that attracts nearby points of the phase space, consisting of points $(x_1, \ldots, x_n)$, are the simplest attractors. Example will be provided in the next sections.

Remark. System (3) had appeared in [11] (see also [12]), in connection with the theory of neuronal networks. It was used also when designing telecommunication networks [13], [1], [2]. Chaotic behaviour was studied in [19], [20].

In what follows we use the qualitative methods, such as phase space analysis, linearizations around the equilibria and the nullclines method. Examples were studied using computer tools for quantitative analysis and visualizations. Calculations were carried out and graphics were created using the program Wolfram Mathematica.

3 Two-element GRN

We consider first the two-element network. The current state of this network is described by the two-dimensional vector $X(t) = (x_1(t), x_2(t))$. This vector can change in time t and our goal is to follow these changes and to predict where it goes in the future. The vector $X(t)$ is conveniently visualized in the (x_1, x_2)-plane, which is the phase plane for the system (4). The evolution of $X(t)$ is governed by the system of differential equations, where on the left side the derivatives are, which can be interpreted as directions for the movements of $x_1(t)$ and $x_2(t)$, and on the right side are formulas for computation these derivatives. If the initial state $X(0)$ is given, the trajectory is defined in phase plane, which generally tends to an attractor. Our goal is to clarify the number, nature, location and properties of attractors.

The system of ODE has the form

$$\begin{cases} x_1' = \frac{1}{1+e^{-\mu_1(w_{11}x_1+w_{12}x_2-\theta_1)}} - x_1, \\ x_2' = \frac{1}{1+e^{-\mu_2(w_{21}x_1+w_{22}x_2-\theta_2)}} - x_2, \end{cases} \quad (4)$$

The regulatory matrix is

$$W = \begin{pmatrix} w_{11} & w_{12} \\ w_{21} & w_{22} \end{pmatrix}, \quad (5)$$

where w_{11} and w_{22} are auto-activation of x_1 and x_2, w_{12} is the impact of x_2 on x_1 and, w_{21} is the

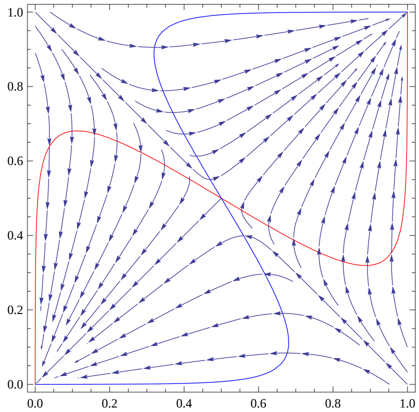

Figure 2: The vector field and nullclines, matrix W as in (6)

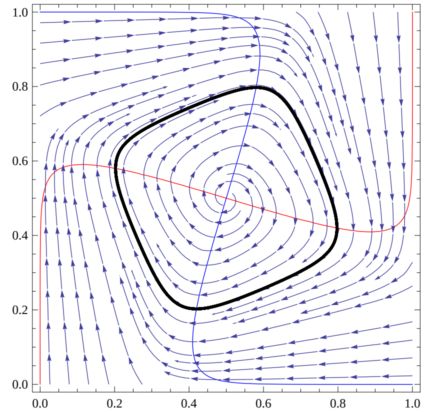

Figure 3: The vector field, nullclines and the periodic attractor, matrix W as in (7)

impact of x_1 on x_2. We recall that positive w_{ij} means activation, while negative is for inhibition, and zero value means no relation. The absolute value of w_{ij} measures the intensity of influence.

Having this in mind, let us investigate the phase portraits of the system (4). First, let the regulatory matrix be

$$W = \begin{pmatrix} 1 & 1 \\ 1 & 1 \end{pmatrix}, \tag{6}$$

This is called full activation. In the picture below we see the vector field, defined by the respective system (4). Trajectories $(x_1(t), x_2(t))$ have to follow the vector field. Any trajectory can be understood as parametrically defined (by time t) curve in phase plane. Looking at the picture, the observer can get impression of the general behavior of trajectories. There are also two nullclines. Nullclines (two of them) are curves, where the vector field is directed horizontally or vertically. The point of intersection of nullclines is special. The vector field is zero there. The respective trajectory is a point, and the corresponding solution is constant, can be written as $x_1(t) = a$, $x_2(t) = b$, where a, b are the coordinates. We see, that two side points are attractive. Our conclusion is that in this case the attractor is a union of two attractive equilibria. It is to be added, that equilibria can exist only in the unity cube $Q_2 = \{(x_1, x_2) : x_1 \in (0, 1), x_2 \in (0, 1)\}$.

Let us switch to the case

$$W = \begin{pmatrix} 1 & 2 \\ -2 & 1 \end{pmatrix}, \tag{7}$$

The phase portrait for this case is depicted in Figure 3. We see circular vector field, which need not necessarily produce closed (circular) trajectories. But this is the case for our choice of parameters. There is a single equilibrium (cross-point of two nullclines) in Figure 3. This point is not attractive, despite of the fact, that trajectories are winding around it. The trajectories spiral out of this critical point. On the other hand, the unity cube Q_2 is the so called invariant set for system (4). This means that the vector field on the boundary of Q_2 is directed inside Q_2. So no trajectory can escape Q_2. As a result of these two opposite trends, the closed trajectory exists, which corresponds to the periodic solution. We see, that this trajectory is attractive. So it is the so called limit cycle. It is a new kind of attractors. Periodic solutions correspond to biological oscillations, and generally they arre of great interest both for mathematicians and biologists.

Remark. More on two-dimensional systems can be found in [14], [15], [16], [18]. Extension of [14] to the n-dimensional case is in [17]. To be able for one to repeat the numerical experiments above, other parameters should be known. In both cases $\mu_1 = \mu_2 = 10$, in the examples corresponding to Figure 2 and Figure 3 the values of θ are respectively $\theta_1 = \theta_2 = 1$ and $\theta_1 = 1.5$, $\theta_2 = -0.5$.

4 Three-element GRN

In this section we treat the three-dimensional networks, described by the system

$$\begin{cases} x_1' = \frac{1}{1+e^{-\mu_1(w_{11}x_1+w_{12}x_2+w_{13}x_3-\theta_1)}} - x_1, \\ x_2' = \frac{1}{1+e^{-\mu_2(w_{21}x_1+w_{22}x_2+w_{23}x_3-\theta_2)}} - x_2, \\ x_3' = \frac{1}{1+e^{-\mu_3(w_{31}x_1+w_{32}x_2+w_{33}x_3-\theta_3)}} - x_3. \end{cases} \tag{8}$$

It is an easy matter to provide examples of attractors, that are sets of attractive equilibria. Their number is finite always and cannot be greater than 27. Instead of considering attractive equilibria, we will look for attractive closed trajectories in three-dimensional phase space. We will need some formulas. The three-dimensional nullclines are defined by the equations

$$\begin{cases} x_1 = \dfrac{1}{1+e^{-\mu_1(w_{11}x_1+w_{12}x_2+w_{13}x_3-\theta_1)}}, \\[2ex] x_2 = \dfrac{1}{1+e^{-\mu_2(w_{21}x_1+w_{22}x_2+w_{23}x_3-\theta_2)}}, \\[2ex] x_3 = \dfrac{1}{1+e^{-\mu_3(w_{31}x_1+w_{32}x_2+w_{33}x_3-\theta_3)}}. \end{cases} \tag{9}$$

Any of these equations defines a three-dimensional surface. On a certain nullcline the vector field, defined by the system (8), is directed in either x_1, or in x_2, or in x_3 direction. The cross-points of nullclines are equilibria, where the vector field is zero. At least one equilibrium must exist and all equilibria are in the three dimensional unity cube $Q_3 = \{(x_1, x_2, x_3) : x_1 \in (0,1), x_2 \in (0,1), x_3 \in (0,1)\}$.

Consider system (8), where the regulatory matrix is

$$W = \begin{pmatrix} k & 1 & -1 \\ -1 & k & 1 \\ 1 & -1 & k \end{pmatrix}. \tag{10}$$

The matrix (10) contains the so called inhibitory cycle, represented by the matrix

$$W = \begin{pmatrix} 0 & 0 & -1 \\ -1 & 0 & 0 \\ 0 & -1 & 0 \end{pmatrix}. \tag{11}$$

This last matrix tells us that the respective network is arranged according the scheme

$$x_1 \Leftarrow x_3 \Leftarrow x_2 \Leftarrow x_1,$$

where $\Leftarrow$ means repression (inhibition). This cycle leads to periodic oscillations. More discussion on this subject can be found in [23], [24], [25], [26]. Let us return to (10) and set $k = 1.2$. The periodic attractor emerges, as we see in Figure 4. Figure 5 shows the graphs of $x_1(t), x_2(t), x_3(t)$. One can deduce that at the beginning these solutions were not periodic, but then they tend to the periodic attractor. The attractor in 3D is presented in Figure 6. Lastly, the solutions of x1,x2,x3 are presented in Figure 7.

Computations show that the attractor in the form of a periodic solution exists for any $k \in (0.9, 3.5)$ for appropriately chosen θ_i. In all cases $\mu_1 = \mu_2 = \mu_3 = 5$.

Consider $k = 3.2$. The periodic attractor exists. There is at least one attractive equilibrium. Therefore attractors of different kind can coexist.

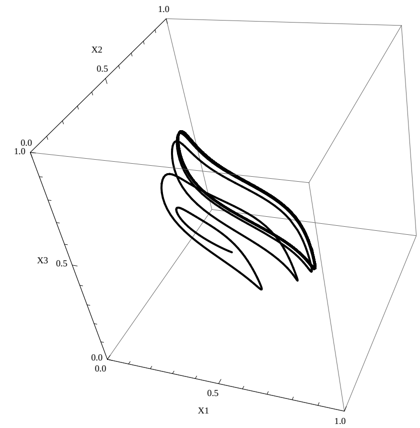

Figure 4: Attractor in 3D, $k = 1.2$

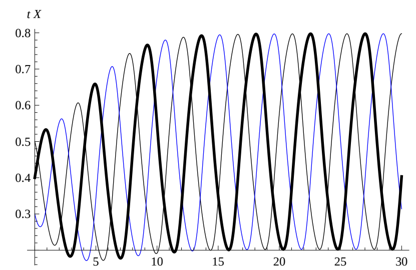

Figure 5: Solutions $x_1(t), x_2(t), x_3(t)$, $k = 1.2$

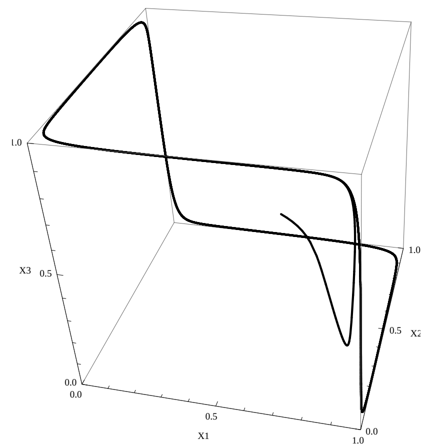

Figure 6: Attractor in 3D, $k = 3.2$

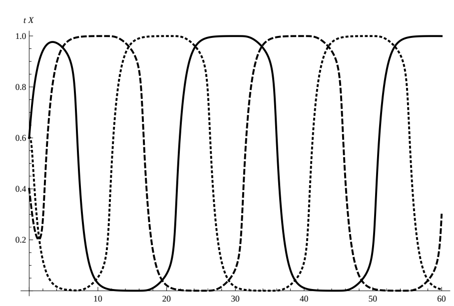

Figure 7: Solutions $x_1(t), x_2(t), x_3(t)$, (solid, dotted, dashed), $k = 3.2$

Remark. More on three-dimensional systems can be found in [19], [21], [22]. Parameters θ_i for any i were chosen as $\theta_i = 0.5k$ in order the equilibrium to be at the center of Q_3, that is, at the point $(0.5, 0.5, 0.5)$.

We conclude that attractors in the form of periodic solutions, coexisting with attractive point equilibria, are possible in three-dimensional systems (networks).

5 Four-element GRN

Consider the fourth-element network and model of the form

$$\begin{cases} x_1' = \frac{1}{1+e^{-\mu_1(w_{11}x_1+w_{12}x_2+w_{13}x_3+w_{14}x_4-\theta_1)}} - v_1x_1, \\ x_2' = \frac{1}{1+e^{-\mu_2(w_{21}x_1+w_{22}x_2+w_{23}x_3+w_{24}x_4-\theta_2)}} - v_2x_2, \\ x_3' = \frac{1}{1+e^{-\mu_3(w_{31}x_1+w_{32}x_2+w_{33}x_3+w_{34}x_4-\theta_3)}} - v_3x_3, \\ x_4' = \frac{1}{1+e^{-\mu_4(w_{41}x_1+w_{42}x_2+w_{43}x_3+w_{44}x_4-\theta_4)}} - v_4x_4, \end{cases} \tag{12}$$

where the regulatory matrix is

$$W = \begin{pmatrix} w_{11} & w_{12} & w_{13} & w_{14} \\ w_{21} & w_{22} & w_{23} & w_{24} \\ w_{31} & w_{32} & w_{33} & w_{34} \\ w_{41} & w_{42} & w_{43} & w_{44} \end{pmatrix}. \tag{13}$$

The attractors are possible in the form of stable equilibria. Periodic trajectories are possible also. We can use the previous example of two-dimensional system to show the periodic attractor.

Let the regulatory matrix be in the form of

$$W = \begin{pmatrix} 1 & 2 & 0 & 0 \\ -2 & 1 & 0 & 0 \\ 0 & 0 & 1 & 2 \\ 0 & 0 & -2 & 1 \end{pmatrix}. \tag{14}$$

Consider the system (12), where the coefficients w_{ij} are as in (14), $\mu_i = 10$, $i = 1, 2, 3, 4$, $\theta_1 = \theta_3 = 1.2$, $\theta_2 = \theta_4 = -0.7$. The attractor is a four-dimensional object, which cannot be viewed, but the two-dimensional (less informative) and three-dimensional projections are available. Two projections are depicted in Figure 8 and Figure 9.

By slightly changing the diagonal elements in (14), consider the new regulatory matrix

$$W = \begin{pmatrix} 0.4 & 2 & 0 & 0 \\ -2 & 0.5 & 0 & 0 \\ 0 & 0 & 0.7 & 2 \\ 0 & 0 & -2 & 0.8 \end{pmatrix}. \tag{15}$$

Other parameters are left unchanged. The new system (12) has another attractor. Some projections of a solution (the initial values are $x_1(0) =$

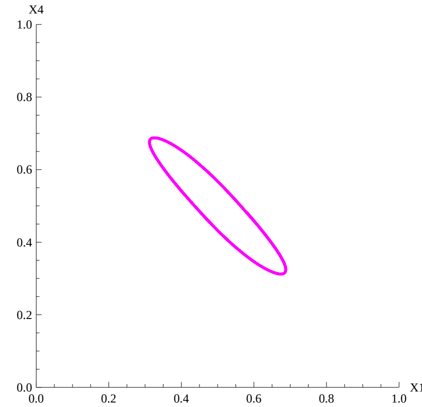

Figure 8: (x_1, x_4)-projection of the 4D attractor.

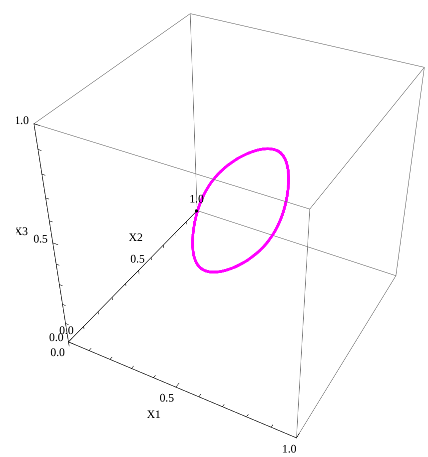

Figure 9: (x_1, x_2, x_3)-projection of the 4D attractor

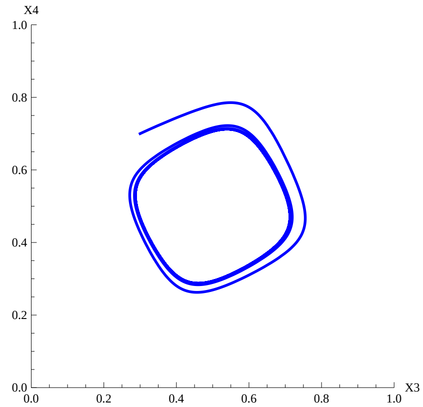

Figure 10: (x_3, x_4)-projection of the 4D solution.

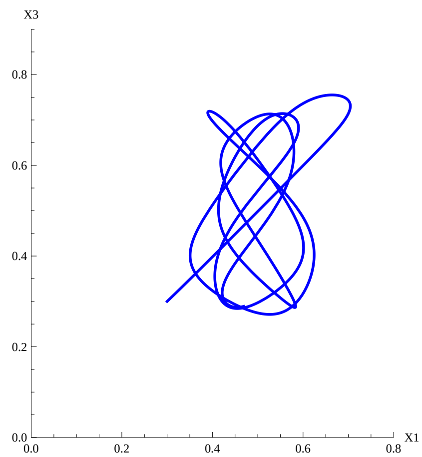

Figure 11: (x_1, x_3)-projection of the 4D solution.

$x_3(0) = 0.3$, $x_2(0) = x_4(0) = 0.7$) tending to this new attractor are depicted in the below four figures from Figure 10, Figure 11, Figure 12, and Figure 13. Similarly, the graphs of each component of the attractor is presented in Figure 14.

The three dimensional projections of the four-dimensional attractor follow.

To be confirmed that this attractor (with the matrix (15)) let us construct the graphs of each component $x_i(t)$, $i = 1, 2, 3, 4$ of the attractor. In the below picture the graphs of each component of the attractor are depicted, $x_1(t)$ thin black, $x_2(t)$ thin blue, $x_3(t)$ thick black, $x_4(t)$ thick blue.

6 Conclusion

The same method of constructing attractors can be used for higher dimensional systems. Any combinations of 2D, 3D, 4D attractors can be combined in a high dimensional system, which will be uncoupled. The respective matrix W would be a block matrix with block elements along the main diagonal. This would be the starting point of finding attractors in realistic large systems, filling the zero spaces by appropriate val-

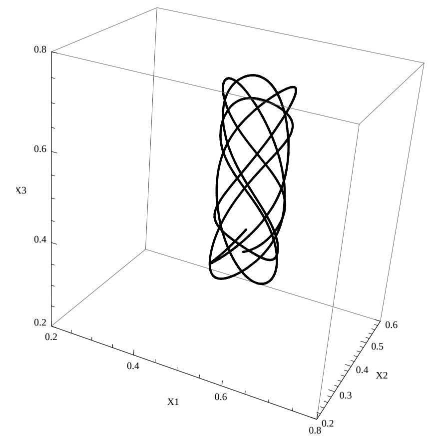

Figure 12: (x_1, x_2, x_3)-projection of the 4D solution.

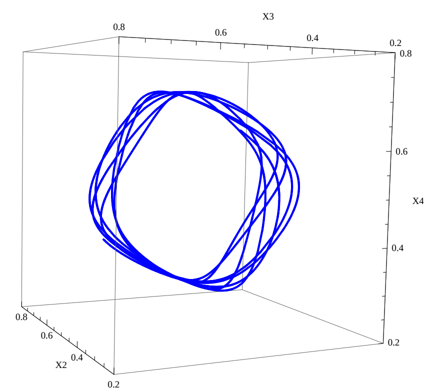

Figure 13: (x_2, x_3, x_4)-projection of the 4D solution.

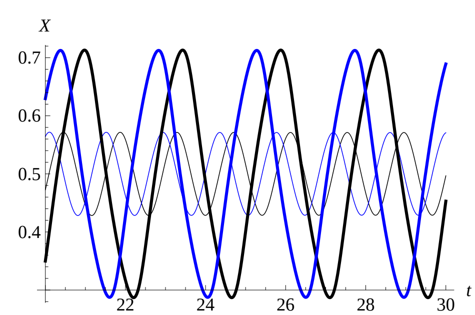

Figure 14: The graphs of each component of the attractor

ues. It is worth to mention, that the network in the work [10] consists of only sixty elements with only 195 adjustable parameters.

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Conflicts of Interest

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