Models of genetic networks with given properties

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Abstract: A multi-parameter system of ordinary differential equations, modelling genetic networks, is considered. Attractors of this system correspond to future states of a network. Sufficient conditions for the non-existence of stable critical points are given. Due to the special structure of the system, attractors must exist. Therefore the existence of more complicated attractors was expected. Several examples are considered, confirming this conclusion.

Key-Words: Mathematical model, dynamical system, attractors, genetic regulatory networks

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1 Introduction

We consider systems of ordinary differential equations of the form

$$\begin{cases} \dfrac{dx}{dt} = \dfrac{1}{1+e^{-\mu_1(w_{11}x+w_{12}y+w_{13}z-\theta_1)}} - v_1 x, \\[2ex] \dfrac{dy}{dt} = \dfrac{1}{1+e^{-\mu_2(w_{21}x+w_{22}y+w_{23}z-\theta_2)}} - v_2 y, \\[2ex] \dfrac{dz}{dt} = \dfrac{1}{1+e^{-\mu_3(w_{31}x+w_{32}y+w_{33}z-\theta_3)}} - v_3 z \end{cases} \tag{1}$$

Such systems arise in the theory of complex networks, such as telecommunication ones [4], genetic networks [3], [2], [7], [1], [6], [11], [12], neuronal networks [9], [5]. More information can be found in the review papers [3], [8] and others. In models of genetic regulatory networks (GRN in short) nonlinear functions on the right side describe interrelation between genes. They communicate by protein expression, sending messages to each other. In such a way a collective reaction of a network is formed. In the system (1) the function $f(z) = \frac{1}{1+e^{-\mu z}}$ is sigmoidal. Sigmoidal functions are monotonically increasing from zero to unity. These functions are most suitable for modeling purposes. The parameters μ_i are positive. The linear part in (1) describes the natural decay of a network if there are no connections between genes. The parameters θ can be any numbers and in many cases they are adjustable. The coefficients w_{ij} are the entries of the regulatory matrix W that describes links between genes. A positive element w_{ij} means activation the i-th gene by j-th one. Negative coefficient means repression (inhibition), zero means no relation. The change of one entry of matrix W leads to rearrangement of the whole network. The collective response of GRN to changes in environment can be developed quickly. The current state of GRN is represented by the state vector $X(t) = (x_1, \ldots, x_n(t))$. The dimension n in system (1) is three. Mathematically $X(t)$ is the solution vector of system (1). Properties of system (1) are such that it has an invariant set in the phase space R^3. This set is a parallelepiped $Q_3 = \{0 < x_i < 1/v_i,\ i = 1, 2, 3\}$. Due to the properties of sigmoidal functions the vector field defined by system (1), is directed inwards of the region Q_3. The trajectories $X(t)$ are therefore trapped in Q_3. The attractors of system (1) must exist in Q_3. Future states of a network are heavily dependent on the number, location and properties of attractors. The structure and properties of attractors for system (1) are to be studied.

Equilibria of system (1) always exist and are located in the domain Q_3. Equilibria are solutions of the system

$$\begin{cases} v_1 x = \dfrac{1}{1+e^{-\mu_1(w_{11}x+w_{12}y+w_{13}z-\theta_1)}}, \\ v_2 y = \dfrac{1}{1+e^{-\mu_2(w_{21}x+w_{22}y+w_{23}z-\theta_2)}}, \\ v_3 z = \dfrac{1}{1+e^{-\mu_3(w_{31}x+w_{32}y+w_{33}z-\theta_3)}}. \end{cases} \quad (2)$$

The system (2) consist of three equations which define the nullclines. Three nullclines can intersect only in Q_3. Indeed, suppose that the critical point (x^*, y^*, z^*) locates outside Q_3. Then some coordinate, say x^*, either is negative or greater than $1/v_1$. This contradicts the properties of the sigmoidal function in the right side (recall that the range of values of a sigmoidal function is $(0, 1)$). The number of intersections is finite, but cannot be zero. A unique cross-point is possible, as examples show.

Our intent in this paper is to clarify the following situation. Imagine that there is a unique critical point (an equilibrium), which is not attractive. The sufficient condition for non-attractivity is positivity of a real part of at least one characteristic number λ. The characteristic numbers can be computed for any equilibrium using the standard analysis of the linearized equation. We will provide the necessary information in the next section. If a unique critical point is not attractive, there are other attractors.

We pass to description of our results in this direction. We provide the sufficient conditions, in terms of the coefficients of W and parameters of the system (1), for a critical point to be non-attractive. We construct then the examples, where our conditions are applicable. In these examples the critical point is unique. Therefore an attractor of more complicated structure should exist. We have discovered them. To be more specific, our intent is to provide conditions for existence of equilibria with the characteristic numbers $\lambda_1 \in R$, $\lambda_{2,3} = \alpha \pm \beta i$, where $\alpha > 0$, $i = \sqrt{-1}$.

2 Problem Formulation

Consider system (1), where $v_1 = v_2 = v_3 = 1$, for simplicity.

The critical points are solutions of the system

$$\begin{cases} x = \dfrac{1}{1+e^{-\mu_1(w_{11}x+w_{12}y+w_{13}z-\theta_1)}} \\ y = \dfrac{1}{1+e^{-\mu_2(w_{21}x+w_{22}y+w_{23}z-\theta_2)}}, \\ z = \dfrac{1}{1+e^{-\mu_3(w_{31}x+w_{32}y+w_{33}z-\theta_3)}}. \end{cases} \quad (3)$$

The linearized system at a critical point (x^*, y^*, z^*) is

$$\begin{cases} u_1' \quad = -u_1 + \mu_1 w_{11} g_1 u_1 \\ \quad +\mu_1 w_{12} g_1 u_2 + \mu_1 w_{13} g_1 u_3, \\ u_2' \quad = -u_2 + \mu_2 w_{21} g_2 u_1 \\ \quad +\mu_2 w_{22} g_2 u_2 + \mu_2 w_{23} g_2 u_3, \\ u_3' \quad = -u_3 + \mu_3 w_{31} g_3 u_1 \\ \quad +\mu_3 w_{32} g_3 u_2 + \mu_3 w_{33} g_3 u_3, \end{cases} \quad (4)$$

where

$$g_1 = \frac{e^{-\mu_1(w_{11}x^*+w_{12}y^*+w_{13}z^*-\theta_1)}}{[1+e^{-\mu_1(w_{11}x^*+w_{12}y^*+w_{13}z^*-\theta_1)}]^2},$$

$$g_2 = \frac{e^{-\mu_2(w_{21}x^*+w_{22}y^*+w_{23}z^*-\theta_2)}}{[1+e^{-\mu_2(w_{21}x^*+w_{22}y^*+w_{23}z^*-\theta_2)}]^2},$$

$$g_3 = \frac{e^{-\mu_3(w_{n1}x^*+w_{n2}y^*+w_{33}z^*-\theta_3)}}{[1+e^{-\mu_3(w_{31}x^*+w_{32}y^*+w_{33}z^*-\theta_3)}]^2}.$$

Properties of a critical point (x^*, y^*, z^*) are described by the three numbers (they are called the characteristic numbers) λ_1, λ_2, λ_3, which can be found from the chracteristic equation. One has

$$\det(A - \lambda I) = 0, \quad (5)$$

where A is 3×3 matrix of the coefficients of the system (4), I is the unity 3×3 matrix.

The equation (5) is complicated, since it requires computation of the partial derivatives g_i at the critical point (x^*, y^*, z^*). It can be simplified, however, in this way. Observe, from (3), that

$$\begin{array}{l} e^{-\mu_1(w_{11}x^*+w_{12}y^*+w_{13}z^*-\theta_1)} = \frac{1}{x^*} - 1, \\ e^{-\mu_2(w_{21}x^*+w_{22}y^*+w_{23}z^*-\theta_2)} = \frac{1}{y^*} - 1, \\ e^{-\mu_3(w_{31}x^*+w_{32}y^*+w_{33}z^*-\theta_3)} = \frac{1}{z^*} - 1. \end{array} \quad (6)$$

Then $g_1 = \dfrac{\frac{1}{x^*} - 1}{\frac{1}{x^{*2}}} = (1 - x^*)x^*$ and, similarly, $g_2 = (1 - y^*)y^*$, $g_3 = (1 - z^*)z^*$.

The entries a_{ij} of the matrix $A - \lambda I$, needed for construction of the characteristic equation, are:
$a_{11} = \mu_1 w_{11}(1 - x^*)x^* - 1 - \lambda$,
$a_{12} = \mu_1 w_{12}(1 - x^*)x^*$,

$a_{13} = \mu_1 w_{13}(1-x^*)x^*,$
$a_{21} = \mu_2 w_{21}(1-y^*)y^*,$
$a_{22} = \mu_2 w_{22}(1-y^*)y^* - 1 - \lambda,$
$a_{23} = \mu_2 w_{23}(1-y^*)y^*,$
$a_{31} = \mu_3 w_{31}(1-z^*)z^*,$
$a_{32} = \mu_3 w_{32}(1-z^*)z^*,$
$a_{33} = \mu_3 w_{33}(1-z^*)z^* - 1 - \lambda.$

Choice of θ-s. The coordinates of a critical point (x^*, y^*, z^*) are solutions of the system (3). Observe, that if $x^* = y^* = z^* = 0.5$, then for θ_i such that

$$\begin{aligned} w_{11} + w_{12} + w_{13} &= 2\,\theta_1, \\ w_{21} + w_{22} + w_{23} &= 2\,\theta_2, \\ w_{31} + w_{32} + w_{33} &= 2\,\theta_3, \end{aligned} \tag{7}$$

the numbers $x^* = y^* = z^* = 0.5$ solve the system (3).

Assumption θ. We assume that θ_i satisfy (7).

Conclusion Θ. The entries a_{ij} of the matrix $A - \lambda I$, needed for construction of the characteristic equation, become:
$a_{11} = \mu_1 w_{11} 0.25 - 1 - \lambda,$
$a_{12} = \mu_1 w_{12} 0.25,$
$a_{13} = \mu_1 w_{13} 0.25,$
$a_{21} = \mu_2 w_{21} 0.25,$
$a_{22} = \mu_2 w_{22} 0.25 - 1 - \lambda,$
$a_{23} = \mu_2 w_{23} 0.25,$
$a_{31} = \mu_3 w_{31} 0.25,$
$a_{32} = \mu_3 w_{32} 0.25,$
$a_{33} = \mu_3 w_{33} 0.25 - 1 - \lambda.$

Choice of μ-s. For easier calculations, we would like to make the products $\mu_i 0.25$ in the above elements equal to unity. Therefore we choose $\mu_i = 4$ for $i = 1, 2, 3$.

Assumption μ. We assume that $\mu_i = 4$ for $i = 1, 2, 3$.

Conclusion μ. The entries a_{ij} of the matrix $A - \lambda I$, needed for construction of the characteristic equation, become:
$a_{11} = w_{11} - 1 - \lambda,$
$a_{12} = w_{12},$
$a_{13} = w_{13},$
$a_{21} = w_{21},$
$a_{22} = w_{22} - 1 - \lambda,$
$a_{23} = w_{23},$
$a_{31} = w_{31},$
$a_{32} = w_{32},$
$a_{33} = w_{33} - 1 - \lambda.$

2.1 Characteristic equation

We are now in a position to construct the characteristic equation for the critical point $(0.5, 0.5, 0.5)$ assuming that Assumption θ and Assumption μ hold. Computing the determinant of the matrix $A - \lambda I$, we obtain the equation

$$\begin{aligned} &\Lambda^3 - (w_{11} + w_{22} + w_{33})\Lambda^2 \\ &-(w_{21}w_{12} - w_{11}w_{22} + w_{31}w_{13} \\ &+w_{32}w_{23} - w_{11}w_{33} - w_{22}w_{33})\Lambda \\ &-(-w_{31}w_{22}w_{13} + w_{21}w_{32}w_{13} \\ &+w_{31}w_{12}w_{23} - w_{11}w_{32}w_{23} \\ &-w_{21}w_{12}w_{33} + w_{11}w_{22}w_{33}) = 0, \end{aligned} \tag{8}$$

$$\Lambda = \lambda + 1. \tag{9}$$

Rewrite (8) in a compact form

$$\Lambda^3 + P\Lambda^2 + Q\Lambda + R = 0, \tag{10}$$

where

$$P = -(w_{11} + w_{22} + w_{33}), \tag{11}$$

$$\begin{aligned} Q = \; & -(w_{21}w_{12} - w_{11}w_{22} + w_{31}w_{13} \\ & +w_{32}w_{23} - w_{11}w_{33} - w_{22}w_{33}), \end{aligned} \tag{12}$$

$$\begin{aligned} R = \; & -(-w_{31}w_{22}w_{13} + w_{21}w_{32}w_{13} + w_{31}w_{12}w_{23} \\ & -w_{11}w_{32}w_{23} - w_{21}w_{12}w_{33} + w_{11}w_{22}w_{33}). \end{aligned} \tag{13}$$

Equation (10) for the variable λ is

$$\lambda^3 + (3+P)\lambda^2 + (3+2P+Q)\lambda + (1+P+Q+R) = 0. \tag{14}$$

2.2 Problem

We can now formulate the problem. Up to now we have made the choice of the parameters v_i, θ_i and μ_i. The critical point under consideration is placed to the location $(0.5, 0.5, 0.5)$ by the choice of θ_i.

Our plan is the following:

1) we make the point $(0.5, 0.5, 0.5)$ non-attractive by the appropriate choice of the entries in the matrix W;

2) under the assumption that this point is unique we are led to the conclusion, that there are no attractive equilibria in the cube Q_3;

3) Then there must exist other attractors.

3 Problem Solution

We assume that there is a single critical point and it is placed in the middle point by an appropriate choice of the parameters θ. We wish to make this point non-attractive by the choice of other parameters and matrix W.

3.1 Routh - Gurwitz criterion and related material

Let us recall the Routh-Gurwitz conditions for the third order equations. Consider

$$a_3 s^3 + a_2 s^2 + a_1 s + a_0 = 0. \tag{15}$$

Our trusted source of information is [10].
Consider the Table:

$$\begin{array}{lcc} s^3 & a_3 & a_1 \\ s^2 & a_2 & a_0 \\ s & \frac{a_2 a_1 - a_0 a_3}{a_2} & \\ s^0 & a_0 & \end{array} \tag{16}$$

This table is called *Routh array.*

Proposition 3.1. *The number of roots in the open right half-plane is equal to the number of sign changes in the first column of Routh array.*

Proposition 3.2. *If 0 appears in the first column in nonzero row in Routh array, replace it with a small positive number. In this case, polynomial has some roots in the open right half-plane (RHP).*

Proposition 3.3. *If zero row appears in Routh array, polynomial has roots either on the imaginary axis or in RHP.*

Proposition 3.4. *If all zeros are in the left half plane (LHP), then all a_k are of the same sign.*

Corollary 1. *If there is sign change in a_k then some zero is not in the LHP.*

Theorem 1. *If $(3+P)$ or $(3+2P+Q)$ or $(1+P+Q+R)$ is negative in (14), then some λ is not in the LHP.*

Example 1. $3+P<0$.
Take $\mu_i = 4$, $3-(w_{11}+w_{22}+w_{33})<0$. All others w_{ij} are taken randomly. To be specific, let $w_{11}=1$, $w_{22}=2$, $w_{33}=3$. Let $w_{ij}=+1$ for $i+j$ even, $w_{ij}=-1$ for $i+j$ odd. So the matrix

$$W = \begin{pmatrix} 1 & -1 & 1 \\ -1 & 2 & -1 \\ 1 & -1 & 3 \end{pmatrix}. \tag{17}$$

is suitable. Choose θ_i as recommended, so $\theta_1 = 0.5$, $\theta_2 = 0.0$, $\theta_3 = 1.5$. The characteristic equations is

$$\lambda^3 + (3+P)\lambda^2 + (3+2P+Q)\lambda + (1+P+Q +R) = \lambda^3 - 3\lambda^2 - \lambda + 1 = 0. \tag{18}$$

The Routh array is

$$\begin{array}{lcc} s^3 & 1 & -1 \\ s^2 & -3 & 1 \\ s & \frac{4}{3} & \\ s^0 & 1 & \end{array} \tag{19}$$

There are two sign changes in the first column of the Routh array.
Solving (18) with respect to λ, obtain

$$\lambda_1 = -0.675131, \quad \lambda_2 = 0.460811, \quad \lambda_3 = 3.21432.$$

The type of the equilibrium at $(0.5, 0.5, 0.5)$ is a 3D saddle point. There are other critical points, so the existence of attractors other than the stable equilibria is not observed.

Example 2. $3+2P+Q<0$.
Let the matrix be

$$W = \begin{pmatrix} 3 & 5 & 2 \\ -1 & 1 & 0 \\ 0 & 1 & -2 \end{pmatrix}. \tag{20}$$

The parameters μ_i and θ_i are chosen as usually. After simple calculations obtain $3+P=1$, $3+2P+Q=-1$, $1+P+Q+R=17$. The characteristic numbers are $\lambda_1 = -3.1$, $\lambda_{2,3} = 1.05 \pm 2.1i$. The critical point at $(0.5, 0.5, 0.5)$ is non-attractive.

Example 3. $1+P+Q+R<0$.
Choose six entries in the regulatory matrix and let the remaining three be arbitrary. Suppose $w_{ii}=0$ for $i=1,2,3$. Let $w_{13}=-1$, $w_{21}=-1$, $w_{32}=-1$. So the matrix W is of the form

$$W = \begin{pmatrix} 0 & w_{12} & -1 \\ -1 & 0 & w_{23} \\ w_{31} & -1 & 0 \end{pmatrix}. \tag{21}$$

Then

$$P=0,\ Q = w_{12}+w_{31}+w_{23},\ R = 1 - w_{31}w_{12}w_{23},$$

$$1+P+Q+R = 1 + w_{12}+w_{31}+w_{23}+1-w_{31}w_{12}w_{23}$$

and the condition $1+P+Q+R<0$ takes the form

$$w_{12}+w_{31}+w_{23} < w_{31}w_{12}w_{23} - 2. \tag{22}$$

The region is visualized in two pictures Fig. 1 and Fig. 2.
The elements $w_{12}=-2$, $w_{23}=-2$, $w_{31}=1$ are admissible.
For the matrix

$$W = \begin{pmatrix} 0 & -2 & -1 \\ -1 & 0 & -2 \\ 1 & -1 & 0 \end{pmatrix}, \tag{23}$$

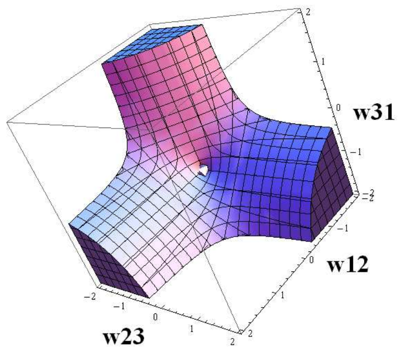

Figure 1: First view.

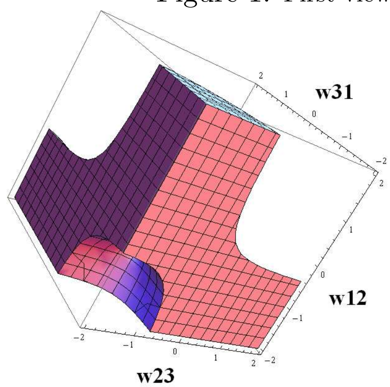

Figure 2: Second view.

parameter $\mu_i = 4$, $\theta_i = (w_{i1} + w_{i2} + w_{i3})/2$ the characteristic equation for the central point $(0.5, 0.5, 0.5)$ is

$$\lambda^3 + 3\lambda^2 - 0\lambda - 5 = 0. \tag{24}$$

The Routh array is

$$\begin{array}{ccc} s^3 & 1 & 0 \\ s^2 & 3 & -5 \\ s & \frac{5}{3} & \\ s^0 & -5 & \end{array} \tag{25}$$

There is one sign change in the first column.

The characteristic numbers for the point $(0.5, 0.5, 0.5)$ are

$$\lambda_1 = 1.1038, \quad \lambda_{2,3} = -2.0519 \pm 0.565236i.$$

The type of this critical point is an attractive focus and repelling in the remaining dimension. The point is not attractive, but there are other critical points and the existence of an attractor other than a stable equilibrium, cannot be guaranteed.

In the above examples we succeded in assigning the critical point $(0.5, 0.5, 0.5)$ the status of non-attracting point. There are, however, other critical points and some of them (or all of them) are attractive. In the next section we provide examples, where assumtions 1 and 2 of subsection 2.2 together are satisfied.

4 More examples

I. Consider system (1), where $\mu_i = 4$, $v_i = 1$, and the regulatory matrix

$$W = \begin{pmatrix} 1 & -a & -1 \\ -1 & 1 & -a \\ -a & -1 & 1 \end{pmatrix}. \tag{26}$$

Suppose $a \geq 0$. If $a = 0$, the matrix becomes

$$W = \begin{pmatrix} 1 & 0 & -1 \\ -1 & 1 & 0 \\ 0 & -1 & 1 \end{pmatrix}. \tag{27}$$

and it contains inhibitory cycle (three -1) and self-activation (three 1). The corresponding system (1) is known to have periodic solutions.

Consider system (1) with the matrix (28). Suppose that the parameters θ_i are chosen appropriately.

Computational experiments show that for $a = 0.1, 0.2, 0.3, 0.4, ..., 0.8$ there exists a periodic solution. There exists a single critical point at $(0.5, 0.5, 0.5)$.

For $a = 0.8$ the values $(3 + P)$, $(3 + 2P + Q)$, $(1 + P + Q + R)$, mentioned in Theorem 1, respectively are $0, -2.4, 1.512$. Therefore a single critical point has the real part in RHP.

The periodic solution exists also, depicted in the Figure 3.

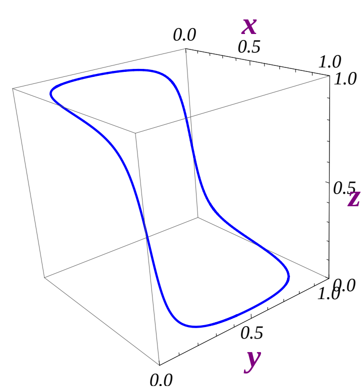

Figure 3: Stable periodic solution for $a = 0.8$

II. Consider Example 2 in the previous section. We have shown that the critical point at the center is not attractive. Visual inspection of nullclines confirm that this point is unique. It has the following characteristic numbers $\lambda_1 = -3.10$, $\lambda_{2,3} = 1.05 \pm 2.10i$.

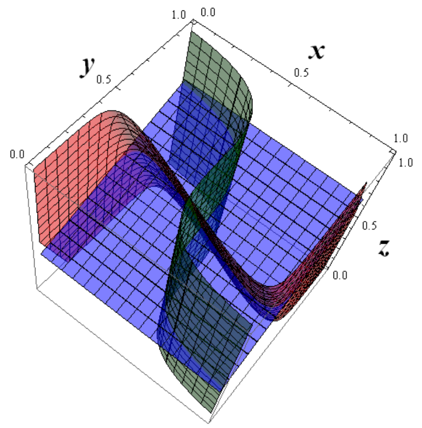

Figure 4: The nullclines in Example II.

Therefore another attractor is expected. It exists in the form of stable periodic solution.

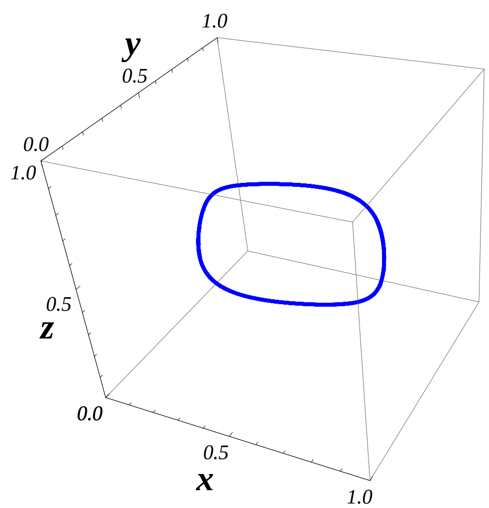

Figure 5: Stable periodic solution in Example II.

III. Consider system (1) with the previous choice of parameters and the regulatory matrix

$$W = \begin{pmatrix} 3 & 5 & 2 \\ -1 & 1 & 0 \\ 0 & 1 & 1 \end{pmatrix}. \tag{28}$$

The values $(3+P)$, $(3+2P+Q)$, $(1+P+Q+R)$, mentioned in Theorem 1, are $-2, 5, 2$. Therefore a single critical point has the real part in RHP. The craracteristic numbers are $\lambda_1 = -0.34$, $\lambda_{2,3} = 1.17 \pm 2.11i$. An attractor exists.

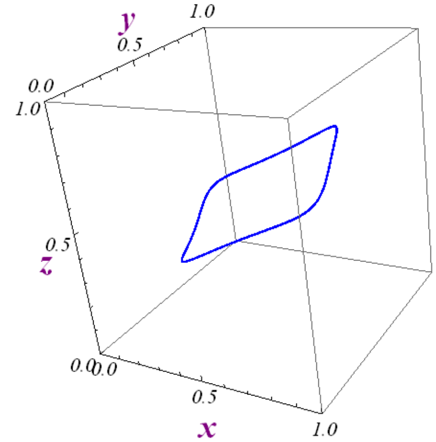

Figure 6: Stable periodic solution in Example III.

5 Conclusion

Using mathematical models can make the process of studying GRN easier and more effective. Given experimental data of some particular GRN, the mathematical model should be adjusted by the appropriate change of parameters. Afterward, the model can be studied using standard mathematical analysis tools. An inverse problem is to take an existed model and try to predict the properties of a real network, studying its model. In our research, we did something in this spirit. We try to select the characteristics of a network (respectively, the elements of the regulatory matrix W) in such a way, that the existence of stable equilibria is not allowed. This can reveal more complicated attractive sets on the phase space. We have obtained such conditions and tested them. In our examples, which were constructed, following the recommendations of Theorem 1, no stable equilibria can appear. Instead, we got stable periodic attractors. In perspective, considering models with several critical points of non-attractive nature, we hope to get attractors of the next level of complicacy. Recall, that the popular Lorenz attractor is based on three equilibria, two of them are non-attractive saddle focuses and one is a saddle point.

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