Remarks on Inhibition

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Abstract: In networks, which arise in multiple applications, the inhibitory connection between elements occur. These networks appear in genetic regulation, neuronal interactions, telecommunication designs, electronic devices. Mathematical modelling of such networks is an efficient tool for their studying. We consider the specific mathematical model, which uses systems of ordinary differential equations of a special form. The solution vector X(t) describes the current state of a network. Future states are dependent on the structure of the phase space and emerging attractive sets. Attractors, their properties and locations depend on the parameters in a system. Some of these parameters are adjustable. The important problem of managing and control over the system, is considered also.

Key-Words: inhibition, differential equations, networks, attractors

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1 Introduction

Networks appear everywhere, since collections of elements of any kind, connected by some links, can be met in nature and everyday life. We focus on evolution of networks with special properties. These networks consist of elements, which will be denoted x_i. They can interact and the rules for interaction are specified using the regulatory square matrix W. Each element can activate or repress the activity of another one, the case of no relation is not excluded. To be specific, in what follows we will consider three-element networks.

The matrix W in this case is 3 × 3 matrix

$$W = \begin{pmatrix} w_{11} & w_{12} & w_{13} \\ w_{21} & w_{22} & w_{23} \\ w_{31} & w_{32} & w_{33} \end{pmatrix} \qquad (0)$$

If, for instance, the element w_{12} is positive, this means that x_2 activates x_1. The symmetrical, with respect to transposition, element w_{21} characterizes the impact of x_1 to x_2. Self-activation of x_i is possible also, then $w_{ii}>0$. Looking ahead, let us say that dynamics of such networks can be described by the system of ordinary differential equations of the form

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

where, besides of the elements w_{ij}, multiple parameters μ and θ appear. Let us mention, that one of the first sources, where this system was studied, is the article [11] (see also [12]). Then, in another context, this system was used by the authors of the papers [1], [13], [17], [23]. It is a component of the mathematical model of genetic regulatory networks [6], [9], [17], [18], [23]. At the same time, this system was used for the purposes of the design of topology of telecommunication networks [1]. It was used also in modelling of neuronal networks [11], [17]. Due to various combinations of elements in the regulatory matrix, there are multiple types of behaviors in a network.

Inhibition is a process, where elements of a network influence each other in a specific way, depending on the nature of a process. In genetic regulatory networks each element (node) is thought as gene, expressing proteins as messages

to other nodes. Some other factors can be included in a network. Phenomenon of inhibition (sometimes called repression) was studied by researchers [4], [19], [20], [23].

We will be focused on systems of differential equations of the form (1) for n=2 and for n=3. We assume also that there is no self-inhibition. Mathematically this means that the diagonal elements are zeros.

The solution vector $X(t)=(x_1(t), \dots, x_n(t))$ is thought as the description of the current state of a model. In turn, the current state of a model can provide significant information of the modelled network. One of the main examples of networks, modelled by systems (1), are genetic regulatory networks (GRN). They exist in any cell of any living organism. These networks are responsible for development of an organism (morphogenesis), reactions to internal and external factors, including the resistance to some diseases [Cornelius], [Grebogy]. The system (1) in a two-dimensional form first appeared in the paper [Wilson]. This paper was devoted to modelling of populations in the neuronal networks. In a n-dimensional form this system was considered in [Brokan, Sadyrbaev, MMAS, 2018].

Our goal in this paper is to discuss some implications, that are typical for inhibition case. New results were obtained also. They are: periodic solutions in three-dimensional (3D, for brevity) systems; by multiple authors, for instance,

The structure of the paper is the following. Section 2 contains brief overview of the existing literature on the subject. The reminder and review of results concerning 2D systems ar included in Section 3. Section 4 is devoted to the study of 3D inhibitory systems. Some suggestions about higher-dimensional inhibitory systems are provided in Section 5. Conclusions section completes the paper. The reference list consists of relevant articles and texts, where the inhibition phemnomenon was studied. This list, definitely, is not full.

2 Literature Survey

This topic lies in the center of biomathematics and is extensively studied in the literature. We mention the works [7],[8],[10],[24], suitable for the first reading on the subject. The works [12],[13],[14] contain information on the system (1) and its genesis. For applications of system (1) in the fields other that GRN, one may consult the papers [1],[12],[13],[23]. Periodic solutions were studied and some example of periodic solutions were obtained in [4], [11],[21],[22]. Applications in medicine were considered in [2],[6]. Some specific problems concerning the study of GRN were treated in the remaining references.

3 Two-element network

The 2D system of the form (1) is

$$\begin{cases} x'_1 = \frac{1}{1+e^{-\mu_1(w_{11}x_1+w_{12}x_2-\theta_1)}} - x_1, \\ x'_2 = \frac{1}{1+e^{-\mu_2(w_{21}x_1+w_{22}x_2-\theta_2)}} - x_2. \\ \dots \end{cases}, \quad (2)$$

The main facts about this system are:

1. The unit cube is an invariant set (no trajectories can escape it);
2. There is at least one critical point inside a unit cube;
3. The vector field heavily depends on the regulatory matrix

$$W = \begin{pmatrix} w_{11} & w_{12} \\ w_{21} & w_{22} \end{pmatrix}. \quad (3)$$

We assume that all elements of this matrix are non-positive, but not all zeros.

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

Geometrical description of possible cases can be found in [5]. Assume that $w_{11}=w_{22}=0$, and two other elements are negative. The typical picture of nullclines together with the vector field, defined by system (2), is depicted in Figure 1, where $\mu_1=\mu_2=6$, $\theta_1= -0.5$, $\theta_2= -1.0$, $w_{12}=-2$, $w_{21}=-1$. The vector field is typical for this case ($w_{11}=w_{22}=0$) and it is not compatible with the periodic solution (closed trajectory).

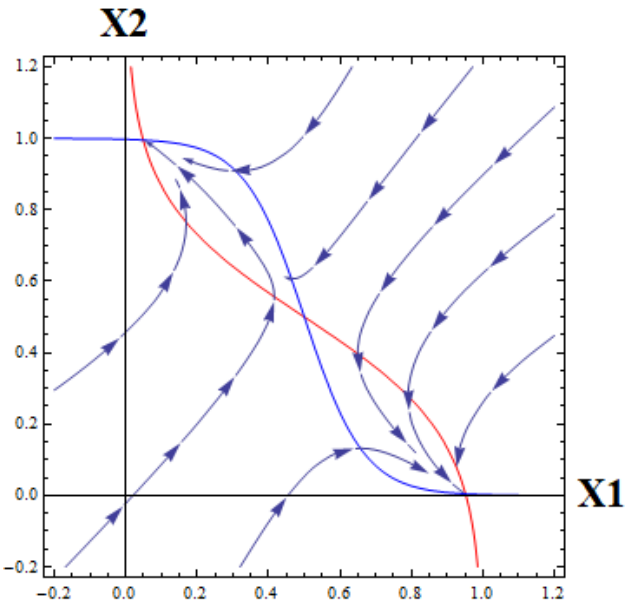

Figure 1.

Differential equations describe gene expression changes as a function of the expression of other genes and environmental factors. Thus, they are adequate to model the dynamic behavior of GRNs in a more quantitative manner [3].

Authors in work [4] give an example of realistic GRN. In this model, the cancerous states are identified with "undesired" attractors. The current state of GRN is described by the vector $X(t) = (x_1(t), \ldots, x_n(t))$, where t is 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.[4]

When mathematical modeling is used to predict the behavior of a GRN, the results need to be compared with experimental data. Developmental GRNs are built hierarchically from simple, recurring building blocks and motifs.[5]

4 Problem Formulation

The general form of writing the n-dimensional dynamical system, that is expected to model a genetic regulatory network, is

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

where $\mu_i > 0$ and θ_i are parameters, and w_{ij} are elements of the n x n regulatory matrix W. 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).

The nullclines of system (1) are given by the equations

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

The geometrical nullclines method is productive in the study of systems of ODE. Knowledge of nullclines allows to approximately feel the vector field, corresponding to a system of ODE. Besides, the critical points (equilibria) are the cross-points of nullclines. To follow the evolution of the vector X(t) one have to understand the architecture of a network. The main elements of this architecture are attractors of the sysem. Since the size of a network in the works [3], [4] is about 60 elements, one should be prepared to deal with relatively large systems. Both numerical and qualitative study of such systems is a challenging problem. In the sequel we will look at systems which are inhibitory. Our aim is to compare inhibition in two-dimensional and three-dimensional cases. show how systems of arbitrary size can be constructed. We provide also the extended example of such system of order six.

5 Three-element GRN

Consider the three dimensional system

$$\begin{cases} x'_1 = \dfrac{1}{1 + e^{-\mu_1(w_{11}x_1 + w_{12}x_2 + w_{13}x_3 - \theta_1)}} - x_1, \\ x'_2 = \dfrac{1}{1 + e^{-\mu_2(w_{21}x_1 + w_{22}x_2 + w_{23}x_3 - \theta_2)}} - x_2, \\ x'_3 = \dfrac{1}{1 + e^{-\mu_3(w_{31}x_1 + w_{32}x_2 + w_{33}x_3 - \theta_3)}} - x_3. \end{cases} \quad (5)$$

Since we focus on inhibition, we assume that all elements of the regulatory matrix are non-positive, but not all zeros. The first nullcline is in the set

$$\{(x_1, x_2, x_3): 0 < x_1 < 1, (x_2, x_3) \in R^2\},$$

the second nullcline is in the set

$$\{(x_1, x_2, x_3): 0 < x_2 < 1, (x_1, x_3) \in R^2\},$$

and the third one is in the set

$$\{(x_1, x_2, x_3): 0 < x_3 < 1, (x_1, x_2) \in R^2\}.$$

All critical points are located in the open cube

$$\{(x_1, x_2, x_3): 0 < x_1 < 1, 0 < x_2 < 1, 0 < x_3 < 1\} =: G.$$

Due to the structure of the system and properties of sigmoidal functions, the vector field, defined by the system of ODE, is directed inward on the border of *G*. Therefore, it is invariant with respect to the system.

The three nullclines definitely intersect at some points of G, and the minimal number of cross-points is one.

We are seeking an answer to the question. What is possible type of a single critical point in case of inhibition? To answer this question, consider the linearized system around a critical point (x_1,x_2,x_3). Let A be the coefficient matrix for this system. We need to know three roots of the characteristic equation

$$\det[A - \lambda E] = 0$$

This equation, with respect to the variable

$$\Lambda = \lambda + 1$$

is

$$\Lambda^3 - C\,\Lambda + B = 0, \qquad (6)$$

Where

$C = (w_{12}w_{21}(-1+x_1)x_1(-1+x_2)x_2\,\mu_1\mu_2 + w_{13}w_{31}(-1+x1)x_1(-1+x_3)x_3\,\mu_1\mu_3 + w_{23}w_{32}(-1+x_2)x_2(-1+x_3)x_3\,\mu_2\mu_3) > 0;$

$B = (w_{12}w_{23}w_{31} + w_{13}w_{21}w_{32})(-1+x_1)x_1(-1+x_2)x_2(-1+x_3)x_3\mu_1\mu_2\mu_3$

Notice that B > 0, if the first factor $(w_{12}w_{23}w_{31} + w_{13}w_{21}w_{32})$ is not zero. C is also positive, if $w_{12}\,w_{21}$, $w_{13}\,w_{31}$, $w_{23}\,w_{32}$ are not all zeros. Recall that parameters μ are positive and coordinates of a critical point are numbers between zero and unity.

Let us formulate some assertions about possible roots of the characteristic equation (2). Our intent is to prove or disprove the assertions below and to construct corresponding examples.

Proposition 1. Equation (6) can have complex conjugate roots.

Proof. We have to construct the example. Set all μ to 4 and choose parameters θi equal to the half of the sum $w_{i1}+w_{i2}+w_{i3}$. This will place the critical point at (0.5,0.5,0.5). The expressions for B and C in (2) become simpler. Namely,

$C = w_{12}\,w_{21} + w_{13}\,w_{31} + w_{23}\,w_{32} > 0,$

$B = -(w_{12}w_{23}w_{31} + w_{13}w_{21}w_{32}) > 0.$

The entries of the matrix

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

satisfy these inequalities.

The nullclines of system (5) intersect only once. A single critical point at (0.5,0.5, 0.5) has the characteristic numbers $\lambda_1 < 0$, $\lambda_{2,3}$ – complex numbers. Computations show that $\lambda_1 = -2.32472$, $\lambda_{2,3} = -0.337641 \pm 0.56228\,i$

The proof is complete.

Proposition 2. Equation (6) can have complex conjugate roots with positive real parts.

Let the regulatory matrix be

$$W = \begin{pmatrix} 0 & -1 & -1 \\ 0 & 0 & -1 \\ w_{31} & 0 & 0 \end{pmatrix}, \qquad (8)$$

where w_{31} is the parameter.

Our intent is to vary this parameter, following changes in the phase space of the system (5).

Let $\mu_1=\mu_2=\mu_3=10$, $w_{31}= -1$, $\theta_1= -1.0$, $\theta_2= -0.5$, $\theta_3= -0.5$. There exists a single critical point with the characteristic numbers $\lambda_1 < 0$, $\lambda_{2,3} = \alpha \pm \beta\mathbf{i}$, $\alpha>0$, **i** is an imaginary unit. This completes the proof.

This critical point is not attractive. An attractor emerges as the stable periodic solution. The closed trajectory is depicted in Figure 2.

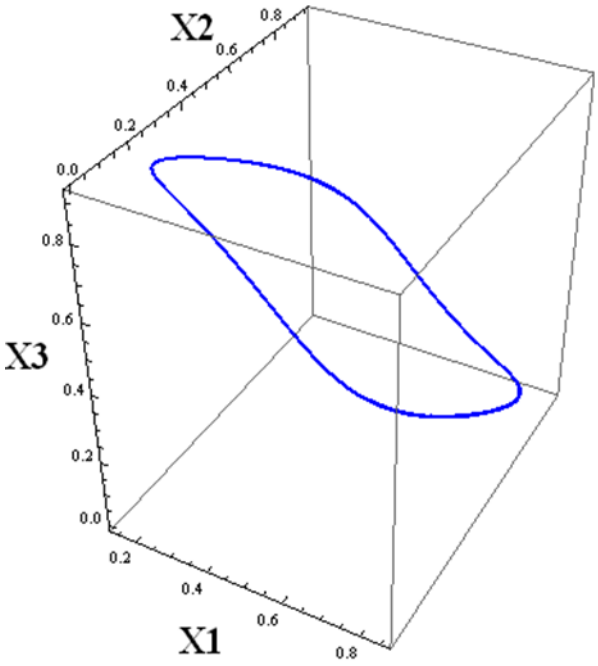

Figure 2. Periodic solution.

The periodic solution disappears if all parameters μ are set to four again.

We continue to increase the absolute value of w_{31}. Let $\mu_1=\mu_2=\mu_3=10$, $w_{31}= -10$, $\theta_1= -1.0$, $\theta_2= -0.5$, $\theta_3= -5$. The parameter θ_3 is changed to put a single critical point to the central location.

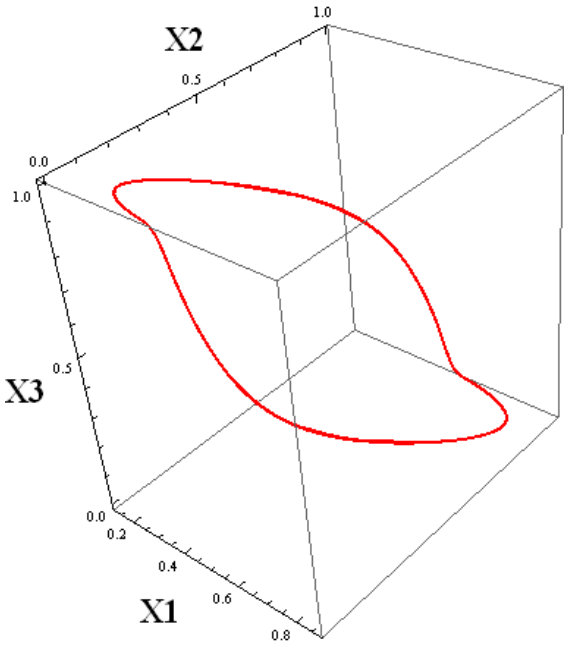

Figure 3. Periodic solution.

It is remarkable fact that the critical point is a three dimensional saddle.

Therefore the following assertion is true.

Proposition 3. Equation (6) can have three real roots.

Proof. Let the regulatory matrix be of the form (4) with $w_{31}= -10$ and other parameters as indicated before Figure 3.

Proposition 4. Equation (6) can have three real roots, of which at least one is positive.

Proof. Let

$$W = \begin{pmatrix} 0 & -1 & -1 \\ -2 & 0 & -1 \\ -1 & 0 & 0 \end{pmatrix} \qquad (9)$$

Then B=1, C=3.

6 Conclusion

The problem of studying genomes and principles of their functioning is one of the most challenging in nowadays biology. These studies require obtaining a huge amount of experimental data, storing and processing them. Elsewhere banks of genomic data are founded and large institutes deal with analyzing them. Mathematical modeling introduces a kind of order in a big amount of data. Periodic processes in genetic networks are of vital importance. Can periodic regimes be obtained in artificial networks where all connections are inhibitory? If the process is governed by an inhibitory regulatory matrix such that a single critical point exists of repelling nature, then an attractive set exists in the form of a stable periodic solution. The critical point can be an unstable three-dimensional focus, as well as a three-dimensional saddle.

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