Networks with Periodic Interactions

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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 the current state of a network for a given value of time *t*. The evolution of a network and future states depend heavily on the attractors of a system of ODE. We discuss this issue for low-dimensional networks and show how the results can be applied to the study of large-size networks. Examples and visualizations are provided. The remarkable feature of our research is that the interactions in a network are supposed to be variable. We focus on the interaction of variable activation-inhibition cycles.

Key-Words: - Mathematical modeling, gene regulatory networks, differential equations, attractors, phase space, variable regulatory matrix.

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1 Introduction

Gene regulatory networks (GRN in short) exist in any cell of any living organism. GRN is 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 other elements. This interaction can be roughly classified and modeled. This is done based on a huge amount of data. By obtaining some kind of regularity in these data, a researcher may build a mathematical model. Mathematical models based on ordinary differential equations (ODE) can predict the future states of a network and describe its evolution. For this, the state space of a system in a model should be investigated. Generally, systems in these models have attractors. Knowledge of attractors and their properties can help one understand the structure and main properties of a modeled network. The system of ODE has multiple parameters, of which the main interest is in the so-called regulatory matrix *W* that describes the interrelations between elements in a model. 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. Experimental data are used extensively in combination with theoretical means to study GRN. 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 have developed extensively. The interested reader can consult the reviews [3], [4], [5] and the articles [6], [7], [8], [9], [10], [11], [12], [13], [14], [15], [16], [17], [18], [19], [20].

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 a phase space, which are called attractors. To understand the principles of GRN, one has first to study attractors in the respective mathematical model.

We focus now on the interrelation between elements of a network. Mathematically this interrelation is described by the regulatory matrix W which is an essential characteristic of the system (1). In the early stages of the study of networks using this system, the elements of W were only 1 (activation), −1 (inhibition), and zero (no relation). Then the intensity of the interrelation was concerned using arbitrary (realistic) real numbers. Nevertheless, these numbers are constant, and it was suggested tacitly that the interrelation is constant. Therefore it is usable only on conventionally small intervals of time. In this manuscript we allow the coefficients to be variable. We provide a number of examples that show that the system with variable matrix W has attractors of various shapes. Due to a large number of variants, we consider here the case of activation inhibition behavior, which is discussed in ongoing sections.

2 Preliminaries

Here is the system of ordinary differential equations:

$$\begin{cases} x'_1 = f_1(-\mu_1 S_1) - v_1 x_1, \\ x'_2 = f_2(-\mu_2 S_2) - v_2 x_2, \\ \qquad \cdots \\ x'_n = f_n(-\mu_n S_n) - v_n x_n. \end{cases} \tag{1}$$

where $S_i = w_{i1}x_1 + w_{i2}x_2 + \cdots + w_{in}x_n - \theta_i$, $f_i(z)$ can be any sigmoidal function. So they are defined for any $z \in R$ and their range of values is (0,1).

Let us simplify things even more. Consider the two-dimensional system:

$$\begin{cases} x'_1 = \dfrac{1}{1 + e^{-\mu_1(w_{11}x_1 + w_{12}x_2 - \theta_1)}} - v_1 x_1, \\ x'_2 = \dfrac{1}{1 + e^{-\mu_2(w_{21}x_1 + w_{22}x_2 - \theta_2)}} - v_2 x_2, \end{cases} \tag{2}$$

which corresponds to the mathematical modeling of a two-element network. Systems of the form

$$\begin{cases} x'_1 = f_1(x_1, x_2), \\ x'_2 = f_2(x_1, x_2) \end{cases} \tag{3}$$

are quite popular among researchers and writers of textbooks for students. One of the reasons is that these systems allow understandable interpretation, using the phase plane. To be definite, set parameters in (2) to $\mu_1 = \mu_2 = 4$, $v_1 = v_2 = 1$, $w_{11} = w_{22} = 0$, $w_{12} = w_{21} = 1$, $\theta_1 = \theta_2 = 0.3$. Choose the initial point for a solution $(x_1(t), x_2(t))$. Let it be at ($x_1(0)$; $x_2(0)$) =(0.8; 0.1). We see in Figure 1 that the trajectory emanating from this point goes to (0.91, 0.91). The graphs of $x_1(t)$ and $x_2(t)$ are depicted in Figure 2. We can predict the future of the process, which is modeled by system (2) with a given set of parameters and the chosen initial data.

What is the conclusion made on the basis of the above considering the two-dimensional system.

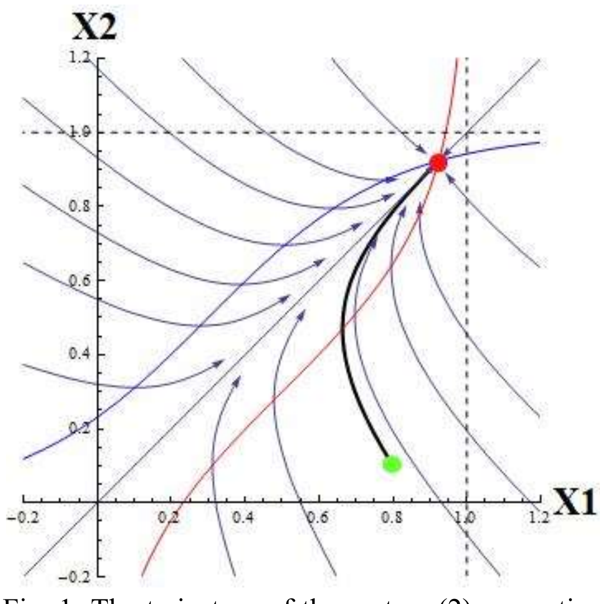

Fig. 1: The trajectory of the system (2) emanating from (0.8, 0.1)

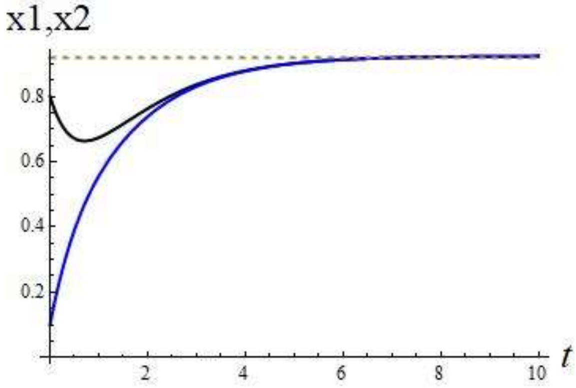

Fig. 2: The graphs of two components of a solution of the system (2) emanating from (0.8, 0.1)

The conclusion is: for a given incline rate (μ_i $=4$) and for given thresholds (θ_i = 0.3) the two-element network, in which an element activates another one with intensity *1* ($w_{12} = w_{21} = 1$), goes to the state (0.9, 0.9) in infinite time.

No other outcomes.

Of course, changing the mode of interaction between elements, as well as changing any parameter, may significantly affect the described scenario. For instance, leave parameters unchanged, and change the sign of w_{21} to –1. The regulatory matrix is:

$$W=\begin{pmatrix} 1 & 1 \\ -1 & 1 \end{pmatrix}. \tag{4}$$

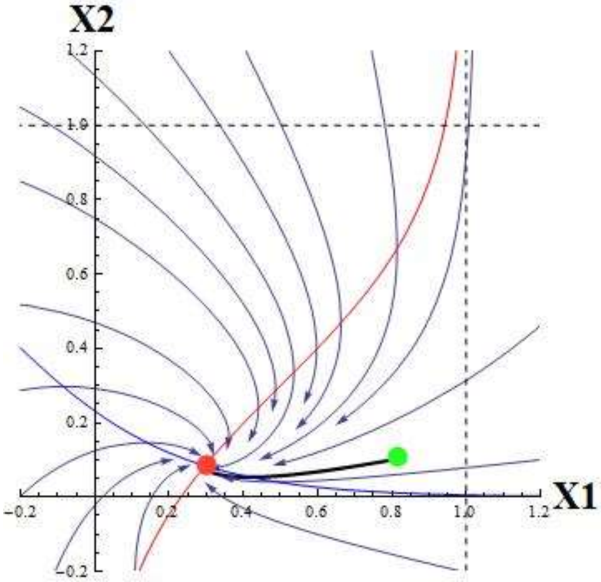

Fig. 3: The trajectory of the system (2), matrix W as in (4), emanating from (0.8*;* 0.1)

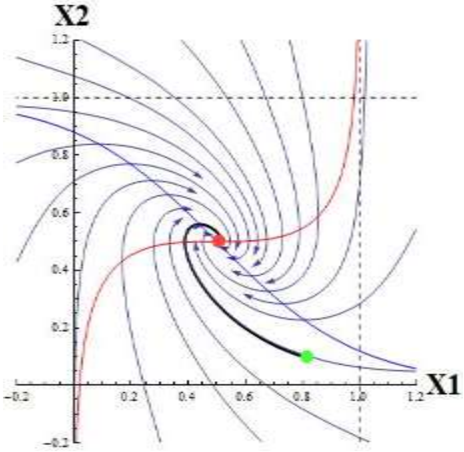

Fig. 4: The trajectory of the system (2), matrix W as in (5), emanating from (0.8*;* 0.1)

The fortune of the trajectory, emanating from the point (0.8, 0.1) is different, it goes (Figure 3) to the point at (0.29, 0.09) (the values are approximate).

Let us make two changes, $w_{11} = 1$, $\mu_1 = 1$.

The regulatory matrix is:

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

The result of changing parameters is shown in Figure 4. Notice that the limit point is now at the center of the unit square. It is the result of the choice of thresholds θ_1 and θ_2. In any of the pictures there are the nullclines:

$$\begin{cases} v_1 x_1 = \dfrac{1}{1+e^{-\mu_1(w_{11}x_1 + w_{12}x_2 - \theta_1)}}, \\ v_2 x_2 = \dfrac{1}{1+e^{-\mu_2(w_{21}x_1 + w_{22}x_2 - \theta_2)}}. \end{cases} \tag{6}$$

The direction of the vector field defined by the system of differential equations (2) is vertical or horizontal, which can be seen in the pictures. The points of intersection of nullclines are the critical points where no direction of the vector field is defined. They serve as attractors in any of the three examples. After this preface, we can outline our plans in this article. The regulatory matrix W in previous studies of many authors was Boolean. Its entries were only *1* for activation, *–1* for inhibition, and *0* for no relation. Then any real number was allowed to be an element of W, characterizing the intensity of interaction. We wish to consider further generalization. It is natural to suggest that interrelations between elements of a network can and ought to change in time. Therefore, in the next section we allow matrix W to be variable. This novelty can change the behavior of solutions significantly. Because of a great variety of possible types of interrelations, we have chosen the combination activation versus inhibition, both in variable settings.

3 The Three-Dimensional Systems and Periodic Attractors

Consider the three-dimensional system, corresponding to a three-element network. It is assumed that the behavior of trajectories of this network is governed by the system:

$$\begin{cases} x'_1 = \frac{1}{1+e^{-\mu_1(w_{11}x_1+\cdots+w_{14}x_4-\theta_1)}} - v_1x_1, \\ x'_2 = \frac{1}{1+e^{-\mu_2(w_{21}x_1+\cdots+w_{24}x_4-\theta_2)}} - v_2x_2, \\ x'_3 = \frac{1}{1+e^{-\mu_3(w_{31}x_1+\cdots+w_{34}x_4-\theta_3)}} - v_3x_3, \end{cases} \quad (7)$$

Assign the parameters values, μ_i=4, $v_i=1$ for $i=1,2,3$. Let the matrix W be:

$$W_{41} = \begin{pmatrix} 2.35 & 0 & -1 \\ -1 & 2.35 & 0 \\ 0 & -1 & 2.35 \end{pmatrix} \quad (8)$$

Set $\theta_1=0.5\ (2.35-1)$, $\theta_2=0.5\ (-1+2.35)$, $\theta_3=0.5(-1+2.35)$.

This choice of θ puts a critical point to the central location (0.5,0.5,0.5). The reader may check that the values x_1=0.5, x_2=0.5, x_3=0.5 satisfy the system

$$\begin{cases} x_1 = \frac{1}{1+e^{-\mu_1(w_{11}x_1+\cdots+w_{14}x_4-\theta_1)}}, \\ x_2 = \frac{1}{1+e^{-\mu_2(w_{21}x_1+\cdots+w_{24}x_4-\theta_2)}}, \\ x_3 = \frac{1}{1+e^{-\mu_3(w_{31}x_1+\cdots+w_{34}x_4-\theta_3)}}, \end{cases} \quad (9)$$

which defines the critical points. The values of parameters μ, θ, w_{ij} are as above chosen. This system has a limit cycle, seen as a closed trajectory. Moreover, this trajectory attracts other trajectories (hence “limit cycle”).

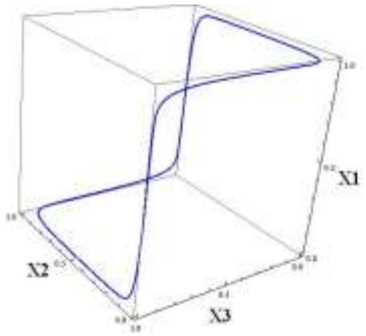

Fig. 5: The closed trajectory of the system (7) emanating from (0.2, 0.4, 0.2)

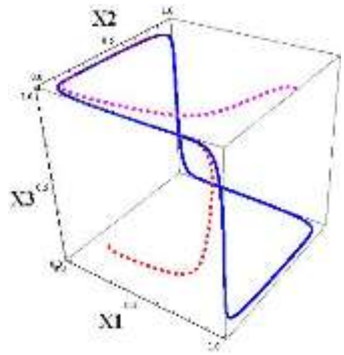

Fig. 6: The closed trajectory of the system (7), attracting two trajectories emanating from (0:2, 0.1, 0.1) and (0.9, 0.8, 0.9)

Looking at the regularity matrix W, we can conclude that there exists an inhibitory cycle (three −1 in different rows and columns) against self-activation represented by three 2.85 in the main diagonal. The struggle between these tendencies results in a periodic solution, represented by the closed trajectory (Figure 5). It is to be said, that further study of this example shows the following. If we put k in the main diagonal,

$$W = \begin{pmatrix} k & 0 & -1 \\ -1 & k & 0 \\ 0 & -1 & k \end{pmatrix}, \quad (10)$$

then for k positive and small the periodic solution does not exist. Instead, a spiral like three-dimensional trajectory enters a single critical point. In some region of values for k the periodic solution exists, and tends to follow the edges of the unit cube (this can be observed in Figure 5).

3.1 Behavior at Small Perturbation

Does the limit cycle lose its properties at small perturbations? We can obtain the partial answer by conducting a numerical experiment. Imagine that the elements in the regulatory matrix are not pure constants, but suffer some perturbations, which can be interpreted as disturbing noise. To experiment, we simply add some bounded functions to several entries of the matrix W. Suppose the matrix is:

$$W = \begin{pmatrix} 2.35 & 0 & -a(t) \\ -a(t) & 2.35 & 0 \\ 0 & -a(t) & 2.35 \end{pmatrix}, \qquad (11)$$

where $a(t) := 1 + \sin t$.

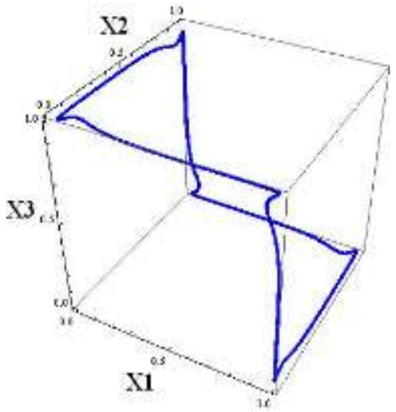

Fig. 7: The closed trajectory of the system (7) with the matrix (11)

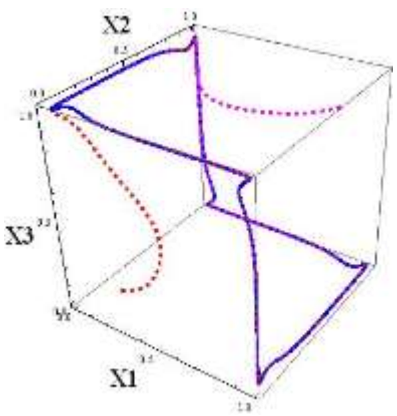

Fig. 8: The closed trajectory together with two trajectories of the system (7) with the matrix (11)

The results of the experiment are shown in Figure 7 and Figure 8, which are counterparts of Figure 5 and Figure 6.

4 Activation Meets Inhibition

Consider system (7) with periodic activation and periodic inhibition. The regulatory matrices are:

$$W1 = \begin{pmatrix} a(t) & 0 & -a(t) \\ -a(t) & a(t) & 0 \\ 0 & -a(t) & a(t) \end{pmatrix}, \qquad (12)$$

$$W2 = \begin{pmatrix} a(t) & 0 & -a(t+1) \\ -a(t+1) & a(t) & 0 \\ 0 & -a(t+1) & a(t) \end{pmatrix}, \qquad (13)$$

and

$$W3 = \begin{pmatrix} a(t) & 0 & -a(t-1) \\ -a(t-1) & a(t) & 0 \\ 0 & -a(t-1) & a(t) \end{pmatrix}. \qquad (14)$$

So inhibition is advancing activation in models with the matrix (13) and delays in models with the matrix (14).

For all three cases a trajectory tending to the attractor is depicted in Figure 9, Figure 10, Figure 11 respectively, the initial conditions are $x_1(0)=0.2$, $x_2(0)=0.4$, $x_3(0)=0.2$.

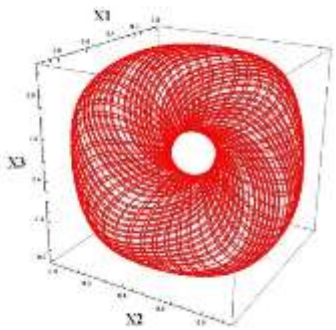

Fig. 9: For the case of matrix (12)

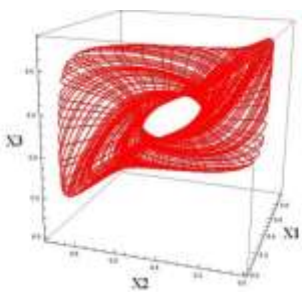

Fig. 10: For the case of matrix (13)

4.1 Activation and Inhibition with Different Periods

Continue considering system (7) with periodic activation and periodic inhibition, but now the period for inhibitory elements is twice smaller than that of activation counterparts. Let the regulatory matrices be:

$$W4 = \begin{pmatrix} a(t) & 0 & -b(t) \\ -b(t) & a(t) & 0 \\ 0 & -b(t) & a(t) \end{pmatrix}, \qquad (15)$$

$$W5 = \begin{pmatrix} a(t) & 0 & -b(t+1) \\ -b(t+1) & a(t) & 0 \\ 0 & -b(t+1) & a(t) \end{pmatrix}, \qquad (16)$$

and

$$W6 = \begin{pmatrix} a(t) & 0 & -b(t-1) \\ -b(t-1) & a(t) & 0 \\ 0 & -b(t-1) & a(t) \end{pmatrix}, \qquad (17)$$

where $a(t) = 1 + \sin t, \quad b(t) = (\sin t)^2$.

In Figure 12, Figure 13 and Figure 14 the trajectory going to the attractor is depicted. The initial values are as before, $x_1(0)=0.2$, $x_2(0)=0.4$, $x_3(0)=0.2$.

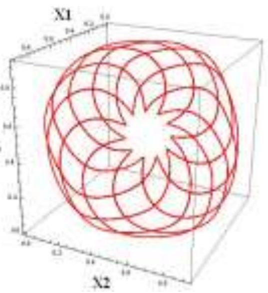

Fig. 11: For the case of matrix (14)

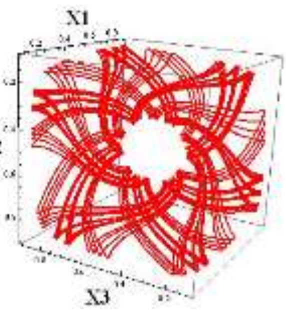

Fig. 12: For the case of matrix (15)

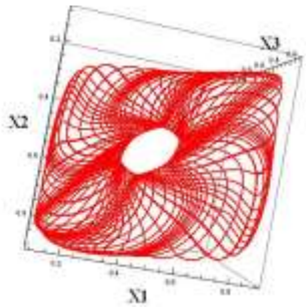

Fig. 13: For the case of matrix (16)

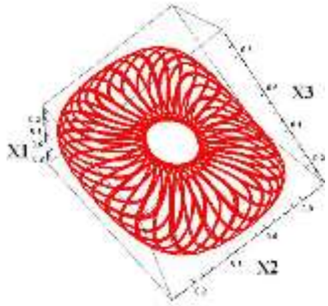

Fig. 14: For the case of matrix (17)

5 Conclusion

A system of ODE describing gene networks and similar networks can be used in the study of phase space and a set of attractors. Since the interrelation between elements in such networks is variable, not static, the systems of ODE with variable regulatory matrices can be used. Activation-inhibition constant matrix produces a periodic attractor. This attractor does not change its main properties under small perturbations in elements of the matrix *W*. For variable matrices, the attractor exists also and resembles the one in the static case. The study of models of gene networks and similar networks can be conducted effectively using the variable elements to model interrelations between elements of a network. Last but not the least, the authors are unaware of studies where *variable* regulatory matrices were employed. Further studies in this direction promise to be fruitful.

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