Book Chapter

On Trajectories of a System Modeling Evolution of Genetic Networks

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Abstract

A system of ordinary differential equations is considered, which arises in the modeling of genetic networks and artificial neural networks. Any point in phase space corresponds to a state of a network. Trajectories, which start at some initial point, represent future states. Any trajectory tends to an attractor, which can be a stable equilibrium, limit cycle, or something else. It is of practical importance to answer the question of whether a trajectory exists which connects two points, or two regions of phase space. Some classical results in the theory of boundary value problems can provide an answer. Some problems cannot be answered, and require the elaboration of new approaches. We consider both the classical approach and specific tasks, which are related to the features of the system and the modeling object.

Keywords

Ordinary Differential Equations; Boundary Value Problems; Mathematical Modeling; Attractors

Introduction

Gene regulatory networks (GRN in short) exist in any cell of any living organism. Genetic networks are responsible for morphogenesis and adaptation to changes in the environment. Elements of these networks interact with each other, developing a general reaction of an organism to changes in the external environment. Biologists have created huge arrays of experimental data, which need to be analyzed, classified and utilized. For this purposes, mathematical models have been created. They are different, using mathematical theories such as Boolean algebras, graph theory, stochastic analysis and more. To

follow evolution of GRN in time, best suit dynamical systems. Models of GRN, based on differential equations, can be treated qualitatively and computationally. On a basis of this treatment, predictions of the behaviors of GRN can be made. The structure of GRN, principles of functioning can be clarified by studying the phase spaces of dynamical systems in a model. Management and control over GRN cam be made possible in some practically important cases. Genetic networks are important in the treatment of various diseases such as multiple sclerosis, chemotherapy for gastric cancer, and leukemia. GRN can be modeled mathematically, and in case of success, the model is to be studied, using analytical and computational approaches. Evolution in time can be traced, following the trajectories of a dynamical system, which describes the behavior of GRN. For this, knowledge of attracting sets is important. This system consists of several ordinary differential equations (ODE), containing multiple parameters. The interrelation between genes is described by the $n \times n$regulatory matrix W. This system is not a particular one. Its modification [1], used in the theory of artificial neural networks, is known to be able to approximate to arbitrary accuracy any dynamical system [2].

We consider the *n*-dimensional dynamical system

$$\begin{cases} \frac{dx_1}{dt} = \frac{1}{1+e^{-\mu_1(w_{11}x_1 + w_{12}x_2 + \cdots + w_{1n}x_n - \theta_1)}} - x_1, \\ \frac{dx_2}{dt} = \frac{1}{1+e^{-\mu_2(w_{21}x_1 + w_{22}x_2 + \cdots + w_{2n}x_n - \theta_2)}} - x_2 \\ \cdots \\ \frac{dx_n}{dt} = \frac{1}{1+e^{-\mu_n(w_{n1}x_1 + w_{n2}x_2 + \cdots + w_{nn}x_n - \theta_n)}} - x_n. \end{cases} \quad (1)$$

where $\mu_i > 0$ and $\theta_i$are parameters, and w_{ij} are elements of the $n \times n$ regulatory matrix

$$W = \begin{pmatrix} w_{11} & \cdots & w_{1n} \\ \cdots & \cdots & \cdots \\ w_{n1} & \cdots & w_{nn} \end{pmatrix}. \quad (2)$$

Such systems arise in the theory of genetic regulatory networks [3,4,5,6,7,8], neural networks [9,10] and telecommunication networks [11].

These systems contain nonlinear terms, represented by the function $\frac{1}{1+e^{-\mu z}}$, and the linear part also. The nonlinear function $f(z)$ is sigmoidal, that is, it is smooth, monotonically increasing from zero to unity, and has a single inflection point. The sigmoidal functions are many, and the Hill and the Gompertz functions can be used as well. The argument of the function $f(z)$can be replaced by the linear combinations of multiple variables $x_1, \dots, x_n$. These variables are interpreted as genes, expressing proteins and thus communicated with each other, developing a common response of the gene network to external and internal influences. In the theory of telecommunication networks x_i are treated as source-destinationpairs, and the optimal configuration of lightpaths is a guestionmark problem.

Our attention to these problems stems from the fact, that they are in a focus of the research on the border of mathematics and biology and the classical mathematical approach should be corrected and adapted to the special needs of practicioners.

Some authors [12,13] interpret this system as a model for not so large real genomic network, which is functioning in an organism suffering from leukemia (a kind of blood cancer). Following Wang et al.[12], the genetic network can be in various states, and some of these states are associated with the disease, while some are considered as "normal". From the mathematical point of view, the respective system of order 60 (only!) has attractive equilibria (critical points) and some of them are conditionally "bad" and some are "normal". The current state of an organism is associated with the state vector $X(t) = (x_1(t), \dots, x_n(t))$, which consists of solutions of the autonomous system (1), representing by trajectories, which are curves, connecting the current state $X(t)$, which depends on the initial conditions $X(0)$, and the "final" state, which is treated as an "attractor".

Two-dimensional Systems

It is reasonable to start with the system of the form (1), which contains only two equations and corresponds to a two-element network. The system has the form

$$\begin{cases} x'_1 = \frac{1}{1+e^{-\mu_1(w_{11}x_1 + w_{12}x_2 - \theta_1)}} - x_1, \\ x'_2 = \frac{1}{1+e^{-\mu_2(w_{21}x_1 + w_{22}x_2 - \theta_2)}} - x_2. \end{cases} \quad (3)$$

and it defines the vector field (x_1, x_2), which can be visualized. Any solution of the system can be viewed as a trajectory$(x_1(t), x_2(t))$, which is usually the curve in the phase plane(x_1, x_2). We will refer to this system as 2D-system. Consequently, the system of three equations will be called 3D-system and so on. Even in 2D-case, the system contains eight parameters, and therefore the solutions of the system can exhibit various behaviors. Signs and values of the elements w_{ij} ofregulatory matrix reflect the character of interrelations between elements x_i. The structure of the phase portraits heavily depends on the nullclines, which are defined by the equations

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

The solutions of the system (4) are critical points, which are called in some contexts "equilibria". The local analysis of solutions of 2D-systems can be conducted by considering the linearized (around a critical point) system and computing some values, called the characteristic values [14]. The three types of behaviors are shown in Figure 1(a,b,c). Usually the trajectories of a 2D-system are attracted by stable equilibria. Sometimes the attracting set is a limit cycle. More complicated structures can be attractors as well.

In the theory of boundary value problems for ordinary differential equations the quasilinear equations were paid special attention of researchers. Fixed point theorems of functional analysis were used to prove the existence of solutions to several quasi-linear problems (e.g, [15,16]). The system (1) is quasi-linear, and its 2D version (3) can be written in a convenient form

$$\begin{cases} x'_1 = -x_1 + f_1(x_1, x_2), \\ x'_2 = -x_2 + f_2(x_1, x_2). \end{cases} \quad (5)$$

The traditional boundary conditions that can be associated with (5), are

$$x_1(0) = A, \quad x_1(T) = B, \tag{6}$$

$$x_2(0) = A, \quad x_2(T) = B, \tag{7}$$

$$x_1(0) = A, \quad x_2(T) = B, \tag{8}$$

$$x_2(0) = A, \quad x_1(T) = B, \tag{9}$$

$$x_1(0) = x_1(T), \ \ x_2(0) = x_2(T). \tag{10}$$

Since $f_1$and f_2 in (5) are continuous andbounded, the above problems are quasi-linear. It follows from thegeneral theory of boundary value problems (BVP) for ordinary differential equations (ODE) [15,16], that the problems (8) and (9) are solvable for any A and B, since the corresponding homogeneous problems

$$\begin{cases} x'_1 = -x_1, \\ x'_2 = -x_2, \\ x_1(0) = 0, \ \ x_2(T) = 0 \end{cases} \tag{11}$$

(and for $x_2(0) = 0, \ x_1(T) = 0$ also) have the trivial solutions only.

This is not the case for the problems (6) and (7), since the homogeneous problems

$$\begin{cases} x'_1 = -x_1, \\ x'_2 = -x_2, \\ x_1(0) = 0, \ \ x_1(T) = 0 \end{cases} \tag{12}$$

(and for $x_2(0) = 0, \ x_2(T) = 0$ also) have nontrivial solutions in the form $x_1(t) \equiv 0, x_2(t) = e^{-t}$.

As to the periodic problem (10), it always has a solution in the form of a constant(x^*_1, x^*_2). This follows from the

geometricalfact that both nullclines in (4) locate in the strips $0 < x_1 < 1$ and $0 < x_2 < 1$respectively and must intersect therefore. The more interesting case is to have a non-constant solution, but additional restrictions are required for this.

The most influential on the behavior of solutions factor, is the matrix W, which is called the regulatory matrix (thus the abbreviation GRN).

Consider three matrices

$$W_a = \begin{pmatrix} 1 & 1 \\ 1 & 1 \end{pmatrix},$$
$$W_b = \begin{pmatrix} 0 & -2 \\ -2 & 0 \end{pmatrix}, \quad (13)$$
$$W_c = \begin{pmatrix} 2 & 1 \\ -1 & 2 \end{pmatrix}$$

and the respective 2D-systems of the form (3). In the theory of genetic networks these types of interrelation between genes are called respectively activation, inhibition, and mixed activation-inhibition case. To be definite, let other parameters be$\mu_1 = \mu_2 = 5, \theta_1 = \frac{w_{11}+w_{12}}{2}, \theta_2 = \frac{w_{21}+w_{22}}{2}$. This choice of θ's puts a critical pointat the central location.

The cross-points of nullclines are marked by the small black disks. Only one critical point is in Figure 1(c). The phase portrait (on the larger scale) of the same system is depicted in Figure 1(d). It is clear that the problem (9) is not solvable for some values of A, B.

All the boundary conditions above mean that solutions are sought which connect subspaces of the extended phase space.

For the purposes of modeling genetic networks, other conditions fit better. Look at Figure 1(a). Both side critical points have their basins of attraction, that is, the sets of initial conditions which are connectable with the respective critical point. Both basins of attraction are separated by separate axes of the middle critical point, which is a saddle. At least in the unit quadrant Q_2, there

are no trajectories, connecting points from different basins of attraction. This means that the BVP with the boundary sets

$$(x_1(0), x_2(0)) = P_1, \quad (x_1(T), x_2(T)) = P_2 \tag{14}$$

are not solvable in Q_2 This boundary problem is over-determined, since the number of conditions (four) is greater than the number of the equations (two).

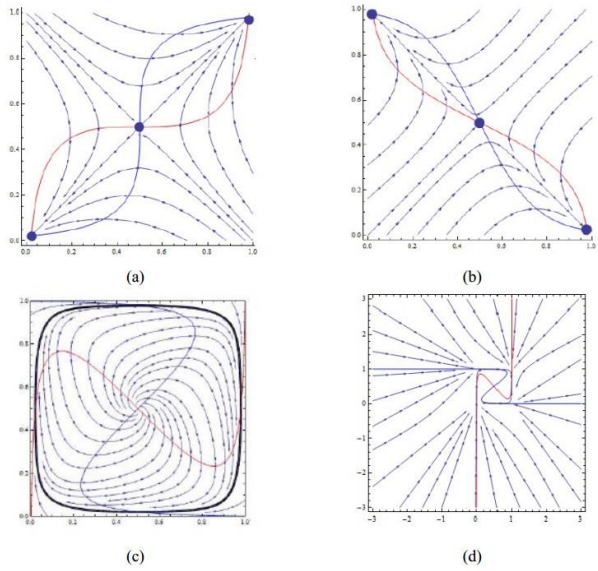

Figure 1: Phase portraits. (a) The phase portrait for the case W_a;(b) The phase portrait for the case W_b;(c) The phase portrait for the case W_c;(d) The scaled phase portrait for the case W_c.

The Alternative Formulation of a Boundary Value Problem

Let A be an attracting set for the system (3) [17]. This means that there exists a vicinity U of A such that for any trajectory Γ with the initial conditions in U this trajectory stays in U eventually and the distance d(Γ,A) tends to zero as t goes to infinity. The corresponding boundary condition can be written as $(x_1(+$

$\infty), x_2(+\infty)) \in A$.Of course, astable equilibrium and a limit cycle are attractors. Let us formulate the problem:

$$\big(x_1(0), x_2(0)\big) = P(0), (x_1(+\infty), x_2(+\infty)) \in A, \quad (15)$$

where T is some number, may be different for differenttrajectories. Since the second condition is looking as depending on T, it can be written in a neutral form $(x_1(t), x_2(t)) \in A$.

Example 1:

Let the 2D-system be with the matrix $W_a$as in (13). Let A_1be the upper stable equilibrium (it is a stable node). The problem is

$$(x_1(0), x_2(0)) = P(0), \ \ (x_1(+\infty), x_2(+\infty)) = A_1. \quad (16)$$

This problem is solvable for any $P(0)$ belonging to the basin ofattraction of the point A_1. The problem has not solutions, if $P(0)$ is in the basin of attraction of the lower stable equilibriumA_2.

Example 2:
Consider the 2D-system, corresponding to the matrix W_m in (13). Let L be the limit cycle which isdepicted in Figure 1(c). The problem is

$$(x_1(0), x_2(0)) = P(0), \ \ (x_1(+\infty), x_2(+\infty)) \in L. \quad (17)$$

Three-dimensional Systems

The classical boundary value problems for the third-order systems of the form (1) can be

$$\begin{cases} x'_1 = -x_1 + f_1(x_1, x_2, x_3), \\ x'_2 = -x_2 + f_2(x_1, x_2, x_3), \\ x'_3 = -x_3 + f_3(x_1, x_2, x_3), \end{cases} \quad (18)$$

are

$$x_1(0) = A, \ \ x_2(0) = B, \ x_1(T) = C, \quad (19)$$

$$x_1(0) = A, \quad x_1(T) = B, x_2(T) = C, \tag{20}$$

$$x_1(0) = A, \quad x_2(0) = B, x_3(T) = C, \tag{21}$$

$$x_1(0) = A, \quad x_2(T) = B, x_3(T) = C, \tag{22}$$

$$x_1(0) = x_1(T), \ \ x_2(0) = x_2(T), x_3(0) = x_3(T). \tag{23}$$

The functions f_i are sigmoidal functions of the form as in (1). They are continuous and bounded, and in accordance with the general theory [15,16], they are solvable, if the linear homogeneous problem has only the trivial solution.

$$\begin{cases} x'_1 = -x_1, \\ x'_2 = -x_2, \\ x'_3 = -x_3, \\ + \ homogeneous \ boundary \ conditions \end{cases} \tag{24}$$

For instance, the problem (18), (21) has a solution for any A, B, C since the homogeneous problem has only the trivial solution for any T.

$$\begin{cases} x'_1 = -x_1, \\ x'_2 = -x_2, \\ x'_3 = -x_3, \\ x_1(0) = 0, \ \ x_2(0) = 0, \ \ x_3(T) = 0 \end{cases} \tag{25}$$

The periodic problem is a special one. It has a solution since any system of the form (1) has at least one critical point (the constant solution).

As in the case of 2D systems, the alternative boundary value problem can be posed in the form

$$(x_1(0), x_2(0), x_3(0)) = P(0), \ \ \left(x_1(+\infty), x_2(+\infty), x_3(+\infty)\right) \in A. \tag{26}$$

Example 3:

Consider the system (1), where$\mu_1 = \mu_3 = 5, \mu_2 = 15, \theta_1 = \theta_3 = 1.5, \theta_2 = -0.25$and the regulatory matrix is

$$W = \begin{pmatrix} 1 & 0 & 2 \\ 0 & -1 & 0.5 \\ 2 & 0 & 1 \end{pmatrix}. \tag{27}$$

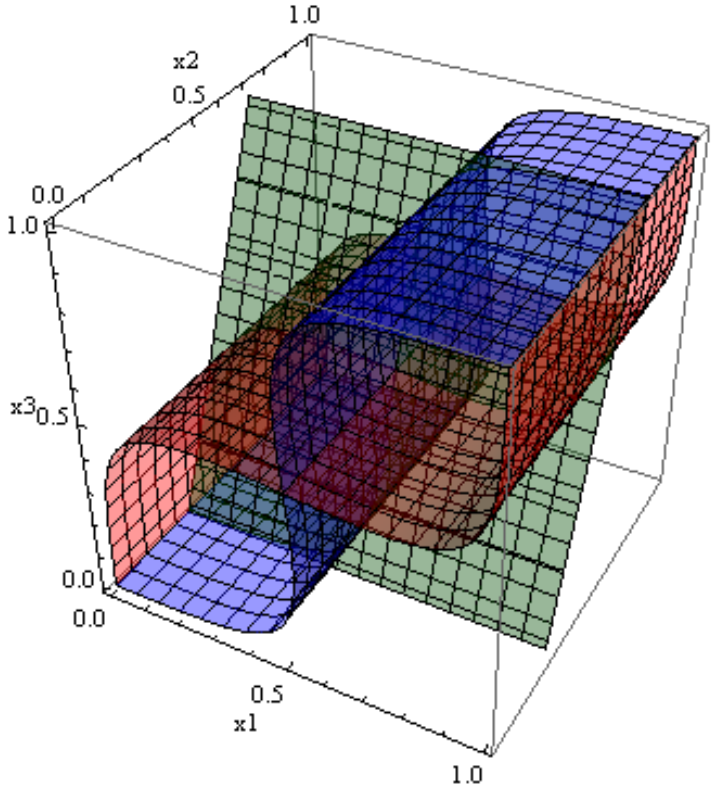

Figure 2: Nullclines. Red: representx_1; green: representx_2;blue: representx_3.

This system has exactly three critical points, which are calculated and depicted as the cross-points of the nullclines in Figure 2. The first one is $(0.001; 0.305; 0.001)$. The linearization around it in a standard way yields the linear system. Let the 3 by 3 coefficient matrix of the linearized system be denoted as *M*. The characteristic equation $det(M-\lambda E)=0$ can be written in the form

$$-\lambda^3 + A\lambda^2 + B\lambda + C = 0, \quad (28)$$

where$A = -6.18; B = -9.33; C = -4.16$. Solving the equation, we have $\lambda_1 = -4.18;\ \lambda_2 = -1.003;\ \lambda_3 = -0.9916$. The type of this critical point is a stable node.

The characteristic equation for the critical point $(0.5; 0.5;\ 0.5)$ is (29), where$A = -4.25; B = 8.56; C = 29.39$. Solving the equation, we have $\lambda_1 = -4.75;\ \lambda_2 = -2.25;\ \lambda_3 = 2.75$. The type of this critical point is a saddle.

The characteristic equation for the critical point $(0.99; 0.69;\ 0.99)$ is (28), where$A = -6.18; B = -9.33; C = -4.16$. Solving the equation, we have $\lambda_1 = -4.18;\ \lambda_2 = -1.003;\ \lambda_3 = -0.9916$. The type of this critical point is a stable node.

Example 4:

Consider $\mu_1 = \mu_3 = 5, \mu_2 = 15, \theta_1 = 1.5;\ \theta_2 = 1, \theta_3 = -0.5$. The regulatory matrix of the system (1) is

$$W = \begin{pmatrix} 1 & 0 & 2 \\ 1 & 1 & 0 \\ -2 & 0 & 1 \end{pmatrix}. \quad (29)$$

There are exactly three critical points. The characteristic equation for the critical point $(0.5; 0.5;\ 0.5)$ is (28), where $A = 3.25; B = -7.69; C = 17.36$. Solving the equation, we have $\lambda_1 = 2.75;\ \lambda_{2,3} = 0.25 \pm 2.5\, i$. The type of the critical point is a 3D unstable focus-node. The nullclines and the graph of solutions are depicted in Figure 3. The self-excited attractor and the dynamics of Lyapunov exponents are depicted in Figure 4.

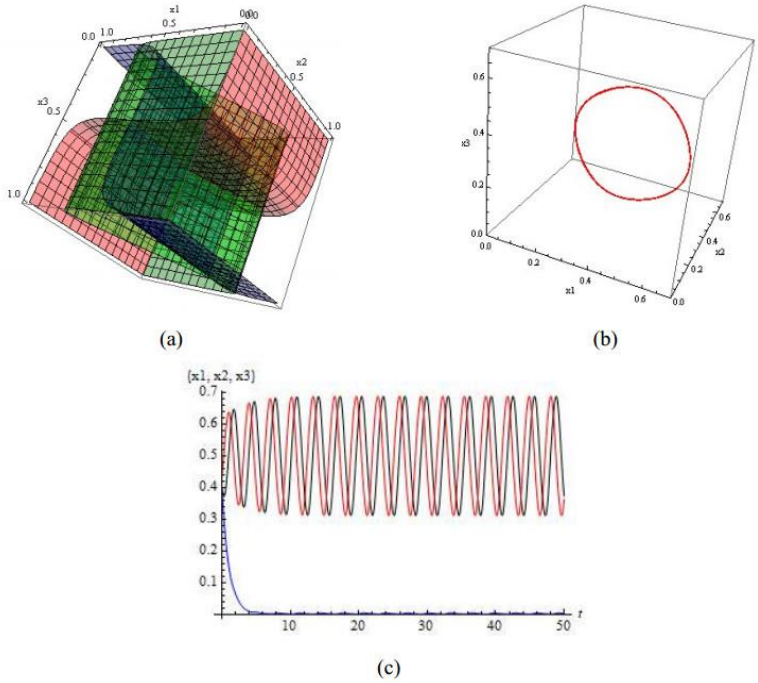

Figure 3: Visualization of nullclines and the periodic solution. (a) The nullclines.x_1-red, x_2-green, x_3-blue. (b) The periodic solution. (c) The graphs of $x_i(t),\ i = 1,2,3$.

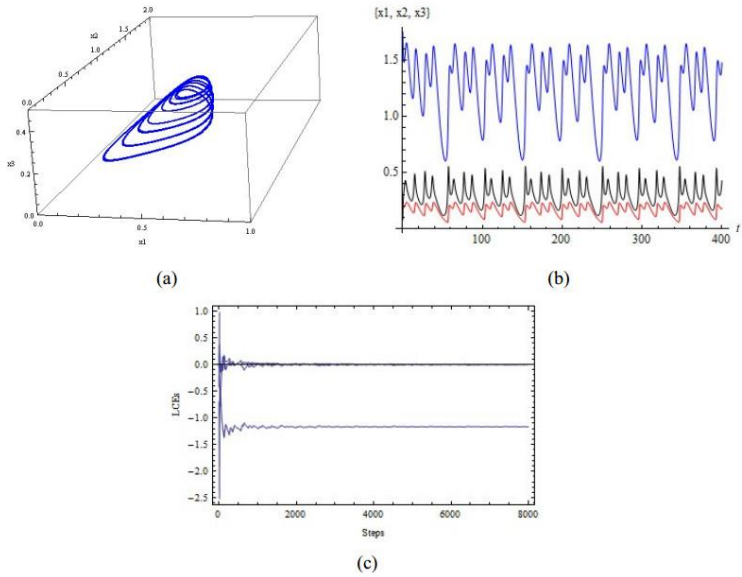

Figure 4: Visualization of self-excited attractor and the dynamics of Lyapunov exponents. (a) The self-excited chaotic attractor; (b) The graphs of $x_i(t), i = 1,2,3$; (c) The Lyapunov exponents, $LE_1 = 0.04$; $LE_2 = 0$; $LE_3 = -1.17$ (obtained by application of the program by M. Sandri [18]).

Example 5:
Consider the system

$$\begin{cases} \frac{dx_1}{dt} = \frac{1}{1+e^{-\mu_1(w_{11}x_1 + w_{12}x_2 + w_{13}x_3 - \theta_1)}} - v_1x_1, \\ \frac{dx_2}{dt} = \frac{1}{1+e^{-\mu_2(w_{21}x_1 + w_{22}x_2 + w_{23}x_3 - \theta_2)}} - v_2x_2, \\ \frac{dx_3}{dt} = \frac{1}{1+e^{-\mu_3(w_{31}x_1 + w_{32}x_2 + w_{33}x_3 - \theta_3).}} - v_3x_3, \end{cases} \quad (30)$$

where $v_1 = 0.65, v_2 = 0.42,\ v_3 = 0.1, \mu_1 = \mu_2 = 7, \mu_3 = 13, \theta_1 = 0.5,\ \theta_2 = 0.3,\ \theta_3 = 0.7$. It is a slight modification of the system from the work [19, 20]. The regulatory matrix of the system (31) is

$$W = \begin{pmatrix} 0 & 1 & -5.65 \\ 1 & 0 & 0.133 \\ 1 & 0.02 & 0.03 \end{pmatrix}. \quad (31)$$

The initial conditions are

$$x_1(0) = 0.3;\ x_2(0) = 1.5;\ x_3(0) = 0.2. \quad (32)$$

There is one critical point. The characteristic equation for the critical point $(0.37; 1.59;\ 0.22)$ is (29), where $A = -1.16; B = -0.42; C = -0.69$. Solving the equation, we have $\lambda_1 = -1.26;\ \lambda_{2,3} = 0.05 \pm 0.74\ i$. The critical point is of the type a 3D unstable saddle-focus. The system is chaotic in the sense that solutions exhibit non-regular behavior.

Conclusions

The boundary value problems of new kind arose from studies of mathematical models, associated with genetic, neural and telecommunication networks. The behavior of GRN on bounded time intervals can be described by systems of ordinary differential equations of the form (1). The interrelation between elements of GRN is encrypted in the regulatory matrix W. The individual properties of genes are described by the parameters μ and θ. In the mathematical model (1) the unit cube Q is an invariant set and trajectories cannot exit it. The nullclines can (and they do) intersect only in Q. The equilibria (critical points) exist. It is possible that they are attractive and the cases, where all the equilibria are non-attractive, are possible also. Then more complicated attractive sets exist, more often they are periodic ones. The boundary value problems of the forms (16), (17), (27) arise naturally in this context. The boundary value problems on finite intervals also can be studied in light of suggestions in the paper [12]. The problem of redirecting a trajectory from the basin of attraction of "bad" attracting set to a "normal" one, changing the adjustable parameters, is of great practical importance.

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