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DEPARTMENT OF ENVIRONMENT AND TECHNOLOGIES

Diana Ogorelova

DYNAMIC MODELS OF BIOLOGICAL NETWORKS

SUMMARY OF THE DOCTORAL THESIS
for obtaining the Doctoral Degree (Ph. D.) in Natural sciences
(Mathematics branch, Differential equations sub-branch)

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The scientific supervisor of Doctoral Thesis:
Professor, Dr.habil.math. Felix Sadyrbaev, Daugavpils University, Institute of Mathematics and Computer Science, University of Latvia.

Official reviewers:

- Dr.math. Prof. Inese Bula (Latvia University, Latvia)
- Dr.math., Assoc.Prof. Sergey Smirnov (University of Latvia, Latvia)
- Professor (Applied Mathematics) Minvydas Kazys Ragulskis (Kaunas University of Technology, Lithuania)

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Comments are welcome. Send them to the secretary of the Promotion Council of mathematics, Parades street 1, Daugavpils, LV-5400, Tel. +37126495316, e-mail: anita.sondore@du.lv

Secretary of the Promotion Council: Dr. math., Anita Sondore.

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GENERAL INFORMATION

The doctoral thesis is devoted to the study of systems of ordinary differential equations that arise in the theory of complex networks. The gene regulatory networks (GRN networks) and artificial neural networks (ANN networks) are networks of this type.

Keywords: differential equations, mathematical modeling, gene regulatory networks, neuronal networks, phase space, attractors, bifurcations.

The object of the promotional work is a certain class of systems of ordinary differential equations (ODE). These systems have a special quasi-linear structure and contain both linear and nonlinear parts. The nonlinear part is represented by sigmoidal functions. The Gompertz function is selected of them.

Aims of research: The aim of the work is to study one class of systems of ordinary differential equations that arise in the theory of gene networks and artificial neural networks. These systems consist of nonlinear and linear parts. The nonlinear part is represented by sigmoidal functions, of which the Gompertz function and the hyperbolic tangent function are used in the work. Special attention is paid to the study of the properties of attractors, the analysis of the evolution of systems, and the prediction of the behavior of solutions.

The research tasks:

- define a system of ODE modeling GRN and using the Gompertz function as a nonlinearity;
- obtain formulas for the study of the critical points of GRN type systems;
- compare the results for GRN systems using Gompertz function with similar systems using other sigmoidal functions;
- transfer the results obtained for GRN systems to systems arising in ANN theory and containing the hyperbolic tangents function as a

nonlinearity;

- compare the results obtained for GRN systems with the results obtained for ANN systems;
- compare the results of examples of periodic attractors in GRN and ANN systems;
- prove the existence of periodic attractors for GRN and ANN systems focusing on similarity of both systems;
- prove the existence of periodic attractors for GRN and ANN systems of order two, three and higher;
- detected sensitive dependence of solutions to ANN systems by calculating Lyapunov exponents;
- provide some observations and remarks on the problem of controllability and management of GRN and ANN systems.

Methods used in the study:

- linearization and local analysis of critical points;
- constructing periodic attractors by using Andronov–Hopf bifurcation from stable focus;
- constructing systems of higher dimensions by using low-dimensional blocks and then coupling systems by adding new elements;
- geometrical analysis of phase plane and phase spaces considering the nullclines;
- analyzing phase spaces and vector fields associated with GRN and ANN systems with respect to invariant sets;
- detecting of sensitive dependence of solutions to GRN and ANN systems by calculating Lyapunov exponents;

- extensive use of computational experiments in studying GRN and ANN systems.

MAIN RESULTS

The promotional work is a set of scientific publications written and published during the years 2015 - 2024. All papers are published in scientific journals or in article books of some conferences. The set of publications contains 14 ([29]-[33], [35]-[41], [43], [54]) scientific articles, seven ([35], [36], [38], [40], [41], [43], [54]) were published in the journal indexed in SCOPUS and one of them ([39]) has been published in the Axioms MDPI (indexed in WoS, Q2) journal.

The results were communicated at several conferences of different levels, including 11 International Scientific Conferences:

1. 82 st International Scientific Conference of the University of Latvia with the paper "REMARKS ON MATHEMATICAL MODELING OF GENE AND NEURONAL NETWORKS" (Riga, February 23, 2024);

2. International Conference of Numerical Analysis and Applied Mathematics 2023 (ICNAAM 2023) with the report "On control over system arising in the theory of neuronal networks" (Crete, Greece, September 11-17, 2023);

3. 26 th International Conference on Mathematical Modelling and Analysis with the report "COMPARATIVE ANALYSIS OF MODELS OF GENETIC AND NEURONAL NETWORKS" (Jurmala, May 30 - June 2, 2023);

4. 65 st International Scientific Conference of Daugavpils University with the paper "On linearization on some system arising in the theory of neural networks, in the neighborhood of a critical point " (Daugavpils, April 20, 2023);

5. 81 st International Scientific Conference of the University of Latvia with the paper "On computation of parameters in Artificial Neural Networks mathematical models" (Riga, February 24, 2023);

6. 61 st International Conference on VIBROENGINEERING with the paper “On a three-dimensional neural network model” (Udaipur, India, December 12-13, 2022);
7. International Liberty Interdisciplinary Studies Conference with the paper “MATHEMATICAL MODELING of THREE-DIMENSIONAL GENETIC REGULATORY NETWORKS USING DIFFERENT SIGMOIDAL FUNCTIONS” (Manhattan, New York, January 16-17, 2022);
8. 1 st International Symposium on Recent Advances in Fundamental and Applied Sciences (ISFAS-2021) with the paper “MATHEMATICAL MODELLING OF GRN USING DIFFERENT SIGMOIDAL FUNCTIONS” (Erzurum, Turkey, September 10-12, 2021);
9. 79 th Scientific Conference of the University of Latvia with the paper “Andronov - Hopf bifurcation in 2D systems” (Riga, February 26, 2021);
10. 78 th Scientific Conference of the University of Latvia with the paper “Gompertz function in the model of gene regulation network” (Riga, February 28, 2020);
11. 77 th Scientific Conference of the University of Latvia with the paper “Z-shaped isoclines in GRN differential system” (Riga, February 18, 2019);
12. 76 th Scientific Conference of the University of Latvia with the paper “Gompertz sigmoidal function in the 2-component network model” (Riga, February 23, 2018);
13. 60 th International Scientific Conference of Daugavpils University with the paper “CRITICAL POINTS FOR SIGMOIDAL FUNCTION” (Daugavpils, April 27, 2018);

14. 12 th Latvian Mathematical Conference with the paper "CRITICAL POINTS FOR SIGMOIDAL FUNCTION" (Ventspils, April 13- 14, 2018);
15. 11 th Latvian Mathematical Conference with the paper "Solvability conditions of the resonant problem" (Daugavpils, April 14, 2016);
16. 57 th International Scientific Conference of Daugavpils University with the paper "Dirichlet boundary value problem for one system of differential equations" (Daugavpils, April 12, 2015);
17. 56 th International Scientific Conference of Daugavpils University with the paper "The Dirichlet boundary value problem for a system of two second-order differential equations" (Daugavpils, April 8, 2014).

1 Introduction

In this work, we consider problems arising in mathematical modeling of networks. We focus on modeling gene regulatory networks and artificial neuronal networks. Networks of this type are everywhere. They consist generally of elements which are usually called nodes and links between nodes. The nature of networks may be different. Networks are present in nature, human society, literally everywhere. They can be enormously large, like networks of astronomical objects, stars, planets, and galaxies. At the same time, they can be very small and even unrecognizable and not seen by unarmed eyes, for example, the gene networks in a living organism. To understand the structure and principles of functioning of networks in nature, scientists should collect huge files of the results of observations. These data are to be collected, systematized, analyzed, and classified. Sometimes and even usually this is a very hard task. To make this task easier, the mathematical modeling can be used. As usually, the mathematical models are objects existing in the virtual realm of mathematics. These objects should be created, step-by-step verifying their adequacy according to the researched phenomena. Experiments should be done in a model. The analysis is of a mathematical nature, and the mathematical tools, standard or created exactly for a particular object of the study, are to be used to analyze the model. The results are recorded, systematized, and classified. Hypotheses are formulated in order to understand better the object of the study. Hypotheses are to be verified, and either to be confirmed or disproved.

Simple networks, like groups of humans, small populations, a number of static objects can be investigated using the mathematical apparatus of the graph theory. Graphs consist of vertices, edges between vertices, and characteristics of both vertices and edges. Sometimes graphs can be visualized and analyzed straightforwardly. For networks of large size, this can be a complicated task. As an example, one might think of transportation networks, networks of industrial objects, and so on.

The structure and properties of networks may change over time, and these are the more interesting networks. Based on the analysis of the past of a network, and knowing its main principles of functioning, one may think about predicting of future states of networks. Depending on the nature of a network, this may be the most important challenge.

To illustrate this, let us speak about genetic networks. The existence of genetic networks was not known before the great finding in the field of genetics and biology in general. Now it is known, that genetic networks are present in any cell of any living organism. It can be imagined as a collection of nodes, which are to be called genes, which communicate with each other. How do they do this? They are sending messages in the form of proteins. These messages are accepted by other genes, and the whole network elaborates common reactions. For instance, a genetic network is responsible for the reaction of an organism to diseases. They govern the most important processes in the growing animal or human. Their activity is decisive in morphogenesis, the process of formation of the internal organs. Due to the investigation of geneticists, biologists, and zoologists, the spots on a leopard, and strips on tigers and zebras appear as the result of programming in genomics, and the formation of these properties takes place under the control of gene networks.

Another example of a network is a collection (huge) of neurons in a human's brain. Neurons accept electrical signals from other elements of a network and produce their own signals, which are transferred further. The collective reaction, quick or not, depending on a situation, helps a human to perform its usual functions, like work, communicating with society, and solving creative and algorithmically defined problems. It was amazing that a human can easily recognize images, which is a difficult task for robots and controllable devices. This type of network belongs to biological neural networks. There are still many problems that can be solved by humans better than a computer or other automaton can do. Attempts to copy the work of a human brain have led to artificial neural networks (ANN briefly). ANN is a collection of units, which are called artificial neurons. These units are connected. They can transmit an accepted signal to other units. An artificial neuron receives signals and transmits them after being processed to other neurons connected to it.

The dynamics of both types of networks, GRN (gene regulatory networks) and ANN can be modeled by ordinary differential equations. Each element of a network is denoted by x_i. The physical meaning of x_i is, of course, different for GRN and ANN. Mathematics as a fundamental science that knows many examples of physical, mechanical, chemical, etc. processes, which are quite different in nature, but described by similar mathematical models. This is the case for GRN and ANN. Both have a finite, but probably very large number of elements, which we will denote by x_i. Each x_i can be measured (mostly imaginary) by a number, which is denoted also x_i, but it is dependent on time, $x_i(t)$. So an investigator deals with a number of functions, which are dependent on each other. The collection of $x_i(t)$, $i = 1, 2, \ldots$, forms the phase space, which mathematically is Euclidian. The relations between elements x_i should be described. One, very rough, way to do this, is to define the so called regulatory matrix, which is denoted usually W. It is $n \times n$ matrix, where n is the number of elements in a network. The element w_{ij} is a number, that characterizes the influence of an element x_j on the element x_i. The convention is, that positive elements of the matrix W mean activation, negativity means repression (also called inhibition), and zero value of w_{ij} means no relation. Once these preparations are made, the system of differential equations can be produced, which describes the dynamics of a network, since functions $x_i(t)$ change in time following the rules, defined by a system of ordinary differential equations (ODE briefly). The great feature of studying the relative system of ODE is that one might use the mathematical apparatus for the study of such systems and to make predictions on the behavior of solutions $x_i(t)$, which are considered now as solutions in a system of ODE. The mentioned systems were defined earlier for GRN networks, and for ANN networks. When we look at those systems, we observe certain similarities. That means that these systems can be studied simultaneously, and results obtained for GRN systems can be used for the study of ANN systems, and vice versa.

This is the main thrust of the presented work.

2 Gompertz function in the model of gene regulatory networks

In the theory of gene regulatory networks, differential systems are of the type

$$x_i' = f(\sum w_{ij}x_j) - x_i. \tag{2.1}$$

This system describes the interrelation between elements (genes) of a gene network. We omit the mechanism of this interrelation and focus on the mathematical aspect. The function $f(z)$ in this model is a continuous bounded monotonically increasing function (that is called *sigmoidal regulatory function*). Matrix W consists of entries describing the relation between nodes of the networks. There are various functions f possessing the desired properties. For instance, the function $f(z) = \frac{1}{1+e^{-\mu z}}$ meets the requirements. The argument z is substituted by $z = \Sigma w_{ij}x_j - \theta$ and it represents the input on a gene with threshold θ for increasing x_i. The function $f(z)$ is a sigmoidal (monotone and bounded) function and 2×2 matrix W consists of entries that take values from the set $\{-1, 0, 1\}$. Systems of this kind appear in gene regulatory theory. The structure of attracting sets is studied.

System (2.2), when containing n equations, describes the dynamics of the artificial network composed of n elements. The interrelation between elements of a network is described by the regulatory matrix W. The positive element a_{ij} means activation of i-th element by an j-th element. The negativity of an element w_{ij} means inhibition, and zero element means no relation. The absolute value of an element means the intensity of space.

In this article, we consider only a two-dimensional case (a network with two elements). The regulatory matrix that corresponds to activation is

$$W = \begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix},$$

and this case was investigated in detail. The inhibition matrix is

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

and behaviour of the system (2.2) for this case, is generally known. In both cases the attractors are stable critical points (stable nodes), and the number of critical points is at most three.

System of the form (2.2) appears in gene regulation theory [2]. It was mentioned that a system of this structure can occur also in the theory of telecommunication networks. Then the elements $x_1, x_2, ...$ represent pairs of communicating bodies, and elements of the regulatory matrices can vary in absolute values and signs.

We wish to consider all cases. Therefore, we allow any elements in W. It was detected that then the number of critical points can increase. We provide a full classification of possible behaviors. Moreover, we give examples of different matrices W, the respective sets of critical points, and their characters. Where possible, typical phase portraits are supplied.

2.1 System

Two-component gene regulatory networks are described by the differential system

$$\begin{cases} x_1' = f(w_{11}x_1 + w_{12}x_2 - \theta_1) - x_1, \\ x_2' = f(w_{21}x_1 + w_{22}x_2 - \theta_2) - x_2, \end{cases} \tag{2.2}$$

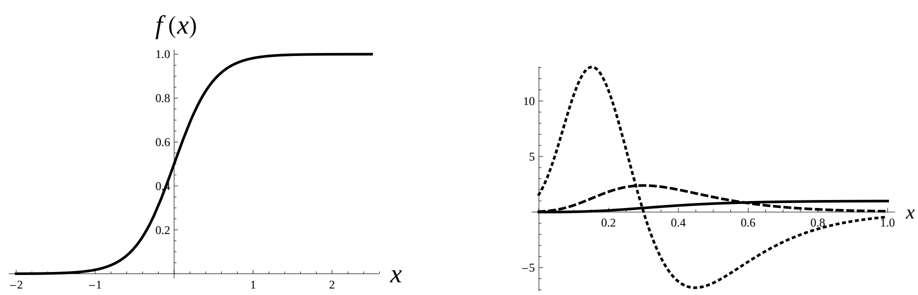
where $f(x)$ is a sigmoidal function.

Definition 1. *A function is called sigmoidal if the following is satisfied.*

1. *$f(x)$ monotonically increases from 0 to 1, $x \in \mathrm{R}$;*
2. *It has exactly one inflection point.*

One example of sigmoidal function is the logistic function $f(z) = \frac{1}{1+e^{-\mu z}}$. This function is used in mathematical models studied in works [7], [9], [22].

Another example of sigmoidal function is the Gompertz function. We use it through the thesis. The graph of f and graphs of f' and f'' are depicted in Fig. 2.1(b) for the values of parameters $\mu = 6.5$ and $\theta = 0.3$. It is convex in some neighborhood of zero and then it is concave. It is bounded by 1 and it is monotonically increasing.



a) Sigmoidal function

b) Solid - $f(x)$, dashed - $f'(x)$, dotted - $f''(x)$

Fig. 2.1

Consider the Gompertz function $f(z) = e^{-e^{-\mu z}}$. This function is sigmoidal in the sense of Definition 1.

The system in extended form is

$$\begin{cases} \dfrac{dx_1}{dt} = e^{-e^{-\mu(w_{11}x_1 + w_{12}x_2 - \theta_1)}} - x_1, \\ \\ \dfrac{dx_2}{dt} = e^{-e^{-\mu(w_{21}x_1 + w_{22}x_2 - \theta_2)}} - x_2, \end{cases} \tag{2.3}$$

where μ and θ are positive parameters. Our goal is to study the phase portrait and the attracting sets of this system.

2.2 System for critical points

It is supposed that $f(z)$ is dependent also on a parameter μ that regulates steepness of the graph of f. We wish to state general properties of the system (2.3).

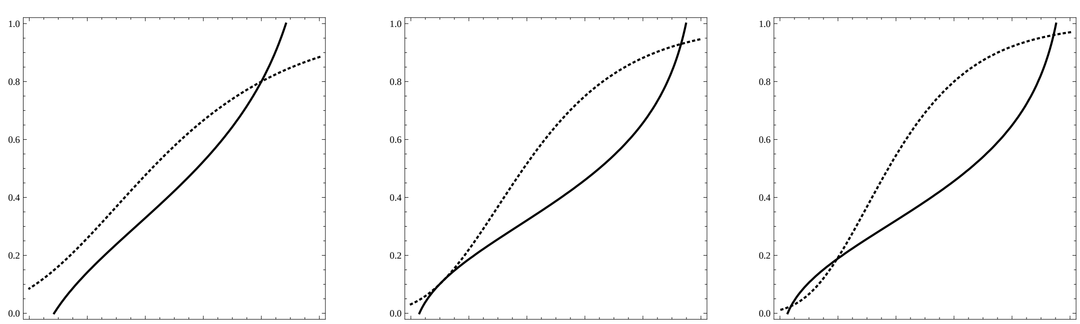
Critical points of this system are solutions of

$$\begin{cases} 0 = e^{-e^{-\mu(x_2 - \theta)}} - x_1, \\ 0 = e^{-e^{-\mu(x_1 - \theta)}} - x_2. \end{cases} \tag{2.4}$$

Lemma 1. *Any critical point is of the form (x, x). Therefore, the coordinate x of a critical point is defined from*

$$x = f(x). \tag{2.5}$$

The graphs of $y = f(x)$ and $y = f^{-1}(x)$ are depicted in Fig. 2.2.



a) $\theta = 0.3$, $\mu = 0.3$, 1 critical point

b) $\theta = 0.3$, $\mu \approx 4.15$, 2 critical point

c) $\theta = 0.3$, $\mu = 5$, 3 critical point

Fig. 2.2

For $\mu < e$, where $e = 2.7182818284...$, we have the relation which is depicted in Fig. 2.2.(a). For $\mu > e$ we have the relation which is depicted in Fig. 2.2.(c).

It is evident that for some values of parameters there is exactly one critical point and for some values of μ and θ there are three points. As an intermediate state we have Fig. 2.2.(b) with exactly two critical points. Our goal is to clarify which values of parameters correspond to 1, 2 or 3 critical points.

2.3 Linearized system

The linearized system in the vicinity of critical point (x_1, x_2) is

$$\begin{cases} u' = -u + \mu e^{-e^{-\mu(x_2-\theta)}-\mu(x_2-\theta)} \cdot v, \\ v' = \mu e^{-e^{-\mu(x_1-\theta)}-\mu(x_1-\theta)} \cdot u - v. \end{cases} \tag{2.6}$$

Since $x_1 = x_2$ the system takes the form

$$\begin{cases} u' = -u + \mu e^{-e^{-\mu(x-\theta)}-\mu(x-\theta)} \cdot v, \\ v' = \mu e^{-e^{-\mu(x-\theta)}-\mu(x-\theta)} \cdot u - v. \end{cases} \tag{2.7}$$

Therefore, by (2.4) and Lemma 1, the coordinate x of any critical point (x, x) satisfies

$$x = e^{-e^{-\mu(x-\theta)}},$$
$$-\ln(x) = e^{-\mu(x-\theta)}.$$

Let us consider $a = \mu e^{-e^{-\mu(x-\Theta)}-\mu(x-\Theta)} = \mu x(-\ln(x))$, then

$$\begin{cases} u' = -u + a \cdot v, \\ v' = a \cdot u - v. \end{cases} \tag{2.8}$$

We get the from $x = e^{-e^{-\mu(x-\theta)}}$ by logarithmation $\ln(-\ln(x)) = -\mu(x-\theta)$. For θ and $x \in (0, 1)$ we get the formula (2.9)

$$\theta = x + \frac{1}{\mu}\ln(-\ln(x)). \tag{2.9}$$

The relation (2.9) is visualized in Fig. 2.3

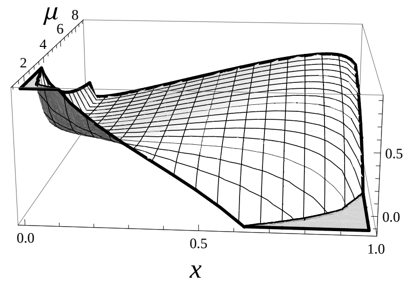
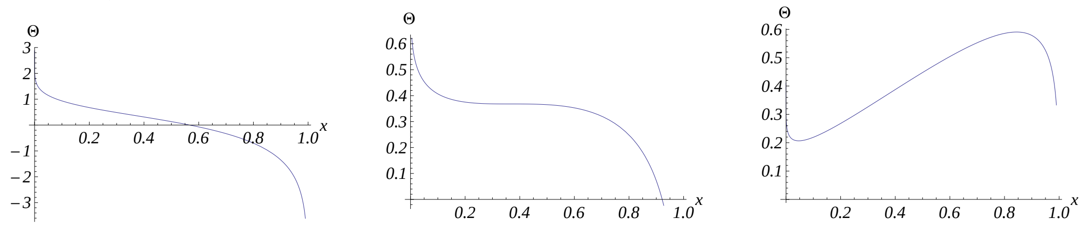


Fig. 2.3 The dependence of θ (for critical point (x, x)) of μ.

Fig. 2.4 shows that for some μ and θ there are respectively one, two or three critical points.

For different μ, the dependence θ of x is visualized below.



a)The dependence of θ of x for $\mu = 1$ b)The dependence of θ of x for $\mu = e$ c)The dependence of θ of x for $\mu = 7$

Fig. 2.4

Look at the second and the third of pictures in Fig. 2.4. There is an interval where $\theta(x)$ is increasing. Let us make an analysis of this.

One has that

$$\theta'(x) = 1 + \frac{1}{\mu} \frac{1}{x \ln x} \tag{2.10}$$

and $\theta'(x) = 0$ if

$$\frac{1}{x \ln x} = -\mu. \tag{2.11}$$

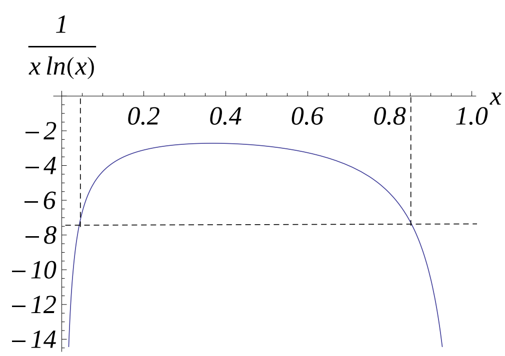


Fig. 2.5 The graph of $\frac{1}{x \ln x}$

The function $\theta'(x) > 0$ if $\frac{1}{x \ln x} > -\mu$. Denote solutions of the equation (2.11) $x_1(\mu)$ and $x_2(\mu)$ respectively. Horizontal dashed line in Fig. 2.5 is for $-\mu$ and two vertical dashed lines are for $x_1(\mu)$ and $x_2(\mu)$.

Consider

$$\theta_1(\mu) = x_1(\mu) + \frac{1}{\mu} \ln(-\ln(x_1(\mu)))$$

and

$$\theta_2(\mu) = x_2(\mu) + \frac{1}{\mu} \ln(-\ln(x_2(\mu))).$$

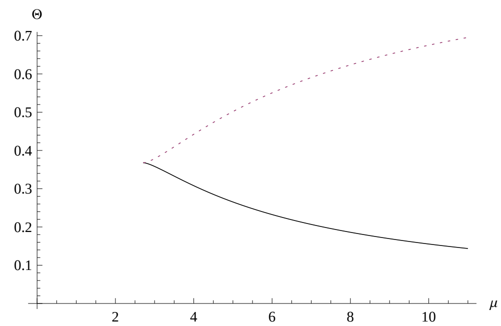


Fig. 2.6 The graphs of $\theta_1(\mu)$ and $\theta_2(\mu)$ together.

The region Ω between $\theta_1(\mu)$ (lower branch) and $\theta_2(\mu)$ (upper branch) corresponds to three critical points of the system, that is, for $(\mu, \theta) \in \Omega$ there are exactly three critical points.

The characteristic equation for the linearized system (2.7) is

$$\det(A - \lambda I) = \begin{vmatrix} -1-\lambda & a \\ a & -1-\lambda \end{vmatrix} = \begin{vmatrix} -1-\lambda & \mu x(-\ln(x)) \\ \mu x(-\ln(x)) & -1-\lambda \end{vmatrix} = \quad (2.12)$$

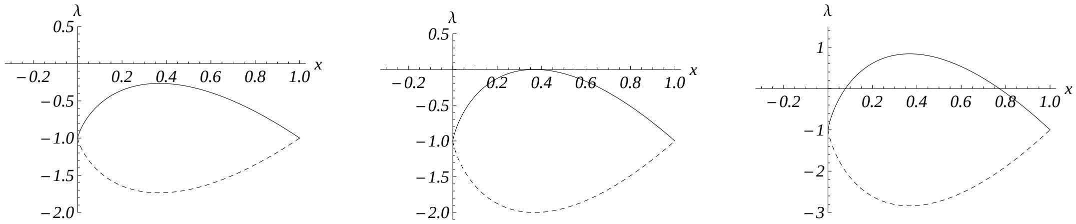
$$= (-1-\lambda)^2 - \mu^2 x^2 (-\ln(x))^2 = 0$$

or $\lambda = -1 \pm a$. Therefore $\lambda_1 = -1 - a$ is always negative and $\lambda_2 = -1 + a$. There are three possibilities for critical points:

1. $\lambda_2 < 0$ then (x, x) is stable node;

2. $\lambda_2 = 0$ then (x, x) is stable degenerate point;

3. $\lambda_2 > 0$ then (x, x) is saddle point.



a) $\mu = 2$ b) $\mu = e$ c) $\mu = 5$

Fig. 2.7 Roots of characteristic equation (2.12), solid line is $\lambda_2 = -1 + \mu x(-\ln(x))$, dashed line is $\lambda_1 = -1 - \mu x(-\ln(x))$, for a) $\mu \in (0, e)$, b) $\mu = e$ and c) $\mu \in (e, +\infty)$

The dependence of λ-s of x and $x = e^{-e^{-\mu(x-\theta)}}$ of θ (for μ given) is depicted in Fig. 2.7.

We observed that attractors for system (2.2) are either stable nodes or degenerate points with $\lambda_1 < 0, \lambda_2 = 0$.

Proposition 1. The system (2.2) cannot have critical points of type focus.

It follows from (2.12), that $\lambda = -1 \pm \mu x(-\ln(x))$ and λ cannot be complex number.

Theorem 1. There are four cases for system (2.2):

1. There is exactly one critical point of the type stable node.

2. There is a unique critical point with $\lambda_1 < 0, \lambda_2 = 0$. It is degenerate stable critical point.

3. There are exactly two critical points, one of them is stable node, another one is degenerate stable critical point.

4. There are exactly three critical points. Side critical points are stable nodes, middle point is a saddle.

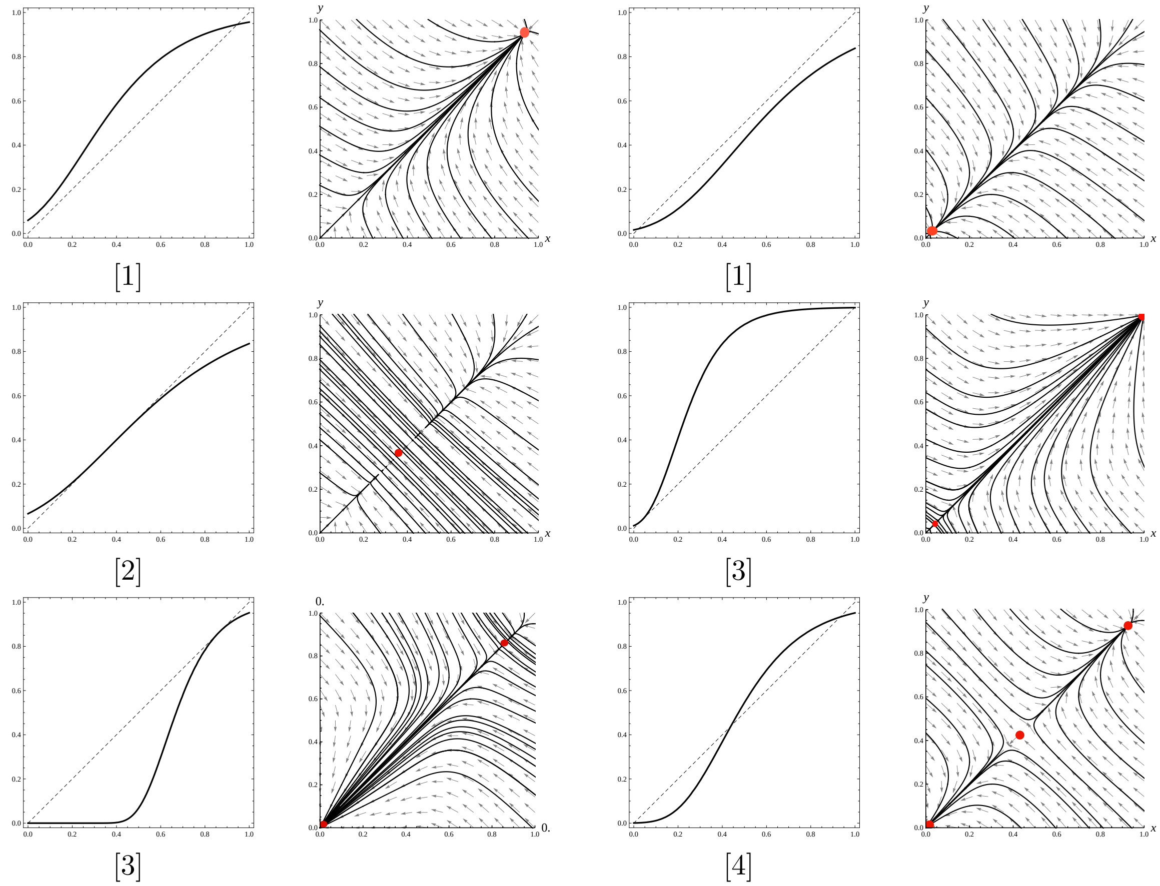


Fig. 2.8 Visualization of Theorem 1

Example 1.

Let us consider $\mu = 3$ and $\theta = 0.3$. There are respectively one critical point $(0.8, 0.8)$. The phase portrait of system (2.3) for one critical point is

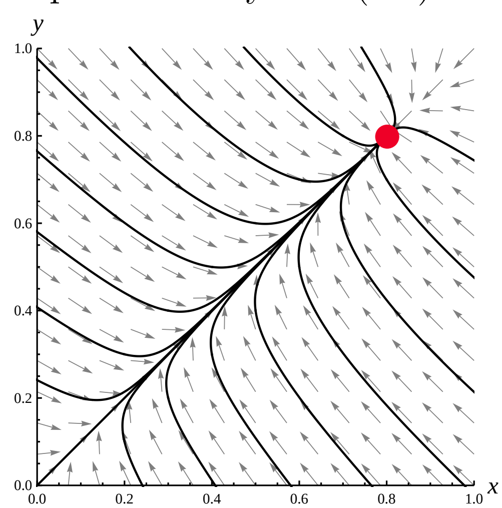


Fig. 2.9 Critical point is a stable node ($\lambda_1 < 0, \lambda_2 < 0$)

Example 2.

Let us consider $\mu = 4.15$ and $\theta = 0.3$. There are respectively two critical points $(0.93, 0.93)$ and $(0.11, 0.11)$. The phase portrait of system (2.3) for two critical points is

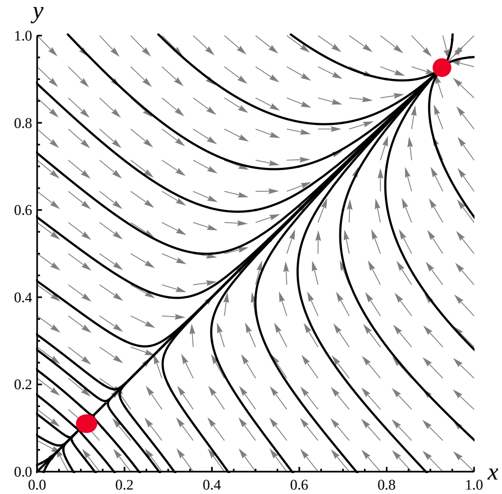


Fig. 2.10 First point is degenerate stable critical point, another one is stable node

Example 3.

Let us consider $\mu = 5$ and $\theta = 0.3$. There are respectively three critical points $(0.02, 0.02)$, $(0.21, 0.21)$, $(0.96, 0.96)$. The phase portrait of system (2.3) for three critical points is

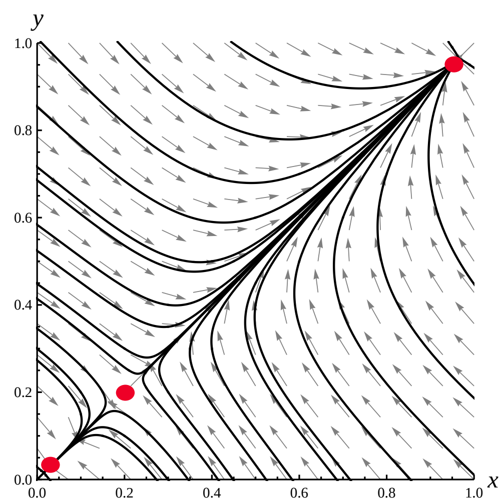


Fig. 2.11 Side critical points are stable nodes, middle point is a saddle

2.3.1 Summing up the results

We have defined the region Ω in (μ, θ)-plane with the properties:

- if $(\mu, \theta) \in \Omega$, then there are exactly three critical points with the properties - two side critical points are stable nodes, middle (central) point is a saddle;

- if $(\mu, \theta) \in \partial\Omega$, then there are exactly two critical points with the properties - the first critical point is stable node, the second is degenerate point $(\lambda_1 < 0, \lambda_2 = 0)$;
- if $(\mu, \theta) \in Q \setminus \overline{\Omega}$, then there is exactly one critical point with the property - it is a stable node;
- the common point of lower and upper branches of $\partial\Omega$ corresponds to a unique critical point with $\lambda_1 < 0, \lambda_2 = 0$, depicted in Fig. 2.15 [2].

2.4 Interrelation

The type of interaction is described by the so-called regulatory matrix $W = (w_{ij})$. The regulatory matrix elements can take any reasonable values. Generally, the system that models interactions and evolution of gene regulatory networks (GRN in short) is (2.3) where $f(z)$ is a sigmoidal function, probably depending on parameters θ_i, and w_{ij} are elements of the regulatory matrix

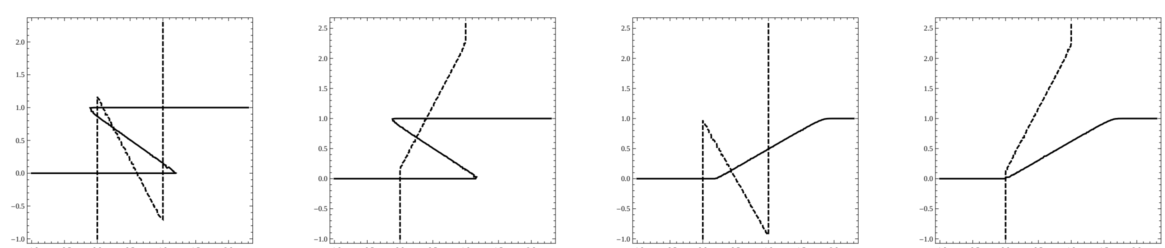
$$W = \begin{pmatrix} w_{11} & w_{12} \\ w_{21} & w_{22} \end{pmatrix}.$$

There exist four cases for type of interaction.

Case A: Activation. The regulatory matrix in this case takes the form

$$W = \begin{pmatrix} * & + \\ + & * \end{pmatrix},$$

where elements w_{12} and w_{21} are positive, but elements w_{11} and w_{22} can take any reasonable values.



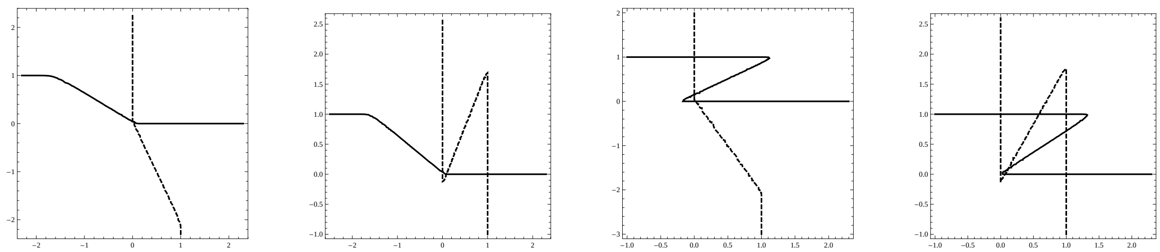
[1] [2] [3] [4]

Fig. 2.12 Visualization of all cases

Case B: Inhibition. The regulatory matrix in this case takes the form

$$W = \begin{pmatrix} * & - \\ - & * \end{pmatrix},$$

where elements w_{12} and w_{21} are negative, but elements w_{11} and w_{22} can take any reasonable values.



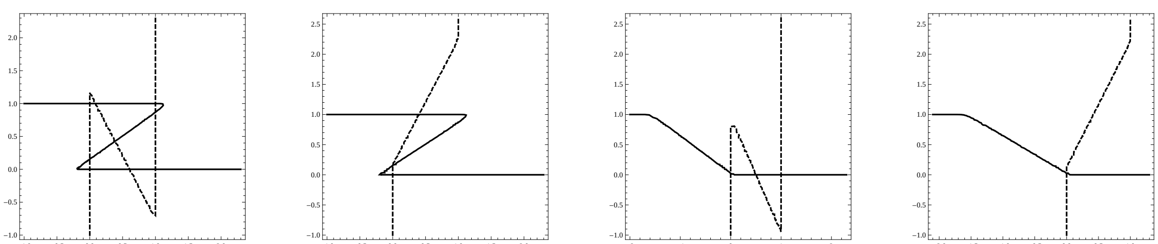
[5] [6] [7] [8]

Fig. 2.13 Visualization of all cases

Case C: Activation - Inhibition. The regulatory matrix in this case takes the form

$$W = \begin{pmatrix} * & + \\ - & * \end{pmatrix},$$

where element w_{12} is positive and element w_{21} is negative, but elements w_{11} and w_{22} can take any reasonable values.



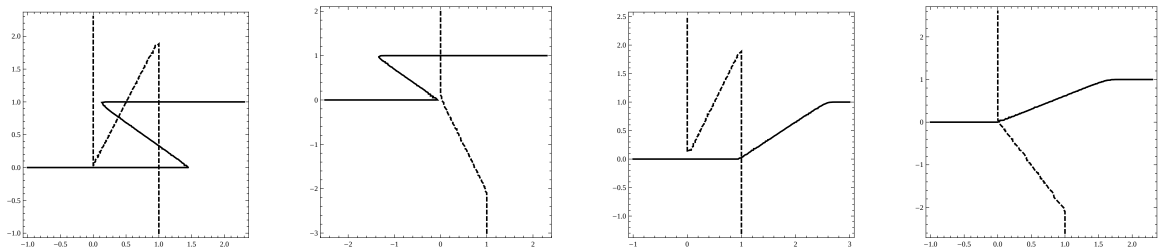
[9] [10] [11] [12]

Fig. 2.14 Visualization of all cases

Case D: Inhibition - Activation. The regulatory matrix in this case takes the form

$$W = \begin{pmatrix} * & - \\ + & * \end{pmatrix},$$

where element w_{12} is negative and element w_{21} is positive, but elements w_{11} and w_{22} can take any reasonable values.



[13] [14] [15] [16]

Fig. 2.15 Visualization of all cases

If μ is large enough in the GRN differential system isoclines have the Z-shaped form. The parameter μ is responsible for the sharpness of the angle of Z. The parameter θ is responsible for the shift of the graph of sigmoidal function, but the elements of regulatory matrix w_{ij} are responsible for the shaped form.

Proposition 2. For the function

$$x_1 = f(w_{11}x_1 + w_{12}x_2 - \theta_1) \tag{2.13}$$

the following is true:

$$x_2 \to +\infty, \qquad x_1 = f(w_{11}x_1 + w_{12}x_2 - \theta_1) \to 1;$$

$$x_2 \to -\infty, \qquad x_1 = f(w_{11}x_1 + w_{12}x_2 - \theta_1) \to 0.$$

Proposition 3. For the function

$$x_2 = f(w_{21}x_1 + w_{22}x_2 - \theta_2) \tag{2.14}$$

the following is true:

$$x_1 \to +\infty, \qquad x_2 = f(w_{21}x_1 + w_{22}x_2 - \theta_2) \to 1;$$

$$x_1 \to -\infty, \qquad x_2 = f(w_{21}x_1 + w_{22}x_2 - \theta_2) \to 0.$$

Corollary. *For the system* (2.2) *exists at least one critical point.*

Proposition 4. For the system (2.2) all critical points (x, y) are in the domain $(0, 1) \times (0, 1)$.

Proposition 5. One characteristic number is zero for the system (2.2) in tangent points of isoclines.

2.4.1 Case A: Activation

We consider the case of the maximal number of critical points (equilibrium states), for example, in the case of a regulatory matrix of the form W= $\begin{pmatrix} + & + \\ + & + \end{pmatrix}$.

For the sigmoidal function $f = e^{-e^{-\mu z}}$ and the particular choice of the regulatory matrix W= $\begin{pmatrix} 10 & 5 \\ 2 & 3 \end{pmatrix}$ the system is

$$\begin{cases} \dfrac{dx_1}{dt} = e^{-e^{-\mu(10x_1+5x_2-\theta_1)}} - x_1, \\ \\ \dfrac{dx_2}{dt} = e^{-e^{-\mu(2x_1+3x_2-\theta_2)}} - x_2. \end{cases} \tag{2.15}$$

It is supposed that $f(z)$ is dependent also on a parameter μ that regulates steepness of the graph of f. We wish to state general properties of the system (2.15).

Critical points of this system are solutions of

$$\begin{cases} x_1 = e^{-e^{-\mu(10x_1+5x_2-\theta_1)}}, \\ \\ x_2 = e^{-e^{-\mu(2x_1+3x_2-\theta_2)}}. \end{cases} \tag{2.16}$$

Two isoclines of system (2.15) are depicted in Fig. 2.16

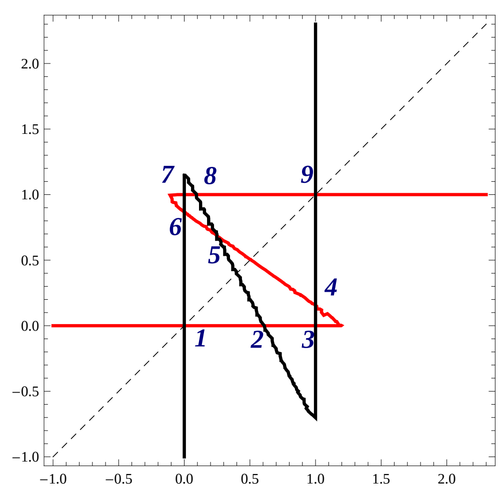


Fig. 2.16 The graph of system (2.15) for nine critical points: $\mu = 20$, $\theta_1 = 6$, $\theta_2 = 2.5$, $w_{11} = 10$, $w_{12} = 5$, $w_{21} = 2$, $w_{22} = 3$

- The type of the first critical point $(0, 0)$ is a stable node ($\lambda_1 = -1, \lambda_2 = -1$).
- The type of the second critical point $(0.6, 0)$ is a saddle point ($\lambda_1 = -1, \lambda_2 = 59.96$).
- The type of the third critical point $(1, 0)$ is a stable node ($\lambda_1 = -1, \lambda_2 = -1$).
- The type of tne fourth critical point $(1, 0.16)$ is a saddle point ($\lambda_1 = -1, \lambda_2 = 16.41$).
- The type of the fifth critical point $(0.26, 0.67)$ is a unstable node ($\lambda_1 = 75.3, \lambda_2 = 8.8$).
- The type of the sixth critical point $(0, 0.87)$ is a saddle point ($\lambda_1 = -1, \lambda_2 = 6.5$).
- The type of the seventh critical point $(0, 0.99)$ is a stable node ($\lambda_1 = -1, \lambda_2 = -0.99$).
- The type of the eighth critical point $(0.1, 0.99)$ is a saddle point ($\lambda_1 = -0.99, \lambda_2 = 43.9$).
- The type of the ninth critical point $(1, 1)$ is a stable node ($\lambda_1 = -1, \lambda_2 = -0.9$).

To confirm the results of analysis, let us provide the phase portrait for the system (2.15).

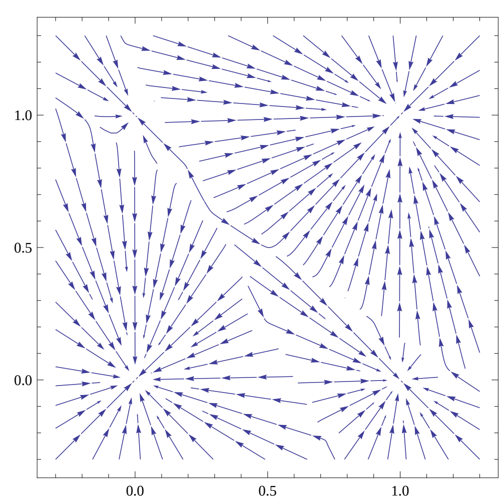


Fig. 2.17 The phase portrait of system (2.15) for nine critical points: $\mu = 20$, $\theta_1 = 6$, $\theta_2 = 2.5$, $w_{11} = 10$, $w_{12} = 5$, $w_{21} = 2$, $w_{22} = 3$

Cases B, C, and D can be investigated analogously.

2.4.2 Summing up the results

In a simple two-dimensional system of differential equations modeling the two-element network, nine critical points are possible. The set of critical points for this case consists of four stable nodes, four-saddle points, and one unstable node. The attractor for this system for selected values of parameters consists of four critical points (1, 3, 7, 9).

3 Mathematical modeling of gene and neuronal networks by ordinary differential equations

In this thesis, we study Neural Networks, called also Artificial Neural Networks (ANN), and their mathematical models, using ordinary differential equations. The motivation for the study of ANN went from the attempts to understand the principles and organization of the human brain. Understanding came that human brains work differently from digital computers. Its effectiveness comes from high complexity, nonlinear mode of regulation, and parallelism of actions. The elements of the human brain were called *neurons*. These elements perform calculations still faster than the fastest digital computers. The human brain is able to perceive information about the environment in the form of images, and, moreover, it can process the received information needed for interaction with the environment.

At birth, the human brain has a ready structure for learning, which in familiar terms is understood as experience. So the neural network is designed to model the way in which the human brain solves usual problems and performs a particular task. A particular interest in ANN stems from the fact that an important group of neural networks performs needed to solve a problem computations through the process of learning. So, following [18], generally, ANN can be imagined as a parallel distributed processor, consisting of simple processing units, which is able to gain experiential knowledge and make it available for use.

Artificial Neural Networks (ANNs) consist of a number of elements that are connected. "Each neuron has a sigmoid transfer function and a continuous positive and bounded output activity that evolves according to weighted sums of the activities in the networks. Neural networks with arbitrary connections are often called recurrent networks" [12]. No conditions are imposed to restrict synaptic values. There are two types of recurrent neural networks: discrete-time recurrent neural networks and continuous-time ones. The dynamics of the continuous-time recurrent neural network with n units can be described by the system of ordinary differential equations (ODE) [16])

$$x_i' = -b_i x_i + f_i(\Sigma a_{ij} x_j) + I_i(t), \tag{3.1}$$

where x_i is the internal state of the i-th unit, b_i is the time constant for the i-th unit, a_{ij} are connection weights, $I_i(t)$ is the input to the i-th unit, and $f_i(\Sigma a_{ij} x_j)$ is the response function of the i-th unit. Usually, f is taken as a sigmoidal function. There are particular response functions that are non-negative. For instance, functions $f_i(z) = (1 + \exp(\mu_i(z - \theta_i))^{-1}$ which are used in [14]. More general cases can be modeled by the system using the function $f_i(z) = \tanh(a_i z - \theta_i)$, which takes values in the open interval $(-1, 1)$. If the recurrent neural networks without input are considered, the system

$$x_i' = f_i(\Sigma(a_{ij} x_j - \theta_i)) - b_i x_i \tag{3.2}$$

can be considered.

The mathematical model using ordinary differential equations, is

$$\begin{cases} \dfrac{dx_1}{dt} = 2\dfrac{1}{1 + e^{(a_{11}x_1 + a_{12}x_2 + a_{13}x_n - \theta_1)}} - 1 - b_1 x_1, \\ \dfrac{dx_2}{dt} = 2\dfrac{1}{1 + e^{(a_{21}x_1 + a_{22}x_2 + aw_{23}x_n - \theta_2)}} - 1 - b_2 x_2, \\ \dfrac{dx_3}{dt} = 2\dfrac{1}{1 + e^{(a_{31}x_1 + a_{32}x_2 + a_{33}x_3 - \theta_3)}} - 1 - b_3 x_3. \end{cases} \tag{3.3}$$

The same system can be written as ([60])

$$\begin{cases} x_1' = \tanh(a_{11}x_1 + a_{12}x_2 + a_{13}x_3 - \theta_1) - b_1 x_1, \\ x_2' = \tanh(a_{21}x_1 + a_{22}x_2 + a_{23}x_3 - \theta_2) - b_2 x_2, \\ x_3' = \tanh(a_{31}x_1 + a_{32}x_2 + a_{33}x_3 - \theta_3) - b_3 x_3. \end{cases} \tag{3.4}$$

The elements of this 3D network are called neurons. The connections between them are synapses (or nerves). There is an algorithm that describes how the impulses are propagated through the network. In the above model, this algorithm is encoded by the matrix

$$W = \begin{pmatrix} a_{11} & a_{12} & a_{13} \\ a_{21} & a_{22} & a_{23} \\ a_{31} & a_{32} & a_{33} \end{pmatrix}. \tag{3.5}$$

Each neuron accepts signals from others and produces a single output. The extent to which the input of neuron i is driven by the output of neuron j is characterized by its output and synaptic weight a_{ij}. The dynamic evolution leads to attractors of the system (3.4) and it was experimentally observed in neural systems. In theoretical modeling, the emphasis is put on the attractors of a system. We wish to study them for the system (3.4).

Similar systems arise in the theory of genetic regulatory networks. The difference is that the nonlinearity is represented by a positive valued sigmoidal function. One of such systems is

$$\begin{cases} \dfrac{dx_1}{dt} = \dfrac{1}{1+e^{-\mu_1(a_{11}x_1+a_{12}x_2+a_{13}x_n-\theta_1)}} - b_1x_1, \\ \dfrac{dx_2}{dt} = \dfrac{1}{1+e^{-\mu_2(a_{21}x_1+a_{22}x_2+a_{23}x_n-\theta_2)}} - b_2x_2, \\ \dfrac{dx_3}{dt} = \dfrac{1}{1+e^{-\mu_3(a_{31}x_1+a_{32}x_2+a_{33}x_3-\theta_3)}} - b_3x_3. \end{cases} \tag{3.6}$$

Systems of the form (3.6) were studied before by many authors. The interested reader may consult the works ([58], [64], [17], [8], [2], [63]). Similar systems appear in the theory of telecommunication networks.

In this section, we study the different dynamic regimes for the system (3.4) which can be observed under various conditions. In particular, we first speak about critical points for the system (3.4) and evaluate the number of them. Then we focus on periodic regimes and study their attractiveness for other trajectories. This can be done, under some restrictions, for systems of relatively high dimensionality. Also, the evidences of chaotic behavior are presented.

3.1 Preliminary results

3.1.1 Invariant set

Consider 3D system (3.4).

Proposition 6. System (3.4) has an invariant set

$$Q_3 = \left\{ \frac{-1}{b_1} < x_1 < \frac{1}{b_1}, \frac{-1}{b_2} < x_2 < \frac{1}{b_2}, \frac{-1}{b_3} < x_3 < \frac{1}{b_3} \right\}. \tag{3.7}$$

3.1.2 Nullclines

The nullclines for the system are defined by the relations

$$\begin{cases} x_1 = [\tanh(a_{11}x_1 + a_{12}x_2 + a_{13}x_3 - \theta_1)]/b_1, \\ x_2 = [\tanh(a_{21}x_1 + a_{22}x_2 + a_{23}x_3 - \theta_2)]/b_2, \\ x_3 = [\tanh(a_{31}x_1 + a_{32}x_2 + a_{33}x_3 - \theta_3)]/b_3. \end{cases} \tag{3.8}$$

3.2 Critical points

The critical points for the system (3.4) are the cross points of the nullclines. They can be found from the system

$$\begin{cases} x_1 - [\tanh(a_{11}x_1 + a_{12}x_2 + a_{13}x_3 - \theta_1)]/b_1 = 0, \\ x_2 - [\tanh(a_{21}x_1 + a_{22}x_2 + a_{23}x_3 - \theta_2)]/b_2 = 0, \\ x_3 - [\tanh(a_{31}x_1 + a_{32}x_2 + a_{33}x_3 - \theta_3)]/b_3 = 0. \end{cases} \tag{3.9}$$

Proposition 7. For the system (2.2) all critical points are in the invariant set Q_3.

The nullclines for the system (2.2) are located in the set Q_3 only.

Proposition 8. At least one critical point exists for the system (2.2).

Remark. The number of critical points may be greater, up to 27, but finite.

Remark. Both assertions are valid for the n-dimensional case also.

Example 4.

Consider the system (3.4) with the matrix

$$W = \begin{pmatrix} 1 & 2 & 0 \\ -2 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} \tag{3.10}$$

and $b_1 = b_2 = b_3 = 1, \theta_1 = 0.8, \theta_2 = 0.3, \theta_3 = 0.2$. There is one critical point $(-0.162;\ 0.399;\ -0.731)$.

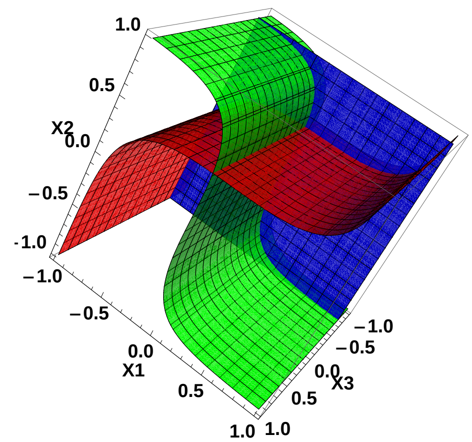


Fig. 3.1 Nullclines for system (3.4) (x_1 - red, x_2 - green, x_3 - blue)

Example 5.

Consider example of multiple critical points and the system (3.4) with the matrix

$$W = \begin{pmatrix} 1.5 & 2 & 0 \\ -2 & 1.5 & 0 \\ 0 & 0 & 1.5 \end{pmatrix} \qquad (3.11)$$

and $b_1 = b_2 = b_3 = 1, \theta_1 = 0.7, \theta_2 = 0.3, \theta_3 = 0.01.$

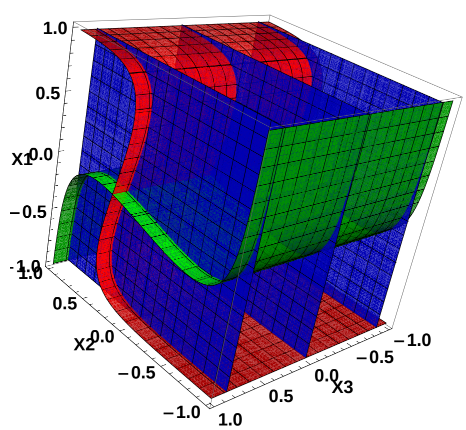


Fig. 3.2 Nullclines for system (3.4) (x_1 - red, x_2 - green, x_3 - blue)

There are three critical points $(-0.067;\ 0.367;\ 0.854)$, $(-0.067;\ 0.367;\ 0.020)$ and $(-0.067;\ 0.367;\ -0.863)$.

3.2.1 Linearization at a critical point

For the system (2.2) the linearized system for any critical point (x_1^*, x_2^*, x_3^*) is

$$\begin{cases} u_1' = -b_1u_1 + a_{11}g_1u_1 + a_{12}g_1u_2 + a_{13}g_1u_3, \\ u_2' = -b_2u_2 + a_{21}g_2u_1 + a_{22}g_2u_2 + a_{23}g_2u_3, \\ u_3' = -b_3u_3 + a_{31}g_3u_1 + a_{32}g_3u_2 + a_{33}g_3u_3, \end{cases} \tag{3.12}$$

where

$$g_1 = \frac{4e^{-2(a_{11}x_1^*+a_{12}x_2^*+a_{13}x_3^*-\theta_1)}}{[1+e^{-2(a_{11}x_1^*+a_{12}x_2^*+a_{13}x_3^*-\theta_1)}]^2}, \tag{3.13}$$

$$g_2 = \frac{4e^{-2(a_{21}x_1^*+a_{22}x_2^*+a_{23}x_3^*-\theta_2)}}{[1+e^{-2(a_{21}x_1^*+a_{22}x_2^*+a_{23}x_3^*-\theta_2)}]^2}, \tag{3.14}$$

$$g_3 = \frac{4e^{-2(a_{31}x_1^*+a_{32}x_2^*+a_{33}x_3^*-\theta_3)}}{[1+e^{-2(a_{31}x_1^*+a_{32}x_2^*+a_{33}x_3^*-\theta_3)}]^2}, \tag{3.15}$$

and coeficent matrix of sistem (3.12) is denoted by A. The characteristic equation for $b_1 = b_2 = b_3 = 1$ is

$$\begin{aligned} \det|A-\lambda I| = -\Lambda^3 + (a_{11}g_1 + a_{22}g_2 + a_{33}g_3)\Lambda^2 + [g_1g_2(a_{12}a_{21} - a_{11}a_{22}) + \\ + g_1g_3(a_{13}a_{31} - a_{11}a_{33}) + g_2g_3(a_{23}a_{32} - a_{22}a_{33})]\Lambda + g_1g_2g_3(a_{11}a_{22}a_{33} + \\ + a_{12}a_{23}a_{31} + a_{13}a_{21}a_{32} - a_{11}a_{23}a_{32} - a_{12}a_{21}a_{33} - a_{13}a_{22}a_{31}) = 0, \end{aligned} \tag{3.16}$$

where $\Lambda = \lambda + 1$.

3.3 Inhibition-activation

Consider the system

$$\begin{cases} x_1' = \tanh(a_{12}x_2 + a_{13}x_3 - \theta_1) - x_1, \\ x_2' = \tanh(a_{21}x_1 + a_{23}x_3 - \theta_2) - x_2, \\ x_3' = \tanh(a_{31}x_1 + a_{32}x_2 - \theta_3) - x_3. \end{cases} \tag{3.17}$$

where a_{12}, a_{13}, a_{23} are negative, a_{21}, a_{31}, a_{32} are positive.

We consider the specific case, when

$$W = \begin{pmatrix} 0 & -1 & -1 \\ 1 & 0 & -1 \\ 1 & 1 & 0 \end{pmatrix} \tag{3.18}$$

and $\theta_1 = \theta_2 = \theta_3 = \theta$. The system then has a single critical point. Let us suppose, that

$$g_1 = \frac{4e^{-2(-x_2-x_3-\theta)}}{[1+e^{-2(-x_2-x_3-\theta)}]^2}, \tag{3.19}$$

$$g_2 = \frac{4e^{-2(x_1-x_3-\theta)}}{[1+e^{-2(x_1-x_3-\theta)}]^2}, \tag{3.20}$$

$$g_3 = \frac{4e^{-2(x_1+x_2-\theta)}}{[1+e^{-2(x_1+x_2-\theta)}]^2}. \tag{3.21}$$

Values of g_i are in the range $(0,1)$. The linearized system now is

$$\begin{cases} u_1' = -u_1 - g_1 u_2 - g_1 u_3, \\ u_2' = -u_2 + g_2 u_1 - g_2 u_3, \\ u_3' = -u_3 + g_3 u_1 + g_3 u_2, \end{cases} \tag{3.22}$$

The characteristic equation can be obtained from

$$A - \lambda I = \begin{vmatrix} -1-\lambda & -g_1 & -g_1 \\ g_2 & -1-\lambda & -g_2 \\ g_3 & g_3 & -1-\lambda \end{vmatrix} \tag{3.23}$$

and

$$\begin{aligned} &\det|A-\lambda I| = -\lambda^3 - 3\lambda^2 + (g_1g_2 + g_1g_3 + g_2g_3 - 3)\lambda \\ &+(g_1g_2 + g_1g_3 + g_2g_3 - 1) = 0. \end{aligned} \tag{3.24}$$

The characteristic numbers are

$$\begin{cases} \lambda_1 = -1, \\ \lambda_2 = -1 - \sqrt{g_1g_2 + g_1g_3 + g_2g_3}\, i, \\ \lambda_3 = -1 + \sqrt{g_1g_2 + g_1g_3 + g_2g_3}\, i, \end{cases} \tag{3.25}$$

where i is an imaginary unit ($i^2 = -1$).

Proposition 9. A critical point of the system (3.17) under the above conditions is 3D-focus, that is, the following is true: there is 2D-subspace with a stable focus and attraction in the remaining dimension.

4 Systems with stable periodic solutions. Andronov - Hopf type bifurcations.

4.1 2D case

We first study the second order system

$$\begin{cases} x_1' = \tanh(kx_1 + bx_2 - \theta_1) - b_1 x_1, \\ x_2' = \tanh(ax_1 + kx_2 - \theta_2) - v_2 x_2, \end{cases} \tag{4.1}$$

where $b = -a = 2$, and $k > 0$ is a parameter.

Choose k small enough to make a unique critical point a stable focus. Then increase k until the stable focus turns to unstable one. Then the limit cycle emerges, surrounding the critical point. This is called Andronov - Hopf bifurcation for 2D systems.

Example 6.

Consider the system (4.1) with the matrix

$$W = \begin{pmatrix} k & 2 \\ -2 & k \end{pmatrix} \tag{4.2}$$

and $k = 0.7, b_1 = b_2 = 1, \theta_1 = 0.2, \theta_2 = 0.4$.

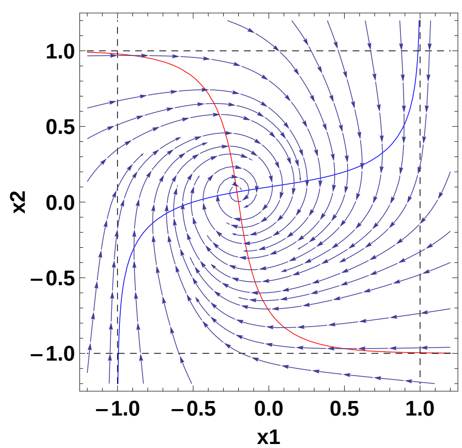


Fig. 4.1 Nullclines and vector field for system (4.1) (x_1 - blue, x_2 - red).

There is one critical point that is stable focus. If the parameter k increases the stable focus turns to an unstable one. Then the limit cycle emerges, surrounding the critical point.

Example 7.

Consider the system (4.1) with the matrix

$$W = \begin{pmatrix} k & 2 \\ -2 & k \end{pmatrix} \tag{4.3}$$

and $k = 1.2, b_1 = b_2 = 1, \theta_1 = 0.2, \theta_2 = 0.4.$

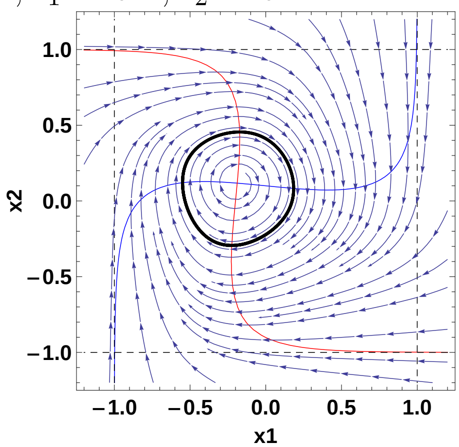


Fig. 4.2 The limit cycle in system (4.1) (x_1 - blue, x_2 - red).

4.2 3D case

Consider now the 3D system with the matrix

$$W = \begin{pmatrix} k & 0 & b \\ 0 & a_{22} & 0 \\ a & 0 & k \end{pmatrix} \tag{4.4}$$

where a, b, k are as in 2D system (4.1). The second nullcline is defined by the relation

$$x_2 = \frac{1}{b_2} \tanh(a_{22}x_2 - \theta_2). \tag{4.5}$$

Choose the parameters so that the equation (4.5) has three roots. Then the second nullcline is a union of three parallel planes.

Example 8.

Consider picture of nullclines. There are three periodic solutions in system (4.5) with the matrix

$$W = \begin{pmatrix} 1.5 & 0 & 2 \\ 0 & 2.7 & 0 \\ -2 & 0 & 1.5 \end{pmatrix} \tag{4.6}$$

and $b_1 = b_2 = b_3 = 1, \theta_1 = 0.2, \theta_2 = 0, \theta_3 = 0.3.$

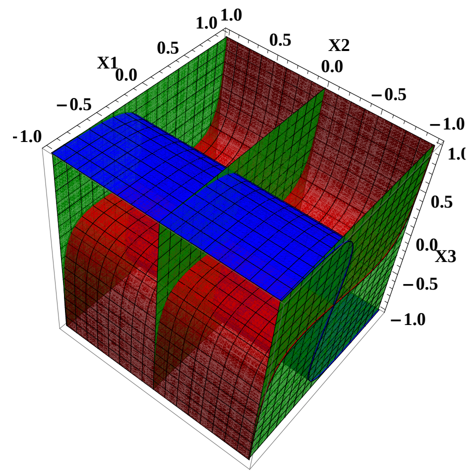


Fig. 4.3 The nullclines of the system (4.5) with the regulatory matrix (4.6).

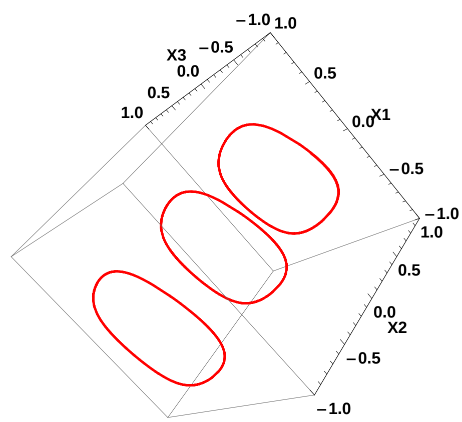


Fig. 4.4 Three periodic solutions of the system (4.5) with the regulatory matrix (4.6).

4.3 Control and management of ANN

First citation from [61]: "Models of ANN are specified by three basic entities: models of the neurons themselves–that is, the node characteristics; models of synaptic interconnections and structures–that is, net topology and weights; and training or learning rules – that is, the method of adjusting the weights or the way the network interprets the information it receives."

In this section, we discuss the problem of changing the behavior of trajectories of a system (3.4). This may be interpreted as partial control over the system. The system has as parameters the coefficients a_{ij}, the values θ_i, and b_i in the linear part. Properties of the system may be changed by varying any of the mentioned parameters.

We would like to demonstrate, how a system of the form (3.4) can be modified so, that trajectories start to tend to some of the indicated attractors. To obtain it, let us consider the system (3.4), which has as attractors three limit cycles. This can be done by three operations: 1) put the entries of the 2D regulatory matrix, which corresponds to the 2D system with the limit cycle L, to the four corners of a 3D matrix A; 2) choose the middle element of the 3D matrix A so, that the equation $x_2 = \tanh(a_{22}x_2 - \theta_2)$ with respect to x_2 has exactly three roots $r_1 < r_2 < r_3$; 3) set the four remaining values of a_{ij} to zero. Set also b_i to unity. After finishing these preparations, the second nullcline will be three parallel planes P_i, going through $x_2 = r_i, i = 1, 2, 3$. Each of these planes will consist of the limit cycle. Two-side limit cycles will attract trajectories from their neighborhoods. The middle limit cycle will attract only trajectories, lying in the plane P_2.

Now, let us solve the problem of control. Let the limit cycle at P_3 be conditionally "bad". The problem is to change the system so, that all trajectories in Q_3 be attracted to the limit cycle which at the beginning of the process was in the plane P_1. Problems of this kind may arise often. In the paper [63], similar problem was treated mathematically for genetic networks.

Solution. Change θ_2 so that the equation $x_2 = \tanh(a_{22}x_2 - \theta_2)$ have now the unique root near the second nullcline the plane, passing near r_1. This operation is possible, since the graph of $\tanh(a_{22}x_2 - \theta_2)$ is sigmoidal, and changing θ_2 means shifting the original plane P_1 in both directions. After that, only one attractor (limit cycle) remains. The problem is solved.

4.4 Summing up the results

The behavior of solutions of systems of the form (3.3) strongly depends on the structure of weight matrix W. Any system (3.3) has at least one critical point in the region $D = \left(\frac{-1}{b_1}, \frac{1}{b_1}\right) \times \left(\frac{-1}{b_2}, \frac{1}{b_2}\right) \times \left(\frac{-1}{b_3}, \frac{1}{b_3}\right)$. No trajectory of the system (3.3) can escape this region. Multiple critical points are possible. Stable nodes, stable and unstable 3D-focuses and saddle points can occur.

5 Conclusions

The work is devoted to the study of systems of ordinary differential equations arising in mathematical models of GRN and ANN.

The main results of the Doctoral thesis are:

- analysis of the phase plane for two-dimensional GRN system with Gompertz nonlinearities, counting critical points and their characteristics;
- formulas for linearization and analysis of critical points in GRN and ANN systems;
- examples of periodic attractors in GRN and ANN systems;
- basic properties of ANN systems with hyperbolic tangent nonlinearities;
- comparison of GRN and ANN systems;
- local analysis of critical points of GRN and ANN systems for dimensions two and three;
- graphical images of nullclines for many relevant to the study cases;
- sensitive dependence of solutions to GRN and ANN systems by calculating Lyapunov exponents;
- control of two-dimensional inhibitory GRN systems;
- control by changing parameters over systems with hyperbolic tangent nonlinearities.

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Iespiests DU Akadēmiskajā apgādā "Saule" –
Vienības iela 13, Daugavpils, LV-5401, Latvija