On controllability of nonlinear dynamical network

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Abstract: We provide the scheme for driving a network modelled by dynamical system from one state ("undesired") to another one. This can be done by changing in time adjustable parameters and require knowledge of the structure of attractors of a system. The process is explained and illustrated by analyzing the two-element network.

Key–Words: network control, attracting sets, dynamical system, phase portrait, gene regulatory networks

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1 Introduction

Living cells in an organism form complicated systems that are now studied by mathematical methods also. The aim of these studies is to understand complexity of these systems and the structure of interrelations. Every element of such systems can influenc others activating or inhibiting them. The gene regulatory system (GRN) is define as network of genes and their activating-inhibiting connections. Different mathematical models are used to analyze networks. Models using differential equations are especially effective since they treat networks as dynamical objects and involve the concept of attractor. Differential equations allow to describe oscillatory behaviour, stationary solutions, cyclical patterns. Nonlinear ordinary differential equations are wide-spread mathematical tools for studying the regulatory interactions between genes. The time-dependent variables $x(t)$ represent the concentration of gene products mRNAs or protein. These variables are positive valued.

It was noticed by biologists that cells of living organisms are adaptable to unknown and unpredictable changes in environment even if these changes are very rapid. It was proposed to use the attractor selection as principal mechanism of adaptation to unknown changes of biological systems.

The main idea of attractor selection is that the system is driven by two components, namely, deterministic and stochastic. Attractors are a part of the equilibrium points in the solution space. Conditions of such system are controlled by very simple feedback. When conditions of a system are suitable (close to one of the attractors), it is driven almost only by deterministic behavior, stochastic influenc is very limited. When conditions of the systems are poor, deterministic behavior influenc is close to zero and in this case system is driven by stochastic behavior. In this case the system randomly fluctuate searching for a new attractor. When this attractor is found, deterministic behavior again dominates over stochastic [7].

On the other hand, the system can be controlled by changing the adjustable parameters (if any). Then stochastic behaviour can be neglected (this is our assumption) and only the deterministic model can be studied. If we use attractor selection mechanism for network resource management, at firs we should defin regulatory matrix W, which shows relationships between node pairs, that is, how each node pair affects each other including itself. Three types of influenc exist, namely, activation, inhibition and no relation, corresponding to positive, negative or zero values of w_{ij}.

In what follows, we provide the example of controlled dynamical system describing an evolving network. The system contains sigmoidal function depending on transformed (via the regulatory matrix W) argument and containing the parameters. Motivated by the paper [6], we provide the scheme of steering the system from "undesired" attractor to "desired" one. The scheme uses two scenarios. The firs is driving the system to desired attractor by changing a single parameter. The perturbation of a parameter is precise in the meaning that an optimal (shortest) path can be selected. The second way to move the system is by changing a single element of the regulatory matrix W. In our examples only bistable systems are considered. No intermediate attractors.

In Section 2 the structure of the system is presented. Section 3 is devoted to detailed description of attractors and their dependence on parameters for a particular choice of the regulatory matrix W. Section 4 describes the process of controlling the system by changing the parameters μ and/or θ. The analysis is supplied by a number of pictures reflectin the results of computational experiments. Section 5 focuses on the process of driving the system to desired attractor by changing an element in the regulatory matrix, i.e. by changing the character of interrelations of elements of the respective network.

2 System

The dynamical system of the form

$$\frac{dx_i}{dt} = f(\sum w_{ij}x_j - \theta_i)v_g - x_i v_g - \eta \qquad (1)$$

is used to model genetic regulatory networks and telecommunications networks [7] as well. The function $f(z)$ is sigmoidal function, that is, monotonically increasing from 0 to 1 as z changes from $-\infty$ to $+\infty$, having only one point of infl xion, like the function $\frac{1}{1+e^{-\mu z}}$, v_g is a parameter that controls deterministic behaviour and η is stochastic term. Neglecting the stochastic terms and assuming $v_g = 1, \theta_i = \theta$ for all i, we can write the dynamical system in extended form

$$\begin{cases} x_1' = f(w_{11}x_1 + \ldots + w_{1n}x_n - \theta) - x_1, \\ x_2' = f(w_{21}x_1 + \ldots + w_{2n}x_n - \theta) - x_2, \\ \ldots \quad \ldots \quad \ldots, \\ x_n' = f(w_{n1}x_1 + \ldots + w_{nn}x_n - \theta) - x_n, \end{cases} \qquad (2)$$

where w_{ij} are entries of the regulatory matrix W. The equilibrium states can be detected from the system

$$\begin{cases} x_1 = f(x_2 + x_3 + \ldots + x_n - \theta), \\ x_2 = f(x_1 + x_3 + \ldots + x_n - \theta), \\ \ldots \quad \ldots \quad \ldots, \\ x_n = f(x_1 + x_2 + \ldots + x_{n-1} - \theta). \end{cases} \qquad (3)$$

The current state of the system is described by the vector $x(t)$. By attractor of the system we mean an attracting equilibrium point. Attractors of systems of the form (2) were studied by the authors in [3] to [5].

3 Description of the state space for system (2)

Generally the state space (phase space) can be complicated and it can be described in particular cases (for different types of interrelations in the network) only. We have proved [4], [5] the following for the case of cross-activation. The below regulatory matrix

$$W = \begin{pmatrix} 0 & 1 & \ldots & 1 \\ 1 & 0 & \ldots & 1 \\ \ldots & \ldots & \ldots & \ldots \\ 1 & 1 & \ldots & 0 \end{pmatrix} \qquad (4)$$

corresponds to this case. All equilibrium states (critical points) are of the form $(x, \ldots, x)$ (we say "lies on the bisectrix").

For the particular choice of $f(z) = \frac{1}{1+e^{-\mu z}}$ system (2) takes the form

$$\begin{cases} x_1' = \dfrac{1}{1+e^{-\mu(w_{11}x_1 + w_{12}x_2 + \ldots + w_{1n}x_n - \theta)}} - x_1, \\ x_2' = \dfrac{1}{1+e^{-\mu(w_{21}x_1 + w_{22}x_2 + \ldots + w_{2n}x_n - \theta)}} - x_2, \\ \ldots \\ x_n' = \dfrac{1}{1+e^{-\mu(w_{n1}x_1 + w_{n2}x_2 + \ldots + w_{nn}x_n - \theta)}} - x_n, \end{cases} \qquad (5)$$

where W is as in (4). It is assumed that μ and θ are positive. In that case the relation between x, μ and θ was established [2], [4]

$$\theta = \frac{1}{\mu}\ln\left(\frac{1}{x} - 1\right) + (n-1)x. \qquad (6)$$

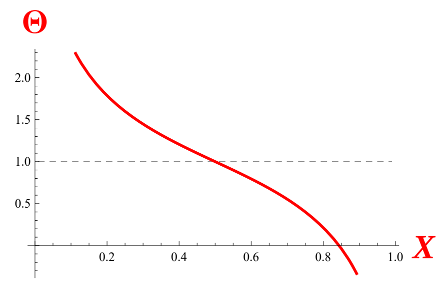

Figure 1: The equation (6) for $\mu = 1$ and $n = 2$

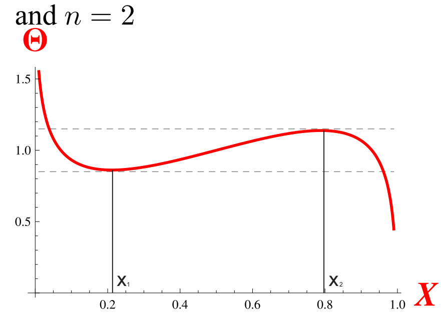

Figure 2: The equation (6) for $\mu = 3$ and $n = 2$

For any $\mu \in (0, \frac{4}{n-1})$ there is exactly one critical point x for every θ, see Figure 1. Consider Figure 2. For $\mu \in (\frac{4}{n-1}, +\infty)$, if θ takes a value between the dashed lines, then there are exactly three values of x, corresponding to three critical points. The case $\mu = \frac{4}{n-1}$ is the special one. There is exactly one x value, corresponding to a single critical point (here $\theta = \theta_1 = \theta_2$). The region Ω (depicted in Figure 3) is bounded by two branches

$$\theta_{1,2} = \frac{1}{\mu}\ln\left(\frac{1}{x_{1,2}} - 1\right) + (n-1)x_{1,2},$$

where

$$x_{1,2} = \frac{1}{2} \pm \sqrt{\frac{1}{4} - \frac{1}{(n-1)\mu}}.$$

The region Ω has the following properties. Exterior and interior in the below formulation mean respectively a set outside $\overline{\Omega}$ in the firs quadrant $\{\mu > 0, \theta > 0\}$ and interior of Ω.

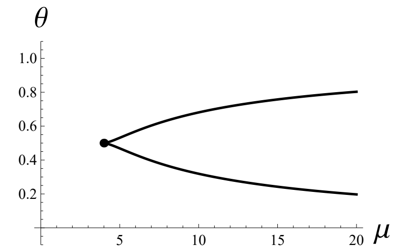

Figure 3: Region Ω between the two branches, $n = 2$.

Theorem.[5] There are at most three positive equilibria (critical points) in system (5). If (μ, θ) is in ext Ω, then there is a unique critical point of the system and all characteristic numbers λ are negative (the point is a sink); if (μ, θ) is in int Ω, there exist exactly three critical points locating on the bisectrix; two side points are sinks (all $\lambda's$ are negative), and the middle critical point is a saddle (there are positive and negative characteristic numbers λ).

4 Driving the system from undesired state to normal one

The problem of driving the system from one attractor to another one generally is complicated. A realistic example was provided in the paper [6]. We provide the following scheme for the cross-activation case described above. Consider the general system (2) that is supposed to have coexisting attracting states (equilibria).

4.1 Description of the schemes

System state at a time moment t is $x(t)$. The phase space of the system is denoted by $P(\mu, \theta, W)$, where μ, θ are parameters in (5) and W is the regulatory matrix. A set of attractors is denoted $A(\mu, \theta, W)$ and it consists of attractors A_1, A_2, and so on. We denote $B(A_i)$ the basin of attraction of an attractor A_i. The phase space with a set of attractors are dependent on parameters μ, θ and on elements of the regulatory matrix W. Elements of the regulatory matrix can be changed and we left aside the problems of technically realization of this. We are interested in mathematical problem of driving the system (5) from "undesired" attractor to "normal" one. In the example given in [6], the "undesired" attractor corresponds to cancerous state. Knowledge of the set of attractors and their basins, understanding of the relation between parameters and the regulatory matrices W can allow for constructive processes of driving a system from one attractor to another. We propose two schemes of such controlling of a network and discuss the respective examples.

Scheme 1 (changing parameters). Suppose $x(t_1) \in B(A_1)$, $A_1 \in A(\mu, \theta, W))$, where A_1 is an "undesired" attractor. Let μ_0 be the initial value of the parameter μ. The system will evolve into an undesired state (attractor) A_1. One wishes to implement control to bring the system out of $B(A_1)$ and steer it into a desired attractor. The goal is to drive the system (5) to A_2, that is treated as normal ("desired") attractor. Suppose that: 1) there exists μ_1 such that $A(\mu_1, \theta, W)$ consists of a unique attractor A_* such that $B(A_*) = P(\mu, \theta, W)$ (attractor A_* attracts all the points of the phase space) and 2) some neighborhood $N(A_*) \in B(A_2)$. Imposing control means that we change the parameter μ from μ_0 to μ_1. This parameter variation takes effect for a finit time since no critical points and their neighborhoods are crossed. Switch μ to the value μ_1 and wait until the trajectory $x(t)$ will reach $N(A_*)$, i.e. there exists $t_2 > t_1$ such that $x(t_2) \in N(A_*) \subset B(A_2)$. Then switch μ back to the previous value μ_0. After control perturbation is withdrawn, the system is restored to its parameter setting before control but its state has been changed, namely, the system will have moved to the basin of attraction of the desired attractor and will approach the desired attractor. The system (5) returns to the previous form and $x(t_2) \in B(A_2)$. The system state tends to a normal state A_2.

Scheme 2 (changing elements of the regulatory matrix W). This scheme is described in Section 5.

Below we describe two ways how to drive the system from one attractor to another one following scheme 1.

4.2 Case: changing μ

Let us illustrate the above scheme considering the system

$$\begin{cases} x_1' = \dfrac{1}{1 + e^{-\mu(x_2 - \theta)}} - x_1, \\ x_2' = \dfrac{1}{1 + e^{-\mu(x_1 - \theta)}} - x_2. \end{cases} \tag{7}$$

The regulatory matrix is

$$W = \begin{pmatrix} 0 & 1 \\ 1 & 0 \end{pmatrix}. \tag{8}$$

4.2.1 The parameter μ escapes the region Ω through the upper branch

Set $\theta = 0.53$. Let $\mu_0 = 8$ and $\mu_1 = 4$. The perturbation of μ is visualized in Fig. 4.

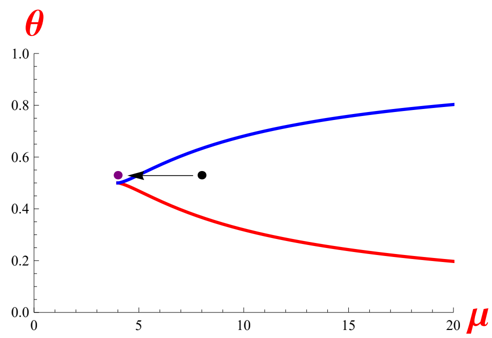

Figure 4: Changing $\mu = 8$ to $\mu = 4$ through the upper branch of Ω.

In Fig. 5 and Fig. 6 evolution of dependence of $\theta(x)$ as μ changes from $\mu = 8$ to $\mu = 4$, where x is the coordinate of a critical point (x, x), is illustrated.

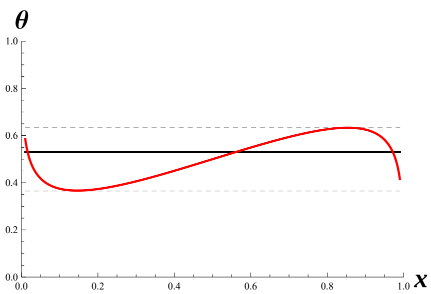

Figure 5: $\mu = 8$, critical points are at $(0.016, 0.016)$, $(0.56, 0.56)$, $(0.972, 0.972)$.

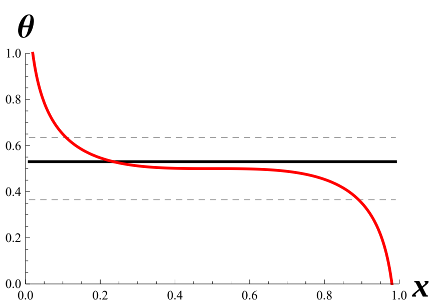

Figure 6: $\mu = 4$, the unique critical point for perturbed system is at $(0.235, 0.235)$.

First, there are three critical points and the upper critical point is treated as "undesired". Currently the system state $x(t)$ is in the basin of attraction of the upper critical point. Changing μ from value 8 to value 4 two upper critical points that are initially at $(0.56, 0.56)$ and $(0.972, 0.972)$ merge and then disappear and only one critical point appears at $(0.235, 0.235)$. Return μ to the value 8. The state $x(t)$ of the system (7) is now in the basin of attraction of the lower critical point at $(0.016, 0.016)$. The system state will tend to the "normal" attractor.

4.2.2 The parameter μ escapes the region Ω through the lower branch

Set θ to the value $\theta = 0.45$. Consider Fig. 7.

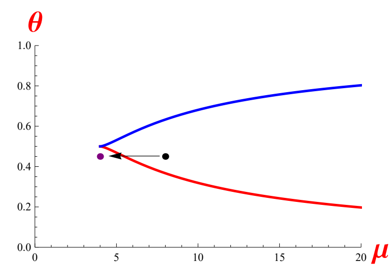

Figure 7: $\mu = 8$ to $\mu = 4$

Evolution of the dependence $(\theta(x)$ is illustrated in Fig. 8 to Fig. 9. Return μ to the value 8. The state $x(t)$ of the system (7)is now in the basin of attraction of the upper critical point at $(0.986, 0.986)$. The system state will tend to the upper "normal" attractor.

5 Case: changing elements of W

Driving the system (7) from the upper attractor to the lower one is possible also by changing some entries of the regulatory matrix W.

Statement. The system (7) can be driven from the upper attractor to the lower one by changing a single element of matrix W.

Let the matrix W be as in (8) and the element $w_{12} = 1$. Let the system state $x(t)$ be in the basin of attraction of the upper critical point shown in Fig. 10. The purpose is to drive the system state to the lower critical point.

Algorithm. Let parameters $(\mu, \theta) = (8, 0.5)$. Change the element w_{12} gradually from 1 to 0.5. The middle and the upper critical points (a saddle and a stable node) approach each other, merge and disappear as shown in Fig. 10 to Fig. 12. Switch the parameter w_{12} back to the value 1. The phase plane is again as in Figure 10. The system state (the vector $x(t)$) is in a close proximity of the lower attractor that is located at the point $(0.021, 0.021)$. The system state will tend to the lower attractor.

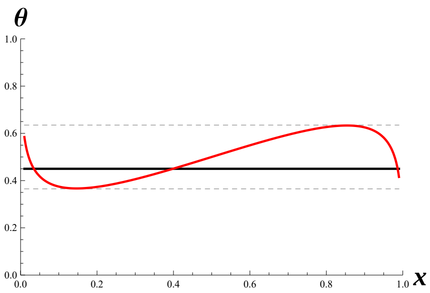

Figure 8: $\mu = 8$, there are three critical points at $(0.035, 0.035)$, $(0.399, 0.399)$, $(0.986, 0.986)$.

We wish to drive the system state $x(t)$ from the lower critical point to the upper one. For this, μ is changed from 8 to 4 (but escape from Ω is through the lower branch). Two lower critical points that are initially at $(0.035, 0.035)$ and $(0.399, 0.399)$ merge and finall disappear and one critical point appears at $(0.806, 0.806)$ remains. The difference with the preceding case (μ crossing the upper branch) is that two lower critical points merge instead of two upper ones.

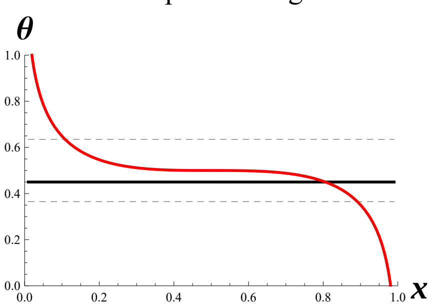

Figure 9: $\mu = 4$, one critical point at $(0.806, 0.806)$ is attractive.

Description. The entire process is visualized in Fig. 13. The system state $x(t)$ is intercepted at upper green point and redirected to the lower green point. It is in the basin of attraction of the lower critical point at The element w_{12} is assigned the value 1 again and the system state will tend to the lower "normal" state at $(0.021, 0.021)$.

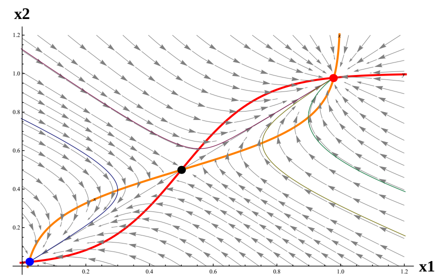

Figure 10: $w_{12} = 1$

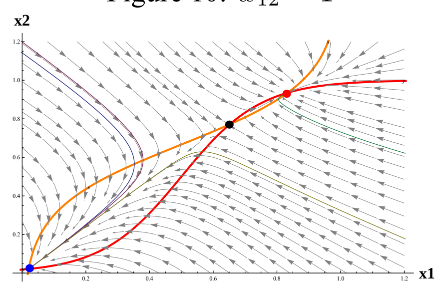

Figure 11: $w_{12} = 0.75$

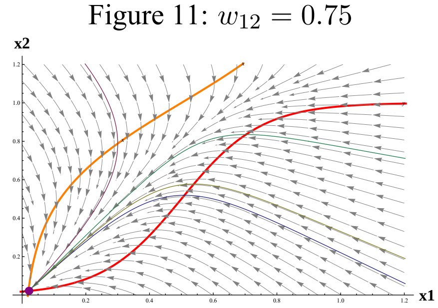

Figure 12: $w_{12} = 0.5$

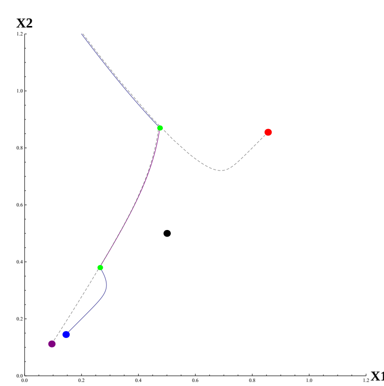

Figure 13: Three critical points at $(0.021, 0.021)$, $(0.5, 0.5)$, $(0.979, 0.979)$, the unique critical point of perturbed system is at $(0.019, 0.021)$

6 Conclusion

The same schemes are valid for the general cross-activation case that is characterized by the regularity matrix (4). If the parameters $(\mu, theta)$ are in the region Ω the system is bistable (it has exactly two attractive critical points). By changing $(\mu, theta)$ to values outside Ω the system is turned to the state with exactly one (attractive) critical point. Only a single parameter (μ in our examples) can be changed to drive a system to desired state. It makes difference whether μ gets out of Ω through upper or lower branches of the boundary $\partial\Omega$. Instead of μ the parameter θ can be used as the control parameter.

The cross-activation system can be controlled also by changing elements of the regulatory matrix W. A single element of W can be used as the control parameter.

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