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On Coexistence of Inhibition and Activation in Genetic Regulatory Networks

Felix Sadyrbaev[1,a)], Valentin Sengileyev[2,b)] and Albert Silvans[3,c)]

[1]*Institute of Mathematics and Computer Science, University of Latvia, Riga, Latvia*
[2]*Daugavpils University, Daugavpils, Latvia*
[3]*Student at Groningen University, Groningen, Netherlands*

[a)]Corresponding author: felix@latnet.lv
[b)]valentin.sengileyev@gmail.com
[c)]albert.silvans@gmail.com

Abstract. Dynamical mathematical models of Genomic Regulatory Networks are considered. We focus on attractors in these models, which has the form of a periodic trajectory. Our observations show that closed orbits can exist in phase spaces of a three-dimensional network with the regulatory matrices, where inhibitory cycle coexists with the activatory one. Examples, illustrations and results of numerical experiments are provided.

INTRODUCTION

The theory of genetic regulatory networks (GRN in short) is an active subject of research in biomathematics. There are several ways of modelling GRN, for instance, boolean algebras, graph theory and more, [1], [2], [3].

We choose to model GRN in terms of dynamical systems, specifically as systems of ODE, which allow to follow the state of these systems in time. The system we wish to study, appears in multiple contexts ([5], [9], [10], [6], [7], [8], [12]). The system we wish to study, in the extended form is

$$\begin{aligned} x_1' &= \frac{1}{1+\exp[-\mu_1(w_{11}x_1+w_{12}x_2+w_{13}x_3-\theta_1)]} - x_1 \\ x_2' &= \frac{1}{1+\exp[-\mu_2(w_{21}x_1+w_{22}x_2+w_{23}x_3-\theta_2)]} - x_2 \\ x_3' &= \frac{1}{1+\exp[-\mu_3(w_{31}x_1+w_{32}x_2+w_{33}x_3-\theta_3)]} - x_3, \end{aligned} \tag{1}$$

where $' = \frac{d}{dt}$, μ_i, θ_i are parameters, and w_{ij} are entries of the *regulatory matrix*

$$W = \begin{pmatrix} w_{11} & w_{12} & w_{13} \\ w_{21} & w_{22} & w_{23} \\ w_{31} & w_{32} & w_{33} \end{pmatrix}. \tag{2}$$

The system (1) describes evolution of a network in time, provided that the interrelation between elements (genes) of a gene network is encoded by the matrix (2). The usual conventions about this matrix are that the element x_j activates (resp.: inhibits) the element x_i, if w_{ij} is positive (resp.: negative). If $w_{ij} = 0$, there is no relation. We omit the mechanism of this interrelation and focus on its mathematical aspects. For more on the application of this model, one can consult [4], [5], [6].

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The decisive role in the evolution of a GRN play attracting sets. The structure of attracting sets of the system (1) is studied. Generally there are stable equilibria. In interesting cases equilibria can be unstable. We study systems where the existense of periodic attractors is possible.

We use the logistic function $z \mapsto 1/(1+\exp(-\mu z))$ in (1), however other options, e.g., the function $x \mapsto \tanh(x)$, the Hill function $x \mapsto x^{\mu}/(\theta^{\mu}+x^{\mu})$ ([6]) and the Gompertz function $x \mapsto \exp[-\exp(-\mu(x-\theta))]$ ([11], [13]) also can be met in the literature.

For (1) the nullclines are given explicitly as

$$
\begin{aligned}
x_1 &= \frac{1}{1+\exp[-\mu_1(w_{11}x_1+w_{12}x_2+w_{13}x_3-\theta_1)]} \\
x_2 &= \frac{1}{1+\exp[-\mu_2(w_{21}x_1+w_{22}x_2+w_{23}x_3-\theta_2)]} \\
x_3 &= \frac{1}{1+\exp[-\mu_3(w_{31}x_1+w_{32}x_2+w_{33}x_3-\theta_3)]},
\end{aligned}
\tag{3}
$$

The critical points (equilibria) are determined by solving the system (3) for x_i. Depending on the choice of parameters μ_i, θ_i, there can be a varying number of critical points.

Due to the structure of the system (1) and the properties of sigmoidal functions, there exists at least one critical point. All critical points are located in the unity cube $Q_3 = (0,1)^3$. The vector field, defined by the system (1), is directed inward on the border of Q_3. Characterization of critical points (equilibria) can be made in the standard way, using the linearized system.

INHIBITION AND ACTIVATION CYCLES

In the examples below the parameters θ_i are set to values, ensuring that the central point $P = (0.5, 0.5, 0.5)$ is an equilibrium.

Regulated auto-activation

Consider the regulatory matrix

$$
W = \begin{pmatrix} k & 0 & -1 \\ -1 & k & 0 \\ 0 & -1 & k \end{pmatrix}. \tag{4}
$$

It represents the inhibitory cycle that can be described schematically as

$$
X_1 \Leftarrow X_3 \Leftarrow X_2 \Leftarrow X_1,
$$

where $\Leftarrow$ means repression of the left element by the right one. The parameter $k > 0$ on the main diagonal means the auto-activation (the term borrowed from [6]). Therefore the respective system

$$
\begin{cases}
x_1' = \dfrac{1}{1+e^{-\mu_1(kx_1-x_3-\theta_1)}} - x_1, \\[2ex]
x_2' = \dfrac{1}{1+e^{-\mu_2(-x_1+kx_2-\theta_2)}} - x_2, \\[2ex]
x_3' = \dfrac{1}{1+e^{-\mu_3(-x_2+kx_3-\theta_3)}} - x_3
\end{cases}
\tag{5}
$$

is driven by the combination of the inhibition cycle with auto-activation. After examination of the system (5) we are led to the conclusion that for k in a certain diapason there exists the periodic attractor.

Regulated inhibition

Another example of combination inhibitory and activatory cycles is associated with the regulatory matrix

$$W = \begin{pmatrix} 0 & -k & 1 \\ 1 & 0 & -k \\ -k & 1 & 0 \end{pmatrix}, \qquad (6)$$

where $k > 0$ is the parameter to be changed. Schematically the inhibition cycle is $x_1 \Leftarrow x_2 \Leftarrow x_3 \Leftarrow x_1$, whereas the activation cycle is $x_1 \Rightarrow x_2 \Rightarrow x_3 \Rightarrow x_1$, where $\Rightarrow$ means activation.

RESULTS

Results for auto-activation case

We consider the system (1) with the regulatory matrix (4). For k small enough, $k < 0.3$, the system has a single critical point P of the type stable focus. For increasing k, the stable periodic solution emerges, which serves as an attractor. For $k = 2$ three critical points appear, but periodic trajectory still exists. For larger k, the periodic attractor seems to be destroyed and nine critical points appear. The attractors for $k = 0.2, 1.0, 2.0$ are depicted in Figure 1.

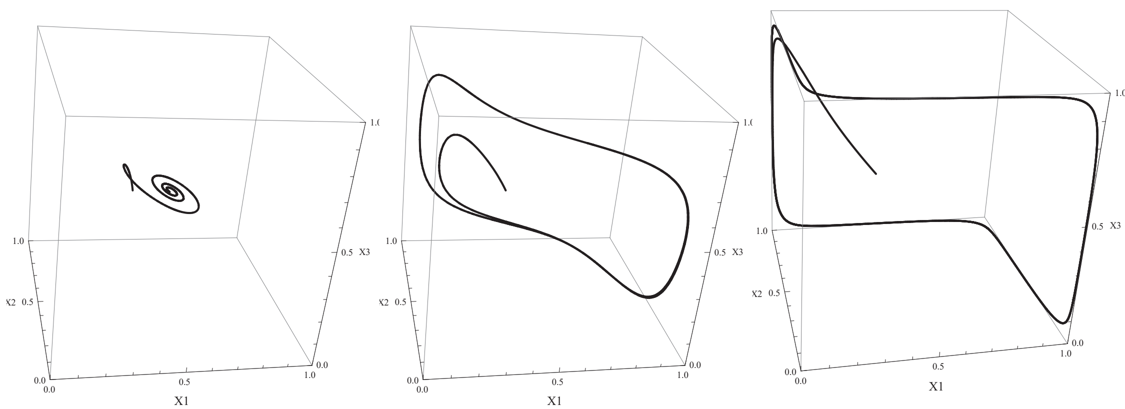

FIGURE 1. $\mu_i = 5$, $k = 0.2$; 1.0; 2.0.

Results for regulated inhibition case

We consider the system (1) with the regulatory matrix (6). For k small enough there are three critical points in Q_3. For $0.2 < k < 2.6$ three points collided to a central one, which is a stable focus. For $k > 2.6$ we observe unstable critical point P and stable periodic solution. The attractors are depicted in Figure 2 for $k = 0.5, 3.0, 16.0$. As k is increased, the attractor becomes more angular.

We have considered two schemes of interrelation of an inhibitory cycle with activation component. First, we analyzed the system with the inhibitory cycle and auto-activation. Secondly, the system with regulated inhibitory cycle was considered. This cycle, when combined with the activation cycle of appropriate form, can produce the periodic attractor.

The conclusion is that coexistence of inhibitory and activation cycles in the system (formally in the regulatory matrix W) leads to periodic attractors, which exist for selected values of k.

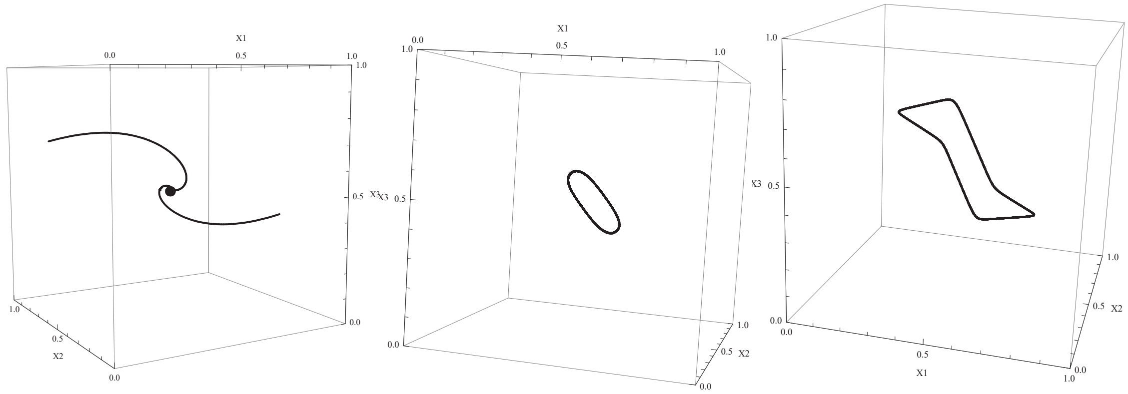

FIGURE 2. $\mu_i = 5$, $k = 0.5, 3.0, 16.0$.

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