



Control in Inhibitory Genetic Regulatory Network Models

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Abstract: The system of two the first order ordinary differential equations arising in the gene regulatory networks theory is studied. The structure of attractors for this system is described for three important behavioral cases: activation, inhibition, mixed activation-inhibition. The geometrical approach combined with the vector field analysis allows treating the problem in full generality. A number of propositions are stated and the proof is geometrical, avoiding complex analytic. Although not all the possible cases are considered, the instructions are given what to do in any particular situation.

Keywords: gene regulatory networks, control, attractors

1. Introduction

Theory of genetic regulatory networks (GRN in short) is in the center of biomathematics. There are several ways of modelling GRN, for instance, boolean algebras, graph theory and more, [1-3]. Modelling in terms of dynamical systems allows to follow evolution of GRN. The system we wish to study, appears in multiple contexts^[4-6] in vectorial form

$$x_i' = f(\sum w_{ij}x_j - \theta_i) - x_i. \quad (1)$$

This system describes interrelation between elements (genes) of a gene network. We omit the mechanism of this interrelation (one can consult [3-5]) 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 $W = (w_{ij})$ consists of entries describing the relation between nodes of the networks. There are various functions f possessing the desired properties. For instance, the function $f(z) = \frac{1}{1 + e^{-uz}}$ meets the requirements. The argument z is substituted by $z = \sum w_{ij}x_j - \theta$ and it represents the input on a gene with threshold θ for increasing x_j . The function $f(z)$ is a sigmoidal (monotone and bounded) function and 2×2 matrix W_{ij} consists of entries that take values from the set $\{-1, 0, 1\}$. The decisive role in the evolution of a GRN play attracting sets. The structure of attracting sets of system (1) is studied. The ability of controlling the network by change of adjustable parameters is in a focus. Let us recall the citation from [5]: "For a given set of parameters, the multiple attractors (for example, stable steady states) and the corresponding basins are fixed. In the absence of stochasticity, for a given initial condition, the system will approach one of the attractors. Each attractor has specific biological significance, which can be regarded as either desired or undesired, depending on the particular function of interest. Suppose, without any control, the system is in an undesired attractor or is in its basin of attraction. The question is how to steer the system from the undesired state to a desired state." The purpose of our article is to show and explain in geometrical and analytical terms, how to do this for system (2).

2. Problem

Two-component gene regulatory networks, where the stochasticity terms are neglected, are described^[7] by the differential system

$$\begin{cases} \frac{dx_1}{dt} = f(-\mu_1(w_{11}x_1 + w_{12}x_2 - \theta_1)) - x_1, \\ \frac{dx_2}{dt} = f(-\mu_2(w_{21}x_1 + w_{22}x_2 - \theta_2)) - x_2, \end{cases} \quad (2)$$

where f 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, $x \in R$;
2. It has exactly one inflection point.

Two typical examples of sigmoidal functions more often used in modelling GRN, are the Gompertz function $f(z) = e^{-\mu(z-\theta)}$ and the logistic function $f(z) = 1/(1 + e^{-\mu(z-\theta)})$. The argument z can be complicated. The 2D system, where f is the Gompertz function, is

$$\begin{cases} \frac{dx_1}{dt} = e^{-e^{-\mu_1(w_{11}x_1 + w_{12}x_2 - \theta_1)}} - x_1, \\ \frac{dx_2}{dt} = e^{-e^{-\mu_2(w_{21}x_1 + w_{22}x_2 - \theta_2)}} - x_2. \end{cases} \quad (3)$$

GRN model in this form was studied in [8-9]. Since we wish to consider systems with any sigmoidal function, we will use the form (2).

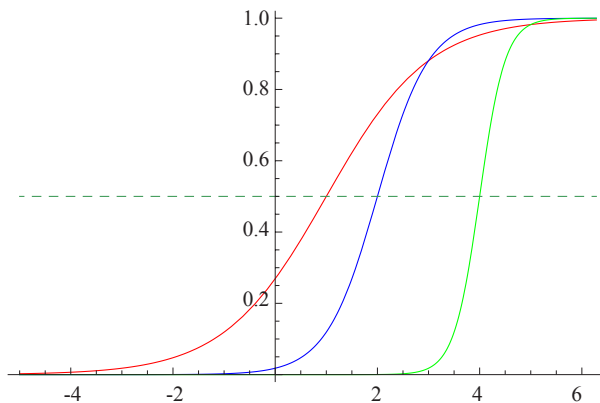


Figure 1. Red: $\mu = \theta = 1$, Blue: $\mu = \theta = 2$, Green: $\mu = \theta = 4$, f is Gompertz function

Since we focus on the inhibition case, we assume that w_{12} and w_{21} are negative. The diagonal elements w_{11} and w_{22} are set to zero, unless otherwise stated.

Problem: Describe possible attracting sets for the inhibition case.

3. Facts

Let us list the main facts about 2D-system (2).

1. The left sides of (2) are zeros on the nullclines^[10] which are given as

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

2. Equilibria (critical points) of system (2) are solutions of the system (4).

3. For w_{11} and w_{21} negative, and $w_{11} = w_{22} = 0$ there are at most three equilibria; the minimal number of equilibria is one. This follows from the S-shape of both nullclines. If w_{11} and/or w_{22} are not zero, then the nullclines may be Z-shaped and the number of critical points can be up to nine.

4. The vector field $(P(x_1, x_2), Q(x_1, x_2))$,

$$P(x_1, x_2) := f(-\mu_1(w_{11}x_1 + w_{12}x_2 - \theta_1)) - x_1,$$

$$Q(x_1, x_2) := f(-\mu_2(w_{21}x_1 + w_{22}x_2 - \theta_2)) - x_2,$$

is directed inward on the border of the rectangle $D = \{0 \leq x_1 \leq 1, 0 \leq x_2 \leq 1\}$ and, therefore, all trajectories of system (2), which start at the border ∂D , enter the region D , and no trajectory escapes. In other words, the region D is invariant under the trajectories of system (2).

5. The nullclines (4) can intersect only in the interior of D . Therefore all equilibria are in the interior of D .

6. If w_{12} and w_{21} are non-zero, and $w_{11} = w_{22} = 0$, and the nullclines (4) intersect transversally, then two cases are possible:

a) there is one equilibrium and it is attractive;

b) there are three equilibria and two of them are stable nodes and one is a saddle point.

7. If nullclines (4) are tangent at some point, then this point is degenerate critical point with one characteristic number $\lambda = 0$.

8. No periodic solutions (closed trajectories) exist in system (2) for w_{12} and w_{21} negative, and $w_{11} = w_{22} = 0$.

9. In the case 6a (one stable equilibrium) any trajectory that starts in D , tends to this equilibrium. The vector field $(P(x_1, x_2), Q(x_1, x_2))$ is directed then to a unique critical point.

10. In the case 6b (two stable equilibria and a saddle point) there are subsets $D_1 \subset D$ and $D_2 \subset D$ such that if the trajectory starts in D_1 , it goes to the first stable equilibrium, if the trajectory starts in D_2 , it goes to the second stable equilibrium.

Some of these facts were known and some were proved in [8-9, 11-14]. Similar technique was used in the works [15-17].

4. Basins of attraction

Let us look at the below pictures Figure 2a to Figure 2c. The first one (Figure 2a) shows two nullclines of the system and three critical points. The middle point is a saddle, both side points are stable equilibria. This can be confirmed by the vector field analysis and the exploration of the respective linearized system. We omit these steps. Each of these equilibria has a basin of attraction, denoted by D_1 and D_2 . Basins of attractions are separated by separatrixes of the saddle point. Any trajectory starting at any time moment at a point in D_1 , will tend eventually to an upper stable equilibrium. Similarly, any trajectory starting at a point in D_2 , will tend to a lower stable equilibrium.

Consider now the problem. Imagine a trajectory started at a point in D_1 . Then its future is predefined, it will go to an upper equilibrium. By some reason (which will be explained later) we need the trajectory to go to a lower equilibrium. We are able to adjust some parameters in system (2), say, θ_1 and/or θ_2 .

Tuning the first nullcline can be done by changing the parameter θ_1 . The result is seen in Figure 2d and Figure 2e. The initial state is seen in Figure 2a. There are two attractors at the side critical points. By changing θ_1 from 0.02 to -1.5 we eliminate the upper attractor, while the second (lower) attractor remains. The trajectory continues, as time increases, to the unique attractor. So by a single operation the trajectory can be redirected to the lower equilibrium.

By changing θ_1 from 0.02 to 0.35 the opposite result can be achieved. The lower attractor is eliminated and the upper one remains. So trajectories that were tending to the lower attractor are redirected to the upper one.

5. Normal and undesired states of GRN

In the work [5] an example of realistic GRN was discussed. The GRN considered corresponds to a kind of cancer, where cancerous states are identified with “undesired” attractors. If the current system states, that is, the vector $x(t)$ is in the basin of attraction of “undesired” attractor, the system (which corresponds to a living organism) will tend to an “undesired” attractor with the negative consequences. The problem is, using adjustable parameters, to redirect the vector $x(t)$ from “undesired” attractor to a normal one. Mathematically (in a model) this can be (sometimes) done by skillfully tuning the system. This is what we did in the preceding section to the two-dimensional system. In the system being considered in [5] the dimensionality of the considered system is not too large (60 nodes, of which three nodes only were attractive). It was mentioned in [5], that also reverse process is available, that is, driving a system into opposite direction. This is another aspect of the problem. We have shown, considering our simple 2D system, that, operating by parameters θ , we can control

the system.

In real situations, management and perturbation of these parameters should be left to biologists and medics. We believe, that in a similar manner systems of higher dimensions can be controlled.

6. Examples

In the below examples $\mu_1 = \mu_2 = 3.0$. The sigmoidal function is the Gompertz one, (3). The numerical data for illustrations are chosen arbitrarily to show the desired behavior of solutions.

Set $\theta_1 = 0.02$ and change θ_2 . Initially $\theta_2 = 0.03$ and the nullclines are depicted in Figure 2a. Increasing θ_2 eliminates the upper stable equilibrium and redirects all the trajectories to the lower equilibrium as shown in Figure 2a. Increasing θ_2 eliminates the upper stable equilibrium and redirects all the trajectories to the lower equilibrium as shown in Figure 2b. If the upper attractor is identified with the normal system state, and trajectories should be redirected to the upper equilibrium, the parameter θ_2 needs to decrease. This is shown in Figure 2c.

The same results can be obtained by changing the second adjustable parameter, θ_1 . The needed operations are explained and illustrated by Figure 2d and Figure 2e.

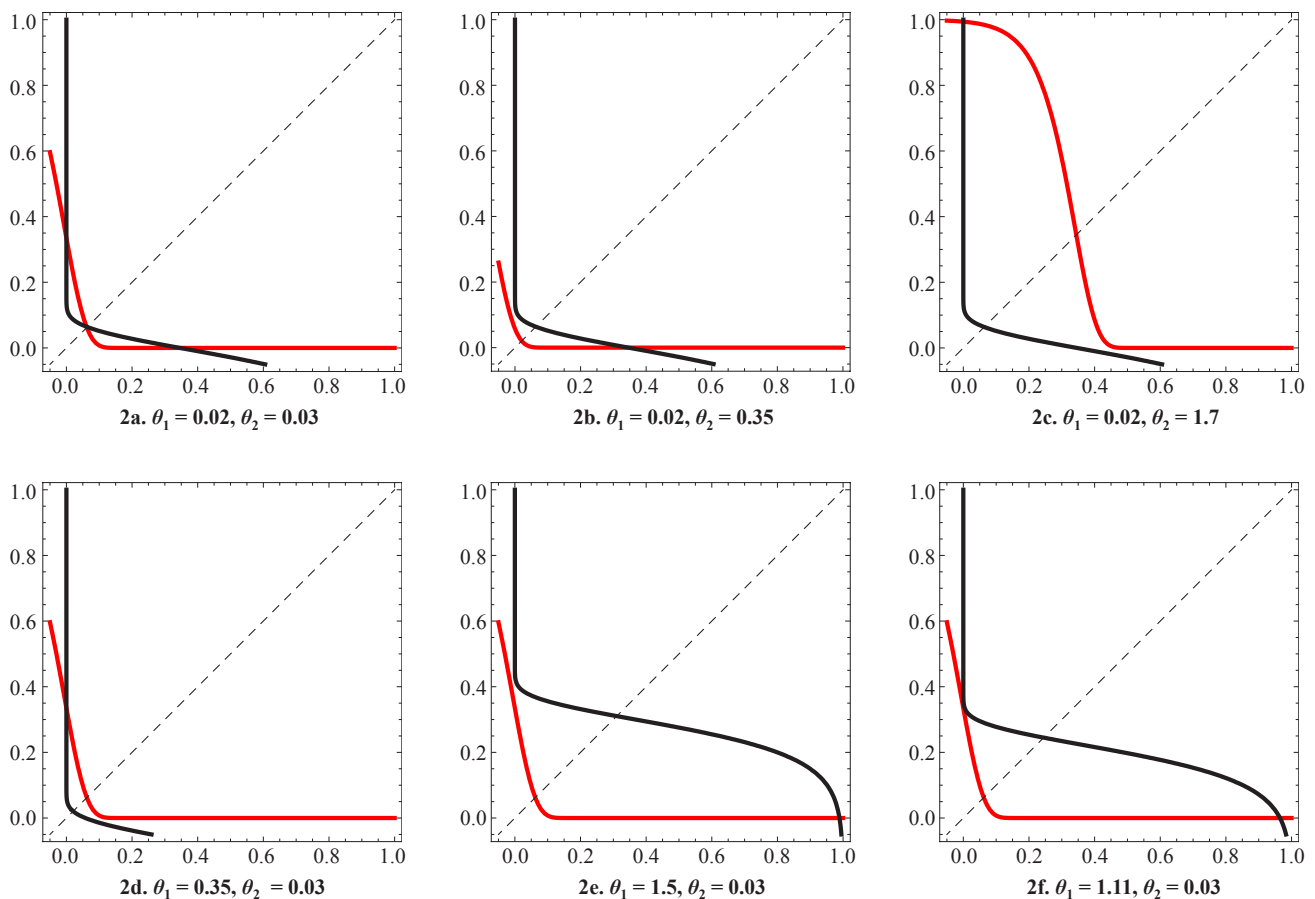


Figure 2. Nullclines for system (3)

It is to be noted, that passage from the initial state (Figure 2a) to other states with a unique equilibrium is through the intermediate “touch” state, when two isoclines are touching each other. There are an “upper” touch and a “lower” touch, leading to a single equilibrium. The “upper” touch is shown in Figure 2f.

7. Analytics

Consider the inhibition case, where the modelling system is

$$\begin{cases} \frac{dx_1}{dt} = f(\mu_1(\alpha x_2 - \theta_1)) - x_1, \\ \frac{dx_2}{dt} = f(\mu_2(\beta x_1 - \theta_2)) - x_2, \end{cases} \quad (5)$$

α and β are negative, $f(z)$ is a sigmoidal function. Suppose that nullclines are located as shown in Figure 2a. The parameters $\mu_1, \mu_2, \theta_1, \theta_2, \alpha, \beta$ are fixed. There are three cross-points, respectively p_1, p_2, p_3 (from upper left to lower right). Two side points, p_1 and p_3 , are stable nodes and the middle point p_2 is a saddle.

Our goal is to control this system, redirecting trajectories to a desired (normal) stable node. For this, we will change θ_1 . Let p_3 be a normal attracting state. Let θ_{1upper} be the value, corresponding to the upper touch point. In the example in Section 6 $\theta_{1upper} = -1.11$ (Figure 2f) and the current value $\theta_1 = 0.02$. Let θ_{1lower} be the value of θ_1 , corresponding to the lower touch point (Figure 3a). The current value of θ_1 , by our assumption, is between θ_{1upper} and θ_{1lower} . For θ_1 values greater than θ_{1lower} the upper attractor remains and all the trajectories tend to it (Figure 3b). For θ_1 values less than θ_{1upper} the upper attractor remains and all the trajectories tend to it (Figure 3c).

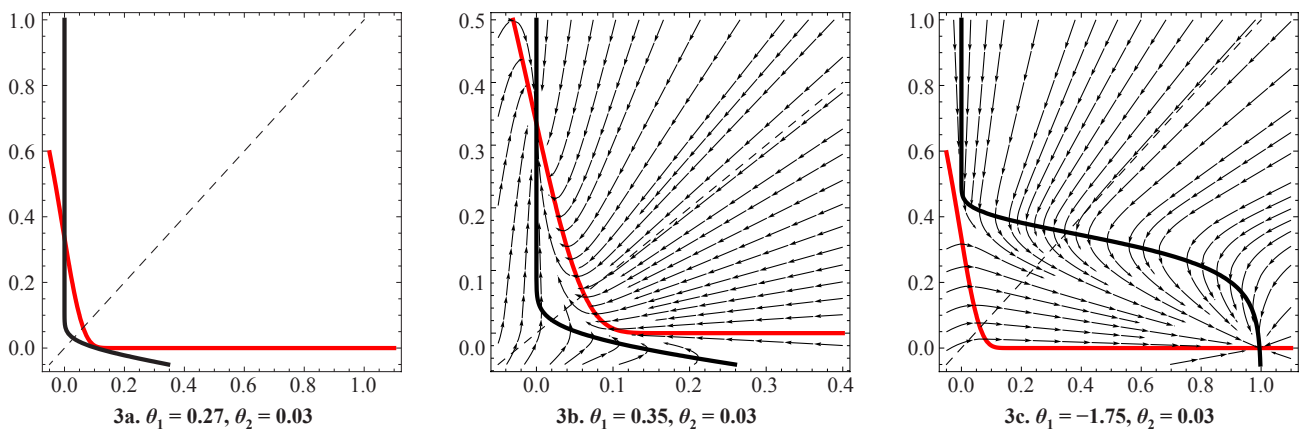


Figure 3. Moving the first nullcline (red)

The nullclines are defined by

$$\begin{cases} x_1 = f(\mu_1(\alpha x_2 - \theta_1)), \\ x_2 = f(\mu_2(\beta x_1 - \theta_2)), \end{cases} \quad (6)$$

It follows that

$$\frac{dx_1}{dx_2} = \frac{\partial}{\partial x_2} f(\mu_1(\alpha x_2 - \theta_1)),$$

$$\frac{dx_2}{dx_1} = \frac{\partial}{\partial x_1} f(\mu_2(\beta x_1 - \theta_2)).$$

At a point, where two nullclines are touching, the relation

$$1 = \frac{\partial}{\partial x_2} f(\mu_1(\alpha x_2 - \theta_1)) \frac{\partial}{\partial x_1} f(\mu_2(\beta x_1 - \theta_2)) \quad (7)$$

must be satisfied.

For given $f, \mu_1, \mu_2, \alpha, \beta, \theta_2$, the values of θ_{1upper} and θ_{1lower} can be found solving the system (6), (7).

Remark. The system can be managed also changing the parameter θ_2 instead of θ_1 . For the touching points of

nullclines then the values θ_{2left} and θ_{2right} should be used.

8. Symmetric case

Consider the particular case

$$\begin{cases} \frac{dx_1}{dt} = f(\mu(-x_2 - \theta)) - x_1 = \frac{1}{1 + e^{-\mu(-x_2 - \theta)}} - x_1, \\ \frac{dx_2}{dt} = f(\mu(-x_1 - \theta)) - x_2 = \frac{1}{1 + e^{-\mu(-x_1 - \theta)}} - x_2, \end{cases} \quad (8)$$

where f is a logistic function and $\mu_1 = \mu_2$ and $\theta_1 = \theta_2$. This corresponds to both elements of GRN acting symmetrically. Mathematically this case can be entirely analyzed.

The system

$$\begin{cases} 1 = \frac{\partial}{\partial x_2} f(\mu(-x_2 - \theta)) \frac{\partial}{\partial x_1} f(\mu(-x_1 - \theta)) \\ x_1 = f(\mu(-x_2 - \theta)), \\ x_2 = f(\mu(-x_1 - \theta)) \end{cases} \quad (9)$$

defines the touching points of nullclines.

For instance, set $\mu = 10$ and let θ be free. Due to symmetry in system (8), a unique equilibrium always exists on the bisectrix and both touch points are also on the bisectrix (Figure 4a and Figure 4b). For the intermediate value $\theta = -0.5$ the nullclines are depicted in Figure 4c.

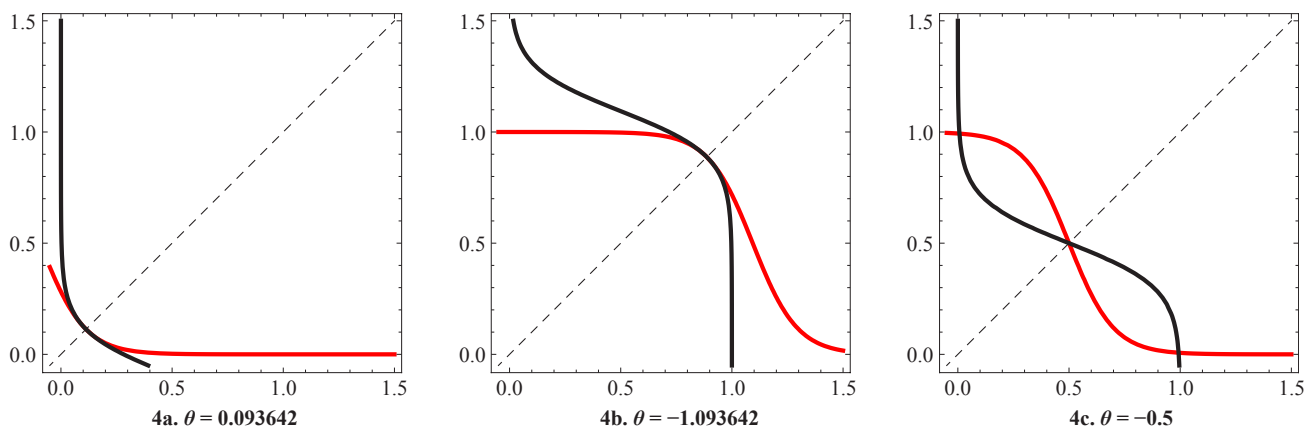


Figure 4. Nullclines for system (8)

The coordinate x of a unique critical point of the form (x, x) satisfies the relation $x = f(\mu(-x - \theta))$. Then

$$\theta = -x + \frac{1}{\mu} \log\left(\frac{1}{x} - 1\right). \quad (10)$$

The characteristic numbers $\lambda_{1,2} = -1 \pm \mu x(1 - x)$ can be obtained by linearizing system (8) around the equilibrium (x, x) . Elementary analysis of $\lambda_2 = -1 + \mu x(1 - x)$ shows that λ_2 can be positive only for $x \in (x_1, x_2)$, where

$$x_1(\mu) := \frac{1}{2} - \frac{\sqrt{\mu^2 - 4\mu}}{2\mu}, \quad x_2(\mu) := \frac{1}{2} + \frac{\sqrt{\mu^2 - 4\mu}}{2\mu}. \quad (11)$$

We can obtain, following the arguments in [14] and using (10) and (11), the figure depicted in Figure 5.

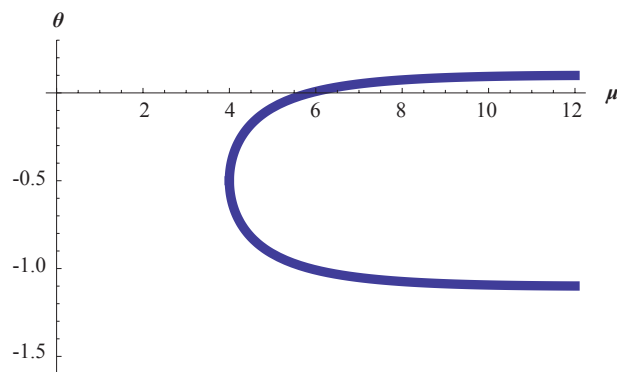


Figure 5. The bifurcation curve $\theta(\mu)$

This figure is defined by two branches

$$\theta_1(\mu) := -x_1(\mu) + \frac{1}{\mu} \log\left(\frac{1}{x_1(\mu)} - 1\right),$$

$$\theta_2(\mu) := -x_2(\mu) + \frac{1}{\mu} \log\left(\frac{1}{x_2(\mu)} - 1\right), \quad (12)$$

where x_1 and x_2 are defined in (11).

9. Conclusions

Typical behavior of solutions in an inhibition models of GRN is described. The possibility of managing and controlling of 2D inhibition GRN systems is emphasized and analyzed in terms of the phase plane. It is shown how to eliminate unwanted attractors and redirect the trajectories of the system in the right direction by changing the adjustable parameters θ . The proposed method is easy to implement, geometrically check, and allows for an accurate mathematical description. This approach is a perspective for studying and managing multi-dimensional systems.

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