Attraction in differential systems arising in network regulatory theory

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***Abstract*—We consider systems of ordinary differential equations that appear in gene regulation networks. Interrelation between nodes of a network is described by the regulatory matrix W. We provide description of attracting sets for various choices of regulatory matrix W or, equivalently, for various types of interrelation in a network. The related examples are considered.**

I. Introduction

The problem of self-regulation in large systems is by no means actual. For instance, in telecommunication systems, where changes are rapid and unpredictable, one can construct an optimal virtual network topology (VNT) [2], [3] by establishing a set of lightpaths between nodes. To treat changing in time (fluctuating) traffic on a VNT, adaptive VNT control methods should be invented, which reconfigure VNTs according to traffic conditions on VNTs. To develope such methods, one way is to observe attractor selection in biological systems that adapt to unknown changes in their surrounding environments and recover their conditions. We consider an attractor selection that models the behavior of gene regulatory and metabolic reaction networks in a cell.

The relations between elements of a network is used to model by the so called regulatory matrix W. In order to deal with possibly simple objects it is proposed that entries of regulatory matrix W can be of only three kinds: -1, 0 and $+1$ that corresponds respectively to inhibition, no relation and activation. Properties of a dynamical system modelling the network strongly depend on the structure of matrix W. The study of related differential systems which are nonlinear, depend on parameters and may be of arbitrary size is a highly nontrivial task.

Even in the simplest cases the analysis of such systems provide nontrivial results. For instance, in the work [8] the simplified system of the form

$$\begin{cases} \dfrac{dx_1}{dt} = \dfrac{1}{1+e^{-\mu(x_2-\Theta)}} - x_1, \\ \dfrac{dx_2}{dt} = \dfrac{1}{1+e^{-\mu(x_1-\Theta)}} - x_2, \end{cases} \tag{1}$$

was considered with the regulatory matrix $W = \begin{vmatrix} 0 & 1 \\ 1 & 0 \end{vmatrix}$. It was proved that this system has no more than three critical points. The complete description of the critical points were given.

It was proven later [1] that for arbitrary dimension n any possible critical point is of the form $(x, \dots, x)$, that is, any critical point locate on the bisectrix. This allows to study the case of a general system consisting of n differential equations for regulatory matrix

$$W = \begin{vmatrix} 0 & 1 & 1 & ... & 1 \\ 1 & 0 & 1 & ... & 1 \\ ... & & & & \\ 1 & 1 & ... & 0 & 1 \\ 1 & 1 & ... & 1 & 0 \end{vmatrix}. \tag{2}$$

This is the so called “cross-activation” case. Full description of critical points was given for this case [1]. The specific region Ω in a (μ, Θ)-plane was obtained with the properties: 1) if $(\mu, \Theta) \in exterior\,\Omega$, then the attracting set consists of one critical point (attraction in all dimensions); 2) if $(\mu, \Theta) \in \partial\,\Omega$, the attracting set consists of two critical points, one attracting in all dimensions (all characteristic numbers are negative) and the second point attracting in $(n-1)$-dimensions and degenerate (the respective λ is zero) in the remaining dimension; 3) if $(\mu, \Theta) \in interior\,\Omega$, then there are three critical points; the middle point is attracting in $(n-1)$-dimensions and repelling in the remaining dimension (the respective λ is positive); the two side critical points are attracting in all dimensions.

In the sequel we consider cases of different regulatory matrices W and provide conclusions on the character of critical points that form the attractors for related differential systems.

General information about networks, kinds of models can be found in the review articles[4], [5], [6], [7].

A. General information

We consider systems of the form

$$\frac{dx_i}{dt} = f(\sum W_{ij}x_j - \Theta)v_g - x_i v_g - \eta, \tag{3}$$

where f is sigmoidal function, W_{ij} are entries of the regulatory matrix W, Θ is a regulatory parameter that can be adjusted, parameter η represents stochastic behavior.

This differential system describes the dynamics of the expression level of the protein on the i-th gene.

The x_i variables represent the deterministic behavior of gene i.

The deterministic and stochastic behaviors are controlled by growth rate v_g, which represents the conditions of the metabolic reaction network.

Regulations of protein expression levels on gene i by other genes are indicated by regulatory matrix W_{ij}, the elements of which take values $-1, 0,$ or $+1$ (due to inhibition, no interaction and activation, respectively).

In what follows we consider the simplified system ($v_g = 1$, $\eta = 0$)

$$\begin{cases} \dfrac{dx_1}{dt} = \dfrac{1}{1+e^{-\mu(W_{11}x_1+W_{12}x_2+...+W_{1n}x_n-\Theta)}} - x_1, \\ \dfrac{dx_2}{dt} = \dfrac{1}{1+e^{-\mu(W_{21}x_1+W_{22}x_2+...+W_{2n}x_n-\Theta)}} - x_2, \\ ... \\ \dfrac{dx_n}{dt} = \dfrac{1}{1+e^{-\mu(W_{n1}x_1+W_{n2}x_2+...+W_{nn}x_n-\Theta)}} - x_n. \end{cases} \tag{4}$$

The sigmoidal functions are many. The sigmoidal function used in our analysis is $f(z) = 1/(1+e^{\mu z})$. The parameter μ indicates the gain rate of the sigmoidal function.

II. Inhibition-activation case

We consider the case where the regulatory matrix is

$$W = \begin{vmatrix} 0 & -1 & -1 & ... & -1 \\ 1 & 0 & -1 & ... & -1 \\ ... & & & & \\ 1 & 1 & ... & 0 & -1 \\ 1 & 1 & ... & 1 & 0 \end{vmatrix}. \tag{5}$$

The differential system takes the form

$$\begin{cases} x_1' = \dfrac{1}{1+e^{-\mu(\quad -x_2-x_3+...-x_{n-1}-x_n-\theta)}} - x_1, \\ x_2' = \dfrac{1}{1+e^{-\mu(x_1 \quad -x_3+...-x_{n-1}-x_n-\theta)}} - x_2, \\ ... \\ x_{n-1}' = \dfrac{1}{1+e^{-\mu(x_1+x_2+ \quad ...+x_{n-2} \quad -x_n-\theta)}} - x_{n-1}, \\ x_n' = \dfrac{1}{1+e^{-\mu(x_1+x_2+...+x_{n-2}+x_{n-1}- \quad \theta)}} - x_n, \end{cases} \tag{6}$$

A. Critical points

Critical points of system (4) are to be determined from

$$\begin{cases} x_1 = \dfrac{1}{1+e^{-\mu(\quad -x_2-x_3+...-x_{n-1}-x_n-\theta)}}, \\ x_2 = \dfrac{1}{1+e^{-\mu(x_1 \quad -x_3+...-x_{n-1}-x_n-\theta)}}, \\ ... \\ x_{n-1} = \dfrac{1}{1+e^{-\mu(x_1+x_2+...+x_{n-2} \quad -x_{n-1}-\theta)}}, \\ x_n = \dfrac{1}{1+e^{-\mu(x_1+x_2+...+x_{n-2}+x_{n-1} \quad -\theta)}}, \end{cases} \tag{7}$$

Since the right sides in (7) are positive but less than a unity, all critical points locate in the figure $(0;1)\times(0;1)\times(0;1)...\times(0;1)$.

Lemma 2.1: Any positive solution of the system (7) is unique.

Proof for 2D system is easy.

Proof. Indeed, the function $x_1(x_2) = \dfrac{1}{1+e^{-\mu(-x_2-\theta)}}$ is decreasing in the interval $[0,1]$. On the other hand, the second of equations (7) can be rewritten as

$$x_1 = \Theta - \frac{1}{\mu}\log\left(\frac{1}{x_2} - 1\right). \tag{8}$$

This function monotonically increases from $-\infty$ to $+\infty$ in the interval $(0,1)$. There is only one point of intersection of the graphs of both functions. □

B. Linearized system

To get the character of possible critical points, consider the linearized system

$$\begin{cases} u_1' = -u_1 - \mu g_1(u_2+u_3+...+u_n), \\ u_2' = -u_2 - \mu g_2(-u_1+u_3+...+u_n), \\ ... \\ u_n' = -u_n - \mu g_n(-u_1-u_2-...-u_{n-1}), \end{cases} \tag{9}$$

where

$$g_1 = \frac{e^{-\mu(-x_2-x_3-...-x_n-\theta)}}{[1+e^{-\mu(-x_2-x_3-...-x_n-\theta)}]^2} \tag{10}$$

$$g_2 = \frac{e^{-\mu(x_1-x_3-...-x_n-\theta)}}{[1+e^{-\mu(x_1-x_3-...-x_n-\theta)}]^2} \tag{11}$$

...

$$g_n = \frac{e^{-\mu(x_1+x_2-...+x_{n-1}-\theta)}}{[1+e^{-\mu(x_1+x_2-...+x_{n-1}-\theta)}]^2} \tag{12}$$

Values of g_1 and g_2 are always positive and less than unity.

The matrix A of the system (9) is

$$A = \begin{vmatrix} -1 & -\mu g_1 & -\mu g_1 & ... & -\mu g_1 \\ \mu g_2 & -1 & -\mu g_2 & ... & -\mu g_2 \\ ... & & & & \\ \mu g_n & \mu g_n & ... & -\mu g_n & -1 \end{vmatrix} \tag{13}$$

$$A - \lambda I = \begin{vmatrix} -1-\lambda & -\mu g_1 & -\mu g_1 & ... & -\mu g_1 \\ \mu g_2 & -1-\lambda & -\mu g_2 & ... & -\mu g_2 \\ ... & & & & \\ \mu g_n & \mu g_n & ... & -\mu g_n & -1-\lambda \end{vmatrix} \tag{14}$$

C. *Specific cases*

1) Two-dimensional system : We consider the specific case

$$W = \begin{vmatrix} 0 & -1 \\ 1 & 0 \end{vmatrix} \tag{15}$$

The differential system looks as

$$\begin{cases} x_1' = \dfrac{1}{1+e^{-\mu(-x_2-\theta)}} - x_1, \\ x_2' = \dfrac{1}{1+e^{-\mu(\ \ x_1-\theta)}} - x_2, \end{cases} \tag{16}$$

Introducing the notation

$$g_1 = \frac{e^{-\mu(-x_2-\theta)}}{[1+e^{-\mu(-x_2-\theta)}]^2} \tag{17}$$

$$g_2 = \frac{e^{-\mu(x_1-\theta)}}{[1+e^{-\mu(x_1-\theta)}]^2}, \tag{18}$$

where values of g_1 and g_2 are always positive and less than unity, the linearized system can by written as

$$\begin{cases} u_1' = -u_1 - \mu g_1 u_2, \\ u_2' = \ \ \mu g_2 u_1 - u_2. \end{cases} \tag{19}$$

$$A - \lambda I = \begin{vmatrix} -1-\lambda & -\mu g_1 \\ \mu g_2 & -1-\lambda \end{vmatrix} \tag{20}$$

$$\det|A - \lambda I| = \lambda^2 + 2\lambda + \mu^2 g_1 g_2 + 1 = 0 \tag{21}$$

$$\begin{cases} \lambda_1 = -1 - \mu\sqrt{g_1 g_2}\, i, \\ \lambda_2 = -1 + \mu\sqrt{g_1 g_2}\, i. \end{cases} \tag{22}$$

It appears that only one type of critical point is possible for the 2D system. Since $\lambda_{1,2}$ are complex numbers, the type of critical point is stable focus.

$$\begin{vmatrix} -1 & -\mu\sqrt{g_1 g_2} \\ \mu\sqrt{g_1 g_2} & -1 \end{vmatrix} \tag{23}$$

Proposition 2.1: The system (16) has only one type of a critical point, namely, stable focus.

2) Three-dimensional system : We consider the specific case

$$W = \begin{vmatrix} 0 & -1 & -1 \\ 1 & 0 & -1 \\ 1 & 1 & 0 \end{vmatrix} \tag{24}$$

We introduce variables g_i to simplify the linearized system

$$g_1 = \frac{e^{-\mu(-x_2-x_3-\theta)}}{[1+e^{-\mu(-x_2-x_3-\theta)}]^2} \tag{25}$$

$$g_2 = \frac{e^{-\mu(\ \ x_1-x_3-\theta)}}{[1+e^{-\mu(\ \ x_1-x_3-\theta)}]^2} \tag{26}$$

$$g_3 = \frac{e^{-\mu(\ \ x_1+x_2-\theta)}}{[1+e^{-\mu(\ \ x_1+x_2-\theta)}]^2} \tag{27}$$

Values of g_i are in $(0;1)$. Linearized system now is

$$\begin{cases} u_1' = -u_1 - \mu g_1 u_2 - \mu g_1 u_3, \\ u_2' = \mu g_2 u_1 - u_2 - \mu g_2 u_3, \\ u_3' = \mu g_3 u_1 + \mu g_3 u_2 - u_3. \end{cases} \tag{28}$$

$$A - \lambda I = \begin{vmatrix} -1-\lambda & -\mu g_1 & -\mu g_1 \\ \mu g_2 & -1-\lambda & -\mu g_2 \\ \mu g_3 & \mu g_3 & -1-\lambda \end{vmatrix} \tag{29}$$

The characteristic equation is

$$\det|A - \lambda I| = -\lambda^3 - 3\lambda^2 - \mu^2(g_1g_2 + g_1g_3 + g_2g_3)(\lambda+1) - \\ -3\lambda - 1 = 0 \tag{30}$$

The eigenvalues λ are

$$\begin{cases} \lambda_1 = -1, \\ \lambda_2 = -1 - \mu\sqrt{g_1g_2 + g_1g_3 + g_2g_3}\, i, \\ \lambda_3 = -1 + \mu\sqrt{g_1g_2 + g_1g_3 + g_2g_3}\, i. \end{cases} \tag{31}$$

We arrive at the proposition.

Proposition 2.2: For any critical point of the respective differential system the following is true: there is 2D-subspace with a stable focus and a attraction in the remaining dimension.

Consider a number of examples illustrating (and confirming) our analysis.

For parameters $\mu = 1$ and $\theta = 0.5$, the critical point is $(0.211336, 0.311244, 0.505645)$. The values of λ for this critical point are

$$\begin{cases} \lambda_1 = -1, \\ \lambda_2 = -1 - 0.36191\, i, \\ \lambda_3 = -1 + 0.36191\, i. \end{cases} \tag{32}$$

In this example the 3D system of the (**??**) has one critical point (stable focus in 2D-subspace and stable node in second subspace).

3) Four-dimensional system : We consider the specific case

$$W = \begin{vmatrix} 0 & -1 & -1 & -1 \\ 1 & 0 & -1 & -1 \\ 1 & 1 & 0 & -1 \\ 1 & 1 & 1 & 0 \end{vmatrix} \tag{33}$$

We introduce new variables to simplify the linearized system

$$g_1 = \frac{e^{-\mu(-x_2-x_3-x_4-\theta)}}{[1+e^{-\mu(-x_2-x_3-x_4-\theta)}]^2} \tag{34}$$

$$g_2 = \frac{e^{-\mu(\ \ x_1-x_3-x_4-\theta)}}{[1+e^{-\mu(\ \ x_1-x_3-x_4-\theta)}]^2} \tag{35}$$

$$g_3 = \frac{e^{-\mu(\ \ x_1+x_2-x_4-\theta)}}{[1+e^{-\mu(\ \ x_1+x_2-x_4-\theta)}]^2} \tag{36}$$

$$g_4 = \frac{e^{-\mu(\ \ x_1+x_2+x_3-\theta)}}{[1+e^{-\mu(\ \ x_1+x_2+x_3-\theta)}]^2} \tag{37}$$

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

$$\begin{cases} u_1' = -u_1 - \mu g_1 u_2 - \mu g_1 u_3 - \mu g_1 u_4, \\ u_2' = \mu g_2 u_1 - u_2 - \mu g_2 u_3 - \mu g_2 u_4, \\ u_3' = \mu g_3 u_1 + \mu g_3 u_2 - u_3 - \mu g_3 u_4, \\ u_4' = \mu g_4 u_1 + \mu g_4 u_2 + \mu g_4 u_3 - u_4, \end{cases} \tag{38}$$

One has that

$$A - \lambda I = \begin{vmatrix} -1-\lambda & -\mu g_1 & -\mu g_1 & -\mu g_1 \\ \mu g_2 & -1-\lambda & -\mu g_2 & -\mu g_2 \\ \mu g_3 & \mu g_3 & -1-\lambda & -\mu g_3 \\ \mu g_4 & \mu g_4 & -\mu g_4 & -1-\lambda \end{vmatrix} \tag{39}$$

The characteristic polynomial is

$$\begin{aligned} &\det|A-\lambda I| = \lambda^4 + 4\lambda^3 + \\ &+\mu^2(g_1g_2 + g_1g_3 + g_1g_4 + g_2g_3 + g_2g_4 + g_3g_4)\lambda^2 + 6\lambda^2 + \\ &+2\mu^2(g_1g_2 + g_1g_3 + g_1g_4 + g_2g_3 + g_2g_4 + g_3g_4)\lambda + 4\lambda + \\ &+\mu^2(g_1g_2 + g_1g_3 + g_1g_4 + g_2g_3 + g_2g_4 + g_3g_4) + 1 = 0 \end{aligned} \tag{40}$$

Denote

$$S_{g1} = g_1g_2 + g_1g_3 + g_1g_4 + g_2g_3 + g_2g_4 + g_3g_4 \tag{41}$$

then

$$\begin{aligned} &\det|A-\lambda I| = \lambda^4 + 4\lambda^3 + \mu^2(S_{g1})\lambda^2 + 6\lambda^2 + \\ &+2\mu^2(S_{g1})\lambda + 4\lambda + \mu^2(S_{g1}) + 1 + g_1g_2g_3g_4\mu^4 = 0 \end{aligned} \tag{42}$$

Set

$$G = S_{g1} - \sqrt{S_{g1}^2 - 4g_1g_2g_3g_4} > 0 \tag{43}$$

then

$$\begin{cases} \lambda_1 = -1 - \frac{\sqrt{2}}{2}\mu\sqrt{G}\,i, \\ \lambda_2 = -1 + \frac{\sqrt{2}}{2}\mu\sqrt{G}\,i, \\ \lambda_3 = -1 - \frac{\sqrt{2}}{2}\mu\sqrt{G}\,i, \\ \lambda_4 = -1 + \frac{\sqrt{2}}{2}\mu\sqrt{G}\,i. \end{cases} \tag{44}$$

Proposition 2.3: For any critical point of the 4D system the following is true: there is two 2D-subspace with a stable focus.

4) Five-dimensional system : Finally we consider the specific case

$$W = \begin{vmatrix} 0 & -1 & -1 & -1 & -1 \\ 1 & 0 & -1 & -1 & -1 \\ 1 & 1 & 0 & -1 & -1 \\ 1 & 1 & 1 & 0 & -1 \\ 1 & 1 & 1 & 1 & 0 \end{vmatrix} \tag{45}$$

Set

$$\begin{aligned} &S_{g1} = g_1g_2 + g_1g_3 + g_1g_4 + g_1g_5 + \\ &g_2g_3 + g_2g_4 + g_2g_5 + g_3g_4 + g_3g_5 + g_4g_5 \end{aligned} \tag{46}$$

and

$$S_{g2} = g_1g_2g_3g_4 + g_1g_2g_3g_5 + g_1g_2g_4g_5 + g_1g_3g_4g_5 + g_2g_3g_4g_5 \tag{47}$$

then

$$\begin{aligned} &\det|A-\lambda I| = \lambda^5 + 5\lambda^4 + \mu^2(S_{g1})\lambda^3 + 10\lambda^3 + \\ &+3\mu^2(S_{g1})\lambda^2 + 10\lambda^2 + \mu^4(S_{g2})\lambda + 3\mu^2(S_{g1})\lambda \\ &+5\lambda + \mu^4(S_{g2}) + \mu^2(S_{g1}) + 1 = 0 \end{aligned} \tag{48}$$

Set

$$G = S_{g1} - \sqrt{S_{g1}^2 - 4S_{g2}} > 0 \tag{49}$$

then

$$\begin{cases} \lambda_1 = -1, \\ \lambda_1 = -1 - \frac{\sqrt{2}}{2}\mu\sqrt{G}\,i, \\ \lambda_2 = -1 + \frac{\sqrt{2}}{2}\mu\sqrt{G}\,i, \\ \lambda_3 = -1 - \frac{\sqrt{2}}{2}\mu\sqrt{G}\,i, \\ \lambda_4 = -1 + \frac{\sqrt{2}}{2}\mu\sqrt{G}\,i. \end{cases} \tag{50}$$

Statement follows.

Proposition 2.4: For any critical point of the 5D system the following is true: there is two 2D-subspace with a stable focus and stable node in remaining subspace.

Our suggestion is that the system (6) for N-dimensions has only one critical point.

For $N = 2K$ the respective λ values of a critical point are pairs of complex numbers, where real parts are equal to -1. The critical point is stable focus on all 2D-subspaces.

For $N = 2K + 1$ the values of λ associated with the critical point are pairs of complex value and the remaining λ is real. All real parts of λ-s values are equal to -1. Critical point is stable focus on all 2D-subspaces and attractive in the remaining dimension.

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