Remark on a system arising in GRN theory

I. Samuilik

Summary. We consider the system of two differential equations that models two-element gene regulatory network (GRN in short). The description of attractors is obtained depending on parameters. Several cases are considered and the respective illustrations are provided.

MSC: 34C60, 34D45, 92B20
Keywords: Nullclines, characteristic equation, critical points.

1 Introduction

The theory of artificial networks ([10]) uses the dynamical systems that describe the dynamic behaviour of a network. The GRN networks are included ([7], [6], [5]). The interested reader may consult the review papers [1], [9]. This system contains multiple parameters that makes the direct analysis difficult. We wish to consider the two-dimensional case in full generality (not neglecting and simplifying the dependence on all parameters). We provide the analysis of some particular cases and supply our analysis by the respective phase portraits. Let us mention some previous works on the subject ([3], [2]).

2 General

We consider the system

$$\begin{cases} \dfrac{dx_1}{dt} = \dfrac{1}{1+e^{-\mu_1(w_{11}x_1+w_{12}x_2-\theta_1)}} - v_1x_1, \\[2ex] \dfrac{dx_2}{dt} = \dfrac{1}{1+e^{-\mu_2(w_{21}x_1+w_{22}x_2-\theta_2)}} - v_2x_2, \end{cases} \tag{1}$$

where μ_i and v_i are positive. The coefficient matrix is

$$W = \begin{vmatrix} w_{11} & w_{12} \\ w_{21} & w_{22} \end{vmatrix}. \tag{2}$$

The nullclines are given by the equations

$$\begin{cases} x_1 = \dfrac{1}{v_1} \dfrac{1}{1+e^{-\mu_1 (w_{11}x_1 + w_{12}x_2 - \theta_1)}}, \\ \\ x_2 = \dfrac{1}{v_2} \dfrac{1}{1+e^{-\mu_2 (w_{21}x_1 - w_{22}x_2 - \theta_2)}}. \end{cases} \tag{3}$$

The function $f(z) = \frac{1}{1+e^{-\mu z}}$ is sigmoidal ([**?**]). Therefore the first nullcline is in the strip $\{(x_1, x_2) : 0 < x_1 < \frac{1}{v_1}, x_2 \in R\}$ and the second one is in the strip $\{(x_1, x_2) : x_1 \in R, 0 < x_2 < \frac{1}{v_2}\}$. Therefore all critical points are located in the bounded box. There exists at list one critical point.

For analysis of critical points we need the linearized system. It is

$$\begin{cases} u_1' = -v_1 u_1 + \mu_1 w_{11} g_1 u_1 + \mu_1 w_{12} g_1 u_2, \\ u_2' = -v_2 u_2 + \mu_2 w_{21} g_2 u_1 + \mu_2 w_{22} g_2 u_2, \end{cases} \tag{4}$$

where

$$g_1 = \frac{e^{-\mu_1 (w_{11}x_1^* + w_{12}x_2^* - \theta_1)}}{[1+e^{-\mu_1 (w_{11}x_1^* + w_{12}x_2^* - \theta_1)}]^2}, \tag{5}$$

$$g_2 = \frac{e^{-\mu_2 (w_{21}x_1^* + w_{22}x_2^* - \theta_2)}}{[1+e^{-\mu_2 (w_{21}x_1^* + w_{22}x_2^* - \theta_2)}]^2}, \tag{6}$$

where (x_1^*, x_2^*) is a critical point under consideration. Notice that $0 < g_i < 0.25$ for $i = 1, 2$.

$$A = \begin{vmatrix} \mu_1 w_{11} g_1 - v_1 & \mu_1 w_{12} g_1 \\ \mu_2 w_{21} g_2 & \mu_2 w_{22} g_2 - v_2 \end{vmatrix} \tag{7}$$

$$A - \lambda I = \begin{vmatrix} \mu_1 w_{11} g_1 - v_1 - \lambda & \mu_1 w_{12} g_1 \\ \mu_2 w_{21} g_2 & \mu_2 w_{22} g_2 - v_2 - \lambda \end{vmatrix} \tag{8}$$

and the characteristic equation is

$$\begin{aligned} &\det|A - \lambda I| = (\mu_1 w_{11} g_1 - v_1 - \lambda)(\mu_2 w_{22} g_2 - v_2 - \lambda) - (\mu_2 w_{21} g_2)(\mu_1 w_{12} g_1) = \\ &\mu_1\mu_2 w_{11} w_{22} g_1 g_2 - \mu_1 w_{11} g_1 v_2 - \mu_1 w_{11} g_1 \lambda - \mu_2 w_{22} g_2 v_1 + v_1 v_2 + v_1 \lambda - \mu_2 w_{22} g_2 \lambda + \\ &v_2 \lambda + \lambda^2 - \mu_1 \mu_2 w_{12} w_{21} g_1 g_2 = \lambda^2 + (v_1 + v_2 - \mu_1 w_{11} g_1 - \mu_2 w_{22} g_2)\lambda + \\ &\mu_1\mu_2 w_{11} w_{22} g_1 g_2 - \mu_1 w_{11} g_1 v_2 - \mu_2 w_{22} g_2 v_1 - \mu_1\mu_2 w_{12} w_{21} g_1 g_2 + v_1 v_2 = 0. \end{aligned} \tag{9}$$

To simplify we can write the characteristic equation as

$$\lambda^2 + B\lambda + C = 0, \tag{10}$$

$$B = v_1 + v_2 - \mu_1 w_{11} g_1 - \mu_2 w_{22} g_2, \tag{11}$$

$$C = \mu_1\mu_2 w_{11} w_{22} g_1 g_2 - \mu_1 w_{11} g_1 v_2 - \mu_2 w_{22} g_2 v_1 - \mu_1\mu_2 w_{12} w_{21} g_1 g_2 + v_1 v_2. \tag{12}$$

3 Particular case

Set $w_{11} = w_{22} = 0$. The regulatory matrix is

$$W = \begin{vmatrix} 0 & w_{12} \\ w_{21} & 0 \end{vmatrix} \tag{13}$$

and the system of differential equations takes the form

$$\begin{cases} x_1' = \dfrac{1}{1 + e^{-\mu_1(w_{12}x_2 - \theta_1)}} - v_1 x_1, \\ x_2' = \dfrac{1}{1 + e^{-\mu_2(w_{21}x_1 - \theta_2)}} - v_2 x_2, \end{cases} \tag{14}$$

The characteristic equation is

$$\lambda^2 + B\lambda + C = 0, \tag{15}$$

$$B = v_1 + v_2, \tag{16}$$

$$C = -\mu_1\mu_2 w_{12} w_{21} g_1 g_2 + v_1 v_2. \tag{17}$$

Case 1.

$$B^2 > 4C, \quad \lambda_{1,2} = -\frac{B}{2} \pm \sqrt{\frac{B^2}{4} - C} > 0$$
$$B < 0 \Rightarrow \lambda_1 > 0 \Rightarrow \lambda_2 > 0.$$

Consider

$$\omega_{11} = \omega_{22} = 0, \quad B = v_1 + v_2, \quad C = v_1 v_2 - \mu_1\mu_2 w_{12} w_{21} g_1 g_2.$$

Proposition 3.1 *If $B^2 > 4C, \quad \lambda_{1,2} \in \mathbb{R}$. The case unstable node is impossible.*

Case 2.

$$B^2 > 4C, B > 0, \lambda_{1,2} = -\frac{B}{2} \pm \sqrt{\frac{B^2}{4} - C}$$

Case 2.1.

$$C > 0, \quad 0 < \frac{B^2}{4} - C < \frac{B^2}{4} \Rightarrow \lambda_2 = -\frac{B}{2} + \sqrt{\frac{B^2}{4} - C} < 0,$$

$$\Rightarrow \lambda_1 = -\frac{B}{2} - \sqrt{\frac{B^2}{4} - C} < 0.$$

Proposition 3.2 *If $B^2 > 4C, C > 0 \Rightarrow \lambda_{1,2} < 0 \Rightarrow$ stable node.*

Consider

$$\omega_{11} = \omega_{22} = 0, \quad B^2 > 4C, \quad C > 0$$

$$(v_1 + v_2)^2 > 4(v_1 v_2 - \mu_1 \mu_2 w_{12} w_{21} g_1 g_2), \quad v_1 v_2 - \mu_1 \mu_2 w_{12} w_{21} g_1 g_2 > 0,$$

$$v_1 = v_2 = 1, \quad 1 > 4(1 - \mu_1 \mu_2 w_{12} w_{21} g_1 g_2).$$

Example 1. Consider $\mu_1 = 5, \mu_2 = 10,\ v_1 = v_2 = 1, \quad \omega_{11} = \omega_{22} = 0, \quad \omega_{12} = -4$, $\omega_{21} = -2$ and $\theta_1 = 0.2, \theta_2 = 0.25$.

Fig. 3.1.

The characteristic equation for critical point $(0.2674; 0.0004)$ is

$$\lambda^2 + B\lambda + C = 0, \tag{18}$$

where

$$B = 2, \tag{19}$$

$$C = 0.969076. \tag{20}$$

Solving the equation we have $\lambda_1 = -1.17585$ and $\lambda_2 = -0.824148$. The type of critical point is a stable node.

Fig. 3.2.

Case 2.2.

$$C < 0, \quad \lambda_1 < 0, \quad \lambda_2 = -\frac{B}{2} + \sqrt{\frac{B^2}{4} - C} > 0.$$

Proposition 3.3 *If* $B^2 > 4C, C < 0 \Rightarrow \lambda_1 < 0, \lambda_2 > 0 \Rightarrow$ *saddle.*

Consider

$$\omega_{11} = \omega_{22} = 0, \quad v_1 = v_2 = 1, \quad \mu_1 = \mu_2 = \mu,$$

$$1 > 4(1 - \mu_1 \mu_2 w_{12} w_{21} g_1 g_2), \quad 1 < \mu^2 w_{12} w_{21} g_1 g_2,$$

Example 2. Consider $\mu_1 = \mu_2 = 8$, $v_1 = v_2 = 1$, $\omega_{11} = 2$, $\omega_{12} = -4$, $\omega_{21} = -1.5$, $\omega_{22} = 2$ and $\theta_1 = 1, \theta_1 = 0.25$.

Fig. 3.3.

The characteristic equation for critical point $(0.50089; 0.00033357)$ is

$$\lambda^2 + B\lambda + C = 0, \tag{21}$$

where

$$B = -2.04806, \tag{22}$$

$$C = -3.05884. \tag{23}$$

Solving the equation we have $\lambda_1 = -1.00266$ and $\lambda_2 = 3.05072$. The type of critical point is a saddle.

Fig. 3.4.

Case 3.1.

$$B^2 < 4C, \quad \lambda_{1,2} = -\frac{B}{2} \pm \sqrt{\frac{B^2}{4} - C} \in \mathbb{C}.$$

Consider

$$\omega_{11} = \omega_{22} = 0, \quad (v_1 + v_2)^2 > 4(v_1 v_2 - \mu_1 \mu_2 w_{12} w_{21} g_1 g_2),$$
$$v_1^2 + 2v_1 v_2 + v_2^2 = 4v_1 v_2 - 4\mu_1 \mu_2 w_{12} w_{21} g_1 g_2,$$
$$(v_1 - v_2)^2 < -4\mu_1 \mu_2 w_{12} w_{21} g_1 g_2.$$

Proposition 3.4 *If* $(v_1 - v_2)^2 < -4\mu_1 \mu_2 w_{12} w_{21} g_1 g_2$ *then all critical points are focuses.*

Corollary 3.1 *The necessary condition for all critical points to be focuses is* $\omega_{12}\omega_{21} < 0$*.*

Example 3. Consider $\mu_1 = 8, \mu_2 = 4,\ v_1 = v_2 = 1$,$\omega_{12} = 2$,$\omega_{12} = -9$ and $\theta_1 = 0.7, \theta_1 = 0.5$.

Fig. 3.5.

The characteristic equation for critical point $(0.0128; 0.0786)$ is

$$\lambda^2 + B\lambda + C = 0, \tag{24}$$

where

$$B = 2, \tag{25}$$

$$C = 1.04354. \tag{26}$$

Solving the equation we have $\lambda_1 = -1 - 0.208672i$ and $\lambda_2 = -1 + 0.208672i$. The type of critical point is a stable focus.

Fig. 3.6.

Consider

$$w_{11} \neq 0, \quad w_{22} \neq 0.$$

Case 3.2.

$$B^2 < 4C, \quad -\frac{B}{2} > 0 \Rightarrow B < 0.$$

Proposition 3.5 *If $w_{11} = w_{22} = 0$, then $B > 0$ and no critical point is unstable focus.*

$$B^2 - 4C = (v_1 + v_2 - \mu_1 w_{11} g_1 - \mu_2 w_{22} g_2)^2 -$$

$$-4(\mu_1\mu_2 w_{11} w_{22} g_1 g_2 - \mu_1 w_{11} g_1 v_2 - \mu_2 w_{22} g_2 v_1 - \mu_1 \mu_2 w_{12} w_{21} g_1 g_2 + v_1 v_2) =$$

$$= v_1^2 + 2v_1v_2 - 2v_1\mu_1 w_{11} g_1 - 2v_1 \mu_2 w_{22} g_2 + v_2^2 - 2v_2\mu_1 w_{11} g_1 - 2v_2 \mu_2 w_{22} g_2 +$$

$$+\mu_1^2 w_{11}^2 g_1^2 + 2\mu_1 w_{11} g_1 \mu_2 w_{22} g_2 + \mu_2^2 w_{22}^2 g_2^2 - 4\mu_1\mu_2 w_{11} w_{22} g_1 g_2 + 4\mu_1 w_{11} g_1 v_2 +$$

$$+4\mu_2 w_{22} g_2 v_1 + 4\mu_1\mu_2 w_{12} w_{21} g_1 g_2 - 4v_1 v_2 =$$

$$= (-v_1 + v_2 + \mu_1 w_{11} g_1)^2 + 2w_{22} g_2(\mu_2(v_1 - v_2 - \mu_1 w_{11} g_1) + 2\mu_1 w_{12} w_{21} g_1) + \mu_2^2 w_{22}^2 g_2^2.$$

Example 4. Consider $\mu_1 = 5, \quad \mu_2 = 5,\ v_1 = \frac{1}{3}, \quad v_2 = \frac{1}{4}, \quad \omega_{11} = 1, \quad \omega_{12} = -1, \omega_{21} = 1, \quad \omega_{22} = 1$ and $\theta_1 = 0.5, \quad \theta_1 = 3.3.$

Fig. 3.7.

The characteristic equation for critical point $(1.87485; 1.27273)$ is

$$\lambda^2 + B\lambda + C = 0, \tag{27}$$

where

$$B = -3.496, \tag{28}$$

$$C = 5.46939. \tag{29}$$

Solving the equation we have $\lambda_1 = 1.74792 - 1.55376i$ and $\lambda_2 = 1.74792 + 1.55376i$. The type of critical point is a unstable focus.

Fig. 3.8.

References

[1] F.M. Alakwaa. Modeling of Gene Regulatory Networks: A Literature Review. J. Computational Systems Biology, 1(1)(2014),102, 1-8.

[2] E. Brokan, F. Sadyrbaev, On a differential system arising in the network control theory, *Nonlinear Analysis: Modelling and Control*, **21**(5):687 – 701, 2016 doi:10.15388/NA.2016.5.8.

[3] E. Brokan and F. Sadyrbaev, Attraction in n-dimensional differential systems from network regulation theory. Mathematical Methods in Applied Sciences, Vol. 41 (2018), Issue 17, 7498–7509 https://doi.org/10.1002/mma.5086

[4] E. Brokan, F. Zh. Sadyrbaev. On Attractors in Gene Regulatory Systems. *AIP Conference Proceedings* **1809**(020010), 2017 doi: 10.1063/1.4975425.

[5] C. Furusawa and K. Kaneko. A generic mechanism for adaptive growth rate regulation. *PLoSComputational Biology*, 4:e3, 2008.

[6] H. D. Jong. Modeling and Simulation of Genetic Regulatory Systems: A Literature Review. J. Computational Biology, 9(1), 2002,67-103. doi: 10.1089/10665270252833208

[7] Y. Koizumi et al. Adaptive Virtual Network Topology Control Based on Attractor Selection. Journal of Lightwave Technology (ISSN :0733-8724), Vol.28 (06/2010), Issue 11, pp. 1720 - 1731 DOI:10.1109/JLT.2010.2048412

[8] S. Mukherjee, S. K. Palit, D.K. Bhattacharya. Is one dimensional Poincare map sufficient to describe the chaotic dynamics of a three dimensional system? *Applied Mathematics and Computation*, **219**(23):11056–11064, 08/2013 DOI:10.1016/J.AMC.2013.04.043

[9] N. Vijesh, S. K. Chakrabarti, J. Sreekumar, Modeling of gene regulatory networks: A review, *J. Biomedical Science and Engineering*, **6**:223-231, 2013.

[10] J. Vohradský. Neural network model of gene expression. The FASEB Journal, Vol. 15 (2001), 846–854.

И.Самуйлик.

Аннотация. Рассматривается система двух дифференциальных уравнений, моделирующая двухэлементную генную систему. Получено описание аттрактов в зависимости от параметров.

I. Samuilik.

Anotācija. Tiek apskatīta divu diferenciālvienādojumu sistēma, modelējot divu elementu gēnu tīklu. Tiek iegūts sistēmas atraktoru apraksts, kas ir atkarīgi no parametriem.

Daugavpils University
Department of Natural Sciences
and Mathematics
Daugavpils, Parades str. 1

Received 9.12.2019