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In Search of Chaos in Genetic Systems

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ABSTRACT A three-dimensional multiparametric system of ordinary differential equations, arising in the theory of genetic networks, is considered. Examples of chaotic behavior are constructed using the methodology by Shilnikov. This methodology requires the existence of saddle-focus points satisfying some additional conditions. As the result, rich dynamical behavior of solutions can be observed, including chaotic behavior of solutions.

KEYWORDS
Mathematical model
Dynamical system
Attractors
Genetic regulatory networks

INTRODUCTION

Genetic regulatory networks are in a focus of investigation of biologists (Peter 2020) and theoreticians (Samuilik and Sadyrbaev 2023; Jong 2002; Schlitt 2013; Vijesh *et al.* 2013). Mathematical models of GRN can be formulated in terms of ordinary differential equations (Barbuti *et al.* 2020). This modeling method is preferable if the evolution of a network is to be studied. Each equation in a system corresponds to an element of a network. So realistic networks and the respective systems are large (Kardynska *et al.* 2023). To understand the principles of functioning of gene networks small networks should be investigated first. The systems of differential equations also consist of several equations only.

The two-dimensional systems can be studied using the phase plane method. The results can be visualized easily and the respective conclusions are at hand. We mention briefly the main properties of two-dimensional systems. They are quasi-linear, and the right sides contain a nonlinear term and a linear one. The nonlinearity is represented usually by a sigmoidal function, such as the logistic one, $f(z) = 1/(1+e^{-\mu z})$ (Samuilik 2022), Hill's function $h(z) = z^{\mu}/(z^{\mu}+\theta^{\mu})$ (Santillan 2008) or Gompertz function $g(z) = \exp(-\exp(-\mu z))$ (Ogorelova *et al.* 2020).

Sigmoidal functions are monotone, smooth and bounded. They are convenient for mathematical treatment and reflect the main properties of a modeled object. To predict future states of a network, a researcher should analyze the mathematical model. The following questions should be answered: 1) Does the system have attracting sets in the phase space; 2) What they (attractors) are; 3) How attractors depend on the parameters of a system; 4) Is it possible to regulate the model by changing parameters. The main issue is, of course, the ability of a model to adequately describe a modeled object. In other words, could a researcher rely on the predictions, formulated when mathematically studied a network. More or less full analysis can be made for two-dimensional (2D) systems. They have attractors, which are stable critical points, limit cycles and their combinations. New information is obtained when studying three-dimensional (3D) systems of the form

$$\begin{cases} \dfrac{dx}{dt} = \dfrac{1}{1+e^{-\mu_1(w_{11}x+w_{12}y+w_{13}z-\theta_1)}} - v_1 x, \\ \dfrac{dy}{dt} = \dfrac{1}{1+e^{-\mu_2(w_{21}x+w_{22}y+w_{23}z-\theta_2)}} - v_2 y, \\ \dfrac{dz}{dt} = \dfrac{1}{1+e^{-\mu_3(w_{31}x+w_{32}y+w_{33}z-\theta_3)}} - v_3 z. \end{cases} \quad (1)$$

Here the three variables x, y, z are for the elements of a network. The dynamics of the system and future states of a network depend on solutions of this system and its attractors. There are many examples of attractors which are stable critical points, stable periodic solutions (limit cycles) and more (Ogorelova *et al.* 2020; Brokan and Sadyrbaev 2016, 2018). There are many examples of three-dimensional autonomous systems, which exhibited chaotic behavior. Recall Lorenz system, Rössler system, Duffing type equations written as 3D-systems, and many nice examples collected by J.C. Sprott (Sprott 2010) and N.A. Magnitskii (Magnitskii and Sidorov 2006).

To find a chaotic attractor, which is none of the above mentioned, is a non-trivial task. "Chaos should occur often in gene regulatory networks which have been widely described by nonlinear coupled ordinary differential equations, if their dimensions are no less than 3. It is therefore puzzling that chaos is also extremely rare in models of GRN," write the authors in (Zhang *et al.* 2012). In (Zhang *et al.* 2012) two tables are provided, which show the number of chaotic samples reached in three-dimensional GRN by

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10^6 tests with random network structures, parameter distributions and initial variable conditions. This number is one. The same measurement within networks possessing the structure of periodic oscillations is 195. We knew only the work (Das *et al.* 2000) where a chaotic attractor was discovered for the system of the form (1).

The attempts to find new chaotic attractors in the system (1) were time and work consuming without any guarantees. Literature review related to the subject led us to early works by L.P. Shilnikov. We plan to study this system under the assumptions formulated in the work (Shilnikov 1965). In this work, a three-dimensional system was considered, which had a saddle-focus type critical point (see also (Gonchenko *et al.* 2019; Deng *et al.* 2017)). Our intent is to construct examples of genetic systems which have a critical point of this type. It is known that the behavior of trajectories in a neighborhood of such point can be complicated. We are looking for chaotic behavior.

SHILNIKOV SYSTEM

In the work (Shilnikov 1965) the following system

$$\begin{cases} \dfrac{dx}{dt} = \rho x - \omega y + P, \\ \dfrac{dy}{dt} = \omega x + \rho y + Q, \\ \dfrac{dz}{dt} = \lambda z + R \end{cases} \tag{2}$$

was studied under the conditions $\rho < 0$, $\lambda > 0$, functions P, Q, R are zeros together with their derivatives at the point $(0,0,0)$.

The linearized system around $(0,0,0)$ is

$$\begin{cases} \dfrac{dx}{dt} = \rho x - \omega y, \\ \dfrac{dy}{dt} = \omega x + \rho y, \\ \dfrac{dz}{dt} = \lambda z. \end{cases} \tag{3}$$

If we assume that ω is positive, then the origin in the system (3) is a saddle-focus with 2D stable focus and repulsion in z-direction. If this repulsion dominates over an attraction in the 2D focus ($\lambda > -\rho$), the behavior of trajectories near the origin in a nonlinear system (2) can be complicated (Shilnikov 1965). Our intent is to construct GRN system with similar properties and to test it on attractors.

Characteristic values for $(0,0,0)$ are $\Lambda_1 = \lambda > 0$, $\Lambda_{2,3} = \rho \pm \omega i$, $\rho < 0$, $\omega > 0$. The phase space around $(0,0,0)$ is the spiral going away of the plane where its (spiral) projection approaches the stable focus. According to (Shilnikov 1965), there is a trajectory of the system (2), which emanates from $(0,0,0)$ and ends in $(0,0,0)$ in an infinite time. It was denoted Γ_0. The following condition according to (Shilnikov 1965) is important for the complicated behavior of trajectories: If $\lambda > -\rho$, then in a vicinity of Γ_0 there are infinitely many periodic solutions.

It was mentioned in (Gonchenko *et al.* 2019, page 9) that there are two interesting cases of a saddle-focus behavior. The first case is called saddle-focus I. Then the equilibrium has a stable 2D manifold and unstable 1D manifold. In terms of characteristic numbers $\lambda_1 > 0$, $\lambda_{2,3} = \alpha \pm \beta i$, $\alpha < 0$, $\beta \neq 0$. Conversely, the saddle-focus II case has $\lambda_1 < 0$, $\lambda_{2,3} = \alpha \pm \beta i$, $\alpha > 0$, $\beta \neq 0$.

EXAMPLES

We wish to construct examples of systems of the form (1), which have critical points with the characteristic numbers $\lambda_1 < 0$, $\lambda_{2,3} = \alpha \pm \beta i$, where $\alpha > 0$. Alternatively, we are interested in the case $\lambda_1 > 0$, $\lambda_{2,3} = \alpha \pm \beta i$, $\alpha < 0$. The notation in this section is independent of the notation in the previous section. We wish also the following condition to be satisfied

$$|\lambda_1| > \alpha. \tag{4}$$

To construct examples, we will use material in the article (Kozlovska and Sadyrbaev 2022). We set $v_i = 1$, $\mu_i = 4$ in the system (1). Suppose that the regulatory matrix

$$W = \begin{pmatrix} w_{11} & w_{12} & w_{13} \\ w_{21} & w_{22} & w_{23} \\ w_{31} & w_{32} & w_{33} \end{pmatrix} \tag{5}$$

is already defined. A critical point can be found from the system

$$\begin{cases} x = \dfrac{1}{1 + e^{-\mu_1(w_{11}x + w_{12}y + w_{13}z - \theta_1)}}, \\ y = \dfrac{1}{1 + e^{-\mu_2(w_{21}x + w_{22}y + w_{23}z - \theta_2)}}, \\ z = \dfrac{1}{1 + e^{-\mu_3(w_{31}x + w_{32}y + w_{33}z - \theta_3)}}, \end{cases} \tag{6}$$

where

$$\begin{aligned} w_{11} + w_{12} + w_{13} &= 2\,\theta_1, \\ w_{21} + w_{22} + w_{23} &= 2\,\theta_2, \\ w_{31} + w_{32} + w_{33} &= 2\,\theta_3. \end{aligned} \tag{7}$$

This choice of θ_i puts a critical point to a central location $(0.5, 0.5, 0.5)$. Notice that the right sides of equations in the system (6) then are equal to 0.5.

Choose $\lambda_1 = -2$, $\lambda_{2,3} = 1 \pm i$. The numbers $\Lambda_1 = \lambda_1 + 1 = -1$, $\Lambda_{2,3} = \lambda_{2,3} \pm i = 2 \pm i$ (do not mix with Λ in the previous section) are solutions (Kozlovska and Sadyrbaev 2022) of the characteristic equation

$$\begin{aligned} &\Lambda^3 - (w_{11} + w_{22} + w_{33})\Lambda^2 - (w_{21}w_{12} - w_{11}w_{22} + w_{31}w_{13} \\ &+ w_{32}w_{23} - w_{11}w_{33} - w_{22}w_{33})\Lambda - (-w_{31}w_{22}w_{13} + w_{21}w_{32}w_{13} \\ &+ w_{31}w_{12}w_{23} - w_{11}w_{32}w_{23} - w_{21}w_{12}w_{33} + w_{11}w_{22}w_{33}) = 0. \end{aligned} \tag{8}$$

For our choice of $\Lambda_1 = -1$, $\Lambda_{2,3} = 2 \pm i$ we obtain the cubic equation

$$(\Lambda + 1)(\Lambda^2 - 4\Lambda + 5) = \Lambda^3 - 3\Lambda^2 + \Lambda + 5 = 0. \tag{9}$$

Comparing (11) and (9), we are led to the conclusion that

$$\begin{aligned} &(w_{11} + w_{22} + w_{33}) = 3, \\ &(w_{21}w_{12} - w_{11}w_{22} + w_{31}w_{13} + w_{32}w_{23} - w_{11}w_{33} - w_{22}w_{33}) = -1, \\ &(-w_{31}w_{22}w_{13} + w_{21}w_{32}w_{13} + w_{31}w_{12}w_{23} - w_{11}w_{32}w_{23} \\ &-w_{21}w_{12}w_{33} + w_{11}w_{22}w_{33}) = -5. \end{aligned} \tag{10}$$

This is an over-determined system of equations to find elements of matrix W. The central point $(0.5, 0.5, 0.5)$ will be a critical point with the characteristic values $\lambda_1 = -2$, $\lambda_{2,3} = 1 \pm i$.

In such a way multiple examples can be constructed. The central point $(0.5, 0.5, 0.5)$ need not be a unique critical point. To find the rest of the critical points (if any), one needs to analyze the location of the nullclines, which are given by the relations (6).

Example of system (1) with the required critical point

Suppose we wish to construct the system with the critical point at $(0.5, 0.5, 0.5)$ and with prescribed characteristic numbers. Since the parameters μ and v are already defined, we need to construct the regulatory matrix W only. The parameters θ will then be defined by the relations (7). Choose the characteristic numbers $\lambda_1 = -0.8$, $\lambda_{2,3} = 0.1 \pm 2i$. The numbers $\Lambda_1 = \lambda_1 + 1 = 0.2$, $\Lambda_{2,3} = \lambda_{2,3} \pm 2i = 1.1 \pm 2i$ are solutions (Kozlovska and Sadyrbaev 2022) of the characteristic equation

$$\begin{aligned} &\Lambda^3 - (w_{11} + w_{22} + w_{33})\Lambda^2 - (w_{21}w_{12} - w_{11}w_{22} + w_{31}w_{13} \\ &+ w_{32}w_{23} - w_{11}w_{33} - w_{22}w_{33})\Lambda - (-w_{31}w_{22}w_{13} + w_{21}w_{32}w_{13} \\ &+ w_{31}w_{12}w_{23} - w_{11}w_{32}w_{23} - w_{21}w_{12}w_{33} + w_{11}w_{22}w_{33}) = 0. \end{aligned} \tag{11}$$

For our choice of $\Lambda_1 = 0.2$, $\Lambda_{2,3} = 1.1 \pm 2i$ we obtain the cubic equation

$$(\Lambda - 0.2)(\Lambda^2 - 2.2\Lambda + 5.21) = \Lambda^3 - 2.4\Lambda^2 + 5.65\Lambda - 1.042 = 0. \tag{12}$$

Comparing (11) and (9), we are led to the conclusion that

$$\begin{aligned} &(w_{11} + w_{22} + w_{33}) = 2.4, (w_{21}w_{12} - w_{11}w_{22} + w_{31}w_{13} \\ &+ w_{32}w_{23} - w_{11}w_{33} - w_{22}w_{33}) = -5.65, (-w_{31}w_{22}w_{13} + w_{21}w_{32}w_{13} \\ &+ w_{31}w_{12}w_{23} - w_{11}w_{32}w_{23} - w_{21}w_{12}w_{33} + w_{11}w_{22}w_{33}) = 1.042. \end{aligned} \tag{13}$$

This is an over-determined system of equations to find elements of matrix W. The central point $(0.5, 0.5, 0.5)$ will be a critical point with the characteristic values $\lambda_1 = -0.8$, $\lambda_{2,3} = 0.1 \pm 2i$.

The regulatory matrix

$$W = \begin{pmatrix} 0 & 0 & 1.042 \\ -1 & 0 & 5.65 \\ 0 & -1 & 2.4 \end{pmatrix} \tag{14}$$

is good. It is not unique, of course.

EXAMPLES WITH ATTRACTORS

We consider system (1), where parameters are μ_i, θ_i, v_i and w_{ij}. In any of our examples we will have a critical point with the characteristic values, satisfying the condition (4). Our goal is to obtain attractors which are neither stable equilibria, nor limit cycles, but something else. We provide 3D visualizations of attractors, as well as graphs of $x(t)$, $y(t)$ and $z(t)$. The behavior of solutions is irregular. We also made a test on the sensitive dependence of solutions on the initial data. For this, we compute Lyapunov exponents. Recall, that there are three Lyapunov curves. If one of them is positive, this is an evidence of the chaotic behavior of solutions. For calculations, we use Wolfram Mathematica programming written by M. Sandri (Sandri 1996) and available online.

Example 1

Consider the three-dimensional system (1) with the regulatory matrix

$$W = \begin{pmatrix} 0 & 0 & 2 \\ -0.82 & -0.2 & 4.55 \\ 0.1 & -0.87 & 1.11 \end{pmatrix} \tag{15}$$

and $v_1 = 0.164, v_2 = 0.1, v_3 = 0.2; \mu_1 = 4.38, \mu_2 = 4, \mu_3 = 3.1; \theta_1 = 0.77, \theta_2 = 1.09, \theta_3 = 0.62$. Let initial conditions be $(0.41; 0.1; 0.4)$. There is the critical point $P = (6.096; 2.085; 1.356)$. The nullclines of the system (1) with the regulatory matrix (15) are demonstrated in Fig.1 and the trajectory of the system (1) with the regulatory matrix (15) is shown in Fig.2.

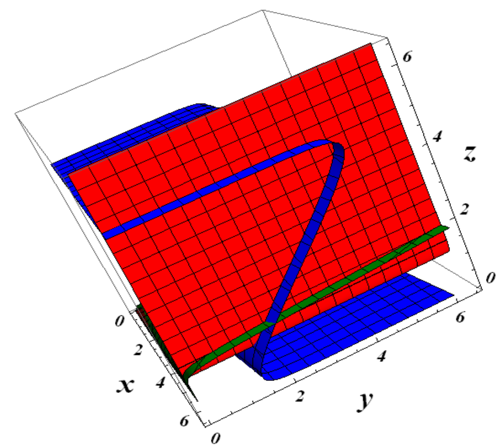

Figure 1 The nullclines of the system (1) with the regulatory matrix (15).

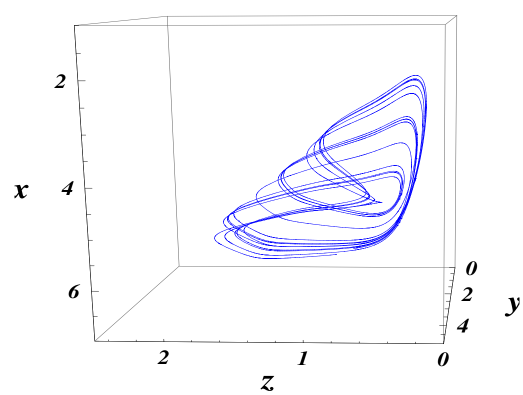

Figure 2 The trajectory of the system (1) with the regulatory matrix (15).

The characteristic values for the critical point P are $\lambda_1 = -0.16, \lambda_{2,3} = 0.12 \pm 1.21i$. This is a saddle-focus II with the condition (4) fulfilled. The dynamics of Lyapunov exponents for the system (1) with the regulatory matrix (15) are demonstrated in Fig.3 and the graphs of the system (1) with regulatory matrix (15) are shown in Fig.4.

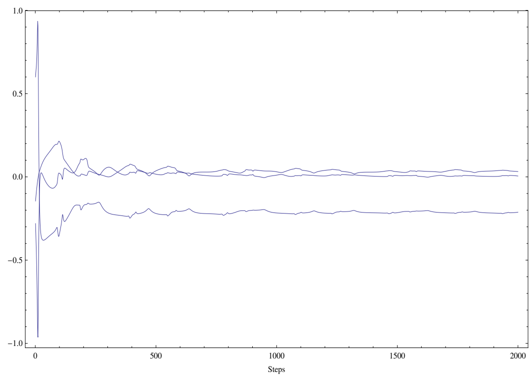

Figure 3 The dynamics of Lyapunov exponents for the system (1) with the regulatory matrix (15).

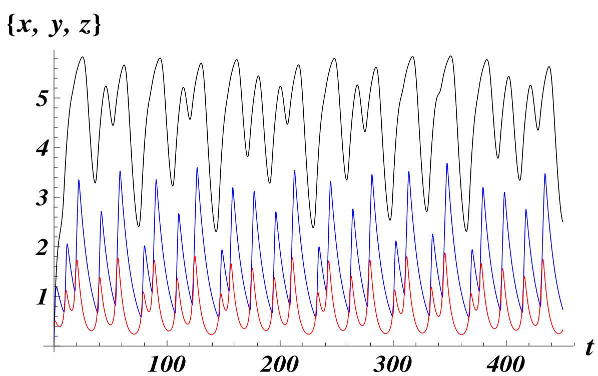

Figure 4 The graphs $(x(t), y(t), z(t))$ of the system (1) with regulatory matrix (15).

The Lyapunov exponents are $(0.032, 0.005, -0.212)$ with the initial condition $(0.41; 0.1; 0.4)$, where $LE_1 > 0, LE_2 = 0$ and $LE_3 < 0$ (Saeed *et al.* 2023).

Example 2

Consider the three-dimensional system (1) with the regulatory matrix

$$W = \begin{pmatrix} 0 & 0.262 & -7.12 \\ 1.46 & 0 & 4 \\ 0.1425 & -1 & 2 \end{pmatrix} \tag{16}$$

and $v_1 = 0.708, v_2 = 0.307, v_3 = 0.767; \mu_1 = 5.63, \mu_2 = 4.538, \mu_3 = 4; \theta_1 = -4, \theta_2 = 4.44, \theta_3 = 0.5$. The initial conditions are $(0.4; 0.9; 0.4)$. The nullclines of the system (1) with the regulatory matrix (16) are demonstrated in Fig.5 and the trajectory of the system (1) with the regulatory matrix (16) is shown in Fig.6.

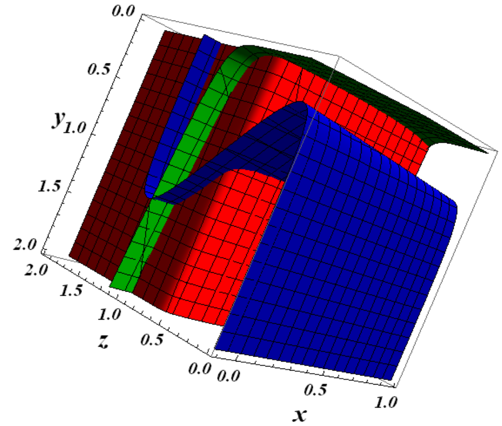

Figure 5 The nullclines of the system (1) with the regulatory matrix (16).

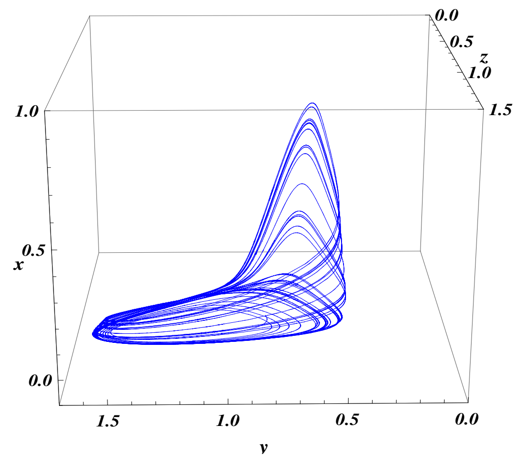

Figure 6 The trajectory of the system (1) with the regulatory matrix (16).

The critical point has coordinates $P = (0; 1.269; 1.085)$. Characteristic values for the critical point P are $\lambda_1 = -0.71, \lambda_{2,3} = 0.02 \pm 1.51i$. This point is a saddle-focus II again. The dynamics of Lyapunov exponents for the system (1) with the regulatory matrix (16) are demonstrated in Fig.7 and the graphs of the system (1) with regulatory matrix (16) are shown in Fig.8.

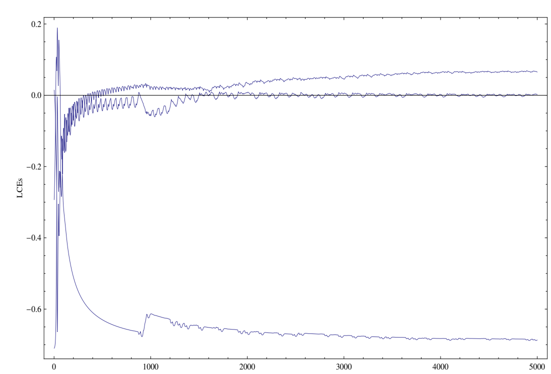

Figure 7 The dynamics of Lyapunov exponents for the system (1) with the regulatory matrix (16).

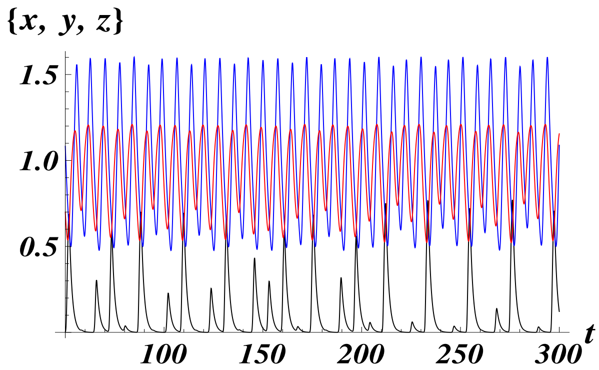

Figure 8 The graphs $(x(t), y(t), z(t))$ of the system(1) with the regulatory matrix (16).

The Lyapunov exponents are $(0.065; 0.002; -0.686)$ with the initial condition $(0.4; 0.9; 0.4)$, where $LE_1 > 0, LE_2 = 0$ and $LE_3 < 0$. The trajectory of Rössler system and the trajectory of the system (1) with the regulatory matrix (16) are shown in Fig.9.

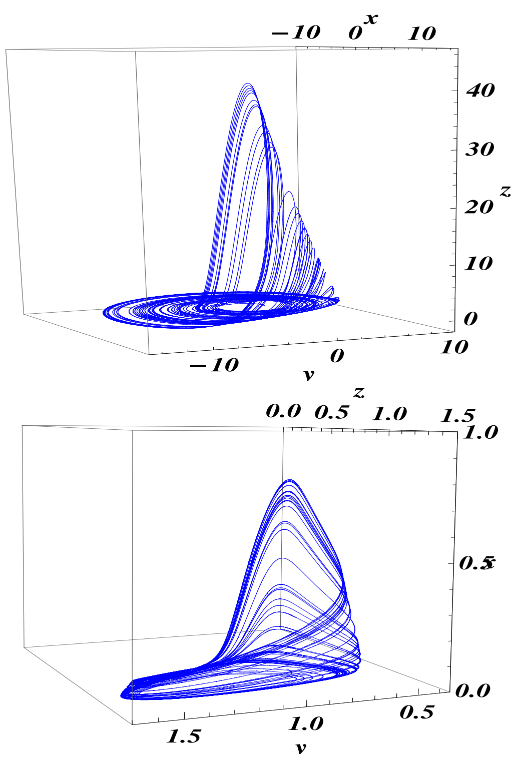

Figure 9 The trajectory of the Rössler system (top picture). The trajectory of the system (1) with the regulatory matrix (16) (bottom picture).

The second attractor looks similar to the Rössler one (Ibraheem and Raied 2022). They are different, however. The Rössler attractor is based on two critical points, one in the basement and the second one in the upper part of the attractor. The critical point in the basement is a saddle focus II point, while the second critical point has one-dimensional unstable manifold and two-dimensional stable one. The attractor in the system (1) with the regulatory matrix (16) has a single saddle focus II type point.

CONCLUSION

Chaotic attractors in GRN are extremely rare, according to the evidences of researchers. So any indications on how to get chaotic behavior are of great importance. In our study, the examples with a critical point of saddle-focus type were considered. The condition $\lambda > -\rho$ was essential. In our examples, we were looking for systems with the critical point of this type. So the number of tests in search of chaos was significantly narrowed. We provide the GRN system having a critical point of saddle-focus type II, where $\lambda_1 < 0$, $\lambda_{2,3} = \alpha \pm i\beta$, $\alpha > 0$, $\beta \neq 0$ and $|\lambda_1| > \alpha$. In two cases the chaotic behavior was confirmed by analysis using the Lyapunov exponents.

Availability of data and material

Not applicable.

Conflicts of interest

The authors declare that there is no conflict of interest regarding the publication of this paper.

Ethical standard

The authors have no relevant financial or non-financial interests to disclose.

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