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(in collaboration with Valentin Sengileyev)

Dynamical systems modeling gene networks

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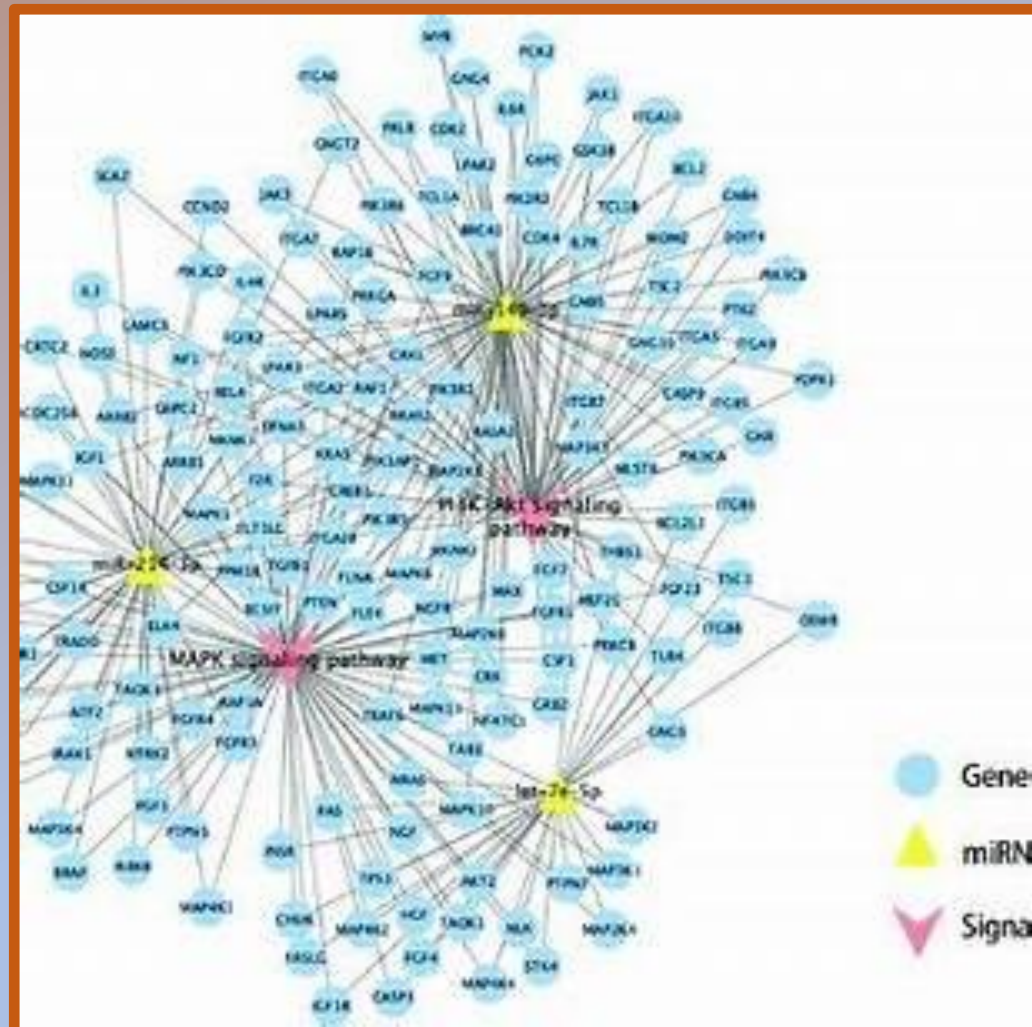
NETWORKS


PI3K-Akt signaling pathway
MAPK signaling pathway
Gene
miRN
Signa

NETWORKS

A **gene** (or **genetic**) **regulatory network** (**GRN**) is a collection of molecular regulators that interact with each other and with other substances in the cell to govern the gene expression levels of mRNA and proteins which, in turn, determine the function of the cell. GRN also play a central role in morphogenesis, the creation of body structures, which in turn is central to evolutionary developmental biology.

NETWORKS

In single-celled organisms, regulatory networks respond to the external environment, optimizing the cell at a given time for survival in this environment.
Wikipedia

NETWORKS

In multicellular animals the same principle has been put in the service of gene cascades that control body-shape. Each time a cell divides, two cells result which, although they contain the same genome in full, can differ in which genes are turned on and making proteins. A major feature of multicellular animals is the use of morphogen gradients. A gene that is turned on in one cell may make a product that leaves the cell and diffuses through adjacent cells, entering them and turning on genes only when it is present above a certain threshold level. These cells are thus induced into a new fate, and may even generate other morphogens that signal back to the original cell. Over longer distances morphogens may use the active process of signal transduction. Such signalling controls embryogenesis, the building of a body plan from scratch through a series of sequential steps. They also control and maintain adult bodies through feedback processes, and the loss of such feedback because of a mutation can be responsible for the cell proliferation that is seen in cancer.

SYSTEM

$X_i(t)$	Gene expression of protein	
t	time	
v_i	Degradation coefficient	
$X'_i(t)$	Derivative	
f	Sigmoidal function	

$$\begin{cases} x'_1 = f_1(x_1, x_2, \cdots, x_n) - v_1 x_1, \\ x'_2 = f_2(x_1, x_2, \cdots, x_n) - v_2 x_2, \\ \cdots \\ x'_n = f_n(x_1, x_2, \cdots, x_n) - v_n x_n. \end{cases}$$

SYSTEM

f (z) – sigmoidal function.

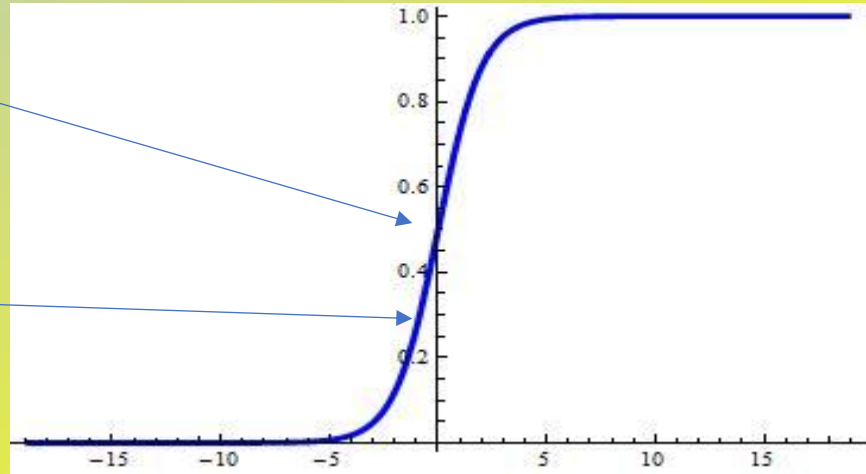
Logistic function $f(z)=1/(1+\exp\{-\mu\,(z-\theta)\})$

Hill's function $f(z)=\frac{z^{\mu}}{z^{\mu}+\theta^{\mu}}$

Gompertz function $f(z)=e^{-e^{-\mu(z-\theta)}}$

μ

θ



SYSTEM

$$\begin{cases} x'_1 = f_1(x_1, x_2, \cdots, x_n) - v_1 x_1, \\ x'_2 = f_2(x_1, x_2, \cdots, x_n) - v_2 x_2, \\ \cdots \\ x'_n = f_n(x_1, x_2, \cdots, x_n) - v_n x_n. \end{cases} \tag{1}$$

Proposition 1. The parallelepiped $Q_n = \left\{ x \epsilon R^n : \ 0 < x_i < \frac{1}{v_i}, \ i = 1, \ldots, n \right\}$ is an invariant set.

SYSTEM

Nullclines

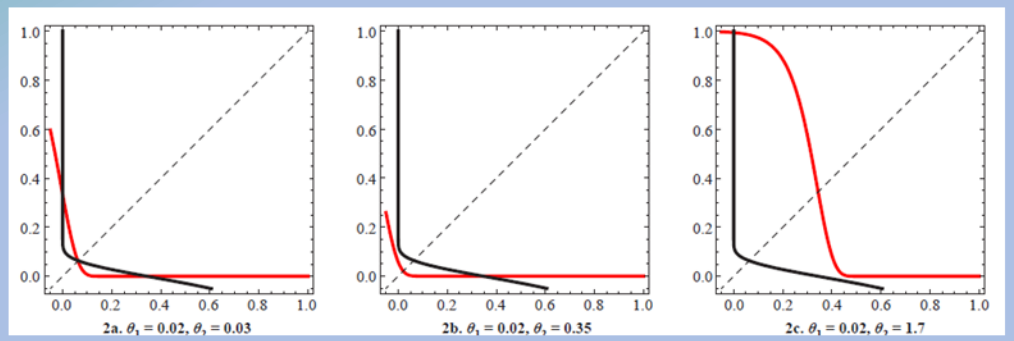
$$\begin{cases} 0 = f_1(x_1, x_2, \cdots, x_n) - v_1 x_1, \\ 0 = f_2(x_1, x_2, \cdots, x_n) - v_2 x_2, \\ \cdots \\ 0 = f_n(x_1, x_2, \cdots, x_n) - v_n x_n. \end{cases} \quad (2)$$

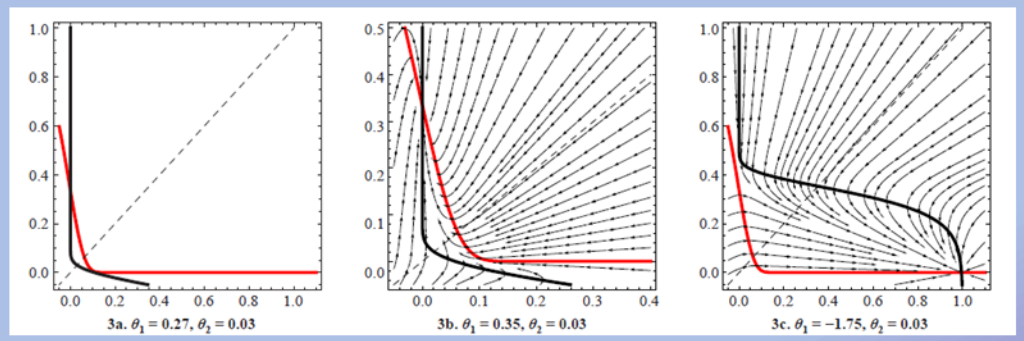
Proposition 2. At least one solution of system (2) exists in $Q_n = \left\{ x \epsilon R^n : \ 0 < x_i < \frac{1}{v_i}, \ i = 1, \ldots, n \right\}$.

Second order systems

$$\begin{cases} x'_1 = \dfrac{1}{1+e^{-\mu_1(w_{11}x_1+w_{12}x_2-\theta_1)}} - v_1x_1, \\ x'_2 = \dfrac{1}{1+e^{-\mu_2(w_{21}x_1+w_{22}x_2-\theta_2)}} - v_2x_2. \end{cases} \quad (3)$$

$$\begin{cases} 0 = \dfrac{1}{1+e^{-\mu_1(w_{11}x_1+w_{12}x_2-\theta_1)}} - v_1x_1, \\ 0 = \dfrac{1}{1+e^{-\mu_2(w_{21}x_1+w_{22}x_2-\theta_2)}} - v_2x_2. \end{cases} \quad (4)$$





D. Ogorelova, F. Sadyrbaev, V. Sengileyev. Control in Inhibitory Genetic Regulatory Network Models. Contemporary Mathematics. Volume 1 Issue 5|2020| 421

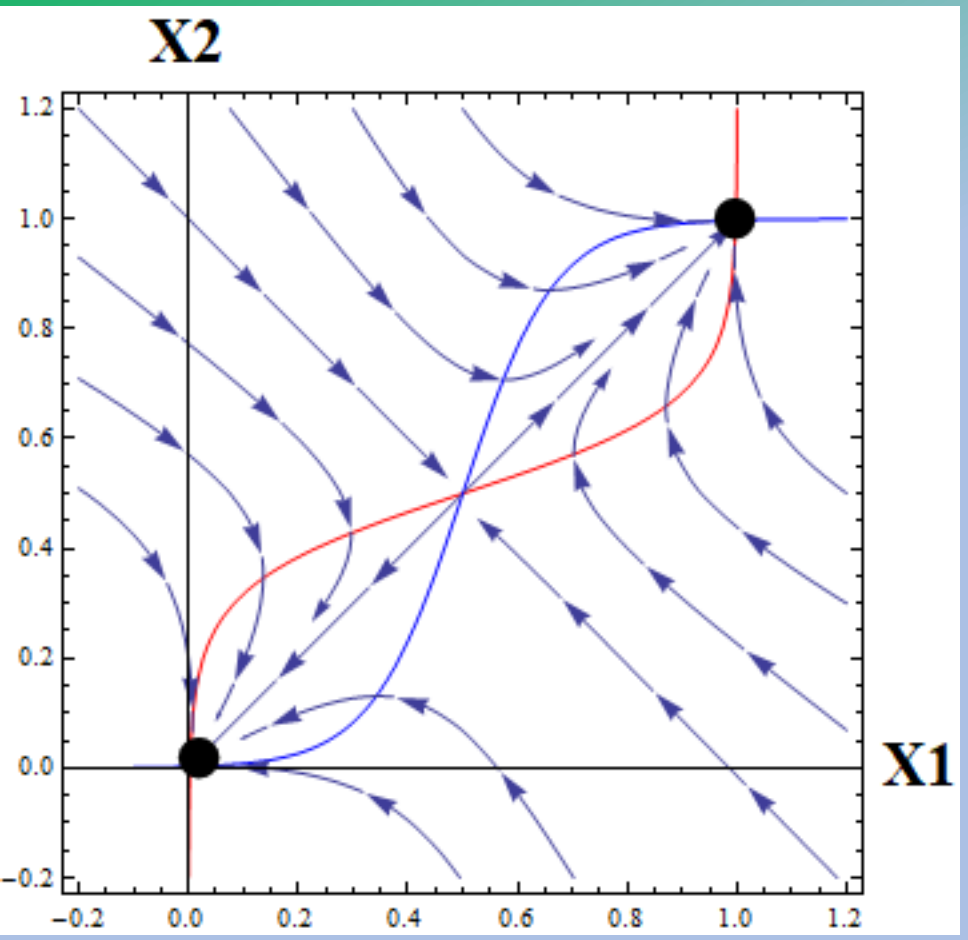
Second order systems

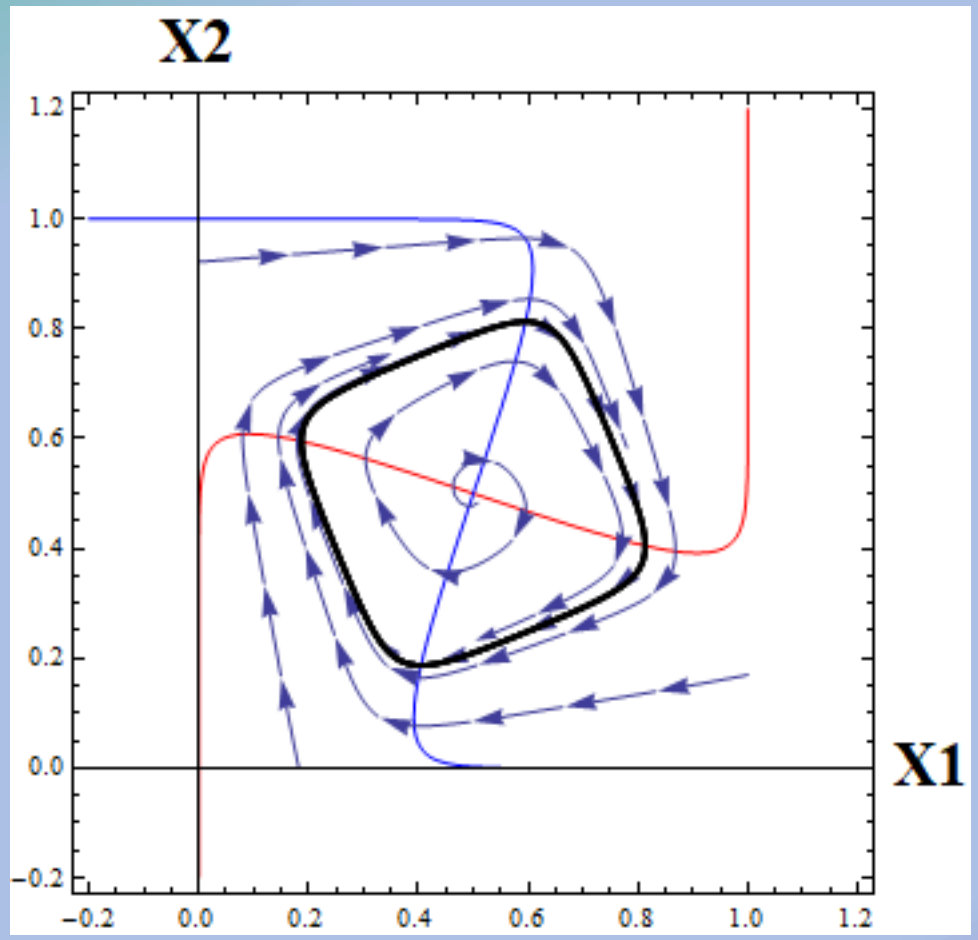
The Wilson–Cowan system primarily was invented for the study of two interacting populations of neurons. Its simplified version

$$\begin{cases} x'_1 = \dfrac{1}{1+e^{-\mu_1(w_{11}x_1 + w_{12}x_2 - \theta_1)}} - v_1 x_1, \\ x'_2 = \dfrac{1}{1+e^{-\mu_2(w_{21}x_1 + w_{22}x_2 - \theta_2)}} - v_2 x_2. \end{cases}$$

is known to have rich dynamics. The higher dimensional versions of system (1) were adapted to model genetic networks, and similar networks in other fields. The three-dimensional version of system (1) contains 18 parameter and the number of parameters increases along with the dimensionality. The central point in the study of this system is to gather information about attractors in the phase space. The dynamics of solutions and evolution of the system heavily depends on the number, locations and properties of attractors. In the proposed talk recent contributions to the theory are reported concerning types, properties and forms of attractors in of the system (1). In particular, a collection of attractors of different shapes is presented.

Second order systems





Second order systems

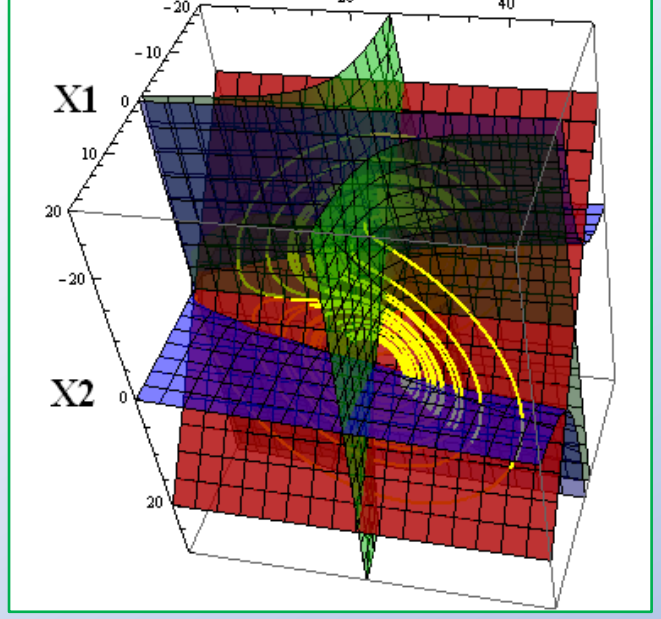
Hugh R. Wilson · Jack D. Cowan ***Excitatory and inhibitory interactions in localized populations of model neurons.*** BiophysIcal Journal Volume 12 1972

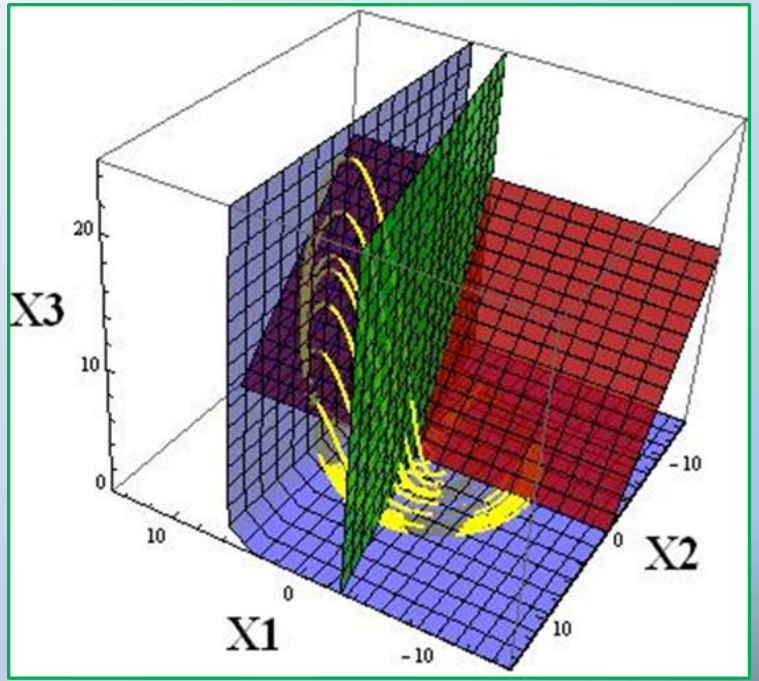
Hugh R. Wilson · Jack D. Cowan ***Evolution of the Wilson–Cowan equations.*** Biological Cybernetics (2021) 115:643–653 https://doi.org/10.1007/s00422-021-00912-7

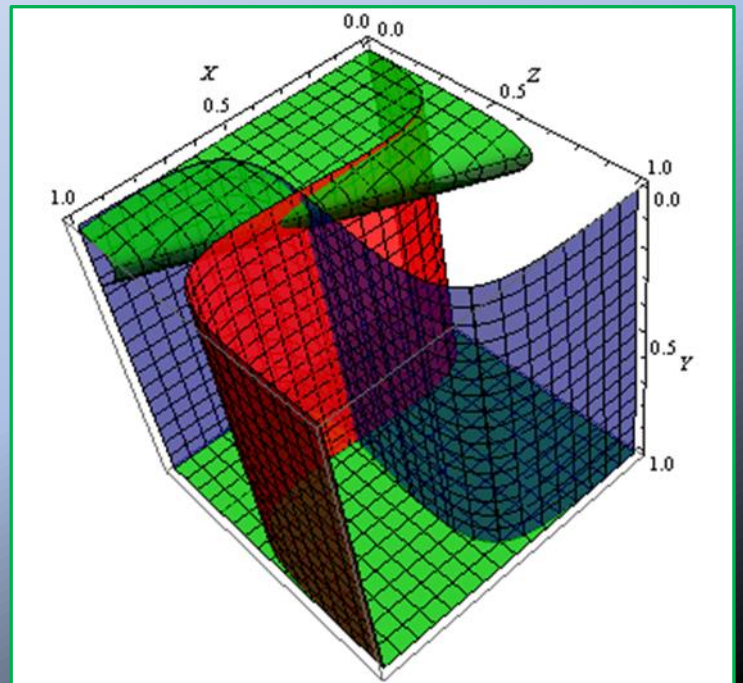
Virginia W. Noonburg. **Differential Equations: From Calculus to Dynamical Systems**. 2nd Edition**,** AMS/MAA TEXTBOOKS, vol. 43, 2019.

Third order system

$$\begin{cases} x'_1 = \dfrac{1}{1+e^{-\mu_1(w_{11}x_1+w_{12}x_2+w_{13}x_3-\theta_1)}} - x_1, \\ x'_2 = \dfrac{1}{1+e^{-\mu_2(w_{21}x_1+w_{22}x_2+w_{23}x_3-\theta_2)}} - x_2, \\ x'_3 = \dfrac{1}{1+e^{-\mu_3(w_{31}x_1+w_{32}x_2+w_{33}x_3-\theta_3)}} - x_3. \end{cases}$$

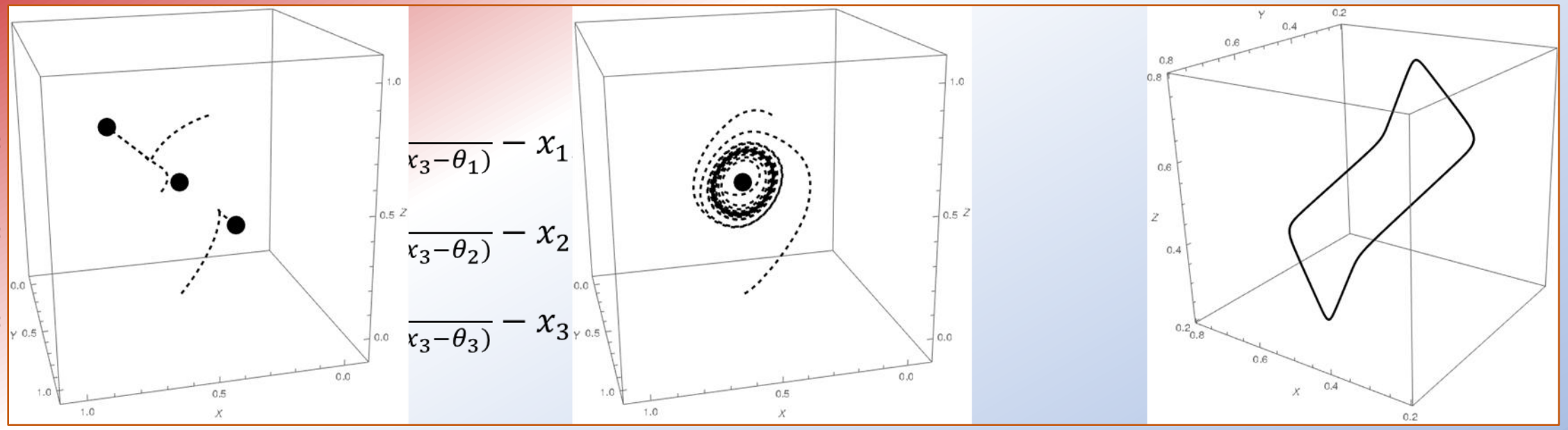


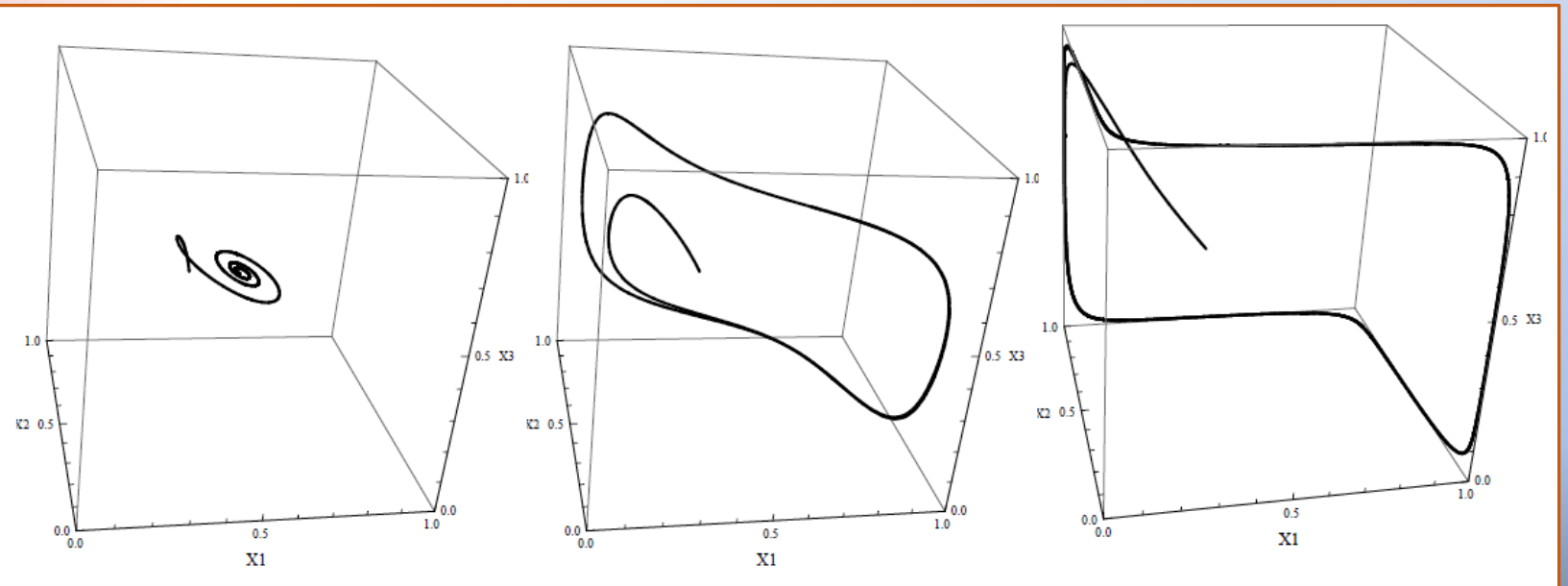




Third order system: attractors

$$\begin{cases} x'_1 = \overline{x_3-\theta_1)} - x_1 \\ x'_2 = \overline{x_3-\theta_2)} - x_2 \\ x'_3 = \overline{x_3-\theta_3)} - x_3 \end{cases}$$





- Sadyrbaev, F., Sengileyev, V., Silvans, A. On Coexistence of Inhibition and Activation in Genetic Regulatory Networks. AIP Conference Proceedings, 2023, 2849(1), 120004

Third order system: regulatory matrix

$$\begin{cases} x'_1 = \dfrac{1}{1+e^{-\mu_1(w_{11}x_1+w_{12}x_2+w_{13}x_3-\theta_1)}} - x_1, \\ x'_2 = \dfrac{1}{1+e^{-\mu_2(w_{21}x_1+w_{22}x_2+w_{23}x_3-\theta_2)}} - x_2, \\ x'_3 = \dfrac{1}{1+e^{-\mu_3(w_{31}x_1+w_{32}x_2+w_{33}x_3-\theta_3)}} - x_3. \end{cases}$$

$$W = \begin{pmatrix} w_{11} & \dots & w_{1n} \\ \dots & \dots & \dots \\ w_{n1} & \dots & w_{nn} \end{pmatrix} \qquad (5)$$

Third order system: regulatory matrix

$$\begin{cases} x'_1 = \dfrac{1}{1+e^{-\mu_1(w_{11}x_1+w_{12}x_2+w_{13}x_3-\theta_1)}} - x_1, \\ x'_2 = \dfrac{1}{1+e^{-\mu_2(w_{21}x_1+w_{22}x_2+w_{23}x_3-\theta_2)}} - x_2, \\ x'_3 = \dfrac{1}{1+e^{-\mu_3(w_{31}x_1+w_{32}x_2+w_{33}x_3-\theta_3)}} - x_3. \end{cases}$$

	x_1	x_2	…	x_n
x_1	1			6
x_2		-2		
….				
…			-4.3	
x_n	0.5			

Fourth order systems

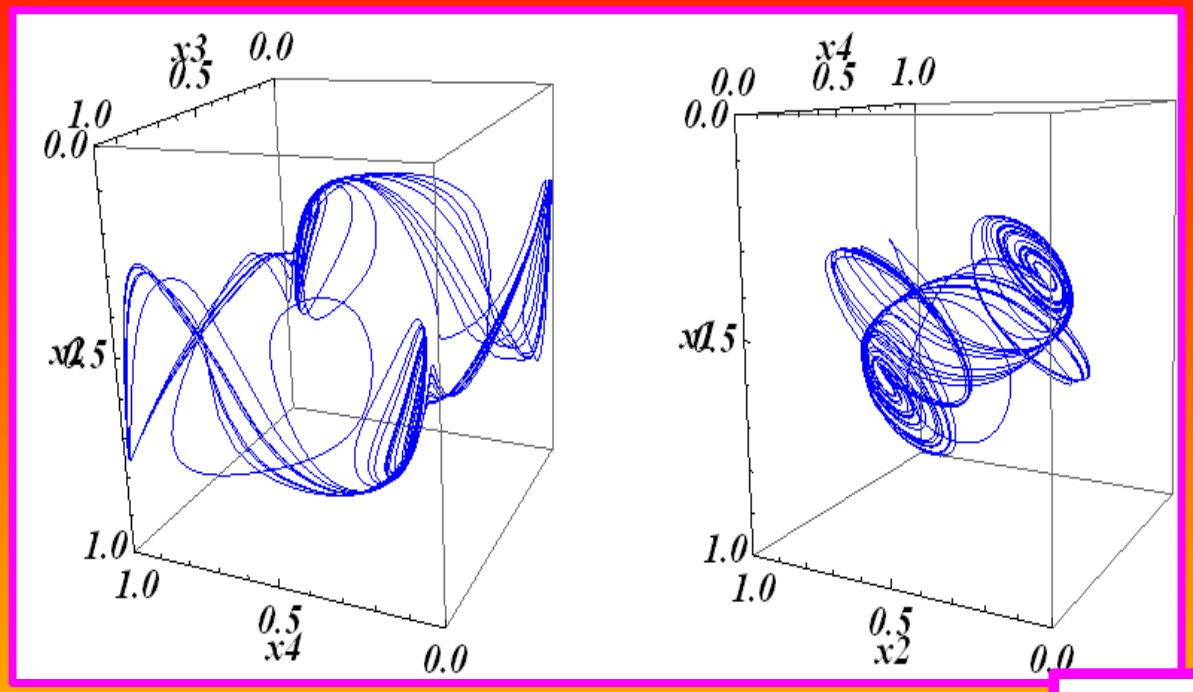
We consider the four-dimensional system

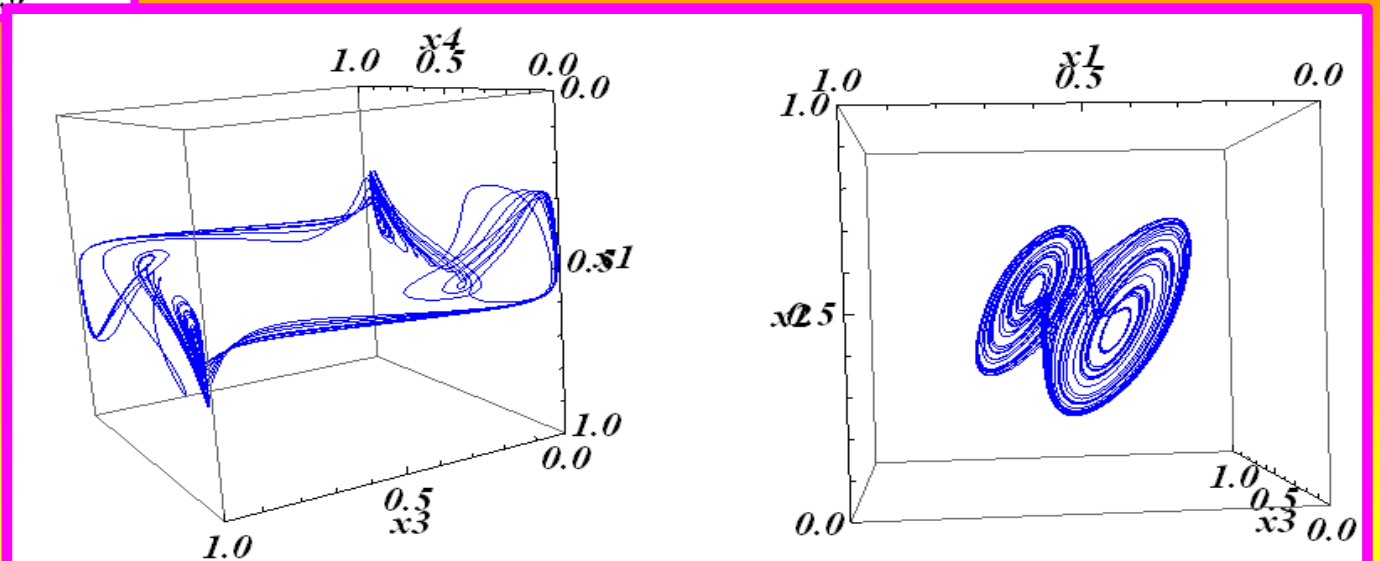
$$\begin{cases} x_1' = \dfrac{1}{1+e^{-\mu_1(w_{11}x_1+w_{12}x_2+w_{13}x_3+w_{14}x_4-\theta_1)}} - v_1x_1, \\ x_2' = \dfrac{1}{1+e^{-\mu_2(w_{21}x_1+w_{22}x_2+w_{23}x_3+w_{24}x_4-\theta_2)}} - v_2x_2, \\ x_3' = \dfrac{1}{1+e^{-\mu_3(w_{31}x_1+w_{32}x_2+w_{33}x_3+w_{34}x_4-\theta_3)}} - v_3x_3, \\ x_4' = \dfrac{1}{1+e^{-\mu_4(w_{41}x_1+w_{42}x_2+w_{43}x_3+w_{44}x_4-\theta_4)}} - v_4x_4, \end{cases} \tag{1}$$

which corresponds to a four-element genetic network.

Out task is to describe possible evolution of GRN, analyzing the system (1). The system is autonomous, so the method of phase space is applicable. It contains multiple parameters, 24 in the system (1).

Fourth order system: chaotic attractor





Fourth order systems

Kozlovska, O.; Sadyrbaev, F.; Samuilik, I. A New 3D Chaotic Attractor in Gene Regulatory Network. *Mathematics* **2023**, *12*, 100. https://doi.org/10.3390/math12010100.

Kozlovska, O.; Sadyrbaev, F. In Search of Chaos in Genetic Systems. *Chaos Theory Appl.* **2024**, *6*, 13–18. https://doi.org/10.51537/chaos.1380419.

Kozlovska, O.; Sadyrbaev, F. Modeling Networks of Four Elements. *Computation* **2025**, *13*(5), 123; **https://doi.org/10.3390/computation13050123**

60-th order system

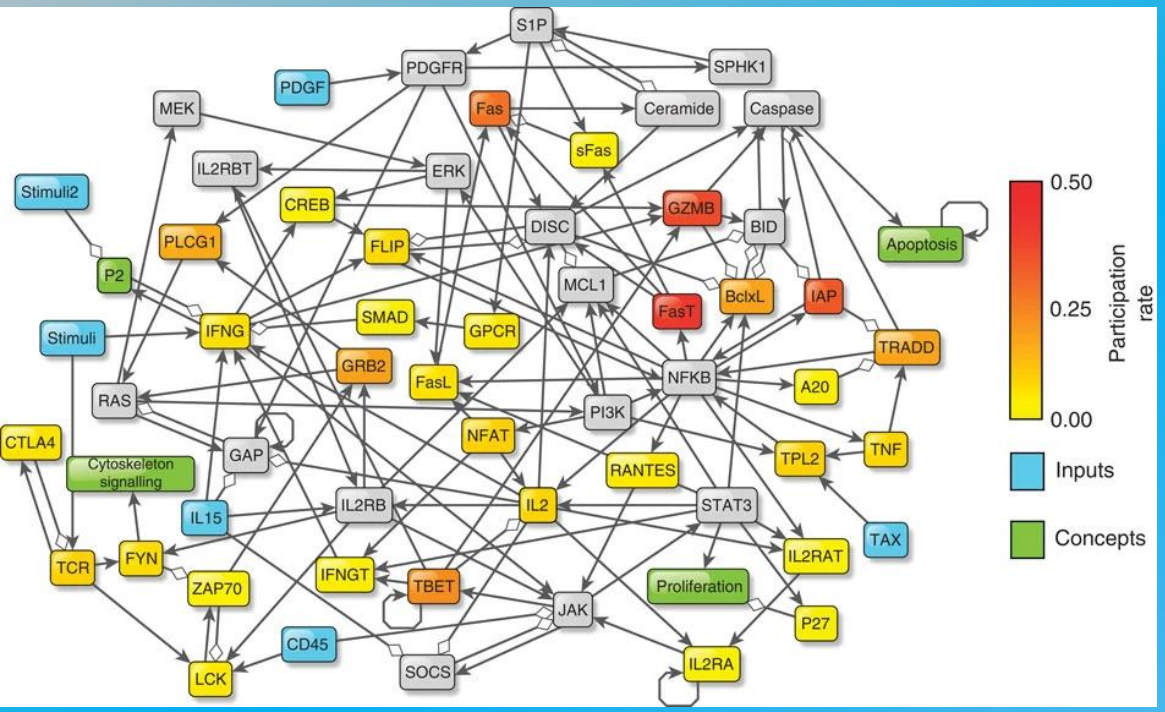


Figure: T-cell survival signalling network governing the development of T-LGL leukemia.

Sean P. Cornelius, William L. Kath & Adilson E. Motter. Realistic control of network dynamics. Nature Communications 4, Article number: 1942 (2013)

60-th order system

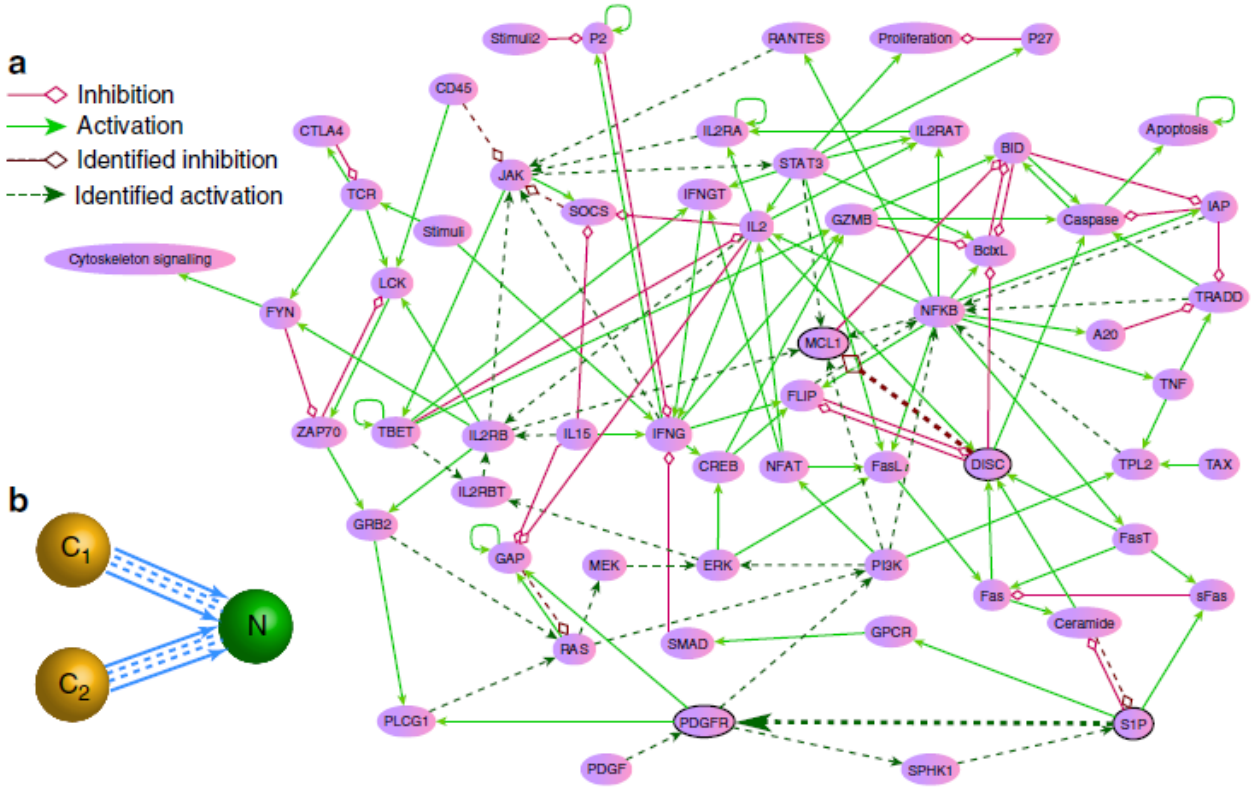
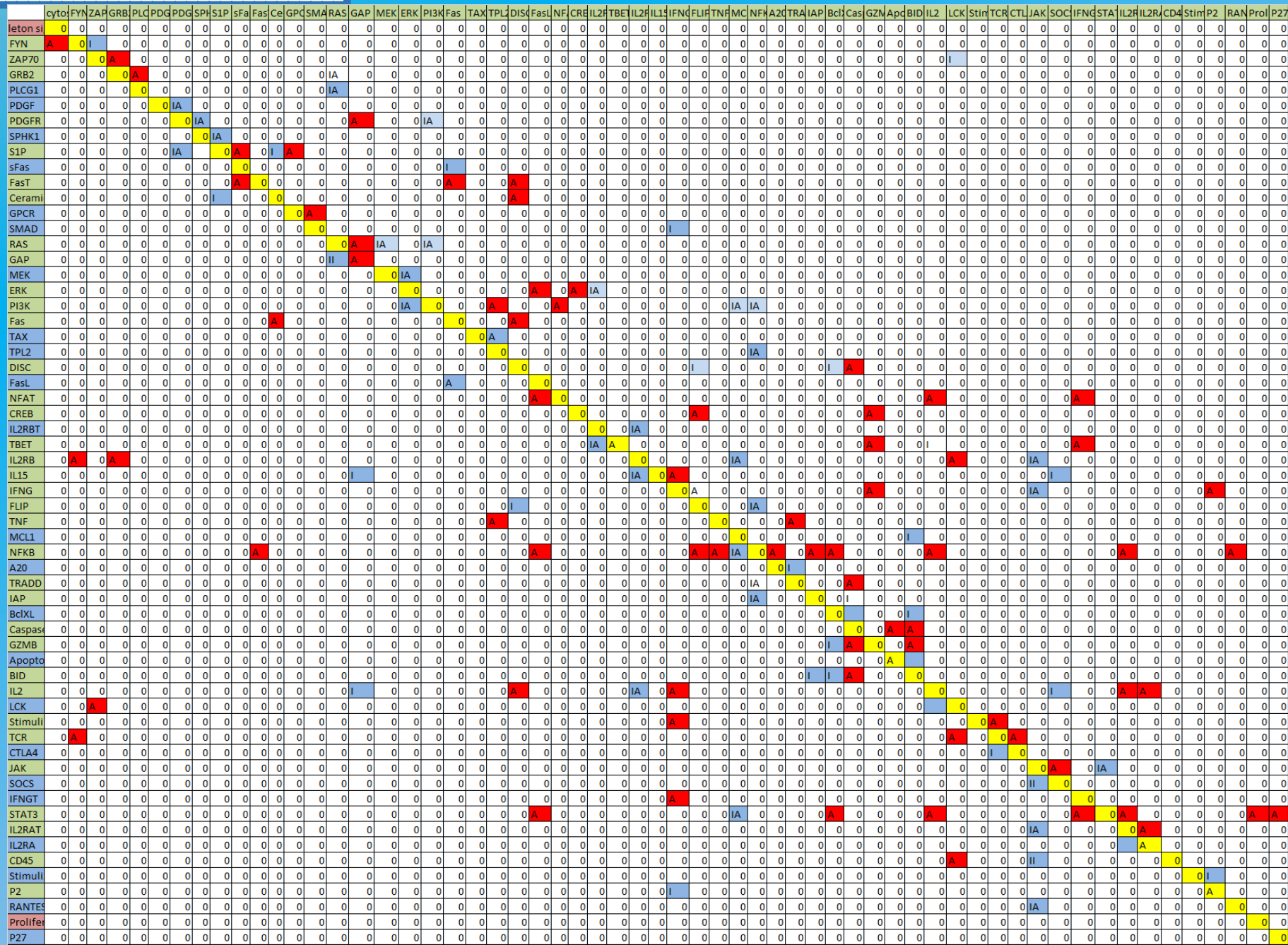


Figure 1 | T-cell survival signalling network and its attractor network. (**a**) Structure of T-cell survival network: each node is labelled with its generic name, and the arrowhead and diamond-head edges represent activation and inhibition regulations, respectively. The inhibitory edges from 'Apoptosis' to other nodes are not shown (for clarity). (**b**) Attractor network of the T-cell network, which contains three nodes: two cancerous states denoted as $\mathbf{C}_1$ and $\mathbf{C}_2$ and a normal state denoted as **N**. The two directed edges in the attractor network are multiple, each containing altogether 48 individual edges corresponding to controlling the 48 edges in the original network, which are indicated by the dark dashed lines, whereas the remaining edges in the original network are signified by the light solid lines. Our detailed computations reveal that parameter perturbation on any one of the 48 edges can drive the system from a cancerous state to the normal state. That is, regardless of whether the initial state is $\mathbf{C}_1$ or $\mathbf{C}_2$, with a proper modification to one of the 48 parameters, the system can be driven to the normal state **N**.

Wang, LZ., Su, RQ., Grebogi, C. *et al.* A geometrical approach to control and controllability of nonlinear dynamical networks. *Nat Commun* **7**, 11323 (2016). https://doi.org/10.1038/ncomms11323

60-th order system: regulatory matrix



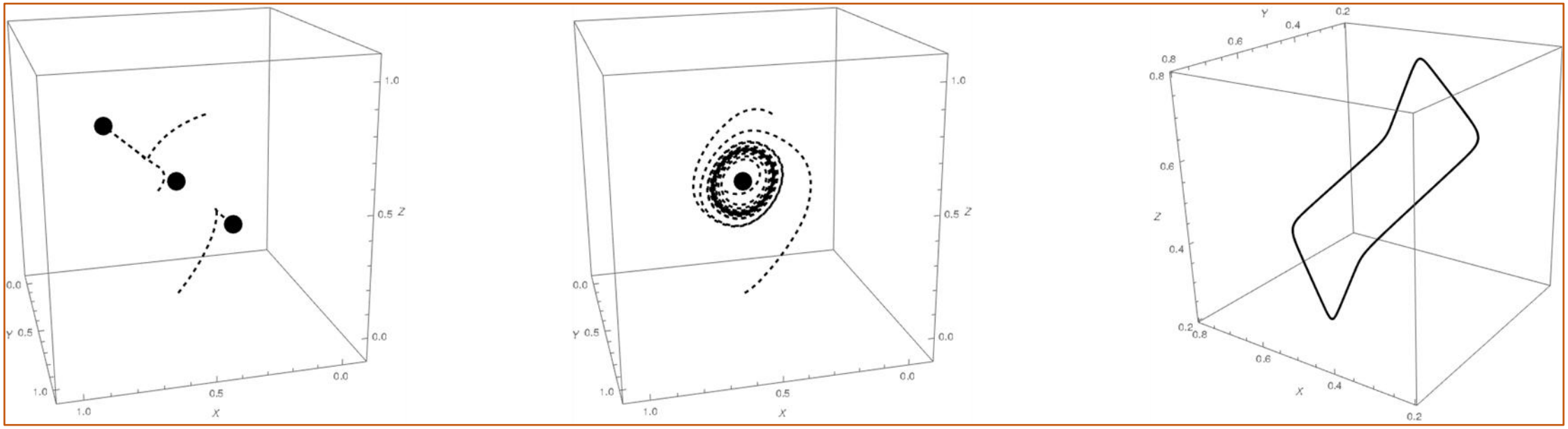
Variable regulatory matrix

$$\begin{cases} x'_1 = \dfrac{1}{1+e^{-\mu_1(w_{11}x_1+w_{12}x_2+w_{13}x_3-\theta_1)}} - x_1, \\ x'_2 = \dfrac{1}{1+e^{-\mu_2(w_{21}x_1+w_{22}x_2+w_{23}x_3-\theta_2)}} - x_2, \\ x'_3 = \dfrac{1}{1+e^{-\mu_3(w_{31}x_1+w_{32}x_2+w_{33}x_3-\theta_3)}} - x_3. \end{cases}$$

Elements w_{ij} are dependent on time, $w_{ij}(t)$

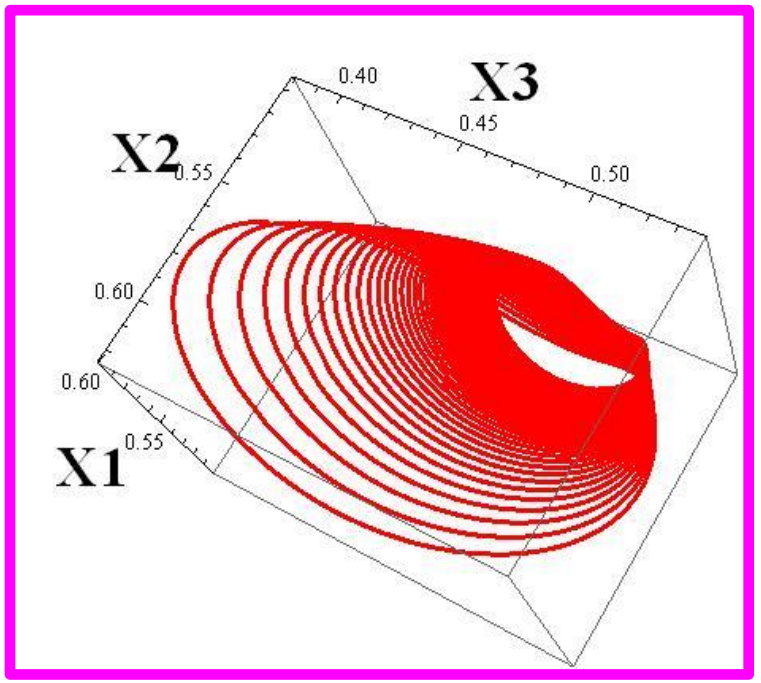
Example (basic). Inhibitory cycle

$$W = \begin{pmatrix} 1 & 0 & -1 \\ -1 & 1 & 0 \\ 0 & -1 & 1 \end{pmatrix}$$



Example 1. Shell

$$W = \begin{pmatrix} (1+m\ \mathrm{Sin}[t]) & 0 & -(p\ \mathrm{Sin}[q\ t+1]) \\ -(p\ \mathrm{Sin}[q\ t+1]) & (1+m\ \mathrm{Sin}[t]) & 0 \\ 0 & -(p\ \mathrm{Sin}[q\ t+1]) \ldots & (1+m\ \mathrm{Sin}[t]) \end{pmatrix}$$

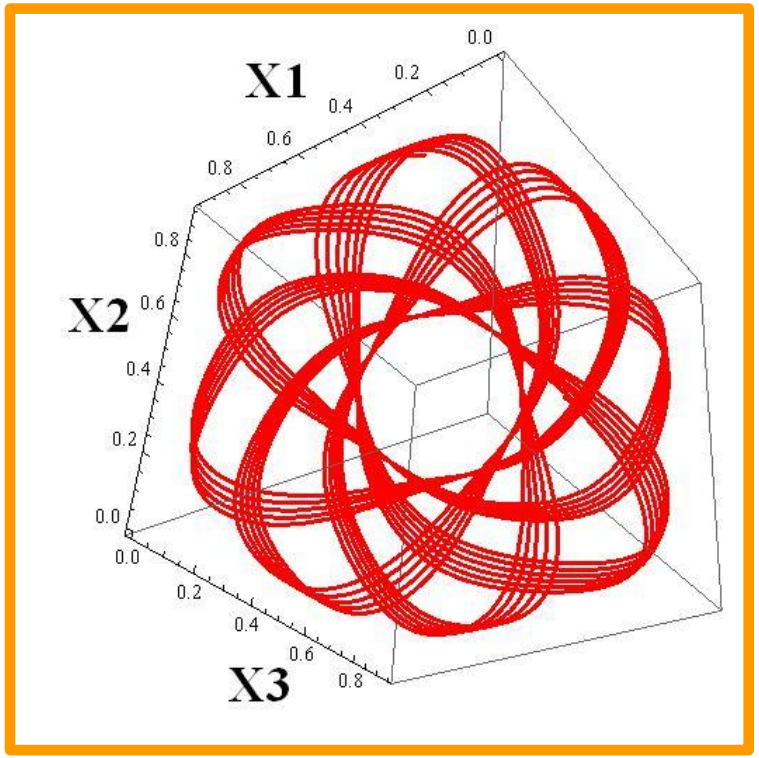


Frequencies of activation and inhibition terms are the same but phases are different

```
p=1; q=1; m=1;
```

Example 2. Belt

$$W = \begin{pmatrix} (1+m\ \mathrm{Sin}[t]) & 0 & -(1+p\ \mathrm{Sin}[q\ t]) \\ -(1+p\ \mathrm{Sin}[q\ t]) & (1+m\ \mathrm{Sin}[t]) & 0 \\ 0 & -(1+p\ \mathrm{Sin}[q\ t]) \ldots & (1+m\ \mathrm{Sin}[t]) \end{pmatrix}$$

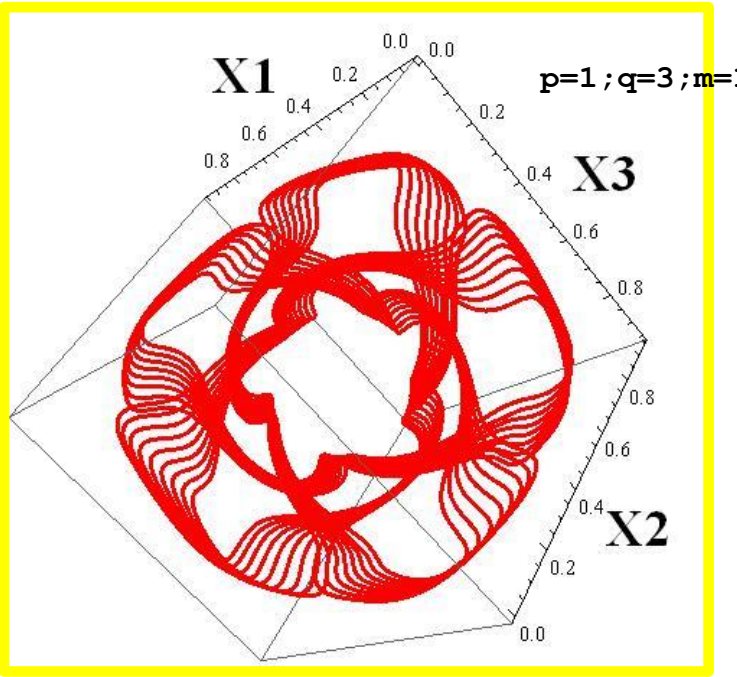


The amplitude of oscillation in inhibition terms is less than 1

```
p=0.5; q=1; m=1;
```

Example 3. Star

$$W = \begin{pmatrix} (1+m\ \mathrm{Sin}[t]) & 0 & -(1+p\ \mathrm{Sin}[q\ t]) \\ -(1+p\ \mathrm{Sin}[q\ t]) & (1+m\ \mathrm{Sin}[t]) & 0 \\ 0 & -(1+p\ \mathrm{Sin}[q\ t]) \ldots & (1+m\ \mathrm{Sin}[t]) \end{pmatrix}$$



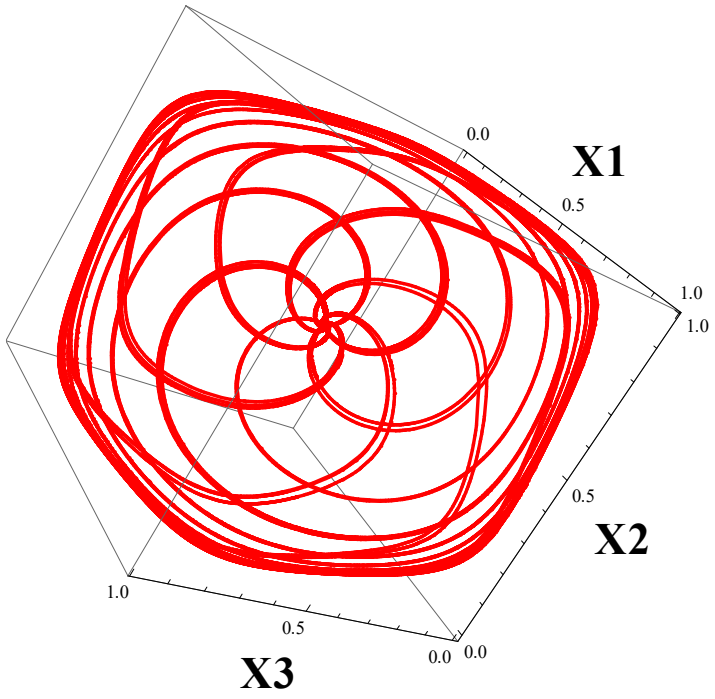
p=1;q=3;m=1;

The frequency of oscillation in inhibition terms is 3 against previous 1

p=1; q=3; m=1;

Example 4. Flower

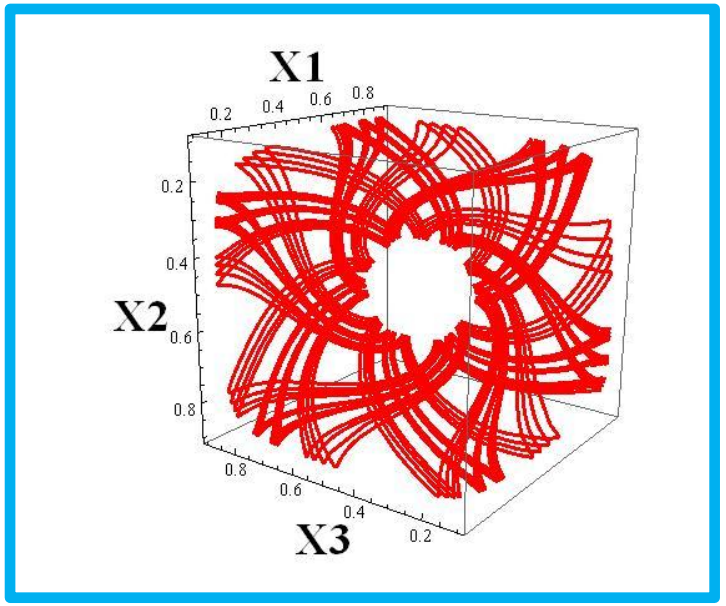
$$W = \begin{pmatrix} (1+m\ \mathrm{Sin}[n\ t]) & 0 & -(1+p\ \mathrm{Sin}[q\ t]) \\ -(1+p\ \mathrm{Sin}[q\ t]) & (1+m\ \mathrm{Sin}[n\ t]) & 0 \\ 0 & -(1+p\ \mathrm{Sin}[q\ t]) \ldots & (1+m\ \mathrm{Sin}[n\ t]) \end{pmatrix}$$




```
p=1; q=0.1; n=0.1; m=1;
```

Example 5. Sharp star

$$W = \begin{pmatrix} (1+m\ \mathrm{Sin}[t]) & 0 & -(\mathrm{Sin}[t]\times\mathrm{Sin}[t]) \\ -(\mathrm{Sin}[t]\times\mathrm{Sin}[t]) & (1+m\ \mathrm{Sin}[t]) & 0 \\ 0 & -(\mathrm{Sin}[t]\times\mathrm{Sin}[t]) & (1+m\ \mathrm{Sin}[t]) \end{pmatrix}$$



The frequency of oscillation in inhibition terms is 2 against previous 1

m=1

Networks with periodic interactions. WSEAS TRANSACTIONS on CIRCUITS and SYSTEMS Volume 24, 2025
Felix Sadyrbaev[1,2], Valentin Sengileyev[1]

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- **Inna Samuilik* , Felix Sadyrbaev, Diana Ogorelova. Comparative Analysis of Models of Gene and Neural Networks. Contemporary Mathematics. Volume 4 Issue 2|2023|**
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- Ogorelova, D., Sadyrbaev, F., Samuilik, I. On Targeted Control over Trajectories of Dynamical Systems Arising in Models of Complex Networks. Mathematics, 2023, 11(9), 2206
- Ogorelova, D., Sadyrbaev, F., Samuilik, I. **On attractors in dynamical systems modeling genetic networks.** Advances in the Theory of Nonlinear Analysis and its Applications, 2023, 7(2), pp. 486–498
- Sadyrbaev, F., Samuilik, I., Sengileyev, V. **Biooscillators in Models of Genetic Networks.** Conference Paper, Springer Proceedings in Mathematics and Statistics, 2023, 423, pp. 141–152

Conclusions and problems

1. Periodic attractors for uncoupled systems;
2. Perturbation of periodic attractors for uncoupled systems;
3. Conditions for guaranteed chaotic behavior under perturbation;
4. Reconstruction of attractor by graphs of a set f solutions;
5. Coexistence of attractors; which are incompatible;
6. When low dimensional projections guarantee the unique reconstruction of attractor;
7. Which attractors have realization in realistic gene networks;
8. Which are possible mathematically, but impossible in reality;
9. Which attractors are undetectable by simple computation of a limited number of solutions;
10. Which are detectable and how many projections are needed for that?
11. What is the lowest dimension of projections needed to uniquely reconstruct an attractor;
12. Can attractors be detected by an algorithm, and how many steps are necessary;
13. There are theorems for existence of periodic solutions; are there theoretical results for the existence of solutions that relate to complicated attractors;
14. If the math model is assumed to be adequate, what is the biological interpretation of them;
15. Applications of any kind.

Thank you for your attention