Mathematical and numerical modeling of gene network functioning.

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Joint work with

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13 октября 2011, ФМШ.

Our main goal is to give a mathematical explanations, and predictions to numerical experiments with nonlinear dynamical systems of chemical kinetics considered as models of gene networks regulated by *combinations* of negative and positive feedbacks.

In our previous publications on the gene networks modeling we have considered the particular cases of very special types of the right hand sides of the equations.

A.N.Kolmogorov, I.G.Petrovskii, N.S.Piskunov
Moscow University Herald, 1937.

1. Some simple gene networks models.

We study odd-dimensional dynamical systems (2k+1)

$$\frac{d\,x_1}{d\,t} = f_1(x_{2k+1}) - x_1; \quad \frac{d\,x_2}{d\,t} = f_2(x_1) - x_2; \ldots \quad \frac{d\,x_{2k+1}}{d\,t} = f_{2k+1}(x_{2k}) - x_{2k+1}.$$

The functions $f_i(u) \to 0$ **are smooth and monotonically decreasing. This corresponds to the negative feedbacks in the gene networks.**

***P 1*. Each system of the type (2k+1) has exactly one stationary point** S_0 **in the positive octant:**

$$x_1 = f_1(f_{2k+1}(f_{2k}(\ldots f_2(x_1)..).$$

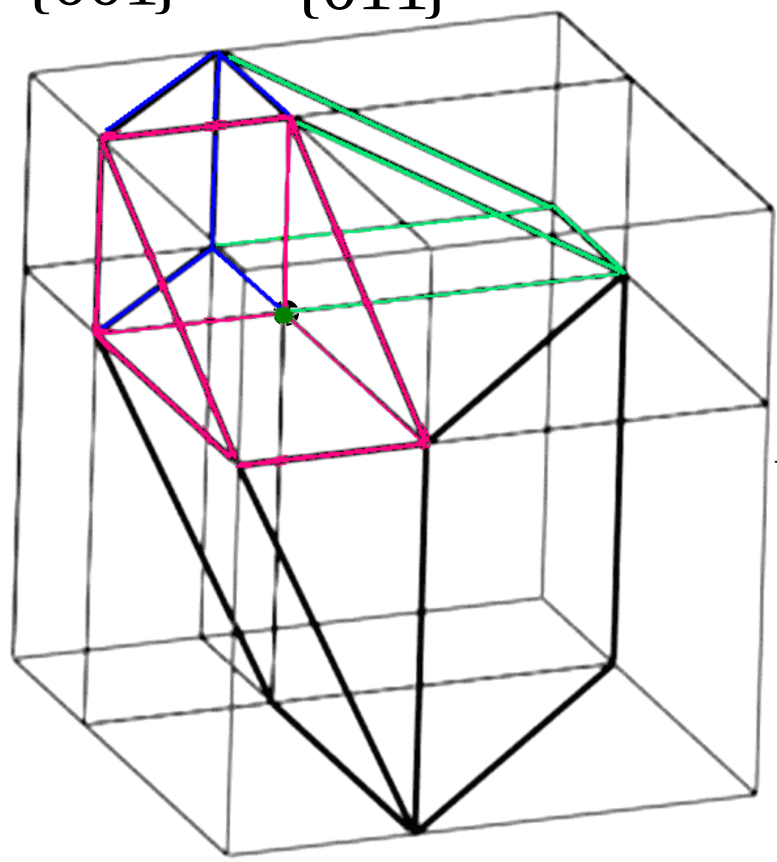
P 2. $Q = [0, f_1(0)] \times [0, f_2(0)] \times \ldots [0, f_{2k+1}(0)]$

is an invariant domain of the system (2k+1). +(2k)

Non-convex 3D invariant domain in Q composed by six triangle prisms.

$$F = \{011\} \bigcap \{001\};$$

$$F_1 = \{101\} \bigcap \{001\}.$$



Hastings S., Tyson J., Webster D. (1977)

$$\{001\} \to \{011\} \to \{010\} \to \{110\} \to \{100\} \to \{101\} \to \{001\}$$

Theorem 1. **If the stationary point S_0 is hyperbolic then the system (2k+1) has at least one periodic trajectory in the invariant domain Q.**

The following diagram (*D*) shows the discrete scheme of some of the trajectories of the system (2k+1).

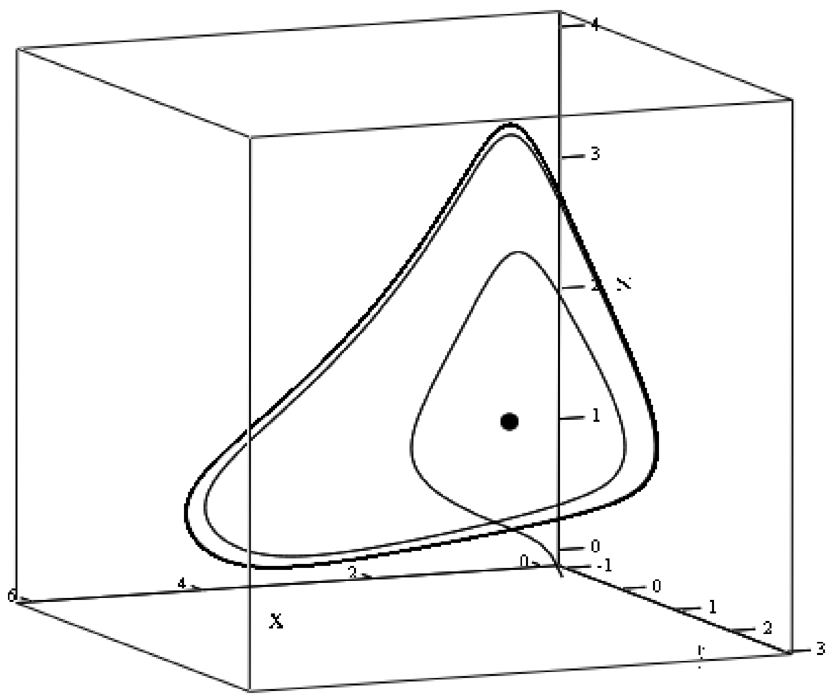
$$\{1010...01\} \to \{0010...01\} \to \{01101...01\} \to \{010010...01\} \to ...$$
$$\to \{1010...0110\} \to \{1010...100\} \to$$

We reduce this invariant domain *Q* to the union of *4k+2* triangle prisms in order to localize the position of the cycle.

Then existence of periodic trajectories follows from the Brower's fixed point theorem.

$$\frac{dx}{dt} = \frac{6}{1+z^5} - x; \qquad \frac{dy}{dt} = \frac{3}{1+x^7} - y; \qquad \frac{dz}{dt} = 7e^{-5y} - z;$$

A trajectory and a limit cycle.



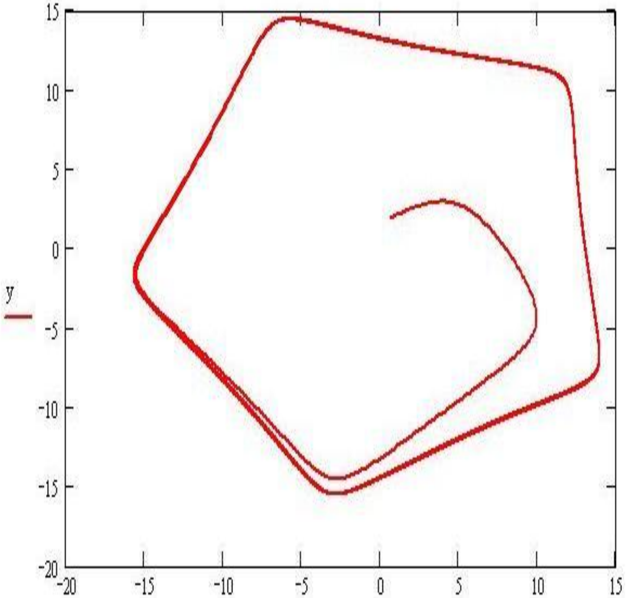
(u1, u2, u3), (rp1, rp2, rp3)

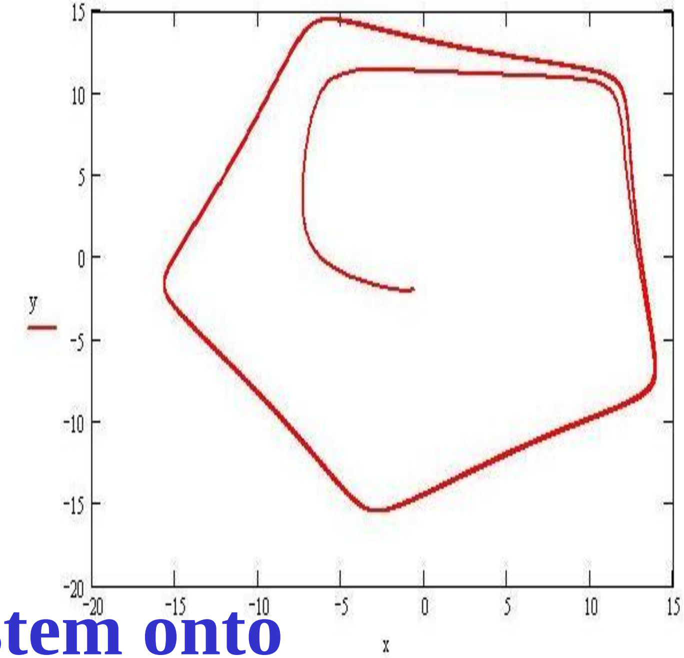
Below we demonstrate projections of trajectories of symmetric 5-D system

$$\frac{dx_i}{dt} = \frac{18}{1+x_{i-1}^3} - x_i, \ldots \quad i = 1,2,3,4,5; \quad S_0 = (2,2,2,2,2).$$

onto 2-D and 3-D planes.

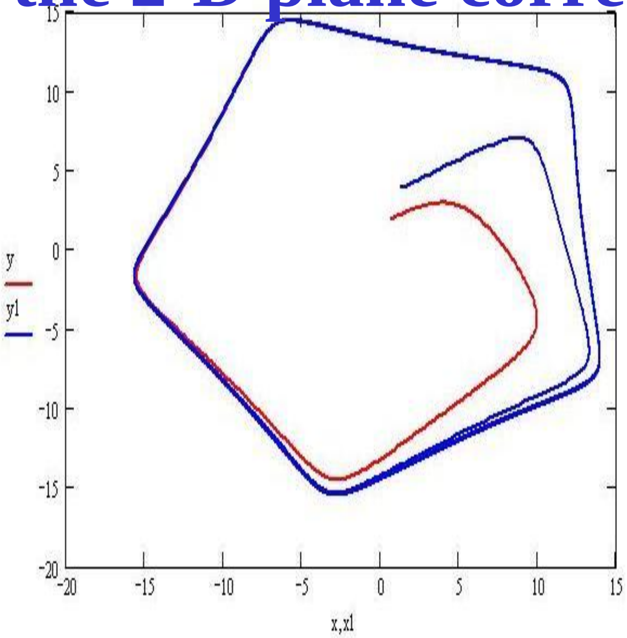
Theorem 1'. **If the dynamical system (2k+1) in the Th.1 is symmetric with respect to the cyclic permutation of the variables then the system has a cycle with corresponding symmetry.**

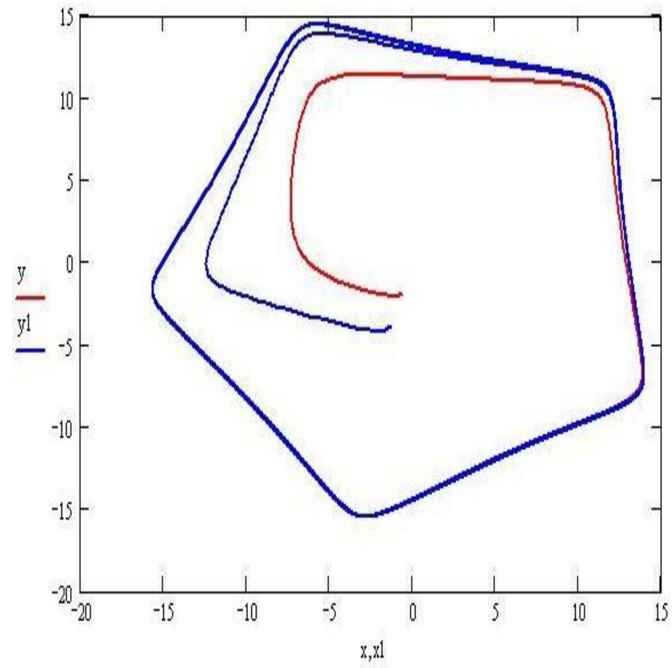




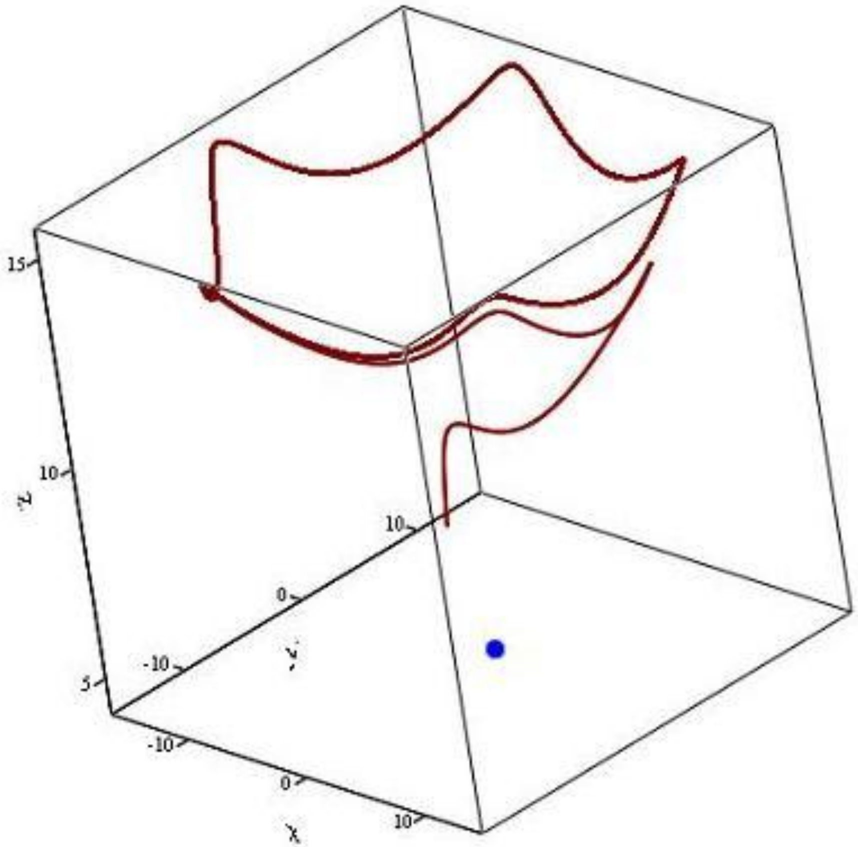
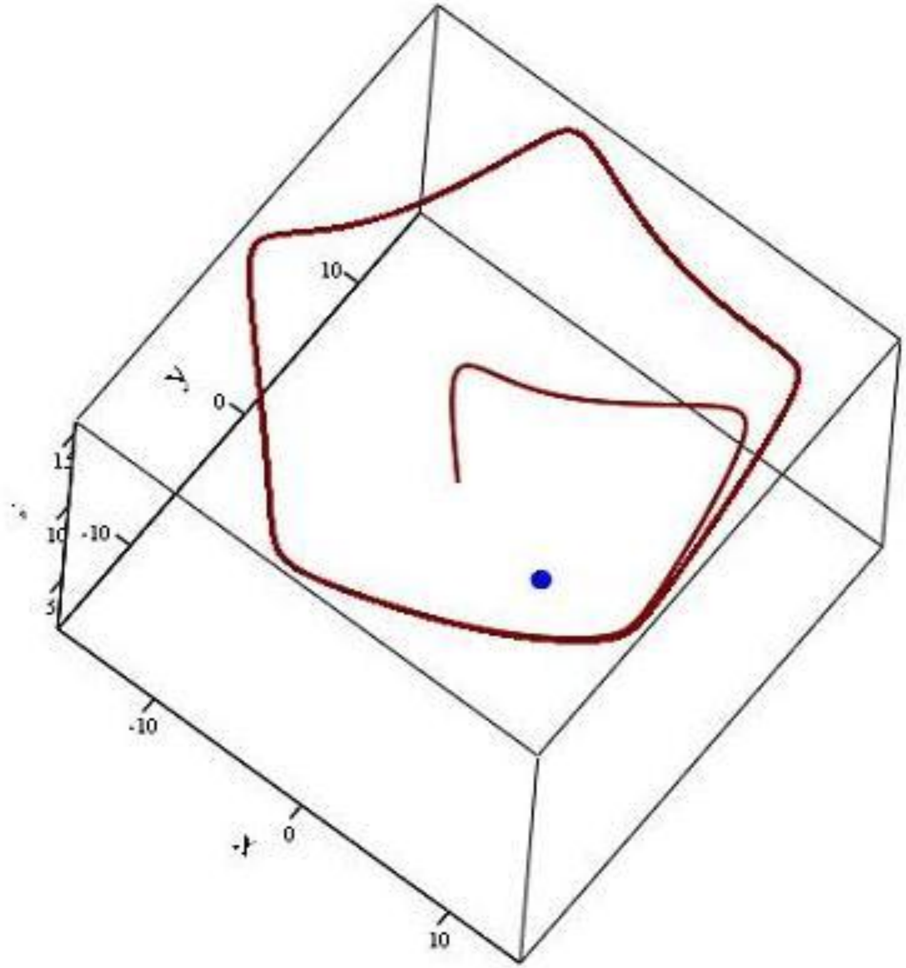
Projections of trajectories of 5-D system onto the 2-D plane corresponding to

$$\operatorname{Re}\lambda_4 = \operatorname{Re}\lambda_5 > 0.$$





Projections of trajectories of the 5-D system onto the 3-D plane corresponding to the eigenvalues with positive real parts and the negative eigenvalue $\lambda_1 < 0$ of the linearization matrix.

The blue spot shows the position of projection of the stationary point.

(x1,y1,z1),(rp1,rp2,rp3)

(x1,y1,z1),(rp1,rp2,rp3)

The characteristic polynomial of the linearization of the system (2k+1) at the stationary point S_0 has the form

$(1+\lambda)^{2k+1}+\Pi^{2k+1}=0.$ **Here** $-\Pi^{2k+1}$ **is the product of all derivatives** $\partial f_i/\partial x_{i-1}$ **at the point** S_0 **.**

We arrange the eigenvalues of this linearization according to the values of their real parts:

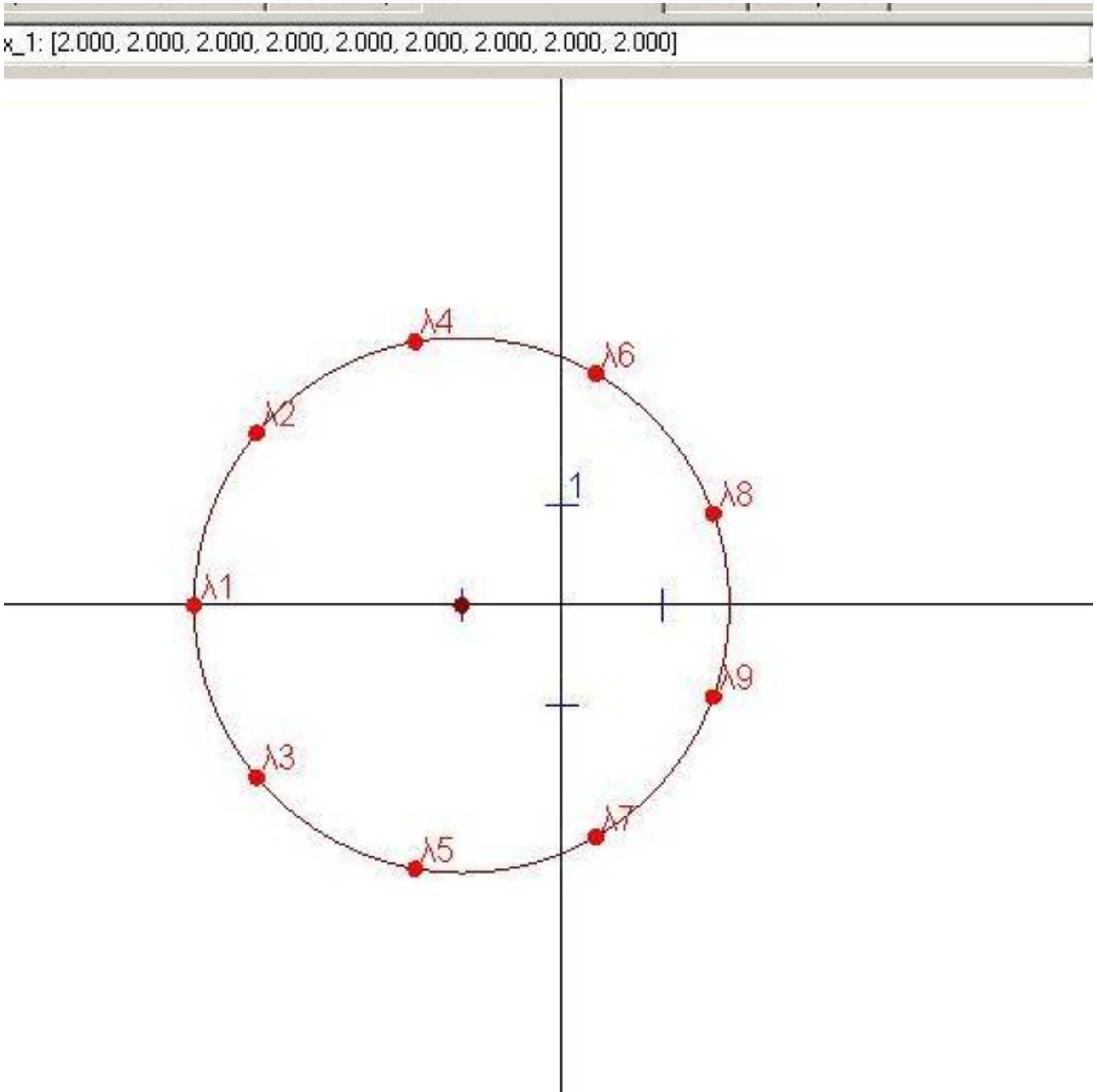
The eigenvalue λ_1 **is real and negative. So,**

$$\lambda_1<\operatorname{Re}\lambda_{2,3}<\operatorname{Re}\lambda_{4,5}<\ldots\operatorname{Re}\lambda_{2k,2k+1}.$$

If the point S_0 **is hyperbolic then none of these real parts vanishes.**

If *k*=2 then $\lambda_1<\operatorname{Re}\lambda_{2,3}<0.$

Eigenvalues of one 9-D symmetric dynamical system

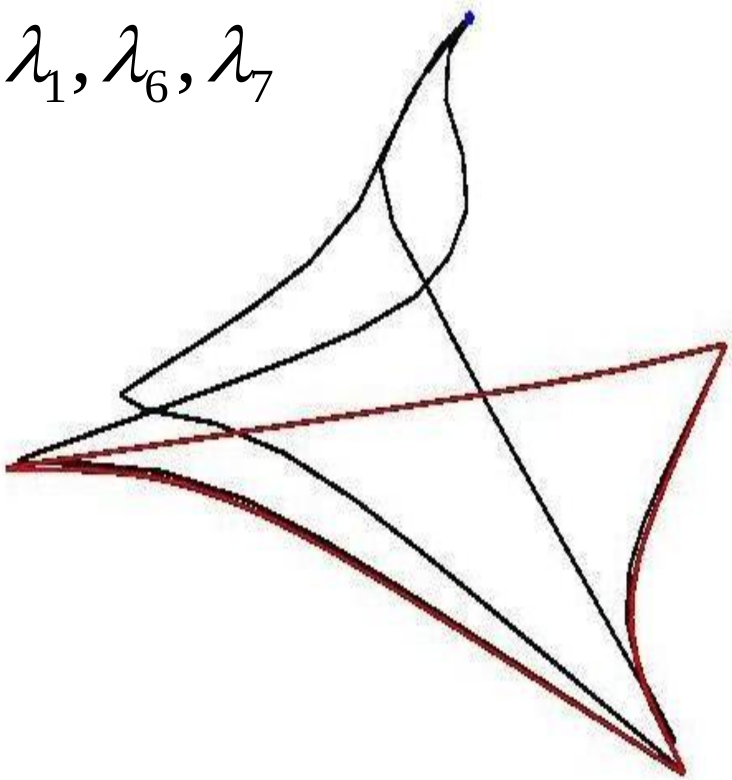


Trajectories of 9-D symmetric system

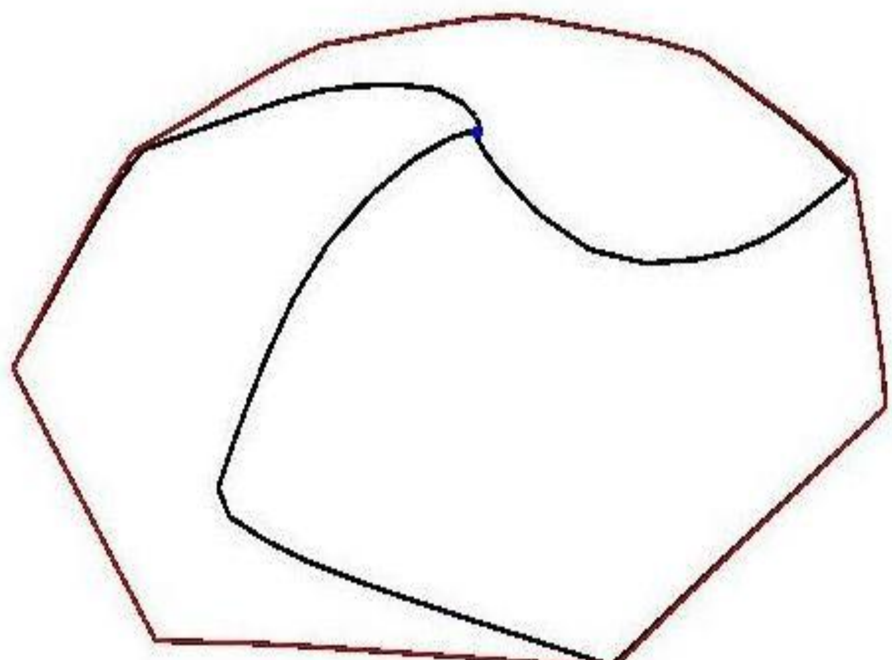
$$\frac{dx_i}{dt} = \frac{130}{1+x_{i-1}^6} - x_i, \ldots$$

projected onto 3D-planes corresponding to different eigenvectors of the linearization of this system near the stationary point. The trajectories are contained in (*D*).

$\lambda_1, \lambda_6, \lambda_7$



$\lambda_1, \lambda_8, \lambda_9$



Similar results can be obtained for the systems of the types

$$\frac{dx_1}{dt} = f_1(x_3) - g(x_1)\ , \quad \frac{dx_2}{dt} = f_2(x_1) - g(x_2),$$

$$\frac{dx_i}{dt} = F_i(x_{i-1}, x_i), \qquad \frac{\partial F_i}{\partial x_i} < 0, \quad \frac{\partial F_i}{\partial x_{i-1}} < 0,$$

etc.

M.Hirsch (1987).

2. Stability questions.

$$\frac{dX}{dt} = A \cdot X + \Psi(X); \qquad \textbf{(VM)}$$

$$A = \begin{pmatrix} -1 & 0 & -\eta \\ -\eta & -1 & 0 \\ 0 & -\eta & -1 \end{pmatrix}; \qquad \Psi(X) = \begin{pmatrix} \eta \cdot z + f_1(z) \\ \eta \cdot x + f_2(x) \\ \eta \cdot y + f_3(y) \end{pmatrix}.$$

$\eta > 0.$

The eigenvalues of *A* can be expressed explicitly:

$$\lambda_1(A) = -1 - \eta; \operatorname{Re} \lambda_{2j,2j+1}(A) = \ldots$$

The transfer matrix

$$\chi(i\omega-1+\nu) := ((i\omega-1+\nu)E-A)^{-1},$$

$$\mu(\nu) = \sup_{\omega} |\chi(i\omega-1+\nu)|.$$

Let $\Psi'(X)$ **be the Jacobi matrix of** $\Psi(X)$,

and let $|\Psi'_X| = \max_i \sup_X (|4\eta + f_i'|)$

$i = 1,2,\ldots$ **be its norm.**

Russel Smith has shown that *if* $|\Psi'_X| < (\mu(\nu))^{-1}$

then the system* (VM) *has a stable cycle (1987).

Actually, he notes that this is not a sharp estimate!!

Theorem 2. **If the system (2k+1) satisfies the conditions of the theorem 1 and**

$$|\eta + f_i'(x_{i-1})| < \eta \cdot \sin\frac{2\pi}{2k+1} \cdot \sin\frac{\pi}{2k+1}$$

for some positive η **then the invariant domain** Q' **contains a stable cycle of this system.**

$$-\eta(1+\sin 2\varphi \cdot \sin\varphi) < f_i' < -\eta(1-\sin 2\varphi \cdot \sin\varphi).$$

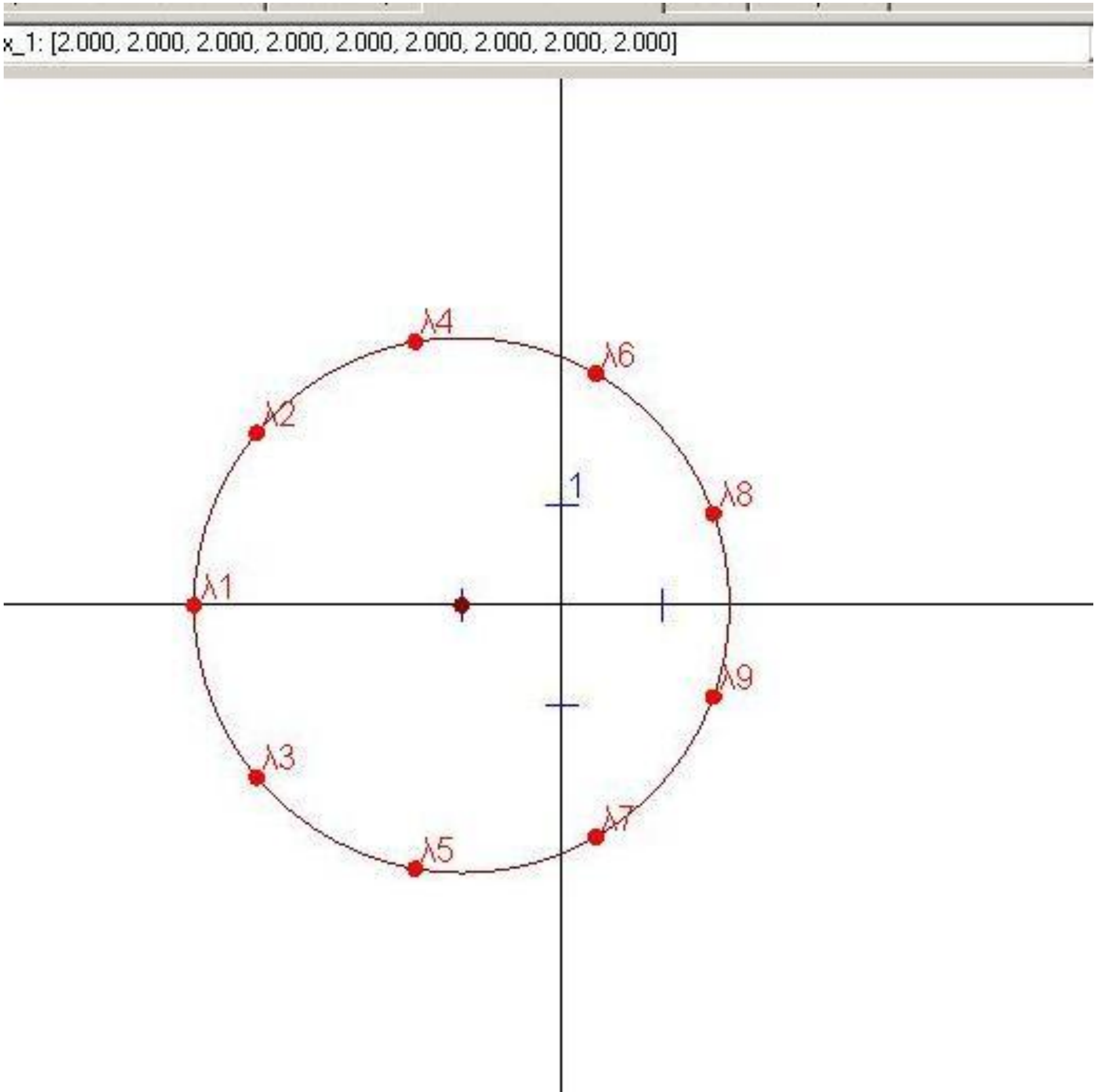
3. Nonuniqueness of cycles in the system (2k+1).

According to the Grobman-Hartmann theorem, each nonlinear dynamical system can be linearized in some neighborhood *W* of its hyperbolic point.

Consider in *W* 2-D planes *corresponding to pairs of the eigenvalues with positive real parts*.
These planes are composed by unwinding trajectories of the dynamical system (2k+1).

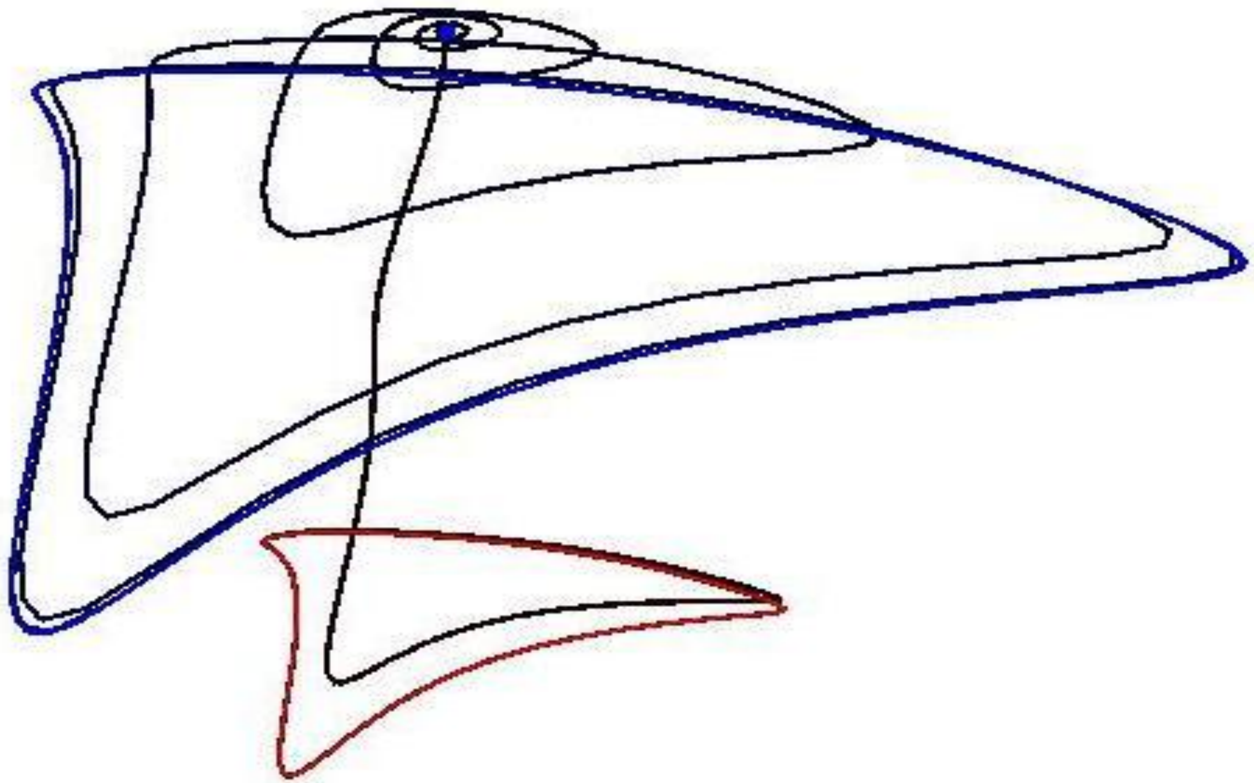
Hypothesis 1: Outside of W different 2-D planes generate different (??) cycles.

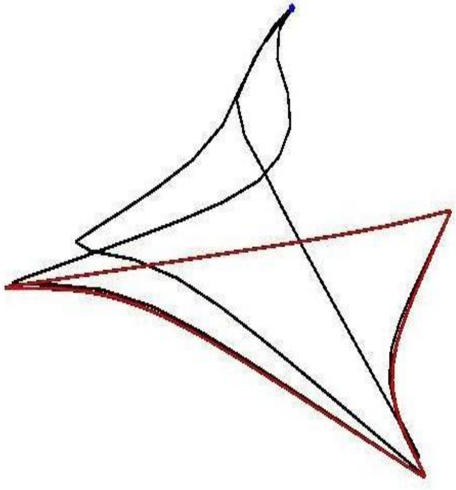
Eigenvalues of one 9-D symmetric dynamical system



Projections of two different cycles of 9-D symmetric system onto 3-D plane $\lambda_1, \lambda_6, \lambda_7$. The second cycle is not contained in (*D*).

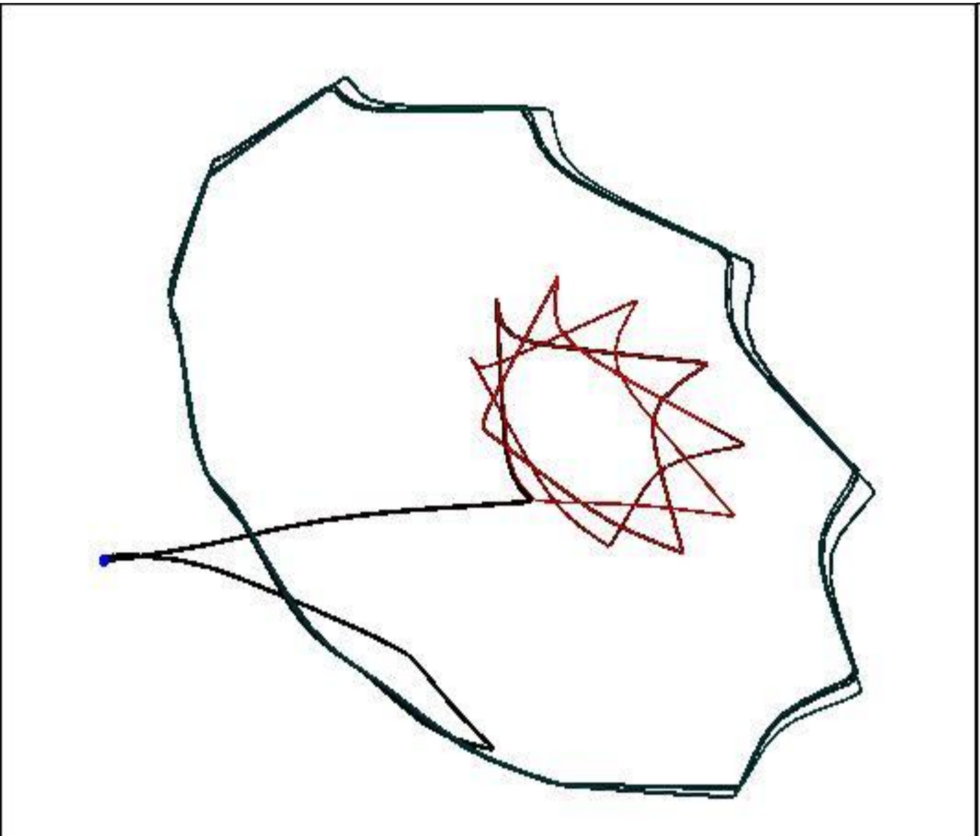
The stationary point is at the top of the picture.

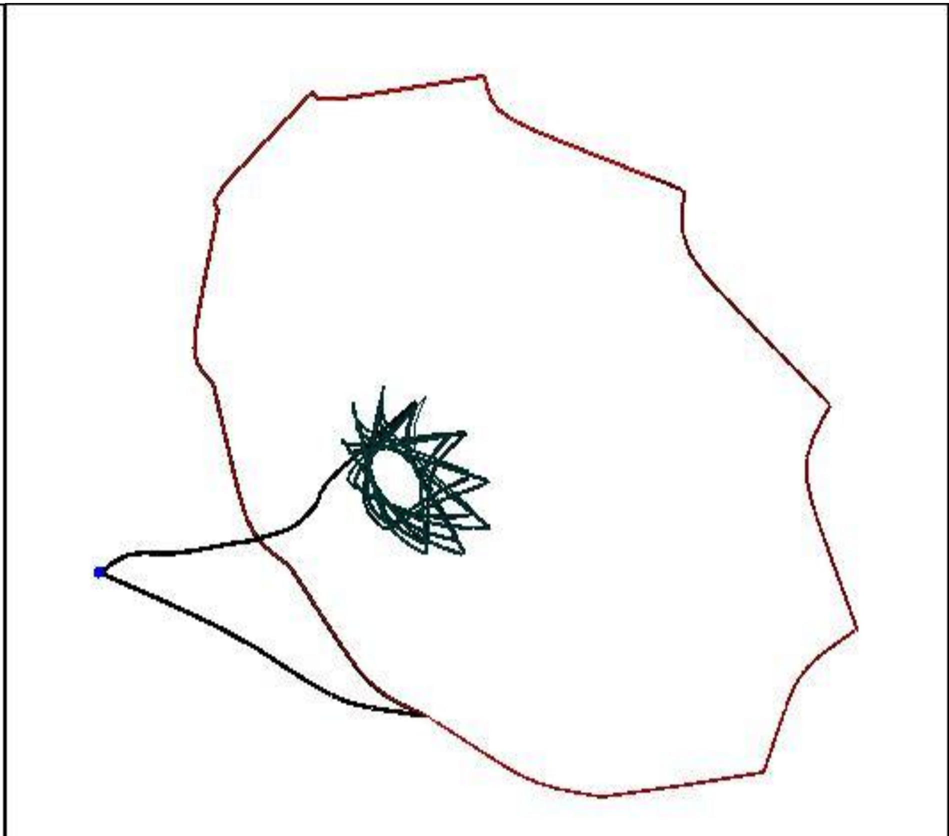




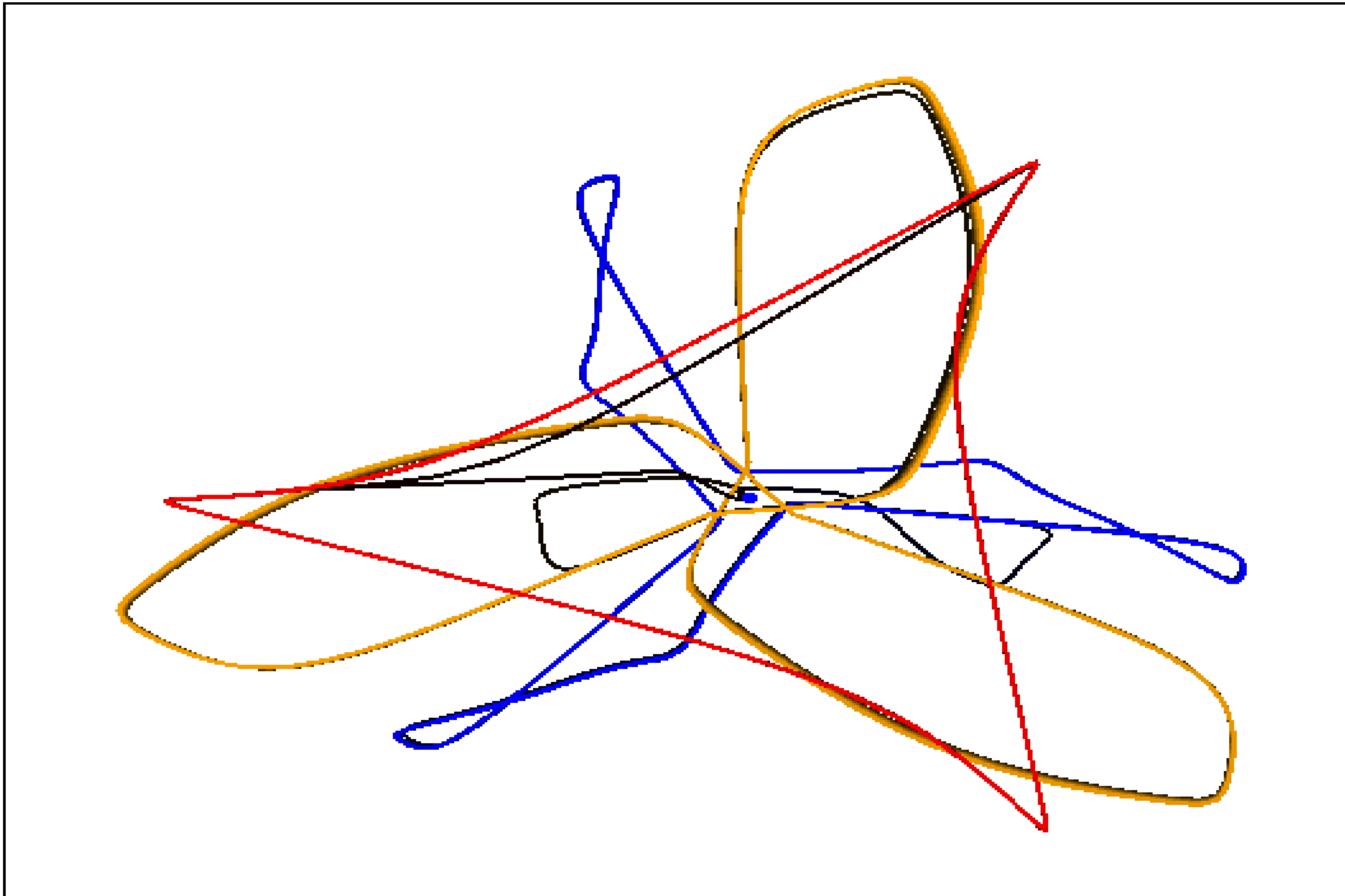
Projections of two different cycles of 11-D symmetric system onto two different 3-D planes

$\lambda_1, \lambda_8, \lambda_9$ left; $\lambda_1, \lambda_{10}, \lambda_{11}$ right.

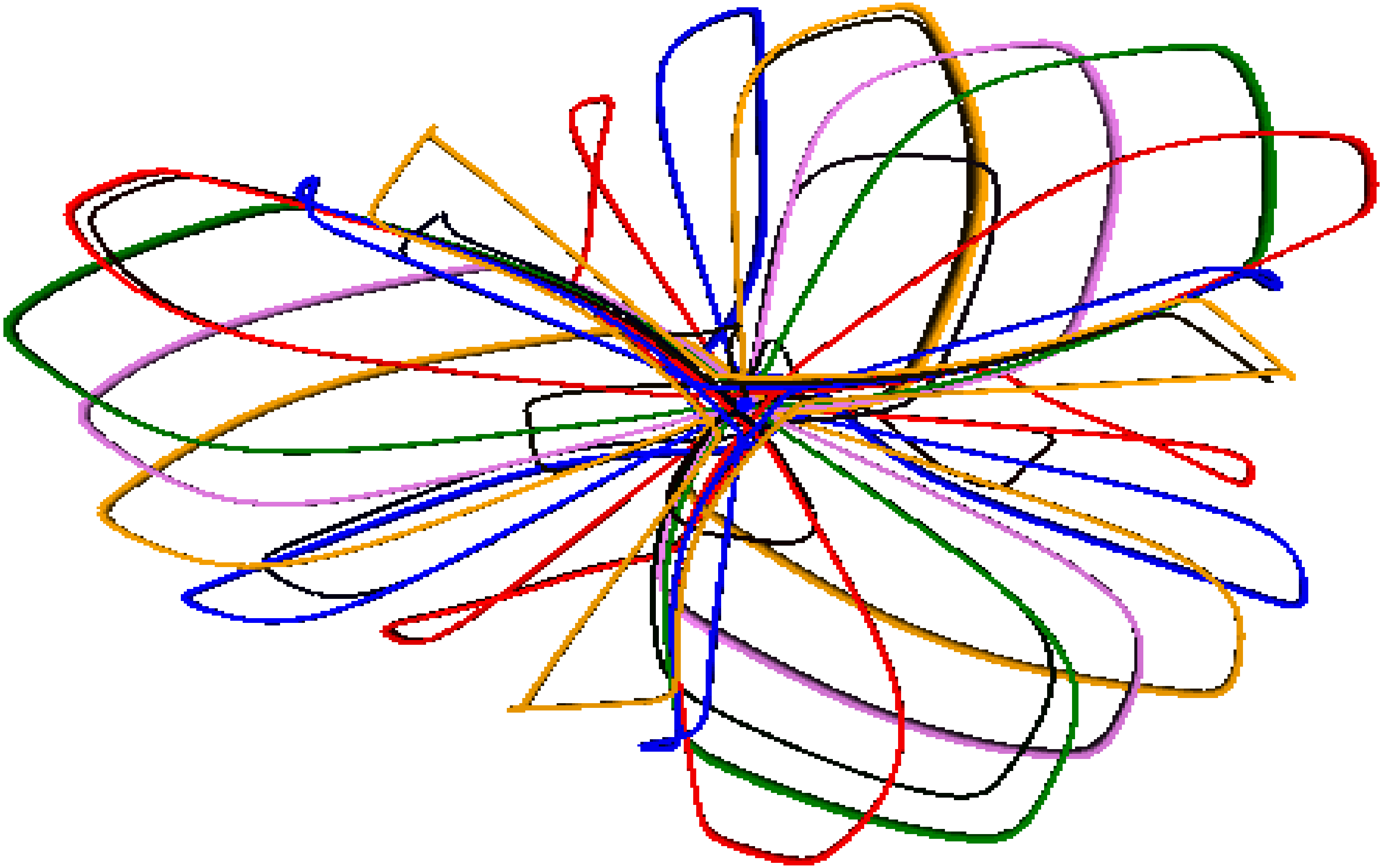




Projections of 3 cycles of 15-dimensional system onto the plane $\lambda_{10}, \lambda_{11}$.



Same system and plane, 5 cycles.
Hypothesis 2: Continuum of cycles???



4. Model of 3-D gene network regulated by a simple combination of negative and positive feedbacks.

system **(ffΛ):**

$$\frac{dx_1}{dt} = f_1(x_3) - x_1 \ ; \quad \frac{dx_2}{dt} = f_2(x_1) - x_2 \ ; \quad \frac{dx_3}{dt} = \Lambda_3(x_2) - x_3$$

$f_1(x_3),\ f_2(x_1) : [0,\infty) \to (0,\infty)$, **Smooth monotonically decreasing** $f_i(u) \to 0$ **for** $u \to \infty$.

$$\Lambda_3(x_2) = \frac{a x_2}{1 + x_2^m}$$

or more general unimodal function.

Let $\Lambda_3(y_M)$ **be the maximal value of** $z = \Lambda_3(y)$ **and** $z = \varphi(y)$ **is the inverse function to** $y = f_2(f_1(z))$.

***Lemma 1*. Let** $\varphi(f_2(0)) > \Lambda_3(f_2(0))$,

and either $f_2(f_1(0)) > y_M$,

or $f_2(f_1(0)) < y_M$, $\varphi(y) < \Lambda_3(y)$ **for** $0 \le y \le y_M$.

Then the system (ffΛ) has exactly one stationary point $S_0(x_0, y_0, z_0)$ **in the positive octant.**

Let $x_A,\ y_A, z_A$ **be defined by** $z_0 = \Lambda_3(y_A)$,

$$y_A < y_M < y_0\,,\ z_A = \varphi(y_A),\ x_A = f_1(\varphi(y_A)).$$

Linearization of system (1) at this point $S_0(x_0, y_{0,} z_0)$ **is described by the matrix with one negative eigenvalue.**

Its other eigenvalues λ_2, λ_3 **are complex.**

Consider the case

$$\operatorname{Re}\lambda_2 = \operatorname{Re}\lambda_3 > 0. \qquad \textbf{(+)}$$

Theorem "1". **If the condition (+) is satisfied then the system (ffΛ): has at least one periodic trajectory.**

The proof is based on existence of an invariant domain of the system (ffΛ). This is the parallelepiped $Q = [0, x_A] \times [y_A, f_2(0)] \times [z_A, \Lambda_3(y_M)].$

Actually, one can construct essentially smaller invariant domain (see below).
Now, existence of periodic trajectories follows from the Brower fixed point theorem, as usual.

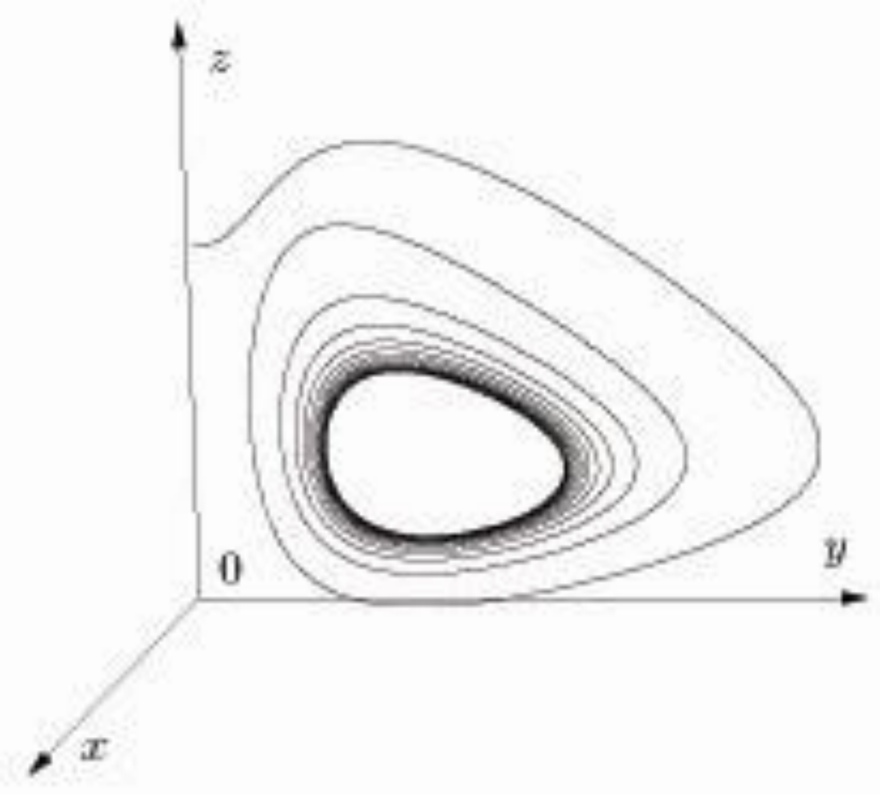
Recall that $z_0 = \Lambda_3(y_A),$

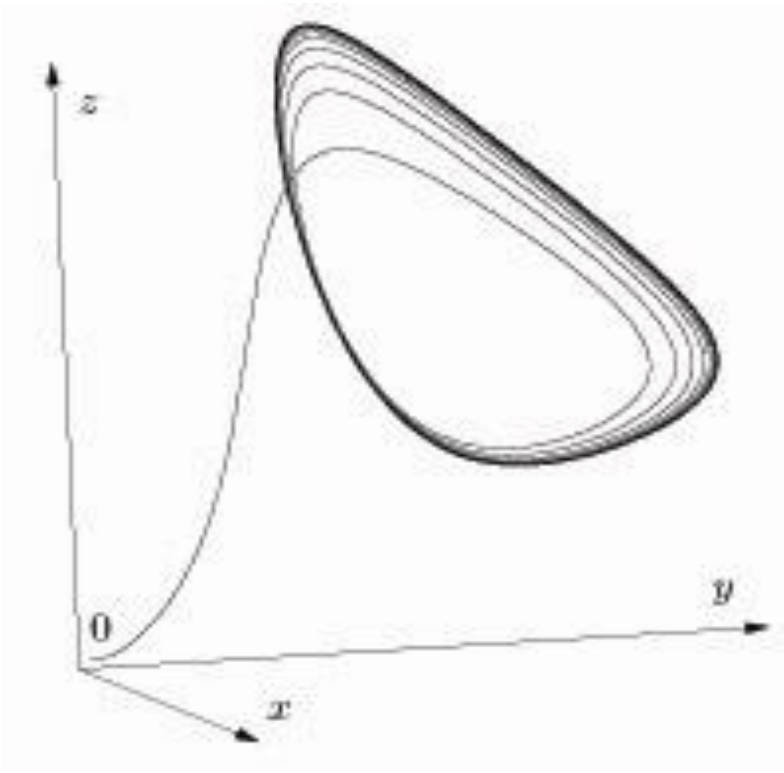
$$y_A < y_M < y_0\,,\; z_A = \varphi(y_A),\; x_A = f_1(\varphi(y_A)).$$

Trajectories of the system (ffΛ)

right: $f_1(z) = \dfrac{10}{1+z^3}$, $f_2(x) = 10 \cdot e^{-0.135x^2}$, $\Lambda_3(y) = \dfrac{17y}{1+y^3}$.

left: $f_1(w) = f_2(w) = \dfrac{10}{1+z^3}$, $\Lambda_3(y) = \dfrac{17y}{1+y^3}$.





5. More complicated gene networks models regulated by *combinations* of positive and negative feedbacks.

system **(fΛΛ):**

$$\frac{dx_1}{dt} = f_1(x_3) - x_1; \quad \frac{dx_2}{dt} = \Lambda_2(x_1) - x_2; \quad \frac{dx_3}{dt} = \Lambda_3(x_2) - x_3;$$

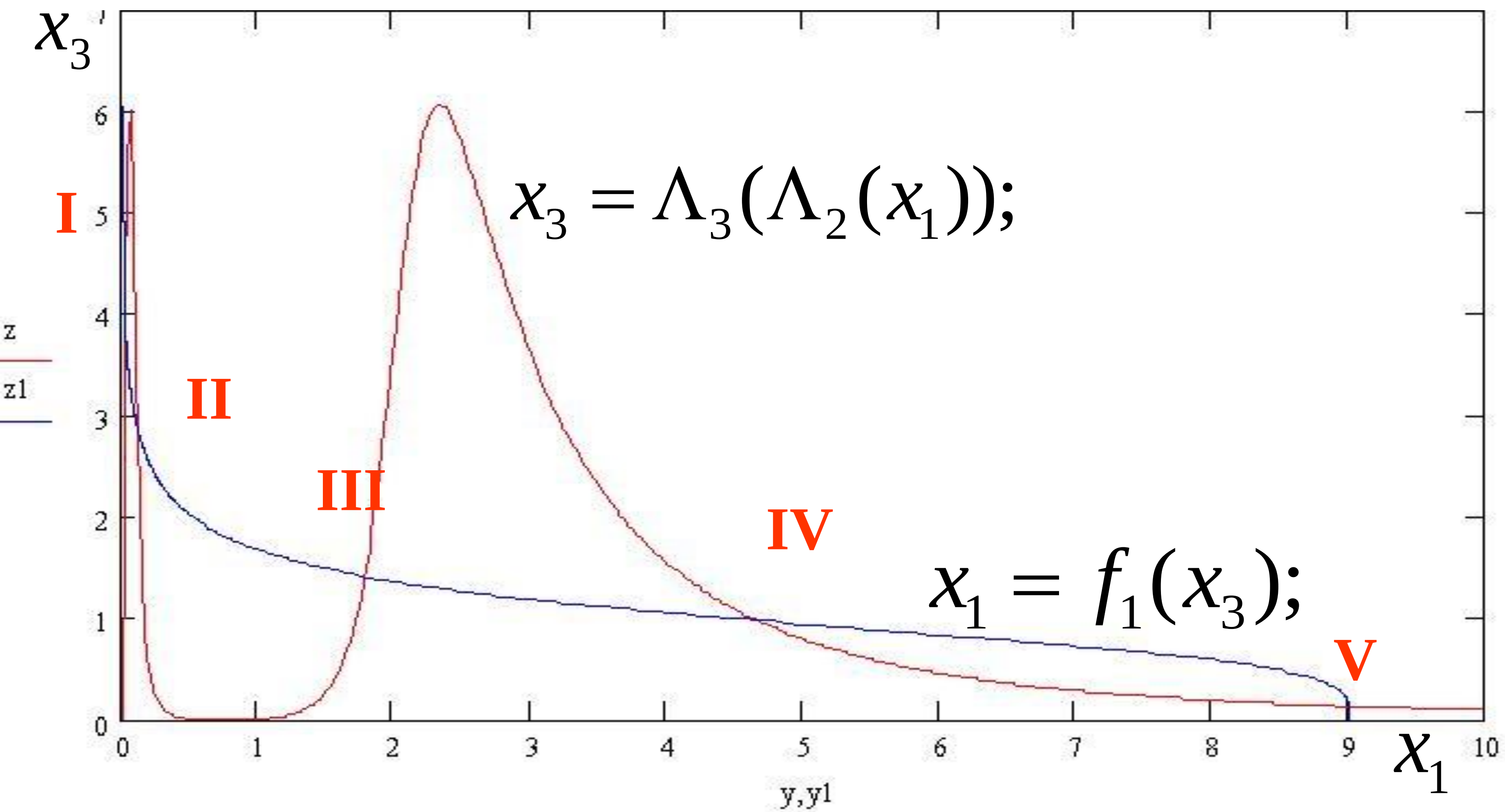
$$f_i(x_{i-1}) : [0,\infty) \to (0,\infty), \quad f_i(u) \to 0 \text{ **for** } u \to \infty.$$

$$\Lambda_j(w) = \frac{a_j w}{1 + w^{m_j}};$$

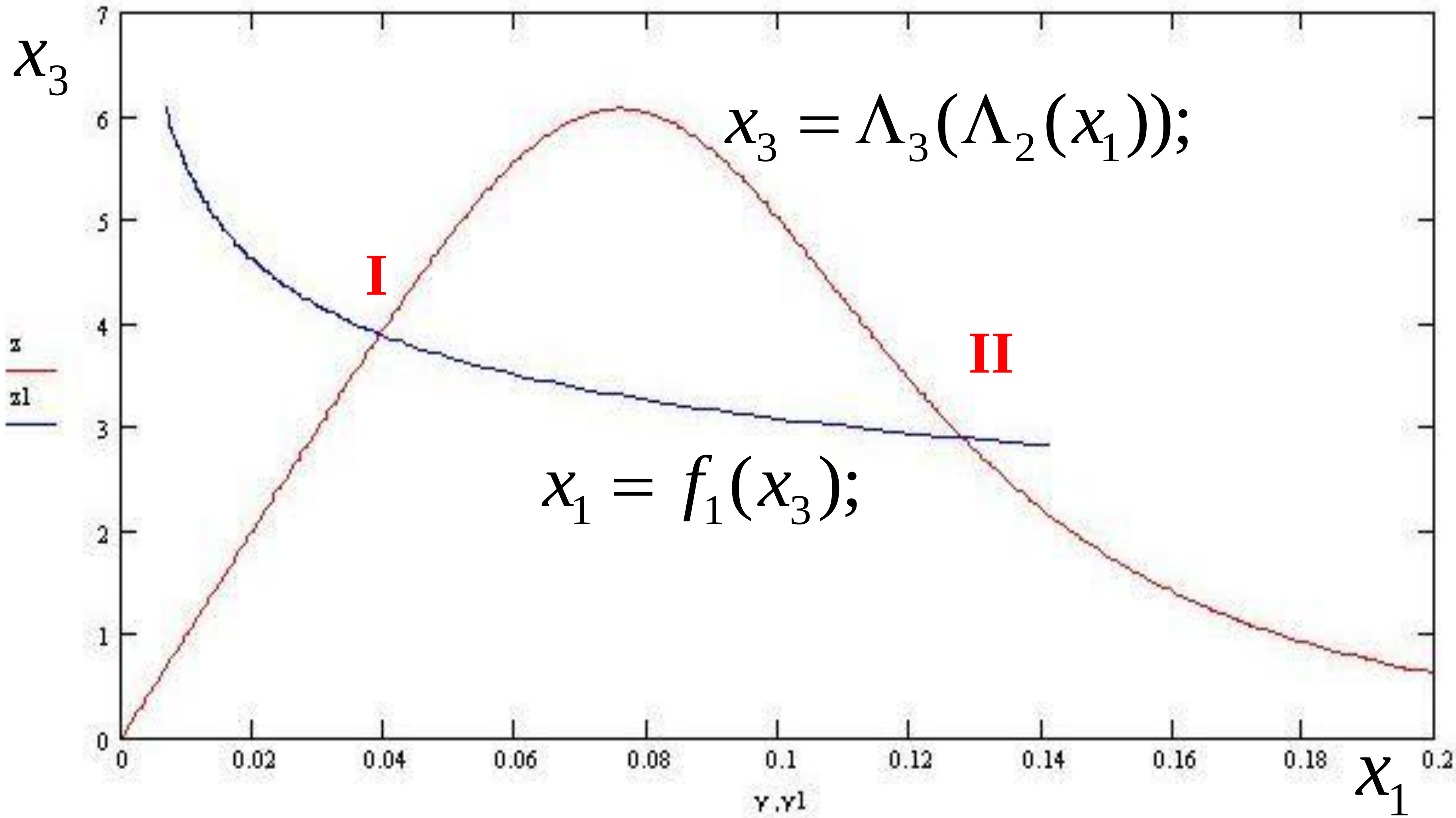
or other unimodal functions.

Stationary points of the system (fΛΛ).

$$f_1(x_3) = \frac{9}{1+x_3^4}; \quad \Lambda_2(x_1) = \frac{10x_1}{1+x_1^4}; \quad \Lambda_3(x_2) = \frac{10x_2}{1+x_2^5}.$$



Stationary points I and II of the system (fΛΛ):

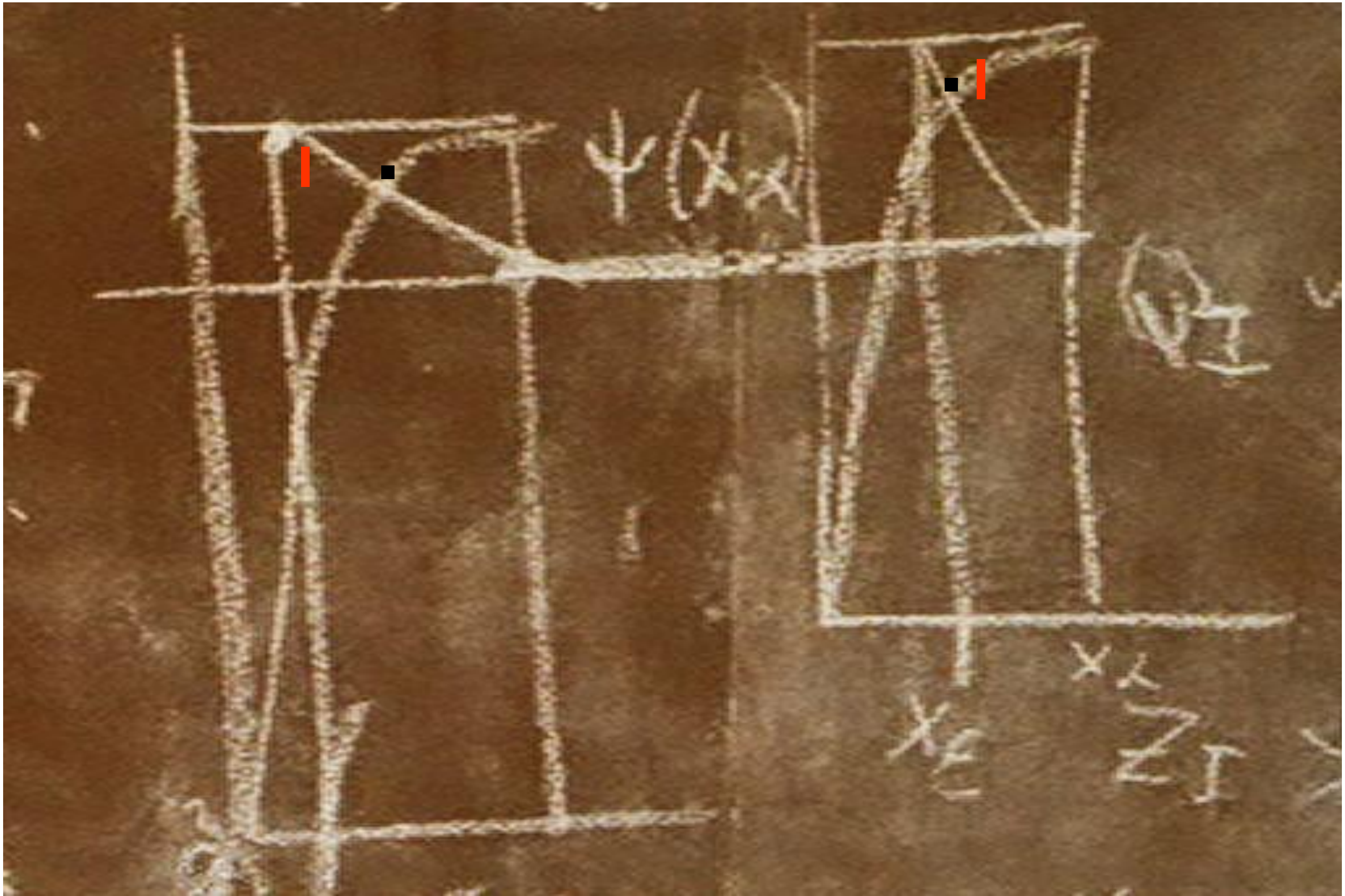


Analogs of the theorems 1 and 2 about existence of a cycle and existence of a stable cycle hold in the neighborhoods of the stationary points I and III.

The stationary point V is stable.

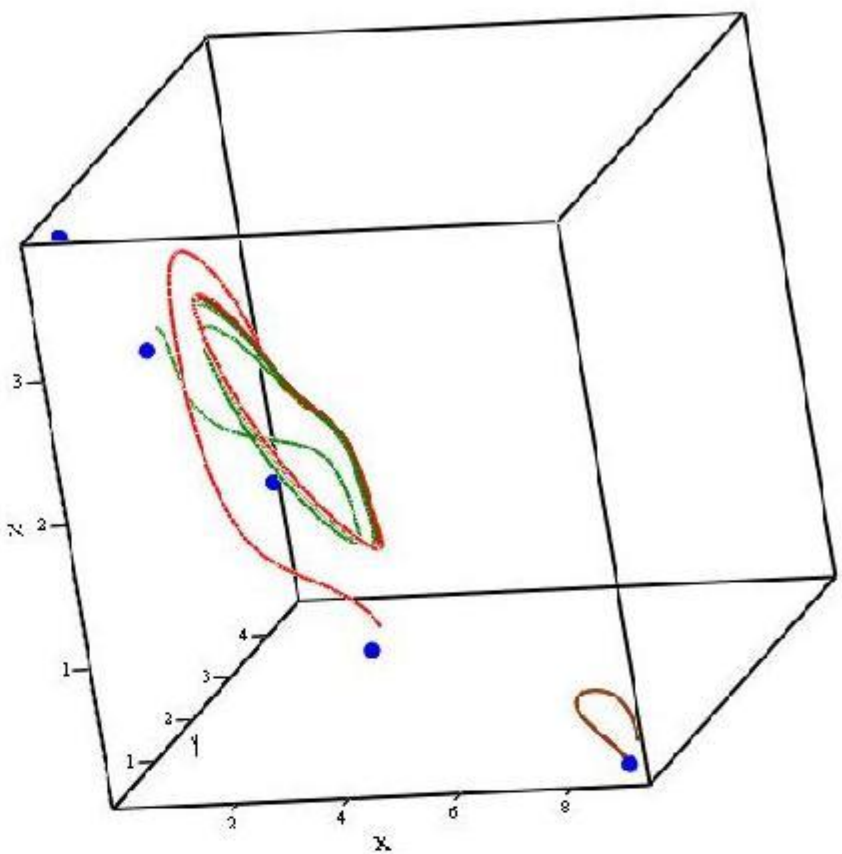
The stationary points II and IV have topological index +1.

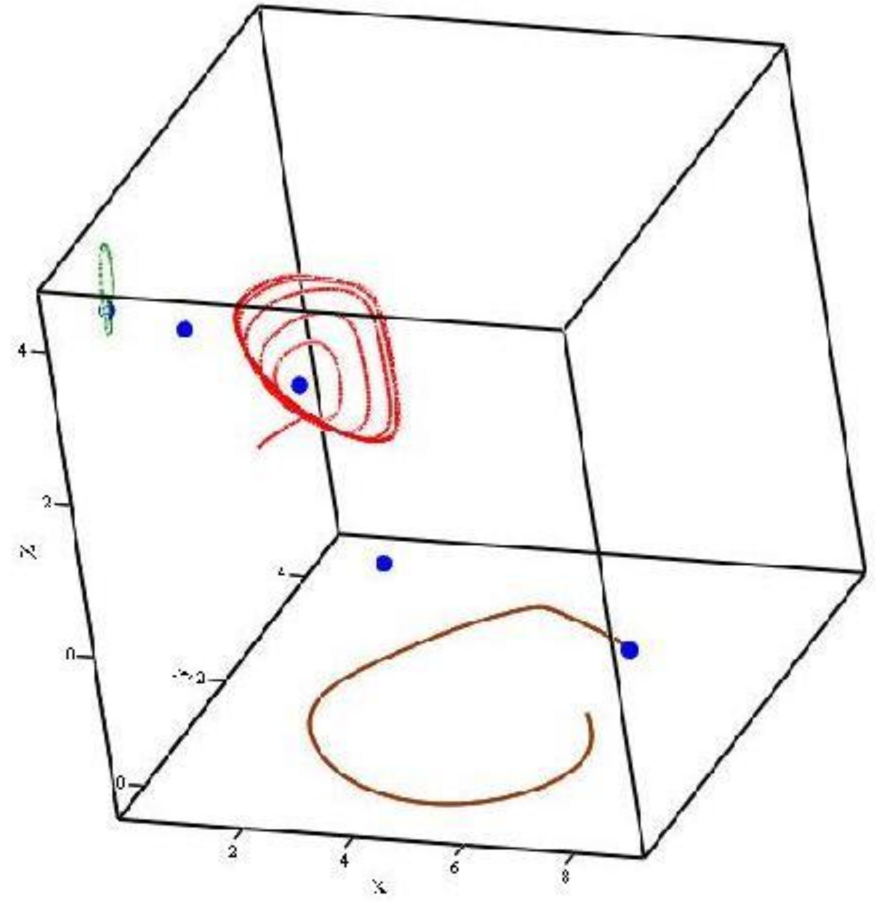
Two variants of constructions of invariant neighborhood of the stationary point I of the system (fΛΛ):



Stationary points and cycles of the system (fΛΛ):

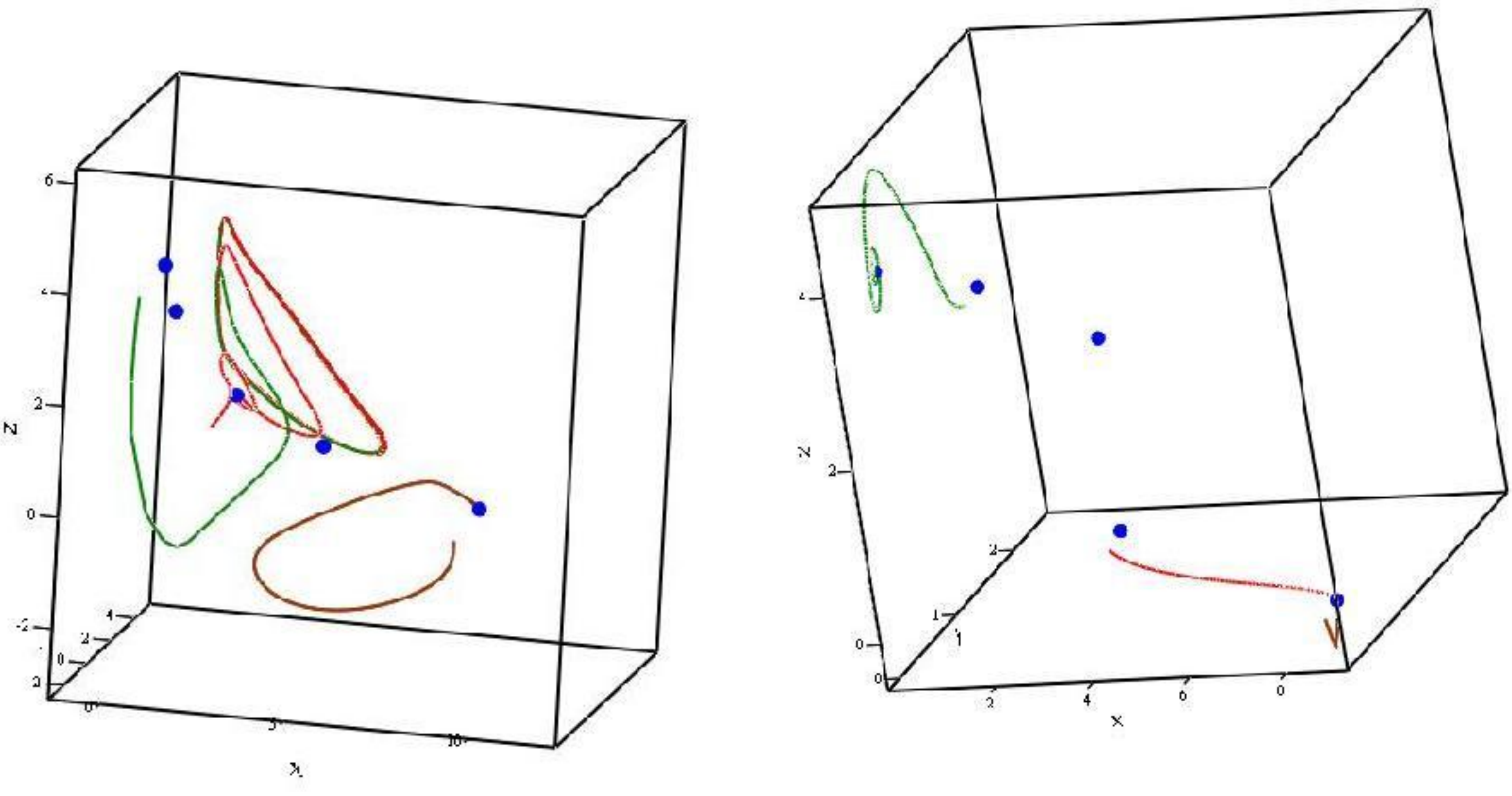
$$f_1(x_3)=\frac{9}{1+x_3^4};\quad \Lambda_2(x_1)=\frac{10x_1}{1+x_1^4};\quad \Lambda_3(x_2)=\frac{10x_2}{1+x_2^3}.$$





u1,u2,u3),(rp1,rp2,rp3),(u11,u12,u13),(u21,u22,u23)

Stationary points and cycles of the system (fΛΛ) (same parameters, other trajectories).



(u1,u2,u3),(rp1,rp2,rp3),(u11,u12,u13),(u21,u22,u23)

5. Glass-Mackey-type systems.

$$\frac{dx_1}{dt} = \Lambda_1(x_3) - x_1; \quad \frac{dx_2}{dt} = \Lambda_2(x_1) - x_2; \quad \frac{dx_3}{dt} = \Lambda_3(x_2) - x_3.$$

$$\Lambda(w) = aw^m \exp(-bw)$$ **Ricker function.**

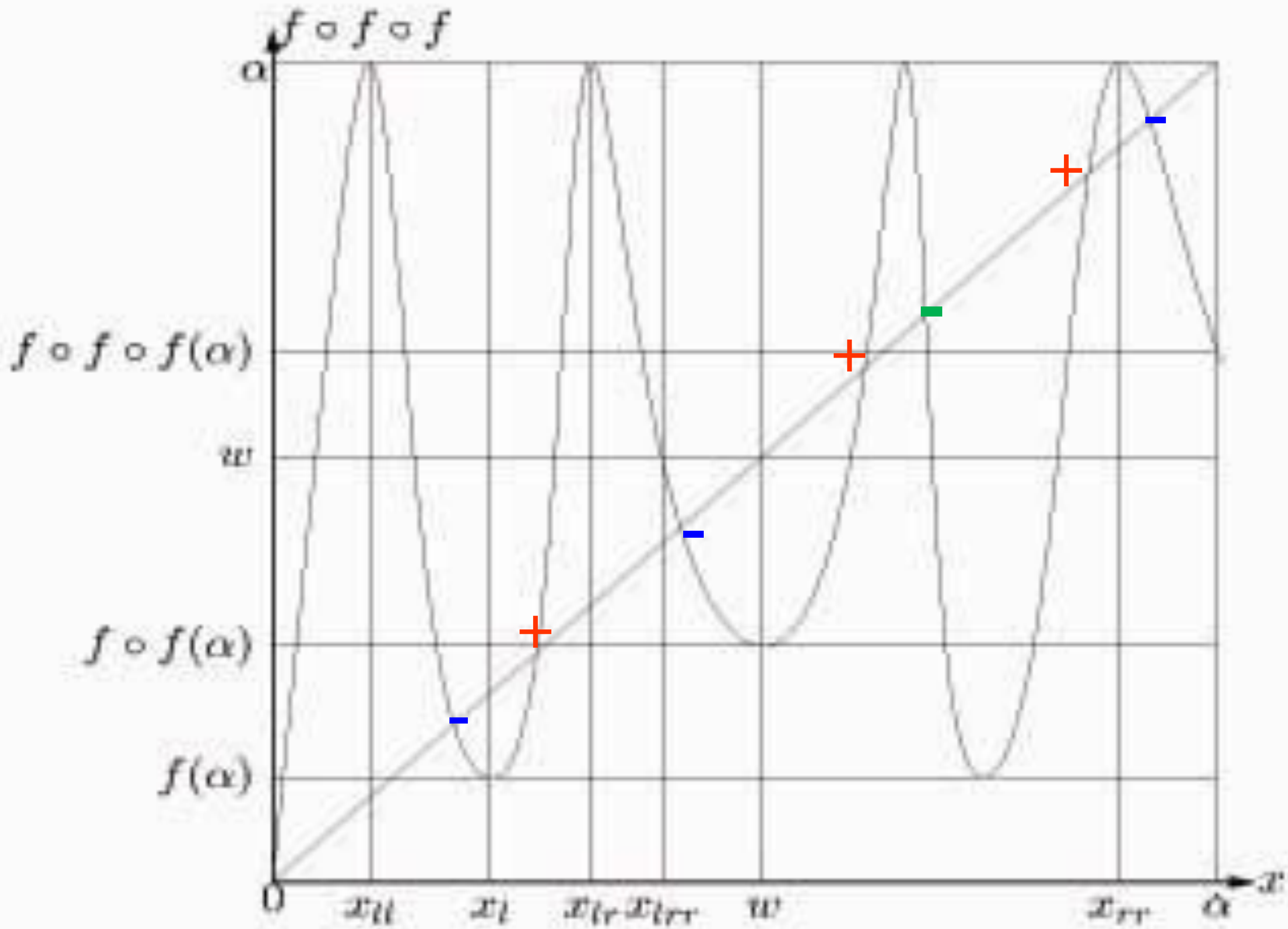
$$\Lambda(w) = \frac{\alpha \cdot w}{1 + w^\gamma}$$ **Glass-Mackey function.** (GM)

$$\Lambda(w) = r \cdot w \cdot (\alpha - w)$$ **Logistic function.** (L)

$$\Lambda_{m,q}(w)=\begin{cases} m\cdot w\ ;\ w\in[0,\alpha/m], \\ 2\alpha-m\cdot w\ ;\ w\in[\alpha/m,(2\alpha-q)/m], \\ q;\ \ (2\alpha-q)/m\le w. \end{cases} \qquad (\Lambda)$$

Each of the systems listed here has exactly 7 stationary points in some invariant domain If the parameters of the system are sufficiently large.

The origin is also stationary point of each of these systems, but it does not seem to be so interesting.



Positions of the stationary points of the Glass-Mackey system (GM).

Topological indices of the stationary points

Topological indices of the points marked by "+"

equal +1, their Conley indices are : $h(+) = S^1$.

Topological indices of the points marked by "-"

equal -1, their Conley indices are : $h(-) = S^2$.

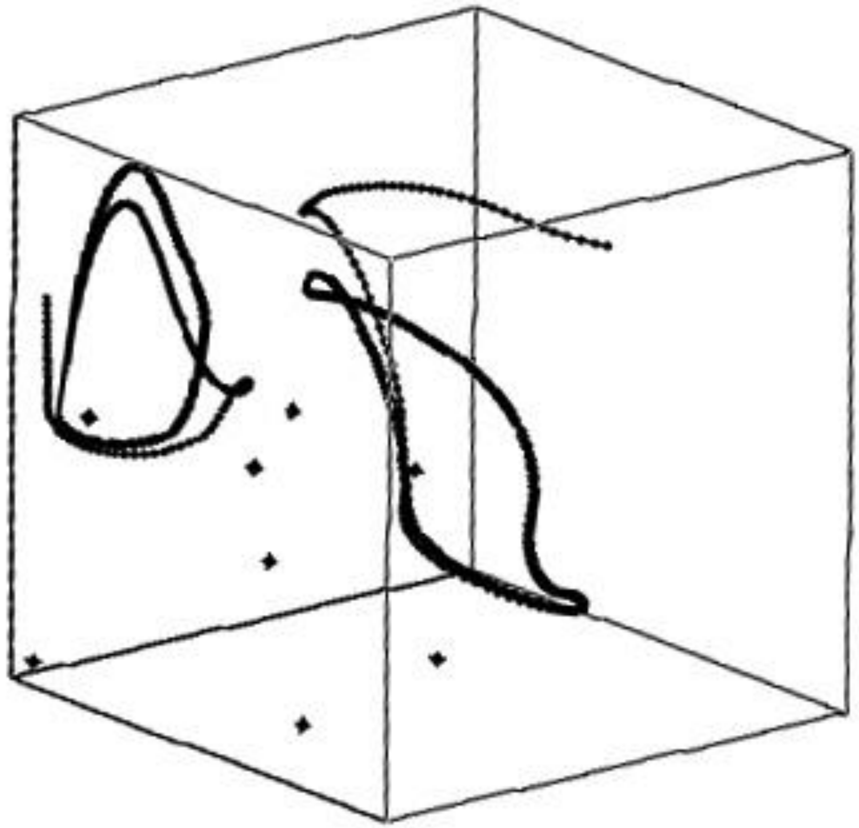
The cycles of the Glass-Mackey type systems do appear near the stationary points with negative indices.

For the stationary point marked by green minus, we have proved analogs of the theorems 1 and 2 about existence of a (stable) cycle.

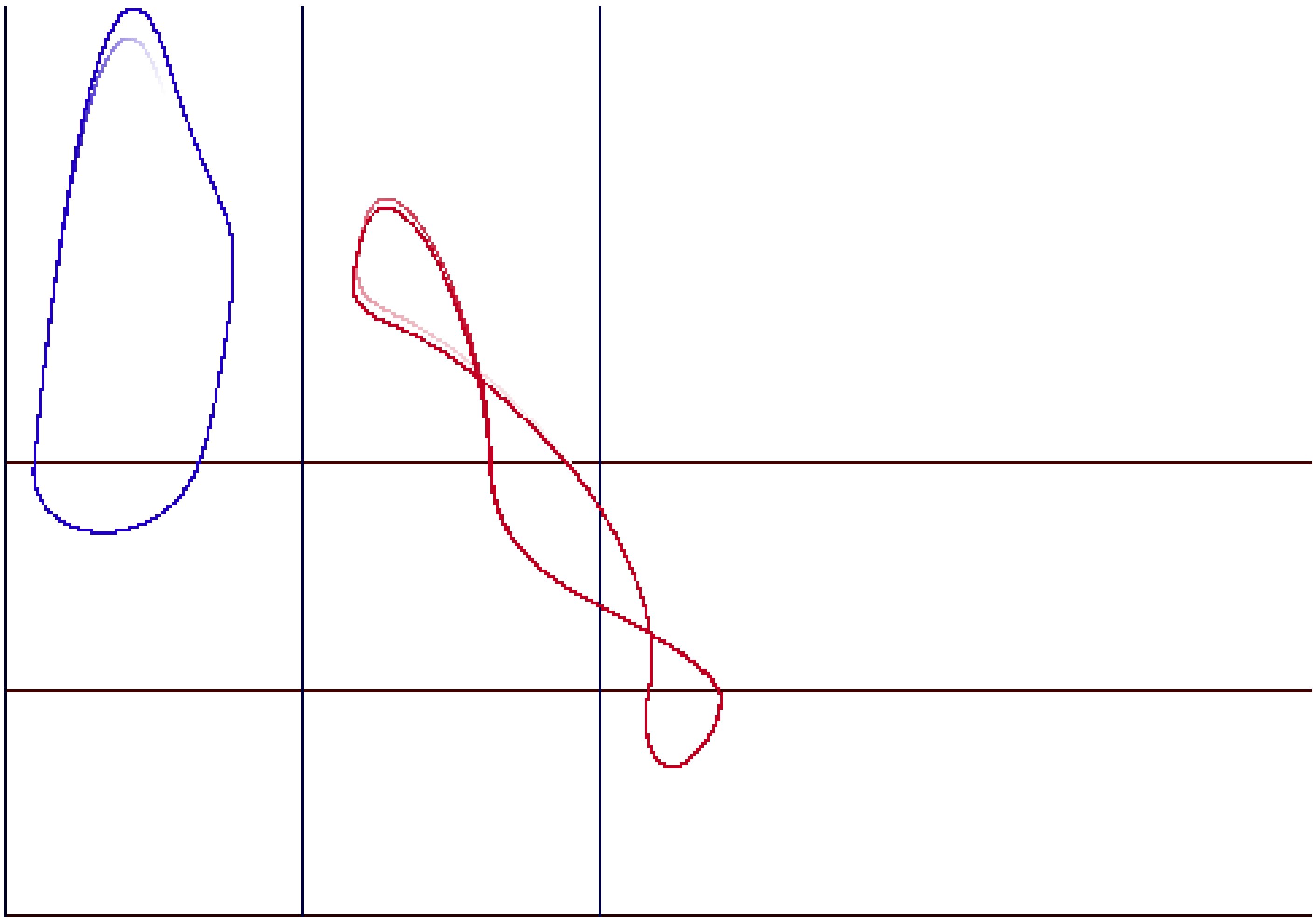
Numerical experiments show existence of cycles near the 1-st, 3-d and the 7-th stationary points marked by blue minuses.

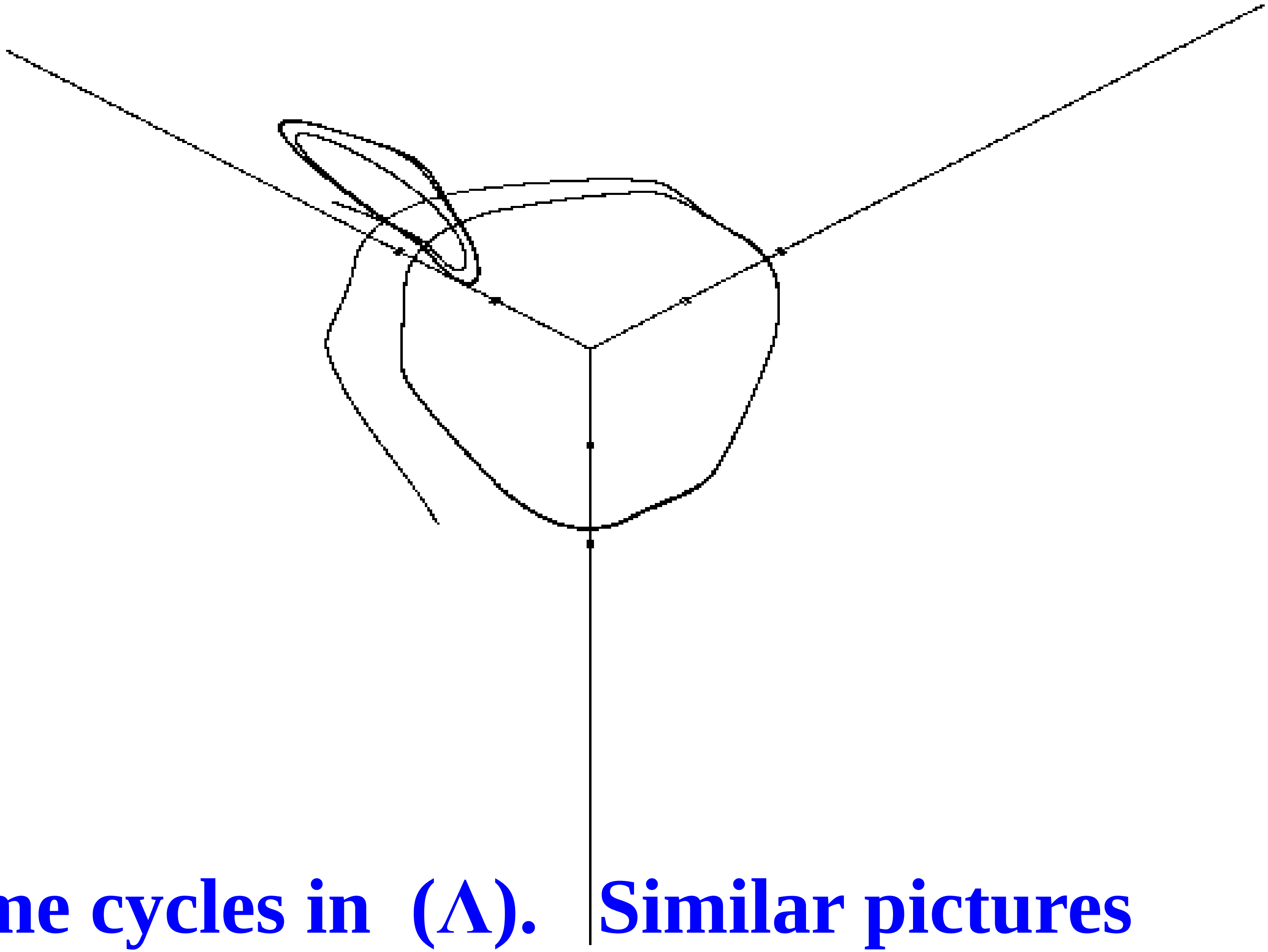
Cycles $C_\Delta(V), C_Z(VII)$ of the system (Λ).

α =10, m=5, q=0.



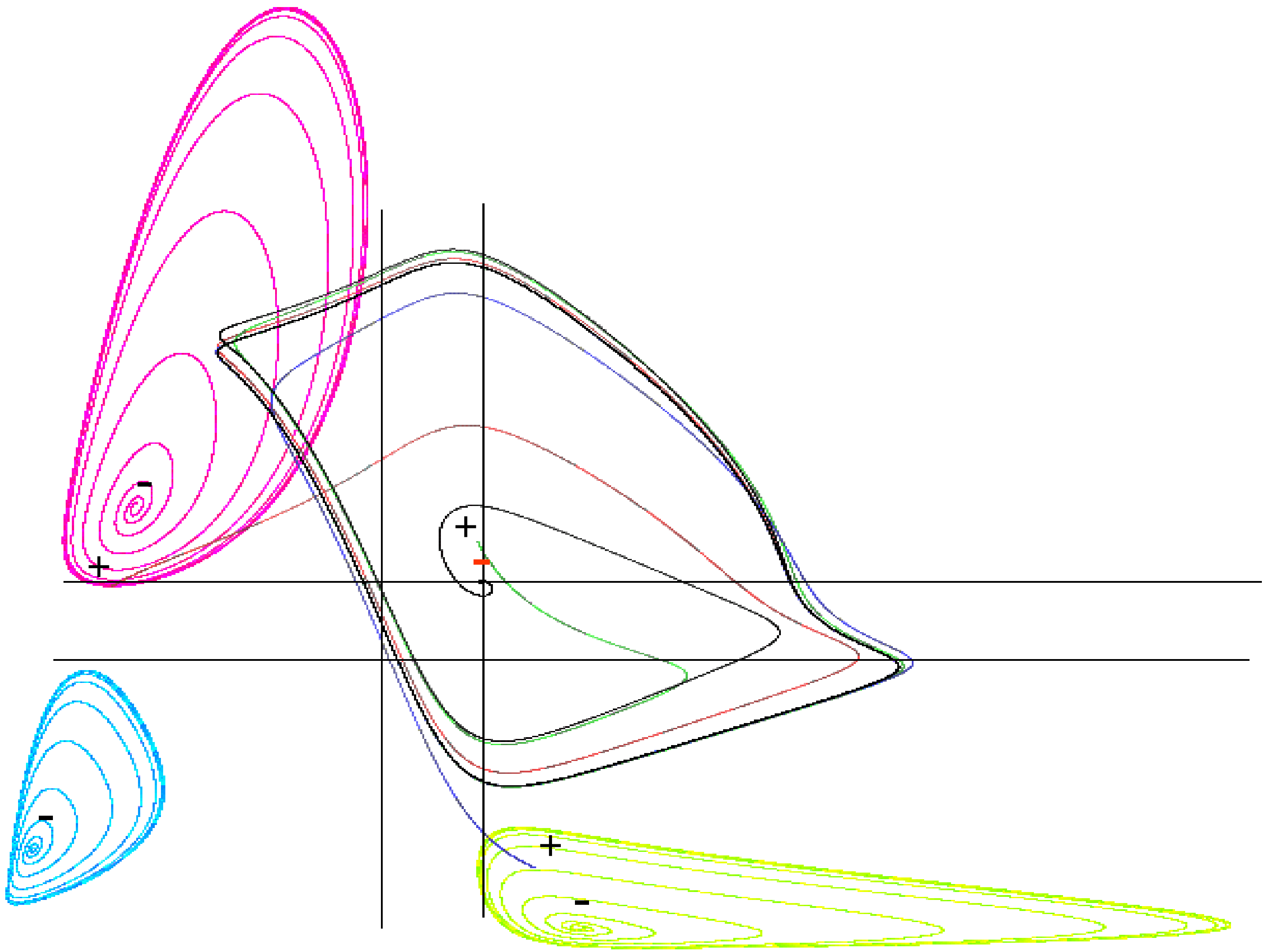
Same cycles of the system (Λ). α =10, m=5, q=0.





Same cycles in (Λ). Similar pictures were observed in the systems (GM), (L).

Cycles $C_\Delta(V)$, $C_X(I)$, $C_Y(III)$, $C_Z(VII)$ **of the system (GM).** α=4.3, γ=17.25. **Projections onto the plane *Z=0*.**



Our current tasks are connected with:

determination of conditions of regular behavior of trajectories;

studies of integral manifolds and

non uniqueness of the cycles,

bifurcations of the cycles;

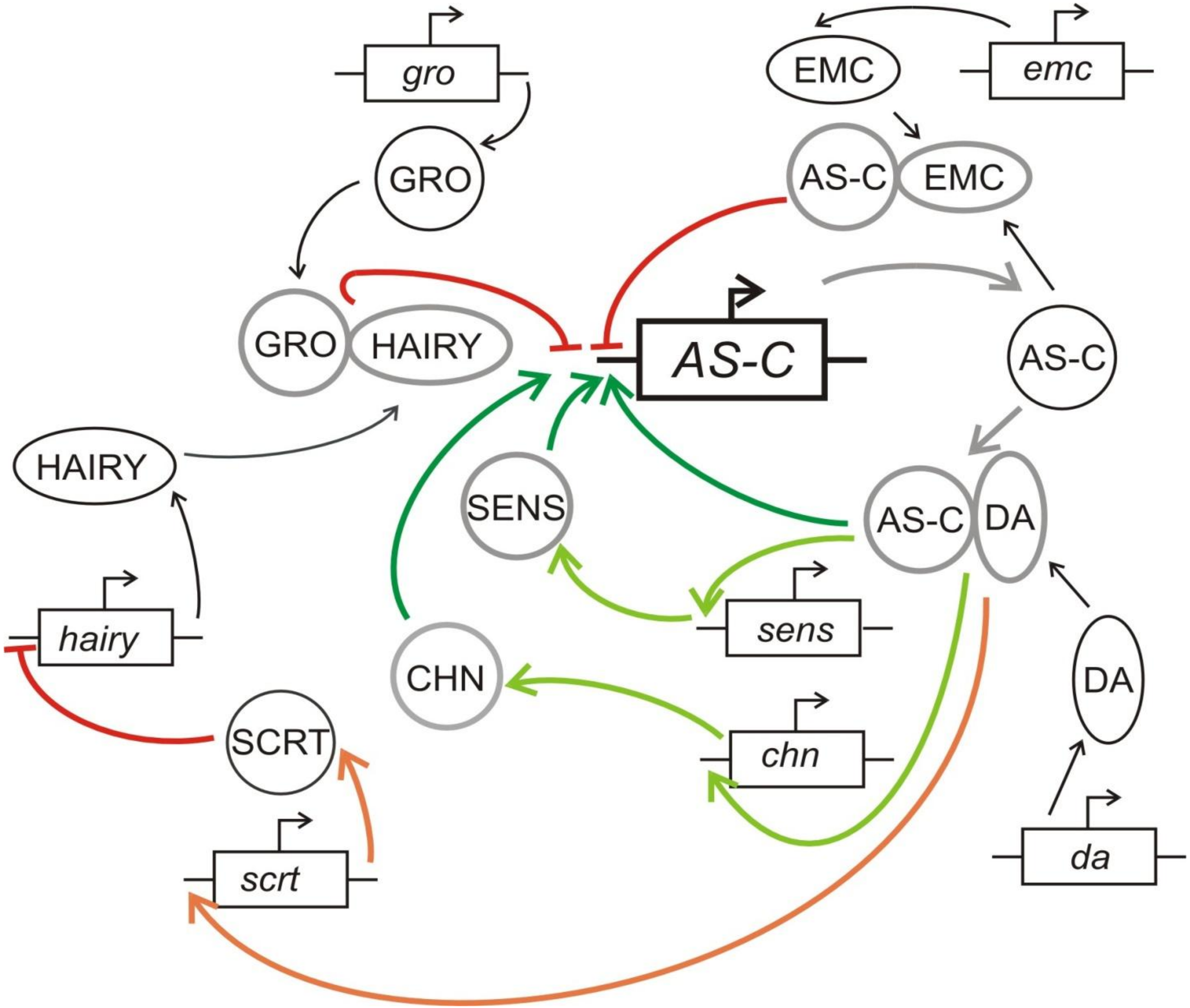
their dependence on the variations of the parameters, and

connections of these models with discrete models of the Gene Networks.

APPENDIX: D.P.Furman, T.A.Bukharina

The Gene Network Determining Development of ***Drosophila Melanogaster*** Mechanoreceptors.

Comp. Biol.Chemistry, 2009, v.33, pp. 231 – 234.

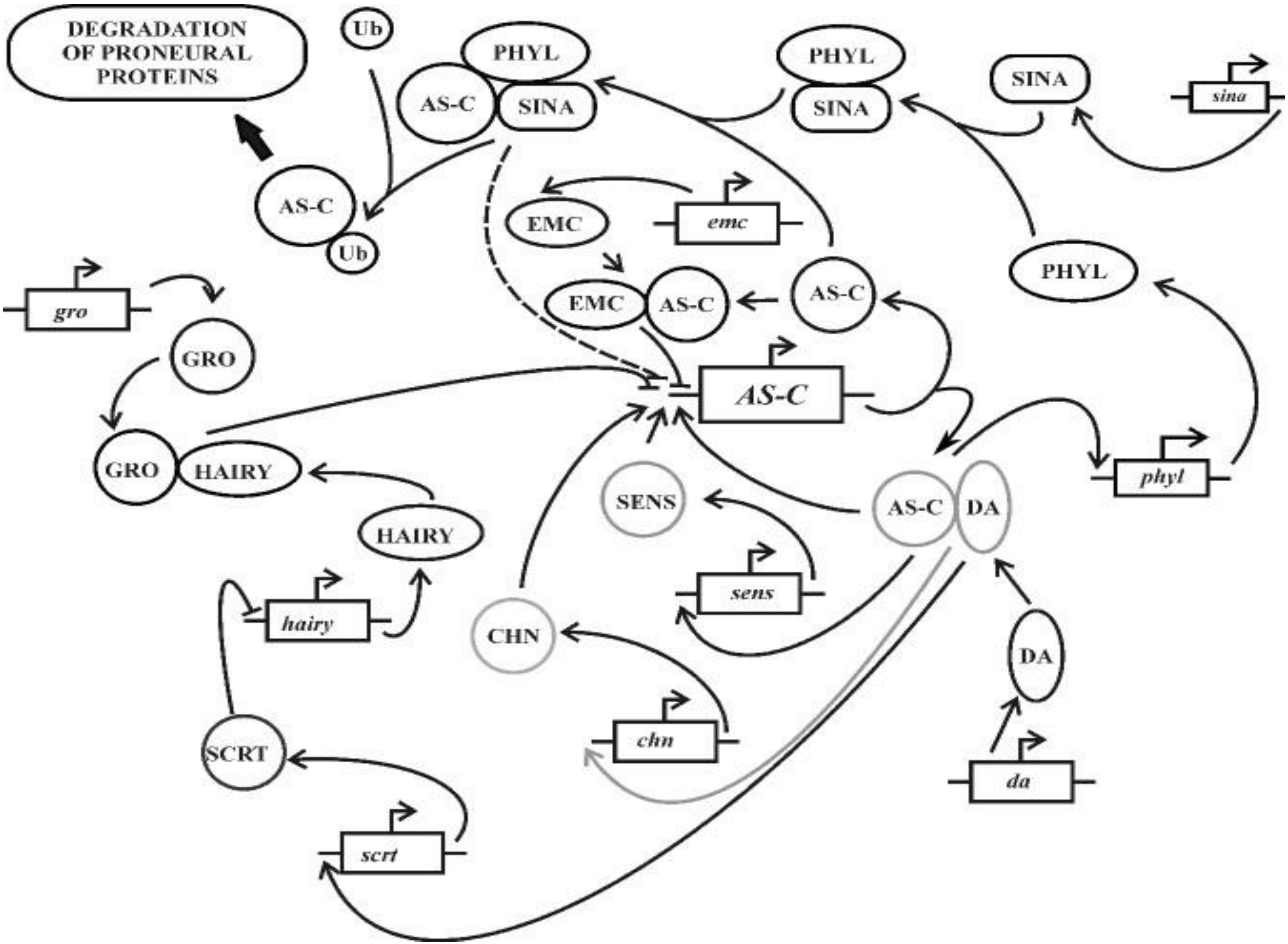


The scheme of the nonlinear system (*DM*), see below.

CHN=*charlatan*.

More complicated model.

A2



We study dynamics of the above gene network model.

$$\frac{dx}{dt} = F_1(x, y, z, w) - x = \frac{\sigma_1(D \cdot x) + \sigma_3(z) + \sigma_5(w)}{(1 + G \cdot y)(1 + E \cdot x)} - x;$$

$$\frac{dy}{dt} = F_2(u) - y = \frac{C_2}{1 + u} - y;$$

$$\frac{dz}{dt} = S_3(D \cdot x) - z,$$

$$\frac{du}{dt} = S_4(D \cdot x) - u,$$

$$\frac{dw}{dt} = S_5(D \cdot x) - w.$$

(*DM*)

x=[AS-C],
y=[HAIRY],
z=[SENS],
u=[SCRT],
w=[CHN]

concentrations.

D=[DA],
G=[GRO],
E=[EMC]

parameters.

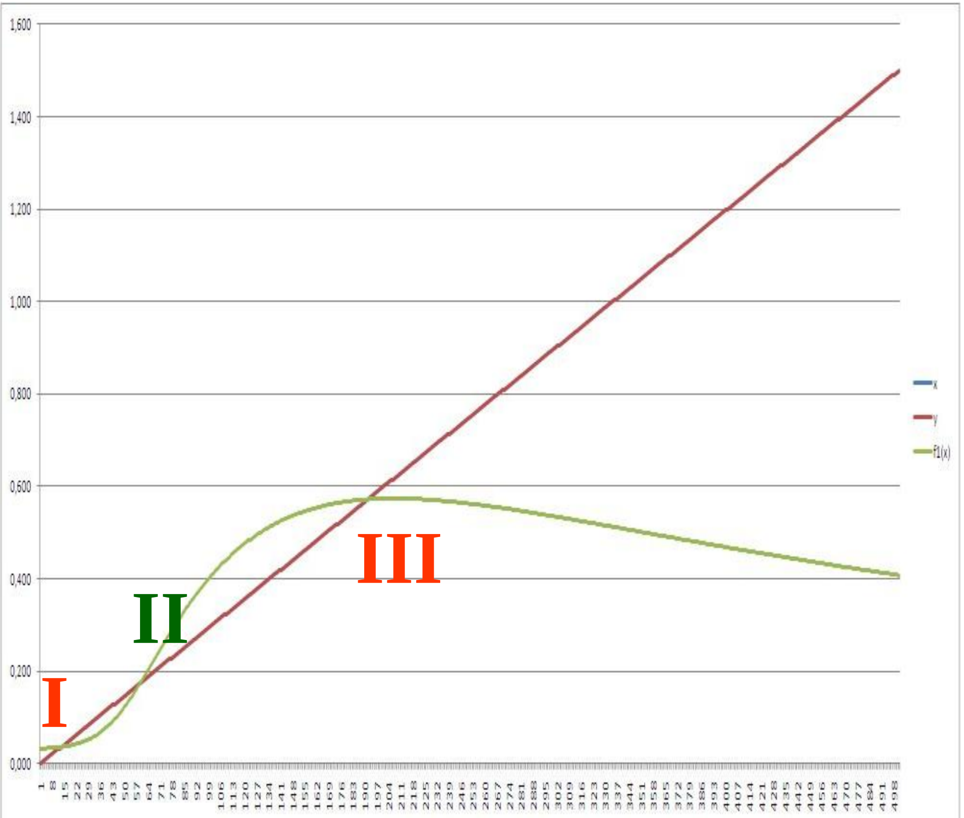
Sigmoid functions

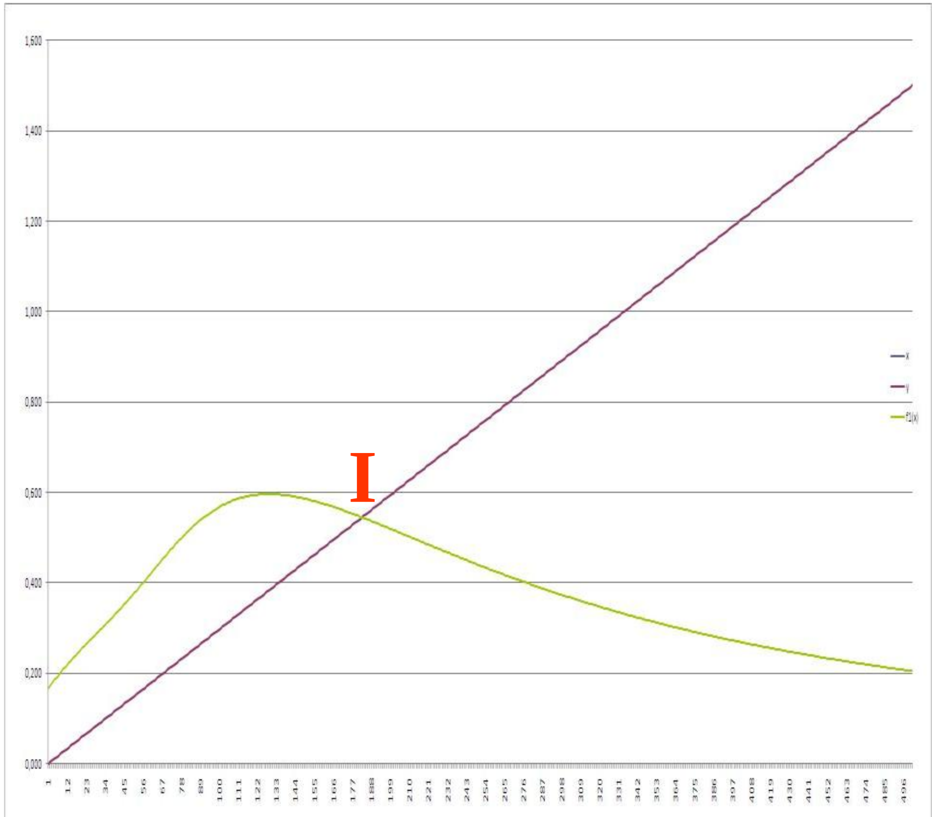
$$S_i(D \cdot x),\ i = 3,4,5; \quad \sigma_j, \quad j = 1,3,5$$

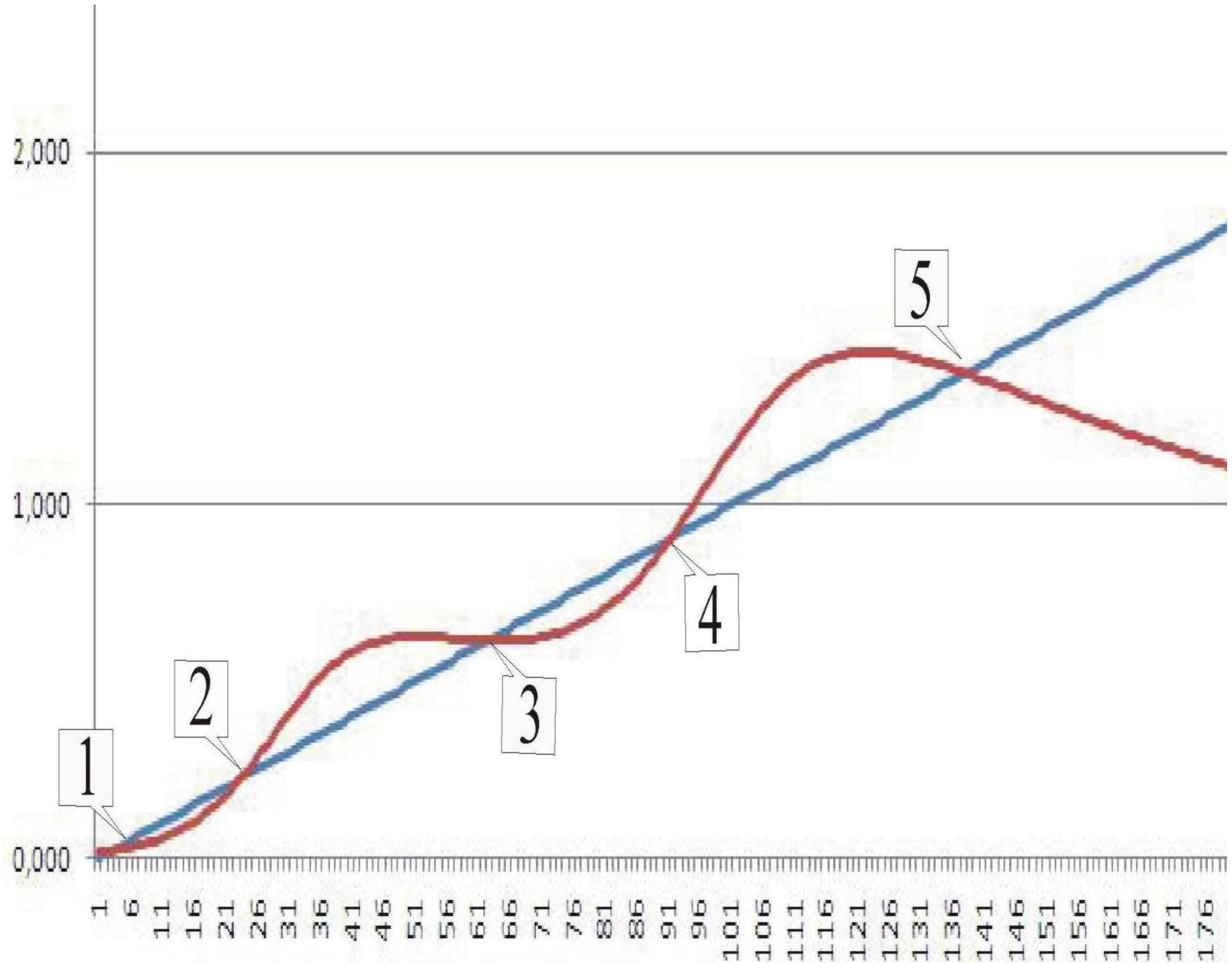
describe the positive feedbacks on the previous slide.

Graph of $f = R(x) := F_1(x, F_2(S_4(D \cdot x)), S_3(D \cdot x), S_5(D \cdot x))$ and the stationary points of the system (*DM*).

Stationary points "I" and "III" are stable,
the point "II" is unstable. ***Ind*(I)=*ind*(III)= -1; *Ind*(II) = +1.**



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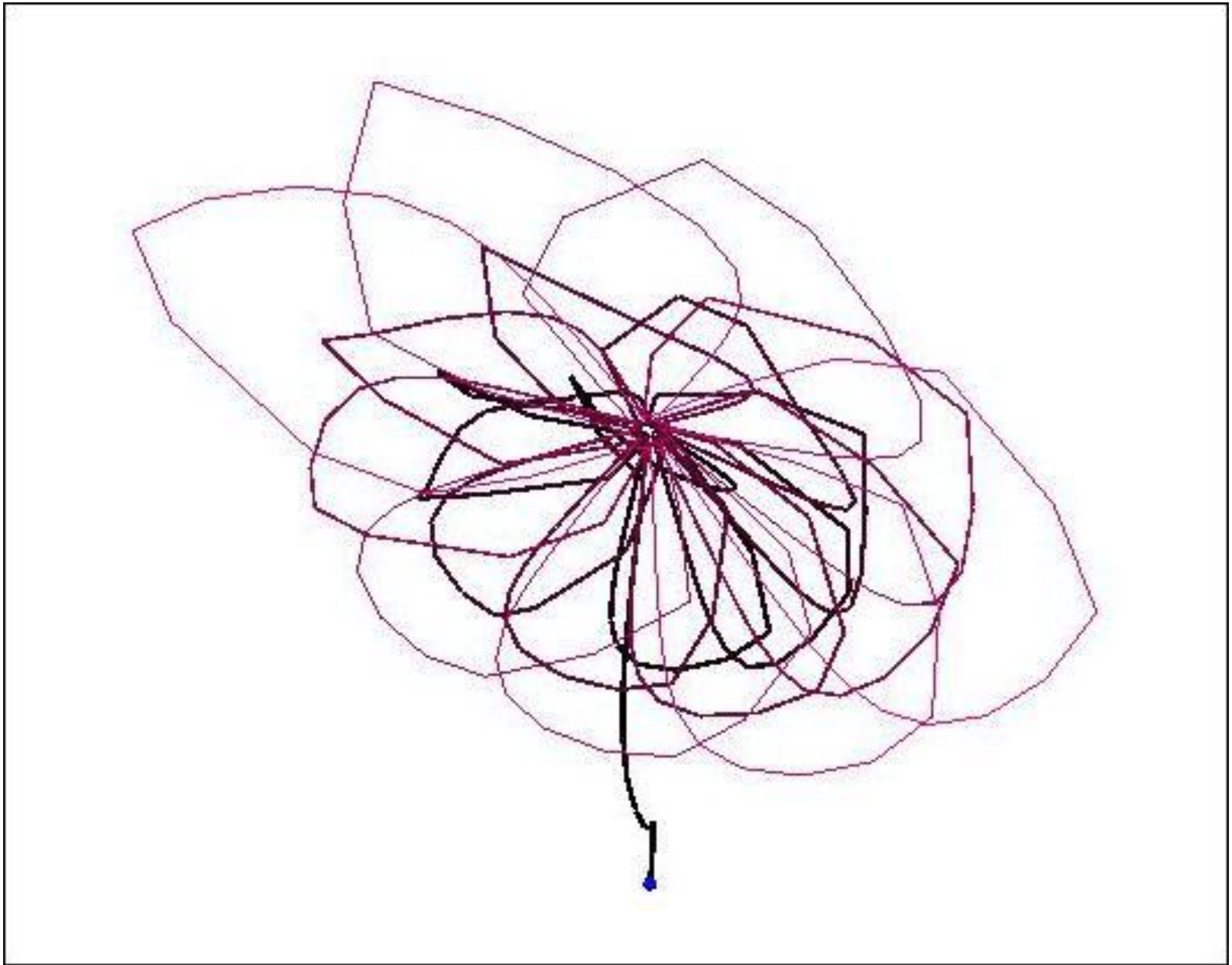
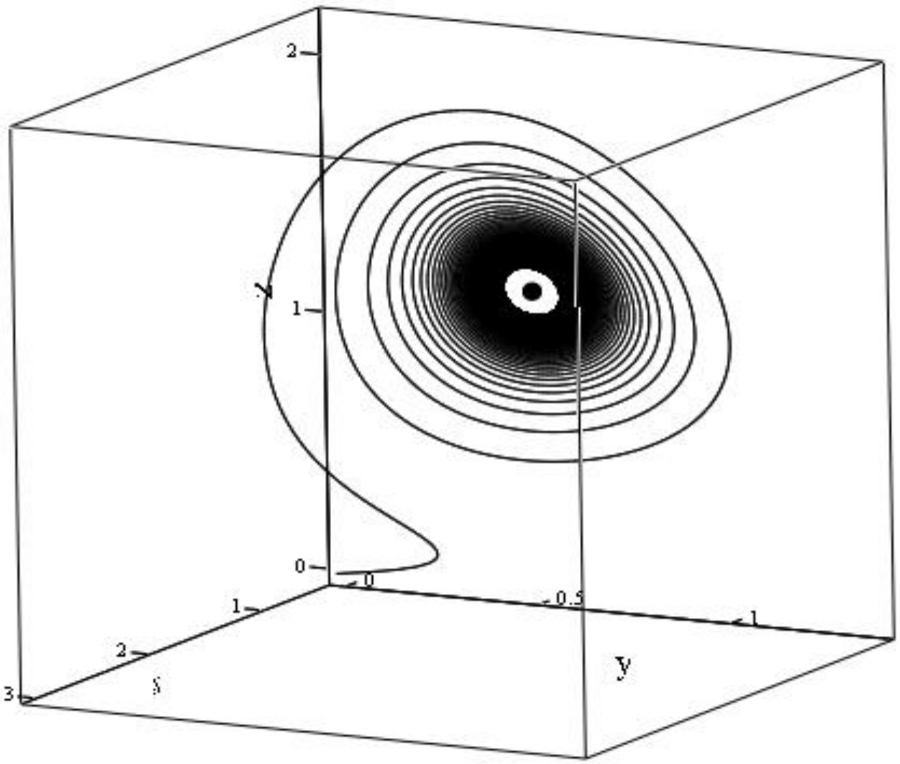
Thank you for your attention



$$\frac{dx}{dt} = \frac{\alpha_1}{1+z^3} - x; \qquad \frac{dy}{dt} = \frac{9}{1+x^3} - y; \qquad \frac{dz}{dt} = \alpha_3 - z(1+y^3);$$



$$\alpha_1 = 8.8$$

$$\alpha_3 = 2.88$$

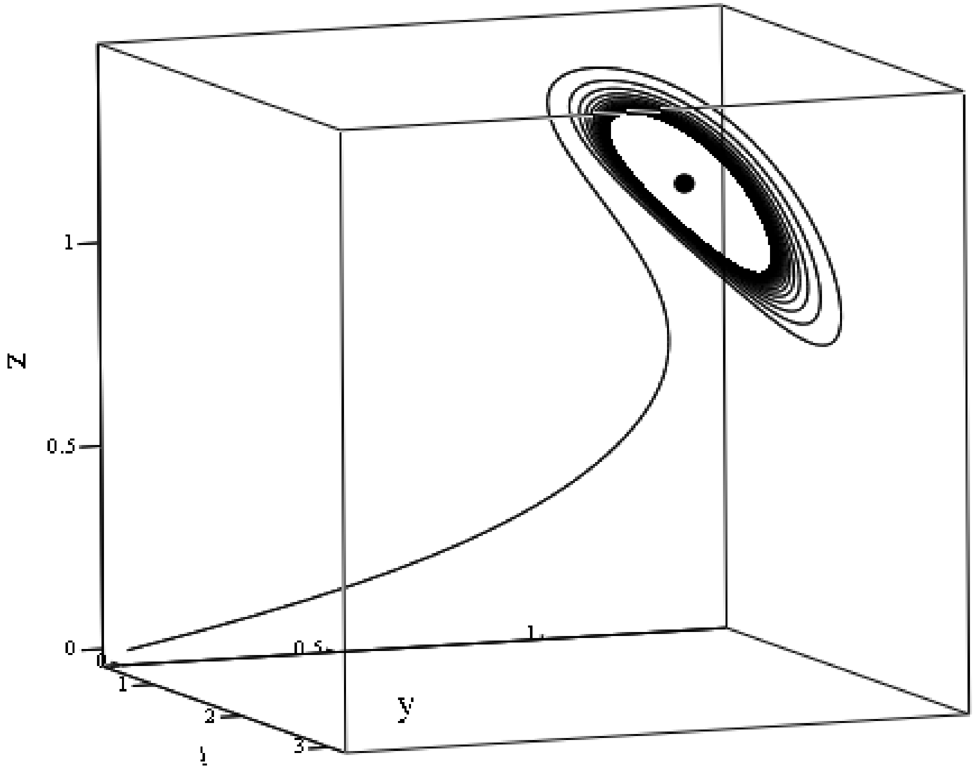
A trajectory convergent to the bifurcation cycle.

(u1, u2, u3), (rp1, rp2, rp3)

(in cooperation with A.G.Kleshchev)

$$\frac{dx}{dt} = \alpha_1 - x(1 + z^3)\,; \qquad \frac{dy}{dt} = \frac{9}{1 + x^3} - y\,; \qquad \frac{dz}{dt} = \alpha_3 - z(1 + y^3)\,;$$

$$\alpha_1 = 6.15,\ \alpha_3 = 2.4$$



A trajectory and a bifurcation cycle.

(u1, u2, u3), (rp1, rp2, rp3)

A trajectory and a bifurcation cycle.