On uniqueness and stability of a cycle in gene network models

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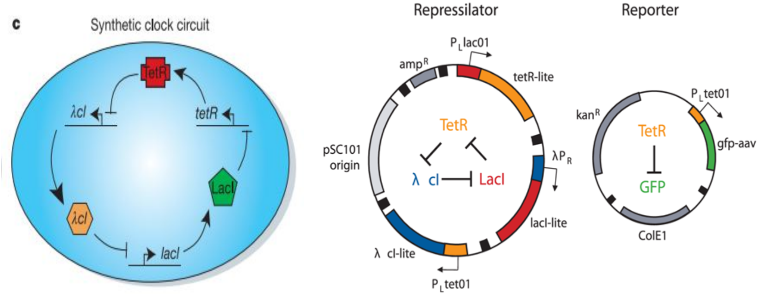
Women in Mathematics

5D-system



c
Synthetic clock circuit
TetR
λcI
tetR
LacI
λcI
lacI
Repressilator
Reporter
P$_L$lac01
amp^R
tetR-lite
TetR
λ cI
LacI
pSC101
origin
λP$_R$
lacI-lite
λ cI-lite
P$_L$tet01
kan^R
P$_L$tet01
TetR
gfp-aav
GFP
ColE1

5D-system

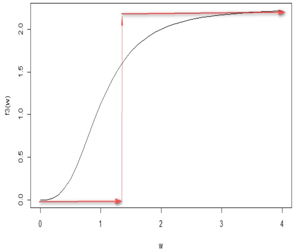


Figure: Γ

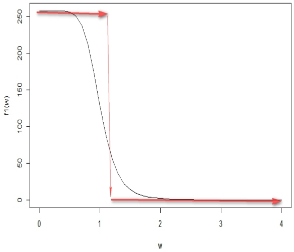


Figure: L

5D-system

$$\frac{dx_1}{dt} = f_1(x_5) - k_1 x_1; \quad \frac{dx_2}{dt} = f_2(x_1) - k_2 x_2; \quad \frac{dx_3}{dt} = f_3(x_2) - k_3 x_3; \tag{1}$$

$$\frac{dx_4}{dt} = f_4(x_3) - k_4 x_4; \quad \frac{dx_5}{dt} = f_5(x_4) - k_5 x_5,$$

k_j are constant and positive,

$$f_j(x_{j-1}) = A_j > 0 \ \text{ at } 0 \le x_{j-1} < 1; \ f_j(x_{j-1}) = 0 \ \text{ at } 1 \le x_j.$$

$j = 1, 2, \dots, 5,$
$j - 1 := 5,\ j = 1.$

5D-system

$a_j := A_j/k_j$

$Q^5 = [0, a_1] \times [0, a_2] \times [0, a_3] \times [0, a_4] \times [0, a_5] \subset \mathbb{R}^5_+$

$x_j = 1\ f_j$,

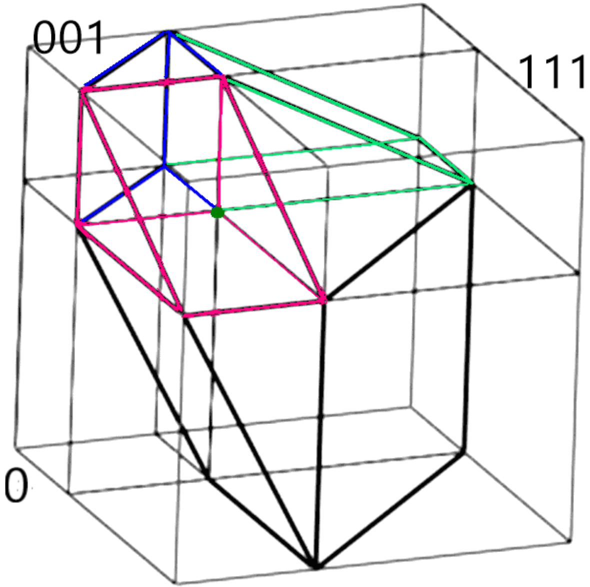
$\{\varepsilon_1\varepsilon_2\varepsilon_3\varepsilon_4\varepsilon_5\}$.

$\varepsilon_j = 0$, $x_j < 1$, and $\varepsilon_j = 1$, $x_j \geq 1$.

$E = (1, 1, 1, 1, 1)$

$\Omega_1 \subset Q^5$

5D-system



5D-system

1. The trajectories of all points of the common four-dimensional face $B_1 \cap B_2$ of every two adjacent blocks B_1 and B_2 proceed either from B_1 to B_2, or from B_2 to B_1.
2.

$$
\begin{array}{ccccccc}
\{10101\} & \longrightarrow & \{00101\} & \longrightarrow & \{01101\} & \longrightarrow & \{01001\} \\
\uparrow & & & & & & \downarrow \\
\{101000\} & & & & & & \{01011\} \\
\uparrow & & & & & & \downarrow \\
\{10110\} & \longleftarrow & \{10010\} & \longleftarrow & \{11010\} & \longleftarrow & \{01010\}
\end{array}
\qquad (2)
$$

5D-system

$$F_0 = \{10101\} \cap \{00101\}, x_1 = 1; \quad F_1 = \{00101\} \cap \{01101\}, x_2 = 1;$$
$$F_2 = \{01101\} \cap \{01001\}, x_3 = 1; \quad F_3 = \{01001\} \cap \{01011\}, x_4 = 1;$$
$$F_4 = \{01011\} \cap \{01010\}, x_5 = 1; \quad F_5 = \{01010\} \cap \{11010\}, x_1 = 1;$$
$$F_6 = \{11010\} \cap \{10010\}, x_2 = 1; \quad F_7 = \{10010\} \cap \{10110\}, x_3 = 1;$$
$$F_8 = \{10110\} \cap \{10100\}, x_4 = 1; \quad F_9 = \{10100\} \cap \{10101\}, x_5 = 1.$$

5D-system

$$\mathfrak{p}_0 : F_0 \to F_1,\ \ \mathfrak{p}_1 : F_1 \to F_2,\ \ \mathfrak{p}_2 : F_2 \to F_3,\ \ \mathfrak{p}_3 : F_3 \to F_4,$$
$$\mathfrak{p}_4 : F_4 \to F_5,\ \ \mathfrak{p}_5 : F_5 \to F_6,\ \ \mathfrak{p}_6 : F_6 \to F_7,$$
$$\mathfrak{p}_7 : F_7 \to F_8,\ \ \mathfrak{p}_8 : F_8 \to F_9,\ \ \mathfrak{p}_9 : F_9 \to F_{10} = F_0.$$

$\mathfrak{P} : F_0 \to F_0$

5D-system

{00101}

$$\dot{x}_1 = -k_1 x_1, \qquad \dot{x}_2 = k_2(a_2 - x_2), \qquad \dot{x}_3 = k_3(a_3 - x_3),$$
$$\dot{x}_4 = -k_4 x_4, \qquad \dot{x}_5 = k_5(a_5 - x_5).$$

$X^{(0)} \in F_0$ $x_1^{(0)} = 1,\ x_2^{(0)} < 1,\ x_3^{(0)} > 1,\ x_4^{(0)} < 1,\ x_5^{(0)} > 1.$
$X^{(1)} \in F_1$

$$\begin{gathered} x_1(t) = x_1^{(0)} e^{-k_1 t},\ x_2(t) = a_2 + (x_2^{(0)} - a_2)e^{-k_2 t}, \\ x_3(t) = a_3 + (x_3^{(0)} - a_3)e^{-k_3 t},\ x_4(t) = x_4^{(0)} e^{-k_4 t}, \\ x_5(t) = a_5 + (x_5^{(0)} - a_5)e^{-k_5 t}. \end{gathered} \tag{3}$$

5D-system

$X^{(1)} = F_1 \cap \mathcal{C}$

$$x_1^{(1)} = x_1^{(0)} \cdot \left(\frac{a_2 - 1}{a_2 - x_2^{(0)}} \right)^{\frac{k_1}{k_2}}; \;\; x_2^{(1)} = 1;$$

$$x_3^{(1)} = a_3 + (x_3^{(0)} - a_3) \cdot \left(\frac{a_2 - 1}{a_2 - x_2^{(0)}} \right)^{\frac{k_3}{k_2}}.$$

$$x_4^{(1)} = x_4^{(0)} \cdot \left(\frac{a_2 - 1}{a_2 - x_2^{(0)}} \right)^{\frac{k_4}{k_2}};$$

$$x_5^{(1)} = a_5 + (x_5^{(0)} - a_5) \cdot \left(\frac{a_2 - 1}{a_2 - x_2^{(0)}} \right)^{\frac{k_5}{k_2}},$$

5D-system

Theorem

If $A_j > k_j$ for all $j = 1, \ldots, 5$, then dynamic system (1) *has the unique cycle in invariant domain Ω_1.*

Theorem

Under conditions of previous theorem, the cycle is stable.

Golubyatnikov V.P., Ayupova N.B. On one cycle in five-dimensional circular gene network model// Journal of Applied and Industrial Mathematics. 2021. (to be published)

PL-system

$$\frac{dx_0}{dt} = L_0(x_5) - k_0 x_0; \qquad \frac{dx_1}{dt} = \Gamma_1(x_0) - k_1 x_1, \tag{4}$$

$$\frac{dx_2}{dt} = L_2(x_1) - k_2 x_2; \qquad \frac{dx_3}{dt} = \Gamma_3(x_2) - k_3 x_3,$$

$$\frac{dx_4}{dt} = L_4(x_3) - k_4 x_4; \qquad \frac{dx_5}{dt} = \Gamma_5(x_4) - k_5 x_5.$$

$$L_{2i}(z) = \begin{cases} k_{2i}(a_{2i} - 1), & -1 \leqslant z \leqslant 0; \\ -1, & z > 0; \end{cases}$$

$$\Gamma_{2i+1}(z) = \begin{cases} 0, & 0 \leqslant z \leqslant 1; \\ k_{2i+1}(a_{2i+1} - 1), & z > 1; \end{cases} \tag{5}$$

$i = 0, 1, 2;$

PL-system

$Q^6 = \prod_{j=0}^{5} [-1, a_j - 1] \subset \mathbb{R}^6_+$

$\{\varepsilon_0\varepsilon_1\varepsilon_2\varepsilon_3\varepsilon_4\varepsilon_5\}$.

$\varepsilon_j = 0$, $x_j < 1$, and

$\varepsilon_j = 1$, $x_j \geq 1$.

Let W_1, W_3, W_5 be the union of 1-valent, 3-valent, respectively 5-valent blocks.

W_1 12 blocks

W_3 40 blocks

W_5 12 blocks.

Bukharina T.A., Golubyatnikov V.P., Furman D.P., Kazantsev M.V., Kirillova N.E. Mathematical and numerical models of two asymmetric gene networks // Siberian Electronic Mathematical Reports, 2018. — V. 15. — P. 1271 – 1283.

PL-system

The main goal is description of behavior of trajectories of the system (4) in the non-invariant domain $W_5 \subset Q^6 \setminus (W_1 \cup W_3)$

$$
\begin{array}{ccccccc}
\{111001\} & \longrightarrow & \{011001\} & \longrightarrow & \{011000\} & \longrightarrow & \{011010\} \\
\uparrow & & & & & & \downarrow \\
\{101001\} & & & & & & \{011110\} \\
\uparrow & & & & & & \downarrow \\
\{100001\} & & & & & & \{010110\} \\
\uparrow & & & & & & \downarrow \\
\{100101\} & \longleftarrow & \{100111\} & \longleftarrow & \{100110\} & \longleftarrow & \{000110\}
\end{array} \tag{6}
$$

PL-system

$\{011001\} \to \{001001\}, \{010001\}, \{011101\}, \{011011\}$
$k_j = 1$

$F_0 = \{111001\} \cap \{011001\}, x_0 = 0; \quad F_1 = \{011001\} \cap \{011000\}, x_5 = 0;$
$F_2 = \{011000\} \cap \{011010\}, x_4 = 0; \quad F_3 = \{011010\} \cap \{011110\}, x_3 = 0;$

$\{011001\}$ $X^{(0)} = (0, x_1^{(0)}, x_2^{(0)}, x_3^{(0)}, x_4^{(0)}, x_5^{(0)})$

$$\dot{x}_0 = -x_0 - 1; \quad \dot{x}_1 = -x_1 - 1; \quad \dot{x}_2 = -x_2 - 1;$$

$$\dot{x}_3 = -x_3 - 1 + a_3; \quad \dot{x}_4 = -x_4 - 1 + a_4; \quad \dot{x}_5 = -x_5 - 1.$$

$$x_5(t) = (x_5^{(0)} + 1)e^{-t} - 1; \quad x_0(t) = -1 + e^{-t},$$

$$x_1(t) = (y_1^{(0)} + 1)e^{-t} - 1; \quad x_2(t) = -1 + (x_2^{(0)} + 1)e^{-t};$$

$$x_3(t) = (a_3 - 1) + (x_3^{(0)} - (a_3 - 1))e^{-t}.$$

$X^{(1)} = (x_0^{(1)}, x_1^{(1)}, x_2^{(1)}, x_3^{(1)}, x_4^{(1)}, 0) \in F_1$

PL-system

$$a_0 = a_2 = a_4; \quad a_1 = a_3 = a_5 \tag{7}$$

$a := a_{2i},\ b := a_{2i+1}$

Theorem

If $a > 1$, $b > 1$ then the system (4), (7) for $k_j = 1$ has an invariant surface $\Sigma \subset W_5$. Trajectories of points of this surface are attracted by the origin.

Golubytnikov V.P. and Minushkina L.S. On geometric structure of phase portraits of some picewise linear dynamical systems.// Tbilisi Mathematical Journal. Special Issue (7-2021), pp. 49 – 56.

6D-system

$$\frac{dm_1}{dt} = -k_1 m_1 + f_1(p_3); \quad \frac{dp_1}{dt} = \mu_1 m_1 - \nu_1 p_1;$$
$$\frac{dm_2}{dt} = -k_2 m_2 + f_2(p_1); \quad \frac{dp_2}{dt} = \mu_2 m_2 - \nu_2 p_2; \qquad (8)$$
$$\frac{dm_3}{dt} = -k_3 m_3 + f_3(p_2); \quad \frac{dp_3}{dt} = \mu_3 m_3 - \nu_3 p_3.$$

6D-system

$k_1 = k_2 = k_3 = 1$, $\mu_1 = \mu_2 = \mu_3 = \nu_1 = \nu_2 = \nu_3$,
$f_1(p) = f_2(p) = f_3(p) = \alpha(1 + p^\gamma)^{-1} + \alpha_0$,
$\alpha + \alpha_0$

Elowitz M. B., Leibler S. A Synthetic Oscillatory Network of Transcriptional Regulators // Nature. 2000. V. 403. P. 335–338.

6D-system

$$Q := \prod_{j=1}^{j=3} \left([0, A_j] \times [0, B_j] \right).$$

$A_j := f_j(0)/k_j$
$B_j := \mu_j A_j/\nu_j$.
$S_0 = (m_1^0; p_1^0; m_2^0; p_2^0; m_3^0; p_3^0)$
$\mu_j m_j = \nu_j p_j$

$$k_1 m_1 = f_1\left(\varphi_3\left(\varphi_2\left(\frac{\mu_1 m_1}{\nu_1}\right)\right)\right),$$

$\varphi_j(p) := \dfrac{\mu_j}{\nu_j k_j} f_j(p)$ $\quad$ $-q_j = df_j/dp\big|_{p=p_{j-1}^0}$

6D-system

S_0:

$$M_6 = \begin{pmatrix} -k_1 & 0 & 0 & 0 & 0 & -q_1 \\ \mu_1 & -\nu_1 & 0 & 0 & 0 & 0 \\ 0 & -q_2 & -k_2 & 0 & 0 & 0 \\ 0 & 0 & \mu_2 & -\nu_2 & 0 & 0 \\ 0 & 0 & 0 & -q_3 & -k_3 & 0 \\ 0 & 0 & 0 & 0 & \mu_3 & -\nu_3 \end{pmatrix}.$$

$$P_6(\lambda) = \prod_{j=1}^{j=3}(k_j + \lambda)(\nu_j + \lambda) + a^6, \quad \text{where} \quad a^6 := \prod_{j=1}^{j=3} q_j \mu_j.$$

6D-system

Lemma

For sufficiently large values of the parameter a the characteristic polinomial $P_6(\lambda)$ has exactly two complex roots with positive real parts and four complex roots with negative real parts.

Theorem

If the characteristic polynomial of M_6 has two roots with positive real parts and four roots with negative real parts the dynamical system (8) has at least one cycle $\mathcal{C}_6$ in the domain $\Omega' = \Omega_1 \setminus (\Omega_1 \cap U)$.

6D-system

Lemma

If a point S_0 is hyperbolic then intersection $U \cap P_1^2$ is in domain Ω_1.

Definition

$W^+(\xi, S_0)$ is *stable manifold of field ξ in a point S_0*, if

$$W^+(\xi, S_0) = \{x \in Q | \varphi_t(x) \to S_0 \quad \text{as } t \to \infty\}.$$

Definition

$W^-(\xi, S_0)$ is *unstable manifols of field ξ in point S_0*, if

$$W^-(\xi, S_0) = \{x \in Q | \varphi_t(x) \to S_0 \quad \text{as } t \to -\infty\}.$$

6D-system

Lemma

Unstable manifold W^- lies in Ω_1. The dimension of W^- is equal to 2.

Theorem

If S_0 is a hyperbolic steady state then each invariant surface containing a cycle of a system passes through S_0.

Kirillova N.E. On invariant surfaces in gene network models.// Journal of Applied and Industrial Mathematics. v.14, No. 4, pp. 666 – 671.

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Thank you for attention!