

Non-uniqueness of cycles in multistage gene networks models

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Motivation and Aim: Conditions of existence and stability of periodic trajectories in various piecewise linear models of circular gene networks functioning were described in [1–3]. At the same time, it was shown that in dimensions $n \geq 5$ these models can possess several cycles, see [2, 4]. Here, we construct a similar 3-dimensional gene network model regulated by negative multistep feedbacks which has at least 3 stable cycles. We describe localization of these cycles in the phase portrait of the corresponding dynamical system.

Methods and Algorithms: Consider 3-dimensional piecewise linear dynamical system

$$\frac{dx_j}{dt} = L(x_{j-1}) - x_j; \text{ here and below, } j=1,2,3; j-1=3 \text{ for } j=1. \quad (1)$$

The function L is monotonically decreasing, it describes negative feedbacks in this circular gene network. Following [5, 6], where generalized threshold functions were studied in modelling of various natural gene networks, we define this function in the following five-steps way:

$$L(w) = 2c \text{ for } 0 \leq w < c - \varepsilon; L(w) = c + \varepsilon \text{ for } c - \varepsilon \leq w < c - \delta;$$

$$L(w) = c + \delta \text{ for } c - \delta \leq w < c; L(w) = c - \delta \text{ for } c \leq w < c + \delta;$$

$$L(w) = c - \varepsilon \text{ for } c + \delta \leq w < c + \varepsilon; L(w) = 0 \text{ for } c + \varepsilon \leq w.$$

Here, $c > \varepsilon > \delta > 0$. As in [1, 3], the cube $Q = [0, 2c] \times [0, 2c] \times [0, 2c]$ in the octant $x_j \geq 0$ is positively invariant, i. e., trajectories of its points do not leave it as $t \rightarrow \infty$. Let us decompose Q by 15 planes $x_j = c - \varepsilon$, $x_j = c - \delta$, $x_j = c$, $x_j = c + \varepsilon$, $x_j = c + \delta$ to 216 blocks. In each of these blocks, the system (1) splits to independent linear differential equations. We enumerate these blocks by 6-symbols multi-indices $\{s_1 s_2 s_3\}$, where $s_j \in \{\alpha, A, 0, 1, B, \beta\}$ as follows: If $0 \leq x_j < c - \varepsilon$ in this block, then $s_j = \alpha$; for $c - \varepsilon \leq x_j < c - \delta$, we set $s_j = A$; if $c - \delta \leq x_j < c$ then $s_j = 0$; if $c \leq x_j < c + \delta$ then $s_j = 1$; if $c + \delta \leq x_j < c + \varepsilon$ then $s_j = B$; and if $c + \varepsilon \leq x_j$ then $s_j = \beta$.

We need this combinatorics for description, and control of trajectories of the system (1), as well as in corresponding numerical experiments. Similar enumeration was used in [1, 3, 7] in the case of one-step functions L .

Results: The cubes $\hat{Q} = [c - \varepsilon, c + \varepsilon] \times [c - \varepsilon, c + \varepsilon] \times [c - \varepsilon, c + \varepsilon] \subset Q$ and $\tilde{Q} = [c - \delta, c + \delta] \times [c - \delta, c + \delta] \times [c - \delta, c + \delta] \subset \hat{Q}$ are positively invariant domains; this can be shown as for the cube Q . Denote by $W_1 \subset \tilde{Q}$ the union of six blocks listed in the circular diagram

$$\dots \rightarrow \{011\} \rightarrow \{010\} \rightarrow \{110\} \rightarrow \{100\} \rightarrow \{101\} \rightarrow \{001\} \rightarrow \{011\} \rightarrow \dots \quad (2)$$

Let $W_2 \subset \hat{Q} \setminus \tilde{Q}$ be the union of 18 blocks listed in the similar diagram

$$\begin{aligned} \dots \rightarrow \{BBA\} \rightarrow \{B1A\} \rightarrow \{B0A\} \rightarrow \{BAA\} \rightarrow \{BA0\} \rightarrow \{BA1\} \rightarrow \{BAB\} \rightarrow \\ \{1AB\} \rightarrow \{0AB\} \rightarrow \{AAB\} \rightarrow \{A0B\} \rightarrow \{A1B\} \rightarrow \{ABB\} \rightarrow \{AB1\} \rightarrow \\ \{AB0\} \rightarrow \{ABA\} \rightarrow \{0BA\} \rightarrow \{1BA\} \rightarrow \{BBA\} \rightarrow \dots \end{aligned} \quad (3)$$

Each of the blocks of the diagram (3) has either a common vertex, or a common edge with one of the blocks of the diagram (2).

Theorem. 1) The domain W_1 is invariant; it contains exactly one cycle C_1 of the system (1); this cycle is stable and travels from block to block according to the arrows of the diagram (2).

2) If $c \geq 4\epsilon$ then the domain W_2 contains at least one cycle C_2 of the system (1), this cycle travels from block to block according to the arrows of the diagram (3).

3) If $\epsilon \geq 4\delta$ then the domain $Q \setminus \hat{Q}$ contains at least one cycle C_3 of the system (1).

4) The cycles C_1, C_2, C_3 are symmetric with respect to the cyclic permutations of the variables x_j . The system (1) does not have asymmetric cycles.

The cycle C_3 travels from block to block according arrows of one bulky circular diagram analogous to (2), (3). The multi-indices which numerate all 30 blocks of this diagram contain symbols α and β , so all these 30 blocks are incident to the boundary of the invariant domain Q .

Figures 1a and 1b show results of some numerical experiments with the system (1) for two collections of its parameters indicated there. In these Figures, one can see all three cycles of the system (1) described in the Theorem. Here, the cycle C_1 is the smallest one, and C_3 is the largest.

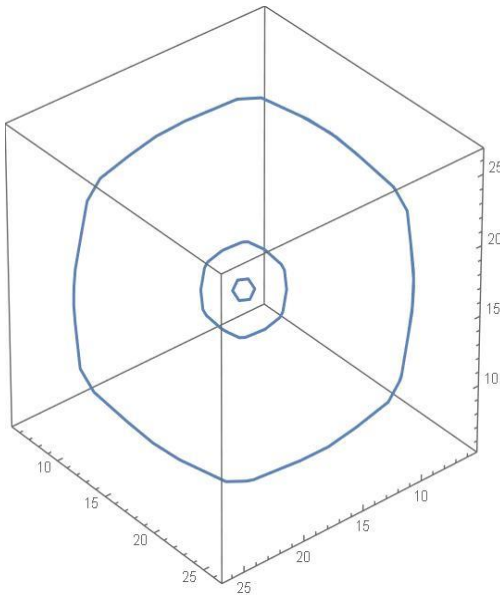


Fig. 1a. Cycles of the system (1);
 $c = 16$; $\epsilon = 4$; $\delta = 1$

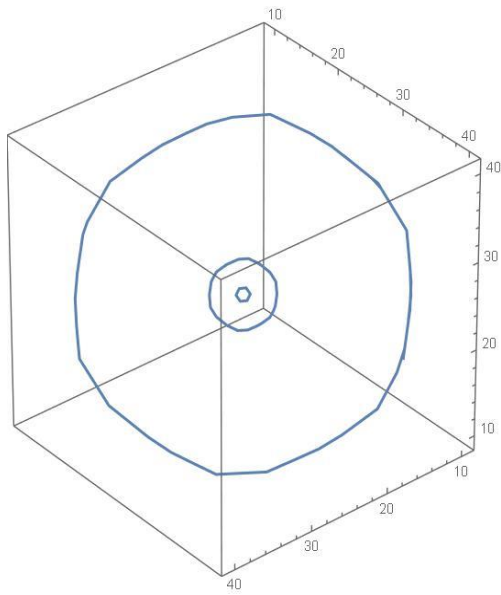


Fig. 1b. Cycles of the system (1);
 $c = 25$; $\epsilon = 5$; $\delta = 1$

Conclusion and Future Work: For nonlinear dynamical systems of the type (1) with one-step functions in their equations considered in [1–4], non-uniqueness of cycles was observed previously in higher-dimensional cases only, see [2, 4]. Using Generalized Threshold Functions approach described in [5], we have constructed here a 3D gene network model which has three cycles. The cycle C_1 is stable, and the system (1) does not have other cycles in the domain W_1 , as in [3]. The cycles C_2 and C_3 give examples

of non-local oscillations, they do not have the bifurcation nature, see [8]. They also should be stable, otherwise we could not see them in the numerical experiments. Similar example of 3D gene network model with two cycles is described in [9].

For these systems of the type (1), we plan to describe invariant surfaces which separate attraction domains of their cycles.

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