RESEARCH OF CYCLIC GENE NETWORK CIRCUITS WITH NEGATIVE TYPE OF REGULATION

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SUMMARY

Motivation: The core of gene networks (GN) is regulatory circuits – genes and proteins with mutually regulated expression. Thus, detection of possible operation modes of regulatory circuits is an important problem of systems biology.

Results: The work presents an efficient method for computing symmetric periodic solutions for cyclic regulatory circuits for model M(n,2). This method includes resolving boundary value problem for equation with delay argument (2) and receiving functional relation $T/\tau$ by means of parameter continuation.

INTRODUCTION

Gene networks (GN) are structurally complex spatial objects composed of hundreds of elements of various natures and complexities, namely, genes and their regulatory regions, RNAs and proteins encoded by these genes, low-molecular-weight compounds, various complexes between enzymes and their targets, etc. The core of GN is regulatory circuits—genes and proteins with mutually regulated expression. Their presence confers on GN a unique ability to respond adequately to changes in external conditions. Thus, detection of possible operation modes of regulatory circuits is important problem of systematic biology. A constructive step in this direction is separation of a finite set of standard elements from natural GN, formalization of the rules for assembling theoretical objects (mathematical models) describing regulatory circuits from these elements, and a systematic analysis of their properties for revealing general biologically significant regularities (Likhoshvai et al., 2003).

In this work we study a model describing the most simple cyclic circuits of molecular-genetic systems.

Mathematical model is presented by autonomous system of n differential equations:

$$\frac{dx_i}{dt} = \frac{\alpha}{1 + \frac{\gamma}{x_{i-1}}} - x_i, i = 1, n, \text{let } i - 1 = 0, \text{let } i - 1 = n. \quad (1)$$

Here, $n$ is number of gene elements in our system. Where $i$-th gene element, $l = 1, \ldots, n$, encodes its protein-regulator. The value of $i$-th component means a concentration of protein has been synthesized as a result of $i$-th gene element expression. The positive term in the right part of $i$-th equation describes a negative type regulatory effect of previous gene element to the efficacy of expression of current element. $\alpha, \gamma$ are positive parameters, which set level of basal activity of expression and nonlinearity of regulator...
effect. All negative type regulation mechanisms consider being identical in the model. Negative term describes degradation process. System is regarded to be dimensionless, that is why time is relative. Those facts were shown before: (i) phase trajectories of system (1) coming from the hypercube $\Xi$ with the edge $\alpha$ remain in $\Xi$, (ii) system (1) always has one stationary symmetric point, which is stable and single on the assumption of $\alpha, \gamma$ – are sufficiently small, (iii) subject to $\alpha, \gamma$ are sufficiently great the symmetric point lose its stability, (iv) if $n$ is even two partially symmetric stable stationary points arise in the system, (v) if $\alpha, \gamma$ are sufficiently great oscillation trajectories which are symmetric appear to exist, (iv) in order to answer the question about their stability we use $(n,k)$ – criterion. The question about quantity of symmetric cycles of (1) is to be examined. Given work presents an efficient method for searching symmetric cycles for system (1), so-called Model M$(n,2)$. The computation is based on the analyses of equation (2), which by itself is a model of auto-repressilator, single gene element able to repress its own expression (Likhoshvai et al., 2005).

METHODS AND ALGORITHMS

Consider the boundary value problem for delay equation that naturally appears from the problem of finding symmetric periodic solutions of system (1). Such solution consists of $n$ identical periodic trajectories, which are shifted for value $\tau$ from each other.

$$\frac{du(t)}{dt} = T\left(\frac{\alpha}{1 + u'(t - \tau)} - u(t)\right),\quad u(0) - u(1) = 0,\quad u(0) - \frac{\alpha}{1 + u'(\tau)} = 0. \quad (2)$$

Investigation of problem (2) is connected with approximate discrete model representation, that appears to be the system of $n$ nonlinear equations for the mesh values of function $u(t)$ (Fadeev, 1990).

For this purpose we integrate both parts of differential equation (2) on interval $[t_i, t_{i+1}]$:

$$u_{i+1} - u_i = \alpha T \int_{t_i}^{t_{i+1}} f(u(t - \tau))dt - T \int_{t_i}^{t_{i+1}} u(t)dt, i = 1, ..., N - 1,$$

Let's denote:

$$F_i = u_{i+1} - u_i + T \int_{t_i}^{t_{i+1}} u(t)dt - \alpha T \int_{t_i}^{t_{i+1}} f(u(t - \tau))dt = 0, i = 1, ..., N - 1, \quad (3)$$

where $T$ – period, $\tau$ – delay, $f(x) = \frac{1}{2}\left(1 + x^2\right)$.

Integrals in (3) are approximately calculated using Hermite parabola

$$\int_{t_i}^{t_{i+1}} u(t)dt = \frac{h_i}{2}(u_i + u_{i+1}) + \frac{h_i^2}{12}(u_i - u_{i+1}),$$

and Simpson quadrature formula

$$\int_{t_i}^{t_{i+1}} f(u(t - \tau))dt = \frac{h_i}{6}\left(f(u(t_i - \tau)) + 4f\left(u\left(t_i + \frac{t_{i+1}}{2} - \tau\right)\right) + f(u(t_{i+1} - \tau))\right).$$
For system (3) we add periodicity condition – second equation (2), and transversality condition – third equation (2). Finally we obtain the system of non-linear rational equations which we solve by Newton method.

We supply our numerical method with mesh adaptation, it holds up computational accuracy for great gradient domains. The adaptation is based on the analytical boundary value problem (1) solution for $\gamma = \infty$. The limiting solution, that is

$$u(t) = \begin{cases} 
(1 - \alpha) \exp(t_1 - t) + \alpha, & t \in [0, t_2], \\
\exp(t_2 - t), & t \in [t_2, T], 
\end{cases}$$

almost coincide with the solution for (2) for $\gamma$ sufficiently great.

**IMPLEMENTATION AND RESULTS**

Using parameter $T$ continuation for boundary value problem (2) we may calculate functional dependence $T/\tau$ from $\tau$ (Fig. 1) and thus to obtain plurality of solutions for model M($n$,2) in the domain of parameter modification (Fadeev *et al.*, 1998).

![Graph](image)

*Figure 1. Dependence of the ratio $\frac{T}{\tau}$ from $\tau$, $\alpha = 25$, $\gamma = 10$.*

Fig. 1 shows dependence $T/\tau$ from $\tau$, according to it, we may conclude that, for example, model M(5,2) has 3 solutions. Components of symmetric periodic solution for model M($n$,2) may differ one from the other for the constant value $\tau$, where by virtue of symmetry $\tau$ must be multiple $1/T$ and satisfy inequality $0 < \tau < 1$. That is why the only values $T/\tau$ receive are 5 and 5/2. For this magnitudes correspond $\tau$ values 6.3313, 0.7503 and 0.4181.

For those $\tau$ we compute the solution of problem (2).

Fig. 2 demonstrates periodic solution for $\tau = 6.3313$. Chart presents dependence $u(t)$, where time is $T$-normalized.
Figure 2. Solution $u(t)$ for (2), $\alpha = 25, \gamma = 10, \tau = 6.3313, T = 15.7331$. Time is relative to period $T$.

**DISCUSSION**

Studying properties of model $M(n,2)$ appears to be an important problem for the theory of gene network. Particularly, this models describe for $n = 2$ molecular trigger and for $n = 3$ repressilator, such constructions were realized by gene-engineering methods (Gardner et al., 2000; Elowitz, Leibler, 2000; Tchuraev et al., 2000). The model have been studied is interesting as well for more complicated molecular-genetic systems construction (Sprinzak, Elowitz, 2005). That is why it is important to reveal in simple regulatory circuits all types of dynamic behavior.

Method have been suggested allows to find efficiently symmetric periodic trajectories in gene network mathematical models class $M(n,2)$. Let us note, that all symmetric model $M(n,2)$ cycles for arbitrary $n$ are cycles of auto-repressilator model. However, question about complicated types of periodical trajectories is not already examined. Computational investigation shows, that for even $n$ partially-symmetric periodical trajectories may be found for model $M(n,2)$. All components of those solutions are divided into two groups; in each group trajectories are identical and shifted from each other for some phase. All such periodic solutions satisfy the system of two equations with delay:

\[
\frac{dy_1}{dt} = \frac{\alpha}{1 + y_2^\gamma(t-\tau)} - y_1, \quad \frac{dy_2}{dt} = \frac{\alpha}{1 + y_1^\gamma(t-\tau)} - y_2,
\]

which present a molecular trigger model, that keeps in mind times of protein-regulator synthesis. Consequently, we could expect molecular trigger to have nonsymmetrical cycle. That is why transient regime from one stationary point to another (switching of molecular trigger) could go through oscillation trajectory, twisting on that cycle arbitrary long. This trajectory is periodic-like. Since the cycle is not stable, fluctuations sooner or later will transfer it to stable regime. In future we are to examine oscillation parameters for more complicated models of molecular trigger in order to appreciate possibility of its existence naturally.

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