TOPOLOGICAL INDEX OF THE *P53-MDM2* CIRCUIT

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Analysis of oscillating regimes in regulatory networks models with multistability properties and with switch-oscillator mechanisms is an important task both from the biological and from the mathematical viewpoints. Unification of discrete and continuous approaches in gene network modeling should be useful for understanding the functioning of the regulation mechanisms of natural and artificial biological systems. Our investigations of the nonlinear dynamical systems as models of the gene networks are based on topological methods elaborated in (Golubyatnikov *et al*., 2006; Gaidov, Golubyatnikov, 2007). Here we study the phase portrait of a system of nonlinear differential equations proposed in (Chikarmane *et al.*, 2007), see also (Lahav *et al*., 2004) as a model of oscillations in the *p53-Mdm2* DNA damage repair network. We construct a domain Q in the phase space such that the topological index of the velocity vector field in Q is nontrivial in presence of the DNA damage and vanishes for small amounts of this damage. This demonstrates a direct relationship between the index of the corresponding velocity vector field and the presence of the DNA damage in this model and exhibits a topological approach to the unification of discrete and continuous gene network modeling.

Key words: gene network models, stationary points, topological index, oscillations.

Introduction

We continue our studies (Golubyatnikov *et al*., 2006; Likhoshvai *et al.*, 2008) of kinetic dynamical systems serving as gene network models. Here, our main aim is to describe multistability in the regulatory network of the DNA damage response system as modeled in (Chikarmane *et al.*, 2007), and to outline important connections of studies of discrete and continuous gene network models. A short exposition of our considerations was presented in (Golubyatikov, Mjolsness, 2008).

The following kinetic system (Chikarmane *et al.*, 2007) represents a model of oscillations in the *p53-Mdm2* circuit. This model contains positive and negative feedback loops in its regulation mechanism. Its phase space is the positive octant R^4_+ in the space of the variables $\{x, y, z, D\}$. Here the positive feedback is related to autocatalysis in *p53*, which activates *Mdm2* as well, and the negative one corresponds to inhibition of *p53* by *Mdm2*.

$$\begin{aligned}
&\frac{dx}{dt} = \Phi_1(x,y,z) = \alpha_0 z + \frac{\alpha_1 \cdot x^6}{k_1 + x^6} - \gamma_1 xy - \gamma_2 x;\\
&\frac{dy}{dt} = \Phi_2(x,y) = \alpha_2 + \frac{\alpha_3 \cdot x^4}{k_2 + x^4} - \gamma_3 y;\\
&\frac{dz}{dt} = z \cdot \Phi_3(z,D) =\\
&\qquad = \frac{\alpha_{1s} \cdot z \cdot (B - z)}{k_{1s} + B - z} - \frac{\alpha_{2s} \cdot z}{(k_{0d} + D)(k_{2s} + z)};\\
&\frac{dD}{dt} = -\alpha_d \cdot D \cdot zx.
\end{aligned} \tag{1}$$

Most of the variables here denote dimensionless concentrations of corresponding species: x=[*p53*], y=[*Mdm2*], z=[*Atm-P*]; z is the switch variable. $D(t)$ denotes the amount of the DNA damage in the network, B = [*Atm*] + [*Atm-P*] appears from the conservation law.

Results

1. For each fixed t_0 consider intersection of 3-D plane $(x, y, z, D(t_0))$ with the positive octant R^4_+.

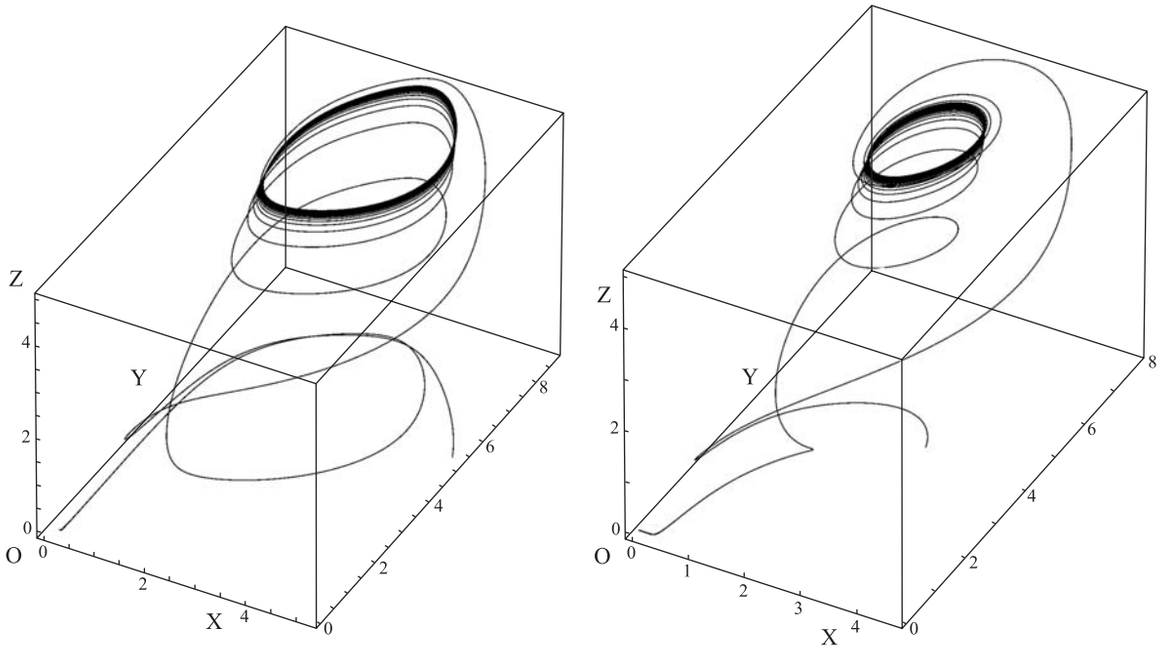

Fig. 1. Behavior of trajectories of the system (1).

B = 5, ε = 4,4. Initial data: $z_0 = 0{,}1$; $D_0 = 10$. Left $n = 5$; $x_0 = 5$; $y_0 = 5$. Right $n = 4$; $x_0 = 4$; $y_0 = 3$.

We call the points where $\frac{dx}{dt} = \frac{dy}{dt} = \frac{dz}{dt} = 0$ · **3-stationary** and consider a domain $Q = [0, C_1] \times [0, C_2] \times [\varepsilon, B] \subset R^3_+(x, y, z)$ with the boundary ∂Q. Here $\gamma_2 \cdot C_1 \geq \alpha_0 \cdot B + \alpha_1$, $\gamma_3 \cdot C_2 \geq \alpha_2 + \alpha_3$, and ε is positive. For small t all trajectories of (1) of the points of ∂Q enter Q. According to (1), $\Phi_3(B, D) < 0$ and $\frac{dD}{dt}$ is strictly negative for all t and positive x and z. If $\Phi_3(0,0) > 0$, then there exists unique $z_1 \in (0, B)$ such that $\Phi_3(z_1, D) = 0$ for all D. $\Phi_2(x, y) = 0$; $\Phi_1(x, y, z_1) = 0$ imply that the summed indices of 3-stationary points in Q coincides with the signed number of roots x of the equation

$$\alpha_0 \cdot z_1 + \frac{\alpha_1 \cdot x^6}{k_1 + x^6} - \frac{\gamma_1 \cdot x}{\gamma_3}\left(\alpha_2 + \frac{\alpha_3 \cdot x^4}{k_2 + x^4}\right) - \gamma_2 \cdot x = 0 .$$

Direct calculations show that for small values of t the sum of 3-dimensional indices of all 3-stationary points in Q equals -1. This corresponds to large values of the DNA damage. For large t and any $\varepsilon \geq 0$ this index vanishes. In this case the DNA damage is small.

The values of all parameters in our numerical experiments were taken close to ones listed in (Chikarmane *et al.*, 2007). It was indicated there that for some intermediate value $D(t)$ during the repair process, the variable x passes through an Andronov–Hopf bifurcation.

Fig. 1 above shows typical behavior of trajectories of the system (1). Here for small values of z_0 and large D_0 trajectories jump to the domain $4{,}4 < z < 5$ and remain there till $D > 0{,}58$.

2. We have seen that the geometric properties of the graphs of the right hand sides of the equations (1), such as spectra of the Jacobian matrices evaluated at the stationary points, conditions of the type $\Phi_3(0,0) > 0$, and the slopes of these graphs, are much more important for bifurcations and other dynamical characteristics of these models than is the concrete analytic representation of Φ_1, Φ_2, Φ_3. Similar observations were made in (Golubyatnikov *et al.*, 2006; Gaidov, Golubyatnikov, 2007) for other models of asymmetric gene networks. General constructions related to the Conley index, see (Salamon, 1990), can be used in the cases of more complicated gene network models.

Conclusion and Discussions

Our analysis of the *p53-Mdm2* oscillatory dynamics is connected with decomposition of high-dimensional models to lower-dimensional ones.

This procedure can be considered as a discretization of a continuous model. Similar decompositions can be used in mathematical modeling of more complicated regulatory networks. The direct relation of the topological index of the repair system (1) with the presence of the DNA damage demonstrates a new approach to gene networks studies. This approach is based on the comparison of properties of continuous models and discrete models of the same gene network. Such a dualism can yield new possibilities in the study of problems in system biology.

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References

Chikarmane V., Ray A., Sauro H.M., Nadim A. A model for *p53* triggered by DNA damage // SIAM J. Appl. Dynamic Systems. 2007. V. 6. № 1. P. 61–76.

Gaidov Yu.A., Golubyatnikov V.P. On some nonlinear dynamical systems modeling asymmetric gene networks // Bul. of Novosibirsk State University. 2007. V. 7. № 2. P. 23–32. (In Russ.).

Golubyatnikov V.P., Gaidov Yu.A., Kleshchev A.G., Volokitin E.P. Modeling of asymmetric gene networks functioning with different types of regulation // Biophysics. 2006. V. 51. Suppl. 1. P. 61–65.

Golubyatnikov V.P., Mjolsness E. Topological index of a model of p53 dynamics triggered by DNA damage // Abstracts of the 6th Intern. Conf. on Bioinformatics of Genome Regulation and Structure (BGRS'2008). Novosibirsk, 23–28 June 2008. Novosibirsk: Inst. Cytol. Genet., 2008. P. 89.

Lahav G., Rosenfeld N., Sigal A. *et al.* Dynamics of the p53-Mdm2 feedback loop in individual cell // Natural Genet. 2004. V. 36. № 1. P. 147–150.

Likhoshvai V.A., Golubyatnikov V.P., Demidenko G.V. *et al.* Theory of Gene Networks // Computational Systems Biology, (Russian) / Eds N.A. Kolchanov, S.S. Goncharov, V.A. Likhoshvai, V.A. Ivanisenko. Novosibirsk: SB RAS. 2008. P. 397–480.

Salamon D.A. Morse theory, the Conley index and Floer homology // Bul. of Lond. Math. Soc. 1990. V. 22. № 1. P. 113–140.