PROBLEMS OF CONTROL OF GENE NETWORKS IN A SPACE OF STABLE STATES


1 Institute of Theoretical and Applied Mechanics, SB RAS, Novosibirsk, Russia, e-mail: latypov@itam.nsc.ru
2 Institute of Cytology and Genetics, SB RAS, Novosibirsk, Russia
*Corresponding author

Key words: gene network, stable state, nonlinear and linear programming, sensitivity matrix

Resume

Motivation: Mutations occurring in genes result frequently in impaired operation of gene networks, causing a diversity of pathologies. Of highest importance is to find the optimal factors and strategies for correcting their functions. This necessitates development of the methods allowing the gene network operation to be controlled.

Results: This work describes statements of problems of control in a space of stable states with reference to gene networks reduced to problems of linear and nonlinear programming. A method for solving nonlinear problems is proposed. A sensitivity matrix for the simplest model simulating cholesterol biosynthesis is constructed and analyzed.

Introduction

Gene network is a set of concertedly expressed genes controlling performance of a particular body function. A group of specific genes together with the following elements form the core of a gene network: (1) proteins encoded by the genes in question; (2) pathways of signal transduction from cell membranes to cell nuclei, providing activation or inhibition of gene transcription; (3) negative and positive feedbacks, either stabilizing gene network parameters at a certain level or, on the contrary, deviating them from the initial value, thereby switching the system into a new functional state; and (4) low-molecular-weight components, switching the gene network function in response to external stimuli (hormones and other signal molecules), energy carriers, various metabolites, etc. (Kolchanov et al., 2000).

Normal gene network operation requires a concerted interaction of all its components in both space and time domains as well as its ability to adequately receive and process the external signals. Impairment of any component may lead to a certain degree of impairment in the gene network operation, resulting in various pathologies. This arises the problem of searching for optimal intervention into gene network operation with minimal side effects. Summing up, the problem of searching for optimal intervention into gene network operation is a problem of control in a broad sense.

An important specific feature of the problem of gene network control is the necessity of solving it in two stages, that is, it is first necessary to find out whether a state required is existing. This brings about the problem of control in the space of stable states (PCSS). Then, if the answer is positive, the problem of searching for optimal realization of the state required in the dynamic process is solved.

A schematic representation of correcting the gene network function on the surface of stable states is shown in Fig. 1. The gene network in a state of pathology A is subjected to controlling effects and transferred to the normal state B. Not all the effects are allowed (crossed out here), as they lead to adverse side effects.

The problems of control have not been yet stated in the context of gene networks. The goal of this work is to fill partially this gap. Here, we are formulating two problems of control of gene network stable states. We are also considering certain approaches to their solution based on considering the sensitivity matrix and solving problems of control “locally”.

Problems of control of stable states

In the context of modern concepts, the operation of a gene network (GN) is described with a system of ordinary differential equations (ODE; Likhoshvai et al., 2001):

$$\dot{V} = f(V, a),$$

where $V$ is the vector of parameters of a GN state and $a$, the vector of internal parameters. Let the values $a = a_*$ correspond to the normal state of gene network. Let GN in the normal state maintain a certain equilibrium state. Formally, this means that the system $f(V, a) = 0$ allows at least one nontrivial solution to exist in the range of positive values $V^*$:

$$V^* \neq 0.$$

Let us designate $T = \tau a$ as normal (basic). Let us consider the state $V^*$ as normal (basic). Let us designate $w = \frac{V}{V^*}$, $\alpha = \frac{a}{a_*}$, $\tau = \frac{t}{T}$, where $T$ is the characteristic time of the process. Then, (1) may be expressed in a dimensionless form as

$$\frac{dw}{d\tau} = T \varphi(w, \alpha).$$

Let the totality of parameters $\alpha$ be divided into three following groups (this partition depends on the particular situation studied):

1) $\alpha_k, \ k \in K$ is the totality of assigned numbers of the parameters displaying changed values that arouse due to mutations;
2) $\alpha_l, \ l \in L$ is the totality of assigned numbers of the parameters used as controls; and
3) $\alpha_m, \ m \in M$ are the rest parameters that are remaining unchanged, that is, $\alpha_m = 1$.

Let us distinguish two statements of the problem of control of stable states.

Problem No. 1. Let us specify

1) Certain values $\alpha_k = \alpha_k^*$ of the parameters from group $K$;
2) The region of admitted values $\alpha_l \in D_l = \{\alpha_l : \alpha_l^{\min} \leq \alpha_l \leq \alpha_l^{\max}\}$ of the parameters from group $L$;
3) Neighborhood of the basic point $B_\Delta = \{w : -1 \leq w \leq 1\}$ and the functional $F = \frac{1}{2} \sum_{l=1}^{L} \beta_l (\alpha_l - 1)^2$, $\beta_l$ are weight coefficients $\sum_{l} \beta_l = 1$.

It is necessary to determine such $\alpha_l$ that $\varphi(\tilde{w}, \tilde{\alpha}_l, \tilde{\alpha}_l)_{\tilde{\alpha}_l = 1} = 0$ (stationary condition), $\tilde{w} \in B_\Delta$ (condition of occurrence in the region), and $F(\tilde{\alpha}_l) = \min_{\alpha_l \in D_l} F(\alpha_l)$.

The functional $F$ characterizes minimal deviations of the parameters from their basic values and, therefore, it is likely that minimal “expenditure” effects will be required for achieving $\alpha_l$.

If PCSS solution requires taking into account the selection of starting point and the trajectory for reaching the basic point within the region specified, we are coming to the formulation of problem No. 2.
Problem No. 2. The stationary point \( \mathbf{w} \) from equations \( \varphi(\mathbf{w}, \mathbf{a}) \bigg|_{\mathbf{a} = 1, \mathbf{a}_m = 1} = 0 \) is determined in addition to the statement of problem No. 1. It is necessary to determine the sequence \( \mathbf{a}_i^j, i = 0,1,\ldots \), such that

\[
\varphi(w^i, a_k, a^j) \bigg|_{a_m = 1} = 0; \quad \varphi(w^{(i)}) \leq 0; \quad \lim a^{(i)} = a; \quad \lim w^{(i)} = \mathbf{w}; \quad \text{and} \quad \mathbf{w} \in B_\Delta; \quad F(\mathbf{a}_i) = \min_{a_i \in b_i} F(\mathbf{a}_i).
\]

Here, the function \( \varphi(\mathbf{w}) \) specify the region of admitted trajectories in the space of states.

The software package Poisk (Latypov, Nikulichev, 1985) may be used for solving problems № 1 and 2. The package has been essentially revised, adapted to the problems of gene network control, and realized in the Delphi-4 environment.

Solving of PCSS requires frequently obtaining of the following information:

- Determining the necessary accuracy for specifying the vector of internal parameters \( \mathbf{a} \);
- Determining the rational composition of control parameters from the totality of \( \mathbf{a} \);
- "Calibrating" the parameters according to their significance; and
- Evaluating the adequacy of the GN model considered.

The most optimal method to solve such problems is application of sensitivity matrix. Sensitivity matrix may be constructed at any stationary point. Let us describe the procedure of its construction.

For definiteness, let us consider the basic point \( \mathbf{a} = 1, \mathbf{w} = 1 \). The initial equations at the stationary point take the following generalized form

\[
\begin{align*}
\varphi(w, \mathbf{a}) = 0, & \quad \varphi = \left[ \varphi_i, i = 0, n \right], \quad w = \left[ w_i, i = 0, n \right], \quad \mathbf{a} = \left[ a_j, j = 0, m \right], \\
\text{and variation form} & \quad J \cdot \mathbf{x} = -C \cdot \mathbf{p}, \quad \mathbf{x} = \delta \mathbf{w}, \quad \mathbf{p} = \delta \mathbf{a}, \quad J = \frac{\partial \varphi}{\partial w}, \quad C = \frac{\partial \varphi}{\partial \mathbf{a}}.
\end{align*}
\]

Then, the solution is as follows:

\[
\mathbf{x} = D \cdot \mathbf{p}, \quad D = J^{-1} \cdot C = \left\{ c_{ij} \right\}, \quad y_{ij} = \frac{x_i}{p_j}.
\]

For a simplified variant of the mathematical model simulating cholesterol biosynthesis regulation (Ratushny et al., 2000), containing 10 equations and 38 parameters, we constructed the matrix of coefficients relating the variations in internal parameters of the mathematical model to the changes in stationary state parameters (sensitivity matrix). Analysis of this matrix allowed us to distinguish three following groups of the parameters used in the model in question: (1) the group of a high effect (comprising only one parameter) with a coefficient of influence amounting to \( \sim 10^2 \); (2) the group of a moderate effect (six parameters) with a coefficient of influence of \( \sim 1 \); and (3) the group of a weak effect (all the rest parameters) with a coefficient of influence equaling \( \leq 0.5 \). A number of parameters of the third group, falling into a separate subgroup, display a very weak effect on the parameters determining the state of the system.

The analysis performed suggests that depending on the problem solved, the sensitivity matrix alone allows the preliminary conclusions on certain possibilities in controlling the system to be made. Moreover, the sensitivity matrix gives useful information while solving the problem of determining the values of model’s variables from measurements of the stationary states of the system. For example, to increase the accuracy of estimating a particular variable, it is appropriate to measure the elements, the coefficients of influence on which with reference to the variable in question is \( \sim 1 \), as the error increases multifold at a low coefficient due to the inversely proportional dependence, whereas time resolution might be inaccessible at a high value of the coefficient.

With reference to PCSS, the sensitivity matrix should be considered when the optimal control is searched for within a small neighborhood of the basic (normal) state (local control). In this case, the PCSS is reduced to solving a sequential set of liner programming problems. A linear programming problem is solved in two following stages. At the first stage, a point \( \mathbf{x}^* \) satisfying the condition for occurrence in the region specified is determined:

Problem L1.

\[
x_i = \sum_{k} y_{ik} p_k + \sum_{l} y_{il} p_l; \quad |x_i| \leq \Delta_i;
\]

\[
F = \sum_{i} c_i x_i = \min_{p_i \in P_i} c_i, \quad c_i \in \{-1,0,1\}
\]

where \( x_i \) is changes in the parameters of the state caused by mutation (the sum over k) and by control (the sum over l) and \( \Delta_i \) specifies the admissible region. The functional \( F \) provides that the point occurs in the region specified. Let us designate the solution of Problem L1 as \( p_i = p_i^* \). Then, the second stage problem is solved.

Problem L2.
\[ x_i = \sum_k \gamma_{ik} p_k + \sum_l \gamma_{il} p_l^*; |x_i| \leq \Delta_i; \]

\[ F^* = \sum_l \text{Sign}(p_l^*) \beta_l p_l \Rightarrow \min_{p_l \in P_l} \]

**Conclusion**

Described here are the statements of the problems of control in a space of stable states applied to gene networks that are reduced to problems of linear and nonlinear programming and the method for solving nonlinear problems. The sensitivity matrix for a simplest model of cholesterol biosynthesis is constructed and analyzed.

**Acknowledgements**

The work was supported in part by the Russian Foundation for Basic Research (grants № 01-07-90376 and 02-07-90359), Russian Ministry of Industry, Science, and Technologies (№ grant № 43.073.1.1.1501), and Siberian Branch of the Russian Academy of Sciences (Integration Project № 65).

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