of textile industry of Russia. For this model, the optimal control problem is investigated for the solvability. For the case of ill-posed dynamic model, the possibility of correction is considered on the base of the approach by I. Eremin.

*Key words*: optimal control problem; correction of models; linear difference model; inconsistent system; inconsistent model.

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# MODELING GENE REGULATORY NETWORKS: MATHEMATICS VS. BIOLOGY

## © A.V. Ponossov, A.I. Shindiapin, V.S. Tafintseva

*Key words*: gene regulatory networks; sigmoid functions; singular perturbation analysis.
We study some properties of the solutions of differential systems describing gene regulatory networks, where instead of linear functions on the right-hand side we consider polynomial functions. We have obtained some different properties of solutions' behavior in the sufficiently close vicinity of singular domains, in particular, walls although in regular domains the dynamics coincide. Thus, linear systems do not describe real dynamics of a gene network.

Consider the system

$$\dot{x}_i = F_i(z_1, ..., z_n) - G_i(z_1, ..., z_n)x_i, \quad i = 1, ..., n, \tag{1}$$

where

$$F_i(z_1, ..., z_n) \geqslant 0, \quad G_i(z_1, ..., z_n) > 0 \quad (0 \leqslant z_i \leqslant 1)$$

are the (regulated) production rate and the (regulated) relative degradation rate, respectively.

Each $z_i$ is a function of the single gene concentration $x_i$, i.e. $z_i = H(x_i, \theta_i, q_i)$. The response functions describe gene interactions in the gene regulatory network. It depends on 2 parameters $\theta > 0, q > 0$. If $q \to 0$, then $H$ becomes the step function with the unit jump at $x = \theta$: $q \to 0$
$\Rightarrow z \to \begin{cases} 0 & \text{if} \quad x < \theta \\ 1 & \text{if} \quad x > \theta \end{cases}$ .

An example is the Hill function given by $z = H(x, \theta, q) = \dfrac{x^{1/q}}{x^{1/q} + \theta^{1/q}}$.

**The Boolean-like formalism**

In (1) let us assume that $q_i \to 0$ for all $i = 1, ..., n$.

This results in

$$\dot{x}_i = F_i(B_1, ..., B_n) - G_i(B_1, ..., B_n)x_i, \quad i = 1, ..., n, \tag{2}$$

where $B_i = 0$ or $1$ are Boolean variables.

This simplified Boolean model (2)

As soon as this formalism is adopted we can make some conclusions resulting in the assumptions which are common in the analysis of gene regulatory networks.

E x a m p l e 1. Consider two scalar functions $f(z, x) = z^3 - 2z^2 + 3z - x$ and $g(z, x) = 2z - x$. They are different, but the difference is not seen within the Boolean-like formalism (where $B^n = B$ for any Boolean variable and any positive $n$), so that $f(B, x) = g(B, x)$. In other words, the systems (equations) $\dot{x} = f(B, x)$ and $\dot{x} = g(B, x)$ are just identical.

That is why a usual assumption put on the right-hand side in the Boolean-like models is linearity of the functions in each variable $z_i$.

T h e o r e m 1. *For an arbitrary $C^1$-system*

$$\dot{x}_i = \overline{F}_i(z_1, ..., z_n) - \overline{G}_i(z_1, ..., z_n)x_i \quad i = 1, ..., n$$

*such that* $\overline{f}_i(\mathcal{B}) = F_i(\mathcal{B}), \overline{G}_i(\mathcal{B}) = G_i(\mathcal{B})$ *for any Boolean vector* $\mathcal{B} = (B_1, ..., B_n)$.

Although the simplified model is Boolean, the actual model is smooth. Can we argue for the assumptions of linearity in each $z_i$ in this case?

The common answer from biologists is «yes», because the sufficiently steep sigmoid function $z = H(x, \theta, q)$ is close to the step function, so that $H^n(x, \theta, q) \approx H(x, \theta, q)$ for small $q > 0$, and in the limit we obtain the equality $H^n(x, \theta, 0) = H(x, \theta, 0)$, so that if we assume that the limit dynamics is good enough to approximate the true dynamics for small $q > 0$, then the assumption of linearity may be put on the right-hand sides of the system. Can this assumption be justified in a rigorous way?

**A more general setting**

The Boolean-like formalism is used in other fields, where the right-hand side may be different from that used in the gene networks. Consider a smooth dynamical system

$$\dot{x} = f(z, x) \tag{3}$$

where $x = (x_1, ..., x_n)$, $z = (z_1, ..., z_n)$, $f_i = f_i(z_1, ..., z_n, x_i)$, $z_i = H(x_i, \theta_i, q_i)$ ($q_i > 0$, $i = 1, ..., n$) (for example, $f_i(z, x) = F_i(z) - G_i(z)x_i$ for gene networks).

In the limit, we obtain the Boolean-like representation:

$$\dot{x} = f(B, x)$$

where $B = (B_1, ..., B_n)$ is a Boolean vector, i. e. $B_i = 0$ or $1$.

E x a m p l e 2. Let us consider two systems

$$\dot{x}_1 = 0.1z_1 + 0.18x_1$$
$$\dot{x}_2 = 2z_2 - x_2,$$

$$\dot{x}_1 = z_1^2 - 0.9z_1 + 0.18x_1$$
$$\dot{x}_2 = 2z_2 - x_2.$$

They are identical within the Boolean-like formalism, as $B_1^2 - 0.9B_1 = 0.1B_1$ for any Boolean $B_1$, so that the two dynamics should be expected to be close to each other for sufficiently steep response functions $z_i = H(x_i, \theta_i, q_i)$, where $q_i > 0$ are small, at least if we rely upon Theorem 1.

**Singular Perturbation Analysis**

We claim that Theorem 1 and the Boolean-like formalism in its classical setting are not sufficient. To see this, we analyze the behavior of the solutions in a vicinity of a threshold value.

For the sake of simplicity we assume in the sequel that $x_1$ is close to its threshold value $\theta_1$ (i.e. $x_1$ is a singular variable), while $x_2, ..., x_n$ stay away from their respective threshold values $\theta_2, ..., \theta_n$ (i.e. they are regular variables). The equation (3) can then be split into the system

$$\dot{x}_1 = f_1(z_1, z_R, x_1)$$
$$\dot{x}_R = f_R(z_1, z_R, x_R),$$

where $x_R = (x_r)_{r \in R}$, $z_R = (z_r)_{r \in R}$, $f_R = (f_r)_{r \in R}$.

Replacing $x_1$ with $z_1 = H(x_1, \theta_1, q_1)$ yields the following equivalent system («the full system»):

$$q_1 \dot{z}_1 = \frac{z_1(1 - z_1)}{x_1} f_1(z_1, z_R, x_1)$$
$$\dot{x}_R = f_R(z_1, z_R, x_R),$$

where $x_1 = H^{-1}(z_1, \theta_1, q_1)$.

To understand the solutions' behavior around the threshold $x_1 = \theta_1$ one uses the stretching transformation $\tau = t/q$ taking the full system into the boundary layer system:

$$z_1' = \frac{z_1(1 - z_1)}{x_1} f_1(z_1, z_R, x_1)$$
$$x_R' = q_1 f_R(z_1, z_R, x_R),$$

where $x_1 = H^{-1}(z_1, \theta_1, q_1)$ and $z_1'$ is the derivative with respect to the fast time $\tau$.

Letting $q_i \to 0$ we arrive at the boundary layer equation

$$z_1' = \frac{z_1(1 - z_1)}{\theta_1} f_1(z_1, B_R, \theta_1),$$

where $B_R = \lim\limits_{q_i \to 0} z_R$.

The behavior of the solutions of the original system around the threshold plane $x_1 = \theta_1$ depends on asymptotic stability of stationary points of the boundary layer equation. For instance, sliding modes only occur if the boundary layer equation has an asymptotically stable stationary point $z_1^* \in (1)$. In this case the limit dynamics in the threshold plane (where $q_i = 0$) obeys the reduced system

$$\dot{x}_R = f_R(z_1^*, B_R, x_R).$$

If there is no stable stationary point inside (1), then either $z_1 = 0$ or $z_1 = 1$ must be asymptotically stable, which gives solutions traveling through the threshold plane $x_1 = \theta_1$ (i. e. no sliding modes can occur).

E x a m p l e 2 (cont.)

Let us look closer at the boundary layer equations for the systems from Example 2.

$$z_1' = z_1(1 - z_1)(0.1z_1 + 0.18),$$

$$z_1' = z_1(1 - z_1)(z_1^2 - 0.9z_1 + 0.18)$$

The singular perturbation analysis shows that the limit dynamics in the linear case and in the polynomial case can be very different. In the other hand, if $q_i \to 0$, then the Boolean-like formalism as it appears in Theorem 1 does not distinguish between polynomials and linear

functions, because $B^n = B$ for any Boolean variable. This means that the conventional assumption of linearity in the Boolean-like formalism does not hold from the mathematical point of view.

**The general boundary layer equation**

The question we want to address below is as follows: What is the minimal degree of the polynomials which would be enough to distinguish between all possible kinds of sliding modes in the limit. The answer is 3.
The equation

$$z_1' = \frac{z_1(1 - z_1)}{\theta_1} f_1(z_1, B_R, \theta_1),$$

where $B_R = \lim_{q_i \to 0} Z_R$, may have many stationary solutions in (1). However, only the leftmost and the rightmost stationary solutions can provide sliding motions in the threshold plane. This is due to the fact that the initial values $z_1(0)$ are either 0 or 1.
Indeed,

$$z_1(0) = \lim_{q_1 \to 0} H(x_1, \theta_1, q_1) = 0 \text{ if } x_1 < \theta_1 \text{ and } 1 \text{ if } x_1 > \theta_1.$$

If $x_1 < \theta_1$, then $z_1(0) = 0$, which means that $z_1(\tau)$ will tend to the stable leftmost stationary point $z_1^{(1)} \in (0, 1)$. If now the total number of stationary solutions in (1) is even, then the rightmost stationary point within this interval $(0, 1)$ is unstable. The plain $x_1 = \theta_1$ becomes attractive on the left and repellent on the right. The other points are not essential for the limit dynamics. That is why the polynomials of degree 2 in $z_1$ can capture this kind of asymptotical behavior.

T h e o r e m 2. *Assume that the boundary layer equation has a nonempty even number of stationary solutions in* (1). *Then the threshold plane* $x_1 = \theta_1$ *will be attractive on one side and repellent on the other.*

In this case an arbitrary $C^1$-function $f$ in the system $\dot{x} = f(z, x)$ can be in the limit replaced with a quadratic polynomial.

Assume now that the number of stationary solutions in (1) is odd. In this case $z_1(\tau)$ will tend either to the leftmost or to the rightmost stationary point which both will be asymptotically stable. The threshold plain becomes therefore attractive on the left and on the right. The other stationary points are not essential for the limit dynamics.

This kind of asymptotical behavior is captured by the polynomials of degree 3 in $z_1$.

T h e o r e m 3. *Assume that the boundary layer equation has a nonempty odd number of stationary solutions in* (1). *Then the threshold plane* $x_1 = \theta_1$ *will be attractive on both sides.* In this case an arbitrary $C^1$-function $f$ in the system $\dot{x} = f(z, x)$ can be in the limit replaced with a cubic polynomial.

**Conclusions**

We considered a gene regulatory network

$$\dot{x}_i = F_i(z_1, ..., z_n) - G_i(z_1, ..., z_n)x_i, \quad i = 1, ..., n,$$

where $F_i, G_i$ are general $C^1$-functions.
We examined the Boolean-like formalism which is meant to describe the limit dynamics of this system when $z_i$ become Boolean.

— The conventional models where $F_i$ and $G_i$ are replaced with multilinear functions (linear in any $z_i$) and which are based on the «<mathematical»> argument that $B^n = B$ for Boolean variables, do not capture at least two essential kinds of the limit dynamics.

— The functions $F_i$ and $G_i$ should be replaced with multicubic polynomials (cubic in any $z_i$) in order that all possible kinds of limit dynamics will be captured.

— These conclusions are also valid for the gene networks with special delays (integral and degenerate).

Поносов А., Шиндяпин А., Тафинцева В. Моделирование генных сетей: математика против биологии. Мы изучаем некоторые свойства решений дифференциальных систем, описывающих генные регулируемые сети, где вместо линейных функций в правой части мы рассматриваем многочлены. Мы получили некоторые новые свойства поведения решений в достаточно близкой окрестности сингулярных областей, в частности стенок, хотя в регулярных областях динамики совпадают. Таким образом линейные системы не описывают реальную динамику генной сети.

*Ключевые слова*: генные регулируемые сети; сигмоидальная функция; метод сингулярных возмущений.

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# ГАШЕНИЕ КОЛЕБАНИЙ УПРУГОЙ СИСТЕМЫ СТРУН

## © Е.Н. Провоторова

*Ключевые слова*: краевая задача на графе; граничное управление; перевод системы из начального в состояние покоя.

В работе рассматривается система из $m$ струн, закрепленных по типу графа-звезды. Такие математические объекты являются основой математических моделей процессов колебаний в антенных конструкциях различных типов. Представлен метод нахождения граничных управляющих воздействий, состоящий в переводе процесса колебаний системы из заданного начального состояния в состояние покоя. Используется спектральная техника (анализ Фурье), позволяющая сравнительно легко преодолевать сложности, порожденные геометрией графа. Главным результатом работы являются формулы, определяющие искомые граничные управления как функции времени.