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Relationship between a Gene Network Graph and Qualitative Modes of Its Functioning

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Abstract—Theoretical investigation of properties of assumed gene networks constructed from elementary units of two types, genetic elements and control links, was carried out. A test was formulated for a subclass of such networks with cyclic structure called S(n,k) networks allowing calculation-free prediction of the network limit properties (the presence/absence and number of stationary and/or cyclic functioning modes) from a graph of the network structure. The data obtained can be useful for constructing gene networks with predefined properties.

Key words: gene network, mathematical model, control, negative and positive feedbacks, limit cycles, stability

INTRODUCTION

A gene network is a group of conjointly functioning genes providing for execution of a vital function, regulation of physiological processes, response to environmental stimulus, etc. [1]. In addition to the genes any gene network includes several types of essential components such as: (i) mRNA and proteins encoded by these genes; (ii) pathways of signal transmission from the cell membrane to nucleus providing for activation of genes in response to external control stimuli; and (iii) external signals, hormones, and metabolites transmitting physiological control influences, thus, switching a gene network modes.

Any gene network includes negative (stabilizing parameters of a gene network at a certain level) and positive feedbacks (deviating them from the initial state, thus, providing for their transition to a new functional state) [2]. Closed control circuits with negative and positive feedbacks provide for autoregulation of gene networks [3]. Control proteins and low-molecular compounds binding target sites in DNA, RNA, and proteins are the molecular basis of such control circuit functioning.

There is a number of deeply explored gene networks: erythrocyte differentiation control, antiviral response, cholesterol biosynthesis in the cell, heat shock response, seed germination control, nitrogen fixation control, etc. [1, 4, 5]. Simulations were built for some gene networks [6–12] and the methods and programming resources for their modeling and numeric investigation of dynamics were proposed [13–22].

Actual problems of the gene network theory includes prediction of qualitative properties of a gene network functioning from the data on its structural and functional organization [23–29].

Qualitative properties of gene network functioning required for understanding the laws of their activity include: (i) the capacity of a gene network to exist in several (or single) stable states with constant concentration of the substances (stationary states); and (ii) continuous oscillating pattern of the changes in a gene network components concentration (oscillations).

In this work we explored the qualitative behavior of assumed gene networks constructed from two elementary units—genetic elements and control links. Numeric analysis of a large number of models of assumed gene networks with cyclic structure allowed us to formulate a test predicting all its limit properties without calculations, i.e., to predict the presence/absence as well as the number of stationery and/or cyclic modes of its functioning. The approaches presented below can be used to describe both gene networks and metabolic systems.

RESULTS AND DISCUSSION

Description of Assumed Gene Network Construction

We shall build assumed gene networks from two types of elementary units: genetic elements and control links.

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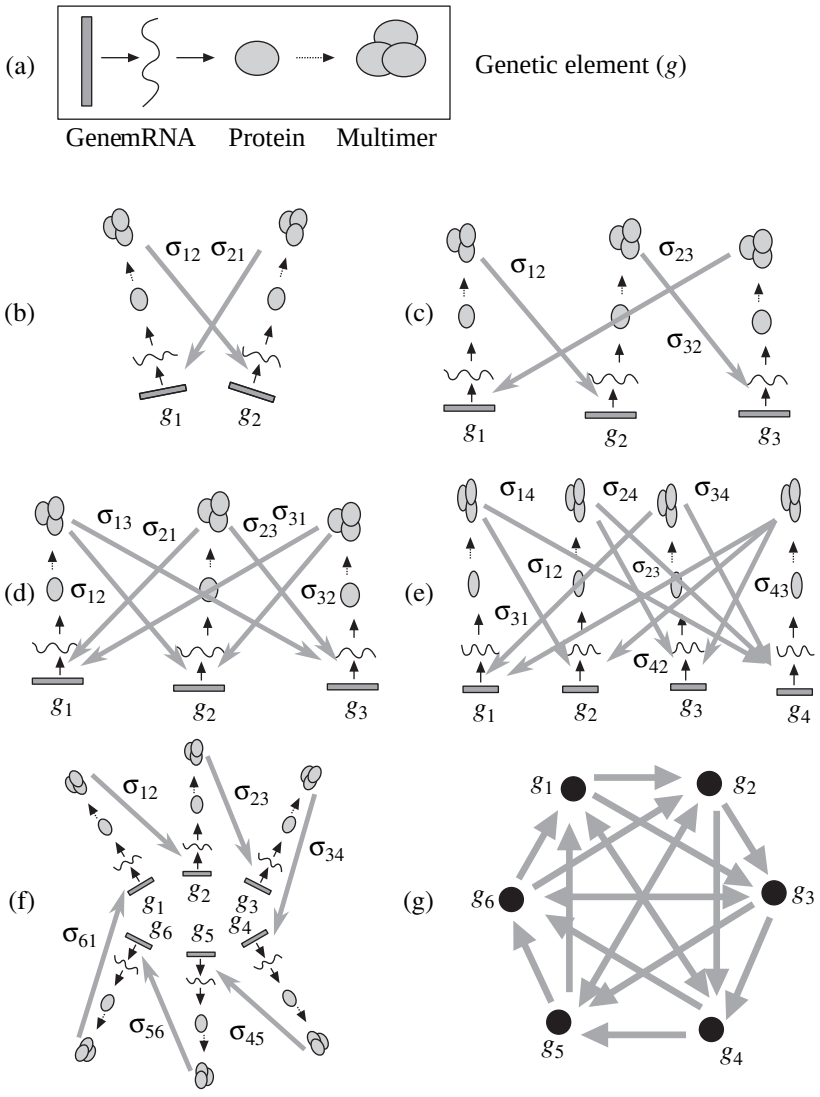

Fig. 1. Examples of assumed gene networks built of two types of standard elements—genetic elements and control links; (a) diagram of a genetic element of assumed gene network, see text for other explanations; (b) gene network S(2,2): (*n*,*k*) test predicts two stable points; (c) gene network S(3,2): (*n*,*k*) test predicts single stable point; (d) gene network S(3,3): (*n*,*k*) test predicts three stable points; (e) gene network composed of four genes and nine control links: calculations reveal single stable point and single stable limit cycle; (f) gene network S(6,2): (*n*,*k*) test predicts two stable points; (g) structural graph of gene network S(6,4): (*n*,*k*) test predicts two stable limit cycles.

Genetic elements (g_1, g_2, …) include a gene, its mRNA, and the protein encoded in this mRNA as well as the processes providing for synthesis of mRNA, protein, and protein multimerization (monomeric form of the protein is considered as a special case in the model). Diagram of a genetic element (G) is given in Fig. 1a. We assume that the products of genes expression have ultimate half-life; hence, a genetic element also includes the processes of mRNA and protein degradation (not shown on the genetic element diagram).

Control links (σ_{12}, σ_{21}, σ_{13}, …) describe the effect of some genetic elements on the other ones decreasing (negative association) or increasing (positive association) synthesis rate of the latter ones. Control links are shown as arrows connecting the genetic elements (Fig. 1a–f). Direction of arrows indicates direction of a control link action. This is also reflected by indices at σ. The first index shows the number of the genetic element affecting functional activity of another genetic element with the number in the second index position. Control link σ_{ij} indicates that the product of genetic element g_i controls the activity of genetic element g_j. For instance, Fig. 1b shows a gene network composed of two genetic elements g_1 and g_2 as well as

two control links σ_{12} and σ_{21} providing for mutual regulation of these elements.

Assumed gene network is any set of genetic elements mutually linked by certain number of control links. Let regulators denote the products exercising control links as well as the corresponding genetic elements. Presumably multimeric forms of proteins are regulators in the general case. Hence, the arrows indicating control links in Fig. 1b–f start from a multimeric protein. We assume that one of gene expression stages preceding synthesis of a regulator product is controlled: transcription, mRNA degradation, splicing, translation, etc. That is why the arrows indicating control links in Fig. 1b–f point to one of intermediate stages of protein synthesis. Examples of six assumed gene networks are presented in Fig. 1. As was already mentioned, the gene network presented in Fig. 1b is composed of two genes g_1 and g_2 as well as two control links σ_{12} and σ_{21}. The gene network in Fig. 1c includes three genes g_1, g_2, and g_3 as well as three control links σ_{12}, σ_{23}, and σ_{31}; the gene network in Fig. 1d includes the same three genes g_1, g_2, and g_3 related by six control links: σ_{12}, σ_{23}, σ_{31}, σ_{13}, σ_{21}, and σ_{32}. In the case presented in Fig. 1e the gene network includes four genetic elements, while those presented in Fig. 1f and 1g include six genetic elements each. The assumed gene network in Fig. 1g is presented as a structural graph (explained below).

Structural Graph of Control Links in a Gene Network

If numbered points denote genetic elements and arrows denote control links, we obtain an oriented graph. Consequently, arbitrary oriented graph can be used to build a gene network if the sense of genetic elements and control links is assigned to the points and oriented edges, respectively. Let us assume that the gene corresponding to the node of the graph is a regulator of activity of the gene corresponding to the node including this edge. Such graph can be naturally called a *graph of structure of a gene network control links* or a *structural graph*. The graph of a gene network structure is exemplified in Fig. 1g. Edge designations are not given not to overload the diagram. Two-way arrows between the nodes correspond to two edges of opposite direction connecting these two nodes. Gene network corresponding to the graph in Fig. 1g includes six genetic elements (*g*1–*g*6) and 18 control links.

Since any oriented graph generates specific assumed gene network, extreme variety of assumed gene networks can be constructed from the genetic elements and control links. For instance, three, four, five, and six genetic elements can give rise to 16, 218, 9608, and 1,540,944 gene networks with different structural graphs without loops, respectively (loop is an oriented edge beginning and ending in the same node which corresponds to autoregulation) [30].

Formal Description of Assumed Gene Network Models

Let there be n genetic elements g_i. Let p_i denote a protein encoded by genetic element g_i. Let $D_i = \{j_1, \ldots, j_{k_i}\}$ denote a set of numbers of genetic elements controlling g_i. It is clear that D_i taken for all $i = 1, \ldots, n$ completely define control links, i.e., define structural graph of the network. Let us describe the dynamics of a gene network functioning according to the following set of differential equations:

$$\frac{dp_i}{dt} = \frac{\left(\alpha_i + \sum_{j \in D_i} \kappa_{i,j} p_j^{h_{i,j}}\right)}{\left(1 + \sum_{j \in D_i} \gamma_{i,j} p_j^{m_{i,j}}\right)} - \beta_i p_i, \quad i = \overline{1, n}. \qquad (1)$$

Here β_i are rate constants of the processes decreasing p_i concentration of the final product of the ith genetic element (degradation, transport from the compartment, etc.); α_i, $\gamma_{i,j}$, and $\kappa_{i,j}$ are coefficients controlling the activity of protein p_i synthesis for regulators p_j; while $h_{i,j}$ and $m_{i,j}$ indicate the rate of p_j influence on g_i activity. In the simplest case $h_{i,j}$ and $m_{i,j}$ have the sense of dimension (in the sense of number of subunits) of the regulator molecule, while in the general case they describe complexity of the control processes and can be non-integral. By implication the parameters β_i, α_i, $\gamma_{i,j}$, $\kappa_{i,j}$, $h_{i,j}$, and $m_{i,j}$ are nonnegative numbers.

Equation (1) demonstrates that if $\kappa_{i,j} = 0$ the jth genetic element is an inhibitor of the ith one, otherwise the influence of jth regulator on the ith element can be either positive and negative. This is defined by the $h_{i,j}$ and $m_{i,j}$ values. If $h_{i,j} = m_{i,j}$ the activation takes place. Otherwise (when $0 < h_{i,j} < m_{i,j}$) for low p_j the activity of ith genetic element will increase with p_j value and decrease at high p_j.

Note that strict inequality $h_{i,j} > m_{i,j}$ can formally be true when unlimited activation takes place. However, we shall confine ourselves to accepting natural additional conditions $h_{i,j} \le m_{i,j}$ and $\kappa_{i,j} = 0$ if $\gamma_{i,j} = 0$ that disallow it.

Clearly, the structural graph of the network completely defines the pattern of system (1). Vice versa, the pattern of system (1) completely defines structural graph of the network. Hence, there is pairwise 1-2-1 correspondence between the assumed gene networks, oriented graphs, and systems of type (1). Hence, oriented graphs have the same sense for systems (1) and gene networks, i.e., they are structural graphs.

Here emerges the question if stationary points and/or limit cycles can be predicted and counted solely on the basis of structural graph of system (1) without numeric calculations?

Here we confine ourselves to analysis of the limit properties of system (1) tracks under the following conditions: $\kappa_{i,j} = 0$, $\alpha_i = \alpha \neq 0$, $\gamma_{i,j} = 1$, $\beta_i = 1$, and $m_{i,j} = m \neq 0$. Hence, we consider the systems with negative control links only and all genetic elements are assumed to have identical genetic properties.

This leaves only two independent parameters in the system: α and m. The parameter α describes the maximum rate of genetic products p synthesis, while parameter m describes the complexity (nonlinearity) of the gene function inhibition by the inhibitors. The desired complexity in the real gene networks can be attained by multimerization of repressor proteins and/or sufficient number of intermediate stages.

Hereafter the systems of type (1) with the abovementioned restrictions will be referred to as (**1**') systems. Numeric calculations demonstrate that (**1**') systems can have both stable functioning modes and limit cycles.

Figure 2 exemplifies numeric calculation for a gene network model composed of four genes g_1, g_2, g_3, and g_4 related by 9 negative associations σ_{12}, σ_{23}, σ_{31}, σ_{14}, σ_{24}, σ_{34}, σ_{41}, σ_{42}, and σ_{43}. The corresponding gene network is presented in Fig. 1e. The calculations were carried out at $m = 3$ and $\alpha = 5$. The most straightforward interpretation of the value $m = 3$ is that trimers are active forms of regulators.

Investigation of these gene networks demonstrated that it has two limit modes of functioning each realized according to the initial data—concentrations p_1, p_2, p_3, and p_4. If the initial concentrations $p_1 = 1$, $p_2 = p_3 = p_4 = 0$ the limit oscillating mode is realized when concentrations of all products periodically and continuously oscillate (Fig. 2a). Figure 2b illustrates the same calculation in phase coordinates ($p2$, $p3$).

In the case of the initial data $p_1 = 1$, $p_2 = p_3 = 0$, and $p_4 = 1.5$ the same system enters the region of stationary mode with constant concentrations of all four components of the model (Fig. 2c).

Let us now consider a special case of (**1**') systems describing gene networks with additional assumption that each genetic element controls activity of the same number $(k - 1)$ of other genetic elements. Let us further assume that the gene network graph is symmetric, i.e., its nodes can be numbered so that each genetic element g_i is inhibited by genetic elements with numbers $m_n(i - 1), \ldots, m_n(i - k + 1)$, where

$$m_n(j) = \begin{cases} j, & \text{if} \quad 1 \le j \le n \\ n + i, & \text{if} \quad i \le 0. \end{cases}$$

Then system (1) is transformed to

$$dp_i/dt = p_i + \alpha/(p^m_{m_n(i-1)} + \ldots + p^m_{m_n(i-k+1)}), \quad i = \overline{1, n}. \tag{2}$$

Test for Determining the Structure of Negative Associations in Symmetric Gene Network, Number of Stable Points, and Limit Cycles from Structural Graph

Gene networks with symmetric structural graphs were called symmetric or S(n,k) networks while the corresponding systems (2) were called M(n,k) models, where n is the number of genetic elements in the network and $(k - 1)$ is the number of a given gene regulators. Examples of five symmetric gene networks are given in Fig. 1 (b, c, d, f, and g). It is easy to calculate that exactly $n - 1$ different symmetric networks exist for a given n.

The table presents the results of numeric analysis of stable functioning modes of all possible variants of symmetric networks with the number of genes from 2 to 9. Analysis included numeric solution of a set of differential equations (2) for various initial concentrations P_i ($i = 1, \ldots, n$). The calculations were carried out at $m = k + 1$ and $\alpha = k + 1$.

For instance, only stable points were revealed in the models presented in rows 1–8 of the table while the models presented in rows 9–11 conversely have no stationary points but have 1, 2, and 3 stationary limit cycles, respectively.

The calculations have revealed 3 stationary points, 2 stationary points, and 2 stationary limit cycles for the model M(3,3) corresponding to the gene network presented in Fig. 1c, model M(6,2) (Fig. 1e), and model M(6,4) (Fig. 1f), respectively.

Let us specifically consider two models out of all presented in the table. The first one is model M(2,2). The calculation has revealed two stationary modes; hence, it describes "molecular trigger"—a gene network S(2,2) in Fig. 1a. Trigger properties of the corresponding gene network have been confirmed experimentally [31, 32] and are manifested as two stationary modes. The second model—M(3,2)—describes assumed gene network S(3,2) (Fig. 1b). The numeric calculations indicate existence of single stationary limit cycle in it. This gene network was also constructed by genetic engineering methods and its oscillating mode has been observed in the experiment [33].

The table demonstrates that the limit properties of systems (2) with various structural graphs indeed differ. However, the differences can be observed within fixed structural graph of a model with different parameters m and α. For instance, M(n,2) models have single stable mode at $n > 1$, $m = 1$, and any positive α. At the same time, we have shown that models M(n,2) (n =

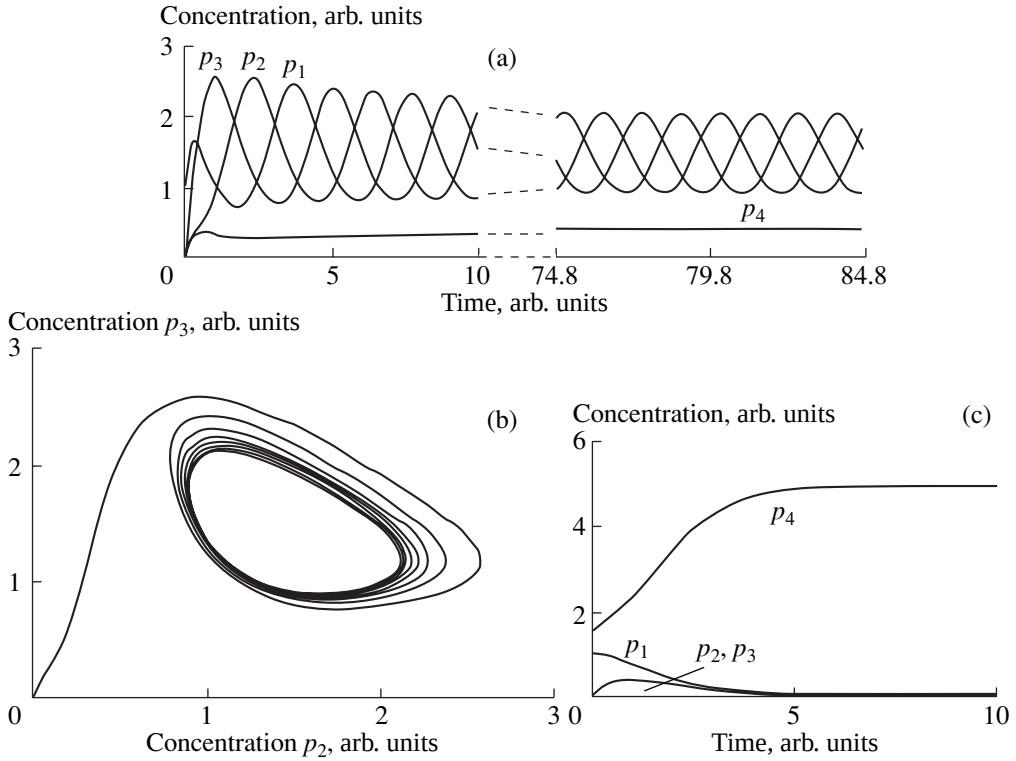

Fig. 2. Example of dynamic behavior of a gene network simulation presented in Fig. 1e with various initial parameters; calculations were carried out at $m = 3$ and $\alpha = 5$; (a) approaching stable limit cycle at the initial products concentrations $p_1 = 1$ and $p_2 = p_3 = p_4 = 0$; (b) phase curve (p_2, p_3) at the same calculations conditions; (c) approaching stationary conditions at the initial products concentrations $p_1 = 1$, $p_2 = p_3 = 0$, and $p_4 = 1.5$.

2, …, 9) have a spectrum of various stable functioning modes (both cycles and stationary states) at $m = 3$ and $\alpha = 3$.

More complex variants of limit behavior of the models with fixed structure at different parameters α and m are also possible. Here emerges the question as to which properties of gene networks depend on the structural graph and which depend on specific values of the parameters? Analysis of the models presented in the table as well as other M(n, k) models allowed us to formulate the following empirical test.

The (*n*,*k*) Test

If n divides evenly by k, there are such m_0 and α_0 that M(n,k) model has k stable singular points at any $m > m_0$ and $\alpha > \alpha_0$. There are no limit cycles in this model. If n does not divide evenly by k, there are such m_0 and α_0 that the M(n,k) model has d stationary limit cycles and no stable points at any $m > m_0$ and $\alpha > \alpha_0$ (d is the greatest common divisor of n and k).

We have also found tests for the general case of (**1**') systems predicting all stationary limit modes of the corresponding gene network functioning from the structural graph. However, they are not presented here because of publication volume limitations.

Note that the (n,k) test does not rule out other functioning modes at $m \le m_0$ and $\alpha \le \alpha_0$ but gives us no information about it.

Practical requirements for the analysis of behavioral dynamics of the real gene networks as well as construction of gene networks with predefined properties deserve numeric investigation of the corresponding mathematical models, analysis of the solution stability, and investigation of the systems behavior for various parameters of the gene networks (e.g., [31, 33]). An integrated approach based on the data obtained from the (n,k) test and methods of numeric analysis can be used in this case. Let us consider two examples.

1. Gene network S(6,6). According to the (n,k) test it should have 6 stable points at certain $m > m_0$ and $\alpha > \alpha_0$. Their search can be performed, for instance, by the previously developed STEP software package [34]. The package is universal and can be used to study arbitrary sets of differential autonomous equations.

STEP investigation of the M(6,6) model for $m > 6$ and $\alpha > 6$ has revealed 83 stationary points and only six of them proved to be stable. Hence, in this case specific values $m_0 = 6$ and $\alpha_0 = 6$ were determined when the (n,k) test is satisfied for the considered gene

List of M(n,k) models and the number of numerically found stable singular points and limit cycles

No.	Model name*	P	C
1	M(2,2), M(4,2), M(6,2), M(8,2)	2	0
2	M(3,3), M(6,3), M(9,3)	3	0
3	M(4,4), M(8,4)	4	0
4	M(5,5)	5	0
5	M(6,6)	6	0
6	M(7,7)	7	0
7	M(8,8)	8	
8	M(9,9)	9	
9	M(3,2), M(4,3), M(5,2), M(5,3), M(5,4), M(6,5), M(7,2), M(7,3), M(7,4), M(7,5), M(7,6), M(8,3), M(8,5), M(8,7), M(9,2), M(9,4), M(9,5), M(9,7)	0	1
10	M(6,4)	0	2
11	M(9,6)	0	3

* See text for explanations; P, number of stable points; C, number of stable cycles (numeric calculations were carried out at $m = k + 1$, $\alpha = k + 1$).

network. In addition STEP package allows us to refine qualitative pattern of S(6,6) gene network behavior for $m < 6$ and $\alpha < 6$. For instance, 13 stationary points including 7 stable ones have been revealed for $m > m_0$ and $1 < \alpha \leq 3$. At $m < 6$ "symmetric solution" is stable for any positive α.

2. Gene network S(6,2). According to the (n,k) test it should have 2 stable points for certain $m > m_0$ and $\alpha > \alpha_0$. The region where the (n,k) test is satisfied revealed by STEP package is defined by the limits $m_0 = 2$ and $\alpha_0 = 2$. Five stationary points and single limit cycle are revealed within it. Only two points are stable, while other points and the limit cycle are unstable.

A detailed description of gene network complex analysis using (n,k) test and numeric methods will be presented in the nearest future at the Web site of the computer system GeneExpress-2 we are now developing.

The approach presented in this work opens new possibilities for analysis of the real gene network structure. We believe that its further development will bring us the solution of practically important problem of constructing gene networks with predefined dynamic properties and limit functioning modes (the number of stationary and/or oscillating variants of the dynamic behavior). The fact that qualitative behavior of a gene network depends on the graph structure and can certainly change after appearance/disappearance of just one control link brings new possibilities to explaining the laws of gene networks evolution (their evolutionary complication, in particular) as well as to interpreting the influence of mutations on functioning of genetic networks and the controlled processes.

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