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APPROACHES TO COMPLEXITY REDUCTION IN A SYSTEMS BIOLOGY RESEARCH ENVIRONMENT (SYCAMORE)

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ABSTRACT

Due to the complexity of biochemical reaction networks, so-called complexity reduction algorithms play a crucial role for making simulations efficient and for dissecting biochemical networks into meaningful subnetworks for analysis. Here, different approaches are presented, which we are developing in the context of a computational research environment for systems biology (SYCAMORE). These approaches are based on time-scale decomposition, sensitivity analysis, and hybrid simulation methods.

1 INTRODUCTION

Systems biology aims at an increased understanding of the biochemical network in the living cell. For this purpose, the focus of experimental and theoretical study has to reach beyond single isolated genes, proteins and reactions to studying increasingly complex systems of biochemical reactions and/or gene and protein interactions. In order to do so, new methods need to be combined with established methods and experimental and theoretical approaches have to be concerted.

For this purpose, we are developing SYCAMORE, a computational research environment for systems biology that supports non-expert users in setting up models and analyzing them. Thus, SYCAMORE links to the appropriate databases and simulation tools (e.g., COPASI 2006) and provides the user with information when to use which of the tools/methods.

One important computational aspect in systems biology is the fact that the increasing size and complexity of studied biochemical systems leads not only to experimental results which are hard to understand, but also to computational results which are not easy to comprehend. Here the so–called complexity reduction aims for two different directions: increasing the speed of simulations and dissecting the biochemical network into smaller subsystems that can be studied independently. The first one is usually achieved by reducing the number of equations mathematically. A smaller number of equations, though, does not guarantee the reduction of the number of biochemical species in the system, since many different species might contribute to one and the same transformed equation. Therefore, a likewise or even more important aspect is to dissect biochemical system into several modules that can be studied independently. This is needed to understand the interplay of specific subsystems. Both directions of complexity reduction have as the common goal not to loose important features. Different approaches to tackle these challenges are developed for the use in SYCAMORE and are described in the following.

The first approach is based on the presence of a wide range of characteristic time-scales in biological systems (from fraction of seconds, e.g., in signal transduction, to several hours, e.g., in some cases of gene expression). The most prominent examples building on the concept of time-scale decomposition are the Computational Singular Perturbation (CSP) method (Lam and Goussis 1994) and the so-called Intrinsic Low-Dimensional Manifolds (ILDM) (Maas and Pope 1992). Several variants of these two methods have been successfully used, e.g., in atmospheric and combustion chemistry modeling (see, e.g., Schmidt et al. 1998). We describe here the adaptation of an ILDM method for the use in the computational decomposition and analysis of biochemical systems with respect to time-scales. In comparison to the ILDM methods for chemical systems, beside the reduction of mathematical equations, our method has an additional focus on the reduction of the underlying biochemical network in a time-dependent manner.

The second very popular approach—sensitivity analysis—has been widely used to analyze chemical and biological systems (Turanyi 1990, Turanyi et al. 1989) primarily to examine their behavior with respect to disturbances or to

determine the robustness of parameter estimation. In addition, principal component analysis can be used to understand the interaction between reactions and their grouped behavior (Tomlin et al. 1995). For SYCAMORE, we are following another strategy, that we believe to be quite promising for investigating biochemical networks — an approach based on parameter scans and second order sensitivities. Increasing the order of sensitivties provides additional information about how first order sensitivities change locally and thus, it is to extend the domain of their local approximative features. Moreover, it allows the consideration of combined effects of two parameter variations. Furthermore, many biological systems keep their properties even if subjected to relatively large parameter fluctuations. So, the knowledge of high order sensitivities could provide a good basis for reducing dimensions (in parameter space) and network dissection.

Another important aspect discussed here is based on the study of the applicability of differential equations for describing reaction systems and the possibility to take intrinsic fluctuations into account using simulations based on discrete particle numbers, e.g., employing Gillespie's algorithm (Gillespie 1976). The latter methodology being of central importance if low number of identical molecules are present in the system. In those cases random effects can not be neglected and one must resort to stochastic methods. Both simulation approaches can be combined however by a hybrid simulation algorithm that we develop and that allows to dissect the system dynamically into a deterministic part and a part that is simulated stochastically. This approach has the advantage, that the computationally demanding stochastic simulation is only used on those subsystems, where it is really needed. The huge computational complexity of simulating the whole system stochastically can be reduced significantly. In addition, the dynamic partitioning and the flexibility to determine the dissection criteria allows to investigate if a certain subsystem of the biochemical network of interest is influenced heavily by intrinsic noise or is stable towards small fluctuations. Thus, the resulting data also help to determine boundaries for subnetworks.

The paper is organized as follows. In Section 2 we present our adaptation of a ILDM method for dynamically dissecting biochemical systems. Section 3 is devoted to our strategies using sensitivity analysis. In Section 4 we shortly describe our hybrid simulation method and discuss how this can aid in network dissection.

2 TIME SCALE DECOMPOSITION

In this section, we describe the adaptation of the method of Intrinsic Low-Dimensional Manifolds (ILDM) to biochemical systems (see also Zobeley et al. 2005). Originally, the ILDM techniques were introduced by Maas and Pope (1992) for the mathematical equations of combustion problems. In contrast, our method has an additional focus on reducing the underlying biochemical network in a time–dependent manner. It can be applied to arbitrary biochemical reaction systems and works independently of assumptions about the specific dynamic regime. Moreover, some numerical differences are introduced as described below.

We assume here that the dynamics of the system are determined by a set of n ODEs together with an initial state $\mathbf{c}_0$:

$$\frac{d}{dt}\,\mathbf{c}(t) = \mathbf{f}(\mathbf{c}(t)), \quad \mathbf{c}(0) = \mathbf{c}_0 \in \mathbb{R}^n.$$

Step 1. As a starting point of analysis a linearization with respect to the state vector $\mathbf{c}_0$ is performed:

$$\left\{ \begin{array}{rcl} \frac{d}{dt}\,\mathbf{c}(t) & = & \mathbf{f}(\mathbf{c}_0) + \mathbf{J}_{\mathbf{c}_0} \cdot (\mathbf{c}(t) - \mathbf{c}_0) \\ \mathbf{c}(0) & = & \mathbf{c}_0 \quad (\mathbf{J}_{\mathbf{c}_0} \text{ Jacobian of } \mathbf{f} \text{ in } \mathbf{c}_0) \end{array} \right. .$$

Step 2. An orthogonal similarity transformation is applied to the Jacobian $\mathbf{J}_{\mathbf{c}_0}$. The resulting matrix $\mathbf{S}$ has real Schur form, i.e., it is a block upper triangular matrix (Golub and Loan 1996):

$$\mathbf{Q} \cdot \mathbf{J}_{\mathbf{c}_0} \cdot \mathbf{Q}^{-1} = \mathbf{S} = \begin{pmatrix} \mathbf{S}_{\text{slow}} & \mathbf{S}_{\text{coup}} \\ 0 & \mathbf{S}_{\text{fast}} \end{pmatrix}.$$

In $\mathbf{S}$ the eigenvalues are reordered by a sequence of Givens rotations

$$\operatorname{Re}\lambda_1 \geq \ldots \geq \operatorname{Re}\lambda_r \gg \operatorname{Re}\lambda_{r+1} \geq \ldots \geq \operatorname{Re}\lambda_n.$$

Step 3. Using the solution of Sylvester equation

$$\mathbf{S}_{\text{slow}}\,\mathbf{Z} - \mathbf{Z}\,\mathbf{S}_{\text{fast}} = -\mathbf{S}_{\text{coup}}$$

we realize that the transformed Jacobian is decoupled additionally:

$$\mathbf{T} \cdot \mathbf{J}_{\mathbf{c}_0} \cdot \mathbf{T}^{-1} = \begin{pmatrix} \mathbf{S}_{\text{slow}} & 0 \\ 0 & \mathbf{S}_{\text{fast}} \end{pmatrix}$$

where

$$\mathbf{T} = \mathbf{Q}^T \left(\mathbf{Id_n} + \begin{pmatrix} 0 & \mathbf{Z} \\ 0 & 0 \end{pmatrix} \right).$$

Step 4. Applying $\mathbf{T}$ to the state $\mathbf{c}$ and reaction rate $\mathbf{f}$ results in a decoupled representation of the system dynamics:

$$\mathbf{x} = \begin{pmatrix} \mathbf{x}_{\text{slow}} \\ \mathbf{x}_{\text{fast}} \end{pmatrix} = \mathbf{T} \cdot \mathbf{c}, \quad \mathbf{g} = \begin{pmatrix} \mathbf{g}_{\text{slow}} \\ \mathbf{g}_{\text{fast}} \end{pmatrix} = \mathbf{T} \cdot \mathbf{f}(\mathbf{T}^{-1} \cdot).$$

Partitioning the reaction system into slow/fast contributions is related to a singular perturbation description of

the ODE system

$$\begin{cases} \frac{d\mathbf{x}_{\text{slow}}}{dt} &= \mathbf{g}_{\text{slow}}\left(\mathbf{x}_{\text{slow}}, \mathbf{x}_{\text{fast}}\right) \\ \varepsilon \cdot \frac{d\mathbf{x}_{\text{fast}}}{dt} &= \mathbf{g}_{\text{fast}}\left(\mathbf{x}_{\text{slow}}, \mathbf{x}_{\text{fast}}\right) \end{cases}.$$

Here, $\varepsilon = \tau_{r+1} = \frac{1}{|\text{Re}\,\lambda_{r+1}|}$ is a singular perturbation parameter. The concentrations of the fast species change with time, but these species can be described by algebraic relations instead of differential equations. The quasi–steady state assumption (QSSA), i.e., $\varepsilon = 0$, yields the associated differential–algebraic system (DAE) for the reduced problem.

Step 5. The number r of "slow" modes plays a crucial role in this approach. We adapt here the criterion suggested by Deuflhard and Heroth (1996): For a given error tolerance $\text{tol} > 0$, the number r of slow modes is chosen such that the corresponding decomposition still satisfies

$$\varepsilon \cdot \left|\mathbf{g}_{\text{slow}}\left(\mathbf{x}_{\text{slow}}, \mathbf{x}_{\text{fast}}\right) - \mathbf{g}_{\text{slow}}\left(\mathbf{x}_{\text{slow}}, \mathbf{x}_{0,\text{fast}}\right)\right| < \text{tol}$$

where the vector $\left(\mathbf{x}_{\text{slow}}, \mathbf{x}_{0,\text{fast}}\right)$ denotes the consistent initial value of DAEs and $\left(\mathbf{x}_{\text{slow}}, \mathbf{x}_{\text{fast}}\right)$ corresponds to the state vector $\mathbf{c}_0$ of ODE system.

Step 6. Another important question concerns the period of time in which the preceding distinction between fast and slow modes can be preserved. To the best of our knowledge, this aspect has not been investigated sufficiently so far. The transition from the original ODE system to the approximating DAE system provides sufficient accuracy merely up to some time δ. This additional time scale ought to be large in comparison with the (shortest) characteristic time τ_{r+1} of the fast modes: $\delta \gg \tau_{r+1}$.

In order to illustrate our theoretical considerations, we analyze here the time scale decomposition in the glycolysis reaction system in yeast as described in Wolf and Heinrich (2000). The model includes the main steps of anaerobic glycolysis, the production of ethanol and glycerol, as well as the effect of intercellular coupling (see Figure 1).

The mathematical model consists of 7 ODEs. The reaction rates $v_2 \ldots v_7$ are described by the law of mass action whereas

$$v_1 = k_1 \cdot \text{glucose} \cdot ATP \cdot \left(1 + \left(\frac{ATP}{K_{ATP}}\right)^q\right)^{-1}.$$

We refer to Wolf and Heinrich (2000) for details of the model.

Depending on the kinetic parameter k_1, the model shows both stationary and oscillatory behavior. We investigate here the case corresponding to small amplitude oscillations reaching the steady state (Figure 2). This specific situation offers the excellent opportunity to observe qualitatively different behavior in complexity reduction on a single run.

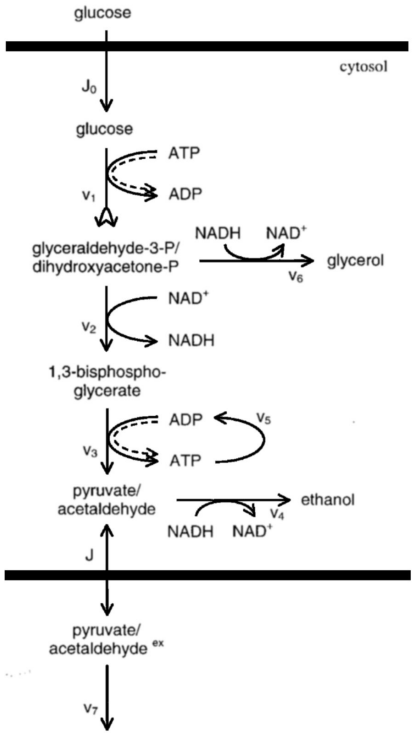

Figure 1: Glycolysis Reaction System in Yeast

The dynamic system represented by 7 ODEs has been analyzed with our adapted ILDM method while propagating along the phase space trajectory obtained by integrating the full system. After steps $1-5$ of our algorithm, the original system of dimension 7 is approximated by a transformed, reduced system consisting of $4-5$ active modes while displaying large amplitude relaxation oscillations. The system can even be represented by a lower number of slow modes (3) while propagating in the regime of sustained regular oscillations (starting at $t \approx 4$).

We compare also the maximal period δ (in which the Schur decomposition of the Jacobian does not change significantly) with the characteristic time scale τ_{r+1} of the slowest "fast" mode (step 6). During large amplitude oscillations (until $t \approx 3$), δ and τ_{r+1} are of the same order of magnitude. For instance: $\delta/\tau_{r+1} \approx 1.037$ at point A $(t = 0.5)$, $\delta/\tau_{r+1} \approx 5.12$ at point B $(t = 1)$. Thus, we cannot justify QSSA for the "fast" modes here.

In contrast, $\delta \gg \tau_{r+1}$ for the regime of small decaying oscillations. For example, at point C $(t = 8)$, $\delta/\tau_{r+1} \approx 152$ allows us to apply this model reduction.

In order to complete our investigation, we perform the analysis of slow modes in terms of contributions of all species concentrations. The information is obtained by analyzing the entries of the transformation matrix $\mathbf{T}$ (see Zobeley et al. 2005). Figure 3 shows the contributions

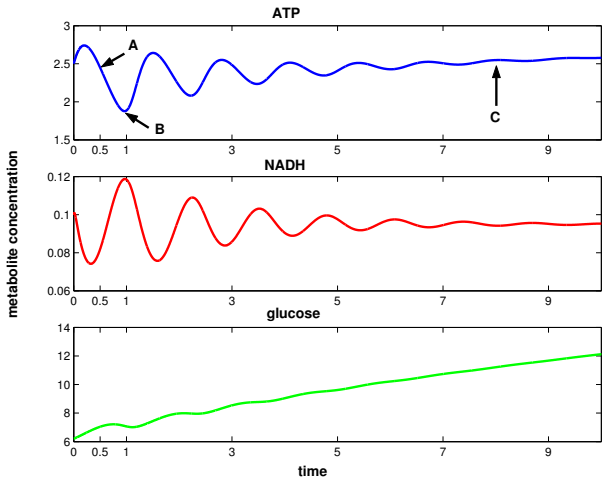

Figure 2: Simulation of the Full Glycolysis Model

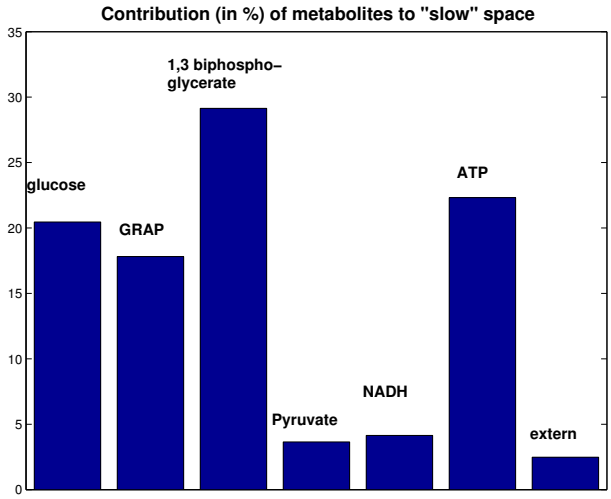

Figure 3: Analysis of the Slow Modes at Point C

of species to the slow space at point C ($t = 8$). Here the contributions of only 4 species are significant. Therefore the "real" reduction of corresponding metabolites is possible.

3 GENERALIZED SENSITIVITIES

One aspect of the complexity of models of biochemical reaction networks is the often rather large number of parameters. Each single enzyme-catalyzed reaction usually has several parameters describing the overall reaction rate as well as effects of saturation, inhibition, activation, etc. The value of many of these kinetic parameters is unknown or not known with sufficient accuracy. Therefore it is important to have methods to study how changing the value of some parameter affects the behavior of the model, or which range of parameter values needs to be considered when we want to study a specific model behavior. Unfortunately, since the reaction networks can have very complicated structures, and the reaction kinetics are nonlinear in most cases, the relation between parameter values and simulation results is not trivial.

So how can the exploration of the parameter space help to reduce the complexity of the model? Obviously, the knowledge about the behavior of the parameters does not reduce the complexity of the model in all cases but it will always reduce the complexity of the problems we (as the modelers) are facing. Knowing, e.g., that a certain parameter does not influence the results very much or that some other parameter can only be in a certain range of values if the system has to be in a steady state helps a lot when fitting the model to experimental data. In addition, the same information can lead to a true dissection of the model. For example, if we find that one set of parameters mostly affects certain model variables and another set of parameters only affects different variables we can try to separate the model into only weakly coupled subsystems.

Entities that describe quantitatively how much changing a parameter value influences some property of a model are called sensitivities. One well established formalism to deal with sensitivities in the context of biochemical reaction networks is *Metabolic Control Analysis (MCA)* (Fell 1997). MCA defines matrices of so-called *control coefficients*. They describe how a steady state of the systems changes if the overall rate of a individual reaction is changed. Usually the coefficients are calculated using an algorithm described by Reder (1988).

This basic notion of sensitivities can be generalized in several ways: First we can consider model properties other than steady state concentration and fluxes. Basically for every property of the model that can be calculated numerically we can also calculate if and how much it changes with any model parameter. As an example, it can be useful to calculate how the frequency and amplitude of a limit cycle oscillation depends on the parameter values. Also, we can calculate the dependency on different parameters. In addition to reaction rates other parameters like inhibition constants are of interest.

Another generalization are second (or higher) order sensitivities. Basic sensitivities as described above are first derivatives of a model property with respect to a model parameter value. We can also calculate second derivatives with respect to one or two parameters. Since biochemical models are usually nonlinear the linear dependency between model state and parameter values that is described by first order sensitivities only holds for a small interval around the state for which they were calculated. Second order sensitivities can provide hints as to how big this interval

is, and they can provide a measure of how much nonlinear effects govern the behavior of the system.

Finally also continuation can be considered as a generalization of sensitivity analysis. Continuation is a numerical method that is well established in the field of nonlinear dynamics—with software packages like AUTO (Doedel 1996)—but that has been used in systems biology only rather recently (e.g., Chickarmane et al. 2005). Continuation follows a solution of the model equations over a whole range of parameter values and also identifies points in parameter space where the stability of a solution changes (bifurcation analysis).

4 HYBRID METHOD

Mathematical models for describing biological phenomena can be divided into two broad categories: continuous or discrete. Most often the continuous models are simulated using deterministic methods (e.g., numerical integration), whereas stochastic simulation methods are utilized for the discrete models. However, this does not always have to be the case. Biochemical networks (e.g., metabolic networks) are usually described by ordinary differential equation systems (ODEs). There exist a variety of very efficient numerical integration methods even for the very stiff ODEs, which often arise in biochemical simulations (Petzold 1983). The actual numbers of particles in the system do not affect the simulation speed. This continuous approach, however, is based on the notion of continuously changing variables. It breaks down in the case of species with only very few particles in the system (e.g., in signal transduction systems), where the concept of concentrations does not hold any longer. In addition internal fluctuations in terms of particle numbers in the system are completely neglected. Those fluctuations again occur primarily when only few molecules are present in the system and can change the overall behavior dramatically. Therefore stochastic simulation methods have been developed (Gillespie 1976, Gibson and Bruck 2000), which consider the discrete nature of the system and simulate it according to individual probabilities for the different reaction events. The stochastic simulation methods reproduce those random fluctuations correctly, but can do that in an efficient manner only for systems containing relatively few molecules.

With the upcoming of more and more complex biochemical models, which for instance combine signal transduction (few particles) and metabolism (many particles) none of the traditional simulation methods alone is appropriate any longer. Therefore a number of hybrid methods (Haseltine and Rawlings 2002, Kiehl et al. 2004, Puchalka and Kierzek 2004, Salis and Kaznessis 2005, Alfonsi et al. 2005) have been proposed that try to combine the advantages of the complementary deterministic and stochastic approaches. Parts of the biochemical system are simulated stochastically to capture the internal fluctuations. Other parts of the system are simulated using deterministic methods at the same. A correct synchronisation of the two parts is essential. The methods proposed so far are different in the partitioning scheme they use and the approximation of variable probabilities between two stochastic events in the system.

The hybrid method developed in our group (COPASI 2006) combines the stochastic simulation algorithm by Gibson and Bruck, 2000 (Next Reaction Method) with a numerical integration of ODEs (4th order Runge Kutta method). The biochemical network is dynamically partitioned into a deterministic and a stochastic subnet depending on the current particle numbers in the system. The user can define limits for when a particle number should be considered low or high. The stochastic subnet comprises reactions involving low numbered species. All the other reactions form the deterministic subnet. The reaction probabilities in the stochastic subnet are approximated as constant during one time step.

The hybrid simulation of a toy system is given in Figure 4. The system describes a simple two-stage decay:

$$A \rightarrow B, \qquad B \rightarrow C.$$

Whenever the particle numbers drop below the user-defined limits (marked time points) the corresponding reactions are simulated stochastically and random fluctuations are captured. Otherwise the faster numerical integration is used for reactions with high-numbered species.

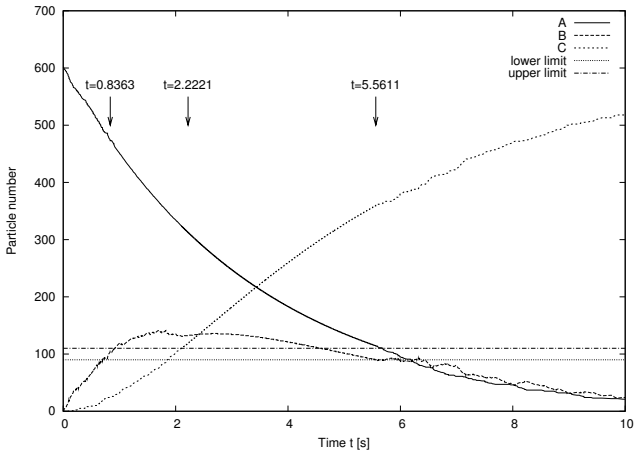

Figure 4: Two–stage Decay

By being able to use the efficient numerical integration for some parts of the system, computational complexity is reduced and simulation speed gained at least for those systems that contain large fractions that can be treated deterministically (compared to a stochastic simulation for the whole system which otherwise would be necessary).

In addition, the user-defined limits for the partitioning of the system allows to study the sensitivity/robustness of individual subnetworks with respect to noise. By changing this limit, one can observe if the resulting trajectory is dramatically changing, e.g., if additional subnetworks are simulated stochastically. If this is the case, these subnetworks exhibit a pronounced sensitivity towards intrinsic noise. Thus, dissection of the whole system with respect to noise-sensitive and noise-robust subnetworks is possible.

5 DISCUSSION

In this article, three approaches to complexity reduction have been considered: time–scale decomposition (ILDM method), sensitivity analysis, and hybrid methods. These approaches are developed for the use in SYCAMORE (a computational research environment for systems biology).

Our modified ILDM approach is based on the assumption that the main part of dynamics, being of real interest for the researchers, belongs to the intrinsic slow manifold. However, we also believe that an effective complexity reduction method should take both fast and slow parts of a trajectory into account adaptively. Such a combined method will be a topic of our future work.

In the field of sensitivities we are developing the generalization of classical approaches, based on the second (or higher) order sensitivities and continuation.

Finally, hybrid simulation methods aid to analyze the systems sensitivity with respect to noise and thus enable researchers to differentiate between subsystems being rather robust (are not easily influenced by intrinsic noise) and subsystems with pronounced sensitivities.

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