DYNAMIC ANALYSIS OF BIOCHEMICAL NETWORK USING COMPLEX NETWORK METHOD

by

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In this study, the stochastic biochemical reaction model is proposed based on the law of mass action and complex network theory. The dynamics of biochemical reaction system is presented as a set of non-linear differential equations and analyzed at the molecular-scale. Given the initial state and the evolution rules of the biochemical reaction system, the system can achieve homeostasis. Compared with random graph, the biochemical reaction network has larger information capacity and is more efficient in information transmission. This is consistent with theory of evolution.

Key words: *biochemical reaction channels, network homeostasis, complex network, dynamical analysis*

Introduction

The last decade has witnessed a new movement of research in the study of complex networks [1-3]. The structure of complex network is irregular, complex and dynamically evolving in time, with the main focus moving from the analysis of small networks to that of systems with thousands or millions of nodes, and with a renewed attention to the properties of networks of dynamical units. Historically, the study of networks has been mainly the domain of a branch of discrete mathematics known as graph theory. Since its birth in 1736, graph theory has witnessed many exciting developments and has provided answers to a series of practical questions [4-8] and it has been shown that many real-world networks share two fundamental properties. The first is called the *small-world* phenomenon that typical distances between vertices are small [9]. The second is called a *power-law degree sequence* that the number of vertices with degree k decays slowly for large k, often resulting graphs to be *scale-free graphs* [10]. Complex networks analysis has been applied for research in biology physics, engineering and even social sciences [11-14]. Take the internet for example; the internet can be considered as a complex network of routers and computers linked by various physical or wireless links [15].

Complex network analysis has been well exploited in system biology by combining mathematical modeling, experiments, and computer simulations. Milo *et al.* [16] employ *network motifs*, patterns of interconnections occurring in complex networks at numbers that are significantly higher than those in randomized networks, to analyze the genetic networks of

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Escherichia coli and *Saccharomyces cerevisiae*. Despite significant variation in kinds of individual constituents and pathways, Jeong *et al.* [17] demonstrated that almost all metabolic networks have the same topological scaling properties and show striking similarities to the inherent organization of complex non-biological systems. Using a graph of 909 interactions among 491 yeast genes and complex network tools, Guelzim *et al.* [18] showed that the number of regulated genes per regulating protein has a broader distribution with a decay resembling a power law. In view of cells and microorganisms, Oltvai and Barabasi [19] and Guggenheim [20] insist that capturing the system-level laws governing cell biology can be represented a search for the deeper patterns common to complex systems and networks in general. However, the existing studies just focus on analyzing biological network statically. Few works study the dynamics of biological network. In this work, we propose a dynamical biochemical reaction network model based on complex network. Given the initial state and the evolution rules of the biochemical network, we demonstrated how the biochemical reaction network achieving homeostasis.

Biochemical reaction network model

In traditional literature, the time evolution of biochemical reacting system is often treated as a continuous and deterministic process [21, 22]. However this approach should not always be taken for granted. More and more studies [23-25] have accepted the fact that the time evolution of a spatially homogeneous biochemical system is a discrete, stochastic process instead of a continuous, deterministic process. In this section, the stochastic biochemical reaction model (SBRM) is proposed to analyze the dynamics of biochemical network. For thermal equilibrium, the concentration of species is the most important index in a fixed volume. The traditional way of defining concentration is that the amount of biochemical species n is variable while the volume v is fixed. This definition is not feasible in view of complex network.

To analyze the evolution process of biochemical reaction network, we define the relative concentration for the species i and j as:

$$C_{ij} = \frac{k}{V_{ij}} \tag{1}$$

where k is a constant and V_{ij} – the relative interaction volume for species i and j. V_{ij} is defined as:

$$V_{ij} = g\,\frac{d_{ij}}{d_{ave}} \tag{2}$$

where d_{ij} is the distance between species i and j, and d_{ave} – the average distance among all the species in the biochemical network. In the evolution process, it is easy to find that the relative volume is varying which will induce new biochemical reaction channels. The probability for constructing a new reaction channels between species i and j is given by:

$$P(x_i, x_j) = \alpha \mathrm{e}^{-\frac{V(i,j)}{\beta V_{\max}}} \tag{3}$$

where α and β are biochemical parameters determined by the activity of biochemical species.

Setting $P(x_1, \ldots, x_N; t)$ as the probability that new biochemical reaction channels will be induced at time t, a_i and b_i as the stochastic reaction constants, the master equation is given by:

$$\frac{\partial P(x_1,..., x_N;t)}{\partial t} = \sum_{i=1}^{N}[b_i - a_i P(x_1,....., x_N;\ t)] \tag{4}$$

To simulate the stochastic evolution of the biochemical reaction system, the algorithm of the SBRM is proposed, as shown in fig. 1.

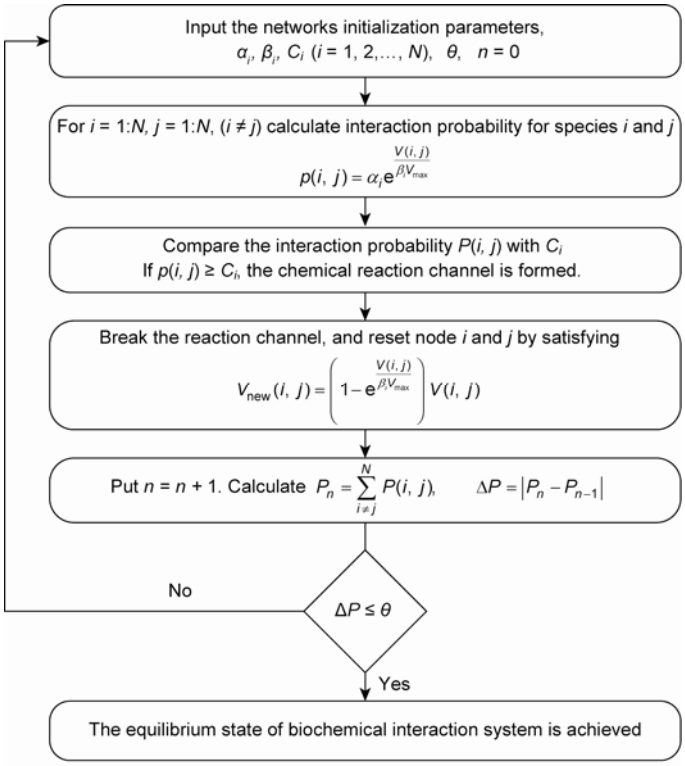

Figure 1. Schematic of SBRM algorithm. θ indicates a very small value judging whether the thermal equilibrium is achieved. C indicates the critical value judging the whether the new biochemical reaction channel is induced

Experiments and analysis

In the evolution process, the interaction probability plays an important role in inducing biochemical reaction channel. As shown in fig. 2, the mean of induced biochemical reaction channels changes from 990 to 6850 along with α varying from 0.1 to 0.85. The variance of of induced biochemical reaction channels changes from 25 to 565 along with β varying from 0.1 to 0.85. It can be found that α is essential for the mean of induced biochemical reaction channels, while β is important for the variance of induced biochemical reaction channels. In system biology, homeostasis of biochemical reaction network is essential. Most biological functions are implemented when equilibrium state is achieved, such as biological adaptation [26] and calcium homeostasis in mammals. Figure 3 shows how the biochemical reaction network achieving equilibrium state. Given the fixed α and β, both the reaction channels and average degree of biochemical species demonstrate that the equilibrium state is achieved at t = 12 s. The biochemical reaction in real-world is always a stochastic process. The average degree and the edges always vary on a small-scale even if the system achieves homeostasis. From fig. 3, we can see that the average degrees are not increasing monotonically.

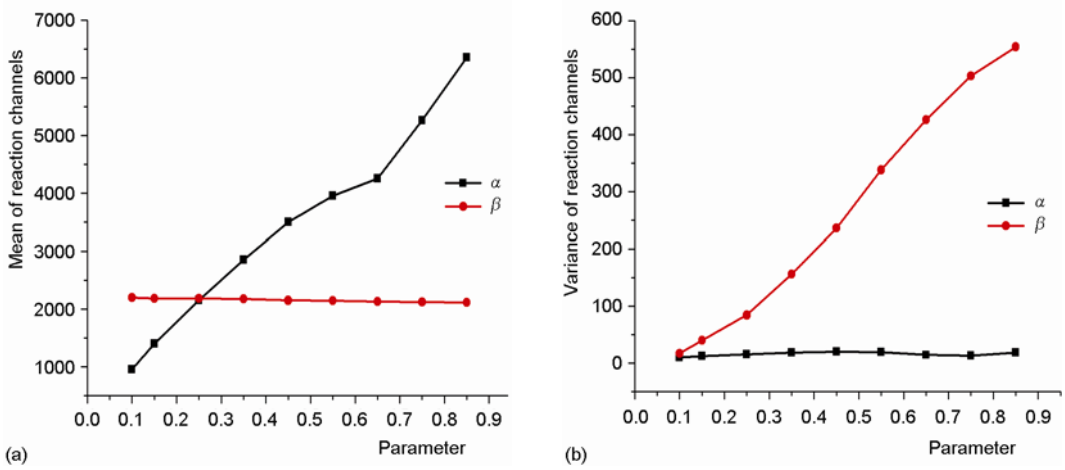

Figure 2. The roles of α and β in the induced biochemical reaction channels

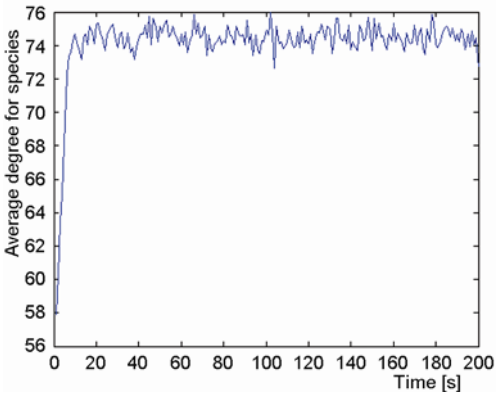

Figure 3. The evolution of average degree for biochemical species: α = 0.4, β = 0.3, and N = 200

Conclusions

In this work, the stochastic biochemical reaction model is proposed. The dynamics of the biochemical reaction system is studied by analyzing the evolution of induced biochemical reaction channels, average degrees, clustering factor, and average path length. The experimental results demonstrated that the existing biochemical network has advantage over a random graph in information processing and homeostasis is the most optimal condition. These findings are consistent with theory of evolution. This work provides a possible direction to study system biology using complex network theory.

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