Modeling and Dynamical Analysis of Molecular Networks

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Abstract. One of major challenges for post-genomic biology is to understand how molecules dynamically interact to form networks which facilitate sophisticated biological functions. Instead of analyzing individual molecules, systems biology is to study dynamical networks of interacting molecules which give rise to life. In recent years, many progress have been made in systematic approaches and high-throughput technologies for systematic studying complex molecular networks. Analyzing these networks provides novel insights in understanding not only complicated cellular phenomena but also the essential principles or fundamental mechanisms behind the phenomena at system level. This paper presents a brief survey on recent developments on modeling and analyzing complex molecular networks mainly from global and dynamical properties of complex molecular networks. Some recent developments and perspectives of analysis on molecular networks are also discussed.

Keywords: Modeling, analyzing, molecular networks.

1 Introduction

Molecular biology has led to remarkable progress in understanding of individual cellular components, and the next main challenge is to understand biological networks composed of the components revealed by reductionism in molecular biology at the system level [1]. As the behaviors of living systems can seldom be reduced to their molecular components, one has to assemble the components into networks so as to understand complex biological processes. More and more scientists are attracted by such a research topics, especially the topological structures and functions of different molecular networks.

Biological functions can only be carried out through precise interactions and regulation of thousands of cellular components such as genes, proteins, and metabolites. Due to the large number components and parameters involved in the networks, it is almost impossible to intuitively understand how the networks execute complex cellular functions. The understanding of complex biological systems requires the integration of experimental and computational research. Therefore, accurate modeling is prerequisite in understanding the biological implications of different topological properties such as path lengths and degree distributions and their behaviors such as circadian rhythms of different molecular networks.

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Furthermore, qualitative or quantitative analysis can also be made, which will contribute to accurate experimentally verifiable predictions.

Molecular networks comprise metabolites, enzymes, proteins, or genes as vertices, which are linked depending on the interactions between them. Modeling these networks may be performed by considering the theory of complex networks because of its universality and ability to mimic systems of many interacting parts. Besides theory of complex networks, nonlinear dynamical theory can also paly an important role in investigating molecular networks due to the dynamical interactions between the cellular components. The dynamics and global properties of molecular networks such as small-world and scale-free topological properties of different kinds of molecular networks are important in understanding biological systems, namely regulation mechanisms, robustness properties, information flow, and perfect adaptation.

In this paper, we present a brief survey on recent developments in modeling and analyzing of complex molecular networks from the viewpoint of systems biology. Attention will be focused on global and dynamical properties of the networks based on theory of complex networks and nonlinear dynamics. Specifically, we first describe some approaches to model molecular networks such as stochastic and deterministic approaches and explain how to construct a molecular network with specific functions, e.g., switches and oscillators, from the theoretical and engineering perspective. Then, we explain how to analyze complex molecular networks, especially their dynamics, robustness, information propagation, and adaptation. Finally, some recent developments and perspectives of analysis on molecular networks will be discussed.

2 Modeling of Molecular Networks

Molecular biology has provided a wealth of knowledge about individual cellular components. Also, the use of high throughput DNA microarray, protein chips, RT-PCR, and other methods to monitor biological processes in bulk is critical. It has led to the realization that it is essential to establish methodologies and techniques to enable us to understand how genes, proteins and small molecules dynamically interact to form molecular networks which facilitate sophisticated biological functions such as circadian rhythms, cell cycle, and cell differentiation and how the global properties mean for different kinds of molecular networks. Therefore, modeling becomes so important that an insight into basic mechanisms and information can be obtained and further detailed qualitative and quantitative analysis and verifiable predictions can be also made.

Several different attempts have already been made to create models of molecular networks. Generally, they can be classified into two categories: reverse and forward engineering approaches.

2.1 Reverse Engineering Approach

Network structures can not be automatically inferred from experimental data based on some principles or universal rules. To identify network structures, two

kinds of approaches - bottom-up and top-down can be utilized based on the experimental data used. The bottom-up approach tries to construct a molecular network based on the compilation of independent experimental data, mostly through literature searches and database request such as KEGG and some specific experiments to obtain data of very specific aspects of the network. This approach is suitable when most of the molecular and their regulatory relationship are relatively well understood.

On the other hand, the top-down approach tries to make use of high-throughput data obtained through new measurement technologies. Many inference technologies have been developed such as singular value decomposition and robust regression [2], steady-state perturbation experiments [3], integration of multiple datasets [4,5], and integrating genetic perturbations [6]. The drawback of the top-down approach is the computational cost. Also, when prior knowledge is well understood, a hybrid method that combines the bottom-up and the top-down approach can also be used so as to reduce the possible space of network structures.

Reverse engineering approach is very useful in building complex molecular networks although the network obtained are generally very abstract. Reverse engineering typically requires the use of simplistic parametric models of a large-scale network, e.g., Bayesian networks, Boolean networks, or linear differential equations, and the parameters of which are adjusted to fit real-world data. Such an approach is very important in understanding their global properties and functional organization such as the scale-free topological properties of metabolic networks [7].

2.2 Forward Engineering Approach

After the abstract models are obtained, some more detailed information is further needed so as to faithfully quantify the information contained in the abstract networks. A natural choice is to use forward engineering approach, where a set of equations are built based on detailed molecular interactions with exact kinetic parameters to achieve biological reality. The underlying biochemistry and regulation mechanisms can be used to quantify the fundamental laws of regulation between molecules.

Forward engineering approach is very useful to handle concrete and complicated molecular systems at more detailed level so as to analyze the regulation mechanism, robustness properties, synthetic network design, and control strategies. So far, many different technologies have been developed including analysis of different regulation process such as effects of nonlinear protein degradation [8], hysteresis in a synthetic mammalian gene network [9], robustness properties [10], construction of relatively simple genetic circuits with specified functions, e.g. switches and oscillators [11,12,13,14,15], and collective behaviors of multicellular networks [16,17,18,19,20,21].

To obtain detailed and exact information in molecular networks, there is a strong need to combine forward engineering and reverse engineering. Reverse engineering approaches provide basic information in molecular networks to fit

to experimental data. Based on the abstract models and further information revealed by molecular biology, forward engineering builds more detailed mathematical models with kinetic-related parameters. From this viewpoint, the model would focus on capturing the intrinsic architecture of molecular networks and their detailed kinetics rather than some basic information.

2.3 Dynamical Modeling of Molecular Networks

Different formalisms can be used to model and simulate detailed molecular networks. All methods can be categorized as static or dynamic, discrete or continuous, stochastic or deterministic [22]. All these approaches can help us qualitatively or quantitatively understand the structures and functions of the molecular networks and their regulatory mechanisms.

Stochastic and deterministic approaches have traditionally been used in modeling dynamical molecular networks. The deterministic approach such as ordinary and partial differential equations neglects the effects of stochastic fluctuations. For example, the rate equation approach, in which the culture is assumed to be homogenous, use the concentrations of cellular components as the variables to describe the dynamics, i.e. the rates of production and decay of these components. The constructed models consist of a system of ordinary differential equations so as to analytical or numerical techniques of nonlinear dynamics can be applied. While For the case of inhomogeneity, other techniques such as partial differential equations are more appropriate to describe the spatially heterogeneous culture.

Although the deterministic approach is relatively easier and some analytical techniques can be applied, the stochastic modeling approach such as master equation approach provides the most detailed level of the dynamics due to the existence of the intrinsic and extrinsic noises. The inherent stochasticity in biochemical processes such as binding, transcription, and translation generates the intrinsic noise. While the variations in the amounts or states of cellular components or the external environment generate the extrinsic noise. Such noises are believed to play especially important roles when species are present at low copy numbers. The power of the stochastic approach lies in its completeness and attention to detail although the simulations are computationally expensive. See [23] for more details on stochastic modeling approaches.

3 Analyzing Molecular Networks

In this section, we give a brief introduction to dynamical analysis, robustness properties, information propagation, and adaptation of molecular networks.

3.1 Dynamical Analysis Molecular Networks

Biological functions can only be carried out through dynamical interactions between the basic cellular components. Therefore, dynamical analysis of molecular

networks is very necessary on how the cellular components interact and form feedback which plays a major role in various aspects of biological processes and physiological functions such as chemotaxis and circadian rhythms. Besides traditional theory of nonlinear dynamics, theory of complex networks, control theory, and stochastic process also plays an important roles in analyzing the dynamics of molecular networks.

Traditional nonlinearity theory, especially stability and bifurcation theory, have been widely used in analyzing network dynamics and cell physiology. For example, the dynamics of cell cycle regulation was analyzed by using bifurcation theory, which tells us how the generic properties of a dynamical system depend on parameter values [24]. The authors showed that bifurcations underlie cell-cycle transitions. The theory of nonlinear dynamics is also used in analyzing all complex dynamics in molecular networks such as circadian rhythms [25] and robustness properties [26].

Control theory can also paly an important roles in analyzing dynamics of molecular networks [27]. For example, monotone control theory can be used to construct molecular networks with specific functions such as switch and oscillators [28,29,11,12,13,14,15]. It can also be used to detect stability and bifurcations in positive-feedback systems [30]. Robust perfect adaptation in bacterial chemotaxis through integral feedback control also has been proposed [31]. It is well known different feedback play different roles in determining networks dynamics [32]. For instance, positive feedback networks can only converge to equilibrium and therefore negative feedback is necessary to produce oscillatory behaviors [33].

Complex network theory can also help us to understand and predict the behavior of molecular networks because many molecular components constitute complex networks. Global properties such as degree distribution, hubs, scale-free properties play important roles in understanding the implication of molecular networks. For example, metabolic networks had small-world and scale-free properties [7,34] and cellular networks such as protein-protein interaction networks, gene regulatory networks, and metabolic networks tend to be disassortative [35]. Such properties can not only ensure the network robustness against random failure of the nodes but also to guarantee an efficient transport and flow processing by avoiding congestion. Gene networks also have similar properties which is a result of evolutionary self-organization via preferential node attachment because the genes with numerous co-expressed partners were found to evolve more slowly than average [36]. The networks of interacting proteins also have the scale-free properties which is the consequence of network's simultaneous tolerance to random errors, coupled with fragility against the removal of the most connected nodes.

Besides the above mentioned techniques, there are some other approaches for mathematical analyzing of biological systems, among which is the stochastic approach due to the inherent stochasticity or randomness in biological processes. Different approaches have been proposed to analyze and control such stochasticity. In many cases, the stochastic and deterministic descriptions of a system

coincide in the sense that the mean behavior of the system can be accurately captured by the deterministic description [37]. When the system is operating near a critical point, however, deterministic and stochastic behaviors may be different. In this case, noises can induce some new phenomena. Noise can also induce new phenomena such as noise-based switches and amplifiers for gene expression [38] and fluctuation-enhanced sensitivity of intracellular regulation [39] in a single cell were also found. Some stochastic simulation algorithms have also been proposed.

3.2 Robustness of Molecular Networks

Robustness, the ability to maintain performance in the face of perturbations and uncertainty, is one of the essential features of biological systems [40]. It is essential for them to be robust against various changes in parameters to cope with genetic variations and external disturbances. It is believed that the structure of the network, rather than specific parameters of the network determine the robustness properties [10].

Understanding the mechanism behind robustness is particularly important because it provides in-depth understanding on how the system maintains its functional properties against various disturbances. For example, robustness of circadian rhythms with respect to molecular noise, parameters, and network structures have been studied [26,41,42,10]. It is found that the robustness maybe related to evolution [43]. Some mechanisms have been found which can improve the robustness. For example, redundancy is a widely used method to improve the systems robustness against damage to its components by using multiple pathways to accomplish the function [1]. The use of explicit control scheme is also an effective approach to improving robustness. The global properties such as scale-free networks are also robust against random failure of the molecules [7].

3.3 Information Propagation in Molecular Networks

Essence of living systems is flow of mass, energy, and information in space and time. The flow occurs along specific networks such as flow of mass and energy in metabolic networks, flow of information involving DNA in transcriptional regulation networks, and flow of information not involving DNA in signaling networks. Thus, the information propagation in molecular networks typically involves intracellular feedback mechanisms and continually sensing their environment through receptors. To determine how cells act and interact we need to understand how information is transferred between and within cells. The information transfer is carried out through integrated exchange of biosignals by cell communication. While the intracellular feedback mechanisms, i.e., the direction and strength of relationships between intracellular components in a pathway determines the information propagation inside individual cells [45].

3.4 Adaptive Molecular Networks

During the evolution of molecular networks, both the network composition and the interactions between components will vary. The adaptive molecular networks are formed on two levels [44]. On one level, the equations of motion are integrated to determine the state of each component. On a second level, algorithms which approximate physical processes in the real system are employed to change the equations of motion. Take the immune network as an example. It has two different types of temporal variation. The first is adjustment of the concentration of each component in response to the couplings, i.e., the relationships between intracellular components. The second is an innovative process, the addition of new components into the system or deletion of old components from the system [44]. The adaptation of molecular networks is a selective property in evolution process.

Besides the construction of adaptive molecular networks from the viewpoints of evolution, there are also two other approaches to constructing a system that exhibits perfect adaptation from the perspective of robust control theory: (i) fine tuning the parameters and (ii) designing a specific structure that creates this property inherently. Robust perfect adaptation in bacterial chemotaxis through integral feedback control is such an example [31].

4 Discussion

In this paper, we have given a brief introduction to modeling and dynamical analysis of molecular networks. It is worth mentioning that the framework on modeling and analyzing molecular networks in this paper is general, and can be widely applied to various areas of real biological systems. Although still in their infancy, theoretical methods for modeling and analyzing of gene regulation processes are indispensable to reveal the essential mechanisms of biological systems because intuitive understanding of their dynamics is usually hard to be obtained only from biological experiments.

Although there are significant advances on modeling and analyzing molecular networks in recent years, the essential mechanisms by which the function arises remain to be fully understood. Many different forms of models have been constructed with various approximation or assumptions, however, the integrative study with as many as possible factors still need further exploration from perspectives of systems and networks. It is an area in need of new theoretical concepts linking dynamical phenomena and molecular networks. In addition, it is also a future topic to exploit the structures of network motifs and modules to model or simplify molecular networks in a biologically plausible manner.

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