EDITORIAL

S**tructure, Dynamics and Function - Dynamical Properties of Large Bio-Molecular Networks**

Bio-molecular systems consist of tens of thousands of molecular species of different chemical nature. These systems have been described as networks, such as metabolic networks [1, 2], protein-interaction networks [3], and transcriptional regulatory networks [4]. The nodes in these networks represent bio-molecular species (e.g. metabolites, proteins, RNAs) and the edges represent functional, causal or physical interactions between the nodes. The abstract representation of bio-molecular regulatory systems as networks is fruitful because it provides the ability to study the systems as a whole while ignoring many irrelevant details [5, 6]. All chemistry and physics is removed (or considered only implicitly) in order to concentrate on the essence of the system: the 'wiring scheme'. As for all abstractions of natural systems, we are doomed to lose some information when we represent bio-molecular regulatory systems as networks [6-8].

Large bio-molecular network have been subjected extensively to topological analysis for over a decade now. Many interesting topological features have been identified and their potential functions have been proposed [5, 6]. However, relating the structure of large bio-molecular network to dynamics and function is still a largely unexplored subject. Studies on dynamical properties have mostly been restricted to very small bio-molecular networks, due to the limited amount of quantitative data. Fortunately, several studies have shown that even without detailed quantitative knowledge, much can still be learned about the dynamical properties of large bio-molecular networks [9-13]. This special issue provides a recent update of the current state of art in relating structure to dynamics applied to large bio-molecular networks.

The goal of the studies reviewed in this special issue is not to study the dynamics of any specific bio-molecular network, but rather to identify topological patterns which imply the possibility of certain dynamical/functional behaviors. By no means can we definitely state that '**structure determines function**' as networks with the same structure could display distinct dynamics depending on their parameter values (for instance the strength or signs of interactions). Networks could for instance display oscillations or reach a stable steady state depending on the specific model parameters. To be able to characterize the true behavior of bio-molecular networks we need the quantitative information of all the parameters. Experimental identification of the large numbers of parameters is currently infeasible, even with modern high throughput techniques.

Nevertheless, we can still learn much about dynamics from topology alone. Inspection of the network topology can immediately **exclude** certain dynamical behaviors completely independent on the parameter values, based on identifying topological conditions which are **necessary** and which are **sufficient**. A simple example is that of an acyclic network (a network without any directed paths which start and end in the same node), which can not display oscillations (which requires the necessary condition negative feedback) nor multi-stationary (which requires the necessary condition positive feedback) [14]. While we can not with certainty state that a network with negative feedback should oscillate or a network with positive feedback should be multi-stationary, as the conditions are necessary but not sufficient, we can with certainty claim the opposite, as a network which lacks the necessary conditions for a particular dynamical behavior is not able to display it.

Indeed, one requires precise information of the functional dependencies between the network nodes and their parameter values in order to be able to conclude which specific dynamics the network displays. Again, this information is virtually completely lacking for bio-molecular networks. Then how can we proceed? What can we still learn from topology? It is easy to show that a particular network structure displays a particular dynamical behavior under one parameter setting, while behaving completely different under another parameter setting, and concluding that structure does not determine function [15]. But rather

1875-0362/11 2011 Bentham Open

than showing the dynamical behavior of networks with specific parameterizations, focus should be put on investigating how the structure determines the 'probability' for a particular dynamical behavior under a wide range of realistic parameter values [9, 16, 17]. While the precise values of each specific parameter are unknown, there is often knowledge (or ability to make educated guesses) on the range of possible values of parameters. This then allows to explore the 'space of possible dynamics' for a given network structure and a chosen 'parameter space'. Such studies might provide insights into why certain network structures have been preferred over others by natural selection. There are many network topologies which could display, for example, oscillatory dynamics, but some might only do so for a small region of parameter space, while other networks might do so for a wide region. If a living cell needs a network displaying oscillations the topology of the latter type, the more robust oscillators, will likely be preferred. Through this approach we might learn how '**structure determines the probability of certain functions**'.

This special issue starts with a review by Ralf Steuer, which first gives a general introduction to modeling bio-molecular networks and then summarizes approaches using Ordinary Differential Equations (ODEs) and Monte Carlo methods to explore dynamic properties of metabolic networks. These approaches enable to explore the dynamical capabilities of a given network topology and to identify which network edges and nodes play important roles in particular dynamics.

Tomáš Helikar, Naomi Kochi, John Konvalina and Jim A. Rogers describe the use of Boolean Networks for modeling the dynamics of protein signaling networks. First, these authors provide a basic introduction to Boolean logic, then highlight the insights obtained through the analysis of such networks (including the groundbreaking work by Stuart Kauffman dating back to the 1960s!), to insights into specific biological systems, and conclude by describing the emergent network properties of signaling networks identified in this framework.

Mika Gustafsson and Michael Hörnquist review how the topological features contribute to the overall stability and/or flexibility of the dynamics of linear ODEs. They elegantly show that a yeast gene network possesses precisely the topological features (and sign distributions) to obtain a perfect balance between stability and flexibility.

José Nacher and Tomoshiro Ochiai take another route. Rather than moving from structure to dynamics, they review efforts which move from dynamics to topology. Their aim is not to identify a specific system which underlies a given gene expression dynamics (i.e. reverse-engineering), but rather to discover general principles, or 'laws', in gene expression dynamics and to argue about what topological features the underlying network must posses consistent with such principles.

Bio-molecular networks should function as a coherent whole. Weihan Li and Changsong Zhou consider networks of oscillators and review findings which provide better insight into how network topology determines the ability of the network to function coherently, i.e. the ability of the network nodes to synchronize.

These reviews summarize the current state of the art in relating the topological properties of large bio-molecular networks to dynamical properties. Further progress in this area will be catalyzed by the current flood of experimental data from modern high throughput omics techniques, but is certainly in need for initiatives dedicated to high throughput determination of kinetic functions and their parameters [18]. In addition, computationally efficient frameworks, ever increasing computational power, novel computational paradigms [19], and novel mathematical techniques [20] will enable to further explore the relations between network topology, dynamics, and biological function.

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