Chapter 9
Topological Analysis of Axon Guidance Network for Homo Sapiens

Xuning Chen
Shanghai University, China

Weiping Zhu
Shanghai University, China

ABSTRACT
Axonal outgrowth is usually guided by a variety of guidance factors, such as netrins, ephrins, slits and semaphorins, and is one of the critical steps for the proper formation of neural networks. However, how the signal molecules function and why some of these play more important roles than others in guiding the axonal directional outgrowth has not been fully understood. In this study, we try to solve the problem by using the complex network analysis method. The signal molecules and interactions are treated as the nodes and edges to construct the axon guidance network model for Homo sapiens. The data of the model are taken from the KEGG database, and an analysis workbench named Integrative Visual Analysis Tool for Biological Networks and Pathways (VisANT) is employed to analyze the topological properties, including the degree distribution and the top co-expressed genes of the axon guidance network. This study has just opened a window into understanding the mechanism of axon guidance.

INTRODUCTION
Axon guidance is one of the critical steps for the proper formation of a neural network (Negishi et al., 2005), which relates to a variety of guidance factors, such as netrins, ephrins, slits, and semaphorins (Dickson, 2002). The growth cone at the tip of an extending axon is highly sensitive to repulsive and attractive guidance cues in its environment. These molecules may be diffusible and work from a distance, or bound to membrane or substrate, or work at a close range. It is the complex integration of these repulsive and attractive signals that guides an axon to its target appropriately. These molecules not only play critical roles during nervous system development but may also regulate the regenerative capacity of neurons during nervous system diseases. Thus, it is necessary to fully understand how these factors

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function and which plays more important roles in the axon guidance network.

Genetics and biochemistry have identified a large set of molecules that affect axon guidance. How all of these molecules exert their effects is less understood. Growth cone signaling mechanisms are highly complex, consisting of numerous dynamic networks of biochemical reactions and signaling interactions between cellular components. This complexity makes it virtually impossible to analyze by traditional methods. Hence, network analysis method has been developed as a platform for integrating information from high-to-low throughput experiments for the analysis of biological systems (Kwoha & Ng, 2007).

A lot of research work has demonstrated that the topological property of a biosystem network implies rich biological functional information (Jeong et al., 2000; Kohn, 1999; Uetz et al., 2000). The network topology-based approach also helps to uncover potential mechanisms that contribute to their shared pathophysiology (Lee et al., 2008). In this paper, we revealed the topological property of the axon guidance network for Homo sapiens by using the complex network analysis method. The results show that some of the nodes are more highly connected than the others in the network. It is as expected that there are a few hubs that dominate their topology to resist random failures in a biosystem.

**MODEL AND ANALYSIS TOOL**

The numerous online pathway databases vary widely in coverage and representation of biological processes. An integrated network-based information system for querying, visualization and analysis promised successful integration of data on a large scale. Such integrated systems will greatly facilitate the understanding of biological interactions and experimental verification (Kwoha & Ng, 2007).

We treated the signal molecules and interactions as the nodes and edges to model the axon guidance network and used the data from the Kyoto Encyclopedia of Genes and Genomes (KEGG) Pathway (Kanehisha, 2009). In order to make these simplifications, it was necessary to neglect some of the details of the biological processes (De Silva & Stumpf, 2005). In reality, axon guidance pathway is highly interconnected and factorizing them into distinct networks will ultimately underestimate the biological complexity.

Many tools exist for visually exploring biological networks including well-known examples such as Cytoscape, VisANT, Pathway Studio and Patika (Suderman & Hallett, 2007). We employed the Integrative Visual Analysis Tool for Biological Networks and Pathways (VisANT) as the analysis workbench. VisANT not only provides network drawing capabilities, including support for very large networks, but it is also one of the first such packages to support creation, visualization and analysis of mixed networks, i.e. networks containing both directed and undirected links. The ability to use nodes to model more complex entities such as protein complexes or pathways allows for more informative visualizations (Hu et al., 2005). A model using the VisANT processing is shown in Figure 1. Signal molecules are the nodes and physical interactions among them are the edges or links in the graph. There are 69 nodes and 67 edges. A single protein/gene is represented as a filled green circle and a meta-node of the multiple proteins/genes is represented as a green box. And “-” indicates that the node is fully expanded (i.e. all connections are shown) whereas the “+” indicates that some links have not yet been displayed.

**RESULTS AND DISCUSSIONS**

In the following sections, we will present a basic theoretical framework oriented to describe and analyze axon guidance networks.