On Attractor Detection and Optimal Control of Boolean Networks

Trinh Van Giang

Doctoral Degree in Information Science

Graduate School of Advanced Science and Technology

Japan Advanced Institute of Science and Technology

Boolean Networks (BNs) are simple but efficient mathematical formalism for modeling and analyzing complex biological systems, such as, gene regulatory networks, signal transduction networks. Beyond systems biology, BNs have widely been applied to various other areas, such as, mathematics, neural networks, social modeling, robotics, and computer science. Besides a plenty of applications, BNs are also interesting mathematical objects that have recently attracted various work in theory. Attractor detection and optimal control of BNs are two crucial but challenging issues of research on BNs. They have also become hot topics in many research communities. However, the existing theories and methods for these issues mainly focus on synchronous types of BNs and few ones focus on asynchronous types of BNs. Moreover, the existing methods are inefficient when the size of the network becomes large or the structure of the network becomes more complex. Hence, we focus in this dissertation on developing theories as well as efficient methods for attractor detection and optimal control of different types of BNs.

In theoretical aspects, we explore a number of new theoretical results that contribute to understanding the dynamics of BNs. First, we discover several relations in dynamics between different types of BNs. In addition, we also obtain several relations in dynamics between BNs and other conventional models. In particular, we demonstrate that these findings pave the potential ways to analyze different types of BNs as well as many other conventional models. Second, we discover several relations between the dynamics of a BN and its network structures. More specifically, we formally state and prove several relations between the dynamics of a BN and a feedback vertex set of its interaction graph. Notably, these relations do not depend on the updating scheme of the BN. Furthermore, we also state and prove a theorem on relations between the dynamics of an asynchronous Boolean network and a negative feedback vertex set of its interaction graph. Finally, we introduce several complexity analysis on three meaningful optimal control problems of deterministic asynchronous probabilistic Boolean networks.

In practical aspects, we develop several algorithms and methods for attractor detection and optimal control of different typical types of BNs. These algorithms and methods are mainly based on the new theoretical results obtained along with the reasonable use of formal techniques. We implement software tools for all the proposed algorithms and methods as well as conduct experiments to evaluate their performance. The experimental results on various classes of networks show that our algorithms and methods outperform the corresponding state-of-the-art ones and can handle large-scale networks. In particular, our method for finding attractors of an asynchronous Boolean network can handle very large networks with up to 1000 nodes in term of randomly generated networks and more than 300 nodes in terms of real biological networks. Notably, the principle that we propose in our algorithms and methods is general, thus enabling us to apply it to many types of BNs as well as paving potential ways to improve these algorithms and methods.

Keywords: *Boolean networks*, *gene regulatory networks*, *attractor detection*, *optimal control*, *formal methods*.