Thesis Summary

Adaptation and Gene Regulatory Networks: Properties and Structural Inference

適応と遺伝子制御ネットワーク：特徴と構造推定

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Networks are ubiquitous in nature. Many natural phenomena, as well as man made objects like internet can be modeled in terms of networks. In the world of biosystems, networks govern the dynamics of many crucial components, ranging from transcriptional networks to signaling systems. Understanding the properties of networks are thus crucial towards developing the understanding of many biological systems. Such an understanding involves two steps: uncovering the topology of the network, and understanding the properties based on the given topology. This thesis is aimed towards understanding both aspects of biochemical networks .

We start our study with exploring the properties of adaptation networks, whose topology is already known. Adaptation is a common response shown by various signaling systems, where a system first responds to the external changes in the environment, and then tries to go back to its previous state. Such a response has been shown to increase the efficiency of response of adaptation systems. It was shown recently that only two network topologies, incoherent feedforward loop (iFFL) and negative feedback loop (nFBL) can show perfect adaptation. But as like other biochemical networks, the performance of these networks is constrained by intrinsic noise which may arise due to factors like small copy number of molecules, diffusion and random fluctuations in reaction coefficients. The relation between response and fluctuations is well understood in equilibrium systems in terms of the Fluctuation Response relation. But such a relation is not understood clearly for nonequlibrium systems like adaptation. This motivated us to explore the relation between adaptive response and its intrinsic noise.

To explore this relation, we studied three node networks of iFFL and nFBL when a steady state perturbation was applied to them. Using numerical simulations, we found that the response magnitude of adaptation networks was always less than the intrinsic noise. To understand this relation properly, we studied these networks analytically. By using linear noise approximation, we obtained the expressions for response magnitude and intrinsic noise. Using the relation between noise strength and the the coupling coefficient for input nodes, we could show the gain noise inequality theoretically. We further also obtained the conditions for iFFL and nFBL when response could achieve its maximum value of noise. This analysis revealed an important difference between iFFL

and nFBL. We found that while iFFL is more robust to parameter variation as compared to nFBL, it is nFBL which offers higher gain and higher gain to noise ratio for adaptation networks. We also showed that in the limit of perfect adaptation, nFBL achieves the gain noise equality as well. In nature, nFBL has been found to occur more frequently as compared to iFFL. Our results may explain this owing to the advantage offered by nFBL over iFFL. We also showed that extrinsic noise is dominated by intrinsic noise for adaptation networks.

After exploring the network properties when the underlying topology was already known, we focused our attention to the study of another class of problems: extracting the network structure using observed states of network components. This reverse engineering problem is important for gene regulatory networks to understand their functioning. Specifically, we studied the gene expression profile data underlying the pluripotent state of Embryonic Stem(ES) cells. We chose to model this system in terms of a Boolean network due to the many underlying advantages offered by it. To be able to do so, we developed a novel algorithm based on the principle of consistency, as discussed in the paper of Akutsu et al. Using this approach, we checked many possible networks, and finally obtained a small number of networks which could successfully reproduce the experimentally observed gene experssion profile. An analysis of the obtained networks yielded information about the regulatory interactions between the given set of transcription factors. A comparison with the available literature showed that while our model recaptures many already known interactions, it also yielded a host of new possible interactions which could play a crucial role in understanding the functioning of pluripotency. In particular, we showed that Esrrb is a crucial regulator of the pluripotent state of ES cells. A number of feedforward and feedback loops also are implicated in the maintenance of pluripotency. A further validation with experiments would thus be the next logical step to compliment our theoretical approach.

In summary, we studied two crucial aspects related to biological networks, and also explored two important systems in terms of adaptation networks and transcription regulatory networks of pluripotent ES cells. We obtained many important insights about both these systems. Though a lot of open problems still remain about both of them, we hope that our effort would shed some light into the how biological systems are governed through the interplay of network structures and outside environment.