

Stability and instability in Gene Regulatory Networks

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Short Abstract —In this work, we investigate the network stability, attractor number and attractor types of ODE models of random gene regulatory networks (GRNs), with different network sizes, connectivity, inhibition fractions and transcription regulation rules. In small network size, mono- and bi- stability dominate the dynamics while oscillations are rare. In large GRNs, though different transcription regulation rules leads to distinct asymptotic behaviors of the network, the network stability is positively correlated with the relative strength of inhibition in similar fashion. Our result shows that increased number of inhibitors destabilizes GRNs and allows for chaos.

Keywords — chaos, gene regulatory networks, inhibition.

I. BACKGROUND

Theoretical modeling of gene regulatory networks (GRNs) is an important topic in systems biology [1]. Much work has been devoted to biological networks with specific topologies and dynamics [2]. In order to understand the general properties of GRNs, and distinguish the network behaviors arose from natural selection and that from randomness of the network, it will be meaningful to investigate the ensemble of GRN models with arbitrary topologies.

Several modeling approaches have been applied to GRNs [1]. Discrete Boolean networks show an order to chaos transition for connectivity larger than 2 [3]. However, real biological networks rarely display chaotic behavior [4], even some of the GRNs are very densely connected. It raises the question about the properties of GRNs on continuous model, which is more realistic approach to biological systems.

II. METHODS

We generated large sets of ODE models for GRNs with random topologies, and investigated the properties of their attractor landscapes. Networks and parameters are sampled by random, and the asymptotic states of each network are classified as steady states, oscillation or chaos according to the maximal Lyapunov exponent. Several forms of gene transcription rates that follow different combinatorial rules of activations and inhibitions are used, such as “AND”, “OR”

and “Additive” rules, and “Combined AND & Additive” rule that represents strong inhibition.

III. RESULTS

In enumerating of all three-node networks, we demonstrate that mono-stable and bi-stables are the dominating landscapes, which appear with probabilities 0.73 and 0.24, respectively. Periodic oscillations (limit cycles) are very rare

In larger networks (N=100), the relation between connectivity and network stability shows a significant dependence on the transcription regulation rules. Networks obeying combined rules result in more non-stationary (oscillatory and chaotic) trajectories in higher connectivity; while networks obeying AND, OR or Additive rules show more steady state behavior when connectivity increases. In the biologically realistic rules, the average number of steady states decreases with network size.

We argue that the distinct behaviors of large GRNs under different transcription rules is due to their different relative strength of inhibitions. We increased the fraction of inhibitions from 0 to 1, and the percentage of trajectories entering chaotic attractors increases drastically. When all gene products are inhibitors, over 50% of the trajectories asymptotically show chaotic behaviors. On the contrast, Boolean Networks are deeply ordered under this condition. Different as different transcription rules are, they show similar positive correlation between maximal Lyapunov exponent and the relative strength of inhibition.

IV. CONCLUSION

Our work helps to build the relation of network structure and dynamics in the GRNs. We also showed that there are distinct regions for stability/instability for Boolean and ODEs. The conclusion that inhibitors destabilize GRNs might have implications in other types of networks and needs more investigations.

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