The Relationship between Microscopic and Collective Properties in Gene Regulatory Network-based Morphogenetic Systems

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Abstract

Gene regulatory network (GRN)-based morphogenetic systems have recently attracted an increasing attention in artificial life and morphogenetic engineering research. However, the relationship between microscopic properties of intracellular GRNs and collective properties of morphogenetic systems has not been fully explored yet. Thus, we propose a new GRN-based framework to elucidate how critical dynamics of GRNs in individual cells affect cell fates such as proliferation, apoptosis, and differentiation in resulting morphogenetic systems. Our model represents an aggregation of cells, where each cell has a GRN in it. We used Kauffman's NK Boolean networks for GRNs. Specifically, we randomly assigned three cell fates to the attractors. Varying the properties of GRNs from ordered, through critical, to chaotic regimes, we observed the process that cells are aggregated. We found that the criticality of a GRN made an optimal partition of basins of attraction, which led to a maximum balance between cell fates. Based on the result, we can conclude that the criticality of a GRN is an important controller to determine the frequencies of cell fates in morphogenetic systems.

Gene regulatory network (GRN)-based morphogenetic systems have been actively developed and their properties have been studied in artificial life and morphogenetic engineering (Doursat, 2008; Schramm, et al. 2012). However, the relationship between microscopic properties of intracellular GRNs and collective properties of morphogenetic systems has not been fully explored yet.

Here, we study the relationship between the critical dynamics of GRNs in cells and cellular functions performed in morphogenetic systems at a collective level. We used Kauffman's NK Boolean network as a model of GRNs (Kauffman, 1969, 1993, 1996). In NK Boolean networks, a dynamic attractor can be considered as a cellular function or a cell type. Thus, staying in different attractors can be interpreted as a dynamical representation of the cellular function. There exists much experimental evidence to support this view of cellular dynamics (Huang et al. 2005; Chang et al. 2008). Based on this view, Huang explained stochastic and reversible switching between cell fates using NK Boolean networks (Huang, 1999; Huang and Ingber, 2000).

Extending Huang's conceptual framework, we implemented NK Boolean network-based morphogenetic systems. In our model, we assumed that a cell has three fundamental cellular functions: proliferation, apoptosis, and differentiation. Our model represents an aggregation of cells, where each cell has an identical random NK Boolean network which consists of 20 nodes. By adjusting in-degree (K) of nodes of a GRN in the model, we can obtain various properties of GRNs from ordered, through critical, to chaotic regimes; K=1 is ordered, K=2 is critical, and K>2 is chaotic [3,4,5]. We generated random GRNs from K=1 to K=4. For each GRN, we randomly chose one attractor and assigned it the cellular function of proliferation. If there is any other attractor available, we chose another attractor randomly and assigned it the cellular function of apoptosis. If there is still any attractor available, we chose an attractor randomly and assigned it the cellular function of differentiation. This means that, if a GRN has only one attractor, it conducts only proliferation. If it has two attractors, it performs proliferation and apoptosis. With three or more attractors, all the cell fates assumed in the model can take place. Fig. 1(a) is a schematic diagram that shows three cell fates randomly assigned in a GRN which has more than three attractors.

Jumping from one cell fate to another may occur in every time step by perturbations in internal gene expression caused by cell-cell interactions within a morphogenetic system. Specifically, cells interact with one another through the transport of signal molecules between the environment and cells. The transport occurs through diffusion by the concentration difference of signal molecules. If the concentration of a signal molecule is beyond a certain threshold, it can control the expression of assigned genes.

Our morphogenetic model starts from one seed cell. The change of concentrations of signal molecules by diffusion leads to the change of gene expression. The altered gene expression finally converges to one attractor. If the converged attractor is proliferation, the cell is divided into two at the next time step. One is mother cell and the other is daughter one. Two cell share the half concentrations of signal molecules of the mother cell before division and they have the same GRN. With the process of proliferation, aggregated cells are composed of all the same GRNs. If the converged attractor is apoptosis, the cell dies. Once the cell becomes dead, it remains as it is for every time step. This is to examine how apoptosis has an influence on morphology based on the biological fact that apoptotic cell death contributes to cell morphology (e.g. the separation of fingers and toes in development). Last, if the converged attractor is differentiation, the cell is regarded as differentiated.

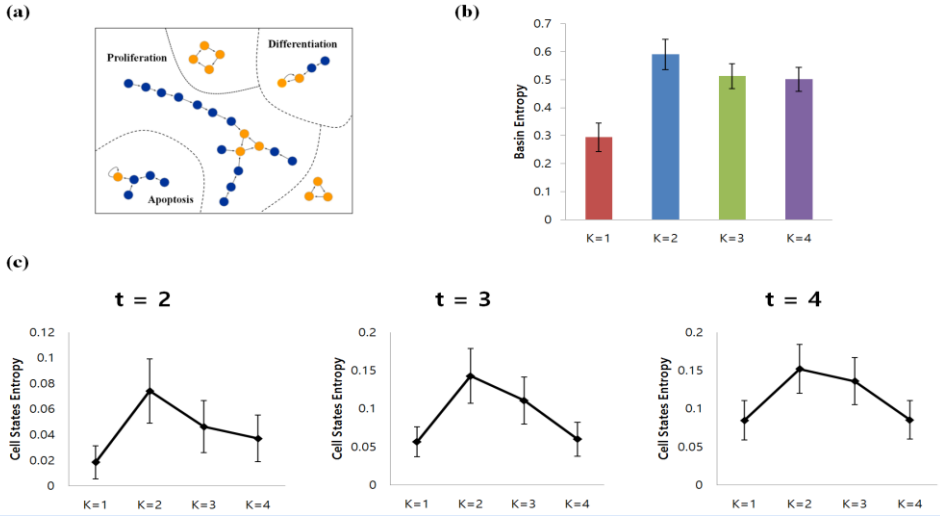

Figure 1: (a) Schematic diagram of randomly assigned three cell fates in a GRN which has more than three attractors. Each node represents a cell's dynamical state. Orange nodes are attractors. (b) Average basin entropy for K = 1–4. (c) Average states entropy of cell fates performed in simulations at each time step for K=1–4.

In our model, we assumed that cells staying in proliferation and differentiation states continue to switch between cell fates.

To investigate the structure of basins for cell fates according to the properties of GRNs, we applied revised basin entropy, using log base two. Basin entropy is a measure of the complexity of information that a system is capable of storing (Krawitz and Shmulevich, 2007). In the context of GRNs, the basin entropy represents the effective functional versatility of the cell. Originally, Krawitz's basin entropy is computed considering all the attractors and their basins. Meanwhile, focusing on the basins into which three cell fates are assigned, we calculated the values of basin entropy based on relative sizes of the basins. Fig. 1(b) shows the average of basin entropy for cell fates from K=1 to K=4. The average basin entropy is highest at K=2, i.e., the GRNs' basins of three cell fates are most evenly distributed at K=2.

For each group, we conducted 100 independent computational simulations of morphogenetic cell growth processes on a 2D spatial grid for t=0–4. By counting the numbers of cells expressing proliferation, apoptosis, or differentiation state at each time step in those simulations, we obtained the average values of cell states entropy based on relative frequencies (see Fig. 1(c)). Because there are too small number of cells at t=1 to capture distinct differences with K, we excluded a graph for the average values at t=1. As seen in Fig. 1(c), the cell states entropy is the highest at K=2 for t=2-4, which means when GRNs are critical, cells are aggregated remaining the most balanced three cell fates at each time step. The result confirmed that GRNs at K=2 have a maximum balance between cell fates. In the evolutionary view, the maximum balance has a significant implication; in any environmental changes, key cellular functions, such as proliferation, apoptosis, and differentiation, must be maintained in balance. Because those cellular functions are expressed by the attractors of a GRN in a cell, if the basins of cellular functions are distributed more evenly, the cell fates can better persist against environmental changes, which may work as a selective advantage in the process of evolution.

Our finding suggests that the criticality of a GRN may play an important role in modulating the frequencies of cell fates in morphogenetic systems. To obtain more theoretical/ empirical support for this suggestion, we plan to conduct large-scale evolutionary simulations of the ecologies of morphogenetic systems where the evolutionary success of multicellular organisms is determined by implicit fitness functions.

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