Mathematical controllability of genomic networks

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Scientists aim to understand, whereas engineers aim to modify and control. In the study by Rajapakse et al. in PNAS (1) these two objectives come together in the context of genomic reorganization during cell differentiation. Cell differentiation, a branch of epigenetics, is a well-analyzed process but one that lacks a mathematical predictive model. Systems biology provides mathematical tools and has recently become a fertile ground for network science (2, 3), specifically in the understanding of the collective dynamics within the nucleus. Indeed, from genetic networks to organizations, one may postulate that a network paradigm is the correct framework to understand life's complexity (4). The complex interactions within a living cell have benefited both from network science concepts as well as from the availability of computing power (3) to provide some modeling tools. What has been lacking, however, is the coupling of genomic network properties and characteristics, with the ability to affect changes at the cellular level. This ability may be especially powerful if one can steer the behavior of a living organism during cell differentiation. Rajapakse et al. (1) provide a convincing mathematical model that explains distinct phases of genomic reorganization consistent with experimental results and suggest that guiding the reorganization toward biologically desirable states may be possible.

Although some descriptive mathematical models are now available, the ability to mathematically study the control of genetic networks has only recently been recognized (5). Such networks may contain millions of nodes, but applying input to special nodes, termed driver nodes, is sufficient to steer the network behavior. The number of driver nodes needed to achieve complete "structural controllability" is determined by the maximum set of links that do not share start or end nodes. Driver nodes are therefore a subset of the large number of nodes in the network, and the number of such nodes was much larger for gene regulatory networks than man-made networks, pointing to the fact that nature has evolved into a harder-to-control (a more robust or lower entropy) state.

In their study (1), Rajapakse et al. take on the problem of controlling genomic networks at a very opportune moment. Although the intent of the research is not to provide a more accurate physical model for gene networks, the authors' ability to image the chromosomal network for a single cell line during differentiation, as well as a mathematical formulation that couples the structural network to the regulatory network in a feedback configuration, provides for a state-dependent network in which a geometric state is modeled using diffusion dynamics. In fact, earlier work (6, 7) has already established the interaction of the structural and functional networks but not the state-dependent network model. A model of the proximity-induced interaction network is a vector differential equation that models the dynamics of the geometric state of all nodes, with the interaction between nodes affected by weights that also depend on the distance between the corresponding geometric states. By including an external signal as an input to the differential equations, a full-fledged, abstract state-dependent dynamical model of the diffusion dynamics in genomic networks is obtained. Although the general model is nonlinear, by linearizing the dynamics around a specific node, a linear model is obtained to explain the behavior of the collective dynamics in nodal domains.

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During cell differentiation, the dynamics of chromosomal networks are therefore modeled by Rajapakse et al. (1) using state-dependent networks. In other words, the state of the system evolves in time but also influences the network structure. The approach has many potential advantages: It actually sheds light on properties and brings in the tools of mathematical control theory that allow for the potential of steering the network into desirable configurations.

State Controllability

In the parlance of control theory, controllability measures the ability to steer the states of a dynamical system throughout a state-space. A more controllable system is desirable, but it may also respond violently to undesirable inputs. Although the study by Liu et al. (5) established the existence of driver nodes that can be used to steer the system, it was focused on the system's structure and did not address the degree of controllability, nor did it express the state-dependent nature of network controllability, which becomes important during cell differentiation. The ability to control from a subset of influential (driver) nodes is also addressed by Rajapakse et al. (1), who show how to select specific nodes and inputs to steer the cell organization toward desirable network equilibrium.

Entropy measures the amount of disorder in a system and, according to the second law of thermodynamics, is always increasing in a closed system. Using the state-dependent network formulation, Rajapakse et al. (1) also present a plausible argument as to why during cell specialization entropy first increases then decreases, leading eventually to a higher-order final state. Entropy is intimately linked to the ability to control, as first described by Kalman et al. (8), and it may be shown to be equal to the determinant of the controllability Gramian. More controllable systems have more possible behaviors (thus are less ordered), and as previously described (9, 10, 11), as the cell specializes, entropy decreases, and a more stable cellular state results in lineage-specific chromosomal topologies. The controllability aspects of the state-dependent network model provide a plausible explanation for the emergence of a self-organized alignment between the architecture and transcriptional networks. It may also explain the unexpectedly large number of driver nodes needed to control gene regulatory networks (5).

Hybrid Systems

Although not discussed by Rajapakse et al. (1), an alternative modeling and potentially useful approach to studying cell differentiation is the use of hybrid systems (12). Hybrid systems are those that have two sets of dynamics: dynamics that evolve over a continuous state-space (they may be in continuous or discrete times) as well as dynamics that evolve

Author contribution: C.T.A. wrote the paper.

The author declares no conflict of interest.

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over a discrete state-space. The state-dependent networks proposed by Rajapakse et al. (1) are actually hybrid systems in which the switching between different modes depends on the state of the network. As the state of the genomic network evolves, the network geometry changes as the state enters the different regions of the state-space. In such formulation, the form or structure of the network jumps between discrete modes, corresponding to the geometric state of the genome evolving into a region that makes the network structure switch. In such a setting, the reachability of certain states (i.e., the ability to reach a certain subset in the state-space starting at some initial conditions) may be studied.

Finally, a potential application of the proposed model of genomic networks is in the area of man-made reconfigurable systems. Nature has evolved a very robust and efficient way to design complex organisms, starting with the same building blocks and a variety of simple rules. Engineering systems that can reconfigure themselves for different functions may be possible by copying the differentiation and reprogramming steps of cellular networks.

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