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Author

Wollman, Roy

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When a stem branches into two or more paths, a dilation occurs, increasing the number of nodes that need to be controlled. Ruths and Ruths distinguish between two types of dilations. In an internal dilation, a path splits into two paths that soon rejoin, much like two lanes of traffic that momentarily split only to merge again soon after (see the figure, panel B). In an external dilation, a path splits without subsequently rejoining, like entering a T-intersection with two dead end streets (see the figure, panel C). An internal dilation does not increase the number of sink nodes, whereas an external one does, by one for each branching.

In the absence of internal dilations, only source nodes and external dilations need to be controlled. When internal dilations are present, the sum of the source nodes and surplus sink nodes gives a lower bound on the number of nodes that need control. In most networks, the number of internal dilations is relatively small, and the bound obtained as the sum of source and surplus sink nodes is therefore fairly tight.

Previous studies have categorized nodes and edges in control structures by considering whether a node always, never, or sometimes needs its independent control (3) and by investigating whether an edge is always, never, or sometimes part of the control structure (1). The degree distribution of a network (that is, the distribution of the number of incoming and outgoing edges of each node) correlates strongly with the number of required independent controls (1). Ruths and Ruths now show that the special role of source and sink nodes in control structures leads to a simple causal link between degree sequence and the size of the driver node set.

Based on the three types of structures that induce the need for independent control (see the figure), real-world and synthetic networks can be profiled by designating all nodes that need to be controlled into source nodes, internal dilations, and external dilations. The control profile of a given network is simply the fraction of nodes in each of these three categories. By investigating a range of directed real-world and model networks, Ruths and Ruths find evidence for three categories of networks, which they call source-dominated, internal-dilation-dominated, and external-dilation-dominated networks.

The authors argue that source-dominated networks, such as neural and social networks, allow relatively uncorrelated behavior across their agents and are thus suitable to distributed processing. Internal-dilation-dominated networks, such as food networks and airport interconnectivity networks, are mostly closed

systems and obey some type of conservation laws. Finally, external-dilation-dominated networks with their surplus sink nodes yield correlated behaviors across their agents that are downstream from a common source, as exemplified by trust hierarchies and transcriptional systems.

The framework appears to assume that there are no intrinsic nodal dynamics. If self-loops (directed edges that connect a node to itself) were present at each node, such that the future state of a node depended on its own current state, all nodes could be driven by a single external control, given that loops and cycles are self-regulating structures (7). However, as the authors point out, if the time scale of interactions with network neighbors is much faster than that of the intrinsic dynamics, it is reasonable not to consider intrinsic nodal dynamics, especially for making comparisons across different types of networks.

Some studied networks will contain false positives and false negatives: The network representation of the system as obtained from empirical data will contain some edges that are not present in the real system, and will not contain some other edges that are present in the real system. Ruths and Ruths' framework may be particularly sensitive to false positives and false negatives, because they could change the classification of nodes in a non-

trivial manner. Furthermore, the data collection processes that introduce false positives and false negatives may be different across different network types. The impact of false negatives could be investigated by subsampling observed networks to determine how sensitive the control profile of a given network and its subsequent classification are to different forms of sampling.

The framework put forward by Ruths and Ruths is elegant in its simplicity and helps us to understand and interpret previous findings. It also points to interesting avenues for future work, such as the development of more realistic models of directed networks in the context of network control. Going forward, the framework provides a useful tool for moving from passively observing networked systems to pursuing control over them.

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DEVELOPMENT

Counting the Ways to Decode Dynamic Signals

Roy Wollman

The social amoeba *Dictyostelium discoideum* decodes an oscillatory signal to measure time.

The role of biological signaling networks is to reliably transmit specific information about the extracellular environment to multiple intracellular downstream effectors, allowing the cell to adjust its physiological state to changing conditions. One mechanism that cells use to enhance the performance of signaling networks is the temporal modulation, or dynamics, of the transmitted signals (1–4). The key role that modulating temporal activity of the signal plays in information transmission makes

signaling dynamics an attractive target for therapeutic approaches that interfere with the transmission of specific types of information through the network (5). The diversity of temporal modulation strategies seen in various signaling networks suggests that there is no single optimal strategy for making use of dynamic information. Therefore, to uncover the benefits of temporal modulation strategies, it is important to understand how the suitability of each type of signaling dynamics is matched to the nature of the particular information that is being transmitted. Some types of information are transmitted through frequency-modulated signals, whereas other types are transmitted through modulation of signal amplitude or duration.

Cell and Developmental Biology Section, Division of Biological Sciences, and Department of Chemistry and Biochemistry, University of California, San Diego, La Jolla, CA 92093, USA, and San Diego Center for Systems Biology, La Jolla, CA 92093, USA. E-mail: rwollman@ucsd.edu

Work by Cai *et al.* (6) on page 1329 of this issue identifies how the social amoeba *Dictyostelium discoideum* decodes a temporally dynamic signal to coordinate its development in response to starvation.

In *D. discoideum*, starvation triggers the chemotactic aggregation of tens of thousands of cells that then coordinate their activities to develop into a multicellular slug, collectively migrate, and form a fruiting body. Such coordinated action of a large number of cells requires reliable communication about gene expression and developmental state. Failure to communicate could cause a subset of the cells to develop at a different pace, resulting in their subsequent developmental arrest and death. Therefore, synchronous and successful development requires a common developmental timer shared by all the cells in the population. Research over the past 40 years has uncovered a complex synchronization mechanism that is controlled by periodic waves of cyclic adenosine monophosphate (cAMP) secreted by the amoebae and propagating throughout the population (7). Pulses of cAMP are necessary for the completion of the developmental program, which suggests that information about the developmental state of cells in the aggregate is encoded in the pulsatile dynamics of extracellular cAMP. However, the mechanism by which this developmental information is decoded by cells has been unknown until now.

Cai *et al.* found that the key signaling circuit that decodes the dynamic cAMP signals in *D. discoideum* involves GtaC, a GATA family transcription factor. GtaC is negatively regulated by cAMP: An increase in the concentration of extracellular cAMP results in the glycogen synthase kinase 3 (GSK3)–dependent export of GtaC from the nucleus to the cytoplasm. Tracking mRNA expression at the single-cell level demonstrated that there is a delay between the cAMP pulse and the resulting decrease in expression of genes positively regulated by GtaC. Because cAMP is known as an activator of gene expression during *D. discoideum* development, its new regulatory role as a delayed inhibitor of gene expression suggested that the circuit that decodes cAMP acts as an incoherent feedforward module. In an incoherent feedforward module, an upstream activator regulates a downstream target through two opposing arms: a fast activator and a slow inhibitor. The delay between the two regulatory arms results in a pulse of target activity.

The identified circuit carries out two key functions: It acts as a low-pass filter and as a counter. The low-pass filter enables the cell to filter out high-frequency cAMP pulses.

Decoding temporal signals. During starvation-induced aggregation in *D. discoideum*, extracellular concentrations of cAMP oscillate. A decoding mechanism of these oscillations that uses the translocation of a GATA transcription factor between the cytoplasm and the nucleus allows cells to count the number of pulses and synchronize the transcriptional programs across the population.

Because the generation of pulses involves a positive feedback mechanism, the system is prone to be noisy, and the ability to be insensitive to short (less than 6 min), high-frequency pulses will increase the robustness of the transition into collective behavior (8). The second function of this circuit is its ability to transform each pulse of cAMP longer than 6 min into a single pulse of transcriptional activity. Therefore, the expression of GtaC-dependent genes will increase approximately linearly as a function of the number of permitted pulses rather than the overall concentration of cAMP (see the figure). By manipulating extracellular cAMP levels, Cai *et al.* demonstrated that the expression of key developmental genes increases with the number of cAMP pulses, supporting the interpretation that cells count the number of pulses to which they are exposed.

The invention of the pendulum clock in 1659 was a technological breakthrough because it allowed the measurement of time with unprecedented accuracy, with an error of approximately 1 min per day (9). A pendulum clock translates an oscillatory input into a time measurement by decoding each cycle as a single action. This transformation

of an oscillatory signal into a count was the key to the incredible accuracy of pendulum clocks relative to previous timekeeping technologies. The circuit identified by Cai *et al.*, similar to the oscillations of the pendulum clock, allows each cell in the collective to translate pulses of cAMP into temporal information. The accuracy of pulse counting as a timekeeping mechanism makes oscillatory encoding a temporal modulation strategy that is adapted to the synchronization challenge faced by *D. discoideum*.

Pulsatile gene expression has now been identified in several experimental systems and has been shown to provide various benefits to cells (10). The encoding of oscillations of cAMP through a population-level signaling circuit that is then decoded by single cells through an incoherent feedforward loop provides a mechanism that can explain how a collection of tens of thousands of cells can synchronize their developmental states. The use of oscillatory dynamics has the potential to facilitate accurate timekeeping by cells in the population, enabling a synchronized transition from a unicellular to a multicellular developmental program.

Signaling networks encode information about events in the extracellular environment into specific signaling dynamics that are then converted (i.e., decoded) into specific actions important for cell physiology (11). The work of Cai *et al.* shows that the coupling of population-level temporal encoding of oscillatory dynamics with single-cell decoding of these pulses into temporal information can act as an accurate developmental timer and thereby provide an important selective advantage for *D. discoideum*. Future studies of signaling dynamics may uncover additional system-specific benefits and costs entailed in the use of various encoding and decoding strategies to transmit biological information through signal transduction networks.

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Roy Wollman (March 20, 2014)

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