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New and Notable

Pattern Selection: The Importance of "How You Get There"

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We all developed from an embryo: along the way, many billions of cells are making decisions on how to differentiate, proliferate, or undergo apoptosis. These cells take cues from each other to differentiate into different tissues, organs, and patterns. Pattern formation is one of the most visible forms of decision-making and has been widely studied; for example, in chemotactic pattern formation (1). The seminal work of Turing (2) showed the basic principle that patterns can form in homogeneous tissue through a generic instability in a system that involves at least two interacting chemical species. Although cells are much more complicated, it is well accepted that a cell's decisions about pattern formation are controlled by gene regulatory networks that coordinate the action of many genes involved in the decision-making, in conjunction with signals from other interacting cells or external media. But precisely which factors affect these decisions? In particular, if there are several stable patterns, which emergent pattern will be selected by the cells that make up a tissue?

A common belief is that the eventual pattern chosen depends primarily on initial conditions. In this issue of the *Biophysical Journal*, Palau-Ortin et al. (3) suggest a different view, from a theoretical study of pattern-formation for the Notch signaling pathway in the *Drosophila* embryo. Surprisingly, their research shows that the pattern chosen may depend more on the dynamical mechanism of spatiotemporal changes of the control parameters than on the initial conditions; a dynamical path in the space of signals may steer the system into one of a number of possible stable patterns. Indeed, according to Palau-Ortin et al. (3), pattern formation seems to be as much about "how you get there" as "where you start"!

Decisions in biological systems often need to be made rapidly and consistently, such as during the development of an embryo; and the outcome may depend not only on the path taken but also on how fast you traverse the path. A mechanism explaining how the final state can depend on the speed is illustrated in Fig. 1. Let us consider a system governed by the asymmetric bifurcation scenario: if we start in state A and change the control parameter λ slowly, state B will be reached. However, a fast change of the control parameter will move a system into state D. This simple example illustrates that the rate of the decision-making can be just as important as any bifurcation scenario or initial conditions. In this case, the selection of final state can be understood in the context of a rate-induced tipping point in an open system (4).

Cellular decisions are fundamental for key cellular processes, including developmental pattern formation, cell differentiation, and the maintenance of pluripotency. In the presence of several stable conditions (and the absence of any clear mechanisms to set initial conditions), these decisions must somehow depend on the form and rate of the dynamical path in the space of controlling parameters. For example, a common genetic switch that sustains decision-making consists of two mutually inhibiting genes under the action of two external signals. Such a switch, because of its bistability (where stable states correspond to the genes in the on-off or off-on states), can be considered as a simple model of the cell differentiation. This genetic switch may be engineered by tools of Synthetic Biology and there are many possible implications for biotechnology, biocomputing, or gene therapy. When the external signals are sufficiently symmetric, the circuit may exhibit bistability, which is associated with two distinct cell fates chosen with equal probability because of noise involved in gene expression. If, however, the input signals provide a transient asymmetry, the switch will be biased by the rate of the external signals. The effect of speed-dependent cellular decision-making can be observed (5) in which slow and fast decisions will result in a different probability to choose the corresponding cell fate. The speed at which the system crosses a critical region strongly influences the sensitivity to transient asymmetry of the external signals. For high speed changes, the system may not notice a transient asymmetry but for slow changes, bifurcation delay may increase the probability of one of the states being selected (6).

Palau-Ortin et al. (3) study a number of scenarios in their article that enables them to control the system into a target pattern that may be homogeneous (H), periodic salt-and-pepper (P), or stripe (S) patterns in an idealized two-dimensional tissue. They consider three types of control: 1) the control is homogeneous, 2) the control acts locally in space, and 3) the control propagates across the tissue. By a number of computational experiments the authors give recipes for how to rapidly and reliably move the system into one of the three target patterns by a path that may be transient. As Palau-Ortin et al. (3) state:

> …key elements for pattern selection are the destabilization of the initial pattern, the subsequent exploration of other patterns determined by the spatiotemporal symmetry of the

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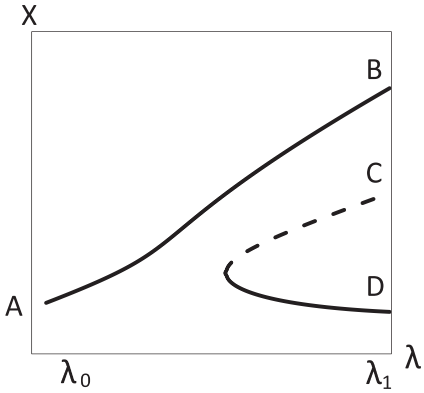

FIGURE 1 An illustration of a simple mechanism responsible for speed-dependent decision-making in terms of a bifurcation diagram where the horizontal axis represents a time-dependent input that changes from $\lambda = \lambda_0$ to λ_1. The vertical axis represents the state of the system X; in this illustration, the system for λ_0 has only one attracting state, while for λ_1 there is bistability. If the control parameter λ changes slowly enough, the system will move from state A to state B. If the change is sufficiently fast, then the system will move from state C to state D; for intermediate rates of change, the details of noise in the system will become significant.

parameter changes, and the speeds of the path compared to the timescales of the pattern formation process itself.

Study of time-dependent bifurcation problems has a long history and there is a considerable literature on noise- and rate-induced escape from attractors in dynamical models. To mention a few of these, Kondepudi et al. (7) considered the combined effect of noise and parameter changes on the related problem of attractor selection in a noisy system, while Nicolis and Prigogine (8) described a mechanism enabling symmetry breaking and pattern selection in nonequilibrium systems. Dynamic bifurcations (9) are a useful approach to the quantitative description of solutions to systems of stochastic differential equations evolving on well-separated timescales. Symmetry breaking and state selection have been shown to play an important role in noisy electronic systems (7). Alagha and Zaikin (10) considered an interplay between asymmetry and noise in erythroid-myeloid differentiation switch, and have shown that timing in a binary cell-fate decision may have important contributions to the immune system when the bias is in favor of the particular cell fate that gives rise to nonimmune cells.

The finding of Palau-Ortin et al. (3) that dynamics and shape of the parameter path can crucially affect the selection of the final pattern seems to be an important and generic mechanism. These effects should allow us to account for rapid pattern formation in developmental biology, clinical diagnostics, and synthetic biology. A next step in the study of path-dependent pattern formation (3) will be a testing of these theoretical findings for experimental and practical applications. Questions that need to be addressed include: Which signals give rise to a specific patterned outcome? How are they generated by the cell? How can parameter paths through bifurcations suggest engineering principles underlying biological systems? Taking parameter paths and timing into account may explain many features of dynamic pattern formation, and gives us a hope of new methods, for example, to treat diseases associated with malfunctioning of these mechanisms. Many related interesting questions are ripe for exploration, including, for example, counterintuitive behavior resulting from the interplay among the system and input asymmetries, the noise, and the spatiotemporal features of the path in parameter space.

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