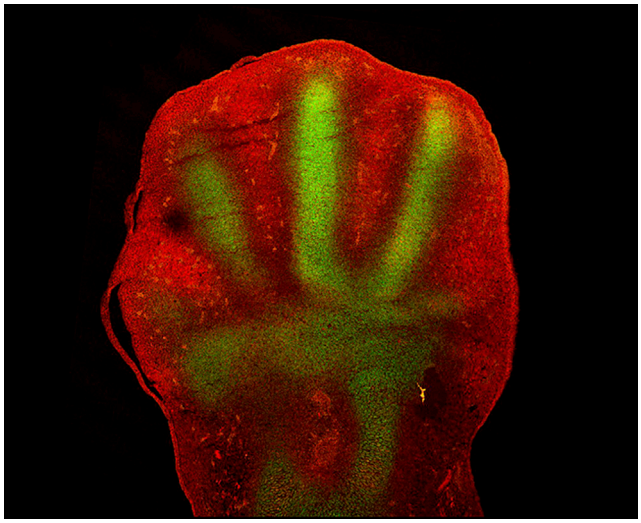
Cell

Biological Code Breaking

The new movie *The Imitation Game* (to be released after this article goes to press), which recounts the Nazi code-breaking triumph of Alan Turing, appears unlikely to devote much screen time to the mathematician's foundational contributions to biology. For cinematic reasons this is perhaps understandable, yet the occasion nevertheless provides a fitting opportunity to reflect on his seminal work "The Chemical Basis of Morphogenesis." In it, he proposed in mathematical terms how an initially homogeneous collection of cells might generate self-organizing morphological patterns. He made many theoretical predictions that were only much later confirmed, and his underlying conceptual framework—exploring the principles of biological self-organization—remains as timely as ever.

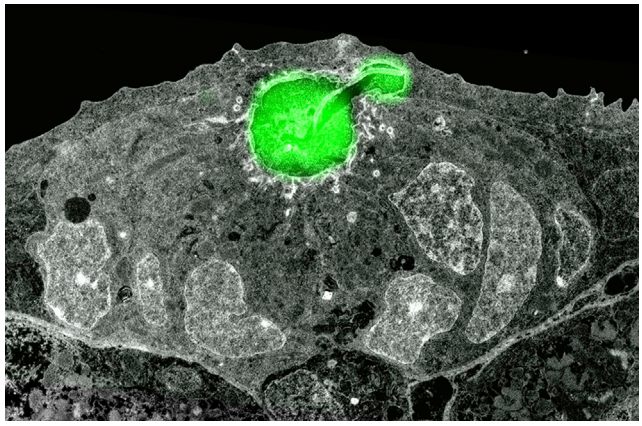


Digit patterning during mouse limb development. Image courtesy of J. Sharpe.

Unknown in Turing's day, there are now numerous beautifully worked-out examples of the phenomena he proposed—systems involving diffusible activators and inhibitors that interact to generate self-organized patterns. The most recent of these, elegantly uncovered by Raspopovic et al. (2014), describes a Turing network involved the formation of digits from developing limb buds. The authors make the observation that *Sox9*, a skeletal marker essential for digit formation, has a periodic pattern of expression in the limb bud at a very early stage, and based on the expectation that diffusible regulators in Turing-like processes would be either in phase or out of phase with *Sox 9* expression, the authors identify pathways differentially activated in *Sox9*$^{+}$ and *Sox9*$^{-}$cells. This analysis implicates the morphogens BMP and WNT, whose involvement with Sox9 is then explored by a combination of simulation and experimental manipulation. A compelling prediction from the modeling, which is borne out in pharmacological experiments in mouse limb bud cultures, is that combined inhibition of BMP and WNT, rather than simply inhibiting or boosting gene expression, is able to actively reorganize the spatial pattern of digits, such that larger digits are formed within the same space, thus resulting in the formation of just four, three, or two digits instead of the usual five.

Reaction-diffusion systems are also found on a subcellular scale. The interaction between MinD and MinE proteins in *E. coli,* for instance, make the two proteins oscillate between cell poles, establishing time-averaged gradients that direct the site of cell division. Zieske and Schwille (2014) have recently succeeded in reconstituting these oscillations in a cell-free system (microengineered soft-polymer compartments) and show that these gradients facilitate the localization of FtsZ, a downstream mediator of cell division, to the center of these simulated cells. These chambers can be readily made in different shapes and sizes, thus permitting the systematic exploration of the role of cell geometry in forming intracellular protein gradients.

Perhaps nowhere has the theme of biological self-organization been more prominently on display as of late than in the organoid field. We are learning from these remarkable in vitro systems that individual cells harbor an extraordinary amount of intrinsic know-how for making complex tissues, a latent ability that is waiting to be unleashed. For example, the key to making gastric organoids, as newly reported by McCracken et al. (2014), is walking human pluripotent stem cells through the normal stages of gastric development (induction of definitive endoderm to primitive foregut to antral specification) with carefully-timed combinations of growth factors. With only this handful of external interventions, the cultured cells do the rest, recapitulating many of the complex features and cell types found in vivo, including the generation of cells expressing markers of stem and endocrine cells. When the ulcer-causing microbe *H. pylori* is introduced into the organoid cultures, an increase in epithelial cell proliferation is observed within 24 hr, illustrating the power of this (and other organoid models) for studying the initiating events in human disease.



Correlative light electron microscopy image of secreted green fluorescent protein concentrated in microlumen. Image courtesy of D. Gilmour.

Although organoids will continue to aid in understanding the conversations cells have with one another that confer self-organizing properties on these systems, equally enlightening insights will come from in vivo exploration, as evidenced by a recent study of the zebrafish lateral line primordium. Durdu et al. (2014) find that among the migrating cells of the primordium, the morphogen FGF selectively accumulates in microluminal structures and that signaling from this central lumen coordinates cell-cell communication to control the deposition and formation of mechanosensory organs. Given that many structures in vitro, such as organoids, and in vivo form lumina, this mode of signal concentration and cellular coordination could prove a widespread mode of tissue self-organization.

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