DEVELOPMENTAL BIOLOGY

The Turing Model Comes of Molecular Age

Molecular analyses of hair follicle formation provide evidence to support the most well-known mathematical model for biological pattern formation.

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What are the underlying mechanisms that give rise to complex patterns in biology? Despite recent advances in biotechnology and mathematical modeling, this still remains a largely open question. As reported on page 1447 of this issue, Sick *et al.* have made a major advance toward answering this question by identifying key molecular players in hair follicle growth and by confirming the validity of perhaps the best-known mathematical model for biological pattern formation (*1*).

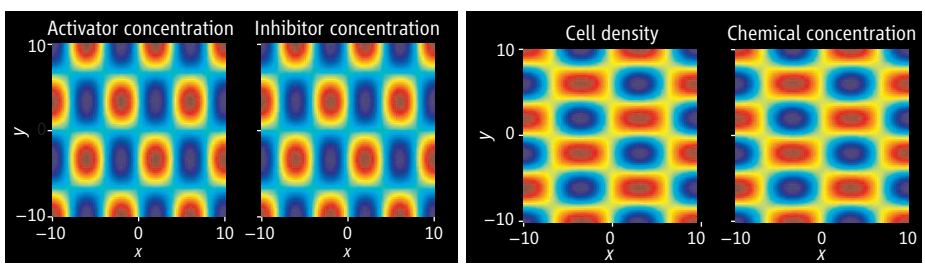
In a seminal paper, Alan Turing proposed that spatial patterns result from a phenomenon he termed "diffusion-driven instability" (*2*). He showed mathematically that small spatial fluctuations in an otherwise well-mixed system of reacting and diffusing chemicals could become unstable, and that amplification of these fluctuations could lead to a spatial pattern of chemicals that he termed morphogens (i.e., substances that stimulate the development of form or structure in an organism). He proposed that this spatial arrangement could serve as a prepattern for development. Turing's work was groundbreaking because the mathematical nature of the resulting patterns is wholly counterintuitive; since their discovery, they have motivated much mathematical research. However, the model has been the subject of controversy because it has been deemed too simplistic and the search for real biological examples has been neglected. Moreover, although diffusion-driven instability has been shown to be present in chemistry, there is substantial evidence in the fruit fly *Drosophila* to refute the model for biology (*3*). The report by Sick *et al*., by providing the first compelling biological evidence for the Turing model, is thus a landmark publication.

The formation of skin appendages (hairs, feathers, etc.) is an excellent paradigm for patterning because these systems are amenable to experimental manipulation. Nagorcka was the first to propose the Turing model to explain hair pattern formation (*4*), but at that stage the molecular biology was lagging behind the theory. It was only in 1998 that Jung *et al*. made the first efforts to link known molecular morphogens with a reaction-diffusion mechanism for feather germ formation (*5*). They showed how the size, number, and distribution of appendages could be modulated by altering morphogen concentrations (*6*).

Sick *et al*. investigated the regulation of hair follicle patterning in developing murine skin. They propose that the protein WNT and its inhibitor DKK are morphogens in the Turing sense. Expression of the protein Dkk1, which inhibits WNT, is actually controlled by secreted WNTs, and both WNTs and DKKs are secreted into the extracellular space where they diffuse, thereby acting over longer distances. Given that the WNT proteins are substantially larger than the DKKs, one would expect a large difference in their rates of diffusion. This makes possible the classical "short-range activation, long-range inhibition" phenomenon that underlies diffusion-driven instability (*7*).

Because hair follicle patterning occurs in waves, the authors used a reaction-diffusion model to set up an initial pattern of follicles. Then, along the same lines as Mooney and Nagorcka (*8*), they assumed these follicles to be chemical sources giving rise to a second wave of hair follicle formation on a larger domain (due to the growth of skin). The model predicts that moderate overexpression of activator (WNT) increases follicular density, whereas moderate overexpression of inhibitor (DKK) during the initial inductive wave increases the interfollicular spacing. Sick *et al*. have verified these predictions experimentally, providing strong evidence for a genetic underpinning of a Turing reaction-diffusion model.

Together the papers of Jung *et al.* and Sick *et al.* show that the skin progenitors are stem cells, in that they are multipotent and may assume appendage or interappendage fates depending on the local chemical environment at the time of specification. In this sense, the molecular components identified by these experiments appear to be acting as morphogens in the true Turing sense.



Biological pattern formation. Two mechanisms can show similar results. (**Left**) Outcome of a reaction-diffusion model (*7*) in which activator and inhibitor react and diffuse. Small random fluctuations in the initial field lead to coinciding spatial patterns of activator and inhibitor concentration. (**Right**) Results of a cell chemotaxis model (*9*) in which cells and chemical both diffuse, with cells also moving up gradients in chemical concentration. Again, small random fluctuations in the initial field lead to coinciding spatial patterns in cell density and chemical concentration. Blue indicates low concentration levels; red indicates high levels.

In principle, a reaction-diffusion model can set up a chemical prepattern before we can visualize changes in cell distribution. That is, it determines sites at which cells will cluster: Regions of high cell density coincide with those of increased morphogen concentration—although the model does not specify how this rearrangement occurs. On the other hand, it is possible for cellular aggregations to form without such a prepattern via simple chemotactic movement in response to gradients in chemical concentration. By way of illustration, the patterns formed by these two different mechanisms are shown in the figure. It is immediately obvious how similar such patterns are.

This highlights one of the difficulties in mathematical modeling: determining which

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is the "correct" model. Now that WNT and DKK have been identified as possible morphogens, this issue can be addressed experimentally. The key requirement, then, is that the results of such experiments are used to test and refine models, ruling some out if the data allow us to do so. The WNT-DKK interaction does appear to be qualitatively of the form necessary for a Turing-type system, but it is now imperative that we try to overcome the experimental challenges in measuring key parameters (rates of production, decay, diffusion coefficients, etc.) so that quantitative tests can be performed to determine whether the system actually is of Turing type. This would then be the first definitive example of the Turing model in biology.

Turing models have been proposed to describe other types of patterns observed in developmental biology. Two applications currently receiving much attention from experimentalists are pigmentation patterning in fish and skeletal development in the mouse limb. Although the evidence for a Turing diffusion-driven instability in these systems is not as strong as that presented by Sick *et al*., their report should stimulate further work in biological pattern formation.

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ASTRONOMY

Variable High-Energy γ Rays from the Elliptical Galaxy M87

High-energy γ rays emanating from intense jets of matter that are associated with certain galaxies provide clues to jet formation.

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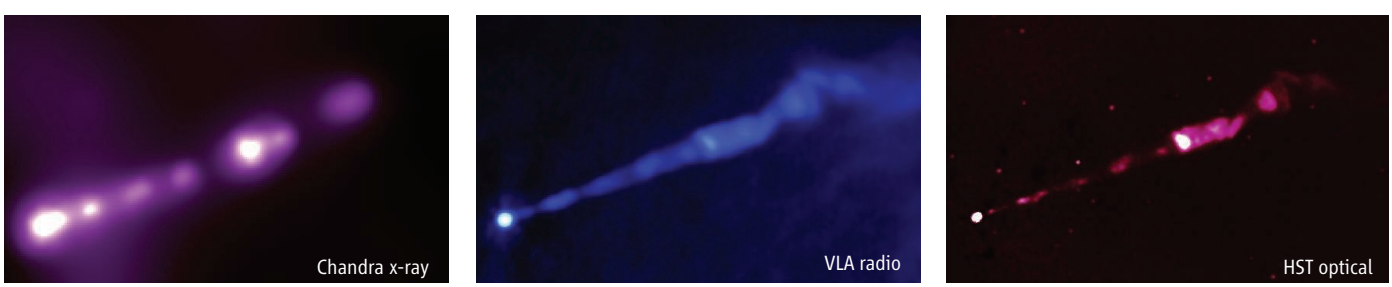
Almost 90 years ago, astronomer Heber Curtis recorded the presence of a "curious straight ray" connected to the nucleus of the giant elliptical galaxy M87. Since then, researchers have acquired high-resolution images of this famous jet at wavelengths from the radio to x-ray bands (see the figure). In these images, the jet appears on only one side of the galaxy nucleus because it is moving in our direction at very close to the speed of light; the side pointed away from us is so dim as to be invisible. Rapid motion of nearby gas and stars reveals that the central engine in this energetic nucleus is a massive black hole. On page 1424 of this issue, Aharonian *et al*. now report observations of M87 at the highest energies of the γ-ray band, which may reveal new details of how the emissions from this galaxy are powered and how the jet is created (*1*).

The first hints of highly energetic teraelectron-volt (TeV) emission from M87 were reported by the High Energy Gamma Ray Astronomy (HEGRA) collaboration in 1998 (*2*). Since 2003, regular observations of M87 have been made by the High Energy Stereoscopic System (H.E.S.S.), sited in Namibia (*3*). Aharonian *et al.* now find evidence of fast variations in the TeV γ emission from the source in H.E.S.S. observations made during a bright phase of the jet in 2005.

The high-energy γ emission varies on a time scale of about 1 day, which is comparable to the time it takes light to cross the black hole and is therefore the shortest natural time scale of the system. This is about 10 times as fast as variations seen from M87 at any other wavelength, which points to an origin for the γ rays close to the black hole. In the optical images, there is a peculiar knot about 100 pc (1 pc = 3.26 light years) along the jet (see right panel of the figure) where some slow variations have been seen, but this is unlikely to be the source of the TeV photons because it would require the jet to be unreasonably tightly collimated there.

Variable TeV γ emission has been seen from other galactic nuclei with jets known as blazars. In these objects, we are looking more or less straight down the jet, which relativistically boosts both the energy of the emission and its observed intensity. For typical conditions, if the jet from M87 were a blazar we would have to be observing the jet within an angle of about 6°. However, the M87 jet is generally considered to be pointing at 30° to 40° or so away from our line of sight, which puts us out of the extreme blazar situation. Measuring the angle with confi-



Energetic jet. The M87 jet imaged at x-ray wavelengths by the Chandra spacecraft (**left**), at radio wavelengths by the Very Large Array (**middle**), and at optical wavelengths by the Hubble Space Telescope (**right**). The view of each panel is 32 arc sec by 21 arc sec. Total length of the arc is 2000 pc.

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