Reaction-diffusion mechanisms

Some chemical systems, such as the famous Belousov–Zhabotinsky reaction, are self-organizing and spontaneously generate spatial patterns of concentration of their components. In two dimensions, the initial distribution of the molecules is uniform, but over time the system forms expanding wave-like patterns. The essential features of such self-organizing systems can be mathematically modeled by chemical reactions between two or more molecules with different rates of diffusion. Such systems are called **reaction–diffusion systems** **or** **Turing mechanisms** (after the mathematician Alan Turing, who was the first to prove that simple repetitive patterns could arise in this way).

For example, consider a closed two-component system of activator and inhibitor molecules in which the activator molecule stimulates both its own synthesis and that of the inhibitor, which in turn inhibits synthesis of the activator, and the inhibitor diffuses faster than the activator (Fig. S12.1). A type of lateral inhibition will occur such that synthesis of activator becomes confined to one region, forming a peak of activator concentration with a given wavelength. If the wavelength stays the same when the size of the system is increased, two peaks will eventually develop, then three, and so on, as the system grows in size (Fig. S12.2). In two dimensions, a pattern of peaks of high concentration of activator can develop like that in Figure S12.3. Conversely, if the system stays the same size, a shortening of the wavelength is needed to generate more peaks.

Reaction–diffusion has interested biologists as, given the appropriate conditions and components, such a mechanism could, in theory, generate periodic patterns such as the spots and stripes on animals, and patterns of repeated structures such as the sepals and petals of flowers and repeated skeletal elements such as the digits of the hand.

The limb has considerable capacity for self-organization, and it has been suggested that reaction–diffusion mechanisms could generate the periodic pattern of skeletal elements. Computer simulations of dynamic interactions between activator and inhibitor molecules in a system of increasing size produce patterns of high concentrations of activator that mimic the pattern of skeletal elements along the proximo-distal axis

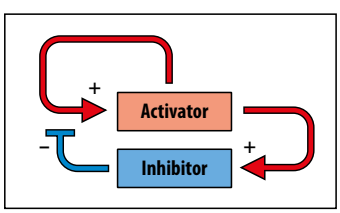


Fig. S12.1

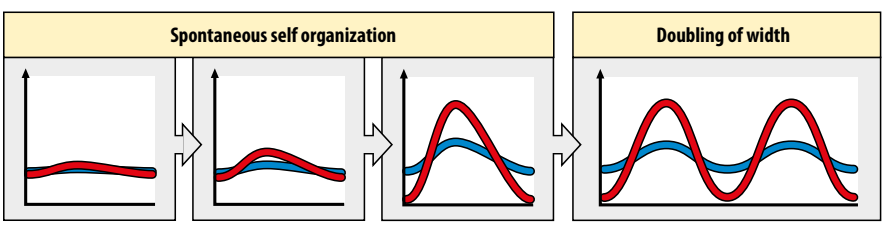


Fig. S12.2

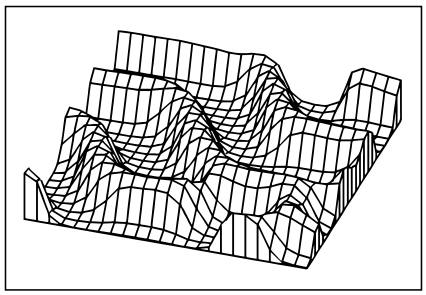


Fig. S12.3 *From Meinhardt, H.:* ***Turing's theory of morphogenesis of 1952 and the subsequent discovery of the crucial role of local self-enhancement and long-range inhibition****.* Interface Focus *2012,* ***2****: 407–416.*

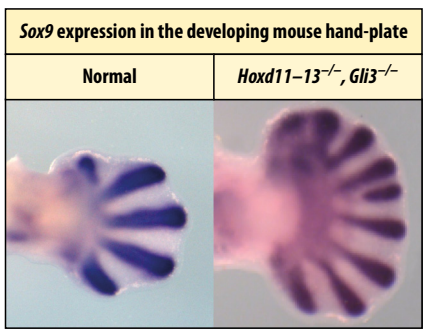


Fig. S12.4 *From Sheth, R., et al.:* ***Hox genes regulate digit patterning by controlling the wavelength of a Turing-type mechanism.*** Science *2012,* ***338****: 1476–1480.*

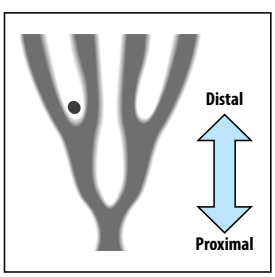


Fig. S12.5

in the limb: one proximal element, then two elements, and finally a number of distal elements (Fig. S12.5).

More recently, reaction–diffusion computer simulations have reproduced the abnormal pattern of stripes of *Sox9* expression in the hand plate of mutant mouse limb buds. In the hand plate of normal mice, five *Sox9*-expressing stripes across the antero-posterior axis fan out from the proximal wrist region towards the distal tip of the hand plate and prefigure the formation of the five digits. The hand plate increases in width going from proximal to distal (wrist to fingertip) as the embryo grows, but the number of digits does not increase. Instead, the stripes become more widely spaced towards the tip (hence looking like a fan). In a reaction–diffusion system, the stripes would represent high concentrations of activator and the fan-like pattern of stripes would be accomplished by changing the wavelength of stripe spacing across the antero-posterior axis so that is longer distally than proximally, thus preventing bifurcations of the stripes that would otherwise occur (see Figure S12.5).

In limb buds that lack antero-posterior positional information as the result of a mutation in *Gli3* (see Section 10.16), the hand plate is broader, and an increased number of *Sox9*-expressing stripes are formed, which also fan out from the wrist region in the same way as in the normal limb (Fig. S12.4). The pattern of stripes seen in the *Gli3* mutant hand plate can be produced by a computer-modeled reaction–diffusion system in which reactions are graded along the proximo-distal axis such that the stripes are oriented towards the tip of the limb and the wavelength (stripe spacing) increases from proximal to distal.

Genetic experiments have recently identified Hox genes as factors that control the wavelength of *Sox9*-expressing stripes in the hand plate. As the dose of Hox genes expressed in the hand plate of *Gli3*$^{-/-}$ mouse embryos is progressively reduced, more and more stripes are crammed into the same-sized hand plate and the stripes may also bifurcate distally. Although the molecular identities of activator and inhibitor that might operate in the limb are unknown, the computational prediction of the activator pattern, using a reaction–diffusion system in which Hox genes modulate inhibitor production and thus the wavelength of the activator peaks, matches the pattern of *Sox9* expression (Fig. S12.6). It is impressive how Turing-type mechanisms can generate patterns that mimic these periodic digit patterns. However, this mechanism does not provide the digits with positional information and therefore cannot generate the differences in the identity of digits at different positions across the antero-posterior axis of the limb.

Reaction-diffusion systems may underlie some of the patterns of pigmentation that are common throughout the animal kingdom, such as the patterns of spots seen in the cheetah and stripes in the zebra (Fig. S12.7). How these patterns are

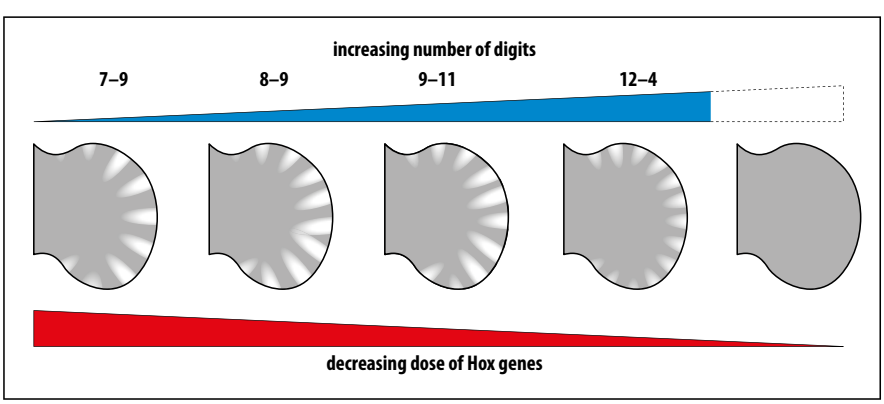


Fig. S12.6

generated is not yet known, but one possibility is a reaction–diffusion mechanism. Assuming that pigment is synthesized in response to some activator, and that synthesis only occurs at high activator concentrations, some animal color patterns can be mimicked by a reaction–diffusion system in computer simulations. The periodic patterns of bristles in insects, feathers in birds and hairs in mammalian skin can also be modeled in terms of this type of reaction-diffusion mechanism and possible candidates for the molecules involved are various signaling molecules, including BMPs and FGFs.

A characteristic feature of reaction–diffusion patterns is that new intermediate peaks appear as the system grows in size. The angelfish *Pomocanthus semicirculatus* provides a remarkable example of striping that could be generated by a reaction–diffusion mechanism (Fig. S12.8). Juvenile *P. semicirculatus*, less than 2 cm long, have only three dorso-ventral stripes. As the fish grow, the intervals between the stripes increase until the fish is around 4 cm long. New stripes then appear between the original stripes and the stripe intervals revert to those present at the 2 cm stage. As the fish grows larger, the process is repeated. This type of dynamic patterning is what would be expected of a reaction–diffusion mechanism. Computer simulations of reaction–diffusion mechanisms can also generate the patterns seen on a wide variety of mollusk shells.

The ocellated lizard (*Timon lepidus*) provides an interesting example of an underlying reaction–diffusion mechanism for skin patterning that, as the lizard grows and the skin forms scales, is disrupted by the change in the 3D structure of the skin. The result is the generation of 'cellular automata' that convert the simple regular skin pattern on juvenile lizards to the labyrinthine pattern of green and black scales seen on adults (Fig. S12.9). The photos show the same animal at 3 months (upper panel) and 3 years (lower panel).

The adult zebrafish has become a useful model for studying the molecular basis of pigmentation patterns. The striking pattern that gives the fish its name is produced by stripes of cells producing black pigment (melanophores) and of cells producing yellow pigment (xanthophores). Although unlike the angel fish, the stripes do not appear to change as the zebrafish grows, experimental ablation of cells in some of the stripes by a laser results in the movement of nearby stripes. The patterns produced are consistent with those predicted by computational modeling of a reaction-diffusion system. Recent analysis suggests however that diffusible molecules are not involved. Instead direct cell-cell contacts transmit signals between pigment cells. It has been suggested that, as both short and long cellular projections are involved, these interactions mimic the different rates of diffusion of the two molecules in a Turing mechanism.

Fig. S12.7

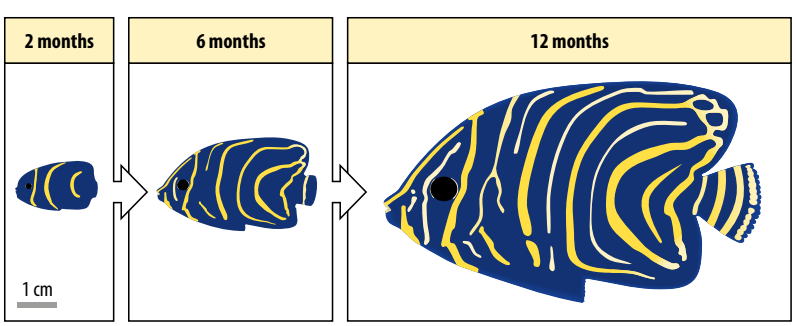
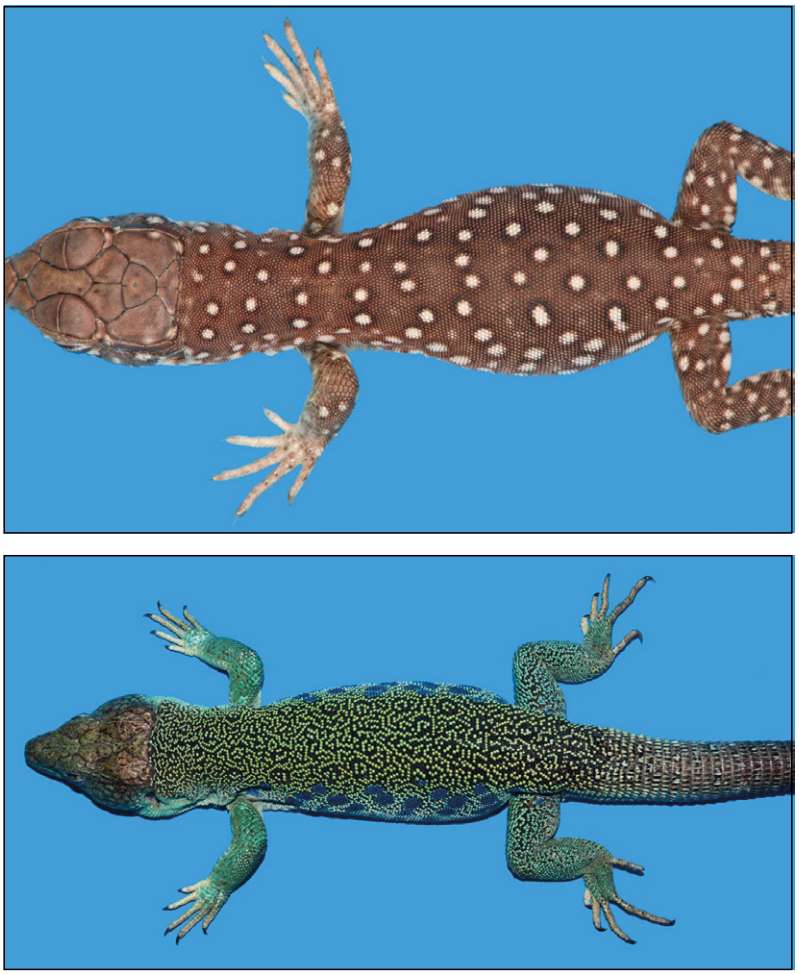


Fig. S12.8

Fig. S12.9 *Research performed in Michel Milinkovitch's laboratory at the University of Geneva, Switzerland. Manukyan, L., Montandon, S.A., Fofonjka, A., Smirnov, S., Milinkovitch, M.C.* ***A living mesoscopic cellular automaton made of skin scales*** Nature *2017,* ***544****: 173-179.*



Further reading

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