

The Mathematics of Patterning

One of the most important mathematical models in developmental biology has been that formulated by Alan Turing (1952), one of the founders of computer science (and the mathematician who cracked the German “Enigma” code during World War II). He proposed a model wherein two homogeneously distributed solutions would interact to produce stable patterns during morphogenesis. These patterns would represent regional differences in the concentrations of the two substances. Their interactions would produce an ordered structure out of random chaos.

Turing's reaction-diffusion model involves two substances. One of them, substance S, inhibits the production of the other, substance P. Substance P promotes the production of more substance P as well as more substance S. Turing's mathematics show that if S diffuses more readily than P, sharp waves of concentration differences will be generated for substance P (Figure 1). These waves have been observed in certain chemical reactions (Prigogine and Nicolis 1967; Winfree 1974).

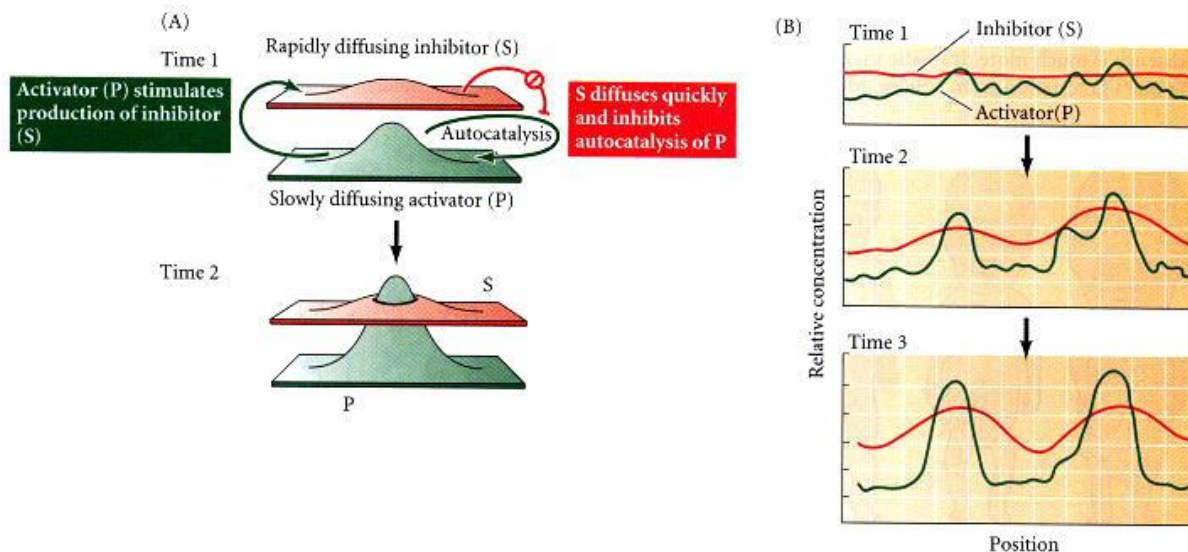


Figure 1 Reaction-diffusion (Turing model) system of pattern generation. Generation of periodic spatial heterogeneity can come about spontaneously when two reactants, S and P, are mixed together under the conditions that S inhibits P, P catalyzes production of both S and P, and S diffuses faster than P. (A) The conditions of the reaction-diffusion system yielding a peak of P and a lower peak of S at the same place. (B) The distribution of the reactants is initially random, and their concentrations fluctuate over a given average. As P increases locally, it produces more S, which diffuses to inhibit more peaks of P from forming in the vicinity of its production. The result is a series of P peaks (“standing waves”) at regular intervals.

The reaction-diffusion model predicts alternating areas of high and low concentrations of some substance. When the concentration of such a substance is above a certain threshold level, a cell (or group of cells) may be instructed to differentiate in a certain way. An important feature of Turing's model is that particular chemical wavelengths will be amplified while all others will be suppressed. As local concentrations of P increase, the values of S form a peak centering on the P peak, but becoming broader and shallower because of S's more rapid diffusion. These S peaks inhibit other P peaks from forming. But which of the many P peaks will survive? That depends on the size and shape of the tissues in which the oscillating reaction is occurring. (This pattern is analogous to the

harmonics of vibrating strings, as in a guitar. Only certain resonance vibrations are permitted, based on the boundaries of the string.)

The mathematics describing which particular wavelengths are selected consist of complex polynomial equations. Such functions have been used to model the spiral patterning of slime molds, the polar organization of the limb, and the pigment patterns of mammals, fish, and snails. A computer simulation based on a Turing reaction-diffusion system can successfully predict such patterns, given the starting shapes and sizes of the elements involved.

One way to search for the chemicals predicted by Turing's model is to find genetic mutations in which the ordered structure of a pattern has been altered. The wild-type alleles of these genes may be responsible for generating the normal pattern. Such a candidate is the *leopard* gene of zebrafish (Asai et al. 1999). Zebrafish usually have five parallel stripes along their flanks. However, in the different mutations, the stripes are broken into spots of different sizes and densities. Figure 3 shows fish homozygous for four different alleles of the *leopard* gene. If the *leopard* gene encodes an enzyme that catalyzes one of the reactions of the reaction-diffusion system, the different mutations of this gene may change the kinetics of synthesis or degradation. Indeed, all the mutant patterns (and those of their heterozygotes) can be computer-generated by changing a single parameter in the reaction-diffusion equation. The cloning of this gene should enable further cooperation between theoretical biology and developmental anatomy.

The Development of Zebra Striping Patterns

Few patterns are more obvious than the alternating black-and-white stripes of the zebra. There are actually three extant species of zebra, and each has a different pattern of stripes (Figure 2). The imperial zebra (*Equus grevyi*) has some eighty stripes perpendicular to the long axis of its body. The common zebra (*E. burchelli*) has 26 wide caudal stripes, some of which extend towards the belly in the rear of the animal. The mountain zebra (*E. zebra*) has some 55 stripes, with three horizontal bands near the hindlegs. Each of these three species are members of the horse genus and can interbreed among themselves and other horses to produce infertile offspring.

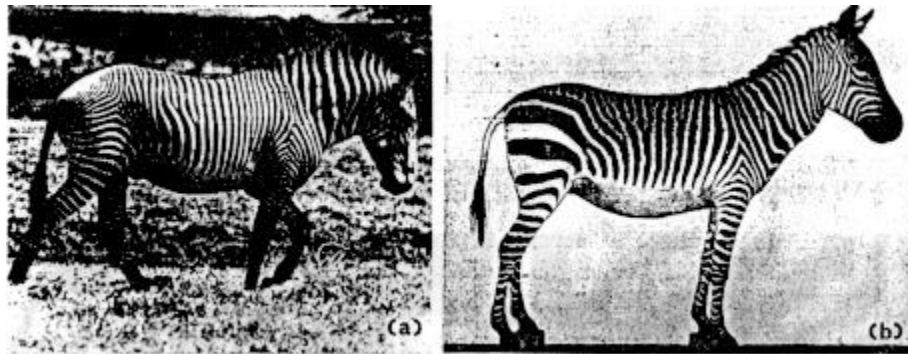


Figure 2 Examples of different species of zebra: (a) The imperial zebra (*Equus grevyi*), photograph by Dr. Denis Mollison; (b) the mountain zebra (*Equus zebra*)

How did the zebra get its stripes?

Ultimate (evolutionary) mechanism

It is generally believed that zebras are dark animals with white stripes where the pigmentation is inhibited. The pigment of the hair is found solely in the hair and not in the skin. The reasons for thinking that they were originally pigmented animals are that (1) white horses would not survive well

in the African plains or forests; (2) there used to be a fourth species of zebra, the quagga (which was overeaten to extinction in the 1800s). The quagga had the zebra striping pattern in the front of the animal, but had a dark rump; (3) when the region between the pigmented bands becomes too wide, secondary stripes emerge, as if suppression was weakening.

Zebra stripes have often been thought to be an adaptation that prevents zebras from being seen by predators such as lions or hyenas. (This hypothesis goes back at least to Rudyard Kipling [1908]). The alternating stripes obscure the outline of the zebra. This may serve as camouflage, allowing the zebra to blend in with its background (Thayer 1909; Marler and Hamilton 1968) and/or it may serve to confuse a predator as to the distance of the fleeing animal (Cott 1957; Kruuk 1972). However, neither of these hypotheses can be easily confirmed. A different hypothesis (Waage 1981) contends that the stripes serve to obliterate a large single-colored region that is favored by biting insects such as the tsetse fly. These flies prefer large, dark, moving animals (Vale 1974).

How did the zebra get its stripes?

Proximate (developmental) mechanism

Jonathan Bard of Edinburgh has hypothesized a mechanism for the production of zebra stripes in the three species of extant zebras (1977, 1981). His model claims that while neural crest cells begin migration at week two of gestation (in the horse), the zebra striping patterns are generated between weeks three and five, depending upon the species. Moreover, Bard asserts that the three patterns of striping are precisely those predicted if the original pattern was the same in each zebra, but was established at different times within this three week period. In the case of the imperial zebra, all the stripes are perpendicular to the dorsal axis, but are thicker towards the neck. This would be expected if the striping pattern originated at week five (Figure 3a). At week five, most of the differential body growth has ceased, except for the neck region, which becomes extended, and the rump, which is slightly shortened. Thus, if the stripes were formed at week five, they should all be parallel, but slightly wider at the neck and narrower at the rump.

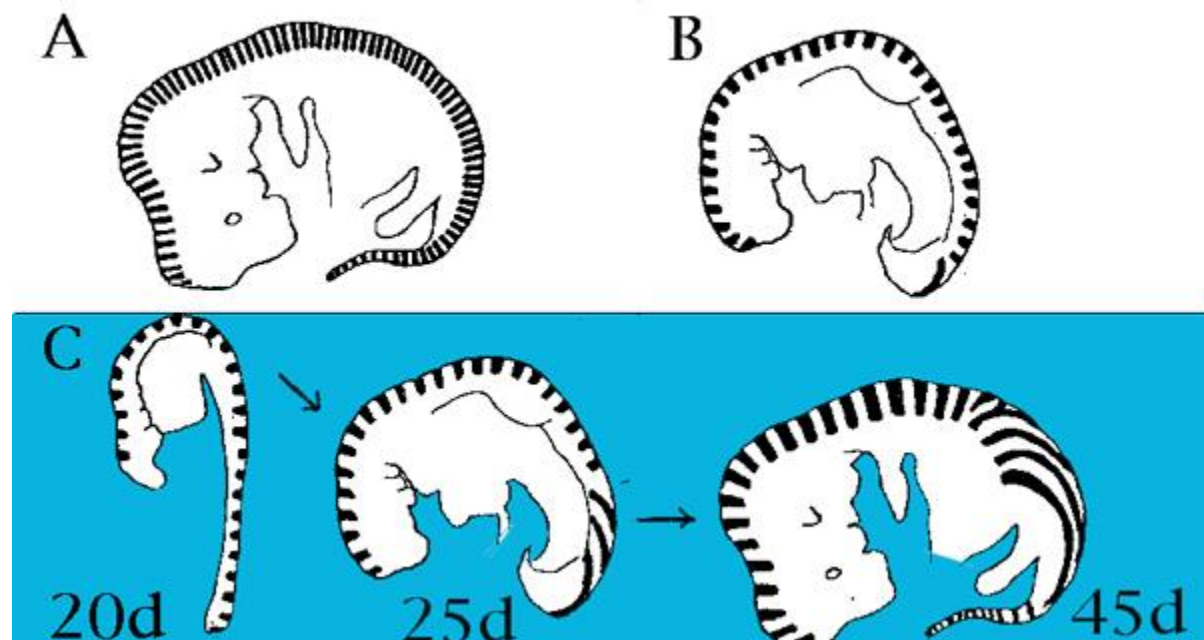


Figure 3 Bard's hypothesis for the generation of stripes in three species of zebras. The spacing and size of the stripes are the same. What differs is the time at which the stripes were generated. If generated during week 3, the stripes begin perpendicular to the anterior-posterior body axis, but become

parallel to this axis in the rump, since the rear of the zebra is still growing. This generates the pattern of common zebra. If the striping pattern is generated during week 4, most of the rump has grown, and the hind stripes are more perpendicular to the body axis. This generates the pattern seen in the mountain zebra. If the striping pattern is generated during week 5, there is space for many more stripes, all of which are perpendicular to the body axis. This generates the striping pattern of the imperial zebra. (After Bard 1977.)

The stripes of the mountain zebra probably form towards the end of week four. If the stripes were originally parallel, those in the rear of the embryo would be pulled back towards the rump by the growth of the hindparts of the horse (Figure 3b). Similarly, if the stripes of the common zebra were generated during the third week of zebra gestation, the differential growth rate of the rump between weeks three and four would also pull the stripes posteriorly (Figure 3c).

Bard's hypothesis that all the stripes originally are the same width and are generated at different times in the three species also explains the numbers of stripes in each species. The common zebra has 26 stripes per side, and the 3-week *Equus* embryo is generally 11 mm long. This gives a spacing of about 0.42 mm per stripe. If the 43 stripes of the mountain zebra were generated in the 17 mm embryo of the 3.75 week zebra, the spacing is also 0.40 mm per stripe. At week 5, the embryo is 32 mm long, and the 80 stripes would yield the spacing of 0.40 mm per stripe. Therefore, the striping patterns of the common zebra, mountain zebra, and imperial zebra can be explained if the stripes are generated 0.4 mm apart in the 3-, 4-, and 5-week embryos, respectively.

It is not known how the pattern is initiated or what activators or inhibitors are being generated. It is difficult to imagine how such a pattern can be generated by preformed maternal instructions, responses to gradients, or regional inductions. It has been proposed that the Turing reaction-diffusion models could produce these alternative pigmented and non-pigmented bands. Murray (1981) has shown that the chevrons at the base of the zebra's limbs are the shape expected by the overlapping of two Turing-type reaction-diffusion systems.

For more on the mathematical background of pattern formation:

* Visit the website of Hans Meinhardt, at <http://www.eb.tuebingen.mpg.de/research/emeriti/hans-meinhardt/home.html>

* See the classic paper Gierer, A. and Meinhardt, H. 1972. A theory of biological pattern formation, *Kybernetik* 12: 30-39

* Visit this website on the life of Alan Turing: <https://www.turing.org.uk/index.htm>

* Read more. <clicking on this sentence should opens the following information, highlighted in yellow:>

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