Caroline Wood

How the leopard gets its spots

The origins of animal patterns

Photos Tiene Alles and Marja Flick-Buijs

The animal kingdom contains an abundance of exquisite natural patterns from the stripes of an angelfish to the spots of a leopard. But how do these arise during early development? ***Caroline Wood*** *explores one theory.*

In 1952, Alan Turing proposed a mechanism to explain how animal patterns are produced. This became known as the 'Reaction-Diffusion Model' and is still the strongest theory for how patterning is controlled. Turing was a mathematician rather than a biologist, and is most famous for deciphering the Nazi Enigma Code during the Second World War. From this experience, he suggested that animal patterns were specified by another type of code, where diffusing molecules acted either as inhibitors or activators. A central idea is that the pattern is not pre-determined but arises spontaneously as a result of the interactions between these molecules.

The central theory

Turing's theory is based on the concept that a process (e.g. spot or stripe formation) occurs when the concentration of an activator reaches a critical level. The concentration of the activator, however, is regulated by feedback mechanisms. The activator produces more of itself through an auto-catalytic mechanism (known as 'positive feedback') yet at the same time also stimulates the production of an inhibitor, which acts as an antagonist to the activator. Because the production of the inhibitor depends on the activator, the highest concentration of activator and inhibitor will occur in the same place, called the focus.

Both molecules diffuse away from the site of production, forming a concentration gradient around the central peak. A key concept of the theory is that the diffusion range of the activator is less than that of the inhibitor. The concentration of the activator is only strong enough to initiate a process at the focus; although this is also where the concentration of inhibitor is highest, sufficient quantities of activator are present here to overcome this negative effect. Because the inhibitor is a more powerful diffusing agent however, the concentration of the activator drops sharply outside the focus point, causing it to be suppressed by the inhibitor.

Key words

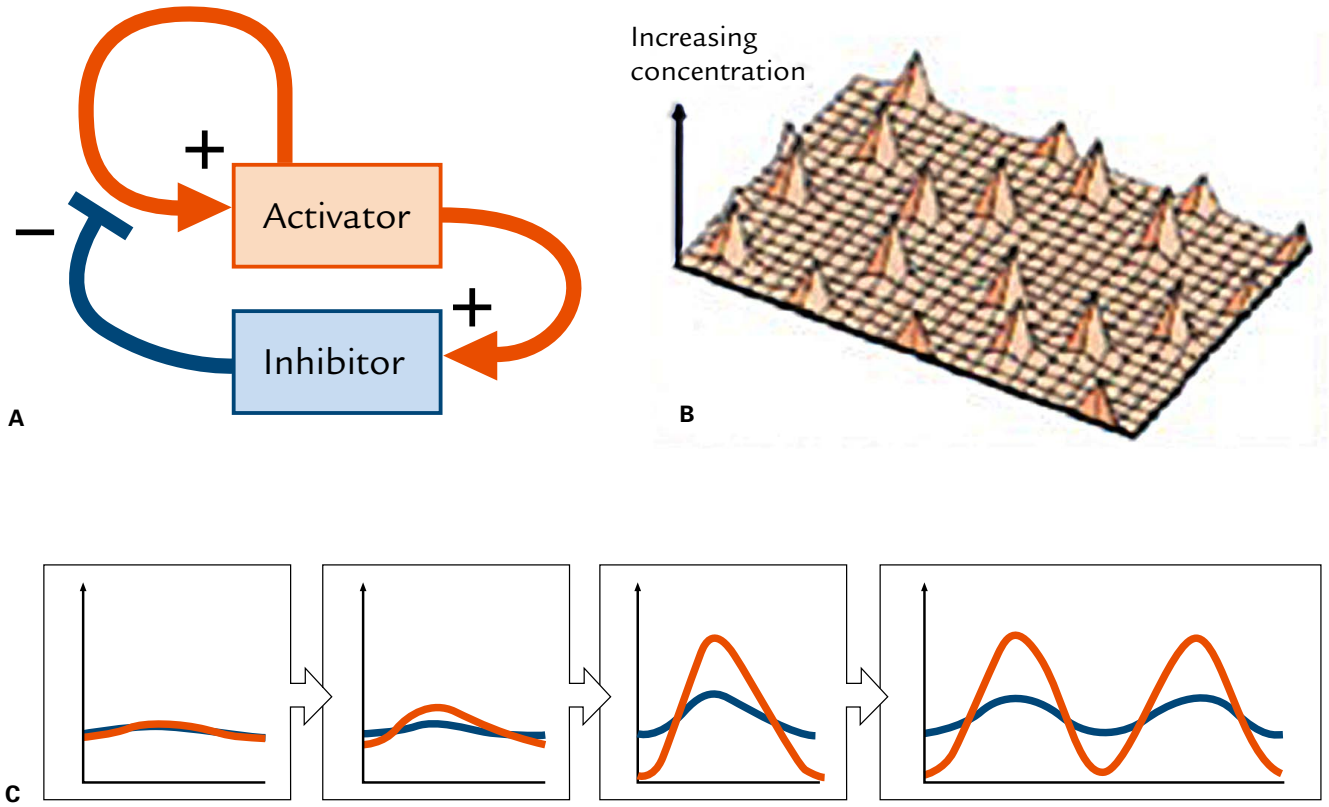
pattern formation

diffusion

feedback

Alan Turing

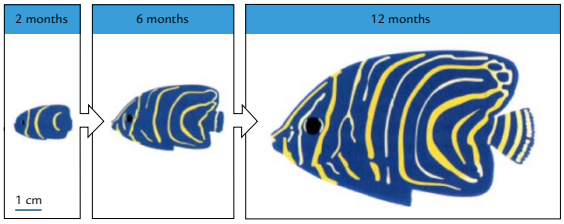
Antagonist: something (a gene, molecule, muscle) which counteracts the activity or effect of another entity (the agonist).



Theory of Turing mechanisms. ***A*** *The patterning process is governed by the activities of diffusible substances that act either as activators or inhibitors. The activator promotes the production of itself, but also increases the concentration of the inhibitor.* ***B*** *This produces distinct peaks of production where the concentrations of both the activator and inhibitor are highest.* ***C*** *These properties allow complex patterns to develop from initially small, random fluctuations in concentration.*

What Turing explains

Turing mechanisms have many attractions for explaining animal patterning. Firstly, they describe how patterns arise spontaneously from a group of cells that all have equal potential to form a patterning element. Because the activator and inhibitor substances are dependent on each other, random fluctuations in concentration resolve over time into sharply defined peaks. Reaction-Diffusion mechanisms also enable the pattern to be maintained as the animal grows. The stripes of the angelfish *Pomacanthus semicirculatus*, for instance, maintain a constant spacing even as the animal grows.



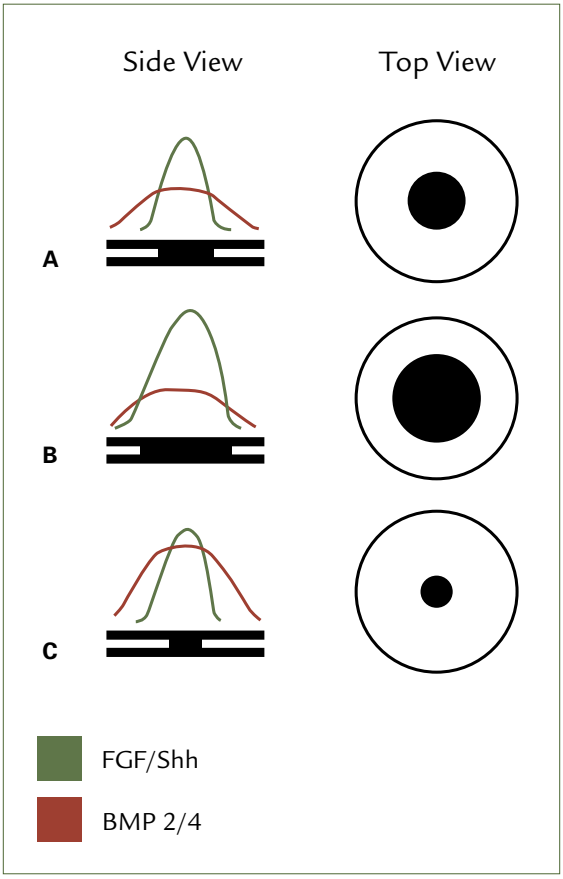
Angelfish stripe patterning. Angelfish stripes maintain a constant distance even as the animal increases in size. This is caused by the gaps between the peaks of inhibitor production widening, allowing new focus points to be established.

The angelfish Pomacanthus semicirculatus

This is the result of new stripes being produced as existing stripes move further apart. According to the Reaction-Diffusion Theory, the stripes represent the areas where the inhibitor substance is produced. As the gaps between the stripes widen, areas with low inhibitor concentrations form, allowing a new focus point to develop and initiate a new stripe. When the parameters of a Turing mechanism were entered into computer modelling software, the programme reproduced the natural pattern observed in angelfish, further supporting a Reaction-Diffusion mechanism.

Forming feathers

Another system that appears to use a Turing mechanism is feather patterning. Feathers develop where cells in the epidermis (the outer layer of the skin) multiply and condense to form an epidermal placode that develops into a feather primordium. Placodes and feather primordia develop in sequence, beginning from the midline and spreading across the flanks. This is promoted by the gene products Fibroblast Growth Factor (FGF) and Sonic Hedgehog (Shh), which have the role of activators. At the foci, Bone Morphogenic Proteins 2 and 4 are also produced, which act as inhibitors. Feather primordia form in the regions where the concentrations of FGF/Shh are high enough to overcome the effects of BMP2 and 4.



Feather placode formation. ***A*** *The formation of epidermal placodes is determined by the ratio of positive inducers (FGF and Shh) and inhibitory substances (BMP 2 and 4). Placodes form where the concentration of positive inducers overcomes the influence of the inhibitors.* ***B*** *If the activator concentration is artificially raised, the placodes will increase in size.* ***C*** *Increasing the level of inhibitors, meanwhile, will result in smaller epidermal placodes.*

Hence, the size of the feather primordia depends on the diffusion range of FGF/Shh and the threshold level at which BMP2 and 4 prevent epithelial condensation. Meanwhile, the spacing between the developing feather follicles is determined by the diffusion range of the inhibitor. In experiments where beads coated with FGF were placed next to chicken skin, the size of the feather placodes expanded so much that they fused together. On the other hand, injecting a synthetic virus coding for BMP2/4 expression caused the feather placodes to reduce in size. Normal feather patterns can form on isolated strips of skin, demonstrating that the pattern arises spontaneously without relying on signals from pre-existing placodes, providing additional evidence of a Turing mechanism.

The pattern and separation of feathers on a chicken's skin can be explained by a Turing mechanism.

Future patterns

The spontaneous production of patterns is an intriguing facet of the field of developmental biology and there is still much debate about the underlying causes. Turing mechanisms have been proposed to govern a large range of processes, including tiger stripes, lung branching, digit formation and even the patterning of mussel beds. Who knows what features they will be implicated with in the future? Although the great mathematician himself is no longer with us, Turing's theories continue to shape our understanding of the mysterious events that occur during early development.

Alan Turing, best known today for his work as a code-breaker during the Second World War, was celebrated in his centenary year 2012.

Caroline Wood is a postgraduate student at the University of Sheffield. She is currently investigating the interactions between parasitic plants and their hosts.