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By Carrie Arnold

New story of animals' spots, stripes

A mathematical model of cell signaling helps explain how animal patterns emerge

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For Rudyard Kipling, the answer of how zebras got their stripes was simple: to hide from predators in the dark and dappled forest of the High Veldt in Africa. But now there's a more scientific explanation, based on a mathematical model of cell-cell signaling, that provides more clues to how stripes and spots and other patterns emerge during animal development.

In a study published this week in *Royal Society Interface,* researchers from the UK showed how cells can communicate with each other via small protrusions. As the protrusions continually form and disappear, neighboring cells receive chemical signals that tell them what color to be. Over time, patterns of spots and stripes appear.

A Plains Zebra, *Equus quagga*, in the Ngorongoro Crater in Tanzania
Image: Wikimedia commons, Muhammad Mahdi Karim

"Our work has shown a novel way in which cells may be able to communicate with one another in order to generate complex patterns," study author Michael Cohen, a mathematical biologist at University College London, told *The Scientist*.

Famed computer pioneer Alan Turing attempted to tackle the problem of how zebras got their stripes in the 1950s. He showed that two molecules known as morphogens secreted from developing cells could interact to form stable patterns like stripes. Signals from the first morphogen told skin cells to be differently colored, whereas signals from the second morphogen told the cells to remain their usual color.

In order for Turing's model to work, these two morphogens had to have very special characteristics. The first morphogen had to stimulate its own production in a positive feedback loop but could only diffuse over very short distances. The second morphogen had to diffuse over much longer distances and also inhibit the production of the first morphogen. Although Turing's model looked good on paper, in reality, morphogens diffused imperfectly and the developing cells didn't always respond as expected.

More recently, biologists such as Sean Carroll have found that evolution can create a variety of patterns from a very small set of regulatory genes. Tiny tweaks in these genes can explain the spacing of hairs and the placement of spots in *Drosophila*. Finding these master switches was a crucial step, but it still didn't explain how these patterns emerged in a developing animal.

Over the years, Cohen and and colleagues have continued to investigate exactly how two morphogens could give zebras their stripes and leopards their spots. The key to this model, Cohen said, was not just in the morphogens but also in the interactions between cells. In one particular type of interaction known as lateral inhibition, one cell sends a signal that prevents its direct neighbors from sending that same signal.

Earlier this year, Cohen showed experimentally that small protrusions in the developing cell membrane could enable the cell to laterally inhibit cells several cell lengths away, not just those with which it is in direct contact. Cohen used his results to mathematically model the development of spaced patterns like a leopard's spots, but he still couldn't explain the formation of stripes.

In the newest paper, Cohen and colleagues demonstrated that a developing cell must receive inhibitory signals from multiple cells before its own signaling was switched off. This model of stripe formation only works if the small protrusions enable contact with a large number of cells, Cohen said. As these cells communicate through these protrusions, "there's a rewiring of the communication network over time," he said. And this rewiring creates what Cohen refers to as "structured noise."

Something similar to structured noise occurs in a large group of people mingling at a cocktail party. Outsiders might only hear a low murmur and see people standing around, but if they pay attention for a longer period of time, they will overhear snippets of conversations and see people socializing with different groups. Cohen and his colleagues acted as these observers watching the cocktail party of animal development, and found that, over time, patterns would emerge from all of this noise.

Biologist Ricard Solé at the Universitat Pompeu Fabra in Barcelona, who did not participate in the research, said that the seemingly irrelevant "noise" allows the cells to stabilize in patterns of stripes and spots. In physics, he said, systems without noise are often suboptimal and unstable. "When you have noise, you can escape from those suboptimal solutions," Solé said.

As the cellular communication system continually rewired itself, some developing cells would sometimes get signals that inhibited them from secreting a morphogen, while at other times those cells would be the ones doing the secreting. This inherently unstable network becomes much more stable as time passes and the cells begin to receive more consistent activating or inhibitory signals. The activating morphogens switch on genes telling the skin cells to turn a different color. These skin cells then activate their neighbors, and ultimately, a pattern of stripes or spots emerges.

"This is the first experimental evidence that cellular systems can use noise to induce order in a pattern-forming system," Solé said. "This work might actually help in looking for potential mechanisms allowing such patterns to get ordered out from cellular noise."

M. Cohen, B. Baum, M. Miodownik. "The importance of structured noise in the generation of self-organizing tissue patterns through contact-mediated cell-cell signalling." *Royal Society Interface*. http://dx.doi.org/10.1098/rsif.2010.0488

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