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Trying to decipher life's patterns from the language of physics and math

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Life comes with a pattern. From the symmetrical double helix that makes up DNA, the genetic blueprint, to the formation of spots on a leopard or stripes on a tiger, patterns are fundamental properties of all living creatures.

In fact, determining how patterns are formed in organisms is a basic question in the field of developmental biology, which seeks to understand how tissues, organs and fully functional life forms develop from a single fertilized cell.

It's an often painstaking discipline, involving the removal or addition of tens or hundreds of genes in a model organism like a fruit fly or round worm, and then waiting to see what develops.

But now, a UCSD physicist is working on a short-cut that could translate the patterns of life into the language of mathematics and then, with the help of high-performance computers, predict the shapes of things to come.

It's a matter of applying what physicists already do in the physical and chemical world to the biological world, according to Herbert Levine, a professor of physics and scientist with UCSD's Institute for Nonlinear Science.

"My career was always involved with looking at spatial patterns in physical and chemical systems," said Levine. "One of my goals was to try to develop some set of understanding that could eventually help in biological systems. So I've started to seriously try to apply these ideas."

If successful, the work could form the basis for a new science of computational developmental biology, in which computers are used to model, visualize and then predict the impact of subtle biochemical changes on a developing organism. From this information, specific experiments could be conducted to confirm or refute the prediction, saving valuable research time in the process.

"What we envision are some fairly simple computational tools that people will be able to use, plug in their data and use it as a way to gain some insight before going off and performing large numbers of experiments," said Levine. "This way you'll be able to narrow it down to a couple of experiments which might be really crucial."

The precise phrase for this new activity is "non-equilibrium systems" or "physics far from equilibrium." The discipline covers any system that is continually driven by some source of external energy and results in an organized pattern, rather than so me random shape.

An example of such a system in the physical world is the weather. The system is continually being driven by the sun's energy and from heat reflected from the Earth's surface. Whether or not it's hot in San Diego on a given day depends, in part, on the amount of energy stored or removed from heat reservoirs located in the desert to the east, or hundreds or thousands of miles to the west in the Pacific Ocean.

By contrast, a system at equilibrium is isolated from external influences, such as heat, gravity and wind. No energy is added or removed. Ultimately, such a system approaches a very steady state, where things look more or less uniform.

In nature, many of the things we observe fall into the category of non-equilibrium systems. Tree leaves or pine needles, for example, result from some pattern-formation principle.

Tiger stripes or leopard spots also exhibit patterns that appear to follow certain principles that, in theory, could be reduced to, and predicted by, mathematical equations.

But before tackling stripes and spots in large cats, for his first experiments Levine decided to study organisms that are far smaller, and much easier: microbes.

"You want to start in a regime where time scales for development are short and investments are small, where the biology is as simple as it could be," said Levine. "It's clear you want to start at the microscopic end of the living spectrum."

Biologists know this as well, which is why studies generally revolve around such esoteric creatures as fruit flies, round worms, nematodes, baker's yeast and soil amoeba. Defining the precise patterns of development among these organisms generally offer insights into similar processes in their more complex cousins higher up on the evolutionary tree including humans.

In one series of studies, Levine and Lev Tsimring of the Institute for Nonlinear Science focused on a common bacteria called Escherichia coli.

The work starts with the experimental observations of others. In this case, it's been recognized that colonies of foraging bacteria form a single ring or an organized pattern of concentric rings. Once these colonies start to slow and stop, the rings collapse and lock into a radial pattern of spots, resembling an old-fashioned wagon wheel.

What's responsible for this pattern-forming behavior? This is where Levine, a theorist, comes in. It's clear, said Levine, the bacteria are responding to some form of chemical signal that halts their growth and rounds them up into clumps of spots. Using a computer model, he confirmed that a chemical attractant released by the bacteria would cause spot-forming activity.

However, the model failed to explain why these spots formed a symmetrical radial pattern. To capture this effect, Levine and Tsimring proposed another model based on evidence that bacterial colonies form spots under some form of stress. Here, the stress would be a build-up of a hazardous waste byproduct in the bacteria's food supply.

Based on this hypothesis, Levine and Tsimring created a series of mathematical equations describing the interplay between the build-up of hazardous waste at a specific location within the bacterial colony, called the triggering field, and the subsequent release of a chemical signal calling for spot formation. The resulting computer model mimicked real-life observations.

"In this model, when the ring expands it doesn't collapse randomly, it collapses preferentially to spots where the attraction mechanism is triggered first, and that depends very strongly where the previous spots were," Levine explains.

In another series of calculations, Levine worked with a soil amoeba formally known as Dictyosteliem discoidieum (from the Greek meaning "netlike tower") or informally called "Dicty" by those who work with it.

For this research, Levine relied heavily on the experimental observations of UCSD biologist William Loomis. To developmental biologists like Loomis, Dicty offers certain advantages that other organisms don't have.

For one, its genome is a relatively small 34 million base pairs, and genes of interest can be mutated, cloned and reinserted to determine their function with relative ease.

Second, the unique way in which the organism moves and forms specialized tissues offers a bounty of information, since the process bears a remarkable resemblance to the way embryos form in much more complex organisms.

When times are good--when food is plentiful--Dicty cells enjoy a free and independent life style. Generally found in the top layers of soil or under leaves in most parts of the world, the cells eat all the yeast and bacteria within their reach until nothing is left. At this time--when food is scarce--the cells send out signals to one another to get together and move.

Within a matter of hours, hundreds of thousands of these cells aggregate and differentiate to form a two-or-three millimeter translucent structure resembling a slug--consisting of a stalk for locomotion and a fruiting body with spores--that is drawn to light or warmth to a new location where food may be plentiful. Once in its new home, Dicty spores are dispersed from its fruiting body to yield thousands of new amoeba-like, free- living cells. The entire process takes about a day.

Among other things, biologists have observed under the microscope that when Dicty cells aggregate, they form a pattern of rotating spirals. Each of these spirals ultimately collapses to form a clump of cells from which a mobile slug evolves.

Once again, it's clear this pattern-forming behavior is initiated by waves of chemical signals, believed to be cyclic adenosine monophospate (cAMP) released by at least one cell. But the release and reception of a chemical signal is not enough by itself to explain the formation of spirals.

In a paper published recently in the Proceedings of the National Academy of Sciences, a team of researchers led by Levine proposed a model suggesting that the initial chemical signal sets in motion two processes in the receiving cell. Its first response is to manufacture its own cAMP which, in turn, is relayed to other nearby Dicty cells. At the same time, the cell sends a second message to a gene inside to create new receptors for cAMP. Soon, entire neighborhoods made up of tens to hundreds of thousands of Dicty cells are randomly building biochemical antennas tuned into cyclic AMP for instructions on where they're supposed to move.

According to classical physics principles, the randomness of these events causes the waves of chemical signals and responding cells to "break," creating spiral tips. When a small spiral of cells invades the territory of another, it may be overwhelmed by the other; the result is a larger spiral, the type seen by biologists under the microscope.

"You can't predict precisely where all the spirals will be," said Levine. "But you can predict an hour or later what the typical spacing between spirals will be."

Levine cautions that his model is only as good as its experimental proof which, he hopes, will soon be forthcoming.

"I know my model is only a caricature of the real biochemistry," he said. "And yes, I know that means there might be some other way which is totally different than the way that I am proposing for getting this spiral.

"But I can't think of such a way and this way works perfectly fine given the data I've seen."

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