Can mathematics solve biological riddles?

The World in Equations

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Observing nature since time immemorial, mankind has always noticed the surprising regularities evidenced by many biological phenomena. Mathematical modeling is now helping explain them

With quite limited capacity to study such phenomena directly, humans have tried to capture the justification underlying these regularities using the tools and knowledge at their disposal. For example, English physician Alexander H. Howe made such an attempt in a book in 1865, reviewing detailed observations of infectious disease epidemics and seeking to explain their occurrence. Aside from quite sensible conclusions identifying large port cities as the source of many such diseases, he also posits some astounding hypotheses. For example, one of the "laws of pestilence" he offers to explain the eighteen-and-a-half-year cycle observed in epidemic occurrences goes as follows: "The length of the interval between successive periodic visitations corresponds with the period of a single revolution of the lunar node, and a double revolution of the lunar apse line." Although absurd by modern standards, this attempted explanation was by no means so strange for its time. Astronomy was then a science held in high esteem, helping the English fleet to ply the world's oceans and the British Empire to flourish. The real causes of infectious disease had yet to be discovered: Louis Pasteur had just begun his research and Robert Koch was then still in medical school.

Many phenomena in the natural world occur periodically, and we are not surprised to find annual, diurnal, or lunar cycles. But other, completely different cycles also occur, ones unjustified by the outside world. Even a quite solid understanding of biological processes does not always suffice to explain why they proceed as they do. Aside from the cyclical occurrence of epidemics, periodic fluctuations are also seen in the population number of certain animal species and the progression of many diseases. Such circumstances can only be accurately explained once a mathematical model is developed to describe these processes.

First models

One of the first models of this type was put forward in 1926 by the Italian mathematician Vito Volterra. His model explained the surprising fluctuations caused in the numbers of predatory fish, and of the species they prey upon, by the reduction in fishing activity during WWI. Immediately after the war, fishermen noted a significant surge in predatory fish numbers in the Adriatic as compared to the prewar period. The phenomenon was hard to explain based on biology alone. Volterra proposed a simple mathematical model that described the relationship between predators and prey. Letting $X(t)$ and $Y(t)$ refer to the population numbers of prey and predators, respectively, these variables satisfy the following pair of differential equations:

$$X' = (a - c\,Y)\,X,$$
$$Y' = (-b + d\,X)\,Y,$$

where a and $-b$ are the growth rates for the two populations and the expressions $-cY$ and dX describe the changes in these growth
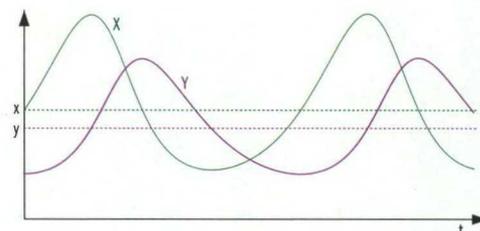
In Volterra's model, the population sizes of prey (X) and predators (Y) fluctuate cyclically. The population of predators can be seen to increase when the population of prey is sufficiently large

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A phytoplankton bloom along the Argentine coast. Due to ocean currents and growth processes, the phytoplankton is not distributed evenly in the ocean but forms interesting fractal forms

caused by the size of the other population. The solutions to this system turn out to be periodic functions, and the average population sizes are $x = b/d$ and $y = a/c$. If the population sizes equal precisely x and y at the outset, they will not vary over time. Using these equations it is easy to conclude that the cessation of fishing will cause an upsurge in predatory fish numbers and a corresponding decrease in the population of their prey, as was seen to occur after WWI. Volterra's model has since been repeatedly modified, with one of its most interesting versions proposed by Soviet mathematician Andrey Kolmogorov. His model has a limit cycle, that is a periodic solution towards which other solutions tend – this can explain the phenomenon of ecosystem stability, i.e. why a system can recover from small, temporary disturbances.

Periodic illnesses

Cyclical, repetitive phenomena play a crucial role for all of life. Some of them, such as the pulse or breathing, proceed throughout an organism's lifetime and their cessation entails death. Other such phenomena, on the other hand, are considered pathological and are disease-related. Many diseases turn out to have a periodic cycle. The mathematician Andrzej Lasota and hematologist Maria Ważewska-Czyżewska, Polish scientists who in the 1970s turned their interest to the temporal course seen in various forms of leukemia, developed a model of hematopoietic system that corresponds quite well with experimental findings. Their model was based on a relatively simple principle. A decrease in the numbers of red blood cells in circulation causes a signal to be sent to the bone marrow, via a hormone called erythropoietin, stimulating blood cell division and differentiation and thereby boosting production of red blood cells. An important role in this process is played by the coefficient h, representing the duration between when the signal is sent and when fully-formed erythrocytes are formed. The model itself then takes the form of a differential equation with the delay parameter h. For a healthy organism h is around 5 days, and then the system is stable. Even when a disturbance affects the system, after some time the organism returns to a state of equilibrium on its own. But a longer time h required to produce erythrocytes, caused by improper functioning of blood cell production mechanisms in the bone marrow, leads the system to become unstable and periodic solutions to appear. In practice that means cyclical changes in the numbers of blood cells in circulation, and certain forms of leukemia do indeed proceed in this way. This mathematical model also enables us to calculate the length of a single pathological cycle, which depends on the time h but is not a simple multiple of it.

The Belousov–Zhabotinsky reaction

A breakthrough in the study of cyclical phenomena came with Boris Pavlovich Belousov's discovery in 1951 of a chemical reaction that showed oscillating behavior, now known as the Belousov–Zhabotinsky (B–Z) reaction. His findings were overlooked in the USSR for many years and only met with the proper interest after knowledge of them reached the

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The charming spots on a Dalmatian's coat are the outcome of reaction-diffusion processes occurring in its body
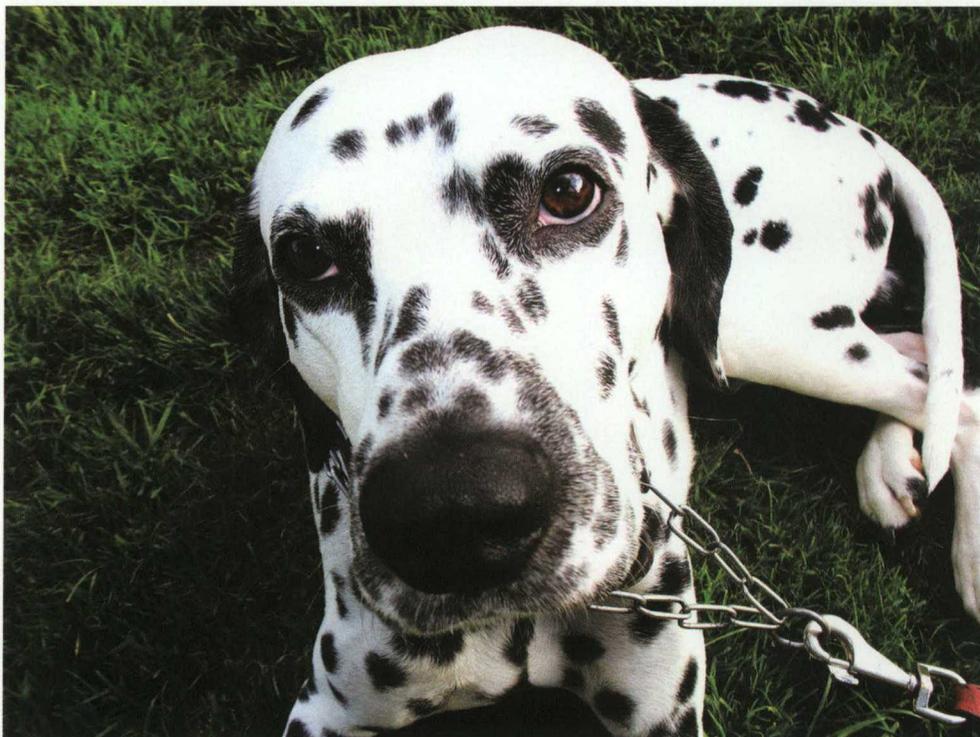
West in the early 1970s. Until then, the prevailing view was that every chemical reaction tended towards equilibrium. Attempts at explaining the periodic behavior of this reaction inspired the Field–Noyes model, developed to describe it, as well as many other mathematical models of biochemical phenomena that show periodic behavior.

The B–Z reaction and similar biological phenomena (plus of course the models that describe them) evidence one more specific property. Namely, they give rise to traveling waves and dynamic spatial non-uniformities – i.e. various kinds of patterns and shapes that change over time. Mathematical models make it possible not only to understand why we witness such periodic or spatially non-uniform processes, but also to calculate such properties as the reaction period and the speed of wave propagation, or even to predict certain kinds of behavior never actually observed before the model revealed the possibility of their occurrence.

Spotted fur and Turing instability

Nature is full of lavish forms and shapes that often astound us with their beauty yet also provoke questions: Why do they occur? Why do they take such form? Such thoughts may be inspired, for example, by the sight of

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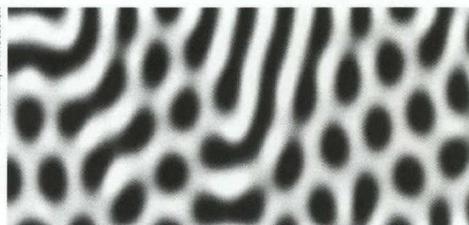
Simulated solutions to reaction–diffusion equations

the spotted coat of a leopard or Dalmatian, the stripes on a zebra or tiger, or the even more colorful wings of a butterfly. The developmental processes by which not just such patches of color but also individual bits of organisms and organs develop are known as *morphogenesis*. The emergence of shapes is governed by certain biochemical factors, greater or lesser concentrations of which cause cells to behave in certain specific ways. While the study of these chemical substances, called *morphogens,* and the cell reactions they trigger belongs to the fields of biochemistry and cytology, the question of how exactly they spread through an organism and why specific forms actually take shape frequently extends beyond the capacity of biology.

Ordinary processes of diffusion tend toward the even dispersal of substances throughout a given medium. But if things always happened that way, a Dalmatian's coat would be uninteresting and uniformly

gray. As it turns out, a properly constructed mathematical model can explain the coloring patterns that are actually observed. In 1952, Turing suggested that without assuming any preexisting shapes, diffusion alone, plus chemical reactions between several different factors, can lead to the occurrence of spatially non-uniform patterns like spots on an animal's fur. The behavior of the spatial distribution of morphogens can be described as a system of nonlinear partial equations of the reaction-diffusion type. Such a system has the interesting property that as the diffusion coefficient increases, the uniform distribution of the morphogen turns into a non-uniform distribution, which leads for instance to the occurrence of black spots on the white fur of a Dalmatian.

Population vs. individual perspective

By observing whole populations from afar, rather than individual organisms up close, we can sometimes notice that they, too, form certain patterns and shapes. Here we are thinking primarily of colonies of smaller organisms like bacteria, ants, and plankton floating in water, or somewhat larger schools of fish. It is hard to imagine that the emergence of such patterns is somehow intentional on the part of each of the individual organisms; rather it stems from their collective behavior and of course the impact of the environment. To properly explain the patterns created by a whole population, one first has to observe the mechanisms by which individual specimens behave and how they react to one another and to the external conditions, and then to build a model that accounts for those mechanisms. Such an individual-level model precisely describing each member of the population usually cannot be studied directly - it has to be properly scaled in order to obtain the macroscopic effect. Seemingly chaotic behavior on the part of individual organisms can lead to the emergence of interesting population-level structure. For example, the fish in a school try to move in the same direction as their neighbors, but their movement seems to be uncoordinated, involving considerable randomness. Despite that, the motion of the school as a whole demonstrates great regularity, which frequently enables it to survive attacks by predators. Similarly, the purely stochastic movement of plankton and their reproductive

process gives rise to interesting fractal structures in the spatial distribution of a population. These phenomena can be captured using quite advanced mathematical models.

All in all, the modeling of biological phenomena enables us to better understand not just natural mechanisms but also the beauty of the world around us. The community pursuing this fruitful field of study includes a number of Polish mathematicians, such as the biomathematical school founded in Katowice by the above-mentioned Andrzej Lasota (which includes the present authors). Other researchers include a strong group in Warsaw led by Mirosław Lachowicz, Jacek Miękisz, and Urszula Foryś, a bioinformatics group led by Jerzy Tiuryn, and a team led by Andrzej Świerniak at the Faculty of Automatic Control, Electronics and Computer Science at the Silesian University of Technology. The European Society for Mathematical and Theoretical Biology has chosen Poland to host its gathering, the "European Conference for Mathematical and Theoretical Biology," which will be held in Kraków in 2011. ■

Further reading:

Grimm V., Railsback S.F. (2005). *Individual-based Modeling and Ecology.* Princeton: Princeton University Press.
Rudnicki R., Wieczorek R. (2006). Phytoplankton dynamics: from the behaviour of cells to a transport equation. *Mathematical Modelling of Natural Phenomena, 1,* 83-100.

Paige Gill - Florida Keys NMS
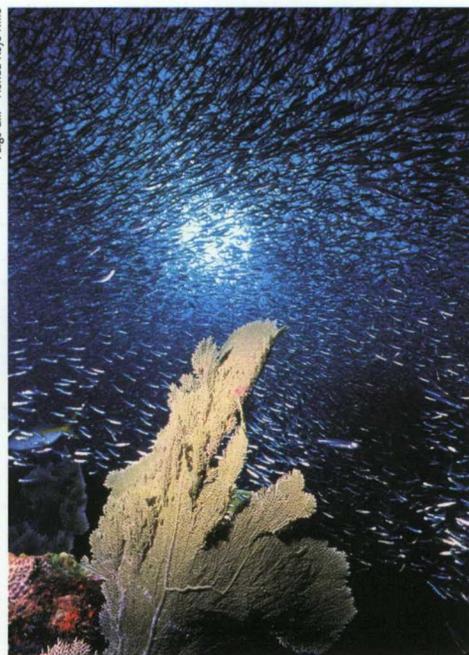
A school of fish behaves like a single organism, even though each fish determines its direction on its own