Chemotactic patterns without chemotaxis

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Advances in computing have made it significantly easier to develop and implement mathematical models of ever-increasing complexity. Whereas, even a decade ago, solving a set of coupled nonlinear partial differential equations required sophisticated training and months of coding, software packages now make it possible for such models to be quickly solved. This has helped to catalyze interest in using computers to simulate every conceivable aspect of cell biology. However, all of the computing power in the world cannot be harnessed to answer the fundamental question of how to use such models to gain insight. Can we improve our understanding of a complicated process by simulating every conceivable part in exquisite detail? If not, what is the right level of detail to include? In PNAS, Cates et al. (1) revisit patterns formed by chemotactic bacteria and demonstrate how an intuitive set of effective models—in which the details of the chemotactic mechanisms are ignored—can nonetheless be used to quantitatively capture the patterns formed.

The danger in modeling complicated processes is well illustrated by the remarkable advances in computer animation. Animators have long used mathematical models to emulate reality, and indeed, in recent years, brilliant and beautiful renditions have been created by modifying physically based equations of motion to make them look like the real thing (2). Although visually compelling, a computer animation of a flame fundamentally differs from a mathematical model of the same phenomenon (3). Whereas an animator seeks to maximize the reality of the image, a modeler aims to understand the mechanistic underpinnings of the phenomenon; with a model, one can ask and develop hypotheses for why the flame has the properties that it does and test these hypotheses in experiments. But from a picture alone, it is impossible to distinguish between computer graphics and a bona fide mathematical model.

Pattern Formation in Bacterial Chemotaxis

Cates et al. (1) study pattern formation in bacterial chemotaxis. Bacterial chemotaxis has long served as a model system for a sensory apparatus (4, 5); beautiful work by Berg and colleagues (5–7) uncovered the cellular basis for how a single bacterium can sense its chemical environment and swim up a gradient. The fundamental idea is that bacteria perform biased random walks, in which "runs," periods in which the bacteria swim straight with constant velocity v, are interrupted by "tumbles," in which the bacteria turn randomly. By measuring a time-weighted average of chemoattractant binding to their receptors, bacteria such as *Escherichia coli* can modulate changes in the frequencies of run and tumble and hence control ascent of a gradient. This system has served as an inspiration for recent efforts to ask questions about design principles of signal transduction networks (8).

Early experiments on bacterial chemotaxis did not focus on the sensory apparatus but instead on the patterns that large collections of chemotactic bacteria create. In 1964, Adler (9) discovered that, when chemotactic bacteria swim through a small tube of rich medium, the bacteria form a dense band that moves at constant velocity. Efforts to reproduce this simple behavior with a mathematical model combining chemotactic bacteria with a single food source showed that constant velocity bands could form only if the chemotactic coefficient (defined as the proportionality constant χ between the drift velocity and the concentration gradient, $v = \chi \nabla c$) diverged to infinity as the attractant concentration vanished (10). The discovery of the cellular underpinnings of the chemotactic coefficient demonstrated that this assumption is invalid (4, 7). Subsequent work demonstrated that steady traveling bands require detailed accounting of the coupling between nutrient consumption and the production or depletion of chemoattractant (11).

Effective models hold great promise for understanding biological systems.

The conclusion that qualitative properties of the chemotactic band require such detailed knowledge of nutrient consumption was disturbing; that such a level of detail was needed for a simple, collective behavior does not bode well for untangling even more complex processes. Perhaps, however, a simpler (yet quantitatively accurate) description is possible.

Enter Cates et al. (1). Rather boldly, they create a model for interacting bacteria in which the direct interaction of bacteria with the attractant or nutrient fields (and indeed, chemotaxis itself!) is ignored completely. Instead, they argue that both the run–tumble behavior and the chemotactic drift of a collection of bacteria can be quantitatively captured by a density-dependent swim speed $v = v(\rho)$, where ρ is the bacterial density. The swim speed is assumed to decrease with increasing bacterial density. With this ansatz, the resulting mathematical model contains chemotactic drift, although now in the direction of increasing bacterial density instead of increasing attractant. Now of course, the bacterial density will tend to be higher in regions where the attractant concentration is higher, and so intuitively the model contains the same type of mechanism as bacterial chemotaxis. However, it "skips a step" by neglecting the chemotaxis entirely and instead asserting that the fundamental quantity is the density-dependent drift velocity.

Strikingly, Cates et al. (1) demonstrate that the model quantitatively reproduces the phenomenology of a set of experiments in bacterial pattern formation. Budrene and colleagues (12–14) demonstrated that the bacterium *Salmonella typhimurium* produces a series of concentric rings that destabilize into high-density "dots." This behavior was reproduced with detailed biochemical simulations but is also strikingly similar to that of the effective model. Moreover, the effective model dictates that the phase space of possible pattern can be described by only two dimensionless parameters, highly reduced from the more complicated model.

Toward an Effective Model

The effective model provides a compelling vision for a quantitative theoretical description of chemotactic cells. The model effectively averages over the details of exactly how individual cells respond to chemical cues, arguing that the most important effect of chemotaxis is to give rise to a density-dependent mobility. This strongly reduces the number of parameters governing the collective response.

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Validation of the model requires several explicit experimental tests: most fundamentally, it needs to be shown that the microscopic motion of the swimming bacteria agrees with a density-dependent velocity $v = v(\rho)$ and the resulting bacterial random walk. If this test works, the framework can be further probed by changing nutrient and attractant concentrations and checking that both the predicted patterns and the bacterial motion are consistent with it. The challenge would then be to develop a first principles understanding of how $v(\rho)$ could arise from the underlying chemical mechanism, so that the effective model can be generalized to other situations.

Can the framework introduced by Cates et al. (1) describe pattern formation in other bacterial types? For example, Budrene and Berg (13, 14) demonstrated in *E. coli* a different pattern-forming mechanism from that shown in *S. typhimurium.* There, a single ring travels with constant velocity and destabilizes into high-density dots (14). The instability leading to dots was shown to be the result of the instability of a collapsing bacterial cylinder (11), which then breaks down into spherical clumps (11, 15). It remains unclear whether the framework proposed by Cates et al. predicts this series of events. Another striking feature of theoretical models of bacterial chemotaxis is their prediction that the bacterial density of a 3D clump can diverge to infinity in finite time (16). It is of some interest to determine the circumstances [i.e., the specific forms of $v(\rho)$] under which the Cates et al. framework predicts this feature, remnants of which are observed in experiments (17).

The work of Cates et al. gives a compelling vision for how biological parameters that are difficult to observe might be subsumed into a much smaller number of effective parameters, whose values are themselves directly connected to the behavior of individual cells and pathways. Their simulations of the effective equations give patterns that "look like" the experiments, but this is much more than computer graphics. Inherent in their description is a fundamental microscopic picture of bacterial motion, which must be verified in detail for the model to be correct.

In the physical sciences, such effective descriptions have had a long and successful history in explaining behavior of complicated systems, sometimes even demonstrating that completely distinct microscopic systems can have identical quantitative macroscopic responses (18). In principle, effective models hold great promise for understanding biological systems as well, although we are only at the beginning stages of their exploration.

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