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The Slime Mold *Dictyostelium* as a Model of Self-Organization in Social Systems

Alan Garfinkel

. . . what wise hand teacheth them to doe what reason cannot teach us? ruder heads stand amazed at those prodigious pieces of nature, Whales, Elephants, Dromidaries and Camels; these I confesse, are the Colossus and Majestick pieces of her hand; but in these narrow Engines there is more curious Mathematicks, and the civilitie of these little Citizens more neatly sets forth the wisedome of their Maker.

Sir Thomas Browne (c. 1663), partially quoting from Henry Power, *Experimental Philosophy*, 1663 (Winfree, 1980)

ABSTRACT

The phenomenon of aggregation in the cellular slime mold *Dictyostelium* has been studied intensely, both as a model for the self-organization of single cells into multicellular organisms and as a source of information about the extracellular function of the chemical messenger, cyclic AMP. There are two basic classes of models: models of individual cells in discrete sets and field theoretic (continuum) models of aggregation. These two kinds of model are designed to answer somewhat different questions, but any explanation of the nature and form of aggregation requires the field approach. An examination of the forms occurring during slime mold aggregation provides important clues to the dynamics of the process and indicates the importance of symmetry breaking and entrainment in self-organization. Analogies are proposed between slime mold aggregation and human social processes.

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Associated with the term *entropy* is a tendency to disorder: structure tends to degenerate into uniformity. In the thermodynamic world, governed by the law of increasing entropy, the Parthenon crumbles into dust and order dissipates. But the opposite tendency is also regularly observed: processes in which structure is built out of the less structured. Such processes built the Parthenon, and, in a similar local defiance of entropy increase, biological evolution produces organisms of increasing complexity. Examples of emergence of complex structure can be found throughout the physical world: if a homogeneous fluid is subjected to sufficient heat or motion, forms develop. The forms are patterns of vortices in the fluid flow, of regularly spaced cells of convection currents, or of waves. In the social world, too, we find examples of emergent forms.

We need concepts with which to understand and explain these kinds of structure-building processes. In the case of the Parthenon, we recognize a guiding intelligence, the unfolding of whose conscious intention explains the development of the structure. But in other cases, such as biological evolution, we want to be able to say what Laplace said to Napoleon: "Sir, I have no need for that hypothesis." What we need are models or theories of how systems can develop or evolve into higher levels of structure or organization.

The term *self-organization* has recently come to be used as the general term for the processes by which order and structure emerge. One of its most important sources is the work of the mathematician Turing (1952), who considered some simple examples in which chemicals, reacting with each other and diffusing through space, produced regular patterns. The point was to show how it is possible for a uniform distribution of substances to display what he called *morphogenesis*: the qualitative leap to a regular pattern or order. His paper has been the inspiration for much recent work in self-organization, and has provided some of its basic philosophical themes.[1] In Turing's scheme, a system of equations has, for one range of its parameters, a homogeneous (i.e., uniform or constant) solution. But as these parameters pass critical points, the homogeneous solution becomes unstable and undergoes *bifurcation*: a splitting-off of a new solution. In these cases there is less homogeneity and more structure than in the original solution. The new solution violates the symmetry of the original configuration, and displays regular patterns in space and/or time.[2]

This approach gives us a general model for explaining pattern formation: find an equation (typically a partial differential equation) that describes the system's interactions, and study the bifurcations of solutions to this equation, especially those in which the prebifurcation state has greater symmetry than the postbifurcation state. These equations may be chemical reaction–diffusion equations, as in Turing's model, the Navier–Stokes equations of fluid dynamics, or more gen-

[1]Turing is better known as the first theoretician of the digital computer: he proposed the basic definitions of machine computability and proved theorems on its limitations. He also wrote about the "thinking" ability of such machines. His areas of interest are linked by the concept of emergence: how can systems display characteristics that do not seem to be inherent in their components?

[2]The idea of explaining morphogenesis as pattern formation in reaction-diffusion equations was also developed by Rashevsky (1940) and by Kolmogorov *et al.* (1937). See also Kametaka (1975).

eralized equations of probability density distributions, such as the various Fokker–Planck equations. The picture that emerges is something like this: several forces interpenetrate a medium. At one extreme (of parameter values), one force completely dominates; at another extreme, another force dominates. But in the twilight regions in which no single force completely dominates, patterns and morphologies form, a moiré of the interactions between forces. For example, in fluids it may be the interaction of viscosity (momentum diffusivity) versus convection, or viscosity versus heat transport. At one extreme, viscosity dominates, and the fluid is (macroscopically) quiescent. But as the parameters pass into critical regions, patterns of vorticity or heat transport are produced.

One kind of pattern formation is the phenomenon of *aggregation*, in which a uniformly distributed substance aggregates into clumps. Aggregation phenomena are found throughout nature. On the cosmic scale, the formation of galaxies is the result of aggregation of stellar material, producing *mesogranularity*: middle-range structures between the scale of individual particles, at one extreme, and the whole space, on the other. On a smaller scale, aggregation phenomena are found in the condensation of vapors into drops and, generally, in processes such as nucleation and granulation. In this chapter we shall be concerned with models of aggregation in biology (and to a lesser degree, in sociology). One example in particular has captured the imagination of many theoreticians, and will be the focus of this chapter: aggregation in the cellular slime mold *Dictyostelium discoideum (Dd)*.

The slime mold is a remarkable creature. It spends one phase of its life as individual amoebae—single-celled animals that move around, eat bacteria, and in other ways lead their own lives. When deprived of food, however, the amoebae aggregate: they come together and fuse into colonies of thousands of cells. Once the merger is complete, the fused colonies migrate over macroscopic distances, and in other ways act as a single organism. This organism, initially homogeneous, later undergoes differentiation: part becomes a foot or base rich in cellulose, and part becomes a fruiting body rich in polysaccharides. Later still, the fruiting body bursts, releasing individual amoebae and completing the life cycle. (A good background reference is Loomis, 1975).

The process of aggregation has been intensively studied. Intrinsically fascinating, it also suggests the possibility of learning some basic truths about higher forms of life. First, the biochemicals involved (ATP and cyclic AMP) form the building blocks for metabolism and communication in all multicellular life forms. Second, the aggregation process seems to offer a model for the evolution of complexity. Cohen (1977) remarks: "In the development of *D. discoideum*, one may really be watching a replay of the basic kinds of events responsible for the appearance of the first multicellular organisms." Third, there is an obvious potential for social analogy. People have already suggested that aggregation in *Dictyostelium* can serve to model the formation of insect colonies, and the analogy to human aggregation, in towns or other collectives, has been hinted at.

Here, I shall consider various models of aggregation in the slime mold. Several philosophical themes will emerge which I think characterize self-organization processes. One is the need for an antireductionist or holistic approach; another is

the role of symmetry-breaking in self-organizing systems. The possibility of analogy to human social processes is also explored.

How can we explain aggregation in *Dictyostelium*? Everyone seems to agree that the amoebae move *chemotactically*, i.e., their motion is in response to a chemical attractant. In this case the attractant, dubbed acrasin,[3] is secreted by the individual cells. In the individual-cell phase, this attractant is ineffective in producing aggregation, and the cells move randomly. Then something happens, and the cells aggregate in response to the attractant. The problem is to show how this occurs. The relevant literature reports empirical research as well as mathematical models. The mathematical models fall into two classes: global models of the aggregation field and models of the individual amoeba cell. Their relationships to each other and to the data are problematic.

The Field Model

The global or field model was developed by Keller and Segel (1970) (see also Segel, 1972) to study the global behavior of the whole system of amoebae, rather than that of the individual cells. They postulate several quantities, which are assumed to be continuously distributed over space. Then they form a set of partial differential equations for the system as a whole. By studying these equations they attempt to explain the formation of patterns of aggregation as a bifurcation in the solution to the field equations. It is therefore an example of the approach of Turing (1952): pattern formation and morphogenesis is explained as the instability of the homogeneous solution to a set of partial differential equations, and the symmetry-breaking bifurcation to a more structured stable configuration.

In this case, the parameters studied are the density of amoebae, $\alpha(x,t)$ at a point x and time t, and the density of acrasin, $\rho(x,t)$. The full model also requires incorporating an acrasinase (destroyer of acrasin) and the reaction product of acrasin and acrasinase, but these are ignored in the simplified model. The model assumes the following: (1) a tendency for amoebae to diffuse, (2) for amoebae to move chemotactically, (3) for acrasin to diffuse, and (4) for amoebae to produce acrasin.

If all the tendencies were connected, then, for certain parameter values, aggregation would not occur, because

$$(2) + (4) < (1) + (3)$$

On the other hand, if the reverse were true, then aggregation *would* occur, as acrasin → aggregation → more acrasin → more aggregation, and so on.

Mathematically, the Keller–Segel model takes the form of a partial differential equation in the two variables $\alpha(x,t)$ and $\rho(x,t)$. The equation governing $\alpha(x,t)$

[3]For *dictyostelium discoideum*, acrasin has been identified as adenosine 3′:5′-cyclic monophosphate, or cAMP for short. See Bonner (1959, 1969) for a good introduction.

is the sum of the two terms representing (1) and (2) above. The diffusion is assumed to follow Fick's law: diffusion follows the gradient $\nabla\alpha$ of the density α from more dense to less dense areas. This term is therefore

$$\nabla \cdot (D_2 \nabla \alpha)$$

where D_2 is the diffusion coefficient for amoebae.[4] The chemotactic aspect is modeled by assuming that the amoebae follow and move along the negative gradient of acrasin density. Hence, this term is

$$-\nabla \cdot (D_1 \nabla \rho)$$

where D_1 measures the sensitivity of amoebae to a given gradient of acrasin. Combining these two, we get the equation for amoeba movement:

$$\frac{\partial \alpha}{\partial t} = -\nabla \cdot (D_1 \nabla \rho) + \nabla \cdot (D_2 \nabla \alpha)$$

Turning to the acrasin density, ρ, they combine the various terms representing the tendencies for acrasin to be used up and to decay, the tendency for acrasin to be produced by the amoebae, and the tendency for acrasin to diffuse, yielding

$$\frac{\partial \rho}{\partial t} = -K(\rho)\rho + \alpha f(\rho) + \nabla \cdot (D\rho \nabla \rho)$$

where $D\rho$ is the diffusion coefficient for acrasin.

Keller and Segel assume a homogeneous (i.e., uniform) equilibrium solution α_0, ρ_0, and study by a linear stability analysis its stability with respect to infinitesimal perturbation. This analysis reveals a condition for the instability of the homogeneous solution: the solution instability will increase if

$$\frac{D_1 f(\rho_0)}{D_2 \bar{k}} + \frac{\alpha_0 f'(\rho_0)}{\bar{k}} > 1$$

where $\bar{k}$ is a constant.

Examining this result qualitatively, they observe that several different mechanisms can produce instability leading to aggregation:

- An increase in D_1 (the chemotactic sensitivity of amoebae)
- An increase in $f(\rho_0)$ (the rate of acrasin production)
- An increase in $f'(\rho_0)$ (the rate at which acrasin stimulates further acrasin production)

[4]If D_2, is constant, this becomes the familiar $D_2\nabla^2\alpha$ of Fick's law. The authors retain the form above, presumably to allow for a variable D_2, although they do not actually consider such a case.

They remark that the first two factors have been observed at the beginning of aggregation. This fact is taken to provide "qualitative evidence for the applicability of our theory."

Critique of the Field Model

The most important thing about the Keller–Segel model is its general philosophical outlook. It models aggregation as morphogenesis in the sense of Turing: first a set of equations is postulated, similar to Turing's reaction–diffusion model, but is complicated in this case by the presence of chemotaxis. Aggregation is then explained as the result of the instability of the homogeneous solution and the bifurcation of a new solution. Their analysis provides a nontrivial criterion for the instability and gives an account of the relative effects of the tendencies that cause it.

Is it a good model? What do we want from a model of aggregation? Any model will explain some phenomena and not others; the problem is to determine which elements of the aggregation process are essential and which can be ignored. Several features of aggregation that do seem important are not explained in the Keller–Segel model. One key feature is the fact that aggregation territories are finite—the amoebae in the medium do not all collect into one single mass but, rather, form a number of territories of roughly equal size spaced throughout the field. This is an important part of the morphology—a stable mesogranularity that is larger than the cell and smaller than the whole field. We ought to be able to give an account of it, but in the simplest versions of the Keller–Segel model, the whole field aggregates into a single mass.

The question then becomes: how can the model be amended to account for this fact? Once aggregation begins, there is nothing in the simplified model to act as a counterforce or countertendency to the collection process. The simplified model ignores the activity of the acrasinase—the enzyme that destroys the attractant. Perhaps the finiteness of territory size is due to the action of this acrasinase. There is some empirical support for this conjecture: it has been observed that high acrasinase levels reduce territory size and that mutants with low acrasinase activity have large territories (Robertson and Cohen, 1974). When we try to include the acrasinase reaction in the full Keller–Segel model, we get a better model, but one that is not mathematically tractable. So far, it has not been demonstrated that the relevant phenomena can be derived from the full Keller–Segel model (Segel, 1972).

Another strategy for explaining the finiteness of territory size, suggested by Keller and Segel, is to assume that there is a threshold in the chemotactic response of the cells to the attractant. These investigators have explored the possibility of adding this assumption to their model and found that it does reproduce some of the desired features but that there are some problems with it. Most importantly, it creates difficulties for their stability analysis. In constructing their basic argument, Keller and Segel used the widely accepted technique of linear stability anal-

ysis. Adding a threshold makes instability depend on the amplitude of the perturbation and requires that it not be small. This need for a good-sized perturbation vitiates the earlier reasoning and invalidates the linear stability analysis they employ.

The entire question of the use of linear stability analysis needs reexamination, for despite its near-universal use, there are serious problems with it. Keller and Segel use it in the usual, accepted fashion: once they have obtained their homogeneous equilibrium solution, linear analysis gives the criterion for instability, which amounts to testing the system for destabilization by infinitely small perturbations. This approach has two drawbacks. First, it provides only local information about the qualitative direction of movement *at* the very point of instability. What happens after that is beyond the scope of this kind of analysis. But questions about what happens after the point of instability (especially: does it oscillate?) are crucial for the success of the model. Second, linear stability analysis is limited in that it tests only the sensitivity of the system to destabilization by *infinitely* small perturbations. It might well be that a given system is stable under vanishingly small perturbation, but unstable under finite perturbation greater than some ϵ, say on the order of the Brownian movement! This criticism illustrates an important fact about continuum models: in order for the techniques of infinitesimal calculus to be applied to any real situation and to produce meaningful results, some kind of scale or gauge must be imposed on the model so that the notion of "small" in the model is not absurdly small from a practical point of view. Any physical continuum disappears on a fine-enough scale, and it is important that the mathematical model of the continuum not commit us to things going on in such a small space as to be physically impossible.

These criticisms should not detract from the basic interest of the Keller–Segel model. In fact, it received very little attention, and no critique ever appeared. Instead, attention shifted away from field-theoretic models toward models of the individual cell. In part, this shift of interest may have been due to the failure of the Keller–Segel model to predict wavelike global oscillation of the aggregation field—a striking and well-confirmed observation. But even more, the shift was probably due to a philosophical antipathy toward holistic models. The essence of the field model lies in viewing the process of aggregation globally rather than focusing on activity inside the individual cell. But most workers in the field seemed convinced that in order to understand the mechanism of aggregation, it is necessary to study in detail exactly what is going on locally. The main argument for this perspective depends on pulsatory oscillation in the individual cell.

During aggregation, the individual amoebae change their characteristic emission of cAMP from a steady low-level output to an output consisting of periodic *pulses*. The duration of these pulses is quite short (< 2 sec) and the interval between them is quite regular (~ 300 sec). A second important feature of the individual cell dynamics is *excitability*: the individual cell during aggregation can emit pulses of cAMP in response to receiving a pulse from another cell above a certain magnitude threshold. There is a time delay of approximately 15 sec in this response (Robertson, 1972).

These phenomena cannot be easily represented in the field model. At the very least, they would require major modifications in the type of equation representing the overall aggregation to account for threshold, delay, and oscillation.

The existence of the threshold, together with the fact that achieving the threshold results in a relatively large output, implies that the acrasin production function has discontinuous slope at the threshold value. This implication means that we are dealing with a partial differential equation with discontinuities of slope sprinkled liberally through space and time. The existence of the time delay for relay creates a further problem: in a field model, a time delay appears as a discontinuity at the individual cell; the cause propagates continuously to the point of the cell, then nothing happens for 15 sec, then a pulse is emitted. The alternative to this discontinuity is to model the process by time-delay equations in which the output at a point x is a function, not just of the instantaneous state at x, but also of the state at x some t seconds past. This alternative enormously complicates the equation. Consider also the function $f(\rho)$, which describes how the local level of cAMP affects its production. If production is oscillatory, then the shapes of f and its derivative are going to be very complicated. These factors make it difficult to represent local oscillation on a field-theoretic model. Because local oscillation seems important in chemotaxis, we see another reason for the focus on the individual cell. Recent work on slime mold aggregation has centered on just the question avoided by the field model: why do the individual cells oscillate?

The Individual Cell Model

Oscillation is often regarded as undesirable, a dysfunction of a system. Examples like business cycles, pipe flutter, bridge and airfoil flutter, wheel shimmy, muscle tremor, as well as periodic diseases like anorexia nervosa and manic-depressive disease made oscillations seem to be unwanted aberrations, rather than a basic function. Recently, there has been recognition of the importance of oscillatory processes in life. For an introduction, see Chance *et al.* (1973) and the excellent survey by Winfree (1980).

In the slime mold, the role of oscillation in the production of cAMP by the cell has several features that are important functionally. Oscillatory production is a much more efficient process from the point of view of resource utilization and of signaling. Given that cells respond to rates of change in cAMP levels, it is more effective to produce cAMP in pulses (Nanjundiah, 1973).

Gerisch and Hess (1974), Goldbeter (1975), Goldbeter and Segel (1977), and Cohen (1977) modeled the workings of the individual cell, taking as the fundamental data to be explained the capacities for pulsing and for relay. They developed models of internal metabolic mechanisms to show how cells can emit periodic cAMP pulses and also how small pulses of *extra*cellular cAMP can elicit large pulses of *intra*cellular cAMP, thereby establishing a "relay" mechanism.

In the model of Goldbeter and Segel (1977), these two phenomena are modeled by an ordinary differential equation in α = ATP concentration, β = intra-

cellular cAMP, and γ = extracellular cAMP, and the reaction is occurring inside a single cell. The equations are

$$\frac{d\alpha}{dt} = v - \sigma\phi$$
$$\frac{d\beta}{dt} = q\sigma\phi - k_t\beta$$
$$\frac{d\gamma}{dt} = (k_t\beta/h) - k\gamma$$

where $\phi = \alpha(1 + \alpha)(1 + \gamma)^2/[L(1 + \alpha)^2(1 + \gamma)^2]$, and everything else is constant.

By numerical integration of the equations, they showed that their model yielded two important behaviors: a small pulse of γ caused a large pulse in β for an appropriate domain of the parameter space, and then, as the parameters changed critically, the same system underwent a transition to regular autonomous pulsing.

There were some problems in reconciling this model with other data, however. In particular, the model called for cyclic variations in ATP level. These are not found in practice, according to Cohen (1977).

An alternative model was suggested by Cohen (1977), who employed qualitative dynamics to develop a model in which the individual cell's cAMP concentration is subject to several interrelated controls, producing a qualitatively described system.[5] As one of its control parameters of this model is slowly increased, the system exhibits successive bifurcations, so that its behavior progresses from

1. Steady-state low-level leakage of cAMP, to
2. Excitability, i.e., the ability to produce the pulses of cAMP in response to external pulses, to
3. Autonomous oscillation of pulses of cAMP, and then to
4. Rapid continuous release of cAMP.

There are some problems with this model. The control parameter that increases slowly with time, causing the bifurcations, is the equilibrium value of cAMP. This assignment yields several false predictions, e.g., that supplying large amounts of cAMP to a cell should induce the sequence of bifurcations. This is not so (Gerisch, 1978). None of the individual cell models takes into account the fact that the cell seems to respond not so much to the cAMP level as to rapid changes in it. It is not clear how to amend such models to represent the dynamics of a pulse input.

[5]The qualitative picture has a certain advantage over writing a single differential equation and then exploring parameter space by computer. The qualitative model is more robust, because it focuses on the general *forms* of the curves involved rather than on the specific equations. Consequently, this approach displays the important causal relations.

My purpose here is not to criticize these models of the individual cell, but rather to ask how, given any model of the cell, we can account for the collective phenomena of aggregation. Let us assume that we have a model of the oscillation and relay properties of a single cell. Explaining aggregation then takes the form of considering various aspects of global behavior, and showing how a model derived by connecting N copies of a single cell can display aggregation morphologies plausibly related to those observed.

The simplest possible model for collective behavior is that of Cohen and Robertson (1971a,b). A single autonomous oscillator has its pulses relayed sequentially by a field of relay-competent cells. This model faces a number of difficulties. To begin with, we have the problem of explaining the levels of cAMP produced during aggregation. The models of the individual cell and the empirical data agree that the relative increase in cAMP level that is brought about by a single cell's pulses is about 20:1 (Goldbeter and Segel, 1977). On the other hand, observations of cAMP levels in the aggregation field indicate that during aggregation overall cAMP levels increase 100:1 (Bonner *et al.*, 1969). Therefore, something that is going on is not simply the sum of independent individual contributions. The basic phenomena of aggregation are essentially *collective* phenomena. Serious difficulties stand in the way of deducing these phenomena from models of the individual cell.

Waves

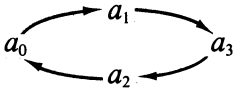
The most important macrophenomenon is the occurrence of *waves* of aggregation. All experimentalists use this term in describing their observations, and it should be possible to explain how it happens. Two attempts to derive wavelike phenomena from detailed models of the individual cell are found in Cohen and Robertson (1971b) and Durston (1973, 1974a,b).

The scheme of Cohen and Robertson is that of a discrete set of relaying cells surrounding a periodic pacemaker. The pacemaker fires, the next cell relays the pulse, and so on, and a wavelike disturbance passes over the field. In the simplest case, we imagine the autonomous pacemaker a_0 signaling to a_1 which signals a_2, and so on. The relay is not immediate, however: it is well established (Cohen and Robertson, 1971b; Gerisch and Hess, 1974) that there is a 15-sec delay between the receipt of a pulse by a cell and its subsequent relay. Compared to this, the cell-to-cell diffusion times are negligible (Cohen and Robertson, 1971b). But this fact has a surprising consequence: the velocity of propagation of the signal ought to be inversely proportional to the density, because higher density implies smaller interamoeba spacing, which implies more relay delays per unit distance. Robertson *et al.* (1972) report a signal propagation velocity of 42 μ/min. In their experiments, they used a preparation with a density of 6×10^4 cells/cm^2. (The laboratory vessel in which the experiments are done is two-dimensional—a plate. Therefore, densities are defined per unit area of field, not per unit volume.) Their velocity observations agree well with those of Gerisch (1968). But in Gerisch's experiments, the densities in question were on the order of 5×10^6 cells/cm^2, or

two orders of magnitude larger. We would have to conclude that propagation velocity is independent of density, which cannot be reconciled with the cell-to-cell relay model.

Several other reports of wave propagation velocity give different results. Gross *et al.* (1976), using densities of 2.5×10^5 cells/cm^2, report propagation velocities ranging from 240 to 467 μ/min, or 6 to 10 times the velocities reported above. It is hard to see how this discrepancy can be explained. Moreover, the authors report a striking fact: the velocity of successive waves decreases linearly with time, a phenomenon for which no explanation exists. Alcantara and Monk (1974) also report velocities on the order of 350 μ/min, which they are unable to reconcile with the data of Gerisch.

The more we examine the cell-to-cell model, the less attractive it becomes. Consider a fairly dense packing of cells. Let a_0 be the autonomous pacemaker, and assume that two cells, a_1 and a_2, are both near a_0, with a_1 slightly closer. The pulse from a_0 reaches both a_1 and a_2, but a_1 slightly ahead of a_2. Fifteen seconds later a_1 fires, just ahead of a_2. What happens to a_2? If a_2 does fire, then by extension to a_3, and so on, there will be huge amounts of cAMP produced immediately. But experiments suggest that being hit by a pulse just as the cell is ready to pulse itself results in the suppression of the pulse (Gerisch and Hess, 1974). But then, if a_2 does not fire (and hence neither do the other cells in the immediate area), the signal will either die out or leapfrog over the suppressed cells until it is too late to suppress the next pulse. In order to predict which of these will happen, we would have to know the exact rate of diffusion, the precise time delay, and exact times of pulse suppression. Moreover, we would need detailed information about the effects on a relay resulting from the receipt of multiple pulses. Consider the following array:



If a_1 and a_2 are equidistant from the pacemaker a_0, they will relay its pulses simultaneously, resulting in *two* pulses hitting a_3. We do not have any information on this, nor any model, to predict what will happen.

Cohen and Robertson (1971a,b) are aware of the leapfrog effect. Using a slightly more complex model of rows of amoebae signaling simultaneously to the next row, they estimate that the pulse will activate the second row away at densities as little as twice the minimum density necessary for signaling. They also estimate that at higher densities there will be multiple row effects. Indeed, Alcantara and Monk (1974) have shown experimentally that in dense populations, "the range of the relayed signal encompasses 4 to 6 cells."

The leapfrog effect obviously matters, and even more important is the multiple-pulse effect, since it is a question not only of the magnitude of the received impulse but also of its direction. What happens when pulses from two different directions hit a cell within a short period? We do not know, either theoretically or empirically.

Some particularly thorny obstacles lie the way of a successful model of wave propagation from the level of the individual cell. If N individual cells are spread across a plane in a discrete model of the aggregation field, the formation of waves with the right properties will be extremely dependent on the position of the cells and diffusion times. There is a sense in which even very good data cannot help us, because the sensitivity of the model calculations will typically be greater than standard experimental error. The calculations necessary to derive the wave phenomena are therefore of such delicacy and complexity that there is little reason to have any faith in them. We must go beyond such local/mechanical theories, at the very least, to a statistical mechanics of ensembles.

Autonomy: The Emergence of "Centers"

Another aspect of global behavior is the small number of aggregation territories. The standard model accounts for this by postulating that only a small number of cells achieve autonomy. These become the center of aggregation. All the other cells have only the capacity to relay and the chemotactic ability to move in response to cAMP. The autonomous center cells give the order to aggregate by pulsing cAMP, and the masses of undistinguished cells obey by moving and relaying the order to others more distant. This is the essence of the best known models of aggregation (Shaffer, 1962, 1964; Cohen and Robertson, 1971a,b; Robertson and Cohen, 1974).

Why do only a small number of cells achieve autonomy, whereas all cells achieve relay-competence? In other words:

- What causes the differentiation into master cells (centers) and slave cells (relays)?
- Why do these two types of cells exist in the proportion that they do?

Perhaps autonomy requires extreme values of some cellular parameters—a property possessed only by a few cells. This conjecture explains the differentiation in the field by appealing to a prior differentiation of the individuals. But any conjecture that locates the field difference in a postulated underlying difference among the individual cells faces a series of objections. First, the emergence of autonomous cells depends both on the density of cells and on their absolute number. Raman *et al.* (1976) report that larger population size at a given density results in relatively *fewer* cells achieving autonomy. For example, at a density of 6×10^5 cells/cm^2, the percentage achieving autonomy was inversely proportional to the population size! On the other hand, for the same densities, the time from first signaling to early aggregation *decreased* with increasing size. So a larger population implies fewer cells achieving autonomy but faster aggregation. This result is obviously inconsistent with a model in which a number of predestined centers emerge and control the others through direct relay. Second, when the center is removed from an aggregation field, reaggregation occurs (Cohen and Robertson, 1971b). Moreover, suspension cultures of nonautonomous but relay-capable cells

agglomerate when gently agitated and then develop into potentially active centers (Gerisch, 1968). A very significant observation is that of Gerisch and Hess (1974), who reported that applications of a few pulses of cAMP to suspension cultures of preaggregation, relay-competent-but-not-oscillating cells produced "precocious onset of oscillations."

It is obvious that these phenomena cannot be reconciled with the idea of an intrinsic difference as the explanation for the emergence of autonomy. The proponents of the individual cell models sometimes acknowledge this but do not account for it. Thus, Raman *et al.* (1976) acknowledge that the emergence of autonomy is "a cooperative phenomenon" but do not explain how this might come about. Cohen (1977) admits that "there seems to be some control mechanism on the emergence of autonomy operating at the population level" but can only appeal to "an as yet unspecified anabolic pathway." If we are to understand the relationships responsible for the emergence of autonomy, we clearly must consider models of the overall field.

The Aggregation Field

Let us consider the differences between a relay-capable device and an autonomous oscillator. Relay-capable devices are triggered responders. Given a small but finite perturbation above a certain threshold, they produce a quick burst of output and then slowly return to equilibrium. Relay behavior can be produced by a cusp catastrophe[6] in the dynamics governing the equilibrium level of the cell, with a stable equilibrium (point attractor) on the upper sheet (Figure 1). Pushing the state sufficiently off the equilibrium causes the jump response (here represented by the state falling off the upper sheet), and then the slow dynamic carries the system back to equilibrium—the relaxation phase.

There are two possible models for explaining the onset of oscillation in a population of coupled relays. The first model assumes that the individual cells, or some of them, as a result of internal processes develop a Hopf bifurcation (point attractor → closed cycle) in their internal dynamics, so that their equilibrium state becomes oscillatory. (See Abraham and Shaw, this volume, for an account of the Hopf bifurcation.) If the amplitude of the oscillator is sufficient to kick the state over the edge, regular spontaneous oscillation will result. Evidence suggests that the oscillating internal variable is adenylate cyclase concentration (Gerisch, 1978). The second model assumes that we are dealing with relay-capable devices coupled so that the state of each can be perturbed by the outputs of others. Then, under the right circumstances, a single random pulse can set up a self-sustaining oscillation in the population. These are inequivalent representations and imply different mechanisms, but it may be very difficult in a given case to tell which one is operating.

[6]Readers unfamiliar with elementary catastrophe theory should consult Thom (1972) and Poston and Stewart (1978), as well as Abraham and Shaw (Chapter 29, this volume).

We now have three possibilities for modeling the aggregation field: (1) as a field of relay devices, (2) as a field of relays driven by a number of autonomous oscillators, or (3) as a field of autonomous oscillators.

Oscillation in the overall field, or even oscillation in individual cells in the field, does not necessarily imply that the individual cells are autonomous oscillators. In fact, fields of relay devices, (1), above, are capable of overall oscillatory behavior of a kind that could be thought to imply case (2) or (3). Small fluctuations in fields of relay devices can set them into an oscillation that mimics the behavior of fields of oscillators. Winfree (1980) has provided an extensive discussion of the relationship between these two different models and offers some criteria for distinguishing between them, but his criteria do not clearly indicate one or the other in the particular case of *Dd* aggregation. Nevertheless, certain clues can be gleaned from the collective behavior of the aggregation field.

It seems likely that the early aggregation field is of type (1) above—a field of relays. In early aggregation, single pulses often propagate through the field (Gerisch, 1968). Kopell and Howard (1974) studied pattern formation in a model chemical reaction and reported that "the excitable (nonoscillatory chemical) reagent is known to produce both periodic wave trains and single pulses, whereas the oscillatory reagent produces only periodic wave trains." Furthermore, the early aggregation field can produce *spiral* waves (Gerisch, 1968; Durston, 1973, 1974a,b). Kopell and Howard (1974), in their study of chemical reaction–diffusion processes, remark that "spirals, as opposed to concentric rings, seem to be easier to achieve in the excitable reagent than in the oscillatory one." But if the early aggregation field is a field of relays, it does not long remain that way. The evidence is strong that the impact of external pulses quickly converts a relay into an autonomous oscillator. For example, Gerisch and Hess (1974) studied the

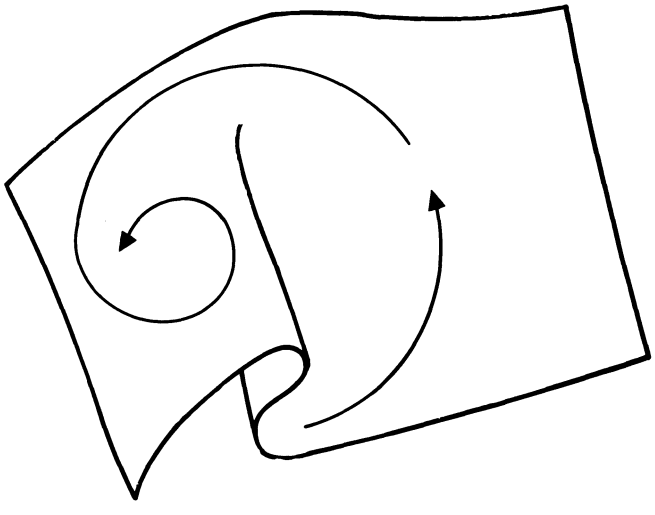


FIGURE 1. Cusp catastrophe representation of relay behavior.

results of applying pulses of cAMP to suspensions of cells at various states of development. They found that application of just two pulses of cAMP to cells at an early stage of development produced "precocious onset of oscillations." Even though none of the cells should have been capable of autonomous oscillation, soon all began oscillating. It seems as if the presence of an oscillator quickly turns the cells around it into oscillators, too. So it seems reasonable to conjecture that the evolution of the aggregation field consists of development from a field of excitable relay elements to a field of oscillators.

It can be objected that the results of Gerisch and Hess imply only that the *field* has become an oscillator, not that the individual cells have done so. Oscillating fields may be composed of nonoscillating relays. But features peculiar to the slime mold *do* indicate that the individual cells become oscillators. The 15-sec delay in the relay response of the individual cell implies that a field of such relays could never achieve global synchrony, because there would always be that 15-sec phase lag between stimulus and response, between signal and relay. A pair of *autonomous oscillators can become entrained or synchronized*—but *not* a pair consisting of *an oscillator and a delayed relayer.* Thus, the most important piece of evidence that we are dealing with a field of autonomous oscillators is the phenomenon of *coherence* (or *entrainment*), in which two or more oscillators bring each other into the same phase, or into an orderly succession of phases, as in the case of traveling waves.

It seems clear that some kind of entrainment does occur in the slime mold aggregation field. Among other things, it is necessary to produce the 100-fold increase in cAMP production that is observed during aggregation, whereas there is only a local 20-fold increase due to the activity of any individual cell. If there were no entrainment, there would be no constructive addition of pulses in the field. In addition, there is direct evidence that phase entrainment takes place among signaling cells. Gerisch and Hess (1974) and Malchow *et al.* (1978) have shown that stimulation of an oscillator by an external pulse tends to advance or retard the phase of the oscillator in just such a way as to produce entrainment: pulses arriving in advance of a scheduled pulse tend to elicit a "premature" pulse from the recipient and to shift the phase of the recipient oscillator forward from that point on. Conversely, pulses received after a regular pulse has been emitted tend to retard the phase of the recipient oscillator.

These considerations suggest that some kind of entrainment is taking place in the developing aggregation field, but they do not tell us what kind or what its role is. Further clues can be gained from a study of the morphologies of aggregation, in keeping with the general approach of inferring dynamics from the shapes and forms of the overall process.

Macromorphologies

Surprisingly little attention has been paid to the macromorphologies found in aggregation fields. Two exceptions are Durston (1973, 1974a,b) and Winfree

(1980). Macromorphologies are important for understanding the mechanisms of aggregation, and significant inferences can be made from their forms. Here is a taxonomy of forms as observed:

- *Target patterns*: concentric rings of aggregation radiating outward from the center.
- *Blobs*: clumps of aggregated cells.
- *Point spirals*: spiral waves of aggregation, emanating from apparently undistinguished points.
- *Whirlpools*: rings of cells (doughnuts) surrounded by spiral spokes of cells, curling into them. These are spiral waves of aggregation surrounding an *empty* core—one with no cells at all! Durston (1974a) describes their development: "The aggregating cells progressively collect into spirally oriented streams and aggregate into a 'doughnut' surrounding the central space. The space diminishes." After a few hours, the doughnut of cells implodes, and the cells form a mound-shaped aggregate "sited at the location of the original open space." The overall morphology is quite striking (Durston, 1973; Figure 2).
- *Spoke patterns*: blobs with radial spokes.
- *Strings*: linear aggregates of cells. These become the spokes of whirlpools and spoke patterns but they are also found free-floating.

There are a number of systematic relationships among these forms at all stages. In the early aggregation field, there are two morphologies: target patterns and point spirals. Both are found in the typical field: target patterns predominate over spirals by about 5:1. Both are stable, although in the late aggregation field, the spirals change to concentric propagation (Durston, 1974a). Both Durston and Winfree suggest that the target patterns are associated with autonomous pacemakers[7] at their center, but spiral waves lack such an autonomous pacemaker. One observation supports this view: in a mutant strain (91A), which makes few pacemakers, spiral waves predominate over target patterns (Durston, 1974b). This observation by itself is not decisive, but both Winfree and Durston seem to feel that there are theoretical reasons for asserting that autonomous pacemakers give target patterns, while spirals arise when there is no autonomous pacemaker. It is not clear what these theoretical reasons are. Why should this be true? The only relevant arguments I can find in Durston and Winfree do not seem to be valid. Durston (1974a) says: "A point source pacemaker region (for example, an autonomously firing cell) which propagates waves through a uniform isotropic medium should propagate wavefronts which are concentric rings." This is apparently an argument from symmetry. But this argument, which is valid for a point source in a *perfectly* uniform, *perfectly* isotropic medium, may fail in a *slightly* nonuniform or nonisotropic medium, which, of course, is what any actual medium is. One must be careful about this, or else we could imagine arguing that whirlpools cannot form in cylindrical tubs of water with a hole at the center of

[7] *Pacemaker* is the generic term for an entraining oscillator.

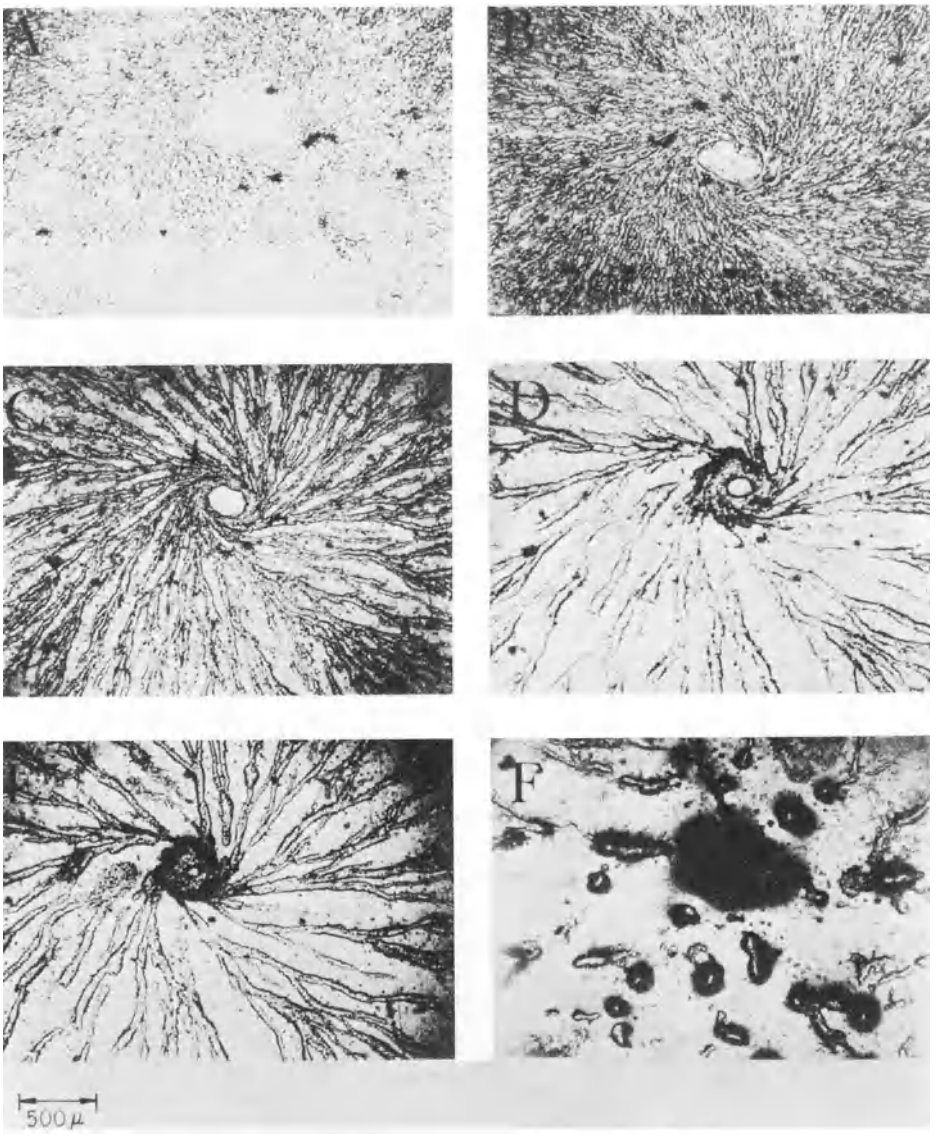


FIGURE 2. Development of an open-centered spiral aggregation center. The figure shows single frames from a low-magnification time-lapse film (× 2.5 to the film frame) of development of the center. Individual cells can only just be seen; the figure shows some details of the coordinated cell movements. (A) Early in development of the center, a cell-free space in an otherwise homogeneous lawn of *Dd* cells on an agar surface has become the focus for a spiral aggregation wave. The wave itself is not visible in the figure, but it induces a visible spiral orientation of the surrounding cells. The space will become the center of an aggregate. (B-E) After 23, 60, 79, and 86 min, respectively, the aggregating cells progressively collect into spirally oriented streams and aggregate into a "doughnut" surrounding the central space. The space diminishes. (F) After 150 min, most of the aggregating cells have entered a hemispherical mound sited at the location of the original open space. (From Durston, 1974a, with permission.)

the bottom. Small perturbations break the symmetry of the initial configuration and produce spiral forms in that case and could here, too.

Winfree (1980, p. 66) says, "It would seem that each wave must first appear somewhere, and that point is its source. But what is manifestly true of concentric ring waves is not necessarily true of rotating spiral waves." This is confusing. Of course, a set of concentric rings has a *geometric* center. But is the geometric center the *cause* of the propagation? Not necessarily. For example, in the case of chemical reaction–diffusion equations with local oscillators, Kopell and Howard (1973) challenge the analogous claim, widely made, that target patterns must have some special cause at their center. Their "working hypothesis" is "that the target patterns exist as a consequence of the interaction of chemical kinetics and diffusion, i.e., that no other physical mechanism plays a significant role. (Most other investigators appear to believe that there is a catalyst in the center of each pattern which affects the frequency of the oscillation . . . . We tentatively believe that the target patterns may form without the intervention of catalysts. . . .)" They do not claim to have proven this, because their derivation of target patterns from overall properties of the field is valid for the whole space except for the point at the center; their space has a hole in it.

Keener (1980) studied reaction–diffusion equations assuming excitable elements, not oscillatory ones, and found solutions by singular perturbation techniques applied to the small parameter ϵ—the ratio of the growth rates of the two state variables in the medium. He found that these methods do not yield any self-sustaining solutions unless the medium has holes (i.e., is not simply connected). In a medium with holes, he shows how self-sustaining spiral waves can arise and then combine to give target patterns. Once again, however, the question of pattern formation in a medium without holes is left open.

What is needed is a study of pattern formation in the slime mold along the lines of the work of Kopell and Howard on chemical reaction patterns. The key questions are:

1. Is the conjecture correct that target patterns have "centers" (autonomous pacemakers) whereas spirals do not?

2. How are spirals generated? [Durston (1973, 1974a,b) suggests that they are created by signals circulating around closed loops of cells, but there is a problem in that all the spirals acquire the same period and form early in aggregation, before the cell-to-cell contacts necessary for closed loops are established.]

3. What are "centers"? Are they special cells distinguished by some preexisting developmental difference? Are they merely fluctuationally different from their neighbors? Or do they have "centerness" thrust upon them by the developing field? Do pacemakers make aggregation fields, or do aggregation fields make pacemakers?

In any event, it seems as if the early aggregation field is a field composed largely of relay elements, with the outward gradients of phase (radial or spiral) characteristic of such elements. In the late aggregation field, actual aggregates of cells form. This involves direct cell-to-cell contact. These forms include blobs, doughnuts, strings, and whirlpools. It is in the late field that we see the evidence of widespread autonomy and entrainment of autonomous oscillators. Gerisch

(1968) took suspension cultures of late, contact-capable cells and transferred them to a plate. They did not form the spiral wave or target pattern configurations characteristic of the early field but, rather, formed into *strings*. This result supports the idea that signal relaying is the key to the radial patterns of the early field and that the late field does not depend on such relays. Instead, these cells, being themselves oscillators, quickly entrained each other and achieved contact. The strings in Gerisch's experiment rapidly proceeded to aggregate by forming a whirlpool with a doughnut at the center. The speed of aggregation is explained by the prevalence of autonomy (and hence the capacity for entrainment). The form of the aggregation into a whirlpool is explained by the absence of strong pacemaker aggregates (blobs). In the absence of a center, the aggregation field creates one: "In this process, aggregation centers usually form through a curling motion of streams."

Interestingly, the one case I have seen of radial (not curled) spokes arose when there was a powerful blob. An experiment of Robertson *et al.* (1972) consisted of placing a microelectrode in a plate of amoebae that pulsed cAMP at a rate simulating a blob. As soon as contact capability was achieved (about 8 hr), the amoebae formed well-defined strings that pointed directly at the center (no curling). Consequently, we can infer that blobs at the center are antagonistic to spiral formation. (This is a feature shared by whirlpools in water and by tornadoes, which also have "empty centers.") On the other hand, where there is high potential for entrainment, but aggregations (blobs) are prevented from forming, the system undergoes oscillation as a whole. This claim is demonstrated by an experiment of Gerisch and Hess (1974) on dense cultures in suspension: a few pulses set the suspension into coherent (simultaneous) global oscillation.

Entrainment helps to explain these morphologies. Were it not for entrainment, there would be a time lag between every pulse and its relay. This fact implies that there would be a constant gradient of phase radiating outward from any signal source. Therefore, the existence of actual aggregates along radial components implies that entrainment must be taking place.

Nanjundiah (1973) developed a mathematical model in the spirit of the Keller–Segel analysis in order to study the phenomenon of streaming. Streaming is the formation of strings of aggregating cells pointing to the center. This breaking of radial symmetry is explained in the Turing manner as an instability to azimuthal fluctuations. Most interestingly, he demonstrates that such streaming depends essentially on "cooperative signaling": "Whenever signalling is *not* restricted to one or a few of the cells, the radially symmetric mode of aggregation is itself unstable against azimuthal fluctuations, and the periphery of an aggregate breaks up to form *streams*." Although the model used is one in which the cells signal steadily, rather than by oscillation, it seems as if this phenomenon also supports the idea that there is widespread autonomy and cooperativity in the late aggregation field.

The common thread uniting these observations is that regions of aggregation are regions of high entrainment of signal, and, conversely, aggregation takes place wherever such regions of high entrainment form. This view helps to explain the patterns observed: the regions of entrainment become the *attractors* of the aggre-

gation dynamic. Therefore, aggregation morphologies can be classified by the nature of the attractors involved. In particular, the spiral patterns and spoke patterns can be identified as marking out *isochrons* (in Winfree's terminology), i.e., regions in which phase is constant. When we look at an aggregation pattern, we are seeing a physical realization of entrainment: the foliation of the basin of attraction into lines of equal phase.

Entrainment

If what I have been saying is correct, then the notion of entrainment is crucial for understanding slime mold aggregation. Entrainment is essential for dynamics of many oscillatory processes, from the circadian rhythms of insects to ovulatory cycles in humans. The problem of modeling entrainment is far from solved and requires much more attention. In particular, the word *entrainment* is used in too many senses. In its most abstract sense it is used to refer to any situation in which small interactions among the individuals of a system have the effect of confining the total state of the system to some limited region of the global state space. In this most general sense, it is simply motion that is not ergodic—that does not wander all over the state space.

Even if we restrict our attention to populations of coupled oscillators, there are still many senses of the word. Most often *entrainment* means *frequency* entrainment, i.e., two or more oscillators interacting in such a way as to equalize their frequencies or bring them to a whole number ratio. Frequency entrainment therefore includes the notion of musical harmony. The idea that harmony consists of a whole number ratio, a rational relationship of frequencies, was known to the Pythagoreans. Abraham and Shaw (Chapter 29, this volume) present a model of frequency entrainment among simple harmonic oscillators.

Although frequency entrainment does occur in slime mold aggregation (and might explain the steady increase in the frequency of oscillation), the notion we have been using is that of *phase* entrainment. Sometimes, this is called "phase-locking" or "synchronization," although both these terms are also used, confusingly, to refer to frequency entrainment. True phase entrainment has not been discussed in any generality, although there are a number of examples of it in various sciences.[8] Winfree (1980) discusses these:

- Populations of crickets entrain each other to chirp coherently
- Populations of fireflies come to coherence in flashing
- Yeast cells display coherence in glycolytic oscillation
- Populations of insects show coherence in their cycles of eclosion (emergence from the pupal to adult form)

[8]See Dewan (1972) for a discussion of types of phase-locking or entrainment for the special case of van der Pol oscillators. A simplified model of phase-locking in biological oscillators can be found in Glass and Mackey (1979) for entrainment by a sinusoidal stimulus.

In addition, we can add:

- Populations of women living together may show phase-entrainment of their ovulation cycles
- Populations of secretory cells, such as in the pituitary, pancreas, and other organs, release their hormones in coherent pulses.

In a laser, there are many atomic oscillators, each emitting light. The transition from ordinary light output to laser light is caused by phase entrainment of the oscillators, so that they pulse light coherently (Haken, 1978).

For slime mold aggregation, a number of simplifying assumptions can be made. First, we are dealing with *pulse* oscillators (so-called "relaxation oscillators"), which are all of roughly the same period and communicate by diffusion. We can therefore give a general form to the problem of slime mold aggregation: we have a large population of pulse oscillators $0_1, \ldots, 0_N$, initially at locations $x_1, \ldots, x_N$ and emitting pulses at phases $w_1, \ldots, w_N$. The pulses then diffuse through the medium by Fick's law, with an added decay term due to the enzyme action of acrasinase. The effect on each phase w_i is then given by the sum of the diffused pulses from the other 0_j, which is then inserted for each 0_i into the known phase response relation. At the same time, the spatial locations of the oscillators are changing due to chemotaxis, so we must add an equation describing the dynamics of the chemotactic movement of each oscillator in response to the sum total of pulses received from neighboring oscillators. In addition, a condition must be added to represent the refractory periods during which the oscillators, after emitting a pulse, are immune to chemotaxis and to being signaled.

These features would comprise the most complete model of slime mold aggregation. The model would be, mathematically, completely intractable, and absolutely nothing can be said about it. The complexity involved is at least that of the general problem of the entrainment of N oscillators, on top of the problem of pattern formation in reaction–diffusion systems added to the N-body motion problem. Any *one* of these problems is insuperable in general form; simultaneously they render the analytic situation hopeless. Our hope thus consists of making numerous simplifying assumptions to bring the problem at least within range of known or imaginable mathematical techniques. Several obstacles stand in the way of a useful representation for this problem. One simplification that is common in oscillator models is to study only the limit behavior as it approaches infinity ("final motions") and to ignore transients. But in this case, it is the transients that we care about, because we are interested in representing the process by which small pockets of entrainment appear and grow. For the same reason, we are prohibited from making another of the standard assumptions used to simplify entrainment problems: throwing out precise spatial information and assuming that our oscillators are coupled by a generic, small, nonlinear perturbation. It is exactly the spatial development of entrainment that we want to study.

But the most serious problem is one that besets any discrete model, i.e., any model in which the aggregation field is represented as a set of N oscillators located at points spread over a plane. Whether or not entrainment takes place in such a

population is extremely dependent on the exact locations, phases, diffusivities, and the like. If we attempt to follow the precise pattern of phase interaction, we can see that the trajectories in question are extremely unstable: if one phase or one location is changed by a small amount, the resulting pattern becomes destabilized. Consequently, we face a problem similar to the one encountered in deriving the phenomenon of wave propagation: the model that reduces the collective phenomenon to the interaction of N discrete individuals has the defect that the (global) overall effect becomes unstable with respect to initial conditions. Moreover, the sensitivity of the overall effect is greater than the degree of error built into the individualistic model by its simplifying assumptions. Consequently, the individualistic model of the collective process becomes useless.[9]

The only hope for a useful model of the phase-entrainment process therefore lies in rising above the level of the individual cells and finding some global model in which the local information is thrown out in favor of some order parameters that describe the average conditions obtaining in spatial neighborhoods. In this respect the situation resembles coherence in the laser or magnetization, in which there is the coherence of orientation of many magnetic dipoles interacting. In cases like these, the strategy that has proved effective is to find global parameters describing the overall state of the system, e.g., the local mean field. These *order parameters*, as Haken (1978) calls them, reflect the degree to which coherence has been achieved in some region. The analogous move in this case would be to consider as our order parameter something like the *distribution of phase* over the aggregation plane. The concentric rings and spirals of the aggregation field correspond to isophase lines (Winfree's "isochrons"). (Alternatively, we could look at the parameter *local degree of coherence of phase.*) It might then be possible to write dynamical equations representing the various influences on local phase coherence, in a manner similar to the laser equations (see, e.g., Haken, 1978).

Some Philosophical Principles

Several methodological or philosophical precepts emerging from this discussion seem to be typical of self-organization phenomena. The first is *antireductionism.* We have seen that modeling aggregation requires us to transcend the level of the individual cells to describe the system by holistic parameters. But in classical reductionism, the behavior of holistic entities must ultimately be explained by reference to the nature of their constituents, because those entities "are just" collections of the lower-level objects with their interactions. Although it may be true in some sense that systems "are just" collections of their elements, it does not follow that we can *explain* the system's behavior by reference to its parts, together with a theory of their connections. In particular, in dealing with systems of large numbers of similar components, we must make recourse to holistic concepts that refer to the behavior of the system as a whole. We have seen

[9]This argument is made in a more general context by Garfinkel (1981).

here, for example, concepts such as entrainment, global attractors, waves of aggregation, and so on. Although these system properties must ultimately be definable in terms of the states of individuals, this fact does not make them "fictions"; they are causally efficacious (hence, *real*) and have definite causal relationships with other system variables and even to the states of the individuals.

Self-organization is therefore inherently antireductionist in that global system parameters are essential for its explanation. The general model of self-organization proceeds by analysis of the qualitative dynamical properties of the overall system variables: the forms of organization are characterized as attractors of the global dynamic, and structural changes from one form of collective organization to another are characterized by bifurcations of the governing equations, as one global attractor gives way to another.

In particular, we have found that we are forced to adopt a field-theoretic, rather than a particle-theoretic, model of the self-organization process. As soon as we begin talking in terms of *waves* and their various properties, we are necessarily talking about a continuous medium and have transcended the level of the individual cell. To return to the subject with which we began, the relationship between the global (Keller–Segel) model and the individual cell model, we see that the essential approach of the global model has been vindicated: there is a need to consider aggregation as a phenomenon occurring in a continuous medium—not one occurring among a discrete set of individual cells. The first version of the Keller–Segel model may have been oversimplified, but some more sophisticated version of it, capable of modeling various kinds of wave propagation, would seem to be necessary for a satisfactory explanation of the patterns of slime mold aggregation.

There may be objections that amoebae are, obviously, discrete entities and that continuum-flavored analyses are mere metaphors, which can in principle be discarded in favor of an underlying model of discrete cells communicating by pulses, in the manner of the Cohen–Robertson (1971a,b) articles. I do not believe that this is right. The methods of analysis now employed depend essentially on the continuum assumption, since they use differential and topological arguments that only make sense in continua. If we increase the magnification so that the continuum disappears, so does the explanation for the phenomena of aggregation. As Winfree observes (1980, p. 270): "In media composed of discrete cells communicating by pulses, the arguments of continuum mechanics and topology have no clear application."

In a certain sense, this commitment to the reality of the continuum is paradoxical. The mathematics used to generate our explanation absolutely requires that the key functions are smooth or continuous in *arbitrarily* small neighborhoods. And yet we know this is false: at sufficiently small distances, the continuum breaks up. The general procedure for resolving such paradoxes is something like this: there is a gauge δ such that for $\delta < \delta_0$ the equations "break down" (lose their validity). In that scale we have to interpolate a finer-grained theory which is valid in the "boundary layer" $\delta < \delta_0$ and reduces to the old theory for $\delta > \delta_0$.

The second major principle operating in the self-organization paradigm is the notion of *symmetry-breaking*. This principle is also a form of anti-reductionism,

because the explanation of global structure proceeds without appealing to underlying differences among the individuals. For example, consider the onset of ferromagnetism in a solid. For temperatures above the critical temperature, there is a uniform distribution of orientations. But as the temperature drops below the critical point, the uniform distribution bifurcates into a sharply bimodal distribution, corresponding to the two possible orientations of the elementary dipoles. How a molecule happens to assume one orientation rather than the other (opposite) orientation is unexplained. Again, if we consider a fluid heated from below, for temperature differences above a critical point, the uniform fluid changes into one with a regular pattern of convection cells, so that some molecules are at the center of convection cells. But there is no intrinsic difference between those molecules and others. The relevant self-organization model here takes the form of equations governing heat transport in the fluid. It shows that for values of the temperature gradient R (called the Rayleigh number) less than the critical R_c, the equations have a solution in which the fluid is at rest, while for R greater than R_c, heat transport overcomes viscous influences, and the steady-state solution bifurcates into a solution with regularly spaced cells of convection currents.

These principles become especially important and take on added significance when the structures in question are social structures, and the individuals are individual people.

Explaining Social Structure: The Emergence of Cooperation

We now turn to social explanation in order to assess the prospects of the self-organization paradigm. First, a word of caution about the dangers of analogy: the history of biological analogy in social theory is not a happy one. From Plato's organic model of the state to the periodic outbreaks of social Darwinism (most recently in discussions of alleged genetic bases for class stratification), biological theories of society have ranged from crackpot to worse. I do not wish to join this tradition of biological reductionism. Rather, I want to suggest that the general lessons and principles of self-organization in the biological sphere are applicable as well in social systems. Therefore, I am investigating a loose analogy, not a reductive explanation.

Even so, this investigation has some interest, for in each historical epoch there has been a rough correspondence between the concepts of biology and physical science, on the one hand, and social theory, on the other. Consider the theory of evolution. The traditional account depicts evolution as gradualist (a continuous gradation of small changes) and individualistic (evolution selects the fittest individuals to survive). With the development of thermodynamics in the late 19th century, the metaphor of entropy percolated quickly into both biology and social thinking as an all-purpose explanation for biological and social degeneracy (see Brush, 1978). Contemporary evolutionary theory has changed radically (see Gould, Chapter 6, this volume). In particular, recent discussions of evolution have stressed its holistic, rather than individualistic, nature, and treat it as a saltatory, rather than gradualist, process.

A similar claim can be made about the other areas of theoretical biology. The self-organization paradigm, with its concepts of antireductive holism, symmetry-breaking, bifurcation, and the like, offers a number of suggestive models for explaining the evolution of social structure. What follows is a somewhat haphazard survey of some topics of current interest in social theory, presented with a view toward exploring the possibilities of analogy.

The fundamental problem of social theorists is to explain the emergence of social structures. As Hobbes saw it, this meant explaining how cooperation occurs, given the fact that it is in each person's individual interest to betray the social contract while everyone else obeys it. For Hobbes, the only solution was the establishment of a *sovereign* to enforce the contract on each individual, but more recent attempts have tried to explain the emergence of a social contract without the authoritarian presence of a sovereign.

In its modern formulation, the problem of explaining how cooperation occurs is expressed as the *Prisoners' Dilemma*[10]: the maximum gain for each individual is to betray the social contract, yet if we all do that, we all lose. How can cooperative behavior possibly arise? The game-theoretic answer to this problem is to define some version of the Prisoner's Dilemma and to study its *Nash equilibria*, i.e., points at which players cannot improve their payoff by making changes just in their own strategies. The question then becomes: is cooperation a Nash equilibrium? If not, is there some weaker form of cooperation that is? How stable is it? What initial states will be drawn to it? Is it subject to bifurcation?

Massive literature on the subject formulates various interpretations and versions of the game and finds various equilibria. Smale (1980) gives a precise formulation of a two-person Prisoner's Dilemma with discrete time and describes a family of Nash solutions that converge over time to cooperation, and that possess global stability (all initial conditions flow to it). The solutions are, roughly, to cooperate as long as our cooperation has not been exploited by the other. Smale exhibits a subfamily of such solutions, S_μ, depending on a parameter μ, so that for $\mu > 0$, S_μ is one of these cooperative Nash solutions, but for $\mu < 0$, the solution bifurcates to noncooperative behavior. This description gives us a simple example of an important phenomenon: a single game, a single set of rules, may have one kind of behavior (competition) for one range of conditions and another (cooperation) for other conditions. That result explains how both responses are possible (without attributing either to "human nature") and how one can change or bifurcate into the other.

It would be useful to have a generalization to continuous choices: suppose each player chooses an amount of money to bet, a time of day to arrive, or a direction to follow (note that the last two are continuous, angular variables). Smale says that his framework can accommodate these conditions, but he does not carry out the proof.

[10]So called because in its standard formulation it concerns two prisoners each separately offered the following deal: Confess and testify against the other, and you will go free and the other will get the maximum sentence. If both confess, they both get fairly stiff sentences; if neither does, they both get a light sentence.

More importantly, it is absolutely necessary to have a generalization of this analysis to an N-person game. N-person games are as different from two-person games as the N-body problem is different from the two-body problem. In particular, coalitions arise in which some people unite to "exploit" others. These coalitions do not have to stem from agreements or even to be known to their members; tacit coalitions can form in a stable way.

A preliminary sketch of some aspects of an N-person Prisoner's Dilemma, from an informal point of view, can be found in Schelling (1978). Applications to some problems in social theory of another version of an N-person Prisoner's Dilemma can be found in Taylor (1976). Neither treatment uses dynamical methods, or establishes stability, bifurcation, and size of attracting basin. As a consequence, it is difficult to extract from their analyses any qualitatively useful conclusions or to tell which effects are stable under which perturbations of the model assumptions.

The key to modeling cooperation is that cooperative solutions in games are *entrainments*, i.e., mutually coherent behaviors. In a model of cooperation as entrainment, global attractors model overall equilibria. Because social conventions (like the working day, driving on the right, feudalism, or speaking English) are essentially coordination equilibria (see Lewis, 1974), the topology of the various attractors in a given system provides the kinematic foundation for theories of social change. We might say, with apologies to Marx, that all history is the history of phase transitions of coordination equilibria.

The global attractor model of the emergence of cooperation displays the characteristic features of the self-organization paradigm. First of all, it is antireductionistic in character. It establishes that the total state of the system will move to a certain attractor despite the absence of individual intentions to achieve that attractor. The global dynamics of the process, especially the existence of a constructive, nonlinear payoff to regions of entrainment, explains the development toward the attractor. This model does not attempt to explain the development of those regions of entrainment by assuming special intentions of "organizers." This removal from intentions enables us to apply game theoretic models to areas in which there are no real intentions or strategies in the conscious sense. Game theory can be introduced into biological evolutionary theory, following Lewontin (1961). We imagine a species playing a game with the environment: one or another genetic strategy is "chosen" (e.g., adaptability to wet environments) and then nature makes its move (lots of rain, or very little rain, and so on). The "payoff" to the species is the reproduction rate achieved. Lewontin (1970) argues that the units of selection in such games are not genes, but whole chromosomes.

Generalizing to the case of several species, we can imagine them playing such a game with each other. This abstraction leads to the notion of an *evolutionarily stable strategy*. The payoffs are again reproductive rates, and an evolutionarily stable strategy is one that evolves toward some stable configuration. Evolutionary stable strategies are Nash equilibria. Taylor and Jonker (1978) present rigorous definitions and prove basic theorems. Auslander *et al.* (1978) examine evolutionarily stable strategies for predator-prey populations and find various situations in which there is no stable strategy. In one case, the prey population displayed cha-

otic behavior, which they suggest may be an adaptive evolutionary strategy, preventing the coevolving predator population from "tracking" it. Chaotic behavior cannot entrain.[11] The concept of an evolutionarily stable strategy, such as a Nash equilibrium in the evolutionary game, allows us to examine the patterns of coevolution of various kinds of species or even of kinds of traits.

One problem that has attracted attention is explaining the evolution of *altruism.* How is it that altruistic tendencies can evolve, if they do not also confer advantage on the individual? For example, in many species of prey (birds, gazelles), the first individual to see an approaching predator will go into a ritualized warning behavior that is very useful to the flock as a whole but that has negative survival value to the individual. Any explanation of this fact will have to go beyond the Darwinian conception of evolution as selecting the fittest *individuals.* The evolution of altruism can be represented as a game in which genetic tendencies play the Prisoner's Dilemma on an evolutionary scale. We imagine a set of genes for cooperation competing with a set for selfish behavior. Can cooperation arise as an evolutionarily stable strategy? The answer seems to be that it can, although controversy still exists and no definitive model has yet emerged (Hamilton, 1964; Trivers, 1971; Axelrod and Hamilton, 1981).

A similar approach has been successful in explaining early stages of molecular evolution. The origin of life in the self-organization of nucleic acids was presumably an evolutionarily stable "strategy" on the part of prebiotic chemicals (Eigen and Schuster, 1977; Schuster *et al.*, 1978; Schuster and Sigmund, Chapter 5, this volume).

Social Structure: Emergence in Economics

In the prototypical market described by Adam Smith, a large number of traders, each having a negligible effect on the market, interact independently to produce a market and a price system. Can we describe the evolution of coalitions, such as cartels and trade unions, in the economic market? There are several discussions of the formation of unions (in the general sense), but they apply only to games in which there are agreements among the players enforced by the analog of Hobbes' sovereign. This is a drawback, since in typical cases there are no agreements to cooperate at all, or there are agreements, but no enforcer. In the case of holders of capital, however, entrained coalitions can form in the absence of any intentions to conspire. Such tacit coalitions can be modeled as stable attractors of the global dynamics, furnishing a basis for a theory of oligopoly. In the case of

[11]For an introduction to chaos, see Abraham and Shaw (Chapter 29, this volume). Chaotic attractors have been found in population dynamics (May, 1976), in a model for the weather (Lorenz, 1963), and have been proposed as models of turbulence in fluids (Ruelle and Takens, 1971). There have as yet been few applications to social theory, despite the fact that the first known instance of chaotic behavior was in a model of the price system, due to Cournot, in 1843—but see Benhabib and Day (1981) for a model in which the effects of actions on preferences, and vice versa, produce chaotic behavior.

trade unions, there is typically an agreement to cooperate, but since the agreement is not enforceable, the situation is really more similar to the self-organizing coalition than it is to the Hobbesian case. Here the self-organization approach can be used to model the development of small regions of entrainment in various areas or industries as well as their subsequent development.

The problem of stable entrainment is relevant also to the "problem of the second-best." A "second-best" problem arises when a system has an equilibrium solution that is optimal with respect to some desirable quantity, but finite perturbations applied to this optimal configuration may produce results much worse than those of other, "second-best" equilibria (Lipsey and Lancaster, 1956; Allingham and Archibald, 1975). Here the problem is a bifurcation of an equilibrium solution to another qualitatively different attractor.

In the market as described by Adam Smith, the situation of the traders is essentially homogeneous. As is well known, however, the homogeneous market, if it ever existed, surely no longer does. Instead, we represent the actual situation, to a first approximation, as a stratified market in which there are two types of traders, owners of capital (buyers of labor power) and nonowners of capital (sellers of labor power). How can this stratification be explained? One approach, based in classical determinism, asserts that there must be some systematic difference between the individuals who end up as capitalists and those who end up as labor. Social Darwinists assert that such differences exist and explain stratification. In the words of William Graham Sumner, for example, the individual differences are that the capitalists possess greater "industry, prudence, continence, or temperance"; for the neosocial Darwinists, it is "intelligence." Despite the difficulty of locating these traits in actual individuals, it is asserted nevertheless that there *must* be some such difference, for how else could stratification be explained? How can there be differences without a difference?

The alternative approach to explain the evident stratification is to assume that there are no significant individual differences. We explain stratification as the increasing instability of a homogeneous solution under increasing competitive pressure, leading to a symmetry-breaking bifurcation to a more structured global state—in this case a system of two strata in stable interaction (Garfinkel, 1981).[12] Social Darwinism can therefore be seen as denying the existence of symmetry-breaking bifurcation in social systems. But what if everyone possessed the desirable individual traits? If the structural features making the homogeneous situation unstable are still present, stratification would take place anyway. In contrast, the broken-symmetry approach locates the explanation of the stratification in structural properties of the system itself. Consequently, it offers an explanation with some theoretical stability as well as greater predictive power.

The general strategy of self-organization as treated here is to explain pattern formation in a macrosystem as resulting from small nonlinearities in the coupling of the individuals. These nonlinearities are negligible for the homogeneous state, whose behavior therefore resembles a (linear) system of independent individuals.

[12]In the language of dynamics, increasing competitive pressure introduces a cusp catastrophe into the distribution of income, thereby transforming it from a unimodal to a bimodal distribution. (See Garfinkel, 1981.)

But as some parameter, such as an external driving force or a density, passes into a critical region, the homogeneous state becomes unstable and the nonlinearities become significant.[13] In this image, the aggregation of capital into a small number of holdings, and the resulting differentiation that takes place, is explained as the development of an entrainment pattern among holders of capital, which in turn is explained as the result of nonlinear payoffs to collections of cooperating (i.e., entrained) holders of capital.

Orthodox economists have trouble explaining this aggregation because of the linear models to which it is attracted. In part, this is due to the ease of solution of linear models, but the attraction is also ideological: linear models obey *superposition*, guaranteeing the independence of individual solutions. This is the algebraic expression of the laissez-faire principle. As can be expected, pattern formation does not arise in such systems. For example, the orthodox economic approach to the two-sector character of the economic market is embodied in the neoclassical production function

$$O = f(K,L)$$

which expresses, for a given production process, the amount O of output that can be produced by combining K units of capital with L units of labor. In the standard treatments of this subject, a theory of distribution (payoff) is derived, according to which the day's output of O is paid back to the contributors of K and L at a rate that is proportional to their marginal contributions to the production process, $\sigma f/\sigma K$ and $\sigma f/\sigma L$. In the standard treatments, this theory of distribution according to marginal contribution is obtained from an application of Euler's theorem to the production function, yielding the desired payoff relation:

$$O = \frac{\partial f}{\partial L} L + \frac{\partial f}{\partial K} K$$

From this it follows that the payoffs to contributors of L and K are determined by purely technical factors (and therefore *not* by political factors, combinations such as cartels or unions, or other cooperative effects).

The trouble with this derivation lies in the assumption that is necessary to apply Euler's theorem: that the production function is *homogeneous of degree one*, i.e.,

$$f(aK,aL) = af(K,L)$$

This restriction says that multiplying the inputs by some arbitrary factor results in multiplying the output by the same factor. This implies complete linear *scaling*: doubling inputs produces a doubled output, and so on. A model that makes

[13]For convection cells in fluids, it is the driving force of heat transport (Rayleigh number); in fluid flow models of vortex formation, it is the driving velocity (Reynolds number); in the transition from an ideal gas, to a van der Waal gas, it is the density; in population dynamics, it is also density, and so on.

this assumption will be unable to explain pattern formation, because payoffs to combinations are exactly equal to what the individual combinants could earn separately. In contrast, the theme of self-organization is that macroscopic pattern formation is the result of small *nonlinear* coupling terms.

Complete (infinitely extendable) scaling never exists in reality. Sometimes we can invoke scaling in regions where the nonlinearities can be neglected. Economic theory has largely confined its attention to those areas, and whatever success it has had is due to the fact that economic reality displayed, until recently, at least some linear growth patterns. Further progress will necessarily involve coming to terms with economic and social nonlinearities.

Conclusion

A number of philosophical themes have emerged from the self-organization paradigm presented herein. All of them represent heresies from the point of view of traditional philosophical concepts. In my opinion, the correct themes are:

1. *Holism.* To explain self-organization one must study the dynamics of global system variables and attractors.

2. *Catastrophic change.* Although Leibniz claimed for all natural processes that *Natura non facit saltum* (nature does not make jumps), the concepts of catastrophe and bifurcation give a richer scientific content to the notion of emergence and make possible models of physical, biological, and social processes in which periods of continuous change are punctuated by episodes of emergence.

3. *Symmetry-breaking.* This principle requires us to explain stratification structurally, without appeal to underlying differences. It denies classical determinism.

In addition to the above themes, I would add the concepts that seem essential in discussing aggregation in the slime mold, especially the notions of *oscillation* and *entrainment.* In the future, the N-torus may be as familiar a model for biological or social space as Euclidean space is now, with pattern formation among coupled oscillators expressed in terms of various forms of entrainment or coherence. Entrainment seems to be the crucial concept in understanding the evolution of social, as well as biological, aggregation and cooperation. This seems to be the real lesson of the slime mold.

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