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Modeling Biological Pattern Formation in Embryology

The mechanisms that generate pattern and form in embryogenesis are unknown. Realistic modeling tries to incorporate known biological facts into coherent and rational physicochemical model mechanisms that orchestrate the pattern formation process. Such models can be used to provide the developmental biologist with possible scenarios for how biological pattern and form are created and to suggest possible experiments that might help to elucidate the underlying phenomena which take place during embryogenesis.

BACKGROUND

Development of spatial pattern and form is one of the central issues in embryology and is included under the general name of morphogenesis. It is now a field of intense and genuine interdisciplinary research between theoreticians and experimentalists, the common aim of which is the elucidation of the underlying mechanisms involved in embryology.

Little is known about the mechanisms that lead, for example, to the cartilage patterns in developing limbs, the specialized structures in the skin such as feathers, scales, glands, and hairs, the spots on leopards, or the miriad of patterns on butterfly wings. The rich spectrum of patterns and structures observed in the animal world evolves from a homogeneous mass of cells and is orchestrated by genes that initiate and control the pattern formation mechanisms: genes themselves are not involved in the actual process of pattern generation. The basic philosophy behind practical modeling is to try to incorporate the physicochemical events, which from observation and experiment appear to be going on during development, within a model mechanistic framework that can then be studied mathematically and the results related back to the biology. These morphogenetic models provide the embryologist with possible scenarios as to how, and often when, pattern is laid down, how elements in the embryo might be created, and what constraints on possible patterns are imposed by different models.

Broadly, two kinds of mechanisms for biological pattern generation have been taken seriously by developmental biologists. (Interpretation of a set of rules, albeit useful at times, does not constitute a mechanism). One is the chemical prepattern approach based on Turing's (1) 1952 theory of morphogenesis coupled with Wolpert's (2,3) concept of "positional information." The other is the mechanochemical approach developed by Oster and Murray and their colleagues (for example, 4–8 and a recent review in 9).

Turing's (1) theory involves hypothetical chemicals—morphogens—that can react and diffuse in such a way that steady-state heterogeneous spatial patterns in chemical concentrations can evolve. Morphogenesis proceeds by the cells interpreting the local chemical concentration pattern, differentiating according to their "positional information" (2,3), and thus forming structures. Here pattern formation and morphogenesis take place *sequentially*. Mechanical shaping of form, which has to occur during embryogenesis, is not addressed in the chemical theory of morphogenesis. Reaction diffusion theory has had a considerable impact on the field, both in promoting theoretical research and in suggesting new experimental investigations. Such reaction diffusion models have been applied to a wide variety of biological problems from animal coat patterns (10) to spatial organization in the embryo of the fruit fly *Drosophila* (11). The books by Meinhardt (12) and Murray (13) describe many applications: other important biological and physiological phenomena are also discussed in the latter.

The Oster-Murray mechanochemical approach directly brings forces and known measurable properties of biological tissue into the morphogenetic pattern formation process. They start with known experimental facts about embryonic cells and tissue involved in development, and construct model mechanisms that reflect these facts. Basically, they take the view that mechanical morphogenetic movements themselves create the pattern and form. The models try to quantify the coordinated movement and patterning of populations of cells. The models are based on the important experimental observations of Harris et al. (14) that early embryonic dermal cells are capable of independent movement and have the ability to generate traction forces through long finger-like protrusions called filopodia. These can attach to adhesive sites on the tissue's extracellular matrix (ECM) and thus

pull themselves along; at the same time, they deform the ECM. This cell traction is resisted by the viscoelasticity of the ECM. The orchestration of the various physical effects can generate spatial aggregation patterns in cell number density, and the models show how the parameters affect the size and shape of the patterns and when they can form. Here pattern formation and morphogenesis occur *simultaneously* as a single process.

CURRENT STATUS

The subject of this article is essentially a field in its own right. In view of the large number of diverse developmental problems that have been modeled by only reaction diffusion and mechanochemical systems, here I shall give a flavor of the field. I restrict the main discussion to the formation of patterns that presage cartilage formation in the developing vertebrate limb and certain skin organ primordia—the early rudiments of these organs—and finally make a few comments on some other major problems of current research interest.

Cartilage Patterns in the Vertebrate Limb

Early limb buds consist of a fairly uniform distribution of cells enmeshed in the ECM. As the limb bud grows, through cell division at the distal end of the bud, patterns of cells or morphogens start to form at the proximal end, and these evolve into patterns of chondrocyte cells that eventually become cartilage.

The current reaction diffusion view, in conjunction with the positional information concept, of this chondrogenic process revolves around the establishment of the appropriate sequence of chemical concentration patterns that appear as the limb grows. Much of the experimental research involves grafting small pieces of tissue from certain areas of one limb bud onto another. The resulting cartilage distribution of the adult limb exhibits abnormal morphologies (see, for example, 3,15,16) such as extra elements, and these depend on when and where the graft is inserted. With experience, these abnormalities can effectively be predicted. The sequence of morphogen prepatterns that can be generated by a reaction diffusion model as the limb bud grows is similar to that observed experimentally. For example, in one type of experiment a double limb is generally obtained (13) along with a broadening of the limb. When the pattern-forming theory is applied to a limb bud that is larger than normal size, further chemical structures appear; when the cross-section is double the normal, a complete double structure is obtained that suggests the appearance of a double limb.

What is lacking from this model mechanistic point of view is firm experimental evidence for the existence and identification of any of the morphogens involved in the reaction diffusion model. Nevertheless, recent important unpublished results from Professor Lewis Wolpert's laboratory in the Middlesex Hospital Medical School (personal communication) seem to indicate that a definite chemical prepattern has been formed before any differences in cell densities or cell types are observed, as required by the mechanochemical mechanism described below.

The Oster-Murray mechanochemical models take a different approach. In the developing limb the cells move around in a meshwork of extracellular material (ECM), moving by exerting traction forces that deform the ECM, which in turn resists the pulling by the cells, thus influencing their movement. Various regulatory chemicals affect the physical properties of the cells and ECM. The model mechanism simply consists of a series of equations that reflect how the cells move, how the forces interact, and how the regulatory chemicals, which are secreted by the cells, influence the physical factors. The geometry and scale of the limb, as it develops, play an important role. A particularly attractive feature of mechanochemical models (as opposed to reaction diffusion models) is that they are capable of directly controlling both the geometry and scale of the limb during development. The sizes of the model parameters are all, in principle, measurable experimentally. Among other things, mathematical and numerical analyses of the model equations show how equivalent effects can be obtained by varying seemingly quite different parameters, which is particularly relevant from an experimental viewpoint.

An important feature of morphogenetic patterns is that they are often laid down sequentially. In the developing forelimb the humerus, marked H in Fig. 1 (which is a typical vertebrate limb skeletal structure) is laid down first, followed by the radius (R) and ulna (U) and so on. The models not only suggest how such a sequence of patterns is initiated but also why certain morphologies are unlikely. This is intimately related to the concept of "developmental constraints," which I briefly describe below and which is of importance in evolutionary theory.

By way of example, let us focus on geometry and scale as the parameters that vary in the developing limb bud and see how these can effect pattern variation. The discussion is based on a detailed mathematical analysis of the model equations. Consider the developing limb bud shown schematically in Fig. 2. We can think of a cell aggregation as a "wave" pattern that can fit into the domain. The regions of higher density of cells become chondrocytes and eventually cartilage. The cross-sectional domain size at AB in Fig. 2a is just sufficient to fit in one "wave." We call this a *focal* condensation (F). It is simply an aggregation of cells that forms when there is sufficient space and enough cells to create it: if the cross-section is too small, no pattern can be initiated. This condensation recruits cells as the limb grows and eventually becomes the humerus: see Fig. 1.

With further limb bud growth, a stage is reached when the cross-sectional area increases sufficiently so that two "waves" can fit into the region as shown in Fig. 2b. The change from a focal aggregation to this Y-form we call a *branching bifurcation* (B). The gaps for joint formation form at a later stage, a precursor of which is the separation of the various parts of the Y. The mathematical analysis indicates that in practice it is not possible to have a limb pattern development which goes from two aggregations to one: this is an example of a developmental constraint that is imposed by the pattern formation mechanism. Another important pattern initiation possibility comes from limb growth without increase in width. Here a focal pattern or one of the legs of a branching pattern can break off longitudinally as shown in Fig. 2c: we call this a *segmental bifurcation* (S).

At this stage we might think that the spatial bifurcations simply increase in complexity as the limb bud grows. It should theoretically be possible, for example, to have a transition from one aggregation to three. The model analyses predict, however, that the combination of pa-

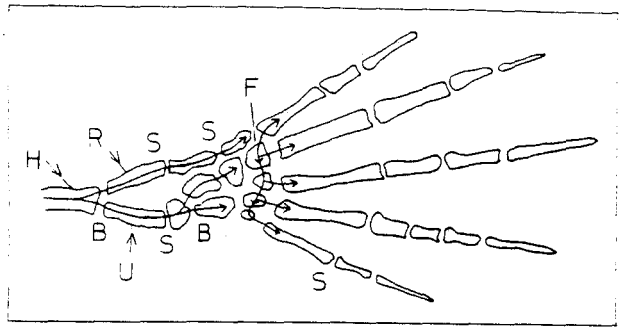

Figure 1 Schematic diagram of the forelimb of a salamander. The lines (with arrows) passing through the bones show how the cartilage patterns are built up from sequences of focal (F), branching (B), and segmental (S) bifurcations illustrated in Fig. 2.

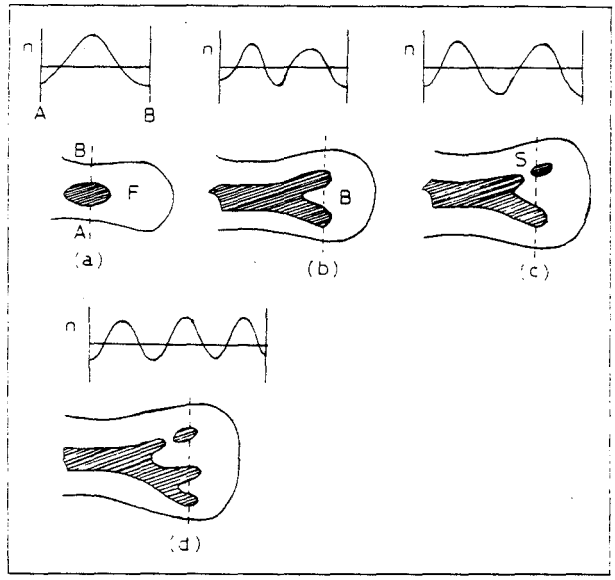

Figure 2 The three types of cell condensations that lead to cartilage formation. In (a) the limb width is sufficient for only one cell aggregation—a focal condensation (F)—to occur. As the limb bud widens with growth, a branching bifurcation (B) can be fitted in as in (b). With further elongation a segmental bifurcation (S) becomes possible as in (c). In (d) we see how a cross-section with three patterns is formed with the set of morphogenetic rules based on only the three bifurcations F, B, and S.

rameters necessary to produce a trifurcation would have to lie within a very narrow range of values. Since biological pattern formation is a robust process, such sensitivity is highly unlikely. Instead, the model suggests that when three aggregations are evident, as in Fig. 2d, they arise from a combination of a branching bifurcation and a segmental bifurcation.

An interesting consequence of the mathematical study of the mechanochemical models is that there is no unique effect which dictates the patterns obtained. Thus, the models can suggest the probable outcomes of varying given physical parameters and hence indicate what type of experiment would be useful in helping to discover the underlying mechanism.

Bifurcation Pattern Sequences Suggest a Theory of Limb Morphogenesis

Although there is enormous diversity in limb morphology, cartilage formation in most vertebrate limbs has a certain similarity of structural organization. From the mathematical study of the two principal theories of pattern formation, we reach the same conclusion regarding the sequence of bifurcating patterns that encapsulates one of the major theoretical hypotheses. It is postulated (17) that all vertebrate limbs could form via the three bifurcation possibilities described above, namely, focal, branching, and segmental bifurcations. Experiments (see 17) on a variety of limbs indicate that, at least with the species studied in detail, this bifurcation scenario is borne out.

If the early limb—for example, that of the salamander (*Ambystoma*) shown in Fig. 1—is treated with the chemical colchicine, which reduces the dermal cell number, the final limb sometimes looks like the paedomorphic, or early embryonic, form *Proteus* that has fewer digits. This suggests that *Proteus* and *Ambystoma* shared a common developmental mechanism. It is thus neither a relevant nor answerable question to ask which specific digits are lost in any such variation caused by a reduction in cell density or as a result of evolution. The *developmental constraints* imposed by a decrease in cell density simply limit the number of aggregation centers possible. This has significant evolutionary implications (17).

Periodic Patterns of Feather Primordia

Vertebrate skin is composed of two layers: an epithelial epidermis overlying a mesenchymal dermis, separated by a fibrous basal lamina. These sheets of epithelial cells can deform and buckle, but there is very little movement of individual cells. On the other hand, dermal cells are loosely packed and motile. The first feather rudiments, the primordia, consist of a thickening of the epidermis, called a placode, and a condensation of dermal cells, called a papilla. The placode is seen by an elongation of the cells perpendicular to the skin, while the dermal condensations are largely the result of cell migration. Whether or not the placodes form prior to the dermal cell papillae is controversial: both layers are essential for skin organ development.

The mathematical analyses of mechanical models (5,18) reflect the known feather germ pattern formation behavior, which takes place in a well-ordered fashion [on the chick, for example; see Davison (19)]. It is also possible to generate similar final patterns with a reaction diffusion model, but it is somewhat contrived. It is less so in the case of hairs, for which a convincing scenario has been proposed (20).

FUTURE DIRECTIONS

Modeling in morphogenesis has now reached the stage whereby several different mechanisms can generate the observed biological patterns. The question is how to distinguish between them so as to determine which may be the relevant mechanism in vivo. These different models, or explanations, for how pattern arises suggest different experiments which may lead to a greater understanding of the biological processes involved. The final arbiter of a model's correctness is not so much in what patterns it generates (although a first necessary condition for any such model is that it must be able to produce biologically observed patterns), but in how con-

sistent it appears in the light of subsequent experiments and observations.

In the case of reaction diffusion models the unequivocal identification of morphogens is crucial. Until this has been done, it is difficult to really test reaction diffusion models experimentally. On the other hand, with mechanical models, which involve cell densities, it is possible to change several of the real parameters. For example, it is possible to reduce the number of cells (for example, by radiation or appropriate chemical treatment). The mechanical model predicts that spacing between patterns will increase (5), and this is borne out by experiments.

In the case of feather and scale patterns, I remarked that the time sequence in which dermal papillae and epidermal placodes formed was unresolved. I also noted that both tissues were essential for the development of the structures. More research effort is now going into models that involve tissue interaction: a first attempt has been made (21) and others are in progress.

Mechanochemical models lend themselves to experimental scrutiny more readily than reaction diffusion models. It is likely that both types of models are involved in development, but until more is known about the morphogens involved, it seems that, at this stage, mechanical models can indicate experimental activity to elucidate the underlying mechanisms involved in morphogenesis in a more productive way.

Potential Future Applications of Mechanochemical Models

The encouraging results described above (and others not described here) obtained from the mechanochemical approach to pattern formation suggest that it might be useful and informative to investigate other areas where cell traction may play a key role. One of these, for example, is wound healing. In the case of burns, epidermal cells at the wound site appear to adopt dermal cell characteristics and are capable of exerting large traction forces, which exert forces at the wound edges. These large traction forces can cause puckering of the skin and can lead to severe scarring and disfigurement. This process could be modeled using the mechanochemical approach, with a view to trying to minimize the traction-caused puckering, by either artifical or other means suggested by the model. Mathematically, this would be a formidable problem, but the potential practical rewards justify a detailed study: first attempts have been reported (9).

A crucially important aspect of this research is the interdisciplinary content. There is absolutely no way mathematical modeling could ever solve such biological problems on its own. On the other hand, it is unlikely that even a reasonably complete understanding could come solely from experiment.

KEY CONTRIBUTORS

This is only a partial list of the many people involved in modeling biological pattern formation. They are, or have been, involved in some of the major modeling developments in the field that particularly relate to the ideas described in this article.

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How the Leopard Gets Its Spots

A single pattern-formation mechanism could underlie the wide variety of animal coat markings found in nature. Results from the mathematical model open lines of inquiry for the biologist

by James D. Murray

Mammals exhibit a remarkable variety of coat patterns; the variety has elicited a comparable variety of explanations—many of them at the level of cogency that prevails in Rudyard Kipling's delightful "How the Leopard Got Its Spots." Although genes control the processes involved in coat pattern formation, the actual mechanisms that create the patterns are still not known. It would be attractive from the viewpoint of both evolutionary and developmental biology if a single mechanism were found to produce the enormous assortment of coat patterns found in nature.

I should like to suggest that a single pattern-formation mechanism could in fact be responsible for most if not all of the observed coat markings. In this article I shall briefly describe a simple mathematical model for how these patterns may be generated in the course of embryonic development. An important feature of the model is that the patterns it generates bear a striking resemblance to the patterns found on a wide variety of animals such as the leopard, the cheetah, the jaguar, the zebra and the giraffe. The simple model is also consistent with the observation that although the distribution of spots on members of the cat family and of stripes on zebras varies widely and is unique to an individual, each kind of distribution adheres to a general theme. Moreover, the model also predicts that the patterns can take only certain forms, which in turn implies the existence of developmental constraints and begins to suggest how coat patterns may have evolved.

It is not clear as to precisely what happens during embryonic development to cause the patterns. There are now several possible mechanisms that are capable of generating such patterns. The appeal of the simple model comes from its mathematical richness and its astonishing ability to create patterns that correspond to what is seen. I hope the model will stimulate experimenters to pose relevant questions that ultimately will help to unravel the nature of the biological mechanism itself.

Some facts, of course, are known about coat patterns. Physically, spots correspond to regions of differently colored hair. Hair color is determined by specialized pigment cells called melanocytes, which are found in the basal, or innermost, layer of the epidermis. The melanocytes generate a pigment called melanin that then passes into the hair. In mammals there are essentially only two kinds of melanin: eumelanin, from the Greek words *eu* (good) and *melas* (black), which results in black or brown hairs, and phaeomelanin, from *phaeos* (dusty), which makes hairs yellow or reddish orange.

It is believed that whether or not melanocytes produce melanin depends on the presence or absence of chemical activators and inhibitors. Although it is not yet known what those chemicals are, each observed coat pattern is thought to reflect an underlying chemical prepattern. The prepattern, if it exists, should reside somewhere in or just under the epidermis. The melanocytes are thought to have the role of "reading out" the pattern. The model I shall describe could generate such a prepattern.

My work is based on a model developed by Alan M. Turing (the inventor of the Turing machine and the founder of modern computing science). In 1952, in one of the most important papers in theoretical biology, Turing postulated a chemical mechanism for generating coat patterns. He suggested that biological form follows a prepattern in the concentration of chemicals he called morphogens. The existence of morphogens is still largely speculative, except for circumstantial evidence, but Turing's model remains attractive because it appears to explain a large number of experimental results with one or two simple ideas.

Turing began with the assumption that morphogens can react with one another and diffuse through cells. He then employed a mathematical model to show that if morphogens react and diffuse in an appropriate way, spatial patterns of morphogen concentrations can arise from an initial uniform distribution in an assemblage of cells. Turing's model has spawned an entire class of models that are now referred to as reaction-diffusion models. These models are applicable if the scale of the pattern is large compared with the diameter of an individual cell. The models are applicable to the leopard's coat, for instance, because the number of cells in a leopard spot at the time the pattern is laid down is probably on the order of 100.

Turing's initial work has been developed by a number of investigators, including me, into a more complete mathematical theory. In a typical reaction-diffusion model one starts with two morphogens that can react with each other and diffuse at varying rates. In the absence of diffusion—in a well-stirred reaction, for example—the two morphogens would react and reach a steady uniform state. If the morphogens are now allowed to diffuse at equal rates, any spatial variation from that steady state will be smoothed out. If, however, the diffusion rates are not equal,

LEOPARD reposes. Do mathematical as well as genetic rules produce its spots?

job a cherry picker may begin the job and then be replaced by a larger mobile crane, which can be positioned to carry out the heavy, complex framing of the building's base. When it is time to construct the lighter-weight, repetitively framed upper floors, a tower crane may be installed. Additional cranes may be brought to the site for finishing the building's exterior as scheduling (or other factors) usually require that the process be expedited. Materials that are very light in weight or compact (bricks, mortar, drywall panels, windows and so on) are more economically lifted in a temporary elevator erected on the outside of the building, thereby freeing the cranes for heavier work.

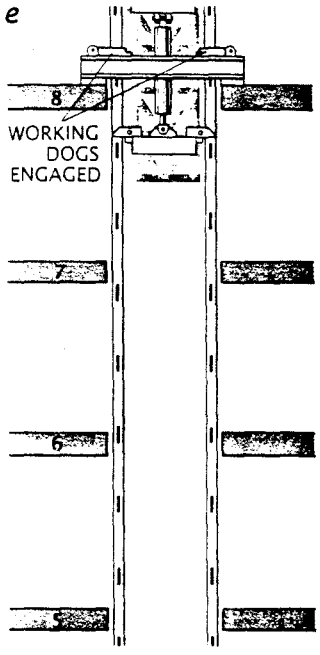
Many forces act simultaneously on a crane, threatening its stability and inducing stress. These include the weight of the load, the pressure of the wind, the weight of the crane itself and the inertia associated with the moving crane components and its load. The resulting effects must of course be constrained by the structural strength of the crane and the earth or building that supports it, but a crane must also have adequate stability to resist overturning. Indeed, mobile cranes are limited more by stability than by strength. The maximum permitted load is set at from 75 to 85 percent of the lifted load that would cause the mobile crane to tip over. Crane designers can maximize the lifting capacity of a machine by minimizing boom weight (for example by utilizing high-strength steel in a latticed boom to reduce self-weight in relation to lift capacity), maximizing the counterweight and providing the widest base possible.

Counterweights on large mobile cranes can weigh as much as 75 tons. They are usually fabricated in sections that are removable and can be shipped separately from the crane itself. When counterweights are combined with the weight of the crane, engine and drive machinery, they add stability to the crane. (If too much counterweight is added, however, an unloaded crane can topple over backward.)

Outriggers that project from the base of a rubber-tired crane provide increased stability by extending the tipping fulcrum away from the body of the machine. Most crane outriggers are sturdy beams that telescope out from each end of the machine chassis. The outer ends of the outriggers are equipped with vertical jacks; when the outriggers are fully extended and the entire crane is jacked up, the crane is operational.

The operator of a mobile crane must exercise judgment, taking into account such factors as the length of the boom and the characteristics of the load, to allow for the effects of wind and inertia. The lifting of a large curtain-wall segment, for example, presents a substantial wind-catching surface and can therefore be carried out only when there is minimal wind velocity. When a crane swings, centrifugal forces project the load outward and stability is decreased; acceleration and braking induce lateral loading on the boom, causing sideways deflection and a corresponding increase in stress.

Tower cranes have automatic limits imposed on their rotational speed and acceleration to control the effects of inertia; mobile-crane operators, on the other hand, must exert that control themselves. But tower cranes are more sensitive to wind because of their fixed position. When major storms arise, the booms on mobile cranes can be lowered out of harm's way, but the booms of tower cranes remain in place and bear the brunt of the storm. As a result, tower cranes must be designed to withstand hurricane conditions. When storms do strike, the usual procedure is to let the boom swing freely, thus providing the least resistance and the smallest surface area to the wind. On days when the wind exceeds 30 miles per hour, all cranes generally cease operation, although most tower cranes are designed to withstand higher winds while working.



then be retracted (*d*), raising the lower crossbeam and automatically disengaging the lower dogs. After the cycle has been repeated several times (five or six floors are climbed at a time in this way) (*e*) the working dogs are once again set in place and the crane becomes operational.

Crane Safety

Crane accidents at urban sites can be dramatic, and they are often followed by outcries that the public is inadequately protected. A crane that loses control of its load or topples over can wreak havoc on the streets below; pedestrians are sometimes killed or maimed. The hazards for construction workers are even greater: construction is a dangerous occupation and crane work is among its greater perils. Can anything be done to ameliorate the situation?

Most serious crane accidents are caused by overload, equipment misuse, excessive wear or damage to the hoisting ropes and failure to follow correct procedures for erection and dismantling (particularly in the case of tower cranes). A smaller but significant number of mishaps result from support failure, inadequate maintenance and collision between the boom and another object. Most of these accidents could be prevented through training programs for construction workers, crane operators and supervisory personnel.

Underlying many crane accidents, however, are errors committed in the planning stage. Safety is compromised when a crane is positioned incorrectly or is inadequate for the job. Crane operators have been known to make heroic efforts as they try to compensate for these inadequacies. Their efforts should be applauded, but the planning shortcomings that led to the selection of the wrong crane in the first place must be condemned. Because congested urban areas are associated with such high potential risk to the public, engineers must play an active role in evaluating sites, planning the lifting operations and selecting the right crane for the job.

Risks can never be totally eliminated from a crane operation (or from any operation in which human judgment is exercised), but they can certainly be minimized. To do so requires diligence on the part of the local authorities who enforce safety regulations and skill on the part of the people responsible for the deployment and operation of cranes.

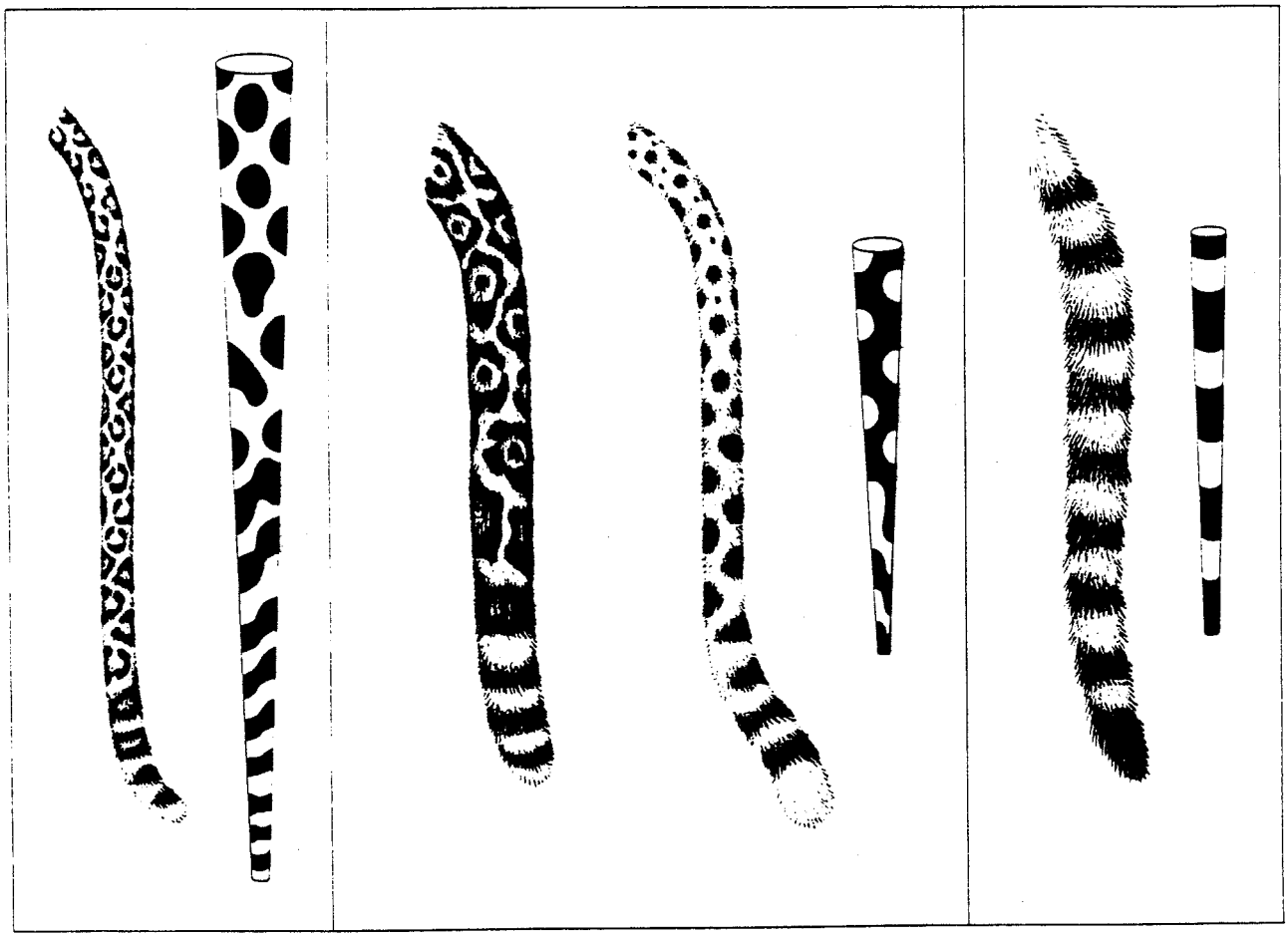
diffusion can be destabilizing: the reaction rates at any given point may not be able to adjust quickly enough to reach equilibrium. If the conditions are right, a small spatial disturbance can become unstable and a pattern begins to grow. Such an instability is said to be diffusion driven.

In reaction-diffusion models it is assumed that one of the morphogens is an activator that causes the melanocytes to produce one kind of melanin, say black, and the other is an inhibitor that results in the pigment cells' producing no melanin. Suppose the reactions are such that the activator increases its concentration locally and simultaneously generates the inhibitor. If the inhibitor diffuses faster than the activator, an island of high activator concentration will be created within a region of high inhibitor concentration.

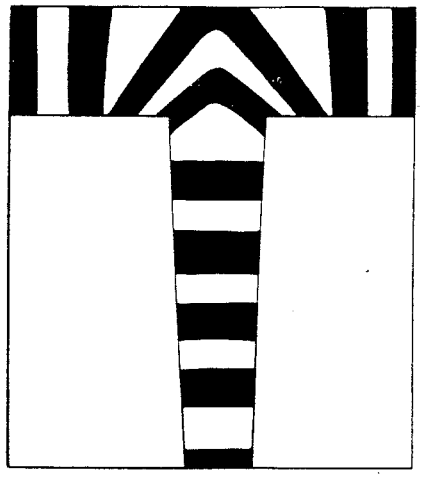
One can gain an intuitive notion of how such an activator-inhibitor mechanism can give rise to spatial patterns of morphogen concentrations from the following, albeit somewhat unrealistic, example. The analogy involves a very dry forest—a situation ripe for forest fires. In an attempt to minimize potential damage, a number of fire fighters with helicopters and fire-fighting equipment have been dispersed throughout the forest. Now imagine that a fire (the activator) breaks out. A fire front starts to propagate outward. Initially there are not enough fire fighters (the inhibitors) in the vicinity of the fire to put it out. Flying in their helicopters, however, the fire fighters can outrun the fire front and spray fire-resistant chemicals on trees; when the fire reaches the sprayed trees, it is extinguished. The front is stopped.

If fires break out spontaneously in random parts of the forest, over the course of time several fire fronts (activation waves) will propagate outward. Each front in turn causes the fire fighters in their helicopters (inhibition waves) to travel out faster and quench the front at some distance ahead of the fire. The final result of this scenario is a forest with blackened patches of burned trees interspersed with patches of green, unburned trees. In effect, the outcome mimics the outcome of reaction-diffusion mechanisms that are diffusion driven. The type of pattern that results depends on the various parameters of the model and can be obtained from mathematical analysis.

Many specific reaction-diffusion models have been proposed, based on plausible or real biochemical reactions, and their pattern-formation properties have been examined. These mechanisms involve several parameters, including the rates at which the reactions proceed, the rates at which the chemicals diffuse and—of crucial importance—the geometry and scale of the tissue. A fascinating property of reaction-diffu-



MATHEMATICAL MODEL called a reaction-diffusion mechanism generates patterns that bear a striking resemblance to those found on certain animals. Here the patterns on the tail of the leopard (*left*), the jaguar and the cheetah (*middle*) and the genet (*right*) are shown, along with the patterns from the model for tapering cylinders of varying width (*right side of each panel*).



ZEBRA STRIPES at the junction of the foreleg and body (*left*) can be produced by a reaction-diffusion mechanism (*above*).

sion models concerns the outcome of beginning with a uniform steady state and holding all the parameters fixed except one, which is varied. To be specific, suppose the scale of the tissue is increased. Then eventually a critical point called a bifurcation value is reached at which the uniform steady state of the morphogens becomes unstable and spatial patterns begin to grow.

The most visually dramatic example of reaction-diffusion pattern formation is the colorful class of chemical reactions discovered by the Soviet investigators B. P. Belousov and A. M. Zhabotinsky in the late 1950's [see "Rotating Chemical Reactions," by Arthur T. Winfree; SCIENTIFIC AMERICAN, June, 1974]. The reactions visibly organize themselves in space and time, for example as spiral waves. Such reactions can oscillate with clocklike precision, changing from, say, blue to orange and back to blue again twice a minute.

Another example of reaction-diffusion patterns in nature was discovered and studied by the French chemist Daniel Thomas in 1975. The patterns are produced during reactions between uric acid and oxygen on a thin membrane within which the chemicals can diffuse. Although the membrane contains an immobilized enzyme that catalyzes the reaction, the empirical model for describing the mechanism involves only the two chemicals and ignores the enzyme. In addition, since the membrane is thin, one can assume correctly that the mechanism takes place in a two-dimensional space.

I should like to suggest that a good candidate for the universal mechanism that generates the prepattern for mammalian coat patterns is a reaction-diffusion system that exhibits diffusion-driven spatial patterns. Such patterns depend strongly on the geometry and scale of the domain where the chemical reaction takes place. Consequently the size and shape of the embryo at the time the reactions are activated should determine the ensuing spatial patterns. (Later growth may distort the initial pattern.)

Any reaction-diffusion mechanism capable of generating diffusion-driven spatial patterns would provide a plausible model for animal coat markings. The numerical and mathematical results I present in this article are based on the model that grew out of Thomas' work. Employing typical values for the parameters, the time to form coat patterns during embryogenesis would be on the order of a day or so.

Interestingly, the mathematical problem of describing the initial stages of spatial pattern formation by reaction-diffusion mechanisms (when departures from uniformity are minute) is similar to the mathematical problem of describing the vibration of thin plates or drum surfaces. The ways in which pattern growth depends on geometry and scale can therefore be seen by considering analogous vibrating drum surfaces.

If a surface is very small, it simply will not sustain vibrations; the disturbances die out quickly. A minimum size is therefore needed to drive any sustainable vibration. Suppose the drum surface, which corresponds to the reaction-diffusion domain, is a rectangle. As the size of the rectangle is increased, a set of increasingly complicated modes of possible vibration emerge.

An important example of how the geometry constrains the possible modes of vibration is found when the domain is so narrow that only simple—essentially one-dimensional—modes can exist. Genuine two-dimensional patterns require the domain to have enough breadth as well as length. The analogous requirement for vibrations on the surface of a cylinder is that the radius cannot be too small, otherwise only quasi-one-dimensional modes can exist: only ringlike patterns can form, in other words. If the radius is large enough, however, two-dimensional patterns can exist on the surface. As a consequence, a tapering cylinder can exhibit a gradation from a two-dimensional pattern to simple stripes [*see illustration on opposite page*].

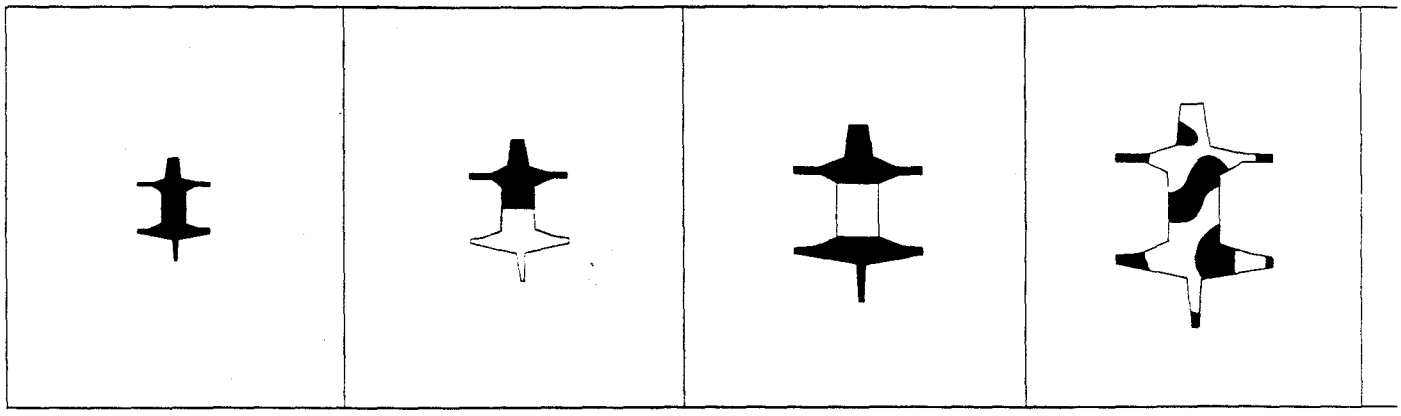
Returning to the actual two-morphogen reaction-diffusion mechanism I considered, I chose a set of reaction and diffusion parameters that could produce a diffusion-driven instability and kept them fixed for all the calculations. I varied only the scale and geometry of the domain. As initial conditions for my calculations, which I did on a computer, I chose random perturbations about the uniform steady state. The resulting patterns are colored dark and light in regions where the concentration of one of the morphogens is greater than or less than the concentration in the homogeneous steady state. Even with such limitations on the parameters and the initial conditions the wealth of possible patterns is remarkable.

EXAMPLES OF DRAMATIC PATTERNS occurring naturally are found in the anteater (*left*) and the Valais goat, *Capra aegagrus hircus* (*right*). Such patterns can be accounted for by the author's reaction-diffusion mechanism (*see bottom illustration on these*

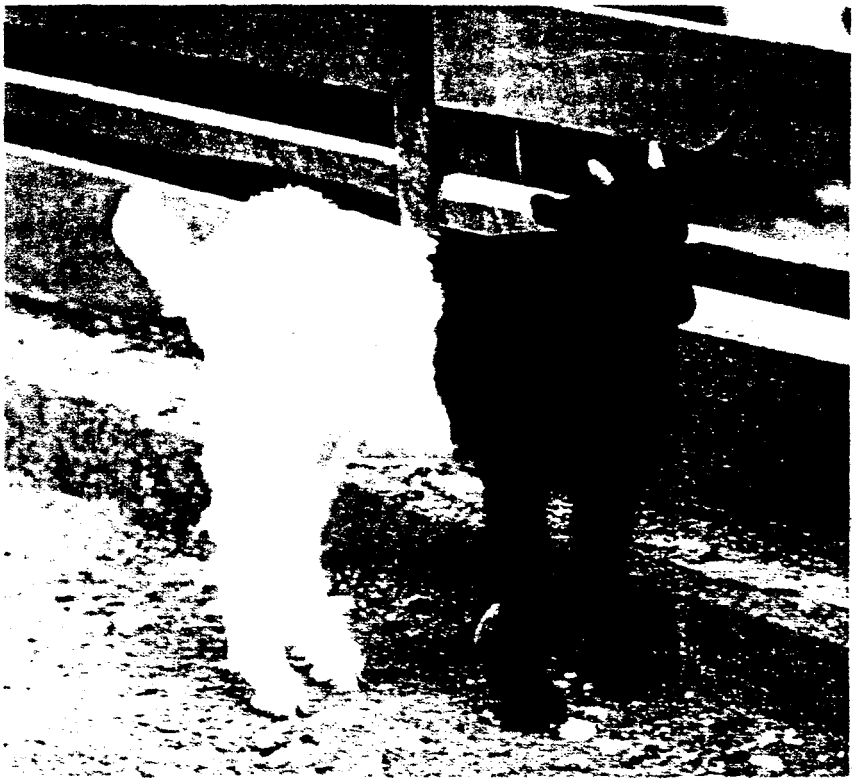
How do the results of the model compare with typical coat markings and general features found on animals? I started by employing tapering cylinders to model the patterns on the tails and legs of animals. The results are mimicked by the results from the vibrating-plate analogue, namely, if a two-dimensional region marked by spots is made sufficiently thin, the spots will eventually change to stripes.

The leopard (*Panthera pardus*), the cheetah (*Acinonyx jubatus*), the jaguar (*Panthera onca*) and the genet (*Genetta genetta*) provide good examples of such pattern behavior. The spots of the leopard reach almost to the tip of the tail. The tails of the cheetah and the jaguar have distinctly striped parts, and the genet has a totally striped tail. These observations are consistent with what is known about the embryonic structure of the four animals. The prenatal leopard tail is sharply tapered and relatively short, and so one would expect that it could support spots to the very tip. (The adult leopard tail is long but has the same number of vertebrae.) The tail of the genet embryo, at the other extreme, has a remarkably uniform diameter that is quite thin. The genet tail should therefore not be able to support spots.

The model also provides an instance of a developmental constraint, documented examples of which are exceedingly rare. If the



SCALE AFFECTS PATTERNS generated within the constraints of a generic animal shape in the author's model. Increasing the scale and holding all other parameters fixed produces a remarkable variety of patterns. The model agrees with the fact that

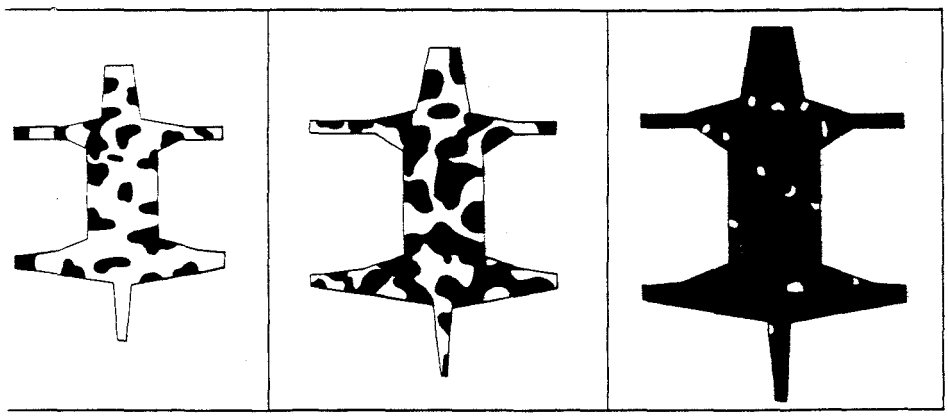


two pages). **The drawing of the anteater was originally published by G. and W. B. Whittaker in February, 1824, and the photograph was made by Avi Baron and Paul Munro.**

prepattern-forming mechanism for animal coat markings is a reaction-diffusion process (or any process that is similarly dependent on scale and geometry), the constraint would develop from the effects of the scale and geometry of the embryos. Specifically, the mechanism shows that it is possible for a spotted animal to have a striped tail but impossible for a striped animal to have a spotted tail.

We have also met with success in our attempts to understand the markings of the zebra. It is not difficult to generate a series of stripes with our mechanism. The junction of the foreleg with the body is more complicated, but the mathematical model predicts the typical pattern of leg-body scapular stripes [*see illustration on page 83*].

In order to study the effect of scale in a more complicated geometry, we computed the patterns for a generic animal shape consisting of a body, a head, four appendages and a tail [*see bottom illustration on these two pages*]. We started with a very small shape and gradually increased its size, keeping all the parts in proportion. We found several interesting results. If the domain is too small, no pattern can be generated. As the size of the domain is increased successive bifurcations occur: different patterns suddenly appear and disappear. The patterns show more structure and more spots as the size of the domain is increased. Slender extremities still retain their striped pattern, however, even for domains that are quite large. When the domain is very large, the pattern structure is so fine that it becomes almost uniform in color again.



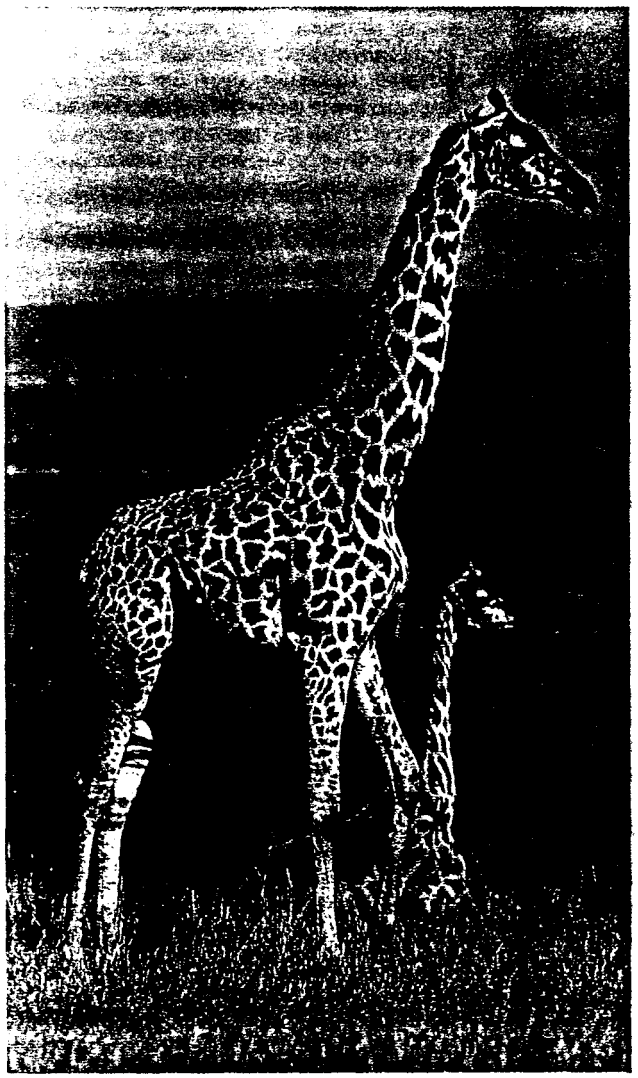
small animals such as the mouse have uniform coats, intermediate-size ones such as the leopard have patterned coats and large animals such as the elephant are uniform.

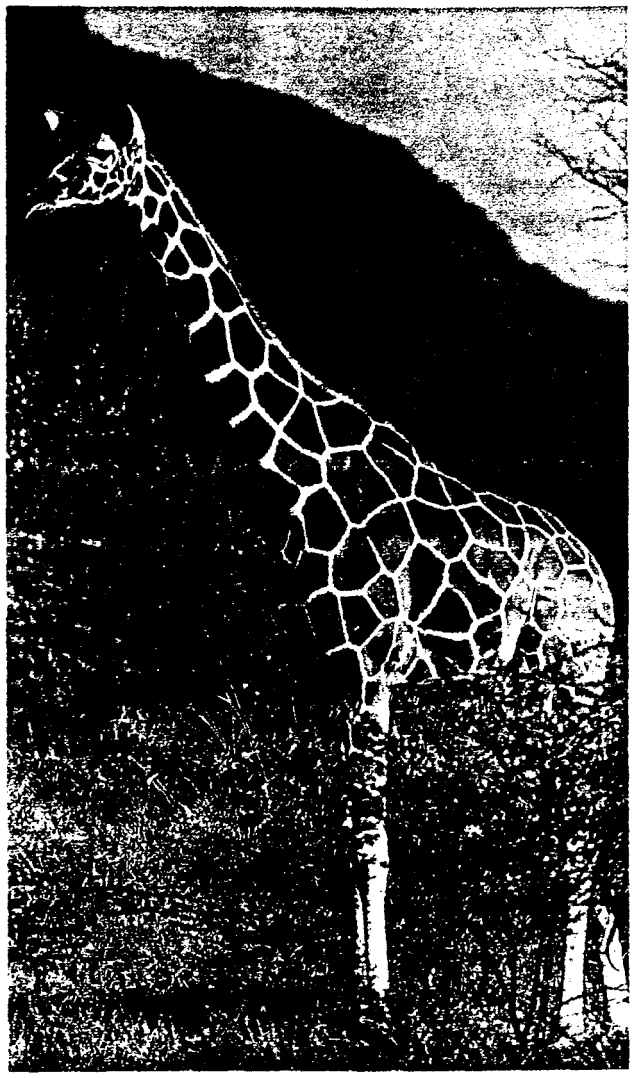
The effects of scale on pattern suggest that if the reaction-diffusion model is correct, the time at which the pattern-forming mechanism is activated during embryogenesis is of the utmost importance. There is an implicit assumption here, namely that the rate constants and diffusion coefficients in the mechanism are roughly similar in different animals. If the mechanism is activated early in development by a genetic switch, say, most small animals that have short periods of gestation should be uniform in color. This is generally the case. For larger surfaces, at the time of activation there is the possibility that animals will be half black and half white. The honey badger (*Mellivora capensis*) and the dramatically patterned Valais goat (*Capra aegagrus hircus*) are two examples [*see top illustration on these two pages*]. As the size of the domain increases, so should the extent of patterning. In fact, there is a progression in complexity from the Valais goat to certain anteaters, through the zebra and on to the leopard and the cheetah. At the upper end of the size scale the spots of giraffes are closely spaced. Finally, very large animals should be uniform in color again, which indeed is the case with the elephant, the rhinoceros and the hippopotamus.

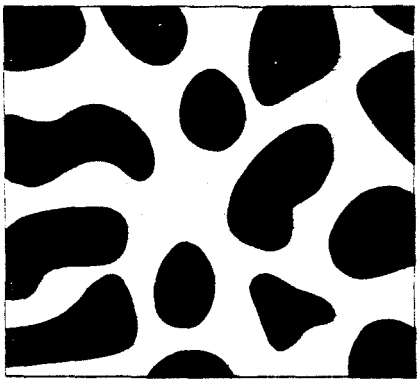
We expect that the time at which the pattern-forming mechanism is activated is an inherited trait, and so, at least for animals whose survival depends to a great extent on pattern, the mechanism is activated when the embryo has reached a certain size. Of course, the conditions on the embryo's surface at the time of activation exhibit a certain randomness. The reaction-diffusion model produces patterns that depend uniquely

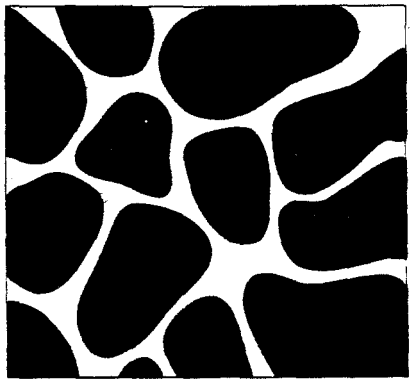
on the initial conditions, the geometry and the scale. An important aspect of the mechanism is that, for a given geometry and scale, the patterns generated for a variety of random initial conditions are qualitatively similar. In the case of a spotted pattern, for example, only the distribution of spots varies. The finding is consistent with the individuality of an animal's markings within a species. Such individuality allows for kin recognition and also for general group recognition.

The patterns generated by the model mechanism are thought to correspond to spatial patterns of morphogen concentrations. If the concentration is high enough, melanocytes will produce the melanin pigments. For simplicity we assumed that the uniform steady state is the threshold concentration, and we reasoned that melanin will be generated if the value is equal to or greater than that concentration. The assumption is somewhat arbitrary, however. It is reasonable to expect that the threshold concentration may vary, even within species. To investigate such









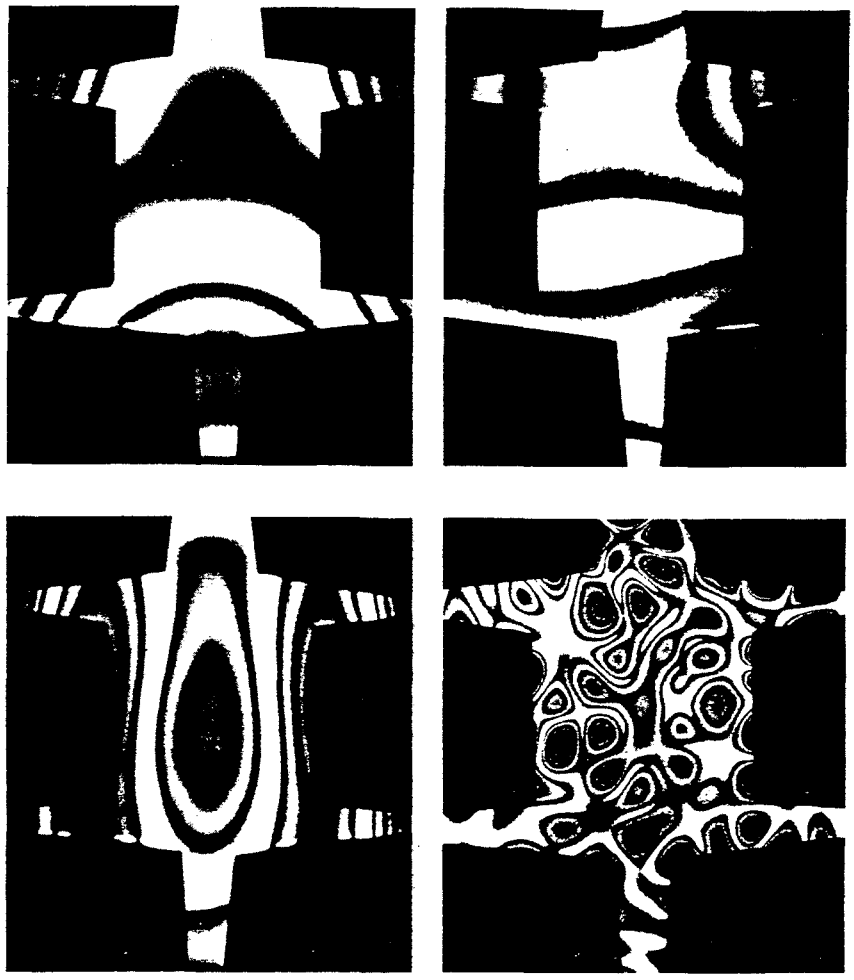
DIFFERENT GIRAFFES have different kinds of markings. The subspecies *Giraffa camelopardalis tippelskirchi* is characterized by rather small spots separated by wide spaces (*top left*); *G. camelopardalis reticulata*, in contrast, is covered by large, closely spaced spots (*top right*). Both kinds of pattern can be accounted for by the author's reaction-diffusion model (*bottom left and bottom right*). The assumption is that at the time the pattern is laid down the embryo is between 35 and 45 days old and has a length of roughly eight to 10 centimeters. (The gestation period of the giraffe is about 457 days.)

effects, we considered the various kinds of giraffe. For a given type of pattern, we varied the parameter that corresponds to the morphogen threshold concentration for melanocyte activity. By varying the parameter, we found we could produce patterns that closely resemble those of two different kinds of giraffe [*see illustration on opposite page*].

Recently the results of our model have been corroborated dramatically by Charles M. Vest and Youren Xu of the University of Michigan. They generated standing-wave patterns on a vibrating plate and changed the nature of the patterns by changing the frequency of vibration. The patterns were made visible by a holographic technique in which the plate was bathed in laser light. Light reflected from the plate interfered with a reference beam, so that crests of waves added to crests, troughs added to troughs, and crests and troughs canceled, and the resulting pattern was recorded on a piece of photographic emulsion [*see illustration at right*].

Vest and Youren found that low frequencies of vibration produce simple patterns and high frequencies of vibration produce complex patterns. The observation is interesting, because it has been shown that if a pattern forms on a plate vibrating at a given frequency, the pattern formed on the same plate vibrated at a higher frequency is identical with the pattern formed on a proportionally larger plate vibrated at the original frequency. In other words, Vest and Youren's data support our conclusion that more complex patterns should be generated as the scale of the reaction-diffusion domain is increased. The resemblance between our patterns and the patterns subsequently produced by the Michigan workers is striking.

I should like to stress again that all the patterns generated were produced by varying only the scale and geometry of the reaction domain; all the other parameters were held fixed (with the exception of the different threshold concentrations in the case of the giraffe). Even so, the diversity of pattern is remarkable. The model also suggests a possible explanation for the various pattern anomalies seen in some animals. Under some circumstances a change in the value of one of the parameters can result in a marked change in the pattern obtained. The size of the effect depends on how close the value of the parameter is to a bifurcation value: the value at which a qualitative change in the pattern is generated.



STANDING-WAVE PATTERNS generated on a thin vibrating plate resemble coat patterns and confirm the author's work. More complex patterns correspond to higher frequencies of vibration. The experiments were done by Charles M. Vest and Youren Xu.

If one of the parameters, say a rate constant in the reaction kinetics, is varied continuously, the mechanism passes from a state in which no spatial pattern can be generated to a patterned state and finally back to a state containing no patterns. The fact that such small changes in a parameter near a bifurcation value can result in such large changes in pattern is consistent with the punctuated-equilibrium theory of evolution. This theory holds that long periods of little evolutionary change are punctuated by short bursts of sudden and rapid change.

Many factors, of course, affect animal coloration. Temperature, humidity, diet, hormones and metabolic rate are among some of them. Although the effects of such factors probably could be mimicked by manipulating various parameters, there is little point in doing so until more is known about how the patterns reflected in the melanin pigments are actually produced. In the meantime one cannot help but note the wide variety of patterns that can be generated with a reaction-diffusion model by varying only the scale and geometry. The considerable circumstantial evidence derived from comparison with specific animal-pattern features is encouraging. I am confident that most of the observed coat patterns can be generated by a reaction-diffusion mechanism. The fact that many general and specific features of mammalian coat patterns can be explained by this simple theory, however, does not make it right. Only experimental observation can confirm the theory.