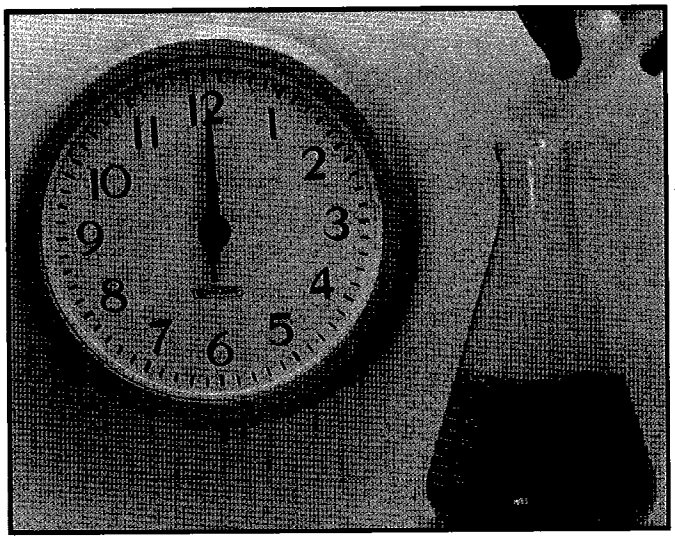

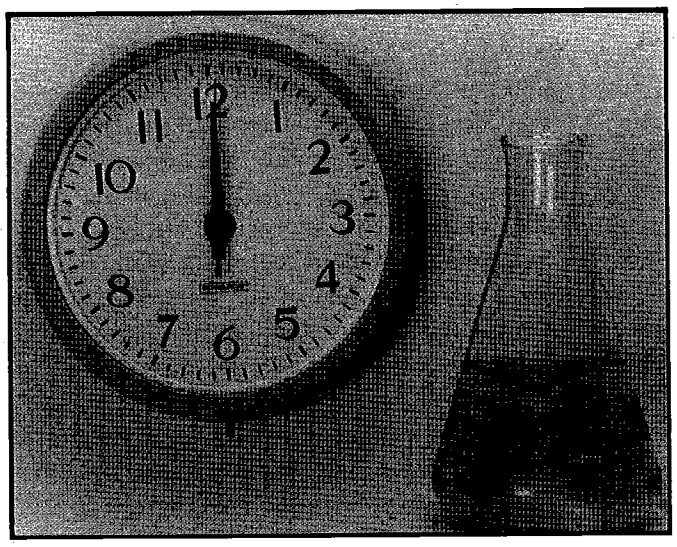

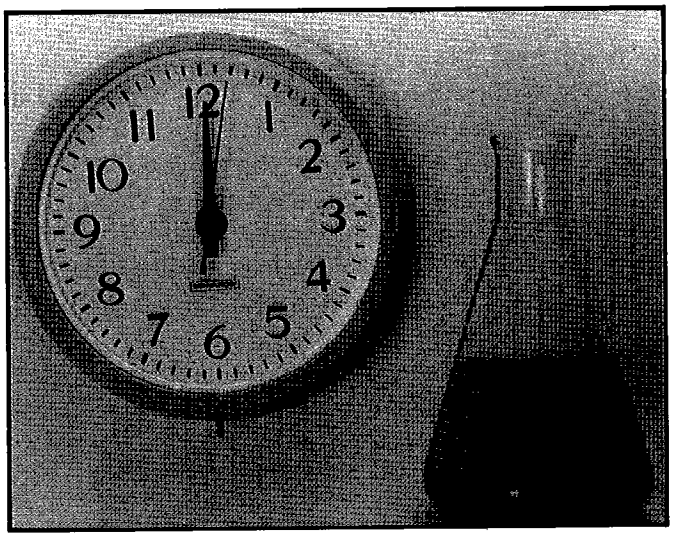

PENDULUMS IN THE TEST TUBE

by Irving R. Epstein

Not long ago a simple inorganic reaction that oscillates periodically would have been thought to violate a natural law. Today such reactions are being systematically designed and studied as analogues of periodic behavior in living organisms.

Show a child a wobbling top, a physicist a pendulum, or a physiologist a beating heart, and they nod with understanding and a certain degree of pleasure. To most people and particularly to most scientists, periodic oscillation is a normal and pleasing mode of behavior for the objects of nature. For the majority of chemists, however, until quite recently the notion of a test tube full of liquid that could periodically change its color from red to blue or green to yellow and back again was an extremely perplexing one.

New advances in chemistry have made chemical oscillation not only credible and accessible but a source of potential insight into a variety of problems in chemistry, biology, the earth sciences, and other disciplines. Although the first chemical oscillators were discovered accidentally, it is now possible to design reactions that display not only oscillatory behavior but other, more exotic phenomena as well.

Early developments

The first evidence for oscillation in a homogeneous chemical reaction was obtained accidentally by W. C. Bray at the University of California at Berkeley in 1921. While studying the way iodate (the IO_3^- ion) catalyzed the decomposition of hydrogen peroxide in solution to oxygen and water, Bray noticed that a brown color characteristic of iodine periodically appeared and disappeared and that bubbles of oxygen were produced in bursts at regular intervals. Bray's discovery encountered more skepticism and indifference than enthusiasm in the chemical community, and it was largely ignored for the next 40 years. This response, or lack of it, was due largely to a widespread but mistaken belief that the laws of thermodynamics forbid chemical oscillation just as surely as they prevent the operation of perpetual motion machines.

A second chemical oscillator, also discovered by serendipity, was found by B. P. Belousov in the Soviet Union in 1958. Again, there was initial resistance to the notion of such behavior, but Belousov and especially his compatriot A. M. Zhabotinsky continued to probe this reaction, in which an organic acid, usually citric or malonic acid, loses carbon dioxide and gains a bromine atom when it reacts in solution with bromate ion (BrO_3^-) in the presence of a metal catalyst such as cerium or manganese. As the reaction progresses, the solution changes periodically from colorless to pale yellow and back. In part because developments in the theory of nonequilibrium thermodynamics had shown that chemical oscillation was neither a physical impossibility nor a scientific fraud and in part because Zhabotinsky published recipes that allowed the oscillations to be reproduced easily in the laboratory, a number of chemists soon became aware of and fascinated by the surprising Belousov-Zhabotinsky (BZ) reaction.

Throughout the 1960s the BZ system was known to a relatively small group of chemists as an entertaining but enigmatic lecture demonstration. Its possible relevance to the built-in biological clocks of humans and other organisms was recognized, and it was the subject of much discussion at a conference in Prague in 1968 on "Biological and Biochemical Oscillators."

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(Overleaf) Sequence of photos taken over a 12.5-second period follow the color changes in the Briggs-Rauscher oscillating chemical system. The reaction, a hybrid of the Belousov-Zhabotinsky (BZ) and Bray systems, changes from colorless to gold to dark blue and back again. A magnetic stirrer, added to keep the reactants well mixed, is responsible for the funnel-shaped vortex in the center of the flask.

(Overleaf) William Shea, Brandeis University

In 1972 Richard Field, Endre Koros, and Richard Noyes at the University of Oregon proposed a reaction mechanism for the BZ system. To a chemist a reaction mechanism represents a complete understanding of the way in which a particular chemical reaction takes place. It consists of a series of "elementary steps"; that is, chemical equations each of which describes an actual encounter between molecules. For example, the overall equation for the combustion of octane, an important process when gasoline is burned in a car engine, is:

$$\underset{\text{octane}}{2C_8H_{18}} + \underset{\text{oxygen}}{25O_2} \rightarrow \underset{\text{carbon dioxide}}{16CO_2} + \underset{\text{water}}{18H_2O}$$

The equation does not imply, however, that the reaction occurs when 27 molecules collide simultaneously to form the appropriate products. Such many-body collisions are wildly improbable. Far more plausible is a scheme in which an initial encounter between one molecule each of octane and oxygen results in the transfer of a hydrogen atom from the octane to the oxygen. Reactive intermediates are thus formed, which react by way of further two-molecule collisions until the final products are formed. Much research in combustion science today is devoted to elucidating just what those further elementary steps are.

The successful formulation of a mechanism that accounted for oscillations in the BZ reaction meant that, in at least one system, chemical oscillation could be understood in the same terms that describe the behavior of any other chemical reaction. Chemical oscillators might be complicated, but they were not magic. The time seemed ripe for an attack on the general problem of what conditions were necessary and sufficient for a chemical system to produce oscillation.

From accident to design

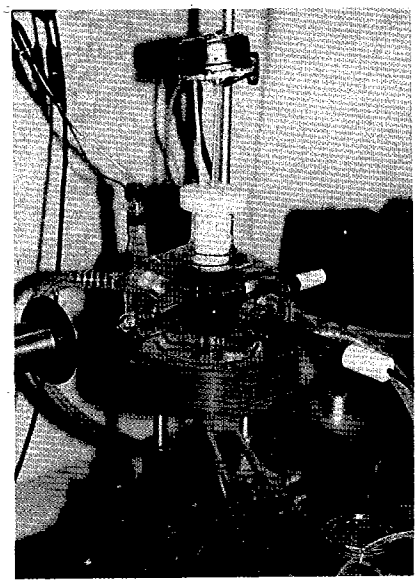
The 1970s produced a number of studies aimed at elucidating the nature of chemical oscillation. Chemists discovered conditions that were necessary—but not sufficient—for a particular mechanism to be capable of oscillation. They were able to show that if no more than two molecules were involved in each elementary reaction or molecular collision, then oscillation required the existence of at least three independent chemical species in the system. Several simple models of chemical oscillators were formulated and analyzed mathematically.

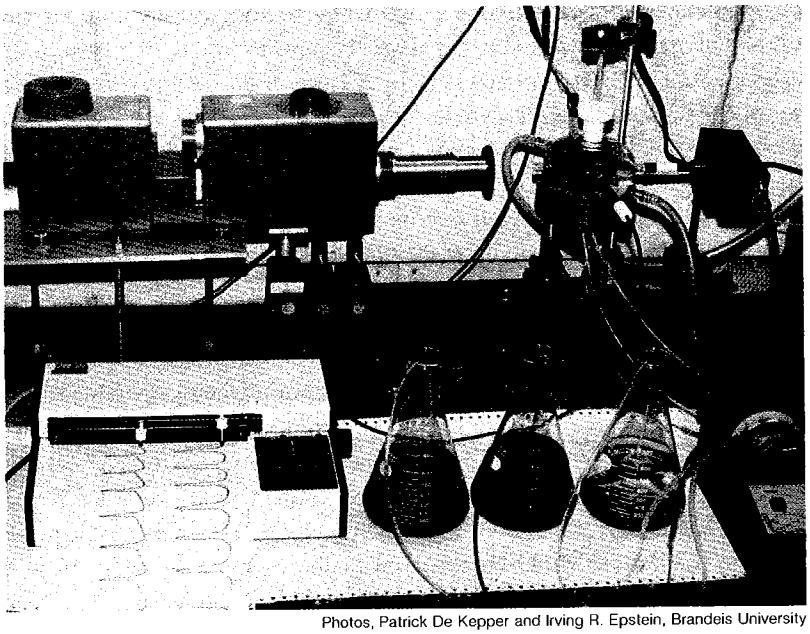
In spite of this progress, by 1980 it had become apparent that no one yet truly understood chemical oscillations and that the number of examples available on which to test general theories was disturbingly small. Aside from the accidentally discovered Bray and BZ reactions, the only known chemical oscillators either were minor variants, in which one or more components were replaced by chemically similar compounds, or were preparations of biological origin. These latter systems generally consisted of a cell-free extract prepared from a living or once-living system, such as yeast or beef heart. On addition of a nutrient such as glucose, oscillations could be observed in the concentrations of oxygen or other molecules involved in various biochemical pathways.

Accident, of course, was not a reliable route to new oscillating reactions. Variants of existing systems gave little new insight into the origins of oscillatory behavior. The biologically based oscillators, though numerous, were far too complex, containing many, often unknown substances, to serve as useful models for constructing or testing theories of chemical oscillation. A deeper understanding thus seemed to hinge on a deliberate search for new chemical oscillators, preferably inorganic ones in order to keep the chemistry as simple and understandable as possible. How might one systematically design a procedure for creating such systems?

The results of nonequilibrium thermodynamics provide one starting point. A reaction reaches chemical equilibrium when it begins to run at the same rate in its forward and reverse directions so that the net amounts of reactants and products do not change. At this point the reaction may be considered finished; for the specified conditions under which the reaction occurred, the maximum amount of reactants has been converted to products. In order to exhibit sustained oscillation, a chemical reaction must be maintained far from equilibrium. One way to do this is to employ an open system, one which exchanges matter, energy, or both with its surroundings. Living things support their oscillatory functions, *i.e.*, life itself, by operating in this fashion. They regularly take in reactants high in available energy—nutrients—from the environment and excrete low-energy products—wastes—to the environment. If either the input or the output flow is stopped, the oscillations soon cease and the organism dies.

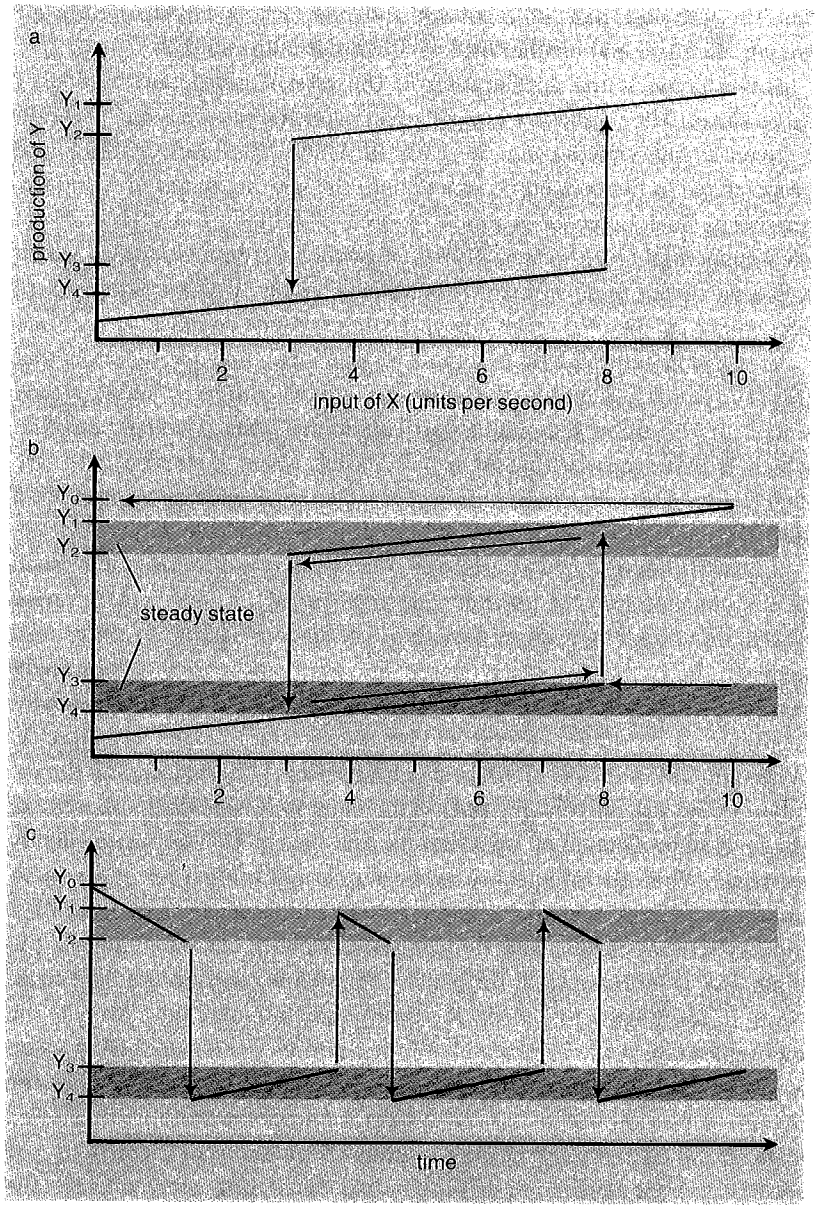
An analogue of this arrangement is to be found in a tool long employed by chemical engineers, the continuous-flow stirred tank reactor (CSTR). Streams of different reactants are pumped into the reactor, which is essentially no more than a beaker with a stirrer and a water jacket around it to maintain constant temperature. The reactants mix and undergo





Experimental arrangement pictured at right was used by De Kepper, Epstein, and Kustin at Brandeis University in 1980 for running the first systematically designed oscillating reaction. The continuous-flow stirred tank reactor (CSTR) can be seen in the upper right portion of the photo and in the close-up above. The reactants—solutions of arsenite, iodate, and chlorite ions held in the three flasks—are pumped continuously into the base of the reactor. A light source and photocell on opposite sides of the reactor monitor the color changes, while electrodes mounted in the reactor sense oscillations in the concentration of particular ions. Periodic changes in color and concentration appear on the chart recorder at the lower left.

Photos, Patrick De Kepper and Irving R. Epstein, Brandeis University



The rationale for designing an oscillating chemical reaction in a CSTR, as described by way of a hypothetical example in text on page 148, is shown in three graphs. Graph a illustrates how a system with two stable steady states can exhibit hysteresis. As one increases the flow of colorless reactant X into the red-colored reactor, the production of blue compound Y first increases slowly (red curve). When the input of X reaches some critical value (here eight units per second), the production of Y rises dramatically (from Y_3 to Y_1), causing the reactor to turn blue. If one then decreases the input of X, the production of Y falls slowly (blue curve), even when X is decreased below the first critical point. Only when a second critical point (three units per second) is reached does the system jump back to the red state (Y_2 to Y_4). Graph b shows what happens to the system when one adds a substance Z that acts selectively to change the available level of X in the reactor. Whereas adding Z decreases the amount of X available to both states of the system, the decrease is much greater in the blue state (horizontal arrow at Y_0) than it is in the red state (horizontal arrow at Y_3). If one fixes the input of X at a high value (say ten units per second) and the system is in the blue state, Z drives down the level of X until the system jumps to the red state; then Z allows the level of X to climb again until the system returns to the blue state. Consequently the system cycles through the path traced in purple. Graph c follows the concentration of Y over time in the bistable system containing the proper amount of Z. The reaction oscillates from one state to another, causing the color of the reactor to alternate between red and blue.

reaction in the reactor and then exit through an outflow tube so that the volume of the system is maintained constant. The composition in the reactor may be monitored, for example, by shining light through it and analyzing the absorbance at a particular wavelength or by connecting electrodes placed in the solution with an external recording device.

The CSTR takes care of the requirement that the system operate far from equilibrium, since reactants are always being refreshed and products removed. But one still needs the right chemistry for oscillation. One fairly obvious necessary condition is that the system possess some sort of feedback mechanism. That is, the product of some reaction in a sequence must influence the rate of some earlier step in the sequence in which that compound or a precursor is produced. Experience suggests

(Facing page) Major chemical oscillators known by the mid-1980s can be grouped into five main families. Solid lines connect related systems within families, while broken lines between families relate systems that share certain characteristics. The BZ reaction, discovered in 1958, belongs to the metal-catalyzed branch of the bromate family; the Bray reaction, found in 1921, and the Briggs-Rauscher system, devised in 1973, are classified in the iodate family. Aside from the above reactions, their minor variants, and oscillators derived from biological systems, all of the listed oscillators have been discovered since 1980.

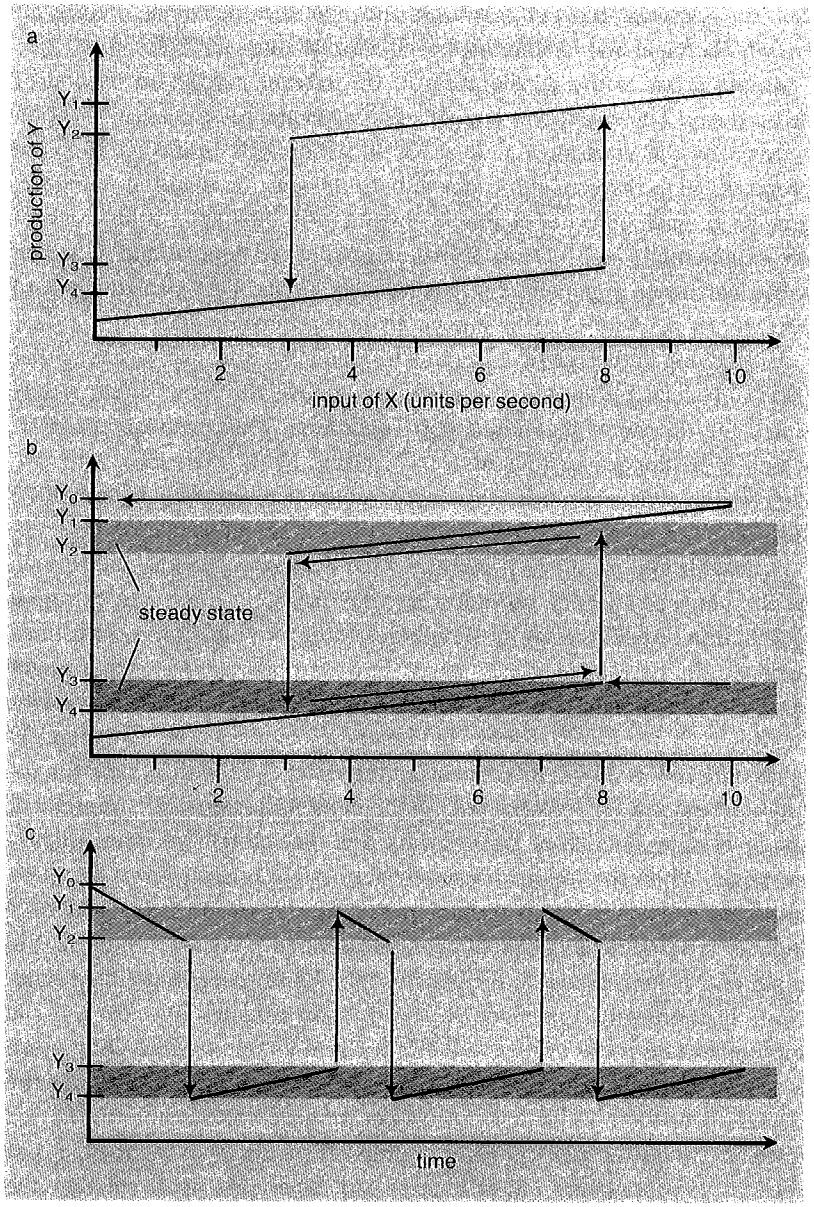
that the simplest type of feedback and one that occurs in nearly all known chemical and biochemical oscillators is autocatalysis.

Autocatalysis is the acceleration of the rate of a reaction by one of its products. The simplest example of an autocatalytic chemical reaction is given by the equation $A + X \rightarrow 2X$, in which X is produced at a rate proportional to the concentrations of both the starting material A and the product X. Such behavior is almost ubiquitous in biology; it is the basis of the exponential (Malthusian) growth of unchecked populations, in which X is a particular organism and A is its food supply. It is a relatively rare occurrence in chemistry, but autocatalytic reactions do exist.

In studying autocatalytic reactions in a flow reactor, one observes that they can show bistability, the existence of two different stable steady states for the same set of reaction conditions. This peculiar behavior, which is analogous to that of a ball rolling along a surface with two depressions in it, can occur only in open chemical systems. It provides a starting point for the systematic design of a chemical oscillator.

A bistable system shows hysteresis. That is, as some control factor such as the concentration of an inflowing reactant or its flow rate is varied first in one direction then in the other, the system undergoes transitions between the two stable steady states. For example, such a system might consist of a solution of a red-colored reactant A and a colorless reactant X, which are fed into a reactor and react to produce a blue compound Y. When the inflow of X is low, the steady-state level of Y is low, and the solution in the reactor remains red. As the input of X is gradually increased, the level of production of Y also grows, and the solution becomes slightly purplish. When the input of X reaches a certain critical level, say eight units per second, a sharp transition occurs, the steady-state level of Y increases dramatically, and the solution suddenly becomes blue. If the input of X is increased still further the solution remains in the blue state. Now, if one begins to reduce X, the solution remains blue even if the input goes below the critical value of eight units per second. Only when a second critical point, say three units per second, is reached does the reverse transition occur and the system jumps from the blue to the red state. Between the two transition points, from three to eight units per second, the solution is either blue or red depending upon whether the system arrived at the present conditions from higher or lower inputs of X. Thus the state of the system depends upon its past history.

A mathematical model developed by Jacques Boissonade and Patrick De Kepper of the Paul Pascal Research Center in Bordeaux, France, leads to an interesting prediction about such bistable systems. In the example above, suppose a substance Z can be found that reacts with the substance in the reactor to change the level of X. If Z reacts sufficiently slowly and if the effect of Z is much greater when the system is in one of the steady states than in the other, then addition of the proper amount of Z to the bistable system will produce a feedback that will cause the system to jump periodically from one branch of steady states to the other; *i.e.*, to oscillate. The Boissonade-De Kepper prediction is an integral part of a systematic method to search for or design new chemical oscillators.



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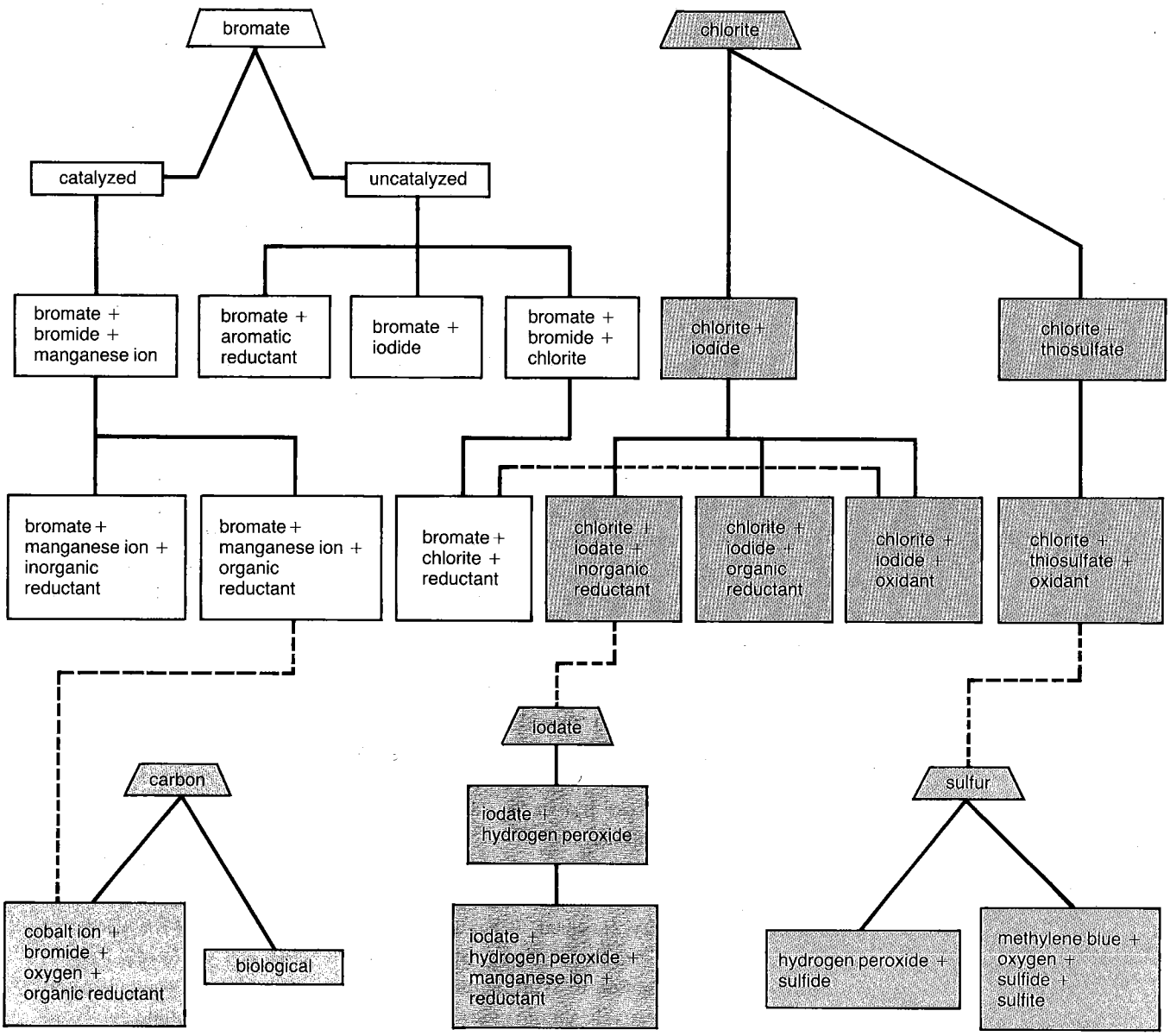


The procedure starts with finding an autocatalytic reaction. Although autocatalysis is not common, several of these reactions are well-known as lecture demonstrations since they give rise to sudden, dramatic color changes. After selecting an autocatalytic reaction, one runs it in a flow reactor to find conditions under which the system is bistable. If bistability is obtained, one then seeks a suitable feedback substance. When the input concentrations are adjusted, hopefully the system will oscillate.

This technique was first applied successfully in 1980 at Brandeis University, Waltham, Massachusetts, by De Kepper, Irving Epstein, and Kenneth Kustin. The autocatalytic reaction involved arsenite (AsO_3^{3-}) and iodate ions, which generate iodide (I^-) as the product. The feedback substance was chlorite ion (ClO_2^-), which actually reacts autocatalytically

with the iodide produced by the first reaction. Thus, two autocatalytic reactions are coupled together, and the color of the system alternates between brown and colorless. Later studies led to the discovery of more than two dozen oscillators involving the chlorite ion.

More oscillators

The first, accidentally discovered chemical oscillators and the later, systematically designed chlorite oscillators are related to each other chemically in a significant way. Each is based on the chemical reactions of an oxyhalogen ion: iodate (IO_3^-) in the case of the Bray reaction, bromate (BrO_3^-) for the BZ reaction, and chlorite (ClO_2^-) for the new systems. That is, in all of these systems the key to oscillatory behavior is an ion consisting of a halogen atom—an element from column VIIA of the periodic table that has all but one of the possible places in its outermost electron shell filled—and several atoms of oxygen.

Why should oxyhalogens be so favorable to chemical oscillation? Could elements from other parts of the periodic table be used as well?

The crucial property of the halogen elements appears to be their ability to support a large number of oxidation states. In other words, iodine, bromine, and chlorine are relatively stable whether they are associated with one electron more or with one, three, five, or seven electrons less than they possess as neutral atoms. This versatility allows them to shift rapidly from one form to another, a requirement for participating in oscillatory processes in which intermediate species are produced and consumed with each cycle.

One might then expect that new types of oscillators should be sought among those elements that also possess multiple oxidation states. Since 1983 success has been achieved with two nonhalogen elements, carbon and sulfur.

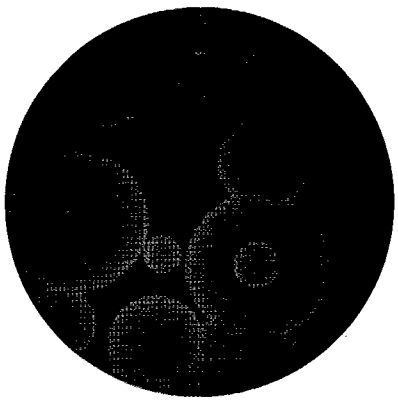
The ubiquity of oscillation in living systems suggests that there exist literally thousands of organic, carbon-based oscillators. Owing to their complexity, however, it has not proven possible to isolate the chemical origin of oscillation in any of them. Scientists at E. I. du Pont's Experimental Station in Wilmington, Delaware, have discovered oscillations in a comparatively simple organic system, the cobalt- and bromide-catalyzed air oxidation of two common organic chemicals, benzaldehyde and cyclohexanone. These reactions, which are similar to industrial processes that produce billions of kilograms of organic chemicals each year, constitute the first two well-characterized organic oscillators. The periodic change in the oxidation state of the cobalt ion causes the system to alternate between pink and greenish-brown.

A similar breakthrough in sulfur chemistry has produced two new oscillators. The first, developed by Richard Field and Maria Burger at the University of Montana, involves the reaction of sulfide (S^{2-}) and sulfite (SO_3^{2-}) ions with dissolved oxygen in the presence of the dye methylene blue. The solution oscillates between blue and colorless. The second sulfur-based oscillator, discovered by Miklos Orban of Eotvos University in Budapest, Hungary, is somewhat simpler in composition, containing

Photo sequence (facing page, top to bottom) taken at half-minute intervals follows the formation of two-dimensional bull's-eye patterns in a thin layer of a modified BZ formula on the bottom of a petri dish. Blue spots appear spontaneously on the red field of the BZ mixture and spread into circles. Shortly thereafter the centers of the circles regain their red color, and new blue spots appear in the same places as the previous ones. As these chemical oscillations continue, concentric rings are built up.

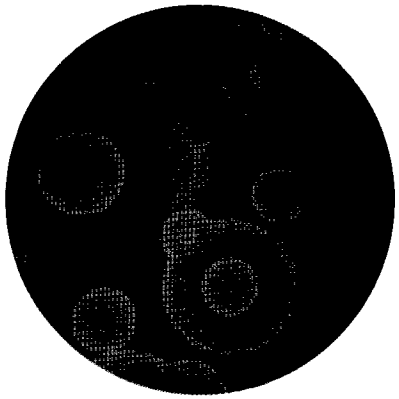
Photos, A. T. Winfree

only sulfide ion and hydrogen peroxide. Since this system alternates between acidic and basic (alkaline) states, the oscillations can be followed in a variety of colors by adding any of a number of color-changing acid-base indicators.

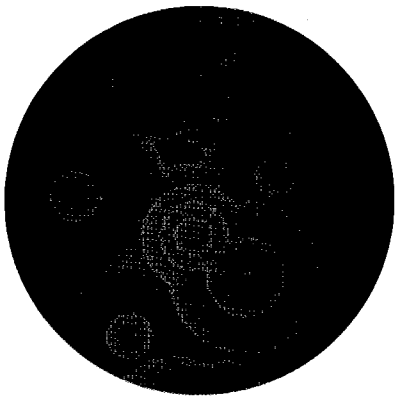


Patterns in space and time

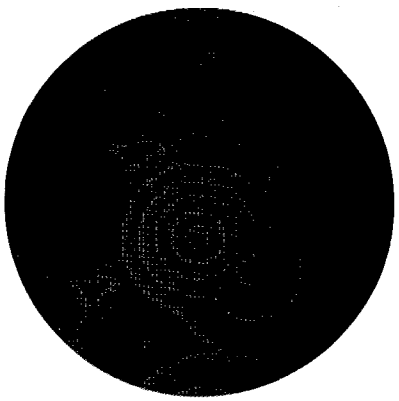
The first studies of chemical oscillation were directed toward eliciting simple, periodic, homogeneous behavior. The systems were required to be well-stirred and uniform. Ideally each cycle of oscillation would be exactly the same as the previous cycle and would contain one maximum and one minimum in each concentration. More recently, by varying the conditions and looking carefully, chemists have discovered fascinating phenomena that are intimately related to the oscillations studied earlier but far more complex.



Perhaps the most striking example is the spontaneous development of spatial patterns in an initially uniform, unstirred medium. If the iron-based oxidation-reduction indicator ferroin is used instead of cerium in the BZ reaction, then the system can oscillate between a red and a blue state. With certain concentrations of the reactants, however, the system is not oscillatory but excitable. Stirred and left undisturbed, it remains in one state, say red, but a small disturbance like a drop of acid can cause it to turn blue and remain that way for several seconds before returning to the stable red state. When this excitable mixture is poured in a thin layer at the bottom of a petri dish and left alone, a remarkable thing happens. After a few minutes one or more blue spots appear. Each of these enlarges and its center turns back to red, so that the spot becomes a ring of blue. As time goes on, a new blue spot forms in each red center and grows into a ring. Soon the dish is filled with sets of concentric blue rings on a field of red. When rings get large enough to touch one another, they annihilate and disappear, leaving behind the red background.



How can such a thing occur? Intuition suggests that any nonuniform pattern that develops in an initially homogeneous medium will soon fade away as a result of diffusion, just as the random motions of molecules tend to disperse a drop of ink placed in a glass of water. But in an excitable and potentially oscillatory system in which autocatalytic reactions are possible, something else may occur. A small fluctuation, perhaps a spontaneous local increase in the concentration of a reactant, may cause a tiny bit of solution to change from red to blue. Since the reaction is autocatalytic, as diffusion spreads the blue material, it causes nearby areas to turn blue as well as the red-to-blue reaction accelerates. The spot enlarges. Soon, however, the central region where the disturbance started returns to its red state. A ring has formed. As the system continues to oscillate, further rings are generated.



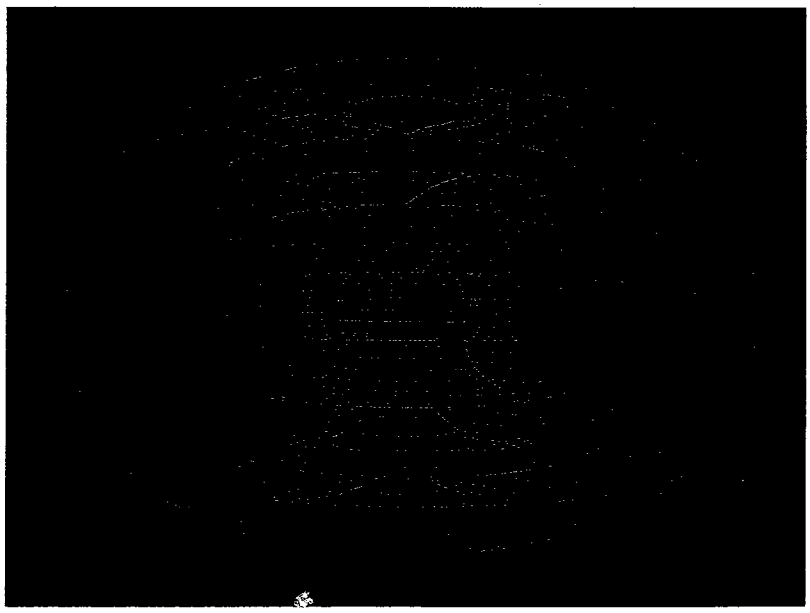
Must such behavior be restricted essentially to two dimensions on the bottom of a petri dish? Early experimenters found that if the layer of solution was too thick, the patterns would not form. Later work showed, however, that beautiful and intricate three-dimensional patterns can de-

Another type of nonsimple behavior is aperiodic oscillation or, as it is sometimes called, chemical chaos. Imagine a pendulum whose swings vary in length, never repeating the same sequence. Although the swings appear random, there is an underlying determinism; given the length of one swing and a knowledge of the system's makeup, one can predict exactly the length of the next swing. Such oscillation is aperiodic, but nonrandom. The chemical analogue of such a system would exhibit a nonrepetitive pattern of highs and lows in the concentrations of its components.

Recently this type of behavior has intrigued mathematicians as well as scientists working with physical systems in a variety of seemingly unrelated fields such as electronics, hydrodynamics, and meteorology. Many of these systems can be described by sets of differential equations that possess solutions known as strange attractors. The solutions correspond to the sort of nonrandom, aperiodic variation described above. They have two other properties of interest, which give rise to their name. They are attractors in the sense that if one starts off the physical system in a state different from that of the attractor, the state changes in such a way as to bring the system ever closer to the attractor. Ultimately the system will exhibit the behavior characteristic of the attractor.

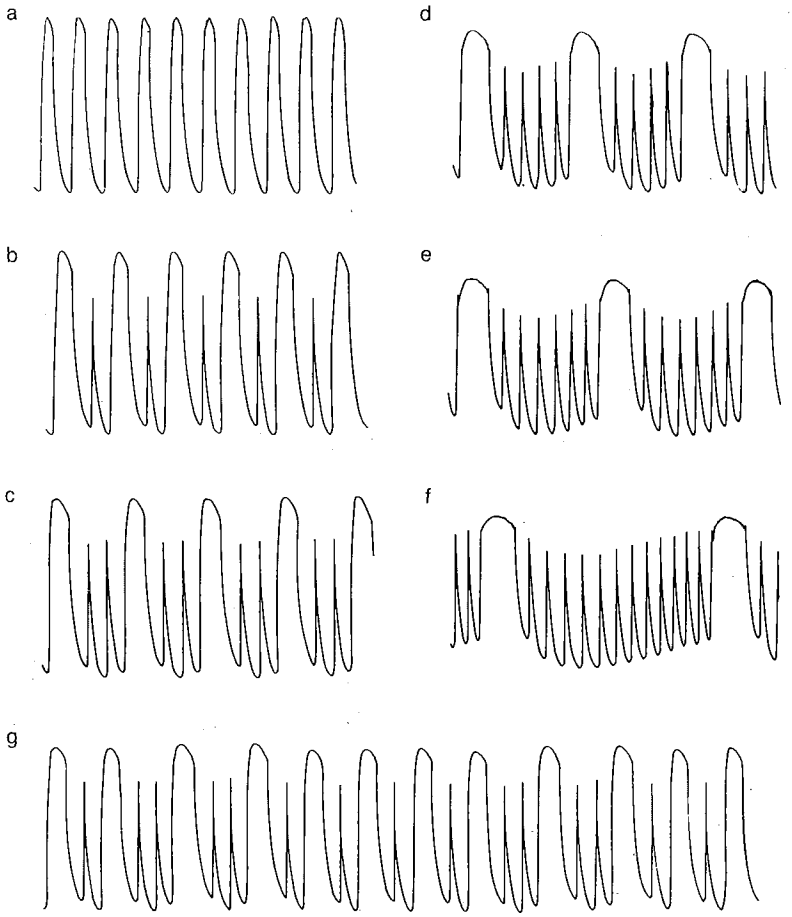
The attractor itself is strange in the sense that if one starts off the system twice, once from each of two almost identical sets of conditions, within a short time the system evolves to two very different sets of conditions. In a system having a strange attractor it is impossible to "perform the same experiment twice." Regardless of the effort, one can never prepare the system with exactly the same starting conditions, and the small initial differences will ultimately grow into major discrepancies.

Chemical oscillators have been shown to possess strange attractors, and in some cases the structure of the attractor has been characterized.



A. T. Winfree

Under appropriate conditions a test tube filled with an initially homogeneous solution of BZ reactants can produce intricate three-dimensional patterns (facing page, left). The most common pattern is the scroll wave (facing page, right), a solid spiral. One variation, in which the ends of the scroll close to form a doughnut-shaped ring, is shown in a computer-generated image (this page, left); sections of the scroll surface have been removed, creating "windows" to inner detail.



Periodic oscillations in a reaction between solutions of chlorite and thiosulfate ions in a CSTR have been found to exhibit a variety of patterns when the input flow of reactants is varied. At low rates ion concentrations show simple large-amplitude oscillations over time (a). As flow rates are raised, the system makes successive transitions to complex periodic modes in which large peaks alternate with increasing numbers of smaller peaks (b–f). Between adjacent modes flow rates can be "fine-tuned" to give aperiodic, or chaotic, patterns that are apparently random mixtures of the two modes. For example, between the periodic oscillations shown in b and c can be found the aperiodic oscillation shown in g.

The first and most thoroughly studied chaotic chemical system was the BZ reaction, but chaotic behavior has been observed in several chlorite reactions and in a biochemical oscillator, the horseradish peroxidase system, as well. Current research is aimed at elucidating the underlying mechanisms of chemical chaos, the processes by which a periodic oscillator becomes chaotic as some element, *e.g.*, a reactant concentration, is varied, and the different types of chaotic behavior.

Expanding applications

As chemical oscillators have become better understood, the principles that underlie them have found application in fields other than chemistry. Three of these fields, all rather closely related to chemistry, are geology, meteorology, and biology.

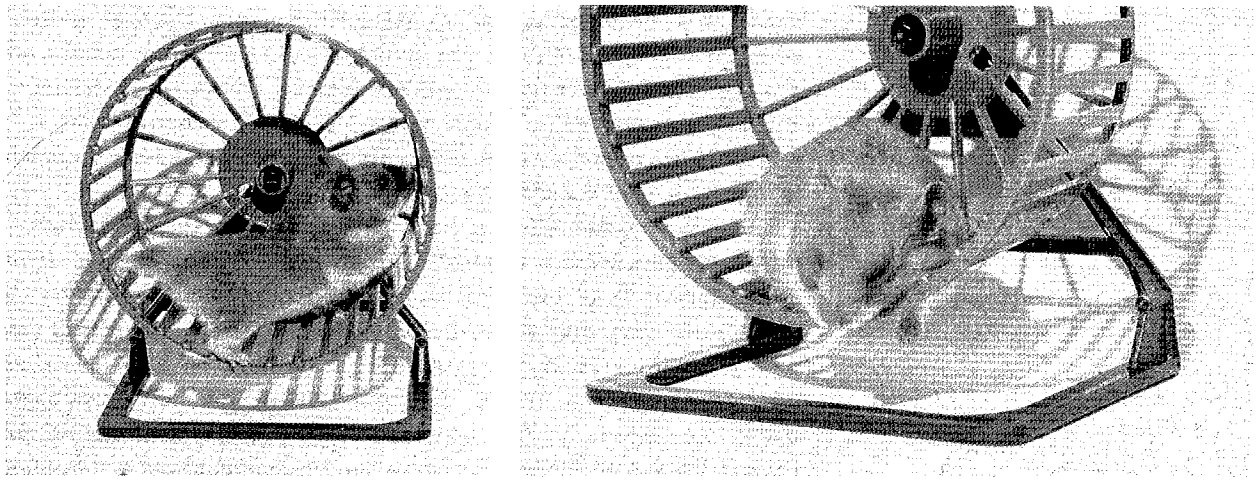
For almost a century chemists have been fascinated by the periodic precipitation patterns known as Liesegang rings. Two separate solutions, each containing one of a pair of ions—such as silver (Ag^+) and dichromate ($Cr_2O_7^{2-}$)—that react to form a nearly insoluble compound, are placed at opposite ends of a tube filled with a gel. As the ions diffuse through the gel toward one another, a precipitate forms—in this case,

silver chromate (Ag_2CrO_4). Contrary to expectations, however, the precipitate does not deposit uniformly, but in a series of sharp, nearly evenly spaced bands. Recent theories account for this phenomenon by invoking the competitive autocatalytic growth of different-sized particles of precipitate coupled to diffusion of the reactants, an explanation analogous to that offered for pattern formation in the BZ system. Scientists are presently using similar theories to model the formation of band and zone patterns in a wide variety of rock formations, despite the vast difference in time and length scales between the geological and chemical systems.

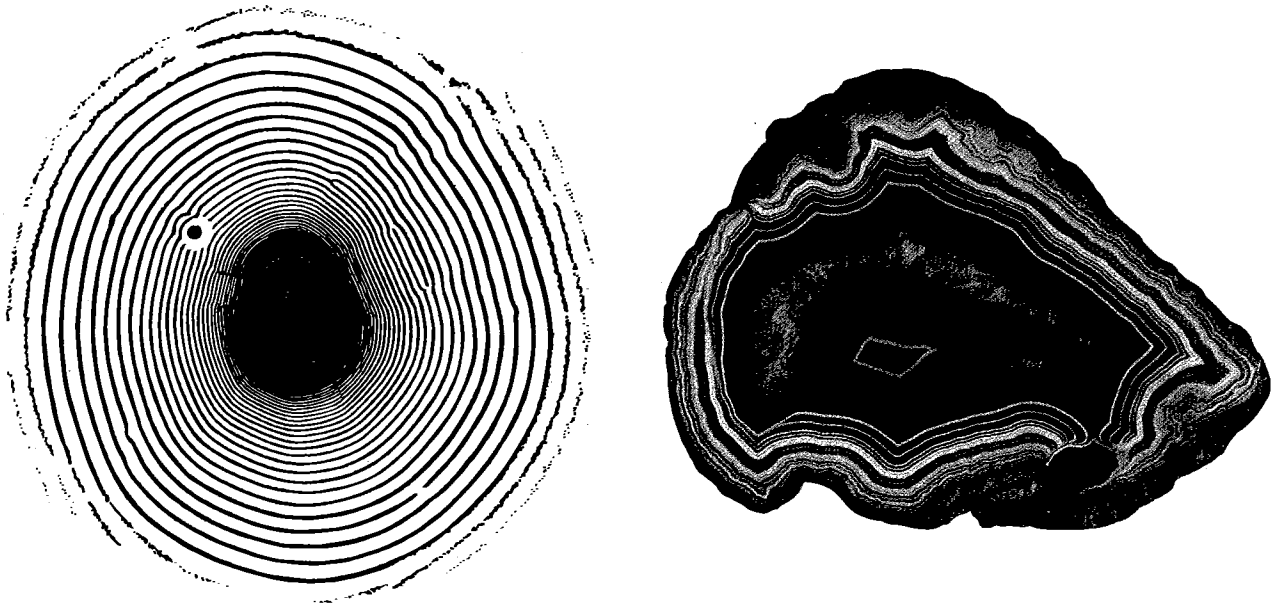
The existence of strange attractors may have profound consequences for the prospects of long-range weather forecasting. One of the earliest models of a strange attractor, proposed by meteorologist E. N. Lorenz of the Massachusetts Institute of Technology, describes the flow of air in the atmosphere. Suppose that the weather is a system that possesses a strange attractor. If forecasters knew the equations that govern the changes in the weather, could they, even in principle, develop good long-range weather forecasting? The answer appears to be no because of the nature of the strange attractor. One never knows the current weather with infinite accuracy. Temperatures are measured only to within a degree, or perhaps a tenth of a degree, wind velocities to within a kilometer per hour or so. If two initial states differing by a tenth of a degree can evolve within days or weeks to situations in which temperatures differ by tens of degrees, then long-range forecasting is an impossiblity.

The field on which studies of chemical oscillators are likely to have their greatest effect is biology. For example, nerve impulses involve the transmission of electrical signals from neuron to neuron across gaps called synapses. The mode of transmission involves messenger molecules called neurotransmitters and the change in permeability of the cell membrane to various ions in response to changes both in neurotransmitter concentrations and in the electrical potential across the membrane. This membrane potential undergoes rhythmic fluctuations, called action potentials. Neurobiologists are beginning to formulate molecular models to account for membrane oscillations based on the idea suggested by

The activity-rest cycle in animals (below), the daily opening and closing of flowers, the 90-minute dreaming cycle of the human brain, and the second-by-second beat of the heart are but a few examples among thousands of the oscillatory behavior apparent in living organisms. Many biologists suspect that most if not all biological oscillation is controlled at the molecular level by chemical oscillators.



Photos, Alan A. Moss



Concentric rings of silver chromate precipitate (above) can be formed by placing a crystal of silver nitrate at the center of a glass plate coated with gelatin containing a dilute solution of potassium dichromate. Recent theories for this phenomenon, called Liesegang rings, give an explanation analogous to that offered for pattern formation in the oscillating BZ system. The banding patterns in agate (above right) and many other minerals closely resemble that of Liesegang rings and are believed to arise by way of the same general mechanism.

(Right) B. M. Shaub

Nobel laureates Alan Hodgkin and Andrew Huxley in 1952 that the membrane contains "voltage-gated" channels for different types of ions. These channels open or shut as the membrane potential passes through a critical value.

One of the most exciting applications of these ideas to problems in biology is a recent proposal by Arthur T. Winfree of Purdue University, West Lafayette, Indiana, that sudden cardiac death syndrome can be understood in terms of the response of a chemical or electrical oscillator to a disturbance. Winfree argues on the basis of theorems in topology that there must be a particular, "singular" stimulus of exactly the right strength and timing that is capable of disrupting the regular oscillation of the heart's natural pacemaker. When this singularity develops it initiates a three-dimensional rotating wave of electrical activity, an action potential, that passes through the cardiac tissue, much as the colored wave of chemical activity passes through a petri dish of BZ reagent. The result of this wave is fibrillation, a rapid, irregular contraction of the heart muscle, which, if it persists, is fatal. The stimulus could come from outside the body or, more likely, from a random impulse from one of the many neighboring nerve cells. Should Winfree's hypothesis prove correct, it might provide important guidance in designing drugs and other therapies to lessen the risk of a sudden cardiac death.

One may speculate whether the mechanisms that produce spatial structure in simple chemical reactions are related to those that are involved in the formation of biological patterns. For example, the similarities between the rings formed in the BZ and other "simple" chemical systems and those seen in the aggregation of the slime mold *Dictyostelium discoideum* are truly striking. *D. discoideum* and other cellular slime molds, demonstrate a remarkable life cycle that has been studied for clues to the way the cells of higher organisms communicate and become

organized. Part of their time is spent as separate, free-living amoebalike cells. When food becomes scarce, they signal to each other chemically and subsequently aggregate into a multicellular structure that culminates in a spore-filled fruiting body. In the earliest stage of aggregation, cells of *D. discoideum* release the substance cyclic adenosine monophosphate (cAMP) at about five-minute intervals and in a way that establishes centers of concentration. Each cell has receptors on its surface that allow it to sense and move toward higher concentrations of cAMP. As aggregation progresses the periodic release of cAMP organizes the moving cells into spiral or concentric circular patterns about the concentration centers. This coupling between temporal oscillation and motion toward a chemical attractant is similar to the interaction of oscillatory chemistry and diffusion in the nonliving BZ system. One may also ponder whether the interaction between diffusion and excitable chemical reactions might provide a means whereby a single, apparently uniform cell could divide into increasing numbers of identical daughter cells, which at some point become irrevocably destined for skin or bone or brain cells.

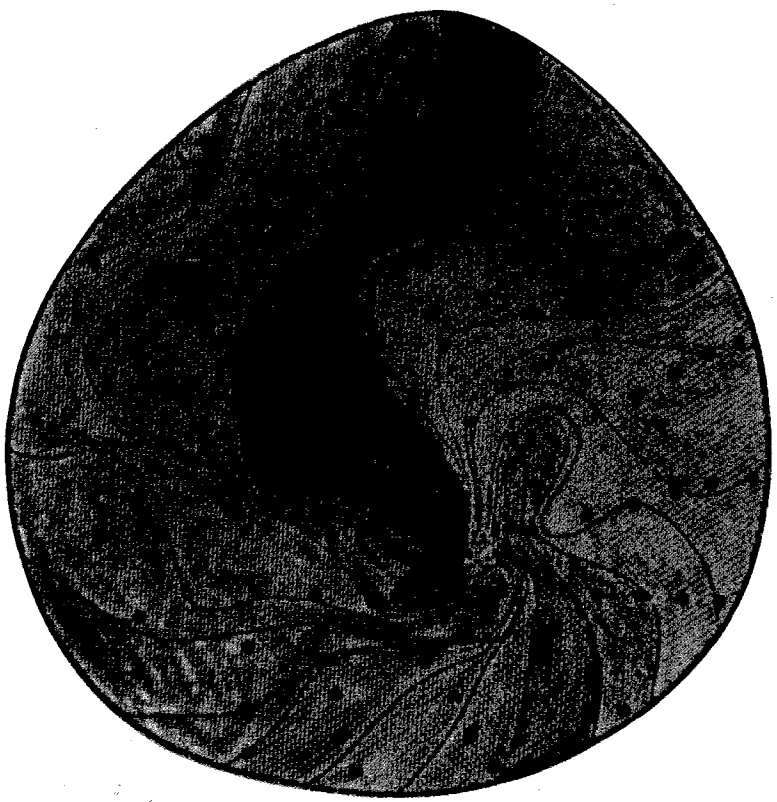
Future prospects

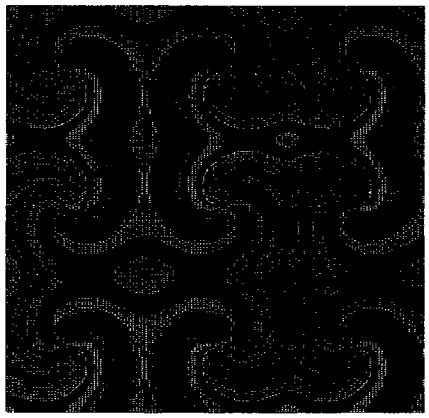
It is hard to predict the next decade for a field that was essentially nonexistent 15 years ago. Some directions seem nearly self-evident while others are highly speculative.

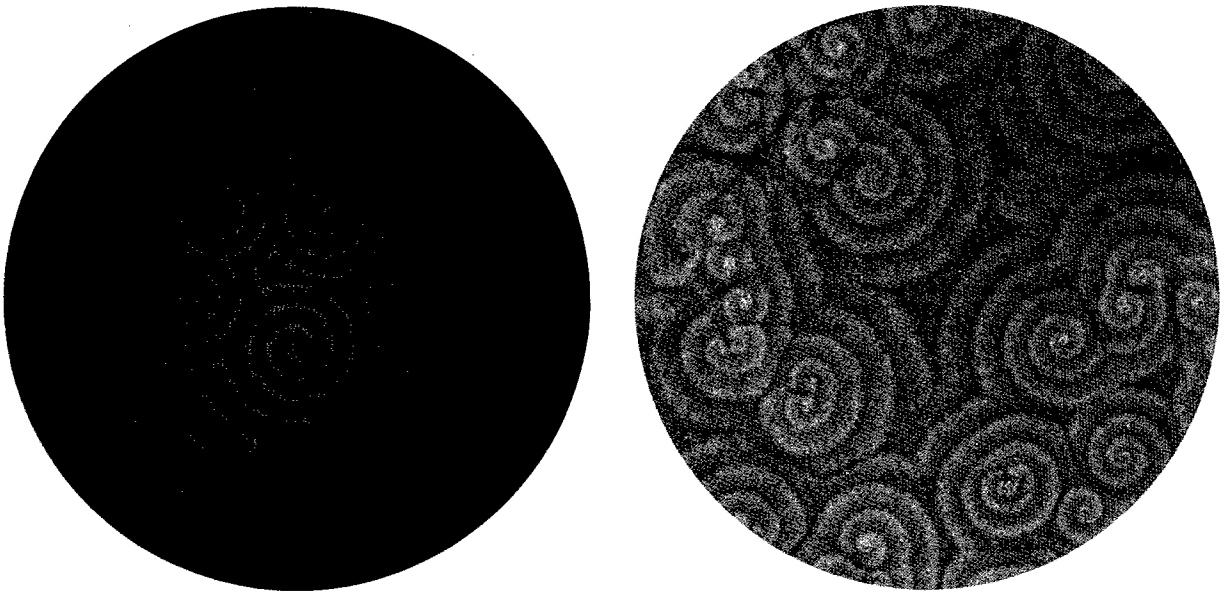
Work is likely to continue on developing new oscillators and on understanding both existing systems and those still to be discovered.

A fatal irregular beating, or fibrillation, of the heart muscle is the only manifestation of an as yet inexplicable category of heart disease called sudden cardiac death syndrome. Both theory and clinical observation suggest that the condition may be caused by a three-dimensional rotating wave of electrical activity—similar to the waves produced in a BZ reaction—that disrupts the regular oscillation of the heart's natural pacemaker. One model of such a wave, a computer-generated square array of counterrotating vortices, is shown below. At the lower left a drawing depicts the electrical activity recorded from the ventricles of a living human heart during open-chest surgery. The tip-on perspective, as if viewed from directly below the heart, reveals a five-cycle-per-second rotating wave pivoting around the apex of the ventricles.

(Left) adapted from information obtained from A. T. Winfree; (right) A. T. Winfree







Spiral waves of oscillating chemical activity in a petri dish of BZ reactants (above) bear a striking similarity to the organized waves of cell movement during aggregation of the slime mold Dictyostelium discoideum *(above right). Both phenomena may hold clues to the way cells of higher organisms communicate during morphogenesis, the complex process by which the cells and tissues of an embryo become patterned into a complete organism.*

(Left) A. T. Winfree; (right) Peter N. Devreotes, Department of Biological Chemistry, The Johns Hopkins University School of Medicine

Biological oscillators are based primarily upon the chemistry of organic compounds and transition metals, particularly systems in which enzymes are involved. Now that the first nonbiological organic oscillators have been found, many more should follow. Scientists have begun to design oscillators based on such transition metals as chromium, cobalt, and vanadium, which support a wide range of oxidation states. Increasingly sophisticated experimental and computational techniques should yield rapid progress in explaining reaction mechanics. While it took 15 years from the discovery of the BZ reaction to develop a mechanism for it, the chlorite-iodide oscillator, of comparable complexity but discovered in 1981, was explained mechanistically within three years.

More attention will probably be devoted to the practical applications of chemical oscillation. Chemical engineers have known for years that industrial reactors which produce large quantities of chemicals occasionally go into oscillation spontaneously. They have developed methods of suppressing this behavior, since an uncontrolled oscillating reactor may escape its usual operating range and either explode or shut down. It makes sense, however, to ask whether certain processes might not be more efficient, in the sense of yielding more product or a higher ratio of desired to undesired material, if they were operated in a controlled oscillatory mode rather than the usual steady state.

The role of chemical oscillation in catalysis is a concept worthy of investigation. Catalysts, substances that speed up a reaction without being changed themselves, are essential factors in almost every process of industrial or biological significance. In order to perform its work, each catalyst molecule or particle must oscillate between two or more different states. In most cases, however, oscillations of the total catalyst concentration have not been observed, either because they occur too fast to be seen without special techniques or because the different portions

of the catalyst oscillate independently of one another so that, on the average, the fraction in any given state is independent of time. Might it be possible to induce the molecules of catalyst to oscillate in phase with one another? And could such coherence increase the efficiency of the catalyst?

Finally, it is likely that studies of chemical oscillators will draw closer to biological and biochemical systems. This approach may take several forms. Experiments with chemical oscillators coupled together either by physical transfer of material from one reactor to another or by sharing a common component in the same vessel have given rise to a complexity of behavior not found in the individual uncoupled system. Further studies of this sort may shed light on the workings of biochemical pathways or structures that may be viewed as a set of linked oscillators.

Investigations of this type attempt in a sense to simulate and gain insight into biological complexity by starting from simple chemical systems and making them increasingly more complicated. An alternative method is to begin with a biological system and dissect it into pieces to which the techniques developed for studying simpler oscillators may be applied. For example, studies are under way to probe whether a single enzyme, phosphofructokinase (PFK), will generate oscillations in a flow reactor. If so, this would be strong evidence that PFK is responsible for the oscillatory behavior of glycolysis, a process used by nearly all living organisms to generate energy-rich adenosine triphosphate (ATP) from glucose.

During the past decade chemical oscillation has become a well-established and well-studied phenomenon. During the coming years scientists will ascertain whether those fascinating beakers of solution that turn from red to blue and back again can help answer such questions as why the heart beats so regularly and why sometimes, unexpectedly, it stops.

FOR ADDITIONAL READING

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