where it apppears to be an integral part of the membranes. They also find a secreted soluble form, which may be different from the membrane protein.

In any event, macrophages enter into direct and specific cell-to-cell contacts with their partners during the initiation of immune responses. The appearance of interleukin-1 on the macrophage membrane may thus help to focus this essential activating signal on just those immune cells that respond to a particular foreign antigen. This finding might explain how interleukin-1 could work without actually being secreted but does not explain how the protein arrives at the membrane in the first place.

Mizel, although he supplied an antibody needed for the Unanue group's work and thus appears as a coauthor on their paper, is not convinced that interleukin-1 works the way Unanue proposes. Mizel, suggests that the membrane-bound form may be on its way out of the cell and not an integral membrane component.

The cloning of the interleukin-1 genes has apparently settled one issue concerning this important lymphokine. There does indeed appear to be a family of the proteins. But many other questions have been raised. For example, the number of proteins that will ultimately be found to belong to that family is currently unknown, as is the manner of their release from the cell and the significance of the membrane-bound and soluble forms.

Also unknown is whether the various family members will differ in their activities. "The assumption that many activities can be ascribed to the one molecule will have to be reinvestigated," notes Steven Gillis of Immunex. Whereas the Immunex workers indicate that there may be differences in the range of activities of their two human interleukin-1's, Mizel notes that the mouse protein appears capable of all the known interleukin-1 functions.

The studies needed to resolve these issues will be greatly facilitated by the new ability to use the cloned genes to produce milligrams of the pure proteins in bacteria, yeast, or mammalian systems. "I have been involved in interleukin-1 research for 10 years," Mizel says. "The things we once dreamed about, we can now do."—**JEAN L. MARX**

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Fractal Fingers in Viscous Fluids

Highly unstable viscous fingers break up into many-branched structures that are suggestive of fractal geometry

An initially flat interface between two immiscible fluids does not move uniformly when pressure is applied to the less viscous of the fluids. In the most general case, the interface can become wavy and then break up into an array of fingers in which each fluid interpenetrates the other, although the average interface position moves in the direction of the pressure gradient.

During the last year, researchers have wondered under what conditions, if any, viscous fingers can exhibit fractal behavior. Fractal objects have a property called self-similarity—that is, they have similar features at all length scales and therefore look the same at all magnifications—and are characterized by an effective fractional dimension, rather than the 1, 2, and 3 of curves, surfaces, and volumes.

The first and so far strongest experimental example of fractal viscous fingers was reported in March by Johann Nittmann and Gérard Daccord of Dowell Schlumberger in St. Etienne, France, and H. Eugene Stanley of Boston University (*1*). Since then a number of results suggesting incipient fractal behavior under somewhat different experimental conditions have or are about to come out. An unanswered question is whether fractal viscous fingers are a general phenomenon or are peculiar to the particular types of fluids used by Nittmann, Daccord, and Stanley.

The three investigators also argued that the numerical model that researchers use to simulate the growth of a class of fractal objects known as diffusion limited aggregates likewise describes the fractal viscous fingers in their experiments. In an interesting turnabout, some theorists are finding that it is possible to extend the diffusion limited aggregation (DLA) model to simulate nonfractal viscous fingering, as well.

Apart from their curious properties, why should fractals be of interest? The answer lies in their self-similarity, which is a kind of symmetry—in this case invariance under a change in length scale. This sort of symmetry has an immense attraction to physicists at the moment, partly because of the crucial role it played in the development of the theory of second-order phase transitions (critical phenomena) in the late 1960's and early 1970's. Understanding how to accurately calculate the properties of physical systems near their critical points, where their behavior is strongly nonlinear, was one of the major triumphs of condensed matter science.

In critical phenomena, self-similarity is closely connected with another property, universality. Since a self-similar physical system looks the same under all magnifications, it has structures that are very large in comparison with the range of basic forces within it. The properties of these large-scale structures depend only on certain long-range symmetries and not on the local details of the forces. This implies that, near their critical points, quite different physical systems that show the same symmetries behave in the same way; that is, universally.

Following the connection of self-similarity with universality by Leo Kadanoff (now at the University of Chicago) and others, Kenneth Wilson of Cornell University was able to rigorously develop it in the renormalization group theory of critical pheonomena that later won him the 1982 Nobel Prize in physics. Now anything that smacks of self-similarity with its attendant promise of unifying diverse phenomena has considerable appeal.

Recently, for example, scientists have been fascinated by the behavior known as chaos that occurs in a wide range of dynamical systems (those that evolve in time), including fluids, that are described by nonlinear equations (*Science*, 5 November 1982, p. 554, and 8 July 1983, p. 140). The behavior is called chaotic because it seems to be wildly unpredictable or noisy, although in fact it is entirely

deterministic. Researchers have found some evidence for universality in nonlinear dynamical systems, but the jury on chaos is still out.

Fractals actually have a lengthy and independent history in the mathematics literature, although the name itself is rather recent, having been coined by Benoit Mandelbrot of the IBM Yorktown Heights laboratory. Mandelbrot is a mathematician by training, but, inspired by the apparent ubiquitousness of fractal behavior in the physical world, he has devoted considerable effort to bridging the gap between mathematics and the physical sciences insofar as fractals go. His text on the subject is a starting point for many newcomers to the field (*2*).

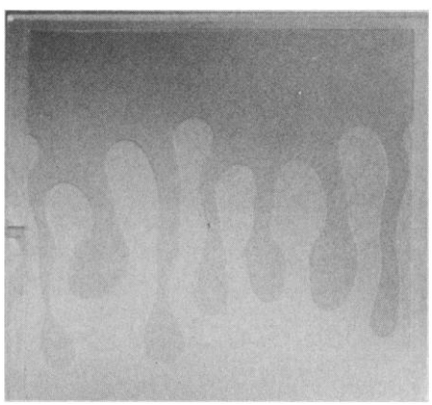
To get a feel for fractals, consider a closed curve on a plane. Ordinarily, measuring the circumference of the curve with a measuring stick gives a finite answer that converges to the true circumference as the size of the stick decreases. If the curve exhibits self-similarity, however, each bump on the curve will have smaller bumps, which in turn have bumps, and so on. As the length of the measuring stick decreases, the smaller and smaller features that are detected must be included in the total. In the limit as the length of the measuring stick becomes vanishingly small, the circumference becomes infinite.

The fractal dimension comes from the relationship between the circumference, as given by the number (N) of measuring sticks of a given length (r) needed to encompass the curve and the length of the measuring stick. For an ordinary curve, which is a one-dimensional object, $N \sim 1/r$, but for a fractal curve, $N \sim 1/r^D$, where D is the fractal dimension of value between 1 and 2. The same reasoning applies to surfaces, where the surface area measured in balls of radius r is proportional to $1/r^2$ for ordinary surfaces but to $1/r^D$ for fractal surfaces, where D is between 2 and 3.

These definitions rigorously apply only in the limit as r becomes vanishingly small, which is not possible to realize in the physical world, where atoms and molecules set the ultimate minimum length scale. However, for practical purposes, the relation need hold only over a suitably wide range of r, a factor of 10 or more, for example. Researchers have no problem with the idea that an object can be fractal only in a certain range of length scales but not in others.

Viscous finger experiments are carried out in a device called a Hele-Shaw cell that comprises two closely spaced glass plates. One way of doing the experiment is to fill the cell with the more viscous fluid and then inject the less viscous fluid at one end. Because the cell is so thin, the two-fluid system is effectively two dimensional. The interface between the two fluids, which is the object of interest, is a curve, which may or may not have fractal properties.

Fluids have several properties that influence viscous fingering. They can, for example, be either immiscible or miscible. In the latter case, it is not possible to maintain a sharp interface and the fingering becomes ill defined. In addition, they can be either Newtonian or non-Newtonian. Newtonian fluids have a well-defined viscosity, while that of non-Newtonian fluids depends on the fluid velocity.



Viscous fingers

Fingering pattern in a critical mixture of isobutryic acid and water in which the viscosity contrast is very low (6).

Most of the literature on viscous fingers deals with Newtonian fluids that are immiscible (at least for the few minutes a typical experiment lasts). One focus has been on the special case in which one fluid has almost no viscosity and in which a single stable finger of the low viscosity fluid forms and grows at a steady velocity down the length of the Hele-Shaw cell.

The parameter that determines the stability of the finger is a dimensionless number called the capillary number and is proportional to the ratio of the interface velocity to the surface tension at the interface between the fluids and to the square of the ratio of the cell width to cell thickness. The most recent research suggests that stable fingers exist over a wide range of capillary numbers, but that they become increasingly susceptible to small perturbations as the capillary number grows, which causes the formation of more complex structures (*Science*, 17 May, p. 834).

One conjecture has been that, as the capillary number becomes very large, the structures become fractals. Part of the reasoning is that the value of the capillary number sets a distance scale (high capillary numbers correspond to small distances) below which perturbations cannot grow. As the distance scale becomes vanishingly small, even the smallest perturbations can grow, so that an incipient finger would grow only a little before bifurcating. Each branch would itself quickly bifurcate and so on, giving rise to a wispy, tree-like structure with a fractal dimension.

There is some experimental and theoretical evidence for this proposition for the two-fluid systems studied in connection with the formation of stable fingers—that is, immiscible, Newtonian fluids with a large viscosity contrast. For example, at Stanford University, Chang-Won Park (now at Union Carbide, Bound Brook, New Jersey) and George Homsy studied fingers of air pushing into a glycerine-water mixture (*3*). As the capillary number was increased (by increasing the driving pressure and hence the interface velocity), the single stable finger first periodically split into two parts, one of which continued to grow and subsequently itself split. At still larger capillary numbers, this so-called tip-splitting behavior becomes irregular and more frequent.

Even more complex structures have been generated by Tony Maxworthy of the University of Southern California, who worked with an air-silicone oil system (*4*). With a relatively wide cell, several fingers start to grow. In the stable regime, one dominates and the others decay. But Maxworthy also observed a regime of instability in which several fingers began tip splitting and developed highly ramified structures before any one finger attained dominance.

A collaboration comprising Eshel Ben-Jacob, Robert Godbey, Tom Mueller, and Leonard Sander of the University of Michigan, Nigel Goldenfeld of the Institute for Theoretical Physics at the University of California at Santa Barbara, and Joel Koplik and Herbert Levine of Schlumberger-Doll Research, Ridgefield, Connecticut, has produced similarly complex fingers (*5*).

These researchers followed an earlier idea of Lincoln Paterson (now at the Australian National University in Canberra) who used a circular geometry in his 1981 experiments and observed tip splitting. The lower viscosity fluid was injected at the center of the Hele-Shaw cell. The idea is that, in the circular geometry, the effective cell width increases as the injected fluid covers a larger area. The effective capillary number rises concomitantly, a large number

of fingers start to grow, and tip-splitting behavior is rampant.

Still another tack was taken by James Maher of the University of Pittsburgh, who investigated fluids of nearly identical viscosity (*6*). He was able to do this by resorting to a binary liquid mixture comprising isobutyric acid and water. At temperatures just below the critical point of the mixture, the system consists of two phases of slightly different density and viscosity and of low interfacial surface tension. By carefully controlling the temperature (to within 1 mK), Maher could control the viscosity contrast.

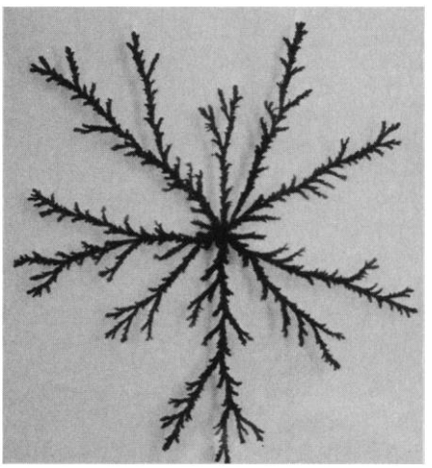
Maher observed that a large number of fingers developed. For the case of almost identical viscosities, the fingers were roughly symmetrical on each side of the average interface position, unlike the case of large viscosity contrast. Moreover, no single finger grew at the expense of the others in Maher's studies. Finally, tip splitting did not occur either, although the interface pattern was quite complex.

Maher's findings qualitatively support numerical simulations of viscous fingering by Grétar Tryggvason (now at the Courant Institute of Mathematical Sciences in New York) and Hassan Aref of Brown University. And, although the connection is less visible than in the cases where repetitive tip splitting takes place, Maher argued that the time dependence of the growth of the fingers was suggestive of fractal behavior.

None of these very recent experiments achieved capillary numbers high enough to clearly reveal the conjectured fractal behavior. Apart from effects due to the walls of the Hele-Shaw cell, which can be considerable, the surface tension is the entity that directly acts to stabilize finger growth. Many fingers or fingers with complex profiles generate a long interface, whereas surface tension acts to minimize the length. As reflected by the scaling in the capillary number, increasing the interface velocity reduces the stabilizing effect of surface tension, but there is a practical limit to how high a pressure one can apply to a Hele-Shaw cell. An advantageous way to generate a fractal structure might then be to experiment with two-fluid systems having a very low surface tension.

Nittmann, Daccord, and Stanley took this head-on approach, but it required a compromise. No one has found a usable set of two Newtonian fluids with a sufficiently low interface surface tension. The researchers therefore resorted to a non-Newtonian system in which water was the low-viscosity fluid and a polymer solution of high molecular mass polysaccharide served as the high-viscosity fluid. These fluids are also miscible, but the mixing time was much longer than the time to do the experiment.

The results were intriguing. The investigators found a single, long, many-branched, wispy finger in a cell of length 0.9 meter, width 0.1 meter, and thickness 0.5 millimeters. This width is larger than in many experiments, which also helps to increase the capillary number. The fingers were similar in appearance to numerically simulated DLA structures. More recent experiments with a radial geometry show a many-armed, spider-like structure (*7*).



Radial fractal fingers

Water injected into the center of a Hele-Shaw cell containing an aqueous polymer solution of high relative molecular weight polysaccharide generates this figure with fractal dimension 1.7 (7).

Interest in the DLA model arose following a 1981 publication by Thomas A. Witten, Jr. (now at the Exxon Research and Engineering Company, Annandale, New Jersey), and Sander of Michigan (*8*). Witten and Sander devised a computer simulation of a growth process in which a seed particle was placed at the origin of a square lattice. A second particle would then be introduced at a random point far from the origin and allowed to walk randomly on the lattice until it reached the seed, whereupon it would stick. The procedure was then repeated a large number of times, building in the process the so-called DLA.

The DLA turns out to be a fractal with dimension measured to be approximately 1.68. A number of physical systems (electrolytically deposited metal films are one example) seem to grow like DLA's. While several groups have explored DLA's in detail by means of computer simulations, a first-principles understanding is not yet in hand. It has not been possible, for example, to calculate from its model what the fractal dimension of a given DLA should be.

Last year, Paterson, who was then at the University of Minnesota, had noted parallels between two-fluid displacements in porous media, where viscous fingering also occurs and for which the Hele-Shaw cell is sometimes used as a model, and DLA's (*9*). Nittman, Daccord, and Stanley took the same path and modified the Witten-Sander DLA model to simulate viscous fingers.

In brief, the seed particle lies at one end of the Hele-Shaw cell, while the random walkers are released from the other. Any random walkers striking the walls before reaching the seed are absorbed by the walls and removed from the simulation. The linear viscous fingers generated in this way visually appear quite similar to the experimental fingers. The measured fractal dimension of the model fingers was only 1.41. However, simulations of still wider Hele-Shaw cells raised the fractal dimension to about 1.6, and the researchers concluded that it would asymptotically reach the DLA value as the width increased further still.

As it happens, the simplest DLA model is not the only one possible. At Chicago, Kadanoff has introduced some new concepts into generalized DLA models with an eye toward using them as a tool for simulating hydrodynamics and viscous fingering, in particular (*10*). His idea is that the original DLA model, which includes only random walkers entering from a great distance, corresponds to the zero surface tension limit. To introduce a surface tension, he allowed for walks from one portion of a growing cluster to another.

The resulting, generalized DLA model obeys the same differential equations as fluid flow in a Hele-Shaw cell. Shoudan Liang and Chao Tang, who are also at Chicago, have since improved the model and have succeeded in reproducing the competition between nonfractal fingers and eventual dominance by one that takes place when the viscosity contrast is high.

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As for fractal viscous fingers, a major question in the mind of some researchers is the role of the non-Newtonian fluid used by Nittman, Daccord, and Stanley. While the use of such a fluid permitted the attainment of the negligible interface surface tension needed to get a fractal, it is also possible that the non-Newtonian character itself played an important role. Until this question is resolved, researchers cannot be sure that fractal behavior is a general characteristic of viscous fingers. Several experiments are planned in the hopes of resolving the issue.

—ARTHUR L. ROBINSON

Hopping Along the Chromosome

Chromosome "walking" has been a familiar exercise to molecular biologists for about 5 years. The technique allows the detailed mapping of relatively long stretches of DNA—nearly 250 kilobases (kb) is the best achieved so far. It has proved valuable for locating specific genes but suffers from the drawback of being tedious. An average walk requires four steps to traverse 100 kb, with each step taking up to 2 months.

A recently developed method, called chromosome "hopping" or "jumping," may have a decided advantage over walking for moving across long stretches of DNA. Hopping currently appears capable of spanning up to 100 kb at a time, about a fourfold improvement over walking. Ultimately, single hops of 500 or even 1000 kb may be possible. Moreover, walking proceeds by the progressive identification of overlapping cloned fragments of DNA and can be stopped in its tracks by a nonclonable region. In contrast, hopping does not require the cloning of all the DNA between the start and stop sites and may thus leap over DNA segments that are refractory to cloning.

The new technique originated independently in Sherman Weissman's laboratory at Yale University School of Medicine and that of Hans Lehrach at the European Molecular Biology Laboratory in Heidelberg. The approaches of the two groups are similar, says Francis Collins, who originally worked with Weissman and is now continuing his hopping research at the University of Michigan Medical School. Both aim at generating "junction fragments," in which the ends of DNA segments of a particular large size, say 100 kb, are brought together while most of the DNA in between the ends is removed (*1*). This is done, as shown in the diagram, by forming circles from the 100-kb pieces and then cutting them with a restriction enzyme. The resulting fragments are small enough to be cloned.

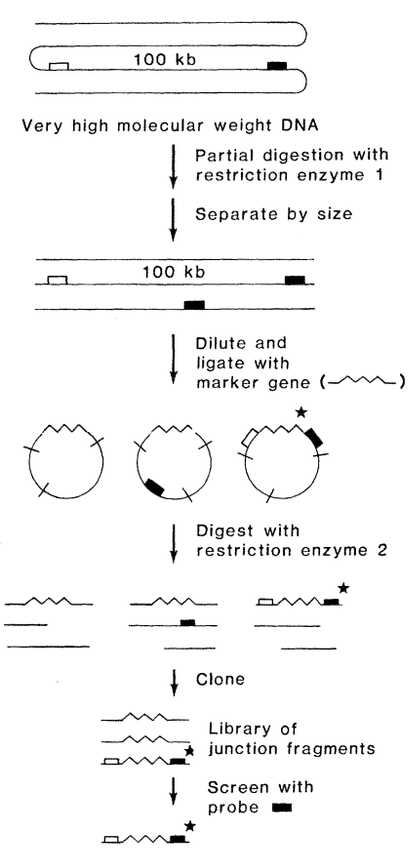
The final result is a library of junction fragments representing the 100-kb DNA fraction. Such a library can be produced in about 2 months, according to Collins, and once produced can be maintained and used indefinitely. Comparable libraries may also be constructed for additional DNA size classes. The library representing the desired length of the hop can then be screened with the probe that defines the start site, a procedure that also requires about 2 months. The junction fragment thus identified serves as a bridge between the start site and the destination and can provide a new probe for initiating a second hop, if that is desired.

The main disadvantage of hopping methods is that they entail a good deal of technical difficulty. Production of the junction fragment library initially requires a preparation of very high molecular weight DNA, and DNA is notoriously subject to mechanical breakage and digestion by cellular enzymes. In addition, DNA fragments longer than 70 kb cannot be separated by conventional gel electrophoresis. However, a new gel electrophoresis procedure, which was devised by David Schwartz and Charles Cantor of Columbia University College of Physicians and Surgeons for separating yeast chromosomes, is proving helpful in this regard (*2*).

Chromosome hopping should help in preparing detailed maps of large gene complexes. In addition, it may be useful for pinning down the defective genes that cause inheritable diseases, many of which are still unidentified. A probe that will identify a DNA sequence that is closely linked to the target gene is required to get the hop under way. Although such probes are currently rare, they are being avidly sought. One has already been found for the genetic locus of Huntington's disease (*Science*, 25 November 1983, p. 913).

The probe identifies a DNA sequence estimated to be some 3000 to 5000 kb distant from the Huntington's locus, a truly formidable distance to walk—but one that may be more amenable to hopping. In fact, Collins is collaborating with James Gusella of Massachusetts General Hospital in an attempt to identify the gene involved in Huntington's disease. As more markers for genetic disease loci are identified, there will be an even greater need for methods for moving rapidly along chromosomes.

—JEAN L. MARX



Scheme for chromosome hopping

The black box denotes the start site of the hop, for which there must be a probe, and the open box represents the destination some 100 kb away. Although it is not absolutely necessary, a marker gene (here denoted by the wavy line) may be inserted into the circles to make it easier to identify the junction fragments that contain the ends of large DNA segments.

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