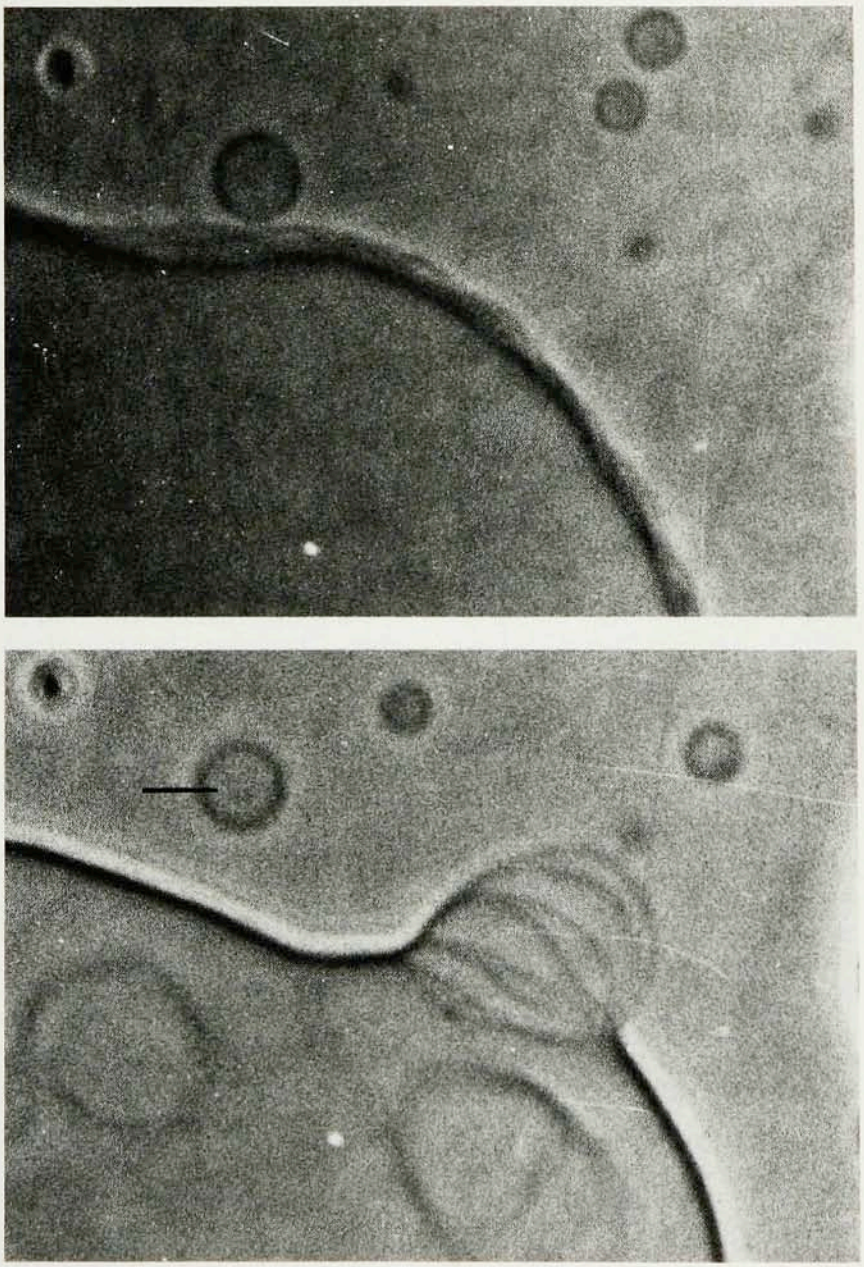
FLUID MEMBRANES REPEL ONE ANOTHER; SOLID MEMBRANES MAY *NOT* CRUMPLE

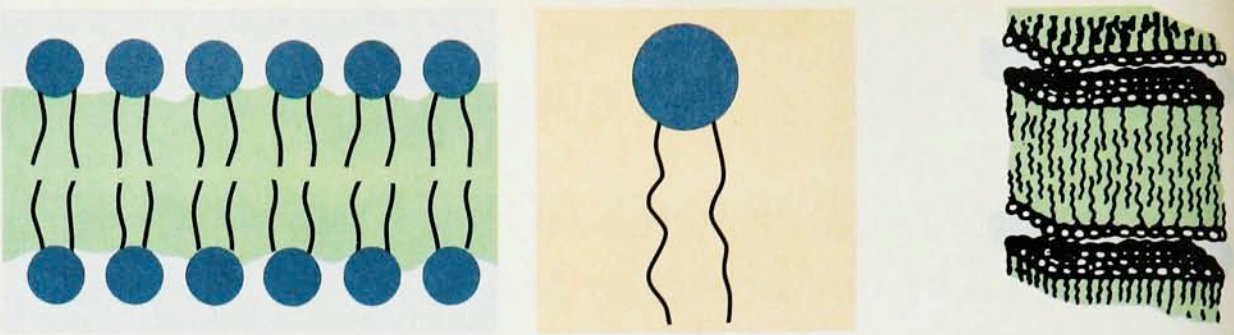
A membrane that is not rigid in the plane, or has zero in-plane shear modulus, is said to be fluid; one that does have a nonzero shear modulus in the plane is said to be solid-like. A fluid membrane shaped, say, like a rectangle will be easily deformed when antiparallel forces are applied along two of its parallel edges. In many cases the interesting excitations, or conformations, of a fluid membrane arise from out-of-plane bending.

Wolfgang Helfrich (Freie Universität, Berlin) argued in 1978 that out-of-plane fluctuations of fluid membranes may cause them to repel one another when they are brought close together, say, to form a stack, if the energy cost of bending the membrane is small (of order of $k_B T$, where T is the temperature).[1] The existence of this repulsion, as well as its inverse-square dependence on the distance between the membranes, was verified in 1986 in a synchrotron x-ray study by a team from Exxon Research and Engineering Company, the CNRS laboratories at Bordeaux and the University of Colorado at Boulder.[2,3] That same year Reinhard Lipowsky (University of Munich) and Stanislas Leibler (CEA Saclay, France) predicted that because of the repulsive interaction a stack of fluid membranes might undergo a phase transition at which the mean separation between the membranes changes continuously from finite to infinite.[4] Michael Mutz (Freie Universität, Berlin) and Helfrich now report observing an "unbinding" phase transition in a stack of fluid membranes; they claim that the transition is similar to the one predicted by Lipowsky and Leibler.[5]

David Nelson (Harvard University) and Luca Peliti (University of Naples) predicted, in 1987, that solid-like membranes would be flat at low temperatures but would undergo a phase transition at some temperature to a crumpled phase in which a typical membrane configuration would be similar to that of a polymer.[6,7] The flat phase has now been seen in extensive molecular dynamics simulations, by Farid Abraham, W. E.



Lipid bilayers in an aqueous solution of NaCl at two different temperatures. The membranes appear as a thick fuzzy line at 22.8 °C (top) because they are unbound and undulate. They appear as a much sharper and darker line at 22.1 °C (bottom) because they are bound. The binding is not complete at 22.1 °C, hence the swollen part in the middle in the right panel. The lipid used was digalactosyldiacylglycerol. The bar represents 10 μm. (Courtesy of Wolfgang Helfrich.)



Amphiphilic molecules. The molecules' polar heads are shown in dark blue in the left and middle panels. The lamellar phase (right) consists of alternating layers of oil (green) and water (light blue) separated by bilayers. A single molecule is shown in the middle; a single bilayer is shown at left.

Rudge (both at IBM San Jose) and Michael Plischke (Simon Fraser University).[8] These authors suggest that self-avoiding solid-like membranes, whose distant parts repel so that they never touch one another, may remain flat at all finite temperatures.

Fluid membranes typically consist of a bilayer of amphiphilic molecules (also called surfactants or lipids). As the name suggests, *amphi*philic molecules have an aliphatic hydrocarbon group at one end, which therefore is hydrophobic, and a polar hydrophilic group at the other. When such molecules are added to oil or water, they arrange themselves in bilayers such that their hydrophilic or hydrophobic ends, respectively, point toward one another and away from the solvent. (See the figure above.) When a surfactant is dissolved in a mixture of oil and water, however, one of the several stable phases formed, the so-called lamellar L_α phase, consists of alternating layers of oil and water, with the surfactant molecules at the water–oil interface, their hydrophilic ends in water and the hydrophobic ends in oil. (See the right panel in the above figure.) The thin layer of oil or water trapped in a bilayer of amphiphilic molecules has several physical characteristics similar to those of biological membranes. The discovery of such bilayers in the early 1960s was therefore hailed as the "reconstitution" of biological membranes in the laboratory. Many biological membranes have a layer that is fluid, but the fluid layer usually is supported by a network of proteins, which give the membrane added rigidity.

Nelson told us that several attempts are now under way to synthesize solid-like membranes. Among candidates for solid membranes: flexible sheet polymers, polymerized Langmuir–Blodgett films, and cross-linked polyacrylamide gel stabilized in the water-rich region between lipid bilayers.

Membranes are two-dimensional objects; their geometry and statistical mechanics are of considerable current interest. Interfaces, which separate two distinct phases, are another example. (The boundary between a fluid and its vapor is an interface.) Membranes need not separate different phases, and unlike interfaces, they differ in composition from the medium in which they are embedded.

Flicker of red blood cells

The current interest in fluid membranes arose in part from attempts to understand the rhythmic movement of red blood cells, which appears as a flicker effect when the cells are observed under a phase-contrast microscope. The flicker phenomenon was first reported in the 1890s, but there seems to have been no agreement on what causes it as late as mid-1970s. For example, stretching of hemoglobin as it absorbs oxygen was among the plausible causes. But the attention shifted to physical possibilities, such as the bombardment of the thin cell membrane by molecules from inside and outside the cell, when the flicker was found to persist even in cells saturated with carbon monoxide, which do not carry oxygen. In 1975, F. Brochard (then at the Université Paris-Sud, Centre d'Orsay) and J. F. Lennon (then at the Institut Pasteur, Paris) proposed that the flicker might arise from undulations of the cell membrane: They showed that if the cell membrane was supposed to be fluid and its thermodynamics were determined solely by the curvature energy, the spectrum of variations in the thickness of the cells due to undulations of the cell membrane was similar to the spectrum observed in the red-blood-cell flicker.[9] (The curvature energy is the elastic energy for out-of-plane bending.) Brochard and Lennon determined experimentally that the amplitude of the change in the cell thickness varies inversely as a power of the frequency of undulation. For frequencies on the order of a few hertz, the measured value for that power was between 1.3 and 1.45; their model gave a value of $^4/_3$.

At about the same time, Heinz J. Deuling (Universität Kassel) and Helfrich cataloged the static shapes of vesicles (or closed fluid membranes) that minimize the curvature energy for given values of surface area and volume.[10] Surprisingly, the shapes of the minimum-elastic-energy vesicles resemble those of red blood cells. The analysis by Helfrich and Deuling takes into account a third parameter, the spontaneous curvature, besides the surface area and volume. A nonzero value of this parameter in a membrane implies that the membrane's equilibrium shape at zero temperature, instead of being flat, has a finite curvature. Spontaneous curvature may arise from asymmetry in the structure of the molecules of the membrane or from the asymmetry in the solvent environment across the membrane.

Numerical simulations (in two dimensions) of fluctuating rigid membranes having different osmotic pressures on the opposite sides, by Leibler, Rajiv R. P. Singh (AT&T Bell Labs) and Michael Fisher (University of Maryland), further support the idea that the stable, nonspherical shapes of closed fluid membranes (or vesicles) are similar to the shapes of red blood cells.[11]

The entropic repulsion

Many electrically neutral biological lipids, such as di-myristoyl-phosphatidylcholine (DMPC) and digalactosyldiacylglycerol (DGDG), also form the lamellar L_α phase when mixed with water. The lipid bilayers are quite rigid—the bending modulus κ is approximately 40 $k_B T$—and the separation between successive layers is on the order of 60 Å. The equilibrium separation of the bilayers is deter-

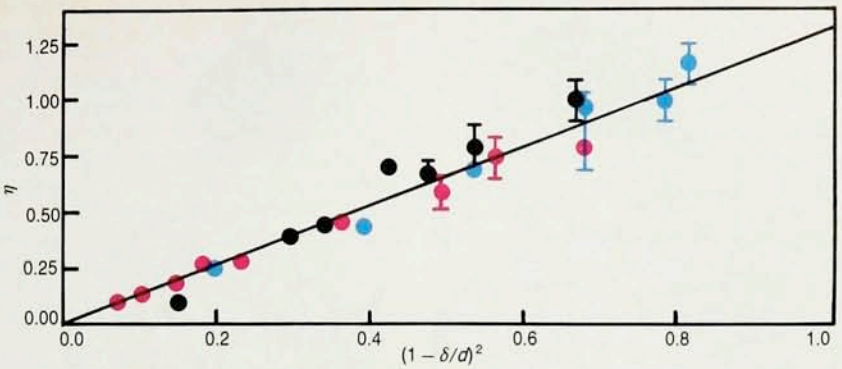
mined by competition among the various forces between them, which include the van der Waals attraction and a short-range repulsive force called the hydration interaction.

Helfrich noticed in the mid-1970s, in his studies of various lecithins (a natural lipid) in excess water, that some of those lipids form *large* vesicles. The observation hinted at an additional long-range repulsion between segments of the fluid membrane forming the vesicles, because the van der Waals interaction—the only long-range force between electrically neutral membranes known at that time—is attractive. The hint led Helfrich to study multibilayer systems; earlier theoretical studies, by Helfrich himself and others, had concentrated on single bilayers. Helfrich's proposal of a repulsive interaction between fluid membranes emerged from this study.

The repulsive interaction Helfrich proposed between fluid membranes is of statistical, or entropic, origin. It arises because two nearby membranes hinder each other's out-of-plane fluctuations. As a result of this hindrance the entropy of a system of two membranes decreases when they are brought close together. The decrease in entropy implies an increase in the free energy that may be interpreted as arising due to a repulsive interaction.

The entropic repulsion varies inversely as the square of the distance between the membranes, whereas the van der Waals interaction at large separation varies as the inverse fourth power of that distance. The repulsion also depends on the modulus for bending rigidity κ as T^2/κ. So membranes that are more easily deformable and undergo large-amplitude undulations also repel one another more strongly.

In the lamellar phase the separation between surfactant bilayers has been found[12] in some cases to be as large as a few thousand angstroms, even though the bilayer thickness is only around 20 Å. This enormous swelling can be interpreted as evidence for the repulsive interaction, because the spacing between the bilayers would remain small if there were no long-range molecular repulsion between them.



Exponent η_1 characterizing the divergence of the x-ray structure factor for a lamellar system, plotted against $(1-\delta/d)^2$, where δ is the membrane thickness and d is the separation between the membranes. The linear behavior confirms Helfrich's theory that a repulsive interaction exists between fluid membranes due to their out-of-plane bending. The data are for dimyristoylphosphotidylcholine membranes (black) and for sodium dodecyl sulfate membranes separating different concentrations of oil and water (blue and red). (Adapted from ref. 3.)

Synchrotron x-ray study

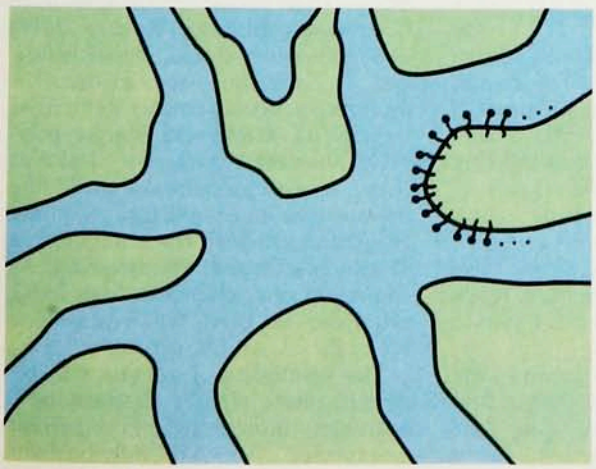
The most definitive evidence to date for the entropic repulsion and its inverse-square dependence on distance has come from a synchrotron x-ray study by Cyrus Safinya, Eric Sirota and Sunil Sinha (all from Exxon Research and Engineering Company) in collaboration with Didier Roux (CNRS, Bordeaux), Greg Smith and Noel Clark (both at the University of Colorado, Boulder).[2,3] The team studied the lamellar phase of the quaternary system consisting of sodium dodecyl sulfate (the surfactant), water, dodecane and pentanol (a cosurfactant). This choice of surfactant and cosurfactant gives a κ value of approximately $k_B T$, so the repulsion in this system is strong enough to overwhelm the van der Waals attraction.

The alternating arrangment of oil and water layers in the lamellar phase cannot be perfectly periodic. This is because the alternation occurs along one dimension only, and periodic, or crystalline, order is not possible in one dimension even though the body in which it occurs is three dimensional. (Lev Landau and Rudolf Peierls were among the first to realize this in the 1930s.) The characteristic signature of a periodic structure—the δ-function Bragg peaks—is therefore absent from the structure factor for x-ray scattering by a lamellar structure. Instead, the structure factor is expected to show singularities at the putative Bragg-peak positions. That is, when the momentum transfer normal to the layers q_m equals $2\pi m/d$, where d is the bilayer separation and m an integer,

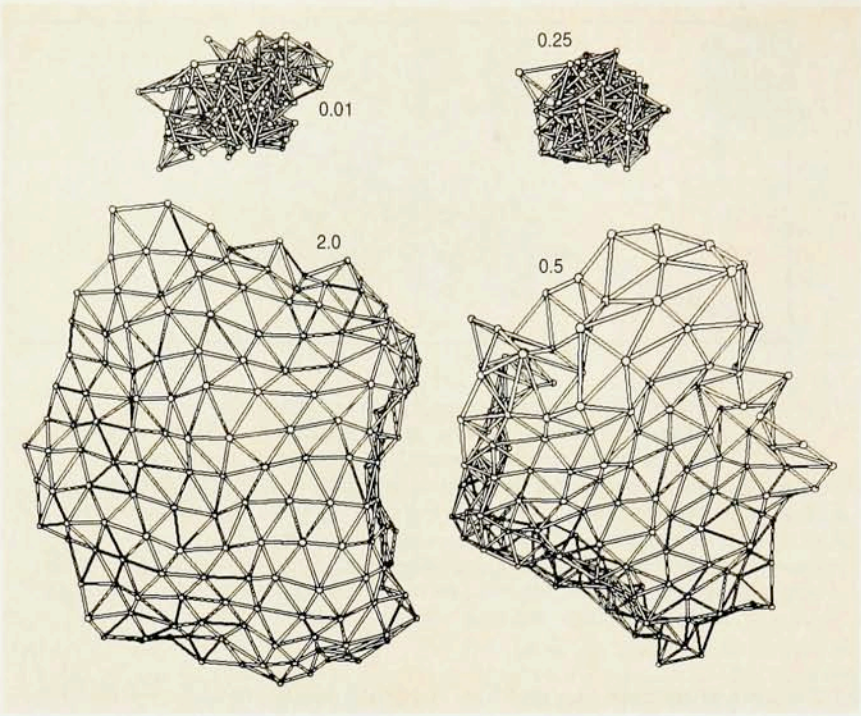
$$S(0,0,q_z) \approx |q_z - q_m|^{-2+\eta_m}$$

The exponent $\eta_m \approx m^2$. The Helfrich theory predicts that $\eta_1(d) \approx (1-\delta/d)^2$, so it depends only on δ, the bilayer thickness. All these features have been confirmed by the Exxon–Bordeaux–Colorado experiments (see the figure above). The experiments used the Exxon beam lines at the National Synchrotron Light Source at Brookhaven National Laboratory.

The Exxon–Bordeaux–Colorado



Microemulsion consists of oil-rich (green) and water-rich (blue) regions, about 100–200 Å across, separated by surfactant monolayers.



Crumpling of a solid membrane. These equilibrium configurations of a triangular network were obtained for different temperatures in a Monte Carlo simulation. The network was 15 units on a side and shaped like a parallelogram. As the temperature decreases (the numbers next to the panels are inversely proportional to temperature), the network changes from crumpled to flat. The particles, placed at the nodes of the network, were allowed to come arbitrarily close to or even touch one another. (Courtesy of David R. Nelson.)

group has also observed that the bending rigidity changes with the relative proportions of surfactant and cosurfactant molecules forming the lamellar phase. Both the surfactant and the cosurfactant are amphiphilic, but the cosurfactants have shorter chains. When the surfactant molecules are partially replaced by those of the cosurfactant, the bending rigidity decreases, the Helfrich interaction becomes stronger, and the lamellar phase becomes even more "swollen."[3]

In their recent confirmation of the unbinding transition, Mutz and Helfrich studied DGDG bilayers in a sodium chloride solution. They spread a few micrograms of DGDG on an object slide, added about 40 microliters of the sodium chloride solution, put a cover glass on top of the slide and sealed the cell, now about 40 microns high. They observed the DGDG at different temperatures using a phase-contrast microscope. The very different configurations of the DGDG at 23.1 °C and 22.4 °C (see the figure on page 17) are evidence for a phase transition at some intervening temperature. Lipowsky and Leibler had predicted the transition to be continuous, which implies that the mean separation between membranes will diverge continuously to infinity if the system can be infinitely diluted. Mutz and Helfrich report seeing no hysteresis, or dependence of the DGDG configuration on how the temperature was varied. The lack of hysteresis, they claim, is evidence in favor of the theory of Lipowsky and Leibler, because hysteretic effects occur more frequently at discontinuous transitions.

Radius of gyration

Fluid membranes of arbitrarily large area are not stable; when the area of fluid membranes in a stack exceeds some critical value, they break up and form isotropic phases—for example, a microemulsion, in which oil-rich or water-rich regions bounded by surfactant monolayers shift and fluctuate constantly.[13] (See the figure on page 19.) If arbitrarily large fluid membranes could be synthesized, theoretical studies show, however, that they would appear *crumpled* at any nonzero temperature.[7] This means that the radius of gyration of a fluid membrane of linear size L varies as L^{ν}, with $\nu < 1$. A flat, stretched membrane, by contrast, will have $\nu = 1$. The significance of the notion of radius of gyration for a membrane is best understood by analogy with its significance in polymer physics.

Many physical properties of a dilute solution of a polymeric solute in a noninteracting solvent depend on the molecular weight of the polymer. This dependence in turn may be expressed in terms of some geometrical properties, such as the radius of gyration. For a polymer made up of N identical monomers placed, say, a unit distance apart, the distance between the free ends, and therefore the radius of gyration, is N units if the polymer is rigid. But a flexible polymer at a finite temperature bends and coils, so its radius of gyration varies as N^{ν}, with $\nu < 1$. The exponent ν has been measured in a variety of experiments, including neutron scattering studies of dilute polymer solutions.[14] It has a value of about $^3/_5$. A value of $^1/_2$ would have indicated that the configuration of a polymer in a solvent is like that of a random walk, or of a Brownian motion, in which the distance moved in N steps varies as $N^{1/2}$.

A value of ν greater than $^1/_2$ suggests that a polymer in a solvent is more extended than a random walk. A random walk may return to points already visited in the walk, whereas monomers in a polymer repel one another. This difference accounts for why the polymer is more extended than a random walk. In fact, the statistical and geometrical properties of polymers agree with those of *self-avoiding* random walks, in which no point may be visited more than once in the course of the walk.

The crumpling transition

Solid-like membranes may be regarded as two-dimensional analogs of polymers. For example, tethered surfaces, a model for solid-like membranes that Yacov Kantor (Tel Aviv University), Mehran Kardar (MIT) and Nelson introduced, resemble fishnets.[15] Each unit—say, monomer—constituting such a surface has a fixed number of neighbors. Unlike polymers, however, for which $\nu < 1$ so that they are always crumpled, solid-like membranes may undergo a phase transition at which the configuration of the membrane, characterized by the value of ν, changes—from being crumpled at high temperatures to being flat at low temperatures.[6,16]

The possibility of an *un*crumpled, or flat, phase of solid membranes is extremely interesting and somewhat unexpected. A surface may be char-

acterized by its normals, and as Alexander Polyakov (Landau Institute for Theoretical Physics, Moscow) and, independently, Peliti and Leibler[7] pointed out, the crumpled and flat phases of membranes may be distinguished by the fact that the normals all point in the same direction in the flat phase, whereas they point in random directions in the crumpled phase. So one may exploit an analogy with magnetic phase trnsitions to study the transition between crumpled and flat phases: The atomic spins all point in the same direction at zero temperature in the ferromagnetic phase, whereas they point in random directions in the paramagnetic phase. But a celebrated theorem, often referred to as the Mermin–Wagner–Hohenberg theorem in condensed matter physics and as the Coleman theorem in field theory, says that a ferromagnetic phase is not possible at any nonzero temperature in a two-dimensional system if the spins are free to point to any point on a circle or a sphere.

Because unit normals to a surface may be directed to any point on a sphere, the theorem seems to rule out the possibility of a flat membrane at any nonzero temperature. There is, however, a difference between spins in magnets and unit normals to a surface that restricts the applicability of the theorem to predicting the possible configurations of a surface: Spins in magnets are coupled only weakly to the vibrations of the lattice, and the exchange interaction between spins has a short range. By contrast, the undulation modes of a surface introduce long-range interactions between the normals.

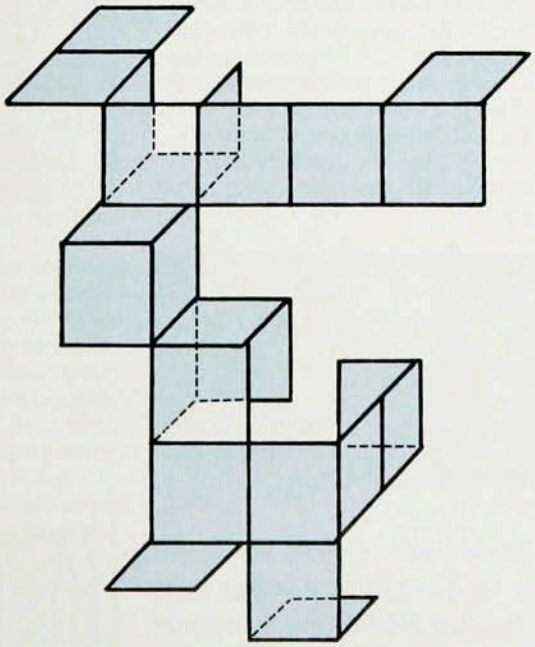
Following the suggestion of a crumpling transition in solid membranes by Nelson and Peliti,[6] Kantor and Nelson studied the properties of tethered surfaces in a Monte Carlo simulation.[16] They found a phase transition at a finite temperature between crumpled and flat phases when the surface is not self-avoiding (see the figure on page 20). For such surfaces, according to Kantor and Nelson, the radius of gyration in the crumpled phase varies as $(\ln L)^{1/2}$, where L is the linear size of the surface in the uncrumpled phase. For self-avoiding tethered surfaces, which are more realistic, the simulations by Abraham, Rudge and Plischke find only a flat phase. But the question of whether such surfaces, like their non-self-avoiding counterparts, also undergo a phase transition into a crumpled phase at a nonzero temperature continues to be debated.

Plaquette surfaces

The partition function for non-self-avoiding solid membranes regarded as continuous sheets is similar to the Feynman path integral representation for the bosonic string theory proposed by Polyakov. The divergence in the specific heat that Kantor and Nelson obtained at the crumpling transition, which shows that the transition is continuous, suggests that there exists a nontrivial bosonic string theory. This is just one example of the themes in current research that are common to studies of random surfaces and relativistic field theories. Another example is the enumeration of configurations of a fixed boundary that are obtained when the elementary squares, or plaquettes, on a hypercubic lattice are connected contiguously (see the figure below). The radius of gyration of such a surface formed from N plaquettes varies as $N^{0.504}$ in three dimensions. The N dependence is similar to that for the radius of gyration of a branched polymer made from N identical monomers.

"It is hard to think of direct experimental realizations of plaquette surfaces," Nelson told us. "Because they resemble branched polymers, plaquette surfaces are rather wild, unruly objects." Studies of such surfaces are important in discrete, lattice versions of gauge theories, however. According to François David (CNRS and CEA Saclay), the connection between gauge theories and plaquette surfaces might be useful in the study of microemulsions.

—Anil Khurana



Plaquette surface.

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