Another Face of Entropy

Particles self-organize to make room for randomness

By PETER WEISS

There's a flip side to the doom and gloom of entropy. The steady march to disorder is not all degradation and the ultimate, bland sameness found so depressing by thinkers from philosopher Bertrand Russell to novelist Thomas Pynchon.

Entropy measures the amount of disorder in any patch of the universe, be it the dust, gas, stars, and planets of a galaxy, a belching steam engine, or the cells of a living organism. The laws of thermodynamics require that entropy must always increase. Rudolf Clausius, the 19th century German physicist, imagined that the relentless increase of entropy would ultimately degrade the universe to a disordered, stagnant confusion—a fate he called the heat-death.

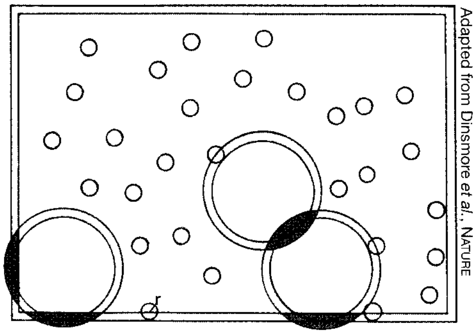
As Russell sadly put it, "all the labors of the ages, all the devotion, all the inspiration, all the noonday brightness of human genius, are destined to extinction." And, Pynchon's character Callisto in the story "Entropy," bemoaned a heat-death of culture as well, "in which ideas, like heat-energy, would no longer be transferred."

Scientists, however, are discovering with apparent glee how often the road to disorder is paved with a little useful order. "Even though it's been known for a long time that entropy can produce order, it's still not fully realized how general that phenomenon is and how rich in potential," says Seth Fraden of Brandeis University in Waltham, Mass.

That potential holds in particular for a submerged realm of objects that are much bigger than atoms but too small to be seen without a microscope. There, remarkable feats of self-assembly take place. Such processes can create intricate molecular structures that, despite appearances, represent an increase of entropy over their ingredients.

It's a realm of special importance to humankind because it encompasses the contents of biological cells. In optics, it's the arena where researchers strive to make the photonic crystals that have been touted as the silicon of future, light-based computing. It's also where scientists grapple with problems of protein crystallization—a vital step toward understanding the functions of many new-found genes.

Although scientists have known since at least the 1940s that entropy can act as an unseen hand to create order, only in the last few years have they begun to suspect—and to demonstrate—how elaborate its handiwork can be. They have found that simply blending microscopic particles of different shapes or sizes in liquids sometimes causes crystalline structures of remarkable complexity to appear. The aimless interactions of the particles creates these structures, even while maximizing entropy as thermodynamics demands.



Adapted from Dinsmore *et al.*, NATURE

Walls and big balls create zones (light blue) where room to roam is lost by some part of each small ball. For instance, a small ball's center is stopped a full radius (r) away, whereas points on its surface roam everywhere. To increase room to move, or entropy, small balls herd large ones into the corners and against the walls and each other. Where surfaces of large balls and walls touch, the restricted regions overlap (dark blue), freeing unfettered volume elsewhere.

In entropy's most virtuoso laboratory performance to date, Fraden and his colleagues at Brandeis University blended plastic spheres and rods in water. The spheres, each no larger than a micron in diameter, were combined with micron-long rods—actually genetically engineered viruses—about 10 nanometers in diameter.

In experiments reported in the May 28 NATURE, the suspended mixtures spontaneously solidified into two types of highly ordered, complex, permanent structures. One is a cake in which layers of vertical rods alternate with a thin frosting of balls—a stacked, or lamellar, arrangement. This pattern reflects the arrangement of phospholipids in cell membranes and the alignment of soap molecules in the surfaces of bubbles.

The other structure, known as columnar, features a regular, crystal lattice of vertical columns of clustered spheres embedded in a horizontal sea of rods all pointing roughly the same way.

Polymers used as glues and soaps commonly take on such structure, a phenomenon that materials scientists have long attributed to an incompatibility between the ends of the polymer molecules. The rods used by Fraden and his colleagues, however, don't have antagonistic ends.

Seeing a glue-like or soap-like structure built purely by entropic forces was "shocking," he says. Other, less durable patterns also emerged, including ropes with lamellar order and chains of rod packets interspersed with spheres.

A new, unpublished study by Arjun Yodh and his colleagues at the University of Pennsylvania in Philadelphia may cast light on how such elaborate structures form.

Since the early 1990s, Yodh's lab has been probing how the organizing influences of entropy arise, how strong they are, and how to control them. In a series of papers dating to early 1994, the researchers have described mixing small beads with large spheres—typically in proportions of thousands of small spheres less than 100 nanometers in diameter for each large sphere, which is 500 or so nanometers across. As the scientists watch, the bigger ones are pushed by their smaller neighbors against the hard, flat walls of containers, where they assemble into crystals.

In other experiments detailed in the January 12 PHYSICAL REVIEW LETTERS, the team observed big balls being forced against the most curved sections of the inner walls of pear-shaped, rigid vessels.

A few simple principles seem to explain where the large spheres go, according to Yodh and other scientists. First, the entropy of the small balls reaches its peak when they have the most room in which to move. Second, the large balls hog more room than just the actual volume that they occupy. Both large balls and walls, by their very presence, create thin regions along their surfaces where some part of each small ball cannot go.

For instance, a small ball's center must stay at least one small-ball radius away from those surfaces. However, those restrictive regions can overlap and cancel each other out where a big ball and a wall or another ball touch. The overlap is even greater at concave walls. By herding the big balls against walls or each other via random collisions, the small balls regain some unfettered volume and raise their entropy.

Of course, the entropy of the big balls drops as they form neat clusters, but calculations show that the overall entropy still goes up, the experimenters say.

In essence, entropy creates an attractive force that is also called a depletion, or excluded-volume, force. The strength of this force, first predicted in 1958 by Japanese physicists Sho Asakura and Fumio Oosawa of Nagoya University, depends on the ratio of small to large spheres and their relative sizes. John Y. Walz of Yale University, a researcher who has measured the minuscule force, describes it as "less than the weight of a single red blood cell in water."

In Yodh's new study, the experimenters again mixed small and large balls. They then tracked the separation of pairs of large spheres to determine the force between them. John Crocker reported the new data in March at a meeting of the American Physical Society in Los Angeles.

At modest concentrations of small spheres, the force was attractive, as expected, decreasing with distance between the spheres. But, at high concentrations of little balls, the force flip-flopped repeatedly, changing from attractive at the closest separation, to repulsive further out, then back to attractive, and so on.

Theorists had predicted this effect, but Yodh's team is the first to measure it between two spheres. Two years ago, Walz and Amber Sharma, also of Yale, saw the same effect while measuring the force between a sphere and a wall. Due to alternating attraction and repulsion, large spheres could become trapped in layers at successive distances from each other.

These entropic forces become significant at scales of, roughly, a few tens of nanometers to a couple of microns. For entropic ordering to take place, particles must constantly jostle each other and be light enough to be randomly agitated by fluid molecules, making gravity negligible. Proteins, DNA, and other macromolecules that crowd a cell's cytoplasm fit the bill, some researchers say.

Most biology researchers have paid no heed to entropic forces because traditional biochemistry focuses on reactions in dilute solutions, away from the cellular "background," says Allen P. Minton, a physical chemist at the National Institutes of Health in Bethesda, Md.

In the late 1970s, however, he and his colleague Philip D. Ross showed how excluded-volume forces could account for an unexplained clumping of sickle-cell hemoglobin in the presence of other proteins that play the role of the small spheres in entropy experiments.

A few years later, Minton and Steven B. Zimmerman, also at NIH, tied entropic forces to the clustering of DNA in cells lacking a nucleus. Currently, Minton is probing the role such forces might play in the binding of proteins to cell membranes and in the assembly of the cell's structural scaffold of protein filaments known as microtubules.

Working with Yodh's group, Dennis E. Discher, a biophysicist at the University of Pennsylvania, is examining whether depletion forces are partly responsible for clumping of blood cells in the body when circulation is blocked. Also, extending Yodh's work to thinner-walled containers, much more like actual cells, Discher hopes to measure the force that can be exerted by a large sphere pushed outward by depletion forces. He speculates that it may be such entropic forces that eject the nucleus from red blood cells before they enter the bloodstream.

"There is a lot of evidence that [entropic forces are] a very widespread and important phenomenon in biological systems," says Minton, a self-proclaimed missionary for the idea. It may be catching on, he adds, given the rising number of invitations he has been receiving to speak and write review papers on "macromolecular crowding," as the phenomenon is known in biology.

In several ways, industry has already recognized the utility of entropic ordering—and also dealt with its down side. In the 1940s, Nobel laureate Lars Onsager predicted a phase transition due to entropic forces. Thirty years later, chemists achieved that phase change among polymer molecules, inducing them to bind together to form ultrastrong fibers such as Kevlar.

In the 1980s, unexpected findings by paint makers fueled a resurgence of interest in entropic ordering. Polymers that had been added to paint to make it flow smoothly were instead causing clumping. The culprit: excluded-volume forces.

The growing appreciation of entropy's penchant for order has unleashed a renewed drive to put it to practical use. Yodh and physicist David Pine of the University of California, Santa Barbara are each trying to exploit entropy to make photonic crystals, which are expected to lead to better microlasers and possibly all-optical computer circuits that are smaller, faster, and create less heat than conventional electronics (SN: 11/15/97, p. 310; 11/16/96, p. 309).

Each is basing his research on their joint discovery that by cutting grooves in the walls of the container to which the spheres adhere, scientists can direct where entropic forces herd large spheres. That finding was detailed in a Sept. 19, 1996 NATURE paper with Anthony D. Dinsmore, now at the Naval Research Laboratory in Washington, D.C.

Now they plan to use the entropy-ordered spheres as seeds for photonic crystals designed so that the walls of their inner pores reflect light in all directions.

Large photonic crystals suitable for manipulating long wavelengths of light, such as microwaves, already exist. Yodh and Pine, however, each intend to create crystals that can handle infrared or visible light, which promise to be far more useful but are difficult to make because they require such fine internal structure.

Nonetheless, Pine believes he is only months away from success. He is using grooves to align spheres of oil suspended in a fluid. He next fills the space around the globules with ceramic materials that tend to scatter light in all directions. When the ceramic hardens, Pine clears out the liquids to leave the desired crystal behind.

Yodh is also using grooves, but he applies beads of similar light-dispersing materials directly to create the crystal. It's a tough challenge because the material is so heavy that gravity enters the equation.

Success for his group might depend on escaping gravity, which is what the researchers intend to do. NASA has awarded them a grant for microgravity experiments on the space shuttle, although a date has not yet been set, Yodh says.

A better understanding of entropic forces might also transform the "black art" of protein crystallization into a reliable process with a firmer scientific footing, Fraden says.

He pledges to devote the next couple of years to that task. He predicts that as scientists attempt to learn what the genes described by the Human Genome Project do, they will reach a bottleneck because their ability to crystallize proteins is limited. Crystals are required to determine the three-dimensional structure of proteins, which give clues to their function.

In the Sept. 26, 1997 SCIENCE, researchers reported computer simulations showing that entropic forces could allow proteins to crystallize readily. In their models, adding polymer particles to a protein suspension induces the formation of dense droplets that act as seeds for crystal formation, say Daan Frenkel and Pieter Rein ten Wolde of the FOM Institute for Atomic and Molecular Physics in Amsterdam.

Also swept up in the revival is Alice P. Gast at Stanford University, whose doctoral thesis 13 years ago quantified the entropy-induced clumping that baffled paint manufacturers. After turning her attention to other things, she is now returning to entropic forces—this time as a way to grow two-dimensional protein crystals.

Experiments on entropy-driven ordering have also caught the eye of physicist Adam J. Simon at Merck & Co., a pharmaceutical firm in West Point, Pa. "If these entropic or depletion forces are playing a role in cellular processes, then there is potential application in the field of drug delivery," he says.

Although excited by new findings and applications, even scientists who have studied depletion forces for years admit that entropy's orderly alter ego can befuddle their intuition. But once you have seen entropy tidy up, the researchers say, you start noticing its touches everywhere. □