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NO ASSEMBLY REQUIRED FOR THESE TINY MACHINES

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CAMBRIDGE - Inside a seemingly sober Harvard laboratory, the Lego mating dance unfolds.

Pale pieces of plastic are riding currents in a twirling flask of warm saltwater. When one piece touches another, it is usually rebuffed, bouncing away. But sometimes the approach is just right, and the two lock together. They are now a couple. As the dance continues, though, something even more meaningful emerges from these chance encounters. Pairs join pairs. Larger sections come together. Soon the water holds a three-dimensional honeycomb of plastic.

And when the honeycomb is allowed to dry, explained researcher **David Gracias**, it contains a surprise. Since each plastic component was built with wiring inside, the resulting structure forms a complete electrical circuit. The circuit is simple - voltage applied to one piece turns on a light in another - yet it was a dramatic scientific first that caught the eye of the computer industry: This is a circuit that assembled itself.

Since the first human fashioned a crude stone tool in the heart of Africa, people have been building things essentially the same way - making pieces, first of wood or stone, later of metal or plastic, and joining them together. Now, though, scientists have begun pursuing a

radical alternative that could fundamentally change everything, including computers, transportation and medicine. Called "self-assembly," the idea is to build components capable of joining together into a complex whole, without an outside builder. It is a concept, they say, that is no stranger than every living thing.

"This is how nature builds all of us," said **Gracias**, who conducted the circuit experiment in the laboratory of George Whitesides, a Harvard chemist who is one of the leading figures in the movement.

Self-assembly is one of the great miracles of life, and one of its profoundest mysteries. A single acorn placed in the ground is able to assemble itself into a vaulting oak tree that thrives on sunlight. A microscopic cell in the form of a fertilized egg can build itself into a squirrel that bounds from branch to branch. And another speck of biological material, not so different from the squirrel cell, can transform itself into a human being who understands that the squirrel is looking for nuts, and winter is on the way.

Physicists, chemists, and other scientists outside of biology are now looking to these creative miracles that take place in what many observers think will be one of the most active areas of 21st century science - the realm of the nanometer (billionth of a meter) where individual molecules operate.

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Nanotechnology is the human tool-making urge taken to its logical extreme, building objects one molecule at a time. In theory, the possibilities include swarms of tiny nano-robots that could be released into a patient's bloodstream to diagnose and fight disease, or materials that are lighter, stronger, or have almost any other property its designer wants.

"We have had the Stone Age, the Bronze Age, and the plastic age," said Shuguang Zhang, who is active in nanotechnology research and is the associate director of MIT's Center for Biomedical Engineering. "The future is the designed material age."

The field is rapidly expanding, with new institutes opening around the country. In the fiscal year 2001, the US government provided \$420 million in nanotechnology research grants, according to the National Science Foundation, which has helped fund research at the Whitesides lab.

But even as the nano-technologists have developed machines that let them manipulate individual molecules, they have begun to confront an enormous practical problem: Building something useful, one molecule at a time, takes too long. And, for the solution, they are hoping to copy biology, where fantastic structures build themselves.

"Why recreate the wheel when nature has already created it for you," asked Paul Hyman, a scientist with NanoFrames LLC, a Boston-based company that hopes to use the rod-like tails of viruses to build self-assembling nanoscale construction scaffolds. "I am in awe of what nature has accomplished."

One of the most awe-inspiring examples of self-assembly is the ability of a cell to copy its own DNA, a process that allows one cell to split into two, and leave each with the full genetic instruction book it needs to operate.

DNA is a long molecule that looks like a twisted ladder, with pairs of chemical bases that scientists refer to with letters for simplicity. A "C" is always joined with "G." A "T" is always joined with an "A." The cell is able to split the ladder and then rebuild the other halves so that it now has two copies of the original. Finding the billions of bases needed, and placing them one at a time, would be a daunting task.

But cells takes advantage of a chemical trick, the fact that each base will only lock in with its pair - the C's will only accept G's, for example.

Instead of having to place the right base at each rung, the cell only needs to make sure that the open ladder is exposed to many bases. Correct bases will slide easily into place, like a key into a lock, and the wrong ones will bounce away. A split ladder of DNA could be placed into a soup thick with base pairs, and the other half will quickly assemble itself. Split this ladder, place each in a similar soup, and there would be two identical strands of DNA.

In a cell, the process is much more complex, but it illustrates the central principles of self-assembly - attraction and what scientists call "recognition." Base pairs of DNA are attracted to each other, but they are looking for the right pair to join with: the "G" will reject a "G," a "T," or an "A," but welcome a "C."

The principle does not just apply to DNA. If pieces are attracted to each other, but discriminating, then they will assemble into more complicated wholes.

"People have all of a sudden realized that most of what goes on in living organisms is based on this idea of one thing recognizing another," said James R. Heflin, an associate professor of physics at Virginia Tech who is using self-assembly to create new kinds of solar cells.

For the cells to work, Heflin is using a substance that will assemble itself on a glass slide in a layer just one molecule thick. Such mono-layers are one of the first applications of self-assembly to engineer structures at the nanoscale.

Other researchers, meanwhile, are taking aim at more-complex structures. One intriguing model is the shell of the abalone, which is 3,000 times tougher than naturally occurring minerals made of the

same substance, according to Angela Belcher, an assistant professor of chemistry and biochemistry at the University of Texas at Austin.

The abalone secretes proteins, Belcher said, which cause calcium carbonate to form thin layers of crystal that overlap like bricks in a house. This structure is the secret of the shell's strength.

Belcher said that she originally became interested in the abalone shell because it is such a remarkable piece of engineering. The animal is able to build the shell using chemistry that is nontoxic, at normal temperatures, and with materials that are readily available.

Now Belcher's lab wants to try to use proteins to get more exotic materials, such as semiconductors, to grow themselves into useful shapes. Eventually, she hopes to have a library of proteins and techniques that would allow scientists to grow a wide range of useful new materials, all engineered at the molecular level the way nature does.

"I want to do the same thing [the abalone does] with materials that nature hasn't had the opportunity to evolve a way to do," Belcher said. If successful, it would be a new paradigm for manufacturing, in which components aren't built so much as they grow.

The array of self-assembly projects now underway is dizzying, including tiny crystals made by the Quantum Dot Corp. of Haywood, Calif., which could be used for medical imaging; or a technique, used by Alien Technology Inc. of Morgan Hill, Calif. which allows tiny integrated circuits to place themselves in products.

Yet all the techniques that scientists dream of are almost embarrassingly simple compared to the feats accomplished every day by life on Earth.

Biology uses self-assembly in many, many layers. DNA assembles itself, and rules the cell. A group of cells organizes into regions of specialized cells. Specialized cells grow into perfectly designed organs, which join up with other organs. One of these organs is a mind, with a web of cells that is constantly rearranging the pattern that connects them.

Eventually the result is a creature with a mind so stunningly complex that it can look at itself and ask: What built me?

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