CHEMICAL POP-UP BOOKS

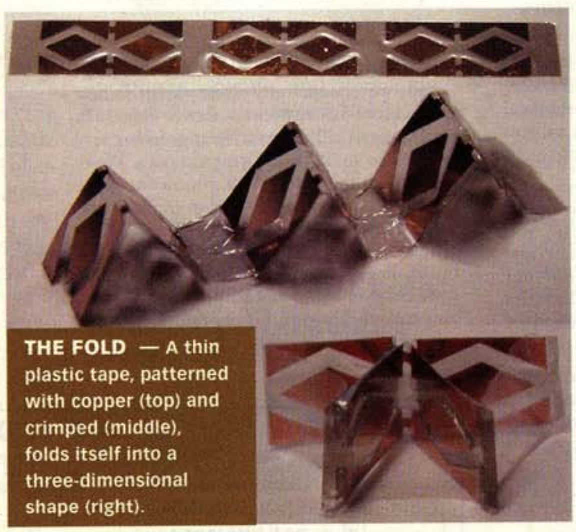
How some devices build themselves

BY AIMEE CUNNINGHAM

Many beasts, buildings, and beauties greet children who open pop-up books: a *Tyrannosaurus rex* with jaws agape, elaborate medieval castles with soaring towers, the Statue of Liberty with her torch held high. These detailed objects take their three-dimensional shape with the turn of a page, arising from intricately folded paper. Today, chemists and engineers are making their own sophisticated versions of pop-up structures. What they lack in whimsy, they may someday gain in practical function.

These objects, which begin as two-dimensional structures, fold themselves into final, functional three-dimensional shapes. Self-folding is one of the methods in a broader category called self-assembly. In that strategy, scientists design structures that build themselves out of specific components, says George M. Whitesides, a chemist and materials scientist at Harvard University. Self-assembly "is a strategy for making complex, multicomponent, three-dimensional things," he says.

Nature is the apotheosis of self-assembly. For example, notes Whitesides, "you and I are self-assembled objects." From our proteins, to our cells, to our bodies, "it all comes together by itself," he says.



THE FOLD — A thin plastic tape, patterned with copper (top) and crimped (middle), folds itself into a three-dimensional shape (right).

Although there is much that scientists don't yet understand about how nature puts things together, they're putting into practice what they've gleaned so far. Researchers are looking for self-assembly strategies for objects too small to be easily constructed by people or robots. "Instead of having robots pick up a billion pieces, the pieces might be able to find their way to where they go," says Whitesides.

Scientists team self-folding strategies with photolithography, a fabrication method that is "a workhorse in the integrated circuit industry," says chemical engineer L. James Lee of Ohio State University in Columbus. While photolithography can create intricate patterns on a two-dimensional surface by adding or removing thin layers, "it is difficult and expensive to use it to make a three-dimensional structure," says Lee.

By combining self-folding with photolithography, "you are able to transform this two-dimensional technology into three-dimensional technology," says David H. Gracias, an engineer at Johns Hopkins University in Baltimore.

The first crop of self-folded creations might include simple electronic devices, drug-delivery vehicles, and miniature chemistry laboratories.

"It seems worth the effort to take this idea outside of biology to see what problems it could solve," says Whitesides.

TAPE SHAPES Protein self-assembly inspired Whitesides' most recent self-folding project. A protein begins as a chain of amino acids, which then folds into a three-dimensional form. The sequence of and interactions among the amino acids dictate the final shape.

To roughly mimic this example, Whitesides, Derek A. Bruzewicz, and their colleagues at Harvard began with a piece of transparent plastic tape 12 micrometers (μm) thick, 3 millimeters wide, and 50 mm long. The team determined the shape that they wanted the tape to fold into and accordingly patterned one surface of the tape using photolithography. The process placed 100-nanometer-thick diamond shapes made of copper. Each diamond can be thought of as an amino acid along a protein chain, says Bruzewicz.

The researchers crimped the tape between metal combs with zigzag teeth. The face of any zig or zag on the tape included a copper diamond. "The crimping is sort of the suggestion" of how the structure will ultimately self-fold into its final shape, Bruzewicz says.

To hold the crimp, the researchers glued the crimped tape to a flat piece of tape and then dipped the patterned tape into solder, coating the copper diamonds with this metal alloy. Next, they placed the whole structure in water heated to a temperature above the solder's melting point, and then gently jostled the structure.

When the solder on two nearby faces of the crimped tape came in contact, the solder naturally minimized its surface area remaining in contact with the water. This bound the two faces, self-folding a portion of the tape. After a few minutes, the tape had completely folded into its predetermined shape. Out of the water, the solder cooled and solidified, locking the shape in place.

After working with a few simpler geometries, the researchers designed a differently patterned tape that folded into a helix. They also created a self-folding light detector by adding copper wires and photodiodes to the flat tape before gluing it to the crimped tape. Once folded, the device detected light from all sides, the team reported in the July 26 *Journal of the American Chemical Society*.

Although the researchers produced a functional device, they are "still at the level of trying to understand the process," says Whitesides.

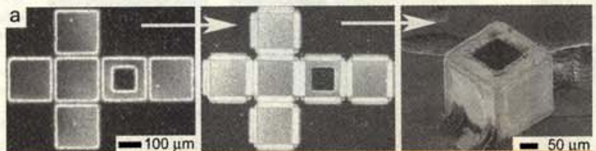
BRUZEWICZ

The team plans to shrink the components it uses in future work, notes Bruzewicz. To explore whether the group's folding strategy might work in commercial electronics, "we want to get [the components] well below a millimeter," he says.

BITTY BOXES Gracias and his team at Johns Hopkins have coaxed two-dimensional patterns to fold into cubes and pyramids. The containers might play host to chemical reactions or transplantable cells, the researchers say.

To build the two-dimensional precursor of their containers, the researchers began with an 8-centimeter-diameter silicon wafer as a support. After laying down a "sacrificial layer" of polymer as an adhesive, the researchers deposited a 100-nm-thick layer of copper.

Making cubes required several steps. First, the researchers used photolithography to pattern onto the metal layer multiple copies of a cross-shaped template of six squares. Each edge of the squares was 200 µm long. Next, the team built up the squares by depositing layers of either nickel or more copper.



BOXING DAY — A metallic, cross-shaped frame (right) receives solder at the squares' edges (middle), which provides the force to fold the cross into a box.

Then, the group added solder to serve as hinges along all the edges of each of the squares. The researchers included an opening on some faces and patterned pores a few micrometers in diameter on other faces.

Dissolving the sacrificial layer released the two-dimensional crosses from the silicon wafer. As with the Whitesides group's tapes, heating the crosses past the solder's melting point triggered the cubes' self-folding. As the liquid solder minimized its surface area, it pulled up the squares to form the sides of the cubes, says Gracias. The cooled solder held together the minuscule boxes.

Gracias has several ideas for using the containers. In the December 2005 *Biomedical Microdevices*, he and his colleagues reported that they had loaded breast cancer cells into boxes 200 µm wide. The cells survived for several hours, and by using magnetic-resonance imaging, the researchers could track the boxes as they moved through liquid-filled channels. Although this work is only preliminary, Gracias says, it might lead to containers useful for transplanting cells that release required chemicals, such as insulin for diabetes or dopamine for Parkinson's disease.

In the Sept. 6 *Journal of the American Chemical Society*, the researchers described self-folding cubes and pyramids, having volumes ranging from 0.2 to 8 nanoliters. In this work, the researchers loaded the containers with reagents and performed chemical experiments. For example, they put a chemical that indicates a solution's acidity into a porous cube made of nickel. They then placed the cube in a solution and used a magnet to move the cube around. The indicator reacted with the solution only along the path where the researchers directed the cube.

Conducting chemistry in specific spots by remote control might find use in lab-on-a-chip systems, says Gracias. These systems provide a platform for miniaturized chemical assays that use far smaller quantities of expensive reagents than assays in traditional beakers do. With the self-folding containers, "we can move chemicals wherever we want them to be," Gracias says.

GEL GEOMETRIES Researchers can also make hydrogel—the material in contact lenses—pop into specified three-dimensional shapes. Lee and his group at Ohio State University have designed self-folding, gel-based structures that they're testing as drug-delivery devices.

Hydrogel structures don't rely on solder to fold into shape. Rather, the repulsive forces between charged molecular groups provide the oomph. Hydrogels are polymers, and certain molecular groups attached to their polymer chains repel each other as the acidity of their environment changes. Because the groups are bound to the material, they can't move far apart, but they can force the material to swell, says Lee.

To exploit this force for folding, Lee and his colleagues combined two hydrogel layers: one that swells a great deal and one that doesn't swell. The team first used photolithography to make a two-dimensional array of specifically shaped, miniature wells in a silicon wafer. The researchers then transferred that pattern to a 10-cm-by-10-cm piece of rubber. They poured one hydrogel into the wells of the rubber and solidified the hydrogel to create the first layer. Then, they added a layer of a different hydrogel. After solidifying that layer, the researchers bent the rubber mold to release the structures from the wells.

When the researchers placed those flat structures into solution, one hydrogel layer began to swell, while the other kept its volume in check. Blocked on one side, the swelling layer expanded on the other, which pulled the whole structure into a three-dimensional shape, explains Lee. The researchers described the structures in the Dec. 15, 2005 *Journal of Physical Chemistry B.*

To make drug-delivery devices, the researchers put a thin square of polymer, which contains the drug, at the center of the hydrogel bilayer. When flat, "the bilayer is like a cross, and the drug is in the middle [square]," says Lee. The drug-carrying polymer also contains an adhesive so that the hydrogel structures will stick to the mucus covering the intestinal tissue.

The researchers plan to place several of the structures inside a capsule that would dissolve in the small intestine. The adhesive would ensure that, once they are released from the capsule, the structures land right-side-down on the mucus. The two-dimensional structure would then fold into a three-dimensional device that Lee likens to a closed fist, with the drug on the palm. After the device grabs onto a bit of the small intestine, the drug would diffuse into the tissue.

In the Jan. 10 *Journal of Controlled Release*, Lee's group reported on initial tests of one of the drug-delivery devices on tissue removed from a pig's small intestine. Within a few minutes, the devices landed and then grabbed the tissue. The devices remained in place for 103 minutes, about 30 minutes longer than a flat, mucus-adhering drug patch did.

With the additional time, more of the drug would be absorbed, says Lee. He adds that the team's next step is to test the self-folding devices, with drug or gene cargoes, in animals.

FIXING FOLDS If self-assembly techniques, including self-folding, are to make a commercial impact, researchers will have to figure out a rigorous system of quality control. Some researchers suggest that in the future, computer chips might self-assemble. Whitesides cautions that when producing such complex devices, "you really can't have any missing pieces."

When Gracias makes his chemistry-experiment containers, for example, only 60 to 90 percent of them fold correctly. In his laboratory, a researcher uses a pipette to pick out the properly folded structures. Large-scale production of the containers would require a more efficient way to pull out the good ones. Without such a procedure "we'd have to figure out how to repair the bad ones," says Gracias.

Whitesides says that as researchers learn more, it might become possible to create new kinds of electronics and displays as well as to begin to uncover nature's assembly techniques. Although the strategy is ubiquitous in nature, for scientists, he says, "self-assembly is just at the beginning." ■

GRACIAS