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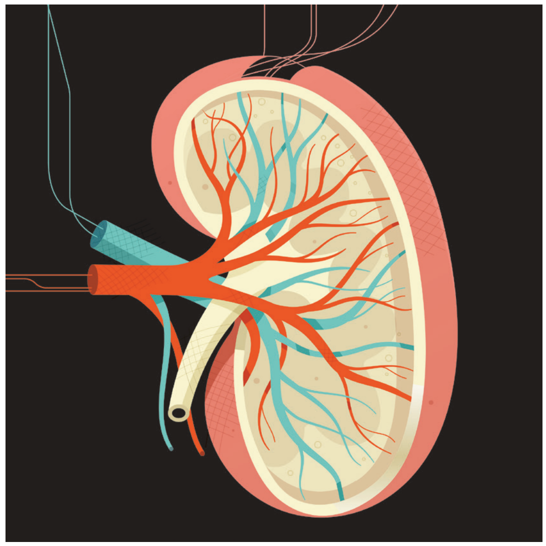

Biomedical Devices: The Emerging Promise of 4D Printing

Engineers are employing advanced manufacturing to develop transformable medical implants.

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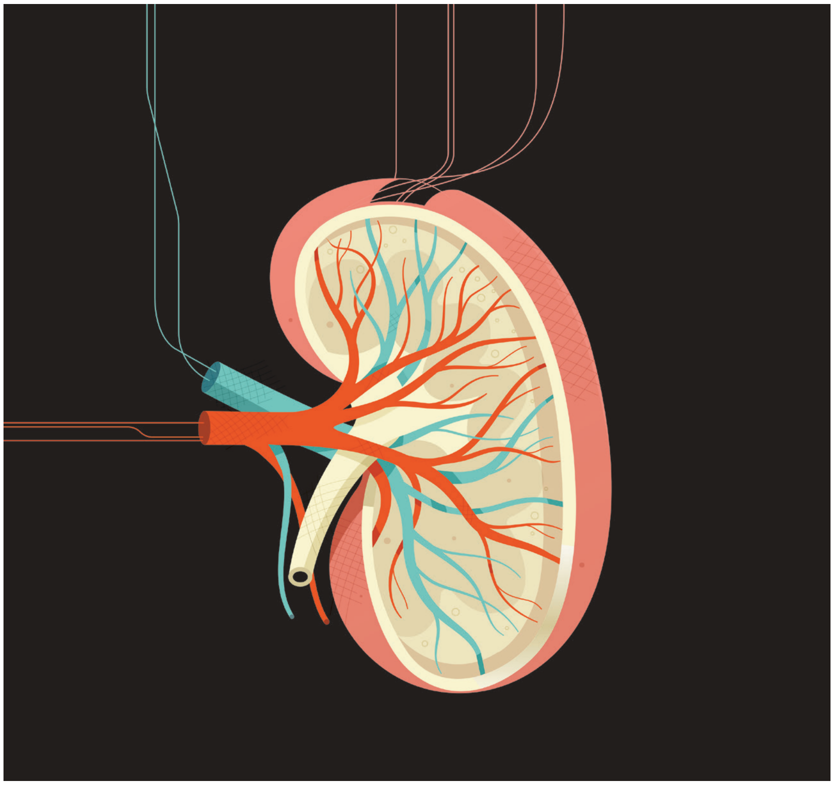

Introduction

The process of 3D printing has quickly evolved from a novelty to a mature, mainstream technology. It is now being put to work in a range of tasks, from building new-product prototypes and producing spare machinery parts to building new homes.

But as 3D printing continues to evolve, we are now seeing the advent of 4D printing, with the fourth dimension being time. In 4D printing, printed objects change in a controlled manner after they are printed—a capability that is further expanding the potential of 3D printing.

In the healthcare industry, 4D printing could improve everything from medical devices to tissue implants. To a great extent, the technology is still in its early stages, and in the hands of researchers. But development is moving quickly, and in some cases, 4D printing is already changing—and saving—lives. And it promises to do even more in the near future.

The Rise of 4D Printing

At this moment, 4D printing is still relatively new, and the term can mean different things to different people. But by most definitions, 4D printing is an extension of 3D printing, the additive manufacturing process that typically builds objects from a computer design file by building up layer after layer of material. 4D printing comes into play when that object can change its shape or properties in a predicable manner in response to an external stimulus, such as light, heat, or chemical reaction.

The concept first took hold when Skylar Tibbits, head of MIT's Self Assembly Lab, gave a TED Talk on the topic in 2013. He showed the audience a strand of material that, when put in water, transformed into the letters MIT, and another strand that assembled itself into a cube. While the examples were simple, the implications were clear. With 4D printing, Tibbits later said, "you don't just print static objects; you print things that turn into other things."

Since then, the 4D printing concept has generated a lot of interest, with observers speculating about the development of car tires that can subtly change shape to handle icy roads, water pipes that can adjust to changing flows, and furniture kits that assemble themselves. As Bastien E. Rapp, head of the Process Technology Laboratory/NeptunLab at Germany's University of Freiburg, told a reporter last year: "Instead of printing only physical structures, we can now print functions. It's like embedding a piece of code in a material—once triggered, it does what you programmed it to do."

For the healthcare community, 4D printing holds a special appeal. For one thing, using the technology is not a great leap for the industry, which is already making good use of 3D printing for everything from organ models that guide surgeons to customized prosthetics and bioprinting, which uses living cells and other biomaterials as an "ink" to print tissue.

With 4D printing, many see an opportunity to take those kinds of activities to the next level. The body is a constantly changing platform that is altered by movement, growth, age, injury, and its environment. Objects that can adapt to those changes—stents that adjust to fit blood vessels, perhaps, or devices that grow with the patient, appear to be a good fit for doctors and researchers looking for ways to treat patients.

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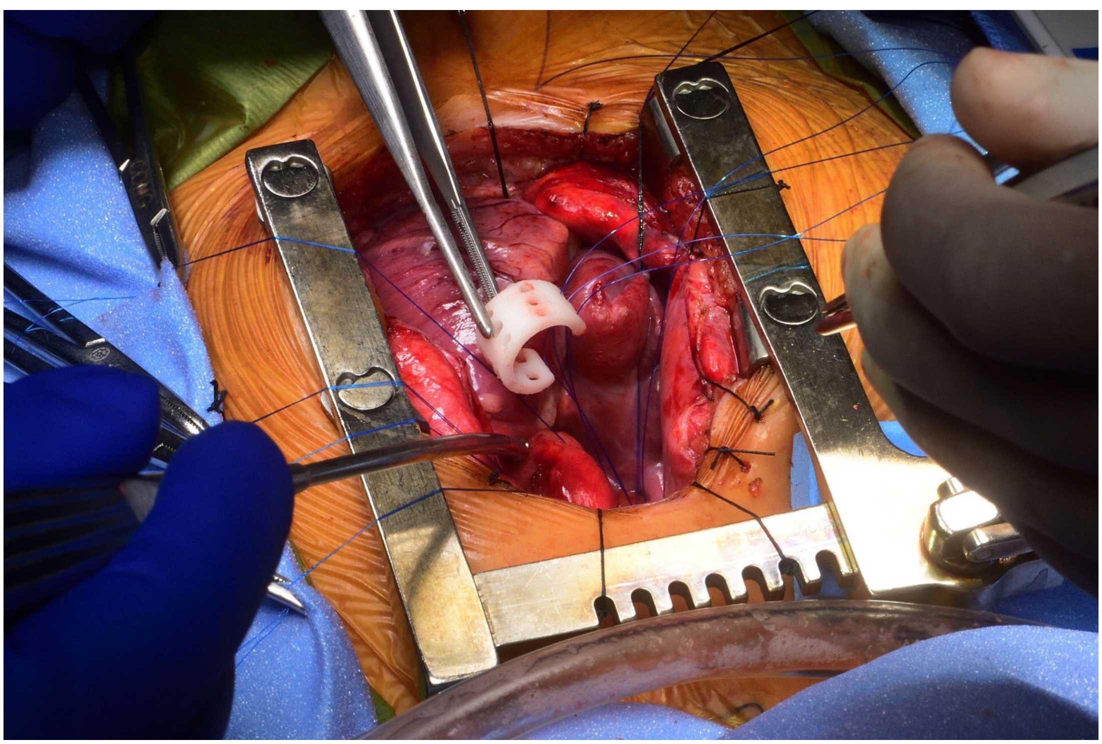
Even the process of getting medical devices in place is likely to be streamlined. "One of the biggest areas we see is the development of devices for minimally invasive procedures," says Scott Hollister, professor at the Wallace H. Coulter Dept. of Biomedical Engineering, a joint department of the Georgia Institute of Technology and Emory University. "So, instead of having a surgeon do open surgery to implant a device in the heart, you'd have a cardiologist who would use a catheter to deliver the device."

That approach is already being used with some devices, but 4D printing could make it feasible to use a wider range of devices and treatments. "If you can fold something into a small shape and then, when it reaches its destination in the body, have it unfold into its intended design shape due to heat or other stimuli, you can avoid large surgeries," says Hollister. "When you do that, you have shorter hospital times, faster recovery, and less risk for infection."

Giving Children a Second Chance

While researchers are working on several fronts to understand the potential of 4D printing in healthcare, Hollister and his colleagues have been putting the technology to practical use. Working with doctors from Childrens Healthcare of Atlanta and the University of Michigan, his team has been using 4D printing to treat congenital problems of the trachea in children. For example, with a condition called tracheomalacia, the cartilage in a baby's trachea fails to develop normally; the airway is thus too weak and "floppy" to hold itself open, making it difficult for the child to breathe. Often, the condition improves by age three or so—but for some children, that isn't soon enough, and doctors may need to perform a tracheotomy and put the child on a ventilator to keep them alive. Or, they may surgically implant a splint that holds the airway open. However, those devices have typically been made of materials such as Goretex, Hollister explains. So, while they hold the trachea open, their fixed size and shape can restrain the trachea's natural growth over time. As a result, the child might have to have additional surgeries to put in larger splints, and ultimately to remove the final splint once the trachea operates normally.

To address that problem, Hollister and his colleagues developed a 4D-printed splint with some unique properties. Using CT scans of the patient, they create a 3D computer model of the trachea, which in turn is used to develop



a CAD model of a virtual splint. “We design the splint individually for the anatomy of the patient,” he says. “And then we 3D-print the splints using laser sintering to build up layers of material.”

The finished splint is essentially a hollow C-shaped tube that doctors suture to the outside of the trachea, where it holds the tissue in place to keep the airway open. Over time, the splint will respond to the pressure created by the growth of trachea tissue. “We’ve designed it so that it will allow growth of the airway, and grow with it,” says Hollister. “As the airway grows, it comes in contact with the splint, and then continued growth will actually push the splint open.”

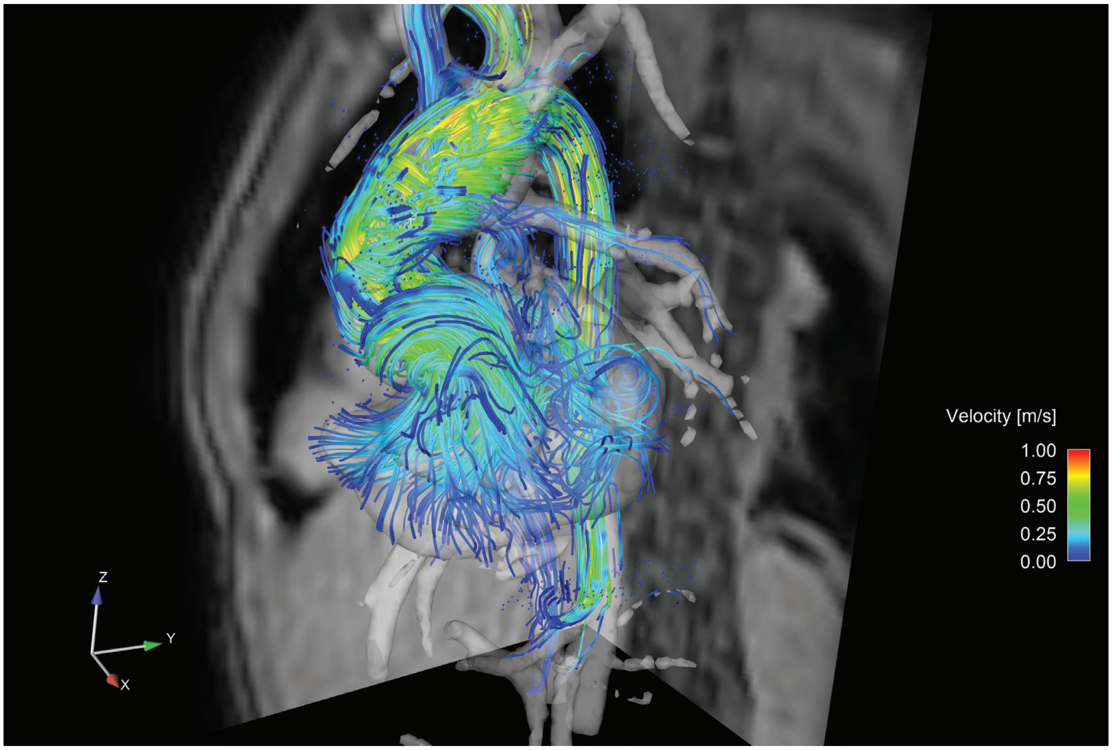
The composition of the splint will also change over time. “We print these with material that is gradually degraded and then excreted from the body, so there is no need to go back and do another surgery later,” Hollister says. That material, polycaprolactone (PCL), was selected because it dissolves slowly over the course a few years, giving the trachea time to grow and repair itself, eventually allowing the child to breathe normally.

Hollister’s team can print as many as 200 splints a day in its Atlanta lab.

The first of these 4D-printed splints was used successfully in 2012 to treat a child who otherwise would have died. Since then, it has been used to treat a number of other children with tracheomalacia or bronchomalacia, a similar problem involving the bronchi leading to the lungs. It was also used to help one child who was born without a trachea, requiring extensive reconstructive surgery.

The process of making these splints is relatively inexpensive and fast. Hollister’s team can print as many as 200 a day in its Atlanta lab. That’s important, because they typically need multiple copies of a splint—some for use in the mechanical and sterilization testing of the batch of devices, and some that are used as “spares” during surgery. “We provide the surgeons with more than they need in the operating room, just in case,” he says. “Even though we base the design on the patient’s scan, there can be issues with scar tissue from previous surgeries that we can’t see or with the resolution of the image itself.” To be safe, the team may have as many as 10 different sizes of splints on hand for the surgeons to choose from.

That capability also underscores another key benefit of 4D printing. Being able to cost-effectively produce custom devices to treat problems in growing children can be “a paradigm change in medicine,” according to Hollister. That’s because it makes it economically feasible to create devices for rare and unique problems—conditions that might not represent a big enough market to justify the development of devices by large companies using traditional methods.



Making Repairs More Effective

Meanwhile, other researchers are working at a more fundamental level and focusing on using the technology to repair tissue in the body. Last fall, the National Science Foundation awarded researchers at George Washington University (GWU) and the University of Maryland (UMD) a grant to investigate the use of 4D-printing to control the differentiation of stem cells into cardiac cells. The researchers—Lijie Grace Zhang, an associate professor in the GWU Department of Mechanical and Aerospace Engineering, and John Fisher, a professor with UMD's Fischell Department of Bioengineering—are working with smart constructs, or scaffolds, that act as platforms to control cell behaviors; with bioinks, which are the substances made of living cells used in 3D bioprinting; and with stem cells, which they are growing into heart tissue. With this work, says Zhang, "we are using 4D printing in our lab to fabricate a smart cardiac tissue patch."

Zhang—whose 4D printing-related research involves a variety of organs and tissue types—explains how 4D printing could help address cardiovascular problems. To repair damaged hearts, researchers have sometimes injected stem cells into the organ. "But the pumping of the heart tends to push those cells out of the heart, where they die," says Zhang. The approach that she and her team are working on involves creating a 3D printed scaffold that holds the stem cells in position until they turn into functioning heart cells—ideally, creating a patch of living heart tissue. She and her team are using long-wavelength near-infrared light, which is less harmful to living tissue than other forms of light, to trigger the material to become flexible, and elongate and contract, once it is in place.

Patches can be built using a laser 3D printing method, stereolithography, in which a laser “draws” patterns in a liquid form of a novel smart scaffold material, working section by section to create a solid structure with the desired shape. The printed structure can automatically change shape based on light or temperature stimulation.

The technology being developed by Zhang could be used to repair other types of problems involving nerves and brain tissue, she says. It also has the potential to enhance the current approach to 3D bioprinted organs, including hearts. While such printed hearts have been created, she says, “they have the shape of a heart, but not the full functions.” She says that 4D printing materials and techniques currently being researched could enable functions such as pumping action and blood flow in these fabricated organs, making them more valuable for the testing of drugs. Someday, she says, this type of research may lead to the 4D printing of working hearts, using a patient’s own cells, that can be transplanted into humans.

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“The very concept of 4D bioprinting is so new that it opens up a realm of possibilities in tissue engineering that few had ever imagined,” UMD’s Fisher said in announcing the NSF grant. “While scientists and engineers have a lot of ground to cover, 4D bioprinted tissue could one day change how we treat pediatric heart disease, or even pave the way to alternatives to donor organs.”

Exploring New Materials

Today, the path forward for the wider use of 4D printing lies less with the printing process itself, and more with the materials being printed. "Material development is really one of the biggest areas of advancement that's needed to bring this technology to the fore," says Hollister. "That's a huge open field."

With that in mind, Hollister's team has developed a shape memory material called poly(glycerol dodecanedioate), or PGD."You can print it in one shape and then essentially fold it or deform it into another state to easily deliver it into the body," Hollister says. "When it warms up to body temperature, it will

retake its initial shape."

This material has the potential to be useful in a variety of situations, such as repairing defects in the heart wall. Often, that is now done with a nickel-titanium patch that can also be delivered via catheter. However, he says, "that's metal, so it's a lot stiffer than heart muscle, and there can be complications with the erosion of the device and bleeding. And it's permanent, so once you put it in, it stays in the heart unless it is removed." By using PGD, he says, "the goal is to make a device that is more in line with the stiffness of heart muscle. It acts more like rubber when it warms up to body temperature." And like the PCL used in the tracheal splints, "it's resorbable, so once it's in place, tissue would grow over it, it would resorb, and you would be left with just the natural tissue in the heart."

The development of new printable materials is the core business at Dimension Inx, a Chicago startup that grew out of laboratory work at Northwestern University. The company makes material for use in repairing and regenerating tissue and organs. Typically, companies in this field make fixed structures with living cells “planted” in them or on them, which are then put into the body to repair a hole or other problem. “What makes us different is that our products are meant to transform into living tissue after they are implanted, without needing to add cells beforehand,” says Adam Jakus, PhD, the company’s co-founder and chief technology officer.

For example, one of the materials made by Dimension Inx, Hyperelastic Bone, is an elastomeric and bioactive ceramic. This synthetic material is mostly calcium phosphate, the same type of ceramic found in human bones. However, it can be produced in an elastic and flexible form, allowing doctors to press-fit it into a location, cut it to size, suture it in place, and so forth.

Jakus notes that there are a variety of potential uses for the material. “In a complex pediatric case, there might be trauma or a birth defect at the base of the skull that in the past would be treated with a permanent structure [holding new cells] that doesn’t grow with the patient. “The Hyperelastic Bone can be used to make that kind of repair.” The treatment would not require added cells or the use of chemicals to stimulate tissue repair. Instead, the body’s cells will integrate with the material and grow into its shape. “The material will transform into bone after implantation over time, so it will grow with the patient,” he says. “Years down the line, if you take an x-ray or CT scan of the location where it was implanted, you won’t see it. It will just be the patient’s new bone.”

The creation of an implant with the material is fairly straightforward, and it can be 3D printed at room temperature through a simple nozzle extrusion

method using a process Dimension Inx calls “3D-Painting”. The 3D-Painting process not only makes it possible to create the right shape and size implant, it is also key to the Hyperelastic Bone’s effectiveness. “The printing technology lets us introduce a lot of 3-dimensional porosity, which is almost impossible to create using traditional manufacturing methods,” says Jakus. “That porosity is really important to the material’s being able to transform and fully integrate with the body and really become a 4D printed material.”

Nanodevices are loaded with medicine, which then diffuse through a nanochannel membrane out into the body.

GWU’s Grace Zhang agrees that the development of new smart biomaterials is the frontier for 4D printing. For the cardiovascular patch her lab is working on, the researchers developed a material called “smart soybean oil epoxidized acrylate,” or SOEA, which lends itself to the laser-based 3D printing processes required, and which changes its properties in reaction to light. The SOEA material is also being used in the creation of small, flat star-shaped objects that, when subject to different stimuli, fold up and then unfold, like a flower opening. This concept could be used to expand pathways for regenerating nerves, or to deliver drugs to a target organ.

Looking ahead, Zhang says that 4D printing could benefit from the development of more types of material suitable for the 3D printing process. In addition, she says, it will be important to develop more approaches to managing the changes that the printed objects go through. “We can change the shape of materials with heat or light or magnetism, for example, but we need to control the smart structures with more precision,” she says. “So we are looking for better mechanisms to do that.”

Keeping it Practical

Not all the challenges facing 4D printing are technical. Regulations for materials and devices used in the human body are, of course, especially strict, and this is a case where regulators have trouble keeping up with fast-moving technology. When the 4D printed tracheal splint was first used to save a child's life, for example, the team had to get an emergency approval from the FDA to use the device, which was given "because the patient was not likely to survive without it," says Hollister.

"A lot of the barriers now for non-musculoskeletal tissue targeted materials are regulatory," says Jakus. "There aren't very clear regulatory pathways to the FDA for any type of 4D printed technology. The problem is that the guidelines and standards were developed for things that aren't supposed to change after implantation, like titanium implants." With traditional medical devices, "change is bad," he says, while with 4D implants, it is a benefit. "So, new standards need to be developed. Fortunately, the standards organizations are aware of this, and they are working on it."

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As they look for new materials and methods, researchers will have to keep an eye not only on regulators, but on the bottom line, as well. For Jakus, new materials need to be "very surgically friendly and cost effective," he says. "That's something we have kept in mind from the very beginning, because with the healthcare system the way it is, the moment something becomes slightly not cost effective, it is not practical anymore. "

There is still work to do, and challenges remain, adds Zhang. But the promise of 4D printing in healthcare is great, the potential benefits are compelling, and, she says, "4D printing has a very broad future in medical applications."

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