HORIZONS IN BIOSCIENCE
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3D Bioprinting
A New Dimension in Tissue Engineering

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THREE-DIMENSIONAL (3D) PRINTING is used to manufacture rocket engines, medical devices, custom-fit athletic shoes, and even other 3D printers. Today, researchers are adapting this exciting technology with the aim of replacing human tissues and organs that have been damaged by trauma or disease.

ADDITIVE MANUFACTURING

A computer-controlled nozzle extrudes a layer of gel in a vaguely oval-shaped outline onto a slide, and then fills it in. It adds another layer with a slightly different shape on top, then another, and another, until the stacked layers of gel begin to take the shape of a human ear. (Figure 1) While it may look like plastic, it is, in fact, constructed with living cells. As the 3D-bioprinted ear incubates in the laboratory, the cells within it multiply and mature, forming cartilage and fat, like that found in a normal ear. Someday, living tissue such as this could be used to replace an ear lost in an accident. (3D bioprinting video)

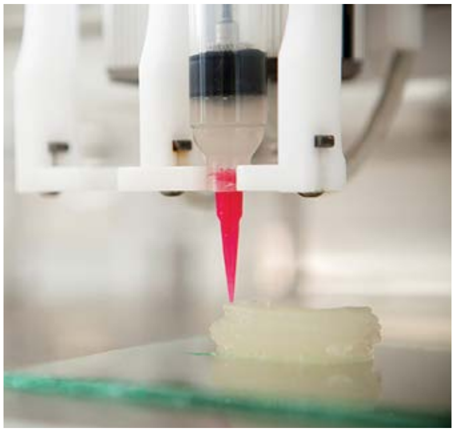

FIGURE 1 / 3D bioprinting of an ear. *Image credit: Lindsay France/Cornell Marketing Group*

In 1984, Charles Hull patented a process he called "stereolithography." Today, we call it 3D printing or additive manufacturing. The concept is simple. Very thin cross-sections are stacked on top of each other to form a three-dimensional object. Additive manufacturing can produce much more complex structures than traditional manufacturing methods that form shapes by removing material from a solid or injecting material into a mold.

3D PRINTING IN MEDICINE

The medical field is already reaping the benefits of 3D printing. Imaging data from computed tomography (CT) scans, ultrasounds, or magnetic resonance imaging (MRI) can produce 3D images in a computer. The computer then digitally "slices" the virtual image into thin layers to generate instructions for a printer to convert the digital object into an exact physical replica.

Precise 3D-printed anatomical models can be used for teaching or to help in surgical planning. For example, surgeons at Children's National Medical Center in Washington, DC used a 3D-printed model of the mid-sections of conjoined twin boys to assist in the surgery to separate them. Because it can match each patient's unique anatomical structure, 3D printing can also be used to construct custom-fit structures such as casts and splints to support injuries, braces to straighten teeth, prosthetic limbs, and even artificial joints and bone implants. (Figure 2)

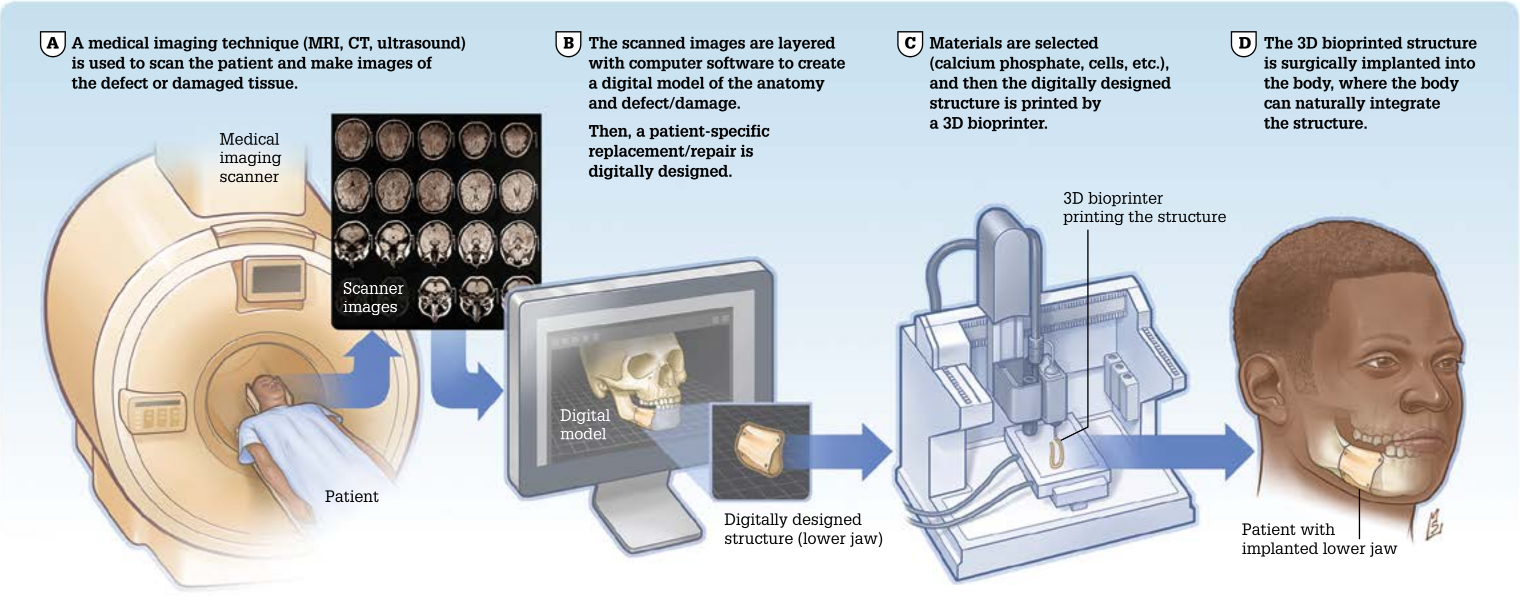

FIGURE 2 / 3D printing process for a mandible defect
Illustration: © Michael Linkinhoker, Link Studio, LLC

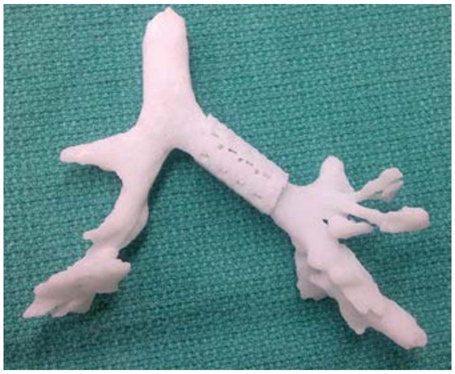

FIGURE 3 / 3D-printed tracheal splint
Image credit: University of Michigan Health System (original article: http://www.uofmhealth.org/news/archive/201305/baby%E2%80%99s-life-saved-groundbreaking-3d-printed-device)

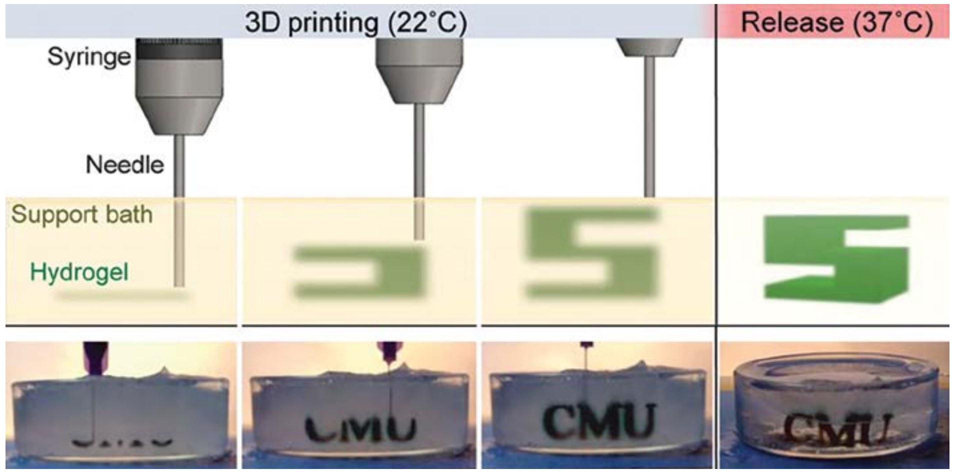

FIGURE 4 / Simulation of 3D printing for a complex biological structure
Image credit: Hinton TJ et al. Three-dimensional printing of complex biological structures by freeform reversible embedding of suspended hydrogels. Science Advances 23 Oct 2015: Vol. 1, no. 9, e1500758 (creativecommons.org/licenses/by/4.0/; Figure 1 – c, d, and e not shown)

As with anything introduced into the body, these implants must be sterile and compatible with living cells. While it is a major challenge in the field, newer printable biocompatible materials are being developed for use in humans—some are synthetic polymers and some are derived from natural products like gelatin or seaweed.

In 2012, doctors at the University of Michigan 3D printed a splint of a synthetic biocompatible polymer to support an infant's defective trachea, which would otherwise collapse, causing life-threatening breathing problems. (Figure 3) Four years later, the child is doing well and the splint is almost completely reabsorbed into his body. Implants that are eventually replaced by the patient's own tissues have the potential to grow with the patient, which is especially important for pediatric patients.

Replacing entire organs that perform biological functions is a complex endeavor. Currently, the only way to replace an organ like a kidney or liver is with a donor organ, but it is not a perfect solution. There is a massive shortage of donor organs, and as many as 22 people die each day on waitlists in the United States. Even patients that receive donor organs face challenges, as they must use immunosuppressive drugs to keep their bodies from rejecting the foreign tissue.

These problems can potentially be overcome using the patient's own cells. Through tissue engineering, cells taken from patients can be grown in the laboratory until there is a sufficient quantity to seed onto scaffolds made of biocompatible materials. The properties of the scaffold material and the addition of growth factors can prompt the cells to grow and develop into the desired tissues. These lab-grown tissues can be implanted back into the patient from whom the cells were harvested without being rejected as foreign tissue.

3D BIOPRINTING

While 3D printing can produce scaffolds for tissue engineering, 3D bioprinting goes a step further by printing materials that contain living cells. For example, clusters of cells of interest are suspended in a gel to form "tissue spheroids." The tissue spheroids and biocompatible scaffold material are bioprinted together by being extruded (pushed out of a syringe-like nozzle), sprayed as tiny droplets (as with an inkjet printer), or propelled by a laser. A bioprinter can position cells within the scaffolding material more quickly and precisely than a human seeding the scaffold by hand. There are also "scaffold-free" printers that construct arrays consisting only of tissue spheroids. The bioprinted tissues then grow in a bioreactor, a system that supplies the physical conditions, mechanical stimuli, and nutrients needed for the printed tissue to develop and mature.

Currently, 3D-bioprinted bits of liver are commercially available to study disease processes in the laboratory and test the effectiveness and toxicity of medications. Investigators are also developing 3D-bioprinted heart, brain, placenta, kidney, and pancreatic tissues, as well as tumor tissues to study cancer and develop treatments. Patient-derived, 3D-bioprinted bone marrow has been shown to produce functional platelets in the laboratory. And a Russian company has produced 3D-bioprinted mouse thyroid glands which, when transplanted into mice without functional thyroid glands, appear to be able to produce the thyroid hormone thyroxine (T4).

Larger tissues present additional technical challenges. Although a layer of tissue just a few cells thick can get the nutrients and oxygen it needs by diffusion, a vascular system is needed to get nutrients and oxygen to cells deep within thicker tissue. In addition, soft tissues can collapse under their own weight during the printing process, so they need to be supported to maintain their internal and external structure. To achieve this, investigators use supporting material to surround the bioprinted tissue or to temporarily fill channels within the tissue. After printing, the supporting material can be removed by changing conditions (heating or cooling, for example) so that it becomes a liquid and can flow out of the channels or away from the outside of the bioprinted tissue. (Figure 4)

Are 3D-printed kidneys just around the corner? Not quite. Printing whole human organs is far in the future, but simpler structures, such as 3D-printed ear, nose, and knee cartilage are closer, as are patches for skin after some successful trials in humans. Investigators are also developing ways to print tissue directly into the human body, by printing new skin on a wound, for example. Technical issues remain, and there are regulatory considerations involved in printing and implanting human tissues in a clinical setting.

The technology for 3D bioprinting is the result of collaboration among scientists and engineers in fields ranging from cell biology to polymer chemistry to mechanical and biomedical engineering and computer science, along with clinicians. While custom-fitted human tissues and organs made from a patient's cells are ambitious goals, the lessons learned in reaching for those goals are already changing lives.

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