

ADVANCES IN MEDICINE

Additive manufacturing: From implants to organs

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Additive manufacturing (AM) constructs 3D objects layer by layer under computer control from 3D models. 3D printing is one example of this kind of technology. AM offers geometric flexibility in its products and therefore allows customisation to suit individual needs. Clinical success has been shown with models for surgical planning, implants, assistive devices and scaffold-based tissue engineering. The use of AM to print tissues and organs that mimic nature in structure and function remains an elusive goal, but has the potential to transform personalised medicine, drug development and scientific understanding of the mechanisms of disease.

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Additive manufacturing (AM) has been labelled a disruptive technology for its ability to produce customised geometrically complex objects in small quantities at low cost.^[1] *The Economist* has called it the third industrial revolution. Unlike traditional manufacturing, which is

subtractive in that large volumes of material are reduced to desired shapes by removing excess, AM constructs 3D objects by adding materials layer by layer under computer control based on 3D models.

AM creates complex shapes yet makes efficient use of raw materials, producing minimal waste and requiring minimal tools.^[2] The

geometric flexibility of the process, mostly attributable to its additive nature, has led to various non-industrial applications, notably those in medicine. Some medical applications of AM include construction of anatomical models for surgery planning, and design and construction of customised prosthetic implants. The raw materials used in AM for these applications include plastics, resins, alloys, stainless steel, titanium, polymers and ceramics.^[1] Layers of material can be built and consolidated in a variety of ways. 3D printing is a fast form of AM and is available in low-cost, low-resolution format. It places production capability in the hands of the designer, facilitated by the availability of computing technology that translates 3D designs into printable files. 3D printers operate similarly to traditional laser or inkjet printers, but with the ink replaced by the materials from which the objects are to be built. They deposit material layer by layer and bind it chemically using a binder sprayed through a nozzle; further strengthening may be achieved with the application of heat. The unbound material is removed chemically. The printer interfaces with computer-aided design (CAD) software to specify the shape of the object.

Patient-specific physical models of anatomical structures serve as an aid for surgical planning to highlight areas of interest and for surgery rehearsal to determine possible complications and reduce operating time.^[2] Such models are produced using AM after CAD translation of volumetric images from 3D modalities such as computed tomography and magnetic resonance imaging. Although 3D visualisation using specialised viewers is available for surgical planning,^[4] 3D images are typically viewed on 2D screens. This limitation can be overcome using physical 3D models. The ability of images to differentiate soft-tissue types remains a constraint, and models of hard tissue are more commonly reported than those of soft tissue.^[5] Physical models have been used successfully in cranio- and maxillofacial, pelvic, neuro-, spine, cardiovascular and visceral surgery.^[3]

Among its potential medical applications, the use of AM in the production of implants, particularly to replace bony structures, is perhaps the best known. AM techniques allow the design of patient-specific prosthetic implants to suit individual anatomy for improved fit, functionality and aesthetics, and to reduce the likelihood of implant failure. Examples include customised mandibles, hips, knees and cranial plates. AM is commonly used in dentistry, and a variety of dental products, such as bridges and crowns, are commercially available.^[2] AM has also influenced the production of hearing aids, devices that require a high degree of customisation for individual fit. Greater ease of regulatory approval for devices worn on the body than for implants has assisted widespread adoption of AM-produced hearing aids, with the result that AM accounts for 99% of those that are placed in the ear.^[6]

In addition to the implantation of fabricated prostheses, surgical techniques adopted to repair defects and replace bone and other tissue that the body is unable to produce include autologous bone grafts (the gold standard – originating from another site in the same patient), allografts (from human donors) or xenografts (from animals). Autografts are associated with long recovery periods, donor site morbidity and a complex graft-shaping process to achieve biomechanical coupling; allografts and xenografts carry the possibility of immuno-rejection, inflammation and disease transmission, as well as poor mechanical performance.^[7] For these reasons, tissue regeneration or engineering approaches are being explored. AM has been used as a tool in tissue regeneration through the production of biocompatible or biodegradable scaffolds – structures that serve as a platform to guide the growth of new tissues to replace damaged or defective ones.^[8] Scaffolds act not only as passive matrices to support cell adhesion or proliferation, but also as vehicles for the delivery of bioactive molecules, nutrients and waste products.^[7] Their functional specifications translate into fabrication requirements for spatially varying structures with high geometric complexity coupled with different biomaterials. Such 'biofabrication' can

be accommodated by AM techniques in combination with CAD and medical imaging.^[8] While tissue engineering is still in its technological infancy, scaffolds have been clinically successful in building bladder and bronchus,^[9] bone, osteochondral tissue, cartilage and skin. Techniques to develop new vasculature are being explored.^[8]

Scaffolding is the traditional tissue engineering approach but has limited ability for cell manipulation and control of cell placement. Incorporating viable cells into biofabricated structures remains a challenge.^[8] Organ printing through controlled deposition of cells or cell aggregates is an alternative to scaffolds, offering more precise cellular positioning.^[10] Manufactured organs are, however, an elusive goal. Patches of organ tissue – including liver, kidney and heart – that have been printed to date have generally not exceeded a few millimetres in area and a few layers in cell depth. Thicker structures would require a vascular system to supply nutrients and oxygen; the requirement for an embedded vasculature and limits to the current understanding of interactions between cells and their environment are challenges to the production of viable organs.^[11] Nonetheless, the ultimate possibility of organ printing *in vivo*, with the aid of a biofabrication device as a surgical tool, has been suggested.^[12]

More immediate applications of tissue engineering transcend its traditional purpose of generating tissues for repair or restoration and lie in the discovery, development and testing of drugs. Biofabrication can produce models of both health and disease. Fabricated tissues can provide a more realistic platform for preclinical testing of pharmaceuticals than the cultured cells and animal models that are currently used. Tissue models can be designed to answer very specific research questions and used as test platforms for new treatments and vaccines.^[13] Personalised therapy is another potential application, e.g. printed models of tumours can be subjected to therapies *in vitro* and their responses used to design patient-specific cancer treatment.^[11]

Engineered tissue models can also be valuable research tools. They have the potential to provide the heterogeneity of mechanics and structure that are lacking in the cellular aggregates currently used in biological studies of disease. They can be used to examine complex cellular pathways and behaviours in a variety of biological conditions to aid the understanding of disease progression and the design of approaches for prevention.^[13]

The ability of AM technology to deliver customised products to suit individual needs holds great promise for personalised healthcare. There have been some clinical successes with AM-based surgical planning, implants, assistive devices and scaffold-based tissue engineering. Biofabrication of tissues and organs that mimic *in vivo* structure and function remains fraught with challenges, but offers exciting prospects and may contribute in significant ways to the 'century of biology'.

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