Review

Printing Technologies for Medical Applications

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Over the past 15 years, printers have been increasingly utilized for biomedical applications in various areas of medicine and tissue engineering. This review discusses the current and future applications of 3D bioprinting. Several 3D printing tools with broad applications from surgical planning to 3D models are being created, such as liver replicas and intermediate splints. Numerous researchers are exploring this technique to pattern cells or fabricate several different tissues and organs, such as blood vessels or cardiac patches. Current investigations in bioprinting applications are yielding further advances. As one of the fastest areas of industry expansion, 3D additive manufacturing will change techniques across biomedical applications, from research and testing models to surgical planning, device manufacturing, and tissue or organ replacement.

Trends

3D printing is a versatile emerging technology that is finding its way through all aspects of human life, and the unique potential of 3D printers can be exploited in different areas of medicine, such as fundamental research, drug delivery, and testing, as well as in clinical practice.

Nearly all current medical non-biological implants, such as ear prostheses or human mandibular replacements, are manufactured at predetermined sizes and configurations that are widely used for patients. 3D printing allows more accurate personalized manufacturing of devices created to the patient's own specifications; a process which is often aided by 3D imaging software.

Surgical planning with 3D printing is already showing promise. As an example, living-donor liver transplantation surgery for patients with end-stage organ disease is complex and can be life-threatening. The use of 3D printed surgical models has been shown to help shorten operative time and decrease donor risk, thereby boosting surgical outcomes.

Bioprinting is being used to create more accurate non-biologic and biologic research models for research purposes in wide variety of applications, including spatial and temporal trauma in cancer research.

3D printing is being increasingly used for the design and manufacturing of living tissues and organs that may one day be implanted into patients.

Printing is a unique technology with a wide range of applications [1–4]. Printers are being used in fields from mass communication to electronics, and recently in medicine [2,5–10]. The invention of 3D lithography by Charles Hull in 1986 also opened up a new avenue for research and industry to make complicated objects not possible otherwise [11]. Numerous sophisticated 3D printed instruments and tools have been created and are being employed in academic laboratories and industry. Moreover, the power of printers has attracted much attention in biomedical fields [2,12,13]. Many researchers are involved in using 2D and 3D printers for various applications such as drug delivery, disease modeling, and tissue and organ engineering [14–17]. Until recently, 3D printers were mostly used for prototyping devices for design and manufacture. More recently, 3D bioprinting has been expanded to applications such as cell and tissue printing.

This article discusses the use of printers for the more recent applications of cell printing, tissue engineering, and regenerative medicine, and reviews the initial work that uses 3D printers for surgical planning models. State-of-the-art printing technologies and their impact on several aspects of health and medicine are discussed. The review briefly examines the general aspects of bioprinting and introduces the most popular printer types such as inkjet, laser-assisted, and extrusion (Box 1). The use of 3D printers in maxillofacial (ear, eye, and jaw) applications, repair of internal organs (liver, heart, and kidney), drug screening and delivery (Box 2), personalized medicine (Box 3), and cancer research is also discussed.

The Basics of Bioprinting

Generally, bioprinting includes three sets of steps; pre-bioprinting, bioprinting, and post-bioprinting activities. Pre-bioprinting involves imaging and digital design in addition to material selection [13]. Computed tomography (CT) and magnetic resonance imaging (MRI) are considered the two most common imaging technologies for medically applied bioprinting. After medical imaging, tomographic reconstruction is performed to achieve segmental 2D images for the layer-by-layer fabrication process [18]. Finally, by using digital

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Box 1. Bioprinter Types and Mechanisms

Inkjet printers are traditionally categorized into two classes, continuous and drop-on-demand [68]. Continuous inkjet printers have high speed capabilities and are able to print on large-scale areas; hence, they are normally used in printing industries [69]. When precision and cost matter, the drop-on-demand inkjet printers are preferred [69]. Thermal and piezoelectric inkjet printers are the most popular drop-on-demand printers [69]. In thermal printers, a heater makes a bubble of ink out of a reservoir and ejects it from the nozzle [68,70]. In piezoelectric drop-on-demand printers, the application of a voltage pulse changes the shape and size of the piezoelectric material and, consequently, a droplet of ink is produced by pressure on the ink reservoir caused by the piezoelectric material [68]. Droplet shape and size can be adjusted by tuning the applied voltage to the piezoelectric material [4].

The mechanism of laser-assisted bioprinting is similar to that of old typewriters. In an old typewriter, there is a ribbon of ink (usually red and black), and templates of the letters that hit the ribbon and make an ink imprint on the paper. Likewise, in laser-assisted bioprinting there is a ribbon containing the biomaterial or cells, and a laser pulse is used to push these out of the ribbon onto the substrate [2]. The patterning is accomplished by changing the substrate location or the laser beam with respect to the ribbon [12]. Because these printers do not use nozzles, they do not experience clogging and are able to print a broad range of materials [12].

The extrusion printers include a stage and one or a few temperature-controlled cartridges (i.e., syringes or pens) that can be loaded with cells, cell-laden hydrogels, and biomaterials to print [2,12,13]. The materials inside the cartridge may be dispensed using a pneumatic or mechanical dispensing system [13,71,72]. The operator can control the extrusion procedure, speed, and the displacement of the cartridge, and/or the stage in *x*, *y*, and *z* directions, by means of a computer software program (Figure I).

Extrusion bioprinters are divided into two categories based on the bioink [12,73,74]. Many groups use extrusion printing to print high-viscosity cell-laden hydrogels and biomaterials [2,12]. After deposition, the hydrogels must be solidified to obtain appropriate mechanical integrity to form a 3D construct. The second approach is using spherical and cylindrical multicellular systems as bioink in addition to supportive and space-holder biomaterials such as agarose [12,15]. After printing, the multicellular systems fuse together and replicate the functional properties of the ECM to make 3D biological samples [75]. The properties of bioinks and the post-bioprinting process are important considerations for the outcome of extrusion printing and need to be addressed in the experimental design [19,21].

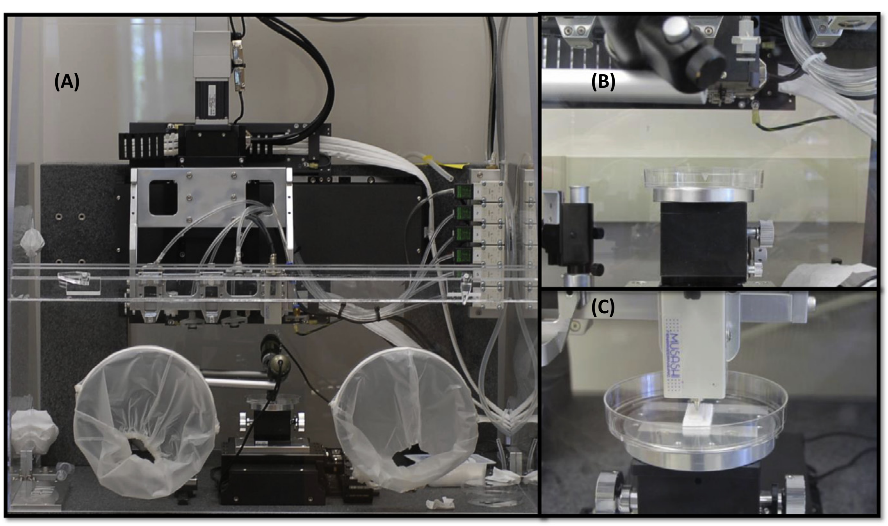

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Figure I. The Extrusion Printer. (A) Extrusion printer equipped with temperature controller inside the printing box, with a pneumatic dispensing system able to print up to six different inks. (B) Printer stage with a camera that enables the researcher to control the printing process. (C) Layer-by-layer printing of a 3D structure.

preparations, the 3D representation of the organ, tissue, or target object is created in stereolithography files (STL files) and transferred to the printer. Material selection, another vital part of the process, is governed by the printer type used and the requirements of the final product [12,19].