REVIEW ARTICLE

# A Brief Overview of the Development of Bioprinting in the Field of Tissue Engineering

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**Abstract**

In the realm of tissue engineering, bioprinting has become a ground-breaking technology that offers creative methods for creating intricate three-dimensional (3D) bioconstructs that closely resemble natural tissues and organs. This review was based on a comprehensive literature search of peer-reviewed articles, review papers, book chapters, and scientific reports indexed in PubMed, Scopus, Web of Science, and Google Scholar. Research on organ transplantation and regenerative medicine has greatly benefited from the combination of biomaterials, living cells, and cutting-edge printing technology. The role of bioinks, biomaterials, and recent technical developments that have enhanced tissue functionality, cell viability, and structural integrity is covered in the article. A summary of the biomedical uses of bioprinting in skin, bone, cartilage, vascular, and organ tissue engineering is provided, along with an overview of the limitations and challenges of 3D bioprinting.

**Key words:** 3D imprinting, biomaterials, regenerative medicine, tissue engineering

## INTRODUCTION

Nowadays, organ transplants are a big concern globally because of the high number of injuries and chronic illnesses that occur each year. However, due to the limited number of available donors, there is a severe organ shortage. To fill this supply deficit, the option is to create plastic structures for the growth of new organs or tissues. The idea behind tissue science is the regeneration of injured tissues or the restoration of organs through the application of engineering, biology, chemistry, physics, and mathematics. A scaffold with a highly porous network that is interconnected is necessary for the appropriate creation of new tissues because it replicates the natural three-dimensional (3D) milieu for migration of cells and infiltration.[1] 3D porous scaffolds have been made by traditional fabrication methods, including electrospinning and freeze-drying. Tissue engineering processes have limited success in promoting *in vitro* and *in vivo* tissue regeneration for specific cell or tissue types. They have limitations in creating an ideal and optimal 3D microcosm that resembles the native tissues in terms of pore size and shape, scaffold architecture, or degradation behavior.[2] This happens because the scaffolds' characteristics do not match those of the freshly created tissue. During the last 10 years, the concept of 3D printing has been put up to address this issue by creating accurate, cell-free 3D scaffolds. Control over the interconnectivity, size, and form of the pores reduces the time required for fabrication and allows for quicker tissue regeneration than with traditional methods.[3] Table 1 presents a comparative overview of conventional manufacturing and 3D printing techniques based on their process, material usage, customization, efficiency, and biomedical applications. Two methods can be used, depending on the types of biomaterials: 3D printing directly and indirectly. Due to the challenges associated with direct printing of natural polymers, indirect printing using 3D printers was created for the creation of 3D scaffolds based on natural polymers. To create the appropriate

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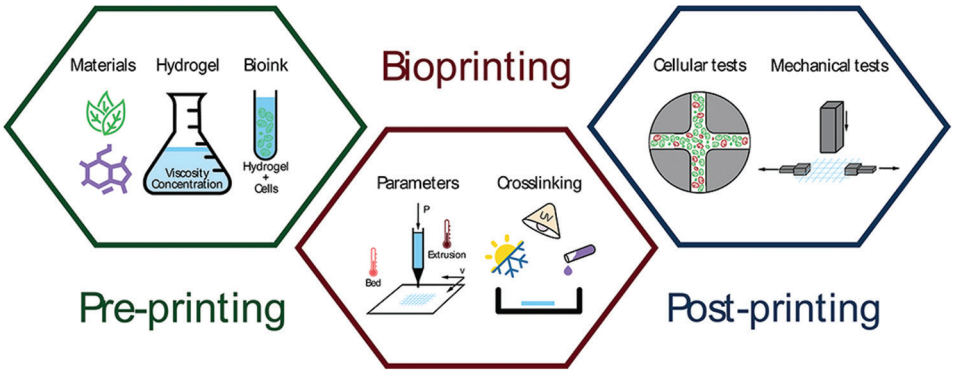



**Figure 1:** 3D bioprinting tissue manufacturing methods

**Table 1:** Comparison of conventional and 3D printing techniques[5]

| Conventional printing | 3D printing |
|---|---|
| Material is cut, molded, or machined into shape | Objects are created layer by layer from digital designs |
| Subtractive or formative production | Additive manufacturing |
| High material wastage | Minimal material wastage |
| Limited ability to produce complex structures | Easily fabricates highly complex geometries |
| Faster for mass production | Faster for prototypes and small batches |
| High tooling and machinery costs | Lower setup cost with digital workflow |
| Suitable for large-scale manufacturing | More suitable for personalized or low-volume production |
| Requires skilled labor and multiple steps | More automated with fewer processing steps |
| A wide range of conventional materials used | Limited but continuously expanding material utilized |

3D scaffolds, this process entails creating a negative mould (often from support fabric) for casting a specific natural polymer, followed by freeze-drying.[4] Figure 1 illustrates the main 3D bioprinting methods used in tissue manufacturing.

## Bioprinting technology

Inkjet bioprinting, extrusion-based bioprinting, laser-assisted bioprinting, and stereolithography bioprinting are the main bioprinting production techniques based on their operational processes. Various bioprinting methods rely on distinct principles and material requirements, considering benefits and drawbacks.[6] Bioprinting fabrication processes are sophisticated additive manufacturing techniques that create 3D biological structures by precisely depositing bioinks, biomaterials, and bioactive chemicals. For low-viscosity materials, inkjet or droplet-based bioprinting offers high speed and cost-effectiveness using thermal or piezoelectric forces to dispense tiny droplets of bioink onto a substrate in a controlled manner.[7] The popular technique, extrusion-based bioprinting, prints huge tissue structures and very viscous biomaterials by constantly extruding bioink through a nozzle employing pneumatic, piston, or screw-driven pressure devices.[8] Laser-assisted bioprinting minimizes clogging problems with the use of laser pulses to deposit bioink droplets onto a receptive surface without the need for a nozzle, while offering greater resolution, precision, and cell survival.[9] Another significant method is stereolithography-based bioprinting, which creates extremely precise and structurally intricate tissue constructions by selectively polymerizing photosensitive bioinks layer by layer using ultraviolet or visible light.[10] The printing resolution, cell viability, biomaterial compatibility, speed, and mechanical characteristics of the finished product vary among these production techniques.[11] By making it possible to create biomimetic tissue architectures that closely mirror natural biological systems, bioprinting fabrication methods have collectively greatly advanced the disciplines of tissue engineering, regenerative medicine and organ fabrication. Figure 2 presents organ 3D bioprinting and its major applications.

## Bioinks and biomaterials used in tissue engineering

Bioinks and biomaterials offer structural support for cell development, proliferation, and differentiation. Living cells are usually mixed with natural or artificial biomaterials with desired physicochemical and biological characteristics to create bioinks. Because of their superior biocompatibility, biodegradability, and resemblance to the original extracellular matrix, natural biomaterials are commonly used.[12] The bioinks/biomaterials utilized in 3D printing are listed in Table 2 with their applications.

## Applications of bioprinting in tissue and organ regeneration

Regenerative medicine in the healthcare industry will soon be dominated by 3D and 4D bioprinting. Vascularization was

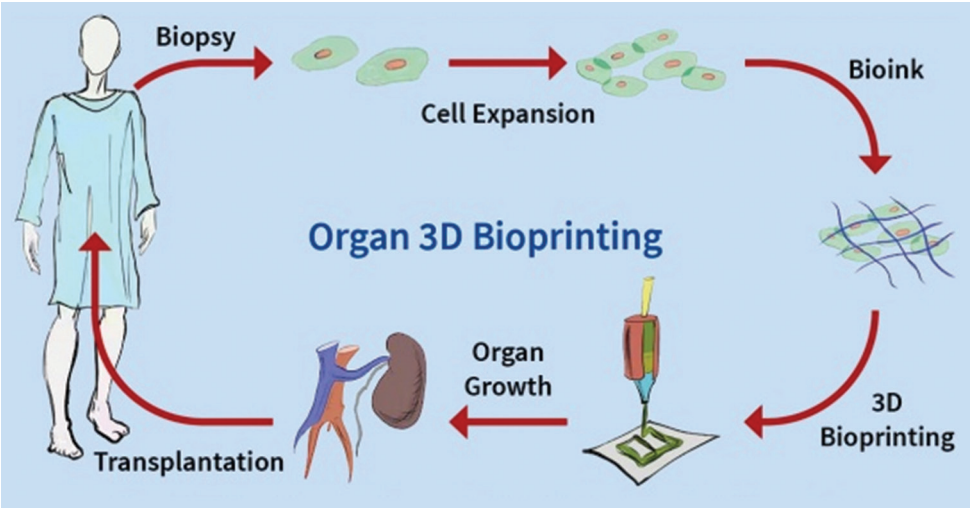



**Figure 2:** Organ 3D bioprinting and its applications. 3D bioprinting to test cosmetics and drugs

**Table 2:** The bioinks/biomaterials utilized in 3D printing with their applications

| Bioink/ biomaterial | Applications in tissue engineering | References |
|---|---|---|
| Alginate | Cartilage, skin, wound healing | [13] |
| Collagen | Skin, bone, and vascular tissue regeneration | [14] |
| Gelatin | Soft-tissue engineering | [15] |
| Chitosan | Bone and skin regeneration | [16] |
| Gelatin methacrylate[16] | Build tissue models for drug screening | [17] |
| Hyaluronic acid | Cartilage and neural tissue regeneration | [18] |
| Fibrin | Vascular and wound healing | [19] |
| Polyethylene glycol | Drug delivery and tissue scaffolds | [20] |
| Polycaprolactone | Bone and cartilage engineering | [21] |
| Polylactic acid | Orthopedic scaffolds | [22] |
| Poly (lactic-co -glycolic acid) | Tissue scaffolds and drug delivery | [23] |
| Hydroxyapatite | Bone tissue engineering | [24] |
| β-Tricalcium phosphate | Bone regeneration | [25] |
| dECM Bioink | Organ-specific tissue fabrication | [26] |
| Stem cell-based Bioinks | Regenerative medicine applications | [27] |

crucial to clinical practice when it came to transplanting human tissue and organs. The tissue microenvironment and cellular viability after bioprinting can promote the incorporation of a vascular network. Tiny pumps in organ-on-chip models can be used to create human-on-a-chip models that examine drug responses across multiple organs simultaneously. To better analyze the experiments using bioprinting, we must use 3D microscopy and culture networks, such as bioreactors and non-invasive monitoring devices.[28] In the future, bioprinting can help diabetic patients by printing pancreatic islet tissues to combat immunological reactions. Various pharmacodynamics can be used to study the environment for customized medications and treatments.[29] To produce 3D models for serious diseases such as cancer, researchers are working to develop sophisticated human tissues. Such a novel application could lead to individualized care for complicated illnesses. Over the past 20 years, smart bio-inks that employ innovative biomaterials to create tailored scaffolds that promote growth in cells have been evolving.[30] Since 2014, the whole 3D bioprinting sector has been dominated by start-ups and numerous R&D companies. In 2016, the market value of 3D bioprinted goods was approximately $680 million. By 2027, the industry predicted that development would reach $1.9 billion.[31] Although *in vitro* and *in vivo* studies have demonstrated that tissue regeneration is viable for application in a variety of therapeutic contexts, there are still obstacles to practical translation. On the higher end of the spectrum, solid organs such as the liver display a complex, 3D variety of unique tissue types that work together to maintain the structural and functional components of the organ.[32] Tissue transplantation, rather than 3D bioprinting, may 1 day be capable of replicating the complex structure and function of hard visceral organs; however, achieving this *in vitro* remains physiologically and technically challenging. One advantage of bioprinting is its high resolution, which permits deposition in arrays ranging from nanoscale to microscale. In the extra processing phase, bioreactors offer an exciting atmosphere for organ maturation; nevertheless, caution must be exercised to minimize the risk of tissue damage during the process of maturation.[33] Bioprinting is currently the best biofabrication method for obtaining the required porosity, geometry, or interconnectivity for complex structures, including solid viscera. It is also anticipated to support major advancements in the field over the next 20 years.

In 2007, Organovo became the first business to deliver functioning bioprinted blood vessels in the 3D bioprinting space.[34] The San Diego-based biotech was at the forefront of the market for a long time because they were an early user of the technology and helped create 3D bioprinted organoids.[35] In addition to 3D tissue models for cosmetic testing, its repertoire quickly grew to include created kidneys as well as liver tissue models for study. However, the requirement for large upfront investments in advancement and research, together with infrastructure construction, frequently raises expectations, as is the case with many novel advances in technology. Even though total market investment matched the initial excitement surrounding the technology, the company's direction change and divestiture were the result of a perceived lack of development. Twelve years after the business's 2007 bioprinting debut, its CEO, Taylor Crouch, announced a change of focus, citing a lack of resources to deal with the challenges presented by the "variation of the biological process and the related lifetime potential advantages" of its main project.[36] Many saw this as an example of a significant issue facing the bioprinting sector: The need for a quick return on investment balanced against long-term commitment. Despite this, 3D bioprinted models are still very important and a key area of research spending for basic scientific studies and drug testing. Numerous challenges in translating to humans.

### The limitations, challenges, and future perspectives of bioprinting

Choosing the best biomaterials is crucial when healthcare tissue is being pre-bioprinted. Although polymers are widely used in 3D bioprinting and tissue engineering, their inadequate cytocompatibility results in unwanted cellular interactions. Premature osteogenic differentiation and bothersome cellular connections might result from excessive biological activity.[37] Alternatively, to replicate the nanostructured scaffold that functions as an extracellular matrix during cell proliferation, new biopolymers and hydrogels are required. However, these printed scaffolds are not ideal for bioprinting due to their weak structural stability.[38] Tricalcium phosphate and bio-ink were mixed in a recent study for bone bioprinting. Existing bioprinting techniques are time-consuming and are unable to produce continuous cells for different tissues. Cell viability may be lost because of cellular structures being altered by the mechanical forces used in the printing process.[39] The development of blood vessel networks in functional tissues is a major bioprinting difficulty since their lack restricts the flow of nutrients in designed tissues, which can lead to necrosis. Therefore, for cell survival, bioprinting vasculature resolution and speed must be optimized.[40]

## CONCLUSION

The creation of organs through imprinting holds great potential for people experiencing organ scarcity. However, it still has certain shortcomings in these particular areas, such as selecting the appropriate material with a variety of real estate and cell types and utilizing different elements and their mutual integration, along with processing with living things or growth promoting the drivers for the building of multifaceted tissues are limiting measures in the manufacturing of numerous distinct alternatives for bionics. First, 3D bioprinting, sometimes referred to as heart printing, has shown great promise in tissue creation and has become a practical production technique for the development of complex systems at the macro and micro scales for use in medical applications. Prospects for the future indicate that this form of technology is evolving.

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