Review Article

3D Bioprinting the Future: Bridging the Gap Between Living Scaffolds and Pharmaceutical Integration

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ABSTRACT

Precisely laying down live cells, biomaterials, and bioactive chemicals to produce intricate Three-dimensional (3D) bioprinting and biological structures a sophisticated type of producing additively has transformed biomedical research and regenerative medicine. Through regulated spatial distribution of cells and materials, Bioprinting in three dimensions seeks to produce live, functional tissues and organs, in contrast to standard 3D printing, which builds non-living components layer by layer. Data collection and model design, signal processing for printer control, and the layer-by-layer creation of the biological construct are the three main steps in the process of bioprintig. The main bioprinting methods are described in this study, along with their mechanisms, benefits, and drawbacks. These methods include Laser-assisted, inkjet-based, and extrusion-based (LIFT), as well as photocuring-based techniques like stereolithography (SLA) and digital light processing (DLP). In terms of materials, uses, and goals, it also distinguishes 3D bioprinting and traditional 3D printing. 3D bioprinting applications are growing quickly in a number of biomedical fields. These include tissue engineering, cancer modelling, Skin regeneration and wound healing, and the use of microbial populations to produce bioproducts. Furthermore, to bioprinting has the potentially transform medication administration and therapy strategies by developing personalized implants and medications. Notwithstanding its quick development and promise, issues like scalability, legal restrictions, and guaranteeing biocompatibility need to be resolved before 3D bioprinting can be completely incorporated into clinical and pharmaceutical practice.

Keywords: 3D Bioprinting, Biomaterials, Biological, Biomedical, Bioproducts.

INTRODUCTION

Three-dimensional (3D) printing, also known as additive manufacturing, is a versatile technology that uses bioprinting of various biomolecules, such as biological macromolecules, biomaterials, and living cells, to construct structured objects [1].

Advancements in tissue bioprinting are critical for advancing research aims and helping the pharmaceutical development process [2]. Generally speaking, there are three stages to bioprinting. Accurate data about tissues and organs must first be gathered in order to define models and select appropriate materials. Secondly, the data is transformed into an electrical signal. that provides the printer with the necessary control to produce the tissues. The last phase is the creation of the stable framework [3]. Selecting the best printing technique or bioink for various application scenarios is crucial; there is no one ideal bioprinting strategy or bioink for all[4]. This article aims to provide a comprehensive explanation of the 3D bioprinting process and the several techniques employed in it, such as stereolithography, extrusion printing, laser-aided bioprinting, and ink-jet printing[5]. In recent years, 3D bioprinting has attracted a lot of attention in the fields of tissue engineering and regenerative medicine, and it will play an increasingly crucial role in shaping the future of precision and tailored medicine[1]. A controlled cell dispersion, precision deposition, affordability, and ease of use are some of the advantages that have resulted in a steady rise in the development and use of 3D bio-printing in recent years [6]. More recently, functional materials that support the growth of microorganisms have also been created via 3D bioprinting. The development and application of bioprinting methods for printing microorganisms in particular holds promise for the creation of an entirely new class of functional materials made by biological processes [7].

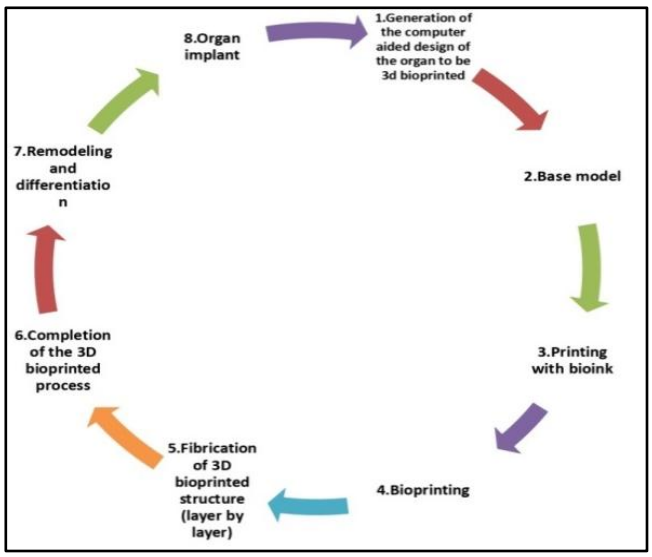

Figure 1: 3D Bioprinting [11]

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In addition to using additive manufacturing techniques, 3D bioprinting technologies create 3D living structures for disease modeling or regenerative medicine purposes by the resins or dyes used for printing integrating living cells into [8]. Scaffolds with high cell density, enhanced bioactivity, and adjustable shape can be produced via 3D bioprinting and used in vitro or even in vivo for regenerative medicine [9]. However, there are a number of obstacles that need to be overcome before. The pharmaceutical industry may make extensive use of 3D printing. Regulatory compliance, quality assurance, and health care professionals' involvement are major challenges that need immediate attention [3]. Creating a biological habitat that is fully integrated and effectively repaired is the only goal of bioprinting [10].

The distinction between 3D bioprinting and 3D printing

Table 1: The distinction between 3D Bioprinting and 3D Printing [10-16]

3D Printing	3D Bioprinting
The three-dimensional process is an additive manufacturing method that creates three-dimensional structures by depositing and hardening successive layers of material.	Three-dimensional (3D) bioprinting, which prints living cells in a predetermined pattern, is one cutting-edge technology that is still in its infancy.
The technique of creating a three-dimensional physical object from a 3D model or digital file is known as additive manufacturing, or 3D printing.	A whole new generation of biologically produced functional materials could be possible with the development and application of bioprinting techniques tailored for printing microorganisms.
The shift from traditional technological approaches to additive manufacturing, represented by formulating 3D printing technologies, represent a revolutionary advancement in the production of pharmaceuticals.	3D Bioprinting can be used to provide novel treatments in the form of organs made especially for sufferers to receive autologous transplants.
Several industries, including the automotive, construction, aerospace, and medical sectors, use three-dimensional printing technologies.	The engineering of a completely integrated and properly repaired biological habitat is the only goal of bioprinting.

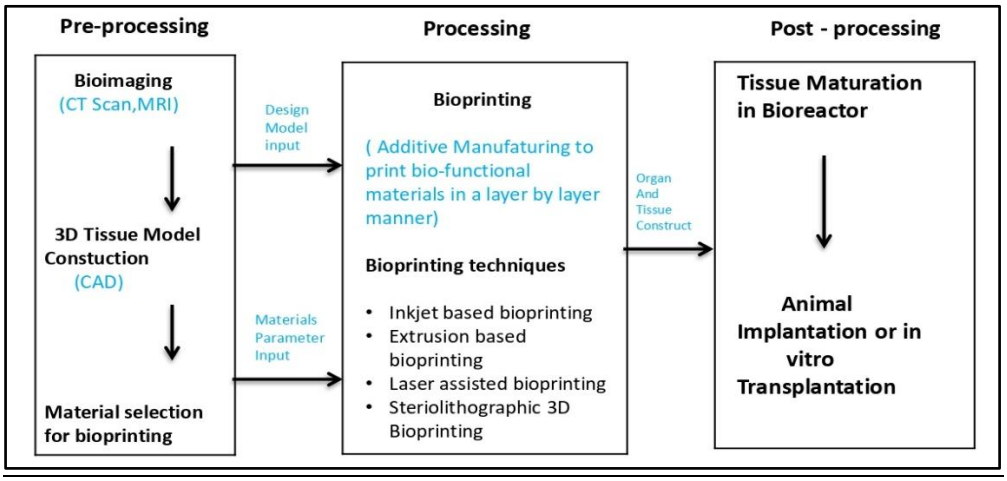

Figure 2: Processes of 3D Bioprinting [17]

TECHNIQUES IN 3D BIOPRINTING

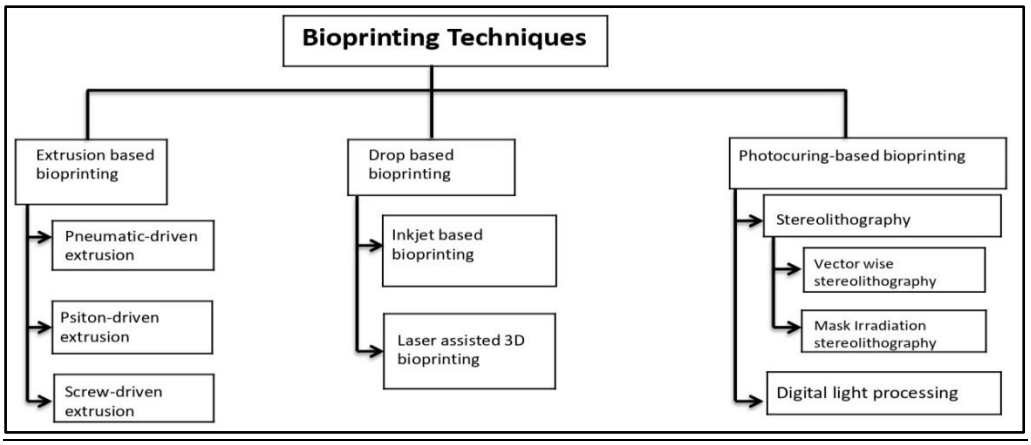

Figure 3: Different techniques used in 3D bioprinting [4]

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I. Extrusion-Based Bioprinter:

In 2002, the first bioprinters based on extrusion were introduced. These printers employ pneumatic or mechanical devices to forcefully deposit hydrogels using screws or pistons. Compared to inkjet-based bioprinters, extrusion-based bioprinters are better able to manage high cell densities, viscosities, and dynamic crosslinking processes [11]. Applying pressure to a cartridge causes the material to constantly dispense via a nozzle, which is the fundamental idea of extrusion printing. Both mechanical and pneumatic force can be used to apply pressure [18].

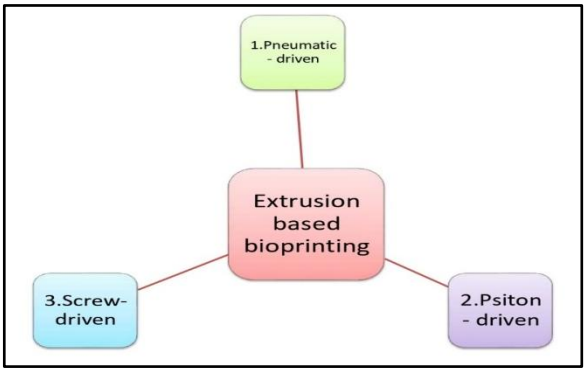

Figure 4: Classification of Extrusion – based Bioprinting [4]

1. *Pneumatically powered extrusion:*

This method uses compressed air to pour liquid. Typically, it consists of a syringe loaded with bioink that is attached to an air pump via pipes and an adapter. Sterilization of the air from the air pump is necessary for pneumatic-driven systems [4].

2. *Piston-driven extrusion:*

Mechanically propelled liquid dispensing devices are known to work better when extruding biomaterials with high viscosities, such as natural or synthetic high-molecular polymers [4].

3. *Screw-driven extrusion:*

Another kind of mechanically propelled liquid dispensing system that offers more volumetric control and facilitates the extrusion of biomaterials with higher viscosities is a screw-driven device [4].

II. Drop Based bioprinting

1. *Inkjet based bioprinting:*

Klebe described the first inkjet-based bioprinter in 1988. Klebe used a commercial Hewlett-Packard (HP) thermal drop on-demand inkjet printer to print a hydrogel solution [11]. This technique uses "bioink," which is just a low viscosity suspension biomaterial that can be employed with living cells on a "bio paper" such as a polymer construct, hydrogel substrate, culture dish, etc [5]. The most popular inkjet-based bioprinting technologies include thermal, piezoelectric, acoustic, microvalve, electrohydrodynamic, and electrostatic inkjets [18].

The two primary ink-jet printing methods are continuous and drop-on-demand (DOD). By applying pressure to the bioink and forcing it out of a nozzle, continuous ink-jet printing produces a continuous jet of droplets. This bio-ink jet is then deflected onto the substrate by applying an electric field. The extra droplets that don't create the desired pattern are diverted to a gutter, where they are gathered for later use. Similar to CIJ, drop-on-demand inkjet printing produces droplets only when needed. As a result, the droplets are expelled using a pressure pulse rather than a constant pressure [5].

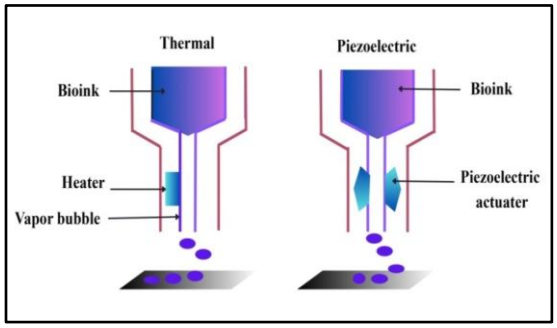

Figure 5: Inkjet based bioprinting [4]

2. Laser assisted bioprinting

Laser-assisted bioprinting, sometimes referred to as laser-induced forward transfer (LIFT), is one of the technologies that is believed to be developing at the fastest rate in the industry. A pulsed laser source, a ribbon that generates biological material, and a substrate that holds the printed material are the three main parts of LIFT printers [1].

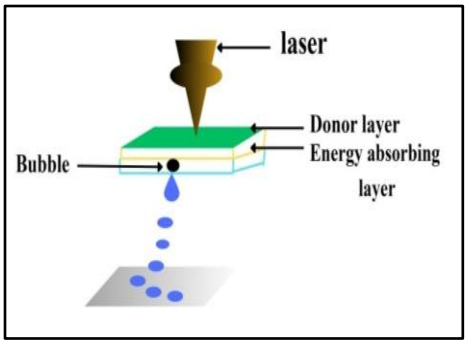

Figure 6: Laser assisted bioprinting [19]

3. Laser Induced Forward Transfer [LIFT]

LIFT is currently used to deposit biomaterials like as cells, DNA, and polypeptides. Originally, it was employed to transport metals. As shown in Fig., a receptive substrate, a bioink-coated ribbon structure, and a pulse laser source are the three main components of a LIFT-based bioprinter. Depending on the optical characteristics and laser wavelength of the bioink, the ribbon structure frequently has a laser-absorbing intermediate layer (typically composed of titanium or gold) between the glass/quartz and bioink layers. The receiving substrate, which is coated with biopolymer or cell medium to ensure the adhesion and subsequent proliferation of the transferred cells, receives rapidly ejected droplets. This substrate is located behind the layer of bioink. The pulsed laser source is typically a

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nanosecond laser with an ultraviolet or near-ultraviolet wavelength; the ribbon structure is essentially a glass/quartz layer that is transparent to the laser radiation wavelength and has a layer of thermosensitive bioink on it (the cells in the bioinadhere to the biopolymer or are uniformly encapsulated in hydrogel) [4].

III. Photocuring-based bioprinting:

The creation of cell-free scaffolds that are seeded after printing is the most popular use of photocuring-based bioprinting. On the other hand, cell-laden photocuring-based bioprinting has also been reported recently. Photocuring-based bioprinting can be further divided into digital light processing (DLP) and stereolithography (SLA) based on various light scanning models [4].

1. Stereolithography:

Charles W. Hull popularized stereolithography for the first time in 1986. This technique uses light to crosslink the bio-techniques [17]. Vectorwise and mask irradiation are the two distinct patterning techniques that have been established. The most common SLA equipment, also referred to as vectorwise scanning galvanometers, these devices scan the surface of resin using a high-resolution UV, IR, or visible light laser beam. The laser will start a spatially controlled radical photopolymerization process at the scanned areas, solidifying the liquid resin. The building platform lowers into the vat after the first layer is constructed, and once it has been uniformly recoated with resin, a second layer is constructed on top of it. On the other hand, projection techniques use a dynamic mask to irradiate and harden the whole surface the resin in a single phase [20].

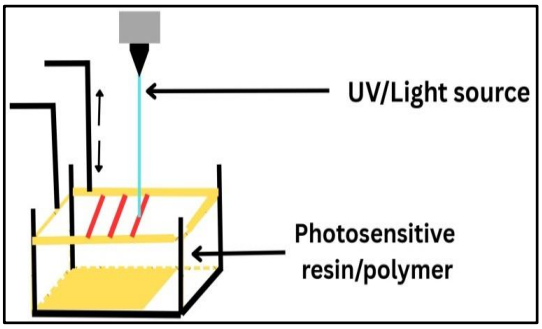

Figure 7: Stereolithopgraphy [20]

2. Digital light processing

DLP forms one complete layer at once, in contrast to SLA, which solidifies a layer at a time. A typical bottom-to-top DLP bioprinter, which starts with the bottom layer and prints each subsequent layer above it, is depicted in Fig. An imaging system above the container; a lifting platform that guarantees lowering a specific height (equal to the thickness of one layer) after one layer is finished being exposed, creating a new layer for photocuring; and a container filled with bioink, such as photocurable hydrogel or photosensitive resin that can solidify when exposed to a laser of a specific wavelength (usually UV light), photoinitiator, cells, etc. In recent years, DLP technology based on DMD dynamic mask has demonstrated improved performance and potential applications [4].

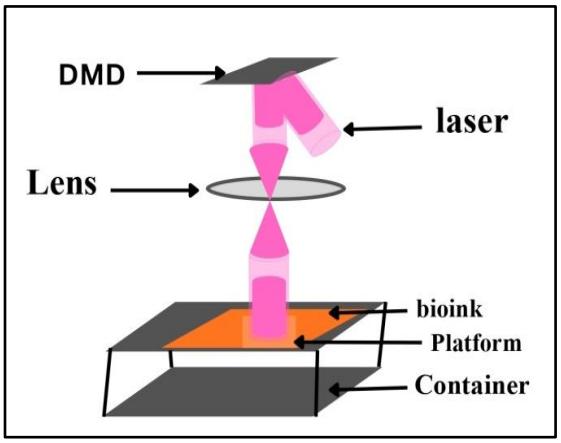

Figure 8: Digital light processing [4].

APPLICATIONS OF 3D BIOPRINTING

1. Management of Burn Injuries and the Healing of Wounds:

3D bioprinting offers the capacity to totally change how injuries and surgeries are treated. It can be especially helpful in healing burned skin. Thanks to the advancement of 3D bioprinters, injured patients can now have their skin produced. Two methods for creating skin to aid in wound healing are ex vivo and in situ bioprinting. A skin construct composed of dermis and epidermis is produced using ex vivo techniques (inkjet, extrusion, and laser-based bioprinting). It is then developed in vitro if needed. It is then placed within the patient's wound. Extrusion-based bioprinting is the fastest and most straightforward ex vivo technique [3].

2. Research on cancer:

Two-dimensional tumor models are frequently employed in cancer research, however since they lack three-dimensional cell-cell and cell-matrix interactions, they are unable to accurately depict the physiologically relevant environment. In order to accurately identify different cell types and microcapillaries as well as to study the formation and spread of cancer, bioprinting has thus provided substantial advantages in simulating the cancer microenvironment. However, there have only been a few studies done in this emerging field, and the application of bioprinting in cancer research is still relatively new [21].

3. Regeneration of tissue

When using bioprinting to create tissues, three primary approaches are considered: microtissue building blocks, autonomous self-assembly, and biomimicry [13].

4. Manufacturing of bioproducts

The advantage of 3D bioprinting is that it makes it simple to rapidly print two or more biological sinks at specific locations in space. This enables the emergence of microbial communities that consider both the geographical closeness and the functional complementarity of implanted

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microorganisms. In the context of 3D bioprinting, biological sinks are specific geographic places where biological components or microorganisms can be purposefully incorporated into a printed product. The development of spatial combinations of whole-cell biocatalysts may offer a fresh approach to investigating microorganism combinations for studies on biomolecule production [7].

5. Biomedical application

Since 3D bioprinting technology can create more individualized based on product enhanced, microbiological habitats based on application circumstances and personal preferences it is undeniably a more promising immobilization technology for the production of medical materials. As a result, immobilization technologies in this sector have more application fields [7].

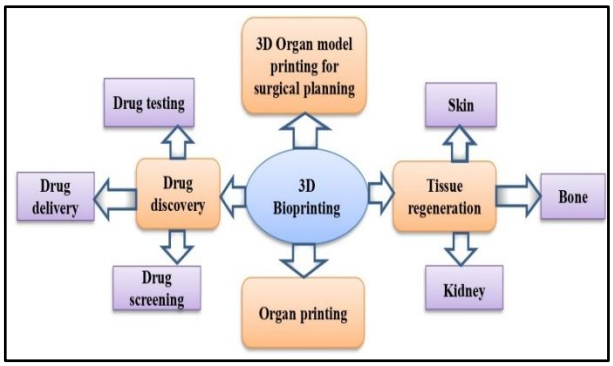

Figure 9: Applications of 3D bioprinting [22]

APPLICATIONS OF 3D PRINTING

1. **Using 3D printing for pharmaceutical purposes in hospitals and pharmacies**

Drug delivery, medical gadgets, tailored treatment, and drug development in pharmacies and hospitals could all be significantly enhanced by 3D printing.3D printing enables the development of streamlined treatment regimens and customized dose forms, enabling the production of individualized pharmaceuticals based on patient-specific needs [23].

2. **3D Printing's Uses in Manufacturing Technology**

3D printing technology allows for unparalleled freedom in component and production design. For the aerospace industry, 3D printing technology makes it possible to produce lightweight parts with intricate and enhanced geometries, which can reduce resource and energy needs [24].

3. **Personalized Medicine:**

Standard pill sizes are produced by conventional facilities. Doctors may alter the precise dosage of medication (D) in a tablet to suit a patient's weight, age, or genetic makeup thanks to 3D printers [24].

4. **Improved Pharmaceutical Delivery:**

A tablet with its core can be mapped into multiple layers using a 3D printer. Imagine it as a tiered cake, with the inside core releasing medication gradually over a 12-hour period while the outside layer melts to provide immediate relief [24].

CONCLUSION

A revolutionary development in additive manufacturing, three-dimensional (3D) bioprinting combines material science, engineering, and biology to create complex biological structures and live tissues. Unlike standard 3D printing, which uses inert materials, 3D bioprinting uses living cells, bioactive chemicals, and biomaterials that are carefully positioned to imitate the microarchitecture of genuine tissues. Drug development, tissue engineering, regenerative medicine, and disease modeling all stand to benefit greatly from this strategy. Various bioprinting techniques, such as extrusion-based, inkjet-based, laser-assisted, and others, depend on the properties of the material, the necessary resolution, and biological compatibility. and photocuring methods—each provide special benefits. Challenges include attaining vascularization; preserving cell viability, guaranteeing regulatory compliance, and increasing output for clinical usage still exist despite tremendous advancements. However, 3D bioprinting's uses are still growing, ranging from tissue regeneration, cancer research, wound healing, and burn therapy to the production of microbial bioproducts. By making it possible to produce medical devices and tailored medicine on demand in healthcare settings, generic 3D printing technologies are also transforming pharmaceutical applications. In conclusion, Despite the fact that 3D bioprinting is still relatively new it is developing quickly and is expected to be a key component of precision medicine and biomedical innovation in the future. Unlocking its full potential and converting laboratory discoveries into clinical and industrial solutions will require ongoing interdisciplinary research, technical advancement, and regulatory development.

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