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Bioprinting: The Future of Healthcare

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ABSTRACT
In 3D Bioprinting techniques three important terms bio fabrication, Bioprinting, and bio assembly are appreciated a lot in the last few years. Uses of Bioprintingin Cells 3D Bioprinting have enormous potential for artificial organ printing and regenerative medicine. Other uses of Bioprinting such as in tissues 3D Bioprinting enables exact layer-by-layer positioning of cells, biochemical agents, and nanomaterials. So far, little attention has been dedicated to the use of 3D Bioprinting in biotechnological applications to investigate hydrogel-liquid phase interactions. According to experts, tissue Bioprinting has the potential to duplicate natural skin by process of employment of 3D printing technology with materials that integrate viable living cells to manufacture tissue for reconstructive surgery.Software and tools are used in Bioprinting and the ultimate goal of Bioprinting is to create completely functional tissues and organs from printed biomaterial constructions. Scientific aspects of Bioprinting commonly 3D Bioprinting raise several ethical and regulatory concerns, including theoretical, source, transplantation and augmentation, animal welfare, economic, safety, and information concerns. This review aids in comprehending the key ideas behind the Bioprinting of tissue structures, their uses, and potential future difficulties with the 3D printing technology involved.
Keywords: *Bioprinting, Biofabrication, Cell expansion, Bioassembly, Extrusion-based Bioprinting, Biomimetic, Biomaterials, Bio inks.*

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INTRODUCTION

Within biology, there are numerous options for learning about Bioprinting to study cells, tissues, organs, and so on. New things are being explored in the studies of Bioprinting such as investigating cellular crosstalk or cellular morphogenesis [1].

Bioprinting was invented around 50 years ago and evolved since 1980 and further. It started from a rapid prototyping technique in which stereolithography (SLA), selective laser sintering (SLS), and fused deposition modeling (FDM) were developed. The fabrication of patient-specific, anatomically precise structures for surgery and orthopedics was the first application of 3D printing in healthcare. Since then, other body parts such as the skull, jaw, hip, and sacrum have been successfully 3D printed by other researchers [2].

This Bioprinting roadmap highlights all of the significant advancements in certain Bioprinting applications such as cell expansion, innovative bio-ink development, stem cell printing, and organoid-based tissue organization. Some of the outlines are anticipated in the improvements of science and technology, as well as the status and problems of present discoveries related to Bioprinting. The development of this field aims at different things such as biomaterials, proteins, bio-inks as well as the large model and cell aggregates. It helps to aim for a comprehensive summary and recommendations for those new to the field for studying the strategies to develop biological models by use of Bioprinting technologies [3].

Bioprinting is a relatively recent method of fabricating constructs that allows great reproducibility and fine control in an automated manner. There is a special type of ink called bio-ink used to create biological models. An ideal bio-ink has good mechanical, rheological, and biological qualities of the target tissues, which are necessary for creating a bio-printed structure of tissues and organs to function properly. Some bio-inks are hydrogel-based, pellet-based, composite, or inks with bioactive molecules [4].

The methods of Bioprinting research have been developed a lot which allows for the creation of very complex 3D structures using living cells. E.g., as in previous 2D cancer models have been significantly improved by bio-printed cancer models. These research models serve as a better platform for understanding cancer pathology, anticancer drug screening, and investigating cancer treatment development by simulating the tumor microenvironment [5].
In recent times the use of Bioprinting techniques in stem cell research is gaining popularity. Biomolecules can be created to direct stem cell differentiation using these approaches. For tissue regeneration, stem cells can also be designed in a high-throughput manner onto flexible implementation patches [6].

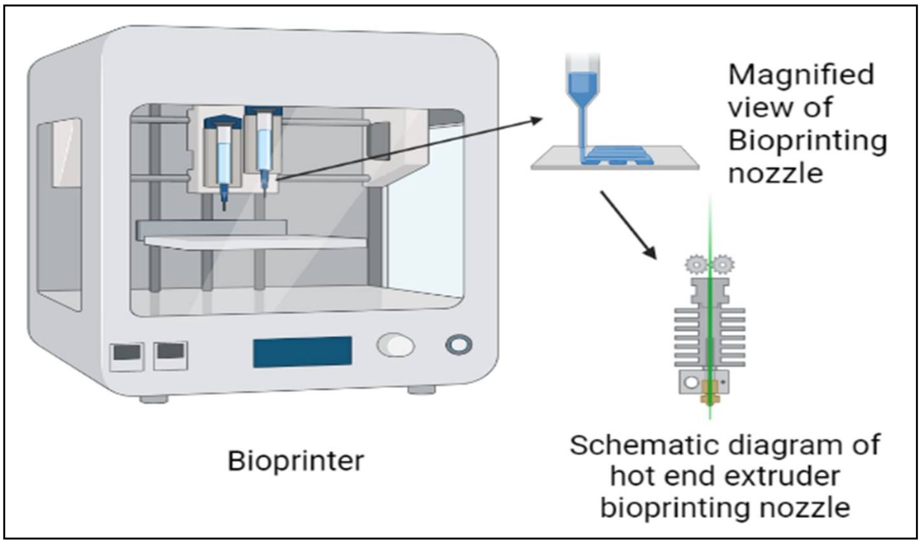

Figure 1:Bioprinter and hot-end extruder Bioprinting nozzle

Neural tissues are engineered with the bio print processes by creating spatial patterns, and scaffolds. The environment required to formulate the neuronal tissues and structures can be achieved by the bioprinter to create complex tissues. Considerations of biomaterials, requirements of spatial arrangement, everything can be studied within Bioprinting [7].
The design criteria for Bioprinting of living tissue and organ structures are presented in this paper. How the different techniques help in creating the anatomical structures with the help of magnetic resonance imaging and computed tomography references. Whether to build tissue construct internal architecture is critical, this is because it provides a porous environment for media exchange, vascularization, tissue development, and engraftment. What future challenges with Bioprinting can be studied under this review [8].

BIOPRINTING

Bioprinting can be defined as the process of employment of 3D printing technology with materials that integrate viable living cells to manufacture tissue for reconstructive surgery. It involves different processes such as biomimicry, mini-tissue building, autonomous self-assembly, and others. There are some ethical aspects, legal aspects, and social aspects called the ELSA framework that is considered in tissue engineering and Bioprinting [9].
The application of 3D printing techniques for tissue engineering is known as three-dimensional Bioprinting. Layer-by-layer exact positioning of biological materials, biochemical, and living cells, with spatial control of the placement of functional components (extracellular matrix, cells, and pre-organized microvessels) to build 3D structures, in 3D Bioprinting.
Traditional 3D printers have been modified to accept cellular inks. Inkjet deposition, laser-assisted desorption, and microextrusion are all options for printers used in Bioprinting [10].

3D Bioprinting Techniques:

There are three important terms related to 3D Bioprinting which include bio fabrication, Bioprinting, and bio assembly. Biofabrication is a more important technique as in this process biologically working objects are created by using living cells, biomaterials, bioactive molecules, cell organelles, and microtissues, with the integration of Bioprinting and bio assembly methods. In Bioprinting patterning and assembling of the living and non-living materials is done with a predetermined 2D or 3D organization to create bio-engineered structures with the help of computer-aided transfer processes [11].

A good bio-printed model can be printed by use of printing process techniques such as digital near-infrared photopolymerization (DNP), material jetting, material extrusion, vat photopolymerization, and free-form spatial printing. Together these techniques allow for noninvasive in vivo 3D Bioprinting of printed tissue constructs. For example, a customized ear-like tissue construct and a muscular tissue repairable cell-laden conformal scaffold were created without the need for surgery. Similarly, the ex vivo irradiation by use of the patterned near-infrared a noninvasive way of Bioprinting through injecting bio-ink subcutaneous route is possible. There are numerous advantages of three-dimensional (3D) printing technology in producing individualized, complex structures with a wide range of medicinal uses. Bioprinting, or the use of bio-ink-containing cells to 3D print living obstacles like tissue or organs, offers a lot of support for medical advancement [12].

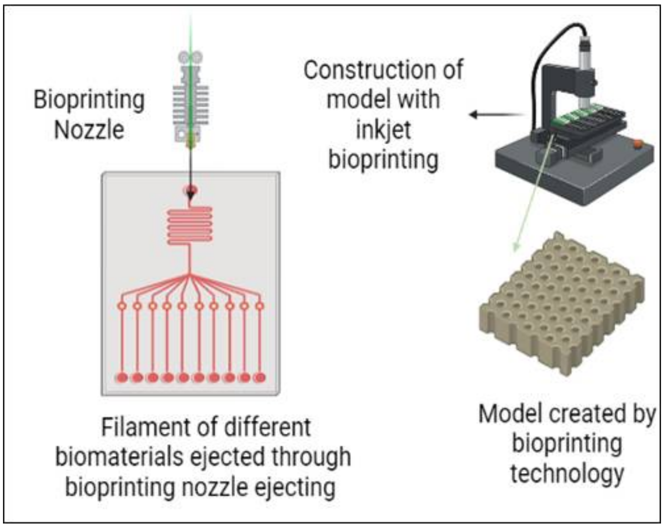

Figure 2: Bioprinting nozzle

Inkjet printing, light-assisted printing, and laser direct writing are all examples of 3D Bioprinting technologies. Surgical implantation or in situ 3D printing at the exposed trauma site is currently the only in vivo application option for 3D-printed macroscale items [13]. Researchers propose a more precise definition of Biofabrication, focusing on its relationship to and application in Tissue Engineering and Regenerative Medicine. Within the topic of BioFabrication, Bioprinting, and Bioassembly should be viewed as complementing techniques [14].

Extrusion-based Bioprinting (EBB) offers a lot of flexibility when it comes to printing different biologics, such as tissues, tissue constructions, organ modules, and microfluidic devices. Despite the many advantages and versatility of printing a wide range of bio-inks, EBB is now facing many difficulties [15].

The invention of the three-dimensional (3D) printer led to substantial advancements in a variety of industries, including fast prototyping. The addition of dynamic responses to stimuli to 3D constructions helped to develop the concept of four-dimensional printing. 4D Bioprinting is being researched for use in drug delivery systems, tissue engineering, and surgery in the clinic [16].

Bio-inks are extruded through nozzles to generate three-dimensional objects in extrusion-based Bioprinting. Bio-inks are biomaterials and living cells that have physical, mechanical, biological, and rheological qualities that influence the quality of printed constructions [17].

Bioprinting is an additive manufacturing technology that uses materials that contain living cells. The printability of bio-ink depends on its qualities before, during, and after gelation. The number of cells in the construct, their proliferation, migration, and contact with the material all influence these features throughout tissue creation [18].

Bioprinting technology has progressed as automation, digitalization, and innovative tissue engineering (TE) methods have come together. When de novo tissues are to be printed directly on the target anatomical region in the living body, in situ,Bioprinting may be preferred [19].

Table 1: Bioprinting Techniques

Sr. No.	Bioprinting Technique	Specific Technique
1	Inkjet	▪ Thermal inkjet photopolymerization (UV) ▪ Inkjet with DC solenoid valve ▪ Thermal inkjet ▪ Inkjet with solenoid valve
2	Extrusion	▪ MHDS Extruded in a syringe by servo motor ▪ Pneumatic extrusion in syringes cross-linking via thrombin solution. ▪ Pneumatic extrusion in syringes 2-stage cross-linking via chemical reaction and UV light ▪ Pressure-driven multi-dispensing nozzles ▪ Pressure-driven nozzles some with thermal apparatus ▪ Mechanically extruded nozzles ▪ Pneumatic extrusion in syringes with electromechanical microvalve Pneumatic dispensing system) ▪ A combination of thermal and pneumatic extrusion systems.
3	Laser-based	▪ Laser-induced forward transfer (LIFT) utilizing near Infrared light (1064nm)
4	Bio-electrospray and cell electrospinning	▪ Bio-electrospray set up ▪ Cell electrospinning

Instruments Used For Bioprinting

In 3D printing, there are a variety of additive manufacturing techniques to choose from. This chapter has focused on well-established techniques that, rather than body parts are more likely to be employed in the creation of medical and other high-value-to-life objects. The highest printing resolutions may be achieved with liquid resin-based methods. The resins that have been approved for use in biomedical implants are, however, limited. Nonetheless, these techniques are being employed to make a wide range of items, and this is expected to grow as material technology advances [20].

Two-dimensional support, such as a well plate or a Petri dish, is used in traditional cell culture. Since 2000, the 3D-Bioplotter has been employed in the pre-clinical field, and it can print many materials at the same time [21].

In the area of biotechnology, 3D printing and Bioprinting in particular are emerging technologies. So far, little attention has been dedicated to the use of 3D Bioprinting in biotechnological applications to investigate hydrogel-liquid phase interactions [22].

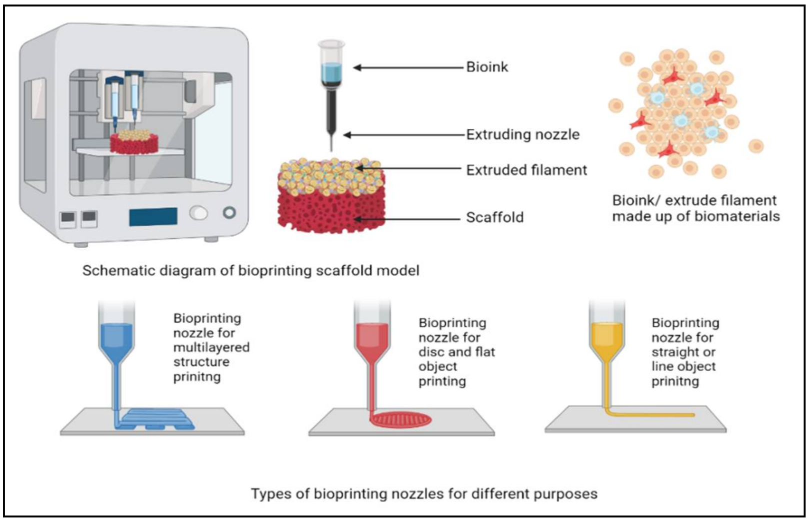

Figure 3: Schematic representation of Bioprinting a scaffold model and different printing nozzles

Software and tools used in Bioprinting

The ultimate goal of Bioprinting is to create completely functional tissues and organs from printed constructions. The secret to this accomplishment has been recognized as technology, which goes hand in hand with the creation of bio-inks. In this sector, computer-aided design and manufacturing (CAD/CAM) play a crucial role [23]. Image-based analysis approaches are non-invasive, time-saving technologies that may be used to characterize printers, assess bio-ink printability, and optimize processes. The goal of this research is to develop an automated, image-based line analysis tool for Bioprinting applications [24].

Three-dimensional (3D) printing technology is regarded as a primary driver of tissue engineering development. A system that can print a variety of biomaterials using different processes is required. The design and integration of a multi-channel 3D bio-printing system are described in this work. For the 3D production of biological material structures, a 3D bio-printing method was designed. It can print a variety of biomaterials using a variety of dispensing methods. To obtain a low-cost, small-sized, and expendable system, the system was built utilizing affordable stages and a rotary table [25]. The fabrication of bioactive structures in a layer-by-layer deposition of cells is done by using bioprinters. This is known as Bioprinting and can only work if it receives commands from software. The increasing usage of open-source software adds to the complexity of the situation, making it more difficult to assess risks and liabilities [26].

Applications of Bioprinting.

- The 3D cell printing additive biomanufacturing allows for the high-resolution manufacture of cell-laden structures using a variety of biomaterials and cells (bio-ink). Several attempts to create tissues and organs using various 3D printing techniques have recently been made [27].
- The composition, geographical distribution, and architecture of the final constructions may all be precisely controlled with 3D Bioprinting. It enables the delicate shapes and structures of targeted organs and tissues to be captured. The Review covers the history of Bioprinting as well as the most recent breakthroughs in apparatus and procedures in a systematic manner [28].
- This technique is a pioneer in the construction of artificial multi-cellular tissues and organs because of its potential to produce regenerative tissues and organs. Researchers are now using a wide range of biomaterials in 3D Bioprinting, as well as a variety of methodologies [29].
- To combat the rise of new infections and infectious diseases, vaccines and treatments must be developed quickly. Layer-by-layer assembly with a 3D Bioprinting system or other technologies is a useful way for producing highly biomimetic and dependable in vitro models in this area [30].
- In the field of tissue engineering, there is a lot of potential for fabricating biostructures. Improved printing resolution (particularly at the nanoscale level) and biomaterial compatibility are two challenges. Hybrid 3D Bioprinting methods combine the advantages of both AM and CM [31].
- Many researchers remain interested in the tissue engineering applications of 3D Bioprinting. 3D scaffolds make it possible to regenerate and restore diverse tissues and organs. They can be used to make scaffolds for biomedical and regenerative medicine, as well as tissue engineering [32].
- Over the last decade, three-dimensional Bioprinting has emerged as a viable method for tissue regeneration. The selection of scaffolds, as well as ensuring safety throughout the process, are both challenges. Other difficulties include vascularization and the survivability of 3D-printed constructions in the body [33].
- It's improbable that a single bio-ink can create a synthetic microenvironment that closely resembles the real thing in the body. As a result, multi-material Bioprinting has become increasingly essential in recent years
- Bio-inks are the materials that are created during 3D Bioprinting and can comprise living cells, extracellular matrix components, cell medium, and/or other additives. Bio-ink printability is described as the ability to control the creation of well-defined droplets, jets, and filaments [34].
- A review of 3D Bioprinting materials such as bioceramics, biopolymers, composites, and metals is undertaken. The importance of employing these materials for craniofacial procedures, as well as their potential to construct facial tissue analogs can be discussed [35].
- The goal of the next generation of bio-inks is to create anatomically-sized 3D scaffolds that are both printable and biocompatible. Utilizing the features of 2D nanomaterials in 3D Bioprinting technology has the potential to transform bio-ink material creation [36].
- Biomedical engineering, implants, medication delivery systems, cardiovascular devices, and wound healing all utilize nanoscaled variants of cellulose. Nanocellulose hydrogel's printability is enabled by its shear thinning behavior and the ability to maintain living cells, allowing for 3D Bioprinting [37].
- The majority of Bioprinting research has focused on the creation of homocellular tissue from a single-cell type. Multiple cell types are patterned in a highly complicated architecture in native

tissues, which are hetero cells in nature. One of the future paths in Bioprinting will be the development of new types of organs, such as bionic organs or organs that do not exist in nature [38].

Scientific Aspects of Bioprinting

3D Bioprinting raises several ethical and regulatory concerns, including theoretical, source, transplantation and augmentation, animal welfare, economic, safety, and information concerns. Bioethical dialogue should be expanded through a multidisciplinary approach involving specialists and the general public [39].

Bioprinting standardization is critical if the scientific community wants to see major biotech and pharmaceutical sector buy-in. This is not a simple task because the bulk of methods published over the previous 50 years was for monolayer cultures, which cannot be simply modified for 3D cultures [40].

Recent advancements in Bioprinting materials have enabled dramatic increases in the resolution and architecture of 3D-printed synthetic tissues [41].

Because of their potential to respond to external stimuli, stimuli-responsive synthetic materials have received interest as biomaterials. It is recommended that stimuli-responsiveness be paired with the hierarchical supramolecular assembly of the materials used to synthetically imitate the cellular microenvironment. We explore the 3D printing of stimuli-responsive materials, as well as the design and development of metamaterials. It is hypothesized that combining these notions with supramolecular chemistry would result in the production of life-like biomaterials with previously unseen features [42].

Bioprinting was originally prompted by the growing demand for guided construction of biomaterials. The analysis investigates the process of obtaining tissue constructions from many phases, spanning numerous technical domains. Each stage has an impact on the performance of created constructions and can influence others [43].

Resolutions

1. Three-dimensional (3D) Bioprinting is an advanced manufacturing technique that employs a variety of biomaterials. Characterizing and fine-tuning bio-ink characteristics before, during, and after printing is critical for producing repeatable and stable constructions. The development of fully defined, functioning bio-ink solutions would be a significant step toward practical therapeutic applications [44].
2. The inkjet process is capable of producing droplets with a volume of a few picoliters, firing thousands of times in a few seconds, and printing in a noncontact way. Inkjet technology is becoming a useful tool in modern medicine for drug research, scaffold construction, and cell deposition [45].
3. Photoactivated materials are increasingly being used in biological and medicinal applications. Light may be used as a catalyst to cause the creation or breakdown of chemical bonds. Light-mediated bio fabrication enables multicellular and multi-material techniques with precision and builds sizes ranging from nanometers to centimeters [46].
4. Shape control, as well as functional control, must be provided through technology. This can be performed by microscopically duplicating the cellular makeup of the native tissue. 3D Bioprinting is a fast-evolving technique for creating modified tissues and organs. Despite recent breakthroughs, there are still numerous obstacles to overcome to construct functioning, biomimetic tissue, and organs for human implantation and drug modeling. The focuses are on advanced multi-material 3D Bioprinting using multi-cartridge printheads and co-axial nozzles [47].
5. Solid fatty acid/ceramic matrices have the potential to be employed as biomaterials for structural implants and controlled-release medication depots. The materials were also proven to be biocompatible in a subcutaneous mouse model and enabled the attachment and development of mesenchymal stem cells in vitro [48].
6. Bacterial polysaccharides have the potential to be a critical battleground in the fight against antibiotic resistance. Antimicrobials are being added to Bioprinting inks to decrease this danger. The study examines the many bacteria-based bio-inks utilized in 3D printing and their prospective uses [49].
7. Epithelial cells are responsible for 90% of all human malignancies. 90% of preclinically approved medicines fail in clinical trials, owing in part to the use of too simplistic in vitro models and a failure to recreate the tumor microenvironment in therapeutic effectiveness testing. The progress of Bioprinting technology opens up the prospect of tailoring materials in a personalized manner and creating biomimetic 3D environments. Because they imitate the TME and recreate cellular and ECM interaction, 3D cell models offer distinct benefits from 2D models. Furthermore,

nanotechnology-based medication delivery systems have been demonstrated to be superior to conventional anti-cancer therapy [50].

8. The deposited bio-ink filaments are exposed to various forms of deformation during extrusion-based Bioprinting. Previously, shape fidelity was checked qualitatively after printing by visual examination. We offer a quantitative assessment of bio-ink form fidelity based on evaluating filament collapse on overhanging structures and filament fusing of parallel printed strands [51].

INNOVATIONS AND CURRENT TRENDS

A printable organ is a man-made device meant for organ replacement that is created using 3D printing technology. 3D printing for the fabrication of artificial organs has been a key research area in biological engineering. Some of the key advantages of 3D printing are the capacity to mass-produce scaffold structures and the high degree of anatomical accuracy in scaffold products [52].

Hydrogels based on methylcellulose are ideal substrates for generating cell sheets for regenerative medicine. To generate substrates with desired and regulated geometries, researchers propose 3D printing of an MC-based hydrogel. The enhanced printing conditions might be utilized to create MC substrates for cell engineering or cell delivery [53].

Bioprinting has developed as a versatile technique in the field of regenerative medicine. One of the most serious issues is a scarcity of materials particularly suited for Bioprinting. Novel biomaterials that are straightforward to deploy in a range of bioprinter platforms are needed [54].

Despite extensive research, the production of bio-inks for Bioprinting of cell-laden constructions remains a barrier to tissue engineering. Dynamic hydrogels allow for more tolerability, improved printing performance, and the production of more life-like settings for ultimate tissue maturation [55].

To load cells for tissue engineering, hydrogels have been widely employed in three-dimensional (3D) printing. Due to the hydrogel diffuses at the junction, a dumbbell form was observed in the printing of lattice structures. Collapses and fusions of neighboring layers would result in error accumulation along the Z axis [56].

Three-dimensional (3D) Bioprinting has demonstrated enormous promise in the fabrication of patient-specific tissue scaffolds and medicinal devices. The nanotechnological method and nanomaterials exhibit unique physical, chemical, and biological features due to their high surface area-to-volume ratios and quantum confinement effects [57].

Many bio-ink formulations have been described for tissue engineering and regenerative medicine applications, ranging from cell-biomaterials-based bio-inks to cell-based aggregates and tissue spheroids. More tunable bio-inks are being developed that are biocompatible for living cells, printable, and mechanically stable after printing [58].

Optimization

3D Bioprinting enhances tumor model orientation in vitro. Hydrogels containing 3.25 percent, 3.5 percent, and 4 percent SA and GL demonstrated improved printability and cell survival. After 15 days, the spheroid size dispersion was in the 50–1100 m diameter range [59]

3D Bioprinting has evolved as a nexus of chemistry, biology, and technology. The approach allows for the creation of biomimetic and functional structures. One of the most significant constraints is the scarcity of printable materials (bio-inks) for tissue engineering [60].

The parameter optimization index (POI) is designed to reduce shear stress acting on the bio-ink and hence on the encapsulated cells. The POI might be used in a variety of 3D Bioprinting applications. Hydrogels, which are water-swollen cross-linked networks, have shown great potential in regenerative medical applications. The Herschel-Bulkley model is presented as a good framework for meaningful material comparisons. [61, 62].

Uses of Bioprinting in Cells

- 3D Bioprinting has enormous potential for artificial organ printing and regenerative medicine. Stem cells provide an infinite cell supply for tissue regeneration and disease research. The capacity to reprogram patient-specific cells promises a better knowledge of disease processes [63].
- Because cancer growth and metastasis entail spatiotemporally shifting cell-matrix interactions, in vitro engineering of tumor milieus is complicated. 3D printed in vitro tumor models may be used to explore disease progression processes, enabling high throughput drug screening, and helping in the development of next-generation molecular therapeutics [64].
- Because of the complexity of the original heart, engineering cardiac tissues and organ models remains a significant problem. We expect that our strategy for creating endothelialized organoids

using 3D Bioprinting technology will find extensive use in regenerative medicine and drug screening [65].

- One of the most important conditions for simulating the tumor microenvironment is the selection of an appropriate bio-ink. Recently, or spheroids have been employed as bio-inks for generating in vitro models. For HTS applications, DBB with low-viscosity bio-inks should be the recommended approach [66].
- The ability to print and analyze 3D bacterial biofilm structures has significant therapeutic implications. MRSA, E. coli, Pseudomonas aeruginosa, and E. coli were all 3D bio-printed [67].
- 3D Bioprinting is a popular approach for producing scaffolds of various materials with predetermined morphologies and geometries. Researchers concentrate on experimental methodologies and current advances in Bioprinting key structural proteins such as collagen, silk, fibrin [68].
- Because of their capacity to deposit single cells with excellent precision and repeatability (1 cell, +/- 2 m, 500 cells/sec), laser-based cell printing techniques are at the forefront. Researchers are focusing on fundamental issues in tissue engineering, such as vascularisation [69].
- Magnetic resonance imaging (MRI) in conjunction with micron-sized superparamagnetic iron oxide (MPIO) particles is a non-invasive approach for monitoring cells in vitro. After in situ Bioprinting onto a mouse calvarial lesion, MRI was able to detect cell patterns [70].
- Drop-on-Demand (DoD) Bioprinting has numerous downsides, including shear stress-induced cell viability loss. To investigate shear stress in the nozzle during printing, a CFD simulation model of a piezoelectric DoD print-head was created [71].
- The biological properties of standard monolayer cell cultures may make it difficult to study virus-host interactions in vitro. According to the researchers, three-dimensional (3D) cultures exhibit more in vivo-like properties and may provide a potential option for characterizing infections [72].
- Direct Bioprinting was used to create a unique 3D coaxial co-culture model in vitro. Novel coaxial multicellular structures were created using a four-layer coaxial nozzle. Collagen solutions containing HUVECs and HUVSMCs were perfused into hollow channel layers [73].

Uses of Bioprinting in tissues

- Three-dimensional (3D) Bioprinting enables for exact layer-by-layer positioning of cells, biochemical agents, and nanomaterials. The bioreactor may be used as a simulator to help in the creation of creating human tissues from 3D cell-laden scaffolds grown in vitro [74].
- The goal of cardiovascular tissue engineering is to repair or replace damaged or inefficient blood arteries, heart valves, and cardiac muscle. Cardiovascular three-dimensional Bioprinting has the potential to be clinically applicable. It may also be used in the laboratory to simulate and understand biological concepts that are at the base of cardiovascular illness [75].
- Three-dimensional Bioprinting of the cardiovascular system has the potential to be clinically useful. Cardiovascular tissue engineering aims to repair or replace damaged or inefficient blood vessels, heart valves, and cardiac muscles. It may also be utilized in the lab to model and comprehend biological ideas at the root of cardiovascular disease [76].
- Cell-printing methods that can build three-dimensional (3D) structures out of biocompatible materials and cells are very appealing for a variety of biomedical applications. The compositions of bio-inks are crucial for both printing processability and the survivability of printed cells [77].
- The technique of generating three-dimensional objects out of biomaterials, cells, and biomolecules is known as Bioprinting. This overview focuses on current Bioprinting research for tissue engineering and its potential for building tissue-mimicking structures. The needs for each approach are explored and contrasted, as are the technical hurdles [78].
- Hydrogel-based bio-inks can be utilized to simulate the extracellular matrix environment of the original tissue, with excellent mechanical and structural integrity for patient-specific tissue regeneration. Bioprinting technologies for a wide range of multicomponent bio-inks are being explored [79].
- By 2020, osteoarthritis is expected to be the fourth biggest cause of disability. Cryo-printing enables the creation of scaffolds with highly repeatable pore diameters and mechanical characteristics that can be readily modified by varying polymer content and print-head temperature [80].
- 3D Bioprinting is a strong tool for addressing one of the most difficult issues in tissue engineering: vascularization. The purpose of this study is to discuss the most recent advances in the field of 3D playing of vascularized tissues. It will include Bioprinting approaches for vascularized

constructions, bio-ink for vascularization, and thoughts on current advancements in 3D printing and biomaterials [81].

- Bioprinting is a 3D manufacturing process that is utilized to accurately distribute cell-laden biomaterials for the creation of complex 3D functioning live tissues or artificial organs. Bioprinting technologies have shown promise in regenerative medicine, generating a range of transplantable tissues such as skin, cartilage, and bone. Current Bioprinting systems have technological problems in high-resolution cell deposition, regulated cell distributions, and vascularisation [82].
- Three-dimensional (3D) Bioprinting is an exciting and new fabrication approach for accurately positioning biologics, such as live cells and extracellular matrix (ECM) components, in the required 3D hierarchical arrangement. We investigate the process factors that influence Bioprinting and bio-ink biomaterials, as well as evaluate important works on bio-printed skin, cardiac, bone, cartilage, liver, lung, brain, and pancreatic tissue [83].
- Three-dimensional (3D) Bioprinting, in particular, is developing as a potentially transformative tool for tissue engineering and regenerative medicine. Based on patient anatomy and biomimicry, the study employed 3D medical scans to fabricate a building with complicated shapes and architecture. This study's findings verified the idea that patient-specific anatomy might be converted to 3D Bioprinting [84].
- 3D Bioprinting has the potential to be a game changer in tissue engineering and regenerative medicine. This work used 3D medical images to design a structure based on patient anatomy and biomimicry. The findings supported the notion that patient-specific anatomy might be transferred to 3D bio printing [85].
- Direct 3D Bioprinting of wounded regions in a surgical context has the potential to greatly increase the precision and efficiency of these treatments. We discuss the present constraints of IOB from an engineering and clinical standpoint, as well as the opportunities for future translation of Bioprinting technologies from bench to bedside [86].
- 3D Bioprinting is gaining traction as a viable approach for creating complex tissue constructions with specific biological components and mechanical qualities. Scientists can now precisely place materials and cells to create functioning tissue models for in vitro drug screening and disease simulation. For possible medicinal applications, we concentrate on the liver, cardiac tissues, vascularized constructions, and cancer models [87].
- Three-dimensional (3D) Bioprinting has the potential to regenerate a variety of tissues, including bone. However, other difficulties, like nutrition and oxygen transport, must be considered. This combined technique has the potential to improve the success rate of implanted tissue engineering constructs for critical-size bone lesions [88].
- Organ and tissue Bioprinting is a new technique in the field of tissue engineering. Several tissues, ranging from poorly regenerative cerebral tissue to highly proliferative skin tissue, have been examined in the context of Bioprinting. The goal of this study is to discuss what has been tried in terms of bio-inks and printing procedures from the beginning to the present [89].
- It appears that artificial tissues/organs for therapeutic use may be created using 3D Bioprinting of living cells and polymers. It is critical to build microstructures that replicate real tissues to generate artificial tissues with biological activities [90].
- 3D Bioprinting has the potential to be a "game changer," with the ability to manufacture human organs on demand, eliminating the requirement for living or deceased human donors or animal transplantation. Despite the paucity of present socioethical interaction with technology, we identify some basic practical, ethical, and regulatory challenges that need to be addressed [91].
- 3D Bioprinting is a cutting-edge technique that allows for the creation of biomimetic, multiscale, multicellular tissues with extremely complex tissue microenvironments. Given the high demand for organ transplantation and the scarcity of organ donors, bio-printing has the potential to alleviate the organ shortage dilemma [92].
- The potential of several natural polymers to enable the adhesion and proliferation of viable cells to bio print cell-laden constructions, bone, cartilage, skin, neural tissues, and blood vessels is discussed in this review [93].
- According to experts at the University of Bristol, tissue Bioprinting has the potential to duplicate natural skin. It entails employing computer-controlled nanoarchitecture and 3D printing to direct the development of cells and scaffolds into spatially controlled patterns [94].
- Patients' demand for organ and tissue regeneration is growing due to a lack of donors and biocompatibility concerns. To solve this, scientists have looked at artificial tissues as a possible

replacement for transplantation. To achieve 3D hard tissues, 3D Bioprinting technologies still face unresolved hurdles [95].

- Producing 3D vascularized cellular constructs of clinically relevant size, shape, and structural integrity is a challenge for tissue engineering. We present an ITOP (integrated tissue–organ printer) capable of producing stable, human-scale tissue constructs of any shape. The ITOP's future development will focus on the generation of tissues for human purposes [96].
- Drug screening, formulation development, transplantation, chemical, and cosmetic testing, and fundamental research might all benefit from bio-printed skin. The increased tissue authenticity over traditional skin equivalent creation, allowing the exact localization of numerous cell types and appendages inside a construct, is a key promise for Bioprinting skin [97].
- Three-dimensional (3D) Bioprinting is a critical technique for the creation of artificial tissue. The classic CAD/CAM technology, which has been utilized in 3D printing for many years, is now experiencing issues [98].
- In vitro tissue/organ models are useful platforms for conducting quantitative drug/chemical research. Bioprinting allows for the creation of complex living tissues, which may be useful for screening new compounds or predicting toxicity. The fundamental goal is to generate physiologically relevant functionalities, which often need sophisticated culture systems [99].
- Bioprinting was first proposed as a remedy for vascularized tissues 15 years ago. The present state of it in academia and industry is appraised subjectively. Progress is recognized, and present constraints in bio printing are examined. Bioprinting is an emerging field that is having a revolutionary impact on the medical sciences. It offers great precision for the spatial placement of cells, proteins, genes, drugs, and biologically active particles. Bioprinting has attracted growing interest worldwide among researchers and the general public [100, 101].
- Bioprinting has evolved as a method that allows for the creation of highly ordered three-dimensional (3D) vascular networks within synthetic tissue constructs. It can aid in the transfer of oxygen, nutrients, and waste products, which is difficult to do using traditional microfabrication processes [102].
- Diseases in which fibrosis plays a significant role cause significant morbidity and death. Our understanding of fibrosis biology is based mainly on data produced in monoculture or coculture environments [103].
- Microvasculature regulates the local mass exchange of oxygen and nutrient-rich blood at the tissue and cell levels. Threedimensional Bioprinting has recently broadened the potential for creating complex microvascular systems. The development of printed biomaterials still faces considerable obstacles [104].
- We provide a unique 3D Bioprinting technology for organ-on-a-chip applications in this paper. On an organ created using the approach, liver function was shown to be greatly improved. Protein absorption was extremely low, allowing for precise measurements of metabolism and medication sensitivity [105].
- There is a growing need for bioengineered blood vessels for use in regenerative medicine and drug screening. Three-dimensional (3D) Bioprinting is a promising method for creating blood vessels or vascularized tissue constructions of varied topologies and sizes [106].
- Vascular health is jeopardized by many factors, including illness and trauma. Endovascular therapies and open vascular reconstruction are the two basic ways to treat vascular problems. Due to size mismatches with the natural vessel and immunogenicity concerns, current prostheses have limits [107].
- Due to the difficulties of the two-dimensional cell, culture techniques to effectively map the structure and function of complex organs such as skin, and three-dimensional (3D) skin models must be developed. Over the previous few decades, a wide range of 3D skin analogs has been produced to explore the intricate features of skin [108].
- Cardiovascular illnesses are the major causes of death worldwide, necessitating the employment of tissue engineering technologies to heal damaged tissues. With the advent of 3D Bioprinting, it is now possible to integrate cells layer by layer, allowing for the recapitulation of cellular heterogeneity and complicated hierarchical structural structure [109].
- In medicine, 3D Bioprinting has been depicted as having the ability to alter various medical therapies, such as giving novel responses to organ injury or organ failure. This article investigates whether there is a limit to what should be bio-printed in medicine, as well as the potential of serious injury connected with human testing [110].

- Corneal transplantation is one of the most effective therapies for severe cases of corneal function loss. Stem cell treatments have yet to be successfully translated into the clinic. 3D Bioprinting is a new technique that may be used to create bio-tissue for therapeutic uses [111].
- Current Bioprinting techniques cannot print using bioactive materials that keep their biological functions. By using dimethyl sulfoxide (DMSO) for low-temperature printing, we were able to successfully insert growth factors into extrusion-printed poly(lactic-co-glycolic acid) scaffolds [112].
- The ultimate objective of Regenerative Medicine is solid organ creation. We look at two new technologies for solid organ manufacturing. Decellularization of cadaveric organs and repopulation with terminally differentiated or progenitor cells is one method. The alternative method is to use 3D Bioprinting to deposit cell-laden bio-inks to achieve complicated tissue architecture [113].
- 3D Bioprinting technology has sparked interest in the development of tissue engineering scaffolds. Bio-inks are the fundamental building elements for the creation of 3D structures. We present scaffold-free bio-inks, such as live cell-only aggregations that do not require a biomaterial carrier [114].
- BioMask was created using the three-dimensional Bioprinting principle and could be customized using clinical images such as computed tomography (CT) data from patients. A porous polyurethane layer, a keratinocyte-laden hydrogel layer, and a fibroblast-laden hydrogel layer comprised the BioMask [115].
- Liver cancer is the third most lethal disease in the world, killing approximately 700,000 people each year. Blood flow in the liver is visualized via permeability testing. The use of 3D printing will aid in the creation of adaptive, dependable, and permeable phantoms for diagnostic imaging [116].

CHALLENGES ASSOCIATED WITH BIOPRINTING

The choice of 3D Bioprinting method, as well as whether or not to use scaffolds (and, if so, which scaffold), are critical considerations. Decellularization of cardiac tissue can produce constructions that nearly resemble natural adult myocardium. As we continue to learn about the native human heart, achieving the optimum cellular composition for cardiac constructions remains a challenge. The fact that changing the makeup of noncardiomyocytes, fibroblasts, and endothelial cells impacts the function, vascularization, and survivability of the 3D bio-printed heart tissue complicates matters [117].

For individuals with terminal lung and tracheal illnesses, transplantation is the only long-term therapy option. However, the scarcity of organ donors and post-implant tissue rejection put a cap on transplantation. A viable strategy to overcome these constraints is 3D Bioprinting for the engineering of lung and tracheal tissue [118].

There are limited examples of effective translation into surgical practice despite expanding laboratory research in the developing field of 3D Bioprinting. If developed successfully, this method might eliminate the requirement for donor locations or immunosuppression by biomanufacturing autologous tissue for repair [119].

In several areas of pharmaceutical and biological discovery and manufacturing, high-throughput methods have become crucial. The technology used to create 3D cell cultures, organoids, and other in vitro models has improved quickly. Here, we talk about how 3D models with high throughput need to be more compatible and how those developments must be made [120].

In the past several years, there has been incredible advancement that has made it simple to create in vitro tissue models. For making the most of this technology, much work needs to be done at several forefronts. The expanding acceptance of the organ and body on chip platforms, as well as their simple scaling up utilizing 3D printing, are highlighted in the review [121].

One of the leading causes of blindness in the world is a corneal disease. Transplantation is now the most common therapy for corneal blindness. Donations are the primary supply of cornea for transplantation, however, this is not nearly enough. A viable strategy for replacing cornea with substitute materials is 3D Bioprinting [122].

Numerous applications of Bioprinting have been discovered in the fields of tissue engineering and regenerative medicine. The power of modeling may be used to forecast and fine-tune experimental settings. We discuss extrusion-based, droplet-based, and laser-based Bioprinting methods in this article [123].

Numerous biological applications, including drug testing, tissue healing, and organ transplantation, may be supported by Bioprinting. The discipline of orthopedics is becoming more interested in 3D Bioprinting due to impressive scientific and technological developments [124].

We examine the most current advancements in 3D Bioprinting for therapeutic applications from this perspective. We concentrate on the design and manufacture of customized 3D-printed cartilage, bone, and skin from the patient's cells. The translation of living biological constructions produced by Bioprinting is extremely difficult [125].

CONCLUSION

In conclusion, Bioprinting is an innovative technology that combines biology and 3D printing to produce living tissues and organs. It presents enormous potential for improvements in personalised medicine, drug development, and regenerative medicine. Overall, tissue engineering and organ transplantation are being approached in a revolutionary way using Bioprinting, raising hopes for better medical results and quality of life. Even while Bioprinting has advanced significantly in recent years, there are still a number of obstacles to be solved before complex organs that are completely functional may be produced for transplantation. The ability to create individualized, useful tissues and organs makes Bioprinting a fascinating and intriguing topic that has the potential to transform healthcare and redefine the future of medicine.

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