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Advances in Bioresearch

REVIEW ARTICLE

A Review On 3d Bioprinting & It's Applications

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ABSTRACT

Bioprinting is a recent development in regenerative medicine. It is essential to construct cell-filled, three-dimensional models that imitate physiological tissues in tissue engineering, drug delivery, and cancer research. Bioprinting can provide patient-specific spatial geometry, managed microstructures, and the positioning of different cell types for the construction of tissue engineering scaffolds. In this concise research, the various production techniques—laser-based, extrusion-based bioprinting, & inkjet-based bioprinting—are explained, discussed, and contrasted. Each strategy's advantages and disadvantages are explored, along with the current stage of each technique's applicability to a variety of tissue types. Successful bio-printed scaffolds are created by using nozzle type of processes like inkjet & extrusion printing. laser-based processes used are stereolithography & laser-assisted bioprinting. These four methods were discovered to have various impacts on print accuracy, resolution, and cell survival.It was discovered that the materials used and their concentrations affect the printing properties. With more current research using numerous ways for combining the advantages of each methodology, each technique has been shown to have its own advantages and downsides.

Keywords: *bioprinting, additive manufacturing, 3D scaffolds, inkjet, extrusion, stereolithography, laser-assisted, rapid prototyping*

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INTRODUCTION

Three-dimensional bioprinting (3D) has been investigated for the production of prosthetics, in vitro models, organs for transplantation, and 3D tissue models for drug testing[1]. The creation of 3D scaffolds that closely mimic natural tissues is new challenge in tissue engineering. Rapid prototyping, also known as additive manufacturing, is a process that builds three-dimensional items layer by layer by adding materials based on computational data from a 3D model. Powder, metals, ceramics, and polymers are all possible materials.

BIOINKS

A key element of 3D bioprinting is bioink, a cell-filled hydrogel material that is typically extruded from nozzle of a specialised bioprinter. Gelatin and collagen, two naturally occurring polymers, have undergone substantial research as potential polymeric supports for bio-inks[1].Bioink should be able to give sufficient mechanical strength and toughness.

Properties of bioink

The generated tissue should preserve the mechanics of tissue-matching.In order to achieve excellent form fidelity during bioprinting, bioink molecules should have tunable gelation and stabilization[2].The bio-ink needs to be biocompatible and capable of biodegradation in accordance with the tissue's natural surroundings. The bio-inks should be able to undergo chemical alterations to create certain tissues.It must possess the appropriate physicochemical features, such as mechanical, biological, chemical, and rheological traits.

BASIC PRINCIPLE OF BIOPRINTING

The precise layers by layers implantation of biological components, biochemicals, and living cells, together with the controlled spatial implantation of functional components onto the 3D structure produced, is the basis of 3D printing. Autonomous self-assembling, mini-tissue units, and biomimicry are its three main pillars.

BIOMIMICRY

After thoroughly analyzing nature, it creates the cellular and extracellular constituents of organs and tissues in precise copies. To achieve biomimicry, certain biological functioning components of tissue must be accurately duplicated[2]. Due to the fact that the materials used in the manufacturing process have a significant influence on cell adhesion, size, and form, the scaffold incorporates control of cell proliferation as well as differentiation [2]. A full understanding of the microenvironment is required, including how various cell types are grouped, the composition of the extracellular matrix, the distribution of soluble and insoluble chemicals, and how biological mechanisms function.

AUTONOMOUS SELF-ASSEMBLING

Autonomous self-assembly is the process of replicating biological tissue using the principles of embryonic tissue and the growth of organs as a guide.It is a scaffold-free version, and a developing tissue's biological component produces its own unique extracellular matrix and cell signals, which offer the autonomous organisation & sequencing needed to build the required microarchitecture[3].This method depends on the fact that the cell acts as the principal regulator of tissue development, dictating the functionality, exact location, shape& structure of the emerging tissue.A thorough knowledge regarding organogenesis as well as developmental processes of embryonic tissues is required for the application of this method.

MINI TISSUE BUILDING BLOCKS

Mini-tissues, or tiny functioning organs& tissues, are created utilizing the bioprinting technique. These mini-tissues, which include kidney neurons, are then produced either by autonomous self-assembly or through biomimicry[3]. They are the tiniest both structurally and functionally unit of the organs. In bioprinting, tissue units that can self-assemble into functional structures are replicated after mini-tissues are assembled into macro-tissues using biologically inspired organization.

PRE BIOPRINTING

The first steps in pre-bioprinting, are the development of the printer-friendly prototype and the choice of substances to be used throughout the process. The procedure begins with the extraction of a tissue samples, which provides the 3D bioprinting approach with a biological model to copy[4].Scan types used include computed tomography (CT) and magnetic resonance imaging (MRI).The images from these approaches are recreated tomographically to produce 2D images.Oxygen and other nutrients are mixed with the cell mass to keep it alive.

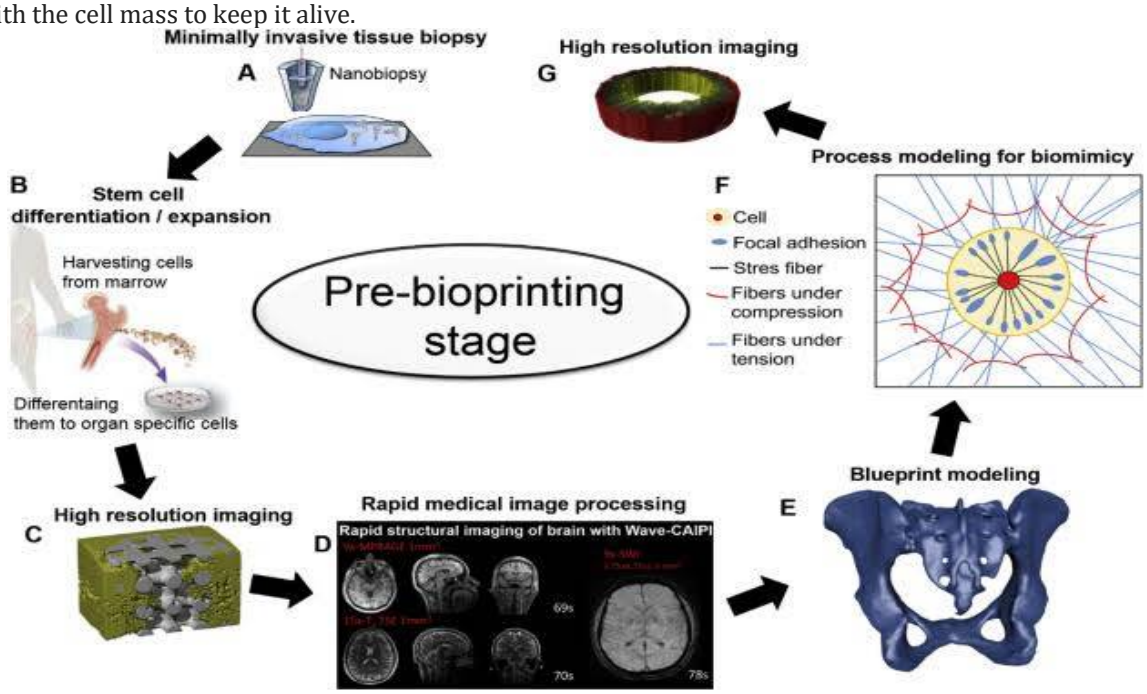
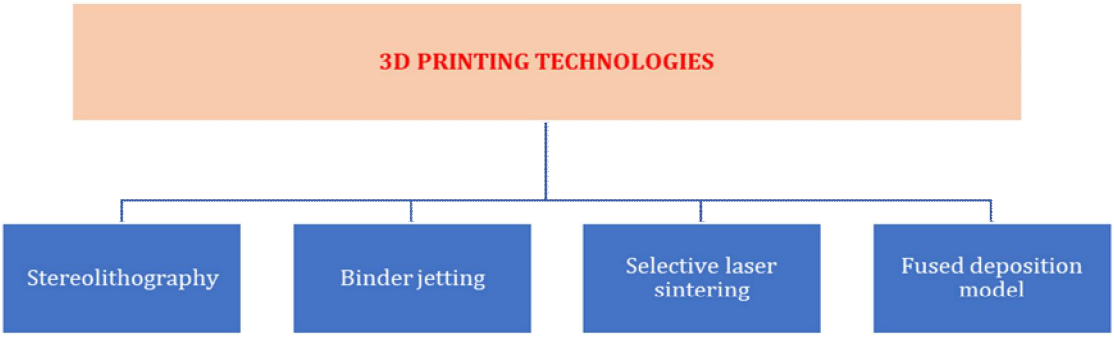


Figure:1 steps involved in pre-bioprinting

BIOPRINTING

The combination is then loaded upon the printer cartridge, which releases the material in according to the generated digital output model[4].The bio-ink is placed in the printer for creating a 3D structure. The bioprinting process begins with the layers-by-layers application of bio-ink to a scaffold to produce a 3D

tissue structure. This step is challenging because it calls for the manufacture of various cells type depending on the organs and tissues that are created.



STEREOLITHOGRAPHY

Stereolithography (STL) technology was created in the late 1980s and is a solid freeform, nozzle-free process. Upon light, a liquid photosensitive polymer composition solidifies. Light-sensitive polymer materials are polymerized using STL, which regulates the light intensity using digital micromirror arrays. This method is mostly used to create structures out of epoxies and acrylics that can cure[5]. There are more photo crosslink able polymers available now, and different resins may be combined to create a single structure. In this top-down system, digital light projection regulates the printing procedure. The manufacturing precision of STL is the greatest compared to other solid freeform processes, and a growing variety of materials may be employed in this method[5]. Additionally, STL can layer-by-layer print light-sensitive hydrogels models, the printing time is totally dependent on structure's thickness.

Despite these advantages, there are still a few drawbacks, such as the lack of suitable biodegradable & biocompatible polymers, unfavourable side effects via toxic photocuring substances that remain in constructs, failure to completely remove the framework that supports them, and the inability to make horizontal gradients in structures[6]. Due to UV-induced DNA damage to cells and skin cancer, the use of UV-sensitive photoinitiators has been discontinued. Wang's 2015 study on the application of tailored visible light in an STL system made use of a commercial beam projection device, bio-inks composed of a mixture of the PEGDA, ((GelMA) methacrylate gelatin, & a photoinitiator based on eosin Y were used in Wang's 2015 investigation on the use of customized visible region light in an STL system.They firstly highlighted the requirement for an IR-blocking water filter and gave a full description of the protocol of a visible light type STL system[7]. The biological printing of the visible light containing curable hydrogels with a 50-m resolution as well as excellent cell survival (85%) for at least 5 days were both accomplished by the researchers utilising NIH 3T3 cells in their trials.

BINDER JETTING: The initial attempts to print living cells were made with the use of specially modified, easily accessible inkjet printers. When inkjet bioprinting was first developed, one issue was that the cells perished during printing since they instantly dried up on the substrate. This issue was solved by encasing the cells& tissues in a polymer that was extremely hydrated; this resulted in the creation of cell-loaded hydrogels. Cells may be positioned precisely using inkjet bioprinting; some experiments have even managed to print only a single cell per printed droplet. Droplets ejected using heat or piezoelectric techniques are used to design cells and biomaterials into the desired pattern.

SELECTIVE LASER SINTERING (SLS): It makes use of powdered material as a basis and joins it with lasers, which are mostly employed to generate acellular anatomical structures in medical applications. Tough models are produced in this way[7].

FUSED DEPOSITION MODEL: Most polymeric materials used in FDM, also known as melt extrusion, are extruded from the nozzle in molten form in set dimensional structure[8]. To fit through the nozzle of the extruder, the bioink must be melted. Tough models are made and acellular scaffolds are produced using it.

POST BIOPRINTING

The final step in the bioprinting process, called post bioprinting, is essential for providing the printed structure stability &solidity[9].To keep biological matter functioning & maintaining its structure, chemical and physical stimulation are required.The cells get information from these stimuli telling them

to reorganise and support tissue growth.The material's mechanical properties might be harmed if this step is neglected, which would reduce the material's usefulness.

WHAT ARE BIOPRINTERS

Bioprinters, they are robotic automatons which is operating based on a several mechanisms. Bioprinters aren't 3D bio printers which can only produce scaffolds devoid of living cells or that can't deliver living cells.Prof. Ralf Mulhaupt's group at Freiburg University in Germany developed the first commercial 3D bioprinter[9].Based on the biomaterials utilised, these bioprinters works according to several mechanisms & are typically employed for a variety of applications.

BIOPRINTER COMPONENTS

a. Head mount

A metal plate that follows the printer's horizontal axis is where the printer's head is fixed[10]. The metal plate is moved from side to side by the motor on the x-axis in order to deposit the biomaterial horizontally.

b. Elevator

At the back of the machine there is a metal track that runs vertically is the lift. The head of printer is moved up and down by the z-axis motor, which powers it.

c. Platform

The platform, which is a coloum located at base of the machine, gives the organ place to rest while it is being manufactured. The platform might be a Petri dish or a scaffold[10]. The platform is moved along the y-axis by a third motor that is part of the printer.

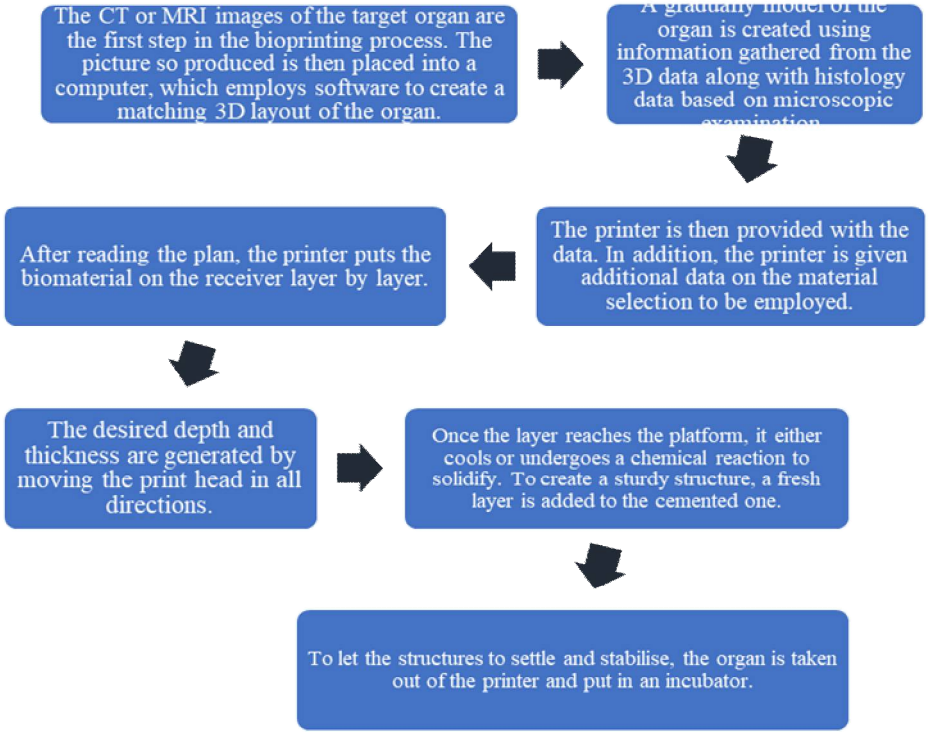
d. Reservoirs

The biomaterial that will be deposited throughout the printing process is held in a reservoir that is situated on the print head.

e. Nozzle

A tiny nozzle\syringe that is located directly exactly above platform forces the biomaterial in print head's reservoir out of the print head

WORKING OF BIOPRINTERS



APPLICATIONS

Tissue engineering

It is One of the most well-known uses of 3D bioprinting is tissue engineering. That makes it possible to create intricate tissues & organs which can successfully replace damaged as well as missing tissues. It takes a lot of effort to incorporate many cell types into complex organ biology and connect vascular

system of veins and arteries, making the production of functional tissues and organs at clinically relevant dimensions challenging. However, a variety of tissues have been successfully printed while maintaining their dimensional stability and usefulness. The following are typical instances of tissues that have been bioprinted for various purposes:

Case study-1

TITLE: Development of 3d bioprinted skin

Using tissue engineering, it is possible to create replacements such as cellularized graft-like commercial items, allografts, acellular dermal substitutes, and autologous split-thickness skin transplants. A 13-layer tissue made of collagen hydrogel may be bioprinted utilising a valve-based, eight-channel bioprinter to create skin tissue. Afterwards, keratinocytes are printed on top of multiple layers of human juvenile skin fibroblasts & acellular collagen to produce constructs with closely packed cells in epidermal layers.The created tissue constructs engraft with their host in stratified epidermal tissue after about ten days. The results of this are the formation of stratum corneum, early signs of differentiation, and some blood vessels. Additionally, skin with infections or diseases might be used as a biomaterial for bioprinting to study the pathophysiology of the disease. Skin tissue may be created using a variety of tissue engineering procedures.

Case study-2

TITLE: Bone and cartilage

They are simple, rigid tissues made primarily of inorganic substances. While other methods, such as salt leaching, gas foaming, & freeze-drying, have been used for creating rigid tissues. 3D bioprinting yields most precise results. Using a thermal inkjet bioprinter, human mesenchymal stem cells obtained from bone marrow are utilized to create polymethacrylate scaffolds using a thermal inkjet bioprinter.To manage the spatial arrangement of the cells, bioactive glass nanoparticles are printed onto the cells.A printed bio-ink for cartilage tissue engineering is created by mixing alginate and nano-fibrillated cellulose layer with the human chondrocytes, a live soft tissue.

Case study-3

TITLE: Blood vessels

The fabrication of tissues &organs rely on vascularization for supplying oxygen and other media to the bioprinted constructions, hence bioprinting of vascular networks is crucial.Extrusion- and laser-assisted bioprinting techniques are both employed in the fabrication of bioprinted vascular networks. Hydrogen gels, such as sodium alginates, chitosan, are directly bioprinted with encapsulated cells in tubular form during bioprinting.The resulting tubular models have enhanced cellular viability and metabolic transport.

Drug development/ screening

High throughput experiments may be performed on 3D tissue models created by bioprinting that closely mimic actual tissue. Additionally, tissue models for such cells can be produced and evaluated based on target cells of developed medications. Epithelial cells are used to create tissue constructions because they are the lining of which a medication enters the circulation. The course of medications and their impact on target cells might be inferred based on investigations on such constructions. Similar to this, bioprinting can be utilised as an alternative method for creating pharmaceuticals. The medications can even be made specifically to each patient by making the right dosages of drug print with the use of a variety of biological inks.It may be preferable to utilise 3D printed composite tablets that include many medications with various rates of release.

Toxicology screening

The method of determining the potential negative effects of chemicals on the people or the environment is known as toxicology screening or testing.Chemicals can include substances such as those found in pharmaceuticals, cosmetics, home products, and industrial processes.It could appear immoral to use a greater number of participants with different metabolisms for studies assessing the toxicity of specific drugs.Animals can be used in some research, but they may not accurately or reliably anticipate human reactions.Instead, 3D bioprinting can offer a highly automated & sophisticated technique that create constructions which resemble the composition &operation of human tissues.Real-time monitoring & high throughput screening of diverse substances are made easier by the deployment of such frameworks. For a very long time, cosmetic chemicals have been tested on models of human-relevant skin tissue. On models that resemble the architecture of human tissue, these experiments examine skin irritation, skin corrosion, skin absorption, and skin sensitization.

Tissue model for cancer research

Long utilised in cancer research, 2D tumour models lack cell-cell interactions and so do not accurately depict the physiologically relevant surroundings. However, 3D bioprinting enables accurate investigation of cancer development and spread by recapitulating the disease microenvironment. With a regulated cell

density and cell-cell spacing, many cell types may be printed concurrently to create multicellular structures in a repeatable manner. To explore cell aggregation, HeLa cells may be bioprinted in gelatin-alginate containing composite hydrogel. These tissues may be utilised to examine the development of cancer as well as the alterations in tissue function and structure that occur throughout time. Additionally, tissue models can be utilised to research the effectiveness of various cancer prevention strategies.

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CONFLICT OF INTEREST
There is no conflict of interest between the authors

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