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# 3-DIMENSIONAL BIOPRINTING IN NEUROSCIENCES: FUTURE STRATEGIES FOR NEURAL REPAIR AND REGENERATION.

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**ABSTRACT** **Introduction:** 3-DBP technology is a perfect example of integration of engineering, biology, material science, technology and robotics. In medicine it has a potential to create tissue constructs giving a Philip to regenerative and transplantation medicine. It enables precise fabrication of 3 Dimensional functional units for regenerative and developmental biology. It is a step in precision medicine where lab grown 3D constructs will replace the native neural tissue. In Neurosciences, research is focused on translation of bio-inspired materials and their application in 3-DBP to yield neural cells and extracellular matrices which can mimic specific structure and function of the brain. It provides an ideal model for drug screening and precision medicine applications. In the near future 3-DBP holds solutions for the many challenges posed in tissue engineering and regenerative medicine for the human brain. As this field progresses, newer applications will emerge which is going to disrupt the practice of neurosurgery in an unprecedented manner. The market size of 3-D printing was approximately $2.2 in 2012. It is expected to reach $10.8 billion by this year. **Observation:** In this paper we review the technological advances made in 3D bio fabrication and strategies which are evolving for neural repair and regeneration. It focuses on research directed towards diagnosis and treatment of neurodegenerative conditions, oncology and neurotrauma including spinal cord injury. The 3-DBP of biological materials (i.e., cells, cell culture media, growth factors, and hydrogels) is based on three major strategies: Laser, droplet, and extrusion based bioprinting. Each strategy impacts the cell viability and functionality in a different way. This innovative technology is already finding applications in Drug Delivery systems, Bioprinting of Vascular grafts, neural cells, bone regeneration and spinal cord injury. **Conclusion:** 3-DBP although in its infancy is poised to yield exciting breakthroughs in the field of neurosciences. Several barriers remain to be overcome through a multidisciplinary approach. It requires active collaborative research between scientists working from bench to bedside. It is technology at its best showcasing the highest form of collective intelligence among individuals from diverse fields sharing a common goal. which is to provide a cure to suffering humanity.

**KEYWORDS :** Dimensional Bioprinting (3DBP), Drug delivery system, polycaprolactone (PCL) scaffolds

## INTRODUCTION

The history of printing dates back to the 15th century when the first printer was invented. It led to an explosive spread of knowledge and information. Five centuries later we are looking at three dimensional printing which is here to push science and technology to a different level. Dimensional Three Bioprinting (3-DBP) is the process of patterning biological materials (e.g., cells, biomaterials, and biomolecules) to fabricate tissue-mimicking constructs using advanced additive manufacturing technologies. During the bioprinting process, biocompatible materials (bio-inks) are used to facilitate the printing and act as matrices (bio-papers) for printed cells, which can then be grown in perfusion vessels (bioreactors) for further cellular and functional maturation.

3D Bo Printers: 3D bioprinters can be commonly classified into four groups based on their working principles. In this section, we introduced seven types of bioprinters: (1) inkjet-based,(2) extrusion-based, (3) laser-assisted, (4) stereolithography, (5) acoustic, (6) microvalve, and (7) needle array bio printers. The type of bioprinter should be carefully selected based on the structural properties of the targeted tissue [1].

**Bio-inks:** Bio inks (termed as printable hydrogels) are another key element for engineering functional tissue constructs. Biomaterials used for the manufacture of bio-inks should be biocompatible, bioprintable, and degradable in the human body without toxic byproducts.Bio inks used in 3DBP include, Natural polymers, Alginate, Chitosan, Gelatin, Collagen,Silk, Fibrinogen, Agarose, Hyaluronic acid, Matrigel, Bioceramics, Synthetic Polymers, Polycaprolactone, Polyethylene glycol,Pluronic F-127,Polyvinyl alcohol and Poly Lactic acid. The ECM supports tissue and arranges cells within connective tissues [2]

It can be harvested and decellularized from tissues such as bone, cartilage, and skin. The ECM contains numerous factors, including collagen, glycosaminoglycans, and elastin, which are advantageous for cell growth and differentiation. Decellularized ECM (dECM)-based bio-inks (also termed as tissue-specific bio-inks) have attracted attention. Decellularization processes that remove cellular components while leaving the ECM have been realized using various methods, including physical, chemical, and enzymatic treatments. The critical limitations of using such tissue-specific bio-inks include batch-to-batch variation and complicated decellularization steps [3].Furthermore, potential residues or toxic detergents after decellularization may impair cellular performance [4]

### Current Applications of 3DBP

Multiple tissues have been successfully fabricated using 3D bioprinting, such as bone, cartilage, osteochondral tissue, blood vessels, liver, and organ-on-a-chip. To improve the printability and viability of bio-inks or to enhance the mechanical strength of the structure, complementary bio-inks have been developed in combination with two or more bio-inks.

**1. Bone tissue:** Lee et al. reported a hybrid scaffold composed of PCL and cell-laden alginate [5].They used PCL as a supportive framework to improve the mechanical strength of the construct. The results showed that the encapsulated cells in the alginate hydrogel were homogeneously distributed and exhibited approximately 84% cell viability, surviving well after 25 days of culture. In another study, Gao et al. evaluated osteogenic and chondrogenic effects when a mixture of PEGDMA–GelMA was used as the bio-ink [6]. Gene therapy represents an ideal approach for bone regeneration while delivering regenerative molecules to the specific tissues [7].

**2. Cartilage:** For cartilage tissue engineering, various strategies have been developed by formulating alginate-based hybrid bio-inks. For improve the resolution of the bioprinted structure, a nanofibrillated cellulose–alginate bio-ink was developed for cartilage tissue engineering [8]. Ni et al. also fabricated hybrid bio-inks consisting of silk fibrin and hydroxypropyl methylcellulose [9]. Adding hydroxypropyl methylcellulose to the silk fibrin formed a double network capable of improving its mechanical strength. The results showed that the mechanical properties of the reported hybrid bio-inks were significantly improved compared with those of a single network.

**3. Osteo Cartilage:** Kosik-Kozioł et al. fabricated a triphasic scaffold consisting of noncalcified cartilage (made of an alginate solution reinforced with short PLA fibers), calcified cartilage (a hybrid scaffold composed of alginate, GelMA, and TCP), and subchondral bone (comprising a printed PCL porous structure modified with acetone and

ultrasound) [10].

**4. Trachea:** Park et al. engineered a tubular structure composed of PCL and alginate [11]. Autologous epithelial cells and chondrocytes were individually encapsulated in 3% alginate. Specifically, the trachea-mimicking structures included five independent layers. The first, third and fifth layers were composed of PCL, between which two bio-ink layers were printed. Afterward, the artificial trachea was transplanted into rabbits, and a respiratory epithelium was successfully formed.

**5. Skin:** The skin is composed of the epidermis, dermis, and hypodermis, which protects tissues and organs as a physical barrier. In the field of skin tissue engineering, several studies have reported that damaged skin tissue can be replaced by engineered artificial skin substitutes [12]. Skardal et al. developed a fibrin-collagen bio-ink and applied it for wound healing [13] specifically, human amniotic fluid-derived stem (AFS) cells and MSCs were separately encapsulated in bio-inks. The growth factors secreted by AFS cells promote angiogenesis and wound closure.

**6. Neural Tissue:** Neural tissue is similar to the abovementioned vascular networks. One study demonstrated that a novel 3D neural minitissue could be designed using a neural stem cell (NSC)-encapsulated bio-ink comprising alginate, agarose, and carboxymethyl-chitosan [14].The results indicated that a uniform distribution of cellular constructs with high cell viability could be engineered using 3D bioprinting. Wu et al. bioprinted a gelatin–alginate-based 3D construct to evaluate biocompatibility for in vitro/in vivo tests [15]]. The results showed that over 90% of the Schwann cells survived after 24 h, and this was maintained over seven days of culture. Moreover, the secretion of a variety of neurotrophic factors by the Schwann cells, which were loaded into the 3D bioprinted construct, was significantly higher than that in the 2D culture.

3-D bioprinting of neural cells to construct brain-like or neuronal structures is highly desirable to model neuronal pathogenesis, regeneration, and networks as well as provide a platform to investigate new therapeutic treatments (e.g., Alzheimer and Parkinson's drugs)[16]. However, one of the main challenges of this approach is the difficulty to recapitulate the brain multi-layers, specifically in the medial or sagittal plane. In addition, patterning neuronal tissues that are functional post-printing remains a challenge.

Recently, a novel bioacoustic levitation assembly (BAL) approach was developed to engineer three-dimensional brain-like constructs [17]. BAL provides a simple, rapid, and biocompatible method to bioengineer multiple layer tissue constructs for a wide array of applications including neuroscience, cardiovascular, and cancer biology.

**7. Blood Vessels:** Recently, Jang et al. biofabricated a vascular scaffold (inner diameter: 4 mm, outer diameter: 5 mm, length: 40 mm) using two different bio-inks: alginate and PCL [18].The artificial blood vessels included three independent layers. The first and third layers were composed of PCL, and 3% alginate was located between these two layers. Afterward, the bioprinted scaffold was transplanted into canines. Owing to the use of autologous MSCs, the cell-laden artificial structure was confirmed to have obtained better endothelialization with little inflammation.

**8. Liver:** Yang et al. bioprinted 3D liver functional tissues using HepaRG cells that combined gelatin and alginate composite bio-inks [19] after verification of the 3D liver-like functional activity using the 3D bioprinted hepatic organoids, the construct was implanted into mice, and it was observed that the mice prolonged their survival in the experimental groups. A liver-like structure was fabricated using a digital light processing bioprinter. The results showed that the cell viability, level of liver functional activities of albumin and blood urea nitrogen, and porosity were significantly higher than those in the absence of dECM. Gori et al. biofabricated a porous structure using composite bio-inks composed of PF127 and alginate . They found printed 3D structures had better liver functional metabolism activity when compared with the 2D cell adherent method.

**9. Spinal cord Injury (SCI) -** So far, no biomaterial based regenerative therapy of SCI is in routine clinical practice. However, a biomaterial technology, the Neuro- Spinal Scaffold, has recently reached clinical trials. Biomaterials used for the treatment of SCI can be in the form of conduits, sheets, scaffolds, fibers, particles and hydrogels. Biomaterials are used to mechanically stabilize the injury site and provide an environment for interactions with host cells, physically fill SCI-associated cavities, reconstituting extracellular matrix and bridging the injury to guide axonal growth across the gap. To guide axonal regeneration, several biomaterial architectures have been investigated, including channels, fibers, scaffolds, and magnetic microgels.

**10. Other applications:** 3D bioprinting can be used to develop a biological substitute that mimics the Structural and physiological functions present in native organs. In vitro model and organ on chips. Cancer modeling for drug screening, Recent technological advancements have accelerated drug design and discovery significantly, but the number of approved experimental platforms is still insufficient due to employment of 2-D monolayer systems. Miniaturized 3-D tissue models are valuable experimental platforms for design, discovery, and development of new generation drugs, since they mimic native microenvironment of the tissues more accurately than 2-D cell cultures [21, 22, 23]. 3-D tissue models have a high potential to evaluate and predict success or failure of drug candidates in preclinical stages [24, 25].

**Limitations**

The selection of bio-ink is another key factor for successful 3D bioprinting. Bio-inks should meet several rudimentary requirements, such as mechanical, rheological, and biological performances. Moreover, to maintain the entire structure over a long period of time, the printed structure requires appropriate stiffness; however, a very high stiffness can potentially impair cell viability.

Striking a balance between Bioprintability and biofunctionality is a major challenge for achieving successful outcomes. Apart from bio-inks, the cell source is another important point for successful tissue engineering. As such, a new method needs to be devised to accelerate cell expansion time without cell damage and mutations [26], The development of microvasculature is important for maintaining the high cell viability of printed constructs over a long period of time. However, the fabrication of a similar native vascular network using current 3D bioprinting is limited because the size of the bioprinted tissues is larger than tens of micrometers [27,28,29].

Recently, 4D bioprinting technology has emerged as a powerful platform, which combines the “time value” with 3D bioprinting techniques. A 4D bioprinter can be constructed using a structure under different stimuli over time. The technique has the potential to engineer a more complex construct using stimuli-response biomaterials that can change the shape of the construct over time [30] .

**CONCLUSION**

Ultimately, bioprinting technology will provide inspiring solutions to address current Challenges in tissue engineering and regenerative medicine [17] by utilizing basic Science, materials science [31], and robotics [32, 33, 34]. 3-D bioprinting is experiencing a rapid transformation from basic research in academic laboratories to an emerging industry due to its potential commercial value in broad fields including pharmaceutical discovery, personalized medicine, and tissue transplantation [35,36 ] . The market size of 3-D printing was approximately $2.2. Billion in 2012; however, it is expected to reach $10.8 billion by 2021[37]. Bioprinters are mainly based on two types of bioprinting technologies: droplet and extrusion bioprinting. Tissue Regeneration Systems provides a patient-customized solution to repair skeletal defects and damages using bioprinted polycaprolactone (PCL) scaffolds [38].

The Food and Drug Administration (FDA) has approved this solution in 2013 as the first 3-D bioprinted implant for skeletal reconstruction and bone regeneration. In addition, Organovo announced the exVive3D™ Liver in 2014[39] that bioprinted human liver tissue mimics were maintained functionally. The exVive3D™ Liver is designed to provide drug testing service to evaluate drug toxicity [40, 41, 42]

Furthermore, the development of a fully closed bioprinting system that integrates printing and post printing processes such as in vitro culture and maturation of tissue constructs is still a challenge. Once the challenges mentioned above are addressed, scaling up bioprinting technologies will potentially improve rapid clinical solutions and advance medical implants. Further, we envision that the integration of

cells and biomaterials through bioprinting with microfluidic technologies are likely to create unique microenvironments for various applications in cancer biology, tissue engineering, and regenerative medicine [43, 44, and 45]. Additionally, developments on high-throughput manufacturing of 3-D architectures will pave the way for further advancements of in vitro screening and diagnostic applications, enabling complex organ constructs.

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