

# 3D Bio-Printing

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**Abstract:-** 3D Bio printing is the process of generating spatially-controlled cell patterns using 3D printing technologies, where cell function and viability are preserved within the printed construct. The first patent related to this technology was filed in the United States in 2003 and granted in 2006.

## I. INTRODUCTION

An increasing demand for directed assembly of biologically relevant materials, with prescribed three dimensional hierarchical organizations, is stimulating technology developments with the ultimate goal of re-creating multicellular tissues and organs de novo. Existing techniques, mostly adapted from other applications or fields of research, are capable of independently meeting partial requirements for engineering biological or biomimetic structures, but their integration toward organ engineering is proving difficult. Inspired by recent developments in material transfer processes operating at all relevant length scales—from Nano to macro—which are amenable to biological elements, a new research field of bio printing and bio patterning has emerged. Here we present a short review regarding the framework, state of the art, and perspectives of this new field, based on the findings presented at a recent international workshop.

## II. HISTORY

3D printing for producing a cellular construct was first introduced in 2003, when Thomas Boland of Clemson University patented the use of inkjet for cells. This process utilized a modified spotting system for the deposition of cells into organized 3D matrices placed on a substrate.

Since Boland's initial findings, the 3D printing of biological structures, also known as bio printing, has been further developed to encompass the production of

tissue and organ structures, as opposed to cell matrices. Additionally, more techniques for printing, such as extrusion bio printing, have been researched and subsequently introduced as a means of production. In 2013, the company Organology produced a human liver using 3D bio printing, though it is not suitable for transplantation, and has primarily been used as a medium for drug testing.

## III. PROCESS

Using 3D bio printing for fabricating biological constructs typically involves dispensing cells onto a biocompatible scaffold using a successive layer-by-layer approach to generate tissue-like three-dimensional structures. Artificial organs such as livers and kidneys made by 3D bio printing have been shown to lack crucial elements that affect the body such as working blood vessels, tubules for collecting urine, and the growth of billions of cells required for these organs. Without these components the body has no way to get the essential nutrients and oxygen deep within their interiors. Given that every tissue in the body is naturally compartmentalized of different cell types, many technologies for printing these cells vary in their ability to ensure stability and viability of the cells during the manufacturing process. Some of the methods that are used for 3D bio printing of cells are photolithography, magnetic bio printing, stereo lithography, and direct cell extrusion. Typically, the first step used is getting a biopsy of the organ. From this examination, certain cells are isolated and multiplied. These cells are then mixed with a special liquefied material that provides oxygen and other nutrients to keep them alive. Finally, the mixture is placed in a printer cartridge and structured using the patients' medical scans. [4]:<sup>4</sup>When a bio printed pre-tissue is transferred to an incubator this cell-based pre-tissue matures into a tissue.

## IV. 3D PRINTING TECHNIQUES

3D printing for the manufacturing of artificial organs has been a major topic of study in biological engineering. As the rapid manufacturing techniques entailed by 3D printing become increasingly efficient, their applicability in artificial organ synthesis has grown more evident. Some of the primary benefits of 3D printing lie in its capability of mass-producing scaffold structures, as well as the high degree of anatomical precision in scaffold products. This allows for the creation of constructs that more effectively resemble the microstructure of a natural organ or tissue structure.

Organ printing using 3D printing can be conducted using a variety of techniques, each of which confers specific advantages that can be suited to particular types of organ production. Two of the most prominent types of organ printing are drop-based bio printing and extrusion bio printing. Numerous other ones do exist, though are not as commonly used, or are still in development.

## V. DROP-BASED BIO PRINTING

Drop-based bio printing creates cellular constructs using individual droplets of a designated material, which has oftentimes been combined with a cell line. Upon contact with the substrate surface, each droplet begins to polymerize, forming a larger structure as individual droplets begin to coalesce. Polymerization is instigated by the presence of calcium ions on the substrate, which diffuse into the liquefied bio ink and allow for the formation of a solid gel. Drop-based bio printing is commonly used due to its efficient speed, though this aspect makes it less suitable for more complicated organ structures.

## VI. EXTRUSION BIO PRINTING

Extrusion bio printing involves the constant deposition of a particular printing material and cell line from an extruder, a type of mobile print head. This tends to be a more controlled and gentler process for material or cell deposition, and allows for greater cell densities to be used in the construction of 3D tissue or organ structures. However, such benefits are set back by the slower printing speeds entailed by this technique. Extrusion bio printing is often coupled with UV light, which photo polymerizes the printed material to form a more stable, integrated construct.

## VII. APPLICATIONS

San Diego-based Organology, an "early-stage regenerative medicine company", was the first company to commercialize 3D bio printing technology. The company utilizes its NovoGen MMX Bio printer for 3D bio printing. The printer is optimized to be able to print skin tissue, heart tissue, and blood vessels among other basic tissues that could be suitable for surgical therapy and transplantation. A research team at Swansea University in the UK is using Bio printing technology to produce soft tissues and artificial bones for eventual use in reconstructive surgery. Bio printing technology will eventually be used to create fully functional human organs for transplants and drug research. This will allow for more effective organ transplants and safer more effective drugs.

## VIII. IMPACT

3D-bioprinting attributes to significant advances in the medical field of tissue engineering by allowing for research to be done on innovative materials called biomaterials. Biomaterials are the materials adapted and used for printing three-dimensional objects. Some of the most notable bioengineered substances those are usually stronger than the average bodily materials, including soft tissue and bone. These constituents can act as future substitutes, even improvements, for the original body materials. Alginate, for example, is an anionic polymer with many biomedical implications including feasibility, strong biocompatibility, low toxicity, and stronger structural ability in comparison to some of the body's structural material. Synthetic hydrogels are also commonplace, including PV based gels. The combination of Acid with a UV initiated PV based cross-linker has been evaluated by the Forest Institute of Medicine and determined to be a very biomaterial. Engineers are also exploring other options such as printing micro-channels that can maximize the diffusion of nutrients and oxygen from neighbouring tissues. In addition, The Defence Threat Reduction Agency aims to print mini organs such as hearts, livers, and lungs as the potential to test new drugs more accurately and perhaps eliminate the need for testing in animals.

## IX. CHALLENGES

While breakthroughs have been made with regards to producing printable organs, its clinical implementation, namely in regards to complex organs, requires further research. Cell proliferation provided by bio printing is conducted in an artificial environment, which is devoid of natural biological signalling and processes; the lack of these qualities inhibits the development of appropriate cellular morphology and differentiation. When present, these conditions allow the printed organ to more accurately mimic *in vivo* conditions and adopt the corresponding structure and function, as opposed to growing as a shaped scaffold of cells.

Another challenge is the need to vascularize artificial structures for cellular sustainability. Vascular structures, such as blood vessels, along with artificial vascular constructs, allow for the diffusion of key nutrients and oxygen. However, they have not been fully integrated into the technique of bio printing.