



Review Article

REVOLUTIONARY EVOLUTION OF BIO-FABRICATION IN TISSUE REGENERATION: A REVIEW

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ABSTRACT

The evolution of Bio-fabrication is by far one of the most rapidly growing fields of research in modern day and with the increasing number of applications it would continue to do so in the future as well. Bio-fabrication is defined as the production of complex living and non-living biological products from raw materials such as cells, molecules, extracellular matrices and other biomaterials. Bio-fabrication is a technology which can be used to convert the designs which are created on computer-aided design (CAD) to 3D constructs consisting of single layered or multilayered models with the help of computer-aided manufacturing (CAM). There are different processes which are used for bio-fabrication such as Inkjet printing, Robotic dispensing, Laser-induced forward transfer and Stereo-lithography which are described in this article.

Keywords: Bio-fabrication, Regeneration, Allograft, Auto graft, Printing, Bio printer

INTRODUCTION

The term Bio-fabrication itself is self-explanatory in which the prefix “Bio-” suggests that either the raw materials which is used or the finished products or both are derived from biological origin and consist of cells, bio-molecules, or other extracellular matrices, and the suffix “-Fabrication” is pertaining to the manufacturing or production steps involved. The basic elements which are similar in both 2D and 3D printing are: the requirement of a printer (3D printer), a print file (3D model file which may be made by using Computer-aided design (CAD), ink (Bio-ink), paper (Printing platform)¹. The rapid growth of Bio-fabrication has a lot to do with the parallel advancements which were made in the field of 3D printing and Molecular sciences. The wide range of applications of Bio-fabrication (both medical and non-medical) such as Human tissue and Organ transplantations, Tissue regeneration and wound healing, Detection of drug toxicities and different assay procedures, as well as the production of animal free leather make it a thrust area for research in the modern day.

Wound healing and tissue engineering: an evolution

Damage to any organ or tissue may be considered for the topic of tissue engineering but as the skin is the primary organ for defense against any external diseases and toxic substances; a brief account of the skin tissue regeneration is provided below. As we know skin consists mainly of three layers: the epidermis which is the most external layer, dermis which is the middle layer providing the mechanical support and integrity to the skin, and hypodermis which is the lowermost layer composed of adipose tissues and blood vessels.² Treatment of the wound is affected by different

parameters such as the wound type (burn, ulceration, and cuts), wound depth and thickness, as well as the health of the individual.

Skin is equipped to be self-healing and regenerating in nature hence in the early days of medicine, the mere use of wound dressings and other traditional techniques would be sufficient to treat any damage to the skin tissue. The use of plant based medicine or extracts was used since very primitive times. Followed by this came the gauze based bandages or pads which were used to give protection to the wound and provide a moist environment with an adequate amount of transfer of gases facilitating the wound healing process. Newer forms of wound dressing also act as drug delivery systems which are able to incorporate the active pharmaceutical ingredient (API) within the dressing and release it according to the need. These advancements were made after 2010 with the growth of Novel drug delivery systems.

Two methods of wound healing which were often used in the late 19th and early 20th century are autograft and allograft. Autograft is a surgical procedure through which skin is removed from one area of the body and transplanted to a different part of the body. Allograft (also known as allogenic or homograft) on the other hand is the transplantation of an organ or tissue from one individual to another of the same species. Both these procedures have their advantages as well as limitations which are shown in Table 1. With the advent of Tissue engineered skin substitutes and Bio-fabrication the limitations of the traditional methods and grafting may be removed and they provide an excellent option for tissue regeneration and wound healing.

Table 1: Different methods of tissue regeneration and wound healing

Method of Treatment	Year of First usage	Definition	Advantages ²	Disadvantages ²
Auto-grafts	Late 19 th century, Ollier and Thiersch's use of pinch graft in 1869. Split-thickness graft in 1872-1886	Autograft is a surgical procedure by which skin is removed from one area of the body and transplanted to another part of the body	Good Adhesion, Pain relief, Reduced chances of rejection	Limited availability at the donor site, Scar tissue would still be left behind, Treatment time is long
Allografts	Early 20 th century, Dr. Alexis carrel transplanted kidney, heart and spleen in animals	Allograft is the transplantation of an organ or tissue from one individual to another of the same species	Availability of tissue is high, May be applied to deep wounds	Immune rejection chances are high, Transmission of diseases
Traditional wound dressing	Very primitive days	This comprises of therapies based on natural origin and plant extracts, gauze based sponges or bandages and pads	Non-expensive, Non-penetrating, Protective in nature	No use of drug products, Unable to provide moist environment
Modern wound dressing	After 2010 modern methods of wound dressing became available	Modern wound dressings are made from a large variety of polymers and drugs combinations.	Able to create moist environment, Incorporation of drug substances as NDDS	High cost, Unable to produce lost skin hence no regeneration
Tissue engineered skin substitutes	Tissue engineering was coined in 1985 by Yuan-Cheng but the first tissue engineered skin substitute was made in 1997-1998. ³	Consists of either cell based or scaffold based structures, which are able to incorporate growth factors, cytokines and other matrix components	Promotes the regeneration of dermis and epidermis layers, Non-contaminant	Manufacturing cost is high, Handling is difficult, Possible immune rejection
Bio-fabrication based tissue regeneration	Bio-fabrication was coined in 1994 and later in 2004 was used by Payne and co-workers to make nanostructured assemblies containing biomaterials	The use of bio-ink in the form of cells and other biologically derived substances as raw materials to design and produce tissues	Immediate and effective relief, with use of cells and biomaterials, Fitting to the anatomical shape of the defect	Requires suitable imaging techniques to be integrated with biofabrication to produce the substitute, High cost

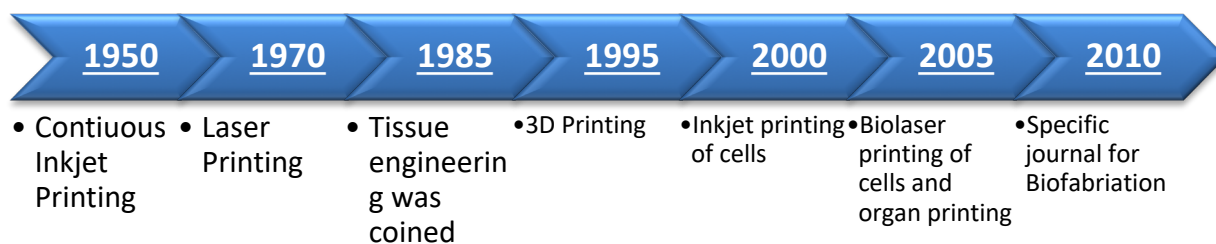


Figure 1: A timeline for the various developments in tissue engineering since its inception

The developments which have occurred over the past 50 years have been the stepping stones to the current success of bio-fabrication. Ever since the concept of 3D printing was first thought of until this date many advancements have been made which are depicted in Figure 1. The two basic requirements which are needed in Bio-fabrication and the formation of 3D tissues and organs are Bio-design and Bio-ink.

As shown in the Figure 2 cells and growth factors are mixed onto a hydro gel or bio-matrices which ensure the cell viability. They act as a support system for the further growth of the cells. Bio-processing is the term which is used to ensure cell adhesion, proliferation and the differentiation of the cells. All this in the end would lead to the tissue growth and the formation of the 3D tissue/organ.

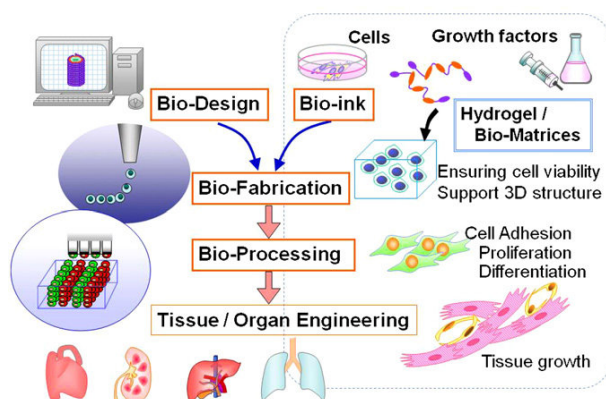


Figure 2: Flowchart depicting the process of Bio-fabrication in tissue/organ engineering⁴

Bio-inks: the building blocks for Bio-printing

Selection of suitable Bio-ink

The bio-ink is the fundamental requirement for the Bio-fabrication and its selection must be done according to the need and specific characteristics. Bio-ink may be defined as the cells, bio-materials, and other extracellular matrices that are required for the fabrication of the 3D construct. Out of the wide range of available bio-inks the suitable selection shall be done based on the following requirements¹:

- Bio-chemicals - (Growth factors, proteins, chemokines, adhesion factors and other bio-materials)
- Physical parameters - (Mechanical and structural strength of the extracellular matrices, interstitial flow)
- Printability - (Capability of the bio-ink to support manufacturing and rapid solidification)
- Physicochemical properties - (Wetting/swelling, structural stability)
- Compatibility - (In case of *in-vivo* implantation the compatibility and biological activity must be assessed)

Bio-printing techniques may be broadly classified into two major categories: Scaffold based bio-printing and Cell based bio-printing.

Scaffold Based Bio-printing

Scaffolds are the porous structures which have suitable geometry and are able to provide support and bio-chemical stimuli to the tissue constructs. In this method the tissue engineering is done by seeding the cells onto the material scaffolds which provide support, stability, and mechanical cues to the cells. They can be fabricated to be inert or have a direct effect on the cell response.⁵ Scaffolds are mainly produced with the help of ink-jet printing or bio-plotting whereby the cells are placed along with the scaffold material or are incorporated within the scaffold material.

Cell Based Bio-printing

Also referred to as the scaffold-free bio-printing technique, it enables the emergence of native tissues in a shorter period of time than the commonly used cell-laden hydro gels. The hydro gel free technique ensures the quick fusion and maturation of the building blocks.⁵ Here the nozzle from which the bio-ink (live cells) is ejected is controlled very precisely in both volume and position. Cells are placed in a layer by layer fashion on top of one another to form the 3D tissue/organ.

Classification of Bio-inks

In general the bio-inks are divided into two categories based on their mechanical strengths: Hard Bio-materials and Soft Bio-materials.

Hard Bio-materials

These types of bio-materials include metallic components, polymers, ceramics and other composites which are derived synthetically or available naturally. Metallic bio-materials have a high applicability in 3D printing due to their mechanical strength and safety features. Some of the common metals used in the 3D printing include titanium and stainless steel¹. The only limitation which is associated with the use of metals as hard bio-materials is metallic corrosion and ageing of the metals. Now-a-days however the safer option of bio-degradable implants is preferred as

opposed to the conventional metallic implants. Some examples include zinc-based bio-degradables and magnesium-based bio-degradable which offer great bio-compatibility and suitable degradation rates.

Some of the other bio-compatible hard bio-materials include ceramics and glasses for dental, bone and joints implantations. They are used here for their special ability of mineralization and cost effectiveness. Poly (lactic-co-glycolide) is another material which is ideally used in case of extrusion based bio-printing along with other such polymeric bio-materials¹.

Soft Bio-materials

Also known as Hydro gels these soft bio-materials are capable to be used in various soft tissues of the body. They are predominantly used in cellular bio-printing based methods in which either naturally occurring polymers such as gelatin, collagen, fibers, chitosan and fibrin are used or synthetic materials such as PEG and their derivatives are used. Each having their own advantages and disadvantages can be used according to the need. The natural polymers are known for their biological activity but are limited in use due to their lack of mechanical strength and immunogenicity. On the other hand the synthetic polymers can be designed according to the need at the specific site.

Hydro gels in general need a pseudo-plastic property if they are to be used in the bio-printing process. Thus their viscosity shall be high enough to keep the hydro gel in the reservoir without letting it flow out of the nozzle, and their viscosity should decrease on the application of shear stress in order to flow through the nozzle. Another desirable property of the hydro gels in the gelation property mainly through cross-linking.⁵

3-D Bio-fabrication techniques

Conventional Fabrication Techniques

Some of the conventional techniques which were used to fabricate scaffolds from natural and synthetic bio-materials were:

Solvent Casting and particulate leaching: This involves the use of a polymer solution which is thoroughly mixed with the salt particles of a fixed diameter. The solvent is then evaporated leaving behind a polymer matrix in which the salt particles remain embedded. This composition is then immersed in water, which leads to the leaching out of salt and leaves behind a porous structure of diameters of up to 500 μm . This method can only be used to fabricate membranes of up to 3 mm thickness.

Gas foaming: In this technique the molded bio-degradable polymers are pressurized at high pressures with gas-foaming agents until the polymers are saturated. Gas foaming agents used are Carbon dioxide, Nitrogen, and fluoroform. This results in the nucleation and the subsequent growth of gas bubbles with sizes ranging between 100 and 500 μm in the polymer. This technique has the advantage of being free from organic solvents. However, it is limited by the fact that the structure which is fabricated would have largely unconnected pores in its structure with a non-porous external surface.

Phase separation: This is a process in which a polymer solution is quenched and undergoes a liquid-liquid phase separation which leads to the formation of phases. Out of the two phases one of them becomes a polymer rich phase and the second one becomes the polymer poor phase. The former polymer rich phase in the end would solidify and lead to the formation of a highly porous

polymer network. By controlling critical process parameters such as the polymer concentration, temperature and the rate of quenching it becomes possible to fabricate various sized micro- and macro- structures. The major advantage of using phase separation technique is that we are able to form nano-scaled fibrous structures which mimic the natural extracellular matrix and also provide a better environment for the cell attachment and functioning.

Melt molding: This is a conventional fabrication technique which involves pouring of the polymer powder and a porogen component into a mold and then heating this to the glass transition temperature of the polymer while applying pressure to the mixture. The raw materials here are able to bind together without the use of solvent system which is very much to the advantage of this technique. The porogen is then leached out and the porous scaffold is dried. The possibility of residual porogen as well as the inability to incorporate biologically active molecules due to the high processing temperatures is the major disadvantages of using melt molding for fabrication purposes.

Freeze drying: In freeze drying the polymer solution is cooled to such low temperatures at which all the materials are in the frozen state and the solvent forms ice-crystals. This forces the movement of the polymer molecules into the interstitial spaces of the frozen solvent. After this, the solvent is removed under a pressure which is lower than the equilibrium vapor pressure of the frozen solvent and we are left with a dry polymer scaffold which consists of interconnected porous micro structure. The porosity of this fabricated scaffold is dependent on the concentration of the polymer solution, and the pore size distribution in the scaffold is dependent on the freezing temperature.⁶

Advanced Bio-fabrication Techniques

Of all the various advanced bio-fabrications techniques which are used, some of the most successful techniques are discussed herein.

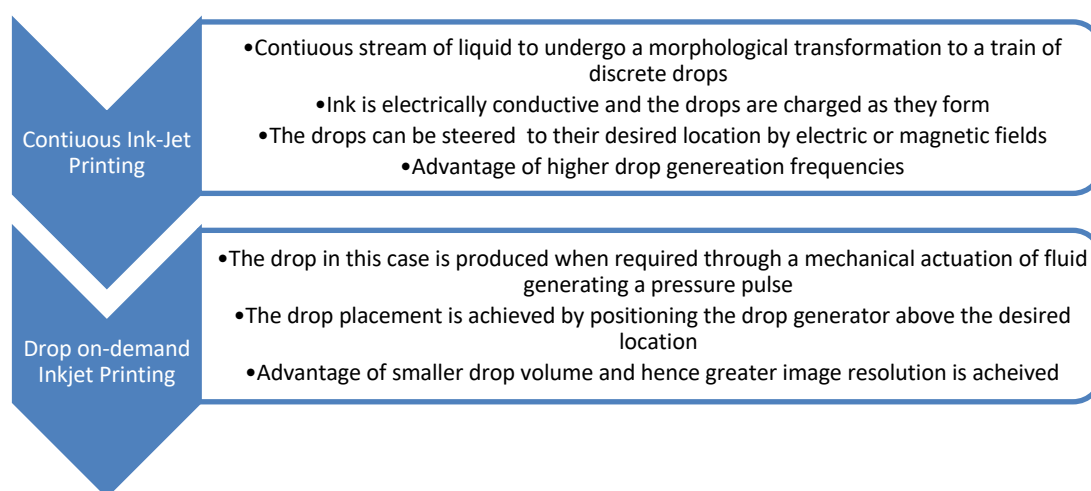
Additive manufacturing (AM) is the proper term to describe the technologies that are capable of creating multilayered 3D objects.

The available additive manufacturing techniques are capable to simultaneously dispense materials which are embedded with live cells or cell aggregates, at controlled locations, enabling the engineering of constructs that closely mimic the original tissue.⁷

Ink-jet Printing

Inkjet printing was originally developed as a graphics and text printing method however in recent times it is also capable of use in bio-fabrication.⁸ It is a digital printing technology in which the image is constructed by the presence or absence of discrete drops of ink (which is termed as Bio-ink when pertaining to Bio-fabrication) on the printed substrate. It is a type of droplet-based bio-printing technique in which the bio-ink used is mainly hydro gels such as Alginate, Agarose, Collagen, Gelatin and Matrigel. The printing process can be considered as two distinct processes: (1) The formation of individual drops that are directed to a specific location on the target substrate and (2) The interaction of the drop with the substrate during and following the impact. Ink-jet printing may be classified into two types based on the two different methods which are used for the droplet formation: (1) Continuous ink-jet printing and (2) Drop-on-demand inkjet printing.⁹

There are two different approaches to use this technology as shown in Figure 3: Thermal inkjet printing and piezoelectric-actuated inkjet printing. In the thermal inkjet printing, small volumes of printing fluid are vaporised by a micro-heater to create the pulse that expels the droplet from the print head. This technique although has some disadvantages such as low droplet directionality and the non-uniform size of the droplets hence has limited use in the 3D Bio-fabrication. On the other hand the Piezoelectric-actuated inkjet printing there is no heating which is used to create the pulse hence no damage to any biological compound present in the inks. In the piezoelectric-actuated inkjet printing a direct pulse is applied to the fluid in the nozzle by an actuator which causes a shockwave that forces the bio-ink through the nozzle and provides some control of the mechanical stress experienced by the cells.



The bio-ink viscosity used in Inkjet printing is less than 10 mPa/s and has a resolution of 10-50 μm , but has one of the highest fabrication speeds ranging up to one lakhs droplets per second.

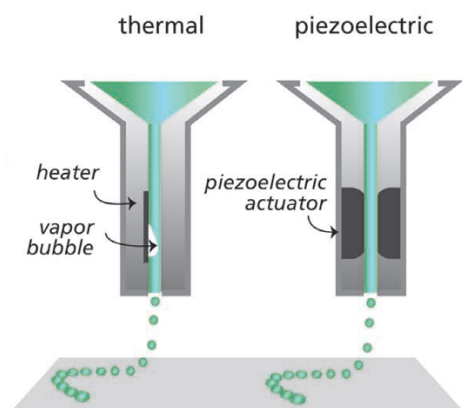


Figure 3: Ink-jet Printing¹⁰

Robotic Dispensing Technique

The most successful attempts to create cell-containing constructs have been through this method in which a robotically controlled extrusion of a material in a continuous manner is done rather than liquid droplets being used. Also known as extrusion based bio-printing, this technology allows the printing of hydro gel encapsulating cells in specific target positions, and has turned out to be the most promising approach for producing 3D organ constructs. The technique is known for its ability to control the flow of bio-ink as well as the rapidity and ease of printing.

There are two main types of bio-inks used in extrusion based cellular bio-printing. One of them is a high viscosity, cell laden solution which is needed to be rapidly solidified into a 3D construct after extrusion. The other type involves the use of spherical and cylindrical multi-cellular systems which may contain supportive biomaterials as the bio-ink such as cell spheroids or cell-laden micro-carriers¹. The technique may make use of either pneumatic, piston or screw type of mechanism to expel the bio-ink from the reservoir as shown in Figure 4. The pneumatic based systems use pressurized air to extrude filaments using a valve-free or a valve-based adjustment and provide a simple and direct method of controlling the flow of the bio-ink used. The piston system makes use of syringes and needles and is suitable to use when the bio-ink fluid has low viscosity. The screw system on the other hand is capable of generating a large amount of pressure to expel the bio-ink and may be used with even high viscosity bio-inks.

The disadvantage of this method though is the low cell viability which is due to the fact that micro-extrusion bio-printing induces shear stress over viscous fluids that contain cells. Hence by using low-viscosity bio-inks, a smaller nozzle diameter and increasing the dispersing speed, higher printing resolution and shorter fabrication times may be achieved.³

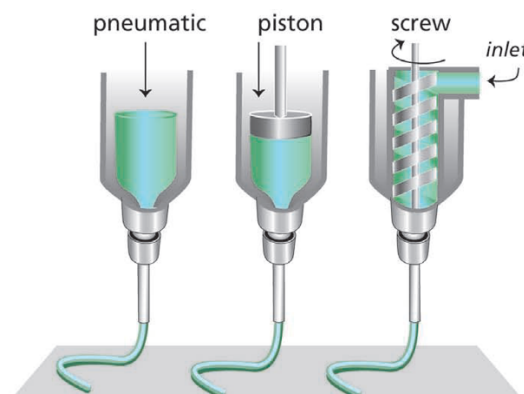


Figure 4: Robotic Dispensing Technique¹⁰

Laser-Induced Forward Transfer (LIFT)

Laser-induced forward transfer is also a droplet based bio-printer system which allows the bioactive materials, proteins, bacteria, and mammalian cells to be placed gently and precisely on any surface. A pulsed laser source is used (as shown in Figure 5) to evaporate a sacrificial layer thereby transferring small amounts of material from the target source to the substrate. The target consists of three layers: A support layer that is transparent to the wavelength of interest, a transfer layer that contains the substance to be transferred, and an absorption layer between the support layer and the transfer layer. A highly focused laser pulse causes the local evaporation of the absorbing layer that generates a high gas pressure propelling the bio-ink compound towards the collector slide.

The major advantages presented by this technique are: (1) Precision with which the deposition of cells/materials occurs in relatively small 3D structures (2) Wide range of bio-inks used with a variety of viscosities (3) Clog-free process without the use of nozzles. The bio-ink viscosity associated with LIFT is from 1-300 mPa/s with a resolution of 10-100 μm . The fabrication speed of LIFT is around 200-1600 mm/s. Due to the above mentioned advantages it has the maximum cell viability of over 95% hence making it able to print skin cell lines as well.

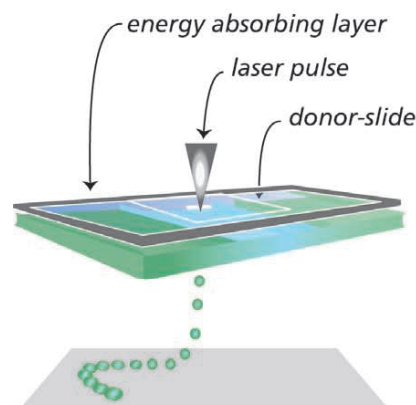


Figure 5: Laser-induced Forward Transfer¹⁰

Stereo-lithography based Cellular Bio-printing

In tissue engineering, a resorbable scaffolding structure is used along with cells biologically active compounds which facilitate (re)generation of tissues either *in vitro* or *in vivo*.¹¹ The scaffold is used only as a temporary support structure to enhance the growth of tissues and cells. Ideally it should degrade into a non-toxic compound as the newer tissues are formed. The manufacturing of these precise scaffolds can be done by stereo-lithography. This technique utilizes the precise and controlled irradiation of light or laser in order to solidify a geometrically 2D pattern layered through selective photo-polymerization in the bio-ink reservoir. This will create a 3D construct which is built by successive 2D layers stacked upon one another in a “layer by layer” fashion.¹¹ The other techniques have a limited resolution of up to 10 μm whereas Stereo-lithographic appearance (SLA) offers an enhanced resolution of 5 μm in the x and y planes and 10 μm in the third dimension. The wide ranges of applications of these techniques of bio-printing include:

Patient specific models and functional parts (With the use of MRI and CT now-a-days it is possible to construct patient specific models of the body parts).

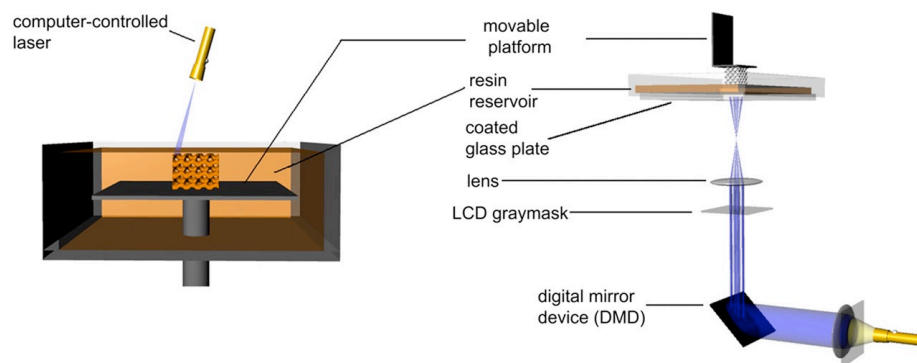


Figure 6: Stereo-lithography instrumentation; Left: Bottom-up system with scanning laser; Right: Top-down setup with digital light projection¹¹

Applications

The most emphasized use of bio-fabrication is the production of human tissues and organs. The shortage of human organs during surgery or transplant is an urgent and serious unsolved medical issue which may be solved if we are able to construct bio-engineered organs or tissues. Many diseases may also be cured by the use of extracorporeal artificial organs or such mimicking devices; an example of this would be the use of extracorporeal liver or kidney.

In-vitro and *in-vivo* applications of Bio-fabrication

Bio-fabrication may also lead to the production of 3D *in-vitro* models of human diseases which may be used instead of the traditional 2D *in-vitro* cell cultures used on petri dishes¹². These models may be created either normal or diseased, by controlling specific locations of several cell types and materials which may increase the accuracy of the drug response. Various examples are available such as¹²:

Mini-liver- By Inkjet printing using alginate as the bio-ink we are able to carry out the animal-free drug discovery

- 3-D Liver Micro-organ-By Extrusion bio-fabrication using alginate as the bio-ink.

Implantable devices (Though limited number of implants have been used till date it is possible to fabricate such implantable devices which could help bone regeneration or tumour removal).

Tissue Engineering (Scaffold based bio-fabrication is done through the use of stereo-lithography)

Hydro gel containing cells (Certain soft bio-materials containing cells can be fabricated with the use of stereo-lithography)

This method is however limited in use due to the lack of choice of photo-polymerizable bio-inks and the high cost of the equipment that are used. Some bio-inks that may be used are polyethylene glycol acrylate/methacrylate, or natural bio-materials such as gelatin, hyaluronic acid, and dextran. Another risk which is often associated with stereo-lithography based cellular bio-printing is the fact that photo-polymerization is driven by a radically induced chemical reaction and these free-radicals have the ability to harm the cell membrane, proteins, and nucleic acids.

- 3-D Cell assays-By Laser bio-fabrication using Fibrin precursors, and HA as the bio-ink to mimic the micro environment.
- Human breast cancer model-By Novo Gen Bio-printing™ (Extrusion method) to create viable breast neo-tissue chemotherapeutic drug response.
- Skin model-By extrusion method using collagen as the bio-ink to create dermal/epidermal like distinctive layers.

Bio-fabrication may also be used to create tissues and organs for implantation *in-vivo*. Hence with 3-D bio-printing technology we are able to produce tissues and organs such as bones, cartilage, blood vessels and heart valves. Thus with the help of advanced bio-printing engineers are able to construct complex tissues/organs by direct and precise placement of the living cells at the specific locations.

Other non-medical application of bio-fabrication in various fields

Animal free production of tissue engineered meat is a solution to the global problem of animal protection. For this to be practical and available in the form of large scale production process the following elements are required: (1) cell source (2) cell media (3) porous scaffold spheres (4) perfusion bioreactors (5) optimal conditions for the cell and tissue differentiation¹². The same can be said for the production of animal free leather which can be produced with the help of bio-fabrication.

Another application of bio-fabrication is in space research in which there is scope for the development of sophisticated cell and tissue based bio-reporters and bio-sensors to check the radiation safety levels.¹³ Thus in the future application of bio-fabrication

we might be able to design, fabricate, and test tissue analogs of human organisms instead of sending manned mission to Mars and the Moon to check the radiation levels and other toxicity studies which are involved in space exploration.

Table 2: A list of companies producing commercially available Bio-printers

Company Name	Country of availability
Envision Tech	Germany
Regen Hu	Switzerland
Poetis	France
Organovo	USA
Rokit	South Korea
3Dynamics systems	USA
Cyfuse Biomedics	Japan
Allevi	USA
3D Bio printing solutions	Russia
Cell ink	Sweden/USA ¹⁴

CONCLUSION

Without a doubt it can be said that the field of bio-fabrication is one which has grown exponentially over the past decade and will continue to do so in the coming years. Various challenges which are faced by the growth of this field include the limited digitalization of the designing methods, the increasing need for the organs and tissues in patients, and the limited resolution of the printing machines. The computer-aided designing programs shall undergo significant improvements which would make it easier for the construction of more precise and micro-structured constructs. Similarly the printing machines resolution must also be enhanced in the future making it capable of printing with a resolution of even smaller than 10 µm which would enable the printing of even the smallest capillaries. These challenges will be faced easily over the next decade with the growth of science and technology which will lead to the simultaneous evolution of bio-fabrication as well.

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