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Review Article

Exploring the Landscape of Biofabrication Methods for Tissue and Organ Engineering

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Societal concerns regarding the persistent shortage of donor organs and tissues have fueled the rapid growth of biofabrication as an unprecedented paradigm in regenerative medicine. In this review, we provide an in-depth overview of the biofabrication approaches for tissue and organ engineering, particularly in the interweaving of engineering and biological principles. We critically review the four main types of bioprinting, such as extrusion, inkjet, laser-assisted, and stereolithography bioprinting in terms of, resolution, compatibility of material with cell type or structure, viability of cells in post-fabrication conditions, and scalability. In addition to the four types of bioprinting, we tackle other scaffold-based and scaffold-free approaches such as electrospinning, cell sheet engineering, and assembly of spheroids. We additionally discuss biomaterials and bioinks developed in the area which can bridge biological processes and mimic nature's extracellular matrix. Recently developed innovations such as 4D bioprinting, smart biomaterials, artificial intelligence integration, and in situ bioprinting are emphasized as well as challenges still faced such as vascularization, mechanical integrity, and post-fabrication maturation. Applications demonstrate a multitude of therapeutic possibilities of biofabrication, from organ-on-chip systems to whole-organ engineering to skin and bone regeneration. The aim of this study is to push the field forward towards the realization of functional, transplantable tissues and organs, by enabling clinical translation and continued research, as well as standardization and interdisciplinary collaboration.

Introduction

The lack of transplantable tissues and organs throughout the world represents a huge medical crisis that has persisted since and remains one of the most important and biggest challenges facing modern medicine [1-3]. In spite of substantial advancements in immunosuppressive therapies and surgical techniques, we continue to see a huge disparity between the need for transplantable organs or tissues when compared to the number of donors [4,5]. When patients experience trauma and develop diseases such as end stage renal disease, hepatic failure, heart failure, or significant loss of tissues there are only a marginal portion of individuals who will get the life-saving transplant in a reasonable time due to a shortage of donors [6].

There is a significant shortage of donor organs relative to the demand; approximately 150,000 solid organ transplants are completed per year worldwide. It's estimated that more than 2 million people each year require organ transplants globally [7]. There were over 103,000 patients on the US transplant list as of 2025. There is, therefore, an urgent need for alternative regeneration strategies, such as advanced biofabrication technologies and bioprinting technology [8].

According to national transplant registries and the World Health Organisation, the global demand for transplantable organs is continually growing; however, the pool of eligible donors remains limited and inconsistent. The shortage of donor organs is primarily attributable to the restricted sources of donor organs and is further exacerbated by logistical, ethical, and socio-cultural factors, including stringent donor-recipient compatibility requirements and low donor registration rates [9].

Making matters worse, the growing number of chronic conditions such as liver cirrhosis, heart disease, and renal failure, cause greater

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discarding of viable donor organs [10]. More broadly, as the average age of the population increases, trauma and degenerative disease increase, giving rise to escalating demands for regeneration therapies, while also overburdening the health care system. The efficacy and availability of donor organs will also diminish with post-transplant complications associated with immunological rejection and chronic immunosuppression [11,12].

Biofabrication contributes a potentially revolutionary role in reducing global shortage of transplantable tissues and organs by allowing for the controlled, automated production of physiologically functional tissues, which are derived using living cells, biomaterials, and bioactive compounds [13]. Biofabrication sets out new opportunities for scalable, customizable, and possibly patient-specific solutions to transplantable tissues and organs which typically rely on the availability of a 'donor' [14,15]. Biofabrication addresses this challenge through several principal strategies:

a) Donor Conflict Mitigation: Biofabrication removes the human element of tissues and organs as bioengineered, laboratory-grown tissues and implants increases supply of grafts etc. [16].

b) Enabling Patient-Specific Constructs: Using a patient's own cells (autologous stem cells for example) allows biofabrication to produce mapped out customized constructs that limit immune response and thus limit immunosuppressed states for life [17].

c) Mimicking Complex Structural and Tissue Architecture: Techniques such as 3D bioprinting, stereolithography, and electrospinning with biofabrication allow researchers to spatially track out the specific type of cells and materials, producing what will in turn simulate the complex microarchitecture and function of tissues (i.e. skin, cartilage, temporal bone, and potentially vascular networks) [18,19].

d) Facilitation for On-Demand Biofabrication: Biofabrication will allow for on-demand biofabrication designs as the rapid prototyping and digital design will provides immediate/easy sped up patient manufacturing process and optimize readiness for instance in emergency situations [20].

e) Platforms for Drug Screening and Disease Modelling: Biofabricated tissue models, by providing regenerative therapies, facilitates therapeutic applications and development of tissue in vitro models for drug screening and disease-mediated research thus reduces demand on organ donor systems [21,22].

The aim of this manuscript is to review and evaluate the spectrum of biofabrication approaches, applied in tissue and organ engineering. It also aims to understand the principles, advancements, and applications of scaffold-based, scaffold-free, bioprinting processes, and new bioprinting technologies. While aiming to explore the roles and importance of biomaterials, bio-inks, and biological components, and to accentuate the integration of bioreactors and microfluidics, it addresses important topics such as vascularization, scalability, and mechanical integrity, whilst attempting to project future trends and research areas, encourage clinical utility, and touch on ethical, translational, and regulatory aspects [23].

Fundamentals of Biofabrication

Biofabrication is the automatic assembly of biologically active materials using living cells, biomaterials, and bioactive agents, and it is a rapidly evolving field it integrates concepts from the contemporary manufacturing and materials sciences and tissue engineering to create 3D structures that mimic the composition and mechanical functionality of natural biological tissues [24,25]. At a foundational level, the aim of biofabrication is to replicate the complexity of natural tissues, by utilizing a variety of strategies such as 3D bioprinting, electrospinning, stereolithography, and self-assembly to organize cells and materials into well-defined spatial structures.

Biofabrication can be applied in a multitude of contexts and projects, for example:

i. Tissue and Organ Engineering: Creating useful structures for regenerative medicine including skin, cartilage, bone, vascular constructs, liver, and cardiac patches [26].

ii. In vitro systems and disease modelling: Developing physiologically relevant models of tissues (e.g. organoids or organs-on-chips) for research on tumour microenvironments, host-pathogen interactions, and disease mechanisms [27].

iii. Drug Discovery and Toxicology Testing: Developing reproducible 3D tissue platforms using high throughput screening for drug testing to lessen the requirement for animal studies [28].

iv. Personalized and Precision Medicine: The use of patient-derived cells to create tissue models or implants that represent individual variability for specialised treatment approaches [29,30].

v. Implantable and Surgical Devices: Biofunctionalized scaffolds and implants for vascular grafts, bone fixation, and wound healing are manufactured [31].

Biological and engineering principles

Biofabrication focuses on using cross-sectional knowledge from biology, engineering, materials science, and medicine to successfully create intricate biological products such as tissue, organs, and useful biomaterials [32]. Biofabrication has three primary techniques: tissue engineering, bioprinting, and bioassembly. The biofabrication of complex biological products incorporates biological principles (i.e., cell behaviour and tissue formation, interactions between biomolecules) with engineering methods to achieve spatially controlled structure and living materials at a high degree of spatial control [33]. These principles are the basis for constructing organ-like and functional tissues.

Biological principles of biofabrication

a) Cell Biology and Cellular Behaviour: Since stem cells offer self-renewal and multipotency for tissue regeneration, primary cells offer native functions but with limited scope for proliferation, and immortal cell lines offer model systems for scalable experiments even when they lose their native behaviour, consideration of cell type is critical to biofabrication [34]. Tissue development is fundamentally based on cellular activities, such as migration for spatial organization, differentiation for unique purposes, extracellular matrix (ECM) secretion for structure, and proliferation for density affording cells [35]. Cell-ECM interactions, mediated by integrins and mechanotransduction signal, influence adhesion, proliferation, and destiny, including paracrine signalling and junctional connections offer coordination within activity, that encompasses moderated freedom. Together, these biological principles create the potential for architecture resembling biological and functional fidelity [36].

b) Tissue Architecture and Microenvironment: To replicate the function of natural tissue using biofabrication, cells, extracellular matrix (ECM) components, and vascular networks must be spatially arranged with precision [37, 38]. Biological gradients are particularly important in influencing cell behaviour, controlling directional cues for tissue development, and inducing maturation of tissue [39]. Biological gradients can be chemical signals such as hormonal growth factors, mechanical signals, and oxygen diffusion. To maintain the viability and functionality of cells, biological scaffolds need to possess vascularization to sustain viable thickness of the tissue construct and deliver nutrients while removing waste [40,41].

c) Developmental Biology Principles: In biofabrication, morphogenesis refers to the process by which genetic instructions and environmental factors organise cell assemblies to become tissues and organs. This process often relies on self-assembly, where cells autonomously organize into functional structures based on inherent biological behaviours [42, 43]. Guiding differentiation pathways through precise biochemical signals and mechanical stimuli is crucial to direct cells toward specific lineages, ensuring the development of functional, tissue-specific architectures [44, 45].

d) Immunological Considerations: In biofabrication biocompatibility is required to avoid immune rejection as it allows the host to see the material and cells as non-threatening. Immune modulation is being developed by biomaterials and tissue constructs that have the capacity to actively modulate, control, and even evade immune responses to elicit integration, reduce inflammation, and increase durability and performance of the artificial tissues [46,47].

Engineering principles of biofabrication

a) Material science and bioink development: The selection of biomaterials is important in biofabrication as it is a compromise between synthetic materials such as PEG and PLGA, which allow controlled degradation and tunable mechanical properties, while natural materials such as collagen, gelatin, and alginate have better biocompatibility, and bioactivity. Bioinks are specially formulated printable materials that contain bioactive chemicals and living cells that allow for precise deposition during bioprinting [48]. The print fidelity and cell viability are contingent upon their rheological properties, which require critical viscosity, shear-thinning behaviour, and rapid gelation [49]. On printing a structure, crosslinking can take place with several techniques such as ionic, thermal, enzymatic, or photo-crosslinking to help improve the mechanical strength, structural stability, and integrity of the printed construct in physiological environments [50].
b) Design and modelling: Biofabrication applications are often implemented using computer-aided design (CAD) which enables the accurate production of scaffold architectures that model the geometry of the original tissue [51]. Computational modelling can be employed to enhance biofabrication by optimising build efficacy before manufacture and for simulating an important range of features, including fluid dynamics, mechanical properties, and nutrient diffusion [52]. Biofabrication techniques follow both top-down and bottom-up methods. For example, in the top-down approach, pre-fabricated formed scaffolds are seeded with cells and while this may confer some degree of structural control, it provides only limited ability to model complex arrangements of cells [53, 54]. The bottom-up method, on the other hand, uses self-organization to create cell-rich micro-units or bio-aggregates for increased biological complexity and tissue functionality.
c) Fabrication technologies: Several bioprinting methods are being used, all with varying constructs [55]. Inkjet bioprinting has a very high speed, but only works with low-viscosity materials, often droplet deposition of bioink is done with heat or piezoelectric forces [56]. Extrusion bioprinting allows larger constructs with stable structures by using continuous extrusions of bioink with embedded cells [57]. Laser assisted bioprinting may be the ideal for small-scale product needs by utilizing laser pulses to deposit bioink on substrates with high accuracy and cell viability [58]. Besides printing, bioassembly makes use of methods like magnetic levitation, or the self-organization of cell aggregates or spheroids, to develop tissues. Microfluidics and organ-on-a-chip for tissue maturation and drug testing also offers small, tightly controlled, mimetic microregulators for tissue microphysiology, where exquisite control might be exercised over fluid flow, nutrient gradients, and mechanical signalling [59].
d) Mechanical and structural integrity: Mechanical integrity is an important requirement in biofabrication, especially for load-bearing tissues (e.g., bone, cartilage, tendon) in which structures must bear physiological load [60]. During or after, may involve mechanical stimuli, e.g., shear stress, compression, or tensile stresses, to enhance tissue maturation by promoting mechanotransduction, the synthesis of the ECM and alignment of cells [61]. Scaffold design is critical based on stiffness like native tissue to aid cell differentiation, porosity based on cell infiltration and nutritional transport, and degradation rate tuned to provide structural support but with replacement or tissue regeneration over time [62].
e) Process control and automation: For clinical translation, reliance, scalability, and regulatory compliance in biofabrication all depend on the standards of practice in the use of biofabrication [63,64]. Automation using both robotics and AI will improve precision, reduce human error, and enable complex productive processes with a dependable quality, high-throughput process [65]. In situ, integrated monitoring with sensors for measurements such as pH, oxygen levels, temperature, and cell viability to monitor conditions in real-time and provide feedback that allow for dynamic adjustments during the process, is an additional consideration to maintain optimal requirements for cell health, structural integrity, and functional tissue growth [66,67].

Integration of biological and engineering principles

A fundamental step in biofabrication relates to the integration of biological and technical concepts. The selection of cell types, and the formation of the tissues' microenvironment would rely on biological knowledge of cellular behaviours like proliferation, differentiation, migration, and interaction with the ECM. Engineering principles can offer sophisticated tools like automated fabrication techniques, CAD-based scaffold design, computational modelling, and 3D bioprinting [68]. Further to the mechanical optimisations enabling acceptable structural integrity and usability, integrating biological and technical principles should allow cells, biomaterials, and signalling cues to be spatially organised in a precise manner [69]. Dynamic bioreactors can also help further integrate biological and engineering aspects and could accelerate the maturation of tissues by also mimicking physiological aspects including mechanical stress, fluid shear, and nutrient exchange in a scalable manner. These integrated aspects are critical to produce biofabricated tissues and organs that are realistic in size, functional and therapeutically relevant [70].
a) Biofunctional constructs: Biofabrication aims to produce biofunctional structures to imitate original tissue structure and function through bio and engineering principles. The development of these structures heavily relies on cell behaviour, morphogenesis, and cell–extracellular matrix (ECM) interactions to encourage survival, differentiation, and functional organization of cells [71]. Engineering plays an additional role with 3D bioprinting, bioassembly and microfluidics to spatially define multiple cell types and positions in biomimetic scaffolds. Biofabrication structures are designed to fulfil nutrient perfusion with embedded vascular networks and optimized material properties to provide adjustable stiffness, porosity, and degradation [72, 73]. ECM synthesis and tissue maturation can be further enhanced by mechanical stimulation from either scaffolds or bioreactors [74]. In conjunction, this will result in a structure that possesses biological function, structure, and stability, and can be used to develop high-throughput drug screening systems, organ models, and regenerative medicine.
b) Dynamic Bioreactors: Dynamic bioreactors that integrate biological and engineering principles are essential for biofunctional constructions developed through biofabrication [75,76]. Dynamic bioreactors represent a biological equivalence to in vivo physiological conditions and create the regulation of mechanical stimuli (e.g. shear stress, compression, and tension), promoting cell proliferation, differentiation, and extracellular matrix formation [77]. From a bioengineering perspective these systems achieve control over oxygenation, fluid transportation, nutrient, and waste exchange required to support densely loaded and vascularised tissues. While some of the latest bioreactors utilize perfusion, delivery of cyclic functional loading, and live-monitoring to support optimal tissue maturation and physiological responses [78,79]. The physiologically responsive and mechanically instigated environment accelerates the development of stable, structured, clinically relevant, and functionally-responsive tissue constructs.
c) Scalability and translational applications: For biofabrication to be scalable with translational capability, one must integrate both biological and engineering principles. On the biological side, this means maintaining functional tissue organisation, phenotypic stability, and cell viability on larger scales [80]. Engineering solutions are automation, robots, and AI-based fabrication. The use of modular bioreactor systems, standardised bioinks and scalable bioprinting platforms allows complex tissues to be mass produced without compromising quality [81]. By in-line monitoring of parameters such as pH, oxygen, and viability, uniformity and consistency across the system can be achieved. This integration of modular process can deliver regenerative medicine, patient specific implants, and high-throughput drug testing by closing the gap between laboratory scale constructs and clinically useful tissues [82].

Biomaterials and bioinks

Biomaterials and bioinks are the basic building blocks of biofabricated tissues and organs, a key aspect of biofabrication. Biomaterials and bioinks are sometimes used to enable cells to function naturally by mimicking the natural extracellular matrix (ECM) to provide biochemically and mechanically synonymous stimuli for tissue formation [83]. The chosen biomaterials and bioinks, their needs and mixes will all affect the aspects of structural integrity, printability, cell viability, and function of the biofabricated construct [84].

Biomaterials used in biofabrication generally split into two broad categories, natural and synthetic. Natural bio-materials such as collagen, gelatin, alginate, fibrin, hyaluronic acid, and decellularized extracellular matrix have good biocompatibility and bioactivity. They provide a biochemically and mechanically representative nature for cells to promote migration, adhesion, and differentiation, and may have variable properties, generally having limited mechanical stability [85]. In contrast, synthetic biomaterials such as polyethylene glycol (PEG), polylactic acid (PLA), and polycaprolactone (PCL), allow more consistent mechanical properties and more predictable degradation rates but generally require some means of surface modification to induce biological behaviour [86]. Bioinks in 3D bioprinting are specialized formulations that resemble biomaterials, living cells, and sometimes bioactive substances (e.g. peptides or growth hormones). An ideal bioink should maintain high cell viability, biocompatibility, be printable in moderate environments, and maintain structural stability after printing [87]. To achieve high-resolution printing and ensure that the printed construct retains dimensional accuracy, the rheological properties of bioinks i.e., viscosity, shear thinning behaviour, and gelation kinetics are also important [88]. Typical composite bioinks are made by using both natural and synthetic materials or by introducing nanoparticles and microcarriers for increased functionality. There are also investigations into stimuli-responsive or "smart" bioinks for use in 4D bioprinting, in which the construction parts will change shape and properties over time in response to environmental stimuli [89].

Types of Biofabrication Methods

Biofabrication employs a variety of advanced manufacturing processes to produce functional biological structures for tissues and organs. There are many definitions available for biofabrication, however most literature combines biological principles with engineering and material sciences to make sophisticated, cell-laden, biomaterial-based structures that replicate natural tissue based upon its form and function [90]. Biofabrication is the fabrication of living cells, biomaterials, and bioactive agents in an organized way to generate structures that maximize the logic of natural tissue while embedding the hierarchical organization acceptable for replacement or repair [91]. Biofabrication is important and useful in the development of regenerative medicine (new organs) therapies, disease models (3D organoid), drug screening platforms, and transplantable tissues and organs because it faithfully reproduces the sought after mechanical, biochemical, and physiological nuances of native tissues [92]. The biofabrication techniques proposed can be categorized generally by the fabrication methodology, material state and manipulation of living cells, based on the complexity, mechanical properties, and biocompatibility required for the targeted tissues. Each method of fabrication has distinct advantages. The type of tissue to be built, if vascularization is needed, and the intended clinical application dictate which fabrication method is appropriate.

Bioprinting techniques

Inkjet bioprinting

Inkjet bioprinting (IBP) is a biofabrication process used to deposit bioinks in a non-contact, droplet-based manner using either thermal, piezoelectric or electrostatic actuation, in either continuous inkjet (CIJ) or drop-on-demand (DOD) mode (as shown in figure 1) [93]. IBP, as a result of the bioprinting mode of operation, allows precise spatial placement of cells and biomaterials; high resolution (20-100 μm); very rapid bioprinting speed; and excellent viability of cells (80-95%) [94]. Due to low performing mechanical stress, IBP allows for very precise spatial placement of cells and biomaterials as well as a high degree of biocompatibility [95]. IBP can primarily use low viscosity bioinks (3-12 mPa.s), such as collagen, fibrin, GelMA and alginate; hence, stable droplet formation and/or prevention of nozzle clogging is achieved with the use of these low-viscosity bioinks [96]. IBP is typically used for cellular patterning, microtissue engineering, biosensing and drug screening applications, where very precise spatial placement and deposition of bioinks is of significant importance [97]. Advantages of using IBP include low cost, scalability and high rates of cell survival in bioprinted constructs. However, disadvantages of using IBP include limitations related to bioink viscosity, the production of satellite droplets, nozzle clogging and the poor mechanical strength of bioprinted constructs; therefore, use of IBP to develop large, vascularized and load-bearing tissues is limited for these reasons. As a result, the clinical application of IBP at present continues to be limited to thin tissues and to develop microscale biological models [98].

Extrusion bioprinting

The most popular form of bioprinting is extrusion bioprinting. It uses pneumatic, mechanical or screw-driven methods to deposit bioink containing cells in layers continuously (figure 2) [99]. This bioprinting method has a broad range of compatible viscosities (i.e. between 30 to 6 x 10w mPa.s). This wide viscosity range enables the use of different materials including collagen, fibrin, gelatin, alginate, GelMA, dECM, ceramic/polymer composites, etc.) [100]. Extrusion bioprinting creates very complicated three-dimensional shapes and very large constructs. The resolution of extruded constructs is moderate (i.e. 100-500μm) with a high degree of cell viability (i.e. 40%-90% depending on the method and materials used) [101]. The extruded materials can be used to create heterogeneous (i.e. mixed and varied) and vascularized tissues using coaxial and multi-nozzle systems [102]. Advantages of this technology include

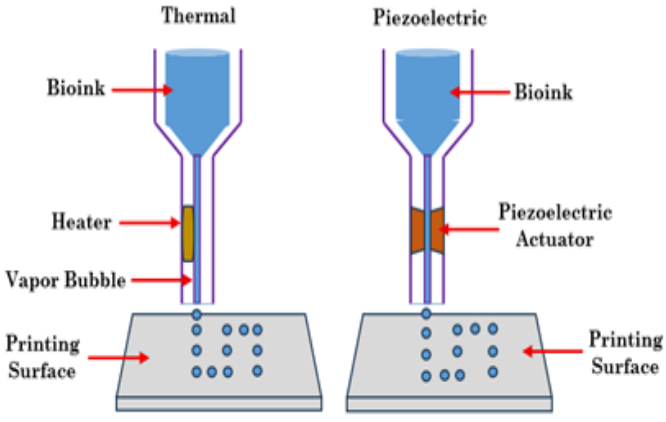

Figure 1: Fabrication Process of Inkjet Bioprinting

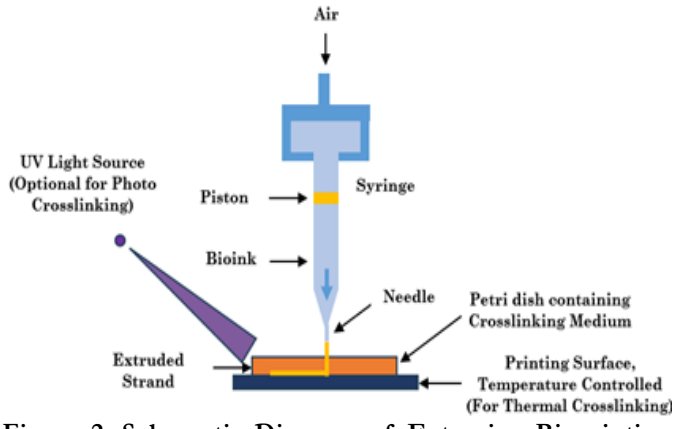

Figure 2: Schematic Diagram of Extrusion Bioprinting Approach

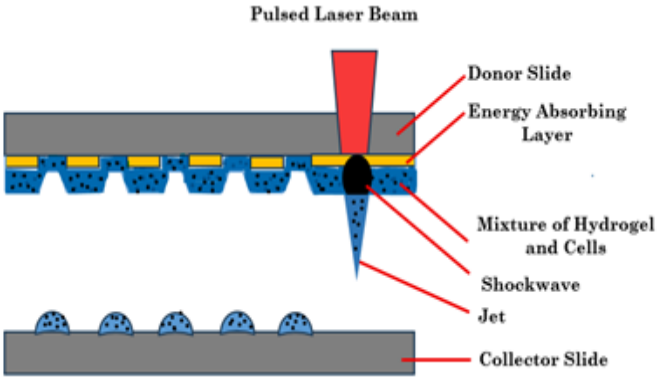

Figure 3: Basic Diagram of Laser-Assisted Bioprinting

a vast number of materials can be utilized as well as commercial scalability, large cell load carrying capacity (i.e., can create many cells/construct), and provide an opportunity to develop constructs that can withstand considerable mechanical forces (e.g. bone, cartilage, vascularized tissue, organoids, etc.). The limitations of this method are low resolution and possible damage to the cells from shear stress produced during extrusion. Due to the design and ease of use, as well as the potential for clinical application have made extrusion bioprinting the most widely used bioprinting technology for regenerative medicine today [103].

Laser-assisted bioprinting

Laser-assisted bioprinting (LAB) employs laser-induced forward transfer (LIFT) to create biofabricated tissue without using a nozzle (figure 3) [104]. By utilizing the energy released by laser pulses to generate a pressure wave in order to transfer bioink micro-droplets onto a target substrate, clogging of the printhead and shear forces that damage cells are reduced significantly, resulting in cell viability levels exceeding 95 percent. LAB is capable of producing printed structures with extremely high resolution (between 10 and 50 microns) and also has the potential to print multiple types and viscosities of bioinks (viscosity range 1 to 300 mPa·s) such as hydrogels, cell suspensions, inks based on extracellular matrix (ECM) components, protein-based, nanoparticle-based, and growth factor-based inks [105]. LAB is an ideal approach for developing tissue constructs used in vascular tissue engineering, skin and neural tissue fabrication, stem cell patterning, micro tissue construction, and biosensor production [106]. Unfortunately, LAB has some limitations, such as the fact that it is relatively expensive when compared to other biofabricating approaches, has low throughput, and has limited scalability when fabricating larger tissues. Although LAB provides exceptional precision and biological performance, translating newly fabricated LAB tissues into clinical applications continues to be somewhat limited-most applications involve either specialized tissue engineering or small-scale biofabrication of tissues suitable for transplantation [107].

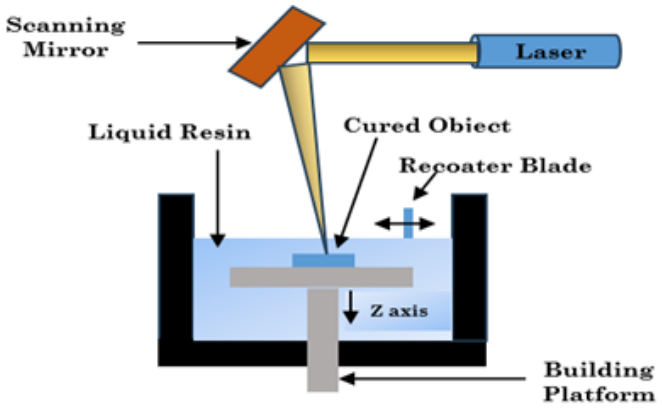

Figure 4: Detailed Construction of Stereolithography (SLA) Bioprinting

Stereolithography bioprinting

Bioprinting using stereolithography (SLA) is a way of producing 3D structures at high resolution by using light to selectively solidify photosensitive bioinks with UV light or visible light through photopolymerization. SLA can produce highly complex geometries with a high degree of accuracy (10-50micron resolution) using either a laser-based SLA or digital light processing (DLP) (figure 4) [108]. It can work with many different types of photocurable bioinks (GelMA, PEGDA, derivatives of hyaluronic acid, etc.) and has been shown to help maintain a 70-90% cell viability in most instances [109]. Traditional photoinitiators, such as Irgacure 2959, are limited by their requirement for ultraviolet (UV) light exposure, poor water solubility, and relatively low initiation efficiency. Recently, there have been some advancements made in the use of visible light (405 nm wavelength) and the addition of more cytocompatible photoinitiators (e.g., lithium phenyl-2,4,6-trimethylbenzoylphosphinate or LAP) to minimize phototoxicity encountered in bioprinting via SLA, leading to an increase in the number of cells that survive [110]. Examples of current applications of SLA bioprinting include use in organ-on-a-chip systems, microfluidic devices, vascular networks, soft tissue constructs, bone/cartilage engineering. Benefits of SLA bioprinting include: high precision, high-quality surface finish, and capability to create complex shapes. Disadvantages/restrictions that limit wider applications of SLA bioprinting are limited availability of photocurable bioinks, possible phototoxicity effects, and lack of mechanical strength of hydrogel bioprinted constructs. Continued innovation in biocompatible bioresins and visible light curing of bioresins is anticipated to improve the potential use of SLA bioprinting in clinical applications [111].

Volumetric bioprinting

A newer technology called volumetric bioprinting (VBP) is designed for biofabrication using light and tomographic light projection to photopolymerize (i.e., harden) photo-sensitive bioinks at the same time, thereby negating the need to build up structures via the traditional layering method [112]. This allows for the creation of cm-size, live-cell constructs around seconds, while providing a high percentage of viable cells (greater than 95%) with minimal mechanical stress [113]. In addition to providing excellent structural fidelity and allowing for complex geometric designs, VBP can produce large, vascularized tissue constructs. Recent studies have shown that VBP can generate perfusable vascular networks, bone and cartilage grafts, liver models, and cardiac patches [114]. Advantages include ultra-fast production time, preservation of cell function, and improved overall structural integrity of constructs. Current limitations of VBP are a relatively limited number of compatible bioinks, difficulties with controlling tissue heterogeneity, lack of standardization for manufacturing processes, and few in vivo studies validating the structures over a long time. Regardless, VBP is expected to be a future platform for fabricating tissues quickly and the engineering of organs [115].

Nanoscribe-based two-photon polymerization

Two-photon polymerization (2PP) is an advanced laser-based fabrication method for the creation of very fine-scale three-dimensional structures using a photosensitive medium. 2PP is based upon the use of a femtosecond pulsed near-infrared laser to simultaneously locally carry out two-photon absorption within the photoactive material. The highly localized nature of the 2PP process allows for the fabrication of highly complex and precise three-dimensional structures with submicron to nanometer resolution and without significantly damaging the surrounding material [116]. 2PP offers highly precise control over scaffold geometry, the ability to create biomimetic microenvironments comparable in structure to native extracellular matrix scaffolds, and the ability to create

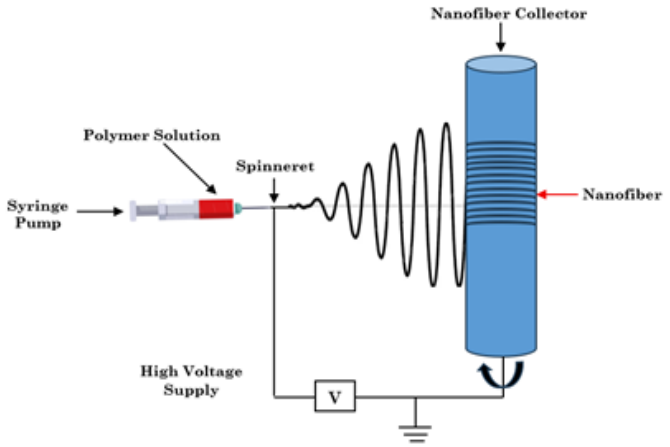

Figure 5: Schematic Representation of Electrospinning Biofabrication Process

microstructures and micro-based devices such as microvascular structures, neural and retinal scaffolds, stem cell instructive microarchitectures, tissue interfaces, and organ-on-chip components. In the near future (2023–2025), there is the potential for 2PP to be used for engineering biomimetic microvascular systems and highly specialized tissue models for use in regenerative medicine and biomedical research [117, 118]. As one of the most accurate biofabrication techniques currently available, 2PP was recently established as the standard for reproducing complex biological microenvironments. However, despite its high precision and resolution, widespread adoption of the 2PP technology has been limited by low throughput, high costs of equipment and operations, limited production volumes, and poor scalability of the fabrications to clinically relevant tissue dimensions [119, 120]. As a result, despite the fact that 2PP has extremely high accuracy and biologically relevant information, it is still mainly a research grade method of developing microscale tissue and modeling diseases and, therefore, is not widely applicable for the manufacture of large-scale transplantable tissue and organs [121].

Scaffold–based biofabrication

Electrospinning

Electrospinning is a biofabrication methodology that creates ultra-thin polymer fiber scaffolds to mimic the native extracellular matrix of the body. An electrically charged solution of polymer is delivered from a Taylor cone to construct the fibers through evaporation of solvent or cooling once ejected (figure 5) [122, 123]. Scaffolds produced using this method have a large surface area, adjustable pore size, and adjustable mechanical properties. Electrospinning works with many different types of polymers, including natural polymers like collagen, gelatin, chitosan, and silk fibroin. Electrospinning also works with synthetic polymers like PCL, PLA, and PEO. Advanced methods can be used to create composite scaffolds by adding living cells into the scaffold while creating the scaffold, such as cell electrospinning and coaxial electrospinning [124, 125]. Cell viability can be as high as 60–90% when using these techniques. The applications of electrospinning are extensive in the fields of bone tissue engineering, vascular grafts, skin regeneration, wound healing and nerve repair as they provide a suitable environment for cell attachment and promote tissue remodelling [126]. Nevertheless, the limitations of cellular infiltration and vascularisation when using dense fibre networks limits the ability to produce thick tissues. As a result, in order for electrospinning to be a clinically relevant tissue engineering application, it is often combined with bioprinting and other hybrid methods [127].

Solvent casting and particulate leaching

Solvent Casting and Particulate Leaching (SCPL) is an established means of creating porous, three-dimensional scaffolds. The process consists of dissolving biodegradable polymers (PLA, PGA, PLGA and PCL) in solvent, adding porogenic particles to produce interconnected pores, casting the mixture in molds, then leaching the porogens out of the scaffold by evaporating the solvent [128]. The result is a scaffold with a high degree of porosity and pores ranging from 100-500 µm, which can facilitate cellular adhesion, proliferation, transport of nutrients, and penetration of tissue into the scaffold (figure 6). SCPL has been successfully used for the creation of scaffolds for bone, cartilage, soft tissue and skin tissue engineering because it is simple to use, inexpensive and works well [129]. Unfortunately, SCPL does not provide much control over the formation of complex geometries, direct encapsulation of cells, or as high of precision as modern bioprinting techniques. Therefore, SCPL can be considered a viable method of producing simple porous scaffolds; however, it is not suitable for producing complex, biomimetic tissue constructs [130, 131].

Freeze-drying (lyophilization)

A scaffold-based biofabrication technique known as freeze-drying (lyophilisation) produces a porous three-dimensional structure through the sublimation of frozen solvent under a reduced pressure environment. In this instance, a polymer solution or hydrogel will be frozen – producing ice crystals, which are then sublimated leaving a well-connected porous scaffold with a pore size between 50 – 500 µm (figure 7) [132, 133]. Numerous natural polymers can be used with this technology including collagen, gelatin, chitosan, alginate, and silk fibroin. Low-

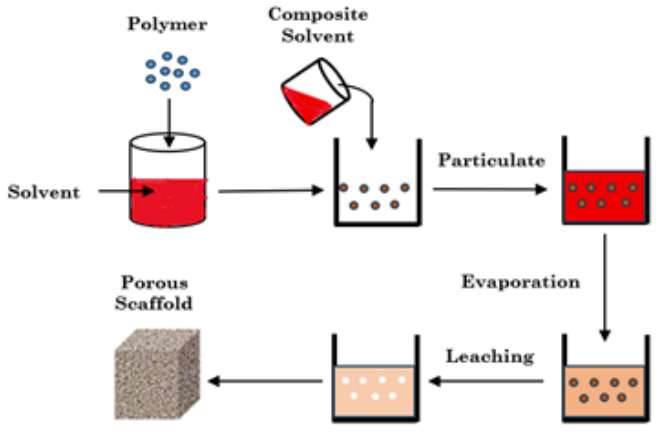

Figure 6: Step by step Illustration of Solvent Casting and Particulate Leaching Process

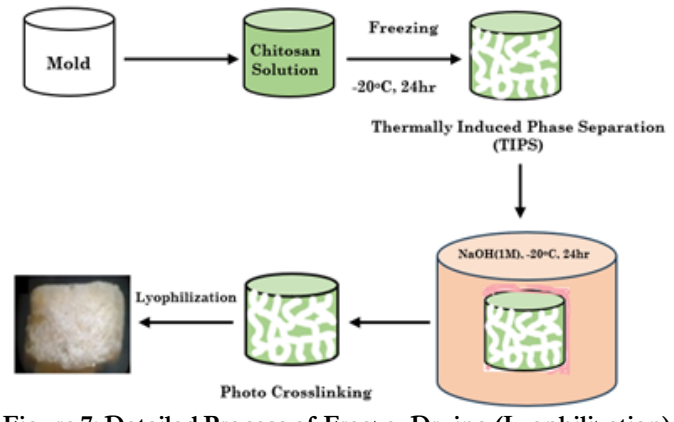

Figure 7: Detailed Process of Freeze- Drying (Lyophilization) Biofabrication

temperature processing of these polymer/hydrogel materials preserves the bioactivity of the biomolecules contained in them; therefore, these materials can be used to produce biocompatible scaffolds [134]. Biocompatible scaffolds not only serve as a way for cells to be anchored to the scaffold during the formation of new tissue, but also provide a channel through which nutrients can diffuse into/out of cells and provide space for the infiltration of new cells into the scaffold. For this reason, freeze dried scaffolds are widely employed as skin substitutes, in the regeneration of bone and cartilage, and in the repair of traumatic wounds [135]. However, in using a freeze-drying method, no direct encapsulation of cells can be done, the ability to design complex, functional architectures are restricted, and the scaffolds produced are not strongly mechanically. Therefore, freeze-drying scaffolds are commonly used in conjunction with other biofabrication techniques to produce scaffolds that are more durable and clinically relevant for constructing tissue [136-138].

Scaffold-free biofabrication

Cell sheet engineering

Cell sheet engineering (CSE) is an innovative scaffold-free and enzymatically-free biofabrication technique that enables the collection of intact biological cell layers along with their native extracellular matrix (ECM) components and intercellular junctions. This process is made possible through two primary techniques: (i) use of temperature responsive surfaces that contain poly(N-isopropylacrylamide) (PNIPAAm) as a substrate for cell growth at 37 degrees C (-98 % of resistive polymer) and detachment at ~20 degrees C; and (ii) temperature-controlled growth and detachment of cells allows for the collection of the complete biological cell layer with all associated ECM components and intercellular junctions [139-141]. CSE provides cellular level resolution (5-20 microns) through the use of multiple types of cells including cardiomyocytes, fibroblasts, endothelial cells, epithelial cells and stem cells, and enables the preservation of bioactivity, in part by preserving the ECM and intercellular signalling, resulting in >90% cell viability and enhanced biological function (figure 8) [142]. Currently, CSE is used for the fabrication of cardiac patches, corneal regeneration, skin substitutes, periodontal tissue repair, and vascular grafting procedures. Unfortunately, smaller tissue thicknesses, lack of vascularization and nutrient diffusion, and limited mechanical strength, generally limit the production of large-scale tissues. Thus, multilayer stacking methods and various methods for vascularization may be required prior to CSE being able to be utilised clinically as large-scale biological constructs [143,144].

Tissue spheroids assembly

As a scaffold-free biomanufacturing method, tissue spheroid assembly uses the inherent abilities of multi-cellular spheroids to organize themselves and join together to form new, functional tissue structures. Spheroids typically range in size from 200 to 500 micrometers in diameter. Spheroids can be manufactured through many different tissue spheroid assembly techniques including hanging-drop culture techniques, low-adhesion microwell techniques, spinner flask methods, and others [145]. There are many different ways to build tissue constructs from these spheroids including by using bioprinting, robotic positioning, magnetic guidance, and micromanipulation techniques (figure 9). Many different types of cells can be used in tissue spheroid assembly including stem cells, endothelial cells, chondrocytes, cardiomyocytes, hepatocytes, and fibroblasts, with consistently high rates (>90%) of cell viability while still maintaining native cell to cell adhesion properties [146,147]. This technology has been extensively used to manufacture a wide array of tissues for specific organ systems, e.g. vascularized tissues, cartilage tissue, cardiac patches, lung models, or microenvironments of tumour cells, providing a unique ability to produce highly biomimetic and organ functional tissues [148,149]. Limitations of this technology preventing clinical application include extended maturation time, limited vascularization ability, and difficulty in controlling the architecture at a large scale, and poor mechanical stability, necessitating use of bioreactors during maturation or using scaffold materials with improvements in mechanical properties.

AI-assisted biofabrication

Biofabrication enhances the process of designing and creating living tissue products using artificial intelligence (AI), machine learning (ML) and predictive modelling (PM) to improve the generating of biologically printed structures such as tissues [150]. With AI-enabled tools like deep learning, generative design, digital twin and real time Analytics, it is possible to enhance the designs of biografts through better scaffold design, bioink formulation, printing parameters and tissue development. AI can automate quality control, predict tissue maturation and monitor processes that can create patient specific products [151].

Recent advancements have shown successful use of AI-assisted biofabrication for improving scaffold designs, making bioinks, and automating processes, predicting the outcome using a digital twin, and controlling bioprinting in real time [152]. AI-assisted biofabrication is changing how the process of developing tissue engineering products is accomplished from manufacturing products based on geometry to manufacturing products based on data. This improves construct quality, reproducibility and personalization [153].

However, the limited number of large high-quality datasets, large computational resources, transparency of AI models, and regulatory validation all limit adoption of AI assisted biofabrication technologies. As such, it is anticipated that the extensive use of AI-assisted biofabrication technologies will be a major contributor to the future development of tissue engineering and patient specific regenerative medicine. Table 1 presents a summary of the machine learning optimized software platforms, version, and computational methodology used in the develop-

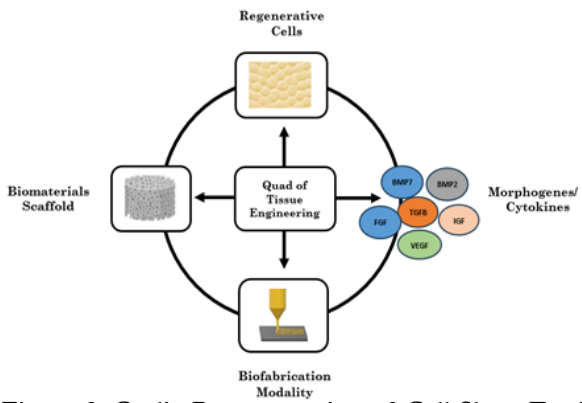

Figure 8: Cyclic Representation of Cell Sheet Engineering Process

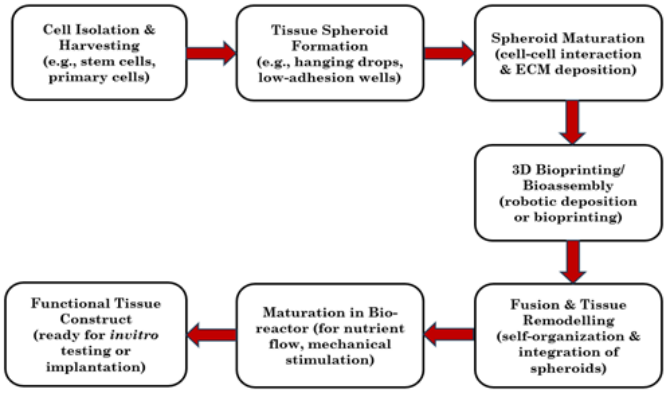

Figure 9: Block diagram highlighting the steps involved in Tissue Spheroid Assembly Fabrication

Table 1: Representative Software Platforms, Versions, and Computational Methodologies Used in AI-Assisted Biofabrication [156]

Category	Software Platform (Version)	Computational Methodology	Primary Function in Biofabrication
Medical Image Processing & Segmentation	Materialise Mimics Innovation Suite (v26–28)	AI-assisted image segmentation, 3D reconstruction, anatomical modeling	CT/MRI segmentation, patient-specific anatomical reconstruction, scaffold design
CAD & Generative Design	Autodesk Fusion 360 (2024–2025)	Generative design, topology optimization, parametric modeling	Patient-specific scaffold and implant design
Advanced Lattice Design	nTop Platform (v5.x)	Computational design, lattice optimization, biomimetic geometry modeling	Complex scaffold architecture and porous lattice generation
Deep Learning Framework	PyTorch (v2.x)	Convolutional Neural Networks (CNNs), Graph Neural Networks (GNNs), Deep Learning	Scaffold optimization, tissue prediction, process monitoring
Deep Learning Framework	TensorFlow (v2.x)	Machine Learning (ML), Deep Learning (DL), Predictive Analytics	Bioink formulation prediction and manufacturing optimization
Medical AI Framework	MONAI (v1.3–1.4)	AI-assisted segmentation, image classification, tissue modeling	Medical image analysis and tissue morphology prediction
Digital Twin Platforms	OpenTwins and custom Python-based Digital Twins	Digital twin modeling, predictive simulation, real-time process control	Virtual representation of tissues and biomanufacturing systems
Finite Element Modeling	COMSOL Multiphysics (v6.1–6.2)	Finite Element Analysis (FEA), multiphysics simulation	Mechanical and transport behavior of scaffolds
Biomechanical Simulation	Abaqus (2023–2025 releases)	FEA, stress-strain analysis, tissue mechanics modeling	Structural and biomechanical assessment of tissue constructs
Data Analytics & Automation	Python (v3.10–3.12), MATLAB (R2023b–R2025a)	Machine learning, Bayesian optimization, statistical modeling	Process optimization, data analysis, automated quality control
Real-Time Manufacturing Monitoring	LabVIEW (2023–2025 releases)	Real-time analytics, feedback control systems	Sensor integration and process monitoring
Cloud-Based AI Computing	AWS SageMaker, Microsoft Azure AI, Google Cloud AI	Distributed machine learning, cloud computing, predictive analytics	Large-scale model training and deployment

ment of scaffolds and biological constructs [154,155].

Biofabrication comprises a wide range of technologies like scaffold-based, scaffold-free, and bioprinting types, that integrate biological and engineering principles to develop biomimetic scaffolds, living tissues, and functional tissue constructs. Owing to different way of fabrication mechanisms, the resulting products exhibits distinct capabilities in terms of resolution, material compatibility, cell viability and performance under mechanical loads, and scalable, thus making these technologies suitable for applications such as organ-on-chip systems, disease models, tissue regeneration and organ engineering. Presently, there is no single biofabrication technology that meets all the criteria needed for successful clinical fabrication of tissues and organs, including precise architectural control, vascularization, mechanical integrity, ability to manufacture at scale, and regulatory compliance. Among the currently available technologies, extrusion bioprinting remains the most well-developed clinically mature platform while volumetric bioprinting, two-photon polymerization, and AI-assisted biofabrication are all emerging transformative technologies with the potential to redefine the landscape of the biofabrication industry.

Consequently, for future progress towards tissue/organ transplantation, hybrids of different biofabrication strategies that combine the large-scale extrusion bioprinting methods, the ultra-high accuracy of volumetric and two-photon technologies, and the predictive capabilities of artificial intelligence can ultimately lead to facilitate the clinical translation of functional, patient-specific, and transplantable tissues and organs. Several biofabrication processes are compared according to a number of factors including principles, resolution, cell viability, compatibility with materials, and their potential biological effects (table 2).

Clinical translation and clinical outcomes of biofabrication technologies in recent years (2023–2025)

Although most biofabrication technologies remain in the preclinical stage, notable translational progress has been reported between 2023 and 2025. Extrusion bioprinting has demonstrated promising outcomes in skin and osteochondral tissue regeneration, while cell sheet engineering has shown encouraging clinical results in corneal and cardiac repair. Electrospun scaffolds continue to exhibit the highest level of clinical adoption in wound healing and tissue regeneration applications. In contrast, emerging technologies such as volumetric bioprinting, two-photon polymerization, and AI-assisted biofabrication have achieved significant preclinical milestones, including the fabrication of perfusable vascular networks, patient-specific tissue constructs, and AI-optimized biomimetic scaffolds. Collectively, these advances highlight the ongoing transition of biofabrication from experimental research toward clinical translation, with electrospinning, cell sheet engineering, and extrusion bioprinting currently demonstrating the highest translational readiness.

Applications of Biofabrication in Tissue and Organ Engineering

One of the significant contributions of biofabrication is the progression of tissue as well as organ engineering [158]. It can provide accurate and customizable methods for regeneration, replacement, or the creation of 3D models of the damaged or diseased biological structures [159]. Through the usage of biomaterials, living cells, and state-of-the-art fabrication technologies, biofabrication accomplishes the design of intricate, functional tissues that are made especially for a single patient's requirements [160]. Some of the major applications are:

Table 2: Comparative Analysis of Major Biofabrication Technologies for Tissue and Organ Engineering [157]

Technique	Principle	Resolution (μm)	Cell Viability	Bioink/ Material Compatibility	Suitable Tissue/ Organs	Advantages	Drawbacks	Clinical Readiness Level
Inkjet Bioprinting	Droplet-based (thermal/ piezoelectric)	20–100	High (80-95%)	Low-viscosity hydrogels, cell suspensions	Skin, cartilage, vascular tissue	High speed, low cost, precise droplet placement	Limited viscosity, nozzle clogging, heat damage	Preclinical validation; emerging skin bioprinting applications
Extrusion Bioprinting	Continuous deposition (pneumatic, piston, screw)	100–500	Moderate to high (80-90%)	High-viscosity hydrogels, cell-laden pastes	Bone, cartilage, skin, heart	Wide material range, high cell density, scalable	Lower resolution, shear stress, slower	Highest translational maturity; early clinical studies
Laser-Assisted Bioprinting (LAB)	Laser-induced forward transfer (LIFT)	10–50	High (>95%)	Viscous materials, cells, nanoparticles	Skin, bone, cartilage, nerve	High resolution, nozzle-free, precise	Expensive, complex, possible thermal damage	Advanced preclinical; limited scalability
SLA Bioprinting	Photo-polymerization (UV/ Visible light)	20–50	High (70-90%)	Photocurable hydrogels (PEGDA, GelMA)	Cartilage, vascular, bone	High resolution, smooth surface, complex structures	Limited bioinks, UV/ light affects viability	Preclinical vascular and cartilage constructs
Volumetric Bioprinting (VBP)	Tomographic light-induced bioink polymerization	20–100	Very High (>95%)	Photocurable hydrogels (GelMA, PEGDA, bioresins)	Vascularized tissues, cartilage, bone, liver, heart	Ultra-fast, high-viability, artifact-free complex fabrication	Limited bioink selection, expensive equipment	Advanced preclinical; high future potential
Nanoscribe-Based Two-Photon Polymerization (2PP)	Femtosecond laser-induced two-photon polymerization	0.1–1	High (>90%)	Photocurable hydrogels and bioresins	Microvascular, neural, retinal, organ-on-chip	Nanoscale precision and biomimetic architectures	Low throughput and limited scalability	Research and early preclinical stage
Electro-spinning	Electric field draws polymer jets into nanofibers	50–500	60-90%	Natural/ synthetic polymers (PCL, PLA, collagen)	Skin, vascular grafts, nerve	Mimics ECM, high surface area, scalable	Limited 3D, post-seeding, poor mechanical strength	Several commercial and clinical products available
Solvent Casting & Particulate Leaching	Polymer + porogen → solvent removal → porous scaffold	100–500 (pore)	Low	Biodegradable polymers (PLGA, PCL)	Bone, cartilage, skin	Simple, cost-effective, tunable porosity	Toxic solvent risk, weak mechanics, no direct cell use	Established scaffold fabrication method
Freeze-Drying (Lyophilization)	Freeze then sublimate solvent → porous scaffold	50–500 (pore)	Low	Collagen, gelatin, chitosan, synthetics	Skin, bone, cartilage	Highly porous, ECM-like, good nutrient flow	Brittle, weak, time-consuming	Widely used in commercial scaffolds
Cell Sheet Engineering	Cell sheets detach preserving ECM & junctions	5-20 (thickness)	Very High (>95%)	Pure cell sheets	Skin, cardiac, cornea	No foreign materials, strong cell-cell interactions	Fragile, limited 3D, size constraints	Early clinical use in corneal and cardiac regeneration
Tissue Spheroids Assembly	Cell spheroids self-assemble into tissues	100–500 (spheroid)	Very High (>90%)	Pure cells, spheroids	Liver, cardiac, vascular	Scaffold-free, high density, biomimetic	Slow fusion, requires bioreactors, long maturation	Early-stage with limited translation
AI-Assisted Biofabrication	Machine-learning-guided scaffold and bioink optimization	Resolution determined by printing platform	Improves cell viability and construct fidelity	Supports hydrogel, polymer, and composite bioinks	Patient-specific tissues, organoids, organs-on-chip	Predictive design, process optimization, personalized fabrication	Large datasets and computational demands	Emerging technology; no independent clinical deployment

a) Skin tissue engineering: Biofabrication plays a major role in the development of full-thickness skin substitutes that include both epidermal and dermal layers [161]. Such constructs find great use in the treatment of burns, chronic wounds, and diabetic ulcers. Through bioprinting, it is possible to accurately localize keratinocytes, fibroblasts, and melanocytes together with ECM components, thus mimicking the structure and function of the original skin [162, 163].

b) Cartilage and bone regeneration: Utilizing biofabrication enables the production of flexible cartilage constructs that exhibit geometry and mechanical properties and load-bearing bone grafts both through scaffold and scaffold-free approaches. Hydrogel or composite bioinks often contain either chondrocytes, MSCs or osteoblasts, to promote tissue-specific development [164,165]. These engineered tissues are applied in joint regeneration, maxillofacial reconstruction, and orthopaedic repair.

Table 3: Clinical Readiness and Translational Milestones in Biofabrication Technologies

Technology	Technology Readiness Level (TRL)	Key Translational Milestones Achieved	Clinical/Translational Outcomes
Inkjet Bioprinting	5–7	Precise droplet deposition; scalable skin and corneal bioprinting.	Multilayered skin substitutes, corneal models, and drug-screening platforms.
Extrusion Bioprinting	6–8	Vascularized tissue constructs; patient-specific bone and cartilage grafts.	Large-animal validation of bone, cartilage, and osteochondral constructs.
Laser-Assisted Bioprinting (LAB)	5–7	High-resolution cell patterning for vascular and corneal tissues.	>90% cell viability and enhanced vascularization.
SLA Bioprinting	5–7	Cytocompatible photocurable bioinks and microvascularized constructs.	Complex tissue architectures with excellent geometric fidelity.
Volumetric Bioprinting	4–6	Seconds-scale bioprinting of vascularized tissue constructs.	Ultrafast bioprinting with enhanced cell survival.
Nanoscribe-Based Two-Photon Polymerization (2PP)	3–5	Submicron scaffold fabrication of vascular & neural architectures and organ-on-chip integration.	Biomimetic microenvironments for stem-cell differentiation and disease modeling.
Electrospinning	7–9	Commercial wound dressings and regenerative membranes.	Clinically approved wound dressing, vascular grafts & membranes
Solvent Casting & Particulate Leaching (SCPL)	7–8	Commercial porous scaffold and biodegradable implant manufacturing.	FDA/CE-approved porous scaffolds for bone tissue and cartilage regeneration.
Freeze-Drying (Lyophilization)	7–8	Biopolymer sponge scaffolds and regenerative wound care matrices.	Porous scaffolds supporting cell infiltration, angiogenesis and tissue integration.
Cell Sheet Engineering	7–9	Clinical studies in corneal, periodontal, esophageal, cardiac, and cartilage repair.	Scaffold-free tissue transplantation with reduced inflammation and improved functional recovery
Tissue Spheroid Bioassembly	4–6	Spheroid-based bioprinting; organoid fusion strategies; scaffold-free tissue maturation systems	Improved cell-cell interactions, ECM formation and tissue biomimicry.
AI-Assisted Bioprinting	3–6	AI-driven bioink optimization, real time print monitoring and process control.	Enhanced bioprint accuracy and predictive quality assurance.

c) Vascular tissue engineering: Creating vascularised tissues is necessary for synthetic organs to survive and integrate [166]. Biofabrication can be used to develop vascular grafts, blood vessels, and capillary networks using endothelial cells and perfusable bioinks [167]. Coaxial bioprinting is one method that allows for the fabrication of multi-layered, physiologically relevant vascular conduits in organ perfusion systems and cardiovascular bypass applications [168].

d) Cardiac tissue engineering: Myocardial repair post-heart attack is achieved with biofabricated cardiac patches and architectures made up of cardiomyocytes, fibroblasts, and vascular cells [169]. The capacity of these synthetic tissues to mimic the heart's electrical and contractile properties may lead to therapeutics for congenital heart defects and heart failure [170].

e) Liver and kidney tissue models: Biofabrication has generated miniaturised liver lobules and nephron-like structures for preclinical and therapeutic applications [171]. Tissue constructs are used to conduct drug metabolism studies, toxicological testing, and modelling of chronic liver or kidney diseases [172]. While it is still difficult to completely replace organs, these models are useful for the study of diseases and drug development.

f) Neural tissue and spinal cord repair: Biofabricated neural scaffolds provide aligned topographies that promote the integration of neuronal and glial cells and axon regrowth [173]. Applications of neural scaffolding include brain tissue models for neurodegeneration, peripheral nerve regeneration, and spinal cord repair [174].

g) Organ-on-chip systems: Organ-on-chip technology simulates physiological organ function in a controlled environment through a combination of microfluidics and biofabrication [175]. These systems are used in the areas of drug development, personalized medicine, and disease modelling, providing reduced reliance on animal testing and greater speed and precision in biomedical research [176,177].

h) Whole organ engineering (emerging): Though still in its early stages, research has begun into biofabrication, which involves vascularised tissue blocks, decellularized scaffolds, and multi-material printing, for the engineering of complex organs, such as the heart, pancreas, and lung [178,179]. Advances in vascularization, innervation, and maturation in a bioreactor may enable the construction of transplantable organs in the future [180].

Significant Challenges

Several fundamental problems challenges limit clinical translation and scalability of engineered tissues and organs, even with major strides being made in biofabrication. Overcoming these challenges will be essential to generate biofabricated constructs that are functional and can be transplanted into patients in the biological, technological, and regulatory spheres.

i. Vascularization of thick tissues: Creating functional vascular and neuronal networks inside thick constructs is one of the most enduring problems in tissue fabrication. Insufficient innervation restricts physiological processes including muscle contraction and sensory transduction, whereas tissues larger than 200 μm suffer from hypoxia and food starvation in the absence of vasculature, which results in cell death. Sacrificial templating lacks natural capillary complexity and necessitates extra endothelialization, but it allows for quick perfusion through predetermined channels with good geometric control. The self-assembly of organoids creates microvascular networks that look like those found in living organisms, but the quality of the building is inconsistent and the speed of how they develop is slow and they cannot be made on a larger scale. Therefore, the hybrid method of creating both self-assembled micro-networks and templated macrovasculature is the best route to take.

ii. Cell acquisition and differentiation strategies: A major limitation is that there are no cells which have significant therapeutic relevance that are patient-specific and functionally mature. A variety of biofabrication methods

will involve using stem cells (commonly referred to as mesenchymal or induced pluripotent stem cells) with the expectation that the stem cells will be able to differentiate to a specific and defined type of cell (such as a hepatocyte or cardiomyocytes). The challenge is ensuring a construct that is uniform in its differentiation, matures those differentiated cells and provides functional stability.

iii. Assessment of material–cell compatibility: Biomaterial selection is important to encourage cell adhesion, proliferation, and function. Nevertheless, many synthetic or semi-synthetic biomaterials are considered to promote good printability but do not provide biological cues for optimal cell contact. While natural biomaterials are typically relatively weak mechanically, they can help with cell survival. Furthermore, it may be difficult to have a sufficient compromise between biodegradability, biocompatibility, and mechanical properties. Lastly, biomaterials should not promote bone remodelling or an adverse immunological response.

iv. Mechanical integrity and structural stability: Many biofabricated tissues, mainly the soft hydrogels that are called bioinks, lack enough mechanical strength, or load bearing capacity; therefore, they can't be functionally used in applications whereby they would be inserted within the human body (e.g., heart, musculoskeletal system and load bearing organs). The main engineering challenge is to build structures that replicate both the mechanical properties and biological function of real tissues.

v. Tissue architecture complexity and cellular diversity: Replicating the intricate 3-dimensional structure and arrangement of cells, ECM, and biochemical gradients presents technical difficulties. High-resolution bioprinting coupled with carefully controlled placement of cells is required for achieving cell-type-specific heterogeneous distributions within tissues (i.e., layered arrangements of epithelial, stromal, and vascular cells in tissue).

vi. Challenges and limitations of bioink: The creation of bioinks that are biocompatible, printable, mechanically stable, and can facilitate cellular function is still developing. Commonly available bioinks require tradeoffs between printability and biological performance limiting their application to a specific type of tissue.

vii. Scalability and process standardization: Translating lab-scale components into clinically relevant sizes, while preserving quality, repeatability and utility, is one of the biggest challenges. Commercialisation and broader acceptance will also be inhibited by a lack of standardised guidelines, legal requirements, and quality control to support biofabrication methods.

viii. Tissue integration and immunological compatibility: Ensuring the last long-term integration of the synthesized tissue with host tissue is difficult and scaffolding systems. Furthermore, diligence will be needed in material selection and immunomodulatory methods are essential to prevent immune rejection, particularly in cases involving allogenic or xenogenic cell sources.

ix. Resolution-viability interdependence: Bioprinting must ensure high resolution to mimic the approximately 150um structure of several native tissues, capillaries, ducts and clusters in cells. However, with increased resolution, typically, either increased crosslinking speeds or smaller nozzles are needed, which tends to increase shear strain, increase temperature, or increase time, all of which can degrade cell viability. This trade-off significantly limits the ability to optimize the printing parameters to achieve high levels of structural fidelity and biological functionality.

x. Biological maturation of fabricated constructs: Bioreactor-based conditioning (through mechanical, electrical and biochemical stimulation) is often necessary for biofabricated tissues to achieve functional maturation. More research is currently being done to develop low cost and tissue-specific maturation methods that promote innervation, vascularization and functionality.

xi. Ethical and regulatory challenges:. The use of genetically-modified materials, human derived stem cells, and biomaterials from animals poses safety, informed consent, immunogenicity and long-term therapeutic concerns. Furthermore, biofabricated tissue can be classified as a biologic, medical device, combination product, or advanced therapeutic pharmacological product meaning regulation of these biofabricated tissues is still fragmented among the various regulatory authorities. The FDA's RMAT (Regenerative Medicine Advanced Therapy) designation is a US example that is intended to accelerate the development of regenerative medicine products while ensuring their safety and effectiveness under the 21st Century Cures Act and the MATURE framework. However, developers face uncertainty since complex biofabricated tissue and organs may not always fit into any of the current regulatory classifications. The diversity of the regulatory approaches taken by various regulatory authorities such as the FDA, EMA and PMDA makes international translation of biofabricated medicine more challenging. There is an increased focus on regulatory requirements for more flexible, harmonized frameworks, particularly due to the ethical uneasiness of some of the applications of biofabrication such as organ duplication and human-animal chimeras.

Future Outlook: Toward Biofabricated Organs-on-Demand

Biofabrication is progressing rapidly toward industrial applications related to more responsive, smart, and clinically relevant tissue engineering technologies. In addition to these anticipated advancements, there will also be opportunities to increase the accuracy, utility, and clinical relevance of biofabricated products. Following are important new directions:

a) 4D bioprinting and smart biomaterials: 4D bioprinting extends 3D bioprinting by incorporating the dimension of time, allowing printed structures to change shape, properties, or functionality in response to an external stimulus (such as temperature, pH, light, or magnetic field). This is achieved by using smart biomaterials that are programmable and responsive to stimuli. Smart biomaterials mimic dynamic physiological environments and then respond to biologically specific changes once implanted, enabling the use of self-morphing tissues, adaptive implants, and targeted drug delivery systems that respond to stimuli characteristic of disease.

b) Artificial intelligence and machine learning integration: Machine Learning (ML) and artificial intelligence (AI) is changing the reliability, automation, and optimization of biofabrication processes. Using AI, Biofabrication is able to create complex tissue patterns, predict cell behaviour, monitor continuous printing, and modify bioprinting parameters in real-time. The use of sensor data and computer vision allows for Quality Control of the printing process by detecting defects such as nozzle clogging, filament breakage, irregularly sized droplets, and misaligned layers. The use of these technologies reduces material waste and improves the quality of the final product as well as the viability of the cells used for fabrication. ML algorithms can also be used to analyze biological, mechanical, and imaging data to optimize performance, develop predictive models, and create customized, repeatable biofabrication processes. The following table shows the name of software, version and computational methodologies used in AI assisted biofabrication.

c) Organs-on-chips and microfluidics coupling: The confluence of biofabrication, microfluidics and organs-on-chips technologies allow for the development of miniature, functional tissue models that mimic organ-level physiology. Collectively, they represent powerful technologies for toxicity test, drug screening, and disease modelling by allowing for controlled perfusion, continuous monitoring, and integration of multi-tissues. Ultimately, combination of 3D bioprinted tissues and microfluidic chip technology can lead to fully integrated, vascularised, and innervated organ models on demand.

d) In situ bioprinting and clinical translation: In situ bioprinting, the action of printing bioinks and cells directly on or within a patient is changing the paradigm towards more personalized regenerative therapeutics. In situ bioprinting sets the stage for precision, patient-specific tissue repair in the operative theatre by creating a replacement or alternative to prefabricated implants. In situ bioprinting could enable real-time tissue repair in orthopaedic operative procedures, burns and trauma, with a significant acceleration of clinical transmission once portable and robotic bioprinters are developed.

e) Standardization and scalability: A major hurdle in clinical translation is heterogeneity of materials, printing processes, and quality controls. Future efforts will focus on bioinks that are regulatory compliant, bioprinters that are scalable, and protocols that are GMP (Good Manufacturing Practice) compliant. High-throughput manufacturing, automation, and batch-to-batch uniformity will be necessary to transition biofabricated

products from the laboratory to routine clinical use.

Conclusion

Biofabrication is already leading the world in regenerative medicine providing accurate, flexible, and scalable techniques for creating functional tissues and organs. As a complementary approach to the current transplantation paradigm, biofabrication can address the limitations of compatibility, donor dependence, and immune rejection, by merging biological principles with advanced engineering. In-depth analyses of the fundamentals, uses, and drawbacks of several important biofabrication processes such as bioprinting, scaffold-based, and scaffold-free approaches—have been provided in this work. The creation of physiologically functional constructions with therapeutic relevance depends critically on the strategic application of biomaterials, the creation of sophisticated bioinks, and the integration of dynamic bioreactors. Although there has been significant progress in the field, vascularization, complex tissue architecture, mechanical support, and regulation, remain major problems. Future advances for biofabrication will come through progress in in situ bioprinting, smart materials, artificial intelligence, and 4D-printing, which all could lead to a little more patient specific responsive and adaptive therapies. Interdisciplinary collaboration, ethical anticipation, and high-quality standardization will all help to advance the pathway for clinical translation. In conclusion, biofabrication has promise for tissue and organ engineering through the creation of living constructs with natural function. Through ongoing searching, innovation, collaboration across sector boundaries we will begin to realize the potential of biofabrication, and its path from the lab to the clinic, ultimately affecting the future of health care.

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