

3D Bioprinting: Emerging Paradigms in Repair, Regeneration, and Microarchitectural Remodelling

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In the field of regenerative medicine three-dimensional (3D) bioprinting emerging as transformative technology focusing on science of biomaterials, cell development, and additive manufacturing to fabricate functional tissues and organs. Wide range of combinations as bioinks composed of living cells, biomaterials, and growth factors, used to design the precise, layer-by-layer deposition mimics the native tissue architecture. Although the recent advances in in situ bioprinting have expanded applications in wound healing and localized repair. However, clinical translation remains limited by challenges such as inadequate vascularization, mechanical instability, bioink variability, and scalability. Ongoing innovations—including multi-material printing, dynamic crosslinking, computer-aided design, and artificial intelligence integration—are enhancing construct fidelity and functionality. This review highlights current progress, biomedical applications, and future directions, with emphasis on strategies to achieve clinically viable, patient-specific tissue and organ replacements.

Keywords: 3D bioprinting, bioink, regenerative medicine, tissue engineering, organ fabrication

Introduction

Over the past few decades, tissue engineering and regenerative medicine (TERM) have emerged as dynamic, interdisciplinary fields, making significant contributions to the development of engineered constructs for a variety of tissues, including skin, bone, cartilage, liver, heart, neural, and vascular systems [1,2]. The clinical demand for such constructs is substantial, driven by a global shortage of donor organs and the limitations associated with conventional grafts and implants. Reflecting this need, the bioengineered graft and implant market is projected to grow at a compound annual growth rate (CAGR) of 14.3% between 2025 and 2030, underscoring both the biomedical and commercial potential of these technologies.

Within this evolving landscape, 3D bioprinting has emerged as a transformative technology, enabling precise, layer-by-layer deposition of cells, biomaterials, and bioactive molecules to fabricate complex, functional tissues. This approach integrates principles of additive manufacturing, biomaterials science, and cellular biology to closely mimic the structural and functional organization of native tissues. The origins of 3D bioprinting can be

traced to foundational advances in additive manufacturing. In 1984, Charles Hull patented stereolithography, establishing the foundation for rapid prototyping and additive manufacturing [3,4]. The first commercial 3D printer, the SLA-250, was introduced in 1988, followed by the coining of the term “3D printer” by Emmanuel Sachs in the 1990s, which enabled fabrication of diverse materials including plastics, metals, and ceramics [5]. By the mid-1990s, additive manufacturing transitioned into the biomedical domain, exemplified by the first applications of biomaterials in tissue regeneration. Between 2001 and 2004, advances such as bladder-shaped polymer scaffolds seeded with donor cells, high-viability inkjet-based bioprinting, and scaffold-free tissue printing marked critical milestones in the field [6,7].

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The introduction of bioprinters like the Novogen MMX in 2009 accelerated commercialization and clinical translation efforts [8,9]. Over the following decade, bioprinting achieved major breakthroughs, including scaffold-free vascular constructs (2009), bioprinted skin and hepatocyte-laden collagen matrices (2010), cartilage and liver tissues (2012), integration of vascularized constructs with circulatory systems (2014), and the fabrication of bioprinted heart valves (2016). Currently, the most widely produced tissues include vascular, cardiac, hepatic, osteogenic, and dermal constructs, highlighting the versatility and growing clinical relevance of 3D bioprinting [10,11].

Contemporary bioprinting research continues to focus on optimizing printing methodologies rather than large-scale commercialization. Three principal modalities—laser-assisted, inkjet-based, and extrusion-based printing—have been developed, each requiring tailored bioinks to balance cell viability, mechanical stability, and print fidelity [12]. Laser-assisted bioprinting offers high precision but poses thermal risks to sensitive cells, whereas inkjet and extrusion approaches provide low shear stress environments compatible with diverse cell types, making them suitable for clinical applications. Experimental applications such as the bioprinted bionic pancreas illustrate both the potential and current challenges of translating complex soft tissues into clinical use. Bioprinting enables precise spatial placement of pancreatic islets within porous scaffolds, improving nutrient diffusion, vascularization, and cell–cell interactions [13]. However, significant challenges remain, including development of ECM-mimicking bioinks, maintaining mechanical stability, and overcoming printer resolution limitations (~100 µm) that impede vascular integration [14]. While tissues like skin, liver, and cardiac constructs have advanced toward clinical implementation, the bionic pancreas remains at an early stage, with success contingent upon improvements in bioink design, vascularization strategies, and high-resolution printing technologies.

In conclusion, 3D bioprinting represents a paradigm shift in TERM, offering patient-specific, scalable, and functional tissue constructs. Continued advances in imaging, bioink engineering, and automated bioprinting platforms are essential to translate laboratory innovations into clinically viable solutions, addressing organ shortages and redefining therapeutic strategies in regenerative medicine [15].

Table 1: Advances of Bioprinting in organ/tissue culture and their impact regeneration/repair

Skin substitutes	Developed for wound healing and the study of skin infection pathophysiology
Blood vessels	Emphasizing geometric optimization, flow dynamics, and molecular diffusion
Heart valves	Utilizing hydrogels and valve interstitial cells (VICs) for high-efficiency constructs
Bone tissue	Focusing on scaffold architecture, pore geometry, cellular viability, and mechanical integrity
Liver tissue	Drug testing and toxicological screening of chemical compounds;

State of the Art: Designing and Printing Strategies:

The recent advancement of the Modern 3D bioprinting integrates patient-specific design, optimized biomaterials, and biologically relevant printing techniques. computer-aided design (CAD) and medical imaging (CT, MRI) generate blueprints for constructs, with soft tissue designs requiring calibration for post-printing fusion and shrinkage [16]. Key printing modalities include: *Inkjet*: High resolution and speed; limited to low-viscosity bioinks; *Extrusion*: Supports viscous hydrogels and multi-materials; widely used but may reduce cell viability due to shear stress; *Laser-assisted*: Enables precise deposition of dense cell suspensions; risk of thermal damage [17]. Emerging techniques like freeform reversible embedding allow printing of soft inks within sacrificial baths. Bioprinting strategies are either: Scaffold-based: Focused on mechanical integrity and nutrient diffusion, and Scaffold-free: Use fusogenic cell spheroids to mimic natural tissue fusion [18].

In situ bioprinting enables direct deposition at wound sites, demonstrated in skin regeneration using handheld or robotic systems. Post-processing is crucial for maintaining the viability of thick, bioprinted tissues. This stage relies heavily on perfusion bioreactors and needle-based irrigation systems, which temporarily supply nutrients and oxygen until a functional vascular network develops. Advanced systems are being designed with detachable porous needles and pressure-controlled drip mechanisms to support perfusion, enable sterile handling, and provide dynamic biomechanical conditioning that accelerates tissue maturation [19]. On the commercial front, platforms such as the BioAssembly Tool (Sciperio/nScript Inc., USA) and Bioplotter (Envisiontech) have advanced

clinical translation by enabling 3D bioprinting of living tissues using combinations of cells and hydrogels [20]. Collaborations with companies like Neatco (Canada) have also led to the development of simple robotic bioprinters. A key direction in the field is the rise of personal fabricators—desktop rapid prototyping devices akin to personal computers [21]. A group at Cornell University designed one of the first affordable, easy-to-assemble systems, demonstrating its application in cartilage tissue engineering. With mass production, costs could fall to as low as US\$250, potentially democratizing access to organ printing technologies.

Despite progress, major challenges remain, particularly in achieving vascularization, reducing bioink costs, and reaching sub-100 μm resolution needed for complex organ fabrication. Thus, for addressing these issues will require continued innovation in bioreactor design, biofabrication systems, and mechanical engineering integration (Fig.1).

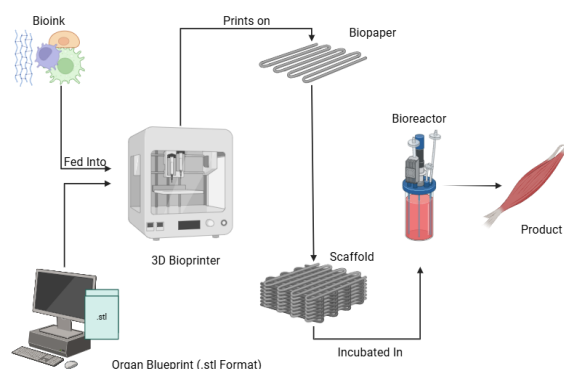


Figure 1 Schematic representation 3D Bioprinting procedure.

• Organ Blueprint and Biopaper in 3D Organ Printing

The concept of an “organ blueprint” represents a software-based computer program that provides detailed instructions for the layer-by-layer deposition of biological components via a dispensing device, based on a CAD file. In practice, this often involves bioprinter-compatible stereolithography (STL) files, which guide the precise architecture of the printed construct [9,22]. A major challenge in blueprint design is the post-processing behavior of soft tissues, which undergo fusion, retraction, compaction, and remodeling after printing. Consequently, organ blueprints typically require scaling adjustments and shape modifications to compensate for these changes, ensuring that the final matured construct conforms to the desired anatomical dimensions. To address this,

tissue compaction, retraction, and remodeling coefficients must be empirically determined and integrated into CAD models. Unlike solid scaffolds, which can be directly modeled from 3D clinical imaging data, soft-tissue blueprints cannot be automatically generated due to the inherent dynamic remodeling of living tissues during maturation [23].

A second critical element in organ printing is biopaper, defined as processable, biomimetic, and tissue-fusion-permissive hydrogels specifically engineered to serve as extracellular matrices during the bioprinting process. Biopaper provides the necessary structural support, cell adhesion sites, and biochemical cues to facilitate tissue formation. A recent comprehensive review highlighted the role of hydrogels as extracellular matrices for organ printing, underscoring their importance in supporting cell viability and function [24]. The development of functionalized hydrogels, such as biomimetic photosensitive matrices incorporating RGD peptides, has significantly improved the survival and integration of printed tissue constructs. The design and synthesis of processable, biomimetic hydrogels (biopaper) thus remain one of the most critical and challenging aspects of organ-printing technology [25]. This area offers a unique opportunity for chemical engineers to apply their expertise in polymer chemistry, biomaterials design, and photopolymerization to create novel extracellular matrix analogs that can both mimic native tissue environments and withstand the mechanical and biological demands of bioprinting.

• Bio-inks

Bioinks are central to the success of 3D bioprinting, combining cells, biomaterials, and biochemical factors to create functional constructs. An ideal bioink must achieve a balance between printability, biocompatibility, and mechanical integrity while preserving cell viability. The architecture of the engineered graft is largely dictated by the choice of bioink, which directly influences tissue fusion, maturation, and the biomimetic fidelity of the printed organ. Inspired by embryonic tissue fusion, organ printing often relies on self-assembled spheroids with viscoelastic and fusogenic properties [26]. Although small-scale spheroid production using methods such as shaking, centrifugation, extrusion, or non-adhesive substrates is well established, scaling this process for standardized robotic dispensing remains a significant challenge, alongside the design of bioink cartridges [11].

Polymeric Bioinks. Wide range of biopolymers used to print the 3D microarchitecture to mimic the native tissue. Natural polymers such as collagen, gelatin,

alginate, fibrin, and hyaluronic acid provide extracellular matrix (ECM)-like cues that support adhesion and proliferation. Gelatin methacryloyl (GelMA), a photopolymerizable hydrogel, has been widely used in cardiac and neural constructs, while fibrin and collagen promote angiogenesis and neurogenesis in skin and nerve regeneration [14]. However, their weak mechanical stability necessitates reinforcement. Synthetic polymers

such as polyethylene glycol (PEG), polycaprolactone (PCL), and polylactic acid (PLA) offer tunable mechanics and degradation rates but lack bioactivity unless functionalized with peptides such as RGD groups [27].

Composite Bioinks. Composite systems combine natural and synthetic polymers or inorganic fillers to enhance both biofunctionality and mechanical stability. Examples include alginate–collagen blends for improved fidelity and adhesion, and hydrogel–ceramic composites such as hydroxyapatite and bioactive glass for osteoconductive applications. Recent advances such as nanoengineered ionic–covalent entanglement (NICE) bioinks have produced resilient bone-like constructs with enhanced mechanical strength [28].

Cell-Seeded Bioinks. Cell-seeded formulations incorporate living cells or spheroids to promote tissue-specific maturation. MSCs, iPSCs, and differentiated

cells such as hepatocytes or cardiomyocytes are widely applied. Co-printing iPSC-derived cardiomyocytes with endothelial cells has yielded vascularized cardiac tissues [29]. For skin bioprinting, keratinocytes remain a major cell source due to their proliferative capacity and resistance to senescence, though challenges such as long expansion times and hypertrophic scarring persist [30].

Hybrid Bioinks. Hybrid formulations integrate polymers, cells, and functional additives such as growth factors, nanoparticles, or decellularized extracellular matrix (dECM). dECM-based inks preserve native biochemical cues and have demonstrated success in liver and cardiac models. Nanoparticles like nanoclay or hydroxyapatite improve mechanics, conductivity, and controlled release [28]. Emerging in situ applications include pore-forming hybrid inks used in handheld extruders for wound repair, enabling simultaneous mechanical support and accelerated healing [30].

Application of 3D printing

3D bioprinting leverages additive manufacturing to create tissue constructs from bioinks containing living cells (Table2). Cytocompatible hydrogels are deposited layer by layer under guidance from CAD files, replicating native tissue architecture [9].

Table 2: Summary table of studies of 3D printed grafts: composition, methodology and outcomes

Organ	Tissue	Methodology	Bioink composition	Pros	Cons
Skin	Whole skin (Multilayer)	Computer-controlled 3D printer	Bioinks composed of viable cells, biomaterials	Provides suitable environment for cell migration, differentiation	-
	Outer layers	Ex vivo (inkjet-, extrusion-, laser-based bioprinting)	Human fibroblasts, human plasma, calcium chloride	High degree of precision and resolution	Lower cellular viability
	Outer layers	In situ bioprinting	Bioink composed of fibroblasts, collagen I, and fibrinogen	Allows for biomaterials to be printed directly into or onto the target/organ	Do not stimulate regeneration of vasculature, nerves, sweat and sebaceous glands
Heart	Cardiac and microvascular tissue	Inkjet bioprinting	Gelatin methacryloyl, heart extracellular matrix hydrogel	Compatible with many biomaterials and maintain remarkable cell viability	Cannot print at high density

		Extrusion printing	Alginate, PEG, fibrinogen	Permits faster, simpler, and more affordable bioprinting	Dispensing pressure and shear stress results in poor cell survival
		Freeform reversible embedding printing	Collagen hydrogels	Overcome the limitations of printing soft and low viscosity bioinks.	Risk of losing viability of cells
Kidney	Parenchymal tissue	Extrusion-based bioprinting	Hydrogels, alginate, PEG	High precision and widely used in industry	Cannot handle high pressure
		Droplet-based bioprinting	Gelatin methacrylate (GelMA), collagen, poly (ethylene glycol) (PEG)	Affordable, ideal for feasibility studies	Thermal and mechanical on cells, expensive
Neurons	Neural tissue Cortical NSCs	Micro-extrusion-based bioprinting	Alginate, carboxymethyl chitosan and agarose	Ability to use high viscosity	Distortion of cell structure
		Inkjet bioprinting	Collagen and fibrin	High speed, availability, low cost	High speed, availability, low cost
Liver	Hepatic cells	Extrusion based bioprinting	Alginate, collagen	Materials with a wide range of viscosities can be constructed efficiently	Low resolution of scaffolds
Bone	All bone tissue	3Dimensional printing	nanoengineered ionic covalent entanglement (NICE) bioink	3d printing using NICE bioink provides mechanically resilient, cellularized structures	NICE bioink is costly so it makes the whole process costly

Traditional scaffold-based methods support cell adhesion and differentiation but are limited by imprecise cell placement, poor vascularization, and labor-intensive assembly [11,13]. Automated bioprinting overcomes these challenges, enabling precise deposition of cells and biomaterials, improving construct fidelity, functionality, and scalability.

Composite Organ Printing integrates diverse cell types, biomaterials, and structural elements to mimic the complexity of native organs. The process typically involves three stages: pre-processing (imaging, model design, bioink formulation), printing (layer-by-layer deposition), and post-processing (maturation in bioreactors) [23]. High-resolution imaging tools such as CT and MRI are essential for accurate 3D model reconstruction, though challenges remain in color capture for skin reconstruction and radiation risks

associated with CT [18,31]. Notably, successful fabrication of layered skin constructs at Hannover Medical School and Laser Zentrum Hannover underscores its translational potential. Laser-assisted bioprinting (LaBP) has emerged as a valuable modality for composite organ printing, enabling high-resolution placement of multiple cell types and bioinks of varying viscosities [32].

Organoids and 3D Models produced via bioprinting offer physiologically relevant platforms for studying development, disease progression, and therapeutic responses. Unlike conventional 2D cultures, bioprinted organoids recreate native cell–cell and cell–matrix interactions within a 3D microenvironment [33,34]. Using stem cell-laden bioinks, self-organizing constructs resembling liver lobules, kidney nephrons,

neural spheroids, and intestinal crypts have been generated, supporting applications in disease modeling, drug screening, and regenerative medicine. For instance, liver organoids printed with alginate–collagen bioinks have provided superior predictive capacity in drug metabolism studies compared to standard in vitro assays [35]. However, challenges persist in vascularization, scalability, and functional integration. Emerging strategies coupling bioprinting with organ-on-chip systems show promise in enabling dynamic perfusion and long-term maturation [36]. Future progress will depend on incorporating vascular networks, immune cells, and multi-tissue interfaces to enhance physiological relevance.

In Situ Tissue Remodeling and Vascular Engineering: Further extend the applications of bioprinting. Vascular graft fabrication relies on selecting appropriate cell types, scaffold materials, and biochemical or mechanical stimuli to induce remodelling in vitro (Figure 2). While endothelial cells (ECs) and smooth muscle cells (SMCs) have been widely used since the 1980s, limited growth capacity has prompted exploration of stem cell–based approaches. Autologous cells remain the preferred option to minimize immunogenicity [37]. Both cellular and acellular grafts are under investigation, with the latter designed to promote host-driven regeneration by tailoring structural, chemical, and degradable features. Preclinical studies highlight the potential of mesenchymal stem cells (MSCs), muscle-derived stem cells (MDSCs), and pericytes to enhance patency and remodeling [38,39]. Nonetheless, evidence indicates that host-derived cells ultimately dominate long-term graft integration. Clinical advances, such as mononuclear cell–seeded biodegradable scaffolds applied in Japan [40,41] and ongoing U.S. trials for congenital cardiac disease [42], demonstrate the translational momentum of these strategies.

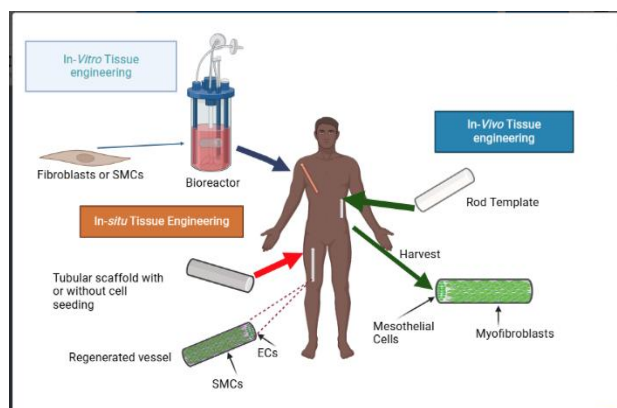


Figure 2: Illustration of In-Situ and In-Vivo Tissue Engineering Respectively

Advancement and future prospective

The rapid advancement of 3D bioprinting is driven by technological innovation and cross-disciplinary integration, with future progress requiring the convergence of computational design, translational biology, and high-throughput manufacturing. CAD and computer-aided manufacturing (CAM) are essential for converting medical imaging data into anatomically accurate 3D constructs, while advanced algorithms and artificial intelligence (AI) now enable optimization of print parameters, prediction of cell viability under shear stress, and the creation of complex vascular networks. Such computationally guided, predictive blueprints are increasingly applied in fields like cardiac tissue engineering, where spatially optimized deposition of endothelial and myocardial cells mimics physiological architecture [43]. Equally critical is translational biology, which addresses challenges in cell sourcing, immunocompatibility, and functional maturation. Autologous stem cells, including mesenchymal stem cells (MSCs) and induced pluripotent stem cells (iPSCs), minimize immune rejection and support patient-specific therapies, while decellularized extracellular matrix (dECM)-based bioinks provide biochemical cues that enhance differentiation and maturation. In situ bioprinting exemplifies clinical potential, as handheld devices have enabled direct fibroblast- and collagen-based deposition into wound sites, although scaling from animal models to human applications still requires rigorous preclinical validation and compliance with Good Manufacturing Practices (GMP) [44].

Alongside these biological advances, the development of high-throughput, GMP-compliant bioprinting platforms with multi-nozzle and automated capabilities is essential for reproducibility and scalability. Innovations such as freeform reversible embedding and high-precision extrusion are driving improvements, while industrial collaborations with companies including Organovo, EnvisionTEC, and Rokit are accelerating applications in skin, liver, and vascular models for pharmaceutical testing and regenerative therapies [45]. Ultimately, the future of 3D bioprinting will depend on the integration of cost-effective, standardized bioinks—particularly ECM-derived hydrogels from donor tissues—with scalable manufacturing systems to enable on-demand, patient-specific graft fabrication and reduce reliance on organ donation.

In brief, 3D bioprinting is redefining tissue engineering and regenerative medicine by integrating additive manufacturing, biomaterials, and cell biology. Applications now include skin grafts, vascular conduits, liver lobules, and cardiac patches, yet clinical

translation is limited by challenges such as vascularization, mechanical instability, high bioink costs, and regulatory barriers. Advances in computer-aided design, translational biology, and scalable bioprinting systems are addressing these gaps, while emerging strategies—such as 4D bioprinting, AI-assisted design, and in situ printing—offer new possibilities for personalized and real-time therapies [46]. Although still evolving, 3D bioprinting holds immense promise to overcome organ shortages, improve drug testing, and enable on-demand tissue fabrication, making it a cornerstone of future regenerative medicine.

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