Recent Advances in Bioprinting and 4D Printing: Materials, Technologies, and Biomedical Applications

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Abstract

Bioprinting and four-dimensional (4D) printing are converging additive fabrication technologies driving transformative progress in tissue engineering, regenerative medicine, and smart biomedical devices. Three-dimensional (3D) bioprinting enables complex, patient-specific constructs using living cells and biomaterials, while 4D printing introduces temporal responsiveness in printed systems via stimuli-responsive materials and programmed transformations. This review synthesizes state-of-the-art developments, including smart bioinks, advanced fabrication platforms, dynamic shape change mechanisms, clinical applications, and key performance outcomes reported in recent literature. We also discuss challenges for clinical translation, scalability, and regulatory adaptation.

Keywords
Bioprinting, 4D printing, smart materials, tissue engineering, regenerative medicine, bioinks

1. Introduction

Additive manufacturing has emerged as a transformative platform in biomedical engineering, fundamentally redefining strategies for tissue fabrication, regenerative medicine, and personalized therapeutics. Among its most impactful innovations is three-dimensional (3D) bioprinting, which enables precise layer-by-layer deposition of living cells, biomaterials, and bioactive molecules to fabricate tissue-mimetic constructs with controlled architecture and spatial heterogeneity [1,2]. Unlike conventional scaffold fabrication approaches, bioprinting allows programmable positioning of multiple cell types and materials within predefined geometries, thereby better replicating native extracellular matrix (ECM) complexity and tissue microenvironments [3–5]. Over the past decade, significant technological advancements have been achieved in extrusion-based, inkjet, laser-assisted, and stereolithographic bioprinting systems, each offering distinct advantages in resolution, speed, scalability, and cell viability [3,4,6]. Parallel progress in bioink development—including natural polymers such as alginate, gelatin methacrylate (GelMA), collagen, fibrin, and hyaluronic acid, as well as synthetic polymers such as polyethylene glycol (PEG)—has improved print fidelity, mechanical stability, biodegradability, and cellular functionality [7,8]. These developments have enabled the fabrication of increasingly complex constructs such as vascularized tissues, bone and cartilage scaffolds, cardiac patches, neural models, and organoids for disease modeling and pharmaceutical screening [5,9].

Despite these advances, conventional 3D bioprinted constructs remain largely static and lack the intrinsic adaptability characteristic of living tissues. This limitation has driven the emergence of four-dimensional (4D) printing, in which time is incorporated as an additional functional dimension, allowing printed constructs to undergo programmed structural or functional transformations after fabrication [10,11]. 4D printing integrates stimuli-responsive or “smart” materials that react to environmental triggers such as temperature, pH, light, moisture, magnetic fields, or biochemical signals [11–14]. Shape-memory polymers, thermoresponsive hydrogels, liquid crystal elastomers, and magnetic nanocomposites are among the key material systems enabling such transformations [12–15]. These materials permit constructs to self-fold, expand, stiffen, degrade, or release therapeutic agents in a controlled manner upon exposure to physiological stimuli [16,17]. The integration of 4D principles with bioprinting has expanded possibilities for adaptive scaffolds, programmable drug delivery systems, self-assembling vascular networks, and responsive biomedical implants [18,19].

The convergence of bioprinting and 4D printing is particularly promising in regenerative medicine, where dynamic mechanical and biochemical cues are essential for tissue maturation and integration. Emerging research demonstrates that stimuli-responsive scaffolds can enhance cell proliferation, alignment, differentiation, and extracellular matrix deposition by mimicking native tissue mechanics and environmental changes [7,19,20]. Furthermore, advances in multi-material bioprinting, computational modeling, and biofabrication strategies are enabling precise control over transformation kinetics and mechanical performance, thereby accelerating translational potential [9,18]. However, challenges remain in ensuring long-term biocompatibility, immune safety, structural stability during transformation, reproducibility at large scale, and regulatory compliance for clinical deployment [6,20]. Continued interdisciplinary integration of materials science, cell biology, bioengineering, and computational design will be critical in advancing dynamic biofabrication technologies toward next-generation smart, patient-specific therapeutic systems.

Table no 1. Comparative Overview of Bioprinting and 4D Printing Developments

Aspect	**3D Bioprinting**	**4D Printing**	**Recent Developments**	**Biomedical Impact**
Definition	Layer-by-layer deposition of bioinks containing living cells	3D printed constructs capable of time-dependent transformation	Integration of smart materials into bioprinting platforms	Dynamic, adaptive implants
Materials Used	Hydrogels (alginate, gelatin, collagen, GelMA)	Shape-memory polymers, thermo-responsive hydrogels, LCEs, magnetic nanocomposites	Development of multi-responsive bioinks	Improved functionality & responsiveness
Stimuli Response	Generally static after fabrication	Respond to heat, pH, light, magnetic field, moisture	Programmable anisotropy & controlled actuation	Minimally invasive deployment

Aspect	3D Bioprinting	4D Printing	Recent Developments	Biomedical Impact
Printing Techniques	Extrusion-based, inkjet, laser-assisted	Multi-material extrusion, DLP, SLA, volumetric printing	High-resolution multi-material systems	Enhanced precision & reproducibility
Applications	Skin, bone, cartilage, liver models	Self-expanding stents, adaptive scaffolds, smart drug delivery	Hybrid 3D/4D bioprinting systems	Personalized regenerative medicine
Challenges	Cell viability, vascularization, mechanical strength	Scalability, reproducibility, regulatory approval	AI-assisted process monitoring	Clinical translation acceleration
Future Direction	Vascularized organ fabrication	Fully autonomous self-transforming implants	Integration with biosensors & IoT	Real-time responsive therapeutic systems

2. Bioprinting Technologies and Bioinks

Major bioprinting modalities include extrusion-based printing, inkjet bioprinting, laser-assisted bioprinting, and volumetric bioprinting. Extrusion systems allow high-viscosity bioinks, whereas inkjet and laser systems provide high resolution. Recent volumetric systems have significantly improved printing speed and structural fidelity.

Bioinks are composed of natural polymers (alginate, gelatin methacrylate, hyaluronic acid), synthetic polymers (PEG-based hydrogels), and composite systems containing nanoparticles for enhanced mechanical strength and bioactivity.

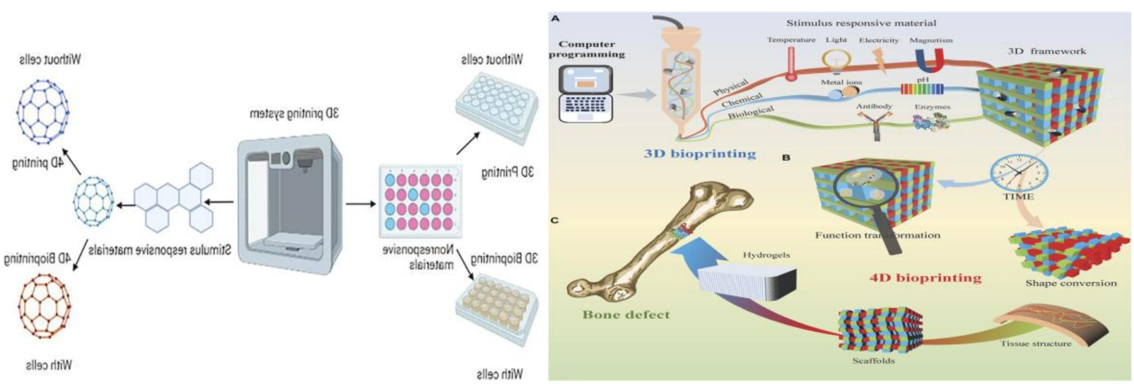

Figure 1: Schematic representation of major bioprinting techniques (Insert high-resolution schematic here).

2.1 Printing Modalities

Bioprinting encompasses several fabrication strategies that differ in working principles, resolution, cell compatibility, and scalability. Among these, extrusion-based bioprinting remains the most widely adopted technique due to its ability to process high-viscosity bioinks and fabricate mechanically stable, large-scale constructs suitable for bone, cartilage, and vascular tissue engineering applications [21,22]. In extrusion systems, bioinks are dispensed through pneumatic or mechanical force, allowing the incorporation of high cell densities and composite biomaterials; however, shear stress during extrusion may affect cell viability if not optimized [21]. Inkjet bioprinting, in contrast, utilizes thermal or piezoelectric actuation to deposit picoliter droplets of low-viscosity bioinks, offering high spatial resolution and precise cell placement, making it suitable for patterning multiple cell types within complex microarchitectures [23]. Laser-assisted bioprinting eliminates nozzle-related shear stress and clogging issues, enabling high-resolution deposition and improved cell survival rates, particularly for delicate cell populations such as stem cells [24]. More recently, volumetric bioprinting has emerged as a breakthrough technology capable of fabricating centimeter-scale hydrogel constructs within seconds through tomographic light projection, significantly reducing printing time while maintaining structural fidelity and cell viability [25]. Additionally, novel approaches such as acoustic wave-assisted bioprinting and context-aware computational design have enhanced printing precision and cellular organization by enabling contactless manipulation of cells and optimization of construct architecture, thereby improving biological performance and reducing fabrication-induced stress [26,27]. Collectively, these technological advancements are driving the transition of bioprinting from laboratory-scale prototyping toward clinically relevant tissue manufacturing.

2.2 Smart Bioinks

The success of bioprinting is fundamentally dependent on the design and functionality of bioinks, which must simultaneously satisfy printability, mechanical integrity, biocompatibility, and bioactivity requirements [28]. Bioinks are typically composed of natural polymers such as alginate, gelatin methacrylate (GelMA), collagen, fibrin, and hyaluronic acid, which closely mimic native extracellular matrix components and promote cell adhesion, proliferation, and differentiation [28,29]. Synthetic polymers, including polyethylene glycol (PEG) and its derivatives, are often incorporated to improve mechanical stability, tunable degradation, and crosslinking control [29]. To further enhance functional performance, nanoparticles such as graphene oxide, carbon nanotubes, gold nanoparticles, and magnetic nanomaterials are blended into polymer matrices to modulate mechanical strength, electrical conductivity, and biological signaling [30]. For instance, alginate-based composites containing conductive nanomaterials have demonstrated improved electrical stimulation capability, supporting synchronized contraction in cardiac tissue models and enhanced neurite outgrowth in neural constructs [30]. Emerging smart bioinks also integrate growth factors, angiogenic peptides, and stimuli-responsive components that enable controlled drug release or dynamic mechanical adaptation, thereby bridging the gap between static scaffolds and biologically active microenvironments [27,29]. Continued optimization of rheological behavior, crosslinking kinetics, and cellular compatibility is essential to ensure reproducibility and translational feasibility in advanced tissue engineering applications.

3. Principles of 4D Printing

Four-dimensional (4D) printing represents an evolution of additive manufacturing in which time is incorporated as an active design parameter, enabling printed structures to undergo predetermined structural or functional transformations after fabrication. This approach integrates stimuli-responsive or "smart" materials—including shape-memory polymers (SMPs), thermo-responsive hydrogels, liquid crystal elastomers (LCEs), and magnetic nanocomposites—that respond dynamically to environmental triggers such as temperature, pH, light, moisture, electric fields, or magnetic stimuli [31–33]. Unlike conventional static 3D-printed constructs, 4D-printed systems are programmed during fabrication to exhibit adaptive behaviors such as self-folding, self-expansion, stiffness modulation, or controlled degradation when exposed to specific external conditions [2,4]. The transformation mechanism is typically governed by internal material anisotropy, differential swelling, phase transitions, or reversible polymer network rearrangements embedded within the printed architecture [33,35].

Shape-memory polymers constitute one of the most widely studied material classes in 4D printing due to their ability to be temporarily deformed and subsequently recover their original geometry upon thermal or other stimuli activation [36]. Thermo-responsive hydrogels, such as those based on poly(N-isopropylacrylamide) (PNIPAAm) or gelatin derivatives, exhibit reversible swelling and deswelling behavior across critical solution temperatures, enabling programmable shape morphing and drug release [35,37]. In controlled laboratory settings, thermo-responsive materials have demonstrated high shape fixity ratios exceeding 95% and shape recovery efficiencies greater than 98%, highlighting their reliability for repeated actuation cycles in biomedical applications [36,38]. Liquid crystal elastomers further expand the functional design space by coupling elastic

deformation with molecular orientation changes, allowing reversible and complex actuation under thermal or photonic stimulation [33,39]. Additionally, magnetic nanocomposites incorporating iron oxide nanoparticles enable remote, non-invasive activation through external magnetic fields, making them particularly attractive for minimally invasive biomedical devices and targeted therapies [32,40].

Collectively, these programmable material systems allow 4D-printed constructs to transform shape, mechanical properties, or biological function in situ, thereby mimicking the dynamic behavior of native tissues. Such capabilities are particularly promising for minimally invasive implants, self-deploying stents, adaptive scaffolds, and controlled therapeutic delivery systems.

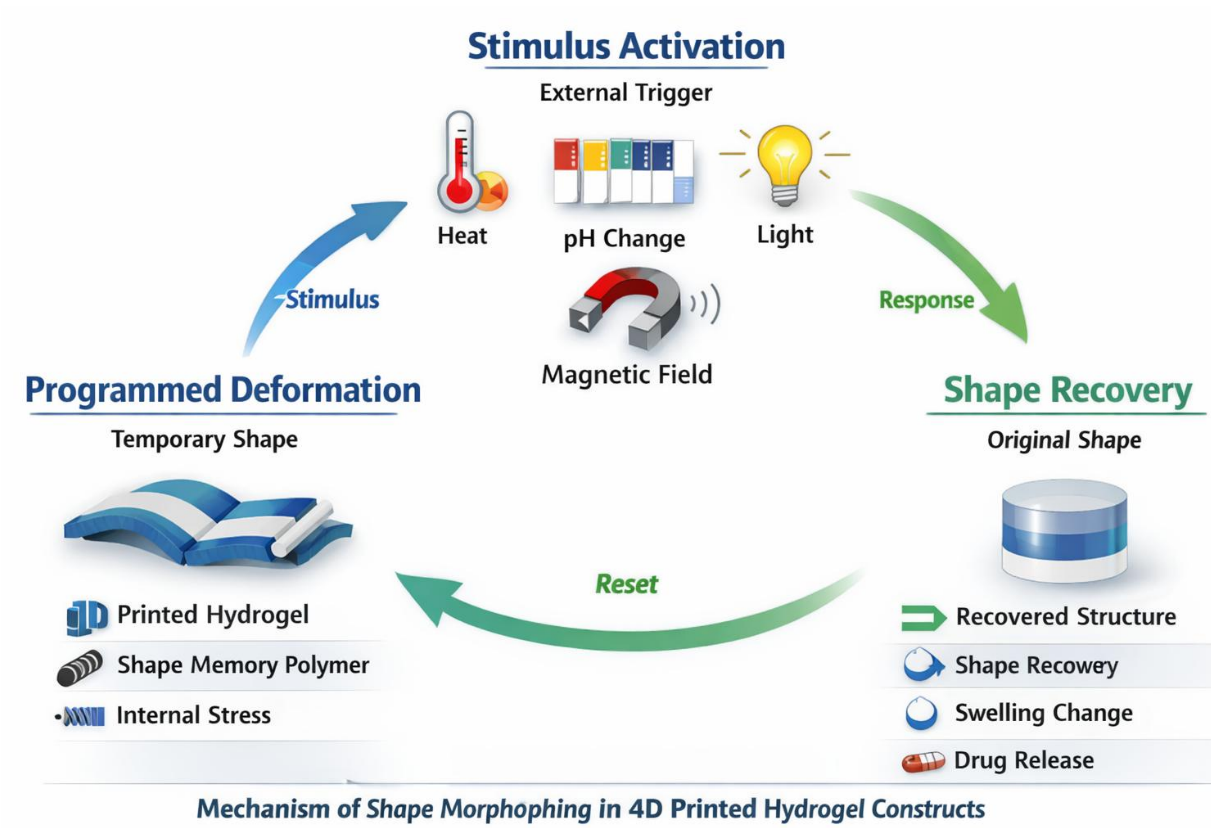

Figure 2: Mechanism of shape morphing in 4D printed hydrogel constructs (Insert schematic diagram illustrating programmed deformation, stimulus activation, and shape recovery cycle).

4. Biomedical Applications

Four-dimensional (4D) printing has emerged as a transformative approach in biomedical engineering by enabling the fabrication of dynamic, stimuli-responsive constructs that adapt to physiological environments over time. In bone and cartilage tissue engineering, shape-morphing scaffolds fabricated from thermo-responsive polymers and hydrogels can be implanted in a compact form and subsequently expand or conform in situ to match defect geometry, thereby supporting cell adhesion, proliferation, and extracellular matrix deposition.[41] Such minimally invasive deployment reduces surgical trauma while improving scaffold–tissue integration. In cardiovascular applications, 4D printed stents composed of shape-memory polymers or biodegradable composites can self-expand at body temperature, offering alternatives to traditional metallic stents and

minimizing complications associated with long-term implantation [43]. Similarly, neural tissue engineering benefits from adaptable scaffolds capable of altering stiffness and geometry in response to physiological stimuli, promoting axonal guidance and reducing mechanical mismatch with surrounding neural tissue [42,44]. Beyond structural regeneration, 4D printing plays a significant role in advanced wound healing systems. Stimuli-responsive hydrogels can dynamically adjust swelling behavior in response to moisture or pH changes in the wound microenvironment, facilitating controlled exudate absorption and sustained release of antimicrobial or anti-inflammatory agents [44,45]. Moreover, 4D printed drug delivery devices can be programmed for pH-triggered, temperature-triggered, or enzyme-responsive release, allowing spatially and temporally controlled therapeutic administration. For example, pH-sensitive systems are particularly advantageous for targeting acidic tumor microenvironments, whereas thermo-responsive platforms can modulate drug diffusion at physiological temperature transitions [45,46]. These programmable delivery systems enhance therapeutic precision, reduce systemic toxicity, and improve patient compliance. Collectively, the integration of smart materials with additive manufacturing enables biomedical constructs that are not only patient-specific but also capable of real-time adaptation within the body, marking a significant advancement toward personalized and minimally invasive medicine.

5. Challenges and Future Directions

5Despite significant advances in 4D printing for biomedical applications, scalability and large-scale manufacturing remain major challenges limiting widespread clinical translation. The fabrication of complex, stimuli-responsive biofabricated systems requires precise control over material composition, crosslinking density, anisotropic architecture, and multi-material interfaces, which can be difficult to reproduce consistently at industrial scale [47,48] . Many smart materials—such as shape-memory polymers, liquid crystal elastomers, and stimuli-responsive hydrogels—exhibit batch-to-batch variability, sensitivity to environmental conditions, and limited mechanical robustness, thereby complicating process standardization and quality assurance [48,49]. Additionally, the integration of living cells in 4D bioprinting introduces further constraints related to sterility, bioink viscosity, cell viability, and long-term functionality, making scale-up more demanding compared to conventional additive manufacturing processes [50].

Manufacturing challenges also arise from the need for high-resolution, multi-material printing systems capable of embedding programmable anisotropy within constructs. Current commercial 3D printers often lack the advanced control algorithms and environmental regulation required for reliable 4D fabrication, necessitating customized platforms that increase production costs [51]. Moreover, reproducibility of time-dependent transformations—such as shape recovery rate, swelling kinetics, and stimulus responsiveness—must meet stringent regulatory standards before clinical implementation, particularly for implantable devices and drug delivery systems [45,46]. Regulatory pathways for adaptive medical devices remain under development, adding further complexity to commercialization.

Future research directions should focus on developing robust, biocompatible smart materials with improved mechanical strength and predictable long-term behavior, as well as scalable manufacturing strategies such as automated multi-material extrusion systems and real-time monitoring technologies integrated with artificial intelligence-based process control [50,52]. Standardization of testing protocols for transformation efficiency, fatigue resistance, and biodegradation kinetics will be essential to ensure translational reliability. Furthermore, interdisciplinary collaboration among material scientists, biomedical engineers, clinicians, and regulatory agencies will accelerate the transition of 4D printed constructs from laboratory prototypes to clinically approved therapeutic platforms [43,46]. Addressing these scalability and manufacturing barriers is critical for realizing the full potential of 4D printing in precision and personalized medicine.

Table .No 2- Key Emerging Trends

Trend	**Description**	**Potential Outcome**
Multi-material Biofabrication	Printing different biomaterials in a single construct	Complex tissue mimicry
AI-Driven Design Optimization	Computational modeling for predicting shape transformation	Improved transformation accuracy
4D Bioprinting with Living Cells	Cell-laden smart hydrogels that change shape	Self-maturing tissues
Remote Actuation Systems	Magnetic/light-triggered constructs	Non-invasive therapeutic activation
Personalized Medicine Integration	Patient-specific anatomical modeling	Custom implants with adaptive behavior

5.2 Biocompatibility & Safety

Biocompatibility and long-term safety evaluation represent critical prerequisites for the clinical translation of 4D printed biomedical constructs. Because these systems are designed to undergo structural or functional transformation in vivo, their interaction with physiological environments must be carefully assessed under dynamic conditions rather than static implantation models [1,2]. Smart materials such as shape-memory polymers, thermo-responsive hydrogels, and composite nanomaterials must demonstrate cytocompatibility, hemocompatibility, and minimal inflammatory response to ensure safe integration with host tissues. Furthermore, the transformation process itself—whether triggered by temperature, pH, magnetic fields, or light—should not induce localized thermal damage, oxidative stress, or unintended tissue irritation [2,3].

Long-term compatibility under physiological conditions is particularly important for implantable devices such as self-expanding stents, scaffolds, and drug delivery systems. These constructs must maintain mechanical integrity, predictable actuation behavior, and structural stability throughout their functional lifespan [1,4]. Degradation profiles require comprehensive evaluation to ensure that by-products are non-toxic, non-immunogenic, and safely metabolized or excreted by the body. In biodegradable 4D printed systems, degradation kinetics must be synchronized with tissue regeneration rates to prevent premature loss of support or prolonged foreign body presence [3,5]. Additionally, immune responses—including macrophage activation, fibrous encapsulation, and chronic inflammation—should be systematically studied using both in vitro and in vivo models before clinical application [2,4].

Regulatory approval pathways further necessitate standardized preclinical testing protocols addressing genotoxicity, systemic toxicity, sensitization, and long-term implantation studies. The adaptive and time-dependent behavior of 4D printed constructs adds complexity to safety validation, requiring extended monitoring to evaluate repeated actuation cycles and fatigue resistance under physiological loading conditions [1,5]. Therefore, rigorous multidisciplinary assessment integrating material science, toxicology, immunology, and clinical expertise is essential to ensure that 4D printed biomedical systems meet safety and efficacy standards prior to human use.

5.3 Regulatory and Ethical Considerations

As these technologies move toward clinical products, robust regulatory frameworks will be required to ensure safety and efficacy.

6. Conclusion

Bioprinting and 4D printing represent transformative advancements in biomedical engineering, bridging material science, additive manufacturing, and regenerative medicine. While 3D bioprinting has enabled the fabrication of patient-specific tissue constructs through precise deposition of cell-laden bioinks, 4D printing extends this capability by introducing time-dependent functionality through stimuli-responsive materials. The integration of shape-memory polymers, smart hydrogels, and multi-material architectures has facilitated the development of dynamic scaffolds, self-expanding implants, adaptive wound dressings, and programmable drug delivery systems. These innovations hold significant promise for minimally invasive procedures, improved tissue integration, and enhanced therapeutic precision.

Despite these advancements, challenges related to scalability, reproducibility, biocompatibility, regulatory approval, and long-term safety must be addressed to enable widespread clinical translation. Standardization of manufacturing processes, comprehensive in vivo validation, and interdisciplinary collaboration among engineers, clinicians, and regulatory bodies are essential to ensure safety and efficacy. Future developments are expected to focus on AI-assisted design optimization, multi-responsive bioinks, vascularized tissue fabrication, and integration with biosensing technologies for real-time therapeutic monitoring.

In conclusion, the convergence of bioprinting and 4D printing technologies marks a paradigm shift toward adaptive, intelligent, and personalized biomedical systems. With continued research and technological refinement, these approaches have the potential to revolutionize regenerative medicine and pave the way for next-generation smart therapeutic platforms.