RESEARCH PAPER

A Comprehensive Review of 3D Bioprinting and Bioinks: From Fundamentals to Clinical Translation

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Abstract

Three-dimensional (3D) bioprinting has emerged as a revolutionary technology at the intersection of engineering, biomaterials science, and cell biology, offering a promising pathway to address the critical shortage of donor organs and advance regenerative medicine. This comprehensive review explores the field of 3D bioprinting, with a particular focus on the central component of this technology: bioinks. Defined as cell-laden formulations, bioinks serve as the living component and must satisfy a complex set of requirements, including biocompatibility, printability, mechanical stability, and biofunctionality. The review provides a detailed taxonomy of bioink materials, categorizing them into natural polymers, which offer inherent bioactivity; synthetic polymers, which provide mechanical tunability; and composite bioinks, which combine the advantages of both to create superior materials. The functional properties of bioinks, from their rheological behavior during printing to their role in guiding cell fate post-printing, are critically examined. Furthermore, the review highlights transformative applications in tissue engineering, such as the fabrication of skin, bone, cartilage, and vascularized constructs, and in the creation of physiologically relevant models for disease modeling and high-throughput drug screening. Despite significant progress, major challenges remain, including the need for functional vascularization, scaling up production, and navigating regulatory pathways. The future of the field points toward the development of smart and personalized bioinks, four-dimensional (4D) bioprinting, and in situ printing techniques. In conclusion, while the fabrication of complex solid organs remains a long-term goal, 3D bioprinting is already generating impactful solutions in medicine and is poised to play an increasingly critical role in the future of healthcare.

Keywords: 3D Bioprinting, Bioinks, Tissue Engineering, Regenerative Medicine, Additive Manufacturing, Biomaterials

How to cite this article: Sonali Sonulkar. A Comprehensive Review of 3D Bioprinting and Bioinks: From Fundamentals to Clinical Translation. Int J Drug Deliv Technol. 2026;16(90s):2085-2093. DOI: 10.25258/ijddt.16.90s.209.

1. INTRODUCTION

Three-dimensional (3D) bioprinting represents a significant technological evolution, transforming from rudimentary printing methods into a sophisticated tool with the potential to redefine medical therapeutics (Agarwal et al., 2020). Historically, printing technology facilitated the dissemination of knowledge through text and images (Lipson & Kurman, 2013). Today, additive manufacturing builds objects layer by layer, extending beyond prototyping to applications in science and education, such as creating fossil replicas or molecular models (Hasiuk, 2014; Watson & Crick, 1953).

The foundational technique of stereolithography, described by Hull (1986), utilized ultraviolet light to cure material layers into 3D structures. This concept was later adapted to create scaffolds for biological materials, leading to the development of aqueous systems capable of printing biological materials for transplantation (Murphy & Atala, 2014). The convergence of these techniques with cell biology and materials science gave rise to 3D bioprinting. Concurrently, 3D printing began producing clinical tools like patient-specific implants (Zopf et al., 2013).

3D bioprinting involves the layer-by-layer deposition of biological materials, biochemicals, and living cells into predefined 3D structures. Strategies include biomimicry, autonomous self-assembly, and mini-tissue building blocks, all aimed at creating functional human tissues for clinical application (Murphy et al., 2020). Technical challenges involve adapting machinery for delicate living cells and replicating the complex micro-architecture of the native extracellular matrix (ECM) with sufficient precision for tissue function (Moroni et al., 2018).

This review examines the landscape of 3D bioprinting for tissue and organ engineering. It will cover the primary strategies for tissue construction, the types of bioprinters and their influence on outcomes, the step-by-step printing process, current technological limitations, and future challenges.

1.1. The Drive to Manufacture Organs

The primary motivation for this research is the severe global shortage of organ donors, making organ manufacturing a critical pursuit in modern medicine (Murphy & Atala, 2014; Vijayavenkataraman, 2023). This endeavor is inherently interdisciplinary, requiring expertise from biology, materials science, computer

science, and clinical medicine (Groll et al., 2018; Mandrycky et al., 2016). The process involves creating digital models, selecting appropriate biomaterials, and combining multiple cell types using advanced manufacturing technologies (Groll et al., 2018; Malda et al., 2013).

A key objective is programming the formation of a functional structure complete with hierarchical vascular, neural, and lymphatic networks—a bioartificial organ. 3D bioprinting, or additive manufacturing, is a leading technology for this task, building organs automatically layer by layer (Kang et al., 2016). Its defining feature is the use of bioinks—formulations of living cells, polymeric hydrogels, and bioactive factors—deposited according to a computer-aided design (CAD) model to construct the organ (Groll et al., 2018). This allows different cell types, each encapsulated in tailored hydrogels, to be placed precisely. These hydrogels create a hydrated, tissue-like environment essential for cell growth, proliferation, and tissue formation (Gungor-Ozkerim et al., 2018).

1.2. Bioprinting's Role in Tissue Engineering

Tissue engineering, focused on repairing tissues using scaffolds and cells, has achieved success in regenerating bone, skin, and cartilage (Chung et al., 2020; Place et al., 2009). However, limitations persist, particularly in precisely arranging multiple cell types and achieving full biological function in complex tissues (Murphy & Atala, 2014).

3D bioprinting addresses these limitations by programmatically controlling scaffold structure, cell distribution, and biological signal placement, enabling the generation of multicellular tissues with near-normal structure and function (Kolesky et al., 2014; Skylar-Scott et al., 2019). It is also a driver of personalized and precision medicine, offering the potential to create patient-specific tissues (Matthews et al., 2022).

It is important to distinguish between general 3D printing and 3D bioprinting. Standard 3D printing is an engineering-focused process for creating intricate structures from materials like plastic or metal, with high precision and reproducibility (Gross et al., 2014). It encompasses techniques like stereolithography (SLA) and fused deposition modeling (FDM) (Derakhshanfar et al., 2018). 3D bioprinting integrates these engineering principles with developmental biology and regenerative medicine. It allows control over the placement of cells, proteins, and drugs, enabling the recapitulation of native tissue microstructure, mechanical properties, and biological functions (Moroni et al., 2018).

A critical consideration is maintaining cell viability. The printing process—speed, pressure, and movement—can stress or kill cells. To protect them, cells are mixed into a bioink, which acts as a temporary, supportive, cell-laden scaffold during printing (Groll et al., 2018). Bioink selection is paramount; it requires appropriate mechanical, biodegradable, and biocompatible properties. Key parameters like viscosity and cross-linking ability significantly impact printing accuracy and cell survival (Ouyang et al., 2016; Paxton et al., 2017). Bioinks are formulated from natural materials (e.g., alginate, collagen) or synthetic ones (e.g., PCL, PEG), each with distinct advantages and disadvantages (Gungor-Ozkerim et al., 2018).

2. FUNDAMENTALS OF BIOINKS

The bioink is the central, living component of bioprinting technology—a formulation that integrates biomaterials, living cells, and bioactive molecules to create biologically functional constructs. The term "bioink" is distinguished from cell-free "biomaterial inks" (Groll et al., 2018). This section details the core concepts, desired properties, classification, and performance evaluation of bioinks.

2.1. Definition of a Bioink

A bioink is a cell-laden formulation designed for processing by a bioprinter into 3D constructs that support cell survival, proliferation, and organization into functional tissue (Groll et al., 2018). Unlike methods where cells are seeded onto pre-formed scaffolds, bioinks combine the scaffold material and cells from the outset, merging printability with cytocompatibility (Donderwinkel et al., 2017). It functions as a temporary, supportive matrix during construction—sufficiently robust to maintain shape during printing yet conducive to cell proliferation and eventual tissue remodeling (Gungor-Ozkerim et al., 2018).

2.2. Properties of an Ideal Bioink

A successful bioink requires a balance of biological and physical properties:

1. Biocompatibility and Cytocompatibility: The bioink must support high cell viability during and after printing, minimizing stress from shear forces or chemical crosslinking processes (Donderwinkel et al., 2017).
2. Printability and Rheological Behavior: The bioink requires optimal viscosity—neither too high to impede extrusion nor too low to prevent shape retention. Many effective bioinks are shear-thinning, becoming less viscous under shear stress for easy extrusion and recovering viscosity afterward to maintain structural integrity (Gungor-Ozkerim et al., 2018).
3. Mechanical Properties and Stability: The printed structure must provide immediate mechanical support and retain its shape during culture without collapsing (Hölzl et al., 2016).
4. Crosslinking Behavior: The gelation process, whether via temperature, ions, enzymes, or light, must

be rapid enough to secure the structure but sufficiently gentle and fast to preserve cell viability (Hölzl et al., 2016).

5. Biodegradability: The bioink should degrade at a controlled rate that matches native matrix production by cells, with safe breakdown products (Hölzl et al., 2016).

6. Biofunctionality: An ideal bioink provides biological cues, such as adhesion sites (e.g., RGD sequences) and growth signals, to direct cell behavior (Chimene et al., 2016).

7. Sterilizability and Shelf Life: For clinical translation, the bioink must be sterile, stable during storage, and reproducible between batches (Chimene et al., 2016).

8. Hardware Compatibility: The bioink must be compatible with the chosen printing technology, such as extrusion-based, inkjet, or laser-assisted systems (Gungor-Ozkerim et al., 2018).

2.3. Classification of Bioinks

Bioinks can be categorized in several ways:

By Material Origin:

Natural Polymers: Derived from nature (e.g., collagen, gelatin, alginate, fibrin), these offer inherent bioactivity but often lack mechanical strength (Hölzl et al., 2016).

Synthetic Polymers: Human-made materials (e.g., PEG, Pluronic) offer tunable mechanical properties but are often biologically inert and require modification with bioactive molecules (Donderwinkel et al., 2017).

Hybrid/Composite Bioinks: Blends of natural and synthetic polymers that combine the bioactivity of the former with the robust mechanics of the latter (Rasouli et al., 2025).

By Function:

Structural Bioinks: Designed to bear loads and provide the primary framework.

Sacrificial Bioinks: Used to print temporary channels or voids (e.g., for vasculature) that are later removed (Gungor-Ozkerim et al., 2018).

Bioactive Bioinks: Incorporated with drugs, growth factors, or nanoparticles for controlled release to direct healing or provide other functions (Donderwinkel et al., 2017).

By Crosslinking Method: Bioinks can be thermoresponsive, ionic-crosslinking, enzymatic-crosslinking, or photocrosslinkable (Hölzl et al., 2016).

2.4. Evaluation of Bioinks

Bioink performance is assessed through quantitative metrics:

Cell Viability Assays: Determine the percentage of living cells after printing, often using live/dead staining (Donderwinkel et al., 2017).

Print Fidelity Metrics: Quantify how accurately the printed structure matches the digital design, measuring parameters like filament diameter and pore size (Gungor-Ozkerim et al., 2018).

Rheological Testing: Analyzes flow properties, including viscosity, shear-thinning behavior, and yield stress, to predict printability (Hölzl et al., 2016).

Mechanical Testing: Measures compressive strength, elasticity, and other properties to ensure constructs can withstand physiological stresses (Rasouli et al., 2025).

3. TYPES OF BIOINKS

The diversity of bioinks is primarily based on polymers that form hydrated, tissue-like environments. These polymers are sourced from nature or synthesized.

3.1. Natural Polymer-Based Bioinks

Natural materials provide inherent bioactivity that cells recognize.

3.1.1. Collagen: The most abundant protein in the human body, collagen contains RGD sequences that promote cell adhesion. However, its weak mechanical properties often necessitate blending with other materials (Xu et al., 2020).

3.1.2. Gelatin: A denatured form of collagen that retains RGD sequences and exhibits higher strength. It is thermosensitive, liquefying when warm and gelling when cool, but its reversibility can limit structural stability (Xu et al., 2020).

3.1.3. Alginate: Derived from seaweed, alginate is biocompatible and gels rapidly via ionic crosslinking with calcium. Its lack of natural cell adhesion sites often requires modification or blending (Xu et al., 2020).

3.1.4. Fibrin: The natural scaffold of blood clots, fibrin is formed from fibrinogen and thrombin. It is highly bioactive, promoting cell adhesion and angiogenesis, and is often used as a substrate for skin printing (Xu et al., 2020).

3.1.5. Hyaluronic Acid (HA): A major component of the ECM, HA is biocompatible and biodegradable. Its high water solubility can lead to instability, but it has been used successfully in multi-layered skin constructs when combined with other materials (Xu et al., 2020).

3.1.6. Chitosan: Derived from crustacean shells, chitosan is easily blended with other polymers and possesses natural antibacterial properties (Fatimi et al., 2022).

3.1.7. Agarose: Sourced from red seaweed, agarose is known for its thermo-reversible gelling and high biocompatibility, though it often requires blending with bioactive components (Benwood et al., 2021).

3.1.8. Cellulose and Silk: Cellulose nanocrystals (CNCs) can reinforce other bioinks, improving strength and printability. Silk fibroin, from silkworms, offers exceptional mechanical strength and versatility (Benwood et al., 2021).

3.1.9. Gellan Gum, Dextran, and Pectin: These natural polysaccharides offer unique properties. Gellan gum improves the printability of soft bioinks, dextran can be chemically modified, and pectin's modifiable nature allows for the addition of custom adhesive signals (Zhang & Wang, 2019).

Given that no single natural material is perfect, the future lies in developing sophisticated blends tailored for specific tissues.

3.2. Cells: The Living Component

The most critical component of a bioink is the cells. Bioprinting complex tissues like skin requires a diverse cell population: fibroblasts for the dermis, keratinocytes for the epidermis, and specialized cells like melanocytes. The ideal source is a patient's own (autologous) cells to avoid immune rejection. Stem cells are a powerful source due to their differentiation potential, but controlling their differentiation and ensuring safety are active research areas (Xu et al., 2020).

3.3. Growth Factors: Biochemical Signals

Tissue formation is guided by biochemical instructions from signaling molecules like growth factors, cytokines, and chemokines. These molecules orchestrate cell division, migration, and differentiation. Incorporating them into bioinks transforms a passive scaffold into an active, instructive environment that guides regeneration (Xu et al., 2020).

3.4. Synthetic Polymer-Based Bioinks

Synthetic polymers provide robust mechanical properties for bioprinting, though they are generally less cell-friendly during printing due to requirements for high heat or solvents.

3.4.1. Poly(ε-caprolactone) (PCL): A biodegradable polyester with a low melting point, PCL solidifies quickly into a strong framework. It is typically printed as a support structure, with cell-laden hydrogels printed into its pores, and is widely used in bone tissue engineering (Place et al., 2009).

3.4.2. Poly(ethylene glycol) (PEG): A highly tunable, biocompatible polymer that forms clear hydrogels. Its inert nature requires modification with cell-adhesive peptides like RGD to support cell attachment (Place et al., 2009).

3.4.3. Pluronic: A temperature-sensitive polymer that is liquid when cool and gels at body temperature. It exhibits excellent print fidelity but degrades rapidly and can be cytotoxic, limiting its use to sacrificial inks for creating hollow channels (Place et al., 2009).

3.5. Composite Bioinks

Incorporating nanomaterials into hydrogels creates composite bioinks with enhanced functionalities.

Gold and Silver Nanoparticles: Can be used for crosslinking control or to create electrically conductive structures (Heid & Boccaccini, 2020).

Magnetic Nanoparticles: Enable control over bioink architecture using external magnetic fields during printing (Heid & Boccaccini, 2020).

Carbon Nanotubes (CNTs): When mixed into hydrogels, create conductive bioinks crucial for electrically active tissues like cardiac and neural. Heart cells in conductive bioinks exhibit stronger beating and improved communication protein expression (Deng et al., 2019).

Hydroxyapatite (HAp): The mineral component of bone. Adding HAp nanoparticles to bioinks enhances mechanical strength and promotes osteogenic differentiation of stem cells for bone tissue engineering (Heid & Boccaccini, 2020).

4. FUNCTIONAL PROPERTIES OF BIOINKS

The success of a bioink depends on its functional properties throughout the lifecycle of a printed construct.

4.1. Printability and Rheology

Bioink behavior during printing is critical. It must extrude easily but hold shape upon deposition. Key concepts include:

Shear-thinning: Viscosity decreases under shear stress during extrusion and recovers afterward.

Thixotropy: The ability to recover viscosity over time is vital for building multi-layered structures without sagging.

Crosslinking Kinetics: Gelation must be optimally balanced—too fast risks nozzle clogging, too slow risks loss of structural fidelity (He et al., 2016; Hölzl et al., 2016; Paxton et al., 2017).

4.2. Mechanical Properties

The printed construct must possess appropriate physical properties.

Stiffness: Cells are mechanosensitive; soft gels (~0.1–1 kPa) guide neurogenesis, while stiffer gels (>30 kPa) promote osteogenesis (Chaudhuri et al., 2016).

Viscoelasticity: Native tissues exhibit both solid-like and fluid-like behaviors. Replicating viscoelasticity is key for load-bearing tissues like cartilage (Chaudhuri et al., 2016).

Porosity: The structure must be sufficiently porous to allow nutrient diffusion in and waste diffusion out, ensuring central cell viability (Duarte Campos et al., 2013).

4.3. Biocompatibility and Bioactivity

The bioink must support high cell viability (Ouyang et al., 2016), minimize immune response (Kharaziha et al., 2021), and provide appropriate biological cues like adhesion sites (Chimene et al., 2016) and growth factors (Groll et al., 2018) to guide tissue development.

4.4. Degradation and Integration

The bioink is a temporary scaffold. It should degrade at a rate matching native matrix production by cells

(Hölzl et al., 2016), with safe byproducts, ultimately allowing full tissue remodeling.

4.5. Smart Bioinks

The next generation of bioinks are "smart" and responsive. They can change properties in response to stimuli like light or temperature (Khan & Tanaka, 2019), self-heal from damage (Maan et al., 2022), conduct electricity for neural and cardiac tissues (Deng et al., 2019), or be printed as gradients to mimic complex zonal tissues like cartilage (Zhang et al., 2021).

5. APPLICATIONS OF BIOINKS

5.1. Tissue and Organ Engineering

5.1.1. Skin: Bioprinting skin is an advanced application for burn victims and chronic wounds. Bioinks containing stem cells have accelerated wound closure by promoting angiogenesis. Distinct epidermal and dermal layers have been printed, creating stable, multi-layered skin with high cell viability (Song et al., 2021).

5.1.2. Bone: For large bone defects, hybrid scaffolds use a strong PCL framework for mechanical support and a cell-laden alginate or gelatin bioink to promote osteogenesis. Incorporating bone-specific signals from decellularized ECM (dECM) or HAp guides patient cells to regenerate bone (Song et al., 2021).

5.1.3. Cartilage: Bioprinting enables the creation of cartilage patches that mimic the tissue's complex zonal structure, where collagen composition and orientation vary from surface to deep layer. This architectural control is crucial for durable, functional replacements (Zhang et al., 2021).

5.1.4. Vascular and Neural Tissues: Creating living vasculature is essential for thick tissues. Strategies include printing sacrificial filaments to create hollow channels later lined with endothelial cells. For nerves, bioinks containing neural stem cells or Schwann cells printed into guidance conduits show promise for repairing nerve damage (Song et al., 2021).

5.2. Disease Modeling and Drug Testing

Bioprinting has an immediate impact in this area. Instead of testing drugs on 2D cell cultures, 3D bioprinted human tissue models (organoids, tissues-on-chips) can mimic diseased livers, tumors, or heart patches. These provide more accurate and ethical platforms for screening drug efficacy and toxicity, potentially saving time and resources by failing ineffective candidates earlier (Mazzocchi et al., 2019).

6. CHALLENGES AND FUTURE PROSPECTS

Despite significant progress, challenges remain on the path to routinely bioprinting complex organs for transplantation.

6.1. Challenges

Vascularization: Creating living, branching, perfusable vascular networks that integrate with host circulation remains a major hurdle (Vijayavenkataraman, 2023).

Resolution vs. Scale: Achieving single-cell resolution is slow, while rapid printing of large organs sacrifices detail. Bridging this gap is necessary (Ozbolat & Yu, 2013).

Multi-Material Challenge: Printing organs comprising multiple cell types and materials simultaneously with high precision requires more complex printers and bioinks (Moroni et al., 2018).

Cell Source: Sourcing billions of healthy, functional cells for organs like the liver or kidney is challenging. Patient-specific stem cells are promising, but scaling up and ensuring maturation inside constructs is non-trivial (Murphy et al., 2020).

Regulatory Hurdles: Regulatory approval pathways for living, bioprinted products are complex, requiring clear safety and efficacy standards (Vijayavenkataraman, 2023).

6.2. Future Prospects

The future of bioprinting points toward increased sophistication and integration:

4D Bioprinting: Using materials that change shape or function after printing in response to physiological cues, creating dynamic, self-assembling structures (Maan et al., 2022).

In Situ Bioprinting: Deploying portable bioprinters in operating rooms to print tissue directly onto wounds, such as printing skin onto burns (Mirshafiei et al., 2024).

Personalized Bioinks: Using patient-specific cells and tailored ECM components to create perfectly matched implants, eliminating rejection risk (Matthews et al., 2022).

Integration with AI and Imaging: Using advanced imaging (MRI/CT) for precise digital modeling of defects and machine learning to optimize printing parameters for individual patients (Mirshafiei et al., 2024).

7. CONCLUSION

In conclusion, 3D bioprinting has evolved from a conceptual technology into a powerful, interdisciplinary field that is advancing drug discovery and regenerative medicine. While the fabrication of whole, functional organs for transplant remains a long-term goal, the pursuit is generating revolutionary technologies and insights that are already saving and improving lives. The continued development of advanced bioinks and bioprinting methodologies promises to play an increasingly critical role in the future of healthcare.

Conflicts of Interest: The authors declare no conflicts of interest.

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