**Bioprinting: Foundations, Advances, and Applications**

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Introduction to the Reading List

Bioprinting has rapidly evolved from an experimental concept to a transformative technology with applications in tissue engineering, regenerative medicine, and disease modeling. This collection of landmark articles serves as a curated reading list for those seeking foundational and cutting-edge knowledge in the field. These articles have been selected based on their contributions to bioprinting techniques, material advancements, and biomedical applications. The heart of bioprinting lies the ability to create three-dimensional, cell-laden structures using specialized materials and precise fabrication techniques. The importance of materials in bioprinting cannot be overstated: the choice of bioinks, materials that support cell viability and promote biological function, is critical to the success of printed tissues. These materials must meet specific criteria, such as biocompatibility, mechanical strength, and the ability to support cell adhesion and differentiation. The development of new bioinks, from hydrogels to protein-based scaffolds, is a driving force behind many of the advances in the field.

Equally important are the various bioprinting strategies employed to achieve high precision and control in fabricating complex tissues. Techniques such as inkjet, extrusion, aspiration and laser-assisted printing each have distinct advantages and limitations. Inkjet printing, for example, allows for fine resolution and high throughput, but it can be challenging when working with viscous bioinks or maintaining cell viability. Extrusion-based bioprinting offers a robust method for printing with high cell densities and supporting the formation of larger tissue constructs but requires careful material optimization to ensure proper structural integrity. Laser-assisted printing, while enabling precise deposition of biomaterials, faces challenges in tissue complexity.

In addition to bioprinting strategies, a significant challenge in the field is the fabrication of functional tissues that mimic the complexity of native organs. Achieving this goal involves overcoming numerous hurdles related to vascularization, tissue maturation, and cell differentiation. While advancements have been made, fabricating tissues that can perform complex biological functions, such as those found in human organs, remains an ongoing challenge.

1. **Advances in Bioinks and Biomaterials**

Material selection is crucial for bioprinting, affecting cell viability, mechanical properties, and tissue function.

Hospodiuk M, Dey M, Sosnoski D, Ozbolat IT. The bioink: A comprehensive review on bioprintable materials. Biotechnol Adv. 2017 Mar-Apr;35(2):217-239. doi: 10.1016/j.biotechadv.2016.12.006. Epub 2017 Jan 3. [PMID: 28057483](https://pubmed.ncbi.nlm.nih.gov/28057483/).

This review article discusses various materials used in 3D bioprinting, referred to as bioinks. It offers a detailed overview of the properties required for bioinks, such as mechanical strength, biocompatibility, and printability. The article examines a diverse range of materials from natural polymers to synthetic compounds and their potential applications in tissue engineering and regenerative medicine.

Hull SM, Brunel LG, Heilshorn SC. 3D Bioprinting of Cell-Laden Hydrogels for Improved Biological Functionality. Adv Mater. 2022 Jan;34(2):e2103691. doi: 10.1002/adma.202103691. Epub 2021 Oct 20. [PMID: 34672027](https://pubmed.ncbi.nlm.nih.gov/34672027/); PMCID: PMC8988886.

This article investigates the use of hydrogels in 3D bioprinting for tissue engineering. It explores how hydrogels can be loaded with various cell types to create complex tissue structures and highlights their advantages in mimicking the extracellular matrix, thereby providing a supportive environment for cell growth and differentiation.

Loebel C, Rodell CB, Chen MH, Burdick JA. Shear-thinning and self-healing hydrogels as injectable therapeutics and for 3D-printing. Nat Protoc. 2017 Aug;12(8):1521-1541. doi: 10.1038/nprot.2017.053. Epub 2017 Jul 6. [PMID: 28683063](https://pubmed.ncbi.nlm.nih.gov/28683063/); PMCID: PMC7546336.

This article reviews shear-thinning and self-healing hydrogels, focusing on their potential as injectable therapeutics and materials for 3D bioprinting. The review covers how these hydrogels adapt to varying shear stresses during printing and recover their structural integrity afterward. These hydrogels show great promise in tissue engineering, wound healing, and drug delivery applications.

Groll J, Boland T, Blunk T, Burdick JA, Cho DW, Dalton PD, Derby B, Forgacs G, Li Q, Mironov VA, Moroni L, Nakamura M, Shu W, Takeuchi S, Vozzi G, Woodfield TB, Xu T, Yoo JJ, Malda J. Biofabrication: reappraising the definition of an evolving field. Biofabrication. 2016 Jan 8;8(1):013001. doi: 10.1088/1758-5090/8/1/013001. [PMID: 26744832](https://pubmed.ncbi.nlm.nih.gov/26744832/).

An authoritative work that refines the terminology of biofabrication and introduces emerging trends in biomaterial development for 3D bioprinting.

1. **Bioprinting Strategies**

These papers established core bioprinting methods, setting the stage for current advancements in the field.

Murphy SV, Atala A. 3D bioprinting of tissues and organs. Nat Biotechnol. 2014 Aug;32(8):773-85. doi: 10.1038/nbt.2958. [PMID: 25093879](https://pubmed.ncbi.nlm.nih.gov/25093879/).

A comprehensive review that discusses various bioprinting technologies (inkjet, extrusion, and laser-assisted) and their biomedical applications, making it a cornerstone reference.

Hinton TJ, Jallerat Q, Palchesko RN, Park JH, Grodzicki MS, Shue HJ, Ramadan MH, Hudson AR, Feinberg AW. Three-dimensional printing of complex biological structures by freeform reversible embedding of suspended hydrogels. Sci Adv. 2015 Oct 23;1(9):e1500758. doi: 10.1126/sciadv.1500758. [PMID: 26601312](https://pubmed.ncbi.nlm.nih.gov/26601312/); PMCID: PMC4646826.

This paper presents the Freeform Reversible Embedding of Suspended Hydrogels (FRESH) technique, a novel method for 3D printing complex biological structures. The technique utilizes support material that can be easily removed after printing, allowing the creation of delicate and intricate structures, such as tissues with embedded cells and proteins.

Daly AC, Davidson MD, Burdick JA. 3D bioprinting of high cell-density heterogeneous tissue models through spheroid fusion within self-healing hydrogels. Nat Commun. 2021 Feb 2;12(1):753. doi: 10.1038/s41467-021-21029-2. [PMID: 33531489](https://pubmed.ncbi.nlm.nih.gov/33531489/); PMCID: PMC7854667.

This study introduces a new 3D bioprinting technique using spheroid fusion within self-healing hydrogels to create high-density, heterogeneous tissue models. The innovative method enables bioprinting of cell aggregates such as spheroids.

1. **Bioprinting of Tissues and Organs**

The following studies highlight how bioprinting is used to create functional tissues and organs for medical applications.

Kolesky DB, Homan KA, Skylar-Scott MA, Lewis JA. Three-dimensional bioprinting of thick vascularized tissues. Proc Natl Acad Sci U S A. 2016 Mar 22;113(12):3179-84. doi: 10.1073/pnas.1521342113. Epub 2016 Mar 7. [PMID: 26951646](https://pubmed.ncbi.nlm.nih.gov/26951646/); PMCID: PMC4812707.

This article focuses on developing bioprinted thick, vascularized tissues. It discusses the creation of tissues with essential vascular networks to ensure proper nutrient and oxygen delivery, an important challenge in tissue engineering. The findings represent significant progress in generating functional, thick tissue constructs for regenerative medicine.

Kang HW, Lee SJ, Ko IK, Kengla C, Yoo JJ, Atala A. A 3D bioprinting system to produce human-scale tissue constructs with structural integrity. Nat Biotechnol. 2016 Mar;34(3):312-9. doi: 10.1038/nbt.3413. Epub 2016 Feb 15. [PMID: 26878319](https://pubmed.ncbi.nlm.nih.gov/26878319/).

This paper introduces a novel 3D bioprinting system that allows for the printing of large-scale tissue constructs with structural integrity. The system addresses previous limitations related to maintaining cell viability and the stability of printed structures. The study aims to advance the creation of complex tissue models for therapeutic and clinical applications.

Dey M, Ozbolat IT. 3D bioprinting of cells, tissues and organs. Sci Rep. 2020 Aug 18;10(1):14023. doi: 10.1038/s41598-020-70086-y. [PMID: 32811864](https://pubmed.ncbi.nlm.nih.gov/32811864/); PMCID: PMC7434768.

This paper provides a comprehensive overview of 3D bioprinting technologies, discussing various techniques and their applications in fabricating complex biological constructs for tissue engineering and regenerative medicine. It focuses on the potential of bioprinting to revolutionize the production of tissues and organs, emphasizing advancements in precision, functionality, and scale.

Skylar-Scott MA, Uzel SGM, Nam LL, Ahrens JH, Truby RL, Damaraju S, Lewis JA. Biomanufacturing of organ-specific tissues with high cellular density and embedded vascular channels. Sci Adv. 2019 Sep 6;5(9):eaaw2459. doi: 10.1126/sciadv.aaw2459. [PMID: 31523707](https://pubmed.ncbi.nlm.nih.gov/31523707/); PMCID: PMC6731072.

A significant contribution addressing one of the biggest hurdles in bioprinting: vascularization. The paper presents a novel method for embedding perfusable vascular channels within bioprinted tissues.

Mandrycky C, Wang Z, Kim K, Kim DH. 3D bioprinting for engineering complex tissues. Biotechnol Adv. 2016 Jul-Aug;34(4):422-434. doi: 10.1016/j.biotechadv.2015.12.011. Epub 2015 Dec 23. [PMID: 26724184](https://pubmed.ncbi.nlm.nih.gov/26724184/); PMCID: PMC4879088.

This work provides a critical discussion on the limitations of current bioprinting techniques and suggests future directions for achieving functional tissue constructs.

Matai I, Kaur G, Seyedsalehi A, McClinton A, Laurencin CT. Progress in 3D bioprinting technology for tissue/organ regenerative engineering. Biomaterials. 2020 Jan;226:119536. doi: 10.1016/j.biomaterials.2019.119536. Epub 2019 Oct 11. [PMID: 31648135](https://pubmed.ncbi.nlm.nih.gov/31648135/).

A recent review covering advancements in tissue engineering applications, including skin, cartilage, and cardiac tissue bioprinting.