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Advances in three-dimensional bioprinting and artificial intelligence for enhanced tumor modeling: Current progress and future perspectives

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Abstract

Over the past decade, the global increase in cancer prevalence and cancer-related mortality has fueled extensive research to enhance the effectiveness of cancer treatments. Such efforts include the fabrication of lab-grown tissues and organs for transplantation, and the development of *in vitro* models for cancer drug testing and screening. Notably, three-dimensional (3D) tissue models offer advantages over two-dimensional cultures and have benefited from recent advancements in cutting-edge techniques like 3D printing, enabling the reconstruction of various tumor models *in vitro*. In this review, we focus on recent progress in *in vitro* 3D tumor models, with particular emphasis on the roles of 3D bioprinting and artificial intelligence. Furthermore, we provide future perspectives on employing bioprinting to develop tumor models that accurately mimic the complexity and heterogeneity of real tumor microenvironments.

Keywords: Tumor model; Three-dimensional bioprinting; Bioink; Artificial intelligence-powered clinical diagnostic aids

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1. Introduction

As one of the deadliest diseases in the world, cancer is a significant challenge in the medical field. In 2020, the International Agency for Research on Cancer reported that cancer is one of the top causes of death globally.[1] The American Cancer Society's latest estimates for 2024 reveal the magnitude of the challenge, with an expectation of 2,001,140 new cancer cases and 611,720 deaths in 2024.[2] Hence, it is crucial to improve cancer prevention, screening, scientific research, and innovation, particularly for malignant digestive tract tumors. However, developing anticancer drugs is a complex and challenging process,[3] and the outcome of late-stage clinical trials is often uncertain.

Therefore, improving cancer prevention and treatment outcomes requires the development of models that can accurately simulate tumor complexity and heterogeneity. Such models are expected to provide us with a deeper understanding of cancer, support drug development and treatment, and ultimately contribute to more success in the fight against cancer.

2. Recent progress in three-dimensional tumor models

In living organisms, cells reside within a three-dimensional (3D) environment, interacting with neighboring cells and the extracellular matrix (ECM). This milieu regulates vital life processes such as proliferation, differentiation, migration, receptor expression regulation, gene transcription and translation, and programmed cell apoptosis. Despite this, two-dimensional (2D) cell and animal models[4] are unable to simulate complex *in vivo* processes in the laboratory. While 2D cultures are easy to control, they do not accurately represent the 3D growth environment and cellular diversity found[5] *in vivo*, which can substantially alter cell behavior. Animal models, though commonly used as experimental substitutes for human studies due to shared physiological and pathological features, involve lengthy and costly experimental procedures. Moreover, the inherent biological differences limit the direct translatability of findings to human conditions. In addition, animal testing raises ethical concerns and hinders the development of new drugs. Nowadays, researchers are increasingly using 3D models to more accurately simulate human cellular and tumor behavior, addressing limitations in existing models. Such models create 3D structures and microenvironments that simulate real-life conditions, enhancing their reliability for tumor biology studies.[6,7] Using 3D cell culture, researchers can choose from various cell types and scaffold materials that provide physical and biochemical support tailored to experimental needs.[8] 3D culture models offer benefits such as accurately simulating different types of tumors at various stages, serving as powerful tools for cancer research and drug screening.[9] Figure 1 represents the progression in terms of increasing complexity to recapitulate the tumor microenvironment (TME) from 2D cell cultures to bioprinted tumor constructs.

These cell models can be broadly categorized into: (i) co-culture systems that combine multiple cell types, (ii) spheroids and organoids formed through cell self-assembly, and (iii) scaffold-supported structures that utilize ECM-mimetic biopolymeric scaffolds to recreate structural and biochemical cues of the native microenvironment. Table 1 compares the standard tumor models, including animal models and 2D versus 3D cultures, across parameters such as modeling ease, survival rates, build

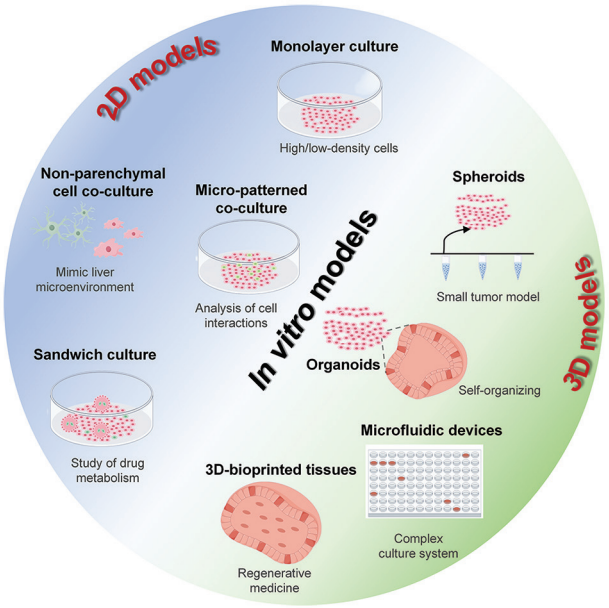

Figure 1. Various cancer models are used in *in vitro* constructs. The figure illustrates the evolution of cell culture models from simple two-dimensional (2D) models to complex three-dimensional (3D) models. Traditional 2D monolayer culture, monolayer co-culture, floating membrane growing cells, and sandwiched monolayer cells are the most common 2D tumor models used in research and drug screening. Cancer cells grown in 3D sphere culture, organoid culture, cancer/matrix cells grown in microfluidic devices, and advanced bioprinted structures are among the 3D cancer models available. Image created by the authors.

time, cost-effectiveness, and biological relevance. Malhão *et al.*[10] successfully inoculated and cultured four human breast cell lines (MCF7, MCF12A, MDA-MB-231, and SKBR3) in multicellular aggregates using a non-stick, low-adhesion culture plate. Watters *et al.*[11] established an organotypic model of the TME of ovarian cancer by co-culturing human mesothelial cells, fibroblasts, and ECM (collagen or fibronectin) and introducing them into ovarian cancer cells. In 2009, Sato *et al.*[12] pioneered experiments with organoid cultures. They cultured small intestinal tissue in a matrix with certain growth factors and unexpectedly discovered approximately six Lgr5 stem cells at the base of the small intestine. Two years after that, a study by Spence *et al.*[13] showed that pluripotent stem cells or embryonic stem cells can be used to create human gut-like organs by differentiating into endoderm and hindgut lineages under defined conditions. From existing models, it is evident that different research teams have made breakthroughs in constructing organoids and TME models using various cell types, and demonstrated the potential of stem cell differentiation and microenvironment simulation in regenerative medicine and tumor research. Designing specific niches for each cell type is critical to avoid the failure of human cancer treatments.

3. Three-dimensional bioprinting for tumor modeling

3.1. Three-dimensional bioprinting

Three-dimensional bioprinting is a revolutionary technology that has emerged as a result of the rapid advancement of 3D additive manufacturing technology and its integration with cells, growth factors, and biomaterials. This technology aims to create biomedical components that closely mimic the properties of natural tissues,[14] opening up unprecedented possibilities in the medical field. 3D bioprinting technology uses computer-aided design to combine cutting-edge technologies from several fields, such as mechanical engineering, materials science, cell biology, and biochemical support. The method typically uses computers, 3D modeling software, polymer materials, and 3D printers. The workflow of 3D bioprinting is shown in Figure 2. These diverse technological factors come together to determine the specific capabilities of 3D bioprinting, showcasing its significant potential and wide-ranging development opportunities.

At present, no universal 3D-bioprinting technique exists that can satisfy all the requirements for ideal tissue fabrication or accommodate every tissue type. In fact, 3D bioprinting technologies have diversified into distinct categories based on their forming principles and printing materials, such as inkjet, laser direct writing, extrusion, and light-curing printing. These technologies have unique advantages and features, contributing to the broader application of 3D bioprinting in the biomedical field. A detailed comparison of these technologies based on critical indicators such as print resolution, print speed,

Table 1. Comparative analysis of commonly used tumor models

Tumor model	Modeling difficulty	Cell survival	Build time	Costs	High-throughput drug screening
Two-dimensional cell model	Easy	Moderate	Short	Low	Suitable
Animal model	Difficult	Moderate	Long	High	Unsuitable
Spheroid	Easy	Low	Short	Moderate	Suitable
Organoid	Easy	Moderate	Short	Moderate	Moderate
Three-dimensional bioprinting	Moderate	Low	Short	High	Moderate
Microfluidic chip	Moderate	High	Short	High	Suitable

Notes: Modeling difficulty refers to the technical complexity in constructing the model, cell survival refers to the viability of cells during/after modeling, build time refers to the approximate time required to establish the model, cost is the relative financial cost, and high-throughput screening refers to the compatibility with automated, large-scale drug testing platforms.

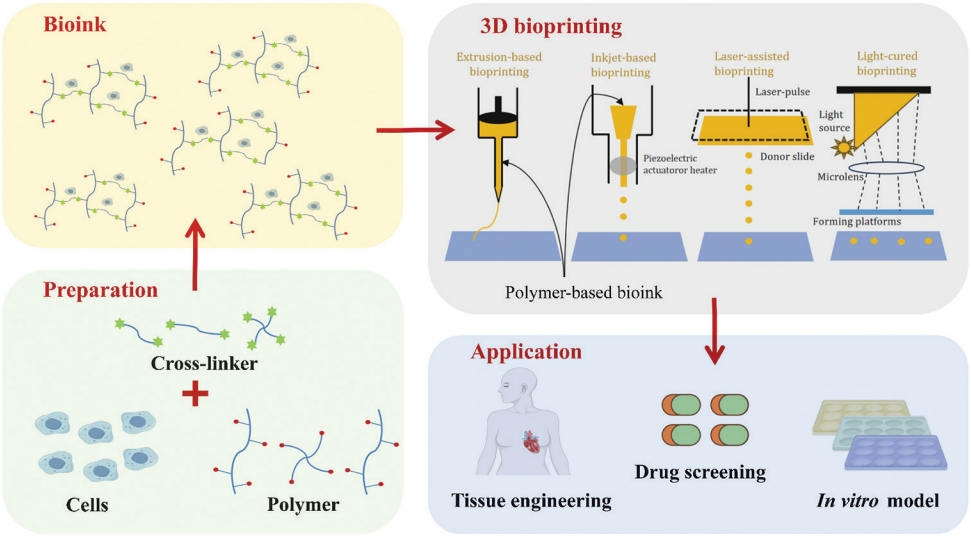

Figure 2. A common workflow of three-dimensional (3D) bioprinting processes. Modeling and designing 3D printable structural objects using computer-aided design software. Before 3D bioprinting, designs could be easily corrected and changed. After preparation, the cells are mixed with the material and the crosslinker, and the bioink is configured. The most suitable printer has to be selected for printing according to different properties and applications. Bioprinted scaffolds can be applied to tissue engineering, drug screening, and *in vitro* culture. The components of cells and the human body were drawn using FigDraw.

cell viability, and material usage is presented in Table 2. Table 2 shows that different 3D bioprinting technologies exhibit significant differences in various metrics. For example, inkjet printing may have better resolution and higher speed compared to other methods, while laser direct writing printing may be superior for cell viability and material efficiency. Extruded and light-cured printing also have unique characteristics and application scenarios. These differences allow researchers to choose the most appropriate 3D bioprinting technology for their needs, promoting advances in biomedical research and innovations in clinical treatments. Moreover, ongoing technological progress continues to yield more efficient, accurate, and reliable 3D bioprinting technologies, which may significantly contribute to human health.

Table 2. Attributes of three-dimensional bioprinting technologies

Causality printing method	Resolution	Printing speed	Cell viability (%)	Material usage
Inkjet-based bioprinting	High	Fast	≥85	High
Laser direct writing bioprinting	High	Middle	≥95	Low
Extrusion-based bioprinting	Middle	Slow	40–80	High
Light-cure bioprinting	High	Slow	≥85	Medium

Similar to office printers, inkjet-based 3D bioprinting uses piezoelectric or thermally driven printheads to precisely eject bioink from an ink cartridge into tiny droplets. These tiny droplets are deposited in layers onto a substrate to construct complex 3D structures of living tissues with fine spatial control[15] (Figure 3A). Inkjet printing technology is well-regarded for its high-resolution capability.[16] Park *et al.*[17] demonstrated precise localization of alveolar cells in a cell culture matrix using inkjet printing technology. A 10-micron-thick model of a three-layer alveolar barrier was created to mimic the structure, morphology, and function of actual lung tissue. In addition, inkjet 3D bioprinters are typically equipped with multiple printheads to print different bioinks simultaneously, which accelerates the printing process.[18-23] However, inkjet printing has limitations due to the low driving pressure of the printheads, which hampers the handling of highly viscous materials and concentrated bioinks. In addition, thermally driven printheads can generate heat when

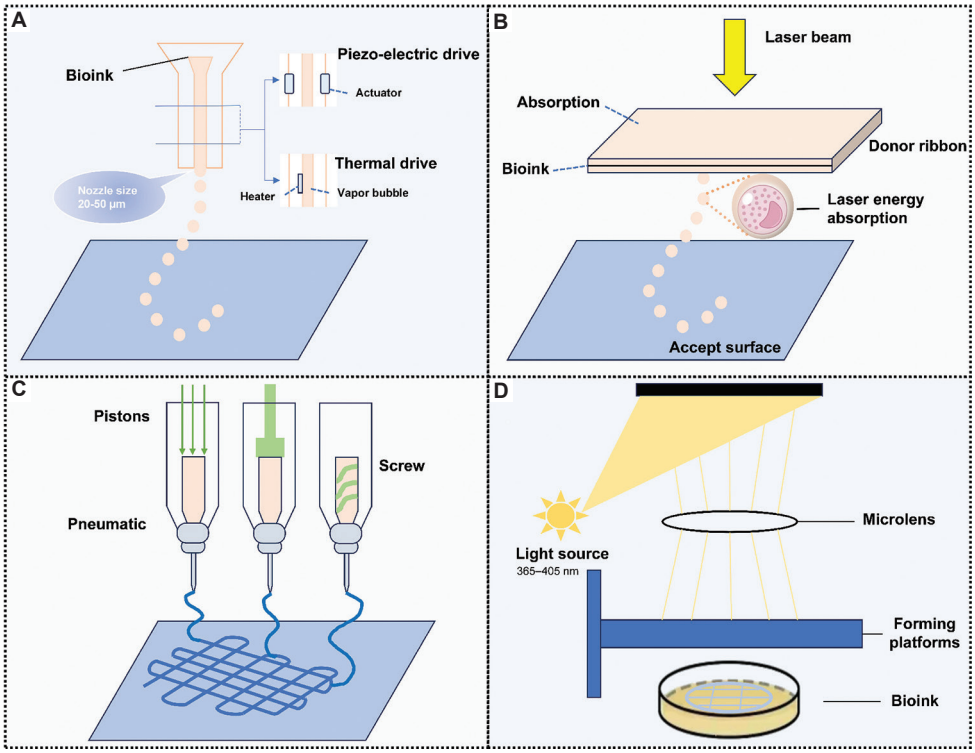

Figure 3. Three-dimensional bioprinting technologies. (A) Droplet-based inkjet bioprinting driven by piezoelectric or thermal actuation. (B) Laser-assisted bioprinting uses a laser beam to transfer bioink from a donor ribbon to an acceptor surface through laser energy absorption. (C) Extrusion-based bioprinting, driven by pneumatic, piston, or screw mechanisms, is suitable for high-viscosity bioinks. (D) Light-assisted bioprinting (e.g., digital light processing) that utilizes patterned light (365–405 nm) through microlens arrays to selectively solidify photosensitive bioinks. Image created by the authors.

printing, which may harm cells, limiting the widespread use of inkjet 3D bioprinting.

Laser direct writing technology was first used to make metal stencils.[24-42] However, in the early 21st century, Odde and Renn[43] first introduced live cell printing using laser direct writing 3D bioprinting technology, which greatly contributed to its rapid development. In this process, bioink is uniformly deposited on a layer that absorbs it. A high-energy laser beam is then used to penetrate the glass substrate and sinter or cure the biomaterial layer by layer in a controlled manner, allowing it to be precisely deposited onto a forming platform[44] (Figure 3B). It is worth noting that laser direct writing technology uses a nozzle-less inkjet printing method. This feature avoids direct contact between the bioink and the processing device, significantly reducing cell mechanical damage. As a result, the cells can maintain a high activity level during the printing process. In addition, laser writing is suitable for printing thick biomaterials, increasing its potential uses.[45]

Extruded 3D bioprinting technology, the most widely used method, is particularly well-suited for printing high-density cells or thick biomaterials,[46] functioning in a manner similar to fusion printing technology.[47] The bioink is extruded in a controlled manner through precise control of the air pressure, piston, or screw. The nozzle's ability to move in the X-Y-Z direction ensures that the bioink is deposited accurately, creating the desired intricate pattern (Figure 3C). This technology has the unique ability to continuously extrude and form continuous fiber-like structures. This feature allows 3D bioprinting[39,42,48-56] technology to effectively print polymers with different viscosities and varying cell concentrations, making it suitable for a wide range of applications. This technology can be used to create structurally robust and morphologically diverse biological tissue models.

In the 1980s, light-curing technology emerged as an advanced process in 3D printing, primarily using photosensitive resins as the principal printing materials.[57] With ongoing technological progress, the potential advantages of applying light-curing technology in bioprinting have begun to be explored innovatively. There are two types of light-curing printing technology: stereolithography and digital light processing (DLP)[29,32,57-65] (Figure 3D). Stereolithography is a special 3D printing method that uses light to selectively solidify bioinks and create precise structures. The material is cured layer by layer, gradually accumulating and stacking to form the desired 3D scaffold.[66] DLP[67] uses ultraviolet or visible light through the digital micromirror device to form 2D shapes, constructing them into 3D structures. Although both stereolithography and DLP share similar principles, they differ in their technical implementation. Compared to other bioprinting methods, light-curing devices are simpler and easier to control. However, the use of ultraviolet light and photoinitiators still poses challenges, as they can potentially damage cells. As research continues and technology advances, light-curing technology is anticipated to have more applications in bioprinting.

Three-dimensional bioprinting technologies have demonstrated distinct advantages in constructing tumor models, and the choice of printing modalities should be closely aligned with the biological characteristics of specific tumor types. Extrusion-based bioprinting, due to its high cell-loading capacity (>10^7 cells/mL) and mechanical stability, is particularly suitable for fabricating matrix-dense tumors such as cholangiocarcinoma and pancreatic cancer. Using this approach, Mao *et al.*[68] successfully recapitulated the fibrotic microenvironment of patient-derived cholangiocarcinoma xenograft, achieving a gemcitabine resistance prediction accuracy of 89% (p<0.01). This success was primarily attributed to the precise simulation of the ECM barrier effect.[68]

For tumors that require accurate vascular network simulation, such as gliomas and metastatic breast cancer, the microscale resolution (~20 μm) of light-assisted bioprinting (e.g., DLP) is essential. Peng *et al.*[69] constructed a vascularized glioma model using DLP technology, in which human umbilical vein endothelial cell-patterned vasculature increased cancer cell migration distance by 3.2-fold, significantly enhancing the model's value for studying blood–brain barrier penetration.[69]

In high-throughput drug screening scenarios, inkjet-based bioprinting facilitates the rapid production of tumor microarrays (>200 models/h), thereby accelerating treatment strategy optimization. For example, Chen *et al.*[70] used inkjet bioprinting to construct a hepatocellular carcinoma model that successfully demonstrated the synergistic effect of sorafenib and radiotherapy, increasing the accuracy of personalized treatment prediction to 82%.[70]

Notably, the functional integration of key components of the TME, such as immune cell infiltration and hypoxic gradients, is becoming a central focus in tumor bioprinting. Cui *et al.*[71] embedded chimeric antigen receptor-T cells into a glioblastoma model, resulting in a 67% increase in T-cell infiltration depth compared to conventional models, offering a more precise platform for immunotherapy research.[71]

These advancements highlight a paradigm shift in bioprinting technology, from generalized tissue fabrication to tumor-specific customized models, with early translational potential demonstrated in patient-derived

organoid- or patient-derived xenograft-based drug sensitivity testing.

3.2. Bioink

Bioink, the core material for 3D bioprinting, is a complex system that includes scaffolding materials, cells, and a variety of biological and chemical factors, as well as crosslinking agents to ensure a smooth printing process. The term was first introduced in a 2003 article on organ printing[72] alongside the concept of biopaper. Initially, bioinks were used in 3D cultures to support cellular components in hydrogels. With advances in bioprinting technology, the incorporation of cellular components such as nuclei and cell clusters has become increasingly important in bioink formulations. Unlike traditional 3D printing materials, bioinks used in 3D bioprinting are typically designed to be biocompatible and often bioactive, with mechanical properties tailored to the target tissue, ranging from flexibility for soft tissue to rigidity for bone applications.[73] Bioinks support cell viability and function, maintain structural fidelity during the printing process, and promote the formation of functional biological constructs. However, an ideal bioink that meets all biological, mechanical, and printability requirements has yet to be fully realized. Researchers must comprehensively consider various factors when developing bioinks, such as the performance of 3D bioprinters (including printing speed, extrusion pressure, and printing temperature), biocompatibility support for cellular activity and growth, degradability, and cell adhesion. Collectively, these constitute the complex challenges of bioink development and serve as the driving force in the field.[74] Hospodiuk *et al.*[75] conducted the first comprehensive review comparing the properties, advantages, and disadvantages of various bioink materials, where they discussed the current limitations of bioink materials and provided insights into future directions, offering a comprehensive view of the present and potential future of bioinks.

Natural hydrogels, derived from plant or animal origins, are highly hydrophilic materials composed of 3D polymer networks crosslinked through physical or chemical bonds and contain a high proportion of water. The unique structure and composition of natural hydrogel make it suitable for a wide range of applications. Type I collagen, renowned for its biocompatibility, has become a widely used material in 3D bioprinting, leading to new possibilities in biomedical engineering.[74] Gelatin is a natural substance made from proteins found in animal skin and bones[76] and is essential in pharmaceutical manufacturing and various industrial applications.[77] Fibrin hydrogel is activated by thrombin to initiate the fibrinogen process, leading to the bonding of fibrin molecules and the formation of a stable fibrin clot.[78]

These commonly used natural hydrogels are highly appreciated for their superior bioactivity. They mimic the ECM microenvironment of body tissues, providing ideal conditions for the growth of printed cells and facilitating cellular communication. In 3D bioprinting, the fluidity of bioinks is critical, as they must solidify and retain their shape rapidly after printing. Therefore, the malleability of bioinks is a key element in successful printing. However, natural hydrogels have limitations under physiological conditions, such as reduced stability and inferior mechanical properties (e.g., strength and toughness) compared to synthetic hydrogels. Therefore, natural hydrogels may not meet the requirements for certain applications. Over the years, research into synthetic hydrogels has increased.[79] Synthetic hydrogels have significantly improved the stability of bioinks by combining physical, chemical, mechanical, and physiological support and incorporating other components. In addition, the mechanical properties of synthetic hydrogels can be adjusted to ensure suitability for 3D printing, providing a broader perspective for 3D bioprinting.[80]

Gelatin methacryloyl has a high mechanical strength and low swelling rate, making it suitable for blending with other hydrogels to enhance cell survival. These properties position Gelatin methacryloyl as a promising biomaterial for tissue engineering.[81,82] Polyethylene glycol-based hydrogels, which have been approved by the Food and Drug Administration for use in the biomedical field, can provide temporary structural support in the fabrication of complex 3D tissue-engineered structures.[74] However, synthetic hydrogels generally exhibit lower intrinsic biocompatibility compared to natural hydrogels, despite being more cost-effective and offering greater tunability in mechanical and chemical properties.[83] Therefore, the choice between natural and synthetic hydrogels can be guided by several factors, including application need, performance criteria, and cost considerations. As shown in Table 3, these considerations can facilitate making well-informed decisions to meet the varying needs of different applications.

Three-dimensional bioprinting technology is widely used in clinical medicine for the fabrication of bone and cartilage,[85] skin,[86] heart, and muscle tissue.[87] While bioprinted tissues and organs can be used to treat diseases, significant challenges in tissue engineering remain. There is an urgent need for bioinks that not only meet essential criteria – such as biocompatibility, appropriate degradation rates, and mechanical strength – but are also cost-effective.

To construct 3D tumor models suitable for different purposes, researchers need to review a wide range of existing studies and identify solutions, such as

Table 3. Comparative summary of common natural and synthetic bioinks used in three-dimensional bioprinting[75,84]

Classification	Bioink	Crosslinking method (time)	Concentration	Formability	Feature resolution	Cell viability (%)	Cellular support capacity
Natural hyaluronic	Collagen type I	Thermal (one to several minutes)	0.025–0.5%	Poor	200–1,000 μm	33–95	High
	Gelatin	Thermal (5 min)	7–20%	Moderate	350–1,000 μm	85–90	High
	Fibrin	Enzymatic (seconds to 6 min)	10–60 mg/mL or 20–50 U/mL	Good	144–750 μm	~74	Moderate
	Agarose	Thermal (minutes to 2 h)	0.3%	Good	250 μm	90–98.8	High
	Chitosan	pH-mediated (2 h)	3%	Poor	400–500 μm	–	Moderate
	Alginate	Ionic (seconds)	0.1–8%	Moderate	400–600 μm	90.8–95	Low
	Hyaluronic acid	Photo/pH-mediated (3–10 min)	1.5%	Good	200–760 μm	–	High
Synthetic hyaluronic	Gelatin methacryloyl	Photopolymerization (10 s–10 min)	5–20%	Good	150–750 μm	63.2–97	High
	Polyethylene glycol	Photopolymerization (up to 19 min)	10–20%	Moderate	168–550 μm	89–90	Moderate
	Pluronic® F-12	Thermal (minutes)	25–30%	Good	150–600 μm	60–91.3	Low

incorporating growth factors, adjusting material ratios, or using different hydrogels, to improve cell survival and phenotypes. Cutting-edge methods such as 3D bioprinting and microfluidics have been used to create effective tumor models for cultivation, with quality evaluation based on cell viability, morphology, proliferation, and differentiation.

Chen *et al.*[88] used 3D bioprinting to develop a colorectal cancer model by constructing a biological scaffold and co-culturing HCT116 human colorectal cancer cells with tumor-associated endothelial cells. The 3D scaffold effectively supported the cells and maintained physiological processes such as cell adhesion, proliferation, stemness retention, and vascular conservation. In the model, the activated stromal stem cells expressed multiple tumor-associated factors and dense ECM. The tumor tissues exhibited transcriptomic features closely resembling those found in real tumors. Sbirkov *et al.*[89] constructed a cost-effective 3D-printed Caco-2 human colon cancer model with a histological appearance that is similar to adenoid tissue. The model's RNA expression profiles were characterized by enhanced cell adhesion, hypoxia-related signatures, upregulation of genes in the epidermal growth factor receptor/Kirsten rat sarcoma viral oncogene homolog pathway, and downregulation of genes involved in cell cycle regulation. Chemotherapeutic drug testing experiments showed that the overall drug resistance of tumor cells in the 3D-printed model increased compared to 2D cultures, closely resembling the drug responsiveness of tumors *in vivo*. The researchers suggested that the platform can be expanded to include primary colorectal cancer samples, making it a promising platform for novel, individualized drug screening.

4. Artificial intelligence (AI) in three-dimensional bioprinting

With the advancement of novel productive forces, 3D bioprinting is encountering increasingly stringent demands. These demands include enhanced biocompatibility and mechanical properties in material selection[90] and the need to attain a high degree of precision and stability during the printing process.[91] In addition, real-time monitoring and adjustment of the printing process are necessary to ensure the quality of the final product. These challenges have driven scientists to explore novel approaches for optimizing 3D bioprinting technology, with the integration of AI opening new opportunities in the field.[92,93]

As a crucial component of modern science and technology, AI can learn and analyze vast amounts of data, extracting patterns to make predictions and optimizations.[94] This capability makes AI widely applicable in 3D bioprinting. AI technology enables intelligent optimization of material formulations,[95] real-time adjustment of printing parameters, and precise control over the final product quality,[96] thereby significantly enhancing the efficiency and quality of 3D bioprinting.

This section aims to explore the specific applications of AI technology in extrusion 3D bioprinting, with a focus on three key areas: bioink formulations, printing parameter optimization, and quality control. First, this section will discuss the role of AI in optimizing bioink formulations, then explore its application in printing parameter optimization, and finally analyze its specific use in defect detection and quality assessment (Figure 4). These discussions aim to provide valuable insights and lessons for the field of 3D bioprinting.

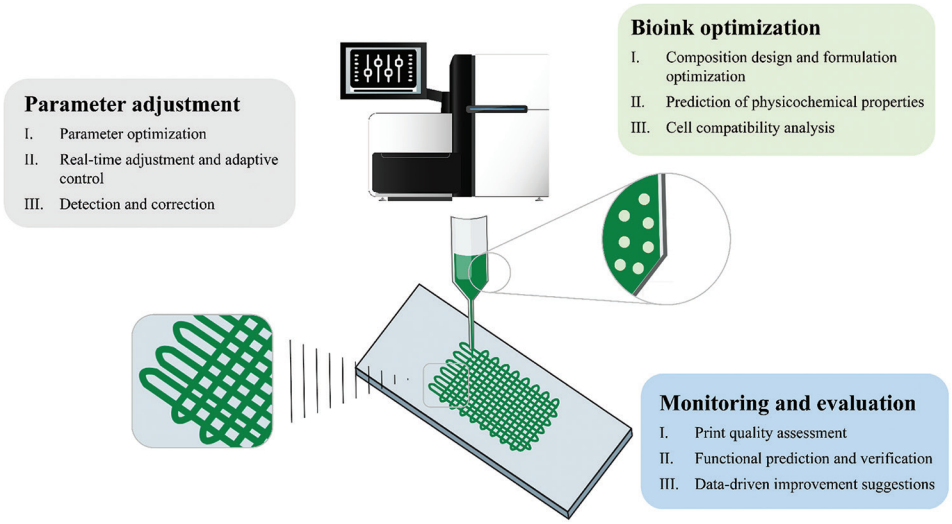

Figure 4. Application of artificial intelligence in three-dimensional bioprinting. Image created by the authors.

4.1. Bioink formulation optimization

In 3D bioprinting, the multi-dimensional nature of characteristic variables complicates the identification of suitable printing conditions. As the foundation of bioinks, the physicochemical properties of biomaterials determine the feasibility of meeting specific printing requirements.[97] However, changes in biomaterial composition and formulation can lead to highly nonlinear variations in these properties. Therefore, given the challenges posed by such complex variables, AI has emerged as a powerful tool for rapid selection and optimization of printing parameters.[98,99]

Chen *et al.*[100] assessed the printability of 210 ink formulations derived from six biomaterials and developed a printability prediction model using a machine learning (ML) algorithm with over 80% accuracy. Hashemi *et al.*[101] utilized a Bayesian optimization algorithm to create a chitosan-gelatin-agarose bioink, which exhibited good cell morphology and viability, along with optimal rheological properties, degradability, and hydrophilicity. These studies demonstrate that ML algorithms can effectively predict print suitability and optimize materials and formulations for specific printing needs. However, this approach is limited, as it only supports formulation screening under specific printing parameters and does not serve as a general modeling method for evaluating biomaterials.

4.2. Printing parameter optimization

In the actual printing process, both bioink and printing parameters jointly determine printability. Therefore, to achieve good printability, it is essential to optimize both simultaneously. Ruberu *et al.*[102] created an optimization algorithm using ink formulation, pressure, printing speed, platform temperature, and ink reservoir temperature as input features, with printability scored quantitatively as the objective. They employed a Bayesian optimization algorithm to iteratively refine the ink formulation and printing parameters, significantly reducing the number of experiments needed to find the optimal values. However, this method still overlooks the material itself. Rheological properties, particularly in hydrogels, such as viscosity, viscoelastic shear moduli, elastic recovery, and shear stress, significantly influence printability.[103] Thus, incorporating the physicochemical properties of materials (e.g., mechanical and rheological properties) into modeling could enable multiscale printability prediction. Lee *et al.*[104] discovered that a high elastic modulus improves shape fidelity and permits extrusion at lower critical yield stresses with the aid of ML. Through multivariate regression analyses, they derived various formulations of naturally derived bioinks that maintain high shape fidelity. This innovative approach to optimizing ink formulations from the perspective of material rheology demonstrates a comprehensive printability assessment by integrating the rheological properties of biomaterials (e.g., shear storage, loss modulus, viscosity, and shear-thinning properties)[95] into the printability evaluation model. By studying the correlation between the rheological properties of materials and printing processes, we can better understand the theoretical basis affecting bioink printability. This allows for a more accurate evaluation of factors such as extrudability, shape fidelity, and cell viability during printing. Establishing a printability evaluation model based on material property interpretability ensures that

the ML model is not just a black box but a scientifically grounded, generalized evaluation model.

4.3. Quality control

Throughout the 3D bioprinting process, AI intervention in automated defect detection and quality assessment is a promising approach for establishing better evaluation criteria with quantitative indexes. Conventional intelligent algorithms can effectively handle basic quality assessment tasks. For instance, the structural similarity method used by Fastowicz and Okarma[105] employs a Monte Carlo approach to randomly select regions for comparison and additional region matching, achieving reliable accuracy in classifying high- and low-quality printed samples. However, such algorithms are insufficient for more complex evaluation characteristics and control requirements. Instead, integrating AI with control systems allows real-time use of evaluation results during the 3D bioprinting process. For example, Paraskevoudis *et al.*[106] assessed the quality of fused filament fabrication 3D-printed objects during printing through AI-based computer vision. Based on the assessment, the printing process can be terminated, or the parameters related to detected defects can be adjusted. This approach is also applicable to real-time extrudability evaluation in 3D bioprinting. In addition, Jin *et al.*[92] developed an anomaly detection system using layer-by-layer sensor images and ML algorithms to distinguish and categorize defects in transparent hydrogel-based bioprinting materials, enabling real-time autonomous correction of process parameters. These methods effectively evaluate and regulate the 3D bioprinting process, leading to efficient printing decisions and high-quality tissue construction in specific target environments. Furthermore, the concept of large models also introduces generalization possibilities for defect detection and real-time regulation in 3D bioprinting. Brion and Pattinson[107] created a large and diverse dataset of extruded 3D prints based on images automatically labeled according to deviations from optimal printing parameters. They employed neural networks and control loops for real-time detection and rapid correction of various errors, demonstrating effectiveness across different 2D and 3D geometries, materials, printers, tool paths, and extrusion methods. Consequently, AI-driven computer vision techniques are increasingly capable of achieving high-quality print result detection, with deep learning networks playing a central role in defect detection and modeling the evaluation of 3D bioprinting outcomes.

5. AI in three-dimensional tumor models

AI technology is progressively transforming the cultivation of 3D tumor models by enhancing image recognition, feature extraction, and data analysis capabilities. These advances have significantly improved the efficiency of model evaluation and the accuracy of drug efficacy prediction. AI not only optimizes culture conditions and reduces reliance on animal experiments, but also enhances the precision of TME modeling, thereby supporting personalized drug screening.[108] For instance, Chen *et al.*[109] developed the spheroid monitoring and AI-based recognition technique, which employs convolutional neural networks to automatically identify the boundaries formed during 3D tumor spheroid culture and quantify their invasive characteristics, thereby improving the assessment of dynamic behaviors during cultivation.[109] Mali *et al.*[110] proposed an end-to-end deep learning pipeline that integrates a U-Net model with a convoluted neural network-based regression network to automatically detect and classify spheroid morphology and cell viability, achieving a prediction accuracy of up to 98%. This provides an effective tool for high-throughput drug screening.[110] These studies offer substantial practical value for optimizing and advancing 3D tumor model cultivation, laying a strong foundation for the multiscale application of AI in this field.

However, it is important to note that current applications of AI in 3D tumor models often lack continuity and integration. Future research should focus on the comprehensive evaluation of specific models such as tumor spheroids, organoids, and matrix-embedded models. This evaluation should be based on a set of indicators, including morphological structure, cell viability and proliferation capacity, cellular heterogeneity, and stemness. Furthermore, the application of multi-objective optimization algorithms may lead to the development of robust AI-based strategies for evaluating and improving 3D tumor models.

6. Three-dimensional bioprinting market

Bioprinting, as a revolutionary technology in the fields of regenerative medicine and tissue engineering, has made significant progress in recent years and demonstrated immense application potential. Technologically, bioprinting is rapidly evolving, with new materials and printing technologies continually emerging, making it increasingly feasible to construct more complex and functional tissues and organs. The current advances in bioprinting technology are primarily reflected in several areas. First, there has been a significant increase in the diversity of bioinks, including natural polymers, synthetic polymers, and composite materials, which more accurately mimic the characteristics of ECM *in vivo*, improving cell viability and tissue functionality.[75] Second, multi-cell type and multi-material composite tissue printing have gradually advanced, better replicating the biological complexity

of tissues, for example, the successful construction of vascularized tissues through simultaneous printing of stem cells, endothelial cells, and supporting cells.[111] In addition, researchers have constructed functional tissues, such as skin, cartilage, and small organ-like structures – by precisely controlling microenvironmental factors (e.g., mechanical strength, porosity, degradability, and the release of bioactive molecules) – which exhibit higher biocompatibility and functionality.[112] Moreover, integration of bioprinting technology with emerging technologies such as AI, nanotechnology, and microfluidics can further enhance printing precision and efficiency, accelerating the development of personalized medicine.[113]

7. Future perspectives

Three-dimensional cell culture technology has demonstrated significant advantages in modern biomedical research, as it can more realistically simulate the complex growth environment of cells *in vivo* than in traditional 2D cultures. In addition, 3D cell culture technology can partly replace animal experiments, reducing the need for animals and ethical concerns. This method boosts the production of cytokines, antibodies, and other vital biomolecules and improves the overall efficiency of cell culture. 3D cell culture provides a powerful tool for in-depth research on the mechanisms of tumor occurrence and development for screening drugs. Cutting-edge technologies for constructing and cultivating 3D models have garnered the attention of researchers to improve the quality of the existing models. In this context, 3D bioprinting has shown several advantages, allowing cells to grow in a 3D scaffold with controlled fine structures to improve the microenvironment for tumors. However, the existing 3D bioprinting techniques have limitations in fully replicating the ECM structures and functions. Specifically, the current challenges include: (i) difficulties in precisely depositing cells and biomaterials to simulate complex structures, leading to models that lack the physiological relevance of actual tumors, and (ii) the inability of bioinks to accurately mimic the biomechanical and biochemical properties of tumor ECM, which hinders the maintenance of cancer cell functions and interactions within the printed tissue. To address these challenges, pioneering efforts on the printing side have explored approaches such as combined coaxial[114] and multi-material printing,[115] enabling the construction of complex, multi-layered tissues that more accurately replicate physiological features in tumor models. AI is anticipated to make significant contributions to these research fields in the near future. Recently, the AI-guided bioink design has facilitated the development of engineered and composite bioinks[116,117] that fulfill specific mechanical and chemical requirements, enabling more effective fabrication of tumor models that better mimic physiological functions and interactions.

Over the past decade, bioprinting has undergone rapid development, driven by multiple factors. The increase in medical demand is one of the main drivers, especially in the fields of organ transplantation and personalized medicine. The persistent global shortage of organs makes bioprinting particularly valuable in fabricating artificial organ and tissue substitutes.[118] In addition, increased research and development investment from governments and research institutions globally and significant capital inflows have accelerated technological development and market growth.[119] Despite its vast potential, bioprinting's market growth still faces regulatory and ethical challenges. For instance, obtaining clinical application approval and certification for printed complex organs or tissues may involve lengthy approval processes. Social and ethical issues must also be considered, particularly in applications involving human cells and gene editing.[120] Beyond medical applications, bioprinting holds significant potential in non-medical fields such as drug development, cosmetic testing, and environmental science. Applications such as 3D-printed liver organoids for drug testing and artificial skin models for cosmetic testing further expand the market for bioprinting.[121]

Looking ahead, the prospects for bioprinting technology are highly promising, with continued rapid development anticipated, driven by ongoing technological innovation, growing market demand, and evolving regulatory frameworks. In terms of technological innovation, future optimizations of bioprinting will focus on achieving higher printing precision and fabricating more complex tissue structures. It will leverage new bioinks, nanomaterials, and microfluidic technologies to achieve more precise control over cells and tissues, which will more accurately simulate complex biological microenvironments.[87] The demand for personalized medicine will further promote the development of bioprinting applications, enabling more targeted treatment plans by combining patient cell and genetic data.[74] In addition, the development of smart bioink materials will significantly enhance the functionality of 3D-bioprinted tissues, such as dynamically regulating cell behavior and tissue function by gradually releasing drugs or growth factors in response to specific physiological or pathological stimuli.[122]

From a market standpoint, the application areas of bioprinting are expected to diversify further. It is anticipated that bioprinting will achieve breakthroughs in areas such as tissue and organ transplantation, new drug development, and toxicity testing, further reducing organ shortages for transplants, optimizing drug development processes, and

lowering research and development costs and time.[123] As technology advances and costs decrease, the bioprinting market is projected to maintain a strong compound annual growth rate over the next decade, especially in emerging economies like China and India, where growth is expected to be faster.[124] However, future market expansion must still address multiple challenges, including the gradual improvement of regulatory standards and the resolution of ethical issues.[125] Further development of bioprinting will depend on strengthening interdisciplinary research and building cross-industry collaborations. Integrating knowledge and methods from multiple disciplines will drive technological advancement and market expansion.[126]

As 3D bioprinting technology evolves, AI integration enables more efficient and precise tasks, such as optimizing bioink formulations, adjusting printing parameters, and enhancing quality control.[95,100-107] Although AI applications in 3D bioprinting have made significant progress, challenges remain, including high dependence on large datasets and limited model interpretability in practical use.[127,128]

To overcome these challenges, future research should focus on developing algorithmic models guided by the physicochemical properties of the printed materials. These models can better cope with the complexity and diversity of different materials and printing conditions, even with limited data. In addition, further exploration of multimodal learning, which integrates diverse data sources such as rheological properties and biological performance data, could improve accuracy and reliability. Shifting toward larger, more accessible datasets and embracing open science principles will foster global research collaboration, further advancing AI-driven 3D bioprinting technologies.[129,130] It is expected that AI is set to become a central force driving innovation in 3D bioprinting, and this incorporation will be beneficial for tumor tissue engineering and unlocking new opportunities in biomedical engineering and regenerative medicine. In parallel, AI is also reshaping the cultivation and evaluation of 3D tumor models; however, systematic research is still needed to establish standardized frameworks for model assessment, enhance consistency across applications, and fully realize the potential of AI-driven optimization in this field.

In summary, 3D bioprinting technology aims to enhance printing accuracy and construct complex tissues, advancing personalized medicine. Market applications will diversify, especially in tissue transplantation and drug development, but regulatory and ethical challenges must be addressed. AI will drive technological innovation, enabling bioprinting to create new opportunities in the fields of oncology, tissue engineering, and regenerative medicine.

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Conflict of interest

The authors declare that they have no conflicts of interest.

Author contributions

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Ethics approval and consent to participate

Not applicable.

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Availability of data

The datasets used and analyzed during the present study are available from the corresponding author on reasonable request.

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