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REVIEW ARTICLE

Robotic-assisted automated *in situ* bioprinting

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Abstract

In situ bioprinting has emerged as a promising technology for tissue and organ engineering based on the precise positioning of living cells, growth factors, and biomaterials. Rather than traditional *in vitro* reconstruction and recapitulation of tissue or organ models, the *in situ* technology can directly print on specific anatomical positions in living bodies. The requirements for biological activity, function, and mechanical property in an *in vivo* setting are more complex. By combining progressive innovations of biomaterials, tissue engineering, and digitalization, especially robotics, *in situ* bioprinting has gained significant interest from the academia and industry, demonstrating its prospect for clinical studies. This article reviews the progress of *in situ* bioprinting, with an emphasis on robotic-assisted studies. The main modalities for *in situ* three-dimensional bioprinting, which include extrusion-based printing, inkjet printing, laser-based printing, and their derivatives, are briefly introduced. These modalities have been integrated with various custom-tailored printers (*i.e.*, end effectors) mounted on robotic arms for dexterous and precision biofabrication. The typical prototypes based on various robot configurations, including Cartesian, articulated, and parallel mechanisms, for *in situ* bioprinting are discussed and compared. The conventional and most recent applications of robotic-assisted methods for *in situ* fabrication of tissue and organ models, including cartilage, bone, and skin, are also elucidated, followed by a discussion on the existing challenges in this field with their corresponding suggestions.

Keywords: *In situ* bioprinting; Robot configurations; Robotic-assisted bioprinting

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1. Introduction

Three-dimensional (3D) printing is a technique that deposits and accumulates materials through computer-aided design and manufacturing to construct physical entities[1]. In the early stages of its technological development, 3D printing was considered merely befitting for the fabrication of functional or aesthetic prototypes, and thus the term rapid prototyping was often adopted to represent this technique[2]. 3D printing is now used synonymously with additive manufacturing since its precision, efficiency, reproducibility, and robustness have been greatly enhanced to the industrial-production level[3]. 3D printing simplifies the processing procedure and minimizes the cost of personalized

production. As an extension of additive manufacturing, bioprinting is a state-of-the-art technology that involves layer-by-layer deposition of a mixture of cells, matrix, and nutrients to produce living tissues and potentially whole organs, such as blood vessels, bones, heart, and skin[4]. By means of this, sophisticated 3D tissues and organs with recapitulated biological functions can be constructed for numerous applications, including drug screening[5], disease modeling[6], pathological and pharmacological analysis[7], as well as regenerative medicine[8]. The use of bioprinting in medical training and testing tasks has advanced in the past two decades. Manifold reports have demonstrated the successful fabrication of various tissues and organs[9] for streamlining early surgical planning models and permanent implants, as well as cell-seeded biocompatible scaffolds or *in vitro* biological models (Figure 1). To create an environment that supports fast and efficient cell growth, cells are often seeded around scaffolds made of biodegradable polymers or collagen, which eventually grow into functional tissue[10]. However, *in vitro* 3D scaffolds have many inherent limitations with regard to their actual clinical applications[11]. Since 2007, *in situ* bioprinting (*i.e.*, *in vivo* bioprinting) has been proposed based on inkjet technology[12]. *In situ* bioprinting can be defined as the direct printing of living cells, growth factors, and biomaterials to create or repair living tissues or organs at a defect site[13]. This technology involves complex shapes, curved surfaces, or even more intricate geometries with heterogeneous compositions, whereas conventional 3D printing usually adds materials layer-by-layer to a flat substrate[14]. Robotic-assisted automated printers or handheld printers are the leading platforms for *in situ* bioprinting. Among these, computer-controlled robots, which can be programmed to aid in biomaterials positioning and manipulation, have shown effectiveness in simplifying and improving the *in situ* operation[15]. Robotic-assisted operation facilitates *in situ* bioprinting with higher accuracy, flexibility, and control. To date, robotic arms with Cartesian, articulated, and parallel configurations have been developed for biofabrication. Moreover, technologies of robotic-assisted minimally invasive surgery can be integrated with 3D bioprinting to improve printing accuracy and dexterity. Particularly, by combining progressive innovations of biomaterials, automation, digitalization, and tissue engineering, robotic-assisted *in situ* bioprinting is becoming more attractive and realistic[16,17], and a number of studies have verified its exceptional potential for use in clinical settings[18-20].

In this review, we discuss the progress of *in situ* bioprinting, with emphasis on robotic-assisted approaches and platforms. The mainstream modalities and advanced methodologies for *in situ* 3D bioprinting are introduced, and the prototypes and commercial products based on different configurations, including Cartesian coordinate, articulated, and parallel robots, for *in situ* fabrication are compared and discussed. The classic utilizations and potential application models for robotic-assisted fabrication of *in situ* tissues and organs, such as cartilage, bone, skin, and liver, are elucidated. In addition, we briefly discuss the existing challenges and provide suggestions for future improvements from the perspectives of individualized medicine, robotics, and information science.

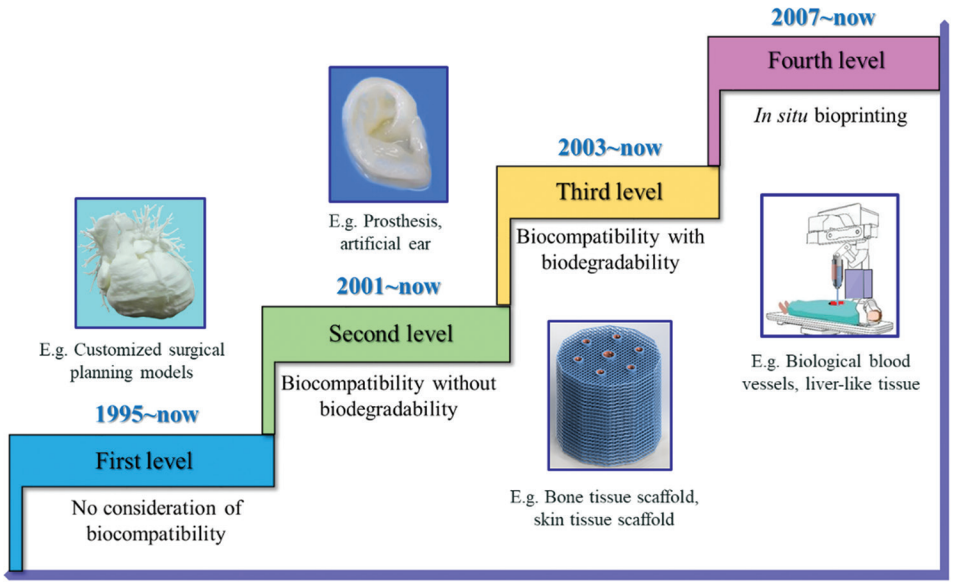

Figure 1. Development of bioprinting.

2. *In situ* bioprinting modalities

2.1. Extrusion-based bioprinting

Extrusion-based bioprinting involves the continuous deposition of bio-ink through syringes or nozzles to construct 3D tissues or organs[21]. Applied pressure, piezoelectric effect, and solenoid dispensing have been employed by bioprinters of this type. Extrusion-based bioprinting generally offers gentle fabrication with high regard for cell viability. One of the most promising features of this technology lies in the fact that multiple cells and biocompatible materials can be simultaneously applied through different nozzles. Furthermore, it is regarded as the most mature solution for *in vivo* clinical applications, owing to its decadal recognition in arthroscopy repair. Commercial bioprinters that are based on this technology have been successfully developed.

2.2. Inkjet bioprinting

In inkjet bioprinting, bio-ink is sprayed onto the deposition substrate via droplet or continuous ejection to establish 3D living constructs[22]. Similar to traditional inkjet printing, this technology has certain merits, including a broad selection of commercial apparatus due to the low cost of machine modification. Ease of multiple printer heads installation facilitates heterogeneous architectures of tissue or organ and ensures a sound printing resolution. An ability to keep integrity is critical as newly printed cells are expected to have long-term survival in the *in vivo* environment. A prompt establishment of mechanical properties through supporting biomaterials is valuable. Since the printing conditions and size are limited, inkjet bioprinting is merely practical for *in vivo* repair or fabrication of exterior structures, such as skin.

2.3. Laser-assisted bioprinting

Laser-assisted bioprinting employs a laser to polymerize bio-ink into solid structures[23]. Laser direct-write techniques have been widely used in this approach. By laser pulses, living cells are selectively transferred from the supply container to defect locations. Stereolithography can also be used for *in vivo* bioprinting to allow precise fabrication of structures with micro or nanoscale resolution. The fact that the heat generated by the laser or exposure to ultraviolet lights may impair cell viability should be considered. Moreover, laser or stereolithography-based techniques may be unsuitable for *in vivo* scenarios due to the machine size. Although the advantage of optics-assisted bioprinting in ultrahigh resolution and precision to meet the requirements of clinical settings, there is still room for improvement in terms of photocrosslinkable biomaterials and photonics techniques.

The aforementioned methods are the most common modalities in bioprinting. Their derivatives, which include acoustic droplet ejection[24], direct-write assembly[25], fused deposition modeling[26], and powder printing[27], have also been developed recently. These printing modalities can be further applied to a variety of printers (or end effectors) mounted on robotic arms for dexterous and precision biofabrication.

3. Bioprinting robots

Robots and handheld devices are commonly employed to achieve *in situ* fabrication of 3D structures with complex shapes and curved surfaces[15]. Robotics can facilitate bioprinting tasks with high accuracy and automation level without exhaustion. Robots have been routinely used in minimally invasive surgical settings[28], thereby paving the way for *in situ* bioprinting[29]. Robot configurations determine the working space, deposition flexibility, and operational precision of bioprinting, of which Cartesian coordinate, articulated, and parallel robots are the main configurations[30]. The typical robotic-assisted bioprinting process is shown in Figure 2.

3.1. Configurations

3.1.1. Cartesian coordinate robots

Conventional 3D printers deposit materials layer-by-layer along the vertical direction (Figure 3A) using the axis-aligned slicing method. A planar surface is often needed to support the printed structure. Adopting this mechanism allows for individualized modeling and rapid fabrication. The procedure involves 3D computer model design and slicing followed by layer deposition of biomaterials through force, sound, light, electricity, and heat. Extrusion-, inkjet-, and optics-based methods can be readily combined with Cartesian coordinate robots. The advantages of this technology for bioprinting include low cost, technology transferability from conventional 3D printing, and a high degree of stiffness of the printing platform, whereas the challenges are evident in anisotropic bioprinting[31]. Since body tissues are anisotropic, different anisotropic material properties along an axis are needed. Moreover, the stair-step effect is non-negligible[32]. During the fabrication of each layer, the motion of the nozzle is restricted to a two-dimensional plane along the direction of gravity. This inevitably results in the staircase effect, where surface distortion occurs between neighboring layers. To improve printing flexibility, Edward Shi *et al.* proposed a method combining Cartesian and curvilinear printing head motion for *in vivo* bioprinting. A biomimetic "tendon cable" soft robot arm was added to a conventional Cartesian three-axis 3D printer to facilitate motion along six independent

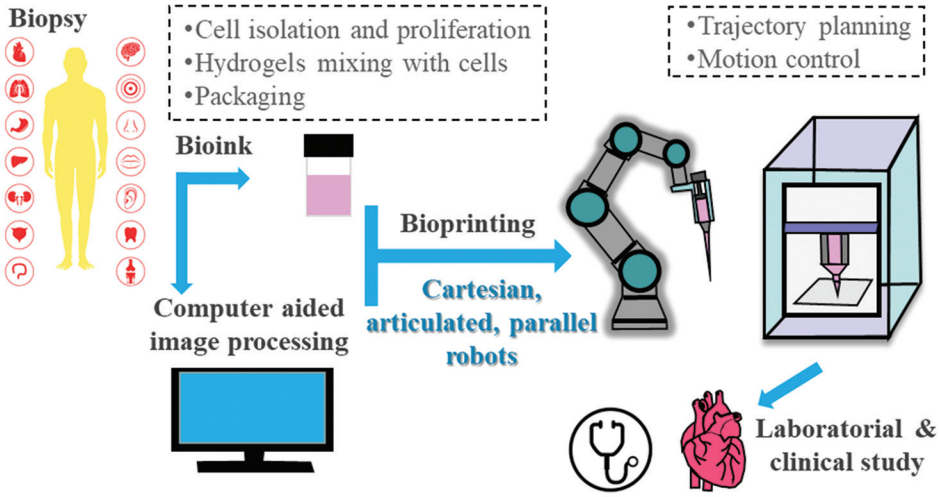

Figure 2. Typical process of robotic-assisted bioprinting.

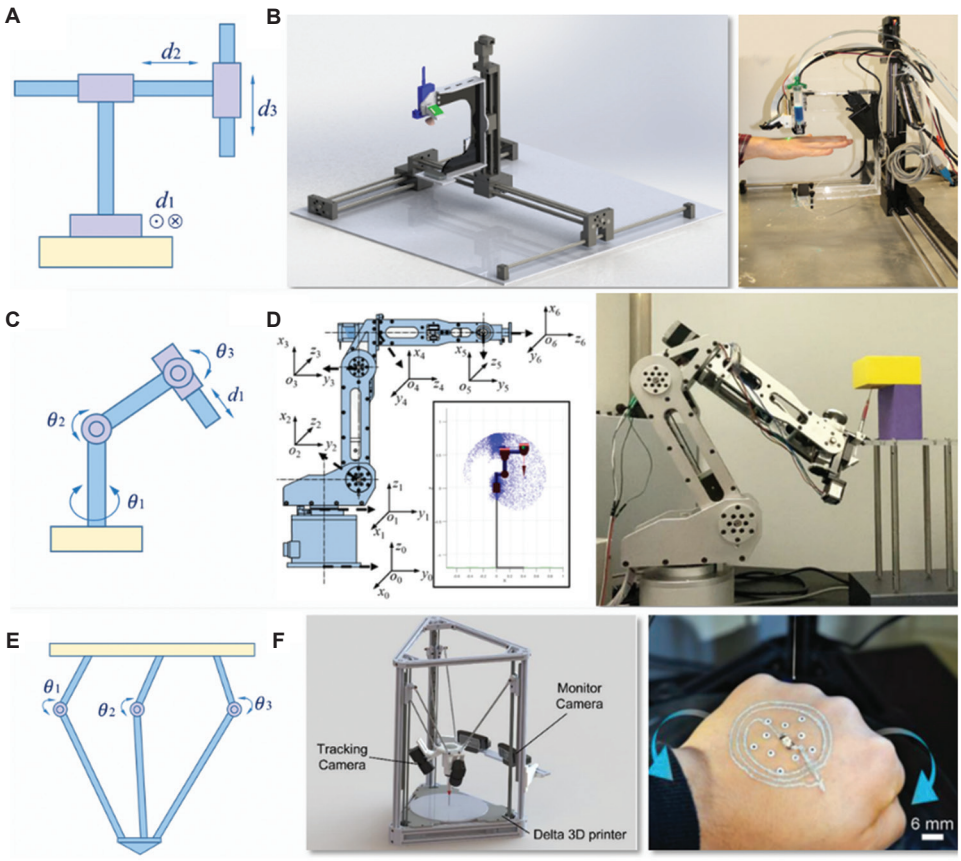

Figure 3. Typical robot configurations for *in situ* 3D bioprinting. (A) Cartesian. (B) Design and material deposition onto a moving hand by the robot[33] (from ref. [33] licensed under IEEE license). (C) Articulated. (D) Design and construction on inverted surface by the robotic bioprinter[41] (from ref. [41] licensed under Creative Commons Attribution 4.0 license). (E) Parallel. (F) Design and adaptive printing on a human hand, which can move freely in the workspace[46] (from ref. [46] licensed under John Wiley and Sons license).

degrees of freedom (DOF)[31]. O'Neill *et al.* demonstrated the feasibility of robotic deposition of biocompatible materials directly onto unconstrained, moving human anatomy (Figure 3B). The robotic platform employed the XYZ gantry system, in which the motions along the axis were actuated by stepper motors[33].

3.1.2. Articulated robots

Articulated robots with 360° rotating joints (Figure 3C) have been developed to overcome the limitations of fixed axes. The number of rotary joints ranges from two to ten or more, and these rotary joints are often powered by servo motors. Most robotic arms have three to six axes, which allow biomaterials to be placed onto curved surfaces with sophisticated profiles from all directions[34]. Articulated robots are more versatile and flexible than other platforms as they have multiple axes and degrees of freedom. Other merits of this anthropomorphic technology include its deployable/foldable ability to reduce the footprint. Moreover, the advanced kinematics algorithms also help to improve the precision of movement[35]. Particularly, as demonstrated by the da Vinci surgical system, articulated robots enable surgeons to perform delicate operations through small incisions[36]. Articulated robots can also enhance *in situ* bioprinting for potential clinical applications. One of the main concerns in the development of the articulated robotic system is the low intraoperative correction ability if the controller fails[37]. In addition, a singularity (a robot end effector becomes blocked in certain directions) may exist[38]. Compared with Cartesian robots, the controlling and programming of articulated robots are more complicated. For instance, redundancy can be exploited to improve manipulability and achieve more dexterous motions, but it may complicate the inverse kinematics[39]. Li *et al.* demonstrated the feasibility of using the industrial 6-DOF robot for direct *in situ* 3D printing in living animal models for injury repair. The osteochondral defect in rabbits could be repaired in about 1 min[40]. Zhao *et al.* used a novel design and an adaptive *in situ* bioprinting robot for rapid biomaterial fabrication on an excisional wound in mice (Figure 3D). The 6-DOF robot successfully provided immediate, precise, and complete wound coverage through stereotactic bioprinting[41]. Zhang *et al.* equipped a printer with a 6-DOF robotic arm, which enabled cell printing on 3D complex-shaped vascular scaffolds from all directions, and proposed an oil bath-based cell printing method to preserve the natural functions of cell after printing[42].

3.1.3. Parallel robots

Parallel robots or delta robots have multiple arms (usually three) connected to a single base mounted above the workspace (Figure 3E). These robots employ articulated robots that use similar mechanisms for movement, and they tend to move delicately and precisely. Since each joint of the end effector is directly controlled by multiple arms, these robots have high efficiency with respect to their moving speed[43]. Other advantages of the parallel configuration include simple structure design and easy installation. The replacement of machine elements is also relatively straightforward. In contrast, issues such as massive linkages and singularity due to parallel linkages may exist in ordinary parallel robots[44]. Zhu *et al.* employed a delta robot printer to print cell-laden hydrogels on live mice to investigate the potential of bioprinting for wound healing[45]. The method also demonstrated feasibility in fabricating smart wearable devices directly on the human body (Figure 3F). Zhao *et al.* developed a micro bioprinting platform that can be installed on an endoscope to enter the human body and process bioprinting. A delta robot was leveraged as the configuration of the printing platform. The delta robot can fold itself down into smaller size when entering the patient's body and unfold before bioprinting[46].

The comparison of robot configurations for *in situ* bioprinting is shown in Table 1.

4. Three-dimensional bioprinted tissues and organs

4.1. Cartilage

Cartilage is an important structural component of the human body. Cartilage injuries are very common, affecting millions of people, and they may result in joint dysfunction. Cartilage is firm but softer and much more flexible than bone. However, blood vessels and nerves are absent in the tissue. Hence, damaged articular cartilage has poor self-healing capacity, and it is difficult to detect early articular cartilage damage. Although autologous chondrocyte implantation, mosaicplasty, and periosteal grafts have been widely adopted as conventional treatments for repairing chondral defects, the reproduction of normal hyaline cartilage with long-term stability and reliable functionality must be improved. The direct repair of cartilage by developing large-scale biomimetic anisotropic constructs with structural integrity, mimicking the native tissue, is challenging. Cui *et al.* developed a 3D bioprinting system with photopolymerization that is capable of cartilage tissue engineering. For repairing defects in osteochondral plugs, poly(ethylene glycol) dimethacrylate with human chondrocytes was printed layer-by-layer, revealing the significance of direct cartilage repair through bioprinting[47]. Sun *et al.* demonstrated anisotropic cartilage regeneration through 3D bioprinting dual-factor releasing and gradient-structured constructs. The fabricated anisotropic cartilage structures showed fine integrity, superficial lubrication, and nutrient supply within deep layers[48]. The dual-factor releasing and gradient-structured cartilage scaffold demonstrated better repairing effect in the rabbit knee cartilage defect model *in vivo* (Figure 4A). Ma *et al.* developed a 6-DOF robot for *in situ* 3D bioprinting to regenerate cartilage and explored

Table 1. Comparisons of typical robot configurations for *in situ* 3D bioprinting

Configuration	Advantages	Disadvantages	Workspace
Cartesian	• Simpler mechanical engineering design	• Nonflexible operation restricted by axes	Restricted
	• Transferability from conventional 3D printing	• Non-negligible staircase effect	
	• High stiffness compared with articulated design	• Unable to print on curvilinear or irregular surfaces	
Articulated	• Excellent flexibility, owing to multiple DOFs	• Low intraoperative correction ability if the controller fails	Large
	• Enhanced by cutting-edge control algorithms	• Singularity issue	
	• Compatible with minimally invasive surgery	• Relatively complex inverse kinematics	
	• High foldability and small footprint		
Parallel	• Simple structure and easy installation	• Massive linkages	Medium
	• Easy replacement of machine elements	• Singularity issue due to parallel linkages	
	• High precision at fast speed		

DOF: Degrees of freedom

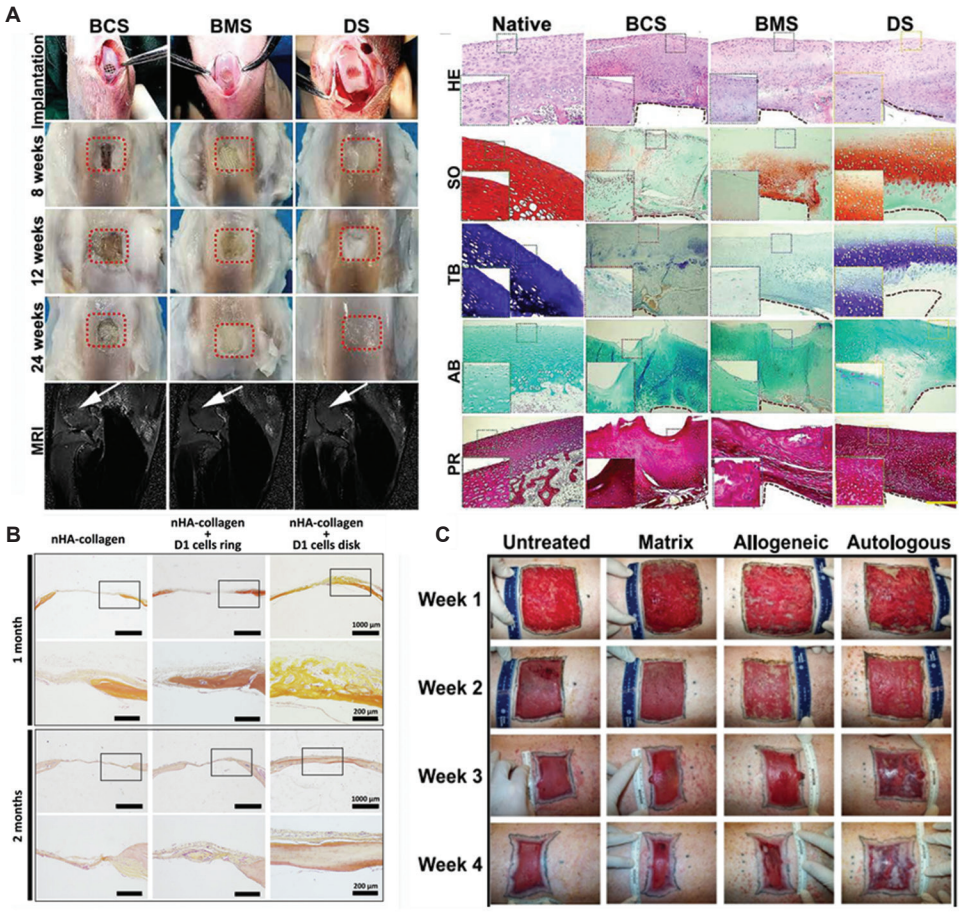

Figure 4. Tests of robotic-assisted bioprinted cartilage, bone, and skin. (A) Scaffold implantation process, and gross appearance of the repaired cartilage at different weeks (left); histological evaluation of the repaired cartilage (right)[49] (from ref. [49] licensed under Creative Commons Attribution 4.0 license). (B) Histology tests of bone repair in a calvaria defect in mice at 1 and 2 months post printing using hematoxylin-eosin-safran staining[40] (from ref. [40] licensed under Creative Commons Attribution 4.0 license). (C) In situ bioprinted autologous and allogeneic fibroblasts and keratinocytes compared to bioprinted fibrinogen/collagen (matrix only) and untreated control over weeks[54] (from ref. [54] licensed under Creative Commons Attribution 4.0 license).

its potential application in clinical settings. The *in vivo* experiment was conducted on rabbits. The arrangement of chondrocytes in the hydrogel implantation and *in situ* bioprinting groups was closer to native cartilage[49].

4.2. Bone

Bone fracture healing and the realization of the function of bones to withstand and adapt to mechanical stresses are results of the synergic effect of bone cells, extracellular matrix, and bioactive molecules. Vascularized bone graft has been recognized as the gold standard in the field of bone healing for four decades. Approximately a couple of million bone grafts are performed yearly across the globe to treat bone lesions. These traditional technologies for repairing defects based on autogenous or allogeneic bone grafts have several limitations, including donor-site availability and morbidity, graft incorporation and remodeling, low biological properties, and high cost. 3D bioprinting provides novel solutions to these enormous clinical challenges. In particular, repairing bone damage by direct *in situ* 3D bioprinting has been viewed as a promising entrance for applying 3D bioprinting in clinical settings. Some reports have evaluated *in situ* 3D bioprinting for clinical use or injury repair, demonstrating the employability of this technology in healing damaged bones. According to Keriquel *et al*., automatic robotic bioprinting can be employed by surgeons to achieve precise cellular implantation at a micron or millimeter scale. Mesenchymal stromal cells with collagen and nano-hydroxyapatite were successfully printed for *in vivo* bone regeneration in a calvaria defect model in mice[50]. After hematoxylin-eosin-safran staining, the histologic evaluation of *in vivo* bone repair in a calvaria defect in mice at 1 and 2 months is shown in Figure 4B. Li *et al.* developed an *in situ* 3D bioprinting technology based on a robotic manipulator to repair long segmental bone defects in a living swine model. By robotic-assisted means, the operation time was significantly reduced, which may be beneficial to patients[40]. Lipskas *et al.* combined 3D bioprinting and robotic-assisted minimally invasive surgery techniques to improve regenerative medicine. They investigated the remote center of motion, which is critical to minimally invasive surgery, followed by biomaterial development. The repair of knee defects was used as an example of the application of *in vivo* 3D printing[51].

4.3. Skin

Skin, which consists of epidermis, dermis, and subcutaneous tissue, is the largest organ in the human body. It serves as a protective barrier against mechanical, thermal, and physical injuries as well as hazardous substances. The skin performs physiological functions, including physiological metabolism and nerve conduction. Its self-regeneration process is slow, in which wounds beyond 4 cm in diameter do not repair well without intervention. Conventional methods for repairing skin wounds include autologous skin transplantation and artificial skin substitutes. The former, which covers the excised total thickness wound with autologous skin graft, has been considered the gold standard treatment. However, the applicability of grafts is limited by the supply of available donor sites; thus, it is difficult to repair skin damage covering a large area. 3D bioprinting is able to deliver bio-inks to specific sites for the reconstruction of damaged skin with biomimetic functions and activities. Recently, there has been remarkable progress in the field of skin bioprinting, which shows great potential in revolutionizing the paradigm of treatment in injury and surgery. By vividly mimicking the layered architecture, consisting of epidermis and dermis, damaged skins have been repaired successfully through bioprinting. Lee *et al.* revealed the potential of 3D bioprinting for tissue engineering using human skin as a prototypical example. The fabricated constructs were cultured and exposed to the air-liquid interface to promote maturation and stratification. The fabricated skin can be viewed as morphologically and biologically representative of *in vivo* human skin tissue, as indicated by histology and immunofluorescence characterization results[52]. Cubo *et al.* performed 3D bioprinting of human bilayered skin using bio-inks containing human plasma, primary human fibroblasts, and keratinocytes. Long-term *in vivo* analysis of the structure and function of the printed skin using an immunodeficient mice model verified that the bioengineered skin obtained by the Cartesian printer was very similar to human skin[53]. Albanna *et al.* conducted validation testing of a mobile skin bioprinting system that offers rapid on-site management of extensive wounds. Through printing layered autologous dermal fibroblasts and epidermal keratinocytes in a hydrogel carrier, the excisional wounds showed rapid closure, reduced contraction, and accelerated re-epithelialization[54].

4.4. Other tissues or organs

Repair and regeneration of other tissues or organs, including muscle, vascular, neural structures, and liver, through 3D bioprinting have also been successfully developed, thus providing potential clinical applications. Chen *et al.* used a combination of 3D printing with digital near-infrared photopolymerization to perform proof-of-concept *in vivo* noninvasive bioprinting. The bio-ink was printed *in situ* into a customized ear-like construct, with chondrification and a muscle tissue, layer-by-layer without surgical implantation[55]. Lee *et al.* constructed vascular channels and created adjacent capillary networks through a natural maturation process based on 3D bioprinting. The connection of capillary networks to the large perfused vascular channels was realized by the presented means[56]. Owens *et al.* fabricated fully biological grafts, composed of cells and cell-secreted material, with reliable reproducibility

through bioprinting. The motor and sensory functions of grafts have been tested using a rat sciatic nerve injury model. The practicability of bioprinting for nerve regeneration has been validated[57]. Zhou *et al*. developed a ferromagnetic soft catheter robot (FSCR) system capable of performing *in situ* computer-controlled bioprinting in a minimally invasive manner. The FSCR was guided by the magnetic field to complete printing with high precision. The *in situ* printing of curved surfaces on a porcine tissue phantom and the liver of a living rat demonstrated the advantages of the intelligent and minimally invasive approach[58].

5. Challenges and suggestions

Although robotic-assisted systems have high operating accuracy and automation and are compatible with minimally invasive surgeries, their applications in clinical settings remain a challenge. *In situ* bioprinting robots are now in the prototype testing phase. Three issues should be addressed before promoting their applications in clinical settings. First, defect scanning, digital model reconstruction, code programming, trajectory planning, and printer calibration are all time-consuming. Furthermore, professional skills are required for human-controlled robotic-assisted operations during intraoperative work; therefore, they may be impractical for resource-limited areas. In addition, *in situ* bioprinting approaches are still restricted to locations near the skin; otherwise, surgery is required for printing on internal organs.

Industry 4.0 technologies, including artificial intelligence (AI), 5G, big data, and cloud computing, have revolutionized many fields. Healthcare and medical sectors are also benefiting from these technologies. For example, the aforementioned time-consuming issue can be minimized by AI-based systems, and teleoperation combined with 5G can help to scale and accelerate the applications of robotic-assisted 3D bioprinting in resource-limited areas. Miniature robotics may be more useful for minimally invasive or noninvasive surgeries. Selectively biodegradable robots with bio-inks for target tissues and organs will be useful for internal repair tasks. Four-dimensional bioprinting technologies, which add time as the fourth dimension, can be integrated with miniature robots to modulate their shapes or functionalities with time. Interdisciplinary collaborations across various fields are essential for fostering more innovations and promoting clinical applications.

6. Conclusions

The potential of *in situ* regeneration of cartilage, skin, and bone in animal models through robotics has been widely recognized. This article reviews the advancements in the field of robotic-assisted automated *in situ* bioprinting. The primary modalities of 3D bioprinting, robot configurations, and the applications in cartilage, bone, and skin repair are discussed. With the accelerated growth of knowledge and advancements of technologies in computer science and manufacturing engineering, *in situ* bioprinting is believed to be feasible in the near future.

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Conflict of interest

There are no conflicts to declare.

Author contributions

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Supervision: Hao Sun
Writing – original draft: Bo Hu, Weikang Zhang, Wantao Xie, Jin Mo
Writing – review & editing: Bo Hu, Weikang Zhang, Wantao Xie, Jin Mo, Hao Sun

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data

Not applicable.

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