Research Progress of Robot Technology in In situ 3D Bioprinting

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Abstract: Three-dimensional (3D) bioprinting is an emerging research direction in bio-manufacturing, a landmark in the shift from traditional manufacturing to high-end manufacturing. It integrates manufacturing science, biomedicine, information technology, and material science. In situ bioprinting is a type of 3D bioprinting which aims to print tissues or organs directly on defective sites in the human body. Printed materials can grow and proliferate in the human body; therefore, the graft is similar to the target tissues or organs and could accurately match the defective site. This article mainly summarizes the current status of robotic applications in the medical field and reviews its research progress in in situ 3D bioprinting.

Keywords: In situ 3D bioprinting; Tissue engineering; Robotic bioprinting platform

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1. Background

Three-dimensional (3D) bioprinting is a novel type of biological manufacturing technology, representing an emerging field of technology that combines the traditional 3D printing with biomedicine. 3D bioprinting has a broad application prospect in solving organ shortage and an important role in tissue engineering repair. The implants are designed based on the medical imaging data provided and can be tailored to the defect site. However, it is not easy to print directly during surgery due to the large size and the complexity of existing 3D bioprinting devices. In addition, pre-production before surgery, printing, and culturing in vitro before transplantation are affiliated with many limitations and risks. Hence, this ushers in the development of in situ 3D bioprinting technology. In situ 3D bioprinting is used to print the defective part of the body directly so that it would grow and proliferate in vivo to repair the defective site. This technique can be put in robot and handheld modes according to the execution mode. In the robot mode, the printing model is first constructed by the computer in advance; then, the slicing software plans the path. Next, the printing device executes the task with the assistance of a robot, thereby increasing the printing accuracy and making the printing process more reliable. In contrast, in the handheld mode, the printing process is controlled by a physician who does not need to build the printing
model and plan the path in advance, while the shape of the model is entirely controlled by the physician. Both modes have their advantages and disadvantages: The robot mode is more efficient but expensive, whereas the handheld mode is more convenient and maneuverable in clinical applications. In recent years, the applications of in situ 3D bioprinting have undergone rapid development, especially in the repair of the skin, cartilage, and bone[7].

Combining robotic synergy and 3D bioprinting technology is an emerging research direction. Compared to the traditional in vitro 3D bioprinting, this novel approach enables direct in situ printing in the clinic for tissue repair. There is no need to print and culture in vitro before transplantation, simplifying the surgical procedures and reducing the risk of surgery. It can help doctors who develop treatment plans that align with the actual situation of a patient with different types of diseases and have a broad application prospect in the field of tissue engineering regeneration.

2. Applications of in situ 3D bioprinting

The skin is the human body’s largest organ, which not only provides a natural barrier against the exterior interferences but also dissipates heat, perspires, and senses external stimuli. Due to the self-renewal ability, the skin is able to recover from mild damage, but it may not be able to repair itself when severely injured. Severe skin damage generally needs to be repaired by skin grafting, which is constrained by limited autotransplantable skin and possible immune rejection in allografted skin[8]. Artificial skin made using tissue engineering techniques can avoid these problems. In situ 3D bioprinting can be used to print tissue-engineered skin for the repair of skin damage directly.

Several in situ biological printing systems for skin repair have been developed in different research institutions and are currently used to conduct related animal experiments. Professor Axel Günther at the University of Toronto has designed a handheld 3D bioprinting device to repair skin damage[9]. The bioink based on fibrin is used, which can be cross-linked with thrombin. Controlled by the operator, the device prints bioinks directly on the site of damage in any shape and size, which then grow and proliferate to form skin tissues. The researchers used this in situ skin bioprinting system on a mouse model of a full-thickness excision wound to repair damaged skin. Studies showed that the experimental in situ skin bioprinting treatment could accelerate wound healing[11]. Professor Dichen Li of Xi’an Jiaotong University proposed a method of in situ 3D bioprinting for treating complex skin and soft-tissue defects. Using this proposed method, the scanned 3D point cloud is directly converted into a multitissue in situ biological printing path, which has a structure similar to the original skin, allowing cells or growth factors to act on the corresponding target tissue layer to better repair the skin damage or defective soft tissues[12].

Articular cartilage plays a key role in the human body, such as weight-bearing, shock absorption, and lubrication. However, it is easily damaged due to osteoarthritis, degeneration, trauma, and some other reasons. The cartilage does not contain lymphoid tissues, blood vessels, or nerve tissues, so it is difficult to repair itself after damage[13,14]. The clinical treatments for cartilage damage are mainly drug treatment, joint cleaning, bone transplantation, etc. Among them, drug treatment and joint cleaning can only temporarily relieve pain but cannot repair the damage. Bone transplantation is slightly more effective but is constrained by a shortage of bone donors and possibility of tissue rejection[15,16]. Therefore, researchers proposed a method to repair cartilage damage using in situ 3D bioprinting directly. Professor Gordon G. Wallace’s team at the University of Melbourne designed a handheld 3D printing device that uses manually controlled coaxial nozzles to deposit bioink with cells directly on the affected area to repair cartilage damage[17,18]. This research team used the device to restore the articular cartilage defect in the sheep’s hind leg. Results showed that the 3D printing device could rapidly repair the damage to sheep’s articular cartilage[19]. Professor Maling Gou’s team at Sichuan University designed a non-invasive in vivo light-curing printing system and used it to print ear cartilage subcutaneously in rats. They injected biological ink subcutaneously into rats, then used near-infrared light to irradiate the bioink through a digital micromirror device, and solidified it according to the desired pattern of ear cartilage. This study demonstrated the possibility of non-invasive biological printing in vivo[20].

The human skeleton is responsible for supporting the body, and when it is damaged, the body’s motor system could be significantly impacted. However, bones have limited ability of self-repairing, especially when there is a large defect[21]. Traditional methods for bone defect repair usually involve the use of implants, which may elicit immune rejection and cannot fuse with the body with ease and fully restore bone functions. Repairing bone defects by in situ 3D bioprinting can prevent these problems to a certain extent and repair bone defect[22].
Professor Jean-Christophe Fricain at the University of Bordeaux proposed a laser-assisted bioprinting method to repair bone defects. The researchers used this printing method to print collagen, nano-hydroxyapatite, and mesenchymal stem cells in situ at the location of the skull defect in a mouse model to repair the defect[23]. This study shows that in situ skull repair is possible and provides a new approach to bone repair.

In situ 3D bioprinting technology is also promising for specific applications in stomatology and ophthalmology. Dental pulp tissue, which is located in the dental pulp cavity, contains nerves, blood vessels, dental pulp stem cells, and other components with sensory, nutritional, dentin forming, defensive, and restorative roles[24]. When irreversible inflammation occurs in dental pulp, the usual treatment is to remove the inflamed tissue and perform root canal treatment. This approach can relieve pain but does not restore the physiological function of the dental pulp tissue. Professor Daniela F. Duarte Campos’ team at the School of Medicine of the Technical University of Aachen in Germany proposed a hand-held 3D bioprinting method for dental pulp tissue regeneration. The dental pulp tissue was printed in the root canal model and then cultured to form vascular tissue, making in situ root canal treatment possible. Nevertheless, in situ 3D bioprinting has particular potential in dental pulp treatment[25]. Professor Juliana Lopes Hoehne of the Federal University of Sao Paulo, Brazil, applied piezoelectric inkjet 3D printing technology in ophthalmic surgeries. They also simulated the in situ bioprinting process in the experiment using pig eyes as the substrate for cell-laden printing and observed their ocular cell growth and proliferation. They demonstrated that this bioprinting technology has the versatility and high precision desired for ophthalmic surgery and could make a big difference in in situ printing. With the constant progress in research in the future, it is expected that ophthalmic implants would become highly personalized for users and attain low immune rejection rates in the future[26].

3. Current status of robotics in the medical field

In the past 10 years, intelligent medical technology has become a popular research direction in the medical field, and this has brought about the emergence of new techniques such as artificial intelligence-based image-aided diagnostic methods. In conjunction with that, the new innovations in the field of surgical robot technology also become potential tools used in surgeries[27,28]. The research in surgical robotics does not support its widespread application in the medical field, nor does it help lower the costs of application. However, surgical robots could provide essential technical support for minimally invasive precision surgery. The evolving needs of prospective patients laid a good foundation for developing surgical robot technology[29]. Surgical robots are faced with obstacles of limited visual perception, low distal dexterity, poor hand-eye coordination, tactile perception obstruction, and non-ergonomics, but these problems are not as significant these days with the advances in microelectronics and algorithms[30]. As a powerful auxiliary surgery aid, surgical robots are increasingly employed in clinical applications worldwide. It is not to replace the surgeons completely, but to integrate the surgical techniques to assist the surgeon and improve their accuracy and success rate in performing surgical operation[31].

3.1 Orthopedic surgery robots

Surgical robots first appeared in orthopedics in the 1930s when Dr. Bauer pioneered the technique of needle biopsies through the posterolateral spine[31]. Medtronic and Mazor Robotics collaborated to develop SpineAssist®, the world’s first spinal surgery robot and one of the most widely used surgical robots to date, which was approved by the United States Food and Drug Administration (FDA) in 2004. SpineAssist® automatically executes its robotic arm to achieve a pre-specified trajectory that maximizes surgical precision and reduces complex movement during surgery. Using SpineAssist® has proven to be more effective in reducing radiation exposure, incidence of complications, operation time, and recovery time[32]. Subsequently, Medtronic’s stealth software technology was combined with Mazor’s robotics to develop the next generation of Mazor X® stealth robotics. It consists of a stand-alone robotic arm with an integrated linear optical camera that assesses the work environment through interactive 3D scanning to avoid collisions and improve predictability and flexibility during surgery[31,32]. Stryker Co. of the United States designed the MAKO Robot Auxiliary system, a semi-automatic robot that was approved by the FDA in 2015. It uses a tactile feedback system and computed tomography scan positioning technique to significantly reduce the probability of complications after single-compartment knee arthroplasty (UKA). However, it increases the cost of surgery and the radiation exposure for patients, both detrimental to its widespread clinical applications[33-35]. The TSolution-One® robot system was developed by THINK Surgical and was approved by the FDA in 2019. The robot system reproduces the precise placement of components in images during preoperative planning, allowing surgeons to create, view, and analyze surgical results in three dimensions[34,36].

3.2 Neurosurgical robot

Neurosurgical robots have been evolving for the past decades. Their advantages are mainly reflected as follows:
(i) Assisting doctors in locating the focus and reducing their surgical burden; (ii) realizing real time or remote control; and (iii) achieving high precision, minor trauma, and less bleeding\textsuperscript{[37,39]}. At present, there are many types of neurosurgical robots in medical use. The Renaissance \textsuperscript{®} surgical robot system from Mazor Robotics features high-precision positioning for minimally invasive percutaneous spinal cord neurosurgery and provides 3D images for intraoperative verification of brain implants. The “Leeyuan” surgical robot system, jointly developed by Beijing University of Aeronautics and Astronautics, the Naval General Hospital, and Tsinghua University, used computed tomography/magnetic resonance imaging data as input data to guide the robot to complete the operation through stereo navigation and completed a minimally invasive brain surgery in 2003. The NeuroMate \textsuperscript{®} robot system developed and manufactured by Renishaw has been certified by the European Union CE. Through stereo vision navigation configuration, the system can perform deep brain stimulation, transcranial magnetic stimulation, and endoscopic surgery with sub-millimeter accuracy. Pathfinder \textsuperscript{®}, developed by Prosurgics and certified by the FDA for neurosurgery in 2004, is a robotic system that uses pre-operative medical images to help physicians perform routine stereotactic brain surgery. In 2010, British researchers upgraded the Pathfinder to achieve the submillimeter positioning precision\textsuperscript{[40]}. Professor Garnett Sutherland at the University of Calgary in Canada developed the neuroArm surgery robot system, which can provide real-time, high-definition 3D image resources and tactile feedback to assist surgeons in performing the surgery. It enables surgeons to view real-time information related to brain function, anatomy, and metabolism during the operation to avoid interruption\textsuperscript{[41]}. In 2016, iSYS1, a new micro-robot system for stereotactic intervention in neurosurgery, was released. Its positioning device is feasible and can be used for frameless stereotactic biopsy and the placement of shunts and catheters in most conditions\textsuperscript{[42]}. The Remebot neurosurgical robot developed by the Department of Neurosurgery of the 306\textsuperscript{th} Hospital of Chinese PLA and Beijing Bai Hui Wei Kang Technology Co., Ltd. can realize frameless, minimally invasive, higher positioning precision brain surgery. Compared with the existing treatment plans, the robot-assisted treatments can significantly reduce the probability of post-operative complications and improve the quality of life of patients\textsuperscript{[43,44]}. The ROSA-Brain surgery robot assistant system by Zimmer Biomet Co. in the United States adopts a 6 degree-of-freedom robotic arm with sensing and dynamic tracking. It has a noticeable effect on deep brain stimulation and reactive nerve stimulation system, and was approved by the FDA for neurosurgery in 2019\textsuperscript{[45,46]}.

4. Robotic technology in \textit{in situ} 3D bioprinting

At present, there are two approaches in the operation of \textit{in situ} 3D bioprinting: Handheld and robotic assistance. By handheld approach, the physicians operate handheld devices to print directly. This approach is more flexible in creating structures, more convenient in operation, and easier in terms of device sterilization. However, the application of this approach is only limited to repairing simple structures. On the other hand, robotic assistance approach combines robotic technology and computer-aided interventions with 3D bioprinting to print under the real-time control of physicians. Compared to the handheld approach, the robotic assistance approach can build a more complex and extensive structure and achieve better precision in repetitive movements, making the printing process more accurate and faster. Robotic assistance approach in 3D bioprinting allows innovations in surgical procedures and treatment plans.

The team of Professor Xingsong Wang at Southeast University, China, designed an \textit{in situ} bioprinting device based on a 6 degree-of-freedom robot. The robot has a rapid tool center point (TCP) calibration system, which can accurately calculate the TCP through the robot’s kinematic model, distance constraints, and measurements of the laser tracker. It helps improve the printing accuracy to a printing surface error of $<30 \mu m$, and osteochondral defects can be repaired in about 60 s. The researchers then used the robot to conduct experiments on the resin model \textit{in vitro} to verify the printing accuracy and on rabbits to assess the healing capabilities of cartilage. Results showed that robot-assisted \textit{in situ} 3D bioprinting can promote cartilage regeneration\textsuperscript{[6]}.

Lipskas \textit{et al.} developed a remote center of motion (RCM) robotic system to treat focal cartilage defects in knee bone. They also designed an end effector that can handle three quick interchangeable end effectors for bone milling 3D printing and a contact probe. The robot is controlled using an Arduino Mega programmable controller and custom firmware and utilizes a ladder interpolation algorithm to generate paths. This method minimizes the risk of stent contamination in regenerative medicine, omits the steps of extracorporeal stent preparation, and reduces the risk of infection\textsuperscript{[47]}.

Fortunato \textit{et al.} developed a robotic bioprinting platform for fabricating 3D structures on complex surfaces. In this research, they built an experimental platform based on the open-source bioprinting robot platform IMAGO\textsuperscript{bot}, used LinuxCNC to control the robot, and developed a path planning algorithm that can automatically project the printing pattern onto the surface of the printing site and calculate the angle of each joint of the robotic arm to ensure the end effector is always perpendicular to the surface\textsuperscript{[48]}. In another study, the
team proposed an in situ bioprinting method based on this platform, used a non-planar slice algorithm for path planning and design, and developed a contact probe as the end execution of the robotic arm device. The probe can realize the surface reconstruction of the defect, record the penetration depth of the penetration point, and help plan the path. Finally, the researchers used the printing method to test anthropomorphic models to repair skull defects\(^{[49]}\).

The team of Professor Xu Tao at Tsinghua University proposed a concept of in situ bioprinting in vivo. They developed a miniature in situ bioprinting robot that can be mounted to an endoscope, which can enter the human body for in situ printing\(^{[50]}\). They use the miniature robot to treat gastric wall injuries. This technology miniaturizes the equipment and implants it into the human body for in situ printing at the microlevel. It is a significant breakthrough and provides new insights for clinical applications. The team also developed a 6-degree-of-freedom printing robot for skin printing, which integrates a 3D scanning system to identify the point cloud information of the defect to plan the printing path. The position of the wound is identified by a binocular camera and feedbacked to the robot control system to form a closed-loop system. In addition, the print head of the robot has three additional degrees of freedom, which can adaptively adjust the printing direction according to the morphology of the skin wound. This helps with its application on complex surfaces. They also developed a bioactive bioink and performed in situ bioprinting on the full-thickness resected wound in mice. The results showed that this robot had satisfying printing performance\(^{[51]}\).

Zhang et al. developed a six-degree-of-freedom bioprinting robot for cardiac tissue fabrication, which supports cell printing on 3D complex-shaped vascular scaffolds. The bioprinting robot consists of a 6 degree-of-freedom robotic arm (UR3), a single-channel Multipette, and a self-developed C++ script to control the entire system. A cell printing method based on the oil bath has been proposed, which better preserves the natural function of cells after printing. This system provides an effective solution for fabricating complex trachea in vitro and printing contractile heart tissue\(^{[52]}\).

In summary, 3D bioprinting robot has a broad application prospect in regenerative medicine, which can effectively simplify surgical procedures, reduce the probability of infection during surgery, and make in situ repair of other organs possible in the future.

5. Conclusion

This paper provides a review of the application of in situ bioprinting and the application of robotic technology in 3D bioprinting. To date, despite the reports on in situ 3D bioprinting, this technique is still at the stage of animal experiments. In addition, both robotics and 3D bioprinting are rarely combined in the innovation of new technologies. However, pioneer research in this area has revealed great potential of the combined technologies in tissue engineering and regenerative medicine. Nevertheless, there are still some difficulties in applying this technology to clinical applications. Breakthroughs are needed in terms of bioink used, control accuracy of the robot execution, recognition accuracy, multi-degree-of-freedom synergy, control software, device size, and so on. It might take some time for the robotic in situ 3D bioprinting technology to be widely used in the clinical settings.

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Conflict of interest
The authors declare no known conflicts of interest.

Author contributions
W.J.W., C.Q.X., and D.K.R. supervised the entire writing process of the review. X.N., S.G.H., W.H., and F.H.Y. wrote the manuscript. S.Y.L. and X.Y.J. edited the manuscript. All the authors approved the review for publication.

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