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EDITORIAL

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Why choose 3D bioprinting? Part I: a brief introduction of 3D bioprinting for the beginners

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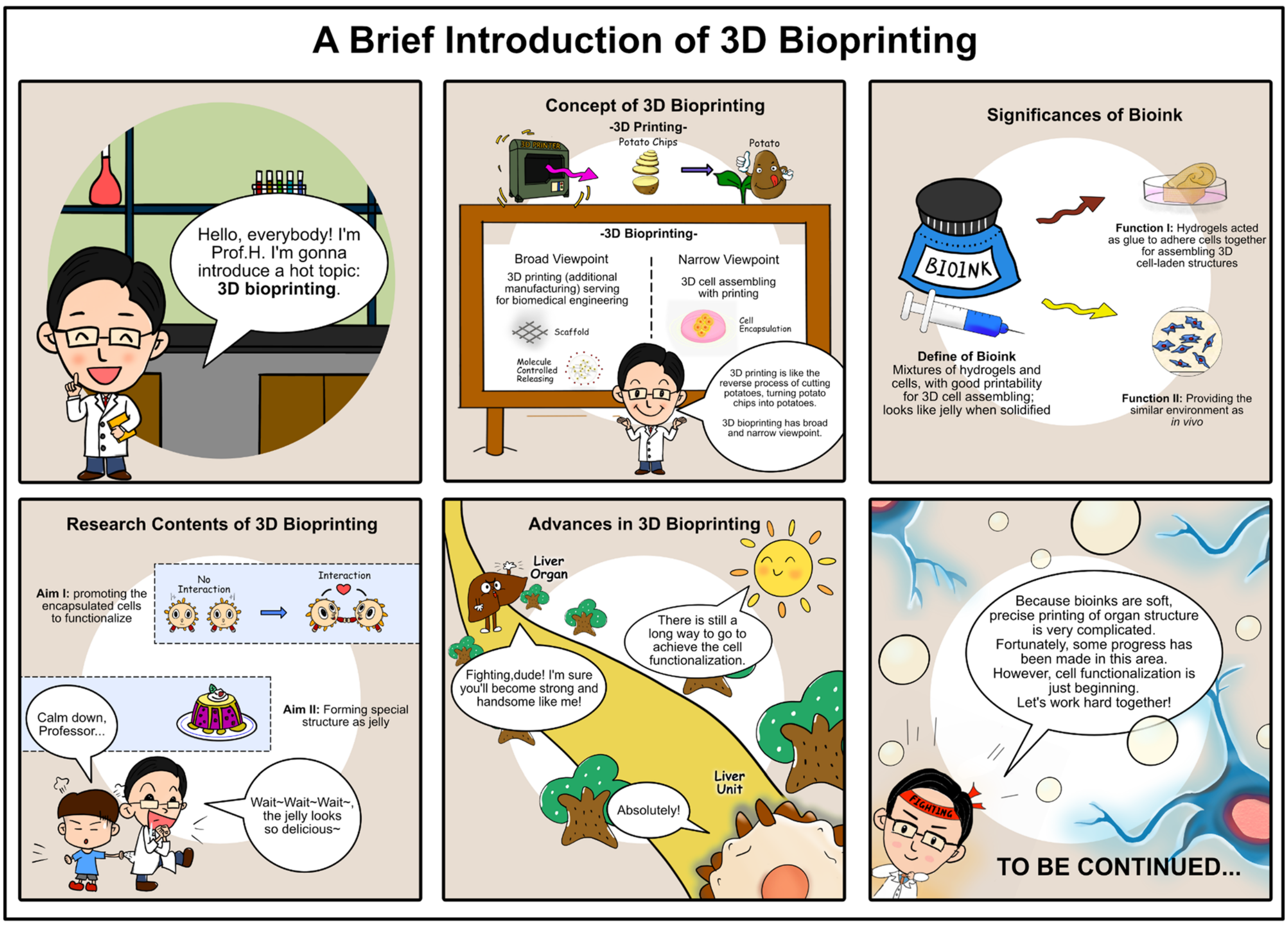
Graphic abstract



Concept of 3D bioprinting

3D printing, also called additive manufacturing, is a layer-by-layer manufacturing method, and it has been implemented in a wide variety of areas. 3D printing could be treated as the reverse process of potato cutting, automatically assembling the chips or slicing into a potato [1]. When this simple idea is met with biomedical engineering, 3D bioprinting is born.

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At present, 3D bioprinting can be seen from two different points of view: broad viewpoint and narrow viewpoint. For the broad viewpoint, 3D bioprinting was established when biomedical applications were realized using 3D printing, such as the printing of medical aids, polymer, ceramic, or metal scaffolds [2–4]. In the narrow viewpoint, this concept simply refers to 3D cell assembling with printing, so it can similarly be referred to as cell printing or organ printing [5–7].

As without laden cells, the bioprinting processing is almost the same as the common 3D printing. Here, this introduction is focused on the narrow viewpoint. The three tasks of 3D bioprinting are very important: preparing bioinks, printing the soft live structures with multiple cells by selected bioprinters, and rebuilding the interaction among cells. These three tasks are what make 3D bioprinting an interdisciplinary of engineering, biotechnology, and medicine. Due to the fact that cells cannot be directly assembled to the 3D structure, it is always needed to prepare bioinks, which can be defined as mixtures of hydrogels and cells with good printability for 3D cell assembling. After being solidified, they look similar to that of jelly and have two functions: (1) acting as glue to adhere cells for assembling 3D live structures and (2) providing a similar environment as in vivo.

Sometimes 3D bioprinting can be confused with tissue engineering and regenerative medicine. Generally speaking, 3D bioprinting is a burgeoning technology of tissue engineering, and all tissue engineering technologies are seeking better tissue or organ regeneration.

Why should 3D bioprinting be chosen?

The manufacturing of tissues or organs in vitro has been a primary goal pursued by humans. This ambitious goal is mainly driven by two demands:

A huge gap in organ transplantation

Currently, the success rate of matching is low all over the world due to insufficient organ donations. As a result, the main thing patients can do is to just wait. In 2016 in the USA, there were roughly 160,000 organ transplant recipients, but only 16,000 organ donors [8]. Therefore, with the combined development in technology and the increased attention given to health, the manufacturing of active organs in vitro is bound to become a research hotspot.

Urgently needed precise models in vitro

At present, drug screening, medical mechanism studies require more precise models in vitro. The traditional solutions are based on 2D cell culture and animal experiments. However, 2D cell culture is different from the 3D environment in vivo, and there may be conflicting results in some cases. Furthermore, many ethical problems exist in animal experiments. In addition, the great differences of the internal environment between animals and the human cannot be ignored. If researchers can reconstruct the 3D environment of tissues and organs in vitro, the deficiencies of the existing solutions would be undoubtedly made up, and the construction of external organs could be widely applied for drug screening and disease mechanism research.

Tissue engineering (TE) became a research hotspot since it was first established by Prof. Fung Y. C. in 1993. Later, Langer et al. published their understanding of TE in *Science* [9]. However, scaffold fabrication is separated from cell adhesion in conventional TE, as it is difficult to deposit different kinds and diverse densities of cells at the desired positions of scaffolds. Therefore, it is difficult to mimic the structures of soft tissues and organs due to the fact that such methods cannot control the distribution of cells. Many researchers have attempted to figure out this bottleneck, which is why 3D bioprinting is proposed. The advantages of 3D bioprinting are the directional manipulation of multicell spatially and the controllable deposition of different cell densities. Currently, 3D bioprinting studies are underway to solve the above demands.

What can be studied with 3D bioprinting?

Manufacturing/printing process

From the view of manufacturing, printing soft tissue should solve many challenges. There are different spatial distributions of each type of cell in different soft tissues. Furthermore, it is difficult to precisely manipulate the bioinks that are soft. The first step is biodesign: understanding the complex structures of tissues and giving reasonable simplification for making them printable. The second step is manufacturing: printing simplified structures in vitro with the suitable bioprinting method and bioink. Three main topics are involved: bionic design of the desired tissue/organ; developing suitable bioinks with high printability for the desired tissues/organs; and developing precise and multicell printing methods to accurately assemble different cells, especially vascular and nerve cells.

Rebuilding tissue/organ functionalization in vitro

The newly printed cell-laden structure is similar to jelly (hydrogel) with bits of fruits (cells). However, in the actual tissues, the cells are interconnected, which have the ability to communicate and cooperate with one another.

Therefore, after the 3D jelly is constructed, the chemical and physical stimulations with enhanced nutrition delivery are needed to accelerate the cross talking of cells. Three main topics are involved: discovering suitable cells for better functionalization; designing suitable cell glues (hydrogels) to better mimic the extracellular matrix (ECM); and vascularization and neutralization in the printed structures.

As an interdisciplinary research, there are many interesting challenges and propositions in 3D bioprinting waiting for to be solved or explored. Also with this development in technology, sociologists are also welcome to collaborate on this goal to share their viewpoints about potential concerns of the balance of technology and life. Some important issues are listed:

- *Cell sources* safety, batching, and stabilization;
- *In vitro organ models* repeatable and standardizable;
- *Large-scale organ prototype* vascularization and long-time survival in vitro;
- *Ethical issue* autologous or foreign cells; the boundary of engineering and ourselves;
- Is it possible Printing@clinic?
- Is it possible to print a brain in vitro?
- Are live, bioprinted structures suitable as normal medical products?
- How many works should be done in vitro, and others left for the self-growth in vivo?

Advances in 3D bioprinting

Printing an organ is underway

In terms of the current progress, the goal of solving the gap of organ transplantation is just the first step in a long process, as the structural properties of organs are rather complicated for two main reasons: (1) many intrinsic mechanisms of development need to be further understood in biology and (2) reengineering the structure of the objective organ is also a huge challenge. For example, vessels seem to be a simple organ. In fact, besides the different layers of cell structure (typical vessels mainly consist of endothelium, smooth muscle, and fibroblasts), the selective permeability, elasticity, and anticoagulation of the vascular wall make it quite difficult to build vessels in vitro for replacing the pathological vessels. In general, one must be patient enough to wait for organ printing to fully develop. It is predicted that organ printing will be firstly broken through at cartilage, adipose, and liver.

Bioprinting of in vitro model is being rapidly developed

The inherent limitations of 2D cell-culture models and animal models for disease study and drug screening have led to an urgent need for in vitro models with the abilities to represent the complexity of human tissues and organs, as well as their in vivo conditions. Referred to as the deposition of pre-prepared bioink based on the principle of additive manufacturing, 3D bioprinting technology has advanced to make it possible for the precise manipulation of specific types of cells and biomaterials to construct the 3D structure, cell–cell/cell–matrix interaction, and in vivo microenvironment with spatiotemporal complexity. With its excellent ability to construct cell-laden structures, 3D bioprinting brings great prospects for precision medicine through the construction of personalized in vitro models. For the effective study of drug screening and disease mechanisms, printed models will be integrated as organs-on-a-chip. Currently, many drug companies are also interested in this area, so it is expected that huge strides will be made over the next decade.

Conclusion

3D bioprinting is a powerful technology that combines biomanufacturing with additional manufacturing. It is a cutting-edge technology related to mechanism, material, biology, and medicine. It provides a new method to explore the complexities of tissue engineering and regenerative medicine. At present, 3D bioprinting has made great progress in the fields of bioink preparation, printing process development, printing equipment development, and medical application research. However, the research of the cell functionalization in the printed structures is just in its beginning stages.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Human and animal rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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