PERSPECTIVE

A perspective on 4D bioprinting

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Abstract: 3D bioprinting has been invented for more than a decade. A disruptive progress is still lacking for the field to significantly move forward. Recently, the invention of 4D printing technology may point a way and hence the birth of 4D bioprinting. However, 4D bioprinting is not well defined and appear to have a few distinct early forms. In this article, a personal perspective on the early forms of 4D bioprinting is presented and a definition for 4D bioprinting is proposed.

Keywords: 4D printing, bioprinting, additive manufacturing, rapid prototyping, tissue engineering.

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1. Introduction

The technology of 3D bioprinting has been invented for more than a decade[1]. A disruptive progress is still lacking for the field to significantly move forward. Recently, the invention of 4D printing technology may point a way. 4D printing technology is invented by Massachusetts Institute of Technology (MIT) and the fourth dimension refers to time[2]. The main difference from 3D printing is that it involves a programmed shape change over the post-printing time. 4D bioprinting is believed to be an extension of 4D printing into biomedical science and engineering. However, in the current literature, there is hardly a report on applying MIT's 4D printing technology to biomedical applications. Indeed, the phrase of "4D bioprinting" can be found in a few recent reviews[3–5], but all briefly mention it without giving further detailed information. At the time of writing, 4D bioprinting is still more of a thing-to-be rather than a well-established matter of fact. Therefore in this paper we would only be able to discuss some early forms of 4D bioprinting and based on which we propose a definition that unifies them.

2. Approaches and Definition

Figure 1 shows three current approaches in 4D bioprinting. They are distinct from each other. The first approach strictly follows MIT's concept of 4D printing, in which a substrate material (e.g., smart biopolymer or responsive hydrogel), upon stimulus, folds into a pre-defined 3D configuration, and the printed cell or tissue materials simply follow the folding of the substrate and form into a desired shape[6]. The second approach is kind of "*in vivo* 4D bioprinting". A 3D printed polymer medical device is implanted first and then accommodates the growth of tissue or organ over the postsurgical period[7]. When the tissue or organ becomes stronger and stronger, the medical device gradually breaks and is absorbed by the body. In this approach, the growth of the tissue could be seen as the stimulation. The third approach involves on-demand

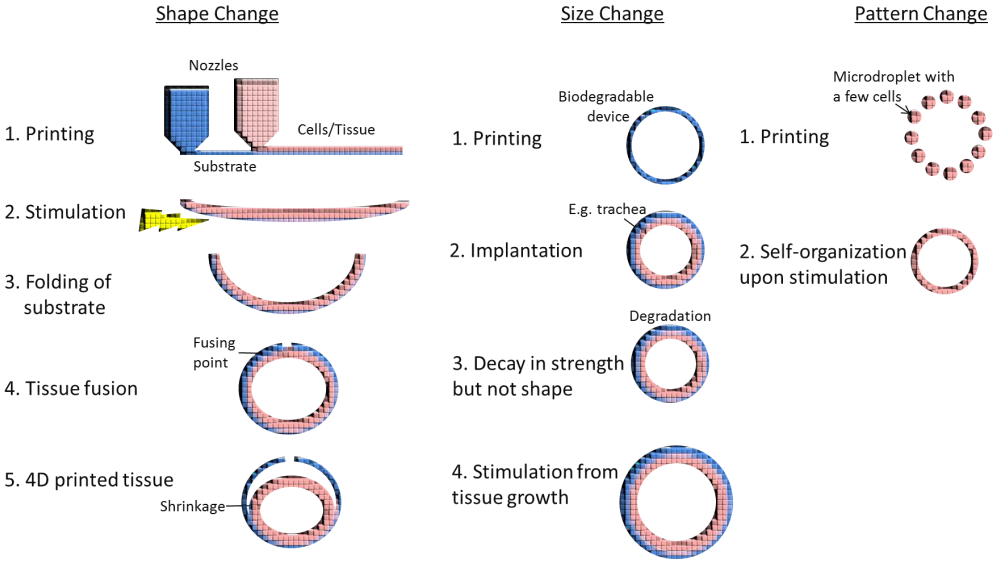

Figure 1. Three approaches in 4D bioprinting.

self-assembly or self-organization. Micro-droplets of cells are precisely deposited into a certain pattern, and then the pattern changes over time due to cell communication and self-organization[8]. In this approach, self-assembly is stimulated to occur, but what could stimulate the pattern to change is not clear yet. It is difficult to compare these three approaches and conclude what is better and what is not, since all are supported by limited study at the current stage. Nonetheless, every approach is interesting and worth further exploration in future.

Since current approaches are different from each other and there is no consensus on the exact form of 4D bioprinting, we would like to propose the following definition for 4D bioprinting to accommodate all current studies and perhaps future studies as well.

4D bioprinting refers to groups of programmable self-assembly, self-folding or self-accommodating technologies which include three main defining or essential components: (i) man-made and not nature-made programmable design, (ii) 2D or 3D bioprinting process, and (iii) post-printing programmable evolving of bioprinted constructs which could be driven by cells or biomaterials and triggered by external signals.

This definition of 4D bioprinting has several features. Firstly, 4D bioprinting is not defined as a single technology. Similar to additive manufacturing, it is defined as a family of technologies based on different principles.

Secondly, there must be a man-made programmable design for self-assembly, self-folding and self-accommodating processes. The process design could be stepwise, relating the type and degree of stimulation to the type and degree of change. The process may or may not be reversible, but it is preferable to have the process being reversible in the design.

Thirdly, the programmable design must be printable by existing bioprinting processes. It could be printing in 2D and then folding into 3D or printing in 3D and then changing into another 3D configuration.

Lastly and most importantly, the self-assembly or self-organization must not occur naturally, but instead it must be driven by cells or biomaterials and triggered by external stimulation, otherwise it does not suit our definition of 4D bioprinting. In 4D bioprinting, the post-printing path in the fourth dimension needs to be manually manipulated. Therefore, fusion of 3D printed tissue spheroids into certain shape is not considered as 4D bioprinting, because tissue fusion process is natural, unless the printed spheroids can hold its as-printed state and start to fuse upon external stimulation. Furthermore, in some reported cases[9], cell contraction and cell migration for cell-driven self-folding and self-assembly is actually also a natural biological process. The folding of the cell origami is not a programmed design, also because the sequence of the folding planes is totally random, neither controlled nor repeatable.

3. Conclusion

In summary, there are clear differences between 3D bioprinting and 4D bioprinting. The major diffe-

rentiating factor is whether there is a stimulation to trigger the as-printed tissue/organ preforms to change over time in a predefined path. In this sense, the combination of 3D bioprinting and bioreactor could be a form of 4D bioprinting, provided the change in tissues/organ can be pre-defined. The future forms of 4D bioprinting would be really unpredictable. However, the differences between 3D bioprinting and 4D bioprinting will continue to widen when more and more research results are available. The early forms of 4D bioprinting may be just the tip of an iceberg; in addition to shape, size and pattern, there could be more other forms of changes in future, such as microstructure, property or even functionality. The era of 4D bioprinting is on its way.

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