Research
3D Printing—Review

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Design and 3D Printing of Scaffolds and Tissues

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ABSTRACT A growing number of three-dimensional (3D)-printing processes have been applied to tissue engineering. This paper presents a state-of-the-art study of 3D-printing technologies for tissue-engineering applications, with particular focus on the development of a computer-aided scaffold design system; the direct 3D printing of functionally graded scaffolds; the modeling of selective laser sintering (SLS) and fused deposition modeling (FDM) processes; the indirect additive manufacturing of scaffolds, with both micro and macro features; the development of a bioreactor; and 3D/4D bioprinting. Technological limitations will be discussed so as to highlight the possibility of future improvements for new 3D-printing methodologies for tissue engineering.

KEYWORDS rapid prototyping, 3D printing, additive manufacturing, tissue engineering, bioprinting

1 Introduction

The concept of tissue engineering was formalized in 1993 when Langer and Vacanti published a historical milestone paper in *Science*, in which the characteristics and applications of biodegradable three-dimensional (3D) scaffolds were first detailed [1]. Ideally, 3D scaffolds should be highly porous, have well-interconnected pore networks, and have consistent and adequate pore size for cell migration and infiltration [2]. In the decade following the publication of this paper (1993–2002), a number of conventional manufacturing techniques were applied to fabricating porous 3D scaffolds, such as fiber bonding, phase separation, solvent casting, particulate leaching, membrane lamination, molding, and foaming [3]. However, all these methods share a major drawback: They do not permit enough control of scaffold architecture, pore network, and pore size, giving rise to inconsistent and less-than-ideal 3D scaffolds. To overcome this problem, researchers proposed the use of 3D-printing methods (also known as rapid prototyping, solid free-form fabrication, or additive manufacturing) to fabricate customized scaffolds with controlled pore size and pore structure [4–6]. Out of more than 40 different 3D-printing techniques in development, fused deposition modeling (FDM), stereolithography, inkjet printing, selective laser sintering (SLS), and colorjet printing appeared to be the most popular, due to their ability to process plastics [7, 8]. As a result, in the second decade of this field (2003–2012), the number of studies in the arena of 3D printing for tissue engineering rapidly multiplied. These studies covered scaffold design, process modeling and optimization, comparisons of 3D-printing methods, post-processing and characterization of 3D printed scaffolds, *in vitro* and *in vivo* applications of 3D printed scaffolds, new scaffold materials for 3D printing, new 3D-printing methods for scaffold fabrication, and even the branching out of an entirely new field—3D bioprinting, or organ printing. Our research group has been extensively involved in this vast wave of research. In this paper, we present our past and current work in this field, and give our perspective on the future of this area as it moves into its third decade (2013–2022).

2 Scaffold architecture design

2.1 Scaffold library

Scaffold architecture design can significantly influence both mechanical property and cell behaviors [9]. We have adopted a bottom-up approach when constructing a 3D scaffold; that is, first making unit cells, and then assembling them into a 3D scaffold. Using this approach, we can fine-tune the mechanical property, based on the porous structure design. We have developed in-house a computer-aided system for tissue scaffolds (CASTS) that can automatically create a highly porous 3D scaffold model with controlled architecture, and precisely match the external surface profile of a native anatomic structure such as bone [10–12]. In this system, nearly 20 polyhedral shapes are selected to form the basic geometry of a unit cell. The scaffold library and the parameters of each unit cell, such as pore size and strut size, can be adjusted, and each polyhedral unit can be repeated automatically in a spatial arrangement and sized to form a block that suits the intended scaffold application (Figure 1). An anatomically shaped porous scaffold can then be created through Bool-

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ean operation between the scaffold block and the actual surface model of the defect tissue. A detailed derivation of the mathematical formulae of the CASTS system for designing and fabricating tissue engineering scaffolds is contained in Ref. [13].

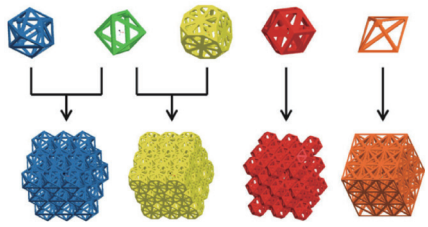

Figure 1. An example of five polyhedral units and their resultant blocks, generated in the CASTS scaffold library.

2.2 Functionally graded scaffold

Natural tissues such as bone usually have a gradient porous structure, so matching mechanical strength and stiffness between porous scaffold design and the target tissue structure is important [14]. There are two types of stiffness gradient in bones: radial gradients in long bones, and linear gradients in short and irregular bones. We have achieved radial gradient design by arranging cylindrical unit cells in a concentric manner so that the porosity decreases linearly from the center to the periphery. This linear gradient occurs as a result of varying the strut diameter along the gradient direction. Therefore, we can tailor the stiffness variation for CASTS scaffolds by adjusting the porosity-stiffness relationship [15]. After modifying and improving the CASTS system, our group successfully fabricated a human mandibular cancellous bone scaffold and a femur bone segment, both with functional gradients [16, 17]. An example of a functionally graded femur bone segment is shown in Figure 2. This process is highly accurate and reproducible. Another method of designing gradient structure is based on shape function and on an all-hexahedral mesh refinement [18]. In this method, a truncated bone is subdivided and represented using various irregular hexahedral elements, which are then converted into various irregular pore elements based on shape function. The entire pore model is obtained after a union operation among the irregular pores, and then the resulting bone scaffold is obtained by performing a difference operation between the contour model and the pore model. Using this method, a well-defined pore size distribution can be achieved for gradient bone-scaffold design. Recently, a new method based on sigmoid function and Gaussian radial basis function has been developed to generate functionally graded structures, and the resulting models can be exported as STL-files and be 3D printed [19].

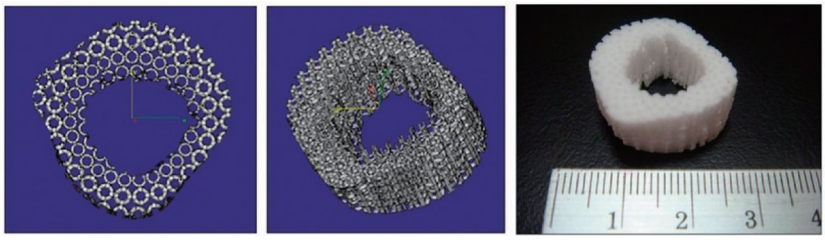

Figure 2. Virtual and physical prototypes of the functionally graded porous scaffold of a femur bone segment.

2.3 Design for vascularization

In addition to mechanical performance, vascularization is a major limitation in tissue engineering, especially when engineering thick or bulk tissues. Researchers have proposed various strategies to enhance or accelerate vascularization, in which scaffold design plays a crucial role [20]. Results show that a designed pore size of 250 μm or above favors the growth of blood vessels more than smaller pore sizes [21]. Also, a high porosity does not necessarily lead to more vascularization, because cell migration and vascularization could be inhibited if there is little interconnectivity between pores [22]. Recently, researchers have developed a tool box for evaluating 3D porous scaffolds [23]. This tool box is based on modular scaffold design, and allows the fine-tuning of scaffold pore size and porosity for vascularization study. Our group is exploring a new concept of hybrid scaffold design to address the vascularization issue. This new approach involves thin porous membranes and filament meshes that alternate in layers to form a 3D scaffold (Figure 3) [24].

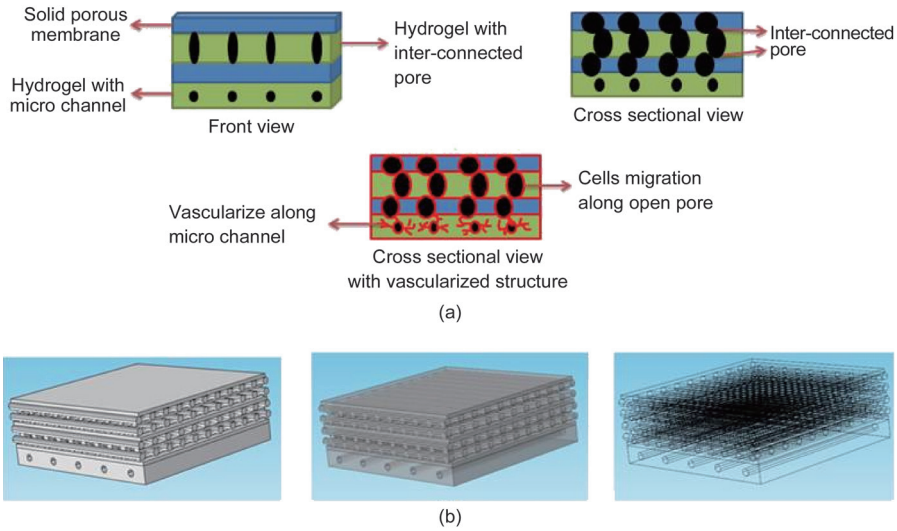

Figure 3. A proposed hybrid scaffold design for vascularization.

3 Direct 3D printing

3.1 Specific forms of materials

At room temperature, the primary forms of materials used for 3D printing are solidifiable fluid, non-brittle filament, laminated thin sheet, and fine powder (see Table 1) [25]. Each form is specific for certain 3D-printing processes. If a material