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Recent Trends and Challenges in Computer-Aided Design of Additive Manufacturing-based Biomimetic Scaffolds and Bioartificial Organs

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Advances introduced by additive manufacturing (AM) methods referred to as solid freedom fabrication (SFF) or rapid prototyping (RP) methods have significantly improved the ability to fabricate porous scaffold structures close in architectures to biological tissues. These technologies have led to the development of innovative porous scaffolds and spatially complex artificial tissues. However, the current approaches face many challenges, such as the lack of an effective design software for printing and prototyping of tissues and scaffolds. In this article, a brief overview of the recent trends and challenges in computer-aided tissue engineering is provided. Future directions are also suggested in order to discuss the challenging technological barriers and provide the overall feasibility of prototyping and printing of biomimetic scaffolds and bioartificial tissues or organs.

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1. Introduction

Recent advances in computer science and its integration with biomaterials and tissue engineering (TE) have led to the emergence of new fabrication technologies for producing three-dimensional (3D) scaffolds and biomimetic tissue constructs.[1-4] Much emphasis has been given in this area to the use of additive manufacturing (AM) methods, sometimes referred to as solid freeform fabrication (SFF) or rapid prototyping (RP) methods. These technologies produce complex objects from a 3D computer-aided design (CAD) digital file by decomposing the object's shape into a series of parallel slices. The shape is then fabricated by adding material layer-by-layer. The AM technique offers the methodology to precisely control over construct architecture, including pore size, shape, orientation, interconnectivity, and branching. Based on the discrete-stacking principle, a wide range of biomaterials, including cells, growth factors, and genes, can be used in AM techniques as structural building blocks.[5] TE emerged in the early 1990s to address limitations of tissue grafting and alloplastic repair. The concept is to transplant a biofactor (cells, genes and/or proteins) within a porous degradable material known as a scaffold. A successful scaffold should balance mechanical function with biofactor delivery providing a sequential transition in which the regenerated tissue assumes function as the scaffold degrades.[6-21] Cells donated by the patient are expanded in culture and are then transferred to the scaffold. The scaffold provides a surface on which cells adhere, thrive, multiply, and generate the extracellular matrix (ECM) of structural and functional proteins that make up a living tissue. Both the scaffold material composition and its internal architecture control the behavior and well-being of the cells seeded inside.[22-28]

Early scaffolds were fabricated by AM technologies from a single biocompatible material. It is now possible to engineer materials that contain biomimetic components to control the cellular microenvironment. The scaffold should be a temporary feature and disappear, through dissolution or degradation, as the cells produce the ECM that defines the tissue.[29-37] Recently, a new approach to TE has been proposed that does not require a solid scaffold structure. In such an approach, cells are formed into clusters, aggregates, or 2D sheets. These are then manipulated or positioned into 3D cellular constructs by using clusters as bricks or sheets as laminates.[22] This methodology has a number of potential benefits over scaffolds. The advanced application of the principles of AM technologies (i.e., layer by layer deposition of cells or matrix) in the area of TE known as bioprinting or organ

printing, is evolving into a promising approach for engineering bioartificial tissues or organs.[38-56] This paper reviews recent trends in porous scaffold design for TE. A brief description of recent achievements in bioprinting is also provided with particular emphasis on the development of an efficient design software for CAD-based 3D organ printing.

2. 3D Porous Scaffold Micro-Architecture Design

In TE, AM techniques enable the easy control of the internal architecture of a scaffold. The biological structure of a native tissue is inherently heterogeneous and complex. Therefore, it is very difficult to exactly reproduce porous scaffold micro-architecture close to a biological tissue. For this reason, many research works in the porous scaffold design are mainly focused on the creation of simplified internal architecture models, functionally equivalent to the tissue to be repaired in terms of porosity and biological properties. In order to manufacture scaffold structures by AM methods, it is necessary to design internal pore architectures via 3D CAD digital models. Conventional tissue scaffolds are fabricated through the foaming of fluid precursors or leaching of pore-generating particles, thereby resulting in a fairly random pore architecture when compared with a scaffold fabricated through AM methods. By fabricating the internal pore architecture through AM methods, it is possible to easily vary the internal architecture of a scaffold, allowing the manufacture of a wide range of pore unit cell libraries. Such unit cell libraries may be created either using CAD software or image-based design approaches.[6,10,57-68] Very recently, efficient methods for designing scaffold pore unit cell libraries have been developed by the use of triply periodic minimal surface (TPMS) pore geometries.[69-79]

Most of the commercial CAD systems are mainly based on solid or surface modeling systems. At the bulk scale, commonly used geometric design methods include boundary representation (B-Rep) and constructive solid geometry (CSG). In CSG-based software, complex models are designed and represented combining basic solid primitives, such as cubes, spheres, and cylinders through Boolean operations, thereby resulting in many problems in the generation of complex scaffold internal pore architectures. In the case of B-Rep, the solid is described through its boundaries, consisting of a collection of vertices, edges, and faces.[54] As model becomes large or if very fine internal architectures are required, B-Rep models dramatically increase in size and become very hard or impossible for current computer systems to visualize and manipulate.[64] For this reason, although there were many researches regarding on the creation of pore unit cell libraries using the commercial CAD systems, most of the suggested libraries are composed of relatively simple geometry, such as sphere, beam, rod, truss, etc. due to the limitation of solid primitive features available.[63] Therefore, it was very difficult to precisely control the resulting biomechanical properties of the scaffolds. In order to improve the time-consuming and tedious manual unit cell modeling and assembling process based on the commercial CAD systems, Chua et al.[63-65] have developed a computer-aided system for the design and manufacture of tissue scaffolds. This research proposed a novel method for the design and manufacturing of a TE scaffold. The proposed approach involves the integration of medical imaging process for the acquisition of anatomic models, 3D CAD modeling for creating the digital scaffold models, and AM technique for fabricating the physical scaffolds. To aid the user in 3D CAD modeling, a standard parametric library of scaffold pore architectures was designed. They used MIMICS^{TM} software to generate a closed volume of the surface in the shape of the patient's bone. The edited surface file was then appended to the generated scaffold block composed of parametric library and a Boolean operation was performed using pro/Engineer CAD system, leaving the scaffold structure in near net-shape of the patient's defect.

Recently, Sudarmadji et al.[66] developed an efficient method for designing a functionally graded scaffold (FGS) with a stiffness gradient that mimics that of a native bone. In order to improve the iterative and tedious design process as well as a heavy reliance on the user's CAD skills required in the design and manufacture of FGS, they implemented an automated FGS production system by providing a database that correlates scaffold porosity values and the corresponding compressive stiffness and integrating it into the design process. To achieve this goal, they newly developed a set of different polyhedral units that can be assembled into scaffold structures. In addition, mathematical relations correlating scaffold porosity and compressive stiffness were also formulated. Although the FGS design process was somewhat automated by their works, most of the suggested libraries were composed of simple pore-making elements, such as octahedron, tetrahedron, triangular prism, hexagonal prism, etc.

In order to overcome the limitations of most CAD-based pore unit cell libraries, more advanced unit cells composed of intricate bio-inspired features have been introduced. Sun et al.[58,67,68] have explored the bioengineering application of reverse engineering (RE) technology in converting computer tomography (CT) or magnetic resonance imagining (MRI)-based images to CAD models. Application of CAD models obtained from CT/MRI-based images allowed exploring many novel approaches in modeling, design, and fabrication of complex tissue scaffolds that have enhanced functionality and improved interactions with cells. Biomimetic features can be based upon real anatomical data regenerated from CT/MRI images, such as channels and porous structures. Using such biomimetic features, they developed three different types of trabecular architectures, such as plate-like primitive for femur, rod-like primitive for spine, and hybrid primitive for iliac crest to design heterogeneous and bioartificial bone scaffolds.

Owing to the rapid advances in AM techniques, a paradigm shift is taking place in the porous scaffold design from CAD-based manual methods[57-68] to computational modeling approaches[69-79] that use mathematically defined internal architectures based on the TPMS pore geometries. The advent of TPMS-based pore architectures has initiated the start of a revolutionary era for the porous scaffold design. The aggregates of cells generally have cells separated by curved partitions. The bio-morphic geometry that best mimics this structural configuration would be surfaces that are continuous through space and divided into two sub-spaces (pore and non-pore) by a non-intersecting two-sided surface. TPMSs are ideal to describe such a biomimetic geometry.[72,73,75-79] The most important advantage of TPMS compared to the pore geometries based on conventional CAD-based manual design methods is the accurate and easy controllability of internal pore architectures, such as pore size, pore shape, porosity, etc. Moreover the

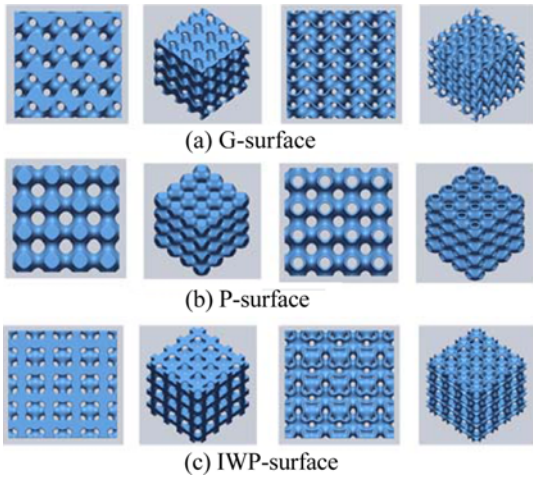


Fig. 1 A variety of TPMS-based unit cell libraries

entire design process can be fully automated by a computer program. Fig. 1 gives a set of examples for the TPMS-based pore unit cell libraries composed of multiple triangular facets generated from marching cube algorithm[80-83] that is an excessively well-known implicit surface visualization algorithm. As shown in Fig. 1, TPMSs are infinite and periodic in three independent directions. Moreover, TPMSs are very smooth and continuous thereby resulting in an optimized pore architecture with fully perfect pore interconnectivity and enhanced interactions with cells. TPMSs are of special interest not only to the tissue engineer, but also to the structural engineer and material scientist because those appear in the natural and man-made worlds, providing a concise description for a variety of physical structures, such as silicates, bicontinuous composites, detergent films, and lipid bilayers.[72]

Rajagopalan et al.[69] designed simple cube types of P-scaffolds and manufactured with the layer-based fabrication device to realize coterminous seeding-feeding networks thereby guaranteeing blood/nutrient supply to the proliferating cells. Melchels et al.[70,71] presented a scaffold design methodology using TPMS. They used K3D surf software to generate CAD files that describe the well known TPMS surfaces of gyroid (G) and diamond (D) architectures. The gradient in pore size and porosity of the gyroid structure was introduced by adding a linear term to the equation for z-values. In their work, it was found that the good accessibility of pores and resulting high permeability of the scaffold result in the more biologically desirable behavior in the seeding of cells and the transport of nutrients and metabolites, either during in vitro or after implantation in the body. They also observed that the mathematically designed tissue engineering scaffolds like a computer designed gyroid architecture fabricated by AM technique show a more than ten times higher permeability than the conventional scaffolds fabricated by salt leaching due to the perfect interconnectivity of pore network of TPMS-based scaffolds. Through the experiments, they proved that gyroid scaffolds show large cell populations in the centre of the scaffold, while salt-leached scaffolds are covered with a cell sheet on the outside and no cells are distributed in the scaffold centre.[73] Hence, the TPMS-based pore unit cell libraries, possessing the advantages of both computational efficiency and enhanced interactions with cells, can be considered as one of the candidates for an ideal pore geometry in the design of next generation scaffolds. However, the

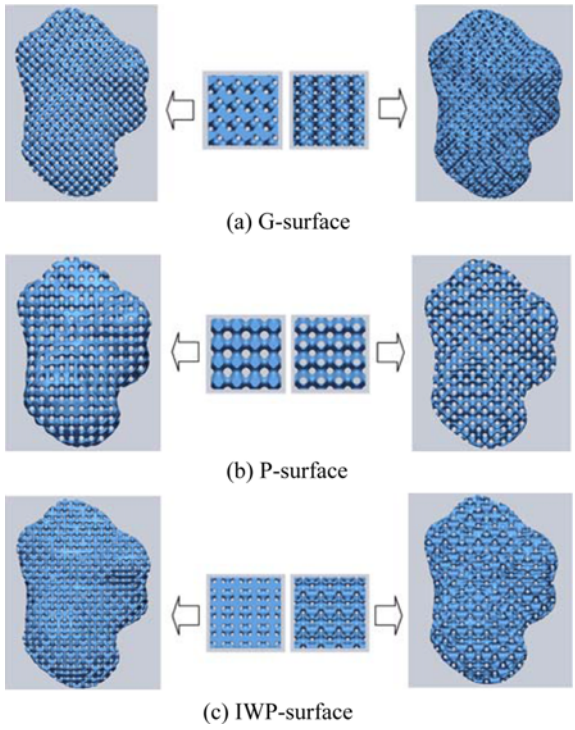


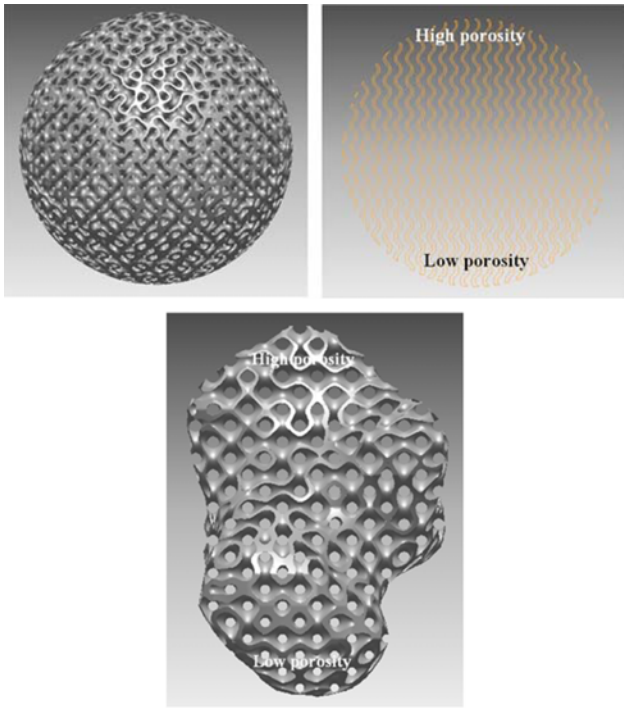
Fig. 2 Tissue engineering porous scaffolds with TPMS-based pore architectures

samples designed and manufactured for the experiments in all the above mentioned works were simple cubic or cylindrical shapes. Very recently, Yoo et al.[72,73] presented a computer-aided porous scaffold design method based on TPMS. For clinically practical applications, they presented an effective method for the 3D porous scaffold design based on distance field (DF) and TPMS. By the application of DF into the Boolean operations of the anatomic model and TPMS-based unit cell library, defects free porous scaffold digital models having the complicated microstructures and high quality external surfaces could be automatically obtained by using the developed scaffold design program. Through the numerical experiments, they showed that the proposed scaffold design method has the potential to combine the perfectly interconnected pore networks based on the TPMS unit cell libraries and the given patient-specific external geometries in a consistent design framework irrespective of the complexity of anatomical models (Fig. 2).

As well as showing the easy controllability of pore architectures and providing the feasibility of clinical application, they also showed that the proposed method can be further improved in terms of design efficiency through recent studies[75-79] related to the functionally graded scaffold design and hierarchical porous scaffold design (Fig. 3). It is undisputable that further advance of AM techniques will significantly improve control over the pore network architecture of scaffolds. Hence, it is highly likely that TPMS-based scaffolds will be used clinically in the near future.

3. CAD-based Organ Printing

CAD-based organ printing which has been defined as computer-



(a) Functionally graded scaffold

(b) Hierarchical porous scaffold

Fig. 3 The easy extensibility of TPMS-based scaffold design method[75,78]

aided 3D tissue-engineering of bioartificial human tissues or organs has initiated the start of an innovative era for the tissue engineering. A fundamental requirement of this process is its capability to simultaneously deliver scaffolding materials, living cells, nutrients, and growth factors at the right time, right position, right amount to form a bioartificial tissue or organ composed of living cells/ECM (or scaffold) for in vitro or in vivo growth.[57] Combination of an engineering approach with the developmental biology concept of tissue fluidity enables the creation of a new 3D printing technology, which will dramatically accelerate and optimize tissue and organ assembly.[40] Computer-aided printing of natural materials such as cells or matrix, is done one layer at a time until a particular 3D tissue form is achieved. However, recent attempts using AM technologies to manufacture bioartificial tissues suffer from the inability to precisely place cells or cell aggregates into the printed scaffolding materials due to the lack of an effective design software for organ printing. Organ printing is distinct from conventional scaffold manufacture using AM techniques because it allows the fabrication of scaffolding materials and the simultaneous or sequential deposition of living cells. Mironov et al.[40] predicted that organ printing will be a promising approach because tissue engineers as well as doctors and their patients, do not have enough time to wait years until engineered tissues and organs become morphologically, biochemically, mechanically, and functionally differentiated. Their prospects for the future of 3D organ printing are being realized by some related recent research works.

The liver is a complex, multifunctional organ that is vital for human survival. In contrast to other simple structural tissues, such as bone and cartilage, the liver must carry out complex metabolic functions. However, the current techniques face many challenges, such as the complex branched vascular and bile ductular systems and the variety of cell types, matrices and regulatory factors involved in liver development. Therefore, the manufacture of an implantable bioartificial liver has long been a dream for many scientists.[1] Wang et al. investigated the overall feasibility of bioartificial liver development. In their recent review paper,[5] some fundamental requirements for the development of a bioartificial liver were addressed. In this paper, a brief review will be given in this viewpoint.

First, a more advanced AM machine will be required to allow the production of more elaborate multi-cellular and multi-material constructs. For instance, multi-nozzle deposition systems should be developed to distribute a high density of the required cells, both efficiently and uniformly, throughout the artificial tissue constructs. By using such an elaborate machine, the biomimetic tissue substitute should be constructed in vitro such that the engineered composite can be transplanted in vivo for the recovery of lost or malfunctioning livers.

Second, more innovative design software should be developed to deliver a range of cell types and ECM and at the same time into 3D structures at accurately chosen positions. While there have been some remarkable studies in the area of the development of 3D artificial organs mainly focused on the 3D cell printer design/manufacture and organ maturation, the researches related to the computerized design software for the development of blueprints for organs have not yet been investigated in the field of 3D organ printing. In order to manufacture artificial organs by AM methods, it will be necessary to make a more intelligent and elaborate computer software. Currently, automatic cells and scaffolding materials distribution algorithm which can realize the 3D organ printing is under development using DF and TPMS-based unit cell libraries. The basic concept and main idea of the methodology are illustrated in Fig. 4.

In fact, the cells exactly know what to do because they have been doing organ forming for millions years. Hence, they know the rules of the organ forming. As we know, a tissue or organ is very well organized according to very stringent rules in cellular sets. It is expected that it will be possible to print an organ composed entirely of living human tissue and let it assemble itself. Assembling from biomolecules and cells to whole functioning printed organs will become only a matter of time. In order to establish this ultimate goal, many tissue engineers

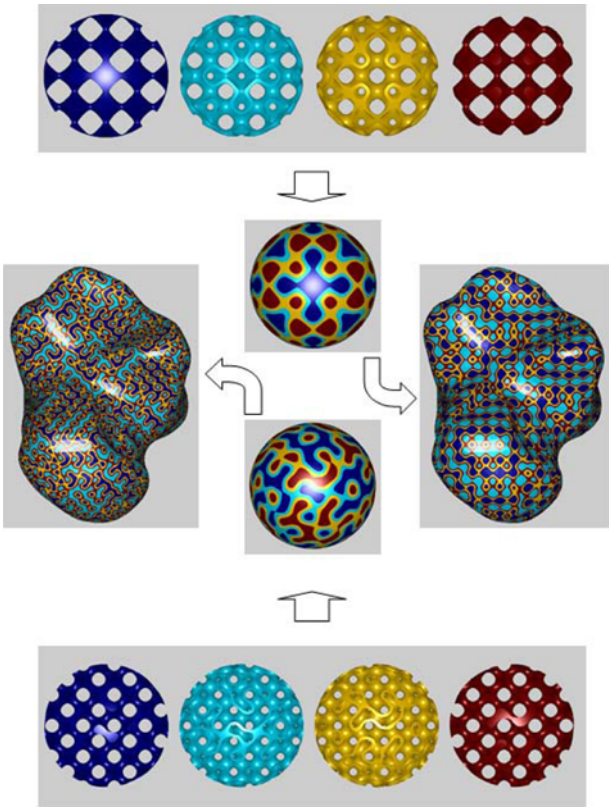


Fig. 4 An automatic cells and scaffolding materials distribution algorithm for 3D organ printing based on the three-dimensionally continuous combination of multiple materials using TPMS-based pore architectures

around the world have begun to print prototype body parts, such as heart valves, ears, artificial bones, joints, nerves, muscles, skin grafts, etc. Now, in order to make more complex organs like a human liver, bioengineers have started to develop more sophisticated manufacture techniques. Among these techniques are microinjection,[86-92] holographic optical tweezers,[93-109] stereolithography,[110-128] selective laser sintering,[129-133] 3D printing,[134-142] fused deposition modeling,[143-146] and bioplotting.[147-154] Regardless of the differences between technologies the ultimate goal of these techniques is to accurately replicate the in vivo environment within an artificial tissue construct.[56]

Therefore, it is expected that, with such advanced manufacture techniques and especially designed software, a range of cell types and biomolecules will be easily and accurately positioned into precise patterns within a specific 3D bulk construct in the near future.

4. CAD-based Biomimetic Scaffold

RE and AM are the two most important techniques in computer-aided medical engineering. RE combined with AM make it possible to design and manufacture very complex human body models that are difficult to create with conventional techniques. The integration of CAD and medical technology is referred to as Bio-CAD. Bio-CAD is widely used in many applications such as computer-aided surgery, structural modeling of tissue, design of orthopedic devices and

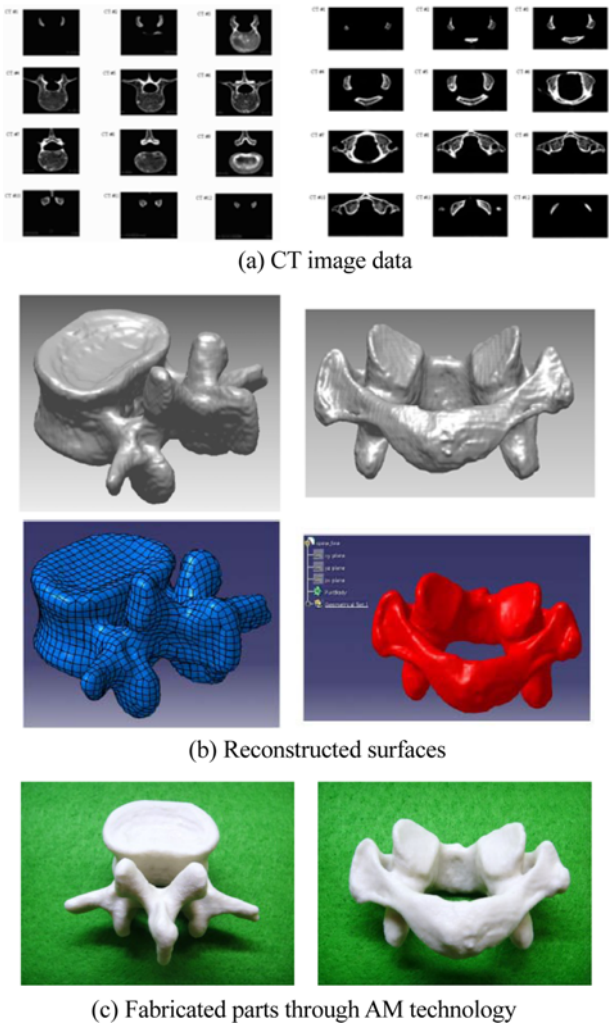


Fig. 5 Automatic reconstruction of human tissue models from CT image data[84,85]

implants, design of tissue scaffolds, etc. Although there were many researches regarding on Bio-CAD model reconstruction, most methods require tedious and time-consuming manual interactions. In general, human body models are obtained by RE process based on non-invasive imaging techniques like CT/MRI. Particularly, CT medical image data is the most popularly used data format for RE in medical engineering. CT medical image is limited by its 2D image presentation in that it does not allow doctors to quickly diagnose illness and explain treatments to patients. Medical models in 3D solid models are therefore very important in the diagnosis and treatment process. Usually, a 3D Bio-CAD model is reconstructed through either segmentation or volumetric representation. 3D Bio-CAD model reconstruction from CT/MRI medical image data has recently become the issue of much attention. It is particularly important in bio-medical engineering since CAD with the help of medical imaging and AM technologies has the capacity to create realistic anatomic models which have diagnostic, therapeutic, and rehabilitatory medical applications.[75]

Two recent studies[84,85] have demonstrated substantial progress in this area (Fig. 5). Through their works, a variety of complex human anatomic models were automatically reconstructed by using the developed computer program without any manual operations of users.

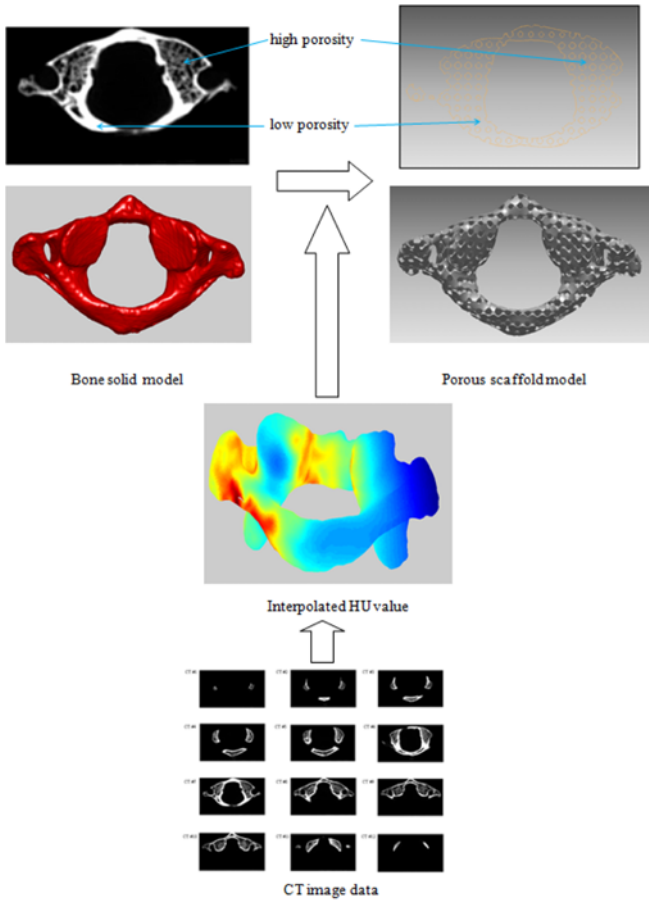


Fig. 6 Generation of a biomimetic porous scaffold model for the spine bone using the heterogeneous implicit solid interpolation method and domain decomposition method[75,84]

They used a heterogeneous implicit solid interpolation method in conjunction with the domain decomposition method to reconstruct perfect 3D bio-CAD models from a sequence of medical image data. In addition, they showed the versatility of the proposed method by designing a biomimetic porous scaffold with controlled porosity and internal architectures (Fig. 6). Since the material gradient information (i.e., porosity distribution) is included within the medical image data, they could design more realistic and biomimetic tissue scaffolds. Firstly, a solid was reconstructed by creating a smooth implicit solid from the geometric positions and Hounsfield unit (HU) values using an implicit interpolation algorithm based on radial basis functions. Secondly, a functionally graded tissue scaffold with bio-mimetically controlled porosity distribution was designed using the internal detail of the tissue obtained from the smoothly interpolated HU value distribution. The interpolated HU value distribution can be considered as the 3D grey-scale density distribution within an anatomical model. Since the HU value is directly related to the material properties, such as density and porosity, the porosity at a spatial location within an anatomical model could be defined uniquely and continuously. Through numerous design results, they showed that it is possible to design a functionally graded tissue scaffold with bio-mimetically controlled porosity distribution closely resembling the biological characteristics of native tissue.

5. Conclusions and Prospects for the Future

Although many tissue engineers have developed a variety of AM techniques for the production of scaffolds and artificial tissues, the majority of published work to date is at a relatively low level of real clinical application. Of course, advanced AM techniques have the potential in the future to enable the manufacture of next generation scaffolds and implantable artificial organs. However, even if we can develop a more advanced AM equipment with unprecedented precision, we will never build a big organ or tissue without a biologically sophisticated software. With a complicated mechanical part like a gear assembly, a 3D CAD system or 3D scanner can create a CAD file in hours and upload the CAD file to a 3D printer. But, there is no equivalent in an organ or tissue. At present, we can make a big and complex mechanical part like an airplane by using CAD/CAM systems. However, a software model of the human organ like a liver is more complicated than the CAD model for an airplane. It will be very difficult or impossible to construct a complete CAD file of a liver by using currently available tools such as commercial CAD software and CT/MRI image processing software.

At present it is not clear to what degree we should mimic natural organs or tissues. However, it is certain that we should deposit a vascular network, cellular aggregates, nutrients, and growth factors at the right time, right position, right amount to form a bioartificial organ or tissue. Recently, a company in USA has teamed to develop CAD programs that could be applied to organ printing. In the near future, we will be able to buy patient-specific CAD blueprints for repairing of our damaged or malfunctioned organs/tissues. Through recent research results, it was found that TPMS-based scaffold design method can provide an important advance in scaffold design because many of the parameters of pore architecture that control the mechanical and biological properties are easily and accurately adjustable. Thus, as discussed previously, it is now possible to model the influence of pore architecture and validate the model by in vitro and in vivo experiments on a range of structures. Moreover, owing to the remarkable advances in AM equipment, it is also possible to provide separate processing of biofactors and scaffold materials allowing simultaneous deposition of them on the same platform. However, there are no blueprints and software models of human organs or tissues that will drive such advanced AM equipment to form implantable artificial organs or tissues.

So far, many researches in this field have shown much progress such as the establishment of a nutrient and metabolite transport system, enhanced cell loading efficiency, and enhancement of cell self-assembly. AM technologies made it possible to have full control over the design and fabrication of bioartificial organs or tissues with highly reproducible complex architectures and variable biomaterial composition. However, further progress needs to be made on the development of more advanced AM devices and more sophisticated software tools for the arrangements of different cells, scaffold materials, and biofactors in precise positions that mimic their respective locations in the organs. The automatic cells and scaffolding materials distribution algorithm (Fig. 4) based on TPMS pore architectures introduced in this paper is likely to be a promising approach for printing and prototyping of bioartificial tissues and more biologically

desirable scaffolds, but further work is needed to demonstrate the full potential of the approach through both in vitro and in vivo experiments.

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REFERENCES

1. Wang, X., Yan, Y., and Zhang, R., "Rapid Prototyping as a Tool for Manufacturing Bioartificial Livers," Trends in Biotechnology, Vol. 25, No. 11, pp. 505-513, 2007.
2. Yan, Y., Xiong, Z., Hu, Y., Wang, S., Zhang, R., and Zhang, C., "Layered Manufacturing of Tissue Engineering Scaffolds Via Multi-Nozzle Deposition," Materials Letters, Vol. 57, No. 18, pp. 2623-2628, 2003.
3. Sakai, Y., Otsuka, M., Kozasa, J., Miyata, F., Furukawa, K. S., and Yamashita, A., "Ultraviolet-Irradiation-based Photofabrication that Simultaneously Produces a Macroporous Structure and Flow Channels Using a Photoreactive Biodegradable Polymer and a Gas-Forming Azoamide Compound," Biochemical Engineering Journal, Vol. 20, No. 2, pp. 163-171, 2004.
4. Yan, Y., Wang, X., Pan, Y., Liu, H., Cheng, J., et al., "Fabrication of Viable Tissue-Engineered Constructs with 3D Cell-Assembly Technique," Biomaterials, Vol. 26, No. 29, pp. 5864-5871, 2005.
5. Wang, X., Yan, Y., and Zhang, R., "Recent Trends and Challenges in Complex Organ Manufacturing," Tissue Engineering Part B: Reviews, Vol. 16, No. 2, pp. 189-197, 2009.
6. Hollister, S. J., "Porous Scaffold Design for Tissue Engineering," Nature Materials, Vol. 4, No. 7, pp. 518-524, 2005.
7. Haynesworth, S. E., Reuben, D., and Caplan, A. I., "Cell-based Tissue Engineering Therapies: The Influence of Whole Body Physiology," Advanced Drug Delivery Reviews, Vol. 33, No. 1, pp. 3-14, 1998.
8. Hollister, S., Maddox, R., and Taboas, J., "Optimal Design and Fabrication of Scaffolds to Mimic Tissue Properties and Satisfy Biological Constraints," Biomaterials, Vol. 23, No. 20, pp. 4095-4103, 2002.
9. Lin, C. Y., Kikuchi, N., and Hollister, S. J., "A Novel Method for Biomaterial Scaffold Internal Architecture Design to Match Bone Elastic Properties with Desired Porosity," Journal of Biomechanics, Vol. 37, No. 5, pp. 623-636, 2004.
10. Fang, Z., Starly, B., and Sun, W., "Computer-Aided Characterization for Effective Mechanical Properties of Porous Tissue Scaffolds," Computer-Aided Design, Vol. 37, No. 1, pp. 65-72, 2005.
11. Hutmacher, D. W., Sittinger, M., and Risbud, M. V., "Scaffold-based Tissue Engineering: Rationale for Computer-Aided Design and Solid Free-Form Fabrication Systems," Trends in Biotechnology, Vol. 22, No. 7, pp. 354-362, 2004.
12. Leong, K. F., Cheah, C. M., and Chua, C. K., "Solid Freeform Fabrication of Three-Dimensional Scaffolds for Engineering Replacement Tissues and Organs," Biomaterials, Vol. 24, No. 13, pp. 2363-2378, 2003.
13. Yeong, W. Y., Chua, C. K., Leong, K. F., and Chandrasekaran, M., "Rapid Prototyping in Tissue Engineering: Challenges and Potential," Trends in Biotechnology, Vol. 22, No. 12, pp. 643-652, 2004.
14. Khalil, S., Nam, J., and Sun, W., "Multi-Nozzle Deposition for Construction of 3D Biopolymer Tissue Scaffolds," Rapid Prototyping Journal, Vol. 11, No. 1, pp. 9-17, 2005.
15. Koegler, W. S. and Griffith, L. G., "Osteoblast Response to PLGA Tissue Engineering Scaffolds with PEO Modified Surface Chemistries and Demonstration of Patterned Cell Response," Biomaterials, Vol. 25, No. 14, pp. 2819-2830, 2004.
16. Taboas, J. M., Maddox, R. D., Krebsbach, P. H., and Hollister, S. J., "Indirect Solid Free Form Fabrication of Local and Global Porous, Biomimetic and Composite 3D Polymer-Ceramic Scaffolds," Biomaterials, Vol. 24, No. 1, pp. 181-194, 2003.
17. Sherwood, J. K., Riley, S. L., Palazzolo, R., Brown, S. C., Monkhouse, D. C., et al., "A Three-Dimensional Osteochondral Composite Scaffold for Articular Cartilage Repair," Biomaterials, Vol. 23, No. 24, pp. 4739-4751, 2002.
18. Williams, J. M., Adewunmi, A., Schek, R. M., Flanagan, C., Krebsbach, P. H., et al., "Bone Tissue Engineering using Polycaprolactone Scaffolds Fabricated Via Selective Laser Sintering," Biomaterials, Vol. 26, No. 23, pp. 4817-4827, 2005.
19. Chu, T. M. G., Orton, D. G., Hollister, S. J., Feinberg, S. E., and Halloran, J. W., "Mechanical and in Vivo Performance of Hydroxyapatite Implants with Controlled Architectures," Biomaterials, Vol. 23, No. 5, pp. 1283-1293, 2002.
20. Woodfield, T. B. F., Malda, J., De Wijn, J., Peters, F., Riesle, J., and van Blitterswijk, C. A., "Design of Porous Scaffolds for Cartilage Tissue Engineering using a Three-Dimensional Fiber-Deposition Technique," Biomaterials, Vol. 25, No. 18, pp. 4149-4161, 2004.
21. Malda, J., Woodfield, T., Van Der Vloodt, F., Wilson, C., Martens, D., et al., "The Effect of PEGT/PBT Scaffold Architecture on the Composition of Tissue Engineered Cartilage," Biomaterials, Vol. 26, No. 1, pp. 63-72, 2005.
22. Derby, B., "Printing and Prototyping of Tissues and Scaffolds," Science, Vol. 338, No. 6109, pp. 921-926, 2012.
23. Sheridan, M. H., Shea, L. D., Peters, M. C., and Mooney, D. J., "Bioabsorbable Polymer Scaffolds for Tissue Engineering Capable

of Sustained Growth Factor Delivery," Journal of Controlled Release, Vol. 64, No. 1, pp. 91-102, 2000.

24. Landers, R., Hübner, U., Schmelzeisen, R., and Mülhaupt, R., "Rapid Prototyping of Scaffolds Derived from Thermoreversible Hydrogels and Tailored for Applications in Tissue Engineering," Biomaterials, Vol. 23, No. 23, pp. 4437-4447, 2002.

25. Zein, I., Hutmacher, D. W., Tan, K. C., and Teoh, S. H., "Fused Deposition Modeling of Novel Scaffold Architectures for Tissue Engineering Applications," Biomaterials, Vol. 23, No. 4, pp. 1169-1185, 2002.

26. Sachlos, E. and Czernuszka, J., "Making Tissue Engineering Scaffolds Work. Review: The Application of Solid Freeform Fabrication Technology to the Production of Tissue Engineering Scaffolds," European Cells and Materials, Vol. 5, No. 29, pp. 39-40, 2003.

27. Vozzi, G., Flaim, C., Ahluwalia, A., and Bhatia, S., "Fabrication of Plga Scaffolds using Soft Lithography and Microsyringe Deposition," Biomaterials, Vol. 24, No. 14, pp. 2533-2540, 2003.

28. Liu Tsang, V. and Bhatia, S. N., "Three-Dimensional Tissue Fabrication," Advanced Drug Delivery Reviews, Vol. 56, No. 11, pp. 1635-1647, 2004.

29. Malda, J., Woodfield, T. B., Van Der Vloodt, F., Kooy, F., Martens, D. E., et al., "The Effect of PEGT/PBT Scaffold Architecture on Oxygen Gradients in Tissue Engineered Cartilaginous Constructs," Biomaterials, Vol. 25, No. 26, pp. 5773-5780, 2004.

30. Leor, J., Amsalem, Y., and Cohen, S., "Cells, Scaffolds, and Molecules for Myocardial Tissue Engineering," Pharmacology & Therapeutics, Vol. 105, No. 2, pp. 151-163, 2005.

31. Karageorgiou, V. and Kaplan, D., "Porosity of 3D Biomaterial Scaffolds and Osteogenesis," Biomaterials, Vol. 26, No. 27, pp. 5474-5491, 2005.

32. Moroni, L., De Wijn, J., and Van Blitterswijk, C., "3D Fiber-Deposited Scaffolds for Tissue Engineering: Influence of Pores Geometry and Architecture on Dynamic Mechanical Properties," Biomaterials, Vol. 27, No. 7, pp. 974-985, 2006.

33. Kneser, U., Schaefer, D. J., Polykandriotis, E., and Horch, R., "Tissue Engineering of Bone: The Reconstructive Surgeon's Point of View," Journal of Cellular and Molecular Medicine, Vol. 10, No. 1, pp. 7-19, 2006.

34. Li, J. P., De Wijn, J. R., Van Blitterswijk, C. A., and de Groot, K., "Porous Ti6Al4V Scaffold Directly Fabricating by Rapid Prototyping: Preparation and in Vitro Experiment," Biomaterials, Vol. 27, No. 8, pp. 1223-1235, 2006.

35. Storrie, H. and Mooney, D. J., "Sustained Delivery of Plasmid DNA from Polymeric Scaffolds for Tissue Engineering," Advanced Drug Delivery Reviews, Vol. 58, No. 4, pp. 500-514, 2006.

36. Kruyt, M. C., Dhert, W. J., Oner, F. C., Van Blitterswijk, C. A., Verbout, A J., and De Bruijn, J. D., "Analysis of Ectopic and Orthotopic Bone Formation in Cell-based Tissue-Engineered Constructs in Goats," Biomaterials, Vol. 28, No. 10, pp. 1798-1805, 2007.

37. Ovsianikov, A., Deiwick, A., Van Vlierberghe, S., Dubruel, P., Moller, L., et al., "Laser Fabrication of Three-Dimensional CAD Scaffolds from Photosensitive Gelatin for Applications in Tissue Engineering," Biomacromolecules, Vol. 12, No. 4, pp. 851-858, 2011.

38. Roth, E. A., Xu, T., Das, M., Gregory, C., Hickman, J. J., and Boland, T., "Inkjet Printing for High-Throughput Cell Patterning," Biomaterials, Vol. 25, No. 17, pp. 3707-3715, 2004.

39. Xu, T., Jin, J., Gregory, C., Hickman, J. J., and Boland, T., "Inkjet Printing of Viable Mammalian Cells," Biomaterials, Vol. 26, No. 1, pp. 93-99, 2005.

40. Mironov, V., Boland, T., Trusk, T., Forgacs, G., and Markwald, R. R., "Organ Printing: Computer-Aided Jet-based 3D Tissue Engineering," Trends in Biotechnology, Vol. 21, No. 4, pp. 157-161, 2003.

41. Unger, R. E., Sartoris, A., Peters, K., Motta, A., Migliaresi, C., et al., "Tissue-Like Self-Assembly in Cocultures of Endothelial Cells and Osteoblasts and the Formation of Microcapillary-like Structures on Three-Dimensional Porous Biomaterials," Biomaterials, Vol. 28, No. 27, pp. 3965-3976, 2007.

42. Phillippi, J. A., Miller, E., Weiss, L., Huard, J., Waggoner, A., and Campbell, P., "Microenvironments Engineered by Inkjet Bioprinting Spatially Direct Adult Stem Cells Toward Muscle- and Bone-Like Subpopulations," Stem Cells, Vol. 26, No. 1, pp. 127-134, 2007.

43. Lee, S. H., Moon, J. J., and West, J. L., "Three-Dimensional Micropatterning of Bioactive Hydrogels Via Two-Photon Laser Scanning Photolithography for Guided 3D Cell Migration," Biomaterials, Vol. 29, No. 20, pp. 2962-2968, 2008.

44. Ong, S.-M., Zhang, C., Toh, Y.-C., Kim, S. H., Foo, H. L., et al., "A Gel-Free 3D Microfluidic Cell Culture System," Biomaterials, Vol. 29, No. 22, pp. 3237-3244, 2008.

45. Rouwkema, J., Rivron, N. C., and Van Blitterswijk, C. A., "Vascularization in Tissue Engineering," Trends in Biotechnology, Vol. 26, No. 8, pp. 434-441, 2008.

46. Mironov, V., Visconti, R. P., Kasyanov, V., Forgacs, G., Drake, C. J., and Markwald, R. R., "Organ Printing: Tissue Spheroids as Building Blocks," Biomaterials, Vol. 30, No. 12, pp. 2164-2174, 2009.

47. Krenning, G., van Luyn, M. J., and Harmsen, M. C., "Endothelial Progenitor Cell-based Neovascularization: Implications for Therapy," Trends in Molecular Medicine, Vol. 15, No. 4, pp. 180-189, 2009.

48. Nichol, J. W. and Khademhosseini, A., "Modular Tissue Engineering: Engineering Biological Tissues from the Bottom Up," Soft Matter, Vol. 5, No. 7, pp. 1312-1319, 2009.

49. Norotte, C., Marga, F. S., Niklason, L. E., and Forgacs, G., "Scaffold-Free Vascular Tissue Engineering using Bioprinting," Biomaterials, Vol. 30, No. 30, pp. 5910-5917, 2009.

50. Fonseca, K. B., Bidarra, S. J., Oliveira, M. J., Granja, P. L., and Barrias, C. C., "Molecularly Designed Alginate Hydrogels Susceptible to Local Proteolysis as Three-Dimensional Cellular Microenvironments," Acta Biomaterialia, Vol. 7, No. 4, pp. 1674-1682, 2011.

51. Huh, D., Hamilton, G. A., Ingber, D. E., "From 3D Cell Culture to Organs-on-Chips," Trends in Cell Biology, Vol. 21, No. 12, pp. 745-754, 2011.

52. Guillotin, B. and Guillemot, F., "Cell Patterning Technologies for Organotypic Tissue Fabrication," Trends in Biotechnology, Vol. 29, No. 4, pp. 183-190, 2011.

53. Fedorovich, N. E., Alblas, J., Hennink, W. E., Öner, F. C., and Dhert, W. J., "Organ Printing: The Future of Bone Regeneration?," Trends in Biotechnology, Vol. 29, No. 12, pp. 601-606, 2011.

54. Giannitelli, S., Accoto, D., Trombetta, M., and Rainer, A., "Current Trends in the Design of Scaffolds for Computer-Aided Tissue Engineering," Acta Biomaterialia, Vol. 10, No. 2, pp. 580-594, 2014.

55. Xu, T., Zhao, W., Zhu, J.-M., Albanna, M. Z., Yoo, J. J., and Atala, A., "Complex Heterogeneous Tissue Constructs Containing Multiple Cell Types Prepared by Inkjet Printing Technology," Biomaterials, Vol. 34, No. 1, pp. 130-139, 2013.

56. Sawdins, M. J., Shakesheff, K. M., Bonassar, L. J., and Kirkham, G. R., "3D Cell and Scaffold Patterning Strategies in Tissue Engineering," Recent Patents on Biomedical Engineering, Vol. 6, No. 1, pp. 3-21, 2013.

57. Starly, B., Lau, W., Bradbury, T., and Sun, W., "Internal Architecture Design and Freeform Fabrication of Tissue Replacement Structures," Computer-Aided Design, Vol. 38, No. 2, pp. 115-124, 2006.

58. Sun, W., Starly, B., Nam, J., and Darling, A., "Bio-CAD Modeling and Its Applications in Computer-Aided Tissue Engineering," Computer-Aided Design, Vol. 37, No. 11, pp. 1097-1114, 2005.

59. Wettergreen, M. A., Bucklen, B. S., Starly, B., Yuksel, E., Sun, W., and Liebschner, M. A. K., "Creation of a Unit Block Library of Architectures for Use in Assembled Scaffold Engineering," Computer-Aided Design, Vol. 37, No. 11, pp. 1141-1149, 2005.

60. Tuan, H. S. and Hutmacher, D. W., "Application of Micro CT and Computation Modeling in Bone Tissue Engineering," Computer-Aided Design, Vol. 37, No. 11, pp. 1151-1161, 2005.

61. Naing, M. W., Chua, C. K., Leong, K. F., and Wang, Y., "Fabrication of Customised Scaffolds using Computer-Aided Design and Rapid Prototyping Techniques," Rapid Prototyping Journal, Vol. 11, No. 4, pp. 249-259, 2005.

62. Wang, C. S., Wang, W. H. A., and Lin, M. C., "STL Rapid Prototyping Bio-CAD Model for CT Medical Image Segmentation," Computers in Industry, Vol. 61, No. 3, pp. 187-197, 2010.

63. Cheah, C. M., Chua, C. K., Leong, K. F., and Chua, S. W., "Development of a Tissue Engineering Scaffold Structure Library for Rapid Prototyping. Part 1: Investigation and Classification," The International Journal of Advanced Manufacturing Technology, Vol. 21, No. 4, pp. 291-301, 2003.

64. Cheah, C. M., Chua, C. K., Leong, K. F., and Chua, S. W., "Development of a Tissue Engineering Scaffold Structure Library for Rapid Prototyping. Part 2: Parametric Library and Assembly Program," The International Journal of Advanced Manufacturing Technology, Vol. 21, No. 4, pp. 302-312, 2003.

65. Cheah, C. M., Chua, C. K., Leong, K. F., Cheong, C. H., and Naing, M. W., "Automatic Algorithm for Generating Complex Polyhedral Scaffold Structures for Tissue Engineering," Tissue Engineering, Vol. 10, No. 3-4, pp. 595-610, 2004.

66. Sudarmadji, N., Tan, J. Y., Leong, K. F., Chua, C. K., and Loh, Y. T., "Investigation of the Mechanical Properties and Porosity Relationships in Selective Laser-Sintered Polyhedral for Functionally Graded Scaffolds," Acta Biomaterialia, Vol. 7, No. 2, pp. 530-537, 2011.

67. Sun, W. and Lal, P., "Recent Development on Computer Aided Tissue Engineering - A Review," Computer Methods and Programs in Biomedicine, Vol. 67, No. 2, pp. 85-103, 2002.

68. Sun, W., Starly, B., Darling, A., and Gomez, C., "Computer-Aided Tissue Engineering: Application to Biomimetic Modelling and Design of Tissue Scaffolds," Biotechnology and Applied Biochemistry, Vol. 39, No. 1, pp. 49-58, 2004.

69. Rajagopalan, S. and Robb, R. A., "Schwarz Meets Schwann: Design and Fabrication of Biomorphic and Durataxic Tissue Engineering Scaffolds," Medical Image Analysis, Vol. 10, No. 5, pp. 693-712, 2006.

70. Melchels, F. P. W., Bertoldi, K., Gabbrielli, R., Velders, A. H., Feijen, J., and Grijpma, D. W., "Mathematically Defined Tissue Engineering Scaffold Architectures Prepared by Stereolithography," Biomaterials, Vol. 31, No. 27, pp. 6909-6916, 2010.

71. Melchels, F. P. W., Barradas, A., Van Blitterswijk, C. A., De Boer, J., Feijen, J., and Grijpma, D. W., "Effects of the Architecture of Tissue Engineering Scaffolds on Cell Seeding and Culturing," Acta Biomaterialia, Vol. 6, No. 11, pp. 4208-4217, 2010.

72. Yoo, D. J., "Computer-Aided Porous Scaffold Design for Tissue Engineering using Triply Periodic Minimal Surfaces," Int. J. Precis. Eng. Manuf., Vol. 12, No. 1, pp. 61-71, 2011.

73. Yoo, D. J., "Porous Scaffold Design using the Distance Field and Triply Periodic Minimal Surface Models," Biomaterials, Vol. 32, No. 31, pp. 7741-7754, 2011.

74. Kapfer, S. C., Hyde, S. T., Mecke, K., Arns, C. H., and Schröder-

Turk, G. E., "Minimal Surface Scaffold Designs for Tissue Engineering," Biomaterials, Vol. 32, No. 29, pp. 6875-6882, 2011.

75. Yoo, D. J., "Heterogeneous Minimal Surface Porous Scaffold Design using the Distance Field and Radial Basis Functions," Medical Engineering & Physics, Vol. 34, No. 5, pp. 625-639, 2012.
76. Yoo, D. J., "Heterogeneous Porous Scaffold Design for Tissue Engineering using Triply Periodic Minimal Surfaces," Int. J. Precis. Eng. Manuf., Vol. 13, No. 4, pp. 527-537, 2012.
77. Yoo, D. J., "New Paradigms in Internal Architecture Design and Freeform Fabrication of Tissue Engineering Porous Scaffolds," Medical Engineering & Physics, Vol. 34, No. 6, pp. 762-776, 2012.
78. Yoo, D. J., "New Paradigms in Hierarchical Porous Scaffold Design for Tissue Engineering," Materials Science and Engineering: C, Vol. 33, No. 3, pp. 1759-1772, 2013.
79. Yoo, D. J., "Heterogeneous Porous Scaffold Design using the Continuous Transformations of Triply Periodic Minimal Surface Models," Int. J. Precis. Eng. Manuf., Vol. 14, No. 10, pp. 1743-1753, 2013.
80. Yoo, D. J., "Filling Holes in Large Polygon Models using an Implicit Surface Scheme and the Domain Decomposition Method," Int. J. Precis. Eng. Manuf., Vol. 8, No. 1, pp. 3-10, 2007.
81. Yoo, D. J., "Three-Dimensional Morphing of Similar Shapes using a Template Mesh," Int. J. Precis. Eng. Manuf., Vol. 10, No. 1, pp. 55-66, 2009.
82. Yoo, D. J., "Rapid Surface Reconstruction from a Point Cloud using the Least-Squares Projection," Int. J. Precis. Eng. Manuf., Vol. 11, No. 2, pp. 273-283, 2010.
83. Yoo, D. J. and Kwon, H. H., "Shape Reconstruction, Shape Manipulation, and Direct Generation of Input Data from Point Clouds for Rapid Prototyping," Int. J. Precis. Eng. Manuf., Vol. 10, No. 1, pp. 103-113, 2009.
84. Yoo, D. J., "Three-Dimensional Human Body Model Reconstruction and Manufacturing from CT Medical Image Data using a Heterogeneous Implicit Solid based Approach," Int. J. Precis. Eng. Manuf., Vol. 12, No. 2, pp. 293-301, 2011.
85. Yoo, D. J., "Three-Dimensional Surface Reconstruction of Human Bone using a B-Spline based Interpolation Approach," Computer-Aided Design, Vol. 43, No. 8, pp. 934-947, 2011.
86. Siniscalco, D., Giordano, C., Galderisi, U., Luongo, L., Alessio, N., et al., "Intra-Brain Microinjection of Human Mesenchymal Stem Cells Decreases Allodynia in Neuropathic Mice," Cellular and Molecular Life Sciences, Vol. 67, No. 4, pp. 655-669, 2010.
87. Bible, E., Chau, D., Alexander, M. R., Price, J., Shakesheff, K. M., and Modo, M., "The Support of Neural Stem Cells Transplanted into Stroke-Induced Brain Cavities by PLGA Particles," Biomaterials, Vol. 30, No. 16, pp. 2985-2994, 2009.
88. Bible, E., Chau, D. Y., Alexander, M. R., Price, J., Shakesheff, K. M., and Modo, M., "Attachment of Stem Cells to Scaffold Particles for Intra-Cerebral Transplantation," Nature Protocols, Vol. 4, No. 10, pp. 1440-1453, 2009.
89. Masuzaki, T., Ayukawa, Y., Moriyama, Y., Jinno, Y., Atsuta, I., et al., "The Effect of a Single Remote Injection of Statin-Impregnated Poly (Lactic- Co-Glycolic Acid) Microspheres on Osteogenesis around Titanium Implants in Rat Tibia," Biomaterials, Vol. 31, No. 12, pp. 3327-3334, 2010.
90. Shishatskaya, E., Voinova, O., Goreva, A., Mogilnaya, O., and Volova, T., "Tissue Reaction to Intramuscular Injection of Resorbable Polymer Microparticles," Bulletin of Experimental Biology and Medicine, Vol. 144, No. 6, pp. 786-790, 2007.
91. Sun, Y. and Nelson, B. J., "Biological Cell Injection using an Autonomous Microrobotic System," The International Journal of Robotics Research, Vol. 21, No. 10-11, pp. 861-868, 2002.
92. Matsuoka, H., Komazaki, T., Mukai, Y., Shibusawa, M., Akane, H., et al., "High Throughput Easy Microinjection with a Single-Cell Manipulation Supporting Robot," Journal of Biotechnology, Vol. 116, No. 2, pp. 185-194, 2005.
93. Ashkin, A., Dziedzic, J., Bjorkholm, J., and Chu, S., "Observation of a Single-Beam Gradient Force Optical Trap for Dielectric Particles," Optics Letters, Vol. 11, No. 5, pp. 288-290, 1986.
94. Ashkin, A. and Dziedzic, J., "Optical Trapping and Manipulation of Viruses and Bacteria," Science, Vol. 235, No. 4795, pp. 1517-1520, 1987.
95. Ashkin, A., Dziedzic, J., and Yamane, T., "Optical Trapping and Manipulation of Single Cells using Infrared Laser Beams," Nature, Vol. 330, No. 6150, pp. 769-771, 1987.
96. Seeger, S., Monajembashi, S., Hutter, K. J., Futterman, G., Wolfrum, J., and Greulich, K., "Application of Laser Optical Tweezers in Immunology and Molecular Genetics," Cytometry, Vol. 12, No. 6, pp. 497-504, 1991.
97. Liesener, J., Reicherter, M., Haist, T., and Tiziani, H., "Multi-Functional Optical Tweezers using Computer-Generated Holograms," Optics Communications, Vol. 185, No. 1, pp. 77-82, 2000.
98. Curtis, J. E., Koss, B. A., and Grier, D. G., "Dynamic Holographic Optical Tweezers," Optics Communications, Vol. 207, No. 1, pp. 169-175, 2002.
99. Sinclair, G., Jordan, P., Courtial, J., Padgett, M., Cooper, J., and Laczik, Z., "Assembly of 3-Dimensional Structures using Programmable Holographic Optical Tweezers," Optics Express, Vol. 12, No. 22, pp. 5475-5480, 2004.
100. Polin, M., Ladavac, K., Lee, S.-H., Roichman, Y., and Grier, D., "Optimized Holographic Optical Traps," Optics Express, Vol. 13, No. 15, pp. 5831-5845, 2005.

101. Hu, S. and Sun, D., "Automatic Transportation of Biological Cells with a Robot-Tweezer Manipulation System," The International Journal of Robotics Research, Vol., No. pp. 0278364911413479, 2011.

102. Ericsson, M., Hanstorp, D., Hagberg, P., Enger, J., and Nyström, T., "Sorting out Bacterial Viability with Optical Tweezers," Journal of Bacteriology, Vol. 182, No. 19, pp. 5551-5555, 2000.

103. Grover, S., Gauthier, R., and Skirtach, A., "Analysis of the Behaviour of Erythrocytes in an Optical Trapping System," Optics Express, Vol. 7, No. 13, pp. 533-539, 2000.

104. Ozkan, M., Wang, M., Ozkan, C., Flynn, R., and Esener, S., "Optical Manipulation of Objects and Biological Cells in Microfluidic Devices," Biomedical Microdevices, Vol. 5, No. 1, pp. 61-67, 2003.

105. Rodrigo, P., Eriksen, R., Daria, V., and Glueckstad, J., "Shack-Hartmann Multiple-Beam Optical Tweezers," Optics Express, Vol. 11, No. 3, pp. 208-214, 2003.

106. Enger, J., Goksör, M., Ramser, K., Hagberg, P., and Hanstorp, D., "Optical Tweezers Applied to a Microfluidic System," Lab on a Chip, Vol. 4, No. 3, pp. 196-200, 2004.

107. MacDonald, M., Spalding, G., and Dholakia, K., "Microfluidic Sorting in an Optical Lattice," Nature, Vol. 426, No. 6965, pp. 421-424, 2003.

108. Wang, M. M., Tu, E., Raymond, D. E., Yang, J. M., Zhang, H., et al., "Microfluidic Sorting of Mammalian Cells by Optical Force Switching," Nature Biotechnology, Vol. 23, No. 1, pp. 83-87, 2005.

109. Jordan, P., Leach, J., Padgett, M., Blackburn, P., Isaacs, N., et al., "Creating Permanent 3D Arrangements of Isolated Cells using Holographic Optical Tweezers," Lab on a Chip, Vol. 5, No. 11, pp. 1224-1228, 2005.

110. Lan, P. X., Lee, J. W., Seol, Y.-J., and Cho, D.-W., "Development of 3D PPF/DEF Scaffolds using Micro-Stereolithography and Surface Modification," Journal of Materials Science: Materials in Medicine, Vol. 20, No. 1, pp. 271-279, 2009.

111. Melchels, F. P., Feijen, J., and Grijpma, D. W., "A Poly (D, L-Lactide) Resin for the Preparation of Tissue Engineering Scaffolds by Stereolithography," Biomaterials, Vol. 30, No. 23, pp. 3801-3809, 2009.

112. Elomaa, L., Teixeira, S., Hakala, R., Korhonen, H., Grijpma, D. W., and Seppälä, J. V., "Preparation of Poly(Epsilon-Caprolactone)-based Tissue Engineering Scaffolds by Stereolithography," Acta Biomaterialia, Vol. 7, No. 11, pp. 3850-3856, 2011.

113. Sohn, Y. S., Jung, J. W., Kim, J. Y., and Cho, D.-W., "Investigation of Bi-Pore Scaffold based on the Cell Behaviors on 3D Scaffold Patterns," Tissue Engineering and Regenerative Medicine, Vol. 8, No. 4, pp. 66-72, 2011.

114. Kim, K., Yeatts, A., Dean, D., and Fisher, J. P., "Stereolithographic Bone Scaffold Design Parameters: Osteogenic Differentiation and Signal Expression," Tissue Engineering Part B: Reviews, Vol. 16, No. 5, pp. 523-539, 2010.

115. Chan, V., Zorlutuna, P., Jeong, J. H., Kong, H., and Bashir, R., "Three-Dimensional Photo Patterning of Hydrogels using Stereolithography for Long-Term Cell Encapsulation," Lab on a Chip, Vol. 10, No. 16, pp. 2062-2070, 2010.

116. Arcaute, K., Mann, B., and Wicker, R., "Stereolithography of Spatially Controlled Multi-Material Bioactive Poly (Ethylene Glycol) Scaffolds," Acta Biomaterialia, Vol. 6, No. 3, pp. 1047-1054, 2010.

117. Choi, J. W., Wicker, R., Lee, S. H., Choi, K. H., Ha, C. S., and Chung, I., "Fabrication of 3D Biocompatible/Biodegradable Micro-Scaffolds using Dynamic Mask Projection Microstereolithography," Journal of Materials Processing Technology, Vol. 209, No. 15, pp. 5494-5503, 2009.

118. Cheng, Y. L. and Lee, M. L., "Development of Dynamic Masking Rapid Prototyping System for Application in Tissue Engineering," Rapid Prototyping Journal, Vol. 15, No. 1, pp. 29-41, 2009.

119. Choi, J. W., MacDonald, E., and Wicker, R., "Multi-Material Microstereolithography," The International Journal of Advanced Manufacturing Technology, Vol. 49, No. 5-8, pp. 543-551, 2010.

120. Narayan, R. J., Doraiswamy, A., Chrisey, D. B., and Chichkov, B. N., "Medical Prototyping using Two Photon Polymerization," Materials Today, Vol. 13, No. 12, pp. 42-48, 2010.

121. Nielson, R., Kaehr, B., and Shear, J. B., "Microreplication and Design of Biological Architectures using DynamicMask Multiphoton Lithography," Small, Vol. 5, No. 1, pp. 120-125, 2009.

122. Weiss, T., Hildebrand, G., Schade, R., and Liefeith, K., "Two Photon Polymerization for Microfabrication of Three Dimensional Scaffolds for Tissue Engineering Application," Engineering in Life Sciences, Vol. 9, No. 5, pp. 384-390, 2009.

123. Luo, Y. and Shoichet, M. S., "A Photolabile Hydrogel for Guided Three-Dimensional Cell Growth and Migration," Nature Materials, Vol. 3, No. 4, pp. 249-253, 2004.

124. Wylie, R. G., Ahsan, S., Aizawa, Y., Maxwell, K. L., Morshead, C. M., and Shoichet, M. S., "Spatially Controlled Simultaneous Patterning of Multiple Growth Factors in Three-Dimensional Hydrogels," Nature Materials, Vol. 10, No. 10, pp. 799-806, 2011.

125. Kloxin, A. M., Kasko, A. M., Salinas, C. N., and Anseth, K. S., "Photodegradable Hydrogels for Dynamic Tuning of Physical and Chemical Properties," Science, Vol. 324, No. 5923, pp. 59-63, 2009.

126. Kloxin, A. M., Tibbitt, M. W., Kasko, A. M., Fairbairn, J. A., and Anseth, K. S., "Tunable Hydrogels for External Manipulation of Cellular Microenvironments through Controlled Photodegradation," Advanced Materials, Vol. 22, No. 1, pp. 61-66, 2010.

127. Lee, S. H., Moon, J. J., and West, J. L., "Three-Dimensional

Micropatterning of Bioactive Hydrogels Via Two-Photon Laser Scanning Photolithography for Guided 3D Cell Migration," Biomaterials, Vol. 29, No. 20, pp. 2962-2968, 2008.

128. Hahn, M. S., Miller, J. S., and West, J. L., "ThreeDimensional Biochemical and Biomechanical Patterning of Hydrogels for Guiding Cell Behavior," Advanced Materials, Vol. 18, No. 20, pp. 2679-2684, 2006.

129. Williams, J. M., Adewunmi, A., Schek, R. M., Flanagan, C. L., Krebsbach, P. H., et al., "Bone Tissue Engineering using Polycaprolactone Scaffolds Fabricated Via Selective Laser Sintering," Biomaterials, Vol. 26, No. 23, pp. 4817-4827, 2005.

130. Leong, K. F., Wiria, F. E., Chua, C. K., and Li, S. H., "Characterization of a Poly-Epsilon-Caprolactone Polymeric Drug Delivery Device Built by Selective Laser Sintering," Bio-Medical Materials and Engineering, Vol. 17, No. 3, pp. 147-157, 2007.

131. Wiria, F. E., Leong, K. F., Chua, C. K., and Liu, Y., "Poly-Epsilon-Caprolactone/Hydroxyapatite for Tissue Engineering Scaffold Fabrication Via Selective Laser Sintering," Acta Biomaterialia, Vol. 3, No. 1, pp. 1-12, 2007.

132. Eosoly, S., Brabazon, D., Lohfeld, S., and Looney, L., "Selective Laser Sintering of Hydroxyapatite/Poly-Epsilon-Caprolactone Scaffolds," Acta Biomaterialia, Vol. 6, No. 7, pp. 2511-2517, 2010.

133. Lorrison, J. C., Dalgarno, K. W., and Wood, D. J., "Processing of an Apatite-Mullite Glass-Ceramic and an Hydroxyapatite/Phosphate Glass Composite by Selective Laser Sintering," Journal of Materials Science: Materials in Medicine, Vol. 16, No. 8, pp. 775-781, 2005.

134. Leukers, B., Gülkan, H., Irsen, S. H., Milz, S., Tille, C., et al., "Hydroxyapatite Scaffolds for Bone Tissue Engineering Made by 3D Printing," Journal of Materials Science: Materials in Medicine, Vol. 16, No. 12, pp. 1121-1124, 2005.

135. Simon, J. L., Rekow, E. D., Thompson, V. P., Beam, H., Ricci, J. L., and Parsons, J. R., "Microct Analysis of Hydroxyapatite Bone Repair Scaffolds Created Via Three Dimensional Printing for Evaluating the Effects of Scaffold Architecture on Bone Ingrowth," Journal of Biomedical Materials Research Part A, Vol. 85, No. 2, pp. 371-377, 2008.

136. Fierz, F. C., Beckmann, F., Huser, M., Irsen, S. H., Leukers, B., et al., "The Morphology of Anisotropic 3D-Printed Hydroxyapatite Scaffolds," Biomaterials, Vol. 29, No. 28, pp. 3799-3806, 2008.

137. Maier, A. K., Dezmirean, L., Will, J., and Greil, P., "Three-Dimensional Printing of Flash-Setting Calcium Aluminate Cement," Journal of Materials Science, Vol. 46, No. 9, pp. 2947-2954, 2011.

138. Butscher, A., Bohner, M., Roth, C., Ernstberger, A., Heuberger, R., et al., "Printability of Calcium Phosphate Powders for Three-Dimensional Printing of Tissue Engineering Scaffolds," Acta Biomaterialia, Vol. 8, No. 1, pp. 373-385, 2012.

139. Fielding, G. A., Bandyopadhyay, A., and Bose, S., "Effects of Silica and Zinc Oxide Doping on Mechanical and Biological Properties of 3D Printed Tricalcium Phosphate Tissue Engineering Scaffolds," Dental Materials, Vol. 28, No. 2, pp. 113-122, 2012.

140. Shim, J. H., Lee, J. S., Kim, J. Y., and Cho, D. W., "Bioprinting of a Mechanically Enhanced Three-Dimensional Dual Cell-Laden Construct for Osteochondral Tissue Engineering using a Multi-Head Tissue/Organ Building System," Journal of Micromechanics and Microengineering, Vol. 22, No. 8, Paper No. 085014, 2012.

141. Shim, J. H., Kim, J. Y., Park, M., Park, J., and Cho, D. W., "Development of a Hybrid Scaffold with Synthetic Biomaterials and Hydrogel using Solid Freeform Fabrication Technology," Biofabrication, Vol. 3, No. 3, Paper No. 034102, 2011.

142. Seol, Y. J., Kang, T. Y., and Cho, D. W., "Solid Freeform Fabrication Technology Applied to Tissue Engineering with Various Biomaterials," Soft Matter, Vol. 8, No. 6, pp. 1730-1735, 2012.

143. Hutmacher, D. W., Schantz, T., Zein, I., Ng, K. W., Teoh, S. H., and Tan, K. C., "Mechanical Properties and Cell Cultural Response of Polycaprolactone Scaffolds Designed and Fabricated Via Fused Deposition Modeling," Journal of Biomedical Materials Research, Vol. 55, No. 2, pp. 203-216, 2001.

144. Zein, I., Hutmacher, D. W., Tan, K. C., and Teoh, S. H., "Fused Deposition Modeling of Novel Scaffold Architectures for Tissue Engineering Applications," Biomaterials, Vol. 23, No. 4, pp. 1169-1185, 2002.

145. Woodfield, T. B., Malda, J., De Wijn, J., Peters, F., Riesle, J., and Van Blitterswijk, C. A., "Design of Porous Scaffolds for Cartilage Tissue Engineering using a Three-Dimensional Fiber-Deposition Technique," Biomaterials, Vol. 25, No. 18, pp. 4149-4161, 2004.

146. Owida, A., Chen, R., Patel, S., Morsi, Y., and Mo, X., "Artery Vessel Fabrication using the Combined Fused Deposition Modeling and Electrospinning Techniques," Rapid Prototyping Journal, Vol. 17, No. 1, pp. 37-44, 2011.

147. Chang, R., Nam, J., and Sun, W., "Effects of Dispensing Pressure and Nozzle Diameter on Cell Survival from Solid Freeform Fabrication-based Direct Cell Writing," Tissue Engineering Part A, Vol. 14, No. 1, pp. 41-48, 2008.

148. Khalil, S., Nam, J., and Sun, W., "Multi-Nozzle Deposition for Construction of 3D Biopolymer Tissue Scaffolds," Rapid Prototyping Journal, Vol. 11, No. 1, pp. 9-17, 2005.

149. Song, S. J., Choi, J., Park, Y. D., Hong, S., Lee, J. J., et al., "Sodium Alginate Hydrogel-based Bioprinting using a Novel Multinozzle Bioprinting System," Artificial Organs, Vol. 35, No. 11, pp. 1132-1136, 2011.

150. Smith, C. M., Christian, J. J., Warren, W. L., and Williams, S. K., "Characterizing Environmental Factors that Impact the Viability of Tissue-Engineered Constructs Fabricated by a Direct-Write Bioassembly Tool," Tissue Engineering, Vol. 13, No. 2, pp. 373-

383, 2007.

151. Yan, Y., Wang, X., Pan, Y., Liu, H., Cheng, J., et al., "Fabrication of Viable Tissue-Engineered Constructs with 3D Cell-Assembly Technique," Biomaterials, Vol. 26, No. 29, pp. 5864-5871, 2005.

152. Barry, R. A., Shepherd, R .F., Hanson, J. N., Nuzzo, R. G., Wiltzius, P., and Lewis, J. A., "Direct-Write Assembly of 3D Hydrogel Scaffolds for Guided Cell Growth," Advanced Materials, Vol. 21, No. 23, pp. 2407-2410, 2009.

153. Rivron, N. C., Rouwkema, J., Truckenmüller, R., Karperien, M., De Boer, J., and Van Blitterswijk, C. A., "Tissue Assembly and Organization: Developmental Mechanisms in Microfabricated Tissues," Biomaterials, Vol. 30, No. 28, pp. 4851-4858, 2009.

154. Skardal, A., Zhang, J., and Prestwich, G. D., "Bioprinting Vessel-like Constructs using Hyaluronan Hydrogels Crosslinked with Tetrahedral Polyethylene Glycol Tetracrylates," Biomaterials, Vol. 31, No. 24, pp. 6173-6181, 2010.