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New Technique:

Digital design of scaffold for mandibular defect repair based on tissue engineering*

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Abstract: Mandibular defect occurs more frequently in recent years, and clinical repair operations via bone transplantation are difficult to be further improved due to some intrinsic flaws. Tissue engineering, which is a hot research field of biomedical engineering, provides a new direction for mandibular defect repair. As the basis and key part of tissue engineering, scaffolds have been widely and deeply studied in regards to the basic theory, as well as the principle of biomaterial, structure, design, and fabrication method. However, little research is targeted at tissue regeneration for clinic repair operations. Since mandibular bone has a special structure, rather than uniform and regular structure in existing studies, a methodology based on tissue engineering is proposed for mandibular defect repair in this paper. Key steps regarding scaffold digital design, such as external shape design and internal microstructure design directly based on triangular meshes are discussed in detail. By analyzing the theoretical model and the measured data from the test parts fabricated by rapid prototyping, the feasibility and effectiveness of the proposed methodology are properly verified. More works about mechanical and biological improvements need to be done to promote its clinical application in future.

Key words: Digital design, Mandibular defect, Scaffold, Tissue engineering
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1 Introduction

The number of human mandibular defects caused by trauma, infection, cancer, congenital malformation, or traffic accident has rapidly increased in recent years. For example, in Europe, approximately 1.5 million patients require bone reconstruction for craniofacial surgery every year, among which mandibular defect accounts for a significant proportion (d′Anquino *et al.*, 2009). In reconstructive surgery, both the shape and the function of missing parts need to be restored. Particularly, the specific function of surgical tissue or organ is very difficult to regenerate. As a part of oral structure, the mandible affects the facial appearance and oral functions (mastication and speech). The restoration of the original bony structure for large mandibular bone defects is very important, and remains a great challenge (Yuan *et al.*, 2007). For repairing the mandibular defect, revascularized bone grafting, including autografting and allografting, is adopted in clinic as the standard method for bone regeneration. However, this method has many defects which limit the operation carrying on and its quality (Jiang *et al.*, 2009). First, blood supply of the bone grafts is a key factor for survival, and the avascular grafts cannot be avoided to be absorbed by surrounding tissue finally, but the vascularization operation is rather difficult and needs to be performed through microsurgery, which limits its application in clinic. Particular to large size defects, the rate of bone

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graft absorption is greater than that of osteogenesis, which makes it difficult for this type of surgery to achieve complete restoration. Another problem is the source of graft, which is limited by the defect size and host viability, and at same time, new trauma cannot avoid graft acquisition. In addition, autologous bone grafts are also limited in supply. For these reasons, tissue engineering (TE), a discipline involving the utilization of composites as bioreactor with cells, biomaterial scaffolds, growth factors, and nutrients to form tissues to recover specific functions of defective organs (Langer and Vacanti, 1993), bears great potential for the restoration of tissue defects. Refinement and development in TE techniques in the past years enhanced the feasibility of bone regeneration with TE methods (Drosse *et al.*, 2008). Some successful repairs of bone defects with TE method have been demonstrated in animals, such as sheep (Abu-Serriah *et al.*, 2004; 2006), canines (Yuan *et al.*, 2007; Zhao *et al.*, 2009), and rats (Jiang *et al.*, 2009). To date, only a few cases of clinical application on patients with biological studies and TE methods have been reported (Gurtner *et al.*, 2008). Although the effect of human mandibular bone defect repair by biological method based on TE has been proven to some degree with clinical experiments (d'Anquino *et al.*, 2009), there is still a long way to go for wide clinical use.

As one of the critical elements of the TE, three-dimension (3D) scaffolds play an important role in cell attachment, proliferation, and guidance of new tissue formation (Fang *et al.*, 2005). To act the role, the scaffolds require various special functions including improved mechanical support to provide structural support and to guide tissue regeneration, shape recovering of defect tissues, degradation to acquire complete tissue replacement, and liquid transportation to import nutrients and export metabolite (Hollister and Cheng, 2007). So the scaffold must be biocompatible, biomimetic, and biodegradable, which determines the scaffold's structure as an intricate internal microarchitecture that is composed of fully interconnected pores and is of similar shape fit into the anatomical defect (Ciocca *et al.*, 2009). Currently, two methods have been proposed for designing scaffolds with controllable structures meeting appropriate design parameters of porosity, Young's modulus, and dissolution. One is the traditional computer-aided design (CAD) method utilizing computational geometry (Sun and Lal, 2002; Sun *et al.*, 2005), and the other is the image-based design method (Adachi *et al.*, 2006). When fabricating the scaffold, the models based on both methods need to be converted from the traditional four-sided region surface model into a digital model represented as triangular mesh (STL file), or need to polygonize from volume model, which is used in manufacturing with rapid prototyping (RP). To complete such tasks, computing efficiency and controllability on microstructure properties (volume porosity and pore size) need to be improved, and complex computation is often needed, as well as conversion error of surface translating introduced (Armillotta and Pelzer, 2008).

A TE-based methodology for the generation of scaffold digital models for human mandibular defect repair is proposed in this paper. As reviewed in the previous paragraph, current approaches, including interactive pore modeling approach in a CAD environment and computational design approach based on volume model, need complex computation and conversion. Furthermore, most research regarding scaffold design focused on fundamental theories and methods, which are not similar to clinical applications for bone defect repair. While in this paper, a solution for mandibular defect repair with scaffold based on TE is proposed. Furthermore, key design methods of external shapes and internal microstructure of repair prosthesis are discussed in detail.

2 Mandibular defect repair strategy with TE

The collective goal of all TE efforts is to create a substitute for the defective organ through preliminary culturing in vitro and further regeneration in vivo. To achieve this goal, the scaffolds, as the bed of cell attachment, growth and differentiation, should be designed with special external shapes and internal structures since they determine the regeneration procedure and results. In order to recover the patient's appearance and oral function, two main problems, i.e., original shape of defect area reproducing and controllable microstructure of scaffold design and fabrication, should be solved. With digital design and manufacturing techniques, such as image processing, mesh modeling, CAD/computer aided manufacturing (CAM), and RP, a bio-substitute of personalized equivalents for the defect area can be designed and fabricated. Furthermore, a whole technique route of TE-based repairing for mandibular defects can be created. The scheme of mandibular defect repair strategies based on TE with scaffolds is shown in Fig. 1. To obtain the original shape of healthy mandible on defect area, computed tomography (CT) images are used to reconstruct the 3D model of bone firstly, then the defect area is separated from the bone, and then prosthesis is designed via mirror or a hole-filling algorithm, in which outer shape can be used as the external shape of scaffold. Compared to the outer shape, internal structure design is more complicated. The required mechanical, biological, and geometrical properties of scaffold determine its intricate micro-structures, which require complicated modeling and calculation. In order to save time on model translation and modeling, the digital design method based on triangular mesh is adopted for scaffold internal structure design. Based on external shape and internal structures, the final scaffold model can be obtained via Boolean subtraction. The scaffold, as the physical model of substitute on defect area, is then fabricated via RP methods, such as the method of selective laser sintering (SLS) with polycaprolactone (PCL) materials (Williams *et al*., 2005), which has been proven to be appropriate for bone regeneration (Más Estellés *et al*., 2008). After surface bio-modification, the fabricated PCL scaffold is then cultured in vitro with cells and growth factors to generate bio-substitute of defect area. Then, through clinical operation, the mandibular defect is resected and the bio-substitute is implanted. After bone generation with scaffolds is completed in vivo, the lost teeth can be rebuilt via dental implantation, restoring the patient's appearance and oral functions.

This methodology combines the research of TE and maxillofacial surgery, and attempts to utilize the achievements on TE to solve existing problems in mandibular defect repair. Some basic theories and techniques of the two fields, such as medical model reconstruction, personalized prosthesis design, and scaffold design, can be utilized or referenced. However, some key works, including digital design of scaffold, material selection, fabrication, and culturing, require exploration and further study.

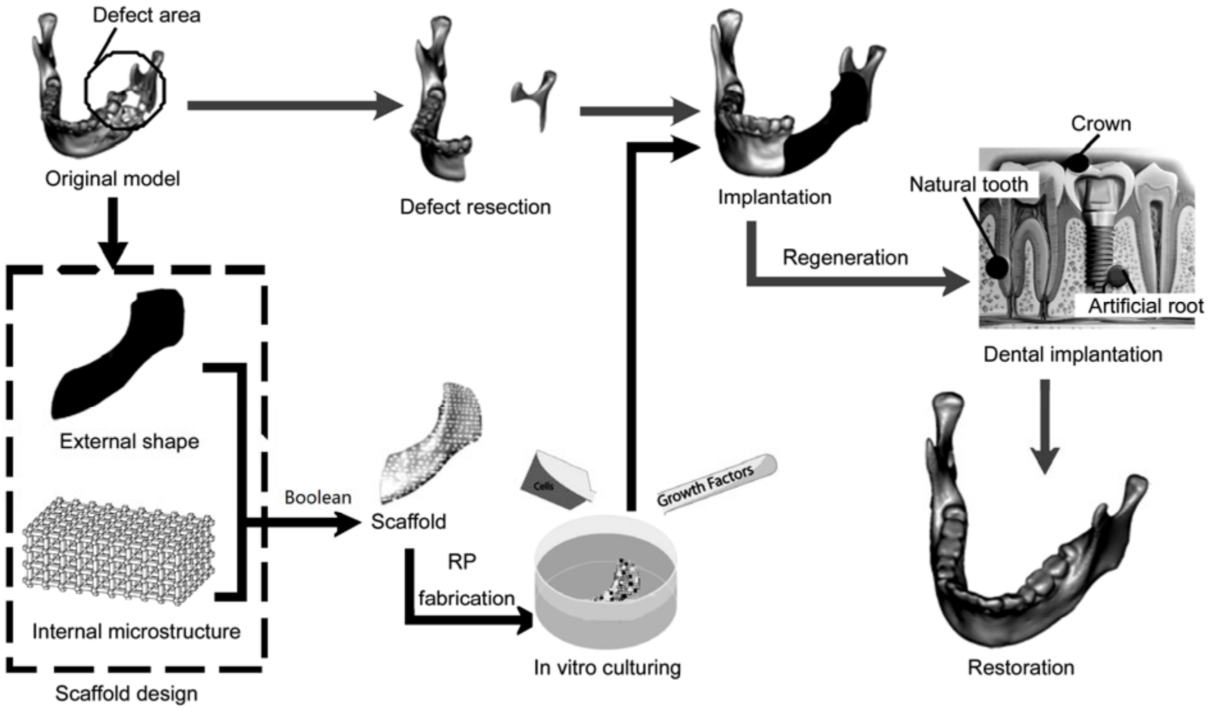

Fig. 1 Scheme of mandible defect repair based on tissue engineering (TE)

3 Scaffold external shape design

The scaffold external shape controls the shape of the bio-substitute for the mandibular defect area, and thus determines the quality of the patient's facial appearance. So, the external shape design is crucial in mandibular defect repair, and is usually complicated due to the complexity of bone structure, which is difficult to represent as a traditional four-sided surface, such as a B-spline surface or a Bezier surface. The digital design method directly based on triangular mesh is adopted to design the external shape of scaffold.

3.1 3D model reconstruction based on CT image

Medical model reconstruction based on CT images is a mature technique, which can be handled with commercial software, such as MIMICS (Materialise NV Corp.). With operations such as mask creation, region growing, and triangular mesh creation, bone models can be rapidly reconstructed, but to meet the needs of scaffold shape design, more complex and trivial works are needed, such as ability to remove image artifacts and to use mask editing for sole mandible separation. In order to guarantee the precision of reconstruction, the scanning space between two adjacent images must be limited to no more than 1 mm. Fig. 2 shows an example of mandibular reconstruction. A total of 124 images are scanned with a 1-mm interval space, with several samples shown in Fig. 2a. With the gray threshold value from 516 to 3071, the bone mask is created as a whole, as shown in Fig. 2b, and the reconstructed 3D model based on this mask is shown in Fig. 2c. With mask editing tools, the mask of mandible is separated from whole bone mask, and the sole mandible 3D model is created, as shown in Figs. 2d and 2e.

3.2 Repair model design

The repair model is becoming more and more important for surgeons, since it can be used to design surgery plans, explain the plan to the patient, and preform titanium implants. In the scaffold design, a repair model is used to design external shape via separating the part on the model according to defect area border, and is designed on original model with mirror or hole-filling algorithms. As shown in Fig. 3, the defect area is located on the left (Position 1) or right side (Position 2) without crossing the central plane, and the mirror algorithm is adopted to design repair model through mirroring healthy side bone to replace the defect. Otherwise, if the defect area crosses the central plane (Position 3), the hole-filling algorithm with surface design is adopted to design the repair model, and quite often the mirror model is used to help this procedure.

An example of repair model design with use of a mirror algorithm is shown in Fig. 4. This figure shows a patient's mandible which has been eroded by cancer. First, the reconstructed model (Fig. 4a) of the original mandible is mirrored through a mirror algorithm to acquire the mirror model (Fig. 4b). Then the defect area is separated from the original model and substituted with the same area on mirror model (Fig. 4c), with a total of three parts being acquired. With mesh-merging algorithm and mesh-smoothing tool, the final repair model is created (Fig. 4d). Fig. 5 shows another example of repair model design of a cancer-eroded mandible. Because the defect is in the middle, the substitute on the mirror model cannot be used to repair the defect fully, as is shown in Fig. 5d. The remaining holes must be repaired with a hole-filling algorithm of surface design, to acquire the final repair model, as shown in Fig. 5e.

3.3 Prosthesis design

Because the structure of human bone is very complex, the original reconstructed mandible model and repair model are both represented as a digital triangular mesh. It is very difficult to translate this mesh model to a traditional four-sided surface model such as non-uniform rational B-spline (NURBS) surface, and translation error cannot be avoided too. In order to obtain the regeneration scaffold with prosthesis shape and microstructure for mandibular defects with TE, Boolean calculation of subtraction between prosthesis and regular microstructure based on the triangular solid model is adopted, so the prosthesis must be designed to satisfy the Boolean calculation.

The prosthesis design was performed on the repair model, as shown in Fig. 6. First, the original model and repair model were matched via importing to one coordinate system, then resection curves of defect areas on original model were drawn, and the regeneration part from repair model with these curves

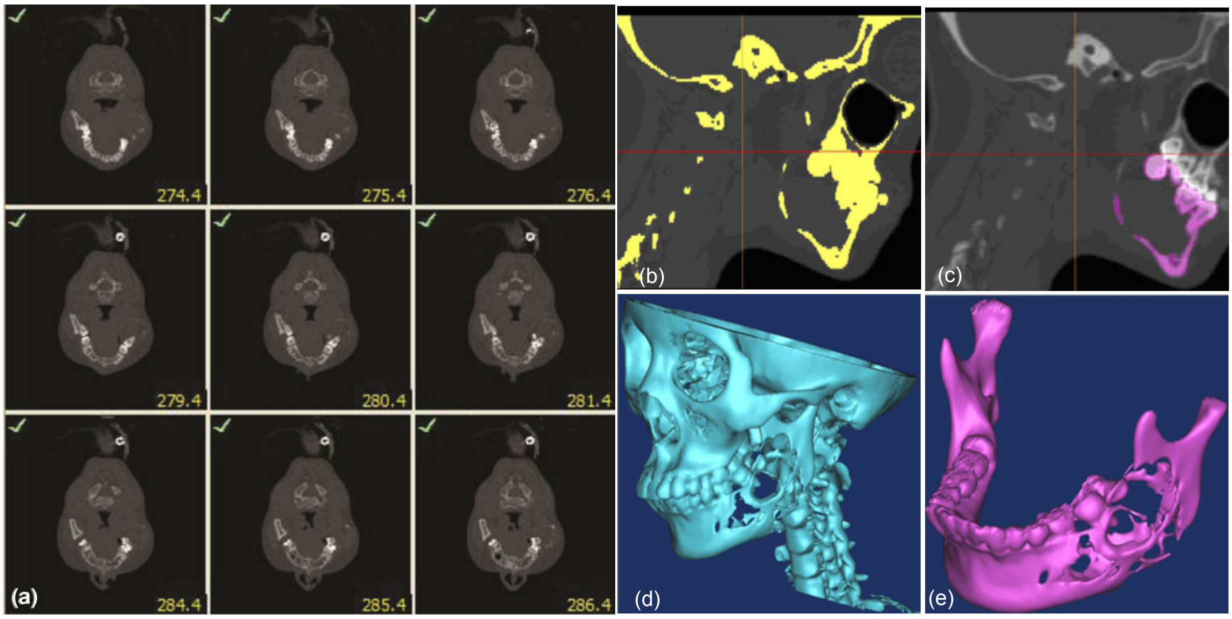

Fig. 2 Mandible 3D model reconstruction
(a) CT images; (b) Bone mask; (c) Separated mask; (d) Whole 3D model; (e) Mandible 3D model

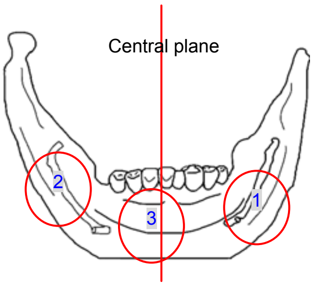

Fig. 3 Defect area positions

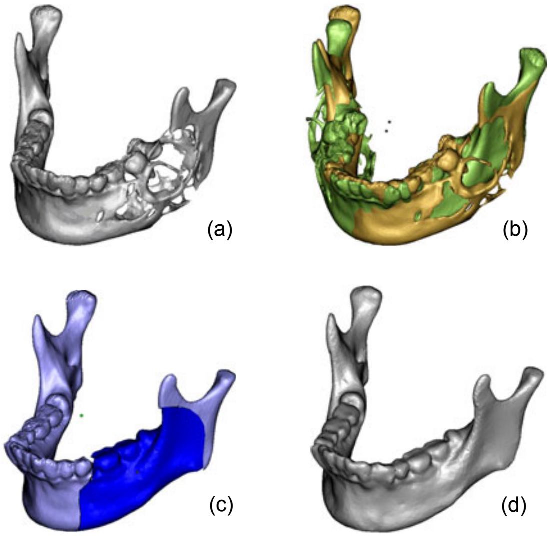

Fig. 4 Repair model design with mirror algorithm
(a) Original model; (b) Mirror model; (c) Defect substitution; (d) Repair model

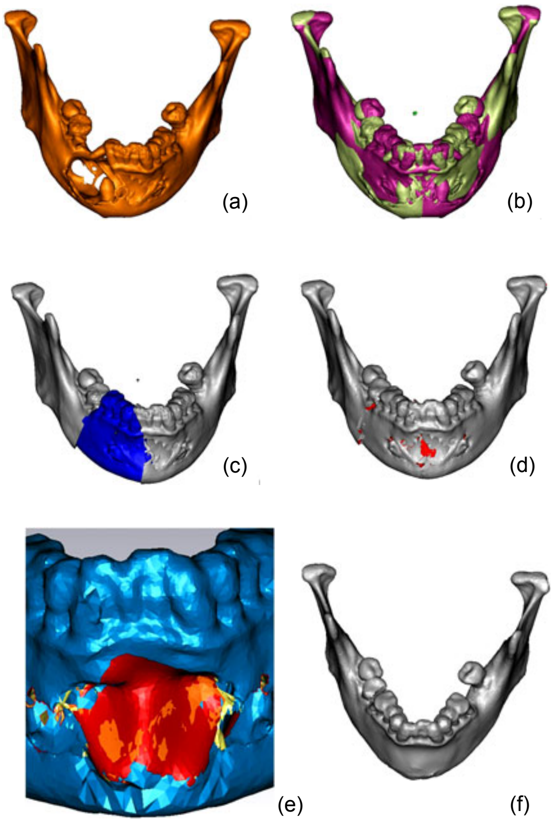

Fig. 5 Repair model design with mirror and hole-filling algorithms
(a) Original model; (b) Mirror model; (c) Defect substitution; (d) Merge model; (e) Hole filling; (f) Repair model

was separated (Fig. 6a). It is simpler obviously to obtain the prosthesis directly separated from the mirror model, but the separated substitute part on the mirror model needs to be redesigned and changed to keep consistent with surrounding borders of mandibular defect, which has been done in repair model design, so separating it from repair model is more precise. To obtain the solid part of the bone prosthesis, the separated substitute then is handled to remove internal holes, with the teeth being removed as well, as shown in Figs. 6b and 6c.

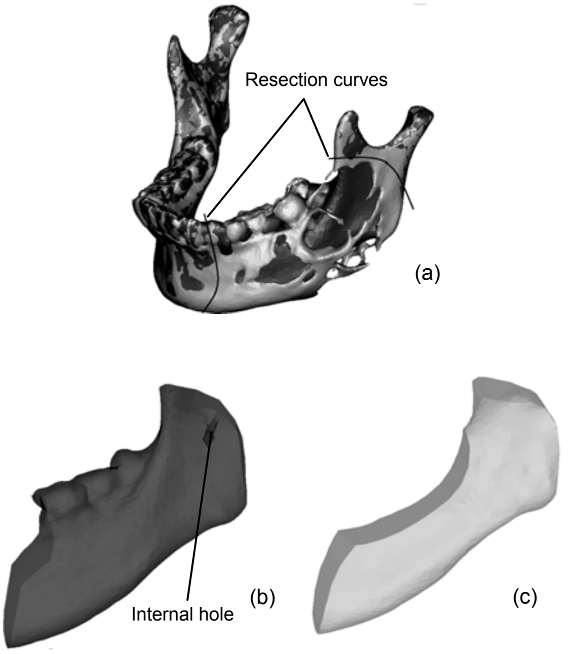

Fig. 6 Prosthesis design
(a) Matching; (b) Separate (transparent view); (c) Prosthesis (transparent view)

4 Scaffold internal microstructure design

Scaffold microstructures not only affect the initial biological and biomechanical properties of the repairing prosthesis, but also determine the bone regeneration process and results via the control of the mechanical environment of the bone-scaffold system (Adachi *et al*., 2006). Appropriate geometrical structures with specific parameters should be designed and a biomaterial with appropriate properties should be selected to satisfy the requirements of biological, biomechanical, and biomaterial functions. On geometrical structure design, two parameters should be considered with one being porosity, and the other being pore size. From existing studies, the porosity is expected to satisfy values ranging from 50% to 90%, and pore size should be from 100 to 500 μm. The final geometrical properties of physical model coinciding with design are determined by the selected fabrication method, such as RP fabrication systems. The two geometrical properties should be kept within an accuracy range of 80%–90%, or the error can be predicted and is compensated for in the design phase (Armillotta and Pelzer, 2008).

4.1 Microstructure design procedure

Considering the facilitation of model format of STL for RP fabrication and complexity of model transfer, the digital design method via 3-matic (Materialise NV Corp.), a piece of software based on triangular mesh, is adopted as the scaffold microstructure design tool. Comprehensively considering the constraints of mechanical and biological properties, the microstructure is designed as a Cartesian reticular structure with nodes on orthogonal grids of three spatial directions. All of the nodes are formed by three orthogonal trusses with a uniform circle section of radius r, which are oriented along the three axes of a coordinate frame x, y, z.

The design procedure of scaffold is shown in Fig. 7. First, create three sketches on coordinate planes XOY, XOZ, and YOZ, and draw a circle with radius r on each the sketch. Then, extrude the sketches to create a Cartesian reticular unit with three orthogonal cylinders. Then, array operations are performed along three coordinate axis directions with appropriate interval distance and copies according to prosthesis dimensions, to create from linear to planner and to cubic pattern consequently. Later, by use of the Boolean UNITE calculation, the negative model of internal structure is obtained. At the end, with Boolean subtraction calculation, the negative model is subtracted from the mandibular prosthesis to get the final internal structure of scaffold.

4.2 Property analysis

The scaffold porosity is one of the most important properties. To calculate the porosity, the calculation model, as the sketch on XOY plane shown in Fig. 8a, is adopted. Considering the uniform property of structure, the central part of the square filled with

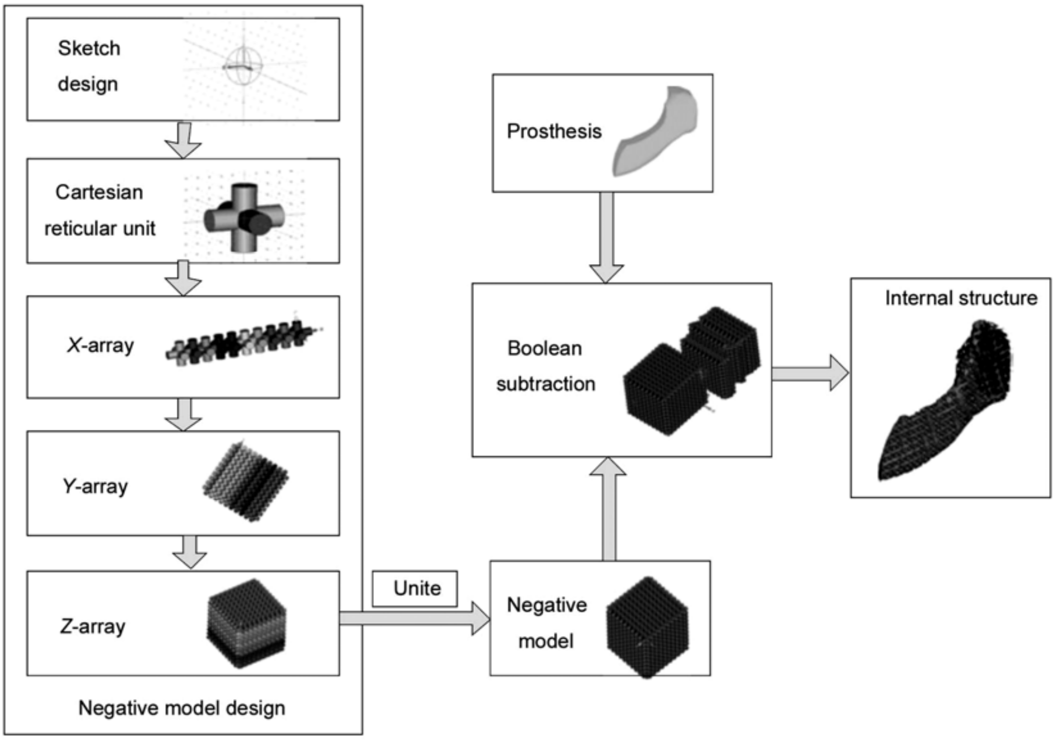

Fig. 7 Procedure of internal structure design

section line is used in the calculation. The square edge length is t, and is filled with a quarter arc in each corner, labeled as 1, 2, 3, 4, which can be combined to form a full circle. In a 3D space, the calculated part becomes a cube with edge length t, and is filled with 12 quarter cylinders which can be combined to equal three orthogonal intersection cylinders along with coordinate axes, similar to the unit in Fig. 8b. When calculating the volume (V), the intersection part as shown in Fig. 8c should be subtracted twice from the whole volume of three cylinders. Then, the porosity (p) can be calculated by the following equations:

$$p_{\text{theory}}=(3V_{\text{cylinder}}-2V_{\text{intersection}})/V_{\text{cube}}\times 100\%,$$
$$V_{\text{cylinder}}=\pi r^2 t,$$
$$V_{\text{intersection}}=(16-8\sqrt{2})r^3,$$
$$V_{\text{cube}}=t^3.$$

When t=3 mm, r=1 mm,

$$p_{\text{theory}}=\frac{3\pi\times 3-2(16-8\sqrt{2})}{27}\times 100\%=69.94\%.$$

Because of the errors existing in the calculation of Boolean subtraction between the prosthesis and the scaffold negative model and the non-uniformity of structures on the scaffold surface, as shown in Fig. 8c, the real porosity is somewhat different from the theoretical one. When t=3 mm and r=1 mm, with the volumes of prosthesis and scaffold acquired from mesh handling software magic RP™, the practical porosity is calculated as follows:

$$p_{\text{practical}}=(V_{\text{prosthesis}}-V_{\text{scaffold}})/V_{\text{prosthesis}}\times 100\%=(13.323-4.425)/13.323\times 100\%=66.79\%.$$

The result is 3.15% less than theoretical porosity.

4.3 Fabrication test

In order to verify the validity of the proposed method and manufacturability of the generated scaffold models, a preliminary test of fabrication was conducted. Fabrication of a scaffold with complex structures is very difficult by way of traditional methods. Solid free-form fabrication (SFF) methods, such as RP, are an integral component of scaffold

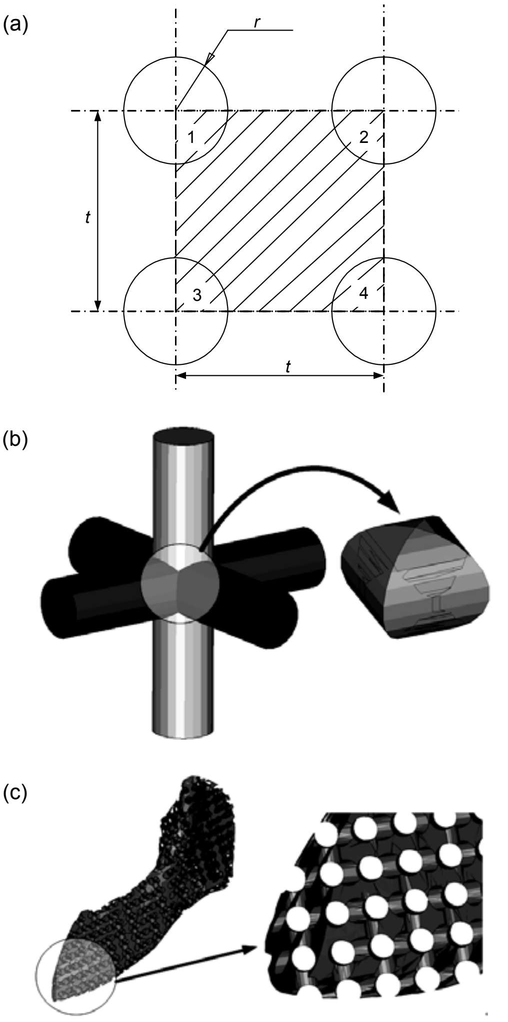

Fig. 8 Porosity calculation
(a) Sketch; (b) A node unit and intersection part; (c) Scaffold

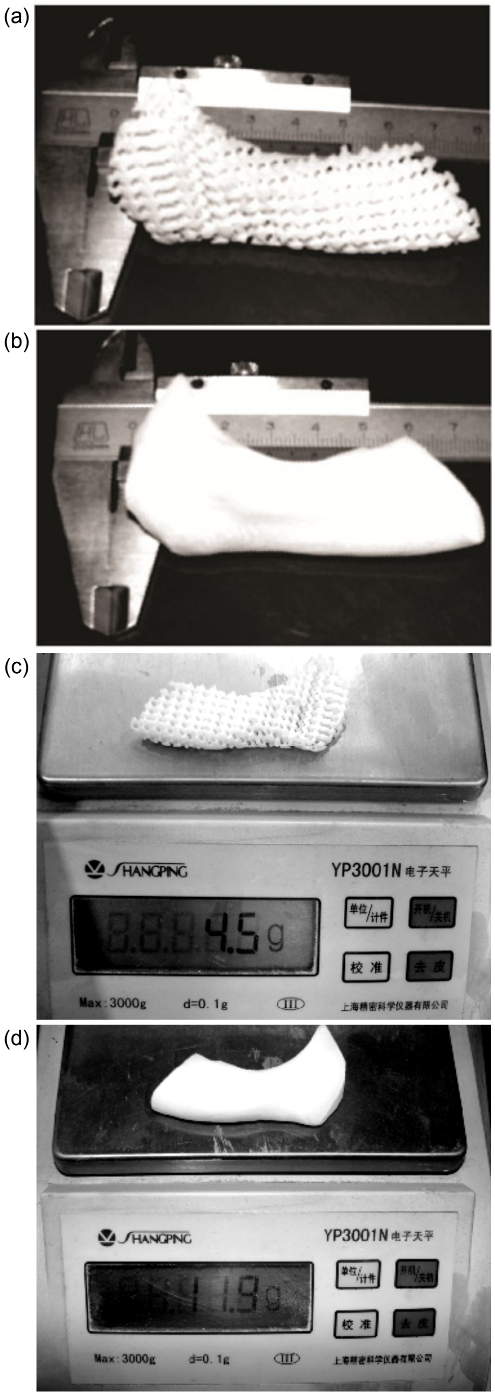

Fig. 9 Fabricated model
(a) Scaffold; (b) Prosthesis; (c) Measuring of scaffold; (d) Measuring of prosthesis

manufacturing, particularly useful for acquiring controllable structures. RP method of SLS with biopolymer materials has been proven to be effective for bone scaffolds to acquire controllable predesigned microstructures (Williams *et al.*, 2005), but the proposed scaffold model with external bone shape and internal connective pores and small size needs to be tested. In order to test the validity of design and fabrication, a scaffold prototype is manufactured with industrial applied materials. Bioactive materials require further biological testing.

A fabricated scaffold for mandible repair via SLS system is shown in Fig. 9. The designed scaffold model with t=3 mm and r=1 mm of structure in Fig. 8 is exported to a Sinterstation HiQ+HiS$^{\text{TM}}$ machine (3D Systems, Velencia, USA) via STL file format. With the use of a common non-biological material of powder (DuraForm™ Polyamide, 3D Systems) used for industrial parts, the scaffold is constructed by SLS processing with the following parameters: preheating temperature of 70 °C, laser beam diameter of 400 μm, laser power of 4 W, and a scanning speed of 1.257 m/s. With a processing thickness of 100 μm, scaffolds were fabricated layer-by-layer in the powder bed. After powder sintering was completed, and the temperature of process chamber was decreased to 70 °C after 2–4 h, the scaffolds were taken out from the powder bed with the whole powder box, and were then extracted from the powder. In order to clean the unsintered powder off of the scaffold's outside surface and in interstices and pores, various tools including a brush, compressed air, and a thin wire were used. Through various measurements and analyses, the fabricated test scaffolds were found to preserve high precision on dimensions and shape with respect to the design model. In order to testify the porosity changes, the scaffolds (Fig. 9a) and the prosthesis without internal pores (Fig. 9b) were fabricated concurrently under the same SLS processing parameters. Their volumes are substituted via mass since they have the same density when they are fabricated in one process at the same time. The mass measuring is shown in Figs. 9c and 9d.

The measured mass is: $m_{\text{prosthesis}}$=11.9 g, m_{scaffold}=4.5 g, so the physical porosity is:

$$p_{\text{physical}}=(m_{\text{prosthesis}}-m_{\text{scaffold}})/m_{\text{prosthesis}}\times100\%=(11.9-4.5)/11.9\times100\%=62.2\%.$$

Therefore, the porosity is decreased with an accuracy of 93%, which is within the requirement of 80%−90% accuracy. One of the reasons for porosity errors is the distortion in SLS processes. Porosity with higher accuracy can be obtained with compensation design based on comprehensive analysis of theory, practical and physical porosities, or by regulating the processing parameters of powder sintering.

5 Discussion

In order to acquire a scaffold with a controllable structure, compatible design and fabrication methods should be used. As reviewed in Section 1, two existing design methods including traditional CAD method (Sun and Lal, 2002; Sun *et al.*, 2005) and image-based design method (Adachi *et al.*, 2006) have been widely used. Compared to them, the most difference of the proposed strategy is that the scaffold design including external shape and internal microstructure is directly based on mesh model. In the traditional design procedure as shown in Fig. 10a, the model must be transferred two times with the first being a surface fitting from mesh model to NURBS model, followed by triangularization from NURBS model to mesh model for RP fabrication. The original bone model reconstructed from CT images is represented by use of triangular meshes for its powerful capacity to render complex details of bone structure, while traditional CAD design method is based on four-sided patches of NURBS, so model transfer via

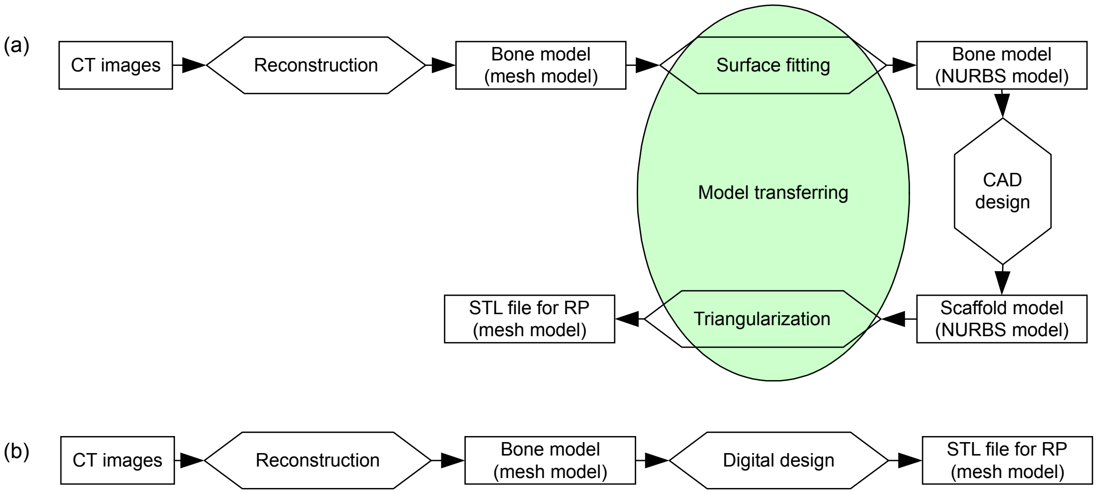

Fig. 10 Comparison of two design methods
(a) Traditional design procedure; (b) Digital design procedure

surface fitting is necessary. On the other hand, scaffold fabrication via RP systems uses an STL file as the data import, so the design model must be transferred to mesh model by triangularization. The two model transfers are too complicated and time-consuming, and transfers errors are also produced. Furthermore, the design of many microstructures on NURBS model will lead to a great amount of calculation time. Compared to the traditional method, the digital design procedure is rather simple and more accurate, because the design work is performed directly on the mesh model and model transfer is avoided, as shown in Fig. 10b.

The scaffold fabrication via SLS of RP can realize controllable structure of physical model from design, but with conventional fabrication techniques including solvent-casting particulate-leaching, gas foaming, phase separation, and others, certain scaffold structures cannot be controlled which include pore size, geometry, spatial distribution of pores, and construction of internal channels (Sachlos and Czernuszka, 2003). Furthermore, conventional methods are incapable of fabrication of human tissue with a specific shape, but it is convenient for RP with layer-by-layer adhesive.

On the other hand, some intrinsic limitations of the proposed methodology should be pointed out: one is that if the mandibular defect area is in the middle (Position 3 as shown in Fig. 3) and is quite large in size, the repair prosthesis cannot be acquired directly through the mirror algorithm, and the original shape of the healthy mandible is difficult to recover via hole filling, which means that some advanced curve and surface design algorithms are needed.

Another limitation is that the digital mesh model is in approximation to geometry. For example, it cannot represent the true quadric surface. As the cylinder shown in Fig. 11, the diameter of the bottom circle is 10 mm and is represented as a series of line segments with lengths of 0.63 mm, and the cylinder surface is represented as a series of rectangles, so geometrical error is unavoidable, which will bring calculation error when Boolean operations are performed between two solid models. Improving approximation precision means more triangular meshes and more time-consuming calculations, so determining how to balance the precision and efficiency is something which needs a comprehensive consideration. Because rational B-spline can truly represent a geometrical model, the conventional CAD method would not encounter this kind of problem on scaffold design.

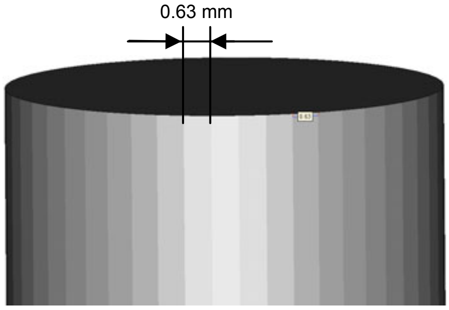

Fig. 11 Digital model of cylinder

6 Conclusions and future works

Mandibular defect is a common oral illness and has been a concern for many years. Aiming at the limitations in clinic repairing methods, a new methodology based on TE with scaffold is proposed in this paper. Digital design methods of substituted scaffold including external shape and intricate interconnected microstructures are discussed and analyzed. With a prototype fabricated via SLS RP system with common non-bioactive material, the validity and accuracy of design and fabrication are tested and analyzed. The comprehensive conclusions can be listed as follows:

1. The proposed method reduces and simplifies the design procedure of the scaffold. Because the digital design method of the scaffold is directly based on triangular mesh, two complex translating calculations between NURBS surface and triangular mesh model are avoided, and model transferring error is decreased.

2. The fabricated test scaffolds prove the feasibility and validity of proposed design and fabrication method to some degree. For the two parameters on fabricated prototype, the accuracy of porosity is 93%, and the pore size is very close to the design model.

3. The repairing strategy of mandibular defect utilizing TE with scaffold is proven to be feasible to some degree. Using the proposed methodology, the prosthesis scaffold with personalized outer shape and intricate internal microstructures is designed and fabricated, and can be used as the bed of bone regeneration and restoration of defect repair after biomaterial substituting and serials bioprocessing.

Until now, the research work is still rather preliminary, and there is a long way to go for clinical use of the proposed methodology for mandibular defect repair. Our future works include: (1) mechanical analysis and testing, (2) biological property analysis and testing, (3) internal microstructure optimization, and (4) biological experiments such as in vitro culturing, animal experiments, in vivo culturing and implanting.

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