

MOULD FOR CASTING TISSUE ENGINEERING SCAFFOLDS AND PROCESS FOR GENERATING THE SAME

Field of the Invention

[0001] The present invention generally relates to technologies of designing and fabricating three-dimensional tissue engineering scaffolds, and more particularly to a mould for casting tissue engineering scaffolds and a process of generating the mould for casting tissue engineering scaffolds, and further to a tissue engineering scaffold fabricated by the mould for casting tissue engineering scaffolds.

Background of the Invention

[0002] Designing and fabricating three-dimensional scaffolds are essential for tissue engineering. For implantable scaffolds, it is desirable to have internal pores and internal channels connecting the internal pores, so that the cells can migrate into the pores and channels and grow therein, resulting in better compatibility of the scaffolds with their host.

[0003] There have been attempts to manually model the micro-architecture within a scaffold using traditional CAD modeling techniques before committing the models for Rapid Prototyping fabrication. However, there are many limitations of employing traditional CAD techniques for modeling the geometry and micro-architecture of tissue engineering scaffolds. The limitations include: highly labor intensive and lengthy; computational resource intensive; requirement of skilled CAD personnel because the process is not automated; and limited scaffold/mould designs because moulds produced using 3D modeling techniques are mainly limited to simple geometric designs.

[0004] The inventors of the present invention have disclosed methods of designing and fabricating a customized three-dimensional porous scaffold by using bitmap templates. "Method For Designing 3-Dimensional Porous Tissue Engineering Scaffold", US Patent Application No. 11/239,008. "3-Dimensional Porous Tissue Engineering Scaffold Designs Using Grow-And-Reduce Pixelization", Singapore Patent Application No. 200504514-1. However, when the designed scaffold is fabricated by Rapid Prototyping Machine, heat is

generated; thus materials for example biomaterials that cannot withstand high processing temperature cannot be used in such automatic fabrication.

Summary of the Invention

[0005] One embodiment of the present invention provides a process for designing a customized three-dimensional porous mould for casting a three-dimensional porous scaffold for an object, wherein the customized three-dimensional porous mould comprises a wall and an internal structure with internal pores and internal channels connecting the internal pores. The process comprises the steps of creating bitmap templates offline, wherein the bitmaps templates are created according to the desired shapes and dimensions of the pores and channels within the mould, preparing two-dimensional images of the object, pre-process the two-dimensional images to remove unwanted portions according to predetermined thresholds, generating the internal structure, and generating the wall of the mould; thereby the customized three-dimensional porous mould is designed.

[0006] In another embodiment of the process, the number of the bitmap templates depends on the size of the scaffold for the object, the resolution of the two-dimensional images of the object, the slice thickness of the two-dimensional images of the object, and the complexity of the internal pores and channels of the mould.

[0007] In another embodiment of the process, the step of creating bitmap templates performs manual drawing of the bitmap templates with any computer graphic software that supports a bitmap file format or using a short algorithm to automatically generate the bitmap templates.

[0008] In another embodiment of the process, the two-dimensional images are medical images that are generated from a technique selected from the group consisting of CT, MRI, Ultrasound or computer-based medical imaging systems.

[0009] In another embodiment of the process, the two-dimensional images are stored in Digital Imaging and Communications in Medicine (DICOM) format.

[0010] In another embodiment of the process, in the step of generating the internal structure, the two-dimensional images are firstly modified by intersecting them with appropriately selected bitmap templates via Boolean operation, resulting in the transferring of the grid pattern on the bitmap template onto the images, and then the internal (micro-

architecture) and external (external geometry) contour data of the modified images are extracted to reconstruct a three-dimensional surface model of the mould. In a further embodiment of the process, the three-dimensional surface model of the mould is reconstructed by surface patching technique.

[0011] In another embodiment of the process, the step of generating the wall of the mould includes creating the cup structure of the mould and expanding the edges of the wall to a required thickness. In a further embodiment of the process, in the step of the creating of the cup structure of the mould, for each slice, two sets of image data are kept, wherein one set is the cleaned images from the step of pre-process the two-dimensional images to remove unwanted portions according to predetermined thresholds without Boolean and the other set is the Boolean images, and wherein no Boolean operation is done for the last slice image that is the base of the cup.

[0012] Another embodiment of the present invention provides a customized three-dimensional porous mould for casting a three-dimensional porous scaffold for an object, wherein the customized three-dimensional porous mould comprises a wall and an internal structure with internal pores and internal channels connecting the internal pores, and wherein the customized three-dimensional porous mould is designed by the process comprising the steps of creating bitmap templates offline, wherein the bitmaps templates are created according to the desired shapes and dimensions of the pores and channels within the mould, preparing two-dimensional images of the object, pre-process the two-dimensional images to remove unwanted portions according to predetermined thresholds, the internal structure, and generating the wall of the mould; thereby the customized three-dimensional porous mould is designed.

[0013] In another embodiment of the mould, the number of the bitmap templates depends on the size of the scaffold for the object, the resolution of the two-dimensional images of the object, the slice thickness of the two-dimensional images of the object, and the complexity of the internal pores and channels of the mould.

[0014] In another embodiment of the mould, the step of creating bitmap templates performs manual drawing of the bitmap templates with any computer graphic software that supports a bitmap file format or using a short algorithm to automatically generate the bitmap templates.

[0015] In another embodiment of the mould, the two-dimensional images are medical images that are generated from a technique selected from the group consisting of CT, MRI, Ultrasound or computer-based medical imaging systems.

[0016] In another embodiment of the mould, the two-dimensional images are stored in Digital Imaging and Communications in Medicine (DICOM) format.

[0017] In another embodiment of the mould, in the step of generating the internal structure, the two-dimensional images are firstly modified by intersecting them with appropriately selected bitmap templates via Boolean operation, resulting in the transferring of the grid pattern on the bitmap template onto the images, and then the internal (micro-architecture) and external (external geometry) contour data of the modified images are extracted to reconstruct a three-dimensional surface model of the mould. In a further embodiment of the mould, the three-dimensional surface model of the mould is reconstructed by surface patching technique.

[0018] In another embodiment of the mould, the step of generating the wall of the mould includes creating the cup structure of the mould and expanding the edges of the wall to a required thickness. In a further embodiment of the mould, in the step of the creating of the cup structure of the mould, for each slice, two sets of image data are kept, wherein one set is the cleaned images from the step of pre-process the two-dimensional images to remove unwanted portions according to predetermined thresholds without Boolean and the other set is the Boolean images, and wherein no Boolean operation is done for the last slice image that is the base of the cup.

[0019] The objectives and advantages of the invention will become apparent from the following detailed description of preferred embodiments thereof in connection with the accompanying drawings.

Brief Description of the Drawings

[0020] Preferred embodiments according to the present invention will now be described with reference to the Figures, in which like reference numerals denote like elements.

- [0021] FIG 1 is a flowchart showing the main steps of the designing and fabricating a mould for casting a three-dimensional porous scaffold in accordance with one embodiment of the present invention.
- [0022] FIG 2 shows a sample of the DICOM medical images.
- [0023] FIG 3 shows a sample of the pre-processed medical image after having removed the unwanted data from the DICOM medical image as shown in FIG 2.
- [0024] FIG 4 is a diagram showing the refinement of the slice thicknesses.
- [0025] FIG 5a shows one bitmap template.
- [0026] FIG 5b shows the negative of the bitmap template shown in FIG 5a.
- [0027] FIG 5c shows a diagrammatic view of forming square pores by overlaying the bitmap templates of FIG 5a and FIG 5b.
- [0028] FIG 5d shows the result of intersecting the Medical Image of FIG 3 with the bitmap template as shown in FIG 5a.
- [0029] FIGS 6a and 6b show an enlarged part of the image of FIG 5d before and after the morphological operation.
- [0030] FIG 7 shows a graphical illustration of the creation of the cup structure of the mould in accordance with one embodiment of the present invention.
- [0031] FIG 8 shows a graphical illustration of the increase of the wall thickness of the mould in accordance with one embodiment of the present invention.
- [0032] FIG 9 shows a mould around the jaw area fabricated by a Rapid Prototyping machine.

Detailed Description of the Invention

- [0033] The present invention may be understood more readily by reference to the following detailed description of certain embodiments of the invention.
- [0034] Throughout this application, where publications are referenced, the disclosures of these publications are hereby incorporated by reference, in their entireties, into this application in order to more fully describe the state of art to which this invention pertains.

[0035] As discussed above, direct fabrication of a three-dimensional porous scaffold may not be feasible when certain biomaterials are utilized because these biomaterials are usually temperature-sensitive. In order to overcome this difficulty, the present invention provides processes for designing and fabricating a three-dimensional porous mould that can be used for casting a three-dimensional porous scaffold, where the mould can be fabricated using a Rapid Prototyping system.

[0036] Now there is provided a more detailed description of the processes for designing and fabricating a customized three-dimensional porous mould for casting a three-dimensional porous scaffold in accordance with one embodiment of the present invention. FIG 1 is a flow chart showing the main steps of the process. It is to be appreciated that while the following description will use specific computer terms and programs for the convenience of explanation, other computer programs may be used if they are applicable for the method of the present invention. In addition, the order of steps in the flow chart is designated only for the convenience of narration. The present invention can be practiced without following the order of steps depicted in FIG 1.

[0037] Referring to FIG 1, the process 1 may start by creating bitmap templates offline 10. As discussed above, a three-dimensional porous mould comprises internal pores and internal channels connecting the internal pores. One aspect of the present invention is to utilize the bitmap templates to create the desired internal pores and channels. Thus, the bitmap templates are created according to the desired shapes and dimensions of the pores and channels within the mould. The number of different bitmap templates that have to be created for a mould depends on many factors including the size of the scaffold, the resolution of the medical images, the slice thickness, and the complexity of the pores and channels. For example, if a square-shaped pore is required, two different bitmap templates that are exact negatives of one another will be prepared, as shown in FIG 5a and FIG 5b. The three-dimensional square pore structure is then achieved by arranging the two different bitmap templates in an alternating manner, as shown in FIG 5c. The shape and dimension of the pores and channels can be controlled by specifying the width of the grids and the spacing between the grids in the bitmap templates. It is apparent that the bitmap templates can be employed to create pores and channels within a mould with any shapes and complexity. However, creating pore shapes with more complex geometries

demands more different bitmap templates and more complex arrangements of the different bitmap templates.

[0038] The creation of bitmap templates can be manual drawing of the template design by using any computer graphic software that supports a bitmap file format. A short algorithm can also be used to automatically generate the required bitmap templates. The methods and algorithms for generating and manipulating the bitmap templates are well known to those skilled in the art, so that no further details will be provided herein. The bitmap templates generated consist of uniform arrays of grids representing the internal structure of the mould and the voids in between the structures. A wide variety of bitmap templates can be created by changing the size, spacing and shape of the grids to give rise to different mould internal micro-architecture designs which possess different micro-structural properties (e.g., porosity, pore shape and distribution and interconnectivity) to suit various Tissue Engineering applications.

[0039] In order to create the three-dimensional porous mould, two-dimensional images are prepared **20**. While medical images from CT, MRI or Ultrasound are used to illustrate the application of the principles of the present invention, it is to be appreciated that the present invention is not so limited. The two-dimensional medical imaging slice data can be generated either by CT, MRI or other types of computer-based medical imaging systems. The generated image slices are stored using a standard file format known as the Digital Imaging and Communications in Medicine (DICOM). FIG 2 shows a sample of the DICOM medical image. Each individual image slice is stored in a single DICOM file. As such, the scanned profile data of a patient is contained in a series of DICOM files, each showing a particular cross-section of the patient's body. Each image slice is separated by a fixed user determined interval known as the slice thickness. The slice thickness directly affects the resolution and accuracy of any three-dimensional models generated using the imaging data slices as an input. The DICOM medical images may be generated by actual scanning or obtained from public databases.

[0040] Then the next step is to pre-process the DICOM files to remove unwanted Data from them **30**. In a typical image slice, the different types of tissues captured by the imaging system are displayed as distinct regions with different pixel intensity. For generating a mould structure, only the profile of certain tissue/tissues (the tissue/tissues which the Tissue Engineered implants are going to replace) on each image slice

corresponding to the region of interest is required. As such, each image slice will be pre-processed to isolate the required data and to remove all unwanted data. FIG 3 shows a sample of the pre-processed medical image after having removed the unwanted data from the DICOM medical image as shown in FIG 2.

[0041] The pre-process for categorizing of required and unwanted data from a DICOM file can be carried out in any possible ways. For example, using a thresholding process for filtering unwanted data, pixels with intensity value less than the threshold value as determined by a user are removed as shown below. As such, the threshold value should be set smaller than the intensity value of the pixels representing the required data.

[0042]
$$f(x) = \begin{cases} 0 & \text{for } f(x) < \varepsilon, \\ f(x) & \text{Otherwise} \end{cases} \quad \text{where } \varepsilon \text{ is the Threshold value}$$

[0043] The removal of unwanted data can also be carried out manually using a specially written algorithm or any image editing software that supports DICOM file format.

[0044] After obtaining the cleaned images of all slices, the process proceeds two parallel operations for generating the internal structure and wall of the mould respectively 40.

[0045] Now the operations of generating the internal structure of the mould will be described first. To create the internal porous micro-architecture of the moulds, the imaging data slices are firstly modified by intersecting them with appropriately selected bitmap templates via Boolean operation. This will result in the transferring of the grid pattern on the bitmap template onto the image slice. To reconstruct the three-dimensional profile of the mould structure, the internal (micro-architecture) and external (external geometry) contour data of the modified image slices are extracted. Surface patching technique is then applied between the contours to create a three-dimensional closed surface model of the mould.

[0046] As mentioned above, there is a slice thickness between two consecutive image slices. In order to use the pre-processed image slices to generate the three-dimensional structure, the slice thickness has to be refined. The refinement may be accomplished in many different ways. One exemplary refinement is shown in FIG 4. The refinement is done by duplicating the sets of the pre-processed DICOM image slice files

and filling the slice thicknesses by inserting the duplicated DICOM image slices into the slice thickness **50**. The number of duplicates to be made for each slice is determined by the thickness of the pre-processed DICOM image slice and the slice thickness. After duplication, the image header data of all the slices has to be re-designated by the user. This modification is necessary to ensure that the inserted slices would be deemed as being a continuous set of 2D images.

[0047] Referring still to FIG 1, after the bitmap templates are created and the image slices are pre-processed, a Boolean intersection operation is then performed between the bitmap templates and the image slices **60**. Using this operation, the grid pattern of the bitmap templates will be transferred onto the image slices and will appear as two-dimensional array of pores and channels. For example, as shown in FIGS 5a and 5b, two sets of bitmap templates being exact negatives of one another are used to generate the squared pores and channels as illustrated in FIG 5c. FIG 5d shows the result of intersecting the Medical Image of FIG 3 and the Bitmap Template 1 of FIG 5a. Different bitmap templates for intersection with the image slices will be required for different geometrical shape and size of the pores generated in the scaffold structure.

[0048] For cases where the pore size is represented by $n \times n$ ($n > 1$) pixels, intersection of the image slices with the bitmap templates may result in the generation of incompletely-formed pores at the edges of the region of interest. If such incomplete pores are not removed from the image slices, they will result in the formation of loose ends of materials sticking out from the scaffold structure during the fabrication process. Such loose ends of materials are not desirable as they can be easily broken off. Thus, a morphological operation is carried out to remove the incomplete pores **70**. This operation checks, identifies and removes all incomplete pores within the image. If an incompletely-formed pore is detected, the intensities of the pixels representing the body of material surrounding the incomplete pore are set to zero (empty space), thereby removing the incomplete pore. FIGS 6a and 6b show an enlarged part of the image of FIG 5d before and after the morphological operation.

[0049] Now the operations of generating the external (wall) structure of the mould will be described in detail. For the mould to function properly, it has to have an enclosed wall for holding the casting slurry/solutions. In one embodiment of the present invention,

the operation of generating the wall comprises two steps: creating the cup structure of the mould **80** and expanding the edges of the wall to a required thickness **90**.

[0050] Now there is provided a detailed description of the creating of the cup structure of the mould **80**. For each slice, two sets of image data are kept; one set is the cleaned image from step **30** without Boolean and the other set is the Boolean image from step **60**. No Boolean operation shall be done for the last slice; the last slice is the base of the cup.

[0051] Now referring to FIG 7, there is provided a graphical illustration of the creation of the cup structure of the mould in accordance with one embodiment of the present invention. Taking a square image as an example, two sets of image data are generated as shown in FIG 7(a). In order to create the cup structure with no leaks at the side, those gaps that will be exposed shall be filled; this is done in one embodiment by using the clean image of the previous slice and the both images of the current slice to perform the Boolean operation. The input images for Boolean operation are shown in FIG 7(b): cleaned image of previous slice; cleaned image of current slice; and Boolean image of current slice. The Boolean operation comprises two steps: 1) as shown in FIG 7(c), the previous cleaned slice and current Boolean slice are Booleaned to generate an initial resultant slice; and 2) as shown in FIG 7(d), the initial resultant slice and current cleaned slice are Booleaned to generate a resultant slice. In other embodiments, instead of doing step 1 in the Boolean operation, the previous Boolean slice can be used as the initial resultant slice. For the last slice, no Boolean operation is necessary as a solid base is required.

[0052] Now referring to FIG 8, there is provided a graphical illustration of the increase of the wall thickness of the mould in accordance with one embodiment of the present invention. To create the wall of the mould, a segmentation technique is first used to create the image boundary as shown in FIG 8(a) and FIG 8(b). After obtaining the edges, wall thickness is being increased by using morphological dilation and erosion. Depending on the thickness required, the process repeats accordingly. The series of in-sequenced Boolean slices together with increased wall thickness slices are then used as inputs to some third party software that converts it into STL file which is suitable for Rapid Prototyping.

[0053] Now referring back to FIG 1, after both internal and external structures are obtained, the Boolean and increased edge thickness image slices are united together by means of using third party software that convert the series of in-sequenced slices into an STL file **100**; and input the file into RP machine for fabrication **110**.

[0054] FIG 9 shows a mould around the jaw area fabricated by a Rapid Prototyping machine using the Inkjet printing technique.

[0055] The materials that are applicable for the scaffold are not limited to any specific type. It could be biodegradable if the scaffold is to be used in providing a support for tissue growth in vivo. For casting technique, materials that can be prepared into slurry/solutions include ceramics, polymers and combination of both materials. The selection of a specific material or materials for making a scaffold depends upon the characteristics of the desired scaffold.

[0056] While the present invention has been described with reference to particular embodiments, it will be understood that the embodiments are illustrative and that the invention scope is not so limited. Alternative embodiments of the present invention will become apparent to those having ordinary skill in the art to which the present invention pertains. Such alternate embodiments are considered to be encompassed within the spirit and scope of the present invention. Accordingly, the scope of the present invention is described by the appended claims and is supported by the foregoing description.

CLAIMS

What is claimed is:

1. A process for designing a customized three-dimensional porous mould for casting a three-dimensional porous scaffold for an object, wherein the customized three-dimensional porous mould comprises a wall and an internal structure with internal pores and internal channels connecting the internal pores, said process comprising the steps of:

creating bitmap templates offline, wherein the bitmaps templates are created according to the desired shapes and dimensions of the pores and channels within the mould;

preparing two-dimensional images of the object;

pre-process the two-dimensional images to remove unwanted portions according to predetermined thresholds;

generating the internal structure; and

generating the wall of the mould;

thereby the customized three-dimensional porous mould is designed.

2. The process of claim 1, wherein the number of the bitmap templates depends on the size of the scaffold for the object, the resolution of the two-dimensional images of the object, the slice thickness of the two-dimensional images of the object, and the complexity of the internal pores and channels of the mould.

3. The process of claim 1, wherein the step of creating bitmap templates performs manual drawing of the bitmap templates with any computer graphic software that supports a bitmap file format or using a short algorithm to automatically generate the bitmap templates.

4. The process of claim 1, wherein the two-dimensional images are medical images that are generated from a technique selected from the group consisting of CT, MRI, Ultrasound or computer-based medical imaging systems.

5. The process of claim 1, wherein the two-dimensional images are stored in Digital Imaging and Communications in Medicine (DICOM) format.
6. The process of claim 1, wherein in the step of generating the internal structure, the two-dimensional images are firstly modified by intersecting them with appropriately selected bitmap templates via Boolean operation, resulting in the transferring of the grid pattern on the bitmap template onto the images, and then the internal (micro-architecture) and external (external geometry) contour data of the modified images are extracted to reconstruct a three-dimensional surface model of the mould.
7. The process of claim 6, wherein the three-dimensional surface model of the mould is reconstructed by surface patching technique.
8. The process of claim 1, wherein the step of generating the wall of the mould includes creating the cup structure of the mould and expanding the edges of the wall to a required thickness.
9. The process of claim 8, wherein in the step of the creating of the cup structure of the mould, for each slice, two sets of image data are kept, wherein one set is the cleaned images from the step of pre-process the two-dimensional images to remove unwanted portions according to predetermined thresholds without Boolean and the other set is the Boolean images, and wherein no Boolean operation is done for the last slice image that is the base of the cup.
10. A customized three-dimensional porous mould for casting a three-dimensional porous scaffold for an object, wherein the customized three-dimensional porous mould comprises a wall and an internal structure with internal pores and internal channels connecting the internal pores, and wherein the customized three-dimensional porous mould is designed by the process comprising the steps of:

creating bitmap templates offline, wherein the bitmaps templates are created according to the desired shapes and dimensions of the pores and channels within the mould;

preparing two-dimensional images of the object;

pre-process the two-dimensional images to remove unwanted portions according to predetermined thresholds;

generating the internal structure; and

generating the wall of the mould;

thereby the customized three-dimensional porous mould is designed.

11. The mould of claim 10, wherein the number of the bitmap templates depends on the size of the scaffold for the object, the resolution of the two-dimensional images of the object, the slice thickness of the two-dimensional images of the object, and the complexity of the internal pores and channels of the mould.

12. The mould of claim 10, wherein the step of creating bitmap templates performs manual drawing of the bitmap templates with any computer graphic software that supports a bitmap file format or using a short algorithm to automatically generate the bitmap templates.

13. The mould of claim 10, wherein the two-dimensional images are medical images that are generated from a technique selected from the group consisting of CT, MRI, Ultrasound or computer-based medical imaging systems.

14. The mould of claim 10, wherein the two-dimensional images are stored in Digital Imaging and Communications in Medicine (DICOM) format.

15. The mould of claim 10, wherein in the step of generating the internal structure, the two-dimensional images are firstly modified by intersecting them with appropriately selected bitmap templates via Boolean operation, resulting in the transferring of the grid pattern on the bitmap template onto the images, and then the internal (micro-architecture)

and external (external geometry) contour data of the modified images are extracted to reconstruct a three-dimensional surface model of the mould.

16. The mould of claim 15, wherein the three-dimensional surface model of the mould is reconstructed by surface patching technique.

17. The mould of claim 10, wherein the step of generating the wall of the mould includes creating the cup structure of the mould and expanding the edges of the wall to a required thickness.

18. The mould of claim 17, wherein in the step of the creating of the cup structure of the mould, for each slice, two sets of image data are kept, wherein one set is the cleaned images from the step of pre-process the two-dimensional images to remove unwanted portions according to predetermined thresholds without Boolean and the other set is the Boolean images, and wherein no Boolean operation is done for the last slice image that is the base of the cup.