ELSEVIER

Computer-Aided Design 37 (2005) 1097–1114

COMPUTER-AIDED DESIGN

www.elsevier.com/locate/cad

Bio-CAD modeling and its applications in computer-aided tissue engineering

W. Sun*, B. Starly, J. Nam, A. Darling

Department of Mechanical Engineering and Mechanics, Drexel University, 3141 Chestnut Street, Philadelphia, PA 19104, USA

Accepted 2 February 2005

Abstract

CAD has been traditionally used to assist in engineering design and modeling for representation, analysis and manufacturing. Advances in Information Technology and in Biomedicine have created new uses for CAD with many novel and important biomedical applications, particularly tissue engineering in which CAD based bio-tissue informatics model provides critical information of tissue biological, biophysical, and biochemical properties for modeling, design, and fabrication of complex tissue substitutes. This paper will present some salient advances of bio-CAD modeling and application in computer-aided tissue engineering, including biomimetic design, analysis, simulation and freeform fabrication of tissue engineered substitutes. Overview of computer-aided tissue engineering will be given. Methodology to generate bio-CAD models from high resolution non-invasive imaging, the medical imaging process and the 3D reconstruction technique will be described. Enabling state-of-the-art computer software in assisting 3D reconstruction and in bio-modeling development will be introduced. Utilization of the bio-CAD model for the description and representation of the morphology, heterogeneity, and organizational structure of tissue anatomy, and the generation of bio-blueprint modeling will also be presented.

Keywords: CAD; Bio-CAD; Biomodeling; Computer-aided tissue engineering; Tissue scaffold design

1. Overview of computer-aided tissue engineering

Recent advances in computing technologies both in terms of hardware and software have helped in the advancement of CAD in applications beyond that of traditional design and analysis. CAD is now being used extensively in biomedical engineering in applications ranging from clinical medicine, customized medical implant design to tissue engineering [1–4]. This has largely been made possible due to developments made in imaging technologies and reverse engineering techniques supported equally by both hardware and software technology advancements. The primary imaging modalities that are made use of in different applications include, computed tomography (CT), magnetic resonance imaging (MRI), optical microscopy, micro CT, etc. each with its own advantages and limitations as described in [1]. Using data derived from these images, computer models of human joints for stress analysis, dynamic force analysis and simulation; design of implants and scaffolds etc. have been reported in published literature [5–7]. This effort to model human body parts in a CAD based virtual environment is also referred to as Bio-CAD modeling.

Utilization of computer-aided technologies in tissue engineering research and development has evolved a development of a new field of Computer-Aided Tissue Engineering (CATE). CATE integrates advances in Biology, Biomedical Engineering, Information Technology, and modern Design and Manufacturing to Tissue Engineering application. Specifically, it applies enabling computer-aided technologies, including computer-aided design (CAD), medical image processing, computer-aided manufacturing (CAM), and solid freeform fabrication (SFF) for multi-scale biological modeling, biophysical analysis and simulation, and design and manufacturing of tissue and organ substitutes. In a broad definition, CATE embraces three major applications in tissue engineering: (1) computer-aided tissue modeling, including 3D anatomic visualization, 3D reconstruction and CAD-based tissue modeling, and bio-physical modeling for surgical planning and

* Corresponding author. Tel.: +1 215 895 5810; fax: +1 215 895 2094.
E-mail address: sunwei@drexel.edu (W. Sun).

0010-4485//$ - see front matter © 2005 Elsevier Ltd. All rights reserved.
doi:10.1016/j.cad.2005.02.002

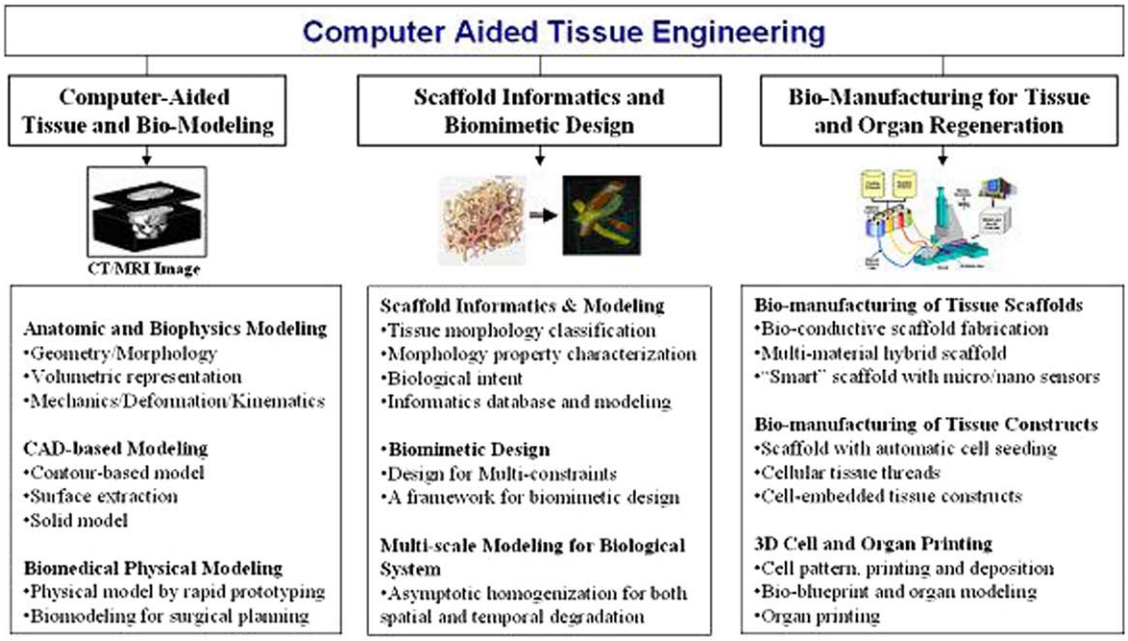


Fig. 1. Overview of computer-aided tissue engineering.

simulation; (2) computer-aided tissue scaffold informatics and biomimetic design, including computer-aided tissue classification and application for tissue identification and characterization at different tissue hierarchical levels, biomimetic design under multi-constraints, and multi-scale modeling of biological systems; and (3) Bio-manufacturing for tissue and organ regeneration, including computer-aided manufacturing of tissue scaffolds, bio-manufacturing of tissue constructs, bio-blueprint modeling for 3D cell and organ printing. An overview of CATE is outlined in Fig. 1. Details of the applications and developments were reported in [1,5,8], respectively.

The extracellular matrix(ECM) that tissue scaffolds attempt to emulate are of great complexity, for integrated within the ECM are instructions that direct cell attachment, proliferation, differentiation, and the growth of new tissue. In order to fulfill its function, an ideal tissue scaffold should be designed to mimic the appropriate structure and characteristics of the desired tissue in terms of biocompatibility, architecture, environment, and chemical composition. In addition, the construction of the scaffold must be achieved at multiple organizational levels, spanning from the micro-scale for cell-printing, to the macro-scale for organ-printing. The scaffold must also have incorporated within it, heterogeneous characteristics in the form of scaffold materials, a controlled spatial distribution of growth factors, and an embedded microarchitectural vascularization for cellular nutrition, movement, and chemotaxis. Consideration of these multiple biological, biomechanical and biochemical issues can be represented by a comprehensive 'scaffold informatics' model. The biological implications of the developed technique and the scaffold informatics model could be significant-ranging from the controlled release of growth factors within a 3D scaffold, to the design and introduction of tissue angiogenesis, creation of a multiple tissue assembly, to the formation of a complex heterogeneous tissue scaffold for soft-hard tissue interface and applications. Central to CATE approach is in its ability of representing such a bio-tissue scaffold informatics model. Bio-CAD modeling plays an important role in this scaffold informatics modeling development by providing the basic morphology, anatomy and organization of the to-be-replaced tissue on which the pertinent biological design intents can be introduced. For example, the definition of the cell-specific scaffolding biomaterials (for cell attachment), the material compositions (for scaffold controlled degradation), pore size, pore shape and ideal topology for inter-architectural connectivity (for cell proliferation, differentiation and new tissue growth), and the prescribed surface chemistry and topography (for cell mechanosensation).

2. Image based bio-CAD modeling technique

Construction of a Bio-CAD model for a specific tissue often starts from the acquisition of anatomic data from an appropriate medical imaging modality. This is referred to as image-based Bio-CAD modeling in which the imaging modality must be capable of producing three-dimensional views of anatomy, differentiating heterogeneous tissue types and displaying the vascular structure, and generating computational tissue models for other down stream applications, such as analysis and simulation. In general, an image based bio-CAD modeling process involves following three major steps: (1) non-invasive image acquisition; (2) imaging process and three-dimensional

reconstruction (3DR) to form voxel-based volumetric image representation; and (3) construction of CAD-based model.

2.1. Non-invasive imaging data acquisition

The primary imaging modalities used in tissue modeling are CT, MRI, and optical microscopy, each with its own advantages and limitations as briefly described as follows. Detailed discussions on using CT and MRI can be found in [1,8]. CT or μCT scans require exposure of a sample to small quantities of ionizing radiation, the absorption of which is detected and imaged. This results in a series of 2D images displaying a density map of the sample. Stacking these images creates a 3D representation of the scanned area. The latest development of micro-CT technology has been successfully used to quantify the microstructure-function relationship of tissues and the designed tissue structures, include to characterize micro-architecture of tissue scaffolds [9,10], to help the design and fabrication of tailored tissue microstructures [11,12], to quantify the bone tissue morphologies and internal stress-strain behavior [13–15], and to non-destructively evaluate the porous biomaterials [16], and to model lung tissue at 10–50 micron resolution [17]. The main advantage of CT and micro-CT as an imaging modality for tissue engineering purposes is reasonably high resolution. MRI provides images for soft tissues as well as for hard tissues, and as such is vastly superior in differentiating soft tissue types and recognizing border regions of tissues of similar density. Dhenain et al. performed micro-MRI scans on mouse embryos and resolution achieved was 20–80 micron voxels. The resulting segmentation isolated each of the major developing organs in the embryo [18]. Using simple region growing techniques and Mimics software [19], the author's group developed a 3D representation for the central nervous system, heart, and kidneys of the subject as reported in [1].

Optical microscopy has limited applications to 3D bio-tissue modeling due to the intensive data manipulation. For example, to examine a sample with high resolution using optical microscopy, it must be physically sectioned to a thickness of between 5 and 80 microns and placed onto slides, providing a square sample perhaps 1 cm $\times$ 1 cm for fine resolution. The division into these slides is a labor intensive process, and the resulting images of the target organ would be thousands of 2D images that must be both digitally stacked into 3D columns as in CT and MRI and arranged in correct X and Y positions. This is computationally and a memory intensive process but within the capabilities of many computer modeling programs. From a practicality point of view, pathologists cannot be expected to examine thousands of individual slides of an entire organ and identify each and every cell in the image. Therefore, it will be a significant challenge to train computers to identify individual cells by their visual characteristics, even with the aid of complex staining. However, differentiating tissue down to the level of the individual cell may still be only possible by using optical microscopy.

Differentiation of tissue in CT scans is accomplished through contrast segmentation, the grayscale value of each voxel determined solely by tissue density. As such, CT is inferior to both MRI and optical microscopy in differentiating soft tissues of similar density. It is much more effective in the modeling of hard tissues and sharply defined density changes, such as the interface between bone and soft tissues. Sometimes, the disadvantage of poor soft tissue differentiation can be addressed with the help of using contrast agents [20,21]. MRI, on the other hand, despite the high tissue differentiation capacity, the resolution is consistently worse than both CT and optical microscopy. However, MRI has been of great use in assembling anatomic atlases of increasingly fine resolution as the technology matures, and find more clinical applications because it does not expose the patient to ionizing radiation.

A hybrid modality approach may be appropriate for determining a more precise 3D model on the same specimen to correct for deficiencies in any single modality. For instance, 3D models derived from MRI and CT could be combined to display heterogeneous soft tissue, for which MRI is excellent, within a high-resolution bone structure such as the skull, for which CT is better suited. A combination of CT and PET has been studied as a means to provide both structural and metabolic information for clinical applications such as precise localization of cancer in the body [22]. A CT/optical microscopy combination might be of use in correcting the histological distortion from the physical sectioning required for optical microscopy, otherwise an ideal modality for high resolution, high tissue differentiation imaging. The CT angiography-derived vascular tree may be a means to help correct this histological distortion in the final model. The optical microscopy method would image the vasculature just as the CT scan would, but the individual vessels might be moved due to cutting distortion in any given slide. By comparing the optical vascular model to the CT-derived vascular model which does not require significant cutting, the histological distortion might be correctable. At the very least, the comparison could determine whether the final model derived from optical microscopy was grossly distorted. An illustration of our study for developing hybrid micro-CT/optical microscopy 3D model, which uses the vascular tree from a micro-CT angiograph to correct distortion in images from optical microscopy sections, is presented in Fig. 2.

2.2. Reconstruction for 3D image representation

A roadmap of the reconstruction of three-dimensional anatomic model from CT/MRI is described in Fig. 3. In the process shown in the roadmap, the CT/MRI images are integrated using 2D segmentation and 3D region growth and this volumetric image data extracts more meaningful, derivative images via three-dimensional anatomic view.

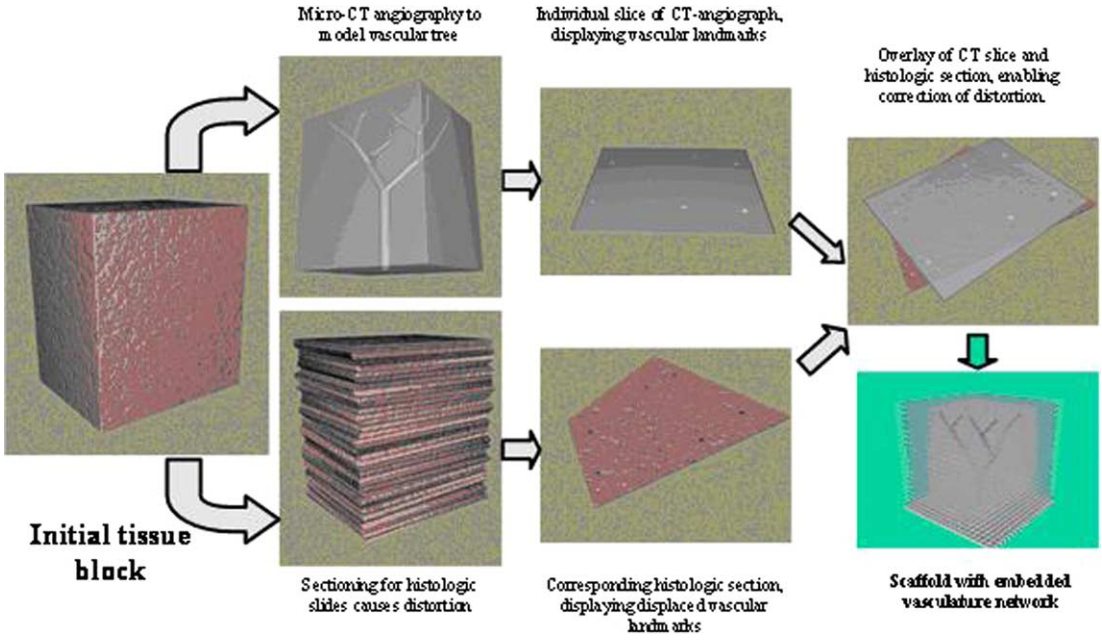


Fig. 2. An illustration of the micro-CT/optical microscopy hybrid model.

The three-dimensional anatomic view produces novel views of patient anatomy while retaining the image voxel intensities that can be used for volume rendering, volumetric representation and three-dimensional image representation. These three-dimensional images lead to the generation of anatomic modeling. Anatomic modeling is used for contour based generation and 3D shaded surface representation of the CAD based medical models. The shaded surface display of 3D objects can involve widespread processing of images to create computer representations of objects. Several visualization issues that cannot be resolved by CAD models provide motivation for the construction of a prototype model. Prototype modeling is done through additive/constructive processes as opposed to subtractive processes. Model slicing and model processing lead to model assisted applications like in surgical planning, preoperative planning, intra-operative planning in computer assisted surgery.

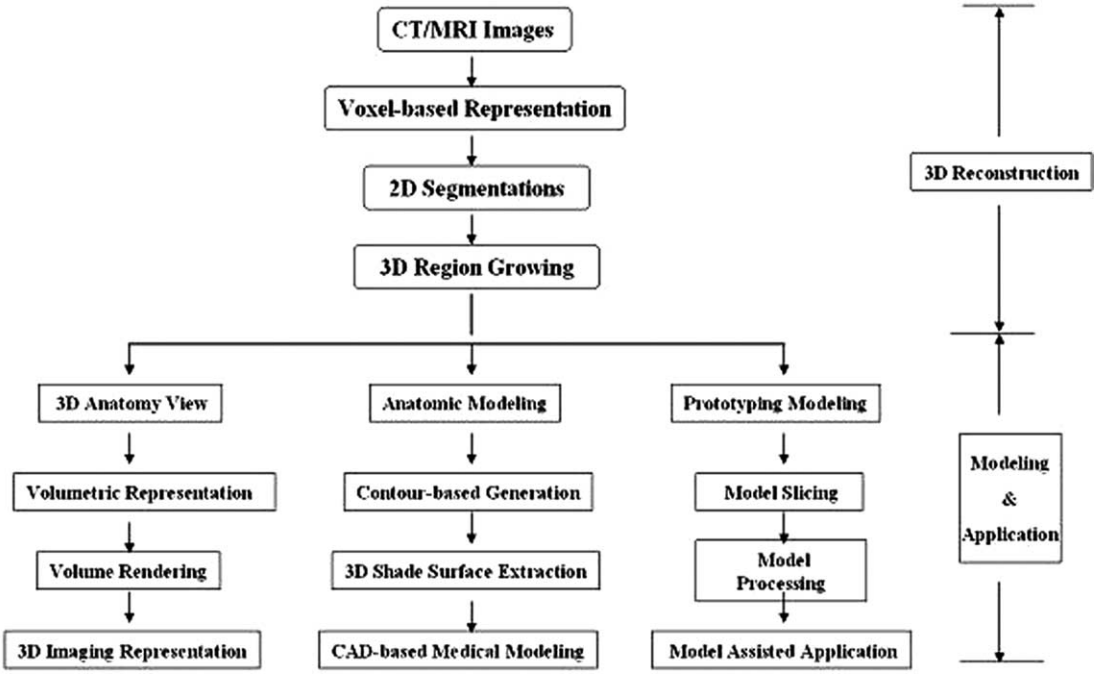


Fig. 3. Roadmap from CT/MRI to 3D reconstruction [8].

Three-dimensional anatomical image and representation is usually constructed through either segmentation or volumetric representation. 2D segmentation is extraction of the geometry of the CT scan data set [23]. Each slice is processed independently leading to the detection of the inner and outer contours of the living tissue, e.g. using a conjugate gradient (CG) algorithm [24,25]. The contours are stacked in 3D and used as reference to create a solid model usually through skinning operations. 3D segmentation [26] of the CT data set are able to identify, within the CT data set, voxels bounding the bone and extract a 'tiled surface' from them. A tiled surface is a discrete representation made of connected polygons (usually triangles). The most popular algorithm is the marching cube algorithm [27,28]. In its original formulation the marching cube method produces tiled surfaces with topological inconsistencies (such as missing triangles) and usually a large number of triangle elements. This method decomposes the complex geometries in 'finite elements' and approximations to the behavior of the system and the quality of approximation depends on the number of these elements and the order of the approximation over each element. In the visualization processing, each triangle is treated as separated polygonal entity and the computational requirements scale up exponentially with the number of triangles. To overcome these difficulties, a new algorithm, Discretized Marching Cube (DMC) algorithm is developed for the 3D segmentation of the CT data set. This algorithm was reported to be able to resolve most topological inconsistencies and maintaining a high level of geometric accuracy through implementing various disambiguation strategies [29].

Beyond the simple reforming of CT scans or MR images into new views [30], three-dimensional modeling and reconstruction provides a new way of viewing the 3D anatomy of the patient. These derived imaging's go beyond simple reformatting to provide a view that integrates across slices to produce 'snapshots' of entire organs or bones. A realistic tissue model is desirable for virtual reality surgery training simulators, mechanical tool design and controller design for safe and effective tissue manipulation. The anatomic tissue modeling should result in efficient and realistic estimation of tissue behavior and interaction forces. The construction of anatomic modeling by either Contour-based method or 3D shaded surface extraction is described in [8].

2.3. Construction of CAD based biomodeling

Although non-invasive modalities, such as CT, Micro-CT, MRI and Optical Microscopy can be used to produce accurate 3D tissue descriptions, however, the voxel-based anatomical imaging representation cannot be effectively used in many biomechanical engineering studies. For example, 3D surface extraction requires either a large amount of computational power or extreme sophistication in data organization and handling; and 3D volumetric model on the other hand, while producing a realistic 3D anatomical appearance, does not contain geometric topological relation. Although they are capable of describing the anatomical morphology and are applicable to rapid prototyping through a converted STL format, neither of them is capable of performing anatomical structural design, modeling-based anatomical tissue biomechanical analysis and simulation. In general, activities in anatomical modeling design, analysis and simulation need to be carried out in a vector-based modeling environment, such as using Computer-Aided Design system and CAD-based solid modeling, which is usually represented as 'boundary representation' (B-REP) and mathematically described as Non-Uniform Rational B-Spline (NURBS) functions. Unfortunately, the direct conversion of the medical imaging data into its NURBS solid model is not a simple task. In last few years some commercial programs, for example, SurgiCAD by Integraph ISS, USA, Med-Link, by Dynamic Computer Resources, USA, and Mimic and MedCAD, by Materialise, Belgium, were developed and used to construct a CAD-based model from medical images. However, none of these programs has been efficiently and widely adopted by the biomedical and tissue engineering community due to the inherent complexity of the tissue anatomical structures. Effective methods for the conversion of CT data into CAD solid models still need to be developed.

We have evaluated and compared following three different process paths for generating a CAD model from medical imaging data: (1) MedCAD interface approach, (2) reverse engineering interface approach, and (3) STL-triangulated model converting approach. The outline of the processes is presented in Fig. 4. The comparison and comments of these three process paths for a case study of femur model generation are listed in Table 1.

2.3.1. Process path 1: MedCAD interface

The MedCAD interface, normally as a standard module of medical imaging process software, is intended to bridge the gap between medical imaging and CAD design software. The MedCAD interface can export data from the imaging system to the CAD platform and vice versa through either IGES (International Graphics Exchange Standard), STEP (Standard for Exchange of Product (STEP) or STL format. The interface provides for the fitting of primitives such as cylinders, planes, spheres etc at the imaging 2D segmentation slices. It also provides the limited ability to model a freeform surface (such as B-spline surfaces). In the example given below, we have used both primitives and freeform shapes to model a femur bone anatomy and report the in Fig. 5. The limitation of using MedCAD interface is the incapability to capture detail and complex tissue anatomical features, particularly for features with complex geometry.

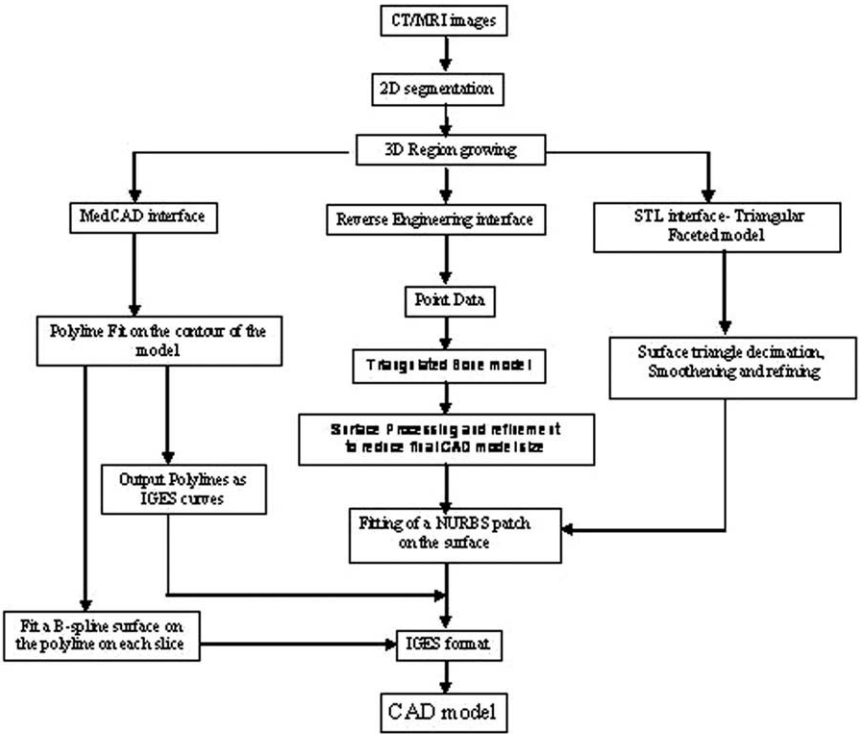


Fig. 4. Process definition to arrive at a CAD model from CT/MRI data.

Table 1
Process comparison-conversion from CT/MRI images to CAD of the proximal femur

Process	Qualities	File size comparisons	Overall
MedCAD interface	Easiest and quickest, but may not be suitable for complex models.	File sizes is small only IGES conversion. IGES: 266KB. CAD (Pro-E): 309KB	Poor
Reverse engineering interface	A longer process but suitable for complex shapes since control is achieved at every level.	Initial file sizes in the point form are not high but final CAD model may involve comparatively higher file sizes. Point: 256KB (7732points). IGES: 266KB (102 NURBS patches). CAD (Pro-E): 298KB	Best
STL interface	Quick method to arrive at a CAD Model but may not work if triangulated surfaces contain errors.	Initial STL file size maybe high resulting in more CAD model IGES file size. STL: 1.82 MB (38252 triangles). IGES: 9.83MB (2316 NURBS patches). CAD (Pro-E): 10.3 MB	Average

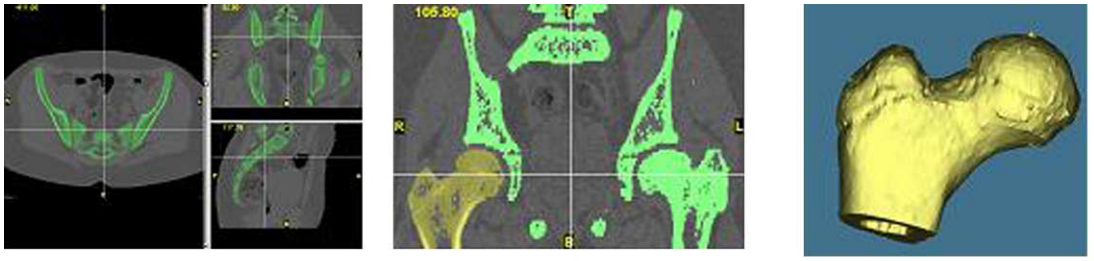


Fig. 5. Image registration, 2D segmentation, 3D reconstruction process.

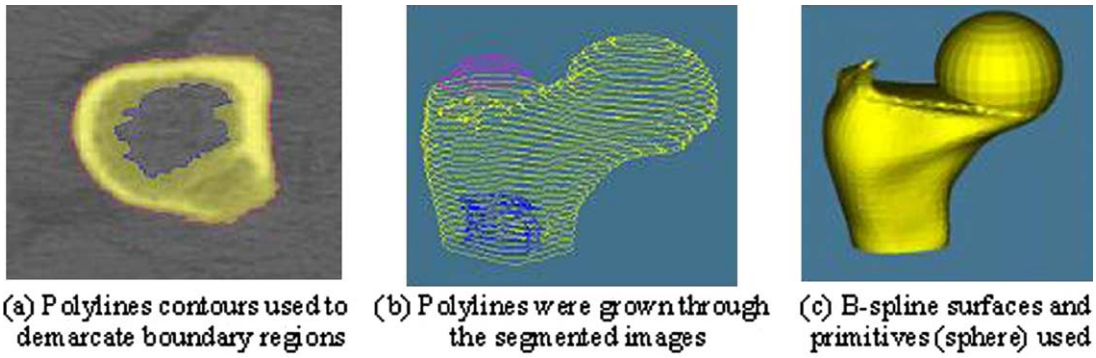


Fig. 6. CAD model construction using MedCAD interface.

2.3.2. Process path 2: reverse engineering interface

The reverse engineering interface approach uses a 3D voxel model created from the segmentation. The 3D voxel model is converted to point data form and the points are loaded into a reverse engineering software (for example, Geomagic Studios by Raindrop Inc. [31]). The points are then triangulated to form a faceted model. The faceted model is further refined and enhanced to reduce the file sizes and unwanted features. The freeform surfaces of NURBS patches are used to fit across the outer shape of the model. Although the process did have a comparatively longer processing time, the results obtained are significantly better than the other two methods. The CAD model is much more aesthetic, stable in configuration, and less error in data transfer formats, particularly for an integrated CAD and FEA application.

2.3.3. Process path 3: STL-triangulated model converting approach

The 3D voxel model can also be converted to the STL file and this STL file can then be imported into reverse engineering software for surface refinement and NURBS surface generation. The difference between this approach and the reverse engineering approach is that this approach uses the STL-triangulated surface as modeling input rather than the point clouds data. Although the process time is more efficient, this approach, however, inherits all limitations of STL format.

2.4. Application example: an imaged based CAD model for femur

This study used the CT images of a proximal femur bone from a small child. In all, 34 slice images were obtained with each of 2 mm sliced segmentation for a height of 68 mm. Once loaded into the MIMICS software, all images were properly registered and aligned for its orientations (Fig. 5a). Next, the region of interest (ROI) was identified and a 3D voxel model of the femur was made. In doing so, an appropriate threshold range was found that could best capture the relevant information contained in the femur. Using this threshold value, all pixels within this range were collected to a color mask within the given segmentation level (Fig. 5b). A region growing technique (available in the software) was applied to form a 3D femur anatomic representation (Fig. 5c).

All three different process paths described above were used to test the CAD model generation. Results are shown in Fig. 6 (MedCAD interface approach), Fig. 7 (reverse engineering approach) and Fig. 8 (STL converting approach), respectively. In the MedCAD example, we have used both primitives and freeform shapes (B-spline) to model the femur anatomy. The process is shown in Fig. 6. Since there was a lack of appropriate primitive features, a sphere primitive feature was used to represent the top of the femur.

Fig. 7a–f shows the process of using reverse engineering approach to construct a 3D femur model. The imported points from the 3D voxel model (Fig. 5c) first need to be cleaned in order to eliminate the noise points. A decimation of points sometimes is also necessary depending on the number of the initial points (Fig. 7a and b). The points are then triangulated to form a faceted model (Fig. 7c). Further surface refining and enhancement (Fig. 7d) is often required for reducing the file sizes and unwanted features. Fig. 7e and f shows NURBS patches used to fit across the outer shape of the model.

Due to the limitation of STL in representing geometry with small, detail and complex features, the CAD model of the femur bone was not well reconstructed as shown in Fig. 8. To overcome this, we need to refine the surface by adding more triangles in STL before the modeling process, or to edit the surface in a CAD environment after the initial model being constructed. In either way, this can lead to a very time consuming process. For models that do not involve complicated features, the STL interface approach can be used to efficiently generate CAD models.

A comparison of three approaches for construction of femur CAD model is given in the following table.

As can be seen from Table 1, the MedCAD process is good if there is primitive applicable. The reverse engineering approach is a preferred modeling approach because of the accuracy, structure fidelity, and the versatility in data transfer to STEP or IGES. The STL process is suitable when medical rapid prototypes need to be made as long as the STL

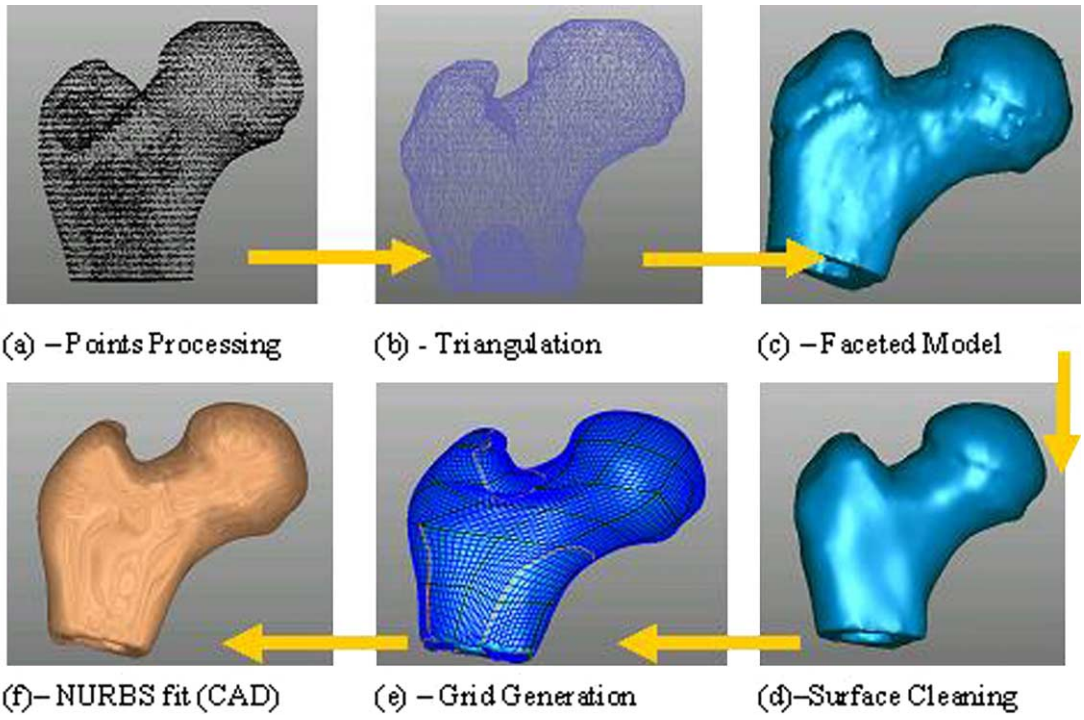


Fig. 7. CAD model construction using reverse engineering approach.

format remains to be the industry standard for medical rapid prototyping.

3. Bio-CAD modeling in CATE: application to biomimetic and tissue scaffold design

Tissue engineering, the science and engineering of creating functional tissues and organs for transplantation, integrates a variety of scientific and engineering disciplines to produce physiologic 'replacement parts' for the development of viable substitutes which restore, maintain or improve the function of human tissues [32,33]. In the success of tissue engineering, three-dimensional (3D) scaffolds play important roles as extra-cellular matrices onto which cells can attach, grow, and form new tissues. Modeling, design and fabrication of tissue scaffolds to meet multiple biological and biophysical requirements is always a challenge in regenerative tissue engineering. This is particularly true when design load bearing scaffolds for bone and cartilage tissue application. In general, this type of scaffolds usually have intricate architecture, porosity, pore size and shape, and interconnectivity in order to provide the needed structural integrity, strength, transport, and ideal micro-environment for cell and tissue ingrowth [34–36]. In addition, thus designed scaffolds often can only be fabricated through advanced manufacturing techniques, such as solid freeform fabrication (SFF) to manufacture complex structural architectures [8,37].

Computer-aided tissue engineering (CATE) advances modeling, design and fabrication of tissue scaffolds [1]. For example, CATE can apply biomimetic design approach to

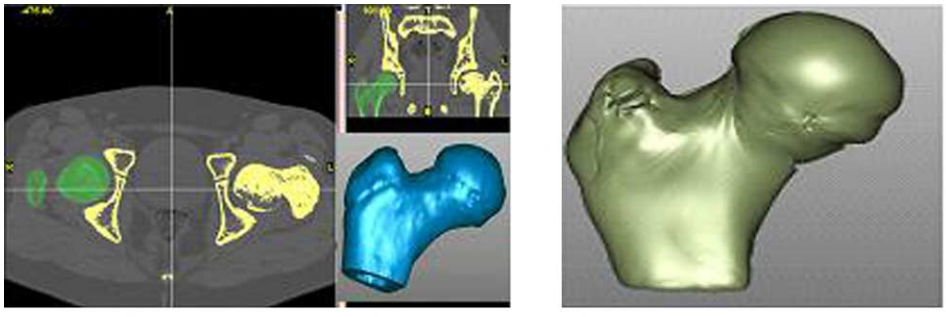


Fig. 8. Conversion from voxel model to CAD model via STL interface.

introduce multiple biological and biophysical requirements into the scaffold design [5]. CATE can also integrate both biomimetic and non-biomimetic features into the scaffold modeling database to form high fidelity and smart scaffolds. Biomimetic features can be based upon real anatomical data regenerated from CT/MRI images, or can be created purely within a CAD environment, such as channels and porous structures. Non-biomimetic features do not imitate nature but can be designed as drug storage chambers, mechanical elements, and attachment interfaces for tubes, sensors, electronics, and other devices. This section will describe using Bio-CAD in CATE for representation of heterogeneous biological tissue structure, for introduction of various design intents of internal and external architecture, porosity, interconnectivity, mechanical properties, vascularization, and drug/growth factor delivery into the scaffold design.

3.1. Biomimetic design for load bearing tissue scaffolds

Load bearing tissue scaffolds need to have certain characteristics of their own in order to function as a true tissue substitute that satisfy the biological, mechanical and geometrical constraints [13]. Such characteristics include: (1) Biological requirement—the designed scaffold must facilitate cell attachment and distribution, growth of regenerative tissue and facilitate the transport of nutrients and signals. This requirement can be achieved by controlling the porosity of the structure, by providing appropriate interconnectivity inside the structure, and by selecting appropriate biocompatible materials; (2) Mechanical requirement—the designed scaffold must provide structural support at the site of replacement while the tissue regenerates to occupy the space defined by the scaffold structure. Scaffold structures need to be defined that have the required mechanical stiffness and strength of the replaced structure; and (3) Anatomical requirement—it must be of an appropriate geometric size that fits in at the site of replacement. Using Bio-CAD modeling, medical image processing and solid freeform fabrication, it is now possible to have all above design requirements be considered in the tissue scaffolds, for example, scaffolds with designed internal architecture, porosity, pore interconnectivity with selected biomaterials and specified geometry.

The CATE based design approach begins with the acquisition of non-invasive images and image processing of appropriate tissue region of interest. This is followed by a three-dimensional reconstruction of anatomical structure using commercially available medical reconstructive and reverse engineering software (MIMICS [19] and Geomagic [31]). The above processes have been described in Section 2. The next step is to characterize tissue structural heterogeneity through a homogenization technique, to define CAD (Pro/Engineer [38]) based tissue anatomic primitive features, and to generate CAD based scaffolding building blocks-representative unit cells. Based on the designed CAD geometrical configuration and the intended scaffolding materials, finite element method (ABAQUS [39]) is applied to determine the corresponding mechanical properties. Those properties are further compared to the replaced tissue mechanical properties characterized through quantitative computed tomography (QCT) method. The unit cells with matching properties are selected as candidates unit cells to make up the tissue scaffold. The candidate unit cells will be further evaluated according to their internal architectures and the intended biological purpose. Using CAD solid modeling based Boolean operations, a set of such selected unit cells would be integrated with the shape of the bone to form the bone tissue scaffold with specified internal architecture and structural properties to match that of the actual replaced bone based on the characterization analysis. Once the complete CAD database of the bone tissue scaffold structure is in place, a process planning and toolpath will be generated based on solid freeform fabrications techniques that would be able to manufacture the designed tissue structures. An overall procedure of the CATE based biomimetic modeling and design for bone tissue scaffold is illustrated in Fig. 9 and further described in the following steps.

3.1.1. CAD in representation of tissue primitives and scaffold unit cells

Biological tissues are inherently heterogeneous structures. At the macrostructure level, tissue exhibits both morphological and mechanical heterogeneity and varies greatly at different anatomical and structural levels. For example, Fig. 10 [12] shows three different types of trabecular architectures as found at different anatomical sites in the human skeleton. In using feature primitive based CAD modeling approach, these architectures can be analogized by three different types of feature primitives: plate-like primitive (for femur), rod-like primitive (for spine), and hybrid primitive (for iliac crest). These primitives can be represented by CAD solid models. These analogies are shown in Fig. 11.

Using feature primitive approach, each primitive discrete volume can be represented by a specific design feature, such as different internal architecture patterns used in common tissue scaffold design, for example, the standard weave, braided, and knit geometric feature of textile fiber patterns can be used as scaffold architectures or muscular pattern in soft tissues. Enabling computer-aided technology can then be applied to develop a CAD-based model based on information provided from the feature primitives, such as desirable feature patterns and architectures, desirable pores, pore sizes and shapes, and its distribution in the scaffold internal structure so that the required biophysical and biological design constraints can be met. A library of thus generated CAD-based unit cells derived from different feature primitive patterns is presented in Fig. 12. In this library, the individual unit cell is designed with different characteristics based on using different scaffolding material,

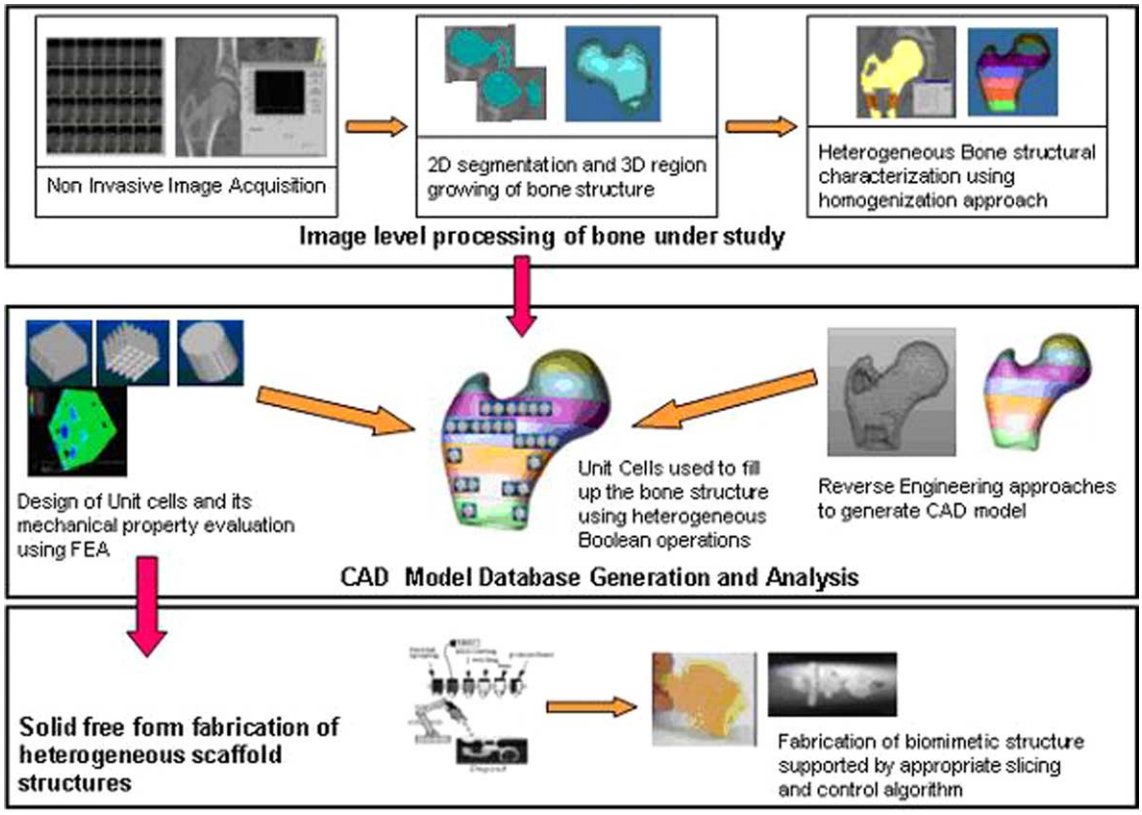


Fig. 9. Overall procedures of modeling and design of biomimetic bone scaffold.

feature primitive pattern, and the spatial distribution of scaffolding material to form unit cell internal architecture for porosity and pore interconnectivity considerations. With an appropriate selection of unit cells, one can design a customized heterogeneous tissue scaffold by tailoring unit cell properties, for example, using different feature patterns to design a specific porosity geometry (for pore size and shape), arranging feature patterns in a specific 3D

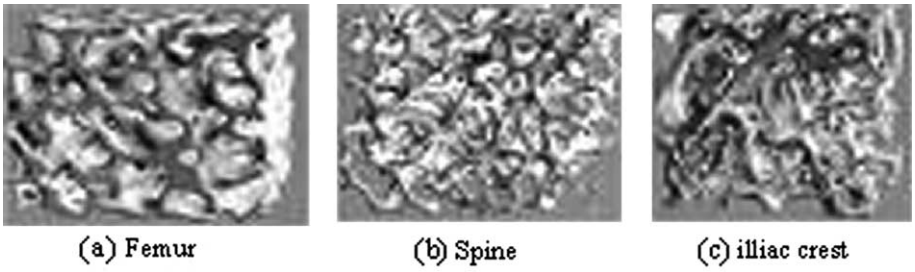


Fig. 10. Variations of trabecular bone architecture.

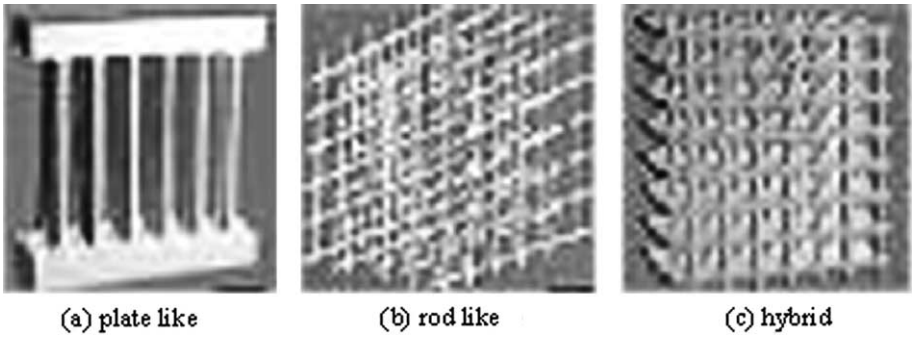


Fig. 11. Analogized feature primitives.

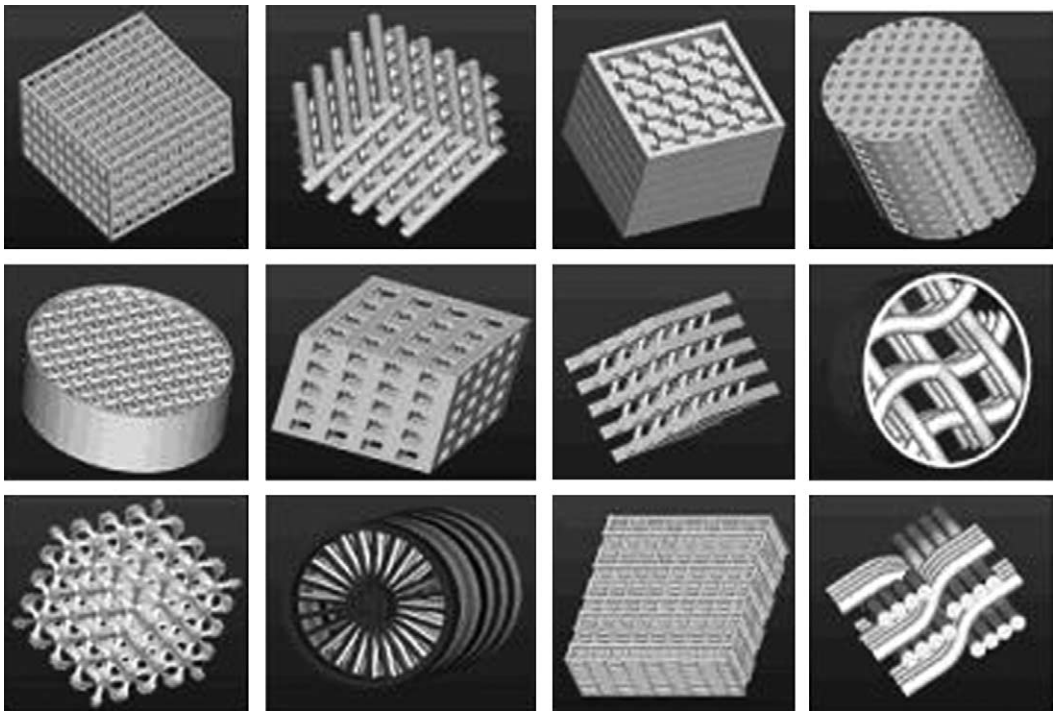


Fig. 12. A library of designed scaffold unit cells based on different feature primitives.

architecture to form a preferable pore distribution and interconnectivity (for cell growing and proliferation), and analyzing or simulating to verify if the designed model meets the scaffold strength and stability requirements.

3.1.2. Characterization of femur property

The CT segmentation of femur was achieved using two different approaches, each approach serving a particular purpose. In the first approach, the whole proximal femur structure was grown into one single color mask representing one single threshold range. With this approach, the average threshold value for the whole structure could be obtained. This average threshold value was in turn correlated to the quantitative computed tomography number (QCT#) represented in hounsfield units (HU) by using a simple relation as follows:

$$\text{QCT\#} = \text{Threshold Value} - 1024 \tag{1}$$

In the second approach described as the homogenization technique, the femur structure was divided into layers and then an average QCT# for each layer found. A collection of slices of the femur was grouped as layers and segmented using different color masks. Each layer thickness was about 10 mm and around seven layers in all. An average QCT number was obtained for each layer in order to characterize the tissue heterogeneity (Fig. 13). The QCT number retrieved from the appropriate layers is then correlated to the density of the bone by a linear interpolation using relations available in published literature. This density can in turn be then related to E, allowing the heterogeneous elasticity of the bone to be defined through the relations obtained as in [40,41].

$$\text{For QCT} < 816 : \rho = 1.9 \times 10^{-3}\text{QCT} + 0.105 \text{ and}$$
$$E = 0.06 + 0.9\rho^2 \tag{2}$$

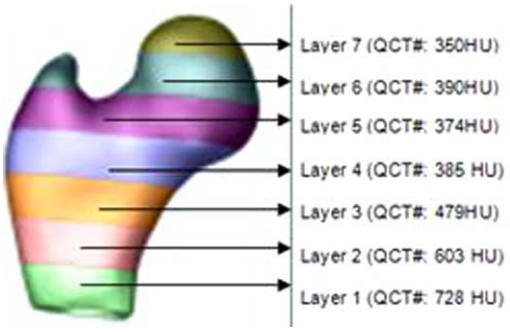


Table 2 Bone Spatial Heterogeneity -7 layer model

Layer #	QCT#	Density (g/cu cm)	E (MPa)
Layer 1	728	1.4882	2053
Layer 2	603	1.2507	1467
Layer 3	479	1.0151	987
Layer 4	385	0.8365	690
Layer 5	374	0.8156	658
Layer 6	390	0.846	704
Layer 7	359	0.7871	617
Average	474	1.0056	970

Fig. 13. Average QCT values measured from CT.

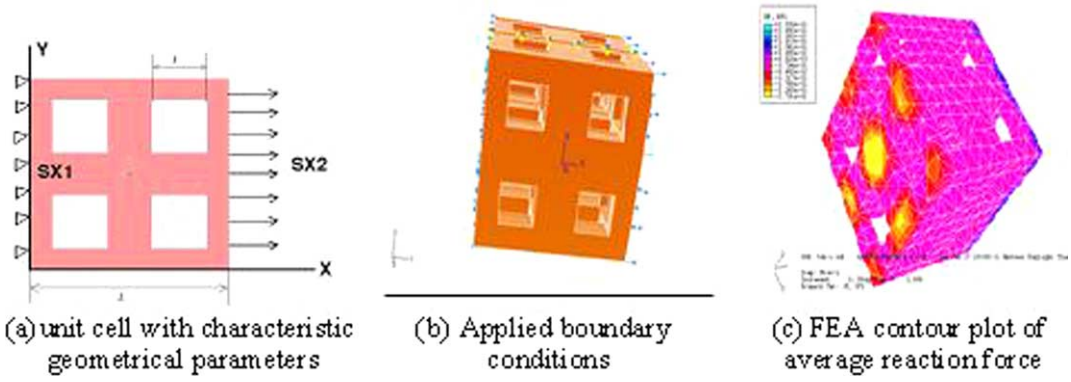


Fig. 14. FEA results of a basic unit cell.

$$\text{For QCT} > 816 : \rho = 7.69 \times 10^{-4} + 1.028 \text{ and } E = 0.09\rho^{7.4} \tag{3}$$

The structural heterogeneity of the bone can thus be defined through the associated bone Young's modulus. The characterization results are as shown in Table 2. The last row in the table indicates the QCT# retrieved when a single color mask was considered. The calculated E is in accordance with published data for cancellous bone- 0.5–1.5 GPa. It is important to note that both cancellous and cortical bone have been considered smeared together as one structure in each layer and hence the slightly higher values obtained by this technique.

Appropriate unit cells would be then integrated with the shape of the bone to form the bone tissue scaffold with specified internal architecture and structural properties to match that of the actual bone based on the characterization analysis.

3.1.3. Selection of designed scaffold unit cell

Finite element analysis (FEA) software (ABAQUS) was used to analyze the designed unit cells to predict their effective mechanical properties. Results of a sample unit cell are presented in Fig. 14 for the unit cell with characteristic geometrical parameters (Fig. 14a), applied boundary condition (Fig. 14b), and the contour plot of the reaction force (Fig. 14c). The unit geometry is $4.5 \times 4.5 \times 4.5$ mm with 4 pore holes on each face. The scaffold cellular unit cell model was generated in Pro/Engineer, and converted to IGES format and then imported to ABAQUS for finite element analysis. A total 8353 4-node tetrahedral elements were used in the analysis. The average reaction force (R_X) was calculated for every node on the constrained surface (Fig. 14c), and used to calculate the effective modulus E_{XX} based on Eq. (4). Results of the designed varying sizes of the unit cell to model various porosities vs. different biomaterials of Hydroxyapatite, L-PGA and L-PLA are presented in Table 2 and plotted in Fig. 15.

$$E_{XX} = \frac{\sigma_X}{\varepsilon_X} = \left(\frac{R_X}{A_{SX2}}\right) / \left(\frac{U_X}{L_X}\right) = \frac{R_X}{0.001 A_X} \tag{4}$$

The relationship of the porosity with the overall geometry of the unit cell for the homogeneous square unit cell with square pore can be found as:

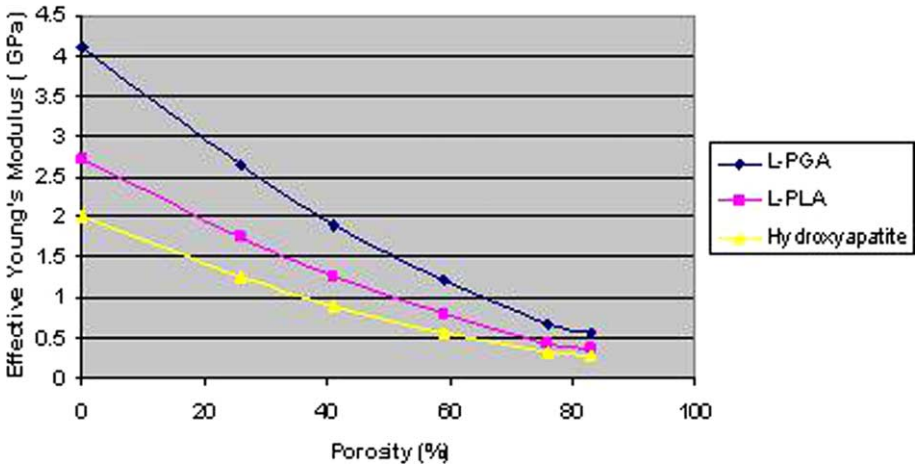


Fig. 15. Effect of unit cell material and porosity on the effective Young's modulus.

Table 3
Effect of unit cell material properties and porosity on the effective Young's modulus

Materials	Young's modulus, E (GPa)	Effective modulus of unit cell at different porosity levels (GPa)				
		26%	41%	59%	76%	83%
Hydroxyapatite	2.0	1.362	0.9	0.6734	0.328	0.2764
L-PLA	2.7	1.7466	1.2564	0.909	0.44	0.375
L-PGA	4.1	2.652	1.7466	1.38	0.673	0.567

$$P = \frac{N[\{Ll^2(f/2)\} - \{(f/2 - 1)l^3N/2\}]}{L^3} \quad (5)$$

where N is the number of the pores in the unit cell; f is the total number of faces that contain pores, L is the size of square unit cell and l is the size of pore (Fig. 14a).

Results of the FEA predictions are summarized in Table 3. From the QCT characterization of the proximal femur, the bone Young's modulus varies from 0.6–2.0 GPA. From a biological point of view, we know that a desirable scaffold structure should have a porosity ranging from 55–70%. In this regard, the unit cell made of hydroxyapatite material with 59% porosity and effective Young's modulus of 0.6734 GPa barely meet both biological and mechanical requirements. L-PLA-based unit cells with around 40–60% porosity do give a better option as a scaffold material for the proximal femur. Candidate unit cells can then be selected from the predicted curves shown in Fig. 6. Once the appropriate unit cell has been identified with the matched porosity, interconnectivity, and mechanical properties, a contour bone structure reconstructed from CT/MRI images will be filled in with the selected unit cell architecture. A constructive heterogeneous solid geometry algebra [42, 43] can be performed combining the unit cell architecture and the replaced bone anatomical structure to achieve the final shape of the replaced bone tissue scaffold.

3.1.4. Define external and internal geometry to meet anatomic compatibility

By reverse engineering CT data with medical imaging reconstruction software and enabling CAD, one can design a tissue implant with controlled external and internal architecture. In the following hypothetical case, we present how a seeded implant would be designed and used for repairing a skull defect after a tumor had been removed.

To create the external structure of the implant we took the CT data, and used the 3D-reconstruction tools in MIMICS to isolate the tumor (Fig. 16a). The STL file for the skull and the STL file for the tumor were then exported from MIMICS and imported into Geomagics. Within Geomagics we used a mirroring operation to mirror the tumor from the right side of the skull to the left side, i.e. the healthy side (Fig. 16b). We then used the Boolean intersection between the tumor and skull to generate a bone implant structure. We then mirrored the implant back across the plane (Fig. 16c and d) to complete the final external architecture of the implant (Fig. 16e). Through this procedure, we essentially replaced the void created by the removal of the tumor, with a mirrored copy of the normal bone structure. Using this method, we were able to create a complex structure that matched the symmetry of the patient's skull.

Upon identifying a candidate sacffold unit cell, we used a Boolean intersection between the scaffold unit cell and tissue anatomic structure within Geomagic to create the final anatomic compatible scaffold (as shown in Fig. 17). The finished scaffold design was then exported to an STL file and a three-dimensional printed prototype is shown in Fig. 18.

3.2. CAD in modeling and representing customized tissue scaffold primitives

To biomimic the natural morphologies of bone through the use of CT and μCT imagery, 3D reconstruction, and modeling techniques, one can further design customized feature primitives for specific tissue structures, morphologies, and functional requirements. For example, a vascular tree system and non-biological drug delivery primitive can all be designed and incorporated into the scaffold system. A set of feature primitives that are represented by the CAD and parametric based model

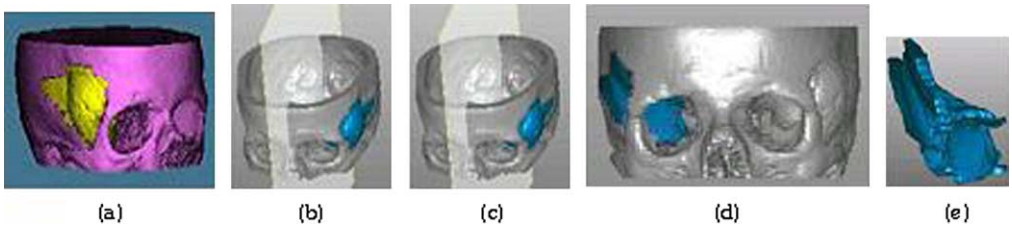


Fig. 16. Steps in creating the external architecture of a tissue implant by using mirroring.

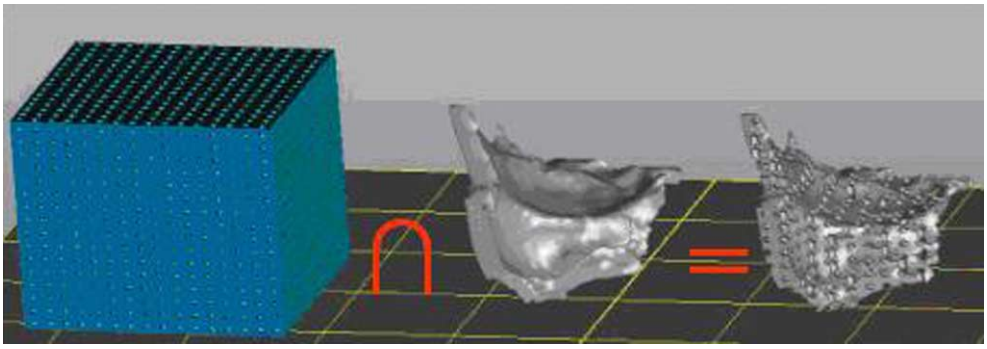


Fig. 17. Example of using Boolean operation to achieve bone scaffold anatomical geometry.

structures can be generated according to different tissue internal architectures, designed topologies, pore size, shape, porosity volume faction, and vascular/drug delivery network. The process of image-based 3D reconstruction from CT and MRI, reverse engineering to develop NURBS based bio-CAD model, and reasoning Boolean algebra for heterogeneous primitive operations defined in the CATE paradigm has laid a critically important foundation for integrating both biological tissue and non-biological artificial elements, such as syringes, drugs, tubes, sensors, electronics, and nano- or micro-scale bio-devices (represented by the feature primitives) for next generation 'smart' and 'functional' scaffolds. Hypothesized applications for using CAD to represent hybrid tissue structures, for vascular tree primitives, and for scaffolds with drug delivery primitives are shown in Figs. 19–21, respectively.

4. Bio-CAD in CATE: CAD-based bio-blueprint model for 3D cell and organ printing

3D cell and organ printing advances solid freeform fabrication to construct 3D object with living biological species, such as specific tissues or organisms. A fundamental requirement of this process is its capability to simultaneously deliver scaffolding materials, living cells, nutrients, therapeutic drugs, and growth factors and/or other important chemical components at the right time, right position, right amount, and within the right environment to form living cells/extracellular matrix (or scaffold) for in vitro or in vivo growth. Cell and organ printing, like any other SFF process, requires (1) a blueprint model, which is a software representation containing bio-information, physical and material information, anatomic and geometric information of to be printed tissue or organ; (2) a process model, which is also a software representation containing the print operation control commands, process planning and toolpath generated for the bio-blueprint model and machine hardware and control system; (3) a process machine, which is a hardware representation that possesses the functionality of the printing; and (4) tissue/organ culture system which can maintain and grow the printed living objects.

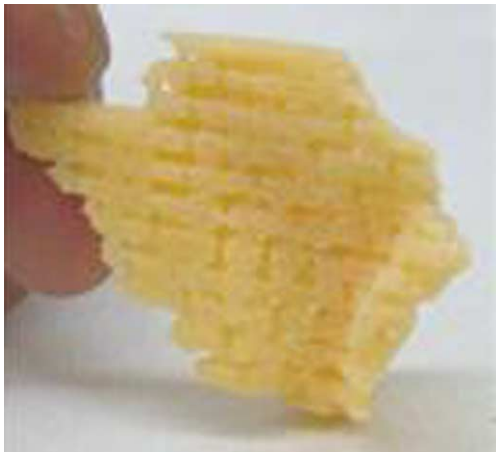


Fig. 18. Fabrication of scaffold.

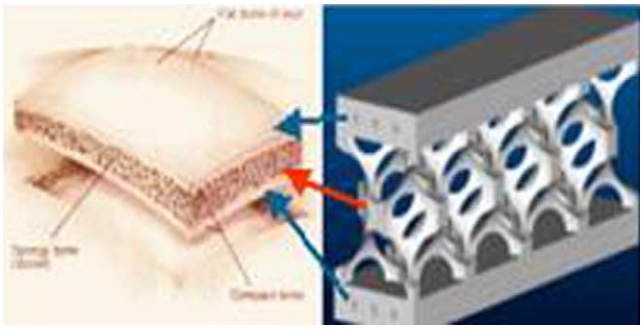


Fig. 19. Customized hybrid feature primitives for cranial tissue.

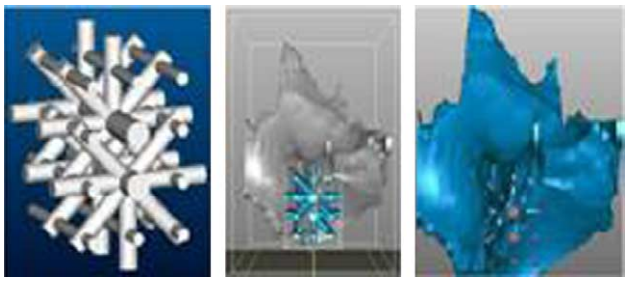


Fig. 20. Scaffold with vascular tree primitives.

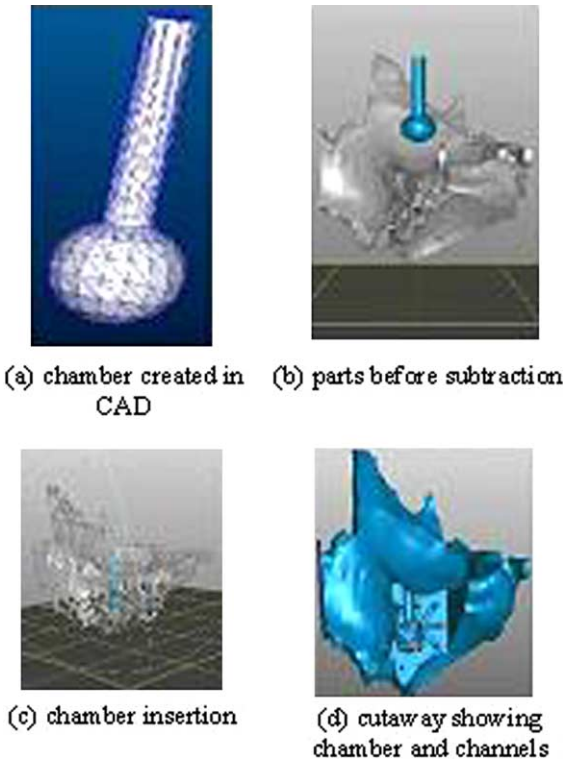


Fig. 21. Scaffold design with an integrated delivery system.

Cell and organ printing requires a description and representation of details of organ anatomy, morphology, tissue heterogeneity and vascular systems at different tissue/organ organizational scales. For example, cell deposition in 3D cell and organ printing is controlled through a process planning program. In the printing process, the toolpath guides the printing head(s) to deposit cells as needed to form a 3D tissue or organ construct. In order to print a specific organ, the toolpath program needs to know detailed data of the geometry of the to-be-printed organ, the organ internal architectures, boundary of the heterogeneous tissues within the organ, and the organ vasculature and its topology. In addition, the toolpath program should also contain the information on cell compositions so it can guide the printing heads to deposit the right cells at the right time and at the right location. The above information often leads to an extremely complicated database, and in most cases, it can only be processed (i.e. information store and retrieve) by a computer-aided design (CAD) model due to the specific requirements on the geometry and topology. We define such a CAD model as a bio-blueprint model for 3D cell and organ printing. Specifically, the functions of the bio-blueprint model will:

(1) describe anatomy, geometry, and internal architecture of a organ (or tissue) of interest, including the tissue heterogeneity, the individual tissue geometry and the boundary distinction within the organ of interest;
(2) define a vascular network and the 3D topology in a organ of interest;
(3) provide a needed database on organ/tissue geometry, heterogeneity, and the associate vascular network that can be used for toolpath generation of 3D cell and organ printing.

The framework of development of bio-blueprint model is outlined through the following major steps:

Step 1: development of a computer modeling representation of a 3D organ.
Step 2: development of a 3D vascularization network.
Step 3: development of a CAD based organ bio-blueprint model.

The bio-blueprint model will be generated based on medical imaging data (obtained from the public domain and/or patient-specific CT/MRI) in order to replicate organ/tissue anatomy, including detailed internal and external morphology, geometry, vascularization, and tissue identification. A CAD-based model relies upon 'boundary representation' by which an organ or tissue anatomy can be explicitly described by the enclosed boundaries, and by the topology between the enclosed boundaries. The CAD-based blueprint model will be constructed at all three organization scales (Fig. 22): (1) the scale of the organ as a whole

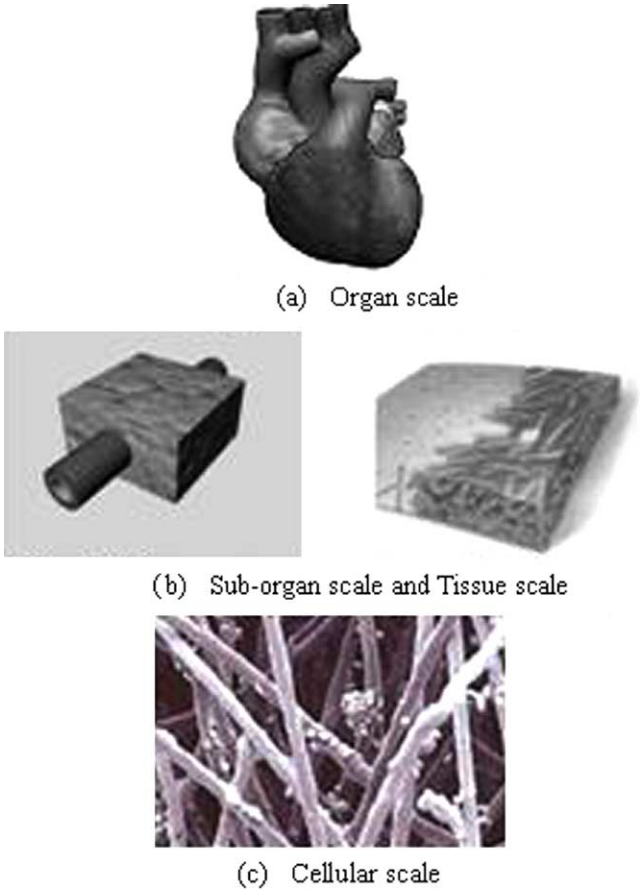


Fig. 22. Hierarchical scales of organ structure.

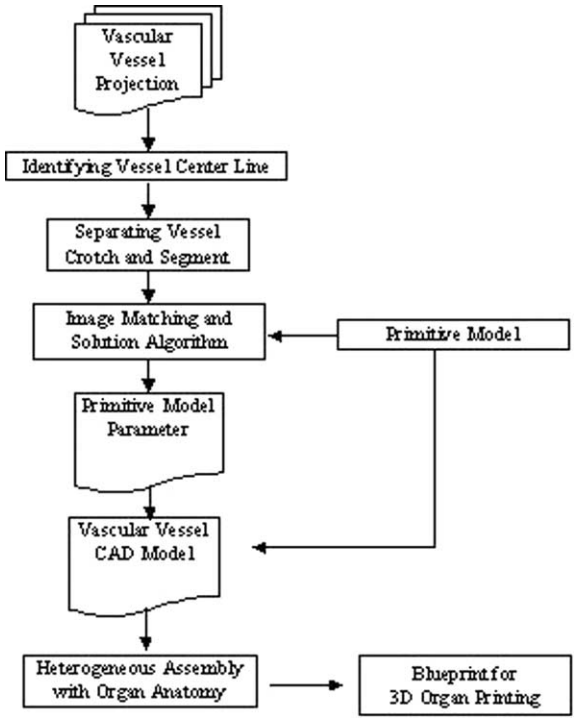


Fig. 23. Process of vascular network modeling.

(the organ's input and output vasculature and ducting, the connections to the nervous system, and anatomical compatibility with the prospective host); (2) the scale of the tissue, or sub-organ (the intended volumetric domain must be seeded with the appropriate type of cells in the correct areas, and consideration must be given to how the cell types will interact with each other); and (3) the scale at the cellular level (the selection of the scaffold material itself and the division of the blueprint model into small blocks enables local selection of scaffold material). A feature primitive based reconstruction method for vascular network is used to generate a 3D biological vascular system for organ growth. In this primitive feature modeling approach, the basic vascular primitives (e.g. crotch or segment) by a set of characteristic parameters are determined from patient specific CT/MRI images, and further use of Boolean operation algebra forms a high level vessel assembly. The vascular feature primitives are represented as NURBS bases, and the parameters in the NURBS equations can be determined through measuring the spatial positions of the vascular CT/MRI images at different projections. Procedures of this reconstruction are schematically illustrated in Fig. 23.

The bio-blueprint model provides the needed biological data for organ anatomy, tissue heterogeneity, and vascular networking. It can be used to introduce and facilitate the design or manufacturing intent (for example, the biological intent of the cell types, combination of cell-growth factor, and tissue heterogeneity; the biophysics intent of the designed cell deposition, extracellular matrix (EM) and structural configuration and neovasculature; and the biochemical intent of the EM surface treatment and desirable cell-cell and cell-matrix interaction). It can also be used to generate process planning for entire organ printing, or to create small units of specialized tissue types and to lay down these bricks in a time-dependent and order-specific pattern throughout the macro-structure of the organ to be printed. For example, creating a biomimetic structure of quartz blocks, laying out the eventual shape of the organ, inserting appropriate vascular network, sculpting tissue scaffolds, and replacing quartz with tissue blocks, the process illustrated from a simplified 2D slice of the kidney in Fig. 24.

5. Conclusion

This paper summarizes a recent research on Bio-CAD modeling and its application to computer-aided tissue engineering (CATE). Overview of CATE and its three major categories, the process of Bio-CAD modeling approach, and the application of Bio-CAD in CATE in the field of biomimetic design, tissue scaffold design, and bio-blueprint modeling were presented. New developments in Bio-CAD modeling development, including 3D reconstruction, tissue primitive feature design, scaffolding unit cell, and computer-aided tissue scaffold manufacturing and bio-blueprint model for 3D cell and organ printing were introduced.

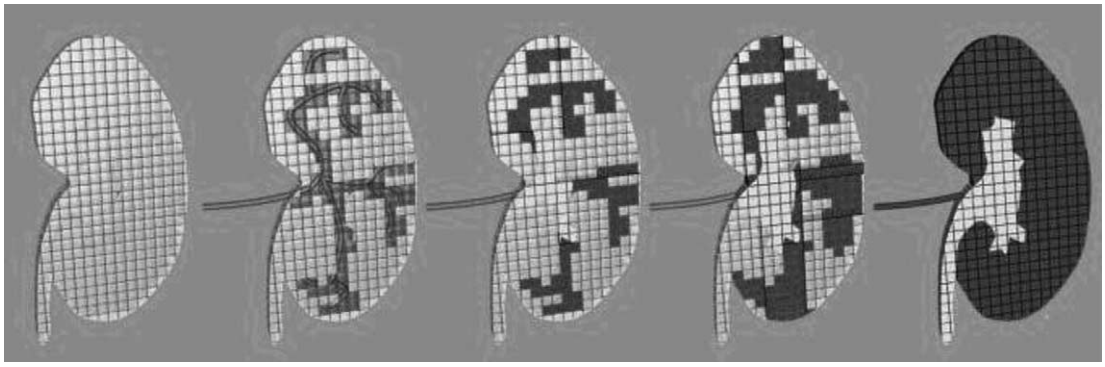


Fig. 24. Schematic process of heterogeneous tissue block assembly for kidney.

The authors have explored the bioengineering application of reverse engineering (RE) technology in converting CT/MRI based images to CAD models and have brought forward different process paths in which this can be achieved. Each process path selected depends on the particular application it is intended for. The MedCAD process path would be suitable in the generation of surface models or models that have less overall complexity. The Reverse engineering interface would be selected when a solid model needs to be made and which would be used for FEA/Dynamic analysis. An iterative process of refining the surface may need to take place since mesh generation can fail in certain cases depending on the complexity of the outer surface. The STL interface is preferred when a rapid prototype of the model is needed for surgical planning or display. These Bio-CAD models can also be used for dynamic simulation to help in a better understanding of the biophysical property of the model under study. The developed approach would benefit in a better design of prostheses and implants. By working on actual rather than computational models, patient specific implants and prostheses can be designed with improved quality and ease of comfort.

Application of Bio-CAD allows exploring many novel approaches in modeling, design, and fabrication of complex tissue scaffolds that have enhanced functionality and improved interactions with cells. Central to CATE is its ability to represent pertinent tissue biological, biomechanical, and biochemical information as computer, and in most cases, CAD-based, bio-tissue informatics model. This model can be used as communication tool between biologists and tissue engineers, and the database of the model serves as a center repository to interface design, simulation and manufacturing of tissue substitutes. In this regard, Bio-CAD provides an essential foundation and facilitates the advance of CATE and tissue engineering from its segmental disciplinary and empirical laboratory based study to integrated empirical, laboratory and computer modeling and simulation based multi-disciplinary research.

CAD and freeform fabrication are the two most important components, as design and manufacturing, in computer-aided tissue engineering. In conjunction CAD with solid freeform fabrication make it possible to design and manufacture very complex tissue scaffolds with functional components that are difficult, if not impossible, to create with conventional techniques. Although a Bio-CAD based CATE is still in its early development stage, it eventually will play a significant role in tissue engineering, especially for tissue scaffold design by providing precisely controlled architecture and multi--material printing for different types of biological factors, cells, and scaffold materials. In a near future, CATE can help to design scaffolds that are built to work as mini-bioreactors, for example, designed with a perfusion system that can be loaded to create mechanical stimuli. CATE can also help to design engineering tissue structures at different hierarchical levels: from microscopic to macroscopic, and ultimately, complex scaffolds could be designed to incorporate bioactive materials to interact with the cell and even have external ports or interfaces to give a physician access to the scaffold for drug administration or monitoring.

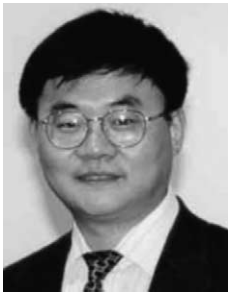
Acknowledgements

The authors would like to acknowledge the funding supports from NSF grants: NSF-9980298, NSF-0219176 and NSF-0427216 for Computer-Aided Tissue Engineering research.

References

[1] Sun W, Darling A, Starly B, Nam J. Computer-aided tissue engineering: overview, scope and challenges. J Biotechnol Appl Biochem 2004; 39(1):29–47.
[2] Hollister S, Levy R, Chu T, Hollaran J, Feinberg S. An image based approach for designing and manufacturing of craniofacial scaffolds. Int J Oral Maxillofacial Surg 2000;29:67–71.
[3] Lal P, Sun W. Computer modeling approach for microsphere-packed bone graft. J Comput-Aided Des 2004;36:487–97.
[4] Wang F, Shor L, Darling A, Khalil S, Sun W, Güçeri S, et al. Precision extruding deposition and characterization of cellular poly-ε-caprolactone tissue scaffolds. Rapid Prototyping J 2004;10(1):42–9.
[5] Sun W, Starly B, Darling A, Gomez C. Computer-aided tissue engineering: application to biomimetic modeling and design of tissue scaffolds. J Biotechnol Appl Biochem 2004;39(1):49–58.
[6] Matsumura T, Sato-Matsumura KC, Yokota T, Kobayashi H, Nagashima K, Ohkawara A. Three-dimensional reconstruction in dermatopathology-a personal computer-based system. J Cutan Pathol 1994;26:197–200.
[7] Taguchi M, Kohsuke C. Computer reconstruction of the three-dimensional structure of mouse cerebral ventricles. Brain Res Protoc 2003;12:10–15.
[8] Sun W, Lal P. Recent development on computer aided tissue engineering-a review. Comput Methods Programs Biomed 2002;67:85–103.
[9] Darling A, Sun W. 3D Microtomographic characterization of precision extruded poly-ε-caprolactone tissue scaffolds. J Biomed Mater Res Part B: Appl Biomater, V 2004;70B(2):311–7.
[10] Lin ASP, Barrows TH, Cartmell SH, Guldberg RE. Micro-architectural and mechanical characterization of oriented porous polymer scaffolds. Biomaterials 2003;24:481–9.
[11] Landers R, Hübner U, Schmelzeisen R, Mühlhaupt R. Rapid prototyping of scaffolds derived from thermoreversible hydrogels and tailored for applications in tissue engineering. Biomaterials 2002;23: 443–4.
[12] Folch A, Mezzour S, Düring M, Hurtado O, Toner M, Müller R. Stacks of microfabricated structures as scaffolds for cell culture and tissue engineering. Biomed Microdevices 2000;2:207–14.
[13] Rietbergen V, Müller R, Ulrich D, Rüegsegger P, Huiskes R. Tissue stresses and strain in trabeculae of canine proximal femur can be quantified from computer reconstructions. J Biomech 1999;32:165–74.
[14] Ulrich D, Hildebrand T, VanRietbergen B, Müller R, Rüegsegger P. The quality of trabecular bone evaluated with micro-computed tomography, FEA and mechanical testing. In: Lowet G et al, editor. Bone research in biomechanics. Amsterdam: IOS Press; 1997. p. 97–112.
[15] Müller R, Rüegsegger P. Micro-tomographic imaging for the non-destructive evaluation of trabecular bone architecture. In: Lowet G et al, editor. Bone research in biomechanics. Amsterdam: IOS Press; 1997. p. 61–80.
[16] Müller R, Matter S, Neuenschwander P, Suter UW, Rüegsegger P. 3D Micro tomographic imaging and quantitative morphometry for the non-

destructive evaluation of porous biomaterials. In: Briber R, Pfeiffer DG, Han CC, editors. Morphological control in multiphase polymer mixtures. Proceedings of the materials research society, 461, 1996. p. 217–22.
[17] Kriete A. 3D imaging of lung tissue by confocal microscopy and micro-CT. SPIE BIOS Conf Proc 2001;4257:469–76.
[18] Dhenain M. Three-dimensional digital mouse atlas using high resolution MRI. Dev Biol 2001;232:458–70.
[19] MIMICS User manual, materialise; 2004.
[20] Krause W, Handreke K, Schuhmann-Giampieri G, Rupp K. Efficacy of the iodine-free computed tomography liver contrast agent, Dy-EOB-DTPA, in comparison with a conventional iodinated agent in normal and in tumor-bearing rabbits. Invest Radiol 2002;37(5):241–7.
[21] Watanabe M, Shin'Oka T, Tohyama S, Hibino N, Konuma T, Matsumura G, et al. Tissue engineered vascular autograft: inferior vena cava replacement in a dog model. Tissue Eng 2001;7(4):429–39.
[22] Karch R, Neumann F, Neumann M, Schreiner W. Staged growth of optimized arterial model trees. Ann Biomed Eng 2000;28:1–17.
[23] Mankovich NJ, Robertson DR, Cheeseman AM. Three-dimensional image display in medicine. J Digit Imaging 1990;3(2):69–80.
[24] Viceconti M, Zannoni C, Pierotti L. Tri2solid: an application of reverse engineering methods to the creation of CAD models of bone segments. Comput Methods Programs Biomed 1998;56(3):211–20.
[25] Viceconti M, Casali M, Massari B, Cristofolini L, Bassini S, Toni A. The standardized femur program proposal for a reference geometry to be used for the creation of finite element models of the femur. J Biomech 1996;29(9):1241.
[26] Viceconti M, Zannoni C, Testi D, Capello A. CT data sets surface extraction for biomechanical modeling of long bones. Comput Methods Programs Biomed 1999;59:159–66.
[27] Lorenson WE, Cline HE. Marching cubes: a high resolution 3D surface construction algorithm. Comput Graphics 1987;21:163–9.
[28] McNamara BP, Cristofolini L, Toni A, Taylor D. Relationship between bone prosthesis bonding and load transfer in total hip reconstruction. J Biomech 1997;30(6):621–30.
[29] Montani C, Scateni R, Scopigno R. Discretizied marching cubes. In: Bergeron RD, Kaufman AE, editors. Proceedings Visualization 94 Congress, IEEE.
[30] Herman GT, Liu HK. Display of three-dimensional information in computed tomography. J Comput Assist Tomogr 1977;1:155–60.
[31] GeoMagic User Manual, Raindrop Geomagic, Research Triangle, NC, USA; 2004.
[32] Langer R, Vacanti JP. Tissue engineering. Science 1993;260:920–6.
[33] Seal BL, Otero TC, Panitch A. Polymeric biomaterials for tissue and organ regeneration. Mater Sci Eng R 2000;34:147–230.
[34] Zeltinger J, Sherwood JK, Graham DA, Mueller R, Griffith LG. Effect of pore size and void fraction on cellular adhesion, proliferation, and matrix deposition. Tissue Eng 2001;7:557–72.
[35] Zein I, Hutmacher DW, Tan KC, Teoh SH. Fused deposition modeling of novel scaffold architectures for tissue engineering applications. Biomaterials 2002;23:1169–85.
[36] Hutmacher DW, Schantz T, Zein I, Ng KW, Teoh SH, Tan KC. Mechanical properties and cell cultural response of polycaprolactone scaffolds designed and fabricated via fused deposition modeling. J Biomed Mater Res 2001;55:203–16.
[37] Yang S, Leong K, Du Z, Chua C. The design of scaffolds for use in tissue engineering. Part 2. Rapid prototyping techniques. Tissue Eng 2002;8(1):1–11.
[38] Pro/Engineer User Manual, PTC, Needham, MA; 2004.
[39] ABAQUS User Manual, ABAQUS, Inc.; 2004.
[40] Rice JC, Cowin SC, Bowman JA. On the dependence of elasticity and strength of cancellous bone on apparent density. J Biomech 1998;21:13–16.
[41] Rho JY, Hobatho MC, Ashman RB. Relations of mechanical properties to density and CT numbers in human bone. Med Eng Phys 1995;17:347–55.
[42] Sun W, Hu X. Reasoning Boolean operation based CAD modeling for heterogeneous objects. J Comput-Aided Des 2002;34:481–8.
[43] Sun W. Multi-volume CAD modeling for heterogeneous object design and fabrication. J Comput Sci Technol 2000;15(1):27–36.



Wei Sun is currently appointed as Associate Professor in the Department of Mechanical Engineering and Mechanics at Drexel University. His research and educational interests are in the interdisciplinary area of CAD/CAM, Computer-Aided Tissue Engineering, Modeling, Design and Simulation of Heterogeneous Structures, and Solid Freeform Fabrication.

Binil Starly is currently a PhD candidate in the Department of Mechanical Engineering and Mechanics at Drexel University, Philadelphia, Pennsylvania, USA. He received his BS degree in Mechanical Engineering from College of Engineering, Trivandrum, India. His current research interests are in the biomimetic design of tissue scaffolds from patient specific image data and the freeform fabrication process planning.

Jae Nam received his BS in Mechanical Engineering from MIT, Cambridge, MA and his MS in Biomedical Engineering from Drexel University, Philadelphia, PA. He is currently pursuing his PhD in mechanical engineering at Drexel University. His research interests include computer-aided tissue engineering, freeform fabrication of heterogeneous tissue constructs, cellular threads, cell viability and cellular tissue engineering study.

Andrew Darling received his BA in Biology in 1998 from the University of Rochester, Rochester, NY, and his MS in Biomedical Science in 2003 from Drexel University, Philadelphia, PA. He is currently a doctoral student in Mechanical Engineering at Drexel University. His research interests have included medical imaging and functional design of tissue engineering scaffolds for cell attachment, diffusion, and structural considerations.