

Transferring Unit Cell Based Tissue Scaffold Design to Solid Freeform Fabrication

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Abstract

Designing for the freeform fabrication of heterogeneous tissue scaffold is always a challenge in Computer Aided Tissue Engineering. The difficulties stem from two major sources: 1) limitations in current CAD systems to assemble unit cells as building blocks to form complex tissue scaffolds, and 2) the inability to generate tool paths for freeform fabrication of unit cell assemblies. To overcome these difficulties, we have developed an abstract model based on skeletal representation and associated computational methods to assemble unit cells into an optimized structure. Additionally we have developed a process planning technique based on internal architecture pattern of unit cells to generate tool paths for freeform fabrication of tissue scaffold. By modifying our optimization process, we are able to transfer an optimized design to our fabrication system via our process planning technique.

1. Introduction

Tissue engineering is a multi-disciplinary field seeking to develop methods and tools for the regeneration of functional three-dimensional tissue [1]. The discipline has developed in the face of society's need for and tissue replacements. In the US alone, there are over 25,000 transplants per year, while over 70,000 remain on the waiting list and over 6,000 people lose their lives waiting for a transplant [2]. One popular method in tissue engineering is to use three-dimensional tissue scaffolds that provide micro-environment for cell adhesion, proliferation, and new tissue regeneration. The scaffold itself also provides a macro-environment that can withstand exterior loading. Scaffold design parameters are usually dictated by the needs of the cell, the *in vivo* conditions at the implantation site, and the method of fabrication. The ability to design and fabricate tissue scaffolds to meet multiple biophysical and biological requirements is one of the greatest challenges in tissue engineering.

The design and fabrication of scaffolds which fulfills multiple parameters requires coupling design and fabrication processes. The design process must be based on micro-architecture, anatomically derived macro-architecture, mechanical properties, pore connectivity, and transport properties. Additionally, this process must be able to incorporate and control scaffold internal architecture in order to accommodate tissue inherent heterogeneity [3]. The micro-architecture of tissue scaffold and the inter-connectivity of pore influence cell behavior by providing spatial distribution and pathways of nutrients and removal of waste materials. Scaffold macro-architecture should be derived from patient-specific information to ensure the scaffold's overall anatomic compatibility. In general, coupling both micro-architecture and

macro-architecture in scaffold design is limited by current CAD technologies as well as by the ability of transferring the design model to standard formats for fabrication [4].

Attempts to fabricate scaffolds have led to the development of several types of processes and the use of different kinds of biomaterials. It should be noted that typical design criteria for scaffolds have centered on pore size, porosity, and elastic modulus [5]. Current scaffold technologies include chemical-based processes such as salt leaching, freeze drying, and Solid Freeform Fabrication (SFF) processes[6]. Chemical-based processes can produce structures with the desired pore sizes and porosities, but have a number of disadvantages, such as uncontrolled and irregular pore shapes, residual solvent harmful to seeded cells, and poor interconnectivity of pore within the scaffold [7]. SFF, on the other hand, provides a direct and reproducible process to fabricate tissue scaffold with controlled pore size, shape, and porosity [8]. Additionally, the SFF techniques enable the integration of using CAD for scaffold design with the scaffold fabrication.

This paper presents an integrated approach of combining a skeletal unit cell based scaffold design with internal unit cell architecture pattern for design and fabrication of tissue scaffolds. This approach permits the transfer of heterogeneous scaffold designs to SFF fabrication processes. Section 2 and Section 3 provide an overview of our unit cell characterization process and our optimization process for unit cell based scaffolds. Section 4 reviews our internal architectural design (IAD) and the incorporation of our optimization process.

2. Unit Cell Characterization

Current research in tissue engineering spans multiple disciplines and multiple scales, such as nano-sized fibers formed through electrospinning [9], cellular biology at the micron scale [10], and orthopedic research at an organ level [11]. This continuing research is discovering how mechanical, biological, and chemical factors influence tissue regeneration. Due to this increasing body of knowledge, we have developed a unit cell based design process that can be applied to design and fabrication of tissue scaffolds and replacements.

2.1 Unit Cells as Multi-Scale Building Blocks

Part of our work has been to develop scaffolds for bone applications [6, 12]. Figure 1 illustrates the scale from which we have gathered information. At the microscale on the left, we have the micro-architecture, which provides the morphological, structural, and mechanical properties [13]. On the far right of the scale there exists the macroscale, at which loading conditions and anatomical geometry can be gathered. By designing unit cells on a mesoscale, which exists between the micro and macro scales, the design considerations generated at the micro and macro scale can be incorporated into our unit cell structures.

Additional, using a unit cell based approach allows generating a biomimetic design based on the heterogeneous interior architecture of a tissue. From the interior structure of the bone, also given in Figure 1, there is a notable change in bone density throughout the tissue. Our process assigns different regions within a tissue with unit cells that mimic the tissue properties of

that region while maintain the connectivity for fluid and material transport between the unite cells within the assembled scaffold.

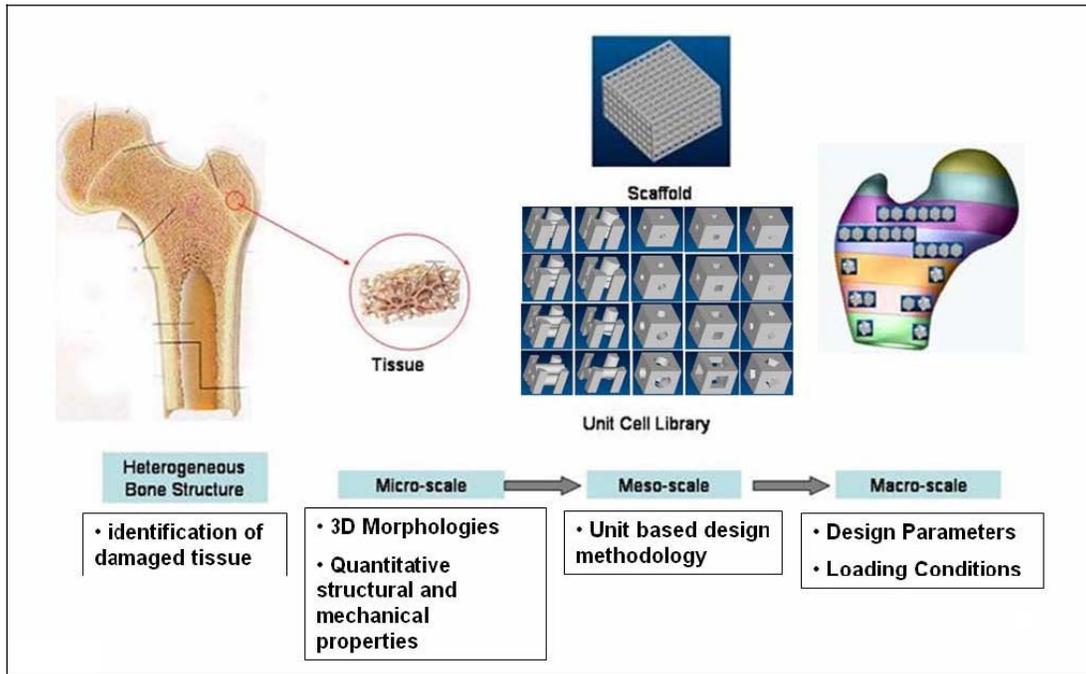


Figure 1: Multi-scale modeling approach for design tissue scaffold replacement: Microscale (left), Mesoscale (middle) and Macroscale (right)

2.2 Unit Cell Characterization

Our unit cell based process requires matching biomimetic designed unit cells to existing tissues. Hence, we have developed a process to characterize a unit cell's properties and structure [14]. Our process consists of analyzing the unit cell's geometric, phase, mechanical, transport, and connective properties as shown in Figure 2..

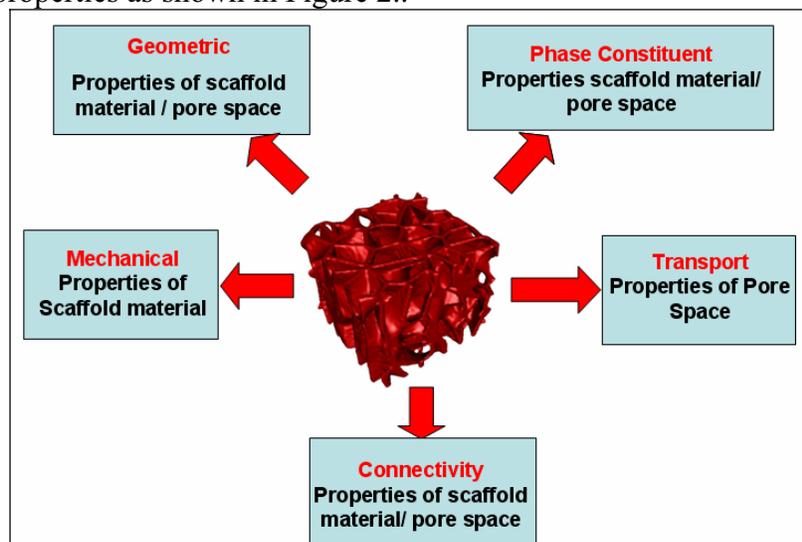


Figure 2: Characterization of unit cells in terms of geometric, phase, mechanical, transport, and connective properties.

2.2.1 Geometric Characterization

Geometric characterization captures the architectural information about each phase present. Presently, we are studying two-phase structures, which contain a scaffold material phase and a fluid phase that fills the pores [14]. During this step, the amount of each phase present, or volume fraction, is collected. The volume fraction of the scaffold material is equivalent to the porosity used in scaffold design. This step also collects pore size, pore area, and pore angle information. This process is completed after generating the unit cell geometry in a CAD software package.

Similarly this geometric characterization captures the unit cell's topological information. The purpose of capturing the topological information is to create connectivity between unit cells to ensure pathways of fluid and material transport through out a scaffold. To do this we convert that CAD representation of the unit cell into a skeletal representation, which is a process that has been utilized by digital imaging applications for the past few decades [15]. The skeletonization process begins with selecting a type of distance transform, such as a circle for a 2D image or a sphere for a 3D object. The distance transform is expanded until it touches two or more boundaries. This process is repeated throughout the object. The skeletal representation consists of the centers of the distance transforms along with their radii. Examples of skeletal representations are given in Figure 3.

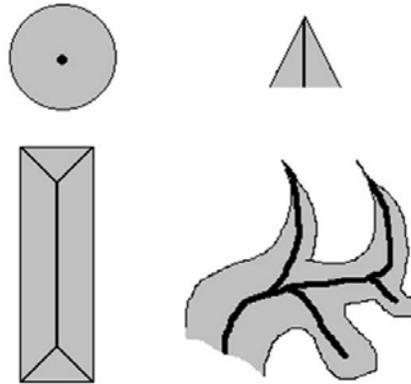


Figure 3: Example skeleton representations of 2D shape.

Skeletal representation enables us to translate and rotate multiple unit cell structures and establish connectivity between unit cells. Using the skeleton representation, one can utilize the Earth Mover's Distance Approach - a many-to-many matching algorithm, to establish connectivity between unit cells [16]. The process for generating the skeletal representation is given in Figure 4. A CAD model or in the case of Figure 4, the negative model or fluid phase model, is generated using existing CAD software. The model is saved as an STL model. This model undergoes voxelization and then skeletonization. Each representation of a unit cell is stored during the characterization process. Section 2.3 gives an overview of our data storage procedure.

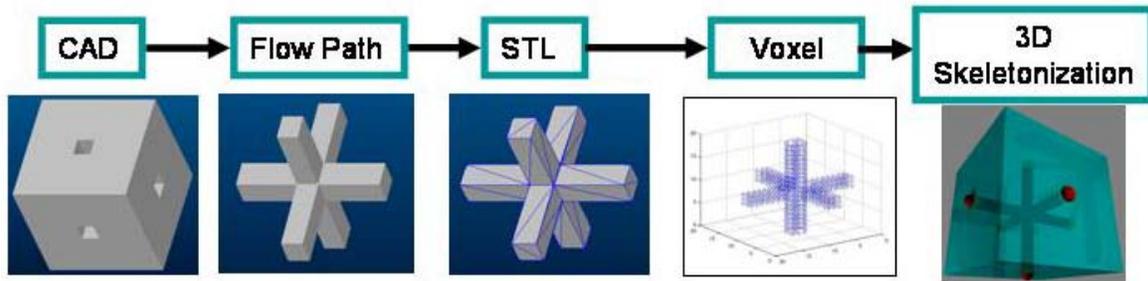


Figure 4: Process to convert a CAD representation to a skeletal representation

2.2.2 Phase Characterization

Phase characterization records the material properties for both phases, which will be used in other steps of this characterization. In the case of the scaffold material, phase characterization records the bulk material properties. Similarly, phase characterization also records the properties of the fluid phase. This information will also pertain to the mechanical and transport characterization steps.

2.2.3 Mechanical Characterization

There are four methods to determine the mechanical properties of a unit-cell: rule-of-mixtures, mechanical testing, finite element analysis (FEA), and a homogenization process [12]. Rule-of-Mixtures averages the properties of the materials found in the sample based on the volume fractions of each phase [17]. Mechanical testing applies a compressive force to a sample that has been fitted with strain gages that measures deformation under stress. The experimental strain data is used to calculate the mechanical properties of the material. This method time consuming due to the need for physical samples [12]. The FEA method creates a mesh of the unit cell. One surface of the unit cell is held stationary while a force is applied to the opposite surface. After the unit-cell undergoes deformation, the amount of strain is reported. Using the known stress via the applied force, the surface area on which it was applied, and the reported strain values, the mechanical properties of the unit-cell can be calculated using Hooke's Law [18].

Finally, a unit-cell can be analyzed using a homogenization process to determine its effective mechanical properties [12]. The unit cell is treated as an anisotropic material, and therefore the Young's modulus, the shear modulus and the Poisson's ratio will be independent of each other. During the preprocessing phase, a mesh of the unit cell is created. The process then goes on to solve six characterized cases for the homogenization equation with inputs from the stiffness matrix, the boundary conditions, and the force vector [12].

2.2.4 Transport Characterization

Similar to mechanical properties, fluid and mass transport rely on the fluid properties in the pore space and the geometry of the unit-cell. The transport properties also rely on the presence of any forced velocities or existing pressures. An initial velocity or pressure determines whether the flow is forced or diffusion in nature [19]. Current modeling systems allow an initial velocity or pressure to be applied. Using an initial velocity, a unit cell is capable of experiencing different velocities, therefore different Reynold's numbers and in turn both laminar and turbulent flow. This means that initial conditions for a given environment also need to be recorded. The components of properties such as velocity will be recorded using a Cartesian coordinate system.

2.2.5 Connectivity Characterization

A structure's connectivity is the degree to which a structure can be cut before creating two distinct structures. The connectivity within a unit cell is dependent on the unit cell topology which can be designed into the unit cell database as unit cell inherent property. Connectivity between unit cells is sometimes defined as the connections created during alignment. We define a connection as having one phase of a structure aligned with any amount of its corresponding phase in a second structure. The criterion for connectivity between unit cells was reported in our previous work [16]. We utilize skeletal representation to select structures that form connectivity using Earth Mover's Distance.

2.3 Data Storage of Unit Cell Information

The data gathered during characterization is generated using different software and on different platforms. For this reason the data is divided into categories and stored in tables. In Figure 5 the category named Unit Cell is depicted along with some of the information it contains. The category contains the information gather during geometric characterization, the meshes created during mechanical characterization, and the different representations generated during characterization.

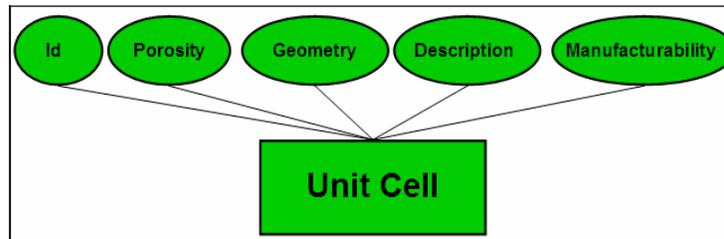


Figure 5 Data storage for the geometric information gathered during characterization. Both the information and representations are stored along with an assigned identification number.

There are two advantages to this data storage system; 1) the ability to expand the type of data gathered during characterization and 2) the ability to form relationships between categories, such as those depicted in Figure 6. The ability to store and locate this information lends itself to our multiple parameter optimization process.

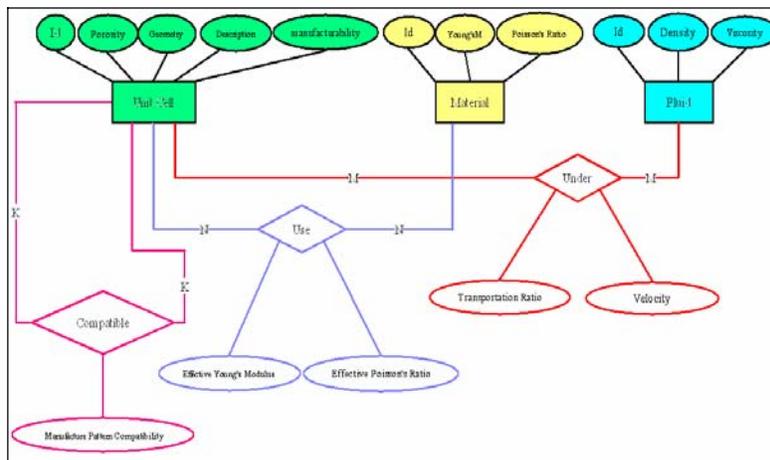


Figure 6: Overall data relationship between the different category tables in the data storage system

3. Design of Tissue Scaffolds under Multiple Parameters

Like any scaffold design, a unit cell based scaffold must meet the biological, mechanical, and geometrical design requirements for a given application. However, unlike conventional scaffold designs, unit cell based scaffold designs need to meet both the local requirement for regions within the scaffold and the global requirements for the entire scaffold. For this reason we have developed a optimization process that concerns multiple parameters for both the local and global scaffold requirements.

3.1 Parameters for Optimization

Optimization needs to be based on biological, mechanical, and connective properties. The biological considerations currently include pore size, porosity, pore area, and material. Likewise the mechanical consideration includes the elastic modulus, the shear modulus, and the Poisson's Ratio for the unit cells. Connectivity between unit cells is measured using the Earth Mover's Distance. These parameters are currently being used during optimization of the scaffold design. Additional, our process requires a target value and a tolerance range for each parameter used during optimization. Since the numerical magnitudes of the parameters vary considerable, we have normalized the unit cell value by the given range. The unit cells with values that reside with the tolerance range are considered for assembly.

To rank the unit cells that meet all the criteria, we have calculated a *fitness* value, F , for each unit cell. The *fitness* value, F , is determined by summing the normalized discrepancy values, D , of all the parameters. The normalized discrepancy is calculated as the error between the target value and the unit cell value after normalization. Each parameter is also assigned a weight factor, w , so that the scaffold design can rank the priority of each parameter.

$$F_i = \sum_{j=1}^{|p|} \left(\frac{1}{2} - D_j \right) w_j \quad (1)$$

3.2 Optimization Process

The overall process is given in Figure 7. The process begins by choosing a base region, region A. A set of candidate unit cells that meet the requirements is selected from the data base. An adjacent region, region B, is selected based on connectivity. The properties of the unit cell candidates for region B are recalculated to account for any changes due to rotation. The unit cell candidates for region B are then compared to the properties of region B. Only the candidate unit cells that fall within the given range are maintained. The fitness values of the unit cells for region A and region B are averaged based on the volumetric contribution of each region to the scaffold. The highest ranking combination is selected for the scaffold structure.

4. Interface with Internal Architectural Design

The unit cell optimization process yields a design that must be transferred to a process planning process to develop the tool path for fabrication. Unlike conventional fabrication techniques, the optimized scaffold design cannot be transferred using STL formats. For this reason, we have developed an internal architectural design (IAD) process.

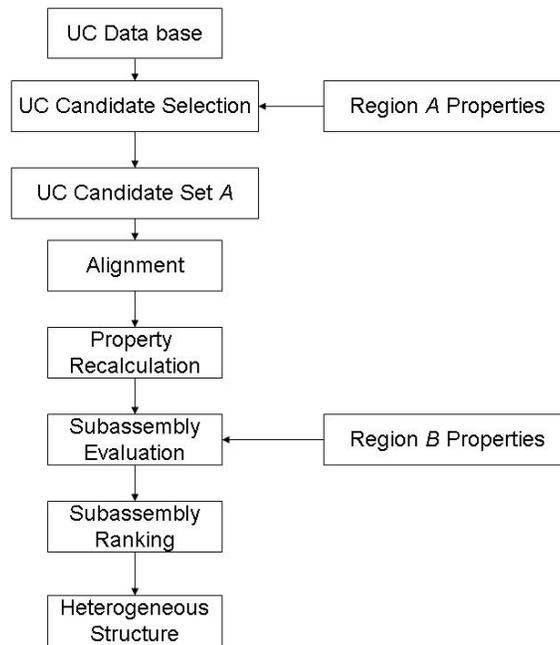


Figure 7: Overview of Alignment Process with Optimization for unit cell based scaffolds

4.1 Internal Architectural Design

There are two major steps in IAD methodology, (1) the determination of the layered processing plane and (2) the generation of a tool path based on internal architecture design. In the first step, the 3D volumetric scaffold is sliced into layers in a model decomposition process. A series of layered processing planes are defined as shown in Figure 8.

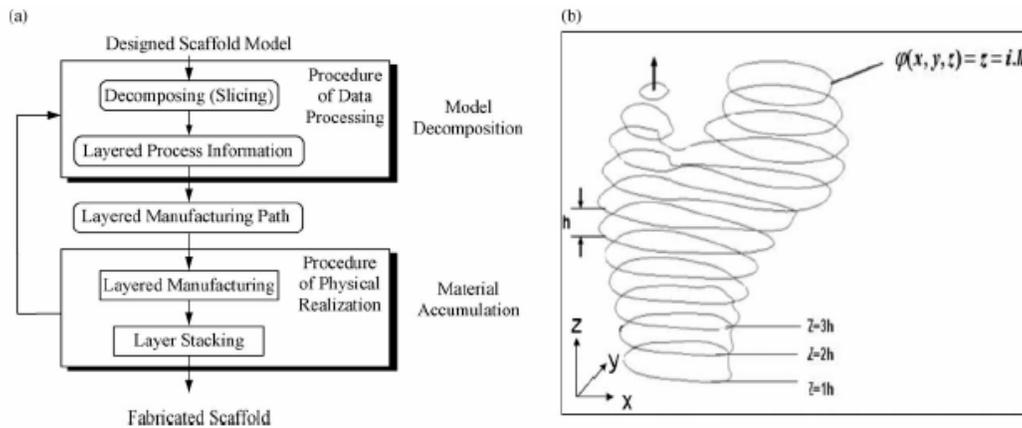


Figure 8: Decomposition and accumulation for layered manufacturing

The process for step 2 is schematically shown in Figure 9. The layered processing planes for the exterior geometries are determined. Given a set of pre-assembled unit-cells, the unit-cells are sliced to determine their characteristic patterns. Then the unit-cell patterns for a given plane are unioned to form the scaffold pattern for that layer. The scaffold pattern is then intersected

with the exterior geometry to remove unwanted regions, thereby forming the interior scaffold pattern. The interior scaffold pattern is then converted into a tool path for SFF fabrication [4].

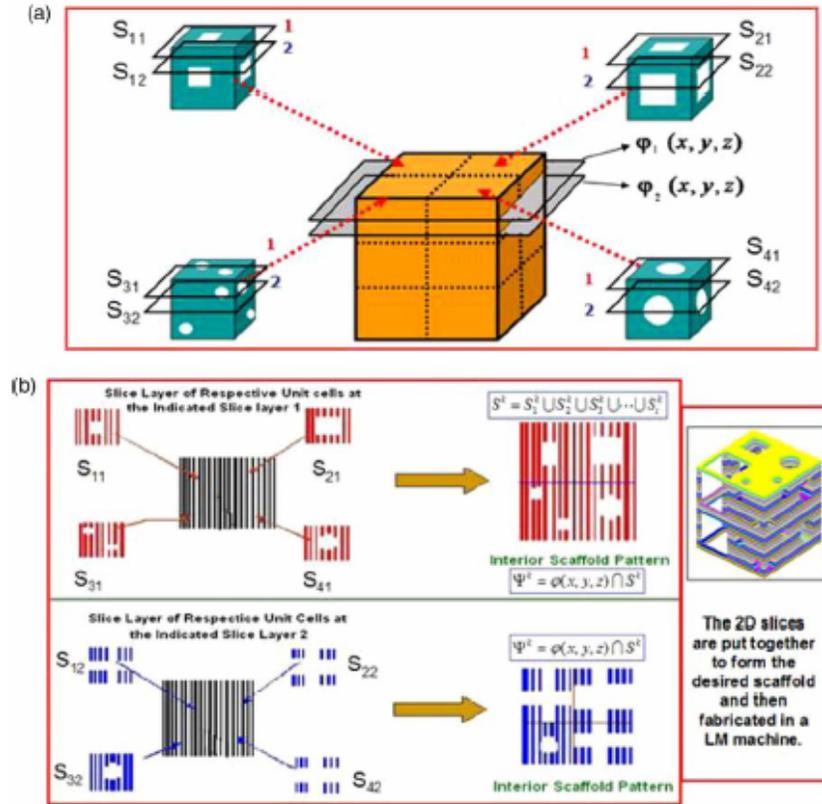


Figure 9: Internal architecture design approach for process tool path generation.
 (a) Slicing of unit cell and scaffold at same slice levels and associating them to regions;
 (b) Intersection of 2D slice patterns onto scaffold 2D pattern to form 3D structure

4.2 Incorporating Data for Internal Architectural Design within the Optimization Process

There are two methods which unit cell scaffold can integrate optimization and IAD for transforming optimized design to a SFF system for fabrication. The first method would modify the existing UC scaffold optimization process and the second would modify the UC scaffold optimization result (Figure 10).

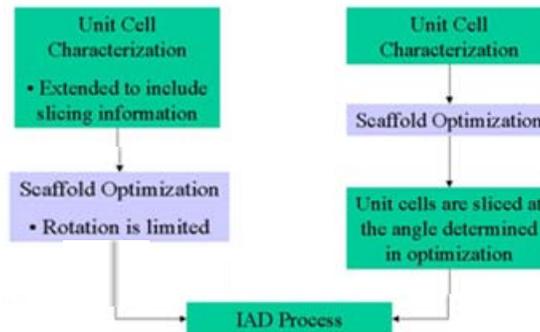


Figure 10: The two methods for integrating the unit cell based scaffold optimization process and the IAD process

4.2.1 Extending the Characterization Process

Perhaps the simplest method to couple these two processes is to extend the data collected during characterization to include unit cell slice information prior to assemble. Since the assemble process also includes an alignment process that allows for rotation, the alignment process can be constrained to limit rotation. Using this method, the relationship graph for the unit-cell would increase in terms of unit-cell geometrical information. The advantage of this method is a relatively uncomplicated transfer of scaffold design to SFF systems. The greatest disadvantage of this method is limiting the number of possible solutions, which could force the creation of much larger unit-cell libraries.

4.2.2 Recharacterization of the Unit Cell after Optimization

The second method requires the unit cell to be re-evaluated after the scaffold design has been optimized. This method would allow the assembly process to retain the ability to rotate a unit-cell during alignment, thereby increasing the possibility of finding a solution to the design requirements. This process would require the rotated skeleton representation to be converted back into a CAD representation and then sliced. The disadvantage of this method occurs due to the possible loss of micro-architecture when converting the information back into a CAD representation. Increasing the resolution to of the skeleton could retain more micro-architecture but would also be more computational expensive. The complexity of the scaffold requirement would dictate the method for transferring the scaffold design. The advantage of using this UC scaffold optimization process lays in the data storage method. At anytime, the characterization parameters can be increase, but the process does not require all characterization information to be used during optimization. This allows the designer to be selective above which the design transfer method.

5. Conclusion

Coupling our scaffold optimization process and the developed IAD process facilitates the creation of advanced scaffold designs that cannot be achieved by conventional CAD modeling approaches. The process combines the advantages of UC scaffold optimization and the IAD process which include:

- Optimization of scaffold design based on multiple parameters. This allows tissue engineers to customize scaffolds for their given application or area of study.
- Both processes have the provision for scaffold designs that have multiple materials, which increases the ability to manipulate cell behavior based on material selection.
- CAD model information is transferred to SFF systems using our IAD process and eliminates the problems inherent to using an STL format during data transfer between the CAD model and the SFF system.
- The problem of memory overhead in CAD software is not present due to the use of skeleton representations in UC scaffold optimization and the separation of outer scaffold shape and interior design in the IAD process.

By combining these two processes, the assumption in the IAD process that the unit-cells have been selected for based on multiple factors is met. It should be noted that the limitations of both

processes are still present. The greatest limitation is the inability to visually examine the design prior to fabrication. The process described in this paper facilitates the design, optimization, and fabrication of 3D material and architectural heterogeneous scaffolds. This work could be further extended to utilize other SFF systems [20, 21] to incorporate more biomaterials for advanced tissue scaffolds.

Acknowledgements

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