Biomimetic Design and Fabrication of Interior Architecture of Tissue scaffolds using Solid Freeform Fabrication

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Abstract: *Modeling, design and fabrication of tissue scaffolds with intricate architecture, porosity and pore size for desired tissue properties presents a challenge in tissue engineering. This paper will present the details of our development in designing and fabrication of the interior architecture of scaffolds using a novel design approach. The Interior Architecture Design (IAD) approach seeks to generate scaffold layered freeform fabrication tool path without forming complicated 3D CAD scaffold models. This involves: applying the principle of layered manufacturing to determine the scaffold individual layered process planes and layered contour; defining the 2D characteristic patterns of the scaffold building blocks (unit cells) to form the Interior Scaffold Pattern; and the generation of process tool path for freeform fabrication of these scaffolds with the specified interior architecture. Feasibility studies applying the IAD algorithm to example models and the generation of fabrication planning instructions will be presented.*

Keyword: *computer aided tissue engineering, scaffold design, interior architecture*

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1. Introduction

The loss or failure of an organ or tissue is one of the most frequent, traumatic and expensive ailments in human health care. The need for substitutes to replace or repair tissues or organs because of disease, trauma, or congenital problems is overwhelming. For example, in the United States alone, as many as twenty million patients per year suffer from various organ and tissue related maladies including burns, skin ulcers, diabetes, bone, cartilage, and connective tissue defects and diseases, more than eight million surgical procedures are performed annually to treat these cases, over 70,000 people are on transplant waiting lists, and an additional 100,000 patients die without even qualifying for the waiting list. The financial cost to care for these patients has been estimated to as much as $400 billion annually on patient suffering from organ failure or tissue loss [1,2]. To address this issue, Tissue Engineering, integrating a variety of

science and engineering disciplines seeks to create functional tissues and organs for transplantation which restore, maintain or improve the function of human tissues, and evolves as one of the most promising therapies in the regenerative medicine [3].

In the success of tissue engineering, three-dimensional (3D) tissue scaffolds play a critical role as extra-cellular matrices onto which cells can attach, grow, and form new tissues. In the growth and migration processes that give rise to tissue function and morphogenesis, cells are influenced by a wide variety of factors including their own genetic programs, its bio-molecular composition, and 3-dimensional scaffolds to direct and induce cell proliferation, migration and differentiation. Modeling, design and fabrication of tissue scaffolds to meet multiple biological and biophysical requirements is always a challenge in tissue engineering. This is further amplified when designing load bearing scaffolds for bone and cartilage tissue application. In these cases, tissue scaffolds need to be designed with intricate architecture, porosity, pore size and shape, and interconnectivity in order to provide the needed structural strength, transport nutrients, and the micro-environment for cell and tissue ingrowth [4-6]. Thus, the designed scaffolds are often required to be made by advanced manufacturing process, such as solid freeform fabrication (SFF) due to the design complexity [7-9].

The scaffold micro-architecture is believed to influence the behavior of cells and the biological function of tissues by providing a nutritional pathway as well as a spatial distribution for cell growth [1, 8, 9]. Designing such micro-architectures within scaffolds has always been limited due to limitations of current CAD technologies either in representation of such micro-structures or the inability to transfer microstructure information to RP machines. The objective of this paper is to develop a process tool path for freeform fabrication of biomimetic designed tissue scaffolds, including a novel Internal Architecture Design (IAD) approach which enables the generation of internal scaffold pattern from characteristic architecture patterns of the scaffold building blocks. The output of such a process would be to have scaffolds with intended interior architecture which would ensure the right pore size, pore shape and interconnectivity throughout the scaffold while making use of current CAD technologies. The next section details current scaffold design techniques and its limitations and the motivation for the development of the IAD technique. The third section details the IAD approach giving details regarding the steps involved. The fourth and fifth section details the implementation of the algorithm and the sample models that were fabricated using this technique. For demonstration purposes we have used the 3DP™ based TheriForm™ Rapid prototype machine in fabrication of the model scaffolds.

2. Current Scaffold Design Process and its Limitations

With the advancement of SFF to be the most favorable approach in the fabrication of scaffolds for tissue engineering applications, CAD has been the default platform in which scaffolds were designed and then converted to machine instructions for fabrication. STL format which has been the de-facto standard of CAD model transfer to RP machines has been mostly used during the scaffold design and fabrication process. The interior architecture of these scaffolds were either designed as a pattern of extrusions, cuts and holes across the surface of the scaffolds in a CAD platform or its interior slice layers were filled in with contours or roads to generate the interior architecture. The former method used by 3DP, SLS, SLA based RP machines for scaffold fabrication while the latter method is used by FDM based machines. Fig

1(a) and (b) outlines the method by which scaffolds are designed in a CAD platform in published literature. Chu et. Al [11] has used an assembly of designed unit cells and then intersected with the scaffold to obtain the interior architecture. Nam et al have used a similar approach in defining the interior architecture. These methods use STL as a means of data transfer to RP machine for final fabrication. This method has limitations as outlined below:

1. STL tessellation involving approximation of surfaces with triangular facets is incapable of representing the scaffold's micro-level pore feature sizes and intricate internal architectures. For example, as model precision demands become more stringent, the number of facets required to adequately approximate the model will increase. This usually ends up with a computing-inefficient STL file due to the extremely large file sizes and inefficient to be used for tool path generation and for freeform fabrication [12, 13];
2. Database in the STL format cannot include other design intents within the model, for example, topology or internal material variations, and its spatial distribution etc.
3. Expensive computing power required when the number of features and cuts in the scaffold become large enough to cause a memory overhead for the CAD software used.

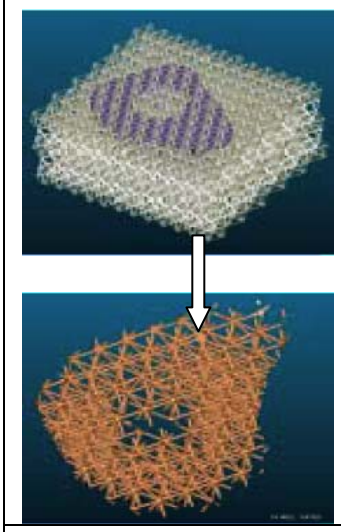

Fig 1(a) Chu et al[11]: Scaffold structure library and assembly.

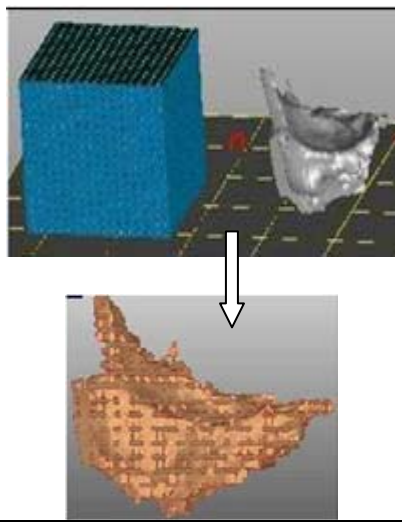

Fig 1(b) Boolean operation to cut out architecture within scaffold [10].

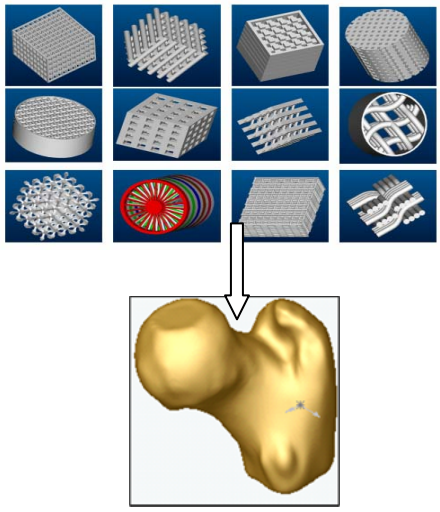

Fig 1(c) How can we design the interior structure of the scaffold – Is it possible?

Although we can use CAD models to represent an individually designed unit cell (such as one shown in Fig. 1(c), CAD is not generally capable of representing a unit cell assembly, for example, using different unit cells to fill in the femur structure as shown in Figure 1(c). Since each unit cell is biomimetically designed with complicated international architecture, the combination of them may result in an even intricate scaffold internal architecture which is beyond the capability of any current commercial available CAD systems [10]. In addition, the STL format which serves as the current industry standard for the data exchange between CAD and freeform fabrication can not be applied to such designed structures.

Therefore, there is a strong demand for developing a new solution to transfer the information of biomimetic designed scaffolds to a process tool path of freeform fabrication techniques and in the design techniques used in the design of scaffolds. We propose to develop a novel solution, an Internal Architecture Design (IAD) approach, to generate process planning instructions for freeform fabrication of biomimetic designed tissue scaffolds. The novelty of the IAD is that it allows the generation of the scaffold process planning without the creation of a unit cell filled 3D CAD scaffold model, thus avoiding the difficulty of using CAD to represent the assembly of the unit cell models. The IAD approach stems from the principle of the decomposition and material accumulation of layered manufacturing [14]. The approach uses the characteristic patterns to represent the individual unit cell 2D interior architectures, and assembles the individual characteristic pattern to form a 2D layered pattern for the scaffold. The processing tool path is generated for every layer based on the layered scaffold pattern, and is then applied to instruct freeform fabrication machines to build 3D scaffold layer by layer. In this way, we do not have to create a real 3D CAD based scaffold model, but still be able to design and control the internal architecture of the scaffold. Detailed development of the IAD approach is outlined as follows.

3. Proposed Methodology for Interior Architecture Design of Scaffolds

Step 1: Determine the layered processing plane ($\varphi(x, y, z)$)

According to the ordered sequences, the 3D volumetric scaffold V is sliced into layers during the model decomposition, and stacked back with materials during the material accumulation. The sequence is a number dispersal in 3-dimensional space V in which the layered manufacturing process is realized. Let's introduce a finite discontinuous real number set C to indicate the discrete layers which V is decomposed:

$$C = \left\{ c_k ; a \le c_1 < c_2 < \cdots < c_{k-1} < c_k < c_{k+1} < \cdots < c_n < c_{n+1} \le b,\ k = 1,2,\cdots,n \right\} \qquad (1)$$

where subscript k represents the number of the kth decomposition in total n layers, and constants a and b represent the values of lowermost and uppermost sequence for a particular object V.

Therefore, corresponding to each C_k, we can define a sequence function $\phi_k(x, y, z)$, and assume it is equal to the ordered number $c_{k,.}$ as shown in Figure 2, we thus define a series of planes in V:

$$\varphi_k(x, y, z) = c_k, \quad k = 1,2,\cdots n \qquad (2)$$

We call those planes the layered processing planes and represent them by a set of scale function $\phi_k(x, y, z)$, with k = 1, 2, …n.. It is important to note that the layered processing plane $\phi_k(x, y, z)$ represents both the indication of the processing layer, and the layered exterior geometry represented by CAD model for the scaffold. In the model decomposition process, the layered processing planes intersect and slice the designed 3D scaffold. In the material accumulation process, the layered processing planes form the processing layers on which material will be added. For example, in Therics' TheriForm fabrication process [15-17], the

layered processing plane is the plane on which the fresh biomaterial powder is spread and printed, while in Drexel's multi-nozzle biopolymer deposition process, the layered processing plane is the plane on which the biopolymer is extruded and deposited. The concept of the decomposition and accumulation, and the layered processing plane is further depicted in Figure 4.

On each thus defined layered processing plane $\phi_k(x, y, z)$ in the volumetric scaffold, we define S^k as a 2D layered scaffold pattern, which can be considered as unions of the partitioned unit cell characteristic patterns:

$$S^k = S_1^k \cup S_2^k \cup S_3^k \cup \cdots \cup S_i^k \tag{3}$$

For simplicity, we assume that the thickness of the slicing layer for unit cells and for the scaffold are all uniform and the same.

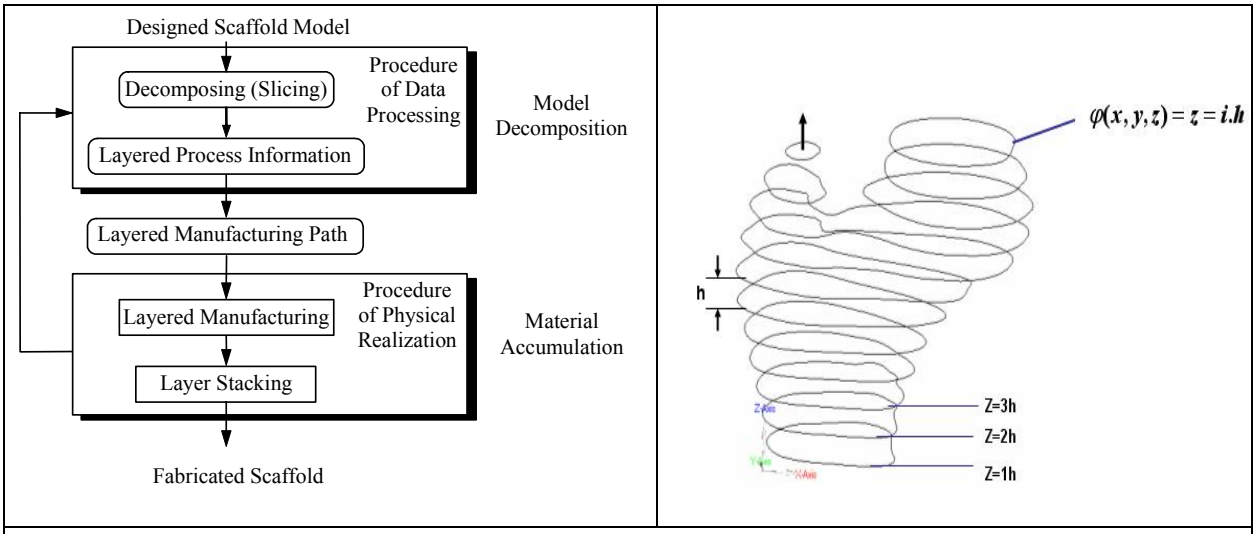

Figure 2: Decomposition and accumulation for layered manufacturing

The external shape of the scaffold is defined by Non-Uniform Rational B-Spline (NURBS) surfaces.We use a direct slicing method to determine the intersection curves of the NURBS model with the given layer (k). Figure 3 shows a step by step procedure on how to calculate the NURBS intersection points. As shown in the figure, a given NURBS surface (depicted as a 2D NURBS curve) is geometrically refined as an adaptive subdivision represented by many smaller domains. We apply bounding boxes to cover up these smaller domains, and find the box that intersects with ray which cast out on the slicing plane. A root finding procedure is initiated to converge at the intersection point. The procedure is then repeated for all rays that are cast onto the slice plane and for every slice plane that intersects the NURBS model. By connecting the intersection point, we can determine the layered processing plane ($\varphi_k(x, y, z)$) and hence determine the outer scaffold shape.

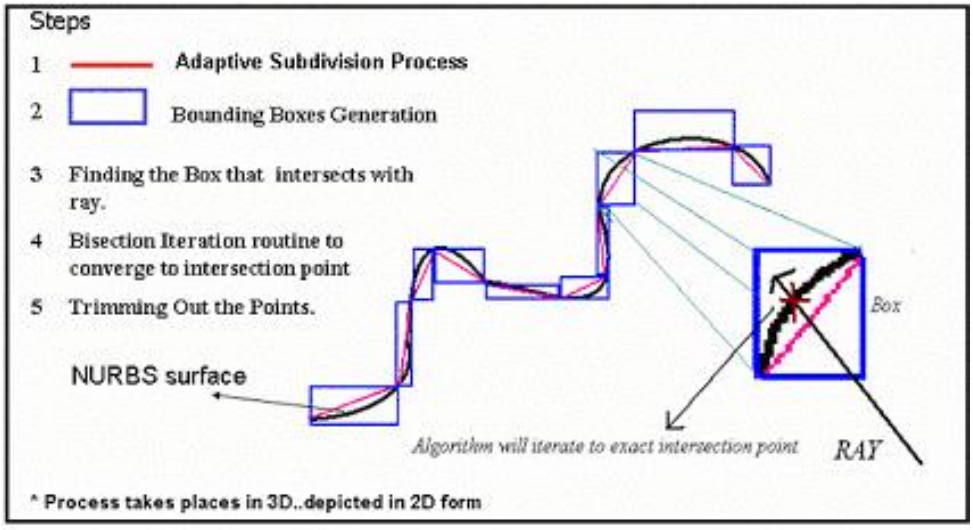

Figure 3: Step by Step procedure on calculation of NURBS intersection points

Step 2: Generate Toolpath based on Internal Architecture Design (IAD)

The layered processing toolpath for freeform fabrication is then generated based on the 2D layered scaffold pattern. The above process can be briefly summarized into the following major steps:

1. Define sub-volume V_i (unit cell) and the spatial position P_i; the discrete layers of V, layered thickness, and the layered processing plane $\varphi_k(x,y,z)$ for scaffold exterior geometries (as defined in Step 1).
2. Determine the unit cell characteristic patterns S_i^j (i = 1,2, …m, and j =1,2, …) by slicing them;
3. Form a 2D layered scaffold pattern S^k (k=1, 2, …n) (or layered Interior Pattern) for a given scaffold sliced layer by a union of all the unit cell patterns;
4. Perform a intersection Boolean operation $S^k \cap \phi_k(x,y,z)$ between the 2D layered scaffold pattern and the exterior scaffold geometry given by φ to remove the unwanted regions of the scaffold sliced layer;
5. Conversion of the Interior Scaffold Pattern to process tool path information for freeform fabrication.
6. Repeating Step 3 to Step 5 till k = n.

We use a square block type unit cells with open pore in the center (as shown in Figure 4) as examples to illustrate the above process. Let's assume that the designed scaffold consists of m unit cells with 4 unit cells being assigned to the top of the scaffold volume (Figure 4). Assume that the number of slices of the scaffold has been determined, the layered processing planes $\varphi_k(x,y,z)$ (k = 1, 2, …n) for the scaffold exterior geometry are known, and the characteristic patterns of the unit cells S_i^j corresponding to the $\varphi_k(x,y,z)$ have been computed and available in the database. The unit cell id P_i within different regions on this layer is used as a key to retrieve the appropriate unit cell characteristic patterns. A scenario has been illustrated as shown

in Figure 4 by taking the case of 2 scaffold slice layers shown as slice layer 1 and slice layer 2. The 2D layered scaffold patterns for scaffold layer 1, S^1, and layer 2, S^2 , are generated by union four unit cell characteristic patterns S_i^1 and S_i^2 (i = 1, 2, … 4), respectively and are shown in the right side of Figure 5. Printing maps consisted of the geometric raster pattern for the slice layer 1 and slice layer 2 are then generated based on S^1 and S^2, as shown in the figure.

By applying intersection Boolean operation between the Interior Scaffold Pattern and the layered processing plane $\varphi_k(x, y, z)$, we then obtain the layered manufacturing maps which will be used for the process tool path generation. The tool path can be generated based on the particular SFF process used. The proposed algorithms is currently implemented in the 3DP™ based SFF technology with possible extension into contour based multi nozzle deposition system. The interior scaffold pattern is used as the initial starting point to generate a raster pattern by determining the entry and exit points for the print head in the case of the 3DP based machine. The calculated intersection points will serve as the starting point for the tool path information for a 3DP based SFF machine. For vector contour based machines, the same scaffold pattern will be used to generate contour vectors by joining the intersection points in a linear technique and forming closed loop vector tool paths.

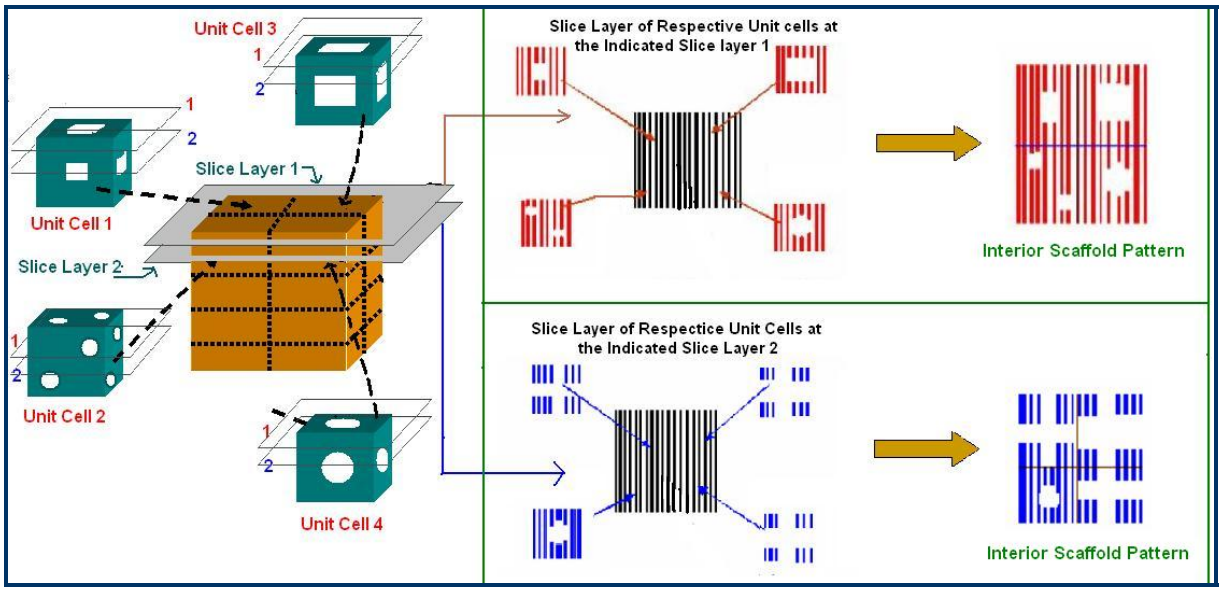

Figure 4: Methodology for Internal Architecture Design

4. Implementation

The steps and algorithms outlined above are implemented within a fabrication planning software to control the different parameters of the fabrication process. The algorithms are implemented in Microsoft's .NET development environment using C# as the programming language. Figure 5 gives the different component modules with the functional flow of data within the fabrication preprocessing environment.

Slicing Module: Once the STEP file of the Scaffold CAD model is read, its geometry and topology will be maintained by the 3D Kernel by which the NURBS surfaces of the model with their topology information will be extracted for the slicing process. Direct slicing of the NURBS surfaces is performed by a Slicing Module, of which the results are packaged into a Slicing Object. The B-rep features of the model are viewed using graphic kernels for easier manipulation and display. Tools are provided for viewing the model and verifying slice layer information for errors that may result in erroneous fabrication. Each cross sectional layer is then extracted from the model based on the slicing parameters and then converted to machine job instructions. A print job database is also maintained for database records and future retrievals.

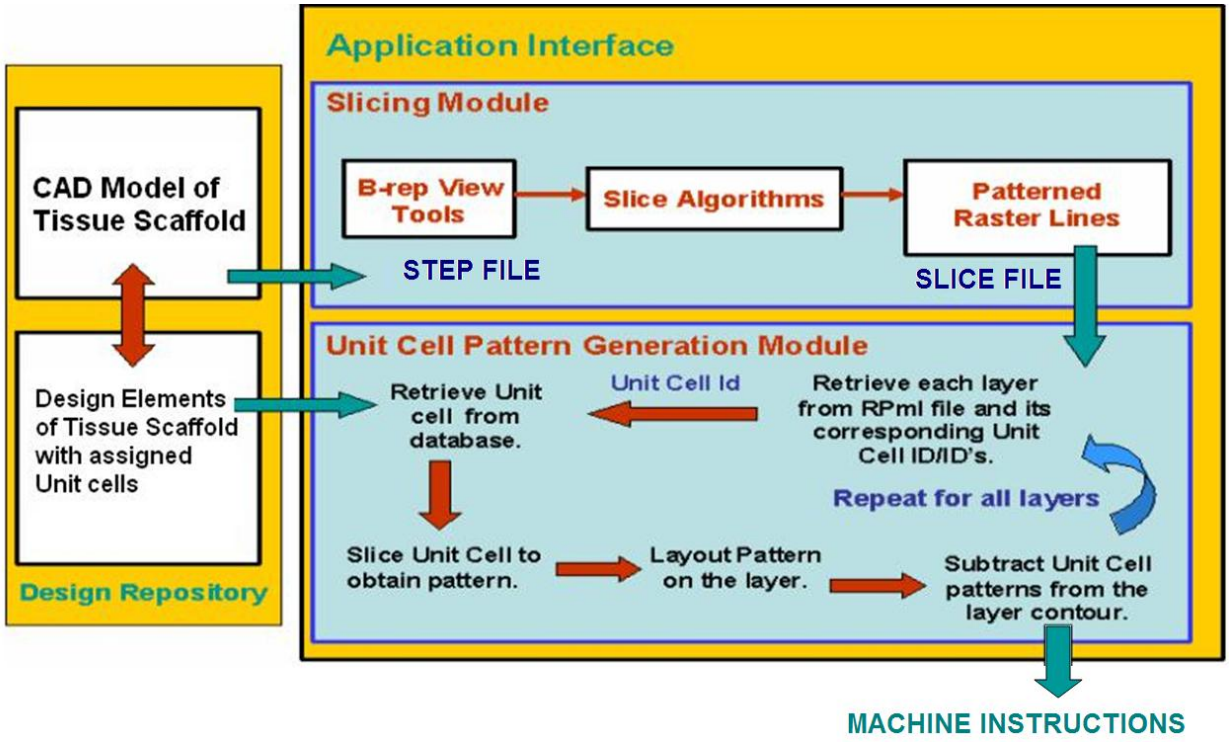

Figure 5: Fabrication Planning Components

Unit Cell Pattern Generation Module: The RP-ml file (containing tool path) from the previous module acts as the input file in this stage. Each layer is extracted from the file along with the microstructure cell ID/IDs it is associated with. The unit cell corresponding to the unit cell ID is retrieved from the design repository and is sliced to obtain the 2-D unit cell pattern. This unit cell pattern is then layered out onto the retrieved layer through a pattern generation algorithm as explained in Figure 5. Once this is completed, the new pattern is intersected with the original pattern of the CAD model retrieved from the RP-ml file to obtain a new set of pattern raster/contour lines. These new set of patterns can be stored in a new XML file format that can be distributed across the web for other applications or converted to machine job instructions to run an SFF based RP machine.

5. Results

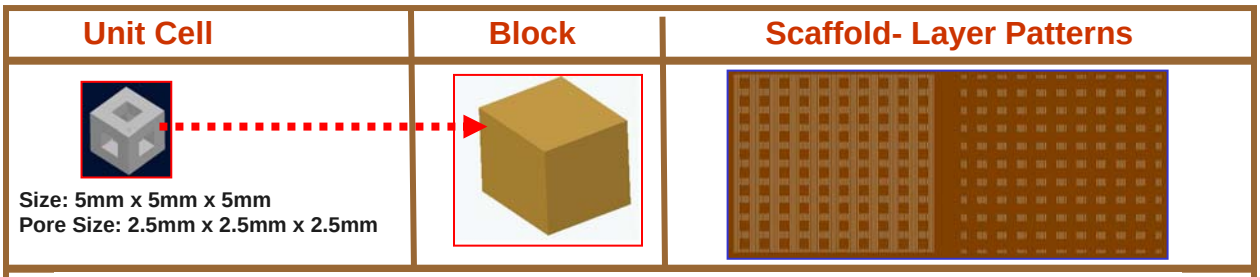

Fig 6(a): Square pore architecture assigned to a Square scaffold structure

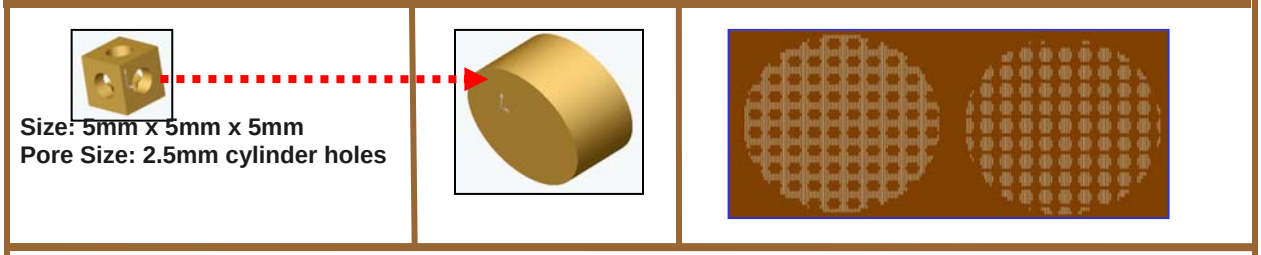

Fig 6(b): Circular Pore architecture assigned to a circular shaped scaffold

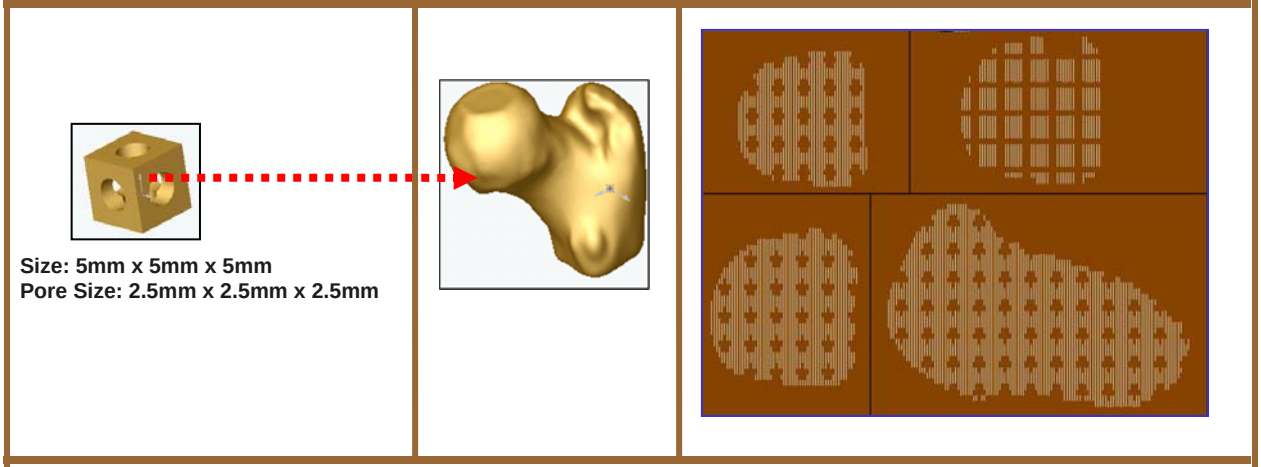

Fig 6(c): A circular pore architecture assigned to an irregular shaped scaffold

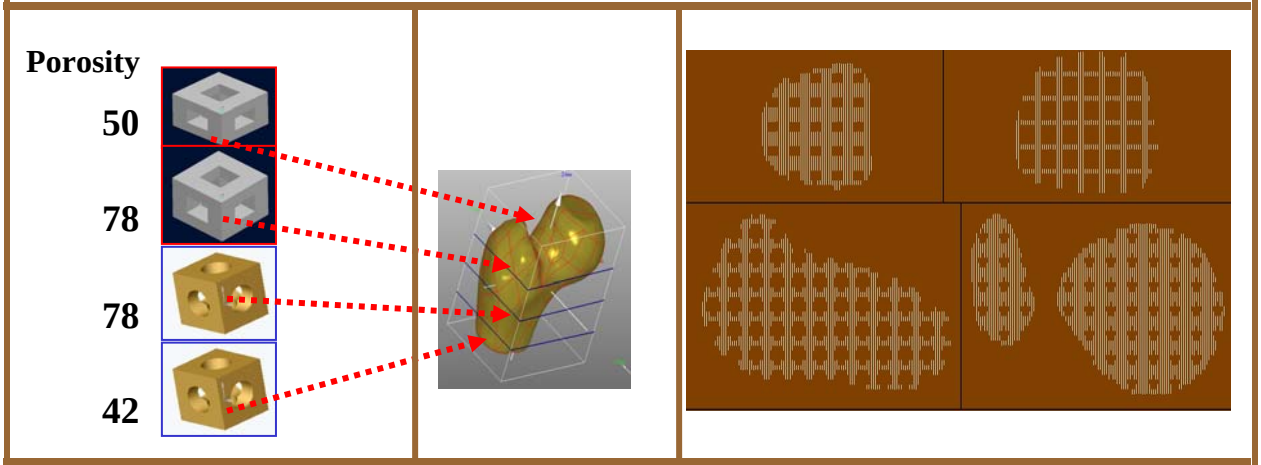

Fig 6(d): Sliced layers of a multi-unit cell scaffold structure

The algorithm was tested with a couple of simple to complex models as shown in Figures 6. The size of the selected unit cell was arbitrarily selected to be a 5mm cube which had characteristic pores of a square pore and cylindrical hole within them. The blocks define the outer shape of the scaffold while the unit cells define the interior architecture of the scaffold. Both the blocks and the unit cells were sliced at equal intervals and stored. The algorithm does not require any huge memory requirements and its run time only depends on the number of slices that make up the block. The size of the unit cell can go further smaller and its size is selected depending on other factors such as the desired pore size, the capability of the selected RP machine and material used. Fig 6(d) shows the bone block structure filled with four different unit cell architectures. Fig 7(a) and (b) shows a cylindrical shaped and a bone scaffold designed using the IAD methodology and fabricated using the TheriForm™ machine. The scaffolds were made out of alumina with a slice thickness of 0.48mm and sintering temperature of 80C. As can be seen, the scaffolds have the required internal architecture as defined by the unit cell. Redefining the unit cell model architecture results in a different interior structure for the scaffold models.

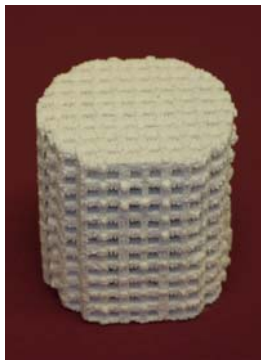

Fig 7(a) Cylindrical Model

Fig 7(b) Bone shaped model

6. Conclusion

The developed IAD methodology provides a more advanced design of scaffolds since each layer can individually be designed to have the desired layer pattern. This pattern is retrieved from the selected unit cell and at the end of the process, the desired scaffold with the outer shape of the block and selected interior unit cell architecture is fabricated. The advantages of the process include:

- The developed approach can help in the design of Biomimetic scaffolds that by current methodologies are impossible to create using CAD or other software. The developed approach does not exclude the use of CAD but uses it as an aid in the design of such scaffolds with macro and micro architecture.
- Interior architecture control of scaffolds along with the provision of multiple material specification and multiple architecture can be specified;
- Direct transfer of CAD model data to RP machines avoiding the bottleneck inherent in the use of the STL format;

- The design of outer scaffold shape and the design of its interior are separated and hence do not present a memory overhead for CAD software. By separating their designs, new architectures with varying properties can be designed and hence aid in the fabrication of better scaffolds for tissue engineering applications.

The layer patterns that are obtained do not work in the same way as laying down hatch patterns within the contour layers. These patterns come with a reason and are generated from the unit cells. The unit cell that needs to be assigned within the block structure is selected based on factors such as the required mechanical and biological properties that have been pre-defined. The process assumes that this selection process has been carried out prior to the generation of process planning instructions. Further details into how these unit cells are selected is described in Sun et al [18-19] and the readers are referred to them for further details.

The described process can be further extended to generate process planning instruction for contour based RP machines such as the FDM and PED [20]. Although the library of unit cells that can be fabricated with these machines are limited, the authors believe that by proper selection of varied contour patterns and sizes, the desired scaffold properties can be obtained. The IAD process developed for the TheriForm machine will be further extended to include contour based machines to be able to fabricate scaffolds with new biopolymer materials and in micron ranges.

7. Acknowledgments

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