Volumetric Histology Data Visualization and Quantitative Analysis

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***Abstract* - This paper presents a framework for histology data visualization based on simplex spline models, which can reconstruct and represent a volumetric histology data for more accurate measurement and analysis. The scanned 2D histology image stacks are first co-registered and segmented to highlight and enhance regions of interests. Then we use our simplex spline based fitting techniques for reconstruction of the segmented 3D volume. Our mathematical framework facilitates tools to quantitatively measure with high accuracy geometric, topological, and other quantities associated with the volumetric histology data. Visualization of the reconstructed data is also faster and more accurate.**

I. Introduction

Traditionally, 2D optical images are prevalently used in histology analysis. We employ volume reconstruction and visualization techniques for generating and visualizing registered stacks of 2D true-color histology images (We name it volumetric Histology Data). Volume visualization of volumetric histology data can exhibit 3D nature of the data, which can reveal more information than 2D images. However, better rendering of histology data requires effective signal processing and image enhancement techniques to process both the slices and the volume to retain small structures and restore fuzzy features. Furthermore, large-scale datasets require efficient algorithms to achieve interactive visualization. The existing visualization techniques still have difficulties to visualize such a large dataset in real time.

To alleviate the situation, we have developed a framework for volumetric histology visualization based on simplex spline model, which can reconstruct and represent a volumetric histology data for more accurate measurement and analysis. The scanned 2D histology image stacks are first co-registered and segmented using our developed software to highlight and enhance regions of interests. Then we use our simplex spline based fitting techniques for reconstruction of the segmented 3D volume. Our mathematical framework facilitates measuring tools to quantitatively measure with high accuracy geometric, topological, and other quantities associated with the volumetric histology data.

In this framework, visualization of the reconstructed data is also faster and more accurate. We have investigated volume rendering via ray casting. During ray-casting extensive sampling and trilinear interpolation along the viewing rays will usually introduce error. In essence, traditional volume rendering is error-prone. Instead, examining our trivariate simplex spline-based formulation, we can compute the basis functions exactly. Therefore, we can efficiently evaluate the integral of densities along a casted ray analytically. In this way, not only can we avoid discretization of the volumetric domain, but we can even avoid performing trilinear interpolation during the viewing-ray discretization. The rendering speed is greatly improved since the evaluation can be done with a close form.

II. Background

Voxel-based analyses and volume visualization are powerful techniques for exploring volumetric datasets. There are basically two major types of volume visualization techniques: isosurface rendering and direct volume rendering. Lorenson and Cline pioneered the Marching Cubes (MC) algorithm [1] that has been frequently used to represent, extract, and visualize the isosurface geometry of (oftentimes voxel-based, regular) volumetric datasets. Each grid point is coded as either inside or outside the object with respect to the surface-defining threshold. The technical essence of the MC algorithm is to generate a triangular mesh that approximates the geometry of an iso-surface by examining each cube (defined by the surrounding grid-points) and producing at most four triangles for each cube based on different configurations of inside-outside vertices. Note that, more triangles per cell (in complementary cases) may be needed in order to prevent creating any holes in the polygonized isosurface. Many variants of the MC algorithm have been published. Dürst [2] discovered that without a careful polygonization of each cell, improperly closed surfaces (i.e., surfaces with “holes”) may occur. To resolve ambiguities for cube types, Montani et al. [3] proposed a slightly altered lookup table that prevents such holes by consistently separating positive vertices on ambiguous faces. Most recently, Kobbelt et al. [4] presented an elegant approach for

fast feature-sensitive surface extraction from volumetric data using directed distance fields, in order to reduce the alias effect. As for direct volume rendering, both volumetric ray-casting [5] and splatting [6] are applicable.

However, there are very few publications on volume visualization and quantitative analysis of volumetric histology data due to the aforementioned difficulties. We conduct our research based on an advance simplex spline model. The histology data used is acquired from the rat root apical bone resorption model [7]. The rat root apical bone resorption model is used to investigate implanted wear induced inflammatory bone resorption and to study a long-term effect of UHMWPE particle injection on tissue profiles of root apical region. Figure 1 shows several samples of histology data after UHMWPE particle injection. H&E staining demonstrated that UHMWPE particle induces significant inflammation and local granuloma change, associated with alveolar bone resorption, as compared with the same region with PBS injection. Van Gilson stain was performed to quantify relative bone matrix collagen changes. UHMWPE particle stimulation dramatically increased the loss of bone collagen content, in comparison with the bone collagen changes in sections of PBS control. In addition to achieve better volume visualization of the histological data (particularly the collagen content), we also aim to find quantitative volume measurements to determine UHMWPE particle-induced bone volume change.

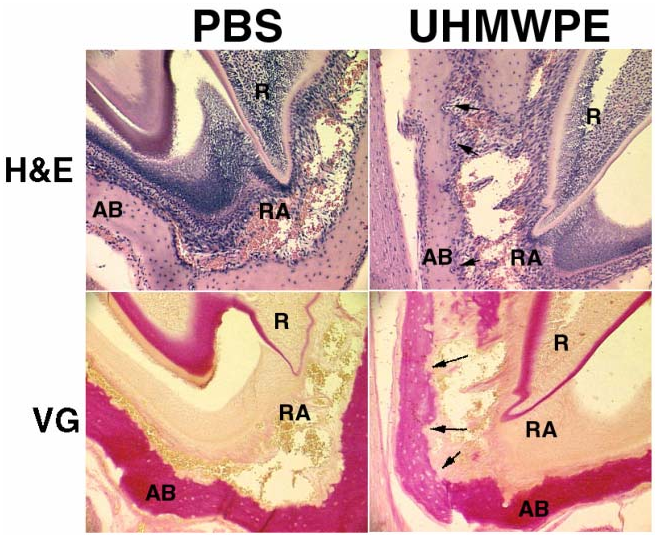

Figure 1. Histological data of UHMWPE particle–stimulated tissue inflammation, osteoclastogenesis, and bone resorption in a rat root apical bone resorption model.

III. Three-Dimensional Simplex Spline-based Model for Data Modeling

The research goal requires an advanced mathematical model to facilitate accurate volume visualization and quantitative analysis. We have developed a simplex spline-based framework, which can reconstruct and represent a volumetric data for more accurate measurement and analysis [8].

In essence, multivariate simplex splines are the volumetric projection of higher dimensional simplices onto a lower dimensional space R^m. A degree n trivariate simplex spline, $M(\mathbf{x}|\mathbf{x}_0, \ldots, \mathbf{x}_{n+3})$, can be defined as a function of $\mathbf{x} \in R^3$ over the half open convex hull of a point set $\mathbf{V} = [\mathbf{x}_0, \ldots, \mathbf{x}_{n+3})$, with $n+4$ knots $\mathbf{x}_i \in R^3$, $i = 0, \ldots, n+3$. The basis function of trivariate simplex splines may be formulated recursively, which facilitates point evaluation and its derivative and gradient computation. When $n = 0$,

$$M(\mathbf{x} \mid \mathbf{x}_0,\ldots,\mathbf{x}_3) = \begin{cases} \dfrac{1}{Vol_{R^3}(\mathbf{x}_0,\ldots,\mathbf{x}_3)}, & \mathbf{x} \in [\mathbf{x}_0,\ldots,\mathbf{x}_3) \\ 0, & Otherwise \end{cases}, \quad (1)$$

and when $n > 0$, select four points $\mathbf{W}= \{\mathbf{x_{k0}}, \mathbf{x_{k1}}, \mathbf{x_{k2}}, \mathbf{x_{k3}}\}$ from $\mathbf{V}$, such that $\mathbf{W}$ is affinely independent, then

$$M(\mathbf{x} \mid \mathbf{x}_0,\ldots,\mathbf{x}_{n+3}) = \sum_{j=0}^{3} \lambda_j(\mathbf{x} \mid \mathbf{W}) M(\mathbf{x} \mid \mathbf{V} \setminus \{\mathbf{x}_{k_j}\}), \quad (2)$$

where $\sum_{j=0}^{3} \lambda_j(\mathbf{x} \mid \mathbf{W}) = 1$ and $\sum_{j=0}^{3} \lambda_j(\mathbf{x} \mid \mathbf{W}) \mathbf{x}_{k_j} = \mathbf{x}$ [9]. Simplex splines have many attractive properties such as piecewise polynomials over general tetrahedral domains, local support, and positivity, making them potentially ideal in general data modeling [10, 11]. During the past 20 years, various types of spline spaces have been proposed by mathematicians [12-15]. The trivariate simplex spline is defined as

$$F(\mathbf{u}) = \sum_{I \in \phi} \sum_{|\beta|=n} \mathbf{c}_{I,\beta} N(\mathbf{u} \mid V_\beta^I), \quad (3)$$

where $\mathbf{c}_{I,\beta}$ is the control point and $N(\mathbf{u}|V^I_\beta)$ is the normalized simplex splines.

Figure 2 shows one example of the reconstructed simplex spline for the volumetric tooth dataset. From the figure we can see that the model is constructed on the volumetric tetrahedral domain.

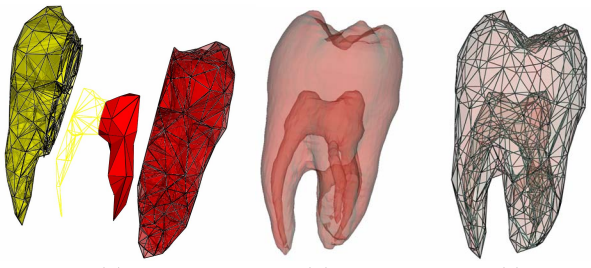

Figure 2. A trivariate simplex spline model for the reconstructed tooth dataset. **(a)** Tetrahedral domain of the tooth dataset. For better visualization, we cut the tetrahedral mesh and show the root canal; **(b-c)** Isosurfaces of the boundary and root canal.

IV. Three-Dimensional Histology Data Modeling and Visualization

In this section we promote our simplex spline-based volume reconstruction and visualization techniques [16] as viable approaches for histology data visualization and analysis. Three-dimensional models of tissue structures can be constructed and rendered to provide realistic interpretations of volume structures not evident in two-dimensional sections. In order to quantitative assessment of 3D histology information, an accurate continuous representation is very critical, which should be easily evaluated anywhere to generate necessary, quantitative information at the desirable resolution. Gradients and higher-order derivatives need to be determined analytically for high-quality visualization. Furthermore, large-scale datasets require efficient algorithms to achieve accurate data modeling and interactive visualization. With our proposed simplex spline-based mathematical model [16], we can provide reconstruction and visualization tools for quantitative analysis and real-time display of 3D histology data. The advantages of the simplex spline model enable data fitting with feature preservation, rapid evaluation, and fast and direct volume rendering.

A. Histology Data Acquisition

The main constituents of the bone tissue include calcium salt and collagen. Collagens of type I is the predominant components in bone tissue. Therefore, the quantity and organization of collagen fibers in bone tissues represents one of the main parameters of bone remodeling in tissue histology. Van Gieson staining is common techniques to accurate quantify the bone collagen change [7]. In this paper, we use Van Gieson stain tissue sections for histology data acquisition. The advantages of using collagen stain tissue sections are as follows: (1) Bone degradation is manifested by both calcium release and collagen depletion. The collagen depletion is always proportional to the loss of calcium. The redness intensities denote the densities of collagen content; (2) Collagen stain images can be clearly interpreted using low amplification viewing (1X ~ 8X), which makes it feasible for volume visualization.. From these standpoints, we believe that collagen stain is of superior advantage than other common histological stains, such as H&E stains.

We cut tissue sections at the interval of 24μm per slice. Before sectioning, we use Laser Marker to physically stain three axes parallel to the cutting sequence direction. Then after sectioning, there are three pre-stained points on each slice, which enables an easier and more accurate alignment procedure for stacking collagen stain images. A panel of stained tissue sections is scanned simultaneously using high-end digital scanner (See Figure 3). These images are captured and reconstructed based on their serial number and laser markers using rigid registration (affine transformations such as rotation and translation). Figure 3 shows a part of samples of scanned sections. The resolution of the images acquired using this approach is detailed enough to show all the necessary histological information for the study of collagen content density. Based on the three pre-stained points on each section we align and register each slice and stack them into a 3D histology data volume. Sometimes a resampling procedure may be necessary to get more realistic 3D histology data.

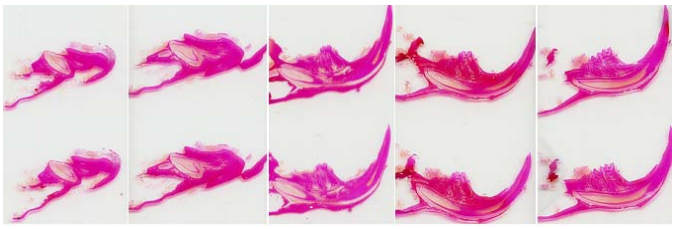

Figure 3. Twelve of scanned rat incisor tissue sections for the volumetric histological assessment.

B. Histology Data Modeling

We use our multivariate simplex spline model to the modeling of redness intensities of histology data, transcending the traditional boundary of spline-based geometric modeling techniques and promoting simplex spines to serve as a powerful data modeling scheme. In order for simplex splines to become a viable and powerful data modeling tool in data modeling, we have to address the issues of data fitting. We have developed very general techniques for data modeling. Different from existing fitting algorithms for parametric representations which usually require a time-consuming parameterization in the pre-processing stage, we directly compute a constrained Delaunay tetrahedralization, which serve as the tetrahedral domain of the trivariate simplex splines.

Assume that $d^h_{I,\beta}$ is associated with control vertices $c_{I,\beta}$, a histology redness intensity data function $\mathbf{d}_h$ over the solid geometry $\mathbf{F}(\mathbf{u})$ can be simultaneously defined as

$$\begin{bmatrix} \mathbf{d}_h \\ \mathbf{F} \end{bmatrix}(\mathbf{u}) = \sum_{I\in\phi} \sum_{|\beta|=n} \begin{bmatrix} \mathbf{d}^h_{I,\beta} \\ \mathbf{c}_{I,\beta} \end{bmatrix} N(\mathbf{u} \mid V^l_\beta) \ . \tag{4}$$

Then, the general problem of fitting volumetric data can be stated as follows: given a set of samples $\mathbf{p}_i = (x_i, y_i, z_i, d_i)$, find a trivariate simplex spline volume s: $R^3 \rightarrow R^4$ that can accurately represent $\mathbf{P}$. We use the position (x_i, y_i, z_i) of the data point $\mathbf{p}_i$ as its parametric value. Therefore, we need to minimize the following objective function:

$$\min E = \sum_{i=1}^{m} (\mathbf{p}_i - \mathbf{s}(x_i, y_i, z_i))^2 \ . \tag{5}$$

The constrained Delaunay tetrahedralization for any volumetric point set is a typical computational geometry problem, whose solution may come from existing standard techniques. For example, we can place a ball at every point, whose radius equals to the shortest distance from this point to its one-ring neighbors. Then, we compute the union of balls to

obtain an occupancy map, which can roughly indicates the boundary of the actual object. We can then use this occupancy map to decide the initial tetrahedralization. After that, we shall perform the decimation procedure to further simplify the tetrahedral meshes in order to arrive at a proper tetrahedral domain for simplex splines. If only the control vectors are considered as variables in Equation (5), the above fitting problem falls into a very special category of nonlinear programming, i.e., unconstrained convex quadratic programming. When considering all the knots as free variables in Equation (5), we will have to calculate the gradient with respect to knots (see Equation (6)). The general data fitting algorithm can be abstracted as:

1. Create a tetrahedral domain for the entire volume, which fully covers the fitted volumetric object;
2. Solve Equation (5) by treating control vectors as free variables;
3. For each node $\mathbf{t}_i$ of the tetrahedralization, if the fitting error in its 1-ring neighboring tetrahedra is larger than a user-specified value, solve Equation (5) by treating the knots associated with $\mathbf{t}_i$ as free variables;
4. For each tetrahedron, if its fitting error is larger than a threshold, then subdivide it into four tetrahedra and repeat (2-4) until the fitting error of every tetrahedron is less than ε.

In applications of data fitting and volume reconstruction, the ultimate goal is to find a trivariate simplex spline approximating the data as accurate as possible. Towards this goal, we prove the following closed-form formula for the directional derivative of trivariate simplex spline volume $\mathbf{s}(\mathbf{u})$ with respect to a knot $\mathbf{t}_{p,l}$ ($p \in N$, $0 \le l < n$) along the direction $\mathbf{v}$:

$$D_{\mathbf{t}_{p,l},\mathbf{v}}\mathbf{s}(\mathbf{u}) = D_{\mathbf{v}}G(\mathbf{u}) + H(\mathbf{u},\mathbf{v}) \tag{6}$$

where

$$G(\mathbf{u}) = -\frac{1}{n+1}\sum_{I\in\Omega, i_j=p}\ \sum_{|\beta|=n+1,\beta_j\ge l}\mathbf{c}^I_{\beta-e^j}N(\mathbf{u}\,|\,\hat{V}^I_\beta),$$

$$H(\mathbf{u},\mathbf{v}) = \sum_{I\in\Omega, i_j=p}\ \sum_{|\beta|=n,\beta_j=l}\mu_j(\mathbf{v}\,|\,X^I_\beta)\mathbf{c}^I_\beta N(\mathbf{u}\,|\,V^I_\beta),$$

and $\hat{\mathbf{V}}^I_\beta = \{\ldots, \mathbf{t}_{p,0}, \ldots, \mathbf{t}_{p,l-1}, \mathbf{t}_{p,l}, \mathbf{t}_{p,l}, \mathbf{t}_{p,l+1}, \ldots, \mathbf{t}_{p,n}, \ldots\}$.

The aforementioned data fitting scheme is expected to function well in many applications such as volumetric reconstruction. Nonetheless, we shall continue to improve the efficiency of our techniques to address histology data natures. The developed volumetric fitting procedure attempts to minimize the total squared distance of the volume data points $\mathbf{d}_i$ to the spline $s(\mathbf{u})$. In practice, certain localized regions may exhibit high-frequency features with much denser point distribution. It is necessarily desirable to introduce new degrees of freedom into the spline representation in order to improve the fitting quality over these high-frequency regions. One strategy is to subdivide any domain tetrahedron whose fitting error is greater than a user controllable threshold. In theory, this local refinement is equivalent with the knot insertion for simplex splines. The new control vectors of the refined domain can be computed with the polar form. Besides local refinement (which essentially maintains all the simplex splines at the same level/scale), we can also resort to hierarchical reconstruction for the same goal of improving the data fitting quality. In the hierarchical reconstruction, we perform the refinement by constructing hierarchical simplices and formulating the reconstructed volume as a series of trivariate simplex splines, i.e., to evaluate $\mathbf{u}\in\Delta I$, we use $s(\mathbf{u}) = s^0(\mathbf{u}) + s^1(\mathbf{u}) + s^2(\mathbf{u}) + \ldots$.

Since the histology data information that we focus on is on the interface between the implant and periprosthetic tissue, it is not necessary to process the entire volume. In Figure 4, (a) shows a histology data with the region of interest marked. (b) shows the corresponding region of interest in the colorized volume. For the quantitative analysis, we actually only need to reconstruct a multivariate simplex spline model for the region of interest.

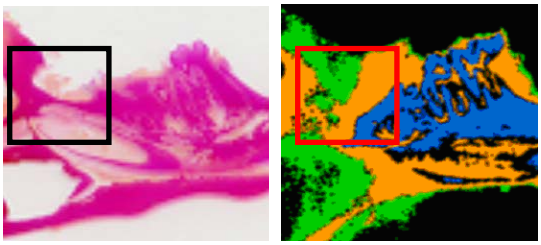

Figure 4. (a) A slice of the histology Data. (b) The corresponding region of interest in the colorized volume.

C. Histology Data Visualization

Besides data modeling, visualization is indispensable in this framework. After data modeling, the histology data is represented as a single analytic function (a multivariate simplex spline function). With this simplex spline-based framework, visualization of the reconstructed data is also faster and more accurate [16]. We have investigated volume rendering via ray casting. During ray-casting extensive sampling and trilinear interpolation along the viewing rays will introduce error. In essence, traditional volume rendering is error-prone. Instead, examining our trivariate simplex spline-based formulation, we can compute the basis functions exactly. Therefore, we can efficiently evaluate the integral of densities along a casted ray analytically.

$$\int_0^L M(\mathbf{x}_c + t\mathbf{d}_c\,|\,\mathbf{V})dt = \frac{n}{n+1}\sum_{j=0}^{3}\lambda(\mathbf{x}_c)\int_0^L M(\mathbf{x}_c + t\mathbf{d}_c\,|\,\mathbf{V}\setminus\{\mathbf{x}_{k_j}\})dt, \tag{7}$$

and when $n = 0$,

$$\int_0^L M(\mathbf{x}_c + t\mathbf{d}_c \mid \mathbf{V})dt = \frac{L}{Vol(\mathbf{V})}. \quad (8)$$

In this way, not only can we avoid discretization of the volumetric domain, but we can even avoid performing trilinear interpolation during the viewing-ray discretization. Considering the nature of histology data, we employ texture-based techniques to further enhance the quality of the visualization and reveal true color information contained in the histology data [17].

Besides ray casting, it is also viable to use tetrahedral projection for direct rendering [18-20], because our simplex spline model can be directly evaluated to define tetrahedral meshes with accompanying data distribution. The tetrahedral projection can be easily accelerated by graphics hardware with the improved performance. Another advantage is that the tetrahedral meshes can be sampled at much higher resolution wherever necessary since the underlying simplex spline model is a continuous representation. Let us now consider *high quality multiresolution isosurfacing*, which is especially important for rendering volumetric histology data. Since the volumetric histology data is reconstructed by a trivariate simplex spline model upon tetrahedra, it is viable to perform marching-tetrahedron [1, 4, 21, 22] isosurfacing to extract isosurfaces from its associated scalar field. Along tetrahedral edges, the process of isosurface extraction employs the original trivariate spline evaluation, which has the potential to avoid introducing sampling artifacts. Since traditional voxel-based systems employ trilinear interpolation, they exhibit aliasing when the voxel grid is scaled or deformed. Aliasing must then be eliminated by filtering most or all of the voxel grids. We avoid this problem by using what is essentially a higher-order C^{n-1} trivariate spline. Inside a tetrahedral cell, we can find a cutting facet that intersects edges of the cell with the user-specified isovalue. The normals at those points can also be computed exactly. Although primary knots may be distributed very irregularly, our approach does not require resampling into a regular voxel raster, which would introduce error. If the modeled object is originally smooth, they will remain smooth even if the control lattice is arbitrarily scaled or even deformed. If they contain C^0 or discontinuity region, these features will also be preserved.

Furthermore, the local evaluation can lead to multiresolution isosurface extraction. When a tetrahedron of the object is detected to cut across the isosurface of its associated field, and its size is larger than a specified threshold, we can evaluate the trivariate simplex spline and upsample it locally to increase the resolution and then perform isosurfacing only on those smaller cells. With the exact on-surface point determination, accurate normal evaluation, and multiresolution capability, our isosurfacing algorithms enable a high-quality isosurface extraction from an unstructured volume. Figure 5 shows the multi-resolution isosurface rendering of the rat root apical bone resorption model at different times.

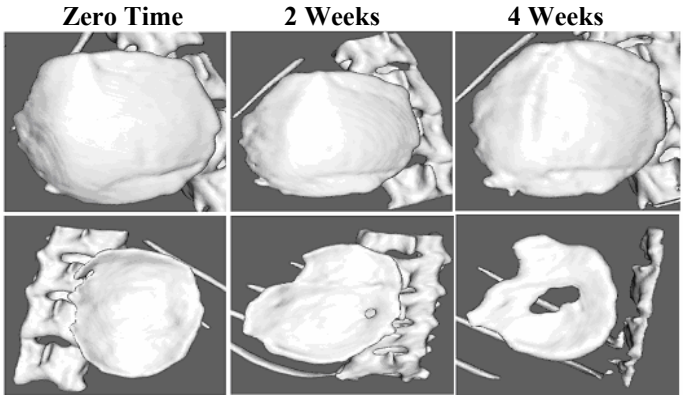

Figure 5. Simplex-spline based marching tetrahedra isosurface rendering.

V. Quantitative Assessment

Since the histology data is represented on the tetrahedral domain, we can easily calculate the quantitative information out of the histology dataset. The tetrahedron can be selected according to x,y,z coordinate indices using a mouse device. Since the multivariate simplex spline model is based on multiresolution tetrahedral domains (see Figure 6(a) and (b)), it facilitates very flexible comparison. The region of interest can be chosen randomly, and even irregularly based on true anatomic locations, etc.

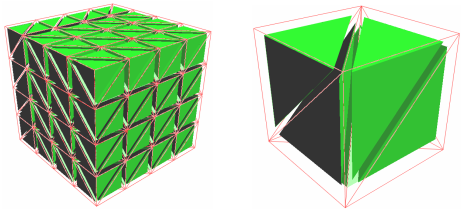

Figure 6. The region of interest can be tetrahedralized into multiresolution tetrahedral mesh prepared for the quantitative assessment. Every tetrahedron can be treated as a MicroUnit for assessment. (a) shows the tetrahedral mesh with the scaled tetrahedron cell in order to exhibit the 3D nature. (b) is the tetrahedral mesh at the lowest resolution.

For a tetrahedron cell of histology data, we measure quantitative information, *normalized cell density* (*collagen density*),

$$D = \frac{\int\int\int_v s(x,y,z)dxdydz}{\|V\|}, \quad (9)$$

where $s(x, y, z)$ is a reconstructed trivariate simplex spline volume for the histology data. $\|V\|$ denotes the volume of the cell. The integration can be calculated analytically for the tetrahedra cell V. Therefore, it is much more accurate than simple summation of all the voxel values inside the tetrahedron cell for calculating normalized cell density.

Quantitative measurements of bone collagen content using our prototype software revealed that saline control mice has much lower bone collagen depletion (16.6% collagen

loss), in comparison with similar regions in UHMWPE particles stimulated mice (36.6% collagen loss, $p<0.05$). Quantitative analysis of implanted bones showed a time-dependent significant alteration of plateau surface contour in pouches with UHMWPE particle stimulation, suggesting the progressive implanted bone degradation (Figure 5).

We have confirmed that injection of wear debris into this region will induce local inflammation, osteoclastogenesis, and bone resorption. The bone loss at apical root tissues can be examined and compared by quantification the reconstructed 3D histology data. More accurately, we use 3D isosurface of the bone segment for volume measurement of bone resorption. The user can pick up a threshold I_0, the volume of the enclosed isosurface in a specified tetrahedron cell can be calculated analytically and accurately as follows:

$$v = \iiint_{d_{CT}(x,y,z)>I_0} dxdydz \ . \qquad (10)$$

With the accurate volume calculation, we can measure the bone resorption along time axis.

VI. Conclusion

In this paper we have presented a framework for histology data visualization based on simplex spline models, which can reconstruct and represent a volumetric histology data for more accurate measurement and analysis. The scanned 2D histology image stacks are first co-registered and segmented using our developed software to highlight and enhance regions of interests. Then we use our simplex spline based fitting techniques for reconstruction of the segmented 3D volume. Our mathematical framework facilitates measuring tools to quantitatively measure with high accuracy geometric, topological, and other quantities associated with the volumetric histology data. Visualization of the reconstructed data is also faster and more accurate. In the future we will improve the framework and apply it to more general microscopic histology data.

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