Spatial Modeling of Bone Microarchitecture

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**ABSTRACT**

We develop and evaluate a novel 3D computational bone framework, which is capable of enabling quantitative assessment of bone micro-architecture, bone mineral density and fracture risks. Our model for bone mineral is developed and its parameters are estimated from imaging data obtained with dual energy x-ray absorptiometry and x-ray imaging methods. Using these parameters, we propose a proper 3D microstructure bone model. The research starts by developing a spatio-temporal 3D microstructure bone model using Voronoi tessellation. Then, we simulate and analyze the architecture of human normal bone network and osteoporotic bone network with edge pruning process in an appropriate ratio. Finally, we design several measurements to analyze Bone Mineral Density (BMD) and bone strength based on our model. The validation results clearly demonstrate our 3D Microstructure Bone Model is robust to reflect the properties of bone in the real world.

**Keywords:** 3D Microstructure Bone Model, Bone Mineral Density (BMD), Trabecular bone, Osteoporosis, Bone strength.

1. INTRODUCTION

Over the past few years, osteoporosis has been recognized as an established and well-defined disease that affects more than 25 million people in the United States.\textsuperscript{1} It is estimated that by 2020, one half of all American citizens over age 50 will be at risk for fractures from osteoporosis and low bone mass.\textsuperscript{2} In 2003, the World Health Organization (WHO) embarked on a project to integrate information on risk factors and bone mineral density (BMD) to better predict fracture risk in men and women worldwide.\textsuperscript{3} The most widely validated technique to measure BMD is dual energy X-ray absorptiometry (DXA). However, major limitations of bone mineral densitometry are that it incompletely reflects variation in bone strength.\textsuperscript{4, 5} A spatio-temporal model of bone could have potential utility because clinical trials for evaluating bone-modulating drugs require very large sample sizes and long study durations to enable meaningful assessment of fracture risk as a clinical endpoint.

To overcome the shortcoming of BMD, computer simulations of bone remodeling attempts to correlate discrete physiological events with observed changes in bone morphology. Previous simulations based on 1D models do not account for the interconnected trabecular structure of cancellous bone or the distribution of remodeling sites that can be only shown in the three-dimensional structure.\textsuperscript{6} Several studies have worked on developing a simulation that is based on a 2D/3D structural model of cancellous bone which allows for the occurrence of trabecular perforation. Extensive studies of structural approaches are done.\textsuperscript{7–9} However, these studies have not incorporated both biochemical reactions of bone remodeling mechanism and BMD of previous measurements into a computer simulation model.\textsuperscript{6}

Bone in human and other mammal bodies is generally classified into two types including Cortical bone, also known as compact bone, and Trabecular bone, also known as cancellous or spongy bone. Trabecular bone is quite porous and more active, more subject to bone turnover, so most research focus on microstructural analysis of trabecular bone. Around the ages of 30-35, trabecular bone loss begins. Women may lose as much as 50%, while men lose about 30%.\textsuperscript{10} Osteoporosis is a systemic disease defined as a reduction in bone mass associated with impaired bone architecture: disruption of trabecular continuity by trabecular perforation, resulting in reduced connectivity of the trabecular bone structure, increased bone fragility and higher possibility of fracture risk.\textsuperscript{11} As shown in Figure 1, bone is not uniformly solid material, but rather has some spaces between its hard elements.

Based on our preliminary study of the 2D bone structure simulation,\textsuperscript{6, 14} we build a 3D bone microarchitecture network. In our preliminary research, one horizontal plane of our 3D bone microarchitecture model has been
studied, which results in a 2D bone structure network, termed BoneNET. In our abstracted bone network model, important components of the bone structure are considered to build a bone model enabling computational analysis in a timely manner without losing the critical bone structure data and biochemical or cellular interactions among bone cells. We will incorporate biochemical or cellular interactions among osteons by applying the methods developed from the pharmacodynamics-cellular bone homeostasis modeling process to understand the metabolic bone reaction. Many studies have examined how the bone microarchitecture contributes to bone strength and their evaluation can improve determination of bone quality and strength. In Figure 2, we show important elements of bone structure and the abstracted bone model, a rod-like structure network for both normal and osteoporotic bone. Attributes of bone microarchitecture are considered and applied to our 3D bone network.

2. MODELING AND METHODS

The procedure for obtaining a three-dimensional model which represents bone architecture contains: 1) distributing points with varying radial density according to the cumulative normal distribution in a circular region. 2) Voronoi tessellation and 3) random pruning of the Voronoi edges. Figure 1 shows the resulting representation approximates a 3D bone-like structure. Importantly, there is a densely connected region resembling cortical bone around the outer periphery and a more loosely connected, less dense region resembling trabecular bone toward the center.
2.1 Distribution of Bone-Forming Foci and Bone Mineral Area

The mean concentration of bone-forming foci \( c(r) \) is expressed as mean number of foci per unit area varied in the radial direction \( r \) according to a cumulative normal distribution (CDF):

\[
c(r) = \frac{c_0}{\sqrt{2\pi}} \int_{-r}^{r} e^{-\frac{(z-\mu)^2}{2\sigma^2}} dz,
\]

(1)

The mean and standard deviations of the underlying normal distributions are denoted by \( \mu \) and \( \sigma \), respectively, whereas \( c_0 \) is a constant of proportionality. In results, we will assess the ability of this equation to describe data from bone imaging. The values of \( \mu \) and \( \sigma \) can be estimated by Nelder-Mead algorithm.\(^{19}\)

2.2 Distribution of Bone Mineral

The edges of the Pruned Voronoi Lattice (PVL) are assigned weights that are interpreted as the circular cross sectional area of the bone mineral in the edge. The distributions of the circular cross-sectional area of bone mineral \( w(r) \) vary in the radial direction \( r \) according a cumulative normal distribution:

\[
w(r) = \frac{w_0}{\sqrt{2\pi}} \int_{-r}^{r} e^{-\frac{(z-\mu)^2}{2\sigma^2}} dz,
\]

(2)

The mean and standard deviations of the bone mineral normal distribution, denoted by \( \mu \) and \( \sigma \), respectively, are fixed at the values used for the distribution of bone forming foci. The \( w_0 \) is a constant of proportionality.

2.3 Voronoi Tessellation

Voronoi tessellation is a mathematical procedure for creating a closed lattice of edges called Voronoi cells from a set of points or Voronoi sites. The boundaries of the discrete polygonal Voronoi regions are straight lines; every point within a given Voronoi cell is closer to its cognate Voronoi site than to any other site. The field of bone forming foci created in section 2.1 provides the set of Voronoi sites that are subject to Voronoi tessellation. The edges of Voronoi cells are interpreted as the structural matrix upon which bone mineral is laid down.

2.4 Stochastic Edge Pruning

Edges in the Voronoi lattice are randomly deleted with a low probability \( p \) according to a Bernoulli distribution \( \text{Bernoulli}(p) \). This creates a lattice with characteristics that more closely approximate observed bone mineral lattices in bone histological specimens. We refer to the lattice remaining after the stochastic edge-pruning step as the PVL. The probability of deletion is an exponential function of the edge weight \( w_i \), which represents the level of bone mineral.

\[
p = e^{-\beta w_i / w_{\text{max}}},
\]

(3)

The \( w_{\text{max}} \) is the maximum value of \( w_i \) and \( \beta \) is a non-dimensional parameter akin to a rate constant that determines the extent of edge pruning.

2.5 Expression for Bone Mineral Mass

The mean mass of bone mineral \( m \) for a given realization of the network model is obtained as the sum over all the edges:

\[
m = \rho \sum w_i l_i,
\]

(4)

The \( w_i \) denotes the cross sectional area of the edge and \( l_i \) is the length of the edge. The true density of bone mineral is denoted by \( \rho \).
2.6 Expression for Bone Mineral Density
The bone mineral density BMD is a projected mass. For a realization of the network model, BMD is obtained from the preceding formula for bone mineral mass as:

\[ BMD = \frac{m}{A_p} = \frac{m}{2R_0 L} = \frac{\rho \sum w_i l_i}{2R_0 L}, \]  

(5)

2.7 Expression for Area Moment
The area moment \( I_z \) is a topological property which is an important determinant of the stress-strain relationships in response to forces that cause bone to bend.

The area moment is computed relative to the central z-axis of the cylindrical geometry. To compute the area moment \( I_z \) due to bone mineral for a realization of the network, the region \( r (0 \leq r \leq R_0) \) is sub-divided into small, ideally infinitesimal, annular regions and the area \( \delta a_i(r) \) of the mineral present at distance \( r \) from the axis are computed. The area moment of inertia is defined as the summation over all the infinitesimal elements in the geometry:

\[ I_z = \sum_i r^2 \delta a_i(r), \]  

(6)

The value of the radius of gyration of the bone \( R_g^2 \) is obtained by dividing the area moment \( I_z \) by the cross-sectional area \( A \). For an circular section of bone:

\[ R_g^2 = \frac{I_z}{A} = \frac{I_z}{\pi R_0^2}, \]  

(7)

2.8 Fraction of Bone Mineral
Let us denote the average volume fraction of bone mineral by \( V_M \) and the corresponding average volume fraction of bone extracellular matrix by \( V_E \).

\[ V_E = 1 - V_M, \]  

(8)

The value of \( V_M \) is given by:

\[ V_M = \frac{1}{\pi R_0^2 L - v_b} \sum_{e} a_i l_i, \]  

(9)

where \( v_b \) represents the volume occupied by blood.

3. EXPERIMENTAL STUDY
In this section, we firstly generate a 3D bone model representing bone microstructure. Then, we conduct the simulation of the Normal Bone Network (NBN) and Osteoporotic Bone Network (OBN). Finally, we provide three measurements including Bone Mineral Density (BMD), Moment of Inertia (MOI) and Fractal analysis to evaluate our bone quality of normal/osteoporotic bone network.
3.1 3D Spatial Model of Bone Microstructure

As the first step of generating 1169 two-dimensional bone random seeds based on cumulative normal distribution (CDF) in Equation (1) as Voronoi center in Figure 3(a), 3D Voronoi sites are generated by uniformly randomly selecting Z-axis within a particular range such as 0 to 0.5. The randomly generated Voronoi sites are the center position of rod-like structures as representatives of mineralized fibers, as shown in Figure 3(b). The number of sites could vary depending on the size and density of a targeted bone structure.

Second, we create Voronoi cell from 3D Voronoi sites in Figure 3(c). In particular, only the Voronoi cells of the extreme vertices are unbounded (i.e. extended to infinity). Each point on the boundary is called an extreme vertex in Figure 3(d).

Third, during the process, an input point is killed if it is no longer contained within boundary. The cell including this particular point will also be removed and Figure 3(e) shows the result of removing cells that extend to infinity.

Fourth, we extract all Voronoi vertices in each edge of pruned Voronoi lattice (PVL), as shown in Figure 3(f).

Fifth, we implement Convex Hull on the union of Voronoi center points and Voronoi vertices in Figure 3(e) and Figure 3(f), and construct the surface for 3D bone model using triangle representation. Then we manually remove the top and the bottom of surface for displaying bone inner microstructure in Figure 4.

![Image](image.png)

Figure 3. The six steps of generating process on 3D bone inner microstructure network.

3.2 Simulation on Normal Bone Network (NBN) and Osteoporotic Bone Network (OBN)

Stochastic Edge Pruning in section 2.4 provides a method to simulate bone network in different phases.

We first generate edges between each connecting two Voronoi vertices in whole PVL, then assign edge weights using normal cumulative density function in Equation (2) according to vertices locations. Second, we try to delete edges by exponential probability with $p$ in Equation (3). The deletion probability $p$ is inversely proportional to $\beta$, denoted by $p \propto \beta^{-1}$. A vertical and horizontal image of 3D bone edge network and microscopic view for both NBN and OBN is shown as Figure 5.
3.3 Measurement based on Bone Mineral Density (BMD)

In section 2.5, a projected area density, referred to as BMD, is normally calculated to assess regional bone density and strength by Equation (5). We investigate the effect of BMD on both Normal Bone Network (NBN) and Osteoporotic Bone Network (OBN). We can manually set up BMD to 0.9 by BMD test result from National Osteoporosis Foundation (NOF). For both NBN and OBN, we implement Equation (5) to solve bone mineral density coefficient $\rho$.

<table>
<thead>
<tr>
<th></th>
<th>NBN</th>
<th>OBN</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\rho$</td>
<td>374.38</td>
<td>146.18</td>
</tr>
</tbody>
</table>

Table 1. Bone Mineral Density coefficient for Normal Bone Network (NBN) and Osteoporotic Bone Network (OBN)

As we expected, results in Table 3.3 clearly show that the structure of NBN is healthier than structure of OBN.
3.4 Moment of Inertia (MOI)

We evaluate the overall strength of bone network with moment of inertia (MOI), which is a measure of an object’s resistance to changes in its rotation rate. Since the nature of bone strength is the resistance to changes from outer forces, MOI is a useful measurement for understanding of bone strength. Equation (6) defines MOI of bone strength, and the area \( \delta a_i(r) \) can be regarded as the cross-sectional area of edge given by Equation (2), because it defines the bone mineral density. The Equation (6) is modified to include a \( w_i \) term which is the weight of an edge and the dot product between the direction of the edge \( \vec{k} \) and the orientation of cross section \( \vec{d}_i \).

\[
MOI = \sum_{e} w_i R_i^2 \cos \theta = \sum_{e} \frac{w_i R_i^2}{d_i \vec{k}}.
\]

(10)

To obtain MOI for both NBN and OBN, we implement Equation (10) and have the following result.

<table>
<thead>
<tr>
<th>MOI</th>
<th>NBN</th>
<th>OBN</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.0914e+006</td>
<td>3.8735e+006</td>
<td></td>
</tr>
</tbody>
</table>

Table 2. Moment of Inertia for Normal Bone Network (NBN) and Osteoporotic Bone Network (OBN).

From MOI calculation result, we can easily find NBN is healthier than OBN because NBN has better resistance from outer force than OBN.

3.5 Fractal Analysis

Fractals are geometric structures that can be used to analyze our trabecular bone structures. Most people are familiar with the topological dimensions such as 1-, 2-, or 3-spatial-dimension. However, some geometrical objects couldn’t be described well with the usual topological dimensions and therefore fractional or fractal dimension is introduced, existing somewhere between the usual topological dimensions. Trabecular bone is a special geometrical object and can be regarded as a hollow bone or solid bone if fractal index is 1.0 or 2.0. Measurements of normal bone or osteoporotic bone usually fall somewhere between these two extremes and so Fractal Analysis is useful in estimating bone strength of different conditions.

2D box-counting algorithm is applied to calculate the fractal index of trabecular bone. Before implementing box-counting algorithm using BongJ, we perform image processing and analysis. We convert grayscale image (Figure 6 (a)) to binary (Figure 6 (b)) by thresholding. Fractal dimension results using 2D box-counting algorithm are shown as Figure 6 (c). Fractal dimension results for both normal bone microscopic view image and osteoporotic bone microscopic view image are the negative value of slope of the line relating the natural logarithms of the number of boxes containing contour and each corresponding box size (Figure 6 (c)).

We then match our Normal Bone Network (NBN) and Osteoporotic Bone Network (OBN) to Normal Bone trabecular architecture (Figure 6. (a) up) and Osteoporotic Bone trabecular architecture (Figure 6. (a) down) by fractal dimension calibration. The input for implementing box-counting algorithm for NBN is Figure 5 (c) upper picture and OBN is Figure 5 (c) lower picture. And the result is shown as Figure 7.

We now discuss the comparison between our NBN and OBN with real trabecular normal bone and osteoporotic bone image based on experiments on fractal analysis using box-counting algorithm. In Figure 6. (c) up, fractal dimension for real normal trabecular bone image is 1.7273, where the similarity fractal dimension obtained using box-counting algorithm on our NBN is 1.7993 in Figure 7. (a). In Figure 6. (c) down, fractal dimension for real osteoporotic bone image is 1.6173, where the similarity fractal dimension obtained using box-counting algorithm on our OBN is 1.6086.
4. CONCLUSION AND FUTURE WORKS

In this paper we develop and evaluate a novel 3D computational bone framework capable of providing: 1) spatio-temporal 3D microstructure bone model; 2) derived quantitative measures of 3D bone microarchitecture; 3) analysis of Bone Mineral Density (BMD) and bone strength. Our study provides an initial framework of developing the spatial component of such a modeling framework and demonstrating how bone microarchitecture, bone composition can be incorporated to obtain some experimental observations in bone biology to explore bone diseases such as osteoporosis.

So, the future works will be focused on a mechanistic understanding of bone microarchitecture and identifying topological network characteristics related to crack propagation characteristics and fracture risk. Using this systematical approach, we hope to provide insights into other clinical problems, such as neurological disorders and leukemia, by identifying the disease progression and prevention.

REFERENCES