ABSTRACT

As prevalence and awareness of osteoporosis increase and treatments of proven efficacy become available, the demand for management of patients with the disease will also rise. It calls for innovative research on understanding of osteoporosis and fracture mechanisms, allowing early and more accurate prediction of bone disease progression. The most widely validated technique for the diagnosis of osteoporosis is Bone Mineral Density (BMD) measurement based on dual energy X-ray absorptiometry (DXA). However, a major limitation of BMD is that it incompletely reflects the variation in bone strength. In this paper we develop and evaluate a novel three-dimensional (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 BMD and bone strength; and (4) A state-of-the-art probabilistic approach to analyze bone fracture risk factors including demographic attributes and life styles. Beyond efficient 3D bone microstructure representation, quantitative assessment is considered not only for identifying critical elements in bone microstructure, but also ensuring effective prediction of bone diseases in advance. The simulation network model of 3D bone microarchitecture and extensive empirical study on fracture risk improve our understanding of bone disease risk arising from the complex interplay of the human BMD assessment result with presence of major risk factors.

Categories and Subject Descriptors
I.6.3 [Simulation And Modeling]: Applications; I.6.4 [Simulation And Modeling]: Model Validation and Analysis; J.3 [Life and Medical Sciences]: Health; H.2.8 [Database Management]: Database Applications—Data Mining

Keywords
3D Microstructure Bone Model, Bone Mineral Density, Bone strength, Osteoporosis, Fracture Risk Factors, Bayesian Network.

1. INTRODUCTION

Osteoporosis, which is a systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue leading to enhanced bone fragility, has been recognized as an established and well-defined disease that affects more than 25 million people in the United States. 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. It requires widespread development of facilities for the diagnosis and assessment of osteoporosis. Traditional thinking on bone’s deterioration has focused on bone quantity-described by the bone mass or bone mineral density (BMD)-as a predictor of fracture risk[10, 4, 8, 16, 29]. The diagnosis of osteoporosis thus centers on assessment of BMD. With the efforts on diagnosis of osteoporosis, relationships between BMD and fracture risks have been widely studied[14, 27]. However, low BMD is actually not the sole factor responsible for the fracture risk. Other factors like bone microarchitecture, demographic attributes and life styles contribute to bone strength, and the evaluation of them can speed up determination of bone quality and strength[13, 11, 24, 15].

In this paper, we begin by introducing 3D bone microstructure modeling and validation methodology. Although bone is a simple composite of a mineral phase which is a calcium phosphate-based hydroxyapatite embedded in an organic matrix of collagen protein, its structure is highly complex. So we identify the important components and properties of bone microstructural units to develop a computa-
Table 1: Common Risk Factors for Osteoporosis

<table>
<thead>
<tr>
<th>Non-modifiable</th>
<th>Modifiable</th>
</tr>
</thead>
<tbody>
<tr>
<td>Older age</td>
<td>Low levels of calcium and vitamin D</td>
</tr>
<tr>
<td>Female gender</td>
<td>Reduced intake of vegetables and fruits</td>
</tr>
<tr>
<td>Family history</td>
<td>Sedentary lifestyle</td>
</tr>
<tr>
<td>Small frame or low body weight</td>
<td>Smoking</td>
</tr>
<tr>
<td>History of broken bones or height loss</td>
<td>Increased use of alcohol</td>
</tr>
</tbody>
</table>

2. METHODS

This section describes our methodology for 3D bone microstructure modeling and measurement, as well as the analysis of bone fracture risk factors.

2.1 Distribution of Bone-Forming Foci and Bone Mineral

The mean concentration of bone-forming foci $c(r)$ is expressed as the mean number of foci per unit area varied in the radial direction $r$ according to a Cumulative Normal Distribution (CDF):

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

where the mean and standard deviations of the underlying normal distributions are denoted by $\mu$ and $\sigma$, respectively, and $c_0$ is a constant of proportionality. We have assessed the ability of this equation to describe data by comparing with bone imaging. The values of $\mu$ and $\sigma$ can be estimated by the Nelder-Mead algorithm [26].

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 to a CDF:

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

where 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, and $w_0$ is a constant of proportionality.

2.2 Voronoi Tessellation and Edge Pruning

Voronoi tessellation is a mathematical procedure for creating a closed lattice of edges called Voronoi cells from a set of points or Voronoi sites [5].

We first generate a field of vertexes as the center of the bone mineral in the network model. The number of vertexes per unit area from the center to the boundary varies in the radial direction according to a CDF:

$$\lambda(r) = \frac{\lambda_0}{\sqrt{2\pi}} \int_{-\infty}^{r} e^{-\frac{z^2}{2\sigma^2}} dz,$$

where the mean and standard deviation of the underlying normal distribution denoted by $\mu$ and $\sigma$ are the same as...
those for the concentration on bone mineral in the continuum model, and \( \lambda_0 \) is a constant of proportionality.

The point distribution is converted to a network using the Voronoi tessellation method [7]. Voronoi tessellation converts a set of points into discrete regions containing of points that are closer to that point than any other points. 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 by Equation 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.

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 as defined earlier. The probability of deletion is an exponential function of the edge weight \( w_i \), which represents the level of bone mineral:

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

where \( w_{\text{max}} \) 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.

### 2.3 Expression for Bone Mineral

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

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

where \( w_i \) 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 \( \rho \).

A BMD test measures the density of minerals in people’s bones, which is the one most important component estimating the strength of bones. Traditionally, the BMD equation is:

\[
BMD = \frac{BMC}{W},
\]

where BMC stands for bone mineral content in the unit of \( g/cm \) and \( W \) stands for the projected area from DXA scan.

We develop a bone quality measurement using our 3D bone structure network model of bone dynamics. With the view of three dimensions, the bone model consists of nodes and edges which are represented by microscopic sphere shapes and microscopic cylinder shapes, respectively. Because the model inherits the nature of the network dynamic modeling properties, we can calculate the structural strength and network density of the bone model. The method gives us the measurements that possibly analyze the condition of the bone model which reflects the variation in bone strength and bone microstructure. Based on this model, we are able to assess the bone strength by the following computational BMD formula:

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

where \( m \) is the mean mass of bone mineral given by Equation 5 and \( A_p \) is the projected area of the bone segment, and the radius of projected area is denoted by \( R_0 \).

### 2.4 Expression for Area Moment

The area moment \( I_s \) 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 \( I_s \) 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:

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

where the value of the radius of gyration of the bone \( R_g^2 \) is obtained by dividing the area moment \( I_s \) by the cross-sectional area \( A \) for a circular section of bone:

\[
R_g^2 = \frac{I_s}{A} = \frac{I_s}{\pi R_0^2}.
\]

### 2.5 Bayesian Networks

After constructing the 3D model, we provide novel insights into understanding of a number of risk factors which are linked to the bone deterioration and may result in an individual’s likelihood of developing the bone fracture. Probabilistic graphical models (PGMs) are a marriage between the probability theories and graph theories that includes both directed graphical model and undirected graphical model. PGMs can be used to model complex probabilistic domain. One important task for PGMs is to find the assignment to each variable that jointly maximizes the probability defined by the model.

Bayesian networks (BNs) are a directed graphical model. The core of the Bayesian network (BN) representation is a directed acyclic graph (DAG) \( G \) whose nodes represent the random variables \( X_1 \) ... \( X_n \) and edges denote dependencies. Conditional Probability Distribution (CPD) for each node \( X_i \) describes \( P(X_i)\mid Pa(X_i) \), where the probability for each parent node of \( X_i \) is denoted by \( Pa(X_i) \). BN represents a joint distribution via the chain rule: \( P(X_1,...X_n) = \prod_i P(X_i)\mid Pa(X_i) \).

As a descriptive model, BN provides a complex joint distribution over a large number of random variables and each variable is directly influenced by only a few other variables. Meanwhile, it is also a flexible model to answer queries about causal reasoning, answer queries about diagnostic reasoning, and answer queries about arbitrary mixtures of the two forms of reasoning.

By modeling an entire joint distribution, BNs can answer any probability query, in particular, any query where we want to find the probability distribution over some variables given evidence about any other variables. In theory, doing inference in BNs is an NP-hard problem. However, the dependency structure from network representation can be exploited by inference algorithms. Also, there are some advanced inference algorithms which can handle with querying very large networks. Furthermore, the graph structure can assist us in inducing cause and effect, and thus understanding and reaching conclusions about the consequences of various risk factors in our specific domain.
3. MODELING OF BONE MICROSTRUCTURE

In this section, we first show the process of 3D bone network modeling in details and realizations of the bone model on DXA scan images. Since DXA scan is broadly used to calculate BMD, important properties of bone strength can be studied by analyzing bone density distribution and BMD of DXA scan images [28, 6]. We use a human femur bone image of DXA scan to analyze properties of the bone density distribution and BMD.

Figure 2 shows the process of DXA scan and results of scan images. From the DXA scan, x-ray images and BMD can be obtained and used as inputs of our mathematical bone network model. Figure 2(c) shows a femur bone image of a patient with osteoporosis by DXA scanning with which we can identify the density distribution of the femur bone. We can calculate the bone density distribution to the bone on the DXA scan images of two patients shown in Figure 2(f) [18, 19, 20, 21, 22, 23].

From BoneNET [23], parameters $\mu$ and $\sigma$ are estimated by minimizing the squared difference between the density distribution from a DXA scan image and the density distribution of the mathematical network bone model. By fitting the parameter values of the model to the density distribution of DXA scan image, the model can realistically reflect the mineral density in bone microstructure which is an important component of bone strength. Based on preliminary parameter study, we show the process of our 3D bone modeling in details and realizations of the bone model on DXA scan images.

In our previous research, one horizontal plane of our 3D bone microarchitecture model has been studied, which results in a 2D bone structure network [18, 19, 20, 21, 22, 23]. In our 3D 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. By stacking up hundreds layered two dimensional bone structure networks, we create a 3D bone structural network shown in Figure 3. The number of layers used in this model can be determined by the research purposes using the model. For example, when a measurement of quantitative BMD is conducted, the number of layers could be less than fifty for reducing computation time on the model. However, the number of layers is an important factor when the degree of bone strength by various forces is the major objective of the measurement. The length and thickness of the bone should be carefully measured before the bone microarchitecture model is created. The general procedure for obtaining a 3D model which represents the bone architecture contains: (1) generating thousands of two-dimensional bone random seeds based on CDF and distributing 3D points with varying radial density according to the CDF in a circular region in Figure 3(a),(b), (2) implementing Voronoi tessellation on 3D distributing points in Figure 3(c), (3) randomly pruning of extended to infinity Voronoi cells in Figure 3(e) after finding extreme vertices which are points on the boundary in Figure 3(d), (4) constructing 3D bone model surface using triangle representation in Figure 3(f), and (5) constructing Normal Bone Network (NBN) and Osteoporotic Bone Network (OBN) by pruning edges. The NBN and OBN construction results from front and top view are shown as Figure 4(a) and (b).
4. UNDERSTANDING FRACTURE RISK FACTORS USING PGMS

4.1 Structured Graphical Models

We extract 11 attributes including questions and prediction results in the FRAX tool \[1\] to construct variables for our Bayesian network in Figure 5. This Bayesian network structure has been designed and analyzed under the help of UB(University at Buffalo) Orthopaedics and Sports Medicine Erie County Medical Center. This is an example indicating the interactions between fracture risk factors (age, sex, body mass index, current smoking, extra alcohol intake, previous fracture, rheumatoid arthritis, secondary osteoporosis, parent fractured hip) and fracture risks (osteoporotic fracture, hip fracture). It provides a statistical model that can unveil and explore many interesting probabilistic dependencies that hold in this domain. For example, Figure 5 shows three potential evidences, osteoporosis, previous fracture and parent fractured hip, either of which may cause a patient to have hip fracture. Thus it can be used for answering queries about any aspect of the domain given any set of observations.

![Figure 5: Fracture risk factors Bayesian network.](image)

We then explore a direct inference method to answer queries such as \(P(X_i) | Pa(X_i)\). The main steps for this inference method include: (1) fixing a network to prepare for inference; (2) conditioning on the evidence; (3) computing the joint distribution and marginalizing out the non-query nodes efficiently; and (4) performing queries on the bone fracture risk BNs. Several observations from bone fracture risk BNs merit further fracture risk investigation and prediction. Figure 6 shows a simple Bayesian network with 7 attributes, together with the conditional probability tables, representing the dependency structure among the variables.

![Figure 6: The CPD for each factor in Bayesian Network.](image)

4.2 Problem Statement and Dataset

Suppose an instance space \(X = \{x_1, x_2, \ldots, x_n\}\), and label space \(Y = \{0, 1, 2\}\) for 3-class corresponding to low risk(L), medium risk(M) and high risk(H) for both major osteoporotic fracture risk and hip fracture risk. We take \(l\) entries as the training data \(X_{train} = \{x_1, \ldots, x_l\}\) and the rest entries as the testing data \(X_{test} = \{x_{l+1}, \ldots, x_n\}\). The task is to predict the labels of the testing data.

We collect the Fracture Risk dataset from the FRAX tool, which contains about 2000 instances and 11 observed variables. All patients are women in the age interval of 55 to 95. The patients’ questionnaire result includes osteoporotic fracture risk percentage and hip fracture risk percentage as shown in the FRAX tool. We also prefer datasets that have few or no continuous features to avoid information loss. We present an appropriate method to discretize multivariate continuous data as follows. We focus on women and men over age 50 and so we divide age interval by index from 0 in Table 2. Body mass index (BMI \(kg/m^2\)) computed from height and weight can be regarded as a risk factor. Since low BMI will lead to an increased risk of fracture, we give the following definition and transfer to binary value to present normal or low BMI from weight and height. Normal BMI = 25.0 \(kg/m^2\) is based on average height of 163 cm (64.17 in) and weight of 66.5 kg (146.61 lb). And low BMI = 21.2 \(kg/m^2\) is based on the average height of 163 cm (64.17 in) and weight of 56.7 kg (125 lb) in Table 3. Osteoporotic frac-

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### Table 2: Age Interval

<table>
<thead>
<tr>
<th>Age</th>
<th>Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>50-54</td>
<td>0</td>
</tr>
<tr>
<td>55-59</td>
<td>1</td>
</tr>
<tr>
<td>60-64</td>
<td>2</td>
</tr>
<tr>
<td>65-69</td>
<td>3</td>
</tr>
<tr>
<td>70-74</td>
<td>4</td>
</tr>
<tr>
<td>75-79</td>
<td>5</td>
</tr>
<tr>
<td>80-84</td>
<td>6</td>
</tr>
<tr>
<td>85-89</td>
<td>7</td>
</tr>
<tr>
<td>90-95</td>
<td>8</td>
</tr>
</tbody>
</table>

### Table 3: BMI Interval

<table>
<thead>
<tr>
<th>BMI</th>
<th>Index</th>
</tr>
</thead>
<tbody>
<tr>
<td>greater than 21.2</td>
<td>0</td>
</tr>
<tr>
<td>less than or equal to 21.2</td>
<td>1</td>
</tr>
</tbody>
</table>
ture risk percentage and hip fracture risk percentage should also be transformed into low, medium and high risk level based on the guideline provided in [17].

4.3 Answering Queries

We now wish to use our BNs to answer probability queries about unknown individuals. Table 4 and Table 5 show examples of estimating the probability of osteoporotic fracture (OST) and hip fracture risk (HIP) in US Caucasian white women, given the observations from the following factors: age(A), sex(S), body mass index(BMI), current smoking(CS), extra alcohol intake(AL), previous fracture(PF), rheumatoid arthritis(RA), secondary osteoporosis(SO) and parent fractured hip(PFH). We note that all of the random variables except age and fracture risk are binary, where the value “1” represents positive and “0” otherwise. For example, the patient is in the age bucket No.3 (65 to 69 years old from Table 2) and other factors are all positive, then our BNs return estimations that the fracture risk is high for both fracture risk cases (the value of prediction “2” has the largest possibility which corresponds to high risk level defined by Problem Statement in Section 4.2).

4.4 Classification Framework

For the fixed directed graphical model as shown in Figure 5, we assume that the age is the root node in the network. The learning of each node is done by computing the full joint distribution over the variables in a network, and then marginalizing out irrelevant variables. We use rudimentary inference engine for BNs. The classification of each case in the test set is done by choosing, as class label, the value of class variable that has the highest posterior probability, given the instantiations of the feature nodes. The classification accuracy is defined as the percentage of correct predictions on the test sets using a 0-1 loss function that measures the full penalty for wrong decisions and no penalty otherwise.

The accuracy on each number of observed variables is an average result. For example, we randomly choose three variables from six given variables in total if only three of them are observed. We then repeat 20 times. Figure 7 shows that predicting hip fracture is tougher than osteoporotic fracture, especially when only a limited number of clinical risk factors are found. Furthermore, patients do not need to provide all evidence to predict their fracture risk, while the accuracy increases as the number of known variables increase. As we expect in Figure 7, the more you know about a patient’s risk factors, the more accurately you can predict the fracture risk.

5. MEASUREMENTS OF BONE QUALITY

In this section, we design mathematical measurements of bone quality from biological, mechanical and geometrical perspectives. And we validate both bone networks NBN and OBN as shown in Figure 4 using these measurements.

5.1 Measuring Bone Strength Based on BMD and MOI

A projected area density, referred to as BMD, is normally calculated to assess regional bone density and strength defined by Equation 7. We investigated the effect of BMD on both bone networks NBN and OBN in Figure 4. We manually set up BMD to a unit by BMD test result according to the WHO (World Health Organization) T-scores report. For both NBN and OBN, we solve bone mineral density coefficient ρ in Equation 7. The larger ρ is, the denser bone network, and vice versa.

We also evaluate the overall strength of the 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 8 defines area moment, and the area $\delta a_i(r)$ can be regarded as the cross-sectional area of edge given by Equation 7, because it defines the BMD. Equation 9 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 $\vec{k}$ as well as the orientation of cross section $\vec{d}_i$.

\[
MOI = \sum_e w_i R_i^2 \cos \theta = \sum_e w_i R_i^2 \frac{d_i}{d_i \cdot \vec{k}},
\]

where $R_i$ is the distance from projected area center to object center.

From Table 6, we can intuitively find that NBN is healthier than OBN because NBN is denser and has better resistance from outer force than OBN.

5.2 Measuring Bone Cross-Sectional Geometry
Fractals are geometric structures that can be used to analyze our trabecular bone structures [2, 25, 9]. Most people are familiar with the topological dimensions such as 1-, 2-, or 3-spatial-dimensions. 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 [2]. 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 [3] is applied to calculate the fractal index of trabecular bone on real DXA image and bone network cross-sectional image. Fractal dimension results are the negative value of the slope of the line relating the natural logarithms of the number of boxes containing contour and each corresponding box size. We match our NBN and OBN to normal bone trabecular architecture and osteoporotic bone trabecular architecture by fractal dimension calibration as shown in Figure 8 using ImageJ tools [9]. Figure 8 left part presents the result of DXA image fractal analysis. We obtain DXA image for both healthy bone and osteoporotic bone and then calculate fractal dimension on both case. Then we process our 3D model part. We first project our 3D model to a compressed 2D image and then calculate the fractal dimension as shown in the right part of Figure 8. The objective is to match the real image fractal dimension with our 3D bone model. The 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. The 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.

6. CONCLUSIONS AND FUTURE WORKS

In this paper, we first developed and evaluated a novel 3D computational bone framework, which is capable of enabling quantitative assessment of bone micro-architecture, bone mineral density and bone’s deterioration. We simulated and analyzed the microstructure of human normal bone network and osteoporotic bone network with different bone loss rate. We then sought to learn relationships between surveyed/self-reported life styles and predicted bone loss rate determined by 3D bone remodeling. We used Bayesian models to analyze bone fracture risk based on demographic characteristics and life styles. This probabilistic graphical model can also answer fundamental questions about fracture risk such as: Are certain life styles more harmful than others? What are the most influential factors to bone fracture deterioration? As a result, people might start to cease drinking alcohol and smoking to protect their bone health. Finally, we designed the measurements in biological, mechanical and geometrical domains to validate our model. The validation results clearly demonstrated our 3D bone model is robust to reflect the properties of the bone microstructure in the real world.

In the future work, we are more interested in a bone-like model representing the arbitrary shape of a real bone sample, which might provide more details such as soft material and hard material in bone microstructure. Moreover, we will try to learn a dependency structure of a Bayesian network automatically if we can collect heterogeneous dataset from distributed sites. For the validation part, we will measure our bone model from some mathematical analysis of bending and buckling parameters of bone structure based on our current mechanical validation approach. Ultimately, this study would provide new insights to the understanding and prediction of bone diseases, such as osteoporosis.

7. REFERENCES
