A Graph-based Approach for Computational Model of Bone Microstructure

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ABSTRACT

Osteoporosis, a condition in which bones become fragile and more likely to break, can greatly affect our health. Nearly half of all women now age 50 will someday have a broken bone due to osteoporosis. The diagnosis of osteoporosis is commonly done by tests that measure the amount of bone mass and predict the risk for fracture. However, the currently available techniques for the diagnosis of osteoporosis are limited due to the lack of good measurements of bone quality.

In this paper, we develop a graph approach to bone microstructure model, which is capable of enabling quantitative assessment of bone mineral density and bone microarchitecture. Our paper focuses on microstructural bone modeling and quantitative characterization of the quality and fractural risk based on the microscopic bone structure. First, we illustrate the process of development on a three-dimensional bone structure model whose properties are similar to those of bone microarchitecture. Next, we list problems of the current measurements of bone strength and quality based on bone mineral density (BMD). Last, we introduce our measurements to quantitatively assess bone quality based on the bone model.

1. INTRODUCTION

Osteoporosis - a systemic skeletal disease characterized by low bone mass and microarchitectural deterioration of bone tissue leading to enhanced bone fragility and a consequent increase in fracture risk - afflicts an estimated 25 million people in the United States [27]. In addition, osteoporosis accounts for approximately 1.5 million new fractures each year, with associated medical charges including rehabilitation and extended treatment facilities of an estimated $10 billion, according to the National Osteoporosis Foundation. Because osteoporosis affects primarily the elderly, the National Osteoporosis Foundation estimates that these costs will increase to $200 billion by the year 2040, as the number of Americans over the age of 65 years grows [2].

Traditional thinking on bone’s deterioration has focused on bone quantity - described by the bone mass or bone mineral density - as a predictor of fracture risk. Measurement of bone mineral density (BMD) has been the central component of any provision that arises from osteoporosis [5]. The diagnosis of osteoporosis thus centers on assessment of bone mass and quality. Except this method, there is no satisfied clinical mean to assess bone quality. Diagnosis of osteoporosis, therefore, mainly depends on the measurement of bone mass until now.

As the efforts on diagnosis of osteoporosis, relationships between BMD and fracture risks have been studied. A study shows BMD of the low hip was an important predictor of fracture risk based on the estimation in a meta-analysis of data from 12 cohort studies of 39,000 men and women [14]. Techniques to accurately assess bone mineral mass in vivo are well established [21]. Current clinical prediction of fracture risk is therefore based primarily on bone mass alone. Nevertheless, a clearer understanding of the role played by bone microstructure in conjunction with bone mass is important for ultimately dealing, as effectively as possible, with bone loss disorders, particularly osteoporosis.

Many evidences show that low BMD is not the sole factor responsible for the fracture risk. A study by Sui Hui provided that aging causes 10 times increase in fracture risk regardless of BMD [12]. Garnero also showed that the increase in BMD might not always give sufficient information to treat patients [6]. This result supports that BMD alone cannot explain therapeutic benefits of antiresorptive agents in treating osteoporosis.

Bone structure is highly complex even thought bone is a simple composite of a mineral phase. As the result of that, the microstructure of bone have been studied to understand strength and quality of bone. Several structural approaches have been done to overcome the shortcoming of BMD. Since computing power has been doubled by every one and a half years, computer simulations of bone remodeling are attempted to correlate discrete physiological events with observed changes in bone morphology [26]. Although producing useful results, these previous simulations are essentially...
based on one-dimensional models, and therefore do not account for the interconnected trabecular structure of cancellous bone or the distribution of remodeling sites that can be only shown in the two-/three-dimensional structure. So several studies have worked on developing a simulation that is based on a two-/three-dimensional structural model of cancellous bone which allows for the occurrence of trabecular perforation, a naturally occurring event. Extensive studies on structural approaches are done [24, 15, 1]; however, these studies have not incorporated both biochemical reactions of bone remodeling mechanism and BMD of previous measurements into a computer simulation model.

2. BACKGROUND

Networks are encountered in a wide variety of contexts, such as social networks, circuit networks, networks of neurons, and terrorist networks. Most of the real world relationships and cooperations among any kinds of objects could be represented by networks. Specifically, many types of biological networks exist, which could be depicted as networks. Bone modeling is one of the most exciting but challenging research area in terms of network modeling.

![Figure 1: (a) The image of human femur bone and the microscopic view of a bone structure are shown. (b) The two-dimension structural bone network model and the microscopic view of the bone model are shown.](image)

As shown in Figure 1(a), bone is not a uniformly solid material, but rather has some spaces between its hard elements. There are two different bone types, one is cortical bone and the other is trabecular bone. Cortical bone is the hard outer layer of bones which is composed of compact bone tissue, so-called due to its minimal gaps and spaces. This tissue gives bones their smooth, white, and solid appearance, and accounts for 80% of the total bone mass of an adult skeleton. Filling the interior of the organ is the trabecular bone tissue (an open cell porous network also called cancellous or spongy bone), which is composed of a network of rod- and plate-like elements that make the overall organ lighter and allowing room for blood vessels and marrow. Trabecular bone accounts for the remaining 20% of total bone mass but has nearly ten times the surface area of compact bone. Figure 1(b) shows our network model which mimics the properties of cortical bone and the trabecular bone based on the different densities from the center to edge.

The standard and routine approach for the diagnosis of osteoporosis is to assess bone mineral density (BMD) using either dualenergy X-ray absorptiometry (DXA) or quantitative computed tomography (QCT). The estimated BMD has shown to be a suitable predictor of fracture risk. However, major limitations of bone mineral densitometry are that it incompletely reflects variation in bone strength and that differentiation of patients with and patients without vertebral fractures is inaccurate [16, 23]. Other factors like bone microarchitecture contribute substantially to bone strength and their evaluation can improve determination of bone quality and strength [23, 13]; yet structural assessment has not been implemented in clinical routine because of a lack of computational bone model. Furthermore, although recent studies have demonstrated the relative importance of architecture and mass as determinants of bone strength, architectural assessment techniques are significantly less developed [25]. Several studies show that accurate prediction of bone strength using BMD alone is very challenging [17].

3. MODEL OF BONE MICROSTRUCTURE

To overcome the lack of measurements of bone quality, we study the problem in a new direction. We develop a microscopic graph-based approach of a bone structure, a computational network model of bone microstructure which is capable of enabling quantitative assessment of bone mineral density, bone microarchitecture, and fracture risk. This study will find valuable methods and measurements on the quantification of bone quality and prediction of bone fracture risks. In what follows, we describe the process of microstructural bone modeling in details.

Based on the bone microstructure, we model a three-dimensional bone microarchitecture network as shown in Figure 2. When we develop 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 structural properties. We focused mineralized collagen fibers as important components from the bone cellular structure point of view.
is a set of nodes and $E$ is a set of edges, $E \subseteq V \times V$, an edge $e = (i, j)$ connects two nodes $i$ and $j$, $i, j \in V$, $W(e)$ is a weight of edge $e$, $e \in E$. An edge in a bone network represents a rod-like bone mineralized fiber and a node in a bone network represents a fiber binding point with which bone cells move and interact with neighboring bone tissues.

As the first step of our modeling process shown in Figure 3(b). The density of points in our model follows an exponential distribution $E(x) = \int_{1}^{\lambda x^{-\lambda - 1}} \lambda x^{-\lambda - 1} dx$, where $\lambda$ is a density slope coefficient and $x$ is the density of mineralized fibers in a $1\text{mm}^2$ area of bone sample images. Next, a bone microstructural network is created shown in Figure 3(c) as a representative of mineralized fibers which are one of the important structural components for bone strength. Based on Voronoi sites, we calculate expected area occupied by each Voronoi site using Voronoi tessellation.

In the next two steps shown in 3(d) and (e), Voronoi sites are removed and randomly selected rods are also removed to pattern properties of bone microstructures. The method of rods deletion step can be adjusted by different study purposes. In this study, two dimensional bone structures are generated by the model whose edges are randomly removed by 6%, 6% and 20% of edges, respectively. In Figure 3(f), different strengths of mineralized fibers are applied to represent the characteristics of trabecular and cortical bone. For simplification of the model, we use a linear function to generate differences on two types of bone structure.

Base on the two dimensional bone model, we can generate a three dimensional bone structure. To generate a three dimensional bone structure, the same processes of two dimensional bone model are applied except 3D Voronoi tessellation process. Instead of generating Voronoi sites in two dimensional circular region, Voronoi sites are generated in three dimensional cylinder area shown in Figure 4(c) and (d). A node and an edge in three dimensional bone structure are shown in Figure 4(c) and (d).

Since this bone model is developed based on image analysis of microscopic figures of bone, properties we have used in this model would not be reliably measured. To make this model more realistic, accurate input data are required, such as density of fibers, average thickness of fibers, and average length of fibers. However, well-understood knowledge with this type of a study would be valuable in the prediction of the bone fracture risk. In the following section, we address existing measurements of the bone quality evaluation and we formulate new measurements of bone quality based on the microstructural bone network.

### 4. Measurements of Bone Quality

A BMD test measures the density of minerals (such as calcium) in your bones, which has been the most important component estimating the quality of your bones. There are several ways to measure BMD. First, dual-energy X-ray absorptiometry (DEXA) is the most accurate way to measure BMD. It uses two different X-ray beams to estimate bone density in your spine and hip. Strong, dense bones allow less of the X-ray beam to pass through them. The amounts of each X-ray beam that are blocked by bone and soft tissue are compared to each other [3]. Second, peripheral dual-energy X-ray absorptiometry (P-DEXA) is used as a type of DEXA test. P-DEXA is not as useful as DEXA for finding out how well a medicine used to treat osteoporosis is working [7].
Third, dual photon absorptiometry (DPA) test uses a radioactive substance to measure bone density [8]. Fourth, ultrasound test is generally used to look for problems. Ultrasound uses sound waves to measure BMD, usually in your heel. Ultrasound is quick, painless, and does not use potentially harmful radiation like X-rays. One disadvantage of ultrasound is that it cannot measure the density of the bones most likely to fracture (the hip and spine) from osteoporosis. It is not used to keep track of how well a medicine used to treat osteoporosis is working [20]. Last, quantitatively computed tomography (QCT) is a type of CT scan that measures the density of a bone in the spine (vertebra). QCT is not usually used because it is expensive, uses higher radiation doses, and is less accurate than DEXA, P-DEXA, or DPA [10].

The previous measurements of bone strength based on BMD have been extensively investigated [9, 20]. However, major limitations of BMD are that it incompletely reflects variation in bone strength and bone microstructure. Based on this method gives us a measurement that possibly analyzes and edges and the relationship among nodes. The following information of network such as the number of nodes and edges, and the density coefficient, respectively. Since every single rod-like microstructure in bone affects the strength of the annular region of the bone structure, the number of neighboring node and then it visits the most dense node among neighboring nodes. The following method gives us a measurement that possibly analyzes the condition of the bone network which reflects variation in bone strength and bone microstructure. Based on this model, we are able to assess the bone strength by the quantitative BMD (QBMD) via

\[
QBMD = \sum_{i=1}^{n} r_i^2 l_i \rho
\]

Figure 5: A diagram for the algorithm of Connectivity-first Scan (CFS) is illustrated. (a) CFS starts from the node \( \nu \) (b) CFS visits the next node with \( \text{Max}(\sum_{i=1}^{l} \varepsilon_i) \) among neighboring nodes. (c), (d) and (e) Execute (a) and (b) until a priority queue (the candidate node list) is empty. (f) Stop node visits and return the scanned path as a result.

**Algorithm 1 Connectivity-first Scan\( (s, \nu, G) \)**

1. \( G \): a space-sensitive graph \( G \) of a bone network
2. \( \nu \): a node as a conjunction point among rod-like microstructures
3. \( s\): \( \nu \) with the minimum value of \( \sum_{i=1}^{l} \varepsilon_i \) such that
4. \( l \): is the number of edges directly connected to \( \nu \),
5. \( \varepsilon \): is the thickness of edge, and the \( \nu \) is the length of edge
6. \( n \): the neighbor node directly connected to \( \nu \)
7. \( \nu \): = \( s \)
8. \text{repeat}
9. Add every \( n \) of \( \nu \) into a priority queue, \( C \)
10. \text{Pop} \( n \) from \( C \)
11. \( \nu = n \) and set visit\( (n) = \text{true} \)
12. Add \( \nu \) into the visited list, \( V \)
13. until isNotEmpty\( (C) \)
14. Return \( V \)

Existing measurements are mostly focused on measuring BMD and predicting overall bone health, which cannot provide the strength of the certain area of bone. Based on our bone model, we can profile the condition of a bone network structure by the following algorithm with which we can analyze a high fractural risk area of the bone structure. We introduce Connectivity-first Scan (CFS) algorithm, modifying the best-first search graph theory algorithm [11]. It is the greedy network path search algorithm which works greatly for finding high probability fracture area in our bone network. It is adapted from the best-first search algorithm that explores a graph by expanding the most promising node chosen according to a certain rule [22].

The CFS process starts from the least dense microstructure node and then it visits the most dense node among neighboring nodes by the rule shown in Figure 5 and Algorithm 1. The CFS selects the first-visit node based on \( \text{Min}(\sum_{i=1}^{l} \varepsilon_i) \) where \( l \) is the number of edges directly connected to \( \nu \), \( \varepsilon \) is the thickness of edge, and \( \nu \) is the length of edge. \( \sum_{i=1}^{l} \varepsilon_i \) of every neighboring node \( n \) is calculated and the node \( n \) with \( \text{Max}(\sum_{i=1}^{l} \varepsilon_i) \) among all neighboring nodes is set to \( \nu \) which is the next visit node. A priority queue was used for (unvisited) nodes sorted by \( \sum_{i=1}^{l} \varepsilon_i \).

<table>
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<tr>
<th>Sample</th>
<th>QBMD</th>
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<tbody>
<tr>
<td>1</td>
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</tr>
<tr>
<td>2</td>
<td>10.38</td>
</tr>
<tr>
<td>3</td>
<td>6.79</td>
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Table 1: QBMD of three samples

To evaluate QBMD and CSF, we generated the three different bone networks based on the bone model shown in Figure 6. For the computational simplicity, two-dimensional bone networks were created on the 1x1 annular region consisting of 6248 nodes and 9509 edges. Figure 6(a), (b) and (c) repre...
Figure 6: The bone network is created which consists of 6248 nodes and 9509 edges. (a) The healthy condition of bone model is shown. There is no glitch on the plot for the normal status of bone model. The sudden increments at around 5500 of $V$ are due to the outside concrete area of the bone network. (b) 6% of bone structure is deteriorated comparing the healthy condition of bone model. The plot shows glitches at the beginning of the result and spikes at the end of the result. The sudden increments at around 4500 of $V$ are the same reason of (a). (c) 23% of bone structure is deteriorated comparing with the healthy condition of bone model. The plot clearly shows glitches and spikes at any points.

In this study, no evaluation method is introduced for computing between our measurements, QBMD and CFS, and the density measurement in practice, BMD. However, it would be an useful theoretical testing framework of bone microstructure to analyze bone structural properties if accurate input data and evaluation processes are available. In addition, this study could be an initial step for further studies on quantitative analysis of bone microstructure and bone quality.

5. CONCLUSION AND FUTURE WORK

We have presented a network model of bone microarchitecture and developed a three-dimensional bone structure model. We introduced the measurement of bone quality based on the bone network model, QBMD, with which the overall bone strength and quality can be analyzed. We also provided the profiling method of bone network, CFS, to analyze a high fractural risk area of the bone structure.

Properties we have incorporated in this model, such as the number of nodes and the weight of edges representing different densities of trabecular and cortical bone, would not be reliably ascertained. Prompt and proper information obtaining from high-quality orthopaedic data is critical for accurate predictions to reduce these uncertainties. However, well-understood knowledge with this type of the model would be extremely valuable in the prediction of the bone fracture risk and the analysis of the bone quality. A feasible strategy on diagnosing the bone using a computational bone model could offer potential for better understanding the bone quality.

The analysis of dynamics on network models has been broadly used for understanding many structural connections and relationships. A study based on the network model shows the defensive effectiveness on network dynamics by damage isolation of strategic self-destruction [19]. Another example of studies on dynamics is the evolution and the hypothetical containment of Avian Influenza outbreak [18]. A network dynamics model on bone remodeling is also one of the interesting but challenging research area because bone is a dynamic and living tissue whose structure and shape continuously adjusts to mainly provide structural framework.

In the future work, we will develop a mathematical model of bone dynamics based on this bone network model. This will be enabling understanding of bone related diseases, such as osteoporosis, as well as bone remodeling processes. Moreover, it will be useful for a theoretical testing framework of bone dynamics to conduct analysis of drug effects.

Eventually, this study will provide new ways to the treatment of bone diseases, such as osteoporosis. By simulating osteoporosis effects, our model can show the microarchitectural bone development of osteoporosis and the effect of existing and new drugs, which has a direct impact on women’s health. Moreover, the simulation paradigm developed in this project may serve as guides in identifying pertinent animal experiments and developing timely clinical preventive and therapeutic programs. Finally, our model can be potential to lend insights into other medical problems, such as neurological disorders and leukemia, by identifying the disease progression and prevention.
6. REFERENCES


