Towards Mouse Bone X-Ray Microscopy Scan Simulation

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Abstract. Osteoporosis occurs when the body loses too much bone mass, and the bones become brittle and fragile. In the aging society of Europe, the number of people with osteoporosis is continuously growing. The disease not only severely impairs the life quality of the patients, but also causes a great burden to the healthcare system. To investigate on the disease mechanism and metabolism of the bones, X-Ray microscopy scans of the mouse tibia are taken. As a fundamental step, the micro-structures, such as the lacunae and vessels of the bones, need to be segmented and analyzed. With the recent advances in the deep learning technologies, segmentation networks with good performance have been proposed. However, these supervised deep nets are not directly applicable for the segmentation of these micro-structures, since manual annotations are not feasible due to the enormous data size. In this work, we propose a pipeline to model the mouse bone micro-structures. Our workflow integrates conventional algorithms with 3-D modeling using *Blender*, and focuses on the anatomical micro-structures rather than the intensity distributions of the mouse bone scans. It provides the basis towards generating simulated mouse bone X-Ray microscopy images, which could be used as the ground truth for training segmentation neural networks.

1 Introduction

Osteoporosis means "porous bone", and is a systemic skeletal disorder. Under a microscope, a bone looks like a honeycomb, where healthy bones have small holes, and osteoporotic bones have large ones. The loss of bone mass weakens the bones and makes bones prone to breaking. Osteoporosis is the most common reason for bone fractures among the elderly [1]. From the macroscopic aspects, osteoporosis can be caused by hormone change, various diseases or medication treatments [2]. From the microscopic aspects, all osteoporosis cases are caused by an imbalanced bone resorption and formation process. Two types of cells are involved in this procedure: when the speed of bone matrix degeneration by

osteoclasts is faster than the regeneration by osteoblasts, bone mass loss and osteoporosis occurs. In the aging European society, osteoporosis is causing both pain to the patients and financial burden to the health care system [1].

To investigate on the metabolism and disease mechanism of bones, the mouse tibia which resemble human bones are utilized as the experimental targets. In one experiment protocol, the sample mouse bones are processed and scanned with the X-Ray Microscope (XRM) [3] to achieve huge data volumes with the resolution up to $0.7 \times 0.7 \times 0.7 \mu m^3$. Inside the bone mass, the lacunae where the osteoclasts and the osteoblasts dwell, and vessels which provide for the cells, are of our interest. Segmentation and further statistical analysis of the lacunae and vessels from the bones in the XRM data are crucial steps towards understanding the micro-structures and metabolism of the bones. With the recent advances of the deep learning technology, various successful segmentation networks have been proposed. However, supervised nets require labeled training data, which is unfeasible to obtain via manually annotation for our task.

In this work, we propose a pipeline to generate binary models of the mouse bone XRM data with the help of *Blender* [4]. The *Blender* is an open-source computer graphics software which can be used for 3-D modeling. Twelve mouse bone XRM datasets are provided to support the simulation procedure. Our pipeline consists of four main steps. Firstly, the shape of the bone is simulated using a combination of classical algorithms. Secondly, irregularly shaped bone cracks created using the *Blender* are indented onto the outer surface of the bone mass. Thirdly, the lacunae inside the bone mass are simulated by seeding several manually created primitives in random locations. Fourthly, the vessels inside the bone mass are simulated by placing manually modeled vessel primitives using a set of rules. The proposed pipeline is straight-forward and can grasp the characteristics of the bone micro-structures. The generated bone models make the fundamental step to simulate training data for supervised deep learning-based methods.

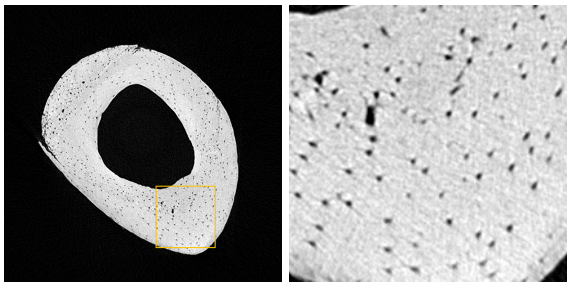
2 Materials and Methods

2.1 Database

A database composed of 12 X-Ray Microscopy (XRM) scans of the mouse tibia is provided. These scans are acquired on a Xradia Versa 520 XRM system. Among them, 6 bone segments are from healthy mice, and the other 6 are from osteoporosis mice. Each mouse tibia has the length of around 2 cm in real, while the XRM volume has the shape of $1980 \times 2024 \times 1999$ pixels with the isotropic resolution of $1.34\,\mu m^3$. The raw data is stored in 16 bit unsigned format, and each volume has the size of around 2 GB.

The XRM scans are used as the modeling targets for the simulation process. In this work we focus on the shape simulation of the mouse bone, thus the high resolution and intensity ranges of the scans are not demanded. To save memory and computation cost, a preprocessing pipeline is applied. Firstly, a Volume Of Interest (VOI) from each scan is extracted by a medical scientist to remove

both ends of the tibia which are not of interest and are often corrupted due to the cone beam artefacts. Secondly, the VOI is binarized using the Otsu's [5] threshold. Thirdly, the binarized VOI is automatically cropped into stacks of shape $1000 \times 1000 \times 200$ pixels. Note that the center of each stack is the weighing center of each bone segment, and we assume that the centerline of the bone segment is parallel to the z-axis within the 200 slices.



(a) (b)

Fig. 1. 2-D x-y slice from a healthy mouse XRM scan in (a), enlarged ROI in (b).

2.2 Simulation for Data Augmentation

In this work, we aim to generate bone shape models with the size of $1000 \times 1000 \times 200$ pixels. The simulation of the bone model is composed of four steps, namely bone shape modeling, bone crack indentation, lacunae simulation and vessel simulation. A combination of classical algorithms are used for bone mass simulation, while the *Blender* [4] is utilized for the bone crack, lacunae and vessel simulation process.

Bone Shape Simulation To obtain binary masks of the bone shape, the Gradient Vector Flow (GVF) [6] method is applied to obtain an anisotropically diffused gradient vector field such that the gradient vectors of the edge map can reach into non-informative homogeneous regions. Then the active contour model [6], which is also regarded as the *Snakes* algorithm is employed to extract the inner and the outer bone shape descriptors. Finally the Statistical Shape Model (SSM) [7] is trained to generate diversed new shapes.

The GVF method aims for an anisotropically diffused gradient vector field $\mathbf{v} = [u(x, y), v(x, y)]$ of the edge map ∇f by minimizing the energy function:

$$E = \int\int \mu(u_x^2 + u_y^2 + v_x^2 + v_y^2) + |\nabla f|^2 |\mathbf{v} - \nabla f|^2 \mathrm{d}x\mathrm{d}y. \tag{1}$$

Minimization of $(u_x^2 + u_y^2 + v_x^2 + v_y^2)$, requires the vector $\mathbf{v}$ to vary slowly; while minimization of $|\nabla f|^2 |\mathbf{v} - \nabla f|$ enforces the resulting field to resemble the gradient of the edge field, especially in regions with high edge responses.

The *Snakes* algorithm is employed to locate the points on the inner and outer contours of each 2-D slice of the mouse bone. A snake is a flexible 2-D discrete line c, and evolves towards the contours along the gradient directions in the GVF field by minimizing the following energy function:

$$E(c) = E_{\text{internal}}(c) + E_{\text{external}}(c) \tag{2}$$

$$E_{\text{internal}}(c) = \sum \alpha \left\| c' \right\|^2 + \beta \left\| c'' \right\|^2 \tag{3}$$

$$E_{\text{external}}(c) = \sum - \left\| \mathbf{v}(c) \right\|^2 . \tag{4}$$

The internal energy term E_{internal} is the weighted summation of the magnitudes of the first and second derivatives of the snake curve c, where α, β are the weighing factors. It controls the length and the curvature of the curve c. The external energy term E_{external} is the negative summation of the GVF field gradient magnitudes at the snake points. Minimization of E_{internal} constrains that the snake curve is short and smooth; minimization of E_{external} pushes the snake points towards the contours where the GVF field has the maximum values.

The *Snakes* algorithm keeps the order and the number of the initialized snake points, thus generates ideal inputs to train the SSM. On each 2-D x-y slice, 1 332 and 400 snake points are utilized to characterize the outer and inner contours respectively. In other words, each bone segment shape is represented as a $(1\,332 + 400) \times 200 \times 3 = 1\,039\,200$ dimensional shape descriptor $\mathbf{x_i}$. The mean vector $\overline{\mathbf{x}}$ of these descriptors is computed and the shape matrix $\mathbf{D}$ is constructed:

$$\overline{\mathbf{x}} = \frac{1}{N} \sum_{i=1}^{N} \mathbf{x_i} \tag{5}$$

$$\mathbf{D} = (\mathbf{x_1} - \overline{\mathbf{x}}, ..., \mathbf{x_N} - \overline{\mathbf{x}}). \tag{6}$$

Singular Value Decomposition (SVD) is then applied on the matrix $\mathbf{D}$ to obtain the eigenvectors ϕ and eigenvalues λ, which are then utilized to create models with new shapes:

$$\mathbf{x} = \overline{\mathbf{x}} + \mathbf{b} \cdot \phi \tag{7}$$

where $\mathbf{b}$ is the multiplicative factor with each element ranging from $-2\sqrt{\lambda_i}$ to $2\sqrt{\lambda_i}$.

Bone Crack Simulation Due to the preparing procedure of the tibia sample, the outer surface of the mouse bones often has cracks as shown in Fig. 1. Here we create indentations onto the outer surface of the bone mass with the help of *Blender*. Firstly, primitives for the cracks are created manually in *Blender* as presented in Fig. 2. The primitive templates are designed to be irregular and asymmetric such that the indented cracks are as diversed as possible. Secondly, 20 seeding points on the outer contour of the bone mass are randomly selected. Thirdly, for each position, a random primitive is chosen, rescaled and rotated within a certain range. Then augmented primitive is used as a structuring element to erode the bone mass.

Fig. 2. Bone crack simulation. Crack templates rendered in Paraview [8].

Lacunae Simulation In bone XRM scans, lacunae are represented as dark cavities that can be approximated using balls, ellipses, or combinations of them. Four particle primitives are designed in *Blender*, as presented in Fig. 3. In each generated bone mass segment, around $150\,k$ center point positions are selected according to prior anatomical knowledge. For each centering point, a lacuna primitive is chosen and augmented with random rotation and scaling.

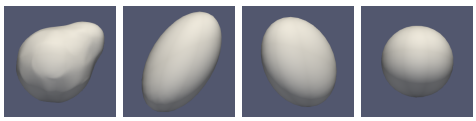


Fig. 3. Lacunae simulation. Lacunae templates rendered in Paraview [8].

Blood Vessel Simulation The blood vessels in the XRM stacks are modeled as tree branches with the *Sapling Tree Gen* plugin of *Blender*. In a 200-slice stack, the vessels have at most one bifurcation. Thus the sapling primitives are designed to have simple structures as shown in Fig. 4. We also contrain that two vessels are at least (100, 100, 20) pixels apart from each other, and should be roughly aligned, deviating i. e. maximum $\pm 30°$ from the direction of the bone axial. In a healthy bone segment sample, the number of unconnected vessels ranges from three to eight.

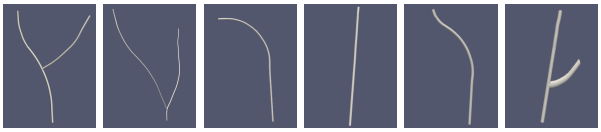
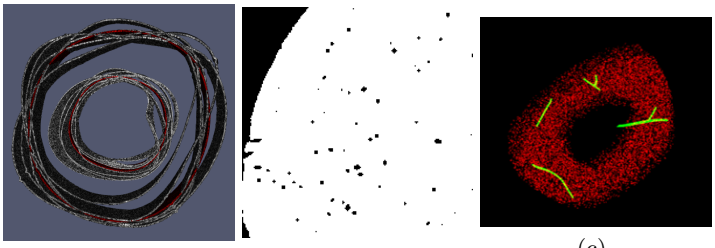


Fig. 4. Blood vessel simulation. Vessel templated rendered in Paraview.

3 Results

The inner and outer contour surfaces of the bone shapes simulated with different settings of the multiplicative factor $\mathbf{b}$ in Eq. 7 are rendered in *Paraview* [8], as shown in Fig. 5(a). The eigen contour surfaces when $\mathbf{b} = \mathbf{0}$ are highlighted in red

color. A patch from a 2-D slice of the simulation result is presented in Fig. 5(b), and the 3-D render of the color-coded lacunae and vessels is shown in Fig. 5(c).



(a) (b) (c)

Fig. 5. Simulated bone contours in (a), an example patch from a 2-D slice of a simulation result in (b), red lacunae and green vessels in (c). (a) rendered in Paraview [8].

4 Discussion

In this work, we propose a pipeline to model the mouse tibia segments and the micro-structures inside. We use the statistical shape model to generate bones of different shapes, and employ *Blender* to simulate the bone cracks, the lacunae and the vessels. Comparing the 2-D x-y slice of the simulation result in Fig. 5(b) and that of the the real XRM data in Fig. 1, a close similarity is observed. The proposed pipeline provides an approach to generate unlimited amount of binarized bone XRM masks, which make the fundamental step towards training data simulation for segmentation networks. In the future, domain adaptation approaches could be applied to train network models with the simulated data; more complicated primitives could be designed to model osteoporosis bones.

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