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Advanced Microscale Mouse Bone Marrow Dosimetry Using Nano-CT Data

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ABSTRACT

Purpose: In the rapidly developing field of radiopharmaceuticals, the skeleton poses a uniquely daunting challenge to any effort to safely employ these powerful tools. The skeleton's wide distribution throughout the body as well as its variability make dose difficult to estimate with current models such as the Mouse Whole Body (MOBY) phantom. Structures like red marrow and bone endosteum play leading roles in radiogenic risk of leukemia and bone cancer. The current method for estimating dose to this vital structure assumes homogeneity of trabecular bone. This is not accurate for short range particles like alphas and betas. Improved dosimetry methods in preclinical models are needed to better understand how to mitigate the risks involved in the use of radiopharmaceuticals. In order improve our understanding, our team has constructed microscale models of mouse bones directly from anatomical data obtained via a Nano-CT. Methods: 5 strain CD-1 mice, ages ranging from 4 weeks to 20 months were sacrificed and 32 selected bones from each individual were harvested. These bones were then scanned with a GE v|tome|x m 240 Nano-CT and their internal structures were assessed. From a combination of scan results and literature values, 3D tetrahedral meshes were constructed to represent these observations. These meshes were then distributed throughout the MOBY phantom's bone trabeculae and doses were simulated using the Particle and Heavy Ion Transport System (PHITS) Monte Carlo code. Results: Image-based trabecular bone and bone marrow were generated with resolution down to 10 µm at maximum. Dosimetry information with these new structures was also obtained. Conclusions: Microscale models of the mouse skeleton were generated directly from anatomical information, allowing for a more anatomically rigorous model of the mouse bone, and dosimetry results were generated. More work is required to determine if the more anatomically rigorous model is also more accurate.

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INTRODUCTION

Red bone marrow (RBM) and bone endosteum are two of the most important targets in bone dosimetry, as both are strongly linked to radiogenic leukemia and bone cancer.[1] However, the complexity of these structures has made accurate models of them difficult to produce until recently. With the gradual improvement of 3D image-based modeling, highly detailed tetrahedral models of bone microstructure have become not just achievable, but extremely useful, particularly for short-ranged decay products such as alpha and low-energy beta particles, where microns matter. Though the mouse is the most common human analogue in preclinical medicine, no detailed image-based models of the mouse skeleton exist for preclinical dosimetry, leaving researchers dependent on current homogeneous models of mouse trabecular bone. This assumption of homogeneity may be acceptable for external beam therapy, given the large distribution of dose relative to the size off mouse bones, but it is far less appropriate for the short-range decay products common in radiopharmaceuticals, potentially compromising the accuracy of dose calculations. In response, we developed models with a resolution of approximately 10 µm for bones within the mouse whole-body (MOBY) phantom,[2] constructed from scans of five CD-1 mice ranging in age from 24 weeks to 20 months.

METHODS AND MATERIALS

Five adult male CD1 mice with ages ranging from 24 weeks to 20 months were sacrificed, and their bones were cleaned of tissue via dermestid beetles. 32 separate skeletal sites were collected and preserved. These were then imaged by a GE v|tome|x m 240 and reconstructed into DICOM images. These slices were cleaned and segmented before being converted into a STL file via a MATLAB algorithm. 0.125 mm^3 cubes of spongiosa from each of the chosen skeletal sites were isolated. The bone image was used as a base for a 50 µm layer of endosteum and the remaining volume filled algorithmically with red bone marrow (RBM) and yellow bone marrow (YBM) in a triangulated mesh. This mesh was then tetrahedralized for use in the Particle and Heavy Ion Transport System Monte Carlo simulations. The mineral bone, endosteum, yellow marrow, and red marrow were defined either using literature data or ICRP 145[3] values adjusted for mice using equation (1):

$$\mathrm{m}_{\mathrm{Endosteum}}^{\mathrm{mouse}} = (m_{\mathrm{RBM}}^{\mathrm{mouse}} + m_{\mathrm{YBM}}^{\mathrm{mouse}}) \cdot \left(\frac{m_{\mathrm{Endosteum}}^{\mathrm{ICRP145}}}{m_{\mathrm{RBM}}^{\mathrm{ICRP145}} + m_{\mathrm{YBM}}^{\mathrm{ICRP145}}}\right) \quad (1)$$

Where m in the equation is the mass of each tissue at a bone site. Each region was then matched with a pre-generated bone marrow segment at the appropriate ratio for that specific bone site. S-values, and specific absorbed fractions were then calculated by equation (2):[4]

$$S(r_{\mathrm{T}} \leftarrow r_{\mathrm{S}}) = \sum_i E_i Y_i \Phi(r_{\mathrm{T}} \leftarrow r_{\mathrm{S}}, E_i) \quad (2)$$

Where E_i and Y_i are energy and yield of the i^{th}emission, $S(r_{\mathrm{T}} \leftarrow r_{\mathrm{S}})$ is the energy deposited in the target tissue per decay in the source, and $\Phi(r_{\mathrm{T}} \leftarrow r_{\mathrm{S}}, E_i)$ is the energy absorbed in the target tissue per decay of the i^{th}emission.

RESULTS

Figure 1 displays the result of our method of Nano-CT image processing to create a model. A 0.125 mm^3 cube of right femoral head bone trabecula was chosen as an example to demonstrate this. The model defines trabecular bone, red and yellow marrow, both inside and outside of the endosteum (shallow marrow). The models were adjusted to match age-specific values found in literature for the volume of each region if available and calculated to compensate for age if not. It was noted trabecular volume decreases and yellow marrow volume increases relative to the total volume with age. **Figure 2** displays the usage of such a model. Dosimetry is ongoing in this project.

Figure 1: Illustrated process of converting the Nano-CT image into a 3D model usable in Monte Carlo Dosimetry

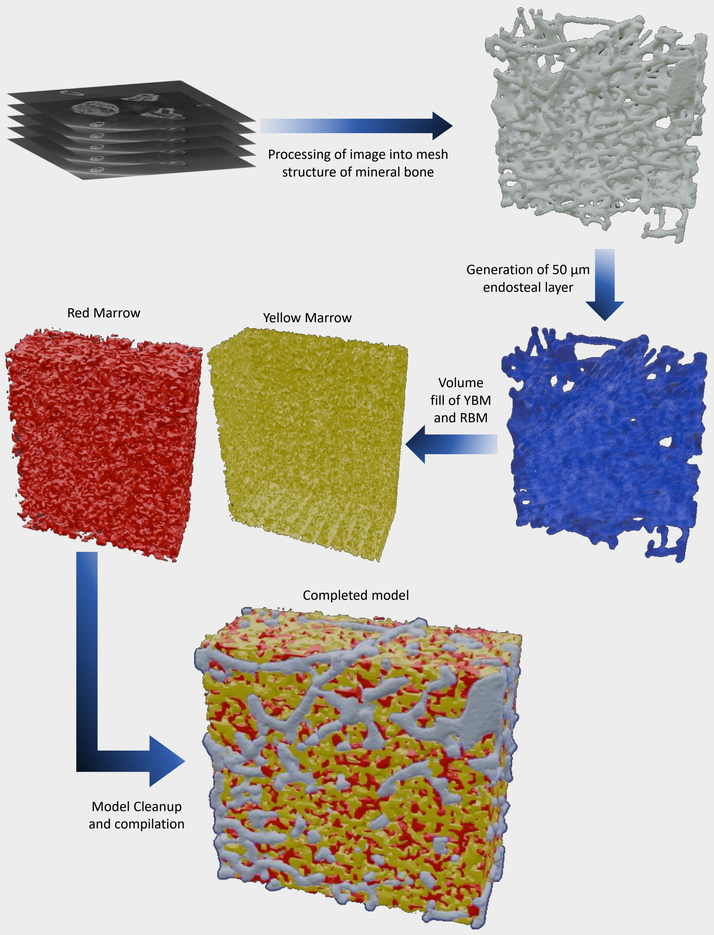
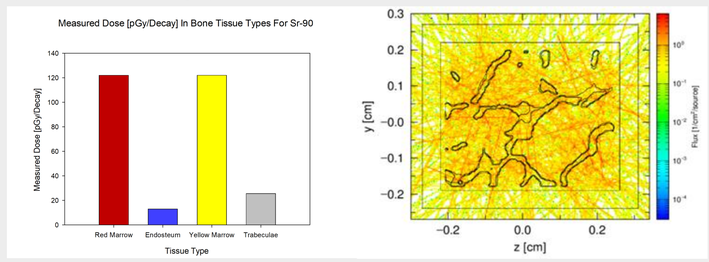


Figure 2: Graph showing use of completed models (left) and fluence track of that particle simulation (right).



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DISCUSSION

The skeleton remains a difficult system to assess dose in due to its high complexity and small structures. Yet, it is vital that we understand how dose is distributed, as some radionuclides have disproportionately large uptake in bone, possibly causing large RBM doses that result in marrow suppression and a host of associated negative patient outcomes. The methodology of this project represents a major step forward in efforts to understand dose distribution in bone marrow, particularly in the field of radiopharmaceuticals. The results of this project are still preliminary, but the feasibility of such models has been confirmed. The mouse models produced in this project should be of great help in assessing the effects of radiopharmaceuticals on bone marrow in preclinical models, well before they are ever used in humans. However, this project could be improved in several ways. First, all dosimetry work was done in male mice, requiring corrections for differences in bone volume ratio for application in female mice. Bone cellularity studies should also be conducted to confirm the accuracy of our conversion from ICRP 145. This project is being conducted in parallel with a similar effort to improve the Mesh-based Computational Reference Phantom (MCRP) in humans, from which most of this methodology was refined before being applied to MOBY. A logical next step after completion of all dosimetry work would be to repeat the process in other human analogs used in preclinical trials such as the rat.

CONCLUSIONS

This project has thus far developed a framework for determining bone marrow and endosteal dose, as well as a model for simulating radiation deposit distribution within tissues. No other model can claim this degree of detail of skeletal dose within mice. Development of this model is a leap forward in mouse phantom fidelity and produces a methodology for further transformation of other preclinical models so that they too are able to accurately assess microscale dosimetry in the skeletal system using modern advancements in imaging technology. However, more work is required to determine if the more anatomically rigorous model is also more accurate.

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