A Skeletal Reference Dosimetry Model for the Adult Female

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Introduction

• In order to predict the risk of bone cancer, an accurate assessment of absorbed dose to skeletal tissues is necessary.
• Acute affects
  – toxicity of hematopoietically active bone marrow
• Red bone marrow
  – hematopoietic stem cells (HSC)
    • Leukemia risk
• Trabecular endosteum
  – osteoprogenitor cells (OPC)
    • Bone cancer risk
• Both the skeletal endosteum and red bone marrow themselves serve as surrogate target tissues for underlying radiosensitive cell populations.
Bone Tissue

- **Remodeling**
  - *Maintain constant* $\text{Ca}^{2+}$ *and* $\text{PO}_4^{3-}$
  - *Mechanical stress*

- **Osteoporosis**
  - *Bone resorption > Bone formation*
  - *Most common bone disease in the United States*
Osteoporosis

- **Risk factors**
  - gender, age, body size, ethnicity, family history
  - lifestyle
- **Measured through bone mineral density (BMD)**
- **BMD (g/cm²)**
  - grams of calcium, other bone minerals

  - low BMD
    - low mineral content
    - less dense bones
    - weaker bones
Bone Imaging Dosimetry Aims

• Target tissue regions are used to determine absorbed fraction
  – Fraction of energy absorbed by the target tissue that was emitted by the source
  – Example: leukemia risk, target is red bone marrow

\[ S(r_T \leftarrow r_S) = \sum_i E_i Y_i \frac{\phi_i(r_T \leftarrow r_S)}{m_T} \]

• Optimize S value by making model specific to the patient
  – Account for patient skeletal size and percentage of active marrow

• MIRD absorbed dose estimate

\[ D(r_T \leftarrow r_S) = \tilde{A}_S \times S(r_T \leftarrow r_S) \]
Accurate Dose Estimates

- Accurate and patient specific models are needed for the best possible dose estimates.
  - Properly model the tissue of interest
    - concentration and distribution of stem and progenitor cells within the hematopoietically active marrow
  - Reliable, scalable, reference models
    - Build a dataset of varying individuals
Objectives

• Develop a comprehensive reference female subject for gender specific skeletal dosimetry.
  – For use in all aspects of radiation protection and medical dosimetry
    • Scalable to a patient
  – Normal Bone health
    • No cancer, normal BMI
  – Provide adjustable mass and absorbed fraction data
    • Account for macrostructure (skeletal size) and microstructure (marrow volume fraction)

\[
(m_{\text{TAM}})^x_{\text{UF-RF}} = (SV)^x_{\text{UF-RF}} \cdot (MVF)^x_{\text{UF-RF}} \cdot (CF)^x_{\text{Variable}} \cdot \rho_{\text{TAM}}
\]
Skeletal Dosimetry Modeling

• We cannot know the microstructure of the patient, nor can we guess the exact amount of energy deposited into a certain tissue beforehand.

• No female model to date
  – Osteoporetic state

• Current model uses multiple sources of data
  – Absorbed fractions → University of Leeds chord distributions
  – Marrow total mass and relative distribution → Mechanic (1926)
  – Reference marrow cellularities → Custer (1974)
  – Bone masses → Trotter and Hixon (1974)
  – Endosteal masses → Leeds S/V ratios & ICRP thickness of 10 μm
Improved Transport

• **Paired Image Radiation Transport (PIRT)**
  – Code developed through University of Florida Bone Imaging and Dosimetry (BID) group
  – Electron tracking through EGSnrc
  – voxel-based, three dimensional model

• **Macrostructure**
  – ex-vivo CT scan of an excised skeletal site
  – manually segmented trabecular spongiosa and cortical bone

• **Microstructure**
  – ex-vivo microCT scan of a cored section of spongiosa
  – 30 μm high resolution
  – segmented using a novel image-gradient approach
    • marrow volume fraction (MVF) obtained
    • full range of marrow cellularity
Paired Image Radiation Transport
Image Based Skeletal Dosimetry

- **Cadaver selection**
  - 64 yr female, 22.51 kg m$^{-2}$, no cancer
- **Whole-body CT imaging**
- **Bone site harvesting**
  - 13 major sites of adult active bone marrow
- **Ex-vivo CT imaging of each excised skeletal site**
  - Volume measurements
    - Spongiosa → combined tissues of trabeculae, endosteum, active and inactive marrow
- **Section skeletal sites – cubes of spongiosa**
- **Microimaging of spongiosa**
  - 30 micron resolution
  - Marrow Volume Fraction
Ex-vivo Volume Estimates

- **Femora**
  - MVF varies
  - Head
  - Neck
Detailed Volume Estimates

- **Cranium**
  - MVF changes drastically between lobes
    - Left Parietal
    - Right Parietal
    - Occipital
    - Frontal
    - Others
      - Ethmoid
      - Sigmoid
      - Temporal
    - Facial
Large Microstructural Differences

- **Cranium, frontal**
  - 40% marrow

- **Femora, head**
  - 71% marrow

- **Due to weight loading**
# Mass Within Trabecular Spongiosa Regions – Active Marrow Skeletal Sites

<table>
<thead>
<tr>
<th>Skeletal Site</th>
<th>Trabecular Spongiosa Regions</th>
<th>Cortical Bone Regions</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Spongiosa Volume (cm^3)</td>
<td>Marrow Volume Fraction</td>
</tr>
<tr>
<td>Os Coxae</td>
<td>407.65</td>
<td>0.87</td>
</tr>
<tr>
<td>Cervical Vert</td>
<td>31.67</td>
<td>0.78</td>
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<tr>
<td>Thoracic Vert</td>
<td>171.51</td>
<td>0.90</td>
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<tr>
<td>Lumbar Vert</td>
<td>151.47</td>
<td>0.91</td>
</tr>
<tr>
<td>Sacrum</td>
<td>83.25</td>
<td>0.96</td>
</tr>
<tr>
<td>Clavicles</td>
<td>25.94</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>13.63</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>12.32</td>
</tr>
<tr>
<td>Femora, proximal</td>
<td>205.94</td>
<td>0.81</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>257.82</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>152.06</td>
</tr>
<tr>
<td>Humeri, proximal</td>
<td>105.76</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>Right</td>
<td>*</td>
</tr>
<tr>
<td></td>
<td>Left</td>
<td>46.30</td>
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<tr>
<td>Scapulae</td>
<td>56.73</td>
<td>0.77</td>
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<td></td>
<td>Right</td>
<td>28.48</td>
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<td></td>
<td>Left</td>
<td>28.25</td>
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<tr>
<td>Sternum</td>
<td>30.59</td>
<td>0.99</td>
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<tr>
<td>Mandible</td>
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<td>0.89</td>
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<td>Ribs TOTAL</td>
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<td>0.93</td>
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<tr>
<td>Cranium</td>
<td>132.62</td>
<td>0.37</td>
</tr>
<tr>
<td>Facial bones</td>
<td>1.86</td>
<td>0.89</td>
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</table>
# Mass Within Trabecular Spongiosa Regions – Inactive Marrow Skeletal Sites

<table>
<thead>
<tr>
<th>Skeletal Site</th>
<th>Spongiosa</th>
<th>Marrow</th>
<th>Endostium</th>
<th>Trabecular Bone</th>
<th>Trabecular Bone</th>
<th>Cortical Bone</th>
<th>Cortical Bone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Volume (cm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>Volume Fraction</td>
<td>Volume Fraction</td>
<td>Volume Fraction</td>
<td>Mass (g)</td>
<td>Volume (cm&lt;sup&gt;3&lt;/sup&gt;)</td>
<td>Mass (g)</td>
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<tr>
<td>Femora</td>
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<td>0.25</td>
<td>0.13</td>
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<td>medullary cavity</td>
<td>42.84</td>
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<td>0.01</td>
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<td>*</td>
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<td>distal end</td>
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<td>Fibula</td>
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<td>0.13</td>
<td>7.15</td>
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<td>0.07</td>
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<td>3.76</td>
<td>8.00</td>
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<td>*</td>
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<td>0.07</td>
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<td>3.39</td>
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<td>Tibia</td>
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<td>0.07</td>
<td>0.13</td>
<td>60.71</td>
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<td>189.69</td>
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<td>medullary cavity</td>
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<td>0.01</td>
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<td>56.37</td>
<td>108.22</td>
</tr>
<tr>
<td>distal</td>
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<td>0.87</td>
<td>0.07</td>
<td>0.13</td>
<td>22.09</td>
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<td>Humeri</td>
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<td>2.55</td>
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<td>*</td>
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<tr>
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<td>26.83</td>
<td>0.95</td>
<td>0.03</td>
<td>0.05</td>
<td>2.55</td>
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<tr>
<td>Ulna</td>
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<tr>
<td>distal</td>
<td>2.97</td>
<td>0.95</td>
<td>0.03</td>
<td>0.05</td>
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<tr>
<td>Radius</td>
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</tr>
<tr>
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<td>3.98</td>
<td></td>
<td>0.02</td>
<td>*</td>
<td>*</td>
<td>20.86</td>
<td>40.04</td>
</tr>
<tr>
<td>distal</td>
<td>14.87</td>
<td>0.95</td>
<td>0.03</td>
<td>0.05</td>
<td>1.41</td>
<td>14.03</td>
<td>26.93</td>
</tr>
</tbody>
</table>
Comparison to ICRP 70/89 – 35 Year Old Female

<table>
<thead>
<tr>
<th>Subject Parameter</th>
<th>ICRP 70 35 y female Mass (g)</th>
<th>UF Reference Female Mass (g)</th>
<th>Difference %</th>
</tr>
</thead>
<tbody>
<tr>
<td>height (cm)</td>
<td>163</td>
<td>160</td>
<td></td>
</tr>
<tr>
<td>weight (kg)</td>
<td>60</td>
<td>61</td>
<td></td>
</tr>
<tr>
<td>BMI kg/m^2</td>
<td>22.58</td>
<td>23.83</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>35</td>
<td>64</td>
<td></td>
</tr>
<tr>
<td>Total Skeleton</td>
<td>7800</td>
<td>6587.96</td>
<td>18.40%</td>
</tr>
<tr>
<td>Bone</td>
<td>4000</td>
<td>3453.52</td>
<td>15.82%</td>
</tr>
<tr>
<td>Active Marrow</td>
<td>900</td>
<td>689.12</td>
<td>30.60%</td>
</tr>
<tr>
<td>Inactive marrow</td>
<td>1800</td>
<td>1345.33</td>
<td>33.80%</td>
</tr>
<tr>
<td>cartilage</td>
<td>900</td>
<td>900</td>
<td></td>
</tr>
<tr>
<td>miscellaneous</td>
<td>200</td>
<td>200</td>
<td></td>
</tr>
</tbody>
</table>

- Assume same cartilage and miscellaneous mass
  - Miscellaneous: teeth, periosteum, blood vessels
- Total Skeletal
  - Sum of bone, active marrow, inactive marrow, cartilage, and miscellaneous
**SAF’s for TAM$\leftarrow$TAM**

- **Specific Absorbed fraction calculated for TAM$_{50}$$\leftarrow$TAM**
  - *Surrogate for HSC population*
  - *All skeletal sites containing active marrow*
SAF’s for all Sources Irradiating the TAM

Repeated for TAM$_{50}$ as a target and all skeletal sites
SAF’s Comparing all Skeletal Sites

- Repeat for all source target combinations
Future Work

• Spatial distribution of blood vessels and hematopoietic stem and progenitor cells within the marrow cavities of human cancellous bone.
  – CD34+ and CD117+
  – Several skeletal sites

• Compare stem cell distributions for compromised marrow states
  – Pre and post-chemotherapy lymphoma patients
  – Better assess temporal status for radiation therapy
This completes my presentation - I would be happy to entertain questions at this time.