BONE FRACTURE PREDICTION USING COMPUTED TOMOGRAPHY BASED RIGIDITY ANALYSIS AND THE FINITE ELEMENT METHOD

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ABSTRACT

In this study two imaging modalities are proposed as a basis for fracture analysis in bone; Computed Tomography (CT) and Positron Emission Tomography (PET).

In the first part of this study, finite element analysis (FEA); CT based structural rigidity analysis (CTRA) and mechanical testing are performed to assess the immediate fracture risk of rat tibia with simulated lytic defects at different locations.

Twenty rat tibia were randomly assigned to four equal groups (n=5). Three of the groups included a simulated defect at various locations: anterior bone surface (Group 1), posterior bone surface (Group 2), and through bone defect (Group 3). The fourth group was a control group with no defect (Group 4). Micro computed tomography was used to assess bone structural rigidity properties and to provide 3D model data for generation of the finite element models for each specimen.

Compressive failure load was predicted using CT derived rigidity parameters ($F_{CTRA}$) and was correlated to failure load recorded in mechanical testing ($R^2=0.96$). The relationships between mechanical testing failure load and the axial rigidity ($R^2=0.61$), bending rigidity ($R^2=0.71$) and FEA calculated failure load ($R^2=0.75$) were also correlated. CTRA stress, calculated adjacent to the defect, were also shown to be well correlated with yield stresses calculated using the average density at the weakest cross section ($R^2=0.72$). No statistically significant relationship between apparent density and mechanical testing failure load was found ($P=0.37$).

In the second part of this study, Positron Emission Tomography (PET) and Computed Tomography (CT) imaging modalities were utilized to study the implementation of a bone remodeling rule for the study of future fracture risk.
Eight rats were inoculated with MDA-MB-231 human breast cancer cells at T0 to induce osteolytic lesions that simulate skeletal metastasis. Fluorine 18 ($^{18}$F) and fluoro-deoxy-glucose (FDG) PET and CT imaging were carried out weekly to correlate changes in local bone mineral density observed using CT, with radionuclide tracer uptake observed in $^{18}$F and FDG PET. Univariate relationships correlating pixel level density to standardized uptake values (SUV’s) were obtained ($R^2=0.4-0.72$). These relationships can be applied in assigning material properties in finite element models studying future fracture risk. Furthermore, a tumor induced bone remodeling rule could be developed to allow determination of future fracture risk associated with a baseline CT scan taken at time T0.

In summary, the results of this study indicate that CTRA analysis of bone strength correlates well with both FEA results and those obtained from mechanical testing. In addition there exist a good correlation between structural rigidity parameters and experimental failure loads. In contrast, there was no correlation between average bone density and failure load. Furthermore, the positron emission tomography (PET) imaging modality offers a promising method of studying future fracture risk using the finite element method.
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NOMENCLATURE

Chapter 4

F_{CTRA}, F_{MECH}, F_{FEA} The CTRA, mechanical testing and FEA based failure load (N)

$\varepsilon_{\text{CRITICAL}}$ The user specified critical strain which defines failure

EI Bending Rigidity (N.mm$^2$)

EA Axial Rigidity (N)

$I_{\text{min}}, I_{\text{max}}$ The moments of inertia associated with principal axis (mm$^4$)

$y$ Distance to neutral axis from center of curvature (mm)

d Distance from eccentrically applied load to centroidal axis (mm)

$q, q_{\text{BONE}}, q_{\text{APP}}$ Pixel level density, bone (equivalent/true), apparent density (g/cm$^3$)

$r$ The distance from the center of curvature to calculated stress (mm)

$R_n$ Radius, distance from center of curvature to neutral axis (mm)

$R$ Radius, distance form center of curvature to centroidal axis (mm)

$A_m$ Geometric parameter used in curved beam equation (mm)

$M_i$ Moment about principal axis (N.mm)

$N$ Eccentrically applied load, (N)

$A$ Cross sectional area (mm$^2$)

$b$ Distance from center of curvature to $i^{th}$ voxel center (mm)

c Distance to inner bound of voxel (mm)

$a$ Distance to outer bound of voxel (mm)

$\sigma_{\text{circ}}, \sigma_{\text{CTRA}}, \sigma_{\text{FEA}}$ The circumferential, CTRA and FEA stresses (MPa)

Chapter 5

$S_v$ Bone surface area density (mm$^2$/mm$^3$)

$\dot{r}$ Net rate of bone apposition/resorption ($\mu$m/day)

$\Delta t$ Time increment (s)

$r_o$ Initial geometrical term in remodeling rule (mm)

$r$ Revised geometrical term after time increment (mm)
CHAPTER 1. INTRODUCTION

1.1 Motivation

One third to a half of all cancers metastasize to bone\textsuperscript{1}. In addition, post mortem examinations of breast and prostate cancer patients show a 70\% incidence of metastatic bone disease\textsuperscript{2}. Pathologic fracture of bones occurs when they can no longer support the loads to which they are subjected to\textsuperscript{3}. Approximately 30\% to 50\% of bone metastases lead to fracture or produce symptoms severe enough to require treatment\textsuperscript{4}.

Micro computed tomography (µCT) and magnetic resonance imaging (MRI) are commonly used to assess bones for defects and to quantify a patient’s fracture risk. Fracture risk is commonly quantified through assessment of the size, location and type of tumor as well as through analysis of a patient’s bone mineral density (BMD). In addition to conventional radiographic techniques, the Mirels’ criteria is also commonly used by clinicians in the assessment of fracture risk in patients with appendicular skeletal metastasis\textsuperscript{2, 4, 5}. Conventional plain radiographic techniques generally lack sensitivity with regard to fracture prediction and while Mirels’ criteria has been shown to be sensitive, it is not specific (91\% sensitive, 35\% specific)\textsuperscript{5, 6}.

In contrast, Computed Tomography based Structural Rigidly Analysis (CTRA) can be used to monitor changes in bone geometry as well as changes in bone material properties. CTRA seeks to define fracture risk based on a bone’s weakest cross section. A bone’s weakest cross section is that which exhibits the lowest value of axial, bending or torsional rigidities, as calculated from computed tomography images of the bone of interest\textsuperscript{3, 7-10}. The CTRA technique can be used to assess the axial, bending or torsional rigidities of appendicular skeletal metastases in a clinical setting. However, this method of quantifying fracture risk has not yet been compared to advanced techniques such as µCT based finite element analysis (FEA). The aim of the first part of this thesis
was to compare these two methods of fracture assessment whilst also introducing a study of compressive failure. Previous studies have investigated the tensile and torsional loading mode and employed CTRA with great success\textsuperscript{[7, 11]}, though these studies did not assess the efficacy of finite element techniques.

FEA has previously been shown to accurately predict fracture load in bone in a number of studies\textsuperscript{[12-15]}. Additionally, studies have been undertaken to correlate the stresses calculated using FEA with those obtained using theoretical closed form solution obtained by utilizing a mechanics of material approach \textsuperscript{[15]}. Despite the simplifying assumptions made using these techniques, highly accurate assessments of the load bearing capacity of bones and stress distributions within femora have been reported in the literature.

As osteolytic metastases are associated with significant bone resorption and commonly result in fracture we have proposed the use of a simulated lytic model for this study. This model allowed the reduction in rigidity associated with the presence of metastatic tumors to be simulated, and the defect site to be controlled.

We hypothesize that CTRA can predict failure load as well as FEA in a simulated osteolytic rat bone defect model. Methods which can measure both bone mineral density distribution and geometry can be used to assess risk of pathologic fracture. Two such approaches presented here are CT Based Structural Rigidity Analysis (CTRA) and Finite Element Analysis (FEA). The use of CTRA as a method for determining fracture risk through verification using FEA is presented. Investigations into correlations between failure load and (1) apparent density, (2) curvature and (3) axial and bending rigidities at the weakest cross section are also undertaken.
1.2 Aim

The aim for Part 1 of this study was to compare two quantitative measures of fracture assessment; the finite element method (FEM) and computed tomography based structural rigidity analysis (CTRA).

In this study a number of simplifying assumptions were applied in order to show that accurate results could be achieved quickly and hence they are applicable in a clinical setting. In the CTRA and finite element modeling undertaken, material properties were assumed to be linear, elastic and isotropic. Additionally, simplified failure criteria were used in both the finite element modeling and in failure loads calculated using theoretical relations in conjunction with parameters derived using the CTRA methods presented. A comparison of the two methods is presented against results obtained from mechanical testing. This study aims to verify that these simplifying assumptions may be applied without detrimental effect on results. The discussion towards the end of Chapter 4 is related to suggesting a number of possible enhancements for method improvements.

In the second part of this study, the Positron Emission Tomography (PET) imaging modality was investigated for use as a measure of local density to provide the necessary input for fracture analysis methods using the finite element method. In this part of the study, the foundation for development of a tumor induced bone remodeling rule is developed. This remodeling rule would allow changes in bone geometry and material properties due to the presence of metastatic involvement of the skeleton to be predicted. Such a tool would be invaluable for predicting future fracture risk associated with baseline CT scans taken at the time of diagnosis. Such information could be applied to both CTRA and FEA techniques of fracture risk assessment in a clinical setting.
1.3 Historical Note

The modern study of long bones and the associated stresses present due to loading in the musculoskeletal system dates back to works by Wolff and Koch\textsuperscript{[16]}. Koch presented a detailed study on the laws of bone architecture in 1917 which gave a detailed geometric description of the femur and outlined a procedure for calculation of stress distributions resulting from a number of different loading conditions. Wolff and Koch compared the stress trajectories in Fairbairn cranes to those observed in the proximal femur, as shown in the figure below.

![Stress Trajectories](image)

**Figure 1:** Stress trajectories in a fairbairn crane and human proximal femur\textsuperscript{[16]}

This work was advanced through mathematical and early FEA analysis of stresses in long bones in the 1960’s and 1970’s\textsuperscript{[17-19]}. The stresses in bone have also been estimated through the use of straight and curved beam analysis. Curved beam analysis in bodies with homogenous material properties has been well established\textsuperscript{[20, 21]}. However, its application to heterogeneous structures, such as bone, needs further study. Recently, curved beam theory and modern finite element analysis have been used by many authors to assess stresses and fracture loads in long bones, particularly the human
femur\textsuperscript{[15, 22-24]} but few if any have coupled FEA with computed tomography based structural rigidity analysis. In FEA models of long bones, bone material is generally assumed to be elastically isotropic for simplicity, though some studies have modeled it as anisotropic, viscoelastic or transversely isotropic\textsuperscript{[23]}\textsuperscript{[15], 22-24]. The assumption that bone is isotropic has been shown to introduce relatively small errors provided a sufficiently fine finite element mesh is used\textsuperscript{[15]}, however in complex problems more sophisticated material models should be used where possible. Cortical bone is a viscoelastic anisotropic material, and a bone’s load bearing capability depends on microstructure and orientation relative to the loading direction as well as on intrinsic material properties such as modulus\textsuperscript{[23]}.

The use of finite element modeling in biomechanical research is now well established. Keyak and co-authors have championed the development of CT/FE modeling of tumor burdened bone using continuum-based models in which element size is on the order of 3 mm\textsuperscript{[26, 27]}. In the study of human cadaveric specimens with and without metastatic lesions in the proximal femur, Keyak et al. reported a strong linear relationship ($R^2 = 0.83$) between predicted and actual strength\textsuperscript{[26]}. In a recent study using micro CT/FE modeling of mouse bones with lytic lesions found a slightly stronger correlation ($R^2 = 0.91$) between predicted and actual strength was observed\textsuperscript{[28]}. A recent study found a similar correlation between predicted and actual strength in the study of rat tibia with simulated lytic defects ($R^2=0.75$). Additionally, studies by Levenston, Crawford, Hart and Beaupre have also advanced the use of bone remodeling algorithms in the finite element method\textsuperscript{[20, 29-33]}.
CHAPTER 2. Bone Composition and Material Properties

2.1 Composition of Bone

Bone is composed of water, collagen, hydroxyapatite mineral and small amounts of proteoglycans and non-collagenous proteins\(^{[34]}\). Mineral in bone consists almost entirely of hydroxyapatite crystals (\(\text{Ca}_{10}(\text{PO}_4)_6(\text{OH})_2\)). Bone material properties are often assessed by taking bone biopsies and testing using histomorphometric techniques\(^{[15]}\). Trabecular bone volume (%), osteoid surface and volume (%), osteoblast surface (%), osteoclast resorption surface (%), and osteoclast number (/mm\(^2\)) are several parameters which are often assessed in such analyses. In order to make assessments of fracture risk, it is necessary to make \textit{non-invasive} assessments of bone material properties. Computed Tomography (CT) provides such an analysis method. It can be used to assess the density of the hydroxyapatite component in bone, and empirical relations have been developed which relate this ash (or equivalent) density to the apparent density, which is the density of the complete structure (mineralized bone plus osteoid). Figure 2 provides an overview of the structural organization of cortical bone.

There are three main classifications of bone: cortical, cancellous and trabecular. The distinguishing factor between these three classifications of bone is the porosity level. Trabecular bone is found at the end of long bones (femur, tibia) and in the vertebrae and typically has a porosity level of approximately 75-95%. Cortical bone is found in the shafts of long bones and also forms the cortex.
or shell around vertebral bodies. It has a porosity of approximately 5-10%. Cancellous bone has a porosity level in the region of 50% and is substantially weaker than cortical bone as a result of this.

2.2 Bone Tissue Properties

The mechanical properties of bone as published in the literature vary widely by species, bone type (trabecular, cancellous or cortical) and orientation. In a recent study of human femora, the modulus of bone was shown to range from between 6.9-25GPa\textsuperscript{[36]}. In diaphyseal femoral bone, the average elastic moduli of osteonal bone was 19.1 ± 5.4 GPa and 21.2 ± 5.3 GPa in interstitial lamellae. In the neck, the average moduli were 15.8 ± 5.3 GPa in osteonal, 17.5 ± 5.3 GPa in interstitial and 11.4 ± 5.6 GPa in trabecular lamellae. This highlights that bone material properties are highly dependent on location and specimen type. The wide variation in material properties highlights the need to define finite element material properties which are relevant to the problem being studied. In finite element studies, the poisson’s ratio is typically set to 0.3. Some authors have reported that varying this parameter in the range 0.2-0.4 typically has an insignificant impact on results\textsuperscript{[37]}, however study specific sensitivity analysis is important. Table 1 below shows typical values of elastic modulus for various species and anatomical sites\textsuperscript{[34, 36-41]}.

<table>
<thead>
<tr>
<th>Species</th>
<th>Anatomic Site</th>
<th>Tissue Modulus (GPa)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>Femoral Head</td>
<td>3.5-8.6</td>
<td>Ulrich et al.</td>
</tr>
<tr>
<td></td>
<td>Vertebra</td>
<td>13.4 ± 2.0</td>
<td>Rho et al.</td>
</tr>
<tr>
<td></td>
<td>Distal Femur</td>
<td>18.1 ± 1.7</td>
<td>Turner et al.</td>
</tr>
<tr>
<td></td>
<td>Femoral Neck</td>
<td>11.4 ± 5.6</td>
<td>Zysset et al.</td>
</tr>
<tr>
<td>Bovine</td>
<td>Proximal Tibia</td>
<td>18.7 ± 3.4</td>
<td>Niebur et al.</td>
</tr>
<tr>
<td></td>
<td>Femur (Long)</td>
<td>20.4</td>
<td>Martin et al.</td>
</tr>
<tr>
<td></td>
<td>Femur (Trans)</td>
<td>11.7</td>
<td>Martin et al.</td>
</tr>
<tr>
<td>Rat</td>
<td>Femur (Long)</td>
<td>18.98 ± 4.78</td>
<td>Cory et al.</td>
</tr>
<tr>
<td></td>
<td>Femur (Trans)</td>
<td>17.65 ± 4.37</td>
<td>Cory et al.</td>
</tr>
<tr>
<td></td>
<td>Tibia (Long)</td>
<td>21.37 ± 1.45</td>
<td>This Study</td>
</tr>
</tbody>
</table>

Table 1: Typical bone elastic modulus properties for various species
A number of authors have developed empirical relations which correlate both apparent and equivalent (or ash) density to modulus (Appendix E), yield strength and ultimate strength. The empirical relation used to carry out the simulation in this study is shown in Figure 3 and correlates the equivalent density in g.HA(hydroxyapatite mineral).mm$^{-3}$ to the modulus in MPa. Bone strength and modulus have both been shown to be highly correlated to density. An understanding of density variations can yield information related to the modulus of tissue at the local level. Bone is not an isotropic material. It is an anisotropic material which is perfectly adapted to withstand the loads to which the skeleton is subjected on a daily basis. Typical anisotropy ratios, where subscript L denotes longitudinal and T denotes transverse[34] are shown in Table 2.

<table>
<thead>
<tr>
<th>Material</th>
<th>$E_L/E_T$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Whole Bone</td>
<td>1.5</td>
</tr>
<tr>
<td>Mineral Phase</td>
<td>1.5</td>
</tr>
<tr>
<td>Organic Phase</td>
<td>1.18</td>
</tr>
</tbody>
</table>

2.3 The Effect of Metastatic Bone Disease

Metastatic lesions can severely reduce a bone's ability to resist loading. When studying metabolic diseases, it is important to note that they have the potential to render bone virtually isotropic[34], modifying the anisotropic nature of a long bone which allows it to resist higher loads longitudinally. As a result, isotropic material assumptions may be a valid simplifying assumption in this form of
study. In the study of metastatic involvement of the skeleton, there are three main lesion types to consider. **Lytic:** tumors where bone destruction occurs. **Blastic:** where bone formation generates a growth on the skeleton. **Mixed:** a combination of lytic and blastic tumor types. **Figure 4** shows large areas of bone resorption in a rat femur which is typical of lytic defect types. Lytic defects reduce the cross sectional area of the weakest cross section and the bending resistance of the weakest cross section through a reduction in the moment of inertia. This severely reduces the bones ability to resist axial and bending loads. This in turn greatly increases the risk of pathological fracture. Ascertaining the risk of fracture and identifying treatment requirements is an ongoing issue for clinicians seeking to evaluate fracture risk. Radiographic imaging techniques such as Computed Tomography (CT), Magnetic Resonance Imaging (MRI) and Positron Emission Tomography (PET) are critical tools for clinicians. In this study, the CT and PET modalities are used and are described in further depth in **Chapter 3.**
CHAPTER 3. Overview of Computed Tomography (CT) and Positron Emission Tomography (PET) Imaging Modalities

3.1 Computed Tomography (CT)

Computed Tomography (CT) provides a non-invasive method to assess both bone structure and density. CT is commonly used to establish the tumor type, staging information and is critical in informing clinicians in choosing a treatment path and in determining the patient’s prognosis. It allows tumor location and extent as well as biologic activity to be assessed. It is very useful for identifying the primary lesion and any associated bone destruction\[^{42}\].

With modern CT scanning technology, resolutions as low as 10.5µm and beyond are now possible. As a result, it is possible to obtain accurate 3D models of long bones. The creation of finite element models using the data generated from CT is now well established\[^{27, 43}\]. Computed Tomography (CT) provides high contrast images which allows the visualization of metastatic involvement of the skeleton (Figure 5). Sequential images through the structure of interest are output. CT involves a moderate to high radiation exposure to the patient and as such exposure should be limited where possible.

![Defect Site](image)

*Figure 5: Sagittal computed tomography image of rat tibia*
3.2 Positron Emission Tomography (PET)

PET, which visualizes the uptake of positron-emitting radiopharmaceuticals by tissue, can be used for whole body scanning to detect metastases in either soft tissue or bone\textsuperscript{[44]}. PET can be used in conjunction with computed tomography to assess fracture risk associated with metastatic involvement of the skeleton. The use of registered PET and CT images (Figure 6) allows clinicians to diagnose and stage disease as well as evaluate response to treatment, thus becoming a standard procedure in cancer imaging. PET-CT has been extensively used for evaluating cancer in a clinical setting, and studies have been undertaken to assess its accuracy\textsuperscript{[45, 46]}. Normal bone is subjected to continuous remodeling through the coordinated activity of osteoclasts and osteoblasts\textsuperscript{[47]}. The $^{18}$F-fluoride radionuclide bone tracer used in $^{18}$F-PET imaging is extracted by bone tissue largely in proportion to bone blood flow, enters and binds to bone tissue, and labels the cells involved in bone turnover. It appears specific for osteoblasts, and thus bone formation. FDG PET has been used to measure glucose metabolism in many types of cancer and can be useful for distinguishing between benign and malignant bone lesions\textsuperscript{[44]}. Malignant tumors with high metabolic rates take up more glucose and FDG than do surrounding tissues. High FDG tracer uptake is observed for osteolytic lesions, where metabolic activity is high, however for osteoblastic activity uptake of FDG is low\textsuperscript{[48]}.

FDG PET images are typically very noisy and as a result image reconstruction can be a problem. As a result, methods such as filtered back projection (FBP) have been developed to tackle this problem\textsuperscript{[49]}. 

![Figure 6: Positron emission tomography scan](image-url)
CHAPTER 4. Finite Element Analysis and Computed Tomography Based Structural Rigidity Analysis of Rat Tibia with Simulated Lytic Defects

4.1 Specimen Preparation

This study was approved by Beth Israel Deaconess Medical Center Institutional Animal Care and Use Committee (IACUC). Twenty female Sprague Dawley rats (~15 weeks old, mass: 250-275 g) were obtained from Charles River laboratories (Charles River, Charlestown, MA, USA). One tibia, selected at random, was excised from each animal and all attached soft tissue removed. The attached fibula was removed prior to scanning with a high speed dremel hand saw. The locations of the simulated lytic defects were chosen to emulate common sites of in-vivo metastatic cancer. Lytic defects were simulated by drilling a hole at the desired location. All defects were made at the apex of the curved section of the bone using a 60 gauge (1.016 mm diameter) carbide drill bit under copious irrigation. The location of the defect for each group is shown in Figure 7, and highlighted in CTRA calculations shown in Appendix C.
The tibiae were randomly assigned to four equal groups (n=5). Three of the groups included a simulated defect at various locations: anterior bone surface Group 1; posterior bone surface Group 2; and through bone defect Group 3. Group 4 was a control group with no defect. Typical Specimens from each group are shown in Figure 7.

4.2 Imaging and Image Analysis

Tibial specimens were mounted in a 0.9% saline filled µCT imaging vial (Ø: 30 mm × H: 50 mm) normal to the cylinder axis. This ensured that all the samples were scanned in the same orientation.

Sequential transaxial images through the entire bone cross section were obtained using micro computed tomography (µCT40, Scanco Medical, AG, Brüttisellen, Switzerland). 30µm isotropic voxel size was chosen in order to provide the required resolution for creating a solid model to perform the FEA analysis. This guaranteed that the scan resolution would be below the size of the edge length (~0.5mm) of the elements in the finite element models. The samples were scanned using an integration time of 250ms and tube voltage and current of 70 kV and 114 µA respectively.
Scan time was 90 minutes per sample. Beam hardening effects can result in the presence of artifacts in the reconstruction as well as a reduction in image quality. Hence, a 1200 mg·cm\(^{-3}\) hydroxyapatite (HA) beam hardening correction was applied to all scans.

Hydroxyapatite phantoms of known density (0, 100, 200, 400 and 800 mg·HA cm\(^{-3}\)), supplied by the manufacturer, were scanned to convert the x-ray attenuation coefficient (\(\mu\)) to the bone mineral density (\(\rho_{\text{EQUIV}} \text{ [g·cm}^{-3}\]) (Figure 8). The equivalent density (\(\rho_{\text{EQUIV}}\)) was converted to apparent density (\(\rho_{\text{APP}}\)) using previously published relations for the mass ash fraction\(^{[50]}\).

### 4.3 Structural Rigidity Analysis

Structural Rigidity analysis is a technique used to predict fracture risk in long bones. The risk of fracture is governed by the weakest cross section of the bone being analyzed. In other words, it is assumed that overall bone strength is governed by the cross section exhibiting the lowest structural rigidity parameters EA, EI and GJ\(^{[3, 7, 9, 10, 51]}\). These parameters are a product of the modulus of elasticity and minimum cross sectional area (EA), modulus of elasticity and moment of inertia (EI) and
shear modulus and polar moment of inertia (GJ). Micro computed tomography images (µCT) are used to assess area and density values of cross sections of interest, as shown in Figure 9. The axial (EA) and bending (EI) rigidities at each trans-axial cross section (30 µm slice spacing) were calculated to ascertain the minimum values for each specimen. The axial rigidity for each cross section was calculated by summing the pixel modulus * pixel area of each pixels in each trans-axial cross section (Figure 9). The maximum (EI$_{max}$) and minimum (EI$_{min}$) bending rigidities for each cross section was found using the relation shown in Figure 9. Internally developed software was used to calculate these variables. Furthermore, ImageJ 1.45i (NIH, Bethesda, MD) and the BoneJ add-on were used to identify the maximum and minimum principal axes (where $I_{xy}=0$) for each cross section (Figure 9a). The weakest cross section of the tibia was then identified by analyzing the resulting axial (EA), minimum bending rigidity (EI$_{min}$) and maximum bending rigidity (EI$_{max}$) at each cross section of the tibia (Appendix C).

In order to calculate a failure load, the rigidity parameters were combined with simple straight beam theory to yield a fracture load based on this CTRA analysis. The CTRA based failure load is defined as:

$$ F_{CTRA} = \frac{\varepsilon_{CRITICAL} \times EA \times EI_{MAX}}{(EI_{MAX} + (EA \times y \times d))} \quad [1] $$

where, $E$ (N.mm$^{-2}$) is average elastic modulus of the weakest cross section, $A$ is the cross sectional area (mm$^2$); $I_{MAX}$ is the maximum moment of inertia (mm$^4$) at the weakest cross section; $y$ is distance from geometric centroid to the bone surface where critical stress is present; and $d$ is the distance
from the eccentrically applied load to the geometric centroid at the weakest cross section. Use of this equation is based on the assumption that the applied moment along the principal axis with the maximum moment of inertia (subscript x in this case) is dominant. Additionally, this equation can also be rearranged and used to calculate stress ($\sigma_{CTRA}$) at points of interest. The CTRA stress ($\sigma_{CTRA}$) was calculated at the defect/minimum cross section, on the sagittal plane and where the stress was compressive (posterior surface). This value was then compared to the FEA stress ($\sigma_{FEA}$) at this point purely to illustrate that both methods were consistent. Results are shown in Tables 3 and 4.

The axial (EA) and bending (EI) rigidities calculated provide knowledge regarding the resistance to axial and bending loads for each tibia in the study. To illustrate this point, Figure 10 gives a simplistic overview of the axial and bending resistance of a beam with rectangular cross section and homogeneous material properties, from which we define the rigidity parameters for axial and bending resistance to loading used in this study.

**Figure 10: Axial and bending rigidity**

\[
\text{Axial Rigidity} = \frac{F}{\lambda/\Delta} = AE
\]

\[
\text{Bending Rigidity} = \frac{1}{\theta} \int M \, dx = EI
\]
Where $\lambda$ is the original length of the structure, and $\Delta$ is the deflection induced by the load, $F$. $M$ is the bending moment applied and $\theta$ ($dy/dx$) is the slope.

For the CTRA analysis undertaken, the elastic modulus was calculated as the sum of the elastic moduli for each voxel in the cross section divided by the number of voxels comprising that cross section using the relation $E = 8362.8 \times q_{\text{EQUIV}}^{2.56}$. The mean modulus of elasticity assigned to all CTRA analyses undertaken was $21.37 \pm 1.45$ GPa, which was approximately equal to published values for the elastic modulus of rat cortical bone$[^{38, 52}]$.

Area and density weighted area moment of inertia at each transaxial cross section was calculated using a module developed for use in conjunction with ImageJ v1.45i (NIH, Bethesda, MD)$[^{53, 54}]$. This software provided a means to derive the required geometric information (cross sectional area and additionally, the moments of inertia associated with the principal axes). Axial (EA) and Bending (EI) rigidities were calculated by summing the density weighted area of each isotropic voxel (30 µm × 30 µm × 30 µm) by its position relative to the density weighted centroid of the cross section, using MATLAB (The Mathworks, Natick, MA, USA). As a result, CTRA is able to account for the relative location of the defect.

Radius of curvature was calculated using geometric centroid positions at the defect/minimum cross section and transaxial slices 3mm axially distant from this location. The radius of curvature was defined at each cross section by constructing a line connecting these three points. This simple
method allowed local variations in curvature to be assessed and for their effects on the fracture load to be investigated. The radius of curvature was only calculated in regions where CTRA analysis identified the cross section as the weakest point of the tibia.

In defining a CTRA based failure load \( (F_{\text{CTRA}}) \), the critical strain which identifies the onset of fracture was set to 1% strain in compression, and 0.8% strain in tension \(^{[3, 51, 55, 56]}\). Further details on the principal strain limit criterion used are provided in the finite element discussion.

4.4 Mechanical Testing

Specimens were tested in an Instron 8511 (Instron, Norwood, MA, USA) load frame under displacement control condition. Specimens were loaded to failure at an axial strain rate of 0.01s\(^{-1}\) under uniaxial compressive. Both ends of the specimens were embedded in Polymethylmethacrylate (PMMA) to provide support.

An ATI – Nano25 F/T 6-axis force transducer (ATI Industrial Automation, Apex, NC, USA) was used to measure loads during testing. The 6-axis load force transducer was used to verify minimal loading on all axes except for the main loading axis. A ball and socket fixture was used in order to ensure specimens were subjected only to uniaxial compression. For all specimens, failure occurred
by brittle fracture, and thus the yield and ultimate stresses were coincident. No plastic deformation was observed and hence a purely elastic model was used to simulate the mechanical testing using FEA. Figure 12 presents representative failed specimens. Specimens were aligned to ensure the moment was applied around the principal axis exhibiting the maximum moment of inertia as calculated using the image analysis methods highlighted. The errors associated with specimen misalignment were thus reduced as far as possible.

4.5 Finite Element Model Creation

Mimics Software v13.1 (Materialise, Leuven, Belgium) was used to construct a 3D solid model of each tibia using sequential transaxial CT images, as shown in Figure 13. CT attenuation thresholds were applied to each transaxial CT image to define the mask (an intensity based thresholding technique) which defined the bone volume. A lower threshold of 400mg.cm$^3$ was applied to
exclude any elements exhibiting a density below this level. This threshold was chosen based on trials undertaken to define the mask used to threshold the original CT data for 3D model generation. This global threshold was applied to all study groups so as to ensure variations in area and moment of inertia associated with operator selection of the mask did not influence comparison of results between groups. Furthermore, special care was taken to minimize the number of surface voids and sharp edges in the 3D reconstruction which could lead to erroneous stress concentrations in the FEA model. Despite the low voxel size (30µm), the finite element mesh generated using the automatic meshing module within Mimics required manual refinement. Initial trials showed that the automatically generated mesh contained an unacceptably high number of elements which failed the in-built ABAQUS requirements for mesh quality (as high as 7% of elements). Upon implementation of the manual refinement, which involved analysis and repair of voids and overlapping triangles in the mesh\cite{57}, this was reduced to less than 1%.

The constructed tibia were meshed using the software package Mimics (Materialise, Leuven, Belgium). Quadratic ten node tetrahedral elements with a mean edge length of ~0.5mm were used. The mesh density was selected based on mesh convergence studies undertaken; each model consisted of approximately 90,000 to 120,000 elements. The mesh was refined adjacent to the defect, with a mean edge length of ~0.15mm in this region. Special care was taken to ensure that the mesh density was gradually decreased as the distance from the defect increased.
In the finite element model, elastic moduli were assigned at the element level based on the bone density. One hundred distinct material properties were assigned to each finite element model. This resulted in a modulus distribution in the complete finite element model from approximately 2GPa to 30 GPa, which matches closely with published values for bone elastic modulus. Poisson’s ratio for all models was set to 0.3 and was chosen based on values previously used in the literature\textsuperscript{[52,56]}.

4.6 Finite Element Model Testing

ABAQUS CAE v6.10 (SIMULIA, Providence, RI) was used to perform all finite element simulations. Boundary conditions consisted of an analytic rigid plate tied to the nodes on the proximal and distal surface of the tibia via a rigid body interaction defined in ABAQUS. An axial displacement of 2mm was then applied to the proximal plate at an axial strain rate of 0.01s\textsuperscript{-1}. The distal plate was held fixed, encastre. This boundary condition was chosen to match the mechanical testing conditions, where each of the specimens was loaded in the same orientation in order to allow regressions to be constructed.

FEA failure load ($F_{\text{FEA}}$) was calculated by recording the percentage of the bone volume strained to 0.8% in tension and 1% in compression at two distinct time points during the analysis. The critical strain values were chosen based on yield strain values published in the literature\textsuperscript{[55]}. Principal strains were monitored for each increment of the finite element simulation, as compressive load was increased, and failure was defined when two percent of the bone volume reached the principal strain limit of 1% in compression and 0.8% in tension\textsuperscript{[55]}. The typical maximum and minimum principal strain distribution for specimens in each group is shown in the results shown in Appendix B. The associated sum of the reaction forces at the fixed nodes was also calculated for each of these time points. A plot of the reaction forces versus the percentage of bone volume which reached the strain limit was created for each specimen. The failure criteria, which was based on 2% of the bone
volume reaching the strain limits selected (1% in compression, 0.8% in tension), was applied to each curve and linear interpolation used to estimate the FEA fracture load. The points used to perform the linear interpolations were chosen to be close to the percentage of bone volume defining failure (2%) which ensured that any errors associated with the use of linear interpolation would be minimized. The 2% failure criteria was established based on the best correlation with the experimental data.

Large deformation and small strain theory was used in all simulations performed in ABAQUS.[58]

4.7 Statistical Analysis

Linear regression analysis was used to assess how well both FE and CTRA analyses can be used to predict failure load when compared to mechanical testing. Investigations into statistical differences between the resulting regression lines and the slope and intercept of the y=x line were also undertaken.

Regressions for mechanical testing failure load against FEA and CTRA derived loads were investigated further using Fisher’s Z transformation test to analyze for statistical differences between the two models. Linear regression was also undertaken to correlate mechanical testing failure load to apparent density, radius of curvature and structural rigidity parameters $E_A$, $E_I_{\text{MIN}}$ and $E_I_{\text{MAX}}$. The resulting coefficients of determination ($R^2$) were used as the criterion by which to compare each of the regression models.

Statistical analysis was performed using the SPSS software package (Version 18.0, SPSS Inc., Chicago, IL, USA). Two tailed values of $P<0.05$ were considered statistically significant.
4.8 Results

All results (group mean and standard deviation are reported) are shown in Tables 3 and 4. All specimens including a simulated lytic defect fractured through that defect, as shown in Figure 12. Control specimens failed across the weakest cross section identified via CT scans (Appendix C). FEA results showed that the maximum stress developed at the defect site for all specimens in groups two (posterior defect) and three (through hole defect), but for no specimens within group one (anterior defect) (See Appendix B). Interestingly, the maximum bending rigidity was higher for the specimens in this group, but this did not result in an increased failure load prediction (See Appendix C).
Table 3: FEA and CTRA results 1.

The parameters reported in the table are $F_{\text{MECH}}$: The mechanical testing failure load, $\rho_{\text{AP}}$: The apparent density of the weakest cross section, $\rho_{\text{BONE}}$: the equivalent (ash) bone density of the weakest cross section, $E_{\text{CTRA}}$: Modulus of elasticity derived using previously developed relations [Cory et al. 2010], $K_{\text{MECH}}$: The axial stress divided by the axial strain from mechanical testing, $F_{\text{CTRA}}$: The CTRA based failure load (Equation 1), $F_{\text{FEA}}$: The FEA estimated failure load and $\varepsilon_{\text{YIELD}}$: The estimated yield strain obtained using CTRA parameters and $F_{\text{MECH}}$ (Equation 1).

<table>
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<tr>
<th></th>
<th>$F_{\text{MECH}}$</th>
<th>$\rho_{\text{AP}}$</th>
<th>$\rho_{\text{BONE}}$</th>
<th>$E_{\text{CTRA}}$</th>
<th>$K_{\text{MECH}}$</th>
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Table 4: FEA and CTRA results 2.

The parameters reported in the table are $\sigma_{\text{CTRA}}$: Stress calculated at defect site/sagittal plane/compressive side using CTRA methodology, $\sigma_{\text{YIELD}}$: Density dependent yield strength calculated using relations from Cory et al. 2010 at defect/minimum cross section (sagittal plane) subjected to compression, $\sigma_{\text{FEA}}$: The stress in FEA at same location as CTRA calculated stress, and $\sigma_{\text{FEA-MAX}}$: The maximum stress in the FEA model, Area: The area of the weakest cross section, EA: The axial rigidity of the weakest cross section, $E_{\text{MIN}}$: The minimum bending rigidity of the weakest cross section, $E_{\text{MAX}}$: The maximum bending rigidity of the weakest cross section.

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<tr>
<th></th>
<th>$\sigma_{\text{CTRA}}$</th>
<th>$\sigma_{\text{YIELD}}$</th>
<th>$\sigma_{\text{FEA}}$</th>
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<td>243.66</td>
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<td>Group 4</td>
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<td>St Dev</td>
<td>33.34</td>
<td>16.96</td>
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<td>7541</td>
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Excellent correlation between mechanical testing ($F_{\text{MECH}}$) and CTRA calculated ($F_{\text{CTRA}}$) failure load is observed. **Figure 14a** shows the relation between $F_{\text{CTRA}}$ and $F_{\text{MECH}}$ ($R^2=0.96$, $P<0.001$). **Figure 14a** also shows that the slope of the regression curve did not deviate from the $y=x$ line [$F_{\text{MECH}} = 1.0662F_{\text{CTRA}} - 4.8006$] ($P=0.80$). In addition, the $y$ intercept was also shown to be not different from zero ($P=0.57$). All statistical analyses performed to compare the regressions generated to the $y=x$ line were performed using Fischer’s Z test transformation.$^{[59]}$

Furthermore, **Figure 14b** shows good correlation between FEA and mechanical testing loads ($R^2=0.75$, $P<0.001$). The FEA failure load ($F_{\text{FEA}}$) accurately predicted the measured failure load from mechanical testing: [$F_{\text{MECH}} = 1.6274F_{\text{FEA}} - 16.493$]; however, unlike CTRA, the FEA predicted failure load regression slope deviated from the slope of the $y=x$ line significantly ($P=0.005$). Yet, the $y$-intercept was shown to be not different from zero ($P=0.51$). Using Fischer’s Z test transformation to compare the FEA and CTRA linear regression models, the difference between the correlations was shown to be significant ($P=0.02$). The CTRA method provided extremely accurate results when compared to mechanical testing. However, the FEA method combined with the principal strain failure criteria, resulted in the slope being significantly different from the $y=x$ line ($P=0.005$). FEA failure loads were generally calculated to be a factor of 1.6 lower than mechanical testing failure loads, which could be attributed to the fact that FEA models generally exhibit increased stiffness when compared to the actual conditions. Increasing the defined strain at failure ($\varepsilon_{\text{ULTIMATE}}$) from 0.8% in tension and 1% in compression yielded a relation which more closely matched the $y=x$ line. However, doing so severely reduced the $R^2$ value and hence the usefulness of this method as a predictor of failure load was limited. Furthermore, increasing the failure strain is biologically unrealistic. Mechanical testing performed has shown that these failure strains are accurate for cortical bone$^{[55]}$, and as such their use in this model is justified. Correlations between
FEA and CTRA calculated failure loads are slightly reduced ($R^2=0.71$, $P<0.001$) but remain significant.

The results obtained using the CTRA analysis methods presented here also confirmed that bone generally fails at a constant strain of 1% in compression, which is independent of modulus.

Correlations shown in Figures 14c and 14d between mechanical testing failure loads and EA ($R^2=0.61$, $P<0.001$) and $E_{\text{max}}$ ($R^2=0.71$, $P<0.001$) show that the bending rigidity of the weakest cross section accounts for 71% of the calculated failure load ($F_{\text{CTRA}}$), and that EA accounts for only 60% of the calculated failure load. Similarly, $E_{\text{min}}$ accounted for 71% of the variation ($R^2=0.71$, $P<0.001$). Neither parameter fully accounts for the failure load due to the presence of both bending and axial stresses, though correlations are strong. Moreover, neither apparent density ($P=0.37$) nor the radius of curvature at the weakest cross section ($P=0.26$) exhibited a strong correlations with $F_{\text{MECH}}$.

An excellent correlation between CTRA calculated stress and the density dependent yield stress is also shown in Figure 15, using the average density at the weakest cross section ($R^2=0.72$, $P<0.001$), as shown in Table 4. In this case, the stress on the sagittal plane at the weakest cross section was calculated in order to make a comparison between the two methods of calculating stress. This method can be expanded to any location, however this is far more resource intensive than FEA in performing this task. This comparison was performed to evaluate the accuracy of the calculations being performed. In contrast, density alone was shown to be a poor predictor of failure (Figure 15).
Figure 14: Linear regressions of mechanical testing failure load to A) CTRA failure load, B) FEA failure load, C) axial rigidity and D) bending rigidity.
Discussion

This study investigated the correlation between FEA, CTRA and mechanical testing based failure loads in a rat bone model of simulated osteolytic defects for the case of uniaxial compressive loading.

The model used here considered four cases of lytic lesion locations, namely through hole defect, anterior defect, posterior defect and a no defect control group. The location of each defect created was strictly controlled. Furthermore, the loading mode used was a simple axial compressive load. It is understood that bone metastases may occur at a variety of locations and be subjected to highly complex loading conditions; however, the model chosen here is thought to answer the clinically relevant question of predicting immediate fracture risk associated with an axial compressive load.

This simulated defect model used here was chosen after being successfully implemented in similar studies\(^7\). Lee et al. have published several papers in this area and have employed the same simulated lytic defect model as used here\(^{60-63}\). The use of a real tumor model would increase the clinical relevance, however the simulated defect model used here simulated the low mechanical properties (modulus, density) associated with lytic defects and hence the drilled defect simulates this reduction.
in load bearing capacity. Despite the success of this simulated lytic defect model in similar studies, it should be noted that the use of the technique does result in defects exhibiting sharp edges. This is seldom, if ever, seen in the case of real tumors. The primary goal of this study was to look at the effects of reduced axial and bending rigidity on the strength of bones and as such the model employed was chosen. Fracture initiation caused by the sharp interface of the defect and its corresponding influence on the fracture load was not considered in the current study but may have influenced the results. This is discussed in further depth in Section 4.10.4. In this study, control of the defect site was important to make an initial comparison between the CTRA and FEA methods employed and hence a simulated lytic defect model was selected to provide this control.

The finite element analyses were performed using linear elastic and isotropic bone material properties. The elastic modulus of each element in the finite element model was based on the density of each element. However, bone has been shown to be a viscoelastic and anisotropic material. The use of transversely isotropic material assignment has been proposed by others[12, 64]; however, in the current study elastic material properties were chosen in order to simplify the FEA analysis undertaken. The application of more advanced material models is discussed in greater detail in Section 4.10.3. The simplifying assumptions used in this study were chosen to limit the computation time as far as possible whilst minimizing the impact on accuracy.

The Computed Tomography based Structural Rigidity Analysis (CTRA) methods presented here can be combined with small displacement and straight beam theoretical approaches of mechanics of materials. It has been shown that the structural parameters obtained from transaxial CT images can be combined with simple equations (Equation 1) to yield both fracture load, stresses and strains. Enhanced results could be achieved through analyzing cross sections perpendicular to either the centroidal axis or the neutral axis when seeking area and moment of inertia parameters for use in
Furthermore, software which calculates the bone stresses within a bone cross section subjected to bending, axial, torsional and transverse shear far-field loading conditions, using quantitative computed tomography (QCT) data, is now available to researchers in this field\textsuperscript{[65, 66]}. This software utilizes inhomogeneous beam theory and is an improvement on the straight beam theory equations presented here. This is discussed further in Section 4.10.2.

The use of curved beam theory as opposed to straight beam theory would likely improve the calculated CTRA stresses and the associated loads, where the defect site was in a region of relatively high curvature. Where the radius of curvature approaches infinity (>5 times the tibia thickness), straight beam theory often gives reasonable results, as we have shown in this study. Future studies should consider defect sites in regions of high curvature in the diaphysis to assess the impact of using straight beam theory in these regions. The use of these methods is discussed further in Section 4.10.2.

Despite the simplifying assumptions made in this study, the CTRA method, in conjunction with the mechanics of materials based approach presented was able to accurately predict the failure loads in a curved, heterogeneous, anisotropic, elliptically shaped cross section bone undergoing large deformations.

The CTRA method, in conjunction with simple beam theory, provided the failure load and stress values adjacent to the defect (Tables 3 and 4). FEA provided the global stress distribution, the stress distribution around the defect as well as an accurate assessment of the failure load (Tables 3 and 4), with a simulation time of less than an hour. However, pre-processing took much longer (>2 hours per specimen). As a result, the time taken to calculate an FEA failure load was far higher than the time to calculate the CTRA rigidity parameters and associated critical stresses and failure loads for each specimen (generally < 30 minutes).
In this study, CTRA and FEA analysis have been combined and assessed as fracture predicative methods associated with axial compressive loading in a simulated osteolytic rat bone defect model. A simplified mechanics of materials approach utilizing CTRA derived rigidities has been shown to be as good as the more sophisticated FEA in calculating the failure load for the case of an axial compressive load. Furthermore, this was performed in a significantly reduced computation time. Whilst the use of patient specific finite element models is perhaps not yet feasible in a clinical setting, the use of CTRA techniques certainly is. The CTRA technique can be used to greatly enhance fracture assessments made using conventional radiographic techniques alone.

Previous clinical studies have utilized the CTRA method in a clinical setting\[3,9\] and similar regression coefficients were obtained ($R^2=0.89-0.95$) for tension, bending and torsion. Similarly, finite element modeling has been performed to predict the strength of bones with osteolytic lesions with excellent results ($R^2=0.91$)\[28\].

The results of this study show CTRA to be an extremely useful method of fracture risk assessment in an osteolytic rat model, where both axial and bending stresses are present. Previously, it has also been shown that CTRA can be used to accurately calculate failure load in the torsional loading mode in the study of rat femurs with simulated lytic defects of various size\[7\].
4.10 Method Enhancements

4.10.1 Overview

The finite element modeling presented in this thesis has been heavily simplified in order to be applied in a clinical setting and show that assumptions such as a purely linear elastic material model and simple strain based failure criteria can be applied with little penalty on result accuracy. The rapid results which can be achieved using these methods have been shown to be fairly accurate in terms of predicting the failure load of rat tibiae subjected to uniaxial compressive loading \((R^2=0.75)\), however improvements to the FEA methodology would allow the fracture load to be predicted more accurately. The aim of the discussion in this section is to present such enhancements and describe work undertaken to address the modeling deficiencies previously highlighted.

To this end, an iterative analysis study was undertaken to analyze the effect that enhancements to the material model and failure criteria used would have on the final \(R^2\) value for the relationship between the mechanical testing failure load \((F_{\text{MECH}})\) to the FEA calculated failure load \((F_{\text{FEA}})\) reported. For simplicity, the material model for these tests was changed from a heterogeneous to homogeneous model. This modeling change was made to allow rapid changes to the finite element modeling variables. This allowed an iterative analysis to be performed which would not be possible for the case of a heterogeneous model incorporating one hundred distinct material properties based on pixel level density, as was the case in the main body of this study.

Additionally, a further parametric study was developed to research the effects of hole sharpness on the fracture load predictive capacity of the model presented (Section 4.10.4). A simulated lytic defect model was presented in the main work of this thesis. This however does not result in defects
which are biologically realistic due to the sharp defect edges present. To ascertain the effect that this has on the predictive nature of the model, a study considering various hole sharpness’s is presented.

In contrast to the FEA methods presented, the CTRA analysis method presented produced a highly accurate means to predict the fracture load despite the simplifying assumptions applied ($R^2=0.96$). Despite this excellent correlation, methodology enhancements are presented in Section 4.10.2 which can be used in regions of high curvature (i.e. diaphysis) to produce an accurate method to determine fracture load.

4.10.2 Curved Beam Analysis

By taking account of curvature, the accuracy of fracture predictive methods that utilize computed tomography based rigidity analysis (CTRA) can be enhanced. A revised Image-J module was developed to analyze cross sections normal to the centroidal axis. Where skeletal metastases are present in regions of increased curvature (for example: at more distal locations than defect shown in Figure 16), this could have a significant impact on the accuracy and validity of predicted CTRA fracture load. In order to fully exploit this method enhancement, the relations used to calculate the fracture load, critical stresses and strains must also be enhanced.

When studying the effects of curvature, the theoretical component of the CTRA method needs to be reviewed. Firstly, the straight beam formula for the circumferential stress in the case of a homogeneous, symmetric, curved beam with bending moment normal to plane symmetry becomes:
\[ \sigma_{\theta \theta} = \frac{N}{A} + \frac{M_x(A - rA_m)}{Ar(RA_m - A)} \] [2]

where \( N \) is the axial load through the cross section of interest, \( A \) is the cross sectional area, \( M_x \) is the moment acting on the cross section about the principal axis, \( A_m \) is a geometric parameter defined below, \( r \) is the distance from the center of curvature to the point of interest, \( R \) is the radius of curvature of the centroidal cross sections (see Nomenclature). Here we note that this term will be the dominant stress term, and that radial and shear stresses are neglected in derivation of Equation 2. This is valid at the surfaces, where principal stresses are greatest, and hence where this analysis method will focus.

As mentioned for the case of straight beam theory, this equation assumes that bending is applied around the x axis (principal axis associated with maximum moment of inertia) dominate, and that this is the primary contributor to the stress value calculated at each point. As we have shown in our analysis, the FEA calculated stress at the defect is correlated to the CTRA calculated stress at the same point for all groups (Tables 3 and 4). The CTRA stress (\( \sigma_{\text{CTRA}} \)) reported in the results tables is calculated by using Equation 1, the straight beam equivalent of Equation 2. As a result, this assumption has been shown to be valid for the case of uniaxial compressive loading studied in this thesis.

All parameters in Equation 2 are easily found using the methods previously presented with the exception of \( A_m \), a geometric parameter defined below in Equation 3 with units of mm. The cross section of the tibia being analyzed is composed of isotropic rectangular voxels. As a result these voxels can be summed to yield the \( A_m \) parameter for each bone cross section as follows:
\[ A_m = \int \frac{dA}{r}, \quad A_m = \sum_{i=1}^{n} A_{mi}, \text{where} \quad A_{mi} = b_i \ln \frac{c_i}{a_i} \quad \text{[Equation 3]} \]

where here, \( b \) is the voxel dimension (30\( \mu \)m), \( c \) is the distance from the center of curvature to the outer bound of the \( i \)th voxel, and \( a \) to the inner bound (i.e. \( c-a = b \) for square voxel dimension)\textsuperscript{[20]}. The revised ImageJ module developed to calculate the geometric properties whilst accounting for curvature also yields this parameter.

To further the development of this approach we now highlight the fact that beam curvature causes the neutral axis to shift away from the section centroid, resulting in a local stress concentration that is a function of the magnitude (sharpness) of the curvature\textsuperscript{[20]}. Previously in this study, it was assumed (albeit incorrectly) that the centroidal and neutral axes were coincident for all cross sections.

As a result, to further this method the neutral axis of the cross section must also be calculated to evaluate the stresses in the bone whilst accounting for curvature effects. The radius from the center of curvature to the neutral axis \((\sigma_{zz}=0)\) is thus defined as:

\[ R_n = \frac{AM_x}{A_mM_x+N(A-RA_m)} \quad \text{[4]} \]

Where \( R_n \) is the radius of curvature from the center of curvature to the neutral axis to the bone cross section, \( R \) is the radius from the center of curvature to the centroidal axis and \( N \) is the normal load acting on that cross section.

These equations provide the basic theoretical foundation to allow a more sophisticated analysis to be developed; however, these equations were developed for isotropic and homogenous materials, and hence must be used with care when studying anisotropic materials such as bone. A discussion of the implementation of further enhancements to this theoretical development to account for the
heterogeneity of the bone is not included here; however, we have shown that straight beam theory provides extremely accurate results in predicting failure load ($R^2=0.96$) and hence the equations presented here offer an excellent framework for further development of this curved beam methodology.

Software which calculates stresses within a bone cross section subjected to bending, axial, torsional and transverse shear far-field loading conditions, using quantitative computed tomography (QCT) data is now freely available and incorporates inhomogeneous beam theory equations for use in validation of finite element models studying fracture risk \cite{65,66}.
4.10.3 Finite Element Modeling Enhancements

4.10.3.1 Material Model Enhancements

In order to enhance the material models used, a greater understanding of bone mechanical properties is required. This often requires extensive mechanical testing and inter-subject variation can severely affect the validity of finite element models looking to solve biological problems. Due to this high inter-subject variation; patient specific finite element models are often employed. The biggest issue to overcome to enhance the material model used is to ascertain the material constants required.

While the multiaxial and off-axis failure properties of trabecular bone play an important role in fracture\textsuperscript{[39, 67, 68]}, experimental data in multiaxial loading is limited, and thus the problem of defining material properties for input into patient specific finite element models is a significant one.

As discussed previously, bone is an anisotropic material and as such the assumption that it is isotropic has an effect on results, albeit insignificant in this study. In addition to anisotropic material models, transverse isotropy can be assigned as the material model in the study of bone failure. Transversely isotropic materials have the same material properties in every direction on a plane normal to a single axis of symmetry\textsuperscript{[69]}. In other words, the material properties are the same in all directions about a common axis of isotropy. An example of this type of structure is a uni-directional carbon fiber laminate. In this case the axis of isotropy is the fiber direction. Using this material model we define a longitudinal, transverse and shear modulus ($E_L$, $E_T$ and $G$ respectively) for each
element comprising the finite element model. These moduli are defined by five independent material constants\(^{[34]}\) and are shown in **Figure 16a** below.

\[
\begin{bmatrix}
\varepsilon_{11} \\
\varepsilon_{22} \\
\varepsilon_{33} \\
\gamma_{12} \\
\gamma_{13} \\
\gamma_{23}
\end{bmatrix} =
\begin{bmatrix}
1/E_p & -\nu_p/E_p & -\nu_{tp}/E_t & 0 & 0 & 0 \\
-\nu_p/E_p & 1/E_p & -\nu_{tp}/E_t & 0 & 0 & 0 \\
-\nu_{tp}/E_p & -\nu_{tp}/E_p & 1/E_t & 0 & 0 & 0 \\
0 & 0 & 0 & 1/G_p & 0 & 0 \\
0 & 0 & 0 & 0 & 1/G_t & 0 \\
0 & 0 & 0 & 0 & 0 & 1/G_t
\end{bmatrix}
\begin{bmatrix}
\sigma_{11} \\
\sigma_{22} \\
\sigma_{33} \\
\sigma_{12} \\
\sigma_{13} \\
\sigma_{23}
\end{bmatrix},
\]

where \(G_p = E_p/2(1 + \nu_p)\) and the total number of independent constants is only five.

**Figure 16a: Stress-strain law for transversely isotropic material model\(^{[57]}\)**

Where data does not permit assignment of a fully anisotropic material model, the transverse isotropy assumption may offer enhanced results with a minimal impact on the time taken to perform a linear elastic, isotropic analysis. As highlighted earlier in this study, linear elastic moduli are often quoted for simplicity in the literature, and few studies have looked at defining the material constants required to utilize a more realistic material model. In order to define these material constants, mechanical testing must be performed. Anisotropy ratios (Table 2) derived from mechanical testing data can be used to define simplified transversely isotropic material models with relative ease.

Transverse isotropy can be relatively easily implemented in bone fracture finite element studies and research has been undertaken in this area. In a recent study, the transverse and longitudinal properties of human bone were studied using acoustic microscopy and nano-indentation techniques to ascertain the anisotropy ratio \((E_L/E_T)\) for human cortical bone\(^{[40]}\). By utilizing the anisotropy ratio derived in conjunction with theoretically derived relationships which relate density to longitudinal modulus\(^{[38]}\), it is possible to accurately define transversely isotropic material properties in patient
specific finite element models. In ABAQUS, transversely isotropic material models can be applied by specifying the elastic moduli, poisson's ratio and shear modulus in each of the principal directions.

The assignment of truly transverse isotropic materials requires the assignment of five *independent* parameter's. However, a simplified model can be used where only two independent parameters are required. An iterative analysis was performed to analyze the effect of material model changes where $E_1 = E_L$, where $E_L$ is derived from the relation shown in Figure 3. Additionally, $E_2 = E_3 = E_T = 0.71*E_L^{[40]}$, $\nu_1 = \nu_2 = \nu_3 = 0.3$ and $G_1 = E_1/2(1+\nu_1)$, $G_2 = G_3 = E_2/2(1+\nu_2)$. All models exhibit homogeneous, linear elastic moduli which are based on the average density of the weakest cross section. To assign truly transverse isotropic properties, relations such as those shown in Appendix E can be used. Where relations for the species or anatomic site being studied do not exist, the simplified model presented can be used.

In addition to presenting the use of transversely isotropic material properties, we also address the issue of allowing for plastic deformations. Furthermore, we assume that the yield surface changes size uniformly in all directions such that the yield stress increases in all stress directions as plastic straining occurs. For simplicity, classical metal plasticity is used as the inputs required to use plasticity models such as Drucker-Prager and Mohr-Coulomb plasticity models are not readily available. The yield stress is calculated using the relation, $\sigma_{\text{yield}} = 106.4*\rho^{2.21}$ from Cory et al$^{[38]}$. The average density of the weakest cross section is used as the input for this relation. For simplicity, no plastic hardening is permitted, and hence an elastic, perfectly plastic model is utilized. In other words, the yield stress does not change with plastic strain.

In order to perform this iterative analysis, a single specimen from Group 3 was analyzed and the results compared to the heterogeneous, linear elastic, principal strain limit modeling and mechanical testing result presented in the main body of this thesis. The failure criteria used in all cases was 2%
bone volume reaching the critical limit of 0.8% in tension and 1% in compression and poison's ratio was set to 0.3.

Table 5: Iterative analysis results and parameters

<table>
<thead>
<tr>
<th>$E_l$ (GPa)</th>
<th>$E_t$ (GPa)</th>
<th>$G$ (GPa)</th>
<th>Apparent Density (g cm$^{-3}$)</th>
<th>Yield Stress (MPa)</th>
</tr>
</thead>
<tbody>
<tr>
<td>19.02</td>
<td>13.50</td>
<td>7.32</td>
<td>2.396</td>
<td>292.99</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Material Model</th>
<th>Failure Load (N)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Linear Elastic, Homogeneous</td>
<td>136.74</td>
</tr>
<tr>
<td>Elastic-Perfectly Plastic</td>
<td>193.92</td>
</tr>
<tr>
<td>Transversely Isotropic</td>
<td>83.29</td>
</tr>
<tr>
<td>Transversely Isotropic, PP</td>
<td>103.04</td>
</tr>
<tr>
<td>Linear Elastic, Heterogeneous</td>
<td>109.32</td>
</tr>
<tr>
<td>Mechanical Testing</td>
<td>93.82</td>
</tr>
</tbody>
</table>

The results of this analysis are described in further depth in Section 4.10.5.

4.10.3.2 Failure Criteria Enhancements

When studying failure in a material such as bone it is important to have a solid understanding of the material properties and its failure behavior. In this study, the tibia exhibited brittle fracture failure (the yield and ultimate stress and strain were coincident). This is not always the case. Furthermore, failure criteria developed for studying failure in homogeneous materials (i.e. metals) are not always relevant. A number of studies have been undertaken to tackle this issue and study the effects of applying various failure criteria to finite element simulations of bone failure mechanisms. Two such
studies consider the Tsai-Wu and Super ellipsoid criteria and will be discussed further here\textsuperscript{[25, 70]}. In addition, authors have also assessed the suitability of the Coulomb-Mohr and Hoffman failure criteria in the study of bone failure\textsuperscript{[27, 71]}.

Whilst the former are related to the study of anisotropic materials, the latter concern failure analysis of linear elastic isotropic materials. The Hoffman and Coulomb-Mohr criterion are highlighted in Equations 5 and 6 below, respectively.

\[
\frac{\sigma_{1i}}{S_{ti}} - \frac{\sigma_{3i}}{S_{ci}} = 1 \quad [5]
\]

\[
\frac{1}{2S_{ti}S_{ci}}[(\sigma_{1i} - \sigma_{2i})^2 + (\sigma_{1i} - \sigma_{3i})^2 + (\sigma_{2i} - \sigma_{2i})^2 + \frac{1}{S_{ti}} + \frac{1}{S_{ci}}][\sigma_{1i} + \sigma_{2i} + \sigma_{3i}] = 1 \quad [6]
\]

where \(\sigma_{1i}, \sigma_{2i}, \sigma_{3i}\) are the principal stresses for element \(i\), and \(S_{ti}\) and \(S_{ci}\) \((S_{ci}>0)\) are the tensile and compressive strengths of element \(i\), respectively. Also, we assume \(\sigma_{1i} > \sigma_{2i} > \sigma_{3i}\). The tensile and compressive yield stresses are calculated for each element \(i\), based on the density. The yield stress is again calculated using the relation, \(\sigma_{\text{yield}} = 106.4*\rho_{\text{(EQUIV)}}^{2.21}\) from Cory et al\textsuperscript{[38]}. Such failure criteria can be used in place of the simple principal strain limit criterion proposed in the body of this thesis. In this thesis, one of the primary goals was to minimize the calculation time and as such a simplified, but accurate, criterion is attractive. However, where this simplified criterion is not valid, Equations 5 and 6 provide an alternative means to evaluate fracture in bone.

It is important to note that the CT data used to generate the finite element models contained in this study cannot yield information related to the anisotropic nature of bone\textsuperscript{[27]}. As a result, it is often not possible to apply anisotropic material models or failure criteria to CT generated finite element models using subject specific material properties. Mechanical testing must be performed to derive
the required material constants and this is only possible in animal or human cadaveric studies. As a result, the Tsai-Wu and Super Ellipsoid criterion are described, but the emphasis of future research into perfecting failure theories used to predict bone fracture should focus on isotropic failure theories which can be more easily applied to CT based finite element models.

Mechanical testing undertaken on bone from various species and anatomical locations has shown that bone fails largely at a constant strain, independent of density\cite{55}. This fact makes a strain based failure criteria an attractive one and was the reason for choosing such a failure criteria in this study.

However, such an approach does not take into account the anisotropic nature of bone. As a result, failure criteria which have been applied successfully in the study of composite materials, which by their nature and design are highly anisotropic to meet certain design requirements, have been applied in the study of bone failure. Two such failure criteria which address this issue are the Tsai-Wu\cite{25} and Super ellipsoid criterion\cite{70}.

The super ellipsoid criterion develops the principal that bone fails at a constant strain independent of density and has been shown to be highly accurate in determining yielding in human bone excised from the femoral neck. The bone in this region has been shown to be essentially homogeneous and isotropic\cite{70}, hence success of this failure criteria should be trialed in additional anatomic sites for accuracy. The yield surface equation contains only four parameters (\(r, c, n\) and \(t\) in Equation 7) and offers an alternative means to assess failure in bone\cite{70}.
where $\varepsilon_i$ ($i=1, 2, 3$) are the principal strains, $\eta_i$ ($i=1, 2, 3$) are the radii, $c_i$ ($i=1, 2, 3$) are the shift in the center coordinates with respect to the origin, $n_1$ and $n_2$ are “squareness” parameters and $t$ is a “flattening” parameter. Further details regarding this model are presented in Bayraktar et al. (2004).\textsuperscript{[70]}

The Tsai-Wu criterion has been investigated in the study of failure in bovine trabecular bone and applied with moderate success.\textsuperscript{[25]} In order to calibrate the criterion for the study of homogeneous, transversely isotropic materials it is necessary to obtain seven coefficients (six from uniaxial testing, the seventh from biaxial tests performed).\textsuperscript{[72]}

Neither criteria have yet been fully studied in relation to bone failure and the literature contains no information regarding correlation coefficients between FEA failure loads predicted using these criteria versus actual mechanical testing loads.

One of the main issues regarding implementation of a failure criteria designed for fiber reinforced composites is due to local variations in bone material properties, which do not exist in fiber reinforced composites. Fiber reinforced laminates are typically designed to have strength requirements which do not vary along a defined axis, to meet a specified design requirement. Failure in bone will be highly localized and hence any failure criterion applied must take account of this. This is a daunting task for the researcher and hence simplifying assumptions which do not have a significant effect on results are highly attractive.
Due to the significant technical challenge of applying anisotropic failure criteria in the study of bone failure, isotropic failure criteria such as principal stress, strain, Coulomb-Mohr or Hoffman criteria are often employed.

### 4.10.4 Hole Sharpness Parametric Study

The drilling technique described in Section 4.1 leads to a well-defined hole with sharp edges, which is a situation seldom seen in biological scenarios. As a result of this, we seek to define the effect this has on results.

Experimental determination of the hole topography and roughness was not undertaken on samples subject to the drilling technique described. In order to study the effects of hole roughness, a means to quantify hole roughness must be defined. Additionally, the creation of three additional models where the surface is artificially roughened in order to more closely model the situation likely to occur in a tumor model would allow this to be investigated. Such defects can be artificially created using the software package Mimics (Materialise, Leuven, Belgium) on specimens scanned where no defect was drilled. A separate mask developed to identify the defect, located at identical coordinates for all three models allows a comparison to be drawn. Only the roughness of the defect edges is varied from model to model, and hence quantification of the effect that hole sharpness has on results can be assessed. The surface roughness is defined by **Equation 5** below.

\[ R_a = \frac{1}{L} \int_0^L |z| dx \quad [8] \]

Where L, z and x are the evaluation length, height and distance along the measurement path, respectively.\(^{[73, 74]}\)
The author hypothesizes that the presence of a sharp edge is likely to cause a stress concentration in the region of the defect, and thus play a role in lowering the fracture load predicted as compared to models where a defect with increased roughness is used, as defined by Equation 8.

Furthermore, an understanding of drilling in cortical bone is required in order to carry out this parametric study. Many studies looking to quantify the effects of various drill types and process are present in engineering journals however such articles in the biological literature are rarer. Two recent articles give an excellent review of current techniques in cortical bone drilling\cite{75, 76}. The focus of most bone drilling studies is in heat generation reduction and in optimizing techniques used in implant fixation. However, such studies provide valuable information related to cortical bone response to drilling procedures.

4.10.5 Discussion

This section highlights possible enhancements to the methodology described in the main body of Chapter 4 in this thesis. The main avenue for improvement concerns the FEA modeling procedure described. The simplified methods chosen as a basis for the study yielded a method which could reasonably predict the fracture load of rat tibia cortical bone ($R^2=0.75$).

Four additional failure criteria have been presented as possible alternatives to the principal strain limit criterion used in the main body of this thesis. These are the Hoffman, Coulomb-Mohr, Tsai-Wu and Super Ellipsoid Models. Additionally, transversely isotropic and elastic perfectly plastic material models have also been presented as potential enhancements. To study the effects of material model assignment on results, an iterative analysis was performed.

In the iterative analysis performed the effect of adopting a transversely isotropic material model and in accounting for plastic deformations using an elastic perfectly plastic material model is presented.
To carry out this analysis, a homogeneous, linear elastic model is used to allow rapid variation of the modeling parameters described. Table 5 presents the parameters used in the iterative analysis.

The use of transversely isotropic material properties enhances the fracture predictive capacity of FEA for this specimen by assigning transversely isotropic material properties a more accurate assessment of the fracture load was achieved. Use of a purely linear elastic model overestimated the failure load significantly, as shown in Table 5. The transversely isotropic, perfectly plastic model most closely estimated the fracture load, overestimating the load by only 9%. The heterogeneous and transversely isotropic models did not produce significantly different values for the failure load and all methods of fracture assessment proved accurate. Allowing for plastic deformation using classical metal plasticity theories increased the predicted failure load for both the elastic and transversely isotropic cases.

5.1 Introduction

The development of a method to study and predict future fracture risk would be of significant importance in clinical studies seeking to predict pathologic fracture caused by metastases. The biological behavior of skeletal metastases can vary widely with some exhibiting slow growth and a low probability of spreading. Conversely, others can be highly aggressive resulting in rapid bone destruction and a high probability of spread\cite{42}. However, the biological behavior of skeletal tumors can be predicted by their clinical, radiological and histopathologic features. As a result, it is possible to provide a model studying future fracture risk with a means to account for this variability and accurately predict the resulting effect on a bone’s resistance to loading.

As a result, a study has been developed to tackle this issue. The work performed in this chapter relates to preliminary studies undertaken to develop and implement a tumor induced bone remodeling rule to be applied to finite element simulations analyzing the effect of metastatic disease progression on the fracture risk of rat long bones.

5.2 Bone Remodeling Overview

Bone remodeling in finite element studies is typically used to assess density distribution changes due to an assumed normal loading history\cite{77}. Adaptive bone remodeling, in which healthy bone adapts to the applied loads has been studied by a number of authors\cite{30-33, 78, 79}. Figure 17 provides an overview of the bone remodeling theory developed by Beaupre et al. in which bone adapts towards a predefined attractor state based on the tissue stress stimulus applied. An excellent example of this
principle is shown in the study of tennis players, where the humerus of the playing arm has been shown to exhibit both significantly increased strength associated with increased density, cross sectional area and moment of inertia\[89\].

![Diagram](image)

Figure 17: Rate of surface remodeling as a function of tissue stress level stimulus\[30,31\]

Studies comparing finite element using bone remodeling algorithms and DXA based assessments of bone mineral density have also been performed and show the predicted density changes to match well with experimental observations\[81\]. In this form of simulation, external geometry of all specimens is typically fixed, and only changes in element level density are permitted. All remodeling simulations initially commence from a structure of homogeneous bone density. The bone algorithm then simulates osteoblastic and osteoclastic cell function in bone resorption and apposition respectively to vary the local element level density throughout the structure. However, in this study,
it will be necessary to account for geometrical variations with time. The figure below illustrates a typical modeling procedure.

Figure 18: Bone remodeling procedure[30,31]
The figure above incorporates the two critical equations which are highlighted below as Equations 9 and 10 for clarity. These equations describe the change in density and bone geometry we seek to define for the case of metastatic disease progression.

\[
\rho = \rho_0 + \dot{r}S_v \rho \Delta t \quad [9]
\]

\[
r = r_0 + \dot{r} \Delta t \quad [10]
\]

where \( \rho \) is the density (g/cm\(^3\)), \( S_v \) is the bone surface area density (mm\(^2\)/mm\(^3\)), \( \dot{r} \) is the net rate of bone apposition/resorption (µm/day), \( \Delta t \) is the time increment (s), \( r_0 \) is the initial geometrical term in remodeling rule (mm), \( r \) is the revised geometrical term after time increment (mm). Full definitions are given in the Nomenclature and further description is given in Beaupre et al\(^{30,31}\).

A number of parameters which describe bone remodeling have been defined outside the scope of finite element simulation. These include mineral apposition rate (MAR), mineral resorption rate (MRR), mineralizing surface (MS), eroded surface (ES), bone formation rate (BFR) and bone resorption rate (BRR)\(^{82}\). As a result, a number of easily defined and obtained parameters exist which can be used to develop the initial remodeling rule sought. These parameters can be obtained using image analysis techniques as established in the literature\(^{82}\).

In the proposed study, a tumor induced bone remodeling algorithm is sought. In contrast to typical studies which analyze bone density variations due to loading variations, the current study seeks to predict density variations due to the presence of metastatic lesions. The model to be developed will be built on the theoretical foundation developed by Beaupre et al\(^{30,31}\), and the study design described in more depth in the sections that follow.
5.3 Method

The eight rats used in this preliminary study were inoculated with MDA-MB-231 human breast cancer cells into the femoral vein with the femoral artery ligated to induce osteolytic lesions that simulate skeletal metastasis at T0 (Time=0 weeks). Unfortunately, this method yielded no skeletal lesions for analysis in this preliminary study. As a result, the following analysis was performed on essentially healthy bone. Future studies should review the animal model, and specifically the inoculation method and cancer cell line used.

Micro-computed tomography images (91µm isotropic voxel size) and Positron Emission Tomography (PET) images (0.87mm isotropic voxel size) of sagittal cross sections through each long bone were compared to understand the bone remodeling process in presence of metastatic involvement of the skeleton\cite{82}. The voxel size was governed by the CT scanning system used, which was capable of scanning an entire animal. The use of a lower voxel size (30µm as in Chapter 4) would have resulted in improved results. Images at various time points were superimposed to gain an understanding of bone apposition and resorption using previously established methods\cite{83,85}. Bone areas present only in earlier measurements were considered resorbed and those appearing only in latter images were considered formed regions.

3D data correlation was performed using the software packages AMIDE (Appendix F for procedure) and sagittal images were compared using a simple algorithm developed using MATLAB (the Mathworks, Natick, MA) as shown in Appendix A. The images were registered using previously established techniques utilizing a semi-automatic algorithm. Automatic algorithms are also available\cite{84,85}. The geometric deformation model is a global three dimensional affine transformation. The deformation model used allows inter-specimen comparison as well as
comparison between images scanned at each time point. This was critical, as although the rat positioning was controlled, it was not possible to ensure the animal was perfectly aligned at each scan point.

All subsequent scans over the course of the study were matched to scans taken at the proceeding time point to ascertain resorbed and formed regions as described above. The voxel size for all CT scans undertaken was 0.091mm. The PET scans had an isotropic voxel size of 0.87mm.

The changes being observed were very small, and hence the relatively large voxel size meant that levels of bone formation or resorption below the voxel dimension could not be observed. Additionally, PET images are typically very noisy and contain a large number of artifacts which can make image registration very difficult. Figure 19 shows the transverse, coronal and sagittal planes for a typical registered $^{18}$F/CT for a single at a single time point.

![Registered $^{18}$F PET and CT scan at 2 weeks (time point a)](image)

In order to compare the tracer uptake for various animals, it is necessary to normalize the tracer uptake. This is done by considering the standardized uptake value variable(SUV)$^{[49]}$. Equation 7 below shows the calculation of the SUV value. For this study a calibration factor of 2.88e08 was applied to convert the units output from PET from bq/cc to g/ml.
\[ SUV = \frac{\text{decay corrected activity (kBq)/tissue (ml)}}{\text{injected FDG dose (kBq)/body weight (g)}} \]  

5.4 Results

Upon registration of the 3D datasets, sagittal cross sections were compared to yield relationships between SUV uptake and the pixel level density (Figure 20). Additionally, profiles through each of the long bones were compared between PET and CT images for various cross sections. Preliminary results showed that density was lower in regions of increased \(^{18}\text{F}\) tracer uptake. In one specimen analyzed, there was a significant relationship between SUV tracer uptake and the pixel level density at a single time point \((R^2=0.72)\) (Figures 20 and 21).

![Figure 20: Sagittal cross section a) \(^{18}\text{F}\) PET and B) CT at 2 weeks (time point a)](image)

There was significant inter specimen variation, and in order to achieve this regression a significant amount of data filtering was required. All SUV values below 0.000129 were excluded from analysis to discount the large amount of data in this region where data was poorly correlated. This threshold value was chosen somewhat arbitrarily but yielded reasonably strong correlations. The assignment
of this threshold is likely to vary from animal to animal and as such should be reviewed for each study performed.

In order to process the large amounts of data, a boxplot analysis was performed as shown in Figure 22 (SUV shown on left, density on right). This analysis showed the large range of data. Three time points were analyzed, a) 2 weeks, b) 4 weeks and c) 6 weeks. Interestingly, the density at time point c seemed to approach a homogeneous state for the cross section analyzed. In order to develop the bone remodeling rule sought, a large range of SUV and pixel level densities is ideal. Unfortunately, the analysis methods detailed here could not be used to successfully derive a trend from one of the preliminary datasets (time point b) and hence no $R^2$ value is reported. Efforts to ascertain a meaningful relationship for this group were unsuccessful due to the large data spread and lack of any relationship between SUV and density as was achieved via data filtering for time points a and c.
In Figure 21 above, the $R^2$ values are reported for time points a and c. $R^2$ values reported are 0.719 and 0.691 respectively. Both datasets were heavily filtered utilizing an SUV threshold to discount all data point below SUV=0.000129 as well as any points with density below 0.8g.cm$^{-3}$. Correlations between the parameters were poor below these thresholds and this filtering was required to yield useful results. A lack of high density data points in group c could point to an issue with the data gathering or may highlight that local density is approaching an attractor state value. In either case, further analysis is required.

5.5 Statistical Analysis

Standardized uptake values (SUV’s) for each animal were plotted against CT-based density. Hydroxyapatite phantoms of known density were used to convert X-ray coefficient ($\mu$) to an equivalent bone mineral density for each pixel. Fit relations were developed based on linear, power law (Figure 21) and exponential relationships. Power law relationships provided the highest $R^2$ value for analyzed specimens. The coefficient of determination ($R^2$) was used as the criterion to compare the different regression models generated. Each fit relation was compared using analysis of
covariance (ANCOVA) and Fishers’ Z transformation test. Boxplots were created at each time point to compare density and SUV values obtained from the analysis.

The SPSS statistical software package (Version 19.0, SPSS Inc, Chicago, IL, USA) was used for data analysis. Two tailed values of P<0.05 will be considered statistically significant.

5.6 Discussion

Although promising, much work needs to be done in order to enhance this method to provide the desired results. High variation between samples, and data collection issues all hampered analysis.

The mismatch between voxel size in the CT and PET images, coupled with the relatively large voxel size in both modalities, made identification of formed and resorbed bone regions at each point difficult. As a result it was difficult to ascertain the regions of osteoblastic and osteoclastic activity.

The mathematical development of the bone remodeling rule was restrained until an understanding of the mechanism being studied could be fully understood. In order to improve this method a reduced voxel size is required in both the CT and PET imaging modalities to allow formed and resorbed areas to be identified.

Additionally, the MDA breast cancer cells used to inoculate the rats in this study is the same strain used successfully in similar rat models. However, in the current study, no bone metastases were

Figure 23: Volume rendering created using 18F PET data
observed in any animals included in the study. As a result, it was not possible to generate the relations desired as all studies were undertaken on what was believed to be essentially healthy bone.

Performing registration of FDG PET data was hampered due to the lack of anatomical information in the FDG PET data. As a result, it was not possible to define a sufficient number of fiduciary markers to allow the semi-automatic registration method to be employed (Appendix F). Conversely, registration of $^{18}$F PET data was relatively simple as a number of easily identifiable markers are present as the entire skeleton appears specific (as shown in Figure 23).

As mentioned previously, there was a high level of inter specimen variation. Within specimen variation from time point to time point was also high, and issues with data processing at certain time points affected results which could have been used to produce a preliminary time dependent bone remodeling rule.

Despite these issues, the method offers a promising means to develop a remodeling rule which can describe changes in geometry and material properties associated with disease progression and/or treatment. Despite the significant data processing issues present, useful results can be obtained by analyzing 3D datasets as outlined within this thesis. The procedures used could be significantly improved upon by automating the analysis undertaken.

The two main points to address prior to advancing this method are for the scan resolution to be increased, and the inoculation method investigated.
Bibliography


Appendix A: MATLAB Image Registration Program

The program below provided a simple means to correlate sagittal projections of PET and CT images. Matching of 3D datasets was performed using this software package AMIDE.

```matlab
\text{% Image Registration Algorithm written by J. Rennick 09202011\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\\nBSE = imread('MID-COMP.tif'); % insert filename of BSE image
DICOM = dicomread('MOUSE_TIB_1L_0000.tif'); % insert filename of DCM image
imshow(DICOM)

cpselect(DICOM, BSE) % opens point selection tool
tform = cp2tform(input_points, base_points, 'affine'); % can also use projective transform if required
registered = imtransform(DICOM, tform,...
    'FillValues', 65536);
figure; imshow(registered);
hold on
h = imshow(BSE);
set(h, 'AlphaData', 0.6)
registered1 = imtransform(DICOM, tform,...
    'FillValues', 65536,...
    'XData', [1 size(BSE,2)],...
    'YData', [1 size(BSE,1)]);

figure; imshow(registered1)
hold on
h = imshow(BSE);
set(h, 'AlphaData', 0.6)
[registered2 xdata ydata] = imtransform(DICOM, tform,...
    'FillValues', 65536);
figure; imshow(registered2, 'XData', xdata, 'YData', ydata)
hold on
h = imshow(BSE);
set(h, 'AlphaData', 0.6)
ylim = get(gca, 'YLim');
set(gca, 'YLim', [0.5 ylim(2)])
analysisimage=registered1-BSE;
imshow(analysisimage);
```
Appendix B: Chapter 4 Finite Element Results
For all strain results, visualization was made in the range 0 to 1.5% strain (in either tension or compression). Peak strains above this level adjacent to the defect appear as dark areas. Stress results are shown in MPa. In all cases the final principal strain and von mises stress plots shows the result distribution at failure.

B.1 Tibia 23L: Group 1 Results
B.1.1 Minimum (Compressive) Principal Strain Plots
B.1.2 Maximum (Tensile) Principal Strain Plots
B.1.3 Von Mises Stress Results
B.2 Tibia 22R: Group 2 Results

B.2.1 Minimum (Compressive) Principal Strain Plots
B.2.2 Maximum (Tensile) Principal Strain Plots
B.2.3 Von Mises Stress Results

![Von Mises Stress Results](image-url)
B.3 Tibia 4R: Group 3 Results

B.3.1 Minimum (Compressive) Principal Strain Plots
B.3.2 Maximum (Tensile) Principal Strain Plots
B.3.3 Von Mises Stress Results

![Von Mises Stress Results](image)

- **S, Mises**
- **SNEG, (fraction = 1.0)**
  (Avg: 75%)
- **S, Mises**
- **SNEG, (fraction = 1.0)**
  (Avg: 75%)
B.4 Tibia 8R: Group 4 Results

B.4.1 Minimum (Compressive) Principal Strain Plots
B.4.2 Maximum (Tensile) Principal Strain Plots
B.4.3 Von Mises Stress Results

![Von Mises Stress Diagram]

**S, Mises SNEG, (fraction = -1.0)**

- 9.695e+02
- 6.250e+02
- 5.208e+02
- 4.167e+02
- 3.125e+02
- 2.083e+02
- 1.042e+02
- 5.208e+01
- 6.000e+00

- 8.762e+02
- 7.250e+02
- 6.208e+02
- 5.167e+02
- 4.125e+02
- 3.083e+02
- 2.042e+02
- 1.008e+01
- 6.000e+00

Avg: 75%

![Von Mises Stress Diagram]

**S, Mises SNEG, (fraction = -1.0)**

- 6.729e+02
- 5.208e+02
- 4.167e+02
- 3.125e+02
- 2.083e+02
- 1.042e+02
- 5.208e+01
- 6.000e+00

- 6.250e+02
- 5.208e+02
- 4.167e+02
- 3.125e+02
- 2.083e+02
- 1.042e+02
- 5.208e+01
- 6.000e+00

Avg: 75%
Appendix C: CTRA Analysis

C.1 Tibia 23L: Group 1
C.2 Tibia 22R: Group 2
C.3 Tibia 4R: Group 3
C.4 Tibia 8R: Group 4

![Graph](image-url)
Appendix D: Anatomical Terminology

This figure below highlights the anatomical planes referred to at various points in this thesis. The human body can be divided into 3 major planes: coronal (frontal) dividing the body into anterior and posterior parts, transverse (or axial) dividing the body into superior and inferior parts, and sagittal dividing the body into right and left parts. These planes can be moved to any position in the body and are typically used for tomographic imaging techniques, such as MRI and CT.

Figure 24: Anatomical planes[34]
Appendix E: Material Property Empirical Relations

The empirical relations below allow analysis using the methods described in this thesis to be employed for various anatomical locations and species.

All equations yield modulus in MPa, with input of density in g.cm\(^{-3}\).[11, 38, 40, 86-88]

<table>
<thead>
<tr>
<th>Species</th>
<th>Loading Mode</th>
<th>Bone Type</th>
<th>Equation</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human</td>
<td>Compression</td>
<td>Trabecular</td>
<td>(E = 472.12 \cdot \rho + 16.171)</td>
<td>Nazarian et. al.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(E = 313.95 \cdot \rho_{ASH} + 16.171)</td>
<td>Nazarian et. al.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(E = 82 \cdot \rho^2 + 70)</td>
<td>Rice et. al.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(E = 1310 \cdot \rho^{1.40})</td>
<td>Lotz et. al.</td>
</tr>
<tr>
<td>Cortical</td>
<td></td>
<td></td>
<td>(E = 9000 \cdot \rho + 1300)</td>
<td>Mitten et. al.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(E = 2610 \cdot \rho^{2.58})</td>
<td>Keller et. al.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(E = 14261 \cdot \rho - 13430)</td>
<td>Lotz et. al.</td>
</tr>
<tr>
<td>Tension</td>
<td></td>
<td>Trabecular</td>
<td>(E = 4577.2 \cdot \rho^{1.4719})</td>
<td>Carter et. al.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(E = 12000 \cdot \rho + 2600)</td>
<td>Mitton et. al.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(E = 33500 \cdot \rho - 32100)</td>
<td>Dong et. al.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(E = 21910 \cdot \rho - 23500)</td>
<td>Snyder et. al.</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>(E = 14570.12 \cdot \rho_{ASH} - 23500)</td>
<td>Snyder et. al.</td>
</tr>
<tr>
<td>Shear</td>
<td>Trabecular</td>
<td></td>
<td>(G = 1234 \cdot \rho - 407)</td>
<td>Arlot et. al.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(G = 1883.969 \cdot \rho_{ASH} - 407)</td>
<td>Arlot et. al.</td>
</tr>
<tr>
<td></td>
<td>Cortical</td>
<td></td>
<td>(G = 12031 \cdot \rho - 12753)</td>
<td>Dong et. al.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(G = 18367.94 \cdot \rho_{ASH} - 12753)</td>
<td>Dong et. al.</td>
</tr>
<tr>
<td>Rat</td>
<td>Compression</td>
<td></td>
<td>(E = 8362.8 \cdot \rho_{ASH}^{2.56})</td>
<td>Cory et al.</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(E = 3711.4 \cdot \rho^{1.87})</td>
<td>Cory et al.</td>
</tr>
<tr>
<td></td>
<td>Tension</td>
<td></td>
<td>(E = 5.92 \cdot \rho - 3106.6)</td>
<td>Nazarian et. al.</td>
</tr>
</tbody>
</table>
Appendix F: PET/CT Registration Procedure

1) 3D data registration is performed using the software package AMIDE (downloaded for free via http://amide.sourceforge.net)

2) Import PET and CT datasets (see figure below)
   a. For PET data, use File→Import File(specify)→Concorde/microPET.
   b. For CT scans, use File→Import File(specify)→Raw data

3) Import settings will depend on individual datasets. Typical input parameters are shown in the figure below

4) Upon import, data sets can be registered utilising the alignment wizard in AMIDE.
   a) Fiducial markers are assigned to easily identifiable geometric landmarks.
Figure 27: Image registration window

Figure 28: Alignment wizard dialog 1

Figure 29: Alignment wizard options
5) Export datasets in a format suitable for further analysis via export data dialog, File→Export Data Set (Analyze NIFTI recommended)

6) Import NIFTI file into ImageJ or similar analysis program (available via http://rsbweb.nih.gov/ij/download.html)

7) Reslice to yield sagittal view as shown in figure below
8) Import slices to MATLAB or similar program for image registration. This step will require use of an affine transformation to register dissimilar datasets more accurately (See Appendix A for simple code example).

9) Data can then be analyzed using methods described previously to develop bone remodeling information.