

## TRANSFER REPORT

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# **Identification of Vertebra Characteristics that Determine Different Mechanical Outcomes of Vertebroplasty**

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# Chapter 1

## Literature Review

### 1.1 Introduction

#### 1.1.1 Spine

The human spine is a complex structure that has a host of biomechanical functions. At each level, there are three joints (a disc and two facet joints) which, along with two vertebrae, muscle and ligamentous tissue form a functional unit. The functions of the spine are: to protect the spinal cord, to provide stability and mobility, and to allow the transmittance of movement of the upper and lower extremities.

The spinal column (Figure 1.1.1) consists of 24 articulating vertebrae and nine fused vertebrae, divided into five regions. These regions consist of seven cervical, 12 thoracic, five lumbar, five fused sacral and three to five fused coccygeal vertebrae, which all vary in size, shape and curvature.

The curvature of the spinal column features lordosis (concave curvature, when viewed from the posterior) in the cervical and lumbar regions and kyphosis (convex curvature) in the thoracic and sacro-coccygeal regions. It has been postulated that the curvature exists to increase rotational stability – moving mass away from the centre line increases the centre of inertia about the skull-pelvis axis. The change in curvature during gait cycle reduces the loads on the skull due to absorption of energy in the tendons and musculature of the surrounding areas. The curvature is created by vertebral geometry in the thoracic and sacral regions, while in the cervical and lumbar regions the curvature is created by the intervertebral disc being wedge shaped.

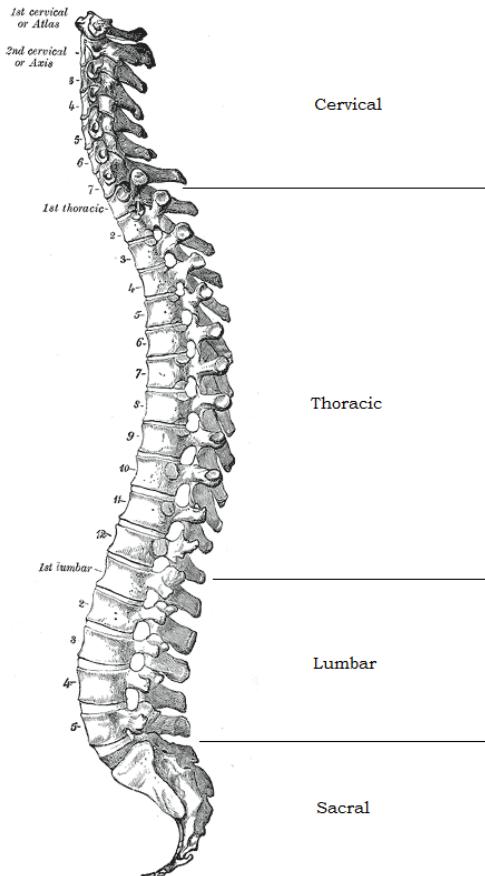


Figure 1.1.1: Curvature of the vertebral column with the four regions labelled. Adapted from [1].

### 1.1.2 Vertebrae

Vertebrae vary greatly between each region and gradually within them. Generally, vertebrae consist of the vertebral body on the anterior portion and the neural arch on the posterior portion along with pedicles and bony processes (Figure 1.1.2).

The vertebral body has a similar structure to long bones, with a low-density trabecular structure internally, with a more dense cortical shell. Due to approximately 80 percent of the compressive load of the spine being carried by the vertebral body [7], the trabeculae are orientated vertically to aid load transfer with horizontal trabeculae providing resistance to compressive buckling. Especially in older patients, often with osteoporosis, the vertebral body can be subject to vertebral fracture, more commonly on the anterior portion, causing anterior collapse and a wedge shape when viewed from the side [7].

Vertebral bodies vary between level in terms of cross sectional area, height and strength, with the axial strength of vertebrae increasing from approximately 1300 N at the third cervical level to over 8000 N at the fourth lumbar level [8]. Similar variations have been found in the bone mineral density (BMD) [9], with the BMD varying with the loads they

are expected to carry. While a reduction in BMD is most often associated with osteoporosis, similar increases in the risk of fracture are attributed to metastatic bone disease.

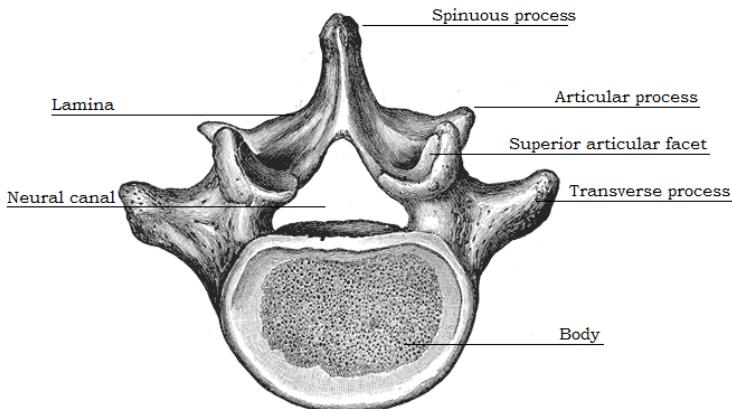


Figure 1.1.2: Superior view of a lumbar vertebrae, with key features labelled. Adapted from [1].

The posterior region of the vertebrae consists of two pedicles, followed by the neural arch and processes. The spinous and transverse processes allow for greater leveraging by the muscles and ligaments while the superior and inferior articular facets of neighbouring vertebrae form the facet (zygapophysial) joints.

Vertebrae at different levels have differing structures to permit their required role. Cervical vertebrae are considerably smaller and lighter than vertebrae at other levels due to the reduced weight they are required to carry (the head and neck, and forces from stabilising muscles). One identifying feature is the foramen transversarium lateral to the vertebral body which allows for the passage of the vertebral artery and vein [10].

The thoracic vertebrae vary substantially through T1 to T12 with the size of the vertebral body gradually increasing and the pedicles changing in orientation and shape. The addition of adjoining ribs through the thoracic region greatly increase the stiffness of the section due to the ligaments and costovertebral joints.

The lumbar vertebrae carry the greatest load of the spinal regions [8] and consequently have the lowest height to width ratio [11]. The end-plates (at the top and bottom of a given vertebra) of this region are in general parallel, suggesting that the lordosis originates from the disc shape rather than the vertebrae.

The sacral vertebrae are fused to form the sacrum which are followed by three to four elements that form the coccyx and fuse in adulthood.

## 1.2 Vertebral Fractures & Vertebroplasty

### 1.2.1 Vertebral Fracture Types

The two most frequent types of vertebral fracture are the compression fracture and the burst fracture. These types originate from different conditions of both the intact vertebrae and the loads applied. To examine the type of fracture, the vertebra is often categorised into three columns from a sagittal view, with the columns being: the anterior , middle and posterior regions [12].

#### 1.2.1.1 Compression Fractures

A vertebral compression fracture (VCF) is a failure of the vertebral body under the anterior column with the middle column remaining intact, a feature unique to this type of fracture [12]. Such fractures can also be identified through compression of the cancellous bone and lack of fragmentation. The two main types of VCF are anterior and lateral, with the mechanism being anterior flexion and lateral flexion respectively. These types can be further divided based on whether the superior or inferior end-plate experienced failure, however failure of the superior end-plate is more common [12]. Radiographically, the anterior height of the vertebral body is reduced with no visible change or damage to the posterior region of the vertebral body [12], although occasionally in juvenile and osteoporotic vertebrae the damage is limited to end-plate impaction [13]. A more extreme case is a vertebral body collapse, found in osteoporotic spines, where occasionally fragments of bone are produced which can violate the spinal canal especially when both end-plates are impacted (such cases are treated as burst fractures) [13].

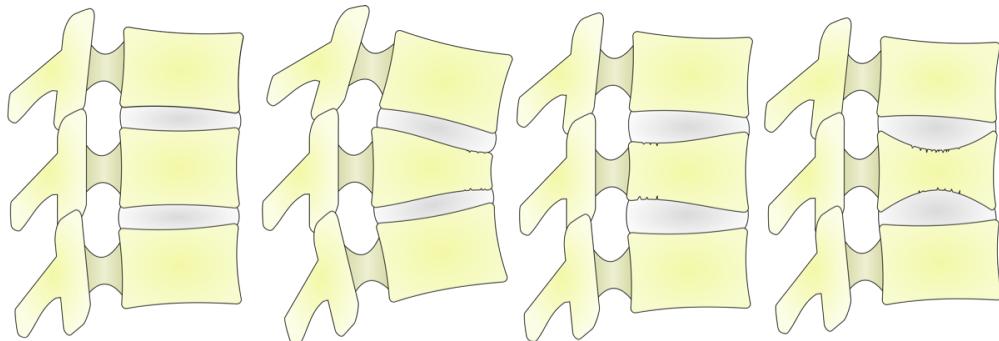


Figure 1.2.1: Types of VCF. Left: Intact FSU. Left-Mid: Anterior wedge fracture. Right-Mid: Posterior wedge fracture. Right: Vertebral body collapse.

A study of 132 anterior VCFs by Denis [12] found that the distribution of fractures favoured the upper lumbar region (L1 was considerably more common) and mid-thoracic (T7 most

common in the thoracic region). Lateral VCFs accounted for only 16 of the 148 VCFs, which were all found to occur in the lumbar region except one case.

### **1.2.1.2 Demographic**

Patients suffering from vertebral compression fractures (VCFs) can experience severe pain for extended amounts of time, dramatically changing daily activities in addition to the pain, through reducing the lower vital capacity and forced expiratory volume when compared to patients without such fractures [14]. Mortality rates were also reported to increase with VCFs in women, with the rate increasing further with the addition of more fractures [14].

Due to VCFs occurring most commonly through the loads applied to the spine exceeding the axial strength of the vertebral body, the demographic of sufferers is dominated by those with osteoporosis or tumours within the vertebrae [14]. The occurrence of osteoporosis is usually age related with the frequency of VCF increasing from 25 percent of postmenopausal women to 40 percent in women aged 80 years old in the United States [15]. However, as discussed by Melton & Kallmes [16], there is difficulty in defining VCFs due to the number of systems developed to define them and the lack of a clear gold standard for classification. This study found that the prevalence varied from 7% to 19% for women in the age range of 50-80 years depending on the method by which the fracture was defined and 4% to 17% for men in the same age range. The prevalence of osteoporotic VCFs in women was found to be twice that of men in an age-adjusted study [17].

VCFs due to tumour infiltration into the vertebrae is another subset of patients and was the motivation for the first image guided percutaneous vertebroplasty procedure in 1984 [18], however it is difficult to assess the rate of such occurrences. The increasing ability to treat osteolytic metastases and myeloma, leave more patients open to vertebral collapse. This is further increased by possible secondary osteoporosis induced by the treatment of malignant lesions [14]. However, specific pathologies and trauma account for a mere 3% and 14% respectively of all clinically relevant fractures [16].

### **1.2.2 Risk Factors**

Many of the risk factors of VCFs are the same as osteoporosis due to their linked nature and can be categorised into potentially modifiable and non-modifiable risk factors [15]. Non-modifiable factors include age, gender, Caucasian race and history of existing fractures;

modifiable factors include insufficient physical activity, calcium and vitamin D deficiency and alcohol and tobacco use [15].

### **1.2.3 Diagnosis**

Approximately two thirds of VCFs are undiagnosed [19] due to back pain often being regarded as a consequence of aging and not reported by patients. Care is often required to ensure that pain is directly related to a VCF and not another spinal entity such as facet arthropathy, herniated disc and spinal stenosis [14]. Indicators for Percutaneous Vertebroplasty (PVP) are often described as pain localised to the area, which lacks suggestions of nerve or cord compression and includes an increase in pain under weight bearing [14]. Vertebral pain for 1-6 weeks that fails to reduce after oral analgesics has also been defined as an indicator [20].

Due to the strong relationship between BMD and bone strength, with stronger vertebrae exhibiting a higher BMD [21], dual energy X-ray absorptiometry (DEXA) or quantitative CT can be used to predict vertebral fractures. Increasingly the ability to assess the bone structure at the clinical level gives a greater ability to clinicians to predict fractures more accurately, due to BMD effectively being a surrogate for the trabecular structure.

### **1.2.4 Vertebroplasty**

The main group of patients that receive PVP are those with either osteoporotic VCFs or those with tumour infiltration. Early use of PVP was limited to those patients who responded poorly to conservative treatments, including analgesics, bed rest, physical therapy and in some cases bracing [14]. However due to the low complication rate of PVP, indication of an osteoporotic VCF is often enough and helps to reduce further compression of the vertebral body [20]. PVP consists of the injection of bone cement into the vertebral body from the posterior side of the body. The addition of cement into an osteoporotic, fractured vertebral body allows stabilisation of the fracture with the aim of reducing pain for the patient.

#### **1.2.4.1 Vertebroplasty Procedure**

Performing vertebroplasty requires careful monitoring during cement injection and cannula placement; this is carried out with the use of fluoroscopic guidance, which helps to limit the possibility of extravasation (cement leakage from the vertebral body). Biplane fluoroscopy

is often used, allowing the procedure to be carried out more rapidly, while single plane fluoroscopy requires checking both lateral and anteroposterior projections [14].

There are three common approaches to the vertebral body: transpedicular, parapedicular, and oblique, shown in Figure 1.2.2. Transpedicular vertebroplasty provides a route into the vertebral body through the pedicle, which acts as a tunnel reducing the risk of dural puncture. Depending on patient vertebrae size and level, the pedicle may be insufficient to allow passage of the vertebroplasty needle and hence other approaches may be required. The transpedicular approach also often requires injection from both sides of the vertebrae into the vertebral body to prevent build-up of cement on one side.

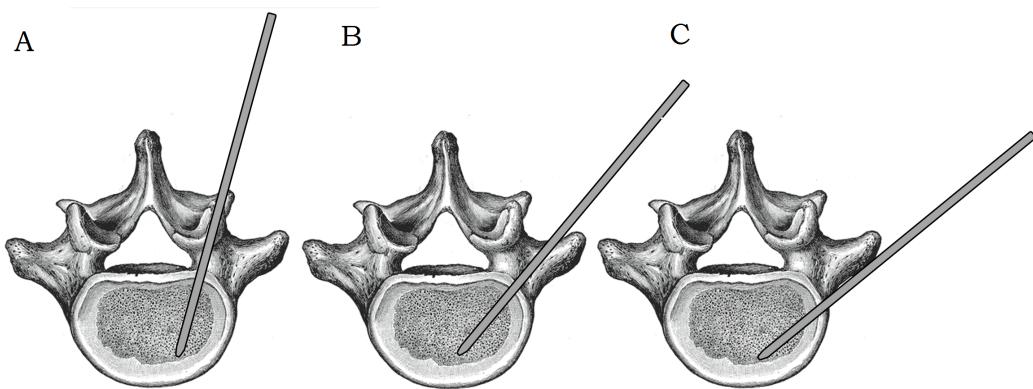


Figure 1.2.2: Three approaches to vertebroplasty. A, transpedicular approach, B, parapedicular approach, C, oblique approach. Adapted from [1].

The parapedicular approach involves the needle being inserted transversely across the pedicle until the vertebral body wall is reached. It has the advantages of allowing the needle to be positioned ideally for injection, removing the need for multiple injections to evenly distribute the cement. Although allowing ideal positioning of the needle tip, it requires the needle to pass close to the basilar vein, therefore increasing risk of puncturing the vein.

Finally, the oblique approach avoids the pedicle entirely, entering the vertebral body in the posterolateral corner and is often used in the thoracic region where the needle can pass over the top of the rib into the vertebral body. Disadvantages of this approach include difficulties in positioning due to the longer needle required and due to the positioning any extravasation at the needle entry point will be around the exiting nerve root [22].

#### 1.2.4.2 Results of Vertebroplasty and Clinical Trials

The pain relief reported following vertebroplasty is currently not fully understood; theories include effects on the nerve endings, both thermal and/or chemical, and the general

Table 1.2.1: Two randomised clinical trials, with their similar inclusion and exclusion criteria and results for the study.

Study Author	Number of patients	Type of pathologies	Inclusion Criteria	Exclusion Criteria	Results for osteoporotic patients
Buchbinder et al. [23]	71 patients, 35 in VP group, 36 in placebo group	Vertebral compression fractures	Pain < 12 months duration and presence of one or two vertebral fractures	> 90 % collapse, presence of spinal cancer, retropulsion of fragments, hip fracture or infection	No beneficial effect of vertebroplasty over a sham procedure at 1 week or at 1, 3, or 6 months among patients
Kallmes et al. [24]	131 patients, 68 VP group and 63 placebo group	Vertebral compression fractures	> 50 years of age 1–3 painful, osteoporotic vertebral compression fractures between vertebral levels T4 and L5. Fracture < 1 year old	Evidence of neoplasm, retropulsion of fragments, hip fracture or infection	No significant difference between groups one month after the procedure on measures of back pain intensity, functional disability, and quality of life

stabilisation of the vertebrae due to the material properties of the cement which can restore the vertebral material properties [4]. The identification of factors that affect pain relief are often difficult to spot, especially with the relatively small patient populations reported in studies, for example the study by Barr et al. [25], with 47 patients was able to find trends showing patients with single level fractures responded better to the procedure. However, the importance of other factors such as degree of kyphosis and compression, age, gender and fracture location require a much larger population in order to obtain any statistical significance.

A large systematic review by Hulme et al. [26] of 69 clinical studies achieved contrasting results to the study described above. A large proportion of patients, 87 %, had pain relief of some degree out of 1552 patients from 32 studies. However, the review also found higher than expected leakage rates, with leakage occurring in 41 % of vertebroplasty procedures and frequent new fractures were found above and below the augmented level. These fractures give an example of the need for larger, comparative, blinded and randomized clinical trials, which could determine whether these fractures are a feature of altered loading,

increased patient activity or whether the new fractures would have occurred regardless of the vertebral augmentation.

The two studies summarised in Table 1.2.1 detail blinded randomised and controlled studies by Buchbinder et al. [23] and Kallmes et al. [24]. These studies raised questions over the risks and evidence for vertebroplasty due to their conclusions that there is no difference between the vertebroplasty and placebo groups. The near simultaneous publication of such results caused many to disregard much of the positive evidence [27] for vertebroplasty. However there are some considerations regarding both of the trials: the inclusion and exclusion criteria detailed in Table 1.2.1 were neither clear nor well defined, failing to take results of MRI scans (Kallmes et al. [24]) and physical examinations (both) into consideration. Such results would link to accepted indications of bone marrow oedema and pain on palpation respectively [28]. In addition to a population bias towards fractures less than six weeks old, there was no statistical significance between chronic and sub-chronic patients (due the small numbers), prohibiting any insight into which subgroups of patients respond best to vertebroplasty. Additionally, the National Institute For Health And Clinical Excellence guidance document suggests that consideration for receiving the treatment should be after six weeks, due to the severity of pain reducing over that time and many patients being pain free at six weeks post fracture [29]. The standard deviation for both pain intensity and Roland–Morris Disability Questionnaire scores were generally high, especially at one month post-procedure. For example the mean ( $\pm$ SD) RDQ score in the vertebroplasty group was  $12.0 \pm 6.3$ , as compared with  $13.0 \pm 6.4$  in the control group. This highlights the need to understand where this variation originates from and hence which subset of patients the treatment is better suited to.

## 1.3 Experimental Studies

### 1.3.1 Trabecular Structure

The biomechanical properties of the vertebrae are known to rely heavily on the trabecular structure, especially the compressive strength and stiffness which relates to the failure behaviour and elastic behaviour respectively. The compressive strength originates from the architecture of the load-bearing trabeculae, which is characterised by thick trabeculae columns or plates oriented vertically and held in place by much thinner horizontal trabeculae. This internal structure changes with age; the vertical plates are reduced to columns through bone remodelling and horizontal supports are often removed [30], [31]. Osteoporosis is

often defined by a reduction in the Bone Mineral Density (BMD) of 2.5 standard deviations below that of a young, healthy member of the population of the same gender. However, reports of poor correlations between the BMD and vertebral fracture rates suggest that a measure of BMD is not sensitive enough to solely determine fracture risks [32], hence the trabecular architecture must be studied using more sensitive and specialised tests.

Methods for studying the trabecular structure of the vertebral body usually involve mechanical testing of the vertebrae, or trabecular bone samples in conjunction with a study of the bone density. The trabecular structure and bone architecture in general can be identified through calculation of the ash density and comparisons of the trabecular structure through histological and  $\mu$ CT examination. The following measurable parameters are usually measured using  $\mu$ CT and/or histological images of the trabecular bone: the bone volume fraction (BV/TV), connectivity density (Conn.D), Structural Model Index (SMI), degree of anisotropy (DA) and the trabecular separation, number and plate thickness (Tb.Sp, Tb.N and Tb.Th respectively) and are discussed in detail in the following papers by Hulme et al. [33] and Mosekilde et al. [34].

The ash density allows comparison of the densities of bone samples through the removal of water and soft tissue in addition to a calculation of the mineral content using an additional measurement of the dry weight. Bone marrow and other remaining soft tissue (fat) is often removed prior to incineration using high-pressure water jets and acetone washes [35]. The dry weight is measured following drying using a recommended 100°C furnace for an hour [35] and the dry density ( $\text{gcm}^{-3}$ ) is the weight divided by the specimen volume. To ash the specimens, they are usually placed in a muffle furnace at 650°C for 18-24 hours [34], [35], which following cooling can be reweighed. The mineral content can be calculated through dividing the ash weight by the dry weight and ash density by dividing the ash weight by the initial specimen volume. However, with the adoption of  $\mu$ CT in most studies regarding trabecular structure, ash density calculations are rarely used in more recent studies.

Other parameters of bone architecture (BV/TV, Conn.D, SMI, DA, Tb.Th, Tb.N and Tb.Sp) are usually defined through  $\mu$ CT scans of the bone and analysis using accompanying software to the  $\mu$ CT scanner. The bone volume fraction, BV/TV, usually quoted as a ratio or percentage, is a measurement of the proportion of the total volume of interest that is bone tissue. Conn.D indicates the number of trabecular connections per volume of interest. The SMI provides a quantification of numbers of different types of trabecular element, usually on a scale from 0 to 3 (from rods to parallel plates) [36]. Tb.Sp and Tb.Th are measured in length and identify the average separation between trabeculae and

the thickness of trabeculae respectively, while Tb.N quantifies the number of trabeculae per unit length. Finally, the degree of anisotropy measures the average alignment of the trabeculae along a specific axis, where a value of one usually specifies isotropic behaviour and less than one equates to various degrees of anisotropy [33].

The region of interest for taking specimens from the vertebral body depends on the nature of the study. If the study requires the capture of an average value for the vertebrae, then the largest possible volume of cancellous bone is required, while avoiding the cortical bone and areas where the basivertebral vein intersects [9]. Other studies have included all cancellous bone between the cranial and caudal endplates and have used subsections of the vertebral body to identify differences and changes with age to specific regions [33].

Bone morphology has been shown to vary greatly between different regions of the vertebrae [33], [37] and between different ages of vertebrae [37], [38]. Animal models are commonly used for the *in vitro* and *in vivo* biomechanical models of the spine while testing the performance of various treatments. However, despite providing a basic understanding of spinal function, the differences in vertebrae at different levels and the changes that the vertebrae experience with ageing mean a single species cannot be used to model the entire spine. Hence many different large mammals have been used, including bovine, ovine, porcine and cervine vertebrae which have already been characterised in the literature [39–41]. These studies compare the anatomical variation in terms of vertebral body width, height and depth, spinal canal size and pedicle height and width. Studies detailing similar anatomical properties for human vertebrae also exist, allowing comparison and assessment of whether a particular animal model is appropriate [10,11]. The anatomical differences found between the animal study papers listed above and the human studies show many differences between all of the parameters, furthering the idea of multiple animals being used for different studies. The studies suggested that sheep spines were much larger than humans, with the vertebral body height being particularly greater [40,41], while the mean vertebral width and depth of the human spine are greater than that of all the animals in the studies (with the exception of the upper thoracic segments in the deer [41]). Much of the geometric and structural variation between human and animal vertebrae may be due to the orientation during walking and therefore load differences. Despite this large difference, muscle forces may add additional loads to the vertebrae, reducing the total loading differences.

A study regarding the trabecular composition of bone samples from the lumbar spine compared: human, dog, pig, cow and sheep and concluded that care was required when choosing a suitable animal model for a particular study, due to the large interspecies differences in terms of Bone Mineral Content (BMC), volumetric BMD (vBMD), height

and area and finally fracture stress [2]. They found that human BMC and vBMD were significantly lower when compared to the other animals in the study, aligning with the greatly reduced fracture stress also reported; the details of this can be seen in Figure 1.3.1. However, the study also reports a higher fracture stress in sheep compared to cows, yet similar values for the BMC and vBMD, with a similar trend also found between pigs (higher BMD) and dogs (lower BMD). Having similar density properties yet high fracture stress, aligns with reports of poor correlations between the BMD and vertebral fracture in the study by Hordon et al [32].

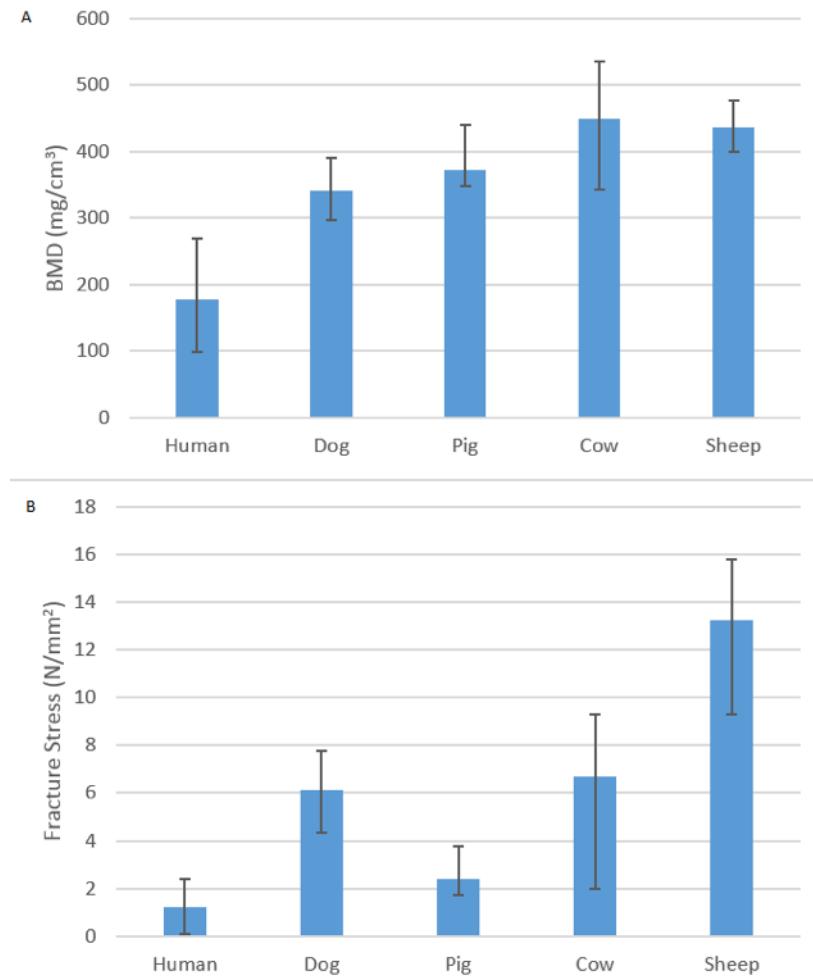


Figure 1.3.1: A, the mean BMD from cylindrical cores taken from the lumbar spine of five different species. B, the mean fracture stress for the same five samples. Bars indicate the range of values. Adapted from [2].

### 1.3.2 Current Studies on Vertebral Fractures and Vertebroplasty

There have been a considerable number of experimental studies that have investigated the effects of vertebroplasty through mechanical testing. Often these studies are carried out in conjunction with computational studies, where properties are defined experimentally and used to validate computational models, for example [42]. These studies are reviewed in

the following section, with a focus on the preparation of specimens and methods and with references to notable findings.

### **1.3.2.1 Specimen Preparation**

Capturing as much data as possible for a given specimen is vital for understanding results and allowing those results to be used in many areas of study. Hence, pre and post-mechanical loading  $\mu$ CT scans (including scans before and after cement augmentation) are usually captured.

To simulate physiologic conditions, specimens are often wrapped in phosphate-buffered-solution (PBS, saline) soaked gauze following dissection [25] and are stored at -20°C and thawed for 24 hours subsubsection before testing at a non-physiological room temperature [43], [44]. This difference between room and body temperature may affect the results, with constituents of the specimens, such as the bone marrow, having different properties at the two temperatures. However, there is a lack of research investigating the effects temperature has on mechanically testing specimens in the literature.

### **1.3.2.2 Mechanical Testing**

The generation of vertebral fractures experimentally attempts to match the natural creation of such fractures; compression fractures are usually generated with an application of force at a low rate, mimicking the gradual creation of fractures in osteoporotic vertebrae over time. Natural burst fractures are usually the result of a traumatic event, high energy impacts causing high rate axial loads through the vertebrae; experimentally burst fractures are usually generated through dropping a load of known mass onto the specimen from a calculated height [43], [45], generating comparative forces to a natural traumatic impact. However, other methods involving biaxial hydraulic testing machines, where high loads (50 – 100 % of the animals body weight) were applied over a short period of time, generating the burst fracture [46].

Mounting of specimens prior to loading in material testing machines allows the position of vertebrae to be maintained during testing, whilst not restricting or confining compression more than necessary. Methods of mounting allow parallel positioning of the exterior surfaces and allow perpendicular loading of the vertebrae along the axis. These requirements for the mounting are usually achieved through potting the specimens in PMMA [43,44,47], semi cured moulding material [48] or low viscosity resin [49].

Methods of loading both a pre-fracture and post fracture/augmentation rely on mimicking the natural loading of the spine, with similar methods being used throughout the literature. Loading is carried out with a materials testing machine, applying loads either under pure axial compression or allowing flexion of the upper endplate through various methods. Methods of applying the “natural” load include applying the load or displacement through a steel ball, requiring a specified loading point and allowing natural motion [43], [44]. Applying bilateral loads through pneumatic cylinders and allowing controlled flexion with simultaneous compression [47] and similarly with the application of two anterior and two posterior loads using pneumatic cylinders positioned so that more of the load was applied to the anterior side causing flexion [49] were other methods used in the literature. The positioning of the applied load differs in the literature varying between the mid point of the superior endplate [50] and one quarter of the distance of the vertebral body in from the anterior margin of the superior endplate [4]. With some studies identifying the effect of loading position on the measured stiffness of the vertebrae [42].

The definition of the point of fracture varies in the literature, most commonly the fracture point was defined as the peak on the recorded load-displacement graph. However, Furtado et al. [44] defined the point of fracture creation as 75% of the original vertebral body height, with the failure strength defined as either the value at the end of the experiment (75% of VB height) or the peak on the load-displacement graph. Pneumaticos et al. [49] defined the point of fracture (or maximum fracture load) using the load-displacement graph, where catastrophic failure could be observed through a sudden jump in the displacement.

### 1.3.2.3 Results of Mechanical Loading

Mechanically loading vertebrae in the study by Furtado et al. [44] showed a significant correlation between failure strength and the product of BMD and endplate area, with the range of failure loads being 900 N to 2200 N for human thoracic vertebrae between T2 and T12. However, the failure load was defined as the load at a deformation of 75 percent of the original vertebral height or the peak load before reaching this deformation, potentially suggesting that the maximum load was not achieved until after 25 percent strain. This may explain the discrepancy between these results and those of Pneumaticos et al. [49] where the average reported failure load was  $6724 \pm 3291$  N for intact specimens using vertebrae between the thoracic levels T2 to T11 from four human cadaveric spines.

#### **1.3.2.4 Experimental Vertebroplasty Compared with Clinical Vertebroplasty**

Experimentally, transpedicular (uni or bi-pedicular) approaches are more common in the literature [44, 47, 49], although extrapedicular approaches have also been used [44].

Although bilateral transpedicular vertebroplasty is the more common clinical procedure [51], unipedicular vertebroplasty is used under some mitigating circumstances often requiring the patient to return for the second injection. A study comparing bilateral and unilateral vertebroplasty found no significant difference between the two procedures in terms of vertebral height and stiffness, possibly attributed to the central positioning of the cement despite the unilateral approach [51]. The authors reached the conclusion that a unipedicular approach is a valid alternative to bipedicular vertebroplasty and may be especially useful during multilevel vertebroplasty by reducing the number of injections and hence risk of cement leaking outside the vertebral walls (extravasation).

#### **1.3.2.5 Results following Experimental Vertebroplasty**

Table 1.3.1: Comparison of the methods used in studies carrying out vertebroplasty experimentally on cadaveric specimens.

Author	Type of specimen	Procedure type & fill volume	Cement Type	Key Finding
Belkoff et al. [52]	Five vertebral bodies (L1-L5) from four female cadaveric spines (age, $80 \pm 5$ years)	Transpedicular, 6 ml fill volume throughout	A bioactive cement, Orthocomp (Orthovita, Malvern, PA) & a PMMA based cement, Simplex P (Howmedica, Rutherford, NJ)	Significantly greater strength following injection of cement, compared to the intact vertebrae
Furtado et al. [44]	Twenty-six single vertebrae from 2 female cadavers (age, 88 and 89 years)	Extrapedicular into anterior third of vertebral body, 20 % volume fill, based on height $\times$ endplate surface area	PMMA with 20 % by dry weight of barium sulfate	Increased failure strength by a factor of 1.72 post vertebroplasty compared to the intact vertebrae
Higgins et al. [53]	Human cadaveric, 61 vertebrae from 5 cadavers with mean age of 81 years	Unipedicular, 10% and 20% cement fill by volume, with unfilled as controls	PMMA	A statistically significant 36% strength increase as compared with the unfilled controls regardless of density levels
Pneumaticos et al. [49]	40 vertebrae from four human cadaveric thoracic spines (age range 65-69 years)	Transpedicular, 6 ml fill volume throughout	PMMA, with 5 to 1 ration of barium sulphate	A reduced failure load post vertebroplasty, although non-significant

The methods used to recreate the vertebroplasty procedure experimentally vary considerably between studies, especially given the sensitivity that certain studies suggest factors such as fill volume have on outcomes. Table 1.3.1 shows the methods and some of the more important variables used in a selection of studies carrying out vertebroplasty on cadaveric specimens. Below is discussion of some of the finer points of the studies, including comparisons to clinical studies.

Identifying the effect of vertebroplasty on intact specimens in the thoracolumbar region, Higgins et al. [53] found the strength was increased by a statistically significant amount of ~36% using 20% fill volume and that when comparing the strength increases with BMD, it was found that those vertebrae with a lower BMD showed a more dramatic increase in the strength. Conversely Graham et al. [54], found that highly osteoporotic vertebrae showed the least improvement compared to intact vertebrae in terms of strength and stiffness.

Higgins found that the upper thoracic vertebrae failed to show any significant result following augmentation of both 10 % and 20 % compared to the intact controls. Belkoff et al. [55] suggested that 7.7 mL of cement was required to restore the original strength of fractured osteoporotic vertebrae, this corresponded to ~24 % volume fill in the lumbar vertebrae tested.

When comparing different cements Belkoff [52] found that in order to obtain a significant increase in the strength 6 mL or approximately a fill of 18 % was required. Similarly, Lee et al. [56], found that between 25 % and 30 % volume fill was required to restore strength to the intact level for lower thoracic and lumbar vertebrae in a clinical study. Graham et al. [54], required a fill volume of 24 % (average 7 mL) to achieve statistical significance, however this did not return the stiffness to the intact level, and only returned the strength to the intact level in those specimens with the highest BMD of their group.

An increase in strength following fracture and augmentation is a desirable outcome especially for osteoporotic vertebrae where returning the strength to that of the intact vertebrae may not prevent fractures. This is often carried out as prophylactic percutaneous vertebroplasty, where the procedure is carried out on vertebrae that are likely to fracture or on levels adjacent to fractured vertebrae already undergoing PVP. Restoring the stiffness however is believed to be responsible for pain relief due to the internal stabilisation and prevention of micro motion, providing a more suitable environment for healing. A study examining the quantity of cement required to restore the strength and stiffness of osteoporotic vertebrae having undergone a compression fracture found that as little as 2 mL of cement is enough

to restore the strength of the vertebrae to the intact value, with the quantity required to restore the stiffness being between 4 mL and 6 mL depending on the level (lumbar vertebrae requiring more cement) [4].

Regarding extravasated cement during the vertebroplasty procedure, Higgins et al. [53] found that an increase in the BMD greatly increased the tendency for cement to leak, however, this typically was from the anterior wall of the vertebra (more favourable than into the spinal canal) and was independent of vertebral level.

Despite previous studies suggesting BMD alone could not be used as an indicator for vertebral fracture [32], Higgins et al. concluded that it was one of the most important factors, conceding however that the BMD measured ex-vivo is not directly comparable to that measured in a clinical setting. This was due to differences in the BMD calculation due to the surrounding soft tissue for the *in vivo* scans.

The results from Furtado et al. [44] using an extrapedicular vertebroplasty approach achieved approximately 25 % fill for specimens which had previously undergone loading to generate a compression fracture, equating to an average volume of cement of approximately 4.5 ml. This augmentation caused a significant increase in the failure load, a factor of 1.72 increasing the average failure load from  $1.61 \text{ kN} \pm 0.49 \text{ kN}$  to  $2.63 \text{ kN} \pm 0.85 \text{ kN}$ . A similar result was achieved by Tohmeh et al. [51], showing that the post augmentation strength is significantly higher than the fractured and intact vertebrae. Pneumaticos et al. [49] found no significant difference between intact and post augmentation intact vertebrae, with an average failure load of  $5.77 \pm 2.13 \text{ kN}$  for the augmented intact specimens with 6 mL of cement injected.

## 1.4 Finite Element Modelling (FE)

The use of finite element models of the spine, spinal segments and vertebrae has been rising rapidly over the past decades. They are being used to model a range of interventions and devices along with being used to aid our understanding of spinal biomechanics. The main benefit of such studies is the ability to test a range of variables and properties for the same model or specimen, with an additional benefit of assessing parameters that cannot easily be measured experimentally, such as stress and strain fields.

Important factors for the generation of biomechanical finite element models have been discussed previously [57]–[58] and include verification, sensitivity testing and validation of models created. The first of these factors is an assessment of the numerical accuracy

of the model; given that most studies use commercially available software for FEA this verification has usually already been carried out, with documentation available. Additional verification can be carried out regarding mesh sensitivity and convergence, where the level of detail of the model is investigated with considerations of accuracy and computational cost. Sensitivity testing determines the sensitivity of a model to various input variables and the errors that these input variables have on the system. Such tests may include the response of the system to various boundary conditions and material properties. Validation of models is a proof that the computational results agree with either *in vitro* or *in vivo* results, however, proof that the results agree with the *in vitro* model do not mean that the model is a valid representation of the *in vivo* scenario.

Due to the importance of trabecular bone in many aspects of bone and spinal research, the methods used to model it are quite detailed throughout the literature. There are currently two dominant approaches to modelling trabecular bone using FEA, discussed in detail by Mengoni et al. [59]. These are  $\mu$ -FE, which expresses the micro structure of the bone explicitly, and continuum level FE models which represent the trabecular structure through a continuous model using an inhomogeneous material property to represent the micro-structure. The increased computational cost of  $\mu$ -FE models, especially for full sized vertebrae and larger functional spinal units, means that many studies use continuum level FEA, despite the reduced level of detail. However, the development of continuum level models allows the use of much larger CT scan data sets, given that the resolution of clinical  $\mu$ CT scanners is upwards of  $1.2\text{ mm}^3$ .

The studies summarised in Table 1.4.1 use various methods to acquire vertebrae geometry, generate models and apply appropriate material properties, either from combinations of scan data and experimental data, or homogenous experimentally defined properties. The variations between methods and results which can be drawn from these studies is described below.

#### 1.4.1 Geometry & Meshing

With the growing availability of  $\mu$ CT scanners and the increasing resolution available with them, studies using *in vitro* measurements and handcrafted geometries such as the study by Higgins et al. [53] in 2007 are being replaced with geometries developed from  $\mu$ CT data. One of the more common methods of generating specimen specific models of vertebrae is the conversion of voxels from down-sampled  $\mu$ CT images into hexahedral elements. The direct conversion of voxels into elements has the advantage of increasing the simplicity of

model generation, however, this requires real specimens (in the form of animal or human tissue) which can be difficult to acquire and scan.

Table 1.4.1: The geometry generation, meshing and material property assignment methods for 7 studies modelling single vertebrae to acquire stiffness and strength data.

Author	Geometry Generation	Material Properties	
		Meshing	
Brown et al. (2014) [60]	Used $\mu$ CT with resolution of $0.074 \times 0.074 \times 0.074$ mm	Using ScanIP software, segmented CT images down sampled to $1 \times 1 \times 1$ mm and meshed in ScanFE using hexahedral elements and tetrahedral elements for the smooth vertebral surface	Material properties assigned using density values from $\mu$ CT. No division between cortical and cancellous bone. Relationship between elastic modulus and BV/TV value investigated
Buckley et al. (2006) [3]	Used $\mu$ CT data with resolution of $1 \times 1 \times 1$ mm	Conversion of voxels to hexahedral elements of size $1 \times 1 \times 1$ mm	Material properties assigned using density values from $\mu$ CT. No division between cortical and cancellous bone
Chevallier et al. (2009) [61]	Used HR-pQCT data with resolution of $0.082 \times 0.082 \times 0.082$ mm	Used $\mu$ CT data to find cortical wall thickness. Surface meshes defined through local triangulation for each cell for the surface and interior cortical wall boundary. Trabecular bone modelled with hexahedrons of size $1.312 \times 1.312 \times 1.312$ mm using GMSH software	Elastic and yield properties assigned to each trabecular element from $\mu$ CT density data

Eswaren et al. (2007) [62]	Used $\mu$ CT data with resolution of $0.03 \times 0.03 \times 0.03$ mm	Conversion of voxels to hexahedral elements of size $0.06 \times 0.06 \times 0.06$ mm. 8 node hexahedral elements using in-house software. Endplates and cortical shell modelled with higher definition using thickness from $\mu$ CT Bone within $180 \mu\text{m}$ of the outer structure was identified as belonging to the cortical shell.	Used a constant material property for entire model
Higgins et al. (2007) [53]	Taken from in vitro measurements of L1 vertebrae, using flat endplates and curved side walls	Composed of 12 node brick elements using in-house code. Used separate mesh for cortical walls and different thicknesses for the endplates and posterior and anterior cortical shell.	Anisotropic through model, using different material properties for cortical shell, endplates and vertebral body.
Kinzl et al. (2012) [63]	Used $\mu$ CT with resolution of $0.082 \times 0.082 \times 0.082$ mm	Used $\mu$ CT data to find cortical wall thickness. Surface meshes defined through local triangulation for each cell for the outer and interior cortical wall boundary, meshed using pentahedra. Trabecular bone modelled with tetrahedra	Material Mapping based on porosity (density). Uses parameters for elastic, plastic and damage behaviour. Uses elasto-plastic material for the cement augmented region
Wijayathunga et al. (2008) [42]	Taken from $\mu$ CT data with resolution $0.074 \times 0.074 \times 0.074$ mm	Hexahedral and tetrahedral elements using ScanFE software, smoothing is applied to vertebral surface to improve geometry	Material properties assigned using density values from $\mu$ CT. No division between cortical and cancellous bone

The cortical surfaces of these models are often rough when just using voxel to element meshing, for example the models created by Buckley et al. [3] in Figure 1.4.1. However, many studies introduce smoothing to the surface of a vertebra model. The error introduced from possible stress raisers when omitting smoothing from the model was questioned by Chevalier et al. [61]. This study suggested that smoothing, in the form of surface meshes representing the cortical walls, successfully removed the stress raisers and artificial damage zones from their models. The studies by the group that produced the Chevalier et al. and Kinzl et al. papers in Table 1.4.1 use methods for fitting the vertebrae surface of the model to that of the scanned specimen, rather than simply smoothing the voxel to element mesh. Kinzl et al. [63] used a “marching tetrahedral” method to extract the surface of the scanned vertebrae from Treecce et al. [64], which uses an adaption of the popular marching cubes method to obtain an iso-surface from discretised three-dimensional data (from  $\mu$ CT data).

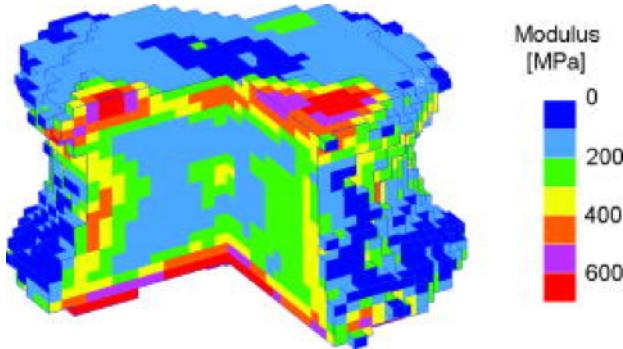


Figure 1.4.1: Voxel finite element mesh of L2 vertebrae used by Buckley et al. with voxel size of 2 mm [3].

There is a reduced difference between the structure of the cortical shell and the cancellous bone structure of the vertebra when compared to other human bones [65]. Despite this, the cortical walls have been shown to share a significant quantity of the load, especially in the axial midsection, where the cross section is narrowest and the load carried by the cortical wall is greatest [65]. An understanding and correct modelling of the load sharing between the cortical wall and trabecular bone becomes more important when considering the variation of the cortical wall with age, location, level and osteoporotic nature of the vertebrae in question [66]. Chevalier et al. [61] found that adding a surface faced cortical shell to their models unloaded the centre trabecular bone and increased the strength and stiffness values of their models to that of their experimental results. Approaches that rely on the  $\mu$ CT greyscale values to assign material properties to elements, give additional stiffness to the cortical walls due to the denser and therefore brighter cortical regions in the  $\mu$ CT images, without the need for modelling the regions separately.

The increased resolution of the Eswaran et al. [62] study allowed for a uniform element size and material assignment for the cortical shell and trabecular bone, relying on the resolution to represent the higher density of bone within this region. In this case, separate meshes were used for the two bone types (cortical and trabecular) to extract information about load sharing between them. However, the required use of a supercomputer to analyse the FE models limits such models being used within research, especially where large datasets are required to investigate population variation.

#### 1.4.2 Material Properties

Material properties for continuum level FE models are in general derived from BV/TV values from  $\mu$ CT greyscale data for each voxel and assigned to the matching element. These density values are used to derive elastic modulus values using a conversion equation. This conversion equation is often optimised to choose the best values for the conversion equations such that the error between experimental and computational results are minimised. Robson Brown et al. [60] performed an investigation into the effect of a linear or non-linear relationship between the elastic modulus and BV/TV. However, due to lower order errors in the form of the tissue modulus and degree of anisotropy, no benefit was found when using the higher order relationship. A good agreement was found with the linear relationship in the Robson Brown et al study when using a similar method in the study by Wijayathunga et al. [42].

Chevalier et al. [61] and Kinzl et al. [63] used other methods of representing the material properties. In these studies an enhanced continuum FE model was used where, rather than using the more common method of converting  $\mu$ CT voxels directly into hexahedral elements, they used high-resolution CT images, which included the cortex and used fabric-elasticity relationships to describe bone morphology. This deviation away from the more common methods used by others [42, 60], potentially allows  $\mu$ CT at lower resolutions to be used, which both reduces computational cost and introduces possibilities for the use of clinically relevant resolutions. The use of lower resolutions was achieved by using 82  $\mu$ m scans and coarsening them to 1.312 mm to mimic common clinical CT scans. With a focus on identifying modelling errors, a study by Pahr and Zysset [67] compared this enhanced continuum FE models with standard methods. This study looked at both the effect of smooth cortex modelling (also used by Chevalier and Kinzl) and the morphology-elasticity relationship. Pahr and Zysset concluded that this method of modelling provided statistically equivalent results for the stiffness of two different models when compared to the more common method, whilst analysing the model at least 100 times faster. This reduction in

time to analyse the models was due to the reduced sensitivity to mesh size, meaning mesh density and therefore number of nodes / elements could be reduced.

### 1.4.3 Modelling Vertebroplasty

The methods used to model vertebroplasty from a selection of studies are summarised in Table 1.4.2. The variation in geometry generation can be seen to vary similarly to studies modelling vertebrae alone, however, in addition to this, the generation of cement geometry and material properties is also presented due to the range of methods used.

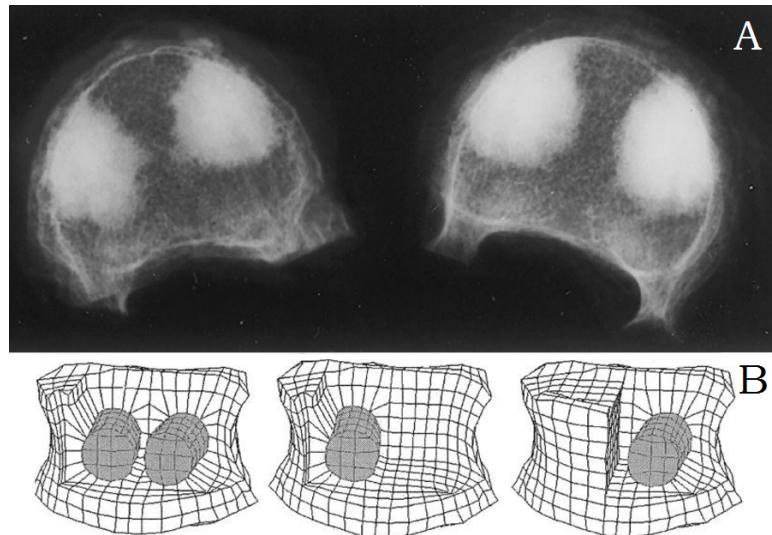


Figure 1.4.2: A: Top view  $\mu$ CT scans of human vertebrae augmented *in vitro*, showing gradual reduction of cement opacity to the edges of the internal cement volume, adapted from Belkoff et al. [4]. B: The augmented model generation for the study carried out by Liebschner et al. [5].

Methods of modelling vertebroplasty usually involve using  $\mu$ CT scans of augmented vertebrae, masking the internal volume of cement though thresholding the greyscale background. However, the methods used in the studies by Liebschner et al., Polikeit et al. and Baroud et al. [5, 68, 69] used approximations of the cement distribution, with the former modelling the distribution according to images from *in vitro* experiments and clinical trial CT scans, while the other studies modelled the cement more approximately. Such approximations of the internal volume of cement can be seen in Fig. 1.4.2:B. The  $\mu$ CT scans in Fig. 1.4.2:A show the much more loosely defined boundaries of the more random internal cement regions, which are created by the trabecular bone that the cement is injected into. The voxels within the defined cement region are often given linear orthotropic elastic properties described by a rule of mixture [70], or more basic material properties with constant elastic modulus and Poisson ration [5, 42, 68, 69].

Table 1.4.2: Method of geometry generation, cement position, location and materials used for five finite element studies of vertebroplasty.

Author	Geometry	Cement position & shape	Cement material
Baroud et al. [68]	Hand modelled , described in Smit et al. 1997, two level model	Used 70% fill of cement	Used previously obtained values for cement infiltrated bone, 46 times stronger, 12 times stiffer than surrounding trabecular bone.
Chervalier et al. [70]	$\mu$ CT scanned pre and post augmentation, model of vertebroplasty combined cement region with non-augmented scan.	Cement position and structure taken directly from $\mu$ CT scans	Bone-cement mixture described by a rule of mixture using a tensor for the isotropic stiffness and for bone stiffness.
Liebschner et al. [5]	Taken from $\mu$ CT data	Cement capsule design, cylinder with rounded edges. Positioned to investigate uni/bipedicular vertebroplasty and centred cement positioning.	Unspecified, PMMA
Pollkiet et al. [69]	Taken from CT scans at 1 mm resolution, manually constructed details not visible. Two level model	Cement modelled as barrels using radiographs as guides. Positioned to investigate uni/bipedicular vertebroplasty including one model with 100 % fill	Constant Young's modulus (3000 MPa) & Poisson ratio (0.41)
Wijayathunga et al. [42]	$\mu$ CT scanned post augmented vertebrae	Identified from $\mu$ CT scan using constant threshold value based on greyscale	Used constant properties for Young's modulus and yield stress. Examined effect of lowering cement modulus to align with that of cement impregnated bone

The studies by Chevalier [70] and Wijayathunga [42] were the only ones to use experimental cement distributions in their FE models. The other studies listed in Table 1.4.2 rely on previously validated models of non-augmented vertebrae, with approximately shaped and placed cement. While such studies can report changes in the overall stiffness, it is difficult to identify how the load is transferred through the internal cement and whether it has been modelled with the correct material properties and boundary conditions for the cement-bone interface. Wijayathunga et al. [42] found large errors between experimental and computational augmented vertebral behaviour, concluding that the representation of the internal cement region as a homogenous material were possibly inadequate. In light of these results the lack of a comparison to in vitro results in the Chevalier et al. [70] study (in order to study prophylactic vertebroplasty) generates questions of the accuracy of cement modelling, in both material properties and boundary conditions.

#### 1.4.3.1 Bone-Cement Interface

Studies have shown that simple approaches to modelling augmentation do not accurately describe the results seen experimentally [42]. Hence, modelling the bone-cement interface is a vital step in portraying the experimental results.

Zhao et al. and Tozzi, Zhang & Tong [71], [72], used a  $\mu$ FE method to investigate the bone-cement interface. They assigned homogenous and orthotropic elastic-plastic properties respectively along with examining the effect of friction between the two surfaces (coefficient of friction 0.3 and 0.4 respectively). Both studies used stepwise compression testing of their trabecular bone-cement samples (open cell rigid polyurethane foam, similar to osteoporotic human trabecular bone and bovine trabecular samples from the iliac crest, Zhao et al. and Tozzi, Zhang & Tong respectively) within a  $\mu$ CT scanner to assess the evolution of stress in a stepwise fashion. These studies found good agreement with computational and experimental data, with Zhao et al. showing that a composite of bone and cement was considerably lower than what would be expected by cement alone or predicted by a rule of mixtures, such as that used in other studies described above [70]. Tozzi, Zhang & Tong found that greater cement penetration or contact area did not increase the compressive strength contradicting the results of Janssen, Mann & Verdonschot [73] in a FE study of cemented total hip arthroplasty. This study examined friction coefficients and morphology under both compression and tension, which along with the results of Tozzi, Zhang & Tong potentially suggest that cement penetration is more important for failure under tension rather than compressive loading. This advocates the idea of buckling trabeculae at the boundary of the cement region and a lack of load transfer into the cement-bone

interdigitated region.

In a similar study to those by Zhao et al. and Tozzi, Zhang & Tong [71], [72], Kinzl et al. [74] examined the effect of PMMA shrinkage due to polymerisation and different interface properties. The shrinkage of PMMA upon polymerisation affects the bone-cement interface due to gaps developing between the two materials caused by the volume change of the PMMA. Kinzl et al. showed that the shrinkage affected their models in two ways, firstly, the loss of volume and creation of gaps reduced the load transmission between the materials and secondly it created residual stresses in the PMMA, causing bone damage at trabecular connections from compressive and shear loading.

Sikora [75] used FE models generated from  $\mu$ CT images of ovine lumbar vertebra to investigate the bone–cement interface. An analytical model of the behaviour of trabecular bone struts embedded in cement was used to impose properties on an interface region defined in the model. The analytical model was used to predict the interdigitation between the two materials and forecast the characteristics of failure between them, it was then used to determine the plastic and elastic properties to apply to the defined interface mesh. The use of the interface layer with explicitly defined properties produced a good agreement with the experimentally determined results for the sample under compression. However, the study was carried out using cylindrical specimens of height 25 mm and diameter 13 mm, hence a further investigation would be required to identify whether this method would prove useful for modelling whole vertebrae.

#### 1.4.4 Discussion of FE studies

Finite element studies modelling vertebrae are currently producing accurate models for single intact vertebrae. The methods employed by Chevalier et al. [61] to reduce the need for high resolution  $\mu$ CT scans and instead use more clinically relevant resolution, present a valuable tool for clinicians. Problems arise however when attentions are turned to modelling vertebroplasty, specifically, modelling how the two materials interact while under compression.

Despite the well validated results for the three  $\mu$ FE interface studies [71], [72], [74], which examined more accurate methods of modelling the boundary between materials, the computational cost of running such simulations on whole vertebrae restricts further research. Especially given the 700 hours on a high performance computer reported by Zhao et al. [71] for a trabecular sample. Hence, methods employed by Sikora [75] require further testing and validation for whole vertebrae in order to strike a balance between agreement

with experimental data and computational cost.

## 1.5 Capture of Population Variation

There is an increasing need for patient variation to be taken into account in pre-clinical testing; however, experimentally there can be difficulties in controlling this variation. Obtaining large quantities of varied tissue can be problematic and time consuming, along with the problems of characterising the variation. Relating to the spine: in vitro studies are limited by tissue availability and controlling and understanding its variability (especially for human studies) and in vivo studies are heavily limited by the invasiveness of any measuring methods. Hence, FE studies present a vital method in assessing the spine. Currently however, the main advantage of FE studies is the ability to run multiple scenarios for the same model (for example using different material properties for implants or different quantities of cement in vertebroplasty studies); this removes variability from the study. In order to use FE studies to examine patient variability across the population then there is a need for large quantities of patient specific models, similarly to experimental work.

Variability in terms of shape, size and density of vertebrae is high between individuals, with even greater variability for those with various pathologies. The effects that this variation has of vertebroplasty is very important, whether certain variables result in more positive outcomes or others suggest more conservative treatments are more suitable. Hence, large sets of models that cover the whole range of variation across the population and then categorised based of vertebroplasty effectiveness, could be used to predict outcomes clinically.

However, these large datasets are difficult to gain access to, for ethical reasons among others [6] and current FE studies usually do not attempt to model population variation and instead use vertebrae specific models from a limited selection of experimental specimens [3,42,63,70]. The alternative to requiring cadaveric specimen or clinical scans is to generate large datasets of vertebral models statistically.

Such statistically generated model studies have been carried out previously for the femur [6,76] and for the knee joint [77,78]. Such studies rely on large databases of CT scans and PCA statistical modelling to represent the shape and BMD distribution of bones.

### 1.5.1 Principal Component Analysis Methods

The purpose of Principal Component Analysis (PCA) is to capture the variation within a given dataset. It allows an understanding of how different variables interact and what variables control the greatest variation. Here, there is a focus on using PCA for shape analysis, but the algorithm can be used for many other types of data. The variation in data is expressed as eigenvalues which become the principal components for the data-set. These eigenvalues or principal components can then be ranked, allowing an understanding of what variables describe the greatest variation in the data-set (for example the general size or length of a bone). With regard to the biomedical field, it has been applied to sets of data containing similar shapes, such as sets of human femurs and knee joints. In these examples it allows an understanding of how the bones vary across the population contained in the given data-set.

Often the first step for PCA is to normalise scaling, rotational and translation differences between the specimens within the dataset. This is carried out via generalised Procrustes analysis (GPA) and is often referred to as a prepossessing step for PCA, it is described in detail by Grassi et al. [6] and Väänänen et al. [76]. Once normalised, matrices are created from columns containing specimens and rows containing the nodal coordinates for each mesh. Using this matrix and the mean coordinates from it, the PCA algorithm can be applied, from which the principal components can be acquired. These principal components describe each mode of variation, ordered in terms of the largest variance. To determine how much variation is contained within each principal component, the eigenvalue for each component can be divided by the sum of all eigenvalues. The first three modes of shape variation for a femur (used here as a convenient example) can be seen in Figure 1.5.1, with the minimum and maximum extremes from each mode of variation seen in the wireframe and shaded model respectively [6].

Similar methods can be used for the BMD and how it varies between specimens. Once models were generated with BMD assigned to each element, another matrix is assembled with rows consisting of the BMD of each element in the mesh. From which a similar method to above can be applied to acquire the principal components and the amount of variation contained within each components.

The understanding of the variation of a data-set and its description in terms of a potentially reduced number of components, allows the generation of virtual specimens that fit within the ranges of the input data set. For example principal components could be altered in terms of their standard deviation about the mean specimen (based on the input data). This

would allow the generation of virtual specimens that fit within the bounds of variation of the current data, but do not currently exist due to possible gaps in the data set. It also means that the variation can be quantified, allowing effects caused by variation to be studied in an iterative fashion. For example, in the case of vertebrae, if changes to the diameter of the spinal canal correlate with process length (a correlation that would be difficult to identify without PCA), then the effect this has on specimen strength can be examined in depth by altering the component that controls this relationship. Models that are described by this relationship and could be generated and solved through FEA, furthering our understanding of the relationship. However, generating models from the statistical models can produce some problems regarding reliability. For example, the generated models heavily rely on the input database, hence the database is required to evenly represent the entire population. There can also be issues with the generating algorithm's ability to produce shapes and materials not present in the starting database [6], [76].

The Grassi et al. study [6] into whether PCA based modelling can be used for the femur concluded that such generated models were able to describe the population of femurs using generated FE models. They found that 50 modes or the first 50 principal components were required to accurately reconstruct the femur while maintaining errors below that originating from pixel size and another 40 to generate accurate density in the models.

In a study by Fitzpatrick et al. [78] statistical shape models were developed in order to identify the relationship between the shape and function of the patellofemoral joint. Here, 26 magnetic resonance scans of the knee were taken, from which FE models of the joint in question were created. PCA was applied to the set of models, from which the first 15 principal components describing the shape were taken, these 15 components accounted for 97.2% of the total geometric variation, with the first component (PC1) counting for 47.7 %. PC1, as is often the case in biological models, described the variation in the size of the joint components, with the next two components describing the position of the patella and details regarding the conformity and depth of the joint. Following modes of variation described more subtle variations in the geometry of the model.

In order to assess the robustness or ability to accurately predict outcomes of the reconstructed bones or joints, the studies [6, 78] use a leave-one-out approach. This approach neglects one specimen from the development of the shape-function models. The final model, based on the included specimens can be used to predict the mechanics or properties of the left out specimen by using the generated FE models.

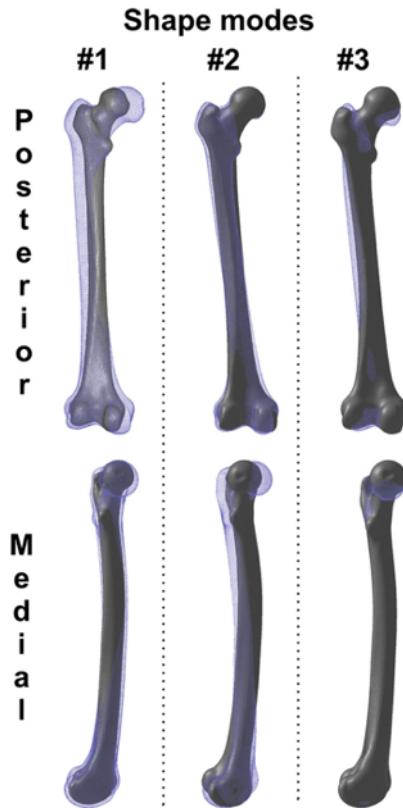


Figure 1.5.1: Femoral shape variations for the first three modes from the PCA. From 115 bones the maximum eigenvalue is shown with the minimum eigenvalue shown in wireframe. Taken from [6].

### 1.5.2 Discussion

The studies described above present useful workflows of generating virtual subjects from a statistical model acquired from a databases of scans. Such methods allow a variety of population based studies, including those regarding the variation of vertebrae across the population.

The ability to generate models not present in the input dataset and hence create a large set of models representing the population allows us to identify relationships not openly visible. For example in the study by Fitzpatrick et al. [78] a 5 mm change in the patella position caused a 25% increase in the contact pressure mid-flexion. This relatively easy quantification of the relationship between geometry and function can easily be transformed to quantify the relationship between vertebral geometry and the mechanical response to vertebroplasty. Equally, such relationships could enable the prediction of vertebral fracture, adjacent level fracture or advise clinicians as to the quantity and location of cement for different patients.

## 1.6 Conclusion

Vertebroplasty potentially provides a valuable method to treat patients with osteoporotic compression fractures, however, the uncertainty regarding its effects, especially regarding certain subsets of patients, mean that further research is required. While the mechanisms of pain relief are not fully understood, certain assumptions regarding the mechanical stabilisation and restoration of stiffness can be investigated. Such investigations may help to understand how patient groups respond to the treatment in different ways.

Current experimental studies have provided a range of useful techniques for mechanically testing vertebrae and for carrying out the vertebroplasty procedure itself. However, obtaining enough vertebrae to represent variation across a population in order understand its effects on different patients is a difficult task and has not been attempted. A possible solution is FE modelling in conjunction with PCA. FE models have been shown to represent the intact vertebrae accurately using both  $\mu$ FE and continuum level models.

Problems arise when modelling the augmented vertebrae, with few studies modelling specimen specific augmented vertebrae and instead modelling vertebrae with arbitrary volumes of cement. Studies that have modelled and validated against experimental results have shown poor agreement, owing to the incorrect modelling of the cement-bone interface or incorrect selection of material properties for the cement-bone interdigitated region.

Finally, principal component analysis has shown its value in the literature presented above allowing the variation in a set of specimens to be accurately described and in certain cases models have been spawned at standard variations away from the mean.

## 1.7 Aims & Objectives

The main aim for the project is to examine whether the outcomes for patients undergoing vertebroplasty are due to underlying biomechanical difference in their vertebrae. To achieve this overall aim three objectives have been defined:

1. To model specimen specific vertebrae accurately, initially using bovine tail vertebrae and later human vertebrae.
2. To carry out vertebra augmentation experimentally and accurately model the results of this augmentation in specimen specific models. This will require an investigation into the cement-bone interface within FE models, allowing the accurate modelling of augmented vertebrae.

3. To use PCA to identify patient subsets that respond differently to the mechanical outcomes of vertebroplasty.

The first objective will require both experimental and computational work-flows. Experimental work will focus on testing methods using bovine tail vertebrae, with an aim to adapt methods to use human vertebrae. Computational work will concentrate on the creation of models of the bovine vertebrae that agree with experimental results for stiffness.

The second objective will involve developing methods of carrying out vertebroplasty on bovine specimens, aiming for clinically relevant volumes of cement using methods similar to those used in a clinical setting. The computational side to this objective is to further the understanding of modelling cement-bone interfaces, allowing accurate models of augmented vertebrae to be made.

To achieve the final objective, an understanding of PCA will need to be developed along with how to apply it to vertebrae. This will include methods of registering the volumes that define the vertebral body, applying the PCA algorithm and producing spawned vertebrae to help understand the variation in vertebrae of the population.

# **Chapter 2**

## **Bovine Tail Vertebrae**

### **2.1 Experimental Methods**

#### **2.1.1 Introduction**

The experimental methods that have been developed and the early results acquired in this sections allow easier transition to using human tissue and provide valuable results for the development of specimen specific finite element models. Currently, experimental work is limited to bovine tail vertebrae due to their plentiful nature and relatively similar geometry to human vertebrae. Studying these vertebrae allow the development of methods for material testing, acquiring  $\mu$ CT scans of the specimens and carrying out vertebroplasty on the specimens. The following section will detail the development of various aspects of the experimental procedure, difficulties encountered and traversed, initial experimental results and finally a discussion of the methods, results and future work.

The steps involved in the developed methods involve dissection of the soft tissue from the vertebrae, potting in PMMA end-caps, scanning using a  $\mu$ CT scanner, compression testing and augmentation, the order of which can be seen in Fig. 2.1.1. Specimen preparation, fracture generation and initial  $\mu$ CT scan was undertaken jointly with Ruth Coe (PhD student, University of Leeds). Vertebroplasty (following initial training attempts) and subsequent loading and scanning was carried out solely by the author.

#### **2.1.2 Specimen Preparation**

Bovine tails were acquired from a local abattoir and frozen to -20°C prior to use. They were defrosted in a 4°C fridge for approximately 24 hours before the initial dissection. The

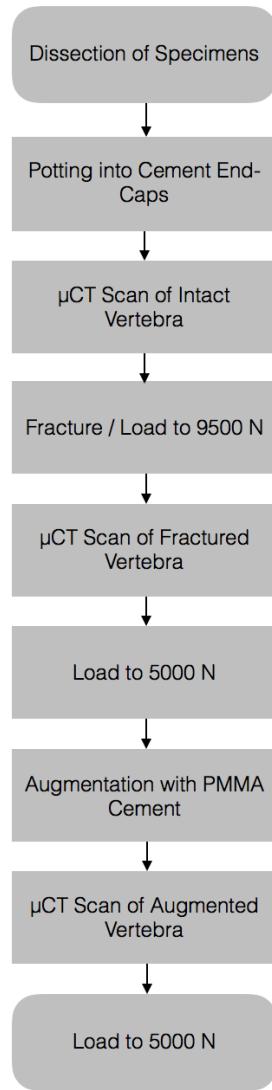


Figure 2.1.1: Flow-chart detailing the experimental process from initial dissection to final load test.

three most caudal vertebral (CC1 to CC3) were kept, discarding the remainder of the tail due to the elongation of the vertebral body further distal of the first three vertebrae. In addition to the elongation of the vertebral body the spinal canal narrows limiting its ability to house a steel rod used for mounting the vertebrae in PMMA end-caps. Soft tissue was removed from the vertebrae as thoroughly as possible, including the intervertebral disc material and material occupying the spinal canal. This was carried out in order to remove potential error when comparing experimental results of stiffness to the vertebra models developed from  $\mu$ CT scans (due to difficulties modelling the soft tissues) and to allow a metal rod through the spinal canal to aid alignment.

Once dissected (and in subsequent breaks between procedure steps) the vertebrae were wrapped in phosphate buffered solution (PBS) soaked tissue, in an attempt to limit the vertebrae from drying. The specimens were potted in PMMA end-caps to allow repeated

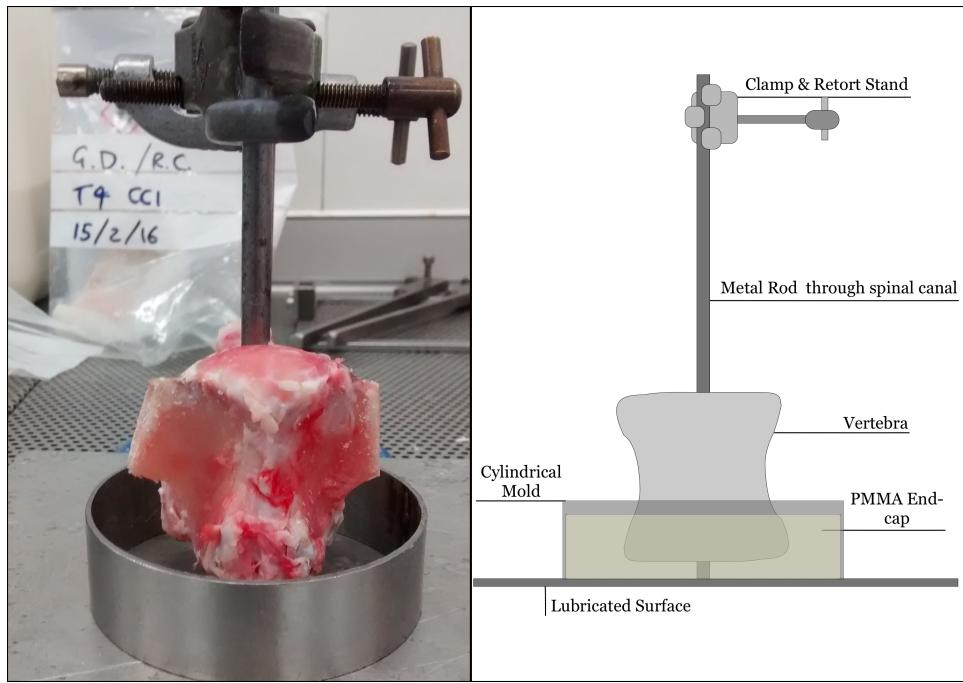


Figure 2.1.2: Photograph and diagram depicting the method of creating end-caps for the specimens.

loading of the vertebrae with the same orientation and positioning, while constraining the vertebrae as little as possible and allowing flexion of the upper endplate. The setup for potting the vertebrae can be seen in Fig. 2.1.2. Vertebrae were held using retort stands and clamps holding a rod placed through the spinal canal. Depending on the level of the vertebrae the spinal canal was packed with foam around the rod forming a snug fit while the vertebrae was held approximately 5 mm above a petroleum jelly lubricated metal surface. Also, depending on the level of the vertebrae, any pedicles that protruded past the limits of the metal cylinders were removed with a hacksaw at their base to prevent issues with the loading and scanning tests which followed, most often this was limited to the most caudal vertebrae and can be seen in Fig. 2.1.2. Lubricated hollow metal cylinders of ~10 cm diameter were used to form the endplate when the 2:1 powder to liquid component PMMA mixture was added. PMMA was added until the endplate of the vertebral body was covered up to the point where the body becomes concave. After approximately 20 minutes the PMMA had sufficiently set to turn over the vertebra and create the end-cap at the other end using the same process with the addition of a level to ensure the creation of parallel end-caps.

Once the PMMA was set the vertebrae were wrapped in more PBS soaked tissue before being frozen or stored in a fridge until the vertebrae were loaded to fracture. The specimens were frozen only if more than 24 hours would pass before the next stage of testing to reduce the number of freeze thaw cycles.

### 2.1.3 Axial Compression

#### 2.1.3.1 Fracture Creation

All specimens underwent axial compression using a material testing machine in order to generate fractures within the vertebral body. Mounted vertebrae were placed between two steel end-plates, the lower of which contains four screws to inhibit lateral motion of the specimen when under load and the upper plate contains similar screws, with the addition of a chamfered hole. This chamfered hole allows the alignment of the specimen so that the loading point was directly below the head of the testing machine using the marker located above the centre of the vertebral body. The steel ball becomes the centre of rotation for the free to rotate upper end-cap. This permitted rotation mimics natural loading of the vertebrae and increases the likelihood of physiological anterior wedge fractures. Details of the setup can be seen in Figure 2.1.3.

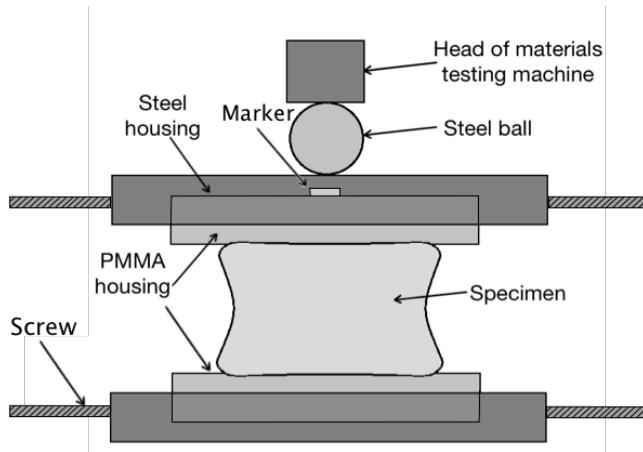


Figure 2.1.3: The experimental setup for axial loading the vertebral specimens.

Loading of the vertebrae starts with a preload from 50 N to 300 N for 10 cycles at a rate of 1mm/minute to remove any viscoelastic effects of any remaining soft tissue. Following the preload, displacement was increased by 1 mm/minute until either the load reached 9500 N (due to the 10 kN load cell limit) or a visible failure occurred on the real-time load-displacement plot during compression. This failure was observed as a peak in load with the compression being stopped once clear decrease in load was observed. Both scenarios can be seen in Fig. 2.1.4.

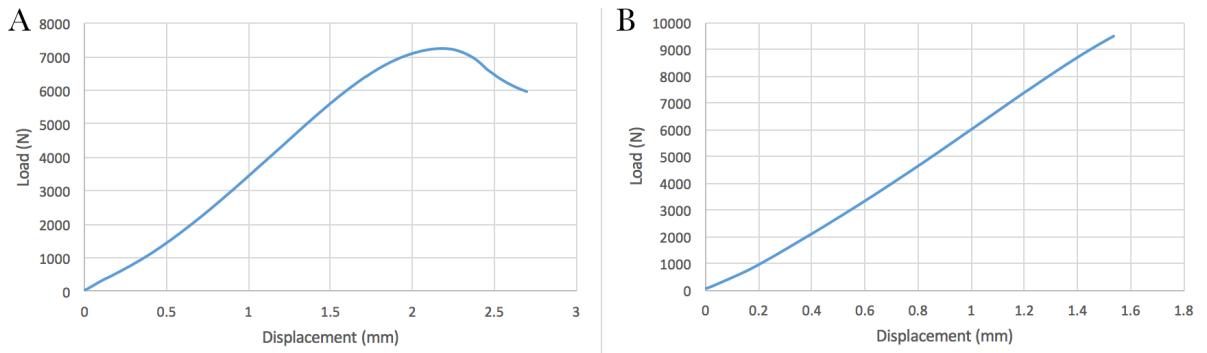


Figure 2.1.4: The difference between failure (A) and non-failure (B) for bovine tail vertebra compressed to a maximum load of 9500 N or until a peak was observed.

### 2.1.3.2 Post Fracture & Post Augmentation Loading & Stiffness Calculation

In order to find the stiffness of the previously fractured and augmented specimens a similar loading procedure was used. However, following the preload, compression was stopped when the load reached 5000 N as a means to limit additional damage and fractures to the vertebrae. This ensured that the vertebral stiffness across the three stages (intact, post-fracture and post-augmentation) was calculated from the same range of loads (0 - 5000 N). To examine the effect that the initial load to failure has on the following loads, both post-fracture and post-augmentation, a control specimen was used. This control (T1 CC3) was only loaded up to 5000 N before ending the test.

The stiffness of the specimens throughout their tests was calculated using a Matlab (Mathworks) script on the raw data from the materials testing machine. The script was adapted from a script written by R. Coe (University of Leeds, 2016). The script allowed the limits of the range of interest to be set and, using a defined segment size, incremented over the data reporting the greatest stiffness found in a segment. The segment size was set to 0.3 mm. The script iterated over the data in overlapping increments of 0.1 mm and the range of interest was set to 0 - 5000 N, this can be seen in Fig. 2.1.5.

If the load-displacement curves were perfectly linear within the “linear region” the stiffness in the three ranges of interest in Fig. 2.1.6 would give an equal value for the stiffness or maximum gradient. However, given that these values were found to differ for the three ranges it suggested non-linear behaviour. As shown in Fig. 2.1.6 the recorded maximum stiffness varies greatly depending on what portion of the load displacement graph was being examined. The average difference between the 0 - 5000 N section and the 0 - 9500 N section was much smaller compared to the 0 - 1500 N section, hence 5000 N was used as the limit on the already fractured vertebrae tests. Due to the slight convergence towards

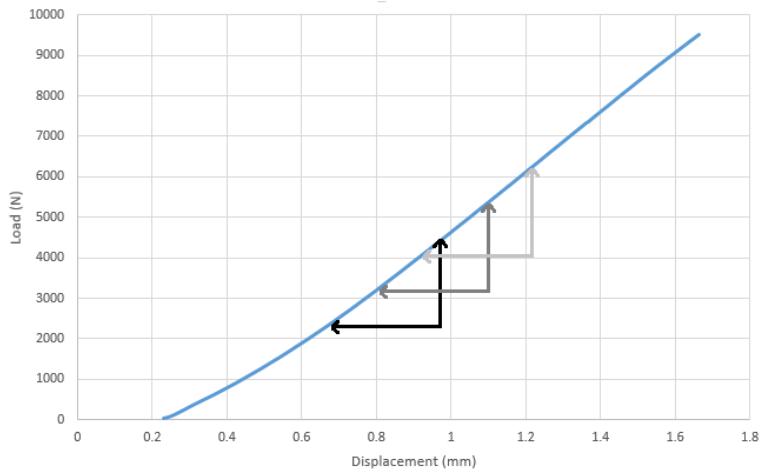


Figure 2.1.5: A typical load displacement curve showing how the gradient was taken from 0.3 mm long sections incremented at 0.1 mm across the length of the curve.

5000 N, this value was seen as a compromise between the risk of further damage whilst still obtaining a genuine value for the stiffness.

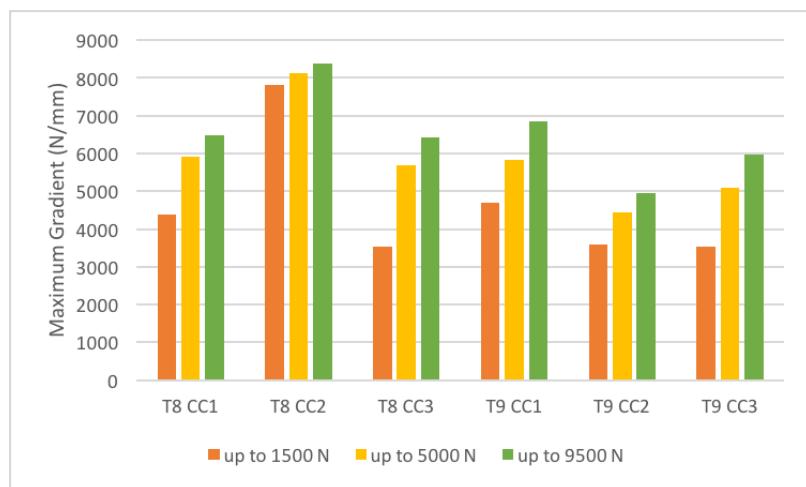


Figure 2.1.6: The difference seen when measuring the greatest gradient (stiffness) using different portions of the load displacement curve. From 0 to 1500 N, 0 to 5000N and 0 to 9500N.

## 2.1.4 Vertebroplasty

The procedure was developed in collaboration with two clinicians (Dr Peter Loughenbury & Dr Vishal Borse) from the Leeds General Infirmary. Subsequent tests of the procedure were undertaken with the aid of Dr Sebastien Sikora, Dr Fernando Zapata Cornelio & Ruth Coe (Research Fellow, Research Fellow & PhD student respectively), while specimens with results presented here were augmented solely by the author. Due to the differences between human and bovine vertebrae it was not possible to perform bi-pedicular vertebroplasty on the bovine specimens using the methodologies established for human vertebra. The

main difficulty was the greatly increased density of the bovine vertebra bone, meaning that rather than pushing the vertebroplasty needle into the vertebra by hand, a mallet and vice to hold the vertebra were required. In addition to this, the force required to inject cement into the vertebral body was greatly increased. The vertebroplasty method for bovine tail vertebra was therefore developed over several iterations due to these difficulties. This sub-section details the initial procedure, the problems encountered and solutions developed to allow a clinically relevant volume of cement to be injected and captured in  $\mu$ CT scans.

#### **2.1.4.1 Initial Procedure**

The procedure was initiated by using bone nibblers to remove the rounded end of both posterior pedicles, providing a surface to start the needle entry. While holding the vertebra in a table mounted vice the needle's markings were used to estimate the depth and angle needed to reach the anterior quarter of the vertebral body. The placement of the needle required care to ensure the pedicle was not damaged through splitting as it was inserted. A mallet was used to insert the needle until it was at the depth required; the procedure was repeated for the other pedicle, reusing the same needle.

The PMMA cement was mixed 1:1 monomer to powder to ensure that it could be drawn up via the syringe and to allow enough time to inject the cement before it thickened and set. This additional setting time and reduced viscosity is also used by clinicians, who use ratios up to 0.74 monomer to powder with no adverse outcomes associated despite the reduced modulus and strength often reported [79, 80]. While the vertebra was held in the clamp of a retort stand, the syringe was attached to the needle, which in turn was inserted into one of the pre-made tracks through the pedicle into the vertebral body. Cement was pushed into the vertebrae using the syringe, until  $\sim$ 3-4 mL was inserted into both sides of the vertebrae, with cement being used to back fill as the needle was removed. The vertebrae were then left for approximately an hour until the cement had set before scanning.

#### **2.1.4.2 Complications and Changes to the Procedure**

Various problems were encountered while carrying out the procedure that required the methods to be adapted. These challenges and their solutions are described below.

**2.1.4.2.1 Vertebral Temperature** The first of these was the difficulty found injecting any cement into the vertebra. With the initial specimens, cement was injected but it

was mainly reserved to the needle tracks rather than the vertebral body. To counter this the vertebrae were warmed to 37°C for an hour or until the internal temperature of the vertebrae had reached this temperature (using a temperature probe in the vertebroplasty needle hole). This meant that the bone marrow inside the vertebrae was no longer solid and therefore could be displaced by the cement making the injection much easier.

**2.1.4.2.2 Radio-opacity of Cement** A second problem was the opacity of the cement on  $\mu$ CT scans, which proved difficult to segment and separate it from the trabeculae in the vertebral body as can be seen in Fig. 2.1.7:A. Here, the cement was indistinguishable from the bone marrow and can only be seen in the needle channel. The solution to this was to mix barium sulphate ( $\text{BaSO}_4$ ) with the PMMA to achieve the radio opacity seen in Fig. 2.1.7:B, where the bright area in the centre of the vertebral body is the injected cement and  $\text{BaSO}_4$  combined. Due to the hydrophilic nature of the  $\text{BaSO}_4$  powder it was important to use a completely dry beaker when thoroughly mixing it with the PMMA powder to limit aggregation of the  $\text{BaSO}_4$ , which can be seen in the bright spots in Fig. 2.1.7:B. The two components were used in a 1:4  $\text{BaSO}_4$  to PMMA powder ratio, mixed 1:1 with the liquid PMMA component.

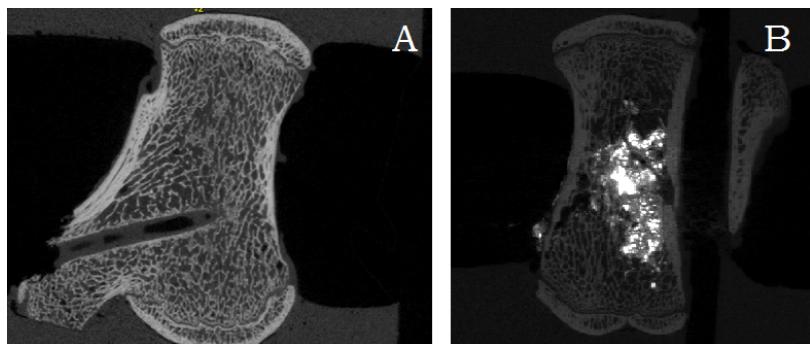


Figure 2.1.7: A:  $\mu$ CT scan of an augmented vertebrae, with some visible PMMA residing in the needle channel. B:  $\mu$ CT scan of an augmented vertebrae using PMMA mixed with barium sulphate.

**2.1.4.2.3 Cement Leaking from Vascular Channels** Preventing the cement from exiting the vertebrae from vascular channels while injecting the cement proved to be another obstacle to achieving a physiologic fill volume for the vertebrae. These channels lead both out the anterior face and from the vertebral body into the spinal canal, this can be seen in Fig. 2.1.8 and 2.1.9. In the body these channels would be filled with vasculature preventing the cement leaking through them. Two main methods were used to stop cement leaking while carrying out the procedure on the bovine tail vertebra. The first was to use the same rod used for mounting the vertebrae in their end-caps to limit the passage of

cement into the spinal canal. The second was to use blu-tac to cover the external vascular channels, wrapped with cling-film to hold it in place. This allowed any bone marrow free passage out of the vertebrae, but enough resistance to limit the flow of cement.



Figure 2.1.8: A:  $\mu$ CT scan of an augmented vertebrae showing the cement leaking from vascular channels on the anterior side. B: Photograph of an augmented vertebrae cut into four quarters showing a vascular channel leading into the spinal canal.

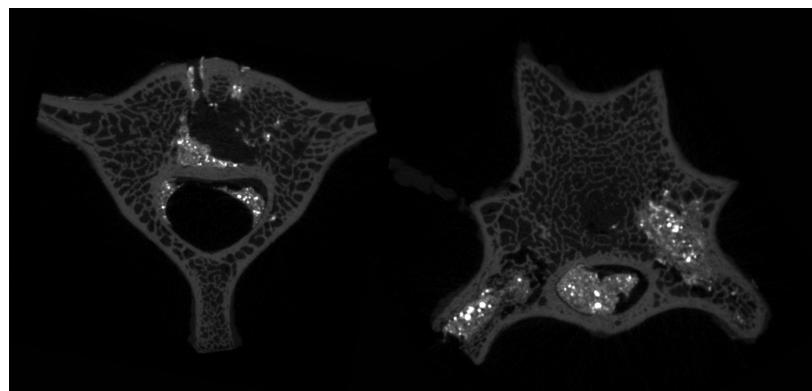


Figure 2.1.9:  $\mu$ CT scans of two vertebra, showing the cement leaking into the spinal canal and out of the vascular channels and the vertebral surface.

### 2.1.5 MicroCT Scanning

$\mu$ CT scans were taken at three occasions during the experimental process. These scans occur before and after the initial load to failure, then following the augmentation of the specimens. The process requires the vertebrae to be defrosted and at room temperature, given that the radio-opacity of water differs between solid and liquid states, hence vertebrae were usually defrosted overnight in a 4°C fridge. Vertebrae were loaded two at a time in a carbon fibre loading cradle designed for the HR-pQCT (XtremeCT, Scanco Medical AG, Switzerland) scanner. The settings used for the scans were: an isotropic voxel size of 82  $\mu$ m, energy settings 900  $\mu$ A, 60 kVp and 300 ms exposure time.

### 2.1.6 Results

The stiffness values for 12 bovine tail vertebra from the first to third vertebra down, shown in Fig. 2.1.10. Of the twelve vertebra only two, the first and second tail vertebra of the second tail (T2 CC1 & T2 CC2), were fractured. The remaining nine (excluding T1 CC3, the control) reached 9500 N and therefore did not fail. It is also difficult to see whether the initial load to failure had any effect on the subsequent loads. This is mainly due to the lack of control specimens and the large variation of results in general following the first load.

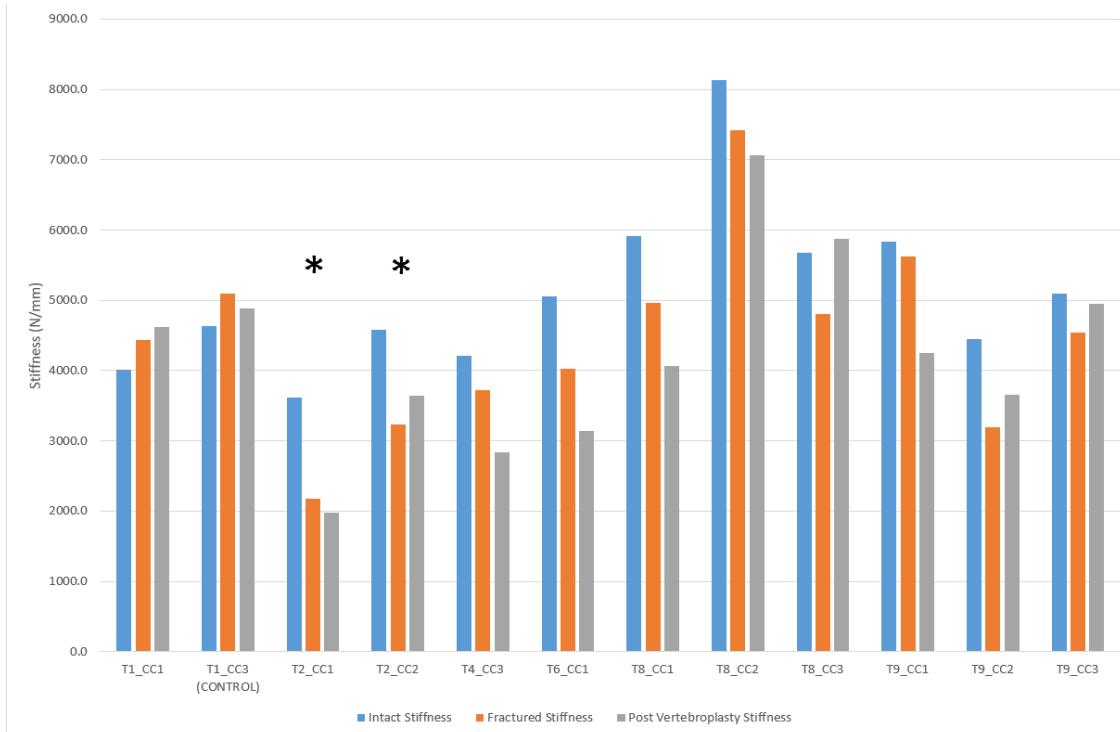


Figure 2.1.10: The maximum stiffness of 12 bovine tail vertebrae between 0 and 5000 N taken from load - displacement data. Showing the stiffness of the intact vertebrae, a post - fracture stiffness and a post - vertebroplasty stiffness for each. \* Indicates those specimens that achieved a clear failure below 9500 N.

The results for the fill volume of cement in the augmented specimens is presented in Table 2.1.1 and was acquired from the down-sampled, segmented models generated from  $\mu$ CT scans. It shows that fill volume varies between 3% and 17% fill and in addition shows a lack of a correlation between fill volume and increase in augmented specimen stiffness over fractured stiffness. Figure 2.1.11 shows the extent of the cement fill for the two vertebrae with the largest fill volume.

The attempt to reduce cement leaking through vasculature during the vertebroplasty procedure can be seen in Figure 2.1.12. The methods employed greatly reduced the quantity of cement observed in both the spinal canal and around vascular channels at the

Table 2.1.1: The volume of cement and the vertebra volume for the 12 specimens used, along with the percentage cement fill and an indication as to whether the stiffnesses of the augmented vertebrae were greater than the fractured stiffness. This information was measured from the down-sampled models generated from  $\mu$ CT scans of the vertebrae.

Vertebrae	Cement Volume (mm <sup>3</sup> )	Vertebra Volume (mm <sup>3</sup> )	Cement Percentage of Vertebra Volume (%)	Increase in Augmented Stiffness over Fractured Stiffness
T1 CC1	2260	32440	6.97	*
T1 CC3	465	27039	1.72	
T2 CC1	663	23285	2.85	
T2 CC2	3405	20373	16.71	*
T4 CC3	1363	25446	5.36	
T6 CC1	830	29332	2.83	
T8 CC1	1257	37357	3.36	
T8 CC2	4489	29248	15.35	
T8 CC3	1041	28403	3.67	*
T9 CC1	2922	45681	6.40	
T9 CC2	2210	38894	5.68	*
T9 CC3	2437	35840	6.80	*

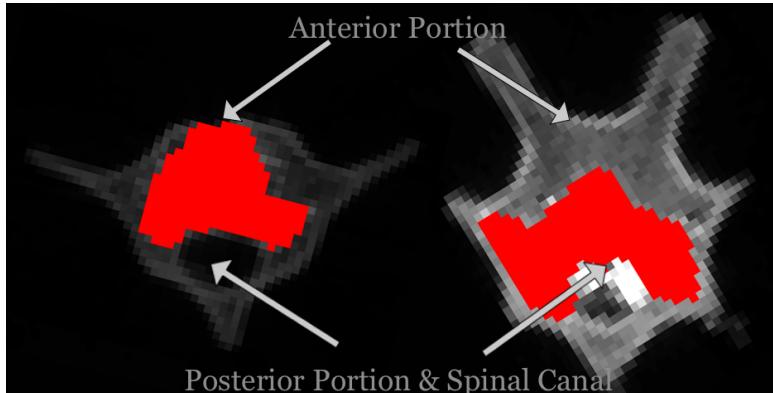


Figure 2.1.11:  $\mu$ CT scans of T2-CC2 (left) and T8-CC2 (right), with cement masked in red, showing the extend of cement fill at the point where the cement was most anterior.

vertebral body surface when compared to scans in Fig. 2.1.9.

The two plots in Fig. 2.1.13 show a lack of correlation between the difference in stiffness after augmentation when compared to both the fractured and intact specimen stiffness and the intact stiffness. Showing that magnitude of any increase or decrease in the vertebral stiffness following augmentation is not caused, or a feature of the initial, intact vertebral stiffness.

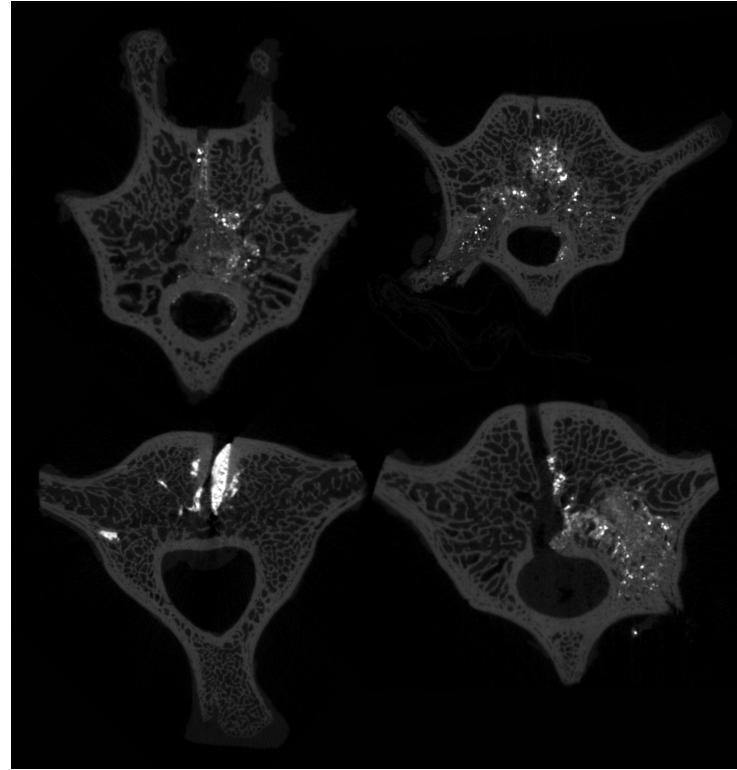


Figure 2.1.12:  $\mu$ CT scans of four augmented vertebra using a steel rod to fill the spinal canal and blu-tac to cover the external vascular channels. Shows greatly reduced cement content within the spinal canal with less cement at the surface of vascular channels.

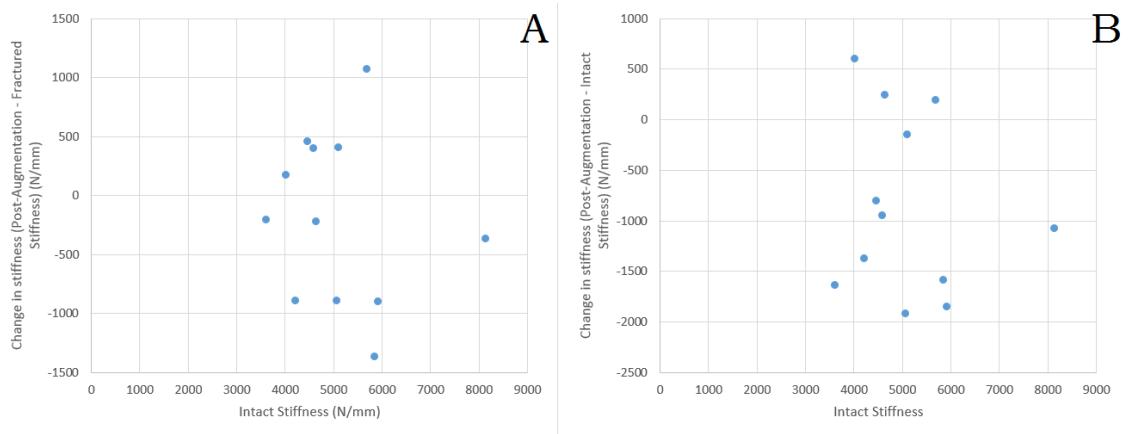


Figure 2.1.13: A: The difference between the post augmentation and fractured stiffness against the intact stiffness. B: The difference between the post augmentation and intact stiffness against the intact stiffness.

### 2.1.7 Discussion

The experimental work carried out so far provides a good basis for both the continued modelling of vertebroplasty (especially modelling the cement - trabecular interface which is discussed in later sections) and to continue the experimental work using human tissue. Understanding the challenges of vertebroplasty (those discussed above), will be invaluable when transitioning onto the much more limited source of human vertebrae.

Regarding the results of stiffness at the intact, fractured and augmented stages, the expected trends were not always clear. Most commonly the intact vertebrae have the greatest stiffness with the fractured stiffness showing a reduced value following the damage created with the initial load to failure. The variation of the decrease (and increase) in stiffness for the fractured vertebrae may have a variety of reasons, although the most likely cause is level of damage caused in the initial “load to failure”. These tests varied between the typical load displacement that includes a failure (Fig. 2.1.4:A) and those that show no sign of failure up to the limit of the load cell (Fig. 2.1.4:B). It is difficult to observe any correlation between these vertebra that showed clear failure (T2-CC1 and T2-CC2), those that reached 9500 N and a reduction in the fractured stiffness. It is not to say that the vertebra that reached 9500 N experienced no damage, with the gradient of the load displacement curve often reducing and plateauing as the 9500 N limit approached. The interesting increase in the fractured stiffness for T1-CC1 compared to the intact stiffness may be explained if it is assumed that the compacted trabeculae following the first load to 9500 N result in a stiffer material for the following tests.

The cement fill volume information shows that a small percentage of cement is injected into the vertebrae on average, with only two vertebrae approaching the clinically relevant 20% fill. Unexpectedly, only one of these two vertebrae showed an increase in augmented stiffness over the fractured stiffness. A possible explanation is that it is not only the fill volume that is important in restoring the vertebral stiffness but the placement too. This is shown when comparing the segmented scans of the two vertebrae with the greatest fill volume with the T2-CC2 specimen showing cement extending to the anterior wall of the vertebral body, while the cement is limited to the posterior and centre of the vertebral body for T8-CC2. This may help to explain why the stiffness of T8-CC2 did not increase following augmentation. The reduction in stiffness following augmentation for seven of the twelve vertebrae may be due to damage caused by the insertion of vertebroplasty needles. Clinically this damage left behind from the needle channels would heal, most likely restoring the stiffness of the vertebrae back to its intact properties.

Another possible area of inconsistency is the temperature at which the vertebra were mechanically tested, while it is ensured that the specimens were fully defrosted they were tested at both fridge temperature (4°C) and room temperature (20°C). The effect of this variation in temperature needs to be identified and depending on the results more closely monitored.

Despite encouraging results regarding the vertebroplasty methodologies it was difficult to achieve the desired quantity of the cement in the vertebral body. This was mainly due to

the difficulty injecting the cement in a smooth manner, which may have been caused by either the tip of the needle becoming blocked following its reinsertion into the needle track, more viscous marrow stopping the displacement of less viscous marrow by the cement or compacted trabeculae around the needle channel that limit the flow of cement past them. One option to test in future work would be side opening needles, which would help guide the cement more accurately to the regions required while circumventing issue with the needle becoming blocked.

The experimental methods currently developed will be of great value when starting experimental work using human tissue albeit many will require adaption due to the differences between the tissue types. These include the density of the bone and methods of inserting the needles, where with the available human tissue being from the elderly, the bones will be most likely be osteoporotic. These bones will require more care to reach the correct region of the vertebral body with the needle and to ensure a clinically relevant volume of cement is used.

## 2.2 Finite Element Modelling Methods

The aims of the finite element section of work were to develop methods that enable the creation of specimen specific models of vertebrae (both bovine tail and human). Initially the focus was on the generation of models that accurately describe the mechanical behaviour of intact bovine specimens, once this was achieved an attempt to model augmented specimens was made. In addition to these larger goals, certain sensitivity tests were carried out, including those to understand the effects that additional meshes have on model stiffness.

### 2.2.1 Model Creation

The computational analyses of linear-elastic finite element models is carried out using a combination the segmentation and meshing software, ScanIP (Simpleware, Exeter, UK) and the simulation software, Abaqus (Dassault Systemes, France). The  $\mu$ CT scans were converted into a finite element mesh using the former software package, this was then imported into the second piece of software to be configured and solved.

The scans acquired from the  $\mu$ CT scanner were converted from the ISQ file format, generated by the scanner software, into the more portable TIFF image format files using an existing in-house matlab script that additionally converts the greyscale of the scan into 256 bins. This conversion from 16 bit TIFF files with 65,536 bins to 8 bit TIFF files was required due to the limitation to 255 material properties within Abaqus, this allows one greyscale value per material property (assuming all 255 greyscale values are represented in the scan). Once the scan has been pre-processed it was imported into ScanIP ensuring that the spacing of voxels was correctly set - in this case  $82 \mu\text{m}$ . Once imported, the location of the loading point was identified to simulate the correct experimental load within ABAQUS; the marker (see Fig. 2.1.3) appears bright on the scan and its centre was taken as the load point, calculated by converting the position into mm. This was achieved by multiplying by the native resolution of  $82 \mu\text{m}$ .

The following parts of model creation were carried out using a Python script from within the ScanIP software. The script carries out the process described below and was generated by the author by carrying out the process manually and in order to understand the steps required and then writing a script to perform those actions. The development of the script removed much of the user variation in the segmentation of each vertebral model.

It was easier to down-sample the image stack prior to segmentation, due to the time

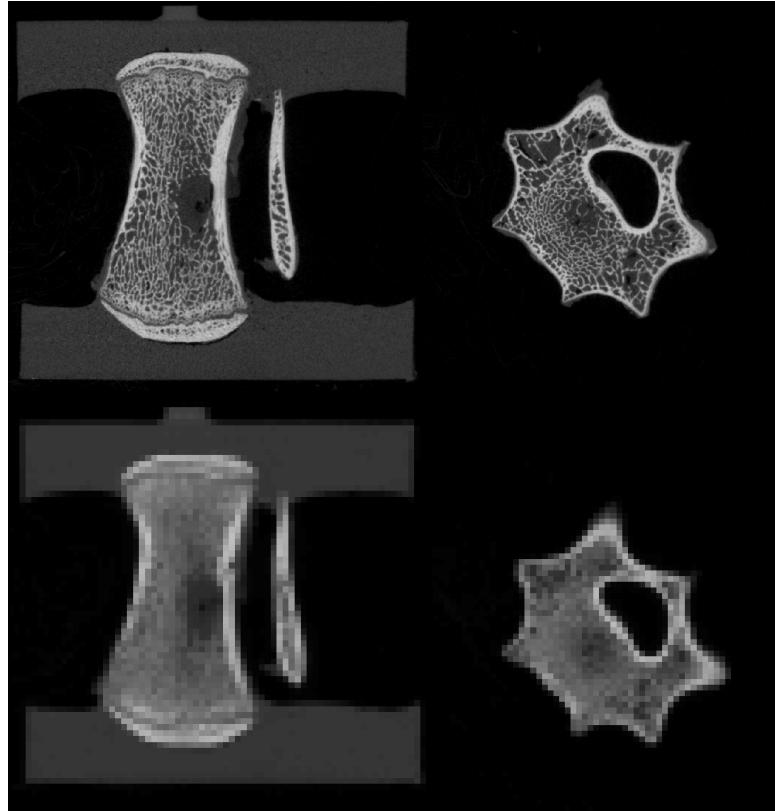


Figure 2.2.1: Side and top view of a vertebral  $\mu$ CT scan showing the effect of the downsample from  $82 \mu\text{m}$  to  $1\text{mm}$  cubed.

required for the software to generate high resolution masks and increased memory usage at higher resolution. The effect of down-sampling can be seen in Fig. 2.2.1. However, in certain cases, for example when modelling vertebral augmentation, in order to attempt to capture the intricacies of the structure and the boundaries between cement and trabecular bone it was favourable to generate the mask prior to down sampling, Fig. 2.2.4. The image stack was down-sampled to voxels  $1\text{ mm}$  cubed, due to previous studies producing sensitivity to mesh size results that showed a good trade off between computational cost and model accuracy [81].

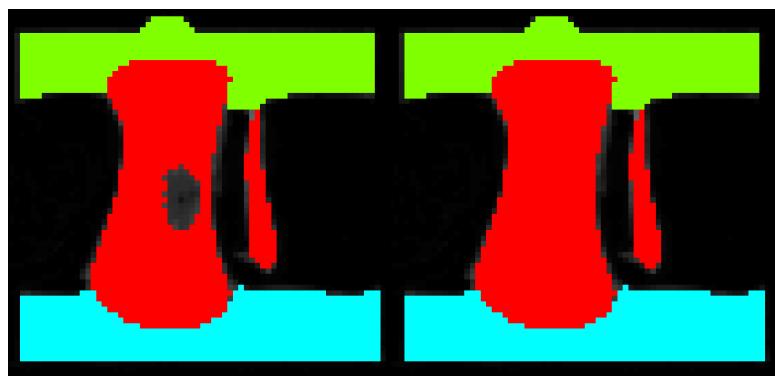


Figure 2.2.2: Side view of a vertebral model showing segemented vertebra, including the internal void that is filled.

Once down-sampled the image stack was segmented into the constituent parts - the vertebrae and cement end-caps. The different regions that were required to be segmented have different greyscale values, hence the general shape of the masks was created through a thresholding tool that selected volumes of the image stack between two bounds. For the end-caps these bounds were usually between greyscale values of 12-22 and, if the specimen was not augmented, the vertebrae between 23-255. For augmented specimens these limits change to 23-65 for the vertebrae and 66-255 for internal cement containing barium sulphate. These values were selected by visually limiting the amount of unwanted material selected within the threshold and maximising the wanted material, for example - selecting as much of the end-caps as possible while limiting the selected background and vertebral material to a minimum. This thresholding can be seen in Fig. 2.2.2. It was preferable to avoid internal voids within each mask, due to the potential for errors that can be thrown once the model is imported into ABAQUS, these were removed with the use of the morphological close and cavity fill tools within ScanIP (Fig. 2.2.2).

The following parts of the method were carried out manually, following the completion of the automatic segmentation python script. The two end-caps were separated into two separate masks by first duplicating the mask and then flood filling each end-cap to form separate masks.

An FE model was created using the previously generated masks and properties for the volume meshing, materials and contacts were set. The grid size for the model was set to  $1 \times 1 \times 1$  using the FE grid algorithm which uses a mix of tetrahedral and hexahedral elements. Material properties were set to homogenous with a density = 1, Young's modulus = 2.45 (GPa) and Poisson's ratio = 0.3 for the end-caps and when appropriate, were set to the internal cement volume. The material properties for the vertebral volume were set to a greyscale based material type using the greyscale background information. The coefficients were set so that both the density and Young's modulus were equal to the greyscale value for that element, allowing the Young's modulus to be set correctly in following steps and as described in Section 2.2.2.

Contacts were set as placeholders to be edited in Abaqus in the steps following. These were contact pairs between each component and another between the superior end-cap and the upper boundary on the Z-axis. The second contact type was a node set between the inferior end-cap and the lower boundary on the Z-axis.

Following this, the FE model was meshed, then exported into an INP file format. The model was then imported into Abaqus where the following configuration was completed by

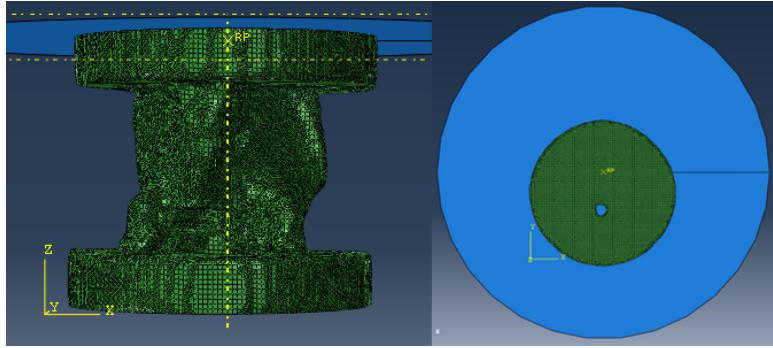


Figure 2.2.3: Side & top down view of a vertebral model showing the alignment of the analytical rigid plane.

a second python script. An analytical rigid plate was created to represent the upper loading platen of the materials testing machine and was centred at the loading point previously found from the marker, this can be seen in Fig. 2.2.3. Once aligned any previous placeholder interactions were removed and a tied interaction was created between the rigid plate and the superior end-cap, along with tied interactions between the vertebra and both end-caps and, if appropriate, to the internal cement volume. An encastre boundary condition was created at the bottom surface of the inferior end-cap removing all rotational and translational movement and therefore mimicking the experimental setup. A displacement boundary condition was applied to a reference node at the centre of the rigid plate and therefore loading position, the properties were set such that 1 mm of displacement occurs in the negative Z direction; lateral motion in the X and Y planes was restricted, while rotation about the loading point was allowed - again mimicking the experimental setup.

The python script was written to set the material properties of the greyscale dependant vertebral elements by setting the Young's modulus to the greyscale value multiplied by a conversion factor (which is discussed in section 2.2.2). The script allowed Abaqus to solve the models and outputs the stiffness for each model. This was calculated by dividing the reaction force at the reference point by the displacement at 1 mm of displacement.

### 2.2.1.1 Augmented Model Generation

In order to attempt to capture the detail of interdigitation between the vertebrae and the injected cement, the masking process was carried out prior to downsampling, seen in Figure 2.2.4. If masked post-down-sample it became difficult to define the cement boundaries and the masked volume was inaccurate when compared to the full resolution scan.

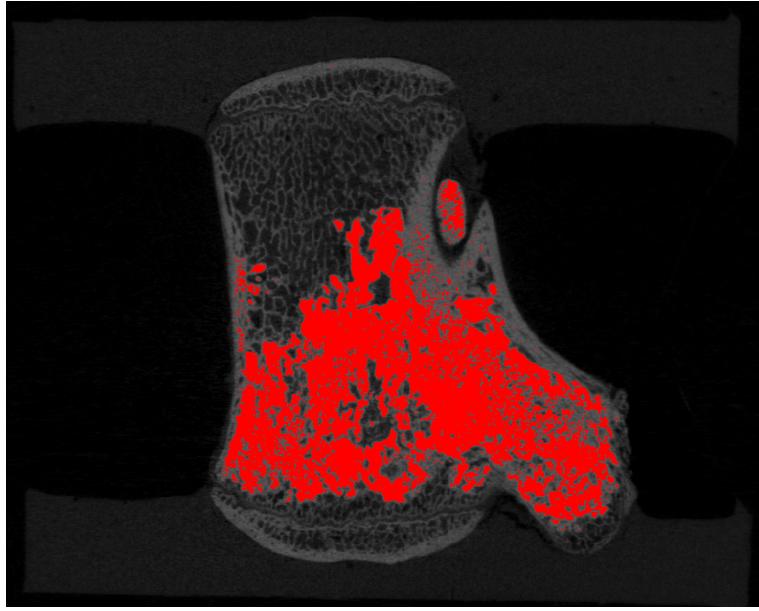


Figure 2.2.4: A lateral slice through an augmented bovine tail vertebra, showing the cement mask in red.

### 2.2.2 Material Properties

Material properties for the bone tissue were modelled elastically using a bone element-specific elastic modulus ( $E_{\text{ele}}$ ) that is dependent on the average greyscale value for the element in question ( $\text{GS}_{\text{ele}}$ ) with the conversion factor between the two being  $\alpha$ .

$$E_{\text{ele}} = \alpha \text{ GS}_{\text{ele}} (\text{GPa})$$

This was required due to each element containing differing quantities of bone and bone marrow due to the continuum level modelling carried out. Hence, a homogenous value for the trabecular bone would not have represented the varying average of material properties seen in each element. Therefore, the conversion factor,  $\alpha$  was used to convert between the greyscale value for each element and the Young's modulus.

This work was carried out in parallel to that described in the experimental sections above, however the experimental and computational methods remained the same. Specimens were divided into two groups of twelve and were used to determine a conversion factor between greyscale and elastic modulus. This additional set of 24 specimens (separate to those used in the above experimental study) was worked on in collaboration with Dr Sebastien Sikora, Dr Fernando Zapata Cornelio & Ruth Coe (Research Fellow, Research Fellow & PhD student respectively). The groups consisted of a calibration group (used to determine the value of  $\alpha$ ) and a validation group. For the validation group material properties were assigned - multiplying the greyscale for each element by  $\alpha$  prior to compressing the

model by 1 mm in Abaqus and was used to validate against the experimental values of stiffness.

The calibration for  $\alpha$ , the conversion factor was carried out using a golden section search scalar optimisation process. Specifically using the Brent method within the opti4Abq toolbox (Marlene Mengoni, University of Leeds). The objective of this toolbox was to find the root mean square normalised difference between the experimental specimen stiffness and the finite element stiffness and iterate until the objective function achieved a value of  $10^{-3}$ .

### **2.2.2.1 Augmented Specimen Material Properties**

For convenience the values for the Young's modulus for the interior cement volume were initially set to that of the inferior and superior end-caps. However, due to the rule of mixtures and the results found in the literature [74, 82], the effect of reducing the Young's modulus was investigated. This was carried out by reducing the Young's modulus in 10 percent increments from a value of 2.45 GPa to 1.225 GPa.

## **2.2.3 Sensitivity Tests**

### **2.2.3.1 Mesh Size Sensitivity**

Element sizes of  $1 \times 1 \times 1$  mm were used throughout, following previous convergence studies on porcine vertebrae [81]. The results of the convergence study on porcine vertebrae showed that reducing the element size below  $2 \times 2 \times 2$  mm led to changes in the model that were smaller than predicted errors originating from other factors, such as experimental errors and the simplification of boundary conditions. However, reducing the element size to  $1 \times 1 \times 1$  mm allows greater resolution when modelling the intricacies of the cement mesh for augmented specimens, the difference between the two resolutions can be seen in Figure 2.2.5.

### **2.2.3.2 Addition of Cement**

**2.2.3.2.1 Sensitivity to an Additional Mask** The addition of cement into the vertebral body created an extra mesh boundary within the mesh containing the vertebral elements. In order to test what effect this may have on the stiffness of models containing an extra mesh boundary, an un-augmented specimen was tested with an extra mesh representing the cement, but with the material properties of its elements set based on

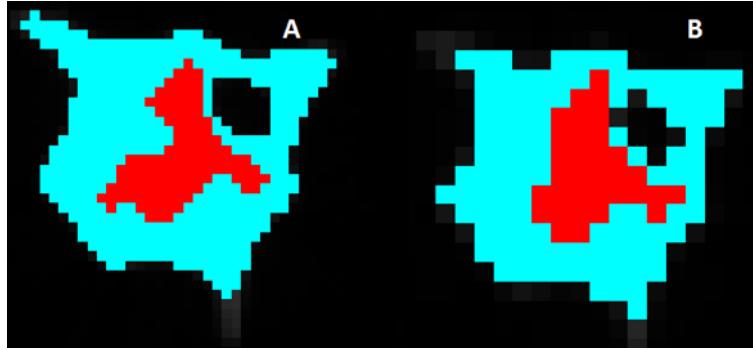


Figure 2.2.5: Mid-slice through an augmented vertebra, cyan: vertebral body, red: cement. A, element size of  $1 \times 1 \times 1$  mm. B, element size of  $2 \times 2 \times 2$  mm.

their greyscale as with the other bone elements. The mask was created by duplicating the vertebral mask and eroding it until the volume was approximately 20 % of its original volume. This allowed testing to be carried out on the effect of the extra mesh alone, while using an augmented specimen would allow a more accurate cement shape, it would hinder setting material properties to that of the bone greyscale and create an additional level of uncertainty. Mesh interactions between the two meshes (internal vertebral surface and the cement mask surface) were set using the contact pair interaction and treated similarly to the interaction between the end-caps and the vertebrae. Following model setup in ABAQUS as outlined in section 2.2.1 the model was loaded in compression to 1 mm and its stiffness was recorded.

There was no difference between the two models, with and without the internal cement mesh, meaning that any changes to the augmented model stiffness was due to the material properties of the cement.

**2.2.3.2.2 Mesh Interactions** The effect of mesh interaction between the vertebral body and the internal cement mesh were tested by comparing a) tied interactions between the two surfaces and b) removing any interaction and merely changing the material properties of the internal cement region (neglecting the contact pair steps described earlier). This was carried out for four augmented specimens following the same setup within ABAQUS as described earlier.

The results can be seen in Table 2.2.1, showing a negligible difference between variations for the four vertebrae models. This difference falls well below the difference between experimental and computation, especially for the augmented specimens, hence the effect of this interaction can be neglected from further test.

Table 2.2.1: The difference between interaction properties, tied and not tied for four augmented vertebrae specimens.

Vertebrae (Tail Number, Vertebral Level)	Tied Interaction (N/mm)	No Tied Interaction (N/mm)	Difference (%)
T2 CC1	5496	5496	0
T2 CC2	8086	8086	0.001
T6 CC1	3686	3686	0.001
T4 CC3	6059	6059	0.0005

### 2.2.3.3 Augmentation Volume & Location Sensitivity

### 2.2.4 Results

The optimisation process gave a value for the conversion factor of 0.012529, allowing conversion between greyscale values for elements and their elastic modulus. This value was used for the bone constituents of the intact and augmented vertebrae presented in Fig. 2.2.6, which shows the agreement between the *in vitro* and *in silico* results for the specimen specific models. The agreement of intact vertebrae was considerably better, with a concordance correlation coefficient (CCC) of 0.49 compared with 0.16 for the augmented vertebrae (Table 2.2.2), with the value increasing to 0.60 if the uncharacteristically stiff T8-CC2 was removed.

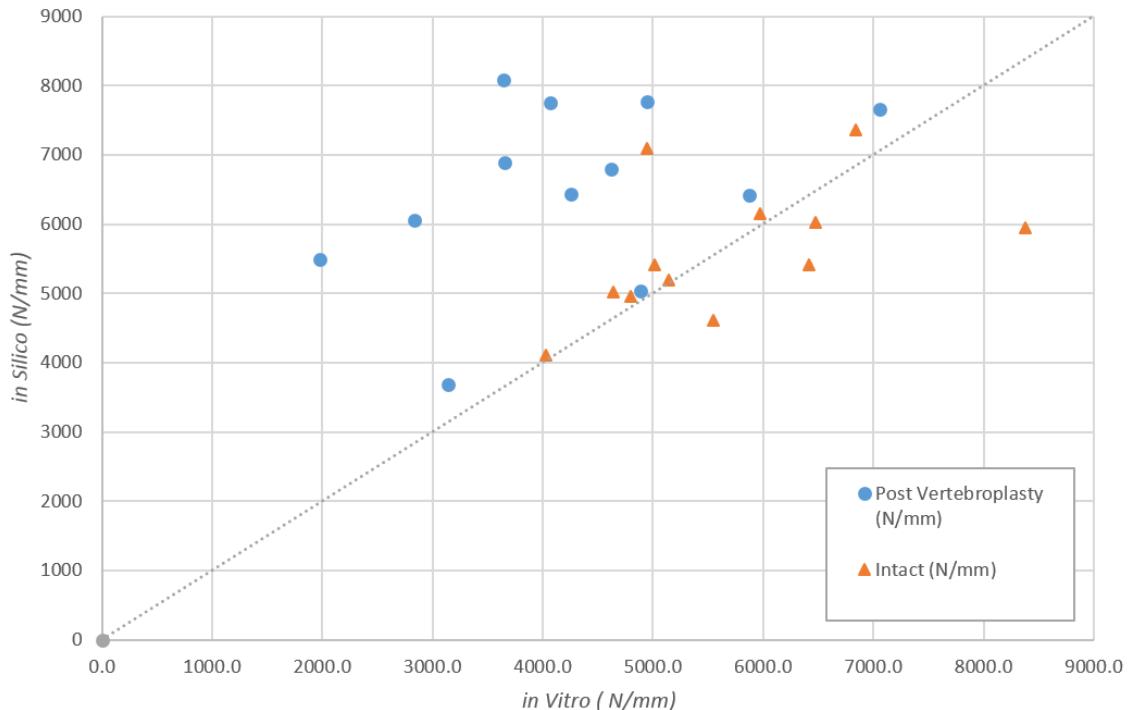


Figure 2.2.6: *in silico* compared with *in vitro* stiffness for intact specimens (triangles) and augmented specimens (circles). The dotted line shows a one-to-one correspondence.

The effect of changing the modulus of the cement volume in the augmented specimens

Table 2.2.2: The mean, standard deviation and concordance correlation coefficient (CCC) of the intact and augmented vertebrae for *in vitro* and *in silico* results.

Intact Specimens	Mean Stiffness	Standard Deviation	CCC
<i>in vitro</i>	5684	1196	
<i>in silico</i>	5610	958	0.4895
Augmented Specimens			
<i>in vitro</i>	4246	1371	
<i>in silico</i>	6507	1298	0.1548

is presented in Fig. 2.2.7. There was a linear decreases in the stiffness of vertebrae with the reduction of the elastic modulus for the internal cement volume. The two vertebrae that show more prominent decreases in stiffness were those vertebrae that contained larger volumes of cement following their augmentation.

The effect that this has on the data with regard to the *in vitro* stiffness results can be seen in Fig. 2.2.8, where the reduction in *in silico* stiffness moves the data points closer to the  $x = y$  line of perfect agreement between the experimental and computational results.

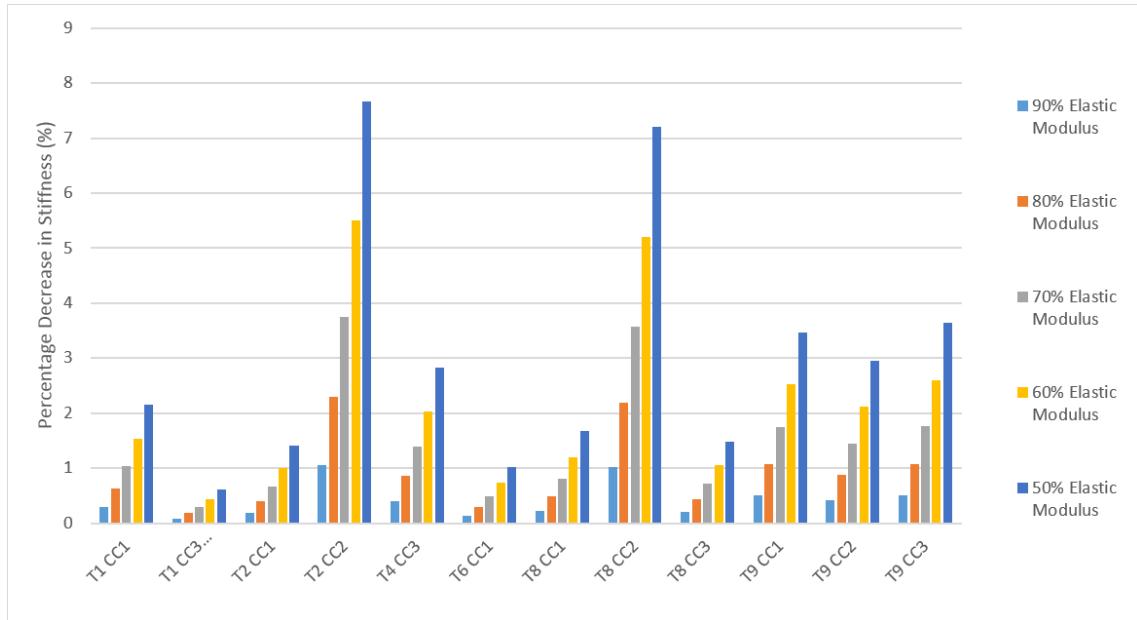


Figure 2.2.7: The percentage decrease in the vertebral stiffness after reducing the elastic modulus of the cement volume within 12 augmented vertebrae.

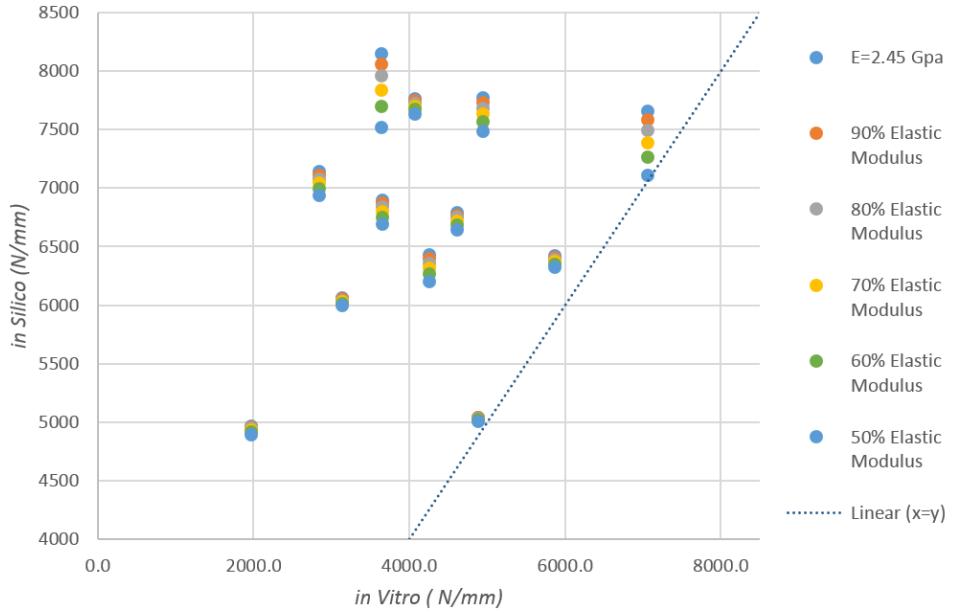


Figure 2.2.8: The effect of reducing the elastic modulus of the cement volume within 12 augmented vertebrae. Shows the in silico stiffness for the six elastic moduli tested against their in vitro stiffness.

### 2.2.5 Discussion

The computational methods developed and results acquired, as with the experimental results, provide a good base for using human vertebrae and for the continued development of augmented vertebra modelling. The methods and automation of the creation of models both greatly reduce the time spent on model generation and reduce human error. This allows a relatively easy translation to human vertebrae, with only minor adjustments to the thresholds that define materials.

The current methods of masking and meshing the internal volumes of cement in the augmented models provides a good method of creating augmented models. The sensitivity tests carried out on the additional mask inside the vertebrae shows that any effects seen are due to the volume of cement and not a simulation problem. Similarly the inclusion of a tied interaction between the two meshes failed to affect the result, something especially useful when considering alternative mesh interaction to model the cement - trabeculae interaction.

The intact models agree well with experimental results, with very similar results for the mean and, excluding anomalous results, a good CCC value, showing that the previously validated conversion factor works well with this set of data and that segmentation and model setup works correctly. The poor agreement with the augmented specimen models and their experimental counterparts was an expected result that agrees with similar studies

in the literature - [42]. In an attempt to produce a better agreement, the elastic modulus of the cement volume was reduced in accordance with the experimental results of Race et al. [82] and similar methods employed by Wijayathunga et al. [42], where the reduction in modulus is expected due to the greater ratio of monomer to powder used, gaps between the bone and cement and pores within the cement. The reduction in stiffness forms a linear pattern as the elastic modulus is reduced, with those vertebrae that show the greatest reduction being those containing the largest volume of cement. While these results do show a reduction in the stiffness, closer to that of the experimental values, it does not explain the disagreement fully. This suggests that a combination of improvements to the augmented models is required.

Future work will utilise the results acquired, especially those relating to the cement modulus and the cement - bone interactions, to understand how to model this interface more realistically and achieve good agreement between experimental and computation results of stiffness for augmented specimens.

# Chapter 3

## Human Tissue

### 3.1 Introduction

Previous studies and earlier chapters have used a range of vertebrae, including bovine, ovine and porcine among others. While all of these vertebrae have important uses for developing methodology and understanding certain characteristics, none share the trabecular structure, thickness of cortical shell, axial strength of stiffness. Hence, in order to understand the mechanical effects of vertebroplasty, human tissue is required.

Here, 14 lumbar vertebrae from four cadaveric spines have been used, with the details shown in table 3.1.1.

Table 3.1.1: Details of the lumbar sections used from four cadaveric spines.

Spine Name	Vertebrae	Sex	Age
G17-11	L1, L2, L3, L4, L5	F	90
G19-11	L1	F	94
G21-11	L1, L2, L3	M	86
G41-11	L1, L2, L3, L4, L5	M	83

### 3.2 Methods

#### 3.2.1 Potting

The geometry of human lumbar vertebrae varies considerably to that of the bovine tail vertebrae from which this methodology is based. This is characterised by much larger posterior elements with the facets extending much lower, below the bottom of the vertebral body. Hence, to correctly pot the human vertebrae much more cement must be used,

especially for the posterior end-cap, in order to cover the bottom of the vertebral body and the extending posterior elements. This means that much more of the posterior elements are constrained, therefore restricting the rotation of the vertebral body endplates under axial load. In addition to this the larger posterior elements which are captured within the PMMA end-caps will transmit load and take a greater share of the load when compared to the bovine tail vertebrae. Given that vertebroplasty attempts to restore the stiffness of the vertebral body and that there is no understanding of specifically how the loads are shared between the vertebral body and posterior element, this presents a problem.

A solution to this is to remove the posterior elements, following such methods as [42, 60], where only the vertebral body is modelled. This allows the stiffness of the vertebral body alone to be captured and modelled. The posterior elements were removed by cutting through the pedicles at the narrowest part, limiting damage to the region.

To pot the specimens that now lack a spinal canal, a retort stand was used to hold the vertebra, ensuring that both endplates were level on average. The specimen was then lowered down into the potting container leaving 5 mm between the bottom of the vertebra and the container. PMMA was poured into the container until the entire of the endplate was touching cement, with the edges of the vertebral body covered. Care needed to be taken to ensure all of the endplate was in contact with cement, given the extent of osteophytes creating non-flat surfaces in some of the more degenerated specimens. The other side of the vertebra was potted in a similar manner, however, due to the constraints of the potting container a measured quantity of cement was poured prior to lowering the vertebra into it. A spirit level ensured parallel end-caps.

### **3.2.2 Loading**

Following previous studies [42], the vertebrae were loaded with an initial maximum load of 800 N for similarly osteoporotic vertebrae. However, after loading two of the initial set of vertebrae the stiffness continued to increase up to maximum 800 N. Following loads up to 2000 N showed that the stiffness reached a maximum between 1300 and 2000 N, with three of the initial four specimens showing some degree of failure in the final 400 N of loading.

#### **3.2.2.1 Maximum Stiffness Measurement**

The maximum stiffness of the vertebra was found in the same fashion as with the bovine tail vertebrae - measuring the stiffness of segments at increments over the length of the

curve. Given that damage, especially for the intact specimens, needs to be avoided the maximum loads used are on the conservative side. This can mean that the maximum stiffness is potentially at the end of the data set or that the stiffness is still increasing at the load cut off. The solution to the latter would require a prediction of the yield point prior to experimental loading (discussed in Section 3.2.5.2), while the former could potentially be solved by using smaller segment sizes when measuring the stiffness from load - displacement results.

To allow the effect of segment size (the length of each section from which the stiffness is found) and increment size (the size of each increment defining the start point of each segment), the maximum stiffness finding Matlab code was rewritten in Python. This function could then be iterated over, reporting the maximum stiffness when using an increment size of between 1 and 100 data points (the distance between two data points corresponds to 0.0017 mm). Changing the increment size becomes a verification of the results using an increment size of 1 data point, given that the only negative of using the smallest possible increment size is computational cost, which is negligible here.

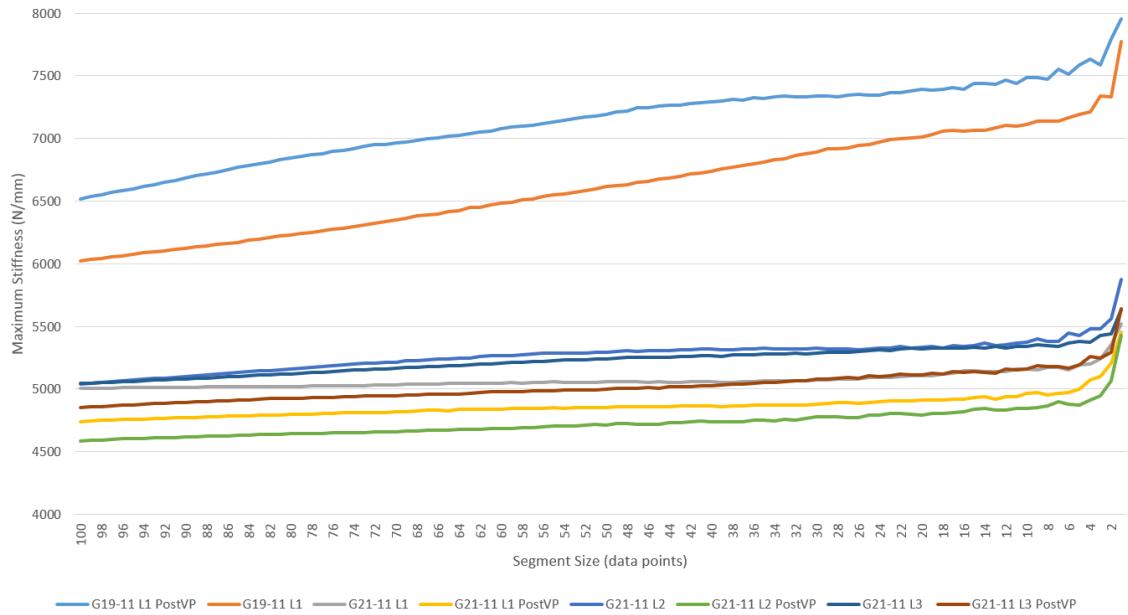


Figure 3.2.1: The effect of reducing the segment size on the maximum stiffness reported from four human vertebrae loaded to 2000 N pre and post augmentation. Using an increment size of 1 data point (0.0017 mm) and segment sizes of 100 to 1 data point (0.17 mm to 0.0017 mm).

Using an increment size of 1 data points width, as shown in Figure 3.2.1 shows a smaller variation across the range of segment sizes compared to using 20 points in Figure 3.2.2. The effect of both segment size and increment size is especially evident for the two G19-11 L1 vertebrae both intact and post augmentation where the stiffness continues to increase until the end of the test at 2000 N. Meaning that there is a much smaller linear region

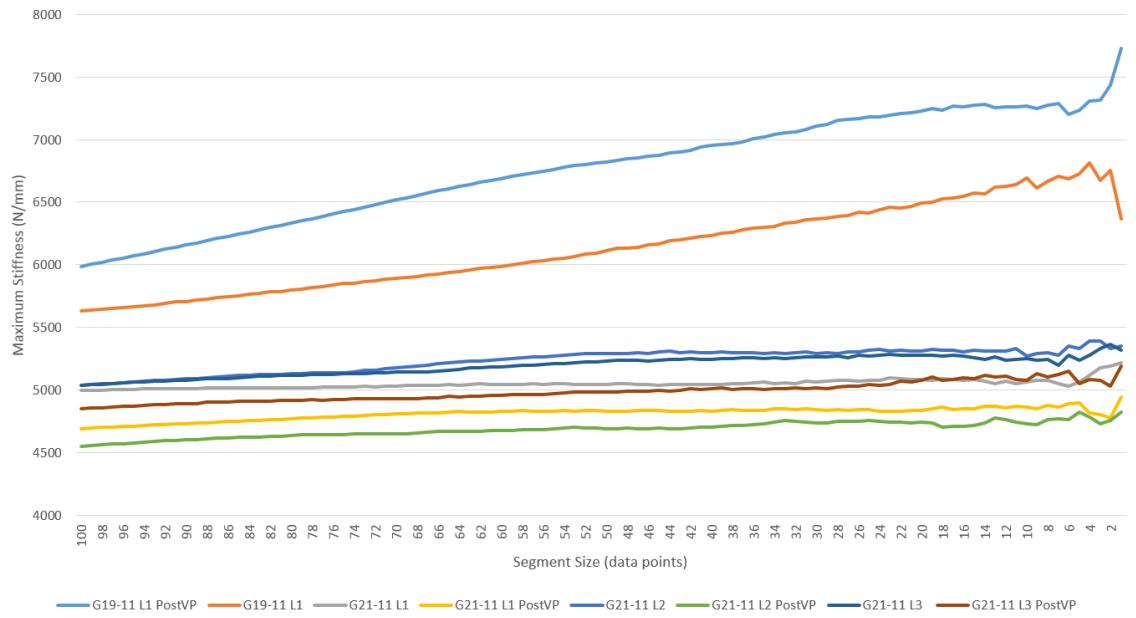


Figure 3.2.2: The effect of reducing the segment size on the maximum stiffness reported from four human vertebrae loaded to 2000 N pre and post augmentation. Using an increment size of 20 data points (0.0037 mm) and segment sizes of 100 to 1 data point (0.17 mm to 0.0017 mm).

for these two specimens, hence requiring a smaller segment size to measure the largest gradient.

Choosing values for the segment size to use moving forwards becomes difficult given the large effect it can have on the measured maximum stiffness (a range of over 1000 N/mm in the case the two G19-11 L1 tests). The segment size needs to be small enough to capture the maximum stiffness while avoiding the noise when using a segment size below 18 data points. Hence, a value of 20 data points was chosen, a value that avoids the noise while being on the plateau of the lines.

### 3.2.2.2 Repeated Loading

Given the nature of the test (attempting to limit damage to the vertebrae) especially during their initial intact load, the ability to derive errors becomes difficult especially from a single load. To attempt to understand this error four vertebrae having undergone augmentation were tested three more times in an iterative fashion, removing each from the load testing machine, testing the next specimen in the set and repeating. Removing the vertebrae from their steel housing (instead of three tests while seated in the steel housing) allowed the error in loading position and setup to be tested along with repeated loading of the vertebrae to be tested.

The results of repeated loading can be seen in Figure 3.2.3. All four specimens show a

reduced stiffness for the repeated loads following the initial load, for which there are a few possible reasons. One possibility for the reduction in stiffness is that it is a consequence of the freeze thaw cycle that occurred between these tests. The second possibility is that the vertebrae were still partially frozen while the testing took place. Finally, it could be due to damage being caused during the initial load to 2000 N, shown in Figures 3.2.4 to 3.2.7 it is possible to see slight failure in the three G21-11 vertebrae, although failure cannot be seen in the G19-11 L1 vertebrae. The frozen bar in Figure 3.2.3 shows how the stiffness increases when the vertebrae are completely frozen, potentially helping to explain the drop in stiffness found in the repeats. Further tests will be carried out with three more repeats following another freeze thaw cycle to attempt to answer this.

The iterative reduction in stiffness for the G21-11 L2 vertebrae can be explained as damage being caused after each iteration. This can be seen in Figure 3.2.6, with the three repeats each showing a yielding before the 1600 N limit and a smaller maximum load and stiffness after each repeat.

Figures 3.2.4 through 3.2.7 show the data for the loading, from which the maximum stiffness values are found. This excludes the initial cyclic loading, starts the loading at 50 N and displacement at 0 mm.

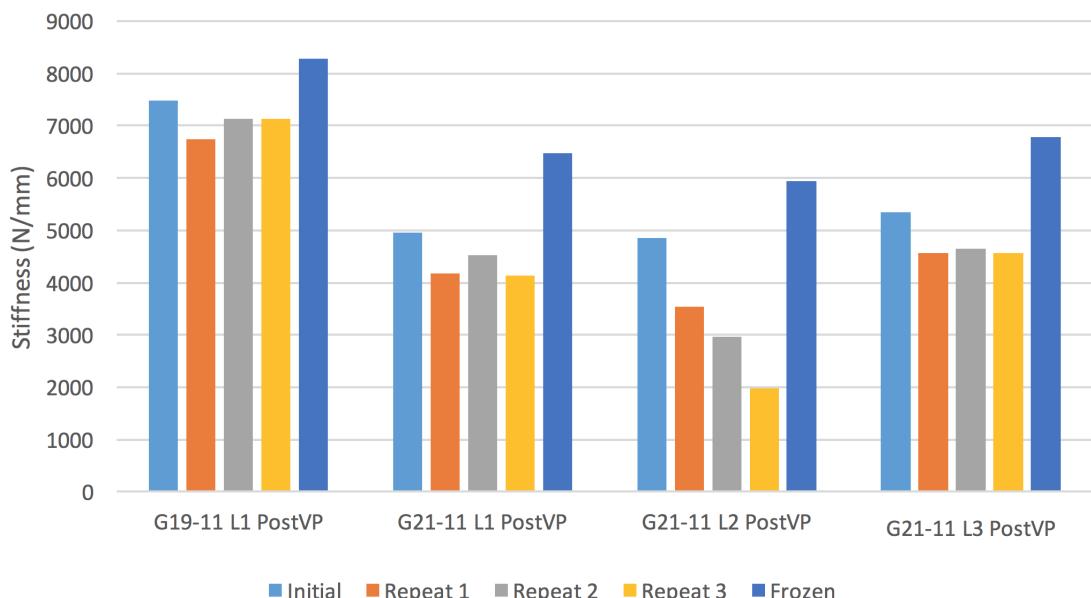


Figure 3.2.3: The stiffness of four augmented vertebral specimens over the course of an initial load, three repeated loads and a load while frozen. The intact specimen was loaded until 2000 N while the remaining four were loaded until 1600 N.

## G19-11 L1

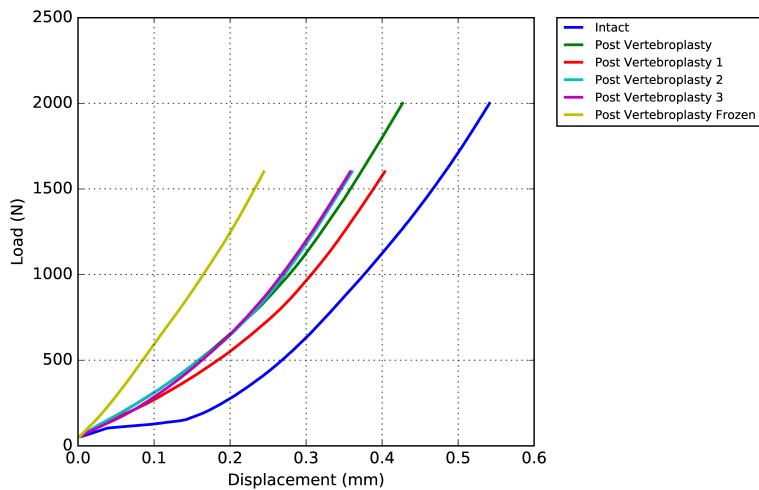


Figure 3.2.4: The load - displacement results for the G19-11 L1 vertebra. Showing results of the intact load and post augmentation load up to 2000 N and the repeats and frozen load up to 1600 N.

## G21-11 L1

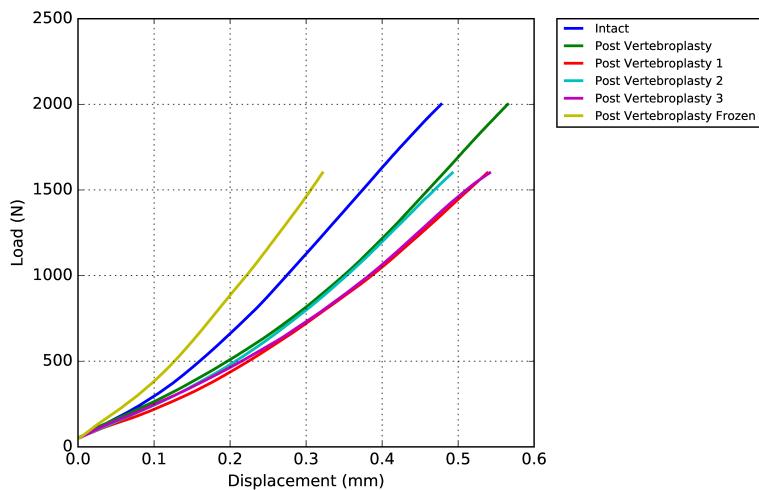


Figure 3.2.5: The load - displacement results for the G21-11 L1 vertebra. Showing results of the intact load and post augmentation load up to 2000 N and the repeats and frozen load up to 1600 N.

### 3.2.3 Vertebroplasty

Despite the development of methods for the augmentation of bovine tail vertebrae, the methods for augmenting human vertebrae were altered due to the different geometry and density. The human vertebrae, being much less dense, did not require the vertebroplasty needle to be inserted with the aid of a mallet. Instead the needle could be pushed by hand through the cortical shell and into the vertebral body.

An additional difference was the approach with the needle, instead of entering the vertebrae

## G21-11 L2

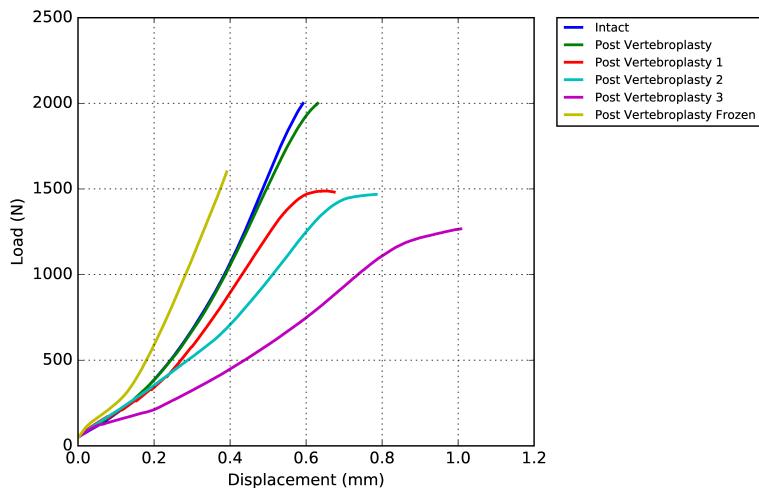


Figure 3.2.6: The load - displacement results for the G21-11 L2 vertebra. Showing results of the intact load and post augmentation load up to 2000 N and the repeats and frozen load up to 1600 N.

## G21-11 L3

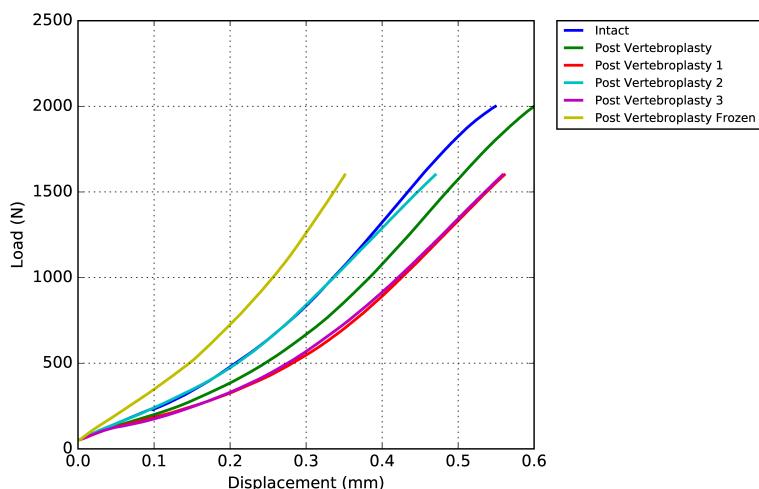


Figure 3.2.7: The load - displacement results for the G21-11 L3 vertebra. Showing results of the intact load and post augmentation load up to 2000 N and the repeats and frozen load up to 1600 N.

through their pedicles an oblique approach was adopted. This was due to variation in pedicle diameter between the L1 - L5 lumbar levels and therefore the potential to damage the region and its load sharing capabilities. The oblique approach therefore avoided creating this damage to the pedicle-canal region, especially for the vertebrae with narrower pedicles and instead created much less damage to the vertebral body.

A final difference to the needle insertion methods was a change to the needle. Here, a side opening needle was used, allowing the cement to be directed into the anterior-centre region of the vertebral body as opposed to directly out of the needle end.

An attempted 20 % fill was used for the vertebrae, measuring the volume of the vertebral body from the  $\mu$ CT scans prior to augmentation. However, despite stopping the injection upon cement leakage through vascular channels leading from the vertebral body surface inwards, cement loss occurred. In addition to this, cement was also lost in the needle itself, where as the cement set the amount of cement remaining in the needle became difficult to measure. This meant that the cement fill could not be measured though the amount of PMMA leaving the syringe due to leakage and needle losses. Hence cement fill volume was measured using segmented  $\mu$ CT scans, the methodology of which is described below.

### 3.2.4 Vertebrae Characteristics

Identifying the different characteristics for the set of lumbar vertebrae has importance in understanding trends and relationships between the experimental and computational results. For example a larger degree of anisotropy and hence more directionality aligned trabeculae would potentially give a more experimentally stiff vertebra, despite otherwise similar characteristics. Given that much of the vertebral characteristics depend on the trabecular structure it is important to understand how this varies between specimens. Furthermore, any calculations originating from a description of the trabecular structure require a correct threshold to be applied to the  $\mu$ CT scan. This threshold describes the limit of the trabecular bone and hence the start of either marrow or empty space. To enable a fair comparison between vertebrae a region of interest was selected from the vertebral body. Given the large variation in cortical shell thickness, along with certain vertebrae containing large osteophytes and other extra bone growth, the region of interest (ROI) was selected to be the largest cylinder that could fit within the vertebral body while not capturing any of the cortical shell.

#### 3.2.4.1 Histograms

In order to understand the spread of brightness' from the set of lumbar the histograms of the ROIs were plotted (Figure 3.2.8).

The lower greyscale values represent the empty space within the ROI which translates to regions where the bone marrow has exited the region, most likely during the freeze thaw cycles. The peak in the histogram at an approximate greyscale value of 16 is due to the bone marrow. The remaining portion of the histogram represents bone, where variation is due to the differences in the mineral content of the bone, with more mineralised bone appearing brighter on  $\mu$ CT scans. The specimens ROIs that contain the brighter values

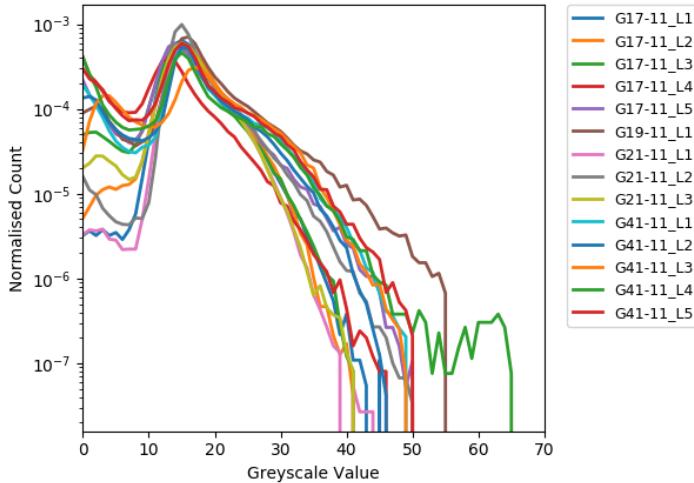


Figure 3.2.8: The normalised (with respect to the volume of the ROI) histogram data for the 14 lumbar vertebrae.

are those that contain osteophytes that contain more dense bone than the other cortical shell, for example G19-11 L1.

### 3.2.4.2 Threshold Optimisation

The full resolution scan is imported into imageJ where the threshold optimisation is carried out. The BoneJ plugin for imageJ is used for all of the trabecular structure metrics, with the optimise threshold tool being the focus here. This tool is run on the region of interest using the default settings for the connectivity options seen in Table 3.2.1. This chooses a threshold based on the peak in a connectivity against threshold plot and reports that value. These values can be seen in Table 3.2.2, showing considerable across the range of vertebrae. However, the differences in these suggested thresholds can grouped with the spine, for example: the G17 spine has a range between 15 to 17, while the G41 spine has an range between 18 to 20. This promotes the idea that these differences are due to the bone mineralisation of the bone, especially given that the G17 spine is from a Female and G41 from a male.

However, given that the chosen value for the threshold will directly impact the reported metrics, a consistent value was chosen of 18. Using lower or higher values for the threshold usually results in the trabeculae being described as thicker or thinner respectively. Hence, the difference in the mineralisation between specimens will still be captured when using a fixed threshold, given that the binary image will be down sampled before material properties are acquired. The results in Table 3.2.3 show the BV / TV data and degree

of anisotropy values for the 14 specimens using the fixed threshold of 18. Similar trends to what could be seen from the optimise threshold results can be seen in the BV/TV data, with grouping between the spines evident. The G17-11 spine has a much lower bone volume fraction compared to the other spines, which suggests a more osteoporotic spine, most likely resulting in less stiff vertebra.

Table 3.2.1: Settings used for the ImageJ plugin, BoneJ: Optimise Threshold.

Options	Values
Tests	11
Range	0.2
Subvolume Size	256
Erosian Cycles	0
Dilation Cycles	0

Table 3.2.2: The suggested threshold from the optimise threshold BoneJ tool for the 14 lumbar vertebrae in the set.

Specimen	Suggested Threshold
G17-11_L1	17
G17-11_L2	16
G17-11_L3	16
G17-11_L4	15
G17-11_L5	16
G19-11_L1	23
G21-11_L1	18
G21-11_L2	19
G21-11_L3	19
G41-11_L1	20
G41-11_L2	19
G41-11_L3	18
G41-11_L4	19
G41-11_L5	18

### 3.2.5 Intact Vertebrae Modelling Sensitivity Tests

Given the aims of the project - to include the models generated here into a larger set of vertebral models for use in statistical shape modelling, it is useful to model the vertebrae in a scanner independent method. A method for doing this (BV/TV modelling method) uses a full resolution scan with the bone regions segmented using a threshold. This full resolution segmented scan is then downsampled to voxels with edge length of 1 mm, meaning that each voxel has a greyscale value proportional to the BV/TV value for the region captured by that voxel. Areas that contain more bone will therefore have a higher greyscale value. This method is purely dependant on the threshold selected defining the bone and hence, given that threshold values can be repeatedly and correctly selected with the methods

Table 3.2.3: BV/TV and degree of anisotropy (DA) values found using the ImageJ plugin BoneJ tools Volume Fraction and Annisotropy respectively using a threshold of 18.

Specimen	BV/TV	DA
G17-11_L1	0.174	0.387
G17-11_L2	0.17	0.364
G17-11_L3	0.137	0.359
G17-11_L4	0.127	0.418
G17-11_L5	0.187	0.341
G19-11_L1	0.391	0.199
G21-11_L1	0.255	0.327
G21-11_L2	0.267	0.231
G21-11_L3	0.281	0.301
G41-11_L1	0.257	0.239
G41-11_L2	0.241	0.338
G41-11_L3	0.244	0.348
G41-11_L4	0.247	0.371
G41-11_L5	0.249	0.186

shown in Section 3.2.4.2, it is scanner independent.

### 3.2.5.1 BV/TV Modelling Method

This method gives the opportunity to keep much of the detail that is often lost when downsampling image data. Specifically, the method described gives the vertebral models much more definition of the cortical shell and internal trabecular structure while maintaining the 1 mm cubed resolution and the computational cost benefits associated with that. The method follows that found in a study by Robson Brown et al. [60] with a few minor changes. The scans are converted from the ScanCo proprietary ISQ format into a stack of TIFF files using an in house Matlab script, which in additionally reduces reduces the 16 bit data to 8 bit images.

The set of vertebral specimens were split at this stage into two sets, allowing an understanding of how the bone volume fraction method affects the results compared to the method described in Section 2.2. To the set using the bone volume fraction method a threshold was applied at the full  $82 \mu\text{m}$  resolution. This threshold was chosen to be a greyscale value of 18, the mean of the values described in section Section 3.2.4.2 and was applied to the scan stacks in imageJ. Once the binary stack was created a Gaussian filter was applied, also within imageJ, with  $\sigma_{x,y,z} = 1$ . This was applied in order to remove speckling found surrounding the end-caps and some of the other noise visible in the scans. The two stacks of images are then imported into ScanIP; carried out by opening one stack of images (the original stack) and then importing a second background (the binary image stack). Both backgrounds are downsampled to voxel sizes of  $1 \text{ mm}^3$ , with the (originally) binary

stack being used to create the mask for the vertebrae and the original stack being used for the end-caps. Greyscale material properties for the vertebral mask are taken from the binary stack, while the remainder of the methods follow the same process as the original method.

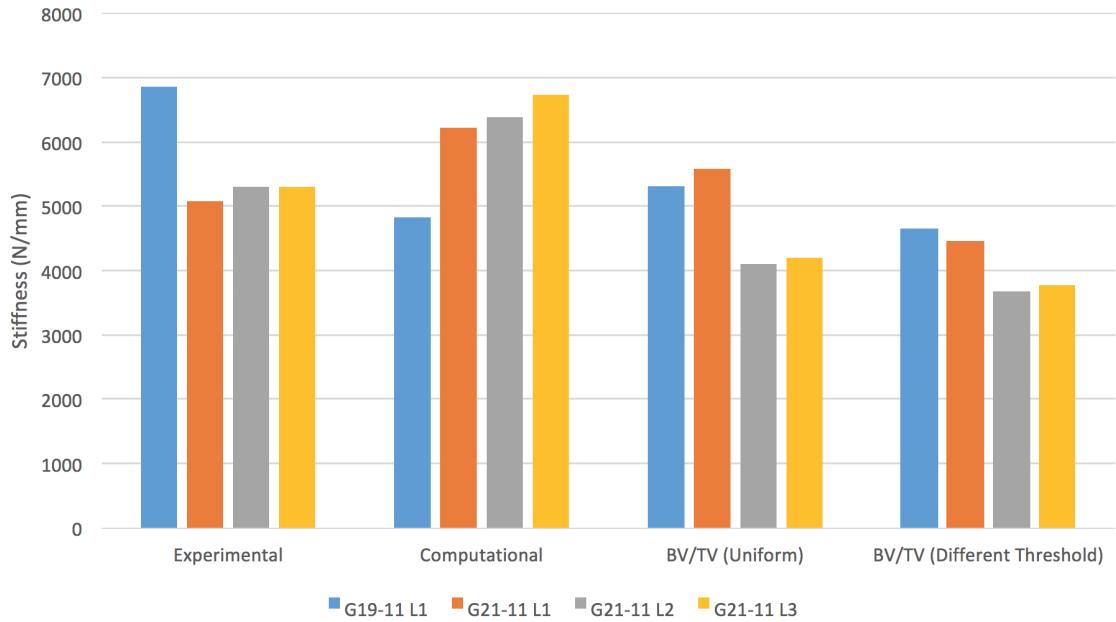


Figure 3.2.9: The stiffness results of three different FE methods for four intact human vertebrae compared to the experimental stiffness results. Interest should be drawn to the ratio between specimen models rather than the values themselves, given that the conversion factors between greyscale values and Young's modulus have not been optimised at this stage. Results show the difference between the currently used method of modelling the vertebrae and the BV/TV based methods (both with uniform thresholds and different thresholds for each specimen).

### 3.2.5.2 Predicting Vertebral Yield Point

### 3.2.5.3 Load Position Sensitivity

In order to understand how the vertebrae respond to different loading positions, eight different positions were tested, shown in Figure 3.2.10. The same boundary conditions, along with the 1 mm of displacement described above were applied to the different loading positions and the change in stiffness was recorded.

The results of the load position sensitivity tests (Figure 3.2.11) show that more posterior loads (above denser bone) result in higher stiffnesses while anterior loads result in a reduced stiffness. Loads lateral to the central loading point resulted in smaller reductions in the stiffness of models.

It also shows that the effect of movements of 1 mm away from the experimental loading

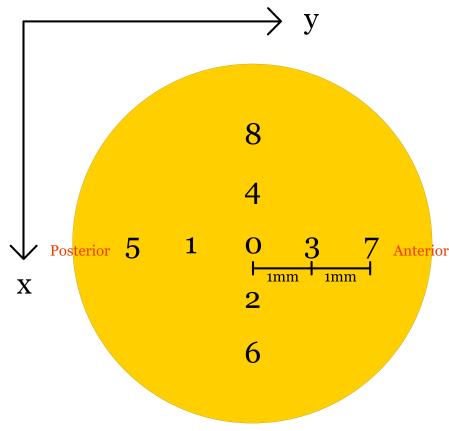


Figure 3.2.10: The loading positions used for the load variation tests. Position 0 is the original, central loading position, with 1 - 4 being 1 mm away from the centre and 5 - 8 being 2 mm away from the centre.

position only changes the stiffness by approximately 5 %. Given the resolution of the models is limited to 1 mm, the accuracy of the selection of the experimental loading positions is also limited to 1 mm. The maximum 5 % change to the stiffness when posterior or anterior may describe some of the error seen when comparing the experimental and computational results.

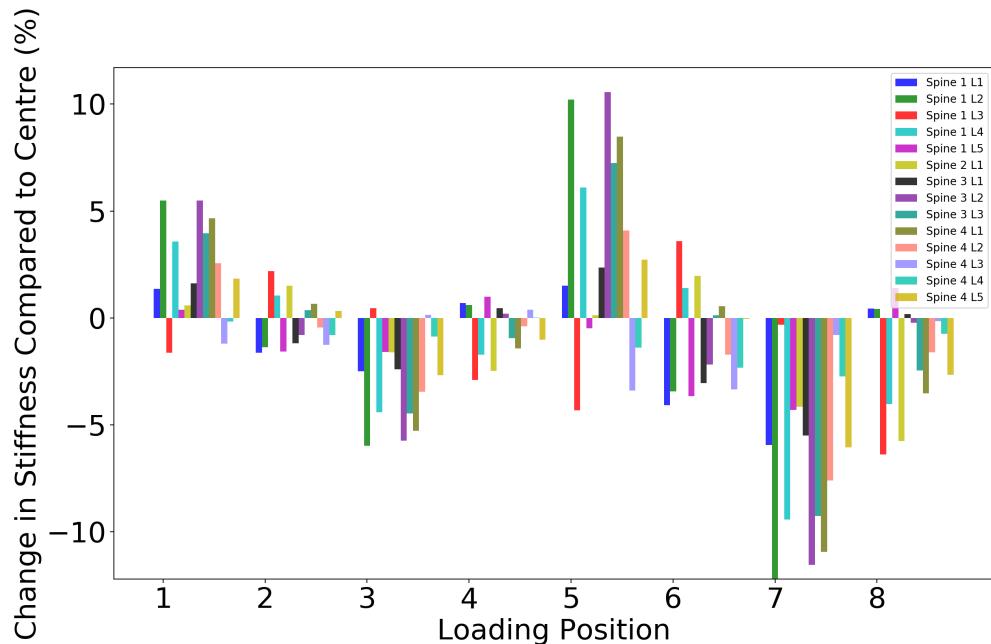


Figure 3.2.11: The effect of the loading position for the human lumbar vertebrae, shown as a percentage change compared to a central loading position.

### 3.2.5.4 End-cap Depth & Contact sensitivity

The stress distribution at the surface of the vertebral body shows high stress at the edges of the cement endcaps, at both the top and bottom of these regions. Experimentally the

endcaps are merely moulded to the shape of the top and bottom of the vertebral body, however, previous work and other studies have used tied contact between the bone and endcaps, removing any motion between the two and locking neighbouring nodes together. Additionally, the depth of these endcaps varies between 5 and 20 mm depending on the shape of the vertebral endplates. The more concave the vertebral endcap was the more cement was required to fill the space forming a flat cement surface.

Given this variation, tests identifying the effect of changing the endcap depth were carried out using FEA models with different depths of  $\pm 1$ ,  $\pm 2$  and  $\pm 3$  mm for the top and bottom endcaps independently and together. Additionally, different interactions between the bone and cement endcaps were tested. This included the current standard method of a tied interaction and replacing this with a frictionless contact between the two materials. Finally the effect of changing the cement endcap depth with the frictionless contact was also investigated. This was carried out given that, experimentally, there is no tied contact between the PMMA and the bone due to the lack of adhesive properties for the PMMA.

### 3.2.6 Modelling Augmentation

Given the limited validation of models achieved using bovine tail vertebrae due to the reasons discussed in Section 2.2.4, a range of different material properties and approaches to modelling the bone-cement interface were investigated. In addition to varying the material properties of the injected volumes of cement, the effect of using a combination of scans from before and after augmentation has been experimented with. To achieve this scans of pre/post augmentation were required to be registered.

#### 3.2.6.1 Registration of $\mu$ CT Scans

Artificial brightening of regions surrounding the internal cement, specifically concentrated areas of barium sulphate and the artefacts this can cause affect the material properties that are applied to the material. To bypass this effect the two models, intact and post-augmentation models can be registered - translating them into the same spacial location. This allows the cement to be defined, masked and modelled based on the post-augmentation scan and the remaining vertebra to be defined from the intact scan, the same background used for the intact models. While the shape of the vertebra may have been changed over the course of its two loads, this change is less than what can be seen at 1 mm resolution. Additionally regions that have experienced damage through the insertion of the needle,

yet do not contain cement will also be neglected using this method. However, the same justification can be made, where this is unlikely to have any affect at 1 mm resolution.

Registration of the images was carried out in 3D Slicer, using scans of the segmented, full-resolution, non-augmented vertebrae and the full-resolution augmented vertebral scans. The method of registration was a landmark based approach using three landmarks for each vertebra, translating the scan of the augmented vertebrae. These points were selected at superior of one pedicle, the inferior of the other pedicle and the inferior anterior of the vertebral body. The selection of these points proved to provide a repeatable registration of the vertebrae, without selecting superfluous landmarks. Once registered the resulting translated augmented vertebrae scan was cropped with respect to the non-augmented scan to prove an aligned and registered pair of scans.

### **3.2.6.2 Registered Scan Model Generation**

The augmented models using the registered scans were created in ScanIP. The initial step was to import the registered augmented scan and applying an initial downsample to a resolution of  $0.5 \text{ mm}^3$ .

## **3.3 Results**

## **3.4 Discussion**

## **3.5 Conclusion**

## **Chapter 4**

# **Principal Component Analysis & Statistical Shape & Appearance Modelling**

### **4.1 Introduction**

#### **4.1.1 Aims of Statistical Shape & Appearance Models**

#### **4.1.2 General Methodology**

Generally SSAMs start with a rigid registration, where rotations and translations are applied to all meshes or models that form the input data set so that they share a common coordinate system. Methods of performing the rigid registration often use an automated approach where certain degrees of freedom are restricted to ensure registration is achieved.

### **4.2 Measuring Vertebral Geometry**

Vertebral volume or the vertebral body volume may be the easiest and most obvious measure of geometric change within a set of vertebra. It has been shown in Chapter 3 that there is a strong correlation between vertebral size and stiffness and so this may be enough for a range of comparisons between spines and individual vertebrae. However, the input set of vertebrae contain a wide range of variation which can be seen visually, which may play an important role in the effect of cement augmentation and is another method of validating the outputs from the PCA generated set of models.

Measuring vertebral geometries in previous studies have either taken the measurements from x-ray scans [83, 84] or  $\mu$ CT scans [85, 86], where the measurements have been made through the moving a cursor to the locations of specific points and reporting the distance between them. While this method may produce accurate results, there is inherent human error associated, the number of measurements is limited to the number of planes available and applying this to large sets of data is time consuming which may lead to further error.

The approach used here involves using the 1 mm voxel resolution models generated in ScanIP (v. 2016) which are used for FE modelling. The mask describing the vertebral body of these vertebrae is exported as a stereolithography file (STL), allowing the surface of the vertebra to be measured. Measuring the vertebra was carried out in Matlab where the STL file was imported forming a point cloud describing the surface from the surface nodes. Once imported the point cloud was split into thirds in each of the three anatomical planes, with the points describing the vertebra within these thirds being stored in nine array variables. Cuboids were then fitted to the 3D arrays, maintaining the correct alignment and therefore prohibiting rotation of the cuboid. The cuboid fits can be seen in Figures ??.

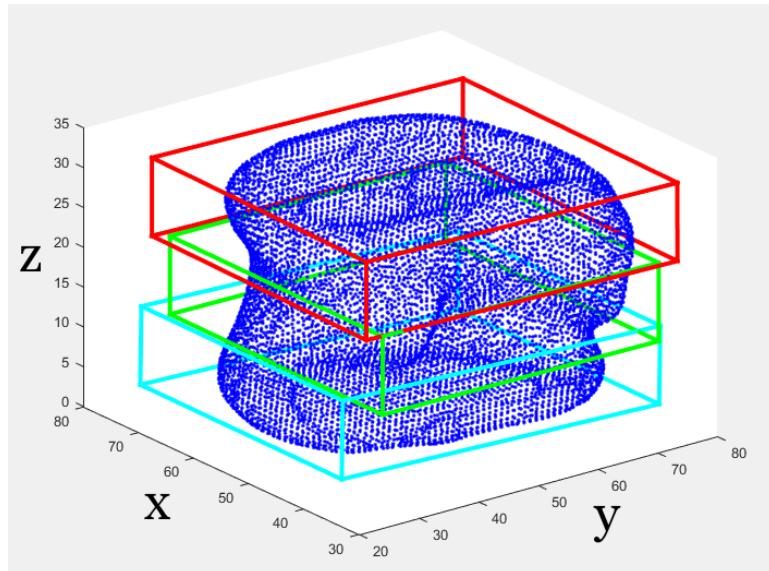


Figure 4.2.1: The three cuboids fitted to the vertebra point cloud in the axial plane.

Measuring the two longer sides of the fitted cuboids gives a total of 18 measurements describing most aspects of the vertebral geometry, these can be seen with their abbreviations in Table 4.2.1. This includes identifying wedge shaped vertebrae, recorded as reduced anterior height compared to the posterior height, left to right wedge shapes, recorded as sagittal left height being smaller or larger when compared to the sagittal right height.

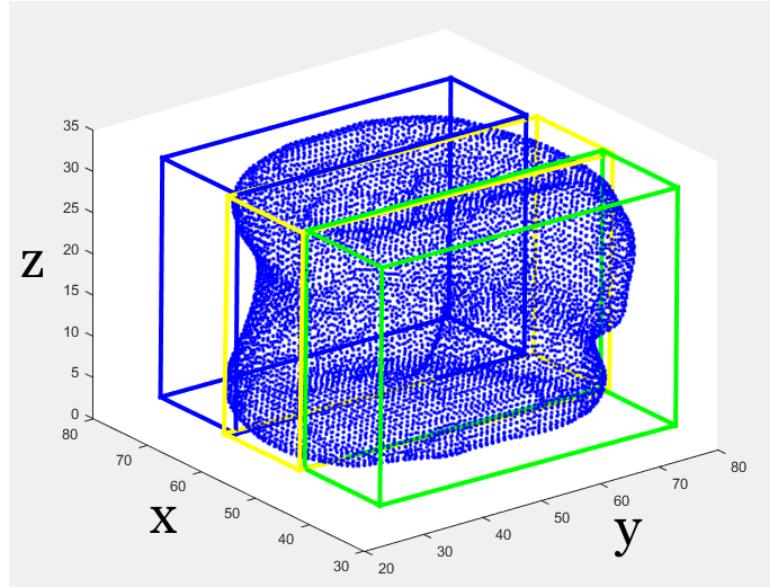


Figure 4.2.2: The three cuboids fitted to the vertebra point cloud in the coronal plane.

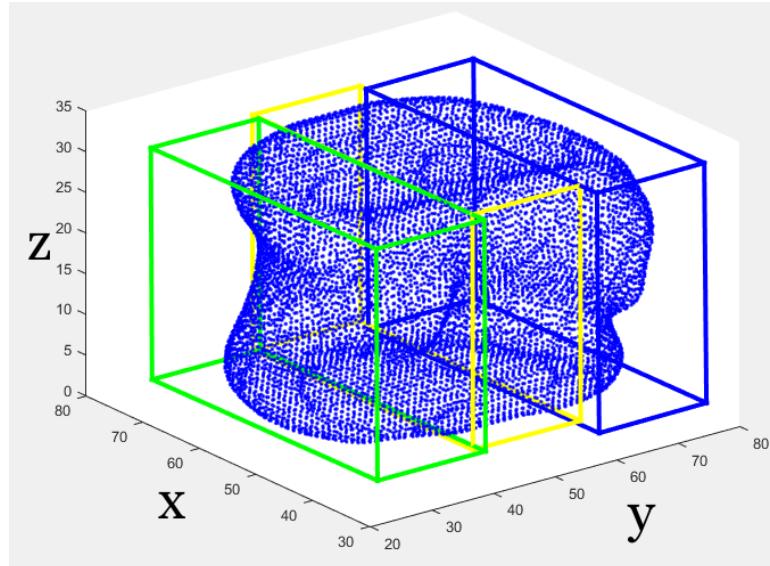


Figure 4.2.3: The three cuboids fitted to the vertebra point cloud in the sagittal plane.

### 4.3 PCA in ScanIP

The plugin for ScanIP that allows principal component analysis and the generation of models described by the principal components consists of five main steps.

The first of these steps is a pre-processing step, converting the masks and backgrounds into necessary formats (.mha & .mhd) for use with the ITK toolkit.

The following step carries out rigid registration of the models, aligning the masks and backgrounds to a shared coordinate system. This is carried out using the ITK library with the registration being measured according to a mean squared image-to-image metric using a gradient descent optimiser. A limit to the number of attempts or steps allowed can be

Table 4.2.1: The measurements and abbreviations taken from the vertebrae.

Measurement	Abbreviation
Sagittal Left Height	SLH
Sagittal Left Depth	SLD
Sagittal Mid Height	SMH
Sagittal Mid Depth	SMD
Sagittal Right Height	SRH
Sagittal Right Depth	SRD
Coronal Anterior Height	CAH
Coronal Anterior Width	CAW
Coronal Mid Height	CMH
Coronal Mid Width	CMW
Coronal Posterior Height	CPH
Coronal Posterior Width	CPW
Axial Inferior Depth	AID
Axial Inferior Width	AIW
Axial Mid Depth	AMD
Axial Mid Width	AMW
Axial Superior Depth	ASD
Axial Superior Width	ASW

set; the default value of 100 steps for each input model was used.

The geometry of each input specimen was described in a deformable registration step, measuring the transform required to morph the mean of the input vertebrae onto each of the input vertebrae. This step utilises the ITK FEM registration filter.

Penultimately, the transforms between the mean and each of the input vertebrae which describe the vertebral geometries are used as inputs for PCA. Here the outputs of the step include the principal components, their eigenvalue, percentage of variation captured in that component and the cumulative percentage variation captured.

Finally, the SSAM produced can be used with the ITK Image Warp filter to generate new mask and background combinations from within the envelope of geometric and material property variation created by the input set, according to the principal components. The plugin allows for the first five principal components (PC1, PC2, PC3, PC4 & PC5) to be used for as variables for model generation, altering the value of the principal components by up to three standard deviations away from the mean in both positive and negative directions.

### 4.3.1 Generating Vertebrae Models

#### 4.3.1.1 Range of Shapes Generated

To attempt to understand what each of the principal components represented in terms of the variation captured by it, models were created at  $\pm 1$ ,  $\pm 2$  and  $\pm 3$  standard deviations away from the mean for the first three principal components independently. In addition to these, the mean model was generated, allowing comparisons of the other generated models against it.

Finally, in order to know whether the range of geometries, material properties and resultant stiffnesses found in the input set was represented in the SSAM within the first three principal components, models were generated which incorporated the variation found in PC1, PC2 & PC3. These models would represent the corners of a cube who's axis would be PC1, 2 & 3 and who's origin would be the mean vertebra. If the majority of input models (68 %, representing the quantity of the population expected to fit within  $\pm 1$  SD of the mean for a normally distributed input set) fit within the limits created by a cube with side length from +1 to -1 SD along each axis for geometric measurements, greyscale background and resultant stiffness, then the variation of the input set will have been captured and represented by the SSAM.

#### 4.3.1.2 FE Model Setup

Once the vertebrae were generated using the plugin the rest of the FE model was set up. This included forming endcaps to mimic the experimental setup and how the input set was loaded. Endcaps were created programmatically within the ScanIP python scripting environment with a diameter of 90 mm, approximately equal to the diameter of the experimental endcaps, with a depth of 6 mm ensuring the superior and inferior tips of the vertebrae were captured with a minimum of 1 mm between the vertebra and end of the cement. The remaining properties for the FE model are identical to those used for the models of the human vertebra which became the inputs to the PCA plugin. This includes a tied interaction between the vertebrae and endcaps and material properties for the endcaps being: Young's modulus 2.45 GPa and Poissons's ratio of 0.3. Material properties for the vertebra used the same greyscale approach as in previous chapters with the Young's modulus for each element being:

$$E = GS \times \alpha$$

Where,  $GS$  is the greyscale value for the current element (between 0 and 255) and  $\alpha$  is the conversion factor. The conversion factor used has the same value used previously for the non-augmented set of vertebrae:  $\alpha = 0.0008184$ . Applying load to the models is carried out as in the previous chapter, with 1 mm of displacement applied to a loading point, with the reaction force being measured to obtain the stiffness. The loading point is found by finding the centre of the vertebral body in the middle slice axially and translating the point axially to the maximum height of the model, including endcaps. The load is then applied through a plate which is tied to the superior endcap.

#### **4.3.1.3 Augmentation in Generated Models**

#### **4.3.2 Validating Generated Vertebrae**

##### **4.3.2.1 Geometry Validation**

Measuring the vertebral geometry 18 measurements

##### **4.3.2.2 Material Property (Greyscale) Validation**

##### **4.3.2.3 Resulting Stiffness Validation**

#### **4.3.3 Measuring & Interrogating Vertebral Variation**

##### **4.3.3.1 Geometry Variation**

##### **4.3.3.2 Greyscale & Material Property Variation**

##### **4.3.3.3 Resulting Stiffness Variation**

#### **4.4 Effect of Injected Cement Volume, Shape & Position**

#### **4.5 Effect of Injected Cement on Vertebral Variation**

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