DISSERTATION

Prediction of Distal Radius Fracture Load Using HR-pQCT-based Finite Element Analysis

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THESIS

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Peter Varga
To my Family,
Nora and Kata
and my Parents
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Abstract

Osteoporosis is a skeletal disease of reduced bone mass, degraded micro–architecture and increased fragility. Distal radius (Colles’) fractures occur earlier in lifetime than other osteoporotic fractures. Efficient non-invasive assessment of fracture risk in the distal radius may therefore help to identify patients at risk early in time, indicate the need for treatment and prevent them from sustaining the predicted fragility fracture. The current gold standard clinical tool for this purpose is densitometry (DXA), predictive capability of which was however shown to be limited as bone mass is not the single contributor to bone strength. The emergence of High Resolution peripheral Quantitative Computed Tomography (HR–pQCT) allows for in vivo assessment of detailed reconstructions of the trabecular microstructure and the cortical shell in the peripheral skeleton. HR–pQCT–based anatomy–specific finite element (FE) modeling may succeed to DXA in predicting fracture risk in the distal radius.

Following an introductory chapter, the studies presented in this Thesis examine if the currently available HR–pQCT–based FE approaches (1) provide adequate predictions of ex vivo Colles’ fracture load and (2) are applicable in the in vivo case.

The first study applies the recently developed smooth–surface–based homogenized continuum FE (hFE) approach on the distal radius, validate it with experimental Colles’ fracture tests and raises numerous research questions which are then addressed in the following studies. The second study introduces an alternative, grayscale image–based approach (SSOD) for assessment of structural anisotropy (fabric) in trabecular bone, aiming to circumvent the need of image segmentation, which is the main weakness of the current methods (e.g. MIL). The third study evaluates how precisely HR–pQCT imaging is able to predict input parameters of the homogenization approach used in the hFE models, volume fraction and fabric, and identifies calibration laws for both of these quantities to match their gold standard (µCT) equivalents. The fourth study shows that HR–pQCT–based hFE modeling incorporating the determined improvements is able to precisely predict experimental fracture load of distal radius sections and have comparable accuracy but lower computational needs than the µFE approach. Finally, the fifth study demonstrates that the FE models of distal radius sections sized according to the in vivo HR–pQCT protocol are excellent predictors of the in vitro Colles’ fracture load obtained in the first study and perform better in this sense than densitometry or morphological analysis. Moreover, distal shift of the standard HR–pQCT region of analysis is shown to increase the power of the prediction.

The herein accomplished research work provides better understanding of the biomechanics of Colles’ fractures. Furthermore, the results suggest that the patient–specific HR–pQCT–based FE simulation represent an improved tool for in vivo fracture risk prediction, which will provide more accurate identification of individuals at risk than the currently available DXA–based approach.

Die nach einem einleitenden Kapitel in dieser Arbeit präsentierten Studien untersuchen, ob die derzeit verfügbaren, auf HR–pQCT basierenden FE Methoden (1) auf den distalen Radius angewandt werden können, (2) präzise Vorhersagen der ex vivo Colles Frakturlasten liefern und (3) auf die in vivo Situation anwendbar sind.


Die hiermit abgeschlossene Forschungsarbeit trägt zu einem besseren Verständnis der Biomechanik von Colles Frakturen bei. Darüber hinaus legen die präsentierten Ergebnisse nahe, dass patientenspezifische, HR–pQCT basierende FE Simulation ein verbessertes Werkzeug für die Vorhersage von in vivo Colles Frakturlasten darstellt, was eine genauere Bestimmung des individuellen Frakturrisikos als die derzeit verfügbaren, auf DXA basierenden Methoden ermöglicht.
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Chapter 1

Introduction

1.1 Bone

Bone is mineralized connective tissue constituting the skeletal system together with cartilage, muscles, ligaments and tendons. The skeleton is responsible for locomotion, provides support for the body in the gravitational field and protects the organs against mechanical effects of the environment. Bones have furthermore significant role in the calcium and phosphorus homeostasis, while red marrow is in charge of hematopoiesis, i.e. formation of blood cells.

Bone material is composed of 50–60\% mineral phase in form of hydroxyapatite crystals, 30–40\% organic constituents (collagen type I, proteoglycans and glycosaminoglycans) as well as 10–20\% bound and free water. This composite is very advantageous from a mechanical point of view as the mineral content provides high stiffness, but the material is not brittle due to collagen which therefore affects strength and ductility. Bones are built of the three main ingredients in a hierarchical manner, as it is depicted in Figure 1.1. Structural organization of bone matter is highly determined by the mechanical function, resulting in two main types of bone which can be distinguished at the macroscopic level (see Figure 1.1, Figure 1.3 and Figure 1.12). Cortical (or compact) bone forms the dense outer shell of bones providing high moment of inertia against bending and torsion. Trabecular (or cancellous, spongious) bone on the other hand is optimized to resist – depending on the anatomical site – specific loadcases with minimal weight. It can be found in the central core of short bones as well as in the epiphysis of long bones, while missing in the metaphyseal regions. These two types differ in porosity and microscopic organization.

Cortical bone is compact as 85–95\% of its volume is occupied by bone matter. It is constituted of an osteonal network with concentric cylindrical lamellae organized around longitudinal voids called Haversian canals which are occupied by blood vessels. These elongated pores are oriented in the direction of the typical loading and this way maximize mechanical resistance. Orientation of the collagen fibers is parallel and has planar alignment within one lamella, but gradually rotated among the individual lamellae resulting in
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Figure 1.1: Hierarchical arrangement of bone: the levels of structural organization (adapted from [1]).

a twisted plywood–like structure [2].

Cancellous bone is characterized by 5–40% volume fraction and accounts for approximately 20% of the skeletal mass. The spongious architecture resembles open–cell foams. It is formed by a network of interconnected trabeculae, which are 50–200 µm in diameter and have various shapes ranging from rod–like to plate–like. The principal orientation of trabeculae follows stress trajectories as it was first observed by Wolff [3]. This micro–structural anisotropy (or fabric) can be quantified with several approaches (see Chapter Three), among which the mean intercept length (MIL) method is the most widely known and used [4]. MIL provides an orientation distribution function (ODF) by measuring the average lengths of bone–marrow interfaces in given directions, as shown in Figure 1.2. When performing the analysis in 3D, the resulting spatial ODF can be approximated with an ellipsoid [5] or a second order tensor [6] which is therefore denominated as fabric tensor (M):

$$ M = \sum_{i=1}^{3} m_i \mathbf{m}_i \otimes \mathbf{m}_i $$

In this equation, $\mathbf{m}_i$ are the eigenvectors of $M$ defining the main fabric orientations ($i = 1, 2, 3$), while $m_i$ ($m_1 < m_2 < m_3$) are the corresponding eigenvalues, from which degree of anisotropy (DA) can be determined ($DA = \frac{m_3}{m_1}$).

The most exciting property of bone from an engineering point of view is that, being a living structure, it is adapting to the mechanical environment with a remodeling process including resorption and formation, which renew its material and repair microdamage. Weight and architecture are hence continuously optimized to the average stresses caused by
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Figure 1.2: Explanation of the mean intercept length method in 2D. As it is shown on the left side of the figure, average bone–marrow distances are measured in several directions (one, with an angulation of $\omega$, is depicted) by counting interfaces (intercepts are shown for one line only). The resulting orientation distribution function is approximated with an ellipse or second order tensor tensor (right), providing the fabric eigensystem ($\mathbf{m}_1$ and $\mathbf{m}_2$ in 2D).

activities of everyday life [3], resulting in a dynamic equilibrium after growth. Diseases like osteoporosis disturb this process and induce disorder in the homeostasis of bone mineral.

1.2 Osteoporosis

Osteoporosis is a skeletal disease perturbing the formation–resorption balance in bone, leading to reduction of bone mass and degradation of micro–architecture. Trabecular bone has a large remodeling surface relative to its volume, therefore it is metabolically more reactive and more strongly affected by osteoporotic processes than compact bone, undergoing thinning, conversion from plate–like to rod–like shape as well as loss of inter–trabecular connectivity. The cortical shell is also deteriorated due to thinning. These changes result in decreased bone strength and increased fragility. Figure 1.3 depicts the effects of the disease on the bone structure by comparing the distal radii of a healthy and an osteoporotic woman having closely the same age.

The official definition of osteoporosis provided by the World Health Organization (WHO) is based on areal bone mineral density (aBMD, projected two–dimensional density) quantified in the femoral neck using dual energy X–ray absorptiometry (DXA). Compared to the mean of young adult (30 years old) Caucasian women taken as reference (T–score), aBMD of -2.5 standard deviations (SDs) was defined as the diagnostic threshold value, below which we talk about osteoporosis, while T–score of -1.0 defines osteopenia, the stage of low bone mass [7, 8]. Figure 1.4 depicts the results of the hip densitometry for a healthy and an osteoporotic case. Women are particularly subjected to threat as their peak bone mass at age 30 is lower compared to men and the hormonal changes of the menopausal
Figure 1.3: High-resolution peripheral quantitative computed tomography reconstructions of the distal radii of a healthy (left) and a severe osteoporotic case (right), demonstrating the effect of osteoporosis on the cortical and trabecular bone structure. Both donors were females with ages 82 and 85 years, respectively.

Stage (drop of estrogen level) cause dramatic decrease with age. The disease affects 30% of all postmenopausal women in the USA and Europe [9, 10]. Both genders lose trabecular bone mass with age, however, the rate and the architectural changes are different: women lose trabeculae, while in men trabecular thinning with more preserved connectivity is more typical [11]. Thinning of the cortical shell and increase of its porosity are as well less pronounced in men and somewhat compensated by the increase of the cortical diameter in both genders [12].

Healing of osteoporosis is primarily based on drug-therapy. There are two main treatment strategies: induce bone formation with anabolic drugs (mainly with parathyroid hormone, PTH), or decelerate bone loss with antiresorptive medication (e.g. bisphosphonates, selective estrogen receptor modulators and calcitonin), some of which are also applicable for prevention. Adequate calcium and vitamin D supplementation as well as exercise are also important for a successful treatment.

The clinically important outcome of osteoporosis is fractures. Osteoporotic fractures are caused by low trauma, i.e. even a low magnitude of the impact force is sufficient to damage the degraded bone structure. Incidence is increasing with age due to progress of osteoporosis and higher risk of falling. Beside the vertebral column and the hip joint, the forearm is the third mostly endangered site. Among the 1.5 million osteoporotic fractures occurring yearly in the USA, approximately 700,000 involve the spine, 250,000 concern the femoral neck and 250,000 affect the wrist [13]. Besides being a disease that proclaims an
Figure 1.4: DXA–based aBMD measurement of the hip joint of a healthy (left, BMD = 0.866 g/cm², T-score = -0.6) and an osteoporotic (right, BMD = 0.580 g/cm², T-score = -3.0) female with closely the same age (75 years). Top: DXA images of the hip joint with the definition of the region of analysis (yellow contour). Bottom: output graphs, the parallel bands show the healthy (green), osteopenic (yellow) and osteoporotic (red) ranges of BMD, respectively T–scores. The result of the diagnosis is indicated with a cross (⊕).
increasing harm to the elderly population, osteoporosis cause heavy financial load on the social health care system through fractures. Treatment costs in the USA were approximated to be 7 billion US$ for proximal femur, 750 million US$ for vertebral and 400 million US$ for forearm fractures in 1995 [14]. Aging of the population in combination with the expected increase of the number of diseased individuals will lead to increased number of fractures resulting in a major financial burden. Early diagnosis and prevention are therefore of increasing interest.

Incidence of distal radius fractures increases in women directly after menopause [15] (see Figure 1.5). Thus, wrist fractures occur earlier in lifetime compared to other osteoporotic injuries and represent an early hallmark of the disease [16, 17, 18, 19, 20, 21]. Forearm fractures were reported to account for more than 25% of all fractures of women in England [22]. Osteoporosis has been shown to be the cause of 70–80% of all distal radius fractures occurring in postmenopausal women [23]. Both BMD [24] and existing fracture [19] of the distal radius predict future fragility fractures of other sites. Fractures, or pre-fracture diagnosis of the distal radius is therefore of particular importance as these could be used to recognize osteoporosis at an early stage as well as to predict and prevent subsequent injuries or other, more severe and life-threatening fragility fractures [25].

1.3 The wrist and its fractures

1.3.1 Anatomy and function of the wrist

Our wrist joint, having a very complex structure and function, ensures large mobility and dexterity of the hand. The wrist is a synovial (also called diarthrodial) joint. It is of elliptic type, allowing no translations and two rotations (Figure 1.6). One of these occurs in the
sagittal plane, around the radio–ulnar axis. It is called flexion when the angle is reduced and
the palm approaches the forearm (having a maximum value of 75°), respectively extension
when rotated in the contrary direction (up to 70°). The other rotation takes place in
the coronal plane, around the dorso–palmar axis. This can be abduction, which is radial
deviation, occurring when the thumb approaches the arm (max: 20°), and adduction (or
ulnar deviation) when rotated in the inverse direction (max: 35°). An other motion of
the forearm, a rotation in the transversal plane around the proximal–distal axis, is called
pronation (or internal rotation, max: 70°) and supination (external rotation, max: 85°).
Nevertheless, these are not direct movements of the wrist but the forearm.

The bony constituents of the wrist are two long bones and eight smaller bones known
as carpals. Figure 1.7 depicts these bones and the metacarpals of the fingers. The forearm
consists of two long bones, the radius and the ulna, both of which are prismatic and tubular.
The radius extends from the inside of the elbow to the thumb side of the wrist, on the lateral
side of the ulna. The distal epiphysis of the radius is larger and it is the main constituent
of the wrist–joint. The ulna is situated on the external side of the forearm, it is longer
and thinner compared to the radius. Its proximal epiphysis is extended and connected to
the humerus. Together they form a hinge–type joint, namely the elbow. The radius and
the ulna are interconnected with ligaments and muscles all over their lengths. Between
the distal epiphyses of the long bones of the forearm one can find the (distal) radio–ulnar
joint with a ligamentous attachment. The eight carpal bones, located in two rows, are
the following (starting at the thumb side): scaphoid (or navicular), lunate, triquetrum and
pisiform in the proximal row; trapezium, trapezoid, capitate and hamate in the distal carpal
row. Each of them is cuboid shaped with six surfaces, four of which is covered with cartilage
to articulate with the adjacent bones and two roughened for ligamentous attachment. The
carpals are packed in a capsule and connected with each other and with the neighboring
bones by means of four groups of articulations. The internal connections in the row are
intercarpal joints, the one between the two rows is the midcarpal joint. The radio–carpal ligaments attach the carpals to the radius and a fibrocartilage disk connects them to the ulna. The connection of the distal row to the metacarpal bones is called carpo–metacarpal articulation.

1.3.2 Wrist fractures

Fractures of the forearm are the most common osteoporotic injuries in post-menopausal women [22]. Ratio between the genders is 4:1 for females:males [16], mainly for two reasons: osteoporosis is more frequent in this group with more severe stage of the disease [13] as well as liability of elderly women to falls is higher [27] compared to the age–matched men. In postmenopausal women, the lifetime risk of sustaining a forearm fracture is 16% [28]. Incidence of wrist fractures remains close to constant after age of 65 in women [17, 18] (see Figure 1.5), most probably because they tend to fall on the hip rather than the hand [15]. Occurrence is mainly related to outdoor falls and increases in winter period [29].

The group of wrist fractures include fractures of the radius, the ulna and the carpal bones as well. Provided that this work is focusing on distal radius fractures, these injuries will be discussed in more details below.

Healing of fractures comprise diagnosis and treatment. The most often applied diagnosis tool is radiography. A pair of X-ray scans are performed in close to perpendicular directions providing projections corresponding to the dorsal–palmar (posterioranterior, PA) and radio–ulnar (lateral) planes. The diagnosis is based on some quantities evaluated on these radiographs: radial length, radial inclination (both measured on the PA view) and palmar tilt (measured on the lateral view). The definitions of these quantities are provided in Figure 1.8 for an intact wrist. Further important aspects of the diagnosis are
intra–articularity (i.e. if the articular surface is involved), comminution (i.e. the number of fragments) and stability of the fracture. Computed tomography (CT) should be involved into the diagnosis in ambiguous or complicated cases where radiography does not provide an adequate basis of evaluation. Magnetic Resonance Imaging (MRI) may be preferential to investigate concurrent soft tissue damage.

Following image assessment, the fracture is classified into certain categories according to specific aspects, aiming the guidance of the decision about the treatment by providing recommendations for action in the distinct cases. Several authors used different classification systems in their studies [31], the most important four of which will be discussed briefly. The Frykman classification [32] was one of the first ones published and rarely used nowadays. It divided fractures into eight groups based on four fracture patterns. The system of Melone [33] was based on the number of fragments and distinguished four types. The AO (Arbeitsgruppe für Osteosynthesefragen) classification [34] put the emphasis on severity and intra–articularity of the fracture, classifying into three main groups which were further divided into specific sub–groups, totalling twenty–seven types. Fernandez & Jupiter [35, 36] based their five–category system on the mechanism of the fracture and suggested treatment mainly according to the type of force causing the injury (bending, shear, compression, or high–velocity impact) as well as impaired soft tissue damage.

Independently of these classification systems, some typical fracture patterns are identified with specific eponyms in the common knowledge. Some of these are listed below in inverse order of importance. Chauffeur fracture (also called Hutchinson or backfire fracture) is an intra–articular fracture of the radial styloid (the projection of bone on the lateral side of the distal radius) occurring when the scaphoid is compressed against the styloid. The eponym originates from the backfire–accident that caused the injury when chauffeurs used cranks to start engines of automobiles. Barton fracture is a shear type intra–articular fracture induced by transverse loading and accompanied with dislocation of the radiocarpal joint. Smith fracture is an extra–articular, transverse fracture of the radial metaphysis with palmar displacement and angulation of the distal fragment. It is caused by high impact in hyperflexion of the hand and often called reverse Colles’ fracture.

Finally, Colles’ fracture, being the most frequent and therefore most important one, will be discussed in more details. The injury is named after Abraham Colles, Irish surgeon and anatomist, who first described it in 1814 [37]. Colles’ fracture is defined as a transverse fracture of the radius located in the ultra–distal 10–12% region (loco typico) with a dorsal displacement and rotation of the distal bone fragment [38, 39]. Majority of distal radius fractures are of the Colles’ type, approximately 80% of which occur in women [16, 40]. It is more frequent in the elderly, caused by low trauma impact [16]. The typical accident of occurrence is falling from standing position when one tries to protect his or her body against impact with the outstretched arm (Figure 1.9). The radiographic signs of Colles’ fracture, as shown in Figure 1.10, are shortening of the radial length, decrease in radial inclination and dorsal tilt.

Treatment of forearm fractures consists of restoration of the radio–carpal planes with closed, arthroscopic, or opened (operative) reduction and maintenance of the recovered geometry for the period of reunion by immobilization. The latter, depending on the severity
Figure 1.8: Radiographs of an intact right wrist with the definitions of the quantities used in fracture diagnosis, based on [30]. Original X-ray images courtesy of the Medical University of Vienna. Left: PA view, right: lateral view. Radial length is the distance of the point D and E, ranging between 10 and 13 mm in healthy case. Radial inclination (α) is the lateral articular angulation defined by axes Y and Z, normal value ranges from 21° to 25°. Both are measured on the PA radiograph (left). Palmar tilt (β) is the angle defined on the lateral view (right side) between the axes Y and Z, with a normal range of 2–20° and average value of 11°.
Figure 1.9: Illustration of the typical accident when sustaining a Colles’ fracture: falling to the outstretched hand.
Figure 1.10: Radiographs of a Colles–fractured right wrist. Left: PA view, right: lateral view. Original X-ray images courtesy of the Medical University of Vienna. In comparison with Figure 1.8, the typical deformations of Colles’ fracture can be observed: radial shortening (length of D–E), reduction of radial inclination ($\alpha$) and inverted palmar (dorsal) tilt ($\beta$).
and stability of the fracture can be simple plaster casting, percutaneous pinning, internal (plate) or external fixations, or combinations of these. In closed reduction, series of control radiographs are necessary to evaluate if restoration was successful and if it is maintained with time. The usual healing period is 6–10 weeks in less complicated cases. Most common complications are wrist pain, reduced degree of motion, joint stiffness and loss of function due to malunion. Arthritis may emerge in intra-articular cases when congruity of the articular surface cannot be restored perfectly and may result in complete fusion of the joint in extremely severe cases. Non-union of the radius is rather rare due to the good blood supply of this area.

1.3.3 Colles’ fracture: from a mechanical point of view

Mechanics of the wrist is considerably complex due to the number of participating bones, ligaments and muscles. The radio-carpal joint is the relevant region from the point of view of Colles’ fractures. It is formed by the radius, a hyaline cartilage layer and three bones of the proximal carpal row: the scaphoid, the lunate, and the triquetrum. The distal radius is triangular in shape and flares distally. Its distal articular surface is a biconcave as it is composed of two concave facets, the scaphoid and the lunate fossa (Figure 1.7).

During a fall to the outstretched arm, the hand is pushed backwards into a hyper-extended (i.e. excessive dorsiflexed) position. Forces are transmitted from the ground through the carpal bones to the long bones of the forearm, causing compression and bending. Two carpal bones transmit bulk of the load to the long bones. Slightly more than half of the full load is carried through the scaphoid in neutral position, which is increased to 60% in extension while reducing the fraction belonging to the lunate [41, 42]. Load sharing among the long bones in neutral position was reported to be dependent on the pronation/supination of the forearm, with approximately two-third carried by the radius [43, 44]. Other studies found 90% of the force transmitted through the radius in neutral position and almost 100% in extension [41, 42]. These results were not supported by a recent work of Rikli et al. using in vivo measurement and reporting majority of the load to be transferred on the ulna side of the joint during active motion of the wrist, however, based on only one patient [45].

Colles’ fracture localizes within the distal 30 mm of the radius [39, 46, 47, 48, 49], at a natural weak spot, the so-called cortico-cancellous junction. Proximally from the radiocarpal joint, the trapezoidal shape of the radius is getting narrow, the size of trabecular domain is decreasing and the cortical bone is still very thin. This zone, being the weakest link in the chain, is where the fracture most probably initiates. The side-support of the ulna may also influence the mechanism. The dorsal angulation of the distal fragment is caused by bending. Contact areas of the radio-carpal joint were found to be dorsally displaced in extension compared to the resting configuration [50, 51, 42, 52] so that eccentricity of the compression force induces bending moment in the long bone principally around the radio-ulnar axis (Figure 1.11), resulting in rotations of the fragment following fracture initiation (see Figure 1.10). This was not in line with the in vivo results of Rikli et al. [45]. During
1.4 Fracture risk assessment

In order to identify individuals at high risk, the goal is not only to diagnose the present stage of osteoporosis but it is also desired to prognosticate the potential of a future fragility fracture. Changes in fracture risk, caused by progress of the disease or, on the contrary, by therapeutic procedures, should also be monitored.

1.4.1 Risk of fracture

The absolute risk of fracture is a complex index affected by numerous factors. It was defined by Kanis as the 'likelihood of fractures over a given period of time' [53]. The clinical approach is to predict risk of fracture directly with specific parameters based on epidemiological data collected in prospective and retrospective clinical studies involving large number of patients. This empirical method allowed for filtering out the relevant factors that significantly correlated with fracture incidence.

aBMD assessed with densitometry does not only provide the recommended diagnostic definition of the disease but delivers information on fracture risk as well. 1.0 SD decrease in the DXA T-score yields to a 1.5-fold increase of fracture risk on average, which factor can range up to 3.5 depending on the site of measurement and injury [24]. Reduced bone min-
eral density was shown to be a strong predictor of fractures [54, 55]. However, DXA is known to have high specificity but low sensitivity [53]; it was reported to be limited in separating fractured and non-fractured patients [56, 57, 58] and a large portion of osteoporotic fractures occur in patients with aBMD within the diagnostic threshold margin [7, 59, 60, 61].

Certain Clinical Risk Factors (CRFs) were identified to be significantly related to fracture risk. These usually have low specificity and sensitivity, but provide a BMD-independent contribution and hence can be used to improve the BMD-based predictions [53]. The most important factors are age [62, 63], gender [16], body mass index (BMI) [64], fragility fracture history [65], parental history of fragility fractures [66], glucocorticoid treatment [67, 68], smoking [69], alcohol consumption [70] and secondary causes of osteoporosis like rheumatoid arthritis [71]. Some of these have dose-dependent contribution, e.g. fracture history or alcohol intake.

The up-to-date clinical approach proposed by the WHO is the Fracture Risk Assessment Tool (FRAX), integrating aBMD and the CRFs into a single measure [72, 73]. With this, specificity of the aBMD measurements is not affected, sensitivity however is improved [74]. FRAX prognoses the ten year probability of an osteoporotic or major clinical fracture based on epidemiological information of the given country. The tool is widely accessible via internet in a questionnaire form (www.shef.ac.uk/FRAX). The procedure of diagnosis starts with the evaluation of the CRFs which must be completed with hip aBMD in case of an intermediate CRF risk in order to enhance the precision of the prediction. One limitation of the FRAX tool is that it does not take account of the dose-dependency of some CRFs, like number of prior fragility fractures or amount of glucocorticoid intake. Furthermore, type of prior low trauma fractures is not specified, although vertebral fractures carry higher risk than fractures at other sites.

Three-dimensional (3D) Quantitative Computed Tomography (QCT) allows for assessment of volumetric BMD (vBMD). The main location of application is the vertebral spine, where it was show to have equivalent, or slightly better predictive power than aBMD [75, 76, 77].

Secondary to the mass of bone, the distribution of its material is the most important descriptor. The development of high resolution 3D image assessment technologies allowed to go beyond bone mass measurements and to gain insight to the micro-architecture. The most commonly used tool is quantitative computed tomography with resolution of a few microns or even below which is therefore called microCT (μCT). MRI may be preferential due to the lack of ionizing radiation, however, this modality is costly, requires long acquisition time, cannot quantify mineralization of bone and the currently available resolution do not compete with the CT technology [78, 79]. Using CT, the trade-offs for the high resolution are high dose and limited sample size which restrict the use to in vitro measurements. Bone biopsies excised mostly from the iliac crests of patients are therefore investigated with μCT (see Figure 1.12). For cortical bone, cortical area, cortical thickness (Ct.Th) and cortical porosity (Ct.Po) are usually quantified. In case of long bones, the further descriptors of cortex are moment of inertia, section modulus and stress-strain index (SSI, density-weighted section modulus). Beyond bone volume fraction (BV/TV), which is highly related to vBMD, the most often investigated indices of trabecular bone are bone surface over
Figure 1.12: µCT reconstruction of a bisected human iliac crest bone biopsy with cortical and trabecular bone.

bone volume ratio (BS/BV), trabecular thickness (Tb.Th), relative number of trabeculae (Tb.N) trabecular spacing (Tb.Sp) [80] and degree of the structural anisotropy (fabric DA) assessed with the MIL method. These parameters were originally quantified on histological bone sections in two dimensions and used to estimate the equivalent spatial measures by assuming plate-like shape of the trabeculae. The emergence of high resolution 3D imaging allowed for assumption-free, truly 3D assessment of these indices [81] providing up to 50% differences in comparison with the 2D approach. Additionally, new, model-independent measures were introduced like structural model index (SMI) [82] and connectivity density (Conn.D) [83, 84]. The main limitations of the biopsy-approach is that it is invasive and not site-specific. Additionally, a random sampling is performed and results may vary with the selection of the region of analysis.

Resolution of the latest high resolution peripheral QCT (HR-pQCT) scanner (XtremeCT, Scanco Medical AG, Switzerland) is 100 µm which is already close or even below the average trabecular thickness allowing for detailed reconstruction of the micro-architecture [85]. Special image filters were developed to increase signal-to-noise ratio and preserve connectivity. Further advantages of HR-pQCT are relative low effective dose (3µSv), precise reconstruction due to the low amount of surrounding soft tissue and high reproducibility [86]. Despite its disadvantages like the relatively small region of analysis (9.02 mm section) and long acquisition time (~3 minutes) the HR-pQCT technology made the distal radius an attractive site for fracture risk assessment. HR-pQCT morphology of the distal radius was reported to provide additional precision to the BMD-based predictions of fractures of the same site.
1.4.2 Decomposition of the risk of fracture

Risk of fracture, in contrary to the approach presented in the previous Subsection, can be considered as a complex factor and decomposed into its basic constituents, probability of falling and factor of risk, as it is shown in Figure 1.13. The methods discussed in the previous Subsection cannot predict incidence and severity of falling [89], neither the magnitude and type of the acting forces. Instead of assessing fracture risk directly, its components should therefore be decoupled and quantified separately. More properly, the prediction should be performed in two steps: first, by predicting the factor of risk by assuming that the accident occurs and correcting for the estimated susceptibility of incidence thereafter.

Probability of falling

The relevant accidents causing fractures in osteoporotic individuals are falls. The definition of a fall provided by the WHO is 'an unexpected event where a person falls to the ground from an upper level or the same level' [90]. Susceptibility of falling is related to sports and active life style, or, on the contrary, to factors associated with diseases and aging like loss of sight [54], balance deficit, reduced muscle mass, immobility, sedative medication, vitamin D deficiency, etc. The risk factors are classified into five categories: medical conditions and its changes associated with aging, medication, nutritional, environmental and lack of exercise [90]. Assessment of risk of falling is difficult and usually performed by means of simple tests
based on analysis of sight, balance and gait. Intervention strategies aiming to prevent falls target one specific aspect (unifactorial) or several risk factors (multifactorial). Exercise, diet and elimination of environmental sources of danger were shown to significantly reduce probability of falling [91].

Assessment of probability of falling is an important, nevertheless inaccurate part of fracture risk prediction. Only 5% of all falls result in an actual fracture [92, 93]. In particular, risk of falling was found not to be strongly related to incidence of forearm fractures [94].

**Factor of risk**

Factor of Safety (FoS) is used in the engineering design and expressed as the ratio of the ultimate and the applied loads. This approach takes the ‘worst case scenario’ into account by assuming that the structure is subjected to extraordinary (i.e. accidental) loads. In case of bones, the inverse of FoS, the factor of risk of fracture (Φ) is generally used, which is therefore defined as the ratio of the fall load and the failure load [95]. The ultimate state is reached, respectively the fracture occurs when Φ is increased above 1.0. This can manifest in two ways:

1. Considering healthy bone as a well designed and optimized structure, the magnitude of the acting forces must increase beyond the normal, everyday level to induce fracture. Beyond accidents, excessive load can occur while doing sports and hence it is more frequent among young, active people, causing high trauma fractures.

2. Bone strength on the other hand can be decreased such that it cannot resist the everyday loads. This case is related to immobility or diseases like osteoporosis, affecting mainly the aged population. Furthermore, decreased muscle mass of the elderly influences the portion of load that the bone is subjected to [96].

The numerator of Φ (i.e. the magnitude and type of the acting forces) includes several uncertain parameters like velocity, height and direction of falling, type of the ground, etc. The accuracy of the prediction can be increased by restricting the analysis to specific cases. In case of the typical Colles-accident for example, the estimation can be based on the height and weight of the patient, assuming that the fall occurs from a standing position [97, 98] and knowing that the majority of falls are directed forwards [99, 100]. Experimental studies concluded that standing-height falls induce forces up to 2500–4000 N, which depends more strongly on the height than the weight of the person, and that falling from a height greater than 0.6 m carries a significant possibility of Colles’ fracture [101].

The denominator of Φ, namely bone strength (or fracture load), is often referred to as ‘bone quality’. To be more precise, ‘bone quality’ was defined as the ‘totality of features and characteristics that influence a bone’s ability to resist fracture’ [102]. For other purposes, it was interpreted such that ‘any clinically relevant modification of bone quality must change bone biomechanical performance relative to bone mass’ [103]. Note, that the first definition
will be used here. There are several factors affecting bone quality, some of which are size, shape, material properties, architecture, microdamage and collagen cross-linking. In vitro experimental studies can directly measure strength with mechanical testing by destroying the bone specimen. Experimental measurements are limited in reproducing some factors of the in vivo case (e.g. muscle tone) and model a specific loading configuration. Still, these are the best available approximations of bone fracture load. Several types of experimental approaches were introduced to quantify strength of the distal radius, including three-point bending and axial compression of bone sections [38]. The most relevant ones for Colles’ fractures are still simulations of falls to the outstretched hand. Different mechanical setups were used to evaluate failure load of the distal radius, ranging from testing forearms with soft tissues to loading isolated radii. Table 1.1 summarizes some of these studies in chronological order.

Table 1.1: Summary of the experimental studies investigating forearm fractures in fall simulations, extended from [38]. F/M/C: Number of specimens (female, male and Colles’ fractured), v: loading rate in mm/sec, Ult. F.: bone strength in kN; a: using intact forearms, b: using intact wrists with carpals, c: using isolated radii; nr: not reported.

<table>
<thead>
<tr>
<th>Study</th>
<th>Ref.</th>
<th>F/M/C</th>
<th>Mean age</th>
<th>v in mm/sec</th>
<th>Ult. F. in kN</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frykman et al. a</td>
<td>[32]</td>
<td>17/21/22</td>
<td>nr</td>
<td>100 kp/min</td>
<td>2.26±1.01</td>
</tr>
<tr>
<td>Myers et al. a</td>
<td>[104]</td>
<td>11/7/16</td>
<td>76±7</td>
<td>25</td>
<td>3.39±0.88</td>
</tr>
<tr>
<td>Myers et al. a</td>
<td>[105]</td>
<td>18/7/19</td>
<td>74±9</td>
<td>25</td>
<td>1.78±0.65</td>
</tr>
<tr>
<td>Spadaro et al. a</td>
<td>[47]</td>
<td>9/12/12</td>
<td>76±12</td>
<td>0.4</td>
<td>1.64±0.98</td>
</tr>
<tr>
<td>Augat et al. c</td>
<td>[106]</td>
<td>13/7/19</td>
<td>85±8</td>
<td>1</td>
<td>2.01±0.91 (F)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>3.77±1.57 (M)</td>
</tr>
<tr>
<td>Augat et al. b</td>
<td>[39]</td>
<td>7/13/17</td>
<td>65±nr</td>
<td>75</td>
<td>2.65±1.49</td>
</tr>
<tr>
<td>Wu et al. c</td>
<td>[107]</td>
<td>Σ13/nr/nr</td>
<td>64±16</td>
<td>75</td>
<td>nr</td>
</tr>
<tr>
<td>Eckstein et al. a</td>
<td>[108]</td>
<td>72/38/85</td>
<td>80±nr</td>
<td>3.3</td>
<td>1.60±0.1</td>
</tr>
<tr>
<td>Lochmüller et al. a</td>
<td>[109]</td>
<td>82/47/102</td>
<td>80±nr</td>
<td>3.3</td>
<td>1.12/2.23 (F/M)</td>
</tr>
<tr>
<td>Pistoia et al. a</td>
<td>[110]</td>
<td>33/21/54</td>
<td>82±9</td>
<td>3.3</td>
<td>1.24±0.46</td>
</tr>
<tr>
<td>Lil et al. a</td>
<td>[31]</td>
<td>72/46/108</td>
<td>81±10</td>
<td>3.3</td>
<td>1.63±0.86</td>
</tr>
<tr>
<td>Muller et al. c</td>
<td>[97]</td>
<td>18/20/21</td>
<td>78±12</td>
<td>100</td>
<td>3.23±0.82</td>
</tr>
<tr>
<td>Ashe et al. c</td>
<td>[111]</td>
<td>10/0/10</td>
<td>79±6</td>
<td>75</td>
<td>2.85±1.61</td>
</tr>
<tr>
<td>Hüdelmaier et al. a</td>
<td>[112]</td>
<td>40/30/51</td>
<td>81±10</td>
<td>1.7</td>
<td>1.86±0.82 (F)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>78±11</td>
<td></td>
<td>3.13±1.32 (M)</td>
</tr>
<tr>
<td>Lochmüller et al. a</td>
<td>[113]</td>
<td>64/66/79</td>
<td>81±9</td>
<td>1.7</td>
<td>1.58±0.76 (F)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>80±9</td>
<td></td>
<td>2.76±1.05 (M)</td>
</tr>
</tbody>
</table>

As failure load cannot be assessed directly in vivo, clinical applications required non-destructive surrogate measures of bone strength. The relevance of these measures were evaluated using results of the in vitro experiments like the ones listed in Table 1.1. Review-
ing these studies, the most important surrogate measures are discussed below.

Bone mass is the primary contributor of bone strength [114] and therefore the most often used predictor. DXA cannot distinguish cortical from trabecular bone and cannot take proper account for bone size either due to its projected nature [115]. Studies reported squared correlation coefficients between aBMD and experimental failure load of $R^2=0.07$ [105], $R^2=0.30$ [110], $R^2=0.44$ [108, 109], $R^2=0.53$ [39], $R^2=0.56$ [107], $R^2=0.59$ [97] and $R^2=0.67$ [113]. Indeed, the best predictions were achieved with site–specific DXA measurements [108].

Slightly improved predictions of fracture load could be obtained using QCT or peripheral QCT (pQCT) vBMD, which can be quantified for the two bone compartments separately. vBMD measurements of the trabecular bone region showed higher predictive power compared to those of the cortical region [47, 106, 112], but was not or not significantly stronger than the total vBMD of both compartments [109].

Bone mineral content (BMC) was reported to be a better predictor of radius strength than BMD, with $R^2$ ranging from 0.48 to 0.88 [104, 47, 108, 109, 110, 97, 112]. In fact, BMC provided the highest correlations with fracture load in many studies [47, 108, 109, 112], suggesting that bone matter is organized in an optimal fashion, as dictated by Wolff’s law. Predictions further improved when BMC of the cortical bone was taken alone [97, 112]. In contrary, a recent study found BMC to be less powerful than density [113].

pQCT imaging allowed for precise assessment of macro–scale geometrical measures of bones. Parameters of the cortical bone of the shaft are usually quantified, including area, thickness, second moment of inertia, section modulus and stress–strain index. Some studies showed that these parameters were stronger predictors than density [104, 105, 106, 116], while others did not support these findings [47, 109, 110, 97, 112].

Further improvement of the technology lead to even higher resolutions, providing insight to the trabecular structure and cortical porosity. Compared to aBMD, slightly improved predictions were achieved by including HR–pQCT–based micro–architectural measures, which however were not or not significantly better predictors as BMC [117, 47, 116, 97]. The $\mu$CT–based biopsy approach failed to improve density–based predictions of fracture load [113], most probably because it was restricted to a randomly sampled subregion instead of analyzing the whole bone structure.

Quantitative ultrasound (QUS) technology allows for non–destructive and radiation–free investigation of bone using speed of sound (SOS) measurement by quantifying attenuation in longitudinal or transverse transmission. It is usually performed in the phalanges or calcaneus, and therefore not site–specific. QUS was found to provide weaker predictions of fracture load compared to mineral density measurements [107, 118, 109, 97, 112].

Instead of following a statistical approach to predict fracture force from density, geometry, micro–architecture or any combination of these, bone strength can be directly computed in a mechanistic way with finite element (FE) modeling. In this method, a virtual mechanical model of the real bone structure is built from the CT images by extracting geometry and, in some cases, density distribution as well. When exposed to the same mechanical environment, well–calibrated FE models can provide very similar – if not identical – responses to their physical analogues. Hence these models are capable of providing accu-
rate predictions of the mechanical properties, like fracture load, directly. In comparison with destructive mechanical testing, an advantage of the FE method is that the sample can be reused to investigate several loadcases. FE analysis was proven to provide better predictions of experimental failure load of the distal radius compared to aBMD and BMC derived from DXA or micro–architectural indices [110] and may therefore be the ideal tool to assess fracture risk of this anatomical site [38, 119]. Furthermore, FE models are able to provide details about how and where a fracture would occur which is clearly not the case for either the density–based or the morphological quantities.

Being an engineering method, FE requires mechanical background information, some parts of which will be summarized briefly in the next Section. The different types of FE models will also be discussed, with emphasis put on the distal radius.

1.5 Finite element modeling of bone

In the course of the structural FE analysis [120], a geometrical model of the examined object is first built which is subdivided into small parts (elements) of finite size. The material behavior (stress response for a given strain) of each element is described by constitutive laws. Using these local formulations, a global equation is assembled that characterizes the full structure. The mechanical environment of a specific loadcase is defined by setting up boundary conditions of force and/or displacement nature. The mechanical response of the structure to a given load is calculated by solving the global equation to satisfy equilibrium. Local quantities of the elements can then be extracted. Finally, the results are interpreted in post–processing steps.

1.5.1 Basics of bone mechanics

Mechanical properties of bone highly depend on the hierarchical level of analysis. Due to their similar material composition, microscopic mechanical behavior of cortical and trabecular bone are similar, if not identical. However cortical and trabecular bone behave differently on the macroscopic hierarchical level due to the differences in their porosity and architectural organization. Apparent (i.e. macroscopic or continuum level) mechanical behavior of trabecular bone is governed by its micro–architecture, while the local anisotropies of the tissue have only secondary importance. For cortical bone, the osteonal organization of the tissue play an important role. Analysis of apparent properties requires the definition of an appropriately sized Volume Element (VE). Selection of too small VE would not provide representative sampling of the microstructure, while an oversized region would lead to exaggerated averaging effect. The ideal size of a cubical region of analysis was identified to be five times as large as the characteristic length of the structure [121], which corresponds to five inter–trabecular spaces, accordingly 4–6 mm in trabecular bone. During quasi–static cycling loading of an adequately sized bone biopsy, three distinct modes appear on the apparent stress–strain curve (Figure 1.14): linear elastic, describing the intact condition;
Figure 1.14: Stress–strain curves resulting from cyclic loading of cortical (left, source: [122]) and trabecular (right, adapted from Keaveny et al. [123]) bone samples in tension. The three deformation modes (linear elastic (E), damage (D) and plastic (P)) are depicted for cortical bone but can be recognized in case of cancellous bone as well.

damage, which is related to energy dissipation and residual strains due to microcracks; and plastic, which appears during unloading and reloading of the damaged structure and may be a result of microcracks sliding. An appropriate mechanical modeling approach has to provide descriptions of all of these phenomena.

**Elasticity**

According to Hooke’s law, stresses and strains of linear elastic solids are related as follows:

\[
\mathbf{S} = \mathbf{S} \mathbf{E}
\]  

(1.2)

where \( \mathbf{S} \) and \( \mathbf{E} \) are the symmetric second order tensors of stress and strain, respectively, while \( \mathbf{S} \) is the symmetric, positive definite, fourth order stiffness tensor. The inverse of \( \mathbf{S} \) is the compliance tensor (\( \mathbf{E} \)), relating stress to strain:

\[
\mathbf{E} = \mathbf{E} \mathbf{S}
\]

(1.3)

Lamellar bone can be considered as an orthotropic material, which have three orthogonal planes of symmetry. Assuming orthotropy, the number of unknowns reduces to nine compared to the twenty–one constants of general anisotropy. The matrix from of Eq. (1.3) is in
this case as follows (Voigt notation is used):

\[
\begin{bmatrix}
E_{11} & E_{22} & E_{33} \\
0 & 0 & \sqrt{2}E_{23} \\
0 & 0 & \sqrt{2}E_{31} \\
\sqrt{2}E_{12}
\end{bmatrix}
= \begin{bmatrix}
\frac{1}{\epsilon_1} & \frac{-\nu_{21}}{\epsilon_1} & \frac{-\nu_{31}}{\epsilon_1} \\
\frac{-\nu_{12}}{\epsilon_2} & \frac{1}{\epsilon_2} & \frac{-\nu_{32}}{\epsilon_2} \\
\frac{-\nu_{13}}{\epsilon_3} & \frac{-\nu_{23}}{\epsilon_3} & \frac{1}{\epsilon_3} \\
\frac{1}{2G_{23}} & \frac{1}{2G_{31}} & \frac{1}{2G_{12}}
\end{bmatrix}
\begin{bmatrix}
S_{11} \\
S_{22} \\
S_{33} \\
\sqrt{2}S_{23} \\
\sqrt{2}S_{31} \\
\sqrt{2}S_{12}
\end{bmatrix}
\tag{1.4}
\]

where \(\epsilon_i\) are the Young’s moduli, \(\nu_{ij}\) are the Poisson’s ratios and \(G_{ij}\) are the shear moduli. These three parameters are designated as engineering constants. \(i = 1, 2, 3\) are the indices corresponding to the three principal axes of symmetry. Furthermore,

\[
\frac{\nu_{ij}}{\epsilon_i} = \frac{\nu_{ji}}{\epsilon_j}
\tag{1.5}
\]

is fulfilled due to the major symmetry of the compliance tensor.

The microscopic lengthscale requires special tools of investigation, one of which is nanoindentation. This technique allows evaluation of microscopic elastic material properties by compressing a nanoscopic tip into the surface of the specimen. Applying this approach on the distal radius, Hoffler et al. found that tissue modulus in the longitudinal direction is around 17 GPa for cortical and close to 15 GPa for trabecular bone [124]. Elastic properties were furthermore reported to be different in dry and wet condition, with the latter being approximately 25% lower [125, 126]. Recently, microscopic anisotropy of femoral and vertebral lamellar bone was quantified using this technique, indenting in two orthogonal directions [127, 128, 129].

Volume fraction was found the be the major determinant of the apparent elastic properties in cellular materials [130]. A power relationship with an exponent of close to two was reported to adequately describe the relationship between BV/TV and elasticity, both in cortical [131] and cancellous bone [131, 132, 133, 134, 84]. A secondary, BV/TV-independent factor affecting elasticity is anisotropy, which is determined by the organization of bone matter. Several studies confirmed that material and structural anisotropies of trabecular bone are closely related [6, 135, 134, 136, 137, 138]. Anisotropy of cortical bone is related to its osteonal microstructure and porosity, providing the highest mechanical resistance in the longitudinal direction.

Several homogenization approaches were proposed to describe the anisotropic material behavior of cancellous bone based on volume fraction and fabric [139]. One of them is the model presented by Zysset and Curnier [140] which assumed orthotropic symmetry. Note, that although it was designed for trabecular bone, it is theoretically applicable for cortical bone as these two types are hypothesized not to be distinct from a micro–mechanical point of view so that compact bone can be considered as dense cancellous bone [131]. In this model, the fourth order compliance tensor is based on volume fraction (\(\rho\)) and the positive
definite second order fabric tensor \((\mathbf{M})\) such that:

\[
\mathbb{E}(\rho, \mathbf{M}) = \sum_{i=1}^{3} \frac{1}{\epsilon_i} \mathbf{M}_i \otimes \mathbf{M}_i - \sum_{i,j=1; i \neq j}^{3} \nu_{ij} \frac{1}{\epsilon_i} \mathbf{M}_i \otimes \mathbf{M}_j + \sum_{i,j=1; i \neq j}^{3} \frac{1}{2G_{ij}} \mathbf{M}_i \otimes \mathbf{M}_j
\]  

(1.6)

With \(m_i (\text{tr}(\mathbf{M}) = m_1 + m_2 + m_3 = 3)\) and \(\mathbf{m}_i\) being the eigenvalues and eigenvectors of \(\mathbf{M}\), respectively, the orthotropic engineering constants can be expressed as:

\[
\epsilon_i = \epsilon_0 \rho^k m_i^{2l}
\]  

(1.7)

\[
\nu_{ij} = \nu_0 \frac{m_i^{l_j}}{m_j^{l_i}}
\]  

(1.8)

\[
G_{ij} = G_0 \rho^k m_i^{l_j} m_j^{l_i}
\]  

(1.9)

In these equations, the subscript \(’0’\) refers to extrapolated properties of the idealized poreless material \((\rho = 1\) case) having at least cubic symmetry. Using these, the full compliance tensor is as follows:

\[
\mathbb{E}(\rho, \mathbf{M}) = \frac{1}{\rho^k} \begin{bmatrix}
\frac{1}{\epsilon_0 m_1^2} & -\frac{\nu_0}{\epsilon_0 m_1^2 m_2^2} & -\frac{\nu_0}{\epsilon_0 m_1^2 m_3^2} & 0 & 0 & 0 \\
-\frac{\nu_0}{\epsilon_0 m_1^2 m_2^2} & \frac{1}{\epsilon_0 m_2^4} & -\frac{\nu_0}{\epsilon_0 m_2^2 m_3^2} & 0 & 0 & 0 \\
-\frac{\nu_0}{\epsilon_0 m_1^2 m_3^2} & -\frac{\nu_0}{\epsilon_0 m_2^2 m_3^2} & \frac{1}{\epsilon_0 m_3^4} & 0 & 0 & 0 \\
0 & 0 & 0 & \frac{1}{2G_0 m_1^2 m_2^2} & 0 & 0 \\
0 & 0 & 0 & 0 & \frac{1}{2G_0 m_1^2 m_3^2} & 0 \\
0 & 0 & 0 & 0 & 0 & \frac{1}{2G_0 m_1^2 m_2^2}
\end{bmatrix}
\]

(1.10)

Bone is known to be viscoelastic. Beyond relaxation and creep, the dependence of stiffness on the velocity of loading can be particularly relevant when analyzing accidental cases as higher loading rate results in higher resistance. However, the above presented model does not include strain rate and the quasi–static results cannot be adapted to impact as the elastic properties of bone do not scale proportionally between these two extreme strain rates.

**Plasticity and damage**

The non–linear material behavior of bone is the result of micro–cracks of its material. Initiation of damage determines plasticity and degradation of the properties in the post–yield phase are regulated by the evolution and accumulation of damage. Strength is an important limit prior to failure, reached when the load–bearing capacity cannot further increase. Non–linear properties are usually investigated and discussed on the macroscopic level. Apparent yield and strength of bone, similarly to the elastic properties, were reported to depend on volume fraction in a close to quadratic manner [131, 132, 141]. Furthermore, these were found to be anisotropic, and, again similarly to elasticity, to be related to fabric
Nevertheless, yield and strength properties are asymmetric, i.e. distinct in compression and tension for both cortical [141] and trabecular bone [143, 123, 144, 142]. Note, that yield and ultimate strain appear to be approximately constant for a given loading case and anatomical site [145, 143, 142].

In accordance with these findings, the model of Zysset and Curnier [140] developed for elasticity was extended to describe plasticity and damage [146, 147]. In this model, the plastic yield function \( Y_P \) was defined as a convex elastic domain of the stress space:

\[
Y_P = \sqrt{S^p : E} - \sigma^p(D) \tag{1.11}
\]

where \( S^p \) is the plastic part of the second Piola-Kirchhoff stress tensor and \( \sigma^p(D) \) is the hardening function. The scalar parameter \( D \) was used to measure the accumulation of damage, ranging from the intact \( D = 0 \) to the totally damaged \( (D = 1) \) stage. The damage threshold function \( Y_D \) was expressed with a generalized halfspace–wise Hill criterion in the stress-space. Asymmetry was taken into account by providing separate descriptions in the tensile and compressive halfspaces that meet at a hyperplane:

\[
Y_D = \begin{cases} 
\sqrt{S^D : F^+ S^D - r^D(D)} \leq 0 & \text{if } m(S^D) \geq 0 \\
\sqrt{S^D : F^- S^D - r^D(D)} \leq 0 & \text{if } m(S^D) < 0
\end{cases} \tag{1.12}
\]

Here, \( S^D \) is the damage stress tensor \( (S^D = \frac{1-D}{D} S) \), \( m(S^D) \) is the plane separating the two stress halfspaces, \( r^D(D) \) governs the evolution of damage and the fourth order tensors \( F^\pm \) are expressed in both half spaces as functions of volume fraction and fabric:

\[
F^{\pm} (\rho, \mathbf{M}) = \sum_{i=1}^{3} \frac{1}{(\sigma_{ii}^{\pm})^2} M_i \otimes M_i - \sum_{i,j=1, i \neq j}^{3} \frac{\chi_{ij}^{\pm}}{(\sigma_{ii}^{\pm})^2} M_i \otimes M_j + \sum_{i,j=1, i \neq j}^{3} \frac{1}{2\tau_{ij}} M_i \otimes M_j \tag{1.13}
\]

where \( \sigma_{ii}^+ \) and \( \sigma_{ii}^- \) are the uniaxial tensile and compressive strengths, respectively, \( \chi_{ij}^+ \) and \( \chi_{ij}^- \) are multiaxial coupling terms, \( \tau_{ij} \) is the ultimate shear stress and \( i, j = 1, 2, 3 \) are the indices of the principal axes. These constants can be expressed as:

\[
\sigma_{ii}^{+/\pm} = \sigma_{ii}^{+/\pm} \rho^p m_i^{2q} \tag{1.14}
\]

\[
\chi_{ij}^{+/\pm} = \chi_{ij}^{+/\pm} \frac{m_i^{2q}}{m_j^{2q}} \tag{1.15}
\]

\[
\tau_{ij} = \tau_{ij} \rho^p m_i^p m_j^q \tag{1.16}
\]
where $\sigma_0^+, \sigma_0^-, \chi_0^+, \chi_0^-, \tau_0$ are properties of the ideal poreless material. With these,

$$F^\pm (\rho, M) = \frac{1}{\rho^2} \begin{bmatrix} \frac{1}{\sigma_0^+ m_1^4} & \frac{-\chi_0^+}{\sigma_0^+ m_1^4 m_2^2} & \frac{-\chi_0^+}{\sigma_0^+ m_1^4 m_3^2} & 0 & 0 & 0 \\ \frac{-\chi_0^+}{\sigma_0^+ m_2^4 m_1^2} & \frac{1}{\sigma_0^+ m_2^4 m_2^2} & \frac{-\chi_0^+}{\sigma_0^+ m_2^4 m_3^2} & 0 & 0 & 0 \\ \frac{-\chi_0^+}{\sigma_0^+ m_3^4 m_1^2} & \frac{-\chi_0^+}{\sigma_0^+ m_3^4 m_2^2} & \frac{1}{\sigma_0^+ m_3^4 m_3^2} & 0 & 0 & 0 \\ 0 & 0 & 0 & \frac{1}{2 \tau_0^2 m_3^2 m_1^2} & 0 & 0 \\ 0 & 0 & 0 & 0 & \frac{1}{2 \tau_0^2 m_3^2 m_2^2} & 0 \\ 0 & 0 & 0 & 0 & 0 & \frac{1}{2 \tau_0^2 m_1^4 m_2^2} \end{bmatrix}$$

(1.17)

Evolution of damage and plastic yield criteria were described by isotropic, exponential hardening laws. The functions

$$\sigma^p(D) = \chi_p (1 - e^{-wD})$$
$$r^D(D) = R (1 + \chi_D (1 - e^{-vD}))$$

(1.18)

were used to define the evolution of the radius of the plastic yield ($\sigma^p(D)$) and damage ($r^D(D)$) criteria, leading to reduced stiffness and hardening at increased level of damage. Here, $\chi_p$ and $\chi_D$ are the plastic and damage hardening coefficients. Other post–yield phenomena like softening and densification of cancellous bone were not modelled in this framework.

The independent constants of this homogenization–based elasticity model and the strength criteria were identified with multiaxial experimental testing of trabecular bone biopsies extracted from several anatomical sites [142]. Hardening parameters were assessed with uniaxial tests of cancellous bone samples [147]. The inclusion of fabric increased the level of prediction for apparent elastic and plastic material properties measured in uniaxial compression [148].

1.5.2 MicroFE

The basic principle of the μFE approach is creating the model directly from the segmented high resolution CT or MRI image by converting all bone (non–zero) voxels into hexahedral elements and neglecting all non–bone (or marrow) regions.

Apparent elastic and plastic properties of trabecular and cortical bone were investigated with μFE models [137, 149, 150, 151, 152]. Bones of several anatomical sites were examined as well, e.g. the femur [153, 154] and vertebral bodies [155, 156, 157]. The introduction of clinical HR–pQCT imaging systems motivated several authors to apply the μFE technique on the distal radius, which became therefore one of the mostly investigated sites. The full distal radius [158, 110, 159] or a bone section obtainable in vivo using HR–pQCT [160, 161, 86] were usually analyzed, while the latter were already utilized in clinical studies [162, 98, 88, 163, 164, 165].
The major advantage of the µFE modeling technique is that the micro–structure of bone is modeled explicitly. Although, to achieve this, it requires a high resolution reconstruction, such that the mechanically relevant elements of the structure are well represented and can be accurately modeled. In order to properly describe bending, four finite elements would be required across the diameter of a structural element. In case of trabecular bone, the ideal CT image resolution is therefore around 30 µm or finer. A further advantage is that, out of the three pre–processing steps of the FE methods (geometry, material properties and boundary conditions), two can be relative easily accomplished. First, the simple voxel conversion technique [166] allows for fast and straightforward generation of the geometrical model, which can be fully automated. Second, due to the structural representation the tissue material model is usually assumed to be homogeneous and isotropic within an element. Furthermore, homogeneity of the properties is commonly assumed among the elements. However, heterogeneous models can be easily generated by scaling the material properties according to the grayscale intensities of the image voxels using to calibration curves [167, 161, 168].

Nonetheless, there are some drawbacks of the µFE approach. First, conversion of high resolution images result in millions of elements which may require outstanding computational power and special solution techniques, even if the analysis is restricted to the linear range. The state of the art largest model was reported by Arbenz et al. [159], including close to 250 million elements. Non–linear simulations are feasible when modeling smaller volumes like biopsies [149, 151, 152], while larger structures like bones demand excessive resources as supercomputers [156, 154, 159]. Second, with the geometry being in such a close relationship with the image, the method is very sensitive with respect to image segmentation. This issue is particularly important in in vivo cases when resolution is relatively low compared to the average dimensions of the trabecular geometry and an adequately detailed description of the micro–structure is therefore not available. A typical case is HR–pQCT imaging, the resolution of which (100 µm) provides one or maximum two voxel thick description of the single trabeculae having an average thickness of 100–200 µm. Due to partial volume effect, connectivity can be easily lost, which leads to loss of the mechanical contribution. In order to avoid this, as discussed above, special image filtering approaches were developed which enhance image quality and signal to noise ratio [85]. Third, due to the regularized geometry, thinner structures are represented with a ‘jagged’ surface. This leads to artificial stress concentrations, which can be eased by improving image resolution or applying smoothing on the mesh [169].

The above reviewed homogenization theory offers a different, continuum–based FE modeling approach, which may help to overcome some of the limitations of µFE, mainly the need of high image resolution and quality as well as extreme hardware requirements. This novel technique may therefore be more suited for a clinical case.
CHAPTER 1. INTRODUCTION

1.5.3 Homogenized continuum FE

The combination of the FE method and the above presented homogenization theory (Subsection 1.5.1) provides a different modeling approach which can be applied on bone, however, the element size must be large enough so that it allows for continuum representation.

Continuum modeling is the only possibility when the available image resolution is limited, which is typical in most clinical applications. Using voxel sizes of 0.5-1.0 mm, QCT cannot resolve the trabecular structure and it is limited in providing adequate representation of the cortical shell. FE models built directly from QCT images are therefore implicitly homogenized as averaging of the densities is performed inherently during scanning. Further coarsening of the images is occasionally used in order to reduce computational cost of the FE analysis. Material properties are calculated from the underlying grayscale intensities of the CT images using calibration equations. As no morphological information is captured during imaging, isotropic material models are usually used [170, 171] or a typical orientation and degree of anisotropy is assumed throughout the full bone domain [172, 173, 174, 175]. Even if using larger elements, homogenized continuum FE (hFE) models are meant to provide as precise representation of the bone geometry as possible, which is again limited by the image resolution. Geometry of the hFE model can be created by simply converting the image voxels or regions of voxels into regular hexahedrons [172, 174, 175], which is straightforward but may result in too rough representation of the bone shape. Alternatively, smooth surface-based geometries can be assessed, which may be meshed with hexahedral [176, 177] or tetrahedral [171, 170, 178] elements. Due to the poor resolution of the CT images, cortical and trabecular bone regions are usually not distinguished [172, 179, 180], although there were attempts to separate the two compartments by simply assuming cortical thickness to be constant [176, 171] or with special image segmentation techniques [181, 175]. QCT–based hFE models of vertebral bodies [172, 180, 174, 175] and femora [182, 170] were usually investigated. These models were shown to be better predictors of bone strength than BMD [182, 172]. Several studies used hFE successfully in clinical studies [171, 179, 183].

hFE modeling is an alternative when the image resolution is adequate to represent
micro-architecture but μFE modeling would require excessive computational resources. Reduced number of elements in this case is meant to decrease the required solution time and memory, and/or allow for non-linear analysis. Homogenization is used here to preserve the essential information, volume fraction and fabric despite the large element size. HR–pQCT provides currently the highest image resolution \textit{in vivo}, which, as discussed above, is still on the edge to comply with the requirements of the μFE approach by endangering trabecular connectivity. The hFE technique therefore may provide not only computationally cheaper, but also improved predictions based on HR–pQCT scans. Using this imaging technique, the distal radius and tibia are the available anatomical sites where the hFE approach may be beneficially utilized. As it was discussed in the previous Sections, fracture load assessment in the distal radius is relevant from a clinical point of view and subject of increasing interest. However, the hFE approach has not yet been applied to this bone.

1.6 Objectives

The aim of this Thesis was to develop a patient-specific HR–pQCT–based finite element tool for predicting fracture load of the distal radius \textit{in vivo}. There are certain requirements that such a tool has to fulfill so that it can be applied clinically. To achieve \textit{validity}, the approach must

- be validated with \textit{in vitro} experimental mechanical tests of the relevant loading case (fall simulation)
- provide more precise predictions than the current gold standard method (DXA).

To achieve \textit{applicability}, the analysis must

- be usable by an operator who has no mechanical background, therefore fully automated and requires no intervention
- include the least number of input parameters (e.g. threshold)
- be reliable and robust
- be performed in reasonable computation time (\(~1\) hour) on a desktop computer.

There are some important \textit{research questions} to be answered, namely if

- μFE or hFE modeling is preferential
- separation of cortical and trabecular bone is necessary for the analysis
- linear simulation can be used or there is a need for introducing nonlinearity
• the region that can be assessed in vivo provides adequate mechanical representation of the full bone.

In the light of these, this thesis targeted the following objectives:

• The first objective was to validate anatomy–based continuum hFE models of the distal radius with experimental fall–simulations.

• A fundamental step of hFE modeling is homogenization, requiring two input parameters, volume fraction and fabric. As current measures of the latter require binary images, a possible improvement was to circumvent segmentation and quantify fabric using grayscale images. The second objective was the design of a method for this purpose.

• The FE models are built from HR–pQCT images, the third objective was therefore the evaluation of the ability of this image modality to predict volume fraction and fabric.

• \( \mu \)FE models have already been used to predict distal radius strength and became the current standard for this task. The fourth objective was hence a detailed validation and comparison of the \( \mu \)FE and hFE methods using simplified and reliable, but still relevant experimental tests of distal radius regions.

• in vivo HR–pQCT scanning is practically limited to a 9mm section of the peripheral skeleton. The last objective was to investigate if FE models of such small sections of the distal radius were able to predict experimental Colles’ fracture load.

1.7 Thesis outline

The present Chapter was meant to provide some basic relevant background information from the fields of anatomy, clinics and mechanics, and to pinpoint the specific aims of this Thesis. The next five Chapters present the steps towards the accomplishment of the defined goals.

• Chapter Two presents an experimental model of Colles’ fracture and investigates whether hFE models are capable of predicting the fracture load assessed mechanically. Even if high correlation were obtained, limitations and possible sources of inaccuracies were identified on both the experimental (embalmed tissue, embedding, machine compliance) and the modeling (input parameters of homogenization, bone–embedding interface, unreasonably large size of the scanned region, lack of comparison with \( \mu \)FE) sides. These motivated further studies and were carefully investigated in the following Chapters.
• **Chapter Three** introduces a novel method, Sampling Sphere Orientation Distribution (SSOD), for quantification of fabric on grayscale images in order to avoid image segmentation, which is known to be a sensitive step. A systematic comparison of SSOD with the gold standard MIL algorithm is reported using human trabecular bone biopsies of six anatomical sites and artificial grid structures.

• **Chapter Four** presents a calibration study of the clinical HR–pQCT with the gold standard \( \mu \)CT system. In particular, the two input quantities of the homogenization approach, volume fraction and fabric are investigated specifically for the distal radius. Several image segmentation techniques and fabric measures are analyzed. Calibration laws are identified to correct for the loss of information due to the lower image resolution of the *in vivo* imaging.

• **Chapter Five** presents an experimental setup for testing the radius section relevant in Colles’ fracture, providing good representation of the fall–case with special care taken to the machine–compliance–free measurement of displacement. It provides further refinements of the hFE models (cortical thickness correction and material model parameters). Finally, it compares the ability of density, micro–architecture, corrected hFE models and the state of the art \( \mu \)FE models to predict the obtained experimental stiffness and strength, respectively.

• **Chapter Six** summarizes the knowledge gained in the previous Chapters to predict the experimental Colles’ fracture strength assessed in Chapter Two with FE models of clinically relevant bone sections and evaluate if these have higher predictive power than density or micro–architecture of the same image regions. Furthermore, it investigates if the standard HR–pQCT section is optimally positioned.

The **last Chapter** summarizes the original contributions of this Thesis, systematically reviews the main results and draws the final conclusions. Furthermore, it provides a list of research questions that aim further improvements but remained opened for future work. Finally, it discusses the possibility to utilize the presented methods in clinical applications.

**Bibliography**


Chapter 2

Validation of a continuum FE model of Colles’ fracture

From the manuscript:

Validation of an anatomy specific finite element model of Colles’ fracture

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Abstract

Osteoporotic fractures are harmful injuries and their number is on the rise. Distal radius fractures are precursors of other osteoporotic fractures. The wrist’s bony geometry and trabecular architecture can be assessed in vivo using the recently introduced HR–pQCT. The goal of this study was the validation of a newly developed HR–pQCT based anatomy specific FE technique including separation of cortical and trabecular bone regions using an experimental model for producing Colles’ fractures. Mechanical compression tests of 21 embalmed human radii were conducted. Continuum level FE models were built using HR–pQCT images of the bones and nonlinear analyses were performed using boundary conditions highly similar to the mechanical tests. Density and fabric based material properties were
Numerical results provided good prediction of the experimental stiffness ($R^2 = 0.793$) and even better for strength ($R^2 = 0.874$). High damage zones of the FE models coincided with the actual failure patterns of the specimens. These encouraging results allow to conclude that the developed method represents an attractive and efficient tool for simulation of Colles’ fracture.

**Keywords:** distal radius, Colles’ fracture, HR–pQCT, finite element, homogenization

### 2.1 Introduction

Osteoporosis is a skeletal disease characterized by loss of bone mass, architectural changes and increased susceptibility to fracture [1]. With a growing population of elderly people in industrialized countries, osteoporotic fractures are expected to increase over the coming decades [2, 3]. More than 50% of osteoporotic fractures occur in patients with a DXA T–score greater than the diagnostic threshold of -2.5 SD [4, 5, 6]. With such a high fracture rate, a more precise method is necessary to identify patients at risk as early as possible.

Site–specific measurements have shown the highest significance for site–specific fracture predictions [7]. Wrist fractures in osteopenic patients tend to occur prior to fractures of the hip and vertebral column [8]. The distal radius is therefore a favorable site for diagnosis of osteoporosis [9]. Colles’ fractures are extra–articular fractures within the distal 10–12% region of the radius. They are the most common distal radius fractures occurring due to axial compression and bending, mainly when falling onto the outstretched hand, leading to a dorsal displacement. Being a peripheral site with relative small amount of surrounding soft tissue, the architecture of the distal radius can be easily and accurately assessed *in vivo.*

The recently introduced High Resolution peripheral Quantitative Computed Tomography (HR–pQCT) provides insight into the trabecular bone structure and access to 3D morphological indices [10, 7, 11].

For the past two decades it has been shown that bone morphology and geometry measurements based on CT images provide additional information to DXA [12, 13, 14]. Patient specific micro–finite element ($\mu$FE) models based on HR–pQCT images provide enhanced prediction of mechanical properties and risk of fracture compared to bone mass or structural parameters [15, 16]. $\mu$FE models are usually limited to estimate ultimate load with linear analyses. Inclusion of nonlinearity is feasible when investigating small biopsies [17], but requires outstanding computational resources and time even if the models are restricted to a bone section [18, 19].

A recently developed surface based FE approach [20, 21] is using a homogenization scheme based on volume fraction and architectural information of trabecular bone [22] obtained from HR–pQCT images. This framework, including bone plasticity and damage, allows nonlinear analysis, which computes stress re–distribution and ultimate load preced-
ing fracture. Still, the computation is performed in a reasonable time frame with moderate resources. Even if the material properties are based on previous experimental results [23, 24], the FE approach needs to be validated for cases of clinical interest.

Previous experimental validation studies on FE models simulating Colles’ fractures have used either intact forearms [15, 25, 26] or a slice of the distal radius [19] for their biomechanical testing. Recreating and measuring forces across the whole wrist is difficult and leads to a testing setup hard to simulate numerically as the exact boundary conditions of the radius remain unknown. A single slice provides a perfect basis for the validation of the FE model, but may be an oversimplification of the loading conditions and may result in unrealistic fracture patterns compared to a full bone.

In this context, the goal of the current study was to design an experimental setup producing Colles’ type fractures with well-defined boundary conditions and applying it to a collection of human radii in order to validate anatomy-specific FE models subjected to the same loading conditions.

2.2 Materials and methods

2.2.1 Sample acquisition and preparation

Twenty-six radii (14 left and 12 right) were obtained from the Institute of Anatomy, LMU, Munich, Germany, after excluding nine specimens due to severe pre-existing arthrosis, previous fractures, or bone cysts using standard X-ray screening in two planes. The bones were excised from 11 male and 15 female formalin-fixed cadavers with an average age of 81 ± 10 years (min = 61, max = 103). Specimen length varied between 205 and 275 mm (238 ± 19), diameter of the epiphysis ranged from 2.0 to 2.8 mm (2.37 ± 0.26) along the dorsal-palmar and from 2.7 to 4.1 mm (3.46 ± 0.34) along the transverse axis. The experiments were in line with the German legislative requirements and approved by the ethical commission of the Medical University of Vienna. The radii were cleaned of soft tissue and the articular cartilage was removed (Dremel 400 Digital at 500R/min) under a light-microscope with 4x magnification. The bones were cut 4 cm proximal to the 1/3 distal side with a Buehler IsoMet Low Speed Saw (Buehler Ltd., USA) and aligned and embedded using purpose built cylindrical aluminum containers and a holding device. Positioning within the containers was achieved by aligning the Lister tubercle and the center of the proximal shaft with the loading axis of the device during testing, resulting in a palmar inclination of approximately 5°. The resulting line of the force therefore was dorsally offset in the sagittal plane and shifted from the center of the radius in the frontal plane towards the scaphoid [27, 28]. The final setup is shown in Figure 2.1. It is a modification of the loading configuration used by Muller et al. [12] adopting Frykmans model [29] using intact radii with a dorsal inclination of 15°. More than 10% of the mechanical tests of that study resulted in non-distal radius fractures which might be explained by the lever arm at the proximal shaft. Our setup was designed to minimize bending at the proximal end and to have the maximum moment act on the epiphysis. Pretests using 15° dorsal inclination showed excessive moments at the
distal embedding, generating tensile stresses on the palmar side which are suspected to be absent in vivo. The inclination was therefore reduced to $5^\circ$, still in line with Frykmans findings. After alignment, the proximal 4 cm of the specimens were cemented into the lower container. Minimal portion of the distal radius was embedded as Colles’ fractures tend to occur in the distal 10–12% of the bone [27, 13, 12, 30]. Following the concept introduced in [12] the distal end was embedded shallowly, approximately 1 mm proximal to the articular surface boundary.

### 2.2.2 HR–pQCT scanning

After the embedding process, the aluminum containers were removed. Small cylindrical gypsum makers were glued onto the top and bottom surfaces of the distal embedding in order to define its geometry on the HR–pQCT images. The embedded specimens were submerged in distilled water in a custom made Plexiglas chamber and scanned with 82 $\mu$m isotropic spatial resolution using an HR–pQCT machine (XtremeCT, Scanco Medical AG, Switzerland). Scanning settings of 60 kVp, 1 mA, 200 ms integration time and 1536x1536 pixels image matrix were used. Number of scanned slices varied between 963 and 1303.
2.2.3 Experimental testing

Following scanning the markers were removed and the radii were kept wet until experimental testing. The specimens were mounted to a servo–hydraulic material testing system (MTS 858 MiniBionix, MTS Systems Corp., USA), using the aluminum containers and loaded to failure. Displacement–controlled uniaxial compression tests were performed with 1 mm/s loading rate [31]. The testing protocol consisted of 10 preconditioning cycles with an amplitude of 0.2 mm, followed by a linear ramp loading. Failure was defined as a 20% reduction in the measured resisting force. In order to classify the fracture, the specimens were carefully removed from the aluminum shells and cut in the dorsal–plantar plane, down to the diapysis, using an Exakt 300CP/R band saw (Exakt Vertriebs GMBH, Germany). Photographs of the cut surfaces were taken with a digital camera and position and pattern of the fracture zones were recorded. Whitened zones were used to identify damaged regions [32]. The fractures were classified according to the AO classification [33].

2.2.4 FE modeling

Cortical and trabecular phases were identified and separated on the HR–pQCT images with an algorithm reported by Pahr and Zysset [20]. The spongious bone volume was meshed with tetrahedral–, while the cortex domain using pentahedral (wedge) quadratic solid elements with an average meshsize of 1.2 mm using an in–house software. A minimal thickness of 0.05 mm was enforced for the cortical elements to avoid holes in the mesh and still prevent a substantial stress transfer. Geometry of the distal embedding was added and meshed with second order solid tetrahedral elements using HyperMesh (Altair Engineering Inc., USA). Its shape was identified using the markers on the HR–pQCT images and simplified with a truncated cylinder. The proximally embedded 4 cm of the shaft was not included into the analysis (Figure 2.2).

Material properties of trabecular bone were modeled using a density and fabric based constitutive law that includes elasticity, plasticity and damage [24]. Elastic material properties were evaluated according to the phenomenological fabric model presented by Zysset and Curnier [22]. The independent unknowns of this model are the extrapolated properties of the idealized poreless material ($\rho = 1$ case): the Young’s modulus $\epsilon_0$, the Poisson’s ratio $\nu_0$ and the shear modulus $G_0$. For trabecular bone, values were taken from the results of multiaxial experimental testing of wet trabecular bone biopsies [23]:

\begin{align}
\epsilon_0 &= 2974.0\, MPa, \\
\nu_0 &= 0.181, \\
k &= 0.972, \\
l &= 0.820
\end{align}

Values for the plastic criteria of this model were taken also from [23]:

\begin{align}
\sigma_0^+ &= 40.69\, MPa, \\
\chi_0^+ &= -0.288, \\
\sigma_0^- &= 55.22\, MPa, \\
\chi_0^- &= 0.310, \\
\tau_0 &= 23.10\, MPa, \\
p &= 1.298, \\
q &= 0.564
\end{align}
Figure 2.2: Steps of the FE model generation from the HR–pQCT image: meshing (left) and assigning volume fraction and orthotropy (principle axes are shown) to the elements of the trabecular bone region (right).

where $\sigma_0^+$ and $\sigma_0^-$ are the uniaxial tensile and compressive ultimate stresses, respectively, $\chi_0^+$ and $\chi_0^-$ are the multiaxial coupling terms and $\tau_0$ is the ultimate shear stress, all of which are properties of a virtual poreless material. The description of the damage evolution was slightly changed compared to [24] by turning off plasticity and reformulating the damage hardening function:

$$r^D(D) = 1 - (1 - \alpha)e^{-kD} \quad (2.3)$$

where $k$ is the power coefficient from Eq. (2.1), $D$ is the scalar parameter used to measure the accumulation of damage ($0 < D < 1$) and $\alpha$ is the ratio of the yield to the ultimate stress, which was selected to be $2/3$. Homogenized orthotropic material properties were assigned to the FE elements by determining the two input parameters of the material law, volume fraction and fabric, from the HR–pQCT images. A 3D structured background grid with an equal gridsize of 3 mm was superimposed onto the 3D HR–pQCT image of trabecular bone. Two variables were quantified at the gridpoints using the image voxels in a spherical (diameter = 7.5 mm) neighborhood around them: bone volume fraction (BV/TV) was converted from the bone
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Mineral density (BMD) values with the relation provided in [34], while fabric was measured using the mean intercept length (MIL) method [35, 36] providing the fabric tensor \( \mathbf{M} \). For the latter, the images were filtered using a Gaussian filter (\( \sigma = 0.8, \text{ supp} = 1 \)) and segmented by setting the threshold level to the 16% of the maximum value of the BMD range. Finally, each element was assigned an individual material property based on linearly interpolated BV/TV and fabric using values at the gridpoints [21].

Cortical bone material was assumed to be homogeneous and isotropic. The above presented elasto–plastic constitutive law was used by setting volume fraction to 1.0 and fabric to isotropic (\( m_1 = m_2 = m_3 = 1 \)). Material properties were taken from [37], reporting a tissue elastic modulus of 16.5GPa for cortical bone of the distal radius in dry stage. This value was reduced first by approximately 23% to account for the wet condition of the tissue [38] and then to 95% in order to convert to apparent property (assuming 5% porosity [39]). Finally, the elastic parameters of the constitutive law were set to \( \epsilon_0 = 12000.0 \text{MPa} \) and \( \nu = 0.30 \). Strength properties were chosen according to the values reported in [40] by scaling them down from the bovine to the human case with a factor of \( \epsilon_{0, \text{bov}} / \epsilon_{0, \text{hum}} = 23.53 \text{GPa} / 12.0 \text{GPa} = 0.512 \):

\[
\sigma_{0}^{\epsilon} = 60.11 \text{MPa}, \quad \chi_{0}^{\epsilon} = -0.577, \\
\sigma_0 = 105.73 \text{MPa}, \quad \chi_0 = 0.310, \\
\tau_0 = 65.32 \text{MPa}, \\
p = 1.0, \quad q = 1.0
\]

(2.4)

The embedding cement (PMMA) was modelled as a linear elastic, homogeneous and isotropic material with Young’s modulus of 3000 MPa and Poisson’s ratio of 0.35. Boundary conditions were set in rigorous accordance to the mechanical tests: nodes of the cortical compartment of the shaft at the top surface of the proximal embedding were fully constrained while vertical displacement was applied to the top surface of the distal embedding (Figure 2.2).

Nonlinear static analyses of the models were carried out with ABAQUS 6.6 (Abaqus Inc., USA). Material behavior was defined for the solver as a user defined material (UMAT). Each FE model included approximately 40,000 quadratic elements (min. 28,268, max. 47,617). The simulations were performed on a computer with 2x2 3.0 GHz Xeon processors and 32 GB RAM in 12 hours of CPU time on average. Memory requirement varied between 6.6 GB and 14.1 GB.

2.2.5 Statistical analysis

Linear regressions were performed with the classical least square method and squared Pearson’s correlation coefficients were computed between the corresponding experimental and numerical quantities of the 21 specimens to evaluate the predictive capability of the FE models.
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Figure 2.3: Left: typical experimental force–displacement curve and its numerical prediction with the definitions of stiffness (K) and strength (F_U). Right: linear regression of the experimental stiffness and strength values.

2.3 Results

2.3.1 Mechanical tests

Out of the 26 radii, three specimens detached from the distal embedding preventing their further use and the experiments failed for two additional ones due to MTS operating errors. Finally, 21 bones were tested successfully. A typical force–displacement curve including the FE prediction is shown in Figure 2.3, left. Ultimate force (F_U^{exp}) was defined as the peak of the curve. Values ranged between 1486.6 N and 7401.9 N (mean and SD: 3802.5 ± 1922.8 N). Linear spring stiffness (K^{exp}) was defined as the steepest slope of the curve prior to failure, ranging from 1666.9 N/mm to 8416.58 N/mm (5398.9 ± 2055.1 N/mm). Experimental stiffness and strength values were correlated, results are plotted in Figure 2.3, right. Qualitative analysis of the damaged bones allowed to conclude that the fracture pattern matched the definition of Colles’ type fracture for 20 out of the 21 cases. For one case, the fracture line could not be identified.

2.3.2 Nonlinear FE

Nonlinear FE simulations of all the 21 specimens tested were successfully completed. Experimental stiffness and strength were compared with the FE results (K^{exp} and F_U^{exp}, respectively, see Figure 2.3, left). For the case of simplicity, linear regressions of these predictions were computed (see Figure 2.4). Using a modified t–test, significance level was p < 0.0001. Location and arrangement of the high damage zones of the FE analyses were qualitatively
Figure 2.4: Linear regression analyses of the experimental values and the FE results, left: stiffnesses, right: ultimate forces ($p < 0.0001$ in both cases).

compared to the actual fracture patterns generated by the mechanical tests in corresponding sections. Figure 2.5 shows the damage plots of the simulations at the ultimate force level and the corresponding images of the fractured bones for eight samples covering the entire range of ultimate forces.

### 2.4 Discussion

Within the scope of this study we presented an experimental validation of a recently developed FE approach with a mechanical model of Colles’ fractures using embalmed human radii.

Several limitations of the presented study need to be discussed. One goal of our study was to create distal radius fractures in a controlled and reproducible way. Our biomechanical model is therefore a simplification of the *in vivo* fracture mechanism which includes the adjacent bones, articular cartilage and soft tissues. An exact reproduction of those conditions would not only exceed reasonable computational capacities but also today’s knowledge of the actual force transmission through the intact wrist. The design was therefore reduced to the essential biomechanical components, namely the lateral and dorsal offset of the force line as well as distribution of the force onto the distal radius. The latter was achieved by the embedding material as the cartilage was removed in order to avoid introducing additional uncertainties into the model. Embedding the distal radius resulted in other limitations which have to be mentioned. All fracture zones seem to be attracted by the embedding–bone interface suggesting that stress concentrations at this boundary influenced the fractures. Preliminary tests on more deeply embedded radii have resulted in fracture initiation and progression at the height of the embedding. The radii were therefore
### Table 2.5: Summary of Failed Bone Samples

<table>
<thead>
<tr>
<th>ID</th>
<th>$F_{t}^{exp}$ [N]</th>
<th>$K_{t}^{exp}$ [N/mm]</th>
<th>In vitro failure</th>
<th>FE damage at $F_{t}^{FE}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>#117</td>
<td>1831.92</td>
<td>3864.95</td>
<td><img src="image1" alt="Image" /></td>
<td><img src="image2" alt="Image" /></td>
</tr>
<tr>
<td>#125</td>
<td>2383.76</td>
<td>4337.74</td>
<td><img src="image3" alt="Image" /></td>
<td><img src="image4" alt="Image" /></td>
</tr>
<tr>
<td>#105</td>
<td>2892.14</td>
<td>4319.11</td>
<td><img src="image5" alt="Image" /></td>
<td><img src="image6" alt="Image" /></td>
</tr>
<tr>
<td>#114</td>
<td>3469.12</td>
<td>4947.24</td>
<td><img src="image7" alt="Image" /></td>
<td><img src="image8" alt="Image" /></td>
</tr>
<tr>
<td>#99</td>
<td>4781.49</td>
<td>7740.68</td>
<td><img src="image9" alt="Image" /></td>
<td><img src="image10" alt="Image" /></td>
</tr>
<tr>
<td>#103</td>
<td>5476.39</td>
<td>6921.96</td>
<td><img src="image11" alt="Image" /></td>
<td><img src="image12" alt="Image" /></td>
</tr>
<tr>
<td>#131</td>
<td>6944.64</td>
<td>7203.27</td>
<td><img src="image13" alt="Image" /></td>
<td><img src="image14" alt="Image" /></td>
</tr>
<tr>
<td>#84</td>
<td>7401.89</td>
<td>8416.58</td>
<td><img src="image15" alt="Image" /></td>
<td><img src="image16" alt="Image" /></td>
</tr>
</tbody>
</table>

**Figure 2.5:** Failure zones of the radius bones (whitened areas) vs. the damage plots of the FE analyses for eight samples.
embedded as shallow as possible resulting in fracture zones still interfering with the dorsal embedding but progressing more proximally in an area common for Colles’ fractures. This also caused three specimens to detach from the PMMA and those were excluded from further testing. Another limitation is the use of formalin fixed specimens. Embalming was reported to influence the signal to noise ratio of the CT images [15] and to alter the tissue properties of bone due to demineralization [41, 42], although the latter effect was found to be small [43]. Due to the limitations of X–rays in resolution and in detection of non–displaced fractures [44] the complete fracture patterns could not be analyzed using this technique. The evaluation was therefore restricted to a single plane by cutting the radii which provided a clear definition of the damaged zones through the whitening effect [32]. Furthermore, the geometry of the distal embedding in the FE model was approximated with simple solids and perfect bone–cement bonding was assumed. This simplification is likely to have slightly altered the initiation of damage and strength of bones in the numerical analyses. The proximally embedded 4cm long shaft region was assumed to provide fully constrained boundary in the model which might be a further source of inaccuracy. Finally, prior to testing all specimens were scanned with X–ray for abnormalities. Even though this does not rule out microfractures, the radii were assumed to be free of any preliminary fractures and therefore an initial damage level (D) of 0 was used for each element.

Despite these limitations, the presented FE approach was shown to be capable of describing the simplified experimental model of Colles’ fracture. Numerical results correlated well with the experimental values for both stiffness ($R^2 = 0.793$) and strength ($R^2 = 0.874$). For comparison, HR–pQCT volumetric BMD determined on the trabecular bone region provided lower correlations with both stiffness ($R^2 = 0.677$) and strength ($R^2 = 0.629$), while full bone BMD had even weaker predictive ability ($R^2 = 0.499$ and $R^2 = 0.319$, respectively). Prediction of strength in our FE models is superior to the one reported by Pistoia et al. [15] ($R^2 = 0.752$). This is most possibly due the complexity and the associated variability of the boundary conditions used in that study. In our case, strength was estimated correctly but stiffness was consistently overestimated for each sample. One of the reasons may be the influence of testing device compliance. The correlation coefficient of 75% between the experimental stiffness and strength showed that stiffness was not a perfect predictor of ultimate force for this experimental setup, most probably due to the bending moment involved.

The evaluation of the results was not restricted to the predictions of the apparent mechanical properties but damage plots of the numerical computations were visualized. Those were found to be in good qualitative agreement with the experimental fracture patterns, underlining the potential of the method.

The presented FE approach allows nonlinear analysis of whole bones with reasonable computation resources and time, which is currently not the case for the µFE methods [19, 18]. The aim of this numerical framework was to predict mechanical behavior of full bones by separating cortical and spongious regions and using homogenized orthotropic material properties of trabecular bone with constants taken from multiaxial material tests of biopsies [23]. The present experimental setup was an application of this approach, no fitting or adjustment of the material parameters were performed. The method is therefore
not restricted to a specific collection of samples or a specific loading type. The encouraging results of this study allow to conclude that the proposed method represents an attractive and efficient tool for Colles' fracture simulation.

Acquisition of HR–pQCT images of the full region analyzed in this work is practically not feasible in vivo. However, since the bulk of damage localizes in the ultradistal part of the radius, selection of a distal section for clinical evaluation is justified. The application of our method restricted to a distal section and its comparison with BMD, morphological indices and other methods will be reported in a future publication.

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Bibliography


Chapter 3

Sampling Sphere Orientation Distribution

From the manuscript:

**Sampling Sphere Orientation Distribution:** An efficient method to quantify trabecular bone fabric on grayscale images

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**Abstract**

A novel Sampling Sphere Orientation Distribution (SSOD) method based on mobile sampling spheres is developed for describing microstructural anisotropy of trabecular bone using grayscale images. Efficient implementation of SSOD on segmented and unsegmented 3D µCT images of human trabecular bone samples from different anatomical locations is demonstrated. The second order fabric tensor of SSOD corresponds well with the one derived from the mean intercept length (MIL) method applied on segmented images. The results of SSOD are extended to higher order fabric approximations and the effect of sampling sphere radius is examined. Finally, performance of the method on artificial microstructures is presented.
Keywords: anisotropy, computer tomography, fabric, mean intercept length, trabecular bone

3.1 Introduction

The architecture of bone adapts to its mechanical environment [1]. This is supported by the fact that the microstructural (or fabric) and the mechanical properties of cancellous bone are closely related [2, 3, 4]. Imaging techniques such as CT or MRI allow to assess the trabecular architecture in vivo with increasing resolution which may be exploited to predict mechanical properties for clinical diagnostics, treatment or follow up.

There are well-known and widely used methods to quantify microstructural anisotropy based on trabecular bone images. Two-dimensional approaches are using stereological methods on planar sections of the architecture while the truly three-dimensional methods are working directly on the volumetric images (arrays). These methods can be sorted in two groups.

One group is formed by the directed secant-based methods based on computation along test-lines superimposed on the image. In these measures, the structure is assumed to be parallel plate-like to compute Tb.Th, Tb.Sp and Tb.N. [5]. Probably the most widely known and applied one is the Mean Intercept Length (MIL) method described in [6]. It is defined as the average distance of two bone/marrow interfaces in a given spatial direction: the total length of the parallel test-lines is divided by the counted number of the interfaces along these lines. In 3D it is done for spatial directions and can be adequately fitted with an ellipsoid as it was proposed in [7] or by spherical Fourier series [8] and therefore described by fabric tensors of increasing order. Cowin [9] introduced the term fabric tensor for the quadratic form associated with an ellipsoid whose eigenbasis is used for quantification of architectural anisotropy. The Line Fraction Deviation (LDF) presented by Geraets [10, 11] is also based on sampling along parallel lines. It was originally applied on 2D radiographs and was recently extended to 3D CT images [12]. The output does not involve approximation or statistics. Although it shows more detailed anisotropy than MIL, quantification occurs with a general orientation distribution function. Intercept Segment Deviation (ISD) measures standard deviation of intercept segments length for the given directions and reported to be more sensitive to anisotropy than MIL [13]. Other 2D directed secant-based methods for characterization of trabecular architecture are described in [14].

Another group is formed by the volume-based methods. Volume Orientation (VO), introduced in [15] is based on the local orientation of the trabeculae that is understood as the direction of the longest lines projected from randomly placed points inside of the bone domain delimited by the marrow phase boundary. Star Volume Distribution (SVD) was presented in [16] as the mean volume of the material as a function of spatial orientation. It is again a point-based method and measures the volume visible from a point placed inside
the bone domain for a given direction. Star Length Distribution (SLD) was proposed in [2] and discussed in [17]. It is a modification of SVD and defined as the average length of lines in a given direction. The review and comparison of the methods MIL, SLD, SVD can be found in [18], while the algorithms for implementation with applications in [19]. Although the volume–based methods generally offer a more detailed anisotropy than MIL they are often approximated with a second order tensor to become suitable for prediction of mechanical properties. These approximations were shown to be good predictors of mechanical anisotropy ([2, 4, 20, 21, 22]. The use of material models for trabecular bone that are based not exclusively on volume fraction but involve architectural information from the fabric tensor give significantly better estimations of the elastic and yield behavior [23, 24]. In methods based of digital topology–based orientation analysis (DTA–O) distinction between plates and rods of the bone architecture is made by skeletonization. The voxel–based local orientations is analyzed to derive global orientations and anisotropy for a given region [25].

The common drawback of all the methods mentioned above is that they require segmented images. The thresholding procedure to generate these binary datasets is an important and delicate step. For low resolution images, voxel size is close to the dimension of the structural elements (partial volume effect) and the trabecular morphology resulting from the segmentation is particularly sensitive to the level of threshold. To circumvent this problem, like for bone volume fraction (BV/TV), grayscale images could be used directly to quantify architectural anisotropy. Recent publications showed different approaches along this idea. Fast Fourier Transform was applied on radiographic images to detect trabecular orientation in 2D [26, 27] and an index of anisotropy was proposed. Bone anisotropy was also evaluated by texture analysis using Gabor wavelets [28, 29] although also only on 2D images. Saha et al. introduced the Tensor Scale Method (TSD) for measuring local anisotropies of small structures such as trabeculae by fitting the largest ellipse (in 2D) in the local density distribution [30, 31]. Each bone–pixel of the analyzed domain is involved to the final result as a homogenization scheme of this local measure is proposed to provide a global anisotropy. This is restricted to elliptical description of the anisotropy and has not been compared to the result of existing methods. It’s robustness with image resolution, rotation, noise and blurring has been shown. Its implementation is restricted to 2D mostly because it is computationally very expensive (more hours as described in [31]) although in [32] some improvements were proposed for increasing the speed. Although TSD is not using explicit segmentation the optimal edge of the local object must be determined that leads eventually to a sophisticated local segmentation with a user–defined parameter. Rotter presented Spatial AutoCorrelation Function (ACF) of 2D images of trabecular bone [33] for quantifying anisotropy from orientational dependence of trabecular thickness and spacing that was later extended in [34] to 3D. It is a probabilistic method that involves all pixels of the image and assumes bone to be a quasi–periodic structure. It was found to be applicable to in vivo datasets and robust with noise, although only rectangular regions can be analyzed. The provided measure is a second order fabric tensor that was compared to MIL in [35] and found to be in a good agreement with it. ACF was also reported to show greater anisotropy, to be faster and more robust to noise, resolution and image shading than MIL. Gray–level Structure Tensor (GTS) is a second order fabric tensor computed
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Figure 3.1: The two phases of the sampling procedure. 1) Initial grid of the sampling spheres and the iterative motion (a single sphere is shown). 2) Addition of the content of the sampling sphere to the container.

from the estimated components of the gradient at every voxel of the 3D image. In [36] it was shown to improve correlation with elastic properties compared to bone mineral density (BMD) alone. The results were compared with MIL.

In this context, the goal of this study is to develop, validate and apply a novel, computationally efficient and robust 3D method to quantify architectural anisotropy of trabecular bone based on grayscale images that provides a second order descriptor but can be extended to higher orders. The organization of this manuscript is as follows. The concept and mathematical formulation of SSOD and its approximation by fabric tensors of increasing order are first exposed. The role of the critical parameters of the method is then explained and illustrated. The SSOD method is then validated by comparing the second order fabric tensor for a collection of 42 trabecular bone samples from six anatomical locations with the one computed by mean intercept length. In a further step, the sensitivity of SSOD with respect to the parameters of the method is examined. Fourth order approximations are analyzed qualitatively for four samples. The potential and limitations of the method are finally illustrated with two artificial open cell microstructures and discussed.

3.2 Method

The Sampling Sphere Orientation Distribution (SSOD) method is designed for unsegmented 3D images with intensities corresponding to relative bone tissue density values or bone volume fraction (real numbers ranging from 0 to 1). We assume our region of interest (ROI) to be a closed convex set within such an image. Our implementation is based on isotropic voxel sizes but it can be easily generalized to operate on images with non–isotropic resolution also (the theory below is shown for this more general case). The basic idea of the method is to sample small, characteristic regions distributed in the ROI and to generate an orientation distribution function with the superposition of their content. The resulting orientation distribution function is then analyzed using spherical harmonics.

A voxel of a 3D digital image can be described by a spatial vector \( \mathbf{y} \) in the global coordinate system of the image emanating from the midpoint of the origin voxel (corner–
voxel) and pointing to the midpoint of the current voxel.

\[ \mathbf{y} = h_1 l_1 \mathbf{e}_1 + h_2 l_2 \mathbf{e}_2 + h_3 l_3 \mathbf{e}_3 \]  (3.1)

Here \( h_k \in \mathbb{N} \) are integers of the voxel-steps needed to reach the given voxel counted from the origin voxel in the three orthogonal directions of the discrete image \( (k = 1, 2, 3) \), \( l_k \) are the voxel lengths and \( \mathbf{e}_k \) are the positive unit vectors of the image coordinate system. In this way the spatial domain of the image \( (I) \) can be understood as a set of vectors that identifies a set of voxels:

\[ I = \{ \mathbf{y} \mid 0 \leq h_1 \leq H_1; 0 \leq h_2 \leq H_2; 0 \leq h_3 \leq H_3 \} \]  (3.2)

with \( H_k \) being the dimensions of the image in voxels. Accordingly, the grayscale value of a voxel is identified as \( \rho (\mathbf{y}) \) where \( \mathbf{y} \in I \).

### 3.2.1 Sampling of the ROI

For the sampling procedure we use spherical regions with a radius \( R \). The center voxel of a sphere is identified by the global vector \( \mathbf{c} \) pointing to its midpoint. The domain of the sampling sphere centered on \( \mathbf{c} \) is a set of vectors:

\[ S_{\mathbf{c}} = \{ \mathbf{y} \in I \mid \| \mathbf{y} - \mathbf{c} \| \leq R \} \]  (3.3)

To determine the sampling points, a periodic grid is projected onto the image and the gridpoints are taken as the initial centers of the sampling spheres identified by the vector \( \mathbf{c}^{(0)} \). The spheres are then free to move from their initial grid positions to the center of gravity of their own local density (grayscale) distribution. This way, they are attracted iteratively towards the center or junction of the heterogeneities to capture their orientation (Fig. 3.1). Since the spheres may overlap with the boundaries of the ROI during such iterations, a frame of zero intensity with thickness of the sphere radius is added around the ROI to prevent interruption of the procedure.

The iterative motion is computed for each sphere individually. At each step, the vector \( \Delta \mathbf{c}^j \) is calculated using the intensity values of the voxels contained in the actual volume of the sampling sphere:

\[ \Delta \mathbf{c}^j_k = \text{Int} \left( \sum_{\mathbf{y} \in S_{\mathbf{c}^j}} \rho^p(\mathbf{y}_k)(\mathbf{y}_k - c^j_k) \sum_{\mathbf{y} \in S_{\mathbf{c}^j}} \rho^p(\mathbf{y}_k) l_k \pm \frac{1}{2} l_k, \ k = 1, 2, 3 \right) \]  (3.4)

where \( p \) is a power used to emphasize the differences between the grayscale values (discussed in Section 3.2.4), \( \text{Int}() \) is used to take the integer part of a real number, \( k = 1, 2, 3 \) denotes the three spatial components and \( S_{\mathbf{c}^j} \) is the domain of the sampling sphere with the center
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Figure 3.2: Iterative motion of the sampling spheres on a real trabecular bone structure (one slice of a 3D image is depicted). Left: initial gridpoints with one sphere shown. Right: final scene with sampling spheres after convergence.

\( c^j \) in the \( j \)th iteration step. The position of the sphere center in the next iteration \((j + 1)\) becomes:

\[
    c^{j+1} = c^j + \Delta c^j
\]

(3.5)

The iterative motion of the sampling sphere stops when all components of the voxel–based difference between the actual center of gravity and the geometrical center of the sphere vanish:

\[
    \Delta c_{k}^{j+1} = 0, \quad k = 1, 2, 3.
\]

(3.6)

Finally, the actual vector of the sphere center defines the final one \( c_f := c^j \).

The sampling grid and the converged positions of the sampling spheres on a 2D section of a 3D trabecular bone image are shown in Fig. 3.2. The frame of zero intensity surrounding the ROI appears as a black frame. Many spheres are found in the marrow space because no significant heterogeneities attracted them away from their original position.

3.2.2 Summation into the container sphere

In the next phase of the proposed SSOD method, a so–called container sphere is defined. It has the same size and discrete domain as the sampling spheres, but is described with a local vector \( \mathbf{x} \) with respect to the midpoint of the central voxel taken as origin:

\[
    \mathbf{x} = n_1 l_1 \mathbf{e}_1 + n_2 l_2 \mathbf{e}_2 + n_3 l_3 \mathbf{e}_3,
\]

(3.7)

where \( n_k \in \mathbb{Z} \) and \( k = 1, 2, 3 \). The domain of the container sphere \((C)\) can therefore be defined as a given set of vectors \( \mathbf{x} \):

\[
    C = \{ \mathbf{x} \mid \| \mathbf{x} \| \leq R \}.
\]

(3.8)
The intensity distribution of all sampling spheres that remained completely inside of the ROI after convergence of their iterative motion is summed into this container. The content of the container sphere (the summed intensity values) is then divided by the number of accepted sampling spheres. An intensity value of a given voxel in the container is nominated by \( p^I(x) \) where \( x \in C \). The process of summation is the following:

\[
(p^I(x)) = \frac{1}{N_S} \sum_{c'_i \in I} p(x) \quad \forall x = y - c'_i \in C
\]

where \( N_S \) is the number of accepted sampling spheres and \( i = 1, 2, ... N_S \). The final content of the container represents an average density pattern of the sampling spheres and thus reflects the overall orientation and structure of the underlying architecture.

The steps of sampling for a single sampling sphere and a simple, 2D binary case are shown in Fig. 3.1 (with the colors inverted). The analysis of a real trabecular bone structure is shown in Fig. 3.2.

As a consequence of the initial assumptions, the container sphere contains positive numbers. To make the information of the container independent from bone volume fraction (bone volume over total volume, BV/TV) of the analyzed image, the minimum contained value is subtracted from all the voxel values. This first normalizing step makes the container image intensity independent:

\[
(p^I_0(x)) = p^I(x) - \min(p^I(x)) \quad \forall x \in C
\]

The intensity values of the container voxels are then made symmetric with respect to the center which thus becomes the center of gravity of the distribution:

\[
(p^I(x)) = \frac{1}{2} \left( p^I_0(x) + p^I_0(-x) \right) \quad \forall x \in C
\]

### 3.2.3 Approximation in the container

In order to characterize the structure in a mathematical way the container is considered as a discretized spatial distribution in the sphere and approximated with generalized Fourier series. The theory below is shown for a continuous vector–scalar function \( \rho^I(x) : \mathbb{R}^3 \to \mathbb{R} \) on \( B(0, R) \), the domain of a sphere with radius \( R \). The Fourier series of our vector–scalar function [37]:

\[
\rho^I(x) = \sum_{k=1}^{\infty} g_k f_k(x), \text{ where } g_k = \langle \rho^I(x), f_k(x) \rangle
\]

where \( f_k(x) \) are the generalized basis functions and \( g_k \) are the corresponding coefficients.

In the present work, we restrict ourselves to the fourth order approximation which represents a good compromise beyond the second order fit commonly used to describe anisotropy of trabecular bone and beneath the computationally more expensive sixth and
higher order approximations [8]. In the fourth order series, three even–ranked tensors appear 
due to the central symmetry of the distribution:

\[ \rho^I_4(x) := \tilde{g}f(x) + \tilde{G} : \tilde{F}(x) + \tilde{G} : \tilde{F}(x), \quad \forall x \text{ in } B(0, R). \] (3.13)

The first three even–ranked tensorial orthonormal basis functions are presented below:

\[ \tilde{f}(x) = 1 \quad (3.14) \]
\[ \tilde{F}(x) = \frac{1}{R^2} \sqrt{\frac{35}{2}} (X - \frac{1}{3}tr(X)I) \quad (3.15) \]
\[ \tilde{F}(x) = \frac{1}{R^4} \sqrt{\frac{1155}{8}} (X - a(I \otimes I + 2I \otimes I) + A \otimes I + 2(I \otimes A + A \otimes I)) \] (3.16)

where \( X = x \otimes x, X = x \otimes x \otimes x \otimes x, a = \frac{1}{15} tr(C), A = \frac{1}{7}(C - \frac{1}{3} tr(C)I) \) and \( C = XI. \)

The second order basis function \( \tilde{F}(x) \) is symmetric (in index notation: \( \tilde{F}_{ij} = \tilde{F}_{ji} \)) and traceless \( (\tilde{F}_{ii} = 0) \), while the fourth order basis function \( \tilde{F}(x) \) is completely symmetric and traceless. Symmetries of a fourth order tensor include the major symmetry \( (\tilde{F}_{ijkl} = \tilde{F}_{klij}) \), the median symmetry \( (\tilde{F}_{ijkl} = \tilde{F}_{ikjl}) \) and two minor symmetries \( (\tilde{F}_{ijkl} = \tilde{F}_{ijk}l = \tilde{F}_{ijlk}) \). A 4th order tensor is completely traceless, if \( \tilde{F}_{kkl} = \tilde{F}_{kll} = \tilde{F}_{kli} = \tilde{F}_{kil} = \tilde{F}_{kii} = \tilde{F}_{iik} = 0 \).

The method for removing all the traces of the fourth order tensor is taken from [38]. The functions \( \tilde{f}(x), \tilde{F}(x) \) and \( \tilde{F}(x) \) form an orthonormal basis and as such they are normalized and orthogonal as shown in (Appendix A). Using this functional basis, the corresponding tensorial coefficients can be calculated:

\[ \tilde{g} = \frac{1}{V_B} \int_{V_B} \rho^I(x) \tilde{f}(x) dV, \] (3.17)
\[ \tilde{G} = \frac{1}{V_B} \int_{V_B} \rho^I(x) \tilde{F}(x) dV, \] (3.18)
\[ \tilde{G} = \frac{1}{V_B} \int_{V_B} \rho^I(x) \tilde{F}(x) dV. \] (3.19)

where \( V_B \) is the volume of the sphere with radius \( R \).

As the container sphere contains positive numbers these so–called fabric tensors will be positive definite \( (\tilde{g} \geq 0, x \cdot \tilde{G}x \geq 0 \) \( \forall x \) and \( X : \tilde{G}X \geq 0 \) \( \forall X = x \otimes x \)).

Hereby we have an approximation of the spatial distribution of the intensities of the container voxels. In order to convert this spatial distribution into an orientation distribution function (ODF), the contribution of each voxel needs somehow to be attributed to orientations only. The fourth order approximation of the new sampling sphere ODF is therefore defined such that its areal integral over the surface of the unit sphere is equal to the volume.
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integral of the spatial distribution $\rho^4(x)$ on the domain of the container sphere:

$$\frac{1}{A_0} \int_{A_0} SSOD_4(n) dA = \frac{1}{4\pi} \int_0^{2\pi} \int_0^\pi SSOD_4(n) \sin(\theta) d\theta d\varphi$$

$$:= \frac{3}{4\pi R^4} \int_0^R \int_0^{2\pi} \int_0^\pi \rho^4_4(x) r^2 \sin(\theta) d\theta d\varphi dr$$

$$= \frac{1}{V_B} \int_{V_B} \rho^4_4(x) dV$$

(3.20)

where $n$ are unit vectors and $A_0$ is the surface of the unit sphere. By simplifying Eq. (3.20), we get:

$$SSOD_4(n) = \frac{3}{R^3} \int_0^R \rho^4_4(x) r^2 dr$$

(3.21)

The fourth order Fourier series $SSOD_4(n)$ of this ODF can also be expressed as:

$$SSOD_4(n) = g f(n) + G : F(n) + \tilde{G} : \tilde{F}(n)$$

(3.22)

The first three even–ranked tensorial basis functions and coefficients of the Fourier series of this ODF are calculated according to [8].

$$f(n) = 1$$

(3.23)

$$F(n) = N - \frac{1}{3} I$$

(3.24)

$$F(n) = N \otimes N - \frac{1}{7} (I \otimes N + N \otimes I) - \frac{2}{7} (\overline{I} \otimes N + N \otimes I) + \frac{1}{35} (I \otimes I) + \frac{2}{35} (I \otimes I)$$

(3.25)

with $N = n \otimes n$. Using Eq. (3.13), Eq. (3.22) and Eq. (3.21), the tensorial coefficients of $SSOD_4(n)$, that will be used to characterize anisotropy, can be related with the corresponding coefficients of the spatial distribution $\rho^4_4(x)$ (defined in Eqs. (3.17-3.19)):

$$g = \tilde{g}$$

(3.26)

$$G = c_2 \tilde{G}$$

(3.27)

$$\tilde{G} = c_4 \tilde{G}$$

(3.28)

with the scalar multiplicators $c_2 = 3\sqrt{\frac{7}{10}}$ and $c_4 = \frac{3}{2} \sqrt{\frac{165}{14}}$.

On the discretized domain of the container sphere, the evaluation of these tensorial coefficients consists in a simple numerical integration (i.e. summation over the voxels) assuming the same density value for the whole volume of a given voxel:

$$g \cong \frac{1}{N} \sum_{x \in C} \rho^4(x)$$

(3.29)
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\[ G \approx c_2 \frac{1}{N} \sum_{x' \in C} \rho'(x') \hat{F}(x') \] (3.30)

\[ G \approx c_4 \frac{1}{N} \sum_{x' \in C} \rho'(x') \hat{F}(x') \] (3.31)

where \( N \) is the number of voxels in the sampling sphere. These coefficients of the approximation are used to characterize anisotropy. The sum of the first two terms defines \( \text{SSOD}_2(n) \), the second order approximation of SSOD. The second order fabric tensor \( \mathbf{M} \) is derived by normalizing this sum with the constant (spherical) part of the approximation \( g \):

\[ \frac{\text{SSOD}_2(n)}{g} = 1 + \frac{G}{g} : \mathbf{F}(n) = n \cdot \mathbf{M}n \] (3.32)

accordingly

\[ \mathbf{M} = \mathbf{I} + \frac{G}{g} \] (3.33)

It leads to an orthotropic symmetry approximation. The fabric tensor is characterized by three positive eigenvalues \( m_j (m_1 < m_2 < m_3) \) and three orthogonal eigenvectors \( \mathbf{m}_j \) where \( j = 1, 2, 3 \) are the three principal directions.

The fourth order approximation allows to describe more complex ODFs with lower symmetries. Similarly to \( \mathbf{M} \) we can define the fourth order fabric tensor \( \mathbf{M}_4 \):

\[ \frac{\text{SSOD}_4(n)}{g} = 1 + \frac{G}{g} : \mathbf{F}(n) + \frac{G}{g} :: \mathbf{F}(n) = (n \otimes n) : \mathbf{M}(n \otimes n) \] (3.34)

accordingly

\[ \mathbf{M} = \mathbf{I} \otimes \mathbf{I} + \frac{1}{2} \left( \frac{G \otimes \mathbf{I}}{g} + \frac{\mathbf{I} \otimes G}{g} \right) + \frac{G}{g} \] (3.35)

An overview of the new SSOD method applied on trabecular bone is presented in Fig. 3.3.

3.2.4 Calibration of the parameters of SSOD

On a grayscale image the movement of the sampling spheres can be altered, e.g. damped, by the background (marrow, noise) voxels if the contrast of intensities between the bone and marrow phase is not high enough. This prevents the spheres from reaching the best final position (for example a structural junction) as the high–valued background signal creates a perturbing force for the intensity driven sphere. This contrast can vary for different image sources and an optimal contrast respectively an optimal movement must be defined. Towards this end, the incremental motion of single sampling spheres on grayscale and the corresponding, properly thresholded binarized images of trabecular bone were tracked and compared. The results of this comparison showed that for our source of images (\( \mu\text{CT}40 \), Scanco Medical AG., Switzerland) the respective movements matched best if the third power of the gray values were used. Accordingly \( p = 3 \) were used in Eq. 3.4.
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Figure 3.3: Overview of the SSOD method: A: Trabecular bone graylevel image. B: Section of the intensity distribution of the final container. C: Second and fourth order approximation of the sampling sphere distribution in the same section.

Figure 3.4: Parts A–C: selecting the size of the sampling sphere: A: too small, B: too big, C: proper size; parts D–F: selecting the size of the sampling grid: A: too sparse, B: too dense, C: proper gridsize.

The size of the sampling spheres is an external parameter and must be determined according to the characteristic structural sizes of the underlaying media (e.g. trabecular thickness and spacing). To discuss this critical issue let us consider for the sake of simplicity two closely parallel structural elements on a 2D binary image. Three possibilities are shown on parts A–C of Fig. 3.4. First, if the diameter of the sampling sphere is too small (assuming sufficiently high resolution) the content of the sphere will appear as isotropic (part A). On the other hand if the sampling sphere is too big, it might include more than one structural element which is misleading for identification of the structural orientation (part B). On part C an optimal situation is depicted with a properly chosen diameter where the content of the sphere reflects the sought architectural information. This means that the diameter of the sampling spheres must be smaller than the pores of the analyzed sample but larger than the thickness of the structural elements, both of which can be estimated for different types of microstructure. For trabecular bone, the optimal diameter must therefore be larger than
the maximal trabecular thickness, but smaller than the minimal trabecular spacing which can be estimated to be respectively 284 µm and 454 µm from the literature [39]. Ideally, it should be close to the upper bound to maximize the precision of the available directional information.

Attention must also be given to the density of the sampling grid, i.e. the initial distance of the sphere centers as shown on parts D–F of Fig. 3.4. Too sparse sampling can lead to loss of important information, as the sampling sphere may have no contact with the relevant structural elements (part A). To avoid this, the sampling regions must overlap in their initial positions. Working with too many sampling regions is computationally inefficient (part B). Taking the spherical shape of the regions into consideration, we selected an overlap equal to the radius (R) of the sphere (part C). Fig. 3.2 shows the application of this rule on trabecular bone.

Effect of the initial gridsize was analyzed on a selected sample of trabecular bone by comparing the results of analyses with gridsize = R and gridsize = 5 voxels for R = 5–12 voxels. For this range the difference between the distinct eigenvalues of M was found to be smaller than 2% and the maximal angular deviation of the corresponding eigenvectors was around 1° while the computation time was significantly more in the second case (approximately 9.5 times in case of R = 12 voxels).

3.3 Results

3.3.1 Results of trabecular bone samples

The SSOD method was tested on µCT images with 26 µm isotropic resolution (µCT40, Scanco) of 42 human trabecular bone biopsies. The samples were selected from six anatomical locations (seven samples for each location): femoral trochanter, femoral neck, T10 vertebra, L2 vertebra, radius and calcaneus, with a broad range of volume fraction (0.0429–0.3737) and degree of anisotropy (1.146–2.301), which is defined as the ratio of the largest over the lowest MIL eigenvalue. The ROI was cylindrical with 6.7 mm diameter and 6.0 mm height for all samples. From the above parameter calibration (Section 3.2.4) and the available image resolution the radius of the sampling sphere was set to R = 7 voxels.

The fabric tensors of the second order approximation of SSOD (SSOD<sub>2</sub>) applied on graylevel respectively binary images were compared to the fabric tensors of MIL and SLD measured on the corresponding binary images. Segmentation was performed by applying a Gaussian filter and using a global threshold value. Fig. 3.5 shows the surface plots of the ODFs of the resulting tensors together with the 3D binary images for four samples covering a wide range of BV/TV. The ODFs of SSOD and SLD are qualitatively very similar and both exhibit a higher degree of anisotropy compared to MIL. Differences between the fabric tensors of SSOD and the gold standard MIL were quantified. For this purpose, the eigenvalues \( m_1 < m_2 < m_3 \) and the associated eigenvectors \( \mathbf{m}_1, \mathbf{m}_2, \mathbf{m}_3 \) of these tensors were compared, respectively. As shown in Fig. 3.6 a strong linear relationship was found between the respective eigenvalues with \( R^2 = 0.972 \). The linear regressions were also calculated sepa-
Figure 3.5: Comparison of the different second order measures of anisotropy for 4 samples: 3D binary images and surface plots of the ODFs of the 2nd order tensors. The samples cover a wide range of BV/TV: C0000747: 4.29%, C0002760: 7.52%, C0002170: 12.00%, C0000317: 37.37%.
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Figure 3.6: Comparison of MIL vs. SSOD$_2$ eigenvalues (grayscale images, R=7).

Analysis of the eigenvectors showed that for samples with higher degree of anisotropy ($DA_{MIL} > 1.2$, 40 samples) the angular deviation from the main eigendirection ($m_3$) of MIL was $1.84^\circ \pm 2.19^\circ$, while for the inferior directions $6.06^\circ \pm 8.40^\circ$ ($m_2$) and $5.66^\circ \pm 8.32^\circ$ ($m_1$). As expected in the case of smaller DA, this angular deviation increases and may become indeterminate when two or three eigenvalues degenerate.

When applying SSOD to the segmented versions of the original images, the eigenvalues and eigenvectors remained close to those computed from grayscale images. In particular, a strong linear relationship ($0.977x + 0.023$) was obtained between their eigenvalues ($R^2 = 0.988$). The separated analysis of the corresponding eigenvalues gave $0.929x + 0.110$, $R^2 = 0.949$ for the main ($m_3$) and $0.893x + 0.107$, $R^2 = 0.824$ respectively $0.866x + 0.067$, $R^2 = 0.852$ for the inferior ones ($m_2, m_1$). Comparison of the associated eigenvectors gave $1.80^\circ \pm 2.20^\circ$ for the main eigendirection ($m_3$) and $5.75^\circ \pm 7.15^\circ$ ($m_2$) respectively $5.13^\circ \pm 7.19^\circ$ ($m_1$) for the two minor directions for 40 samples.

3.3.2 Influence of the size of the sampling spheres

Despite the suggested guideline to select the appropriate sampling sphere radius, its influence on the fabric tensor was examined. The analysis of the same 42 bone samples was repeated for sampling sphere radii from 5 to 12 voxels. The SSOD method was applied on both the original grayscale and the segmented images.

The results of SSOD$_2$ were again compared with the MIL results. The parameters of the linear regressions between the corresponding eigenvalues for different value of $R$ were plotted on Fig. 3.7. Based on the correlation coefficient value the best agreement between SSOD$_2$ and MIL is obtained for $R = 7$ on both grayscale and segmented images. However
CHAPTER 3. SAMPLING SPHERE ORIENTATION DISTRIBUTION

Figure 3.7: Influence of sampling sphere radius on the linear regression of MIL vs. SSOD\textsubscript{2} eigenvalues: slope and intercept (left) and correlation coefficient (right).

Figure 3.8: Influence of sampling sphere radius of MIL vs. SSOD\textsubscript{2} eigenvectors, angular deviations of the corresponding directions: grayscale (left) and segmented images (right).
the match of the directionality also has to be accounted for in this comparison. For this the angular deviations of the eigenvectors were measured on 40 samples (with higher DA). The results are presented as bar plots for the different size of the sampling sphere in Fig. 3.8. An important basis of comparison is the agreement in the direction corresponding to the highest eigenvalue. In cases close to transverse isotropy, the two minor eigenvectors may deviate to a large extent. This comparison showed the best agreement for sampling sphere radius of 7 voxels which again supports our choice. In fact, these results of SSOD$_2$ are robust in the analyzed range of sampling sphere radii $R$ as the mean of the relative angular deviations in the $3^{rd}$ direction is approximately $2.2^\circ$ for grayscale images (the absolute value compared to the MIL ranges from $1.84^\circ$ to $4.05^\circ$).

### 3.3.3 Fourth order results of trabecular bone samples

To verify the potential and limitations of the fourth order approximation of the SSOD method in detecting higher order anisotropies the ODFs of SSOD$_4$ were qualitatively compared with the ODFs of the $4^{th}$ order approximation of MIL and SLD for the same four samples that were shown above at the second order analysis. SLD was involved into this comparison as it is known that for this measure the fourth order approximation of the ODF is more accurate [17]. A preliminary study showed that SSOD$_4$ shows more details if the sampling sphere is bigger. On the other hand the value of $R$ cannot go too high according to the geometrical guidelines mentioned above. Therefore a slightly bigger radius was chosen compared to what we had in the analysis of SSOD$_2$. Here, the selection was $R = 9$ voxels. The surface plots of the ODFs are shown on Fig. 3.9 for the different measures. This comparison suggests that by involving the fourth order part of the approximation SSOD$_4$ shows more structure than MIL$_4$ but less details as SLD$_4$. It also allows to conclude that for lower values of BV/TV SSOD seems to be closer to SLD while for denser structures the impact of the fourth order part is smaller. Note that the results of SSOD on grayscale images are close to the ones obtained from the corresponding binarized images also in case of the $4^{th}$ order approximations. A quantitative comparison of the fourth order fabric tensor goes beyond the goal of this initial study.

### 3.3.4 Artificial structures

The capability of SSOD$_4$ in capturing orientation patterns was shown also on 3D images of artificial structures. An orthogonal regular grid structure with cubic symmetry was created and analyzed with SSOD. Thickness of the beams and the gridsize was equal in all spatial directions. Assuming $20\, \mu m$ isotropic spatial resolution thickness of the beams was set to 10 voxels and a gridsize of 24 voxels was chosen to achieve a volume fraction compatible with trabecular bone (approximately 20%). The ROI was a $5.44^3 mm^3$ region assembled from $8 \times 8 \times 8$ cells of this grid pattern. From the spacing of the grid, the radius of the sampling sphere was set to 11 voxels. A subvolume of $3 \times 3 \times 3$ cells of the ROI can be seen in the first row of Fig 3.10 together with the second and fourth order approximations of
Figure 3.9: Comparison of different fourth order measures of anisotropy: surface plots of the ODFs of the 4<sup>th</sup> order tensors for the 4 samples shown on Fig. 3.5.
MIL, SLD and SSOD. The cubic symmetry invisible when the second order approximation is used becomes visible when the fourth order one is computed.

A modification of the previous grid structure was also prepared. The thickness of the columns in the vertical direction was enlarged by 2 voxels and the horizontal rods were thickened by 2 voxels. Therefore the minimal spacing become 22 voxels, so \( R = 10 \) was selected for the analysis. The structure and the computed 4\(^{th}\) order tensors are shown in the second row of Fig 3.10. These artificial structures suggest that SSOD\(_{4}\) is capable of discriminating structures with cubic or tetragonal symmetry from isotropic symmetry.

### 3.3.5 Computation time

In order to evaluate the computational efficiency of the implemented method a grayscale, \(200 \times 200 \times 200\) voxels subregion of a trabecular bone image with 26\(\mu m\) resolution was analyzed with SSOD. This corresponds to a representative volume element (VE) of approx. \(5 \times 5 \times 5\) \(mm^3\) for trabecular bone [40]. Computation was performed and the CPU times were measured on a standard PC (Athlon64 3500 (2.2 GHz), 2 GB RAM) for different radii of the sampling spheres. Processing time (with the convention \(gridsize = radius\)) for the optimal selection of radius (\(R = 7\)) was 10.2 s. It increased approximately linearly with the change of the sampling sphere size with some deviations due to the motion of the spheres. In the extremes, computing time was 9.0s for \(R = 5\) and 14.6s for \(R = 12\).

### 3.4 Discussion

The novel Sampling Sphere Orientation Distribution method presented in this paper is designed to quantify structural anisotropy of open cell materials from 3D grayscale images. It samples the Region Of Interest with mobile spheres that are attracted by structural elements. The density contents of these sampling spheres are summed up and averaged within a container of identical shape. The resulting density distribution is converted into an Orientation Distribution Function that is expanded in Fourier series to identify the 2\(^{nd}\) and 4\(^{th}\) order fabric tensors. The 2\(^{nd}\) order fabric tensor can be used in previously published fabric–mechanical property relationships, while the 4\(^{th}\) order one may be used in higher order relationships as the elasticity tensor is a tensor of fourth order and it can be decomposed to a second and a fourth order ODF.

The performance of SSOD was investigated on 42 human trabecular bone samples from a wide range of anatomical locations, volume fraction and degree of anisotropy. In fact, segmented images can be considered as a special case of grayscale images and SSOD can also be applied on binary images. As a first result, the SSOD of the grayscale images is in good agreement with the SSOD of the segmented ones. This property ensures a solid basis for comparison with classical characterization methods used for segmented images such as MIL or SLD. In particular, the eigenbases of the second order tensor approximation of SSOD were computed and compared with the ones computed with MIL. Linear
Figure 3.10: Artificial grid structures: subvolumes with second and fourth order approximations of fabric.
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relationships with high coefficients of determination were obtained between the eigenvalues and small angular deviations were found between the associated eigenvectors, especially for samples with high DA. This finding ensures that SSOD can be used in fabric–mechanical property relationships anchored on a second order fabric tensor.

The effect of sampling sphere radius was then analyzed. While this parameter demonstrated a detectable influence on the second order results, the best agreement with MIL was obtained for a radius of 7 voxels, which corresponds to the theoretical estimation proposed in Section 3.2.4. Nevertheless, the correlations between eigenvalues and angular deviations between eigenvectors proved to be reasonably robust within a ±14% (about 1 voxel) variation of the radius.

The capabilities of the fourth order approximation of SSOD were qualitatively shown on four trabecular bone examples. Furthermore the method was tested on two artificial grid structures. The inclusion of the fourth order term in the Fourier expansion of SSOD accounted properly for the cubic and tetragonal symmetry of these structures. In this respect, the structural discrimination power of SSOD appears to be closer to SLD than to MIL.

Despite these encouraging results, SSOD exhibits a number of limitations. First, the method was designed for trabecular bone and can be applied to open cell structures with a volume fraction typically smaller than 0.5. The method is not appropriate for porous materials with high volume fraction such as compact bone because the pores will be avoided in the motion of the spheres. Second, the ROI must be defined as a closed convex set that is larger than the size of the sampling sphere. In fact, the continuum or statistical homogeneity assumption underlying quantification of an architectural property suggests that the linear dimensions of the ROI should include 5 intertrabecular spacing i.e. 3–7 mm depending on volume fraction. Due to the motion of the sampling spheres, some parts of the image are not involved in the final analysis. On the other hand, spheres from different grid points may converge to the same structural element which intensity is therefore added several times in the container. It can be argued that the purpose of the sphere motion is precisely to capture the most relevant structural details and that the algorithm attributes consequently more weight to structural elements that attract more spheres. As MIL is known to be additive, the same property was examined for SSOD. Additivity means that the ODF of two objects within an image is the sum of the ODF weighted by the relative mass of these objects. This property is not exactly verified by SSOD for two reasons. (1) The motion of the sphere may lead to some interaction between the objects if they are close enough. (2) The shift of the container intensities with respect to the lowest value will induce an arbitrary intensity level that is related but not rigorously equal to the relative mass. Nevertheless, SSOD is invariant with respect to addition of a constant and is homogeneous of degree one, i.e. multiplication of an image by a constant leads to the same SSOD multiplied by the same constant. Normalization of the fabric tensors imply that beyond invariance with respect to addition of a constant they are also invariant with respect to the multiplication of a constant. This property ensures that the description of architectural anisotropy is independent of volume fraction or bone apparent density.

Computational efficiency of SSOD appears to be attractive compared to other meth-
ods working on grayscale images such as TSD or spatial autocorrelation analysis, but re-
 mains inferior to MIL which implementation in the same hardware and software environment
 is approximately 4 times faster. This difference clearly represents the price for including
 the intensity information.

To conclude, SSOD is found to be a reliable and efficient method to quantify anisotropy
of human trabecular bone from 3D grayscale µCT images. The second order fabric tensor
of SSOD is closely related to the one computed with MIL on corresponding segmented im-
ages, but SSOD, like for instance SLD, can capture more subtle anisotropy features than
MIL as shown by the fourth order approximations on trabecular bone samples respectively
on artificial cubic and tetragonal structures. Sensitivity of the novel SSOD method with
respect to image resolution for the sake of implementation in fabric–elasticity relationship
will be explored in future work.

Acknowledgements

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SLD methods.

Appendix A

Orthonormality of the basis functions of the Fourier series:

- $\mathbf{F}(\mathbf{x})$ is normal to $\mathbf{f}(\mathbf{x})$, as $\mathbf{F}(\mathbf{x})$ is traceless:

$$
\frac{1}{V_B} \int_{V_B} \mathbf{f}(\mathbf{x}) \mathbf{F}(\mathbf{x}) dV = \mathbf{0}. \tag{3.36}
$$

- $\mathbf{F}(\mathbf{x})$ is normalized:

$$
\frac{1}{V_B} \int_{V_B} \mathbf{F}(\mathbf{x}) \otimes \mathbf{F}(\mathbf{x}) dV = \mathbf{I}, \tag{3.37}
$$

where $\mathbf{I}$ is a 'properly' traceless fourth order identity tensor, that fulfills:

$$
\mathbf{I} A = A, \ \forall A \ (tr(A) = 0) \tag{3.38}
$$

$\mathbf{I}$ can be expressed the following way:

$$
\mathbf{I} = \mathbf{I} \otimes \mathbf{I} - \frac{1}{3} \mathbf{I} \otimes \mathbf{I} \tag{3.39}
$$

with $\mathbf{I}$ being the second order identity tensor and $\otimes$ is the symmetric tensorial product
explained below in index notation:

$$
\mathbf{P} = \mathbf{Q} \otimes \mathbf{R} \quad P_{ijkl} = \frac{1}{2} (Q_{ik} R_{jl} + Q_{il} R_{jk})
$$
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The explanation for (3.37):

\[ \tilde{G} = \frac{1}{V_B} \int_{V_B} \rho_A(x) \tilde{F}(x) dV \]
\[ = \frac{1}{V_B} \int_{V_B} \left( \tilde{g} f(x) + \tilde{G} : \tilde{F}(x) + \tilde{G} : \tilde{F}(x) \right) \tilde{F}(x) dV \]
\[ = \frac{1}{V_B} \int_{V_B} \tilde{G} : \tilde{F}(x) \tilde{F}(x) dV \]
\[ = \frac{1}{V_B} \int_{V_B} \tilde{F}(x) \otimes \tilde{F}(x) dV : \tilde{G} \]
\[ = \hat{I} : \tilde{G}. \] (3.40)

as \( \tilde{G} \) is independent of \( x \).

- \( \tilde{F}(x) \) is normal to \( \tilde{f}(x) \) and to \( \tilde{F}(x) \) as \( \tilde{F}(x) \) is completely traceless:

\[ \frac{1}{V_B} \int_{V_B} \tilde{f}(x) \tilde{F}(x) dV = 0 \] (3.41)
\[ \frac{1}{V_B} \int_{V_B} \tilde{F}(x) \otimes \tilde{F}(x) dV = 0 \otimes 0 \] (3.42)

- \( \tilde{F}(x) \) is normalized:

\[ \frac{1}{V_B} \int_{V_B} \tilde{F}(x) \otimes \tilde{F}(x) dV = \hat{I}, \] (3.43)

where \( \hat{I} \) is a 'properly' traceless eighth order identity tensor, that fullfills:

\[ \hat{I} A = A, \forall A \ (A \ is \ completely \ traceless). \] (3.44)

\( \hat{I} \) can be expressed as:

\[ \hat{I} = \mathbb{I} - \frac{12}{13} \mathbb{I} - \frac{11}{35} (\mathbb{I}^{sy} \mathbb{I} + \mathbb{I} \mathbb{I}^{sy}) \]
\[ + \frac{13}{35} \mathbb{I}^{sy} \mathbb{I} \mathbb{I}^{sy} - \frac{5}{7} \mathbb{I}^{cr0} + \frac{4}{7} (\mathbb{I}^{cr0} \mathbb{I}^{sy} + \mathbb{I}^{sy} \mathbb{I}^{cr0}) \]
\[ - \frac{6}{7} (\mathbb{I}^{sy} \mathbb{I}^{cr0} \mathbb{I}^{sy}) \] (3.45)

where the eight order tensors in index notation:

\[ \mathbb{I} = \frac{1}{8} (\delta_{im} \delta_{jn} \delta_{ko} \delta_{lp} + \delta_{io} \delta_{jp} \delta_{km} \delta_{ln} + \delta_{in} \delta_{jm} \delta_{ko} \delta_{lp} + \delta_{im} \delta_{jn} \delta_{kp} \delta_{lo} + \delta_{in} \delta_{jm} \delta_{kp} \delta_{lo} + \delta_{ip} \delta_{jx} \delta_{km} \delta_{ln} + \delta_{io} \delta_{jp} \delta_{kn} \delta_{lm} + \delta_{ip} \delta_{jx} \delta_{kn} \delta_{lm}) \] (3.46)
\[ \mathbb{I} = \delta_{ij} \delta_{kl} \delta_{mn} \delta_{op} \] (3.47)
\[ \Pi^{c_r} = \Pi^{c_r} \Pi \text{ with } \Pi^{c_r} = \delta_{im} \delta_{jn} \delta_{kl} \delta_{op} + \delta_{ij} \delta_{km} \delta_{ln} \delta_{op} \quad (3.48) \]
\[ \Pi^{c_y} = \Pi^{c_y} \Pi \text{ with } \Pi^{c_y} = \delta_{im} \delta_{jn} \delta_{kn} \delta_{lp} \quad (3.49) \]

The explanation for (3.43):

\begin{align*}
\tilde{g} &= \frac{1}{V_B} \int_{V_B} \rho^I(x) \tilde{F}(x) dV \\
&= \frac{1}{V_B} \int_{V_B} \left( \tilde{g} \tilde{f}(x) + \tilde{G} : \tilde{F}(x) + \tilde{G} \cdot \tilde{F}(x) \right) \tilde{F}(x) dV \\
&= \frac{1}{V_B} \int_{V_B} \tilde{G} \cdot \tilde{F}(x) \tilde{F}(x) dV \\
&= \frac{1}{V_B} \int_{V_B} \tilde{F}(x) \otimes \tilde{F}(x) dV \cdot \tilde{G} \\
&= \Pi \cdot \tilde{G}. \quad (3.50)
\end{align*}

as \( \tilde{G} \) is independent of \( x \).

Bibliography


Chapter 4

Calibration of HR–pQCT with respect to volume fraction and fabric

Extended from the manuscript:

Assessment of volume fraction and fabric in the distal radius using HR–pQCT

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Abstract

The aim of this study was to investigate the capabilities of the state of the art HR–pQCT technique to predict mineral content, volume fraction and fabric of trabecular bone structure compared to the gold standard µCT. Four cadaveric human forearms were scanned with HR–pQCT and the dissected radius epiphyses with µCT. After registering the images, bone mineral density (BMD), volume fraction (BV/TV) and fabric were computed on corresponding cubical regions of interest for both image sources. In particular, the effect of the segmentation procedure on BV/TV was analyzed. Assessment of fabric was performed with three different methods comparing their efficiency and robustness against resolution change. The
results showed that in order to achieve optimal results at the lower image resolution, different filtering and thresholding approaches needed to be selected for different tasks. Therefore, to preserve BV/TV, the BMD–based volume fraction provided best match with the reference values of µCT, while in case of Mean Intercept Length (MIL) fabric a Gaussian filter and a histogram–based threshold were optimal. Using the latter, MIL was found to be more robust against resolution change than the other approaches. Additionally, we proposed two models for describing the mathematical transformation that the second order fabric tensor undergoes when the resolution of the input images changes. As a conclusion, we found that the investigated properties of trabecular bone structure can be adequately predicted from the lower resolution technique that is available in vivo for peripheral bones, when proper image processing and corrections are applied.

Keywords: HR–pQCT, fabric, image registration, distal radius, trabecular bone

4.1 Introduction

Fracture of the distal radius is one of the most common osteoporotic fractures [1]. As it often occurs earlier in lifetime it may help to predict and prevent osteoporotic fractures of the other endangered skeletal sites like the hip or the vertebral column [2]. Besides bone mineral density (BMD), architecture is an important parameter that characterizes the mechanical properties of trabecular bone [3, 4] but requires high resolution representation of its structure. Micro–computed tomography (µCT) imaging provides detailed reconstructions but the sample size is limited to very small volumes like biopsies and measurements are therefore restricted to in vitro cases. With the introduction of High Resolution peripheral Quantitative Computed Tomography (HR–pQCT), it became possible to obtain insight into the trabecular bone structure of the distal sites like the wrist under in vivo conditions [5]. The currently available resolution of this technique is below the average trabecular thickness which makes it capable of capturing the trabecular architecture. It may therefore improve the assessment of bone quality and prediction of fracture risk compared to classical densitometry (DXA), the current gold standard method, which takes solely 2D mineral density into account [6, 7]. HR–pQCT derived morphological properties have limited accuracy and predictive capability compared to the standard µCT measurements [8, 9, 10], mostly due to lower resolution and signal to noise ratio.

Finite element (FE) methods are proven to enhance fracture risk prediction by computing mechanical properties [11, 12, 13] using patient–based models. A currently developed FE technique [14] is using a homogenization approach [15, 16] and therefore needs volume fraction and fabric (architectural anisotropy) of the trabecular bone structure. The inclusion of fabric information has been shown to improve the capability of this model to predict mechanical properties of vertebral bodies [17]. The gold standard method for quantifying
fabric, Mean Intercept Length (MIL), requires segmentation of the input images. Thresholding is a delicate step especially on lower resolutions like the HR–pQCT images where the trabeculae are represented as few voxel thick structures and connectivity can be easily lost. This was the main motivation for introducing grayscale image–based methods for quantifying the fabric information [18, 19, 20, 21, 22, 23]. Degradation of fabric properties due to the limited image quality of HR–pQCT is not known in details and might affect the prediction of mechanical properties provided by the FE models.

The goal of the present study was to calibrate bone mass, volume fraction and fabric information assessed from HR–pQCT with the \( \mu \)CT based quantities as reference. The effect of different image filters and thresholding procedures on volume fraction was investigated. For the description of fabric, three different methods were analyzed and compared: MIL and two recently introduced grayscale image based approaches, Spatial Autocorrelation Function (ACF) [22] and Sampling Sphere Orientation Distribution (SSOD) Chapter Three. Robustness of these methods was analyzed by comparing their results and performance on the HR–pQCT and the \( \mu \)CT images.

4.2 Materials and methods

4.2.1 Bone samples

Four formalin fixed cadaveric human arms (2 left, 2 right) of three donors (2 males, 1 female, mean age 87±11 years) were received from the Institute of Anatomy, Ludwig Maximillians University (LMU) Munich. The donors had agreed to dedicate their bodies to LMU several years prior to death. The specimens were stored frozen until the scans were performed. Following thawing for 12 h at room temperature, the lower arms were dissected and the hands were removed.

4.2.2 Imaging

The cadaveric forearms were initially scanned with HR–pQCT, XtremeCT (Scanco Medical AG, Switzerland) using the standard settings (60 kVp, 1 mA, 100 ms integration time, 82 \( \mu \)m image voxel size, 1536x1536 pixels image matrix), of the in vivo scanning protocol. However, the length of the scanned region was extended compared to the original protocol in order to increase the number of regions of interest. The scans included the distal 72.16 mm (880 slices) part of the radius starting at the most distal end of the bone and extending proximally.

The arms were then dissected, and the radii were extracted and cleaned from soft tissues. The distal 70 mm of the bones was cut and prepared for scanning with \( \mu \)CT40 (Scanco, settings: 70 kVp, 114 mA, 200 ms integration time, 18 \( \mu \)m isotropic spatial resolution, 2048x2048 pixels image matrix). In two cases, the radii needed to be cropped in order to fit into the largest sample holder having an inner diameter of 35 mm. The specimens
were submerged in distilled water, and air bubbles were removed by exposing the flooded samples to vacuum for 10 min. A 36 mm long region was scanned (2000 slices), starting right below the distal articular surface of the bone and extending proximally.

4.2.3 Registration

The radius was separated from the adjacent bones on each XtremeCT (XCT) images using the in–built semi–automatic contouring procedure of the scanner. The µCT images were first rotated in order to maximize the number of rectangular regions that fit in the trabecular phase. These images were than coarsened with a factor of 4 for the registration process resulting in 72 µm voxel size and the grayscale values surrounding the radius bones were masked using a fill procedure. The XCT images were registered with these resampled µCT images using the 3D spatial rigid registration methods of the C++ library ITK framework (Kitware Inc., USA). In order to minimize the computation time, the XCT images were cropped along and rotated around the z (vertical) axis with a visually estimated angle to match the µCT images and therefore provide an initial configuration for the registration. The iteration process was driven by a regular step gradient descent optimizer to minimize the cost function. In order to avoid inaccuracies due to the different signal–to–noise ratios and possible calibration differences of the two sets of images, the cost function was computed from a mutual information measure. For this purpose, the Mattes mutual information was selected which was sampled from 50% of the XCT image voxels and histograms with 50 bins were used [24]. The transformed image was resampled into the voxel–grid using linear interpolation. The result was verified both by the final cost function values and by visual inspections.

4.2.4 Regions of interest

Cubical regions with 6 mm side length (equal to 333 voxels on the µCT and 73 voxels on the XCT images) were selected and cropped from the trabecular bone phase of the registered XCT images. The corresponding regions were cropped automatically from the µCT images having 18 µm voxel size. Seventy–seven regions were obtained in total. Midplane images of one of these regions are shown in Figure 4.1.

4.2.5 BMD and BV/TV

The grayscale values of the images were converted into BMD units (HA mg/cm³) using the calibration curves of the µCT and the XCT scanners, respectively. Mean BMD values of the regions were computed and compared for the corresponding regions of the two sets.

The µCT images were filtered using a Gaussian low–pass filter (σ = 1.2, support = 2) and segmented using a grayscale histogram based threshold: the value separating the bone and the marrow peaks was identified for each specimen separately using the summed
Figure 4.1: 3D and midplane images of a cubical region of interest. Columns: 3D view, planes with normals X, Y and Z, respectively; rows: µCT and XCT images in grayscale as well as segmented using different filters (Gaussian (Gauss) and Laplace–Hamming (LH)) and thresholding (optimal (Opt) and fixed–valued (Fix)) approaches.
Chapter 4. Calibration of HR-PQCT

Histogram of all regions with the procedure proposed in [25]. This method was shown in a previous (unpublished) study involving small human trabecular bone biopsies to provide an excellent match of the volume fraction measured using the Archimedes principle and also applied by Meinel et al. [26]. It will be referenced as ‘optimal’ approach below.

Segmentation of HR–pQCT images is a delicate issue. On this relatively coarse resolution, a slight modification of the threshold value has a high influence on the resulting structure as connectivity may be changed. Therefore, following the standard XCT evaluation, a density–based BV/TV volume fraction (BV/TVd) was calculated assuming 1200 HA mg/cm$^3$ to be the density of fully mineralized tissue [5]. Still, the XCT images had to be segmented for the MIL method. The threshold value was determined for each specimen from the summed histograms similarly to the $\mu$CT case (‘optimal’) following filtering with Gaussian filter ($\sigma = 0.8$, support = 1) in one case and Laplace–Hamming (LH) filter in a second case. The LH filter was reported to enhance preserving the trabecular architecture during segmentation [27]. It is used in the standard in vivo evaluation protocol of the XCT in combination with a global threshold value (40% of the maximal grayscale intensity value) to compute trabecular number and fabric. We investigated this procedure as a third thresholding approach, which will be referenced as ‘fix’.

4.2.6 Fabric

Fabric describes the orientation and extent of the microarchitectural anisotropy of cellular materials. There are various ways to determine this property. In this study, we examined three methods for quantifying fabric: the gold standard MIL and two lately introduced grayscale image–based approaches.

The MIL method was originally described in [28] as the average distances of bone–marrow interfaces in given spatial directions. For the definition of these interfaces, it requires segmented images. The resulting spatial distribution can be approximated with an ellipsoid [29] or tensors of different order [30] providing the so called fabric tensors [31]. Nowadays this method became the gold standard way of quantifying fabric. The spatial distribution of MIL was computed here using scanning lines. This procedure was found to provide identical results to the triangular surface–based approach of the CT manufacturer. MIL fabric was computed for the three sets of differently segmented XCT images and the one providing the best results in terms of resolution sensitivity was selected for the comparison with the two grayscale–based methods.

The basic idea of using Spatial Autocorrelation Function (ACF) for characterization of bone fabric was introduced in [32]. It is a statistical method based on the grayvalues of the images that is applicable on rectangular regions of quasi–periodic structures like trabecular bone. ACF can be assessed by shifting the image along a given direction and correlating the shifted and the original image on the common domain. Mean trabecular thickness (Tb.Th) and spacing (Tb.Sp) values are then estimated [22, 33]. As the measurement of Tb.Sp was reported not to be reliable and therefore inaccurate, it was not used in the current study. Our implementation followed the description given in [22] by performing the computation
CHAPTER 4. CALIBRATION OF HR-PQCT

in the Fourier domain.

Sampling Sphere Orientation Distribution (SSOD) introduced in Chapter Three is also using the grayscale information and therefore does not require segmentation of the input images. In the frame of this method, small spherical regions are sampled from the characteristic spots of the underlying architecture. From the superposition of the content of these spheres, an orientation distribution function (ODF) is extracted that is approximated using spherical harmonics. In this study, the second order approximation defined the SSOD fabric tensor. The single input parameter of the method is the size of the sampling spheres, which can be selected according to the rule that the diameter should be as big as possible, but smaller than the Tb.Sp and bigger than the Tb.Th of the structure. In case of the $\mu$CT images sphere radius $(R)$ was selected to be 12 voxels in Chapter Three, resulting in a diameter $(d)$ of 25 voxels corresponding to 450$\mu$m. When processing the XCT data $R = 3$ voxels, respectively, $d = 7$ voxels were used based on results of a preliminary study where this value of $R$ leads to the closest agreement between typical $\mu$CT and HR–pQCT voxel sizes [34].

Quantification of fabric was performed with all three measures for both the $\mu$CT and the XCT image regions. Different approaches provide different measures which are rarely convertible and also hard to compare [35]. Computational performance and resolution sensitivity are objective measures that can be used as basis of comparison. Performance of the methods was evaluated and compared by measuring computation time. The effect of the resolution and quality difference between the $\mu$CT and the XCT images was analyzed by investigating the degradation of both the extent and the directionality of fabric anisotropy for all three methods. In case of MIL, results of the different filter types and thresholding approaches were additionally compared. Second order tensorial approximations of all three measures were used as these exhibited smaller sensitivity against resolution change compared to the ellipsoidal fits. The spectral decomposition of the second order fabric tensor $M$ provides its eigensystem:

$$M = \sum_{i=1}^{3} m_i \mathbf{m}_i \otimes \mathbf{m}_i$$ (4.1)

where $m_i$ ($m_1 < m_2 < m_3$, $tr(M) = m_1 + m_2 + m_3 = 3$) are the three positive fabric eigenvalues, $\mathbf{m}_i$ are three orthogonal eigenvectors and $i = 1, 2, 3$ are the three principal directions. Changes in the fabric orientation were measured by calculating spatial angular deviations of the corresponding eigenvectors, respectively. To describe the degradation of the extent of anisotropy, two models were proposed. The first model defined an affine transformation, $T_{\text{aff}}$:

$$\muCT m_i = \alpha(XCT m_i - 1) + 1$$ (4.2)

which represented a simple linear regression fit to the pool of the corresponding eigenvalues. The second model was based on a power transformation, $T_{\text{pow}}$:

$$\muCT m_i = \frac{3}{\sum_{i=1}^{3} XCT m_i^\gamma} XCT m_i^\gamma$$ (4.3)
Both $T_{aff}$ and $T_{pow}$ were described in more details in the Appendix. In fact, $T_{aff}$ and $T_{pow}$ do not affect the fabric eigenvectors but transform the fabric eigenvalues. Degree of anisotropy (DA) of the second order fabric tensor is defined as the ratio of the largest and the smallest eigenvalue. The two models established for the degradation of the eigenvalues (Eq. (4.2) and Eq. (4.3)) were adopted for DA. In case of $T_{aff}$, the relation for DA was the following:

$$\mu_{\text{CT}} DA = \frac{\mu_{\text{CT}} m_3}{\mu_{\text{CT}} m_1} = \frac{XCT m_3 - 1}{\alpha(XCT m_1 - 1) + 1},$$ \hspace{1cm} (4.4)

while for $T_{pow}$:

$$\mu_{\text{CT}} DA = \frac{\mu_{\text{CT}} m_3}{\mu_{\text{CT}} m_1} = \frac{XCT m_3}{XCT m_1} = XCT DA^\gamma.$$ \hspace{1cm} (4.5)

4.2.7 Statistics

BMD and volume fraction values of the XCT image were compared with the corresponding $\mu$CT values using linear regression analysis and coefficients of determination ($R^2$) were computed. Bland–Altman plots were used for qualitative comparison of the quantities of the two image sources. Parameters of the affine and the power models were evaluated for the fabric eigenvalues using Eq. (4.2) and Eq. (4.3), respectively. Squared Pearson’s correlation coefficients and root mean square errors (RMSE) were calculated. Deviations of the predictions of both models ($T_{aff}$ and $T_{pow}$) from the $\mu$CT DA values were measured with squared Pearson’s correlation coefficients, and values of $\alpha$ as well as $\gamma$ were obtained from the fits of the eigenvalues. Means and standard deviations of the absolute angular deviations between the corresponding fabric eigenvectors of the XCT and the $\mu$CT images were computed for the three eigendirections, respectively.

4.3 Results

4.3.1 BMD and BV/TV

During the qualitative analysis of the images, air bubbles were found on the $\mu$CT scan of one of the four specimens indicating that air was not perfectly removed prior to scanning in that case. This resulted in altered average BMD values and influenced the optimal threshold through the grayscale histogram in regions cropped from this sample ($N=13$). This part of the data was therefore excluded from the analysis which was then performed using the remaining $N=64$ regions of three specimens from two donors.

Comparison of the mean BMD values of the regions derived from the two different image sources is depicted in the first row of Figure 4.2. The regions perturbed by air bubbles were displayed separately in the BMD correlation plot to show the alterations, but not included into the regression analysis. $\mu$CT BV/TV values ranged from 6.6% to 26.9% (mean±SD: 15.46 ± 4.72%). The second row of Figure 4.2 shows the relation between the
CHAPTER 4. CALIBRATION OF HR-PQCT

XCT BV/TVd and the μCT volume fractions, and the further rows present the results of the different filtering and thresholding approaches.

The segmented images were analyzed visually as well. This qualitative comparison showed that for HR–pQCT images the LH filtering technique provided better results: when comparing with μCT, the architecture and connectivity of the bone structure seemed to be better preserved as for the Gaussian filtered case where some smaller, thinner parts disappeared and the larger patterns were still too thick. Results of the thresholding procedures are shown in Figure 4.1 for one region.

4.3.2 Comparison of μCT and XCT fabric

ODFs of the different methods as lines and their second order approximations as surface plots are shown for both the μCT and the XCT images for three regions in Figure 4.3. The regions were selected to cover the available volume fraction range. Results of MIL evaluated on the Gaussian filtered and 'optimal' thresholded XCT images are depicted on this figure. In case of SSOD, the surface is shown alone as it provides the approximation directly. Black lines show the orientations of the main axes of the fabric tensors.

Figure 4.4 shows the SSOD eigenvalues together with the affine (left) and the power (right) models for the transformation between μCT and XCT fabric. Parameters of the two model identified for the eigenvalues (Eq. (4.2) and Eq. (4.3)) with $R^2$ and RMSE values are summarized in Table 4.1 for each method. Squared correlation coefficients between the μCT DA values and the predictions of both model are summarized in Table 4.2. Parameters of the simple linear regression analysis of the DA values, relying on no model of the eigenvalue degradation, are also shown in Table 4.2 for comparative purposes.

Table 4.1: Parameters of the affine and the power models describing the relation between XCT and μCT fabric eigenvalues, for each fabric measure: slopes, correlation coefficients and root mean square errors of the affine relation ($\alpha$, $R^2_{aff}$ and RMSE$_{aff}$); power exponents ($\gamma$), correlation coefficients ($R^2_{pow}$) and root mean square errors (RMSE$_{pow}$) of the power model.

<table>
<thead>
<tr>
<th>Method</th>
<th>Affine model</th>
<th>Power model</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>$\alpha$</td>
<td>$R^2_{aff}$</td>
</tr>
<tr>
<td>MIL (Ga,Opt)</td>
<td>1.189</td>
<td>0.985</td>
</tr>
<tr>
<td>MIL (LH,Opt)</td>
<td>1.195</td>
<td>0.982</td>
</tr>
<tr>
<td>MIL (LH,Fix)</td>
<td>1.217</td>
<td>0.974</td>
</tr>
<tr>
<td>ACF</td>
<td>1.336</td>
<td>0.961</td>
</tr>
<tr>
<td>SSOD</td>
<td>1.341</td>
<td>0.978</td>
</tr>
</tbody>
</table>
Figure 4.2: Comparison of bone mineral density (BMD) and volume fraction (BV/TV) between XCT and µCT. The first row depicts the BMD analysis. Results of the different density (BV/TVd) and segmented image (Gaussian (Ga) filter with 'optimal' (OPT) threshold, Laplace-Hamming (LH) filter with 'optimal' and 'fix' (FIX) thresholds) based approaches used for XCT volume fraction assessment are shown in the further rows. Columns: regression analysis (left) and Bland–Altman plots (right). Regions containing bubbles are shown on the linear regression plot of BMD only and were not included in the analysis.
CHAPTER 4. CALIBRATION OF HR-PQCT

Figure 4.3: ODF (denoted by ‘d’), and ODF together with the surface plot of its 2nd order approximation and with the main fabric orientations in black (denoted by ‘a’) of the different methods shown for 3 samples covering the available range of BV/TV: F1: 8.5%, B5: 15.8%, A2: 26.9% (measured on the μCT images).
CHAPTER 4. CALIBRATION OF HR-PQCT

Figure 4.4: Comparison between the Sampling Sphere Orientation Distribution (SSOD) fabric eigenvalues of XCT and $\mu$CT together with the affine (left) and the power model (right).

Table 4.2: Comparison of XCT and $\mu$CT fabric degree of anisotropy (DA) for each method: parameters of a simple linear regression, and squared Pearson’s correlation coefficients of the predictions of the affine ($R^2_{\text{aff}}$) and the power ($R^2_{\text{pow}}$) models.

<table>
<thead>
<tr>
<th>Method</th>
<th>Slope</th>
<th>Intercept</th>
<th>$R^2$</th>
<th>$R^2_{\text{aff}}$</th>
<th>$R^2_{\text{pow}}$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIL (Ga,Opt)</td>
<td>1.115</td>
<td>0.031</td>
<td>0.701</td>
<td>0.705</td>
<td>0.701</td>
</tr>
<tr>
<td>MIL (LH,Opt)</td>
<td>1.079</td>
<td>0.031</td>
<td>0.672</td>
<td>0.681</td>
<td>0.673</td>
</tr>
<tr>
<td>MIL (LH,Fix)</td>
<td>0.928</td>
<td>0.291</td>
<td>0.578</td>
<td>0.592</td>
<td>0.579</td>
</tr>
<tr>
<td>ACF</td>
<td>0.830</td>
<td>0.643</td>
<td>0.377</td>
<td>0.377</td>
<td>0.371</td>
</tr>
<tr>
<td>SSOD</td>
<td>2.083</td>
<td>1.614</td>
<td>0.421</td>
<td>0.467</td>
<td>0.423</td>
</tr>
</tbody>
</table>

A rose plot of the angular deviations for $\mathbf{m}_3$ and $\mathbf{m}_1$ of the SSOD fabric tensor is depicted in Figure 4.5. The mean values and the standard deviations of the angular deviations are summarized in Table 4.3 for the three eigenvectors of each method. Note that, in case of the first and second eigenvectors, the angular deviations become arbitrary when the sample is transverse isotropic that is often the case for trabecular bone. Main emphasis should therefore be put on the analysis of the angular deviations of the major eigenvectors ($\mathbf{m}_3$).
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Figure 4.5: Angular deviations between fabric eigenvectors of XCT and µCT. Left: explanation of the measured angles. Right: values of the SSOD method; the distance from the origin (radial axis) is the angular deviation of the third (the major) eigenvectors (angle $\theta$) and the value plotted on the circular axis is the angular deviation of the first (the minor) eigenvectors (angle $\varphi$), both given in degrees.

Table 4.3: Angular deviations ($\Delta m_i$, $i = 1, 2, 3$) between XCT and µCT fabric eigenvectors for each of the methods, mean and standard deviation (SD) values given in degrees.

<table>
<thead>
<tr>
<th>Method</th>
<th>$\Delta m_1$ (degree)</th>
<th>$\Delta m_2$ (degree)</th>
<th>$\Delta m_3$ (degree)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>MIL (Ga,Opt)</td>
<td>7.09</td>
<td>7.62</td>
<td>7.71</td>
</tr>
<tr>
<td>MIL (LH,Opt)</td>
<td>7.78</td>
<td>9.00</td>
<td>9.13</td>
</tr>
<tr>
<td>MIL (LH,Fix)</td>
<td>10.92</td>
<td>13.82</td>
<td>12.85</td>
</tr>
<tr>
<td>ACF</td>
<td>15.27</td>
<td>14.96</td>
<td>15.81</td>
</tr>
<tr>
<td>SSOD</td>
<td>13.79</td>
<td>17.02</td>
<td>14.77</td>
</tr>
</tbody>
</table>

4.3.3 Computational performance of the different methods

Computation times of the different methods were measured on a standard PC (Athlon64 3500, 2.2 GHz, 2 GB RAM) using the µCT image (with $333^3$ voxels) and the XCT image (with $73^3$ voxels) of the same sample, having an average BV/TV value. In case of the larger dataset, CPU times were 62.0, 39.2 and 88.7 s for MIL, ACF and SSOD, respectively, while in case of the smaller image, 5.5, 3.5 and 0.9 s for the methods in the same order. The time needed for image thresholding for MIL was not included into these values. Memory requirements were analyzed for the µCT regions. In our implementation, memory usages
were comparable for MIL and SSOD (450 MB and 470 MB, respectively) and more than three times as much (1.7 GB) for ACF due to the FFT computations.

4.4 Discussion

In this study, we investigated the capabilities of the state of the art HR–pQCT technique in comparison with the gold standard \( \mu \)CT imaging to predict mineral content, volume fraction and fabric of trabecular bone in the human distal radius. The scanning procedure and positioning of the cadaveric arms in the XCT were performed according to the in vivo protocol. Length of the scanned region was different from the standard value but had no effect on the image quality. This way, the results of this study can be extended to the in vivo case.

4.4.1 BMD and BV/TV

The correlation of the BMD values was found to be very high, although XCT tended to underestimate bone mineral density compared to \( \mu \)CT. These differences most probably arose due to the partial volume effect, the different scanning setup, and geometrical and scattering differences of the two CT systems [36]. Based on the established relation, the presence of bubbles during the \( \mu \)CT scan of one specimen resulted in underestimation of BMD with a values between 4.5 and 56.5 \( HA \, mg/cm^3 \) (mean±SD: 26.3±17.4) (Figure 4.2). Exclusion of this sample from the analyses of the entire study was therefore necessary.

Segmented image–based BV/TV values were highly affected by the filtering and thresholding procedure. The threshold value determined from the grayscale histogram (‘optimal’) provided too high bone volume fraction values for XCT compared to \( \mu \)CT for both filter types. Usage of the Gaussian filter resulted in a consistent, more than two times overestimation of volume fraction. The LH filter produced two separated groups of data that corresponded to the two donors and therefore it was not appropriate for setting up a global relationship.

As a third possibility, the segmentation method of the standard patient protocol of the XCT software was investigated using the combination of the LH filter and a fixed global threshold value (‘fix’). This approach provided a direct multiplicative conversion between the BV/TV values of the two CT–s with a correlation close to 95%. These results are in a good accordance with the findings of Burghardt et al. [8] \( (BV/TV_{\mu CT} = 0.86 \times BV/TV_{XCT} - 8.0\% , \ R^2 = 0.97, \) using 11 trabecular bone biopsies extracted from human femoral heads) and even better with the results of MacNeil and Boyd [9] \( (BV/TV_{\mu CT} = 0.78 \times BV/TV_{XCT} + 0.3\% , \ R^2 = 0.70 \) for 9.02 mm thick human distal radius slices, using 38 \( \mu \)m resolution \( \mu \)CT images). Note that, in both studies, a global threshold value was used for the segmentation of the \( \mu \)CT images.

Prediction of volume fraction based on XCT density provided stronger correlation than any other segmentation method allowing us to conclude that BMD may be the
strongest predictor of BV/TV in in vivo applications. This supports its use in the patient protocol of the scanner. Still, volume fraction was underestimated by BV/TVd, which is again in a good correspondence with the results of [8] \((BV/TVd_{\mu CT} = 1.12 \times BV/TVd_{XCT} - 3.0\%, R^2 = 1.0\) for biopsies) and with [9] \((BV/TVd_{\mu CT} = 1.5 \times BV/TVd_{XCT} + 1.2\%, R^2 = 0.86\) for radius slices).

4.4.2 \(\mu\)CT and XCT MIL fabric

Among the investigated XCT thresholding approaches, the best prediction of the \(\mu\)CT MIL fabric could be obtained using the Gaussian filter with ‘optimal’ thresholding, despite the exaggerated volume fraction of this combination. The LH filter preserved the trabecular bone architecture qualitatively better than did the Gaussian but this advantage seemed to be lost when computing MIL fabric. The overall architecture and connectivity appeared to be well represented with the use of the Gaussian filter, even if loosing smaller details and overestimating size for the bigger patterns. These effects remained invisible for the method due to its nature. The ‘fix’ approach provided the weakest correlation and the largest deviation from the gold standard suggesting that this segmentation technique may not be the best one for fabric assessment.

We proposed two models for the description of the degradation that the 2nd order fabric tensor (with \(tr(M) = 3\) scaling) undergoes during resolution change of the input images, resulting in decreased extent of anisotropy when increasing the image voxel size. One of them, \(T_{aff}\) is linear and can be interpreted as the change in the ratio of the orthotropic and isotropic constituents of the tensor. The other one, \(T_{pow}\) is a power model relating the fabric tensors directly. Both models have a single parameter that represents the extent of degradation. These parameters were quantified for the given coarsening step and anatomical location. There were no significant differences found in their predictive capabilities. For DA, slightly higher correlation coefficients were found with the affine model. Additionally, the latter is easier to compute and hence might be more favorable when the eigenvalues are available, while the power model is still applicable even if the DA values are provided alone.

Linear regression relation of the \(\mu\)CT and the XCT ‘fix’ DA values was compared to the ones reported in [9] \((DA_{\mu CT} = 0.53 \times DA_{XCT} + 1.1, R^2 = 0.67\), [8] \((DA_{\mu CT} = 0.85 \times DA_{XCT} + 0.32, R^2 = 0.90)\) and in [10] \((DA_{\mu CT} = 0.91 \times DA_{XCT} + 0.41, R^2 = 0.93\). In agreement with these, \(\mu\)CT DA was found to be higher than XCT DA. Correlation of DA is relatively low as DA, being a ratio, amplifies the errors on the eigenvalues. However, \(R^2\) was considerably lower in this study compared to the above mentioned ones. The explanations of this might be differences in number and anatomical location of the samples and that both latter studies used trabecular bone biopsies which might increase the image quality of the XCT. Furthermore, DA was evaluated on the whole trabecular bone regions of 9.02 mm thick distal radius slices in [9] and degree anisotropy is averaging out and hence reducing if the analyzed region of a cellular material is much larger than the representative volume element. In contrast to these, 64 small cubical ROIs were analyzed in our work that were scanned in situ with the XCT.
4.4.3 Comparison of the grayscale fabric measures to MIL

For comparison with the two grayscale methods, results of MIL using Gaussian filtering and 'optimal' threshold were selected as reference. MIL provided the most accurate prediction of the eigenvalues and there was no clear preference between the two investigated grayscale-based approaches. Comparison of the DA values supported the outcomes of the eigenvalue-analysis. The affine model provided higher correlation coefficient than the simple linear regression for all methods, which verifies the proposed description.

When investigating the deviations of the eigenvectors, only smaller differences were found among the methods. MIL seemed to be the best in this perspective as well. Considering only the main eigenvectors ($\Delta m_3$), the mean error produced by SSOD, being the largest one, was still less than 5°. Errors of the two other directions were considerably higher for the grayscale approaches suggesting that these methods are less robust in a close to transverse isotropic case. Note, that – as mentioned above – the distinction of the two directions belonging to the similar eigenvalues becomes less important in such cases.

ACF was found to be less robust against resolution change in this work compared to what was reported in [33], most probably due to the fact that coarsening was simulated by a low-pass filter in that study which does not truly represent the real image degradation: although trabecular structures were blurred, the voxel sizes remained the same.

Computation speed is critical for applications and was compared for our implementations of the three methods. In case of the small (XCT) regions, SSOD was the fastest, nevertheless, it was 1.5 times slower than MIL and more than twice as slow than ACF when processing the larger data. For the $\mu$CT regions, ACF needed the least time to provide results, although the memory requirement was substantially higher compared to the other approaches.

4.4.4 Limitations

Limitations of this study need to be discussed. First of all, the cadaveric arms were embalmed. Exposure to formalin might result in lowered bone-marrow contrast [11] and therefore influence the thresholding procedure. Another limitation is that only four specimens from three donors were used and with the exclusion of one specimen due to air bubbles on the $\mu$CT image this was reduced to three arms from two donors. Nevertheless, a total of 64 regions of interest were analyzed. The confidence intervals of the regression parameters showed that there were no significant effects of the donors for BMD and BV/TVd but some significant effects for MIL fabric that may be attributed to the distinct trabecular architecture between the male and female donor.

4.4.5 Conclusions

This study showed that BMD, volume fraction and fabric of trabecular bone can be predicted with an adequate accuracy using HR-pQCT images and the correct post-processing steps.
Nevertheless, all quantities had to be converted to match values of the gold standard \( \mu \text{CT} \) technique. Conversion rules of these parameters were identified between XCT and \( \mu \text{CT} \) images of the human distal radius. According to our findings, the BMD–based BV/TVd provided the best prediction of volume fraction, but underestimated the values of the gold standard. Predictions based on XCT volume fraction, like the morphology–mechanical property relationships presented in [16, 37], would therefore underestimate bone stiffness and strength. This would lead to overestimation of fracture risk in the finite element models using these relationships if no corrections are applied. In terms of MIL fabric, the closest prediction was achieved by applying a Gaussian filter and using the grayscale histogram–based ('optimal') threshold value for the XCT images, superceding the performance of the default procedure ('fix') of the scanner. Nevertheless, the 'optimal' segmentation would most probably result in false Tb.N values. Even if there is no need to threshold the input images for the grayscale image–based methods, which means one less source of errors, the widespread MIL method was found to be less sensitive to the image quality loss of the XCT resolution. Errors of the prediction of the directionality, although being relatively small, cannot be properly accounted for. XCT eigenvalues needed to be transformed to match the \( \mu \text{CT} \) results, underestimation of DA would result in lower contrast of the orthogonal mechanical properties.

In terms of efficiency, SSOD performed best among the three methods on smaller image volumes belonging to the XCT resolution. This can be preferential in applications like the finite element method with a homogenization scheme [14] on \textit{in vivo} HR–pQCT datasets where there is a need to quantify individual fabric for a large number of small regions. The actual goal of this FEM approach is to predict the homogenized mechanical behavior of trabecular bone regions from the CT images, which is not identical to predicting fabric and there might be better predictors of mechanics than MIL. Investigation of this question is the subject of a further study.

Acknowledgments

The authors would like to thank Mrs Maiko Matsuura and Prof. Reinhard Putz for providing the cadaver arms. We acknowledge Dr. Dieter Pahr for the implementation of the MIL method.

Appendix

Two models were proposed to describe the transformation \( T : M \rightarrow \tilde{M} \) that the second order fabric tensor suffers due to the resolution and quality change of the input images, while assuming its directionality and scaling unchanged (\( MM = \tilde{M}M, trM = tr\tilde{M} = 3 \)). The first model defined an affine transformation \( T_{aff} \):

\[
\mu^{CT}M = \alpha^{XCT}M + \beta I = \alpha^{XCT}(M - I) + (\alpha + \beta)I = \alpha^{XCT}(M - I) + I.
\]
In this equation, $\alpha + \beta = 1$ had to be fulfilled in order to preserve the trace of the tensor. $T$ therefore scales the anisotropic part of the fabric tensor while leaving the isotropic part unaffected. The parameter $\alpha$ is the measure of this scaling, in extreme case $\alpha = 0$ would lead to isotropy and $\alpha = 1$ would mean identity of the two tensors.

In the second model, the two fabric tensors were related using a power function, defining a different transformation, $T_{pow}$:

$$\mu^{CT}M = \delta^{X^{CT}M^\gamma} = \frac{3}{tr(X^{CT}M^\gamma)} X^{CT}M^\gamma$$

Here, $\delta$ was derived again from the constraint of scaling ($trM = 3$). This relation would yield to $\delta = 1$ and $\gamma = 1$ in perfect fit of the two tensors. Isotropy, as an extreme case can also be achieved with $\delta = 1$ and $\gamma = 0$.

**Bibliography**


Chapter 5

Validation of an HR–pQCT–based homogenized finite element approach using mechanical testing of ultra–distal radius sections

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Manuscript in preparation for submission.

Abstract

Osteoporotic fractures of the distal radius, majority of which are of the Colles’ type, occur relatively early in lifetime and could predict risk of fracture of other, more endangered anatomical sites. HR–pQCT–based \(\mu FE\) analysis was shown to better predict fracture load of the distal radius than the gold standard DXA or morphological measures. As an alternative to \(\mu FE\), homogenization–based FE (hFE) approach may provide at least equivalent predictive power with reduced computational needs. The aim of this study was to validate the hFE approach with compression tests of twenty–five distal radius sections extracted at
the location which is relevant in Colles’ fractures. An experimental setup was designed to perform compression tests with allowing rotations by means of a ball joint and to measure machine–compliance–free displacements. A calibration sub–study of the parameters relevant for the hFE modeling was performed to evaluate the inaccuracies arose due to the limitations of the HR–pQCT imaging with respect to μCT. HR–pQCT–based hFE models of the distal radius slices were then built and their ability to predict experimental stiffness and strength was compared to those of the density–based parameters, morphological indices and μFE models assessed from the same input images. BMC was found to be the best predictor ($R^2=0.86$) of bone strength among the density–based and micro–architectural measures. The both FE methods were not only the strongest predictors of fracture load, but provided quantitatively correct values. With the correction factors identified in the calibration sub–study, the hFE approach provided closely as strong predictions of ultimate force ($R^2=0.94$) than μFE ($R^2=0.95$), although was computationally cheaper. The results of this validation study suggest that FE simulation can be used as an efficient and precise tool to predict Colles’ fracture load.

**Keywords:** distal radius, Colles’ fracture, HR–pQCT, finite element, homogenization

### 5.1 Introduction

Osteoporosis is a skeletal disease leading to increased fragility due to bone mass loss and micro–architectural degradation. Non–invasive assessment of fracture risk becomes therefore of increasing interest. The clinical prediction of fracture risk relies currently on projected areal bone mineral density (aBMD) quantified using densitometry (dual X–ray absorptiometry, DXA) [1]. aBMD is taken as a surrogate measure for bone strength and was reported to be limited in predicting risk of osteoporotic fractures [2, 3]. Distal radius fractures, which are predominantly of Colles’ type, are among the three most common osteoporotic fractures [4]. Occurring earlier in lifetime than hip and vertebral fractures, they could be used as a warning sign for increased fracture risk at other sites [5].

The emergence of High Resolution peripheral Quantitative Computed Tomography (HR–pQCT) allows detailed analysis of the bony microstructure of the distal radius in vivo [6]. In the past years, HR–pQCT–based, anatomy–specific micro finite element (μFE) analysis has undergone substantial progress and became the gold standard in predicting Colles’ fracture load as well as failure load of various radial slices [7, 8, 9, 6, 10]. μFE models have been proven to provide increased prediction of bone strength and risk of fracture compared to DXA and morphological indices [7, 11, 6]. A previous study already showed that μFE analysis can predict mechanical properties of radius slices [9]. However, this study was not restricted to the region where Colles’ fracture typically occur. The distance between the radial styloid and the fracture localization was found by Spadaro et al. to vary between 13
 CHAPTER 5. VALIDATION OF HFE AND µFE WITH RADIUS SLICES

and 24 mm [12], other studies reported 22 ± 4 mm [13] and 28 ± 6.1 mm [14] for the same quantity. With radial height ranging from 10 to 13 mm [15], the zone where the occurrence of Colles’ fracture is expected starts right proximal to the distal subchondral plate of the radius and extends 20–25 mm proximally.

µFE models of bones or bone sections are usually restricted to linear analyses providing essentially stiffness [16, 9, 17]. A recently developed surface–based homogenized FE approach (hFE) is using a homogenization scheme including volume fraction and architectural anisotropy information (fabric) of trabecular bone, based on high resolution CT images [18, 19, 20]. It allows for nonlinear analyses including plasticity and damage using moderate resources within reasonable computation time. As previously shown in Chapter Two, results of the hFE method were strongly correlated with experimental results of a Colles’ fracture model. Although, the exact values could not be well predicted, especially for apparent stiffness, which was consistently overestimated. These deviations were most probably caused on the one hand by the limited resolution of HR–pQCT (∼ 100 µm), which did not allow for detailed reconstruction of the trabecular micro-architecture and the thin cortical regions [21], and on the other hand by image noise affecting the measurement of mineral density. More specifically, Chapter Four showed that, HR–pQCT, in comparison with the gold standard µCT, does not provide exact values of the two input parameters of the homogenization scheme, volume fraction and fabric, which therefore require calibration and conversion. However, it was not demonstrated, if the correction of these inaccuracies improves the performance of the hFE models.

Taking all these factors into consideration, the aim of this study was to validate the alternative, continuum level hFE approach with mechanical tests of human ultra distal radius slices extracted from the typical location of Colles’ fracture. In order to accomplish this, the specific goals were to (1) design and perform experiments with well–defined boundary conditions which provide good approximations of the in vivo conditions of the fall case and can be easily modeled using FE; (2) identify the calibration laws for the HR–pQCT quantities of volume fraction, fabric as well as cortical thickness for the in vitro case and implement these into the hFE models; (3) compare the ability of the corrected hFE models to predict experimental stiffness and strength with the density–based and micro–architectural parameters; and finally (4) compare the calibrated hFE approach with the µFE method.

5.2 Materials and methods

5.2.1 Sample preparation

Fourteen pairs of fresh frozen cadaveric radii were received from the Department of Applied Anatomy, Medical University of Vienna, Austria. All procedures were performed in full agreement with the ethical regulations of the Medical University of Vienna. Donors were ten females and four males with mean age of 81.2 ± 13.7 years (min/max: 59/97ys). The bones were stored frozen at -20°C until further manipulations and in between the steps of the experiment. Following cleaning from soft tissues, 20.5 mm thick sections of the radii were
cut proximal to the distal subchondral plate (diamond bandsaw, 300 CP, Exakt Gmbh, Germany). Both cut surfaces of the specimens were polished using a 500 particles/inch sandpaper (PM5, Logitech Ltd, Scotland) to obtain parallel plane surfaces. Sample height was measured at least at four locations around the cortical perimeter using a digital caliper and the polishing procedure was repeated until the intra-specimen differences in height became smaller than 0.05 mm. Final height varied between 19.03 and 20.17 mm with 19.87±0.23 mm on average.

5.2.2 HR–pQCT scanning

The specimens were submerged in 0.9% saline solution and exposed to vacuum for fifteen minutes in order to remove air bubbles. The bone sections were then scanned with HR–pQCT (XtremeCT, Scanco Medical AG, Switzerland) in 0.9% saline solution using a custom made waterproof Plexiglas chamber. A special fixation system was used to ensure parallel alignment of the cut planes of the bone sections and the CT slices within the chamber (Figure 5.1). Scanning setting were 60 kVp energy, 1 mA current, 100 ms integration time, 1536x1536 pixels image matrix and 82 µm isotropic voxel size. Length of the scanned region was slightly larger than the height of the specimens to avoid data loss. Slight misalignment between the sample cut planes and the scanning slices were corrected by rotating the 3D images with visually evaluated angles using the software tools of the XtremeCT (IPL). The images were then cropped to remove the remaining inaccuracies of the cut plane boarders. Difference between the physical height of the specimens and the corresponding dimension of the images was 0.123±0.050 mm on average (min. 0.048 mm, max. 0.224 mm). Figure 5.2 shows the photograph and the 3D HR–pQCT reconstruction of a specimen.
5.2.3 Morphological analysis

Cortical and trabecular bone compartments of the HR–pQCT images were separated using a 3D fill algorithm [18]. Morphological indices were computed according to the standard patient evaluation procedure of the XtremeCT (XCT) using the inbuilt software tools (IPL). Mean cross sectional area (A), apparent volumetric bone mineral density (vBMD) and bone mineral content (BMC) were quantified for both compartments separately and for the full volume as well. DXA-like areal bone mineral density (aBMD) was evaluated by projecting the 3D images into the plane along the dorsal-palmar axis and dividing BMC by the projected area. This approach was shown to provide aBMD of 9 mm thick radius sections which is highly correlated with conventional radial DXA measurements [22]. The default XCT evaluation protocol was used to quantify standard density–based and morphological indices [23]. Trabecular bone volume fraction (BV/TVd) was estimated from the vBMD values by assuming vBMD of fully mineralized tissue to be 1200 HA mg/cm$^3$. The images were then segmented with a combination of a Laplace-Hamming (LH) filter and a fixed global threshold value (40% of the maximal grayscale intensity). Trabecular number (Tb.N) was measured directly with a ridge extraction algorithm. Due to the limited resolution, trabecular thickness (Tb.Th) and separation (Tb.Sp) were computed from BV/TVd and Tb.N using the plate assumption. Average cortical thickness (Ct.Th) was estimated as the ratio of the cortical volume and the mean of the inner and outer cortical surfaces.

5.2.4 Mechanical testing

Prior to experimental testing, wet condition of the specimens was ensured by submerging them into 0.9% saline solution for at least one hour. Displacement controlled compression tests of the bone sections were performed using a hydraulic loading system (MiniBionix 858, MTS System Corp., USA). Rotation of the upper loading plate was allowed by means of
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Figure 5.3: Left: alignment of the anatomical planes of the specimen with the LVDTs and the center of mass with the loading axis using sample–specific printouts. Right: experimental setup of the compression test.

a ball joint (Figure 5.3, left). Sideways slip of the specimens was inhibited by sandblasted metal contact surfaces of the loading device, providing high friction contact. Center of mass of the distal 4% part of each specimen was calculated using the HR–pQCT images and was carefully matched with the vertical axis of the ball joint before loading (Figure 5.3, right). The experiments were performed with a quasi-static displacement rate of 5 mm/min [24, 25]. Loading protocol consisted of 10 preconditioning cycles with 0.08 mm displacement to enhance the contact between the loading plates and the specimen, as well as a monotonic loading up to large deformation. Force was measured using a 100 kN load cell (U3, HBM, Germany). Displacement was recorded with the actuator of the MTS and, concurrently, with three linear displacement sensors (linear variable differential transformers, LVDTs, WA20, HBM) positioned around the specimen in a circle having a diameter of 135 mm and distributed equally around the perimeter in 120$^\circ$ divisions. The use of this independent measurement ensured direct, machine–compliance–free quantification of the displacement and allowed assessment of the inclination of the upper plate during loading. The resulting force–displacement curve was then analyzed. Stiffness was measured as the highest slope of the quasi–linear part of the curve following the initial toe–region, ultimate force was defined as the peak value of the curve. Rotation of the upper loading plate was calculated using the displacements recorded by the three LVDTs. As the position of the specimen was standardized with respect to the peripheral LVDTs (Figure 5.3, right), the total inclination could be decomposed into two rotation components corresponding to the anatomical dorsal–palmar and radial–ulnar deviations.

5.2.5 $\mu$FE modeling

$\mu$FE models of the radius slices were built using the same segmented HR–pQCT images that were used to quantify morphology by converting all image voxels corresponding to bone into linear hexahedral elements. Isolated regions of the images, i.e. floating bodies
were removed with a cleaning procedure. Number of elements varied between 2.05 and 6.34 millions and was 3.81 ± 1.19 millions on average. Isotropic, linear elastic material properties with Young’s modulus of 15.0 GPa and Poisson’s ratio of 0.3 were assigned to each element of both the cortical and trabecular compartments [26]. Boundary conditions were set in accordance with the high friction compression test: displacements of the lower cut surface was constrained in all spatial directions, nodes of the upper plane were fixed in–plane and displaced in axial direction. Rotation of the upper plate was neglected in the simulations as it was found to be < 1° in the experimental result (see later). Figure 5.4 depicts the μFE model with the applied boundary conditions. Linear analyses of the models were performed with an open source large scale element–by–element solver (ParFE, [17]) using a computer with 2x2 3.0 GHz Xeon processors and 32 GB RAM. Apparent stiffness was evaluated as the ratio of the resulting force and the imposed displacement. Fracture load was estimated using the effective tissue strain–based approach of Pistoia et al. [7], by scaling the results linearly until the effective tissue strain was higher than 7000 μstrains in 2% of the elements. Elastic strain energy (ESE) of the cortical and trabecular regions was calculated to evaluate the mechanical contributions of the two compartments.

5.2.6 Calibration sub–study for the hFE modeling

A sub–study was conducted aiming to provide calibration laws for the preparation of the HR–pQCT–based hFE models. Two main issues were investigated (see Figure 5.5): (1) assessment of homogenized elastic properties of trabecular bone using the XCT images and (2) quantification of the error in cortical thickness measurement of XCT. Part (1) consisted of two sub–parts: (1A) identification of the relation between the XCT–based and the gold standard (μCT) quantities, volume fraction and fabric, required for the homogenization–approach [27, 28]; and (1B) assessment of the homogenized elastic engineering constants. The methods applied in part (1a) were similar to those used in Chapter Four, where these calibration laws were identified in a close to in vivo configuration. The different scanning protocol applied in the present work necessitated re–evaluation of these relationships.
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For the purposes of this sub–study, 6 cadaveric arms were received from the Medical University of Vienna (three left and three right, exact age and gender unknown but similar to those of the main study). The radii were dissected from the forearms. The samples were then cleaned, cut, polished and scanned with HR–pQCT following the protocol described above. The bone sections were then submerged into 0.9% saline solution, and, after removal of air bubbles using vacuum, scanned with µCT (µCT40, Scanco Medical AG, Switzerland) using the settings of 70 kVp, 114mA, 200ms integration time, 2048x2048 pixels image matrix and 18 µm isotropic spatial resolution. It was necessary to slightly crop the cortex of two specimens in order to fit the inner diameter of the sample holder (35 mm). The corresponding XCT and µCT image pairs were then registered using 3D rigid image registration (ITK, Kitware Inc., USA).

Calibration of volume fraction and fabric (1A)

Small cubical trabecular bone Regions Of Interest (ROIs) of $5.33^3$ mm$^3$ size were cropped from corresponding locations of the XCT and µCT images. Volume rendering of the µCT and XCT images of an arbitrarily selected ROI example are shown on Figure 5.6. Eighty–one regions were obtained in total with volume fraction ranging from 9.46% up to 28.15% (mean and SD: 16.45 ± 3.89). The two input parameters of the homogenization approach, volume fraction and fabric, were quantified for the ROIs of both image modalities using the methods described in Chapter Four. A grayscale histogram–based (optimal) thresholding procedure was used to segment the µCT images [29]. XCT volume fraction was on the one hand assessed from vBMD (BV/TVd), and on the other hand was computed from the LH filtered and segmented images (see Subsection 5.2.3). Fabric was evaluated using three methods: Mean Intercept Length (MIL), Star Length Distribution (SLD) [30], which - similarly to MIL - is a segmented image–based method, as well as Sampling Sphere Orientation Distribution (SSOD) that is using the grayscale image information and was introduced in Chapter Three.
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Figure 5.6: $\mu$CT (left) and XCT (right) images of a typical cubical region of interest used in part (1) of the calibration sub–study.

Calibration laws between XCT volume fraction and $\mu$CT BV/TV, as well as between XCT fabric and $\mu$CT fabric were established in this sub–study. In agreement with the findings of Chapter Four, BV/TVd provided better prediction of $\mu$CT BV/TV than the segmented image–based volume fraction (see later in the Results section). Hence, BV/TVd of the XCT images were used in the homogenization step of the hFE model generation.

**Morphology–elasticity relationship (1B)**

The stiffness tensors of the 81 ROIs were computed with virtual mechanical tests [31]. Micro finite element ($\mu$FE) models of the bone cubes were built from the $\mu$CT images using the methods described above (Section 5.2.5). The images of the ROIs needed to be resampled from the original 18 $\mu$m to 27 $\mu$m voxel size in order to fit the available computing resources (2x2 3.0 GHz Xeon processors and 64 GB RAM). Resampling was performed on the original grayscale images which were then segmented using the grayscale histogram–based thresholding procedure [29]. Linear isotropic material properties were used with Young’s modulus of 15 GPa and Poisson’s ratio of 0.3. Six linear analyses, three compression and three shear load cases were performed in case of each specimen to assess the anisotropic stiffness tensor (Abaqus 6.6, SIMULIA, USA). Homogeneous displacement (kinematic uniform) boundary conditions (KUBC) were used as these were shown to provide similar mechanical response as the in situ conditions of trabecular bone [32, 19]. The elastic orthotropic engineering constants of the constitutive law based on volume fraction and fabric are the following [27]:

$$E_i = E_0 \rho^k m_i^{2l}$$  \hspace{1cm} (5.1)
are the Young’s moduli,
\[ \nu_{ij} = \nu_0 \frac{m_i}{m_j} \]  
(5.2)

are the Poisson’s ratios and
\[ G_{ij} = G_0 \rho^k \pi^l m_i m_j \]  
(5.3)

are the shear moduli in the three principal direction \((i, j = 1, 2, 3)\). Here, the parameters \(\rho\) and \(m_i\) are volume fraction and fabric eigenvalues, respectively, which can be quantified using the CT images. The constants of the law are \(E_0\), \(\nu_0\) and \(G_0\), which are properties of an idealized poreless solid, while \(k\) and \(l\) are power coefficients. Multiple regression analysis \([28]\) was used to evaluate these constants using the above assessed, \(\mu\)CT–based BV/TV and fabric as well as the \(\mu\)FE results of the ROIs. \(E_0\) was enforced in this computation to be equivalent to the input Young’s modulus of the tissue (15 GPa). Logarithm of the spectral decomposition of the stiffness tensor was used to compute the least square fit \([19]\) which ensured that the relation was valid for both stiffness and compliance. Absolute angular deviations were measured between the corresponding eigenvectors of the second order fabric tensor and the orthotropic stiffness tensor to evaluate how well the directionality of the mechanical properties was predicted by the orientations of the architectural anisotropy.

The multiple regression and the angular deviations were computed using MIL, SLD and SSOD, in order to evaluate which of the three fabric measures investigated here provides the closest prediction of stiffness. The same set of volume fractions was used for the repeated evaluations and second order tensorial approximations of all fabric measures were taken. As MIL was found to be the closest predictor of stiffness (see in more details in the Results section), it was selected as the fabric measure to be used in the hFE models.

**Cortical thickness correction (2)**

Cortical thickness (Ct.Th) values measured on the HR–pQCT images were compared to the ones identified on the \(\mu\)CT images using the four specimens for which the cortex remained intact during scanning. Triangular mesh of the cortical–trabecular boarder surface was generated and Ct.Th was measured at the nodes of this mesh along the nodal normals, using the voxel–based thickness maps of the CT images extracted with a fill algorithm \([18]\). Nodes of the top and bottom cut planes of the specimens, providing invalid lengths, were not included into the analysis. Measurements of \(N = 2214\) corresponding locations were used to evaluate the conversion rule between the Ct.Th values of the two imaging systems.

**5.2.7 hFE modeling**

Smooth surface–based continuum (homogenized) finite element models of the specimens were built from the HR–pQCT images using the approach described in \([19]\). Steps of the hFE model generation are shown in Figure 5.7. First, bone compartments were distinguished during meshing, cortical region was discretized with pentahedral, trabecular region
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Figure 5.7: Details of the hFE model generation: separation of cortical (A) and trabecular (B) compartments; geometrical meshing (C, with a subvolume masked in order to show the elements); mapping material properties based on the underlying HR-pQCT image (D, part of the model is shown with an HR-pQCT slice showing BMD); assignment of volume fraction (E) and anisotropy (F, with distribution of the maximal Young's modulus shown) to the elements of the trabecular bone phase; and applying boundary conditions (G).
with tetrahedral elements (Figure 5.7A,B). Thicknesses of the cortical elements were adjusted according to the calibration law identified in the sub-study. Approximate element size was 1.3 mm, the meshes included 9818 ± 2057 quadratic elements on average (min: 5981, max: 14292).

Density (Figure 5.7E) and MIL fabric (Figure 5.7F) were then assessed and used for the evaluation of the homogenized orthotropic material properties of the tetrahedral elements of trabecular bone. Elastic constants of the calibration sub-study were used. Non-elastic material behavior of trabecular bone was described using a constitutive law including plasticity and damage [33]. Having the set of elastic constants newly identified in the sub-study, material constants of this constitutive laws were adjusted to fit previous experimental results of human trabecular bone biopsies [34]. Cortical bone was modeled as a homogeneous, poreless, transversely isotropic material with the major axis corresponding to the longitudinal direction of the bone while radial and circumferential properties were assumed to be the same. Material properties were taken from nanoindentation results [26]. Degree of material anisotropy was approximated to be 1.393, using multi-directional nanoindentation data of human vertebral cortical bone [35]. Local coordinate system of the cortical elements (pentahedrons) were identified and used as the material orientations: normals of the outer surface triangles were taken as the radial, and the vertical (z) orientation of the model as the longitudinal material direction.

Boundary conditions, similarly to those of the µFE models, were set to approximate the experimental conditions: the bottom plane was fully constrained and axial compressive displacement corresponding to 1.6% strain was applied on the nodes of the top cut surface with their movement constrained in the transverse plane (Figure 5.7G). Nonlinear finite element analyses of the axial compression tests were performed (Abaqus 6.6, SIMULIA, USA). Computations were performed using the same computer architecture as in case of the µFE models.

Apparent stiffness was defined as the initial slope, apparent strength as the peak of the resulting force-displacement curve. Mechanical significances of cortical and trabecular bone phases were evaluated by calculating percentages of the elastic strain energy absorbed by the elements of the cortical (Ct.ESE), respectively trabecular (Tb.ESE) bone compartments, at the linear stage of loading (0.16% strain).

### 5.2.8 Statistics

Squared Pearson’s correlation coefficients between the morphological parameters and the experimentally measured stiffness and strength were calculated. Linear regression analyses were performed between the results of both FE methods and the experimental test results to evaluate the predictive power of the two numerical approaches, with respect to stiffness and strength, respectively. Results of the two FE methods were compared to each other with linear regressions. Fisher’s Z-transformation was used to detect significance of the difference between the power of the geometrical, density-based and FE results to predict
Figure 5.8: Results of the mechanical tests for an arbitrarily selected specimen. Left: force-displacement curves measured with the LVDTs and with the MTS crosshead, with definitions of stiffness ($K_{\text{exp}}$) and ultimate force ($F_{U}^{\text{exp}}$). Right: inclinations of the upper loading plate assessed with the LVDTs, transformed into the dorsal–palmar ($\alpha_x$) and radial–ulnar ($\alpha_y$) planes, red line with * indicates the timepoint when the ultimate force was reached.

5.3 Results

Two out of the twenty-eight specimens had to be excluded from the study during sample preparation due to pathological deformities.

5.3.1 Experimental tests

Each of the twenty-six samples were successfully tested mechanically. Figure 5.8 shows a typical force–displacement curve and the rotation of the upper loading plate. Failure force was reached in dorsal inclination with rotation angle smaller than one degree for all specimens and the dorsal rotation was preserved in the high deformation range in twenty-four cases.

Concurrent recording of the displacements with the sensor of the MTS at the crosshead and the LVDTs allowed for comparison, which was performed using the evaluated apparent stiffnesses and presented in the left side of Figure 5.9. The two systems provided highly correlated, but considerably different results. Measures provided by the LVDTs, being machine–compliance–free, were taken as the exact values and used later on. Corre-
Figure 5.9: Analysis of the mechanical results. Left: comparison of the apparent stiffnesses measured with the LVDTs and with the MTS crosshead. Right: linear regression plot of the experimental (LVDT) stiffness and strength. The outlier is marked with ⊥, the equation is shown for the analyses including (w) and excluding (w/o) this specimen. The regression line is depicted for the w/o case.

A correlation of $R^2 = 0.872$ was found between experimental (LVDT) stiffness and strength. One specimen was found to be an outlier using Q-Test (95% confidence level). By excluding the outlier, the correlation coefficient increased to $R^2 = 0.911$ (see Figure 5.9, right). This specimen was excluded from all further parts of the study, which were therefore conducted with twenty-five samples. Experimental spring stiffnesses varied between 6839 N/mm and 42491 N/mm with a mean and standard deviation of 23490.3 ± 9620.5 N/mm, ultimate forces ranged from 948.0 N up to 4704.0 N and were 2792.4 ± 1111.2 N on average.

5.3.2 Morphological parameters

Table 5.1 summarizes the mean values and standard deviations of the morphology analysis results and their correlation coefficients with experimental stiffness and strength.
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Table 5.1: Means and standard deviations of the HR–pQCT measures as well as the squared Pearson’s correlation coefficients with experimental stiffness and strength. Bold numbers indicate high coefficients of determination \((R^2 > 0.7)\). Significances: *: \( p < 0.05 \), **: \( p < 0.01 \), ***: \( p < 0.001 \), ****: \( p < 0.0001 \).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>( R^2(M_{\text{exp}}) )</th>
<th>( R^2(M_{\text{U}}) )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_{\text{tot}} ) (cm(^3))</td>
<td>6.841 ± 1.515</td>
<td>0.305**</td>
<td>0.436***</td>
</tr>
<tr>
<td>( V_{\text{trab}} ) (cm(^3))</td>
<td>5.864 ± 1.457</td>
<td>0.177*</td>
<td>0.295**</td>
</tr>
<tr>
<td>( V_{\text{cort}} ) (cm(^3))</td>
<td>0.995 ± 0.254</td>
<td><strong>0.783</strong>*</td>
<td>0.682***</td>
</tr>
<tr>
<td>( A_{\text{tot}} ) (mm(^2))</td>
<td>345.6 ± 75.3</td>
<td>0.288**</td>
<td>0.410***</td>
</tr>
<tr>
<td>( A_{\text{trab}} ) (mm(^2))</td>
<td>295.3 ± 72.9</td>
<td>0.162*</td>
<td>0.270**</td>
</tr>
<tr>
<td>( A_{\text{cort}} ) (mm(^2))</td>
<td>50.2 ± 12.6</td>
<td><strong>0.777</strong>*</td>
<td>0.665***</td>
</tr>
<tr>
<td>( \text{BMC}_{\text{tot}} ) (HA mg)</td>
<td>1230.9 ± 440.5</td>
<td>0.930***</td>
<td>0.862***</td>
</tr>
<tr>
<td>( \text{BMC}_{\text{trab}} ) (HA mg)</td>
<td>587.8 ± 259.1</td>
<td><strong>0.730</strong>*</td>
<td>0.757***</td>
</tr>
<tr>
<td>( \text{BMC}_{\text{cort}} ) (HA mg)</td>
<td>643.1 ± 231.8</td>
<td><strong>0.771</strong>*</td>
<td>0.638***</td>
</tr>
<tr>
<td>( \text{aBMD} ) (HA g/cm(^2))</td>
<td>0.254 ± 0.07</td>
<td><strong>0.864</strong>*</td>
<td>0.735***</td>
</tr>
<tr>
<td>( \text{vBMD}_{\text{tot}} ) (HA mg/cm(^3))</td>
<td>181.6 ± 55.9</td>
<td>0.487***</td>
<td>0.315**</td>
</tr>
<tr>
<td>( \text{vBMD}_{\text{trab}} ) (HA mg/cm(^3))</td>
<td>99.7 ± 32.4</td>
<td>0.634***</td>
<td>0.484***</td>
</tr>
<tr>
<td>( \text{vBMD}_{\text{cort}} ) (HA mg/cm(^3))</td>
<td>630.7 ± 87.8</td>
<td>0.485***</td>
<td>0.380**</td>
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<tr>
<td>( \text{BV/Tvd} ) (%)</td>
<td>8.31 ± 2.70</td>
<td>0.634***</td>
<td>0.484***</td>
</tr>
<tr>
<td>( \text{Tb.N} ) (mm(^{-1}))</td>
<td>2.64 ± 0.07</td>
<td><strong>0.773</strong>*</td>
<td>0.633***</td>
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<tr>
<td>( \text{Tb.Th} ) (( \mu )m)</td>
<td>31.2 ± 9.4</td>
<td><strong>0.607</strong>*</td>
<td>0.463***</td>
</tr>
<tr>
<td>( \text{Tb.Sp} ) (( \mu )m)</td>
<td>347.1 ± 19.0</td>
<td><strong>0.740</strong>*</td>
<td>0.588***</td>
</tr>
<tr>
<td>( \text{Ct.Th} ) (( \mu )m)</td>
<td>394.6 ± 90.4</td>
<td>0.374**</td>
<td>0.266**</td>
</tr>
</tbody>
</table>

5.3.3 \( \mu \)FE analysis

CPU times of the \( \mu \)FE analyses ranged from 74.4 to 190.4 min with 125.2 ± 30.8 min on average, although parallel computation was used which reduced the real (wallclock) solution time. Required memory varied between \( \sim \)10 GB and \( \sim \)27 GB, approximately. Table 5.6 presents the means and standard deviations of the \( \mu \)FE results as well as their correlations with the experimental values. Linear regressions between the corresponding measures of the \( \mu \)FE models and the mechanical tests are shown in Figure 5.10 for stiffness and strength.

5.3.4 Results of the calibration study

The relations identified between XCT BV/TV assessed with the two approaches (BV/Tvd and LH–segmented) and \( \mu \)CT BV/TV are shown in Figure 5.11, left. Linear regression between the XCT and \( \mu \)CT MIL fabric eigenvalues is depicted on the right side of Figure 5.11. The slopes of the linear regressions were 1.75, 1.76 and 1.58, while correlation coefficients \((R^2)\) were 0.936, 0.958 and 0.963 for MIL, SLD and SSOD respectively. The angular devi-
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Figure 5.10: Comparison of the experimental and the $\mu$FE results linear regression analyses. Left: apparent stiffness, right: ultimate force.

Figure 5.11: Calibration curves (linear regression lines) identified between the XCT and $\mu$CT quantities of the parameters used in the homogenization approach. Left: BMD–based (BV/TVd) and segmented image–based (LH) BV/TV of XCT vs. $\mu$CT BV/TV, right: eigenvalues of the second order MIL fabric tensor compared between the two image modalities.
Figure 5.12: Cubical trabecular bone sample with the corresponding fabric and stiffness. Surface plots of the second order fabric tensors of all the three measures (MIL, SLD and SSOD), and the original anisotropic and the approximated orthotropic fourth order stiffness tensors are shown.

Angular deviations measured between the corresponding fabric eigenvectors of the HR–pQCT and the µCT images are summarized in Table 5.2, for all three investigated fabric measures.

Table 5.2: Angular deviations between the corresponding HR–pQCT and µCT fabric eigenvectors, evaluated for the three fabric measures, MIL, SLD and SSOD. Mean and standard deviation (SD) values are given in degrees.

<table>
<thead>
<tr>
<th>Method</th>
<th>$\Delta e_1$ (degree)</th>
<th>$\Delta e_2$ (degree)</th>
<th>$\Delta e_3$ (degree)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>MIL</td>
<td>10.75</td>
<td>13.92</td>
<td>13.95</td>
</tr>
<tr>
<td>SLD</td>
<td>9.08</td>
<td>13.77</td>
<td>11.31</td>
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<tr>
<td>SSOD</td>
<td>12.09</td>
<td>14.89</td>
<td>14.87</td>
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</tbody>
</table>

Figure 5.12 depicts a cubical ROI together with the corresponding fabric and stiffness tensors. The result of the multiple regression analysis between volume fraction, fabric and the µFE stiffness tensors is depicted in Figure 5.13 for the case of MIL. The identified elastic engineering constants of the constitutive law of the homogenization approach and the correlation coefficients are summarized in Table 5.3 for all three fabric measures. Table 5.4 presents the angular deviations between the corresponding eigenvectors of the orthotropic stiffness tensors and the second order tensors of the three fabric measures. Angular deviations of the three methods were comparable in the main (third) directions, while MIL provided the highest correlation with the stiffness tensor and therefore it was selected to be used in the hFE models. The constants of the yield and damage criteria of the constitutive law, re–evaluated from the experimental results of [34] using the MIL–based elastic constants of Table 5.3, are presented in Table 5.5.
Figure 5.13: Result of the multiple regression analysis of the homogenization-based material model, using MIL as fabric measure. The components of the stiffness tensor corresponding to Young’s modulus, shear modulus and Poisson’s ratio are shown.

Table 5.3: Elastic engineering constants of the homogenization-based constitutive law and coefficient of determination of the multiple regression analysis, evaluated for the three fabric measures, MIL, SLD and SSOD.

<table>
<thead>
<tr>
<th>Method</th>
<th>$\epsilon_0$ (fixed)</th>
<th>$\mu_0$</th>
<th>$\nu_0$</th>
<th>k</th>
<th>l</th>
<th>$R^2$</th>
</tr>
</thead>
<tbody>
<tr>
<td>MIL</td>
<td>15.0 GPa</td>
<td>5.035 GPa</td>
<td>0.227</td>
<td>1.745</td>
<td>1.333</td>
<td>0.951</td>
</tr>
<tr>
<td>SLD</td>
<td>15.0 GPa</td>
<td>5.034 GPa</td>
<td>0.227</td>
<td>1.724</td>
<td>0.823</td>
<td>0.948</td>
</tr>
<tr>
<td>SSOD</td>
<td>15.0 GPa</td>
<td>5.039 GPa</td>
<td>0.227</td>
<td>1.703</td>
<td>0.546</td>
<td>0.941</td>
</tr>
</tbody>
</table>

Table 5.4: Angular deviations between the corresponding eigenvectors of the second order fabric tensor and the orthotropic stiffness tensor, evaluated for the three fabric measures, MIL, SLD and SSOD. Mean and standard deviation (SD) values are given in degrees.

<table>
<thead>
<tr>
<th>Method</th>
<th>$\Delta e_1$ (degree)</th>
<th>$\Delta e_2$ (degree)</th>
<th>$\Delta e_3$ (degree)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mean</td>
<td>SD</td>
<td>Mean</td>
</tr>
<tr>
<td>MIL</td>
<td>6.32</td>
<td>7.80</td>
<td>6.65</td>
</tr>
<tr>
<td>SLD</td>
<td>4.41</td>
<td>6.18</td>
<td>4.76</td>
</tr>
<tr>
<td>SSOD</td>
<td>7.98</td>
<td>8.62</td>
<td>8.47</td>
</tr>
</tbody>
</table>
Figure 5.14: Comparison of Ct.Th measured on the XCT and the µCT images and the calibration equation (linear regression).

Table 5.5: Constants of the homogenization–based plasticity and damage constitutive law, evaluated for MIL using the results presented in Table 5.3 and the data presented in [34].

<table>
<thead>
<tr>
<th>σ₀⁺</th>
<th>σ₀⁻</th>
<th>χ₀⁺</th>
<th>χ₀⁻</th>
<th>τ₀</th>
<th>p</th>
<th>q</th>
</tr>
</thead>
<tbody>
<tr>
<td>96.0 MPa</td>
<td>128.0 MPa</td>
<td>-0.263</td>
<td>0.310</td>
<td>56.3 MPa</td>
<td>1.745</td>
<td>0.632</td>
</tr>
</tbody>
</table>

In the second part of the calibration sub–study, we found that a linear relationship was appropriate to describe the conversion rule between the cortical thicknesses measured on the XCT and µCT images. Figure 5.14 presents the measurements of the four specimens and the resulting calibration law (linear regression line).

5.3.5 hFE analysis

Average computation time was 81.3 ± 35.4 minutes, required memory remained below 4 GB. The hFE and the experimental force–displacement results of the sample shown in Figure 5.8 are compared in Figure 5.15. Stiffnesses and ultimate forces of the hFE models were compared with the corresponding experimental results using linear regressions. Results are shown in Figure 5.16. Table 5.6 presents the stiffness and ultimate force results of the hFE models as well as their correlation coefficients with the experimental quantities. Comparison of the values summarized in Table 5.1 and Table 5.6 allowed to conclude that the best predictions could be achieved using the FE methods. Still, these were not significantly
CHAPTER 5. VALIDATION OF HFE AND \( \mu \)FE WITH RADIUS SLICES

Figure 5.15: Comparison of the hFE and the experimental force–displacement results of the sample shown in Figure 5.8.

Figure 5.16: Results of the linear regression analyses between the experimental and the hFE results, for stiffness (left) and strength (right), respectively.
better than BMC or aBMD in predicting stiffness and than BMC in predicting ultimate force. Note, that the distribution of elastic strain energy density between the two bone compartments, reflecting load–sharing between the phases, was closely the same in the two types of FE models. Figure 5.17 shows the comparisons between the results of the two FE approaches for stiffness and ultimate force, respectively.

Figure 5.17: Linear regression analyses between the results of the μFE and the hFE models, left: apparent stiffness, right: ultimate force.

Table 5.6: Mean and standard deviation values of the μFE and hFE results of the radius sections, as well as the squared correlation coefficients with experimental stiffness and strength. Bold numbers indicate high correlation coefficients (R² > 0.7). Significances: N.S.: p > 0.05, ****: p < 0.0001.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean ± SD</th>
<th>R²(K^exp)</th>
<th>R²(F_U^exp)</th>
</tr>
</thead>
<tbody>
<tr>
<td>μFE stiff. (kN/mm)</td>
<td>24.80 ± 9.56</td>
<td><strong>0.956</strong>**</td>
<td><strong>0.881</strong>**</td>
</tr>
<tr>
<td>μFE ult. force (kN)</td>
<td>2.80 ± 1.04</td>
<td><strong>0.954</strong>**</td>
<td><strong>0.948</strong>**</td>
</tr>
<tr>
<td>μFE % Tb.ESE (%)</td>
<td>46.4 ± 7.4</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>μFE % Ct.ESE (%)</td>
<td>53.6 ± 7.4</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>hFE stiff. (kN/mm)</td>
<td>25.37 ± 8.28</td>
<td><strong>0.945</strong>**</td>
<td><strong>0.860</strong>**</td>
</tr>
<tr>
<td>hFE ult. force (kN)</td>
<td>3.23 ± 1.13</td>
<td><strong>0.939</strong>**</td>
<td><strong>0.935</strong>**</td>
</tr>
<tr>
<td>hFE % Tb.ESE (%)</td>
<td>45.2 ± 8.1</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
<tr>
<td>hFE % Ct.ESE (%)</td>
<td>54.8 ± 8.1</td>
<td>N.S.</td>
<td>N.S.</td>
</tr>
</tbody>
</table>
5.4 Discussion

The presented mechanical testing setup was developed to provide well controlled loading environment of distal radius sections, which was a simplified, but still realistic representation of the in situ conditions. Rotation of the upper loading plate was allowed with a ball joint and the region of analysis was restricted to a 20 mm section of the distal radius which is the most relevant in Colles’ fractures [12, 13]. The apparent stiffness obtained with the LVDTs was highly correlated with the concurrent MTS cross–head measurement, but the latter provided approximately 20% lower values on average due to inclusion of machine compliance. This emphasizes the need of the independent displacement–assessment technique. The high apparent spring–stiffness values resulted from the relatively small sample height (20 mm). Experimental stiffness and strength results were only moderately correlated compared to the relation reported in [9] for four adjacent sections of the distal radius. This is most probably due to the fact that only one bone region was tested in the present study. During evaluation of the experimental result, an outlier was identified. Further investigations of this specimen are in progress using nanoindentation.

Among the microarchitectural measures, Tb.N provided the strongest predictions of the experimental results, while area and volume of the cortical region were the best geometrical predictors. Weak relation between mechanical properties and cortical thickness was found. The density–based parameters had stronger predictive power than the geometrical and microarchitectural measures. The projected (areal) mineral density performed better than vBMD. With the exception of BMC of the trabecular region, all indices were better predictors of stiffness than strength. The highest correlation coefficient was obtained with BMC of the total sample, for both strength and stiffness.

Geometry of the \( \mu \)FE models was based on segmented images assessed with a combination of a Laplace-Hamming filter and 40% threshold. This segmentation technique was found in the calibration sub–study to overestimate volume fraction with a factor of 1.52 on average. The \( \mu \)FE models provided quantitatively correct predictions of the experimental stiffnesses using experimentally identified material constants of bone tissue reported in [26]. These suggests that the gain of mechanical resistance caused by the overestimation of volume fraction might have been compensated by the loss of connectivity in the trabecular network due to segmentation of the limited resolution images. Pistoia et. al [7] used Young’s modulus of 10 GPa in their \( \mu \)FE models, although did not present the comparison of experimental and predicted stiffness, and used coarser image resolution to generate the meshes. Additionally, the tissue–strain–based criterion presented in that study overestimated fracture load. Even if a higher elastic modulus (15 GPa) was used in the present study, the constants of this criterion were not changed compared to [7]. The reason for this choice was that the effective tissue strain level (0.7%) of the criterion was assumed to be constant [36]. Using these settings, both stiffness and ultimate force of the mechanical tests were well predicted in the present work. This set of \( \mu \)FE–parameters seems therefore to be the proper one for XCT image resolution and compressive loading case of distal radius sections. In contrary, MacNeil and Boyd found Young’s modulus of 6829 MPa in their
CHAPTER 5. VALIDATION OF HFE AND $\mu$FE WITH RADIUS SLICES

study with back-calculation using the experimental stiffness [9]. Comparison of their experimental data with the mechanical results assessed here using the MTS cross-head and the LVDTs suggested that the experimental stiffnesses presented in that study might have been affected by machine compliance, which finally lead to the lower tissue elastic modulus of $\mu$FE models.

A single set of isotropic material constants were used in the $\mu$FE models for cortical and trabecular bone tissues. Assignment of individual properties to the two compartments and implementation of anisotropy of the cortex may further improve the level of prediction.

The HR–pQCT – $\mu$CT calibration laws identified in the sub-study for volume fraction and fabric were different from the ones obtained in Chapter Four. This mismatch was mainly caused by the different XCT scanning protocols of the two studies, as lack of surrounding soft tissues could not be perfectly compensated by submerging the specimens into water and resulted in different scattering. Furthermore, the thresholded images were not cleaned in that previous study. Slope of the volume fraction calibration law for HR–pQCT BV/TVd was different compared to Chapter Four (1.12 vs. 1.30), while similar values were found for the intercept (3.51% vs. 2.92%) and correlation coefficient (0.948 vs. 0.953). The relations for the LH–segmented XCT image–based BV/TV were slightly different from the previously presented ones (slope: 0.746 vs. 0.733, intercept: -2.10 vs. 0.919 and R$^2$: 0.932 vs. 0.946). MIL fabric calibration was more strongly affected by image resolution change than in Chapter Four (slope: 1.75 vs. 1.22, R$^2$: 0.936 vs. 0.974). Better correspondence was found in case of SSOD (slope: 1.58 vs. 1.34, R$^2$: 0.963 vs. 0.978). In line with the findings of Chapter Four, SSOD was the best in terms of correlation coefficient (considering the MIL results obtained from the LH–filtered and ‘Fix’–thresholded images of Chapter Four). Concerning the angular deviations of the main (third) fabric eigenvector, MIL and SSOD had similar precision, which is in agreement with Chapter Four, and SLD was the most accurate.

Cortical thickness was found to be systematically overestimated by XCT with a factor of 1.25 which is in line with the findings of a previous study [21], although Ct.Th was measured with a different approach in that work. The substantial noise in the comparison of the HR–pQCT and the $\mu$CT measurement of the thicknesses was mostly the result of the fill–algorithm used to extract the cortical shell domain from the images. This procedure consisted of morphological opening and closing operations which, although were adjusted to the actual image resolution, resulted in different patterns on the HR–pQCT and $\mu$CT images as these latter provided more detailed and correct representation of the porous structure of the cortical shell.

$\mu$CT MIL was found to be the best predictor of $\mu$FE stiffness as it provided the strongest correlations in the multiple regression analysis. In terms of directional deviations, the third direction - belonging to the highest eigenvalue - is the most important as the two other might be flipped when the sample is close to transverse isotropic. Considering the third direction only, there were only small differences between the three fabric measures and all of them provided accurate predictions. Still, SLD was the most accurate from this point of view.

In the second part of the calibration sub-study, a new set of material constants as
well as correction factors for volume fraction, fabric and cortical thickness were identified. These were then implemented into the hFE models, which were therefore based purely on geometrical information and material data at the lower hierarchical level and no fitting was performed with the experimental results. Despite the use of these refinements, the hFE models overestimated stiffness of the less compliant specimens and overestimated failure load consistently for all samples. When evaluating the constants of the homogenization law, homogeneous displacement boundary conditions (BCs) were used in the μFE analyses of the cubical ROIs to determine the stiffness tensor. These BCs were shown to overestimate apparent mechanical properties of cancellous bone [37], which may partially explain the overestimation of stiffness in the hFE models. Although, when analyzing models of full vertebral bodies, hFE with KUBCs was found to provide a good match with μFE [19] suggesting these type of boundary conditions to be appropriate when trabecular bone surrounded by cortical shell is analyzed. As trabecular bone is assumably differently constrained when it is situated in the middle of the core and when neighbored by cortex, different set of homogenization constants might be needed for these two cases, with KUBC providing the proper calibration for the latter. Further investigation of these research question and the remaining inaccuracies of the hFE models were beyond the scope of the present work and will be targeted in future studies.

Substantially better predictions of experimental stiffness and ultimate force were obtained with both FE approaches compared to any of the density–based or micro–architectural indices, which corresponds to the findings of previous studies [7, 8, 38]. In particular, both μFE and hFE provided significantly better predictions of fracture load than aBMD. However, the FE methods were not significantly better than aBMD and BMC in predicting stiffness, and than BMC in predicting ultimate force.

In accordance with a previous study [19], the hFE and μFE results were highly correlated, although the μFE models provided more exact and slightly more precise predictions of the experimental results. The good correspondence was reinforced by the distribution of the reaction force between the two bone compartments that was found to be similar for the two types of numerical models. CPU times of the linear μFE models were comparable to the ones of the non–linear hFE models, although the latter could not take advantage of parallel processing. Nevertheless, the nonlinear hFE simulations could be performed using less memory. Furthermore, linear analyses of the hFE models (not reported here) took approximately 12 minutes of CPU time on average.

Experimental stiffness was strongly correlated with ultimate force, which is in agreement with a previous study [9], still, this is most probably valid in this specific loading case only. FE ultimate force although was a much better predictor of experimental fracture load than FE stiffness, which argues for the assessment of strength either with a nonlinear hFE analysis or with post–processing of the linear μFE analysis results.

Several limitations of the study needs to be discussed. First, sections of the distal radius were used. The goal of the present study although was not exact reproduction of Colles’ fractures but, as pointed out above, investigation of a simplified and highly controlled loading case. The boundary conditions of the experimental setup provided therefore a simplified configuration compared to the assumed in situ loading conditions of the distal
radius in Colles’ fracture. By allowing the rotation of the upper loading plate and centering the axis of the applied load with respect to the center of mass of the distal part of the radius sections, the experiments were able to reproduce the dorsal inclination typical in Colles’ fractures. Second, dissected specimens were scanned without surrounding soft tissues that might affect the grayscale–calibration of the scanner, which is valid for the in vivo case. Additionally, compared to the standard HR–pQCT protocol, a larger region of analysis was selected, which was positioned differently. Result of this study hence cannot be directly extrapolated to the clinical setup. The reason for the enlarged sample height was that the standard 9 mm thick region of the distal radius might have been too small to provide a good mechanical representation of Colles’ fracture, the occurrence of which was found to be distributed within a larger zone [12, 13]. Third, rotation of the upper plate was neglected in the FE simulations by applying constrained axial compression. The inclusion of dorsal bending is expected to further increase the level of prediction, whereas only marginally, while making the analysis more complicated as it would require the axis of rotation to be defined. Still, outstanding predictions were achieved even with these simplified boundary conditions. Fourth, cortical bone was modelled as a poreless structure in the hFE models and orientation of anisotropy was constant. Refinement of the modeling procedure to include these characteristics is currently in progress. Fifth, number of specimens was too low and the results were therefore limited to indicate trends rather than detect significant differences between the correlations of the investigated parameters and methods, especially BMC and FE.

To conclude, the strong predictive power of BMC suggested that the distribution of matter in bone is optimized naturally to provide maximal stiffness and strength against the typical loading pattern, which is a combination of axial compression and bending in case of the distal radius. This is in line with Wolff’s law. The results also allowed to conclude that BMC, which can be obtained using DXA as well, could be used as an efficient predictor for bone strength and even better for stiffness in the distal radius. However, BMC, being a surrogate measure, provided high correlation only, while the FE methods delivered direct and quantitatively correct predictions of the experimental measurements. The obtained results demonstrated that both the μFE and the hFE approaches were capable of predicting failure load and apparent stiffness of the distal radius section relevant in Colles’ fracture with an accuracy of 94–95% and 95–96%, respectively, within reasonable computation time. These emphasize the potential of the FE methods to improve the assessment of fracture risk in the distal radius and suggest that the FE analysis might be the most appropriate tool for this purpose when HR–pQCT images are available.

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Bibliography


Chapter 6

Validation of distal radius section FE models to predict Colles’ Fracture

Extended from the manuscript:

HR–pQCT based FE analysis of the most distal radius section provides an improved prediction of Colles’ fracture load in vitro

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Abstract

The remarkable performances of High Resolution peripheral Quantitative Computed Tomography (HR–pQCT) make the distal radius a favorable site for early diagnosis of osteoporosis and improved Colles’ fracture risk assessment. The goal of this study was to investigate if the HR–pQCT based micro finite element (µFE) method applied on specific sections of the distal radius provides improved predictions of Colles’ fracture load compared to bone min-
eral content (BMC), bone mineral density (BMD), or morphological indices. HR–pQCT based BMC, BMD, morphological parameters and μFE models of 9 mm thick bone sections were used to predict stiffness and strength of 21 distal radii assessed in an experimental model of Colles’ fracture reported in a previous study. The analysis was performed on two bone sections: a standard one recommended by the HR–pQCT manufacturer and a second one defined just proximal to the distal subchondral plate. For most of the investigated parameters, significant differences were found between the two sections and correlations with experimental fracture load were higher in the most distal section. BMC provided a better estimation of Colles’ fracture load \( R^2 = 0.942 \) than aBMD or any other morphological indices. The best prediction was achieved with μFE analyses of the most distal slice \( R^2 = 0.962 \), which provided quantitatively correct ultimate forces. To conclude, this study showed that HR–pQCT based BMC of a 9 mm bone section was a strong predictor of experimental Colles’ fracture load of the distal radius and μFE analysis provided additional power. Further improved predictions could be achieved by analyzing the ultra–distal section just proximal to the subchondral plate.

**Keywords:** distal radius, Colles’ fracture, HR–pQCT, finite element, homogenization

### 6.1 Introduction

Osteoporosis is a skeletal disease comprised of reduced bone mass and degraded architecture, resulting in increased fragility [1, 2]. Fracture risk is determined by the probability and intensity of falling as well as the mechanical resistance of bones. Quantification of the latter is the cardinal principle of all diagnostic tools. DXA based areal bone mineral density (aBMD) has been shown to have a strong association to almost all types of fractures [3, 4, 5]. Still, its capability in predicting fracture risk is limited as bone strength is not associated with bone mass alone [6, 7] and at least 50% of all osteoporosis related fractures occur in patients diagnosed as non–osteoporotic [8, 9]. Additional information can be provided by CT based morphometric and geometric measurements of bone micro–architecture, nevertheless, micro–structural parameters were reported not to perform significantly better than aBMD [10, 11, 12, 13].

Structural parameters as well as aBMD have been assessed at various skeletal sites, primarily the spine, femoral neck and distal radius. The distal radius is a favorable site for diagnosis of osteoporosis for several reasons. First, forearm fractures have been shown to account for up to 25% of all bone injuries [14, 15, 16], the majority of which are Colles’ fractures. Second, radial aBMD is capable of predicting fragility fractures at all sites [17]. Third, distal radius fractures occur earlier in lifetime to other fragility fractures [18, 19, 20] and might therefore act as predictors of increased bone fragility of other sites [21, 22, 23]. Finally, the wrist is a peripheral site with small amount of surrounding soft tissues
that allows imaging with the recently introduced High Resolution peripheral Quantitative Computed Tomography (HR–pQCT) [24]. This technique has the highest in vivo resolution currently available, providing insight into the 3D trabecular bone micro–architecture which further improves predictions of fracture risk [25, 26, 27].

Mechanical properties of full bones can be directly assessed with virtual mechanical tests using micro finite element (µFE) simulations, integrating geometry, micro–architecture and tissue material properties [28, 29, 30, 31]. Specimen specific HR–pQCT based µFE models have been shown to better predict mechanical properties and risk fracture compared to aBMD or micro–structural parameters [28, 26, 7, 32]. Due to computational needs, µFE models are usually limited to linear analyses where bone strength is estimated from the elastic stiffness. While the use of non–linear material laws is feasible when analyzing smaller regions like biopsies [33, 34], it requires outstanding computational resources when investigating full bones or larger bone sections [35, 31, 36]. The strain–based criterion suggested by Pistoia et al. allows estimation of the ultimate load using the results of a linear analysis [28].

Having the majority of forearm fractures localized in the ultradistal radius (UDR), the distal 3 cm adjacent to the articular endplate [22], this region is assumed to be the weakest within the bone. It is composed primarily of trabecular bone and corresponds to the location of Colles’ fracture. The standard analysis protocol of the HR–pQCT is based on a ~9 mm wide bone section of the UDR, starting 9.5 mm proximal to the landmark plateau of the distal articular endplate formed by the intersection of scaphoid and lunate fossa [37]. This standard section has two potential limitations. First, it has not been well demonstrated if this section of limited size provides a good representation of the structural mechanics for Colles’ fracture, i.e. if it is an appropriate region of analysis for fracture risk assessment. Pistoia et al. [38] showed that µFE models of 10 mm distal radius slices (starting 6 mm proximal from the reference line) were able to explain 66% of the variation in experimental forearm fracture load. Second, it is questionable whether the standardized section encompasses the weakest zone of the distal radius where the fracture would localize. This issue was most recently addressed by Mueller et al. who reported the best predictions of forearm failure load to be assessed with analysis of the most distal region adjacent to the subchondral plate [39]. This finding is in line with the results of Eastell et al. [40] who found that the location of Colles’ fracture is at a mean distance of 22 mm ± 4mm proximal from the tip of the radial styloid with the height of the proc. styloideus radii being approximately 11.6 ± 1.6mm [41].

The aim of this study was therefore to evaluate (1) if analysis of a single 9 mm section of the radius can predict distal radius ultimate load of a recently developed experimental model of Colles’ fracture (Chapter Two), (2) if the standard or the most distal region provides the better prediction and (3) if µFE analysis provides a better prediction than the density–based measures or micro–architectural indices.
CHAPTER 6. \( \mu FE \) SECTION MODELS OF COLLES’ FRACTURE

6.2 Materials and methods

6.2.1 Samples, HR–pQCT scanning and experimental tests

As described previously in more details in Chapter Two, an experimental model of Colles’ fracture with well controlled boundary conditions was developed and applied on twenty-one intact formalin fixed human radii obtained in conformance with the ethics guidelines of the Ludwig–Maximilians University in Munich, Germany (12 left and 9 right, 8 male, 13 female, mean age: 82.2 ± 9.3 years). The bones were cut 4 cm proximally to the 1/3 distal site, positioned in 5° dorsal inclination and embedded at both ends. The specimens were placed in a custom–made water chamber and scanned with 82 µm isotropic voxel size using HR–pQCT (XtremeCT, Scanco Medical AG, Switzerland). Scanning settings were 60 kVp energy, 1 mA current, 200 ms integration time and 1536x1536 pixels image matrix. The specimens were then tested to failure in monotonic, quasi–static, displacement–controlled compression following ten preconditioning loading cycles while recording force and displacement. Figure 6.1 shows the experimental setup on the left and a typical resulting force–displacement curve on the right side. Apparent bone stiffness was determined as the slope of the linear part of the curve, and the peak value defined the fracture load. The fracture pattern was analyzed visually after testing on a distal cut surface prepared in the dorsal–palmar plane through Lister’s tubercle. For the purposes of the present study, two sections of the HR–pQCT reconstructions of each radii were selected and further analyzed. The first section was sized and positioned in accordance with the standard in vivo protocol of the XtremeCT: 9.02 mm (110 slices) thick region located 9.5 mm proximal to
the endplate landmark. A second section of the same size was selected strictly adjacent to the most proximal point of the subchondral endplate (Figure 6.2). Both sections were cut perpendicular to the longitudinal axis corresponding to the loading axis of the mechanical tests.

6.2.2 Evaluation of HR–pQCT morphology

Cortical and trabecular bone compartments were separated on the HR–pQCT images using an automated in–house fill algorithm [42] (Figure 6.3A,B) as the separation procedure provided by the manufacturer couldn’t be successfully applied on the in vitro images as shown also by Buie et al. [43]. Morphological parameters were assessed using the Image Processing Language (IPL) software of the HR–pQCT manufacturer. Cross sectional areas were computed and averaged over the height of the samples for the trabecular (A_trab), cortical (A_cort) and total bone (A_tot) image regions. Bone mineral content (BMC) was calculated by integrating the density values of all voxels contained by the specimen volume. DXA–like areal BMD (aBMD) was evaluated by projecting the 3D images to the plane along the dorsal–palmar axis and dividing BMC by the projected area [44]. Volumetric bone mineral density (vBMD) of the trabecular (vBMD_trab), cortical (vBMD_cort) and full region (vBMD_tot) was quantified. Density based volume fraction of the trabecular phase (BV/TV_d) was assessed from vBMD_trab by assuming the density of fully mineralized bone to be 1200 mg HA/cm^3. Image noise was reduced on the grayscale images with a Laplace–Hamming filter and segmentation was performed using a global threshold value selected as 40% of the maximal grayscale intensity [45]. Segmented image based micro–architectural indices were then measured using the algorithms of the standard patient evaluation. Trabecular number (Tb.N) was directly measured with a 3D ridge extraction algorithm [46], while trabecular thickness (Tb.Th) and spacing (Tb.Sp) were determined from Tb.N and BV/TV_d using the plate model assumption [47]. Cortical thickness was calculated from bone surface (BS) and volume (BV) of the triangulated surface representation of the cortex with Ct.Th = BV/0.5BS. All parameters were quantified for the standard and the most distal section, respectively.

6.2.3 µFE modeling

µFE models of the radius slices were built from the segmented HR–pQCT images by converting all bone voxels into linear hexahedral elements. Number of elements varied between 0.98 and 3.21 millions (mean 1.78 millions) in the standard, respectively between 1.24 and 3.79 millions (mean 2.11 millions) in the most distal sections. Bone tissue was assumed to be a homogeneous and isotropic material with Young’s modulus of 15.0 GPa and Poisson’s ratio of 0.3 following the concept of Chapter Five. These indeed correspond to nanoindentation results [48]. Boundary conditions were set to approximate the in situ condition of the section: the most proximal plane was fully constrained, while axial compressive displace-
Figure 6.2: Selection of the two (standard and most distal) 9 mm thick sections on the HR–pQCT image of the distal radius.
CHAPTER 6. \( \mu \)FE SECTION MODELS OF COLLES’ FRACTURE

Figure 6.3: Image processing: separation of cortical (A) and trabecular (B) compartments, \( \mu \)FE model with boundary conditions (C).

ment was applied on the nodes of the distal cut surface with their movement constrained in the transverse plane (Figure 6.3C). Linear analyses of the models were performed with an open source large scale element–by–element solver (ParFE, [36]) using a computer with 2x2 3.0 GHz Xeon processors and 32 GB RAM. Mean CPU time was 16.3 minutes (min. 8.2, max. 30.2 min) for the standard and 24.3 minutes (min. 8.2, max. 98.0 min) for the distal sections. Apparent stiffness was evaluated as the ratio of the resulting force and the imposed displacement. The ultimate load was estimated with the force level that caused Strain Energy Density (SED)-based effective tissue strain of 0.7% in 2% of the elements according to [28] and Chapter Five. Contributions of cortical and trabecular bone phases were investigated by calculating percentages of the elastic strain energy absorbed by the cortical (Ct.ESE) and trabecular (Tb.ESE) bone compartments.

6.2.4 Statistical analysis

Means and standard deviations of the investigated quantities were calculated. Differences of the standard and the most distal regions were computed in percentages of the standard section values and tested for significance with a two–tailed paired Student t–test. Squared Pearson’s correlation coefficients were used to evaluate capabilities of the numerical results of the sections in predicting the experimental stiffness and Colles’ fracture load of the distal radii. Multiple regression analysis was perform to determine if combinations of BMC, BMD and microarchitectural parameters provide improved correlation compared to the single linear regressions.
6.3 Results

6.3.1 Experimental tests

As described in Two, the mechanical tests of the distal radii resulted in Colles' fractures except for one specimen for which the fracture zone could not be identified. Experimental ultimate forces ranged from 1486.6 N to 7401.9 N (3802.5 ± 1922.8), linear spring stiffnesses varied between 1666.9 N/mm and 8416.58 N/mm (5398.9 ± 2055.1). Correlation coefficient between stiffness and strength was $R^2=0.75$.

6.3.2 HR–pQCT analysis and $\mu$FE of the two sections

The standard and the most distal sections were found to overlap for each specimen (Figure 6.2), with a mean common domain length of 4.1 ± 1.2 mm (ranging from 2.0 to 6.3 mm). Means and standard deviations of the HR–pQCT–based volumetric and areal BMD, BMC, morphological parameters as well as $\mu$FE variables for both sections are summarized in Table 6.1.

Table 6.1: Mean and standard deviation values of the HR–pQCT measures and the $\mu$FE results for the standard and the distal sections of the radii. Differences between the two are given in percentages of the standard section values with significance expressed with paired Student $t$–test $p$ values.

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standard region</th>
<th>Most distal region</th>
<th>Diff. in %</th>
<th>$p$ value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$A_{\text{tot}}$ (mm$^2$)</td>
<td>369.0 ± 110.0</td>
<td>495.3 ± 116.5</td>
<td>34.2</td>
<td>$&lt;10^{-4}$</td>
</tr>
<tr>
<td>$A_{\text{trab}}$ (mm$^2$)</td>
<td>303.4 ± 102.0</td>
<td>442.9 ± 109.0</td>
<td>46.0</td>
<td>$&lt;10^{-4}$</td>
</tr>
<tr>
<td>$A_{\text{cort}}$ (mm$^2$)</td>
<td>65.5 ± 20.5</td>
<td>51.7 ± 18.3</td>
<td>-21.1</td>
<td>$&lt;10^{-4}$</td>
</tr>
<tr>
<td>BMC (HA mg)</td>
<td>590.8 ± 263.3</td>
<td>614.8 ± 313.6</td>
<td>4.1</td>
<td>0.190</td>
</tr>
<tr>
<td>aBMD (HA g/cm$^2$)</td>
<td>0.240 ± 0.080</td>
<td>0.221 ± 0.086</td>
<td>-8.06</td>
<td>0.002</td>
</tr>
<tr>
<td>vBMD$_{\text{tot}}$ (HA mg/cm$^3$)</td>
<td>178.8 ± 58.4</td>
<td>134.9 ± 49.2</td>
<td>-24.6</td>
<td>$&lt;10^{-4}$</td>
</tr>
<tr>
<td>vBMD$_{\text{trab}}$ (HA mg/cm$^3$)</td>
<td>88.0 ± 41.2</td>
<td>94.3 ± 40.6</td>
<td>7.16</td>
<td>0.114</td>
</tr>
<tr>
<td>vBMD$_{\text{cort}}$ (HA mg/cm$^3$)</td>
<td>565.8 ± 66.4</td>
<td>466.8 ± 61.1</td>
<td>-17.5</td>
<td>$&lt;10^{-4}$</td>
</tr>
<tr>
<td>BV/TV$_d$ (%)</td>
<td>7.33 ± 3.43</td>
<td>7.85 ± 3.39</td>
<td>7.16</td>
<td>0.114</td>
</tr>
<tr>
<td>Tb.N (mm$^{-1}$)</td>
<td>1.33 ± 0.28</td>
<td>1.41 ± 0.24</td>
<td>6.32</td>
<td>0.004</td>
</tr>
<tr>
<td>Tb.Th (µm)</td>
<td>52.7 ± 18.3</td>
<td>53.9 ± 16.7</td>
<td>2.28</td>
<td>0.550</td>
</tr>
<tr>
<td>Tb.Sp (µm)</td>
<td>746 ± 235</td>
<td>682 ± 175</td>
<td>-8.55</td>
<td>0.007</td>
</tr>
<tr>
<td>Ct.Th (µm)</td>
<td>436 ± 97</td>
<td>301 ± 61</td>
<td>-30.9</td>
<td>$&lt;10^{-4}$</td>
</tr>
<tr>
<td>$\mu$FE stiff. (kN/mm)</td>
<td>96.5 ± 39.4</td>
<td>84.6 ± 44.8</td>
<td>-12.3</td>
<td>$&lt;10^{-4}$</td>
</tr>
<tr>
<td>$\mu$FE ult. force (kN)</td>
<td>4.50 ± 1.79</td>
<td>4.05 ± 2.01</td>
<td>-9.95</td>
<td>$&lt;10^{-4}$</td>
</tr>
<tr>
<td>$\mu$FE % Tb.ESE (%)</td>
<td>38.4 ± 13.8</td>
<td>61.1 ± 10.3</td>
<td>59.1</td>
<td>$&lt;10^{-4}$</td>
</tr>
</tbody>
</table>
Cortical area decreased with the distal shift of the section most likely due to thinning of the cortical shell. Combined with a reduction of cortical density, this might explain the drop in vBMD<sub>tot</sub>, despite the increase of the total area. There was no significant inter-section difference for BMC and Tb.Th. With increased Tb.N and decreased Tb.Sp, BV/TV<sub>d</sub> (or vBMD<sub>trab</sub>) was slightly but not significantly higher for the distal section. The most distal section was found to be more compliant in the µFE simulations and the computed failure load was also lower. In accordance with the areal measurements, the portion of the load carried by the trabecular bone increased distally. Compared to the standard section, the load sharing among the two compartments inverted in the most distal region, where it was dominated by the trabecular phase.

Table 6.2 summarizes squared Pearson’s correlation coefficients between all investigated parameters of the sections and the experimental results of the distal radii (p<0.001 in all cases).

Table 6.2: Correlations (Pearson’s R<sup>2</sup>) between the parameters of the sections and the experimental results of the distal radii (p<0.001). Bold numbers are used to highlight the highest values (R<sup>2</sup> >0.8).

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Standard region</th>
<th>Most distal region</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>stiff&lt;sup&gt;exp&lt;/sup&gt;</td>
<td>F&lt;sub&gt;U&lt;/sub&gt;&lt;sup&gt;exp&lt;/sup&gt;</td>
</tr>
<tr>
<td>A&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>0.273</td>
<td>0.520</td>
</tr>
<tr>
<td>A&lt;sub&gt;trab&lt;/sub&gt;</td>
<td>0.170</td>
<td>0.377</td>
</tr>
<tr>
<td>A&lt;sub&gt;cort&lt;/sub&gt;</td>
<td>0.582</td>
<td>0.682</td>
</tr>
<tr>
<td>BMC (HA mg)</td>
<td>0.715</td>
<td><strong>0.897</strong></td>
</tr>
<tr>
<td>aBMD (HA g/cm&lt;sup&gt;2&lt;/sup&gt;)</td>
<td>0.770</td>
<td>0.781</td>
</tr>
<tr>
<td>vBMD&lt;sub&gt;tot&lt;/sub&gt;</td>
<td>0.409</td>
<td>0.295</td>
</tr>
<tr>
<td>vBMD&lt;sub&gt;cort&lt;/sub&gt;</td>
<td>0.201</td>
<td>0.070</td>
</tr>
<tr>
<td>BV/TV&lt;sub&gt;d&lt;/sub&gt;</td>
<td>0.561</td>
<td>0.579</td>
</tr>
<tr>
<td>Tb.N</td>
<td>0.442</td>
<td>0.341</td>
</tr>
<tr>
<td>Tb.Th</td>
<td>0.505</td>
<td>0.548</td>
</tr>
<tr>
<td>Tb.Sp</td>
<td>0.457</td>
<td>0.336</td>
</tr>
<tr>
<td>Ct.Th</td>
<td>0.161</td>
<td>0.057</td>
</tr>
<tr>
<td>µFE stiffness</td>
<td>0.702</td>
<td><strong>0.916</strong></td>
</tr>
<tr>
<td>µFE ult. force</td>
<td>0.707</td>
<td><strong>0.924</strong></td>
</tr>
<tr>
<td>µFE Tb.ESE</td>
<td>0.507</td>
<td>0.771</td>
</tr>
<tr>
<td>µFE Ct.ESE</td>
<td>0.475</td>
<td>0.499</td>
</tr>
</tbody>
</table>

Apart from the area measurements, R<sup>2</sup> of all parameters were higher for the most distal region. BMC of both sections correlated equally well with stiffness. aBMD provided higher correlations that vBMD, although BMC was the best predictor of fracture load amongst all density based and morphological parameters. During the multiple regression
analysis none of the density based or micro-architectural indices provided significant contribution to the predictive power of BMC. The best prediction of failure load was achieved with μFE analysis. Linear regressions between the experimental ultimate forces and the section μFE results are shown on Figure 6.4. Colles’ fracture load was overestimated by the μFE analysis using the standard section and better predicted using the most distal section. μFE stiffness correlated strongly with μFE strength for both the standard ($R^2 = 0.998$) and the most distal ($R^2 = 0.998$) sections. Still, experimental ultimate force was slightly better predicted by μFE strength ($R^2 = 0.924$ and $R^2 = 0.962$) than μFE stiffness ($R^2 = 0.916$ and $R^2 = 0.957$ for the standard and the most distal sections, respectively).

### 6.4 Discussion

In order to validate the use of HR-pQCT for assessment of fracture risk in the distal radius, density-based and micro-architectural parameters as well as μFE biomechanical variables of 9 mm bone sections were quantified and compared with experimental Colles’ fracture load obtained in a previous in vitro study. The predictive power of the variables from the standard and the most distal sections were systematically compared.

The specimens used in this study represent an elderly population. Densities and micro-architectural parameters of the standard section lay hence in value ranges typical for individuals with increased fracture risk [26, 7, 27, 32]. Some deviations with respect to previously reported values can be found, as the measurements were performed on cadaver
samples. Therefore, the obtained results should rather be compared to *in vitro* studies [49, 31].

Specimen length in the experimental tests (distal 1/3 of the radius) was not the same as in the numerical models (distal 9.02 mm section). This dissimilarity resulted in one order of magnitude difference between the physical and µFE (spring–) stiffnesses. Additionally, the simulated boundary conditions of the radius sections might have not been the same as the *in situ* ones provided by the epiphysis. Nevertheless, experimental Colles’ fracture load of the distal radius was well predicted by the µFE models of the most distal section. To achieve this, correct tissue Young’s modulus (15 GPa) and strength criteria parameters, which were previously identified in Chapter Five, had to be used in HR–pQCT–based µFE models. The herein presented predictive power of the µFE simulations suggests, in agreement with the findings of Chapter Five, that the strain–based strength criteria, which was originally identified for a different configuration and image resolution [28], is appropriate for HR–pQCT–based section models of the distal radius when linear analysis is solely available.

Interestingly, the correlation between FE and experimental ultimate load was higher for the distal section model than for the entire distal radius model (for which $R^2=0.793$ and $R^2=0.874$ were found for stiffness and strength, respectively, in Chapter Two). The boundary conditions and the bone–embedding bonding was approximated in those full bone models and lead to inaccuracies which were circumvented in the simple analyses of the present study. A further source of the differences might be the use of different FE modeling techniques in the mentioned and in the present study, although the µFE and hFE approaches were shown to provide closely identical results in case of vertebral [50] and radial (Chapter Five) slices.

BMC of the radius section was a better predictor of the experimental results than any of the density–based or morphological indices, which is in agreement with findings of previous studies [51, 11, 28] as well as Chapter Five. This suggests that bone matter is distributed and organized such that it’s well optimized for the typical loading case which is a combination of compression and bending in the ultra–distal radius epiphysis, the weakest part of the bone where fractures most often occur. This finding is in line with Wolff’s law. Besides BMC, high predictive power of geometrical and density–based parameters of cortical bone was reported in other studies [10, 12], which was not supported by our results. µFE ultimate force provided however even higher correlations with the experimental failure load than BMC. This confirmed that the FE model is the appropriate synthesis of all the significant parameters like overall geometry, cortical thickness, heterogeneity of volume fraction and anisotropy of the trabecular core. Moreover, the FE analysis provides strength that can be directly used for fracture risk assessment.

In this specific, simplified, uniaxial loading case of the section, stiffness was found to be a good predictor of strength, which is in line with experimental findings of MacNeil and Boyd [31] reporting a correlation of $R^2=0.977$. This argues for the assessment of bone strength through stiffness calculation using a simple linear analysis which requires less computational effort. Still, µFE ultimate forces provided better prediction of the experimental ultimate forces than µFE stiffnesses in both sections. When there is a need to investigate not only the ultimate force but the failure mode or fracture pattern, non–linear models
should be used as it was demonstrated in Chapter Two.

To the knowledge of the authors, the herein presented correlation between experimental Colles’ fracture loads and FE analysis ($R^2 = 0.962$) is the highest reported in the literature. Similar studies using intact cadaver forearms reported correlations of $R^2 = 0.66$ [38] and $R^2 = 0.73$ [39]. The use of isolated radii with better defined and controlled boundary conditions is a plausible explanation for the stronger correlations obtained in the present study.

The results of this study showed that Colles’ fracture strength of the distal radius measured in the recently developed experimental setup could well be predicted with the analysis of a distal, 9 mm thick bone section. This supports the use of such a section in clinical applications. Nevertheless, the presented data suggests that the standardized position of the section may not be optimal. On the one hand, our FE results indicated, in agreement with [52], that the most distal section was weaker and might be the weakest region of the distal radius where a possible fracture would localize. This was strongly supported by the fact that the $\mu$FE ultimate force of this section provided quantitatively correct prediction of Colles’ fracture load. On the other hand, all investigated parameters, with the exception of bone area, better predicted failure load when assessed from the section just proximal to the distal subchondral zone than from the standardized section of the HR–pQCT manufacturer. This is in line with the study of Mueller et al. [39] who found that the most distal section, out of five consecutive regions, provided the best prediction for failure load of the forearm and the prediction decreased proximally. These suggest that the standard section should either be shifted distally, or, with the improvement of the imaging technology, extended to the edge of the articular surface. As proposed in [52], the most proximal end of the subchondral endplate could act as the landmark for such measurements. Re-definition of the clinical region although would raise questions on reproducibility which was shown to be remarkably good for the standard section [37, 53]. A recent study using fourteen cadaveric samples reported high $in vitro$ reproducibility [52], including the most distal section. Still, $in vivo$ reproducibility studies, including movement artifacts and patient handling and positioning problems, have to be conducted using the most distal section. Furthermore, automatic recognition of the radial contours on the HR–pQCT images could be more complicated on the distal region due to the thin cortical wall and the radio–ulnar joint.

Several potential limitations of the current study have to be discussed. First, the relatively modest sample size on the one hand limits extrapolation of the results to a larger population and on the other hand did not allow meaningful statistical testing of differences between the correlation coefficients of the predictive parameters of the two investigated sections. Nevertheless, the sample size corresponds to the typical number used in experimental studies. Second, aBMD was based on the projected HR–pQCT images which is not the same as the DXA measurements, resembling the clinical gold standard. This method however was shown to provide highly correlated results with conventional radial DXA measurements of 9 mm thick radius sections [44]. Third, loading conditions of the radii in the mechanical tests were idealized and somewhat distinct from the anatomical situation. A more accurate modeling of the latter, which would require the inclusion of carpal bones,
articular cartilage, ligaments and muscle contraction, was beyond the scope of the current study. The experimental setup presented in Chapter Two was designed to provide well controlled boundary conditions, which represent a simplified version of the \textit{in vivo} case by including the key biomechanical elements, namely the dorsal and lateral offset of the compressive force. Fourth, the specimens were embalmed. Long–term formalin fixation was reported to affect mechanical properties causing significant differences in Young’s modulus but not in ultimate stress of cortical bone tissue [54]. Signal to noise ratio of the CT images was found to be also influenced [28], while negligible alterations have been shown in bone mineral composition or mineral density [55, 56]. Fifth, the experimental measurements were affected by the compliance of the testing device, which was not quantified. As it was demonstrated in Chapter Five, this can lead to significant differences during quantification of stiffness. Assessment of ultimate force however, being the most relevant parameter determined, remained unaffected. Sixth, the HR–pQCT measurements were performed on the intact bones, lack of surrounding soft tissues might have had a minor influence on density and micro–architectural parameters. To compensate for this, the specimens were scanned submerged in water, the attenuation coefficient of which is close to soft tissues. Finally, cortical and trabecular bone were distinguished during \textit{µ}FE modeling although their material properties were identical [48]. Furthermore, cortical bone was modelled as an isotropic material, however it is known to be orthotropic [57]. Including orthotropy was not possible due to lack of radius–specific material properties and was therefore beyond the scope of this study.

Despite these potential limitations, this study showed that (1) experimental Colles’ fracture load can be well predicted using HR–pQCT scan of a 9 mm section of the radius. Restricting the region of analysis to such a section is advantageous for two reasons. First, clinically, as it means less measurement time and patient dose and second, computationally, as it reduces costs of the FE analysis. (2) In general, results of the most distal section exhibited stronger correlations with the experimental values compared to the ones of the standard section. Additionally, the \textit{µ}FE analysis of the most distal section correctly predicted \textit{in vitro} Colles’ fracture load of the distal radius and therefore might be most relevant region to be analyzed. (3) BMC of the sections was found to be highly correlated with Colles’ fracture load and therefore could be used as a surrogate measure when FE analysis is not available. The best predictions was provided by the FE analysis which can be performed using no extra examination beyond the HR–pQCT scan with reasonable computational resources and time and might therefore be the ideal tool to be used in fracture risk prediction in the distal radius.

\textbf{Acknowledgments}

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Bibliography


Chapter 7

Conclusions

7.1 Summary of original contributions

The aim of this Thesis was the development and validation of a patient–specific, HR–pQCT–based finite element modeling approach to predict distal radius strength, which can be applied in vivo to evaluate factor of risk (Φ) for a typical Colles’ fracture accident. Towards this end, the studies presented in Chapters Two to Six targeted specific research questions and provided the following results:

1. Chapter Two showed that the homogenized FE models (hFE) can predict experimental Colles’ fracture load better than BMD, however, some details of the mechanical setup and the numerical approach were found to require improvements and refinements to achieve a better basis for validation.

2. Chapter Three presented a novel method, SSOD, to assess trabecular bone fabric needed for the homogenization step directly on the grayscale images, and therefore exclude one source of errors from the hFE model generation by avoiding the delicate step of segmentation of the HR–pQCT images. SSOD was shown in the following Chapters to be at least as efficient as the gold standard MIL method in predicting elasticity and almost as robust with respect to image resolution change.

3. Chapter Four concluded that volume fraction and fabric assessed from HR–pQCT images are however good predictors of the corresponding quantities of μCT, but do not provide exact values and need to be corrected before used in the homogenization approach to predict mechanical properties.

4. With simplified, but highly controlled experimental tests of the distal radius section relevant in Colles’ fracture, Chapter Five showed FE modeling to better predict stiffness and ultimate load than density–based and morphological measures. With the presented refinements and improvements, the hFE modeling was found to be closely
as strong predictor as the current standard $\mu$FE simulation. Nonlinear hFE analyses required closely the same CPU time, but much less memory than the linear $\mu$FE runs. This study validated the two FE approaches, both of which provided quantitatively correct predictions of the experimental results without artificial adjustments.

5. Chapter Six demonstrated that $\mu$FE simulations of 9 mm distal radius sections are excellent predictors of in vitro Colles’ fracture load. The approach was therefore found to be applicable in the clinical case where the region of analysis is restricted to such a section. $\mu$FE provided stronger correlations than mineral density, mineral content or morphology. Additionally, compared to the default HR–pQCT protocol, higher correlation coefficients and quantitatively correct numerical prediction of the ultimate force could be assessed when the region of analysis was selected adjacent to the subchondral endplate.

7.2 General discussion

The work presented in this Thesis was initiated with the study presented in Chapter Two, during the accomplishment of which several research questions emerged. These were investigated in details in the further Chapters, while the ultimate goal – the applicability under clinical conditions – was kept in mind.

Chapter Two presented an experimental setup with well defined boundary conditions for inducing Colles’ fractures on intact radii, which was meant to provide a strong basis for validation of the new type of continuum–based hFE models. In order to have well controlled and reproducible boundary conditions, a simplified setup was necessary, which was still capable of producing fractures of Colles’ type. Numerical results showed that the hFE modeling presented by Pahr and Zysset [1] could be applied successfully on the distal radius and the nonlinear analysis was able to predict the experimental ultimate force. The hFE models were not calibrated to this specific anatomy and loading case, material properties were taken directly from previously reported experimental tests of trabecular bone biopsies [2]. Mostly due to the well defined boundary conditions of the experiments, the obtained predictions were better than those of the previously reported Colles’ fracture studies using intact arms and involving FE [3, 4]. The previous finding that FE analysis is a better predictor of Colles’ fracture load than the density measurement [3] was verified.

Nevertheless, the study presented in Chapter Two had several limitations, some of which were due to the experimental setup (bone tissue was embalmed, embedding affected the fracture lines, machine compliance influenced the measurement of stiffness), while others were modeling–related (HR–pQCT–based volume fraction and fabric were inaccurate but not corrected, bone–embedding contact was assumed to be perfect bonding, the size of the scanned region was unreasonably large compared to the in vivo protocol, no comparison with $\mu$FE was performed). The following Chapters aimed to improve and further validate the hFE technique, to compare it to the standard $\mu$FE approach and to evaluate applicability under quasi–clinical conditions. The achieved improvements and acquired observations
will be discussed in the following subsections according to specific aspects.

7.2.1 Mechanical test

Some limitations of the mechanical setup of Chapter Two did not allow for exact validation. Embalming process was reported to alter mechanical properties (mainly stiffness) of bones and affect CT images quality. The use of embedding included an additional source of error as it affected the fracture lines. Moreover, the PMMA–bone contact was not investigated in more details and was simplified in the FE models to be perfect bonding. Machine compliance, which was not quantified, was shown in Chapter Five to introduce significant differences when measuring stiffness even in case of more simple setup. However, the more important fracture load measurement was not affected by this deficiency.

Most of these limitations were eliminated in the experimental setup presented in Chapter Five, which indeed focused on the relevant section of the distal radius where Colles’ fracture localizes. In that study, fresh specimens were used which were not embedded as the cut surfaces of the bone sections were loaded directly. Furthermore, the independent measurement of displacements ensured machine compliance–free quantification of stiffness. These improvements and simplifications provided a stronger basis for validation and allowed for stronger and more precise numerical predictions compared to Chapter Two.

7.2.2 Homogenization

One source of errors of the hFE approach causing inaccurate predictions in Chapter Two was related to the evaluation of the homogenized mechanical properties of the continuum elements. Namely, the input parameters of the homogenization approach used during the hFE model generation, volume fraction and fabric, were measured directly on the HR–pQCT images. Chapter Four concluded that these quantities evaluated on this limited resolution were however highly correlated with the gold standard ($\mu$CT) equivalents, but did not provide exact values and needed therefore to be corrected. The relevant conversion rules were identified for the in vivo case in Chapter Four and actualized in Chapter Five for the in vitro scanning setup.

Volume fraction

Volume fraction was evaluated from BMD in the hFE models of Chapter Two in order to avoid image segmentation which is known to be a delicate step on the HR–pQCT resolution with volume fraction being very sensitive to the selection of the threshold level. This choice was verified later, in both Chapter Four and Five, as BMD of the HR–pQCT was found to be a better predictor of $\mu$CT BV/TV than any segmented image–based volume fractions. Nevertheless, this density–based prediction underestimated the real volume fraction and resulted in incorrect mechanical properties. As discussed in the Introduction, volume fraction
is the main determinant of stiffness and strength. Therefore, its correction was an essential step during hFE model generation in Chapter Five.

**Fabric**

The other input of the homogenization approach, fabric, was quantified for the hFE models of Chapter Two with the MIL method, which required binarized images. To go around the requirement of thresholding, Chapter Three introduced the SSOD method which was developed to quantify fabric directly on the grayscale images. SSOD was found to be in a good agreement with, but not directly convertible to MIL.

The single input parameter of SSOD, the diameter of the sampling sphere, could be considered as a trade-off for not having to segment the input images. In fact, this size is not arbitrarily selected. Knowing the average trabecular thickness and spacing, the ideal sphere diameter depends only on the image resolution. The theoretically prescribed size was confirmed in Chapter Three to be the best numerically, by involving trabecular bone specimens from six anatomical locations which covered a broad range of volume fraction.

SSOD cannot be applied on very low resolution images as it requires a sufficiently detailed discretized sampling sphere to provide a meaningful orientation distribution. The 82 $\mu$m voxel size of HR–pQCT was found to be the lower limit in this sense. The ideal radius ($R$) of the sphere according to the theory would be two voxels in this case but $R = 3$ was found in a preliminary study to provide the best match between the fabric tensors of the high resolution $\mu$CT images and the recoarsened ones having a resolution close to that of HR–pQCT [5]. This suggested that the gain of information due to the use of the correct diameter is smaller than the loss caused by the poor discretization of the sphere.

Chapter Four compared SSOD with the MIL and the Spatial Autocorrelation Function (ACF) methods by focusing on the sensitivity with respect to change of image resolution and signal to noise ratio. This was accomplished by comparing the fabric tensors evaluated on the $\mu$CT and the HR–pQCT images. SSOD was found to be the fastest of the three approaches when processing HR–pQCT images. Robustness of SSOD and the other grayscale image–based method, ACF, was found to be similar. Surprisingly, MIL was the most powerful in this sense, nevertheless, proper image segmentation steps were required to achieve the best results. When using the standard image segmentation of the HR–pQCT, sensitivity of MIL was comparable to that of SSOD. This was confirmed in a similar comparison accomplished in Chapter Five. Note that, in the latter study, unlike Chapter Four, the samples were scanned without surrounding soft tissues and the segmented images were cleaned of separated voxel islands before computing MIL.

A sub-study of Chapter Five investigated the ability of three fabric measures, MIL, SLD and SSOD to predict anisotropy of elasticity in cubical volume elements of trabecular bone. There were only minor differences between the three approaches. Nevertheless, these results were based on trabecular bone samples extracted exclusively from the distal radius. Analysis of other anatomical sites having different cancellous micro-architecture might lead to different results. Additionally, second order fabric tensors of all three measures were
used in this study. MIL was reported to be closely described by a second order measure of fabric, while SLD may include fourth order information. SSOD is also able to provide higher order approximation of its orientation distribution function. The abilities of the fourth order tensors of SLD and SSOD to describe lower symmetries were already demonstrated in Chapter Three when analyzing artificial grid structures. These measures with higher order approximations may eventually better predict the fourth order elasticity tensor than MIL.

### 7.2.3 FE vs. density and morphology

Both Chapters Five and Six showed, in accordance with previous findings [6], that BMC is a very strong predictor of experimental Colles’ fracture load and that it performs better than aBMD. The density–based measures were found to be more strongly correlated with ultimate load than the geometrical and morphological indices, none of which could provide significant contribution to the predictive power of BMC in Chapter Six. These suggest that the organization of mineral in the distal radius is well optimized to provide mechanical resistance against the combination of compression and bending. Colles’ fracture strength hence depend almost solely on the amount of the matter, which confirms Wolff’s law. Nevertheless, the FE approaches were found to be better predictors of both experimental stiffness and strength than BMC in both Chapters Five and Six. These differences however did not reach the level of significance, which is most probably mainly due to the limited number of samples used in the experimental studies. More data is required to support these findings.

The density–based and morphological parameters have been related to bone strength in the literature using a broad range of statistical tools. Nevertheless, the determined relationships may vary between anatomical sites and loading configurations. Beyond the better correlation, a further, more important advantage of the FE method is that it provides the numerical equivalents of the investigated mechanical parameters, stiffness and strength, which can therefore be directly compared to the experimental results. The FE simulations did not only provide the strongest correlations among the investigated measures in Chapters Five and Six but predicted stiffness and fracture load in a quantitatively correct way. A validated FE model should provide correct mechanical response in other loading cases as well, albeit this issue was not analyzed in this Thesis which addressed one specific injury of the distal radius occurring in a typical accident.

It is important to emphasize that the FE method requires exactly the same input data as the density–based and morphological analysis of the HR–pQCT instrument. Therefore it provides more accurate prediction of $\Phi$ than these latter without the need of any further examinations of the patient.

### 7.2.4 hFE vs. $\mu$FE models

Several pros and cons of the two FE modeling approaches were mentioned in the Introduction. These are further discussed below in the light of Chapter Five, which compared the
improved hFE models to the standard μFE models directly, on the basis of experimental results.

Generation of the smooth surface–based hFE geometry is complicated compared to the simple and fast voxel conversion technique of the μFE models as the two bone compartments has to be meshed separately. However, an automated, fast, robust and reliable algorithm was developed by Pahr and Zysset for this purpose [1], which was successfully applied for vertebral bodies in previous studies [7, 8] as well as for the distal radius throughout this Thesis. In the μFE models, compartment separation is necessary only if distinct material properties are attributed to the two bone phases, which might add further precision to the predictions. It may be also required when the mechanical contribution of trabecular and compact bone is in the focus of interest, which is rarely the case in clinical applications.

Computation of the homogenized properties in hFE models is a time consuming step which is missing in the μFE models, however, the continuum representation may be the strength of this approach. As mentioned in the Introduction, μFE models are exposed to loss of trabecular connectivity due to segmentation of the HR–pQCT images. The Laplace-Hamming filter seems to be successful in enhancing the signal to noise ratio and emphasizing the high–intensity structural elements, still, it is ineffective against the partial volume effect. hFE models are more shielded against this phenomenon due to their continuum nature and the use of grayscale images.

Nonlinear analyses of the hFE radius section models required closely the same computation time and much less memory than the parallel–computed linear analyses of the μFE models in Chapter Five. The former therefore is better suited to lower resources and allow for usage of standard personal computers. Note that the solution strategies of the two models are not the same as the latter require special, iterative, element-by-element solvers [9]. The results also suggest that a linear simulation may be sufficient when investigating Colles’ fractures. Namely, the ultimate force of the ultra–distal section is an excellent predictor of Colles’ fracture load of the distal radius (Chapter Six), and stiffness and strength of the bone section are closely related (Chapter Five, in line with [10]). CPU time of a linear hFE model is only a few minutes and more than ten times less compared to the one of the corresponding μFE simulation. Nevertheless, nonlinear simulations can still be beneficial by providing extra information about fracture localization as it was demonstrated in Chapter Two, where the high damage zones of the hFE models were found to be in good qualitatively agreement with the experimental fracture patterns.

The hFE models were closely as powerful in predicting experimental spring stiffness and fracture load as the μFE models. Nevertheless, some possible further improvements of the hFE approach, which are expected to add extra accuracy to the predictions, were not investigated in Chapter Five. Probably the most important of these is the inclusion of porosity and real orthotropy of the cortical shell, which is currently under development. The slightly lower accuracy of the hFE models obtained in Chapter Five provided the main motivation for the use of the μFE approach in Chapter Six. Still, with the further improvements, hFE may have at least as strong predictive power as μFE and may be the preferred tool of such predictions. Beyond being computationally less expensive, a further advantage is that the calibrated hFE method provides a versatile tool which enables modeling of bones
of different anatomical locations and various loadcases using the same set of parameters, which might therefore be unique. This seems not to be true in case of the \( \mu \)FE approach. Nevertheless, the distal radius is not the anatomical location where the advantages of the hFE approach would prevail, for mainly two reasons: its failure is dominated by a single type of fracture (Colles’) occurring in a simple loadcase; and the fracture localizes within a relatively small domain, which can be analyzed with \( \mu \)FE using reasonable computing resources.

Surprisingly, the correlation coefficient between the prediction of the distal radius section FE model of Chapter Six and the experimental Colles’ fracture load obtained in Chapter Two was slightly higher than the one between the section FE model and the corresponding experiment in Chapter Five. Some of the several potential sources of differences are the distinct experimental setup, different sample height, the unequal number of specimens, use of formalin fixed vs. fresh bones, and the effect of statistical sampling.

7.2.5 Region of analysis

Chapter Two investigated a relatively long part (one third) of the distal radius which was nine to twelve times as large as the region that is reasonably obtainable using HR–pQCT under clinical circumstances. The analysis in Chapter Six was therefore restricted to 9 mm sections that correspond to the standard size assessed in vivo. These thin bone slices were found to be surprisingly powerful predictors of the experimental Colles’ fracture load measured in Chapter Two. In fact, the FE models of the sections better predicted ultimate force than those of the full bones. This suggests that (1) the errors committed during modeling of the full bones’ boundary conditions and the bone–embedding bonding were successfully eliminated by the section analysis; (2) the constraints and the loading applied in the section FE models provided reasonably good representation of the experimental in situ mechanical environment of these regions; (3) the analysis of such a section can adequately predict full bone strength.

Chapter Six showed that the most distal section of the radius was weaker and better predictor of Colles’ fracture load than the standard HR–pQCT region. These findings are in line with conclusions of previous studies [4, 11] and suggest that the most distal section captures the less resistant region of the radius, which is hence the most relevant to be analyzed when investigating full bone strength. This was further supported by the fact that the analysis of the most distal section provided quantitatively correct predictions of Colles’ fracture load in Chapter Six using the \( \mu \)FE approach validated in Chapter Five. Re-definition of the most distal section to be the standard region of analysis in the HR–pQCT measurements would nevertheless have to face some difficulties, as it was discussed in Chapter Six.
7.3 Outlook

7.3.1 Future work

The studies presented in Chapters Two to Six accomplished several steps towards the ultimate goal, the development and validation of a FE–based tool for Colles’ fracture load prediction. Still, additional work is needed to examine the numerous research issues that remained opened here. Some of the not yet investigated research questions are listed below, answering of which may help to further improve the presented methods and predictions:

- How well the fabric approaches can predict mechanical anisotropy? In particular, do the fourth order fabric measures (SLD, SSOD) carry any extra information which would allow them to better describe apparent elasticity and strength of trabecular bone than the second order MIL?
- What benefits can be achieved with further improvements of the hFE models, most importantly the inclusion of the cortical inhomogeneity?
- How well the results of the hFE and \( \mu \)FE approaches correspond to each other when investigated in details (e.g. comparison of strain energy distributions)?
- What are the experimental orthotropic tissue properties of the cortical shell in the ultra–distal radius (using nanoindentation and material testing)?
- Can size and location of the distal radius section optimized so that its FE analysis provides an even better prediction of Colles’ fracture load?
- How do the mechanical properties of the distal radius compare between quasi–static and accidental loading rates using the same experimental setup?
- What is the real mechanical environment of the distal radius in the \textit{in vivo} fall situation, including effects of muscle activation, ligaments, cartilage and surrounding bones?

The latter may be one of the most important questions. Answering it is however not possible at the current stage of research as the wrist represents such an extremely complex mechanism that its complete understanding and overview is not yet available. There was no consensus found in the literature between \textit{in vitro} [12], rigid body modeling–based [13] and \textit{in vivo} [14] measurement techniques even in simple cases like pure extension and flexion.

7.3.2 A tool for clinical studies

This Thesis confirmed the potentials and reinforced the relevance of the FE method in bone biomechanics by demonstrating its ability to predict Colles’ fracture load. The results presented here strongly supported the applicability of the HR–pQCT–based FE method under
clinical conditions as (1) it was validated with experimental tests (Chapter Five), (2) it provided the best available predictions of the \textit{in vitro} Colles’ fracture load (Chapter Five) and (3) models of the \textit{in vivo} HR–pQCT protocol–based bone sections were found to be precise predictors of ultimate load of the distal radius (Chapter Six). There were no significant differences found between the applicability and predictive ability of the two investigated FE approaches and both of them fulfill the requirements specified in the Introduction. Namely, both (1) are fully automated as the steps from the HR–pQCT image to the fracture load require no intervention; (2) were successfully applied on numerous specimens without problems in model generation or solution and (3) can be performed in less than one hour without requiring extraordinary computational power.

This Thesis focused on the prediction of fracture load, which is the denominator of factor of risk. Evaluation of $\Phi$ requires a second input, the accidental load. This, as mentioned in the Introduction, could be estimated by making assumptions about the type of accident which accordingly would narrow the range of possible types and magnitudes of the acting forces. Colles’ fracture is a relatively less complicated case from this point of view as in elderly it occurs mostly when falling onto the outstretched hand. Simplified approaches were therefore proposed \cite{15, 16} which assumed – as a worst case scenario – that the radius is subjected to the total falling force, magnitude of which was estimated based on the height and weight of the patient based on previous results of experimental studies \cite{17}.

The $\mu$FE modeling protocol presented in Chapter Six is already being used in two clinical studies currently running in the Vienna General Hospital and involving HR–pQCT imaging of the distal radius. Briefly, one of these is a cross–sectional study aiming to evaluate the ability of the FE–based $\Phi$ to discriminate between patients having positive and negative wrist fracture history, while the other one is a longitudinal study addressing follow up of the change in $\Phi$ for a group of patients having a specific disease. Patient information is registered in both cases which allows for quantification of the acting load and the HR–pQCT–based FE simulation is meant to provide the resistance of the distal radius. The latter requires the same input as the morphological analysis of the HR–pQCT instrument, the HR–pQCT image and a contour defining the radius.

As pointed out earlier, Colles’ fracture represents a hallmark of osteoporosis. Wrist–fractured patients should therefore be warned, provided with lifestyle advises and treated for osteoporosis if necessary. Unfortunately, this chain of actions is not yet widely applied. Less than 5% of the patients sustaining a distal radius fracture are investigated for osteoporosis \cite{18}. Better follow–up of these people at obvious risk would help to avoid consecutive osteoporotic fractures. Moreover, utilization of the proposed HR–pQCT–based FE tool may provide improved predictions compared to the currently used densitometry and help to identify these individuals earlier in time, even before sustaining the first fragility fracture.
Bibliography


List of Symbols

\( \alpha \) radial inclination, or the ratio of the yield to the ultimate stress, or multiplier of the fabric eigenvalues
\( \alpha_x \) inclination of the upper loading plate in the dorsal–palmar plane
\( \alpha_y \) inclination of the upper loading plate in the radial–ulnar plane
\( \beta \) palmar tilt
\( \Delta m_i \) angular deviation between corresponding eigenvectors of tensors
\( \Delta c^j \) motion increment of the sphere in step \( j \)
\( \epsilon_0 \) Young’s modulus for a poreless material
\( \epsilon_i \) Elastic modulus in the \( i \) direction
\( \gamma \) power coefficient of the fabric eigenvalues
\( \mu \text{CT} \) micro computed tomography
\( \mu \text{FE} \) micro finite element
\( \nu \) Poisson’s ratio
\( \nu_0 \) Poisson’s ratio of a poreless material
\( \nu_{ij} \) Poisson’s ratio in the plane \( ij \)
\( \Phi \) factor of risk
\( \varphi \) angular deviation of the minor eigenvectors of fabric tensors
\( \rho \) bone volume fraction
\( \rho(y) \) grayscale value of a voxel at location \( y \) of the image
\( p^j(x) \) intensity value of a voxel at location \( x \) within the container sphere
\( \sigma \) standard deviation of the normal distribution used for the Gaussian filter
\( \sigma_0^+ \) and \( \sigma_0^- \) uniaxial tensile and compressive strength for a poreless material
\( \sigma_{ij}^+ \) and \( \sigma_{ij}^- \) uniaxial tensile and compressive strength along axis \( i \)
\( \sigma_p^+ \) plastic yield stress
\( \sigma^p(D) \) hardening function
\( \tau_0 \) shear strength for a poreless material
\( \tau_{ij} \) shear strength in the plane \( ij \)
\( \theta \) angular deviation of the major eigenvectors of fabric tensors
\( \chi_0^+ \) and \( \chi_0^- \) tensile and compressive stress interaction coefficients for a poreless material
\( \chi_D \) damage hardening coefficient
\( \chi_{ij}^+ \) and \( \chi_{ij}^- \) multiaxial coupling terms of the tensile and compressive stress
\( \chi_p \)  
plastic hardening coefficient

\( \omega \)  
orientation of the mean intercept length measure

2D  
two dimensional

3D  
three dimensional

\( A_0 \)  
surface of the unit sphere

\( A_{\text{tot}} \)  
total mean area

\( A_{\text{trab}} \)  
mean area of the trabecular compartment

\( A_{\text{cort}} \)  
mean area of the cortical compartment

AO  
Arbetsgruppe für Osteosynthesefragen

ACF  
autocorrelation function

\( \text{aBMD} \)  
areal bone mineral density

BC  
boundary condition

BMC  
bone mineral content

\( \text{BMC}_{\text{tot}} \)  
total bone mineral content

\( \text{BMC}_{\text{trab}} \)  
bone mineral content of the trabecular compartment

\( \text{BMC}_{\text{cort}} \)  
bone mineral content of the cortical compartment

BMD  
bone mineral density

BMI  
body mass index

BS  
bone surface

\( \text{BS/BV} \)  
bone surface over bone volume ratio

BV  
bone volume

\( \text{BV/TV} \)  
bone volume fraction

\( \text{BV/TVd} \)  
density–based volume fraction

\( C \)  
voxel–domain of the container sphere

c  
global image vector identifying the center voxel of a sphere

Conn.D  
connectivity density

CPU  
central processing unit of a computer

CRF  
clinical risk factors

CT  
computed tomography

CT.ESE  
elastic strain energy in the cortical compartment

Ct.Po  
cortical porosity

Ct.Th  
cortical thickness

\( d \)  
sphere diameter

\( D \)  
damage scalar variable

\( D_{100} \)  
mean density

\( D_{\text{comp}} \)  
cortical density

\( D_{\text{trab}} \)  
trabecular density

DA  
degree of anisotropy

DTA-O  
digital topology-based orientation analysis

DXA  
dual energy X–ray absorptiometry

\( E \)  
second order strain tensor

\( E \)  
fourth order compliance tensor
LIST OF SYMBOLS

\[ E_0 \] elastic modulus for a poreless material
\[ E_{ij} \] Cartesian components of the second order strain tensor
\[ e_k \] unit vector in direction \( k \)
\[ ESE \] elastic strain energy
\[ F^+ \text{ and } F^- \] fourth rank strength tensors
\[ F^{\text{exp}} \] experimental ultimate force
\[ \mathcal{F}(n) \] fourth order tensorial Fourier basis function of an ODF
\[ \mathcal{F}(x) \] fourth order tensorial orthonormal basis function
\[ F(n) \] second order tensorial Fourier basis function of an ODF
\[ F(x) \] second order tensorial orthonormal basis function
\[ f(n) \] zero order tensorial Fourier basis function of an ODF
\[ f(x) \] zero order tensorial orthonormal basis function
\[ F_U^{\text{exp}} \] experimental ultimate force
\[ f_k(x) \] generalized basis functions
\[ \text{FE} \] finite element
\[ \text{FFT} \] fast Fourier transformation
\[ \text{Fix} \] fix–valued threshold
\[ \text{FoS} \] factor of safety
\[ \text{FRAX} \] Fracture Risk Assessment Tool
\[ G_0 \] shear modulus of a poreless material
\[ G_{ij} \] shear modulus in the plane \( ij \)
\[ \mathcal{G} \] fourth order tensorial Fourier coefficient of an ODF
\[ \mathcal{G} \] fourth order tensorial coefficient
\[ G \] second order tensorial Fourier coefficient of an ODF
\[ \mathcal{G} \] second order tensorial coefficient
\[ g \] zero order tensorial Fourier coefficient of an ODF
\[ \mathcal{g} \] zero order tensorial coefficient
\[ g_k \] coefficients of the generalized basis functions
\[ \text{Ga} \] Gaussian filter
\[ \text{GTS} \] gray–level structure tensor
\[ H_k \] dimensions of the image in voxels, in direction \( k \)
\[ h_k \] number of voxel-steps in direction \( k \)
\[ \text{HA} \] hydroxyapatite
\[ \text{hFE} \] homogenized continuum finite element
\[ \text{HR–pQCT} \] high resolution peripheral quantitative computed tomography
\[ I \] spatial domain of the image
\[ \mathbf{\hat{I}} \] 'properly' traceless eighth order identity tensor
\[ \mathbf{\tilde{I}} \] 'properly' traceless eighth order identity tensor
\[ I \] second order identity tensor
\[ \text{IPL} \] image processing language (Scanco Medical AG)
\[ \text{ISD} \] intercept segment deviation
\[ \text{ITK} \] Image Tool Kit, C++ library
<table>
<thead>
<tr>
<th>Symbol</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>$K^{\text{exp}}$</td>
<td>experimental stiffness</td>
</tr>
<tr>
<td>$k$</td>
<td>porosity exponent for the fabric-based elasticity</td>
</tr>
<tr>
<td>$k_{ij}$</td>
<td>$ij$ component of the vertebral stiffness matrix</td>
</tr>
<tr>
<td>KUBC</td>
<td>kinematic uniform boundary conditions</td>
</tr>
<tr>
<td>$l$</td>
<td>anisotropy exponent for the fabric-based elasticity</td>
</tr>
<tr>
<td>$L$</td>
<td>total length for the mean intercept length method</td>
</tr>
<tr>
<td>$l_k$</td>
<td>voxel lengths in direction $k$</td>
</tr>
<tr>
<td>LFD</td>
<td>line fraction deviation</td>
</tr>
<tr>
<td>LH</td>
<td>Laplace–Hamming (filter)</td>
</tr>
<tr>
<td>LVDT</td>
<td>linear variable differential transformers</td>
</tr>
<tr>
<td>$M$</td>
<td>fourth order fabric tensor</td>
</tr>
<tr>
<td>$\mathbf{M}$</td>
<td>second order fabric tensor</td>
</tr>
<tr>
<td>$m_i$</td>
<td>eigenvalues of $\mathbf{M}$</td>
</tr>
<tr>
<td>$\text{mathbf{m}}_i$</td>
<td>orthotropic eigenvectors of $\mathbf{M}$</td>
</tr>
<tr>
<td>MIL</td>
<td>mean intercept length</td>
</tr>
<tr>
<td>MIL$_4$</td>
<td>fourth order approximation of MIL</td>
</tr>
<tr>
<td>MRI</td>
<td>magnetic resonance imaging</td>
</tr>
<tr>
<td>$N$</td>
<td>number of samples; or number of voxels in the sampling sphere</td>
</tr>
<tr>
<td>$\mathbf{n}$</td>
<td>unit vector</td>
</tr>
<tr>
<td>$N_S$</td>
<td>number of accepted sampling spheres</td>
</tr>
<tr>
<td>$n_k$</td>
<td>voxels steps in direction $k$</td>
</tr>
<tr>
<td>ODF</td>
<td>orientation distribution function</td>
</tr>
<tr>
<td>OPT</td>
<td>optimal threshold</td>
</tr>
<tr>
<td>Opt</td>
<td>optimal threshold</td>
</tr>
<tr>
<td>$p$</td>
<td>porosity exponent for the fabric-based damage criterion, or power of the grayscale intensity</td>
</tr>
<tr>
<td>PA</td>
<td>posterioroanterior</td>
</tr>
<tr>
<td>PMMA</td>
<td>polymethylmethacrylate</td>
</tr>
<tr>
<td>PTH</td>
<td>parathyroid hormone</td>
</tr>
<tr>
<td>$q$</td>
<td>anisotropy exponent for the fabric-based damage criterion</td>
</tr>
<tr>
<td>QCT</td>
<td>quantitative computed tomography</td>
</tr>
<tr>
<td>QUS</td>
<td>quantitative ultrasound</td>
</tr>
<tr>
<td>$R$</td>
<td>constant for the evolution of damage criterion</td>
</tr>
<tr>
<td>$R$</td>
<td>sampling sphere radius</td>
</tr>
<tr>
<td>$r$</td>
<td>sphere radius</td>
</tr>
<tr>
<td>$R^2$</td>
<td>squared Pearson’s correlation coefficient</td>
</tr>
<tr>
<td>$r^D$</td>
<td>radius of the damage criterion</td>
</tr>
<tr>
<td>RAM</td>
<td>random access memory</td>
</tr>
<tr>
<td>RMSE</td>
<td>root mean square error</td>
</tr>
<tr>
<td>ROI</td>
<td>region of interest</td>
</tr>
<tr>
<td>$\mathbf{S}$</td>
<td>second order stress tensor</td>
</tr>
<tr>
<td>$\mathbf{S}$</td>
<td>fourth order stiffness tensor</td>
</tr>
<tr>
<td>Symbol</td>
<td>Description</td>
</tr>
<tr>
<td>--------</td>
<td>-------------</td>
</tr>
<tr>
<td>$S_{ij}$</td>
<td>Cartesian component of $S$</td>
</tr>
<tr>
<td>$S_{ijkl}$</td>
<td>Component $ijkl$ of the stiffness tensor $S$</td>
</tr>
<tr>
<td>$S^D$</td>
<td>Damage stress tensor</td>
</tr>
<tr>
<td>$S^p$</td>
<td>Plastic part of the stress tensor</td>
</tr>
<tr>
<td>SD</td>
<td>Standard deviation</td>
</tr>
<tr>
<td>SED</td>
<td>Strain energy density</td>
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<tr>
<td>SLD</td>
<td>Star length distribution</td>
</tr>
<tr>
<td>SLD$_4$</td>
<td>Fourth order approximation of SLD</td>
</tr>
<tr>
<td>SMI</td>
<td>Structural model index</td>
</tr>
<tr>
<td>SOS</td>
<td>Speed of sound</td>
</tr>
<tr>
<td>SSI</td>
<td>Stress strain index</td>
</tr>
<tr>
<td>SSOD</td>
<td>Sampling sphere orientation distribution</td>
</tr>
<tr>
<td>SSOD$_2$</td>
<td>Second order approximation of SSOD</td>
</tr>
<tr>
<td>SSOD$_4$</td>
<td>Fourth order approximation of SSOD</td>
</tr>
<tr>
<td>SVD</td>
<td>Star volume distribution</td>
</tr>
<tr>
<td>$T_{aff}$</td>
<td>Affine transformation</td>
</tr>
<tr>
<td>$T_{pow}$</td>
<td>Power transformation</td>
</tr>
<tr>
<td>Tb.ESE</td>
<td>Elastic strain energy in the trabecular compartment</td>
</tr>
<tr>
<td>Tb.N</td>
<td>Trabecular number</td>
</tr>
<tr>
<td>Tb.Sp</td>
<td>Trabecular spacing</td>
</tr>
<tr>
<td>TSD</td>
<td>Tensor scale method</td>
</tr>
<tr>
<td>Tb.Th</td>
<td>Trabecular thickness</td>
</tr>
<tr>
<td>TV</td>
<td>Total volume</td>
</tr>
<tr>
<td>UDR</td>
<td>Ultradistal radius</td>
</tr>
<tr>
<td>UMAT</td>
<td>User material subroutine for the ABAQUS software</td>
</tr>
<tr>
<td>$v$</td>
<td>Damage hardening coefficient</td>
</tr>
<tr>
<td>$V_B$</td>
<td>Volume of the container sphere</td>
</tr>
<tr>
<td>$V_{tot}$</td>
<td>Total volume</td>
</tr>
<tr>
<td>$V_{trab}$</td>
<td>Volume of the trabecular compartment</td>
</tr>
<tr>
<td>$V_{cort}$</td>
<td>Volume of the cortical compartment</td>
</tr>
<tr>
<td>$\nu$BMD</td>
<td>Volumetric bone mineral density</td>
</tr>
<tr>
<td>$\nu$BMD$_{tot}$</td>
<td>Total volumetric bone mineral density</td>
</tr>
<tr>
<td>$\nu$BMD$_{trab}$</td>
<td>Volumetric bone mineral density of the trabecular compartment</td>
</tr>
<tr>
<td>$\nu$BMD$_{cort}$</td>
<td>Volumetric bone mineral density of the cortical compartment</td>
</tr>
<tr>
<td>VE</td>
<td>Volume element</td>
</tr>
<tr>
<td>VO</td>
<td>Volume orientation</td>
</tr>
<tr>
<td>$w$</td>
<td>Plastic hardening coefficient</td>
</tr>
<tr>
<td>WHO</td>
<td>World Health Organization</td>
</tr>
<tr>
<td>x</td>
<td>Local spatial vector within the container sphere</td>
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<tr>
<td>XCT</td>
<td>XtremeCT scanner</td>
</tr>
<tr>
<td>y</td>
<td>Spatial vector in the global coordinate system of the image</td>
</tr>
<tr>
<td>$Y^D$</td>
<td>Damage threshold function</td>
</tr>
<tr>
<td>$Y^p$</td>
<td>Plastic yield function</td>
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</table>
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Conferences


