An Image-Based Method to Measure Joint Deformity in Inflammatory Arthritis

by

Travis Foster Henchie

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Approved:

Prof. Karen Troy, Thesis Advisor: ________________________________

Prof. Todd Bredbenner, Committee Member: ________________________________

Prof. Glenn Gaudette, Committee Member: ________________________________

Prof. Songbai Ji, Committee Member: ________________________________
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List of Abbreviations

3D: three-dimensional
2D: two-dimensional
RANKL: receptor activator of nuclear factor κB ligand
ACPA: anti-citrullinated protein antibodies
RF: rheumatoid factor
HLA: human leukocyte antigen
IL: interleukin
TNF: tumor necrosis factor
MMPs: matrix metalloproteinases
MCP: metacarpophalangeal (joint)
PIP: proximal interphalangeal
MCB: metacarpal base
PsA: psoriatic arthritis
RA: rheumatoid arthritis
CASPAR: Classification of Psoriatic Arthritis
SHS: Sharp/van der Heijde
CPD: Coherent Point Drift
GMM: Gaussian mixture model
UMMMC: University of Massachusetts Memorial Medical Center
RMSE: root mean squared error
ROC: receiver operator curve
OMERACT: Outcome measures in rheumatology arthritis clinical trials
PsAMRIS: Psoriatic Arthritis Magnetic Resonance Imaging Score
RAMRIS: Rheumatoid Arthritis Magnetic Imaging Score
CT: computed tomography
HR-pQCT: high resolution peripheral quantitative computed tomography
MRI: magnetic resonance imaging
HU: Hounsfield Units, a measure of x-ray intensity
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1 Abstract

Background

Quantifying joint deformity in people with rheumatoid arthritis (RA) and psoriatic arthritis (PsA), using high resolution peripheral quantitative computed tomography (HR-pQCT), remains problematic because it is difficult to estimate where the healthy joint surface would have been.

Methods

The second metacarpophalangeal of RA, PsA and healthy subjects were imaged with HR-pQCT. Using the bone surfaces of the healthy cohort as a reference, the method predicted the healthy surface of each individual diseased bone surface. Quantifiable outcomes were measured based on differences between the predicted healthy surface and the actual diseased surface. Sensitivity studies were conducted to measure precision, and the algorithm was validated against artificially created deformities with known geometries.

Results

Subjects with PsA and RA had significantly greater occurrences of erosion based surface outcomes than the healthy cohort. Sensitivity analyses revealed precision errors of up to 0.26 mm. Validating the algorithm showed an average accuracy error of 0.12 mm (4%) for detecting erosions and 0.27 mm (20%) for detecting periosteal bone growths.

Conclusions

The new method allows for visualization and quantification of surface changes within the affected joint by identifying areas of erosion and periosteal bone formation. Surface based outcomes are a novel way to interpret and further quantify articular bone changes affected by PsA and RA.

Keywords: non-linear surface transformation, coherent point drift, HRpQCT, CT, imaging, inflammatory arthritis, MCP, method
2 Introduction

Psoriatic arthritis (PsA) and rheumatoid arthritis (RA) are chronic inflammatory diseases occurring in patients with autoimmune disorders and psoriasis [1–3]. A combination of mechanical stress and inflammation in individuals with PsA results in the formation of periosteal bone growth (osteophytes or enthesophytes) at tendon/ligament insertion sites, and articular erosions within the joints [1, 4, 5]. Erosion formation typically occurs in early disease at the proximal enthesis, but in later stages, spur formation occurs at the distal end of the ligament attachment site [6]. The frequency and size of the abnormalities and the number of affected joints are associated with poor clinical outcomes [3]. Some individuals exhibit extremely destructive and disfiguring forms of the disease with erosions and periosteal bone formation leading to disability [7, 8]. The metacarpophalangeal joints of the hand are common areas for these bone changes. Because these changes are irreversible [9], earlier detection and prevention may lead to improved patient care.

Radiographic imaging is the most common modality to identify and assess characteristic features of both RA and PsA including joint erosions, joint space narrowing, bony proliferation and formation [10, 11]. However, radiography has relatively low sensitivity for the detection of degenerative features in early disease stages, and these features are often poorly defined due to the progression of periosteal bone formation adjacent to erosions [10]. Computed tomography (CT), magnetic resonance imaging (MRI) and ultrasound imaging are gaining clinical popularity. These technologies are capable of detecting early stages of disease and monitoring joint changes during disease progression with greater sensitivity than that of plain radiographs [12–16].

High-resolution peripheral computed tomography (HR-pQCT) is a low radiation dose imaging technique with the ability to assess three-dimensional (3D) bone structure in the peripheral bones
at an isotropic voxel resolution range of 63 - 246 µm [17]. HR-pQCT is gaining popularity and clinical accessibility as a means to quantify bone degradation in RA patients, with multiple studies reporting results on the visual analysis of erosion presence, number and size, and user reliability [18–23]. Several publications report positive results for semi-automated algorithms capable of segmenting erosions in patients with RA from cortical interruptions in the bone surface [20, 24–28]. These methods show good results in erosion identification and quantification in image data where erosions are easily defined. However, current algorithms designed to measure erosion and bone formation characteristics require user intervention to identify an erosion by manually locating seed points or assisting in segmentation where the algorithm has leaked into the trabecular bone region. In addition, quantifying erosion geometry presents methodological challenges because it depends on the subjective estimation of the original (missing) bone surface. Estimating the original bone surface becomes inaccurate in severely damaged joint areas, or when periosteal bone develops adjacent to erosions. Similar challenges are encountered when measuring periosteal bone growths.

Quantifying deformities of the bone at the articular joint surface is critically important in understanding the extent of disability as a result of skeletal deformity. Thus, a general goal of this research is to utilize the increasing availability of HR-pQCT in a clinical setting to provide accurate, detailed images of bone topography, which allow for the development of objective measurement methods that have been previously unavailable. As has been the case in many other diseases, patient outcomes may be improved as a result of more sensitive and less subjective measures of progression of joint damage. The long-term goal is to improve the treatment of arthritic diseases by providing accurate, objective and clinically relevant diagnostic tools that may be used to quantify and predict disease progression.
Here, we present and validate a new approach using HR-pQCT images to detect and quantify diseased bone surface comprised of both erosions and periosteal bone growth on 3D surfaces. The algorithm is designed to predict the prior healthy bone surface from the geometry of a diseased bone surface using a probabilistic approach and a set of healthy bone surfaces as a reference. We validated the algorithm by creating artificial erosions and periosteal bone growths. Finally, we applied the algorithm to images from patients with PsA and RA. We report potentially clinically relevant outcome measures between diseased cohorts and a healthy cohort, highlighting the algorithm’s capability in objectively detecting diseased bone surface in a repeatable manner.

**Specific Aim 1:** To develop and validate a novel algorithm capable of predicting a healthy bone surface from the geometry of a degraded bone surface, as a result of RA or PsA. The algorithm will implement a modified coherent point drift code to non-linearly scale, translate and warp a generic reference bone surface to the shape of the unhealthy bone surface whilst retaining desirable healthy features for correspondence between two dissimilar shapes. The predicted healthy surface will be used to discriminate between healthy bone surfaces and unhealthy bone surfaces of the 2nd MCP joint by computing various outcome measures. To validate the algorithm performance, outcome measures will be computed from artificially created deformities with known geometries. Comparisons between the predicted healthy surfaces of the original bone surface and the manufactured diseased bone surface will be compared to one another, and the accuracy of the outcomes will be compared to the corresponding actual values.

**Specific Aim 2:** To analyze morphological variations in the MCP joint between patients with RA or PsA and matched healthy individuals using outcome measures derived from differences in the healthy predicted bone surface and the diseased bone surface. A One-way ANOVA will be used to compare outcomes of healthy, RA, and PsA patients. Post hoc t-tests with Bonferroni corrections
will be run to detect between-group differences. To determine the degree to which the algorithm-calculated metrics are associated with disease-related bony features, a stepwise discriminant analysis will be implemented to blindly classify between healthy and diseased surfaces. Lastly, the sensitivity of the algorithm to producing outcomes will be determined by varying the number, order and sex of the healthy input surfaces.

**Hypothesis:** The algorithm will be sensitive to detect surface deformities between RA or PsA and healthy bones, and differentiate between healthy and diseased bone surfaces. This hypothesis will be supported if the algorithm produces accurate and repeatable measurements of outcomes, consistent prediction of healthy surfaces from the diseased surfaces and show significant differences between outcomes of the diseased and healthy cohort.

## 3 Literature Review

A review of the pertinent literature for this study is presented here. Current clinical techniques for detecting bone deformities in patients with RA or PsA using several imaging modalities and scoring systems are evaluated. An overview of the current environment for quantifying bone degradation is reviewed to understood how the technique presented here will contribute and compare to current methodologies. An overview of reported research-focused algorithms designed to detect abnormalities using cutting-edge imaging equipment is presented with comments on the advantages and disadvantages of each. Finally, an outline of the data transformation algorithm, Coherent Point Drift, is summarized and the merits are discussed with relevant examples highlighting the benefits of this technique for the study presented here.
### 3.1 Rheumatoid Arthritis

Rheumatoid arthritis (RA) is a chronic, progressive inflammatory condition characterized by synovial proliferation in the joint space and within the trabecular bone region, often associated with erosive arthritis [29]. A primary factor in the inflammatory process includes overproduction and overexpression of tumor necrosis factor (TNF), which is caused largely from interactions between T and B lymphocytes, synovial-like fibroblasts, and macrophages [30]. This process drives the overproduction of many cytokines such as interleukin 6 and immunoglobulin-like receptor activator of nuclear factor κB ligand (RANKL), which leads to inflammation and joint destruction by invasion of fibroblasts in the cartilage [3, 9, 30]. These receptors and RANKL facilitate differentiation toward osteoclasts [3]. Final differentiation into bone-resorbing osteoclasts is then achieved following contact with the bone surface [9]. These osteoclasts absorb bone in an unrestricted process because of an immune imbalance [29].

Autoimmunity as a result of inflammation is an indicator of structural damage in RA by the presence of anti-citrullinated protein antibodies (ACPA) and rheumatoid factor (RF) autoantibody in the serum of patients with RA [3, 30, 31]. ACPA is found in 70 - 90% of RA patients and has high disease specificity (90 - 95%), and RF is found in 60 - 80% of RA patients [31]. These antibodies are common biomarkers for indicators of structural damage in joints before the onset of synovitis.

Bone erosions are defined as breaks in the cortical bone surface, and often include loss of the adjacent trabecular bone to form voids in the bone structure [3]. Bone erosions are major outcome measure in RA patients to determine the severity of the disease and degree of disability [3, 32]. Thus, quantifying bone erosions is a major instrument for disease diagnosis and tracking disease progression in drug therapy trails. In RA, bone erosions can be defined as ‘U’ shaped voids [33],
often characterized by the diameter of the cortical break, the depth of the erosion and the volume. Depths of erosions have been reported from 1.9 to 4.9 mm and volumes from 5 mm$^3$ to 120 mm$^3$, with a commonly reported average volume of 30 mm$^3$ [22, 34–37]. Erosion formation occurs most frequently at the radial aspects of the finger joints, whereas the ulnar aspects are less affected, and the palmar and volar surfaces of the joints have far less to no presence of lesions [3]. The areas susceptible to erosion as described are associated with ligament insertion sites to the bone surface, which translate mechanical forces to the bone and may induce microdamage [38]. Also, inflamed tendon sheaths, which pass over the bone surface, enable the spread of inflammation from the tendon to the articular synovium [38]. Understanding the nature, geometry and location of erosions is important in defining what an erosion is when creating an algorithm to detect these features. Having a better understanding of the erosive process and what bony features are designated as arthritic erosion in a clinical environment aids the development process and outlines the necessities for the algorithm’s outcomes to be relevant in the clinical environment.

### 3.2 Psoriatic Arthritis

Psoriatic arthritis (PsA) is classified as an inflammatory arthritis associated with psoriasis and is sero-negative for RF [1]. PsA is a genetically inherited autoimmune disease where T-cell derived cytokines are an important factor [1, 2] Peripheral PsA in the hands and feet have been associated with HLA-B38 and HLA-B39 and PsA spondylitis with human leukocyte antigen (HLA) class 1 [1]. The trigger for the onset of infection has yet to be identified, but trauma and biomechanical stress have been linked to entheses up-regulation of pro-inflammatory cytokines in genetically susceptible individuals [1, 2, 4]. Joints and inflamed entheses in PsA are attacked by a lymphocytic infiltrate with an abundance of activated T-cells and T-cell-derived cytokines, including interleukin (IL)-1, IL-2, IL-10, interferon, and TNF [1]. TNF over-expression within the joint plays
a role in abnormal bone remodeling, which is a characteristic feature of PsA, leading to increased production of matrix metalloproteinases (MMPs) and cartilage destruction [1]. As described in RA, TNF stimulates the differentiation of cells into eventual mature osteoclasts with activation of RANKL leading to bone erosion [2].

PsA is characterized by a wide range of musculoskeletal features occurring in defined patterns at various joint locations in the body [2, 39]. In PsA, the effected distal joint distribution tends to occur where all the joints of a single digit are more likely to get affected than the same joints on both sides, which is typical of RA [2]. One of the classifications of PsA is the asymmetry that occurs in the distal interphalangeal joints. Further indicators of PsA include the presence of enthesitis and tenderness [2]. PsA leads to deformation within the joints where the shortening of digits occurs because of severe joint or bone lysis, with telescoping of digits in severe cases and bony fusion has been reported [6]. These skeletal changes are observed in radiographs as the classic pencil in cup and ankylosis [2]. Typical clinical features of PsA include dactylitis, nail lesions and psoriasis. Also, PsA is characterized by periarticular bone remodeling associated with bone spur formation [40].

In PsA, bone spurs occur frequently at the radial sides of the MCP joints (for the metacarpal head) [40]. Bony spurs can be referred to periosteal bone growths osteophytes depending on the proximity to the ligament insertion sites of the joint. These features are predominantly defined by frequency and height, and described as convex dome shaped lesions [40]. A maximum growth height of 1.6 mm was reported, but heights exceeding 2 mm have been reported [41]. Similar to detecting erosions, having an understanding of the geometry and location of periosteal bone growths helps identify these deformities when outlining the definitions for algorithm development. It is important to note that in PsA periosteal bone growths and erosions can occur adjacent to one
another. The algorithm therefore should be able to detect these two features in terms of the range of differentiation from the original healthy surface.

### 3.3 Image based scoring

**Radiography** is commonly used to estimate the progression of rheumatoid arthritis and determine the effects of anti-rheumatic treatment. There are various radiographic scoring methods that are clinically applicable, but most techniques tally individual deformities and assess joint narrowing to produce a final score representing the extent of joint damage. [42–44]. Radiography is often used as a benchmark for research developed techniques.

The Sharp/van der Heijde radiographic scoring method is the most widely used in assessment of rheumatoid arthritis, and has undergone several modifications [42, 45, 46]. The standard approach for the Sharp van der Heijde scoring method assesses 17 areas for erosion: 5 proximal interphalangeal (PIP), 5 metacarpophalangeal (MCP), 1st metacarpal base (MCB), trapezium and trapezoid as one, scaphoid, lunate, triquetrum and pisiform as one, radius and ulnar for each hand and wrist. Similarly, the method assesses 18 areas for joint space narrowing. Each erosion is scored as 1 point, with a maximum of 5 points per area of interest. This results in an erosion score ranging from 0 to 170. Joint space narrowing scored on a scale from 0 to 4, where 1 point represents slight narrowing, 2 points for diffuse narrowing of less than 50% of the original space, 3 points for narrowing exceeding 50% and 4 points for ankyloses or space closure. The joint space narrowing score ranges from 0 to 144.

Molenaar et al [47] reports joint damage in patients with rheumatoid arthritis during clinical remission using the Sharp/van der Heijde scoring method. The scoring method successfully
measured remission in 52% of the patients, with a decrease in score from initial recordings to two year follow up recordings. The radiographs were scored by two observers with an intra-observer correlation and variation was 0.98 and 0.99, respectively, which suggests the method can be consistent for multicenter longitudinal studies.

Several other scoring methods exist, most of which use a linear scale scoring system similarly to the Sharp/van der Heijde method. Examples of these scoring methods include Genant et al [48], Kaye et al [44] and Larsen et al [43]. Several modifications and various methods were derived from the Larsen method [49, 50], all of which utilize a linear scoring system to assess multiple joints.

Some disadvantages of radiography include the necessity for high resolution film and proper exposure for reproducible image results. Furthermore, identical subject position is required for serial radiograph acquisition to obtain accurate scoring comparisons of damage progression. It can often take months for joint damage to become detectable on radiography, which doesn’t represent the current disease state causing a mismatch in between clinical signs and radiographic progress. The radiographic scoring methodologies view the degradation from inflammatory arthritis as a holistic score encompassing multiple joints, which requires a trained clinician to subjectively identify these singular deformities. This approach can become subjective and is not sensitive to small changes in individual joints, which may not be beneficial to patients seeking to remedy specific joint disability. The method presented in this study aims to overcome the low diagnosis resolution by being able to characterize bone deformation on a single joint at multiple time points without the subjectivity from user input.
Magnetic resonance imaging (MRI) can be a useful tool in evaluating early signs of rheumatoid arthritis in both 2D and 3D assessments. This imaging modality can detect pre-erosive synovitis present in the joint space and trabecular bone region of the infected joint.

Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) [51] has developed Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) for the evaluation of joint damage in PsA in hands using MRI [52, 53] evaluating multiple joints and patient disability. Similarly, Rheumatoid Arthritis Magnetic Imaging Score (RAMRIS) exists for evaluating RA [14, 54]. The OMERACT system defines an erosion as a sharply marginated bone lesion, which needs to be visible in two planes and corresponding cortical break needs to be seen in at least one plane [14]. The scoring system for OMERACT RAMRIS is summarized in Table 1, as per Ostergaard et al [14].

Table 1: Scoring system for OMERACT RAMRIS [14]

<table>
<thead>
<tr>
<th>Pathology</th>
<th>Locations</th>
<th>Scoring Scale</th>
<th>Description</th>
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<tr>
<td>Synovitis</td>
<td>3 wrist regions: distal radioulnar, radiocarpal, intercarpal and carpometacarpal joints, and each MCP joint. Excluding the 1st carpometacarpal and MCP joint.</td>
<td>Scale: 0-3, Score 0 is normal, and 1-3 is mild, moderate and severe, respectively. The severities are determined by thirds of presumed maximum volume of proliferating tissue within the synovial compartment.</td>
<td></td>
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<tr>
<td>Bone erosions</td>
<td>Each bone is scored separately: carpal bones, distal radius, distal ulna, metacarpal, metacarpal heads, phalangeal bases.</td>
<td>Scale: 0-10, based on the proportion of eroded bone compared to the assessed bone volume. Score 0 is no erosions, 1 is 10% if bone eroded, 2 is 11-20% of bone eroded, etc.</td>
<td></td>
</tr>
<tr>
<td>Bone oedema</td>
<td>Each bone is scored separately (same as erosions).</td>
<td>Scale: 0-3, based on proportion of bone with oedema. Score 0 is no oedema, Score 1 is 1-33%, score 2 is 34-66%, score 3 is 67-100% of bone oedematous.</td>
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Marzo-Ortega et al [55] carried out a study using MRI to assess metacarpophalangeal joint disease in early psoriatic and rheumatoid arthritis. Twenty patients, 10 with RA and 10 with PsA were assessed with dynamic contrast-enhanced MRI of swollen MCP joints. Synovitis, periarticular bone erosions and oedema were scored according to the OMERACT system for RA and PsA. A
sensitivity test showed good intra-observer reliability (94.3% agreement) by an experienced reader, indicating reliable consistent data sets. The results from the study illustrated MRI can determine number, size and locations of erosions in both RA and PsA and can produce differentiating results between pathologies. This finding appears to be significant for synovitis alone, and the severity of bone erosion in RA and PsA could be observed, but no quantifiable measure was discussed.

A similar conclusion to the Sharp/van der Heijde scoring method can be made for the OMERACT systems, where a disease state score may be somewhat repeatable for a holistic view of a patient over multiple joints. Producing a score using the OMERACT system requires the user to grade the percentage of bone missing from the volume of interest. Firstly, this approach is subjective in 10% increments, and there is no standardization for bone volume of interest. This could cause inaccurate scoring if different bone volumes are used to score the same image when a percentage missing bone is used as a metric. Linear scoring methods for quantifying erosions rely on a judgment of the percentage of bone missing from the original bone morphology. Without a reference to where the healthy bone surface used to be, this judgment could become highly sensitive for quantification of individual joints. Furthermore, if the bone is severely degraded, the quantification becomes more subjective. The presented method will predict the original healthy surface in a reliable and repeatable manner to increase the accuracy of measuring bone degradation on single joints.

**High resolution peripheral quantitative computed tomography (HR-PQCT)** is a non-invasive, low radiation method for assessing bone microarchitecture in both the trabecular and cortical regions of the distal tibia and radius [19], including the carpal and metacarpals of the hands, wrists, ankles and feet. Currently, HR-pQCT is commercially available as XtremeCT (SCANCO Medical
AG, Brüttisellen, Switzerland), for research purposes and not yet readily used in a clinical environment.

Methods for quantification of erosions have been developed for CT and HR-pQCT [24, 27, 56], but a “Gold standard” for erosion and osteophyte assessment is yet to be established. Some popular outcomes for erosion and osteophyte measurement include number of bone lesions, volume of bone lesions in comparison to total bone volume and location of bone lesions within the joint. HR-pQCT is predominantly used to measure bone structural changes over time, serving as assessment of disease progression as a result of drug therapy rather than initial diagnosis.

A study by Stach et al [21], investigates the periarticular bone structure of patients with RA and compares the outcomes to healthy equivalents. In this study, the investigators develop a method to quantify erosion sites, osteophytes and surface changes using HR-pQCT in both 2-dimensional and 3-dimensional reconstructions. High resolution 82 µm isotropic voxel scans were carried out on 58 RA patients and 30 healthy individuals. The various bone lesions were semi-quantitatively scored in each joint according to a 4 grade system (0 to 3), as per Table 2 [21]. The grading was based on the maximum diameter of the erosion, maximum distance between original and new cortical lining for osteophytes and percentage of degraded area for surface changes. However, the maximum diameter was determined by sequencing through 2-dimensional slices, which will not necessarily reveal the maximum diameter of the erosion as erosions are generally complex 3-dimensional shapes. Also, it is sometimes difficult to identify the original cortical lining to define the height of osteophytes from this original reference point.
Table 2: Summary of grading system used in Stach et al [21]

<table>
<thead>
<tr>
<th></th>
<th>Grade 0</th>
<th>Grade 1</th>
<th>Grade 2</th>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Erosion Score</strong></td>
<td>No evidence of erosions</td>
<td>1 questionable erosion with a cortical break less than 1.9 mm</td>
<td>2 or more erosions with cortical break less than 1.9 mm or 1 erosion with cortical break greater than 1.9 mm</td>
<td>Destruction of normal joint structure</td>
</tr>
<tr>
<td><strong>Osteophyte Score</strong></td>
<td>No evidence of osteophytes</td>
<td>Small osteophytes less than 1 mm (height)</td>
<td>Osteophytes greater than 1 mm (height)</td>
<td>Osteophytes leading to destruction of normal joint structure</td>
</tr>
<tr>
<td><strong>Surface Change Score</strong></td>
<td>No surface changes</td>
<td>Surface changes less than 25% of original surface</td>
<td>Surface changes between 25% and 50%</td>
<td>Surface changes greater than 50%</td>
</tr>
</tbody>
</table>

The degree of bone degradation as a result of RA was semi-quantitatively calculated by using a weighted formula encompassing all scores for the various joints and lesion types to produce a final compound score. Interestingly, small bone lesions less than 1.9 mm in diameter were detected in both healthy and RA subjects. Lesions greater than 1.9 mm were highly specific to RA subjects and found predominantly in the radial compartment. This suggests, the ligament insertion sites play a role in erosion formation. Cortical fenestration, defined as regions of severe cortical thinning where trabecular-like structures are visible (Figure 1) [21], were found in RA patients and healthy controls. The severity of this fenestration is highly sensitive to thresholding changes when processing the HR-pQCT images, and highlights the importance of thresholding standardization [21]. As this fenestration is a characteristic of thresholding and occurs in both healthy and diseased patients, it would be acceptable to consider disregarding cortical breaks within this description. This is particularly important for bone surface-only based analyses, where cortical breaks leading directly into the trabecular region are undesirable.
Figure 1: 3D rendering of metacarpophalangeal joint showing fenestration. (A) Has a higher threshold than (B), and illustrates the substantial difference affected surface area [21].

A similar assessment strategy was implemented by Finzel et al [40] to characterize bone spur (osteophyte) formation in patients with PsA. HR-pQCT imaging was used to assess the number, size and distribution of bone spurs. Patients with PsA were required to fulfill the criteria of the Classification of Psoriatic Arthritis (CASPAR) [57]. The 2\textsuperscript{nd}, 3\textsuperscript{rd} and 4\textsuperscript{th} MCP joints were scanned using isotropic 82 µm voxel image resolution, 80 slices distal and 242 slices proximal of the upper margin of the metacarpal head [40]. Localization, number and size of bony spurs were evaluated according to palmar, ulnar, dorsal and radial quadrants of the metacarpal heads and phalangeal bases. The sizes of the osteophytes were measured as the distance between the original cortical surface and the new proliferated cortical lining. The bone spurs were scored according to height as follows: 0 = no bone spur, 1 = bone spur < 1mm, 2 = bone spur > 1mm and 3 = large widespread bone spurs. It was found that an increased number of bone spurs were identified in the 2\textsuperscript{nd} and 3\textsuperscript{rd} metacarpal head compared to the 4\textsuperscript{th} MCP joint and phalangeal bases. Also, bone spur formations were found predominantly on the radial quadrant [40]. This finding contradicts similar findings as reported by Stach et al [21], in which osteophyte formation showed a formation prevalence to the palmar and dorsal quadrants. Limitations of the study [40] include: 1) the reliance on observers to identify osteophytes. These lesions are not always clearly identifiable especially for growths < 1
2) Measuring the height of the osteophytes by estimating the original cortical surface topography.

As previously mentioned, there is no current gold standard methodology for scoring bone lesions using CT scanning techniques. However, several publications report positive results on the visual analysis of erosion presence, number and size, and user reliability as a means to quantify bone degradation in RA patients [18–23]. Poggenborg et al [56], carried out a study to characterize bone proliferation in patients under adalimumab therapy using HR-pQCT and radiography. HR-pQCT and radiography were performed concurrently at various study timepoints for direct comparison, on 41 patients with PsA. The HR-pQCT scans were carried out on the 2nd to 5th MCP joints, with a resolution of 0.4 x 0.4 mm and slice thickness of 0.8 mm [56]. The CT images were scored according to the definitions of the Outcome Measures in Rheumatology Clinical Trials (OMERACT) PsA magnetic resonance imaging scoring system (PsAMRIS) [52]. The erosion scoring is graded on a scale of 0 to 10, as discussed previously. In the radiographic images, erosions were scored using the modified Sharp/van der Heijde (SHS) for PsA [58] and scored from 0 to 3. Results from this study found a significant correlation with disease duration and age. Erosions occurred more frequently in the 2nd and 3rd metacarpal heads than the other MCP joints and phalangeal bases. This method is very similar to Dohn et al [36, 59], using OMERACT RAMRIS scoring system and HR-pQCT as a benchmark for RA patients. These studies investigated a longitudinal comparison between CT, MRI, radiography and ultrasonography. Isotropic voxel (0.4 x 0.4 x 0.4 mm) HR-pQCT images were scanned on the 2nd to 5th MCP joint of 52 RA patients. The reports conclude MRI and US have high sensitivity towards erosion detection, and MRI showed greater correlation to CT in erosion detection than radiography.
3.4 Three Dimensional Algorithms for measuring bone deformities

Duryea et al [27] developed a semiautomated three dimensional segmentation method to quantify carpal bone volume changes on wrist CT scans for arthritis assessment. The goal of this research was to decrease the segmentation time of each carpal bone for a quicker more user-friendly volume measurement. A hand phantom was used as the initial test subject where artificial erosions were created in the model to simulate arthritis progression, before the system was used on in vivo subjects. The algorithm involved manually selecting the region of interest with the carpal present. Then, the reader was required to scroll through each slice and place a seed point near the center of the carpal. The software then uses an edge tracking routine based on grey scale differentiation. Once the first slice was successfully segmented, the reader instructed the software to move onto the next adjacent slice and use the initial contour as a starting template. An active contour refinement tool based on grey scale gradient cost function was implemented to better refine the contours. The root mean squared standard deviation for the total carpal volumes was 21 mm$^3$ for the phantom and 44 mm$^3$ for the in vivo subjects [27]. This method works well on bone with easily identifiable deformities for a user to input the erosion location. However, this method does not aid the user in identifying deformities and requires intervention at the cortical break site.

Topfer et al [60] developed a precise semi-automated three-dimensional segmentation method for quantification of bone erosions in HR-pQCT scans. The outcome measures included erosion volume, surface area and shape parameters. The aim was to assess anti rheumatic therapies by determining dimensional changes of erosions. HR-pQCT scans with a resolution of 120 µm of the second to fourth MCP joint were obtained from patients with RA. The segmentation algorithm required a user to identify each erosion and place a seed point within each of them. A closed spherical surface is iteratively inflated until it stops at voxels with a high gray values. This forms
the volume of interest within the erosion. However, often the sphere would leak into the trabecular region if the erosion was not closed. The leaked sphere is then iteratively eroded until each leaked volume is separated from the main erosion. These separate leaked areas are then dilated until all volumes are reattached. This method seems to require a substantial amount of manual adjustment when the automated segmentation does not correctly represent the erosion. Furthermore, the observer is required to identify each erosion, which is not always obvious and may induce incorrect assessment. This method works well for monitoring small changes in individual erosions.

Peters et al [25, 61] report a fully automated algorithm for detection of small cortical breaks in HR-pQCT images of metacarpophalangeal joints. The aim of the study was to develop a sensitive and objective tool to identify cortical interruptions for aid in detecting erosions. HR-pQCT scans of the 2nd MCP joint were acquired from 8 diseased patients and 3 healthy individuals at 82 µm isotropic voxel resolution. In this study, the threshold to detect erosions was set at 4 voxel thickness (0.328 mm) determined as a function of the average metacarpal cortical thickness. The minimum intra-cortical interruption volume that can be detected by the algorithm is 20 voxels (0.011 mm³) [61]. The algorithm detected cortical breaks from a series of voxel dilations and erosions whereby the cortical region of the bone is isolated to a 4-voxel depth. Any discontinuities in the segmented cortical bone is identified as a cortical break. The author noted the significantly higher occurrence of cortical breaks in the bone surface compared to other studies. It was not clear if a sensitivity analysis was carried out on changing the thresholding criteria, as the algorithm may be detecting fenestration as previously discussed. Many of the detected cortical breaks may not necessarily represent bone degradation as a result of disease. Furthermore, this algorithm is very sensitive motion artefacts, and a problem of many false positive results was reported. This algorithm may
be useful in aiding other segmentation techniques that require seed points for erosion detection.
For our study, a similar outlook is presented.

To summarize, the method reported in this current study aims to address the shortcomings of past algorithms particularly in the requirement for user interaction to subjectively identify sites of erosion or growths. The proposed method accounts for a true 3D surface when predicting the layout of the original healthy surface from the surface of a degraded bone. Also, this method has the potential to be fully automated after the bone surface has been segmented for analysis with no requirements for manual manipulation to estimate missing surface.

### 3.5 Coherent Point Drift

Coherent Point Drift (CPD), as developed by Myronenko and Song [62], is a non-linear data transformation algorithm and is the primary image registration technique used in this study. This algorithm aids in predicting healthy surfaces from diseased bone surfaces. The goal of this registration is to find correspondence between two sets of points and the resultant transformation that maps one point set to the other. In the context of this study, the points in a given point set are vertices strategically placed on the 3D bone surface. This algorithm is noted to be robust to noise, outliers, and missing points [63], which we deem beneficial in predicting missing bone surface.

Non-rigid point set registration uses non-linear approximations for alignment and the distances between points are not necessarily conserved during the transformation. CPD considers the alignment of two point sets as a probability density estimation problem, where one point set represents Gaussian mixture model (GMM) centroids and the other one represents the reference point set [63]. The Gaussian centroids are transformed from their initial position to their final position in a restricted sequential motion process [64]. To maintain smoothness in the underlying
transformation a motion coherence constraint is implemented as proposed by the Motion Coherence Theory [65], where closely associated points move in a coherent, controlled manner. Several parameters within the code could be manipulated where a trade-off between data fitting and smoothness regularization existed. The interaction between points could be tailored to increase the conformity of a cluster of points or maintain a pure translation transformation. Lastly, the capture range for each Gaussian mixture component could be set. For a detailed derivation of the CPD algorithm, refer to [62, 66].

Zhang et al used CPD to produce 3-dimensional reconstructions of patient specific femurs for computer-assisted diagnosis and surgery [67]. The study method extracted the patient specific femur edge (2-dimensional) and using the CPD algorithm, non-rigidly fitted the patient femur edge to an ideal reference femur shape, from which a 3D model was rendered. Dupej et al [68] used CPD for face matching registration. The face shape registration was used to track the progression of cleft pallet corrective surgery with age over several years. Mirzaalian et al [69] used coherent point drift to find correspondence between matching moles on the backs of patients from images taken at different time points. The CPD algorithm provided a useful platform to track changes in mole structure, size and any additional mole formation, which helps in detecting malignancies. The overarching theme of the CPD algorithm is the robustness against noise and missing data. These attributes are favorable to our study in predicting missing bone as a result of erosion or identifying outliers in the form of periosteal bone growths. As the topology of degraded bone has a substantial variation, the CPD algorithm is well suited to estimate data points where large amounts are missing or data points are inconsistent with the general shape as observed in bone surfaces degraded from arthritis.
3.6 Literature Review Conclusion

Individuals suffering from RA and PsA experience joint degradation in the form of bone erosions and/or periosteal bone growths. The MCP joint is a common area of disease presence with erosions commonly forming in the radial aspects and growths also on the radial sides. Erosions typically take the form of ‘U’ shaped voids ranging in depth from 1.9 to 4.9 mm, which is relevant for clinical diagnosis. Similarly, growths are described as convex dome shaped protrusions where maximum heights can exceed 2 mm. Imaging modalities are used to recreate the diseased bone surface in 3D for a deeper understanding of deformity shape, of which HR-pQCT has the highest resolution. As a result, HR-pQCT is often used as the standard for comparisons when researching other imaging modalities. Several algorithms have been developed for quantification of deformity volume or size and used to monitor drug therapies with greater sensitivity than what is currently clinically available. The majority of these algorithms require human input to identify deformity locations or modify incorrectly segmented regions of interest. Furthermore, many of these algorithms cannot predict where the original bone surface used to be and require users to guess. This inherently introduces subjectivity and errors, especially when the deformities are very large or not easily identifiable. The CPD algorithm is capable of using existing data in a set to predict missing data by using samples of ideal data sets. The algorithm is reported to be robust against missing points and outliers, which are good attributes for predicting missing or original bone surface. The present study will address the limitations of current automated algorithms to diagnose bone degradation in arthritic patients by systematically predicting the healthy surface of an imaged diseased surface to make quantifiable measurements of bone erosions and periosteal growths. Inherently, this method is capable of objectively, repeatably and automatically identifying sites of bone degradation in a 3D space. This is advantageous over other methods, which require subjective
user input to identify erosions or growths before measurements are made in a 2D slice-by-slice process. Furthermore, the present study introduces an algorithm with the novel ability to detect erosions and growths adjacent to one another on the same degraded bone surface.

4 Methods

4.1 Subjects and Image Acquisition

*In vivo* images of the second metacarpophalangeal (MCP) joint were acquired using HR-pQCT (XtremeCT, Scanco Medical AG, Brüttisellen, Switzerland). The region of interest consisted of 330 slices with 82 µm isotropic voxel size spanning a length approximately 15 mm of the distal metacarpal head and 12 mm of the proximal phalangeal base (Figure 2).

The HR-pQCT images were acquired for three cohorts: healthy individuals, subjects with RA and subjects with PsA. Imaging was carried out on the predominantly affected hand of 17 RA patients (age 61±18 years, 12 females, 5 males) and 17 PsA subjects (age 60±18 years, 7 females, 10 males), whom were enrolled from the Rheumatology Division at University of Massachusetts Memorial Medical Center (UMMMC). Each patient had radiographic confirmation of erosions and periosteal bone formation on the imaged hand. The healthy cohort consisted of 12 subjects (age 52±14 years, 7 females, 5 males), devoid of known immuno-deficiencies. All subjects provided written informed consent for this approved study.
4.2 Surface Transformation Algorithm

Overview

The algorithm designed to calculate bone surface abnormalities is summarized in Figure 3, and consists of the following steps: (1) the respective phalangeal base and metacarpal head are segmented from the HR-pQCT images using a fixed intensity threshold and converted into 3D triangulated surface meshes; (2) Corresponding anatomical points are applied to the cohort of healthy surfaces; (3) A generic healthy surface of the MCP joint is generated by averaging the corresponding points on the healthy surfaces to produce healthy reference surfaces; (4) The healthy reference surfaces are non-rigidly transformed to the shape of each diseased subject surface, whilst retaining the original healthy features; (5) periosteal bone growth and erosions are defined as regions where the surface of the diseased bone deviates from the transformed healthy bone surface.
A detailed work flow instruction is provided in Appendix I, outlining the steps to produce the outcome measures from patient images.

Figure 3: Illustration of algorithm overview as describing the dependent chronological order of events to estimate a healthy bone surface from a diseased surface.
Three-dimensional surface generation

HR-pQCT images were converted to three-dimensional (3D) triangulated surface meshes (Mimics 18 & 3Matic 10, Materialise NV, Leuven, Belgium, 2015) in preparation for surface-to-surface registration. The internal trabecular bone region was excluded in this analysis. The pixel data representing bone was segmented using a fixed density threshold of 0.41 g/cm³ throughout all images. A binomial blur filter was then applied in 3 iterations to each CT slice to reduce noise, as only the outer bone surface was of interest.

Varied amounts of motion artifacts were observed during the scan process and 3D surface generation. A smoothing factor of 0.5 was applied in 10 iterations during the surface generation to remove any small artefacts and irregular triangulation, as available in the Mimics 18 and 3Matic 10 software (Materialise NV, Leuven, Belgium, 2015). For larger motion induced surface irregularities, manual segmentation techniques in 3D and per slice basis (2D) were used at the user’s discretion. Furthermore, a customized code (MATLAB 2015a, The MathWorks, Inc., Natick, MA, US) was implemented during the image acquisition process to align all images between stacks. The entire imaged region of interest was composed of three image stacks (110 slices each), which were misaligned during image construction from raw data. This misalignment would result in an inaccurate surface topology during 3D surface generation. Lastly, to reduce cortical fenestration in the segmented mask because of poor imaging quality, a surface wrap was specified for the 3D surface with a gap closing distance of 0.2 mm. This distance was chosen as per observations made in this study and fall below the size of fenestration cortical breaks observed in [21]. Cortical breaks smaller than 0.2 mm were deemed not clinically relevant and therefore, where necessary, were excluded.
Scaling and orienting surfaces

To define a common analysis region, all the surfaces’ (metacarpals and phalanges) centroids were aligned and volumes scaled to a specific reference size and orientation. This was carried out using a rigid probabilistic transformation [62] as defined by a subsection of the CPD algorithm, where only translation, rotation and scaling transformations are carried out. This included mirroring all left-hand surfaces to a right-handed orientation. The scaled and aligned healthy 3D meshes were truncated proportionally, according to a fixed distance from the joint space, 12 mm for the metacarpal head and 9 mm for the phalangeal base. The truncation is carried out using a specialized code in MATLAB 2015a (The MathWorks, Inc., Natick, MA, US). This served to reduce variability between subjects of different sizes by normalizing inter-subject bone size and spatial position.

Creating a healthy reference surface

A single “generic” healthy reference surface was produced from the $k = 12$ healthy subject surfaces. The proportioned healthy surfaces were characterized by $M = 10,000$ vertices (average vertex point-to-point resolution of 0.28 mm) positioned at corresponding anatomical locations (Figure 4A). This allowed for a point-to-point correspondence between each $n – \{\text{number of healthy surfaces}\}$ in the form of comparable point sets [70–73]. This was carried out by mapping the dense, template point set $Y = (y_1, \ldots , y_M)$ in $\mathbb{R}^3$ to each healthy surface point set $X = (x_{11}, \ldots , x_{kn})$ using a non-rigid, modified Coherent Point Drift (CPD) transformation [62, 66]. The CPD algorithm is a probabilistic Gaussian mixture model (GMM), non-rigid transformation technique used to register two dissimilar point sets [66, 74]. The result was a single healthy reference surface (Figure 4B), generated by averaging the Euclidean space between all the $k = 12$ corresponding transformed template point sets $Y’$ to get a single average point set, such that:
Healthy Reference Surface = \( \frac{\sum_{i=1}^{k} V'_i}{k} \), where \( i = 1, ..., k \).

Figure 4: (A) Healthy reference vertices calculated by averaging vertices assigned to corresponding locations on the healthy cohort bone surfaces. (B) The corresponding healthy reference surface generated from the vertices.

Estimating healthy surfaces from diseased patient scans

To differentiate between healthy and diseased surface regions, the healthy reference surface was non-rigidly transformed to each patient surface mesh. The result was a new bone surface with healthy features that had similar size and geometry to the diseased surface. To accomplish this, a CPD algorithm was adapted to warp the reference healthy surface mesh (Figure 5A) into the shape of each patient specific diseased surface mesh (Figure 5B), whilst retaining the “healthy” features. This allowed prediction of the geometry of a patient healthy surface (Figure 5C) from the diseased surface.

Figure 5: (A) The reference healthy surface is non-linearly transformed into the shape of the (B) diseased bone surface using CPD. The transformed surface is now considered the (C) estimated healthy surface of the original diseased surface.
The CPD algorithm lets the user choose parameters to essentially control the rigidity of the non-linear transformation. A reference point set can be transformed to the exact shape of the target point set (less rigid) or retain more features of the reference point set (more rigid) controlled predominantly by two parameters: $\beta$ and $\lambda$. Parameter $\beta$ controls the organization and strength of interaction between points in a set. Small values of $\beta$ correspond to locally smooth transformation, vice versa large values of $\beta$ will produce pure translation transformation [64]. Simply, parameter $\beta$ maintains the order and relation between points representing a surface to retain the shape of the reference point set. Parameter $\lambda$ represents the trade-off between data fitting and smoothness regularization [64], which in part controls the rigidity of the transformation and has a small role in controlling the capture size (or kernel size) of the GMM component. The capture size is important as there exists an ideal ratio between this and the volume/size of the surface and its features to be transformed.

Initial tests are carried out to help determine the ideal combination of parameters to suit the metacarpophalangeal joint and a typical erosion volume. For a similar size, low complexity 3D object the code was initially supplied with $\beta = 3$ and $\lambda = 2$. This preliminary process entailed transforming a healthy surface to the shape of an unhealthy surface with varying parameter values, increasing from low to high. Observations from preliminary algorithm runs suggest higher $\beta$ values retain more of the reference surface’s healthy features, whilst lower values of $\lambda$ provide better transformation shape matching to the diseased surface. After several iterative steps of surface transformations, an acceptable value of $\beta = 11$ and $\lambda = 2$ are chosen from visual confirmation (Figure 6). Several random examples of predicted surfaces from the iterative process are provided in Figure 6 with varying values of $\beta$ and $\lambda$ compared to the original diseased bone surface.
Additional parameter testing is carried out to determine if the chosen parameters are acceptable for the proposed application in terms of predicting healthy bone surface in the presence of a typical erosion. To do this, a known volume of 26 mm³ is removed from a healthy bone surface segmented in Mimics 18 software (Materialise NV, Leuven, Belgium, 2015) to represent a typical erosion. A generic reference surface is transformed to the bone surface with the manufactured erosion. The predicted volume of the erosion is measured from the difference in volume between the transformed surface (predicted healthy surface) and the bone surface with erosion. Also, the predicted healthy surface volume is compared to the original healthy bone surface (without manufactured erosion) to indicate the accuracy of the predicted healthy bone surface to a real surface. These steps are repeated for increasing values of $\beta$ in increments of two starting at 1 through to 11. An acceptable $\beta$ is chosen when the CPD code ignores the erosion and predicts the original healthy surface at the erosion region of interest. Thereafter, multiple simulations are run by varying the parameter $\lambda$ from 1 to 9. The ideal combination of $\beta$ and $\lambda$ predicts a healthy surface at the erosion site and transforms to the shape of the original bone surface (no erosion). The parameters have successful outcomes when the measured erosion volume tends to zero and the total predicted bone volume tends to the original healthy bone volume.
In Figure 7 below, the measured bone volume tends to zero as $\beta$ increases with ideal parameter values being 7 or greater. In Figure 8, the predicted healthy bone volume tends the original bone volume (no erosion) as $\lambda$ decreases with values less than 2 being ideal in this scenario. Therefore, the chosen parameters of $\beta = 11$ and $\lambda = 2$ are acceptable values for this application. However, further sensitivity tests on multiple bone sizes, multiple deformities and degrees of disease degradation are required to increase accuracy. It must also be noted that the outcome measures reported here are dependent on the chosen parameters or the CPD code.

*Figure 7:* The effects of parameter $\beta$ on the measured erosion volume. Ideally, the parameter should cause the transformation to not be affected by the erosion and accurately predict the healthy surface. Therefore, an erosion volume of 0 is desirable.
Figure 8: The effects of parameter $\lambda$ on the measured erosion volume. Ideally, the parameter should help the transformation predict a healthy surface with the same volume as the original bone surface. Therefore, a predicted bone volume close to the value of the original bone volume is desirable.

Quantifying surface deformity

We characterized surface deformity as the deviation of the patient bone surface from the corresponding predicted healthy surface. A negative distance represented bone erosion (Figure 9, Detail A), whilst a positive distance represented periosteal bone growth (Figure 9, Detail B). These distances, calculated over the entire 3D surface, were used to develop outcome measures to describe the degree of bone degradation as a function of surface deviation, described below.

1. **Mean distance between surfaces**: the extent of the deviation between the predicted healthy surface and the diseased surface was represented as an average distance, where a large mean distance indicated a greater occurrence of surface deviation in either the positive or negative direction. A negative distance would indicate more erosions, and vice versa for growths.
2. **Maximum positive distance and maximum negative distance between surfaces:**

   Maximum periosteal bone growth height (positive distance) and erosion depth (negative distance) were expressed in mm.

3. **Average Standard deviation of distances between surfaces:** described the surface variation of the diseased bone surface. It was assumed bone surface with greater standard deviation between the predicted healthy surface and diseased surface was an indication of greater joint degradation.

4. **Percentage surface area of periosteal bone growth and erosion (%):** The total bone surface area determined to be “diseased” (i.e., comprised of abnormal erosions or growths) was represented as a percentage of the total analyzed surface area. A threshold of 0.6 mm was selected from the sensitivity analysis, described in Section 0, where distances exceeding this threshold were considered “diseased”. This outcome was further categorized into areas of erosion and periosteal bone growth, each expressed as a percent of the total surface area.

5. **Number of independent erosion sites and bone growths:** The number of standalone erosion sites and periosteal bone growths were tallied for each surface.
In this context, to measure the distance between the predicted healthy surface and the diseased bone surface: the healthy surface is defined as a point cloud with 10,000 vertices distributed over the surface and the diseased surface is defined as a triangulated mesh. Each triangulation is characterized by three vertices and a face normal. The algorithm calculates the shortest line connecting a point on the healthy surface and a 3D triangulation on the diseased surface using the direction of the respective face normal. The nearest point on the surface as well as the distance is returned as a measurement. The distance is signed according to face normals to identify on which side of the surface the query point resides. Using the triangulation as the boundary condition for area when searching for a respective face for each point in the face normal direction, restricts the algorithm from calculating non-representative distances.

Figure 9: Cross-sectional profile of metacarpophalangeal joint with diseased surface (red) overlaid the corresponding predicted healthy surface (blue). In Detail A, the graphic illustrates a negative distance between the predicted healthy triangulated surface to the nearest diseased surface vertex in the normal direction of the respective triangle plane (erosion). Similarly, Detail B shows an example of a positive distance (periosteal bone formation).
4.3 Sensitivity Analysis

To determine the degree to which the calculated parameters depended upon the specific reference surfaces used to produce the generic healthy surface, we conducted a sensitivity analysis using various healthy surface combinations. To accomplish this, we quantified the maximum periosteal bone growth height for three randomly selected diseased surfaces using the various reference surfaces with different combinations of healthy bone surfaces. The percent mean difference of the outcome was calculated for each reference surface group. Mean and SD were calculated for each diseased surface. The reference surface groups are made of various combinations of healthy surfaces as listed below:

1. **Randomized surfaces:** To determine the extent to which the specific healthy surfaces included within the generic surface mattered, nine different combinations of three healthy surfaces were selected to create different generic surfaces. The three healthy surfaces were chosen from a pool of twelve healthy surfaces by a random number generator implemented in MATLAB 2015a (The MathWorks, Inc., Natick, MA, US).

2. **Number of surfaces:** To determine how many healthy surfaces were required to create a reliable generic healthy reference surface, the number of healthy surfaces used to create the generic surface increased from two to twelve.

3. **Gender specific surfaces:** To determine whether gender-specific reference surfaces were appropriate, we compared all-male (n = 6) and all-female (n = 6) reference surfaces to female data. The raw and percent difference between female:male and male:female pairs were calculated for four diseased female surfaces.
4.4 Validation

To quantify the accuracy and limitations of the algorithm, a series of artificial erosions and periosteal bone growths with known dimensions were manufactured on five different healthy surfaces. Algorithm-based measures, maximum erosion depth, maximum growth height, number of individual erosions and number of individual growths were compared to the actual known values. The deformities were constructed by manual manipulation of the already segmented HR-pQCT image masks.

Three sizes of erosion were constructed as ‘U’ shaped voids as described in [33]. Erosions were defined by the diameter (Ø) of the cortical break (assumed to be circular) and the depth (L) of the erosion, as shown in Figure 10. The volume (V) and diameter-to-depth ratio was used as a metric to describe each category of erosion and maintain inter-surface consistency in erosion construction. Erosions ranged from 1.9 to 4.9 mm in depth. Refer to Table 3, summarizing the geometry and description of each deformity.

Similarly, three sizes of periosteal growths were constructed as convex dome shaped protrusions (Figure 10). Dimensions and shapes for both erosions and growths were selected based on clinical reports [22, 34–37]. Periosteal growths ranged from 0.6 to 1.9 mm in height with varying height-to-diameter ratios (Table 3).
All types of artificial erosions and growths were placed individually on each of the five healthy surfaces. To detect multiple deformities and erosions and growths adjacent to one another is an important tool for clinical diagnosis of joint degeneration, especially in cases of psoriatic arthritis. The extent to which the algorithm can detect a combination of deformities is evaluated by applying: all three types of erosions on each of the five healthy surfaces (multiple erosion group), all three growths (multiple growth group) and a combination of all erosions and all growths on the five healthy surfaces (combined group), as defined in Table 3. The various deformities and combinations thereof resulted in 90 different simulations.
Table 3: Description of artificial deformities manufactured on healthy bone surfaces for algorithm validation. Each category described was applied to 5 different healthy bone surfaces.

<table>
<thead>
<tr>
<th>Simulation Category: Deforrmity ID</th>
<th>Geometry (approximate)</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Ø (mm)</td>
<td>L (mm)</td>
</tr>
<tr>
<td>Erosion 1</td>
<td>3.0</td>
<td>4.3</td>
</tr>
<tr>
<td>Erosion 2</td>
<td>2.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Erosion 3</td>
<td>3.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Growth 1</td>
<td>3.0</td>
<td>2.0</td>
</tr>
<tr>
<td>Growth 2</td>
<td>2.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Growth 3</td>
<td>3.5</td>
<td>1.0</td>
</tr>
<tr>
<td>Multiple Erosions</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Multiple Growths</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Combined erosions and growths</td>
<td>NA</td>
<td></td>
</tr>
</tbody>
</table>

We assessed: (1) the ability to detect an erosion or growth, by systematically varying the cut-off threshold, starting at zero and increasing to approximately 4.5 mm for erosions and 3 mm for growths. This metric was the minimum distance between surfaces to be considered an erosion or growth and was determined from the average Youden’s Index of the sensitivity and specificity plots for the erosions detected on the 5 healthy surfaces. (2) The accuracy of erosion depth calculations. This was calculated as the root mean squared error (RMSE) of the measured versus actual depth or height of the deformity. (3) The overall fit of the diseased bone predicted healthy surface onto the corresponding healthy bone predicted healthy surface. A predicted healthy surface was generated for the original healthy bone surface and a predicted healthy surface was generated for the manufactured “diseased” surface, where the overall fit was expressed as the mean distance between the predicted and actual surface, in those regions without artificial erosions and growths.

4.5 Application to Patient Cohort

After determining the best performance parameters from the sensitivity and validation studies, the algorithm was applied to the healthy and diseased patient cohorts. The various outcome measures as listed in Section 4.2 were calculated for each cohort:
The data normality was checked using both Kolmogorov-Smirnov and Shapiro-Wilk tests. One way ANOVA was used to compare the listed outcomes of healthy, RA, and PsA patients. Post hoc t-tests with Bonferroni corrections were used to detect between-group differences in data sets with normal distributions. Kruskal-Wallis One Way Analysis of Variance on Ranks with post hoc Dunn’s Tests were carried out on several data sets with non-normal distributions. A criterion of $\alpha=0.05$ was deemed significant. To determine the degree to which the algorithm-calculated metrics were associated with disease-related bony features, stepwise discriminant analysis was used to blindly classify two mixed groups: 12 healthy plus 17 RA patients, and 12 healthy plus 17 PsA patients.

5 Results

5.1 Sensitivity Analysis

The surface matching algorithm was not very sensitive to: the number of surfaces used to create the generic healthy surface, the specific healthy surfaces used and categorizing the healthy surfaces into female or male specific.

When the number of surfaces used to create the generic healthy surface was increased from 2 to 12, the calculated maximum periosteal growth for the diseased surfaces that were tested varied from 0 up to 129 $\mu$m. This corresponds to maximum mean percentage difference of 26% (Table 4).

Different combinations of healthy surfaces were used to create the generic healthy surface, which resulted in the calculated maximum periosteal growth to vary from 39 up to 260 $\mu$m. This corresponds to a maximum mean percentage difference of 34% (Table 5).
Categorizing the reference surface into female and male specific healthy surfaces and computing the maximum periosteal bone growth for four different female bone surfaces, revealed the algorithm to be unsensitive to this input. The maximum difference in predicted periosteal bone growth was 150 μm (Figure 11).
Table 4: The effect of number of healthy surfaces used to generate the generic healthy reference surface. Here, sensitivity was calculated as the percent difference between the outcome of interest (max positive distance) when calculated with the candidate healthy reference, versus the average value. i.e., percent difference = (candidate dist – mean dist)/mean dist.

<table>
<thead>
<tr>
<th>Number of healthy surfaces used in reference surface</th>
<th>% difference of max positive distance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diseased Surface 1</td>
</tr>
<tr>
<td>2</td>
<td>4%</td>
</tr>
<tr>
<td>3</td>
<td>26%</td>
</tr>
<tr>
<td>4</td>
<td>3%</td>
</tr>
<tr>
<td>5</td>
<td>0%</td>
</tr>
<tr>
<td>6</td>
<td>2%</td>
</tr>
<tr>
<td>7</td>
<td>1%</td>
</tr>
<tr>
<td>8</td>
<td>2%</td>
</tr>
<tr>
<td>9</td>
<td>4%</td>
</tr>
<tr>
<td>10</td>
<td>16%</td>
</tr>
<tr>
<td>11</td>
<td>4%</td>
</tr>
<tr>
<td>12</td>
<td>5%</td>
</tr>
<tr>
<td>Mean max positive distance</td>
<td>0.498 mm</td>
</tr>
</tbody>
</table>

Table 5: The effect of specific combinations of three healthy surfaces, denoted as combinations A-I, were used to generate the generic healthy reference surface. Sensitivity was calculated as the percent difference between the outcome of interest (max positive distance) when calculated with the candidate healthy reference, versus the average value. i.e., percent difference = (candidate dist – mean dist)/mean dist.

<table>
<thead>
<tr>
<th>Three-surface combinations to generate the healthy reference surface</th>
<th>% difference of max positive distance</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Diseased Surface 1</td>
</tr>
<tr>
<td>A</td>
<td>5%</td>
</tr>
<tr>
<td>B</td>
<td>6%</td>
</tr>
<tr>
<td>C</td>
<td>7%</td>
</tr>
<tr>
<td>D</td>
<td>15%</td>
</tr>
<tr>
<td>E</td>
<td>7%</td>
</tr>
<tr>
<td>F</td>
<td>11%</td>
</tr>
<tr>
<td>G</td>
<td>34%</td>
</tr>
<tr>
<td>H</td>
<td>17%</td>
</tr>
<tr>
<td>I</td>
<td>8%</td>
</tr>
<tr>
<td>Mean max positive distance</td>
<td>0.506 mm</td>
</tr>
</tbody>
</table>
Figure 11: The effect of categorizing the reference surface to female or male specific. Each female specific surface and each male specific surface was mapped to four different female surfaces (A - D), from which the maximum periosteal bone growth was computed. The differences in the growth prediction for each surface pair is presented and is used as an indication of the sensitivity of the algorithm to this input. The error bars represent 1 standard deviation of the between surface differences for each prediction.

5.2 Validation

A cut-off threshold of 0.6 mm was able to detect both erosions and periosteal growths with 87.5% sensitivity and 86.8% specificity, as per the receiver operator curve (ROC) in Figure 12. The specificity-sensitivity plots for detecting erosions, periosteal bone growths and a combination of both are shown in Figure 13, from which the cut-off threshold was determined. This cut-off was used for all subsequent calculations.

Overall, the algorithm predicted erosion depth more accurately than periosteal bone growth height (Figure 14). Erosion depth RMSE was 4 ± 3% of the actual value, corresponding to an average precision error of 50 μm. The heights of periosteal bone growths were predicted to within 20 ±
13\%, corresponding to an average precision error of 210 \mu m. The majority of deformity predictions were under-predicted, 72\% of erosion depths and 94\% of growth heights. The algorithm was best at measuring deep, narrow erosions, and worst at measuring wide, gradual periosteal growths. Overall fit between surfaces was excellent, with an average distance of 0.08 mm. The linear regression from a one-to-one plot (Figure 15) produced a gradient of 0.93, indicating a close fit to the perfect prediction (gradient 1).

![ROC Curve](image)

Figure 12: Receiver operator curve for varying the cut-off threshold in detecting multiple erosions and growths adjacent to one another on the same bone surface.
Figure 13: Decision plots for choosing cut-off threshold from the sensitivity and specificity to determine diseased bone surface. The sensitivity and specificity are plotted for detecting erosions (A), periosteal bone growths (B) and detecting deformities on surfaces with a combination of erosions and growths adjacent to one another (C).
Figure 14: The relative error between the predicted values and the actual values of the deformity measurements represented as a percentage of the size of the deformity. Relative error = (predicted value – actual value)/actual value %. Erosion depths are illustrated in blue and periosteal bone growths in red.
Figure 15: Results from a one-to-one comparison of the predicted deformity values to the actual deformity values. Erosion depths are illustrated in blue and periosteal bone growths in red. The black line represents a perfect prediction to the actual value equivalent and the dashed grey line shows the linear regression of all predicted data points.

5.3 Application to Patient Cohort

The algorithm objectively illustrated areas of abnormal bone degradation and growth, accompanied by corresponding output data from which bone surface topology could be further analyzed (Figure 16). In the metacarpal head, patients with PsA and RA had maximum positive distances (periosteal bone growth) that were 55% and 57% greater than in the healthy cohort. Similarly, PsA and RA patients had maximum negative distances (erosions) for both the metacarpal head and phalangeal base that were over 85% greater than the healthy cohort (Table 6).
Patients with PsA had significantly greater percentages of the metacarpal head and phalangeal base surface area that were eroded compared to the healthy cohort (Table 6). The algorithm detected significantly more erosion sites on the metacarpal head in both PsA and RA patients, compared to the healthy cohort. Finally, the maximum depth of erosions was significantly greater in both the metacarpal head and phalangeal base of RA subjects, and the phalangeal base of the PsA subjects.

The outcome variables were able to discriminate healthy versus RA patients better than healthy versus PsA patients. At the metacarpal head, erosion depth and average surface matching successfully discriminated 96.6% of healthy and RA patient surfaces from each other (11/12 healthy and 17/17 RA surfaces). At the phalangeal base, a combination of erosion depth, periosteal growth height, percent surface eroded and surface variability correctly classified 100% of healthy and RA patient surfaces. At the metacarpal head of healthy and PsA patients, the number of erosion sites and average surface matching discriminated 86.2% correctly (12/12 healthy and 13/17 PsA surfaces). However, at the phalangeal base, erosion depth alone was selected, which discriminated 72.4% of surfaces correctly (12/12 healthy and 9/17 PsA surfaces).
Table 6: Results comparing mean outcome measures of healthy subject surfaces to PsA diseased subject surfaces and RA diseased subject surfaces. Differences between PsA and RA surfaces are included. The outcome measures are reported as mean values ± standard deviation.

<table>
<thead>
<tr>
<th>Outcome Measure</th>
<th>Metacarpal Results</th>
<th>Phalangeal Base Results</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Healthy surface</td>
<td>PsA Diseased Surface</td>
</tr>
<tr>
<td>Mean distance between surfaces (mm)</td>
<td>-0.07 ± 0.04</td>
<td>-0.05 ± 0.07</td>
</tr>
<tr>
<td>Maximum positive distance between surfaces (mm)</td>
<td>0.60 ± 0.13</td>
<td>0.93 ± 0.45</td>
</tr>
<tr>
<td>Maximum Negative distance between surfaces (mm)</td>
<td>-0.71 ± 0.28</td>
<td>-1.31 ± 0.65</td>
</tr>
<tr>
<td>Average Standard deviation of distances between surfaces (mm)</td>
<td>0.22 ± 0.05</td>
<td>-0.32 ± 0.17</td>
</tr>
<tr>
<td>Percentage surface area of periosteal bone growth (%)</td>
<td>0.1% ± 0.2%</td>
<td>3.8% ± 6.4%</td>
</tr>
<tr>
<td>Percentage surface area of erosions (%)</td>
<td>0.6% ± 1.2%</td>
<td>6.7% ± 8.7%a</td>
</tr>
<tr>
<td>Number of independent erosion sites</td>
<td>0.8 ± 1.1</td>
<td>2.9 ± 2.7a</td>
</tr>
<tr>
<td>Number of independent bone growths</td>
<td>0.9 ± 1.0</td>
<td>4.5 ± 3.5</td>
</tr>
</tbody>
</table>

*a* Significant difference (p<0.05) for outcome measures between healthy and diseased surfaces.

*b* Significant difference (p<0.05) for outcome measures between PsA and RA diseased subject surfaces.
In this study, an objective algorithm was developed to quantify three-dimensional bone surface abnormalities based on HR-pQCT images. The algorithm uses a generic healthy surface to predict the healthy surface topology of diseased bone. This allows for visualization and quantification of surface changes within the affected joint by defining areas of erosion and periosteal bone growth.

Figure 16: The visual outputs of the algorithm showing areas of erosion (blue) and periosteal bone growth (red). The heat map represents the distance between the subject bone surface and the corresponding predicted healthy surface. Two examples of diseased surfaces are illustrated in (A) and two examples of healthy surfaces in (B). The prevalence of erosion and bone growth is noticeably observable. The dashed ellipse in the top right panel illustrates a large ridge of abnormal periosteal growth.

6 Discussion

In this study an objective algorithm was developed to quantify three-dimensional bone surface abnormalities based on HR-pQCT images. The algorithm uses a generic healthy surface to predict the healthy surface topology of diseased bone. This allows for visualization and quantification of surface changes within the affected joint by defining areas of erosion and periosteal bone growth.
formation. The sensitivity of these measures to input parameters was evaluated, and sets of outcome measures were compared in healthy subjects and patients with both RA and PsA.

The data show the algorithm is not particularly sensitive to changing the number of input surfaces, the specific surfaces, or the sex of the surfaces used to generate the generic healthy reference surface. Based on this data, and the assumption that including more healthy surfaces in the generic model would improve generalizability, all 12 healthy surfaces were used. For large data sets it may be beneficial to categorize surfaces into age, size and gender, for example, to reduce unwanted noise or variability in the generic healthy reference surface and produce a more representative reference surface.

The algorithm was partially validated by comparing measurements to artificial erosions and periosteal growths with known geometry. Based on these data, a cut-off value of 0.6 mm was identified to best detect an unknown and mixed set of erosions and periosteal growths. The algorithm had difficulty in detecting and measuring large diameter and low height periosteal bone growths because it is challenging to identify convex growths on an already convex bone surface. The transition between healthy surface and diseased surface for periosteal bone growths is less obvious as the surface gradient remains consistent in some cases, especially for wide flat growths. However, the algorithm accurately identified erosion sites and growths adjacent to one another, which has clinical relevance especially in PsA patients. The sensitivity and specificity for detecting the presence of both erosions and periosteal growths was excellent (nearly 90%), and both features could be detected with an accuracy of 210 μm. This development is in line with Specific Aim 1. To the author’s knowledge previous studies have not been successful in identifying erosions and growths adjacent to one another, or this outcome has not been reported yet. It must be noted this preliminary validation is only valid for the cohort presented and the several manufactured
deformations characterized. The validation outcomes may change with an increased number of cohort samples and deformation types. The initial validation presented is limited to the several deformities manufactured, which serves as a base for extending the validation to more types and shapes of deformities.

Several of the outcome variables generated here have clinical relevance. We observed that erosion depth was consistently and significantly greater in both patient groups compared to the healthy cohort. Several other variables may be important, although the combination of small sample size and variable patient surfaces meant that the present study was underpowered to detect between-group differences. We found that a combination of erosion depth, number of erosion sites, periosteal growth height, percent surface eroded and surface variability could blindly discriminate between healthy and diseased bony surfaces, as outlined in Specific Aim 2. Based on these features, the algorithm was better able to discriminate RA than PsA versus healthy subjects. The present group of patients with PsA had bone surfaces that included a variable mix of erosions and abnormal periosteal growth, whereas the patients with RA had predominantly erosions. Surface area based outcomes are a novel way to interpret and further diagnose articular bone surfaces affected by PsA and RA. Further validation of these surface features, especially association with clinical markers of disease severity, is needed to fully understand their potential clinical relevance and utility. These results prove the hypothesis stated to differentiate between healthy and diseased bone surface.

The present algorithm compares the diseased surface to an estimated healthy surface, to objectively quantify differences in surface morphology. This general approach is frequently used during surgical planning for unilateral deformities, in which the intact/healthy limb is imaged and mirrored onto the diseased/injured limb [75]. In the case of inflammatory arthritis, both hands may
be affected, and previous images may not be available. Here, we address this problem by predicting the geometry of a healthy bone surface from the geometry of the diseased bone surface. This healthy surface can serve many purposes in understanding disease progression and quantifying joint changes. Our algorithm does not require human intervention during the image registration process and is inherently an objective method to produce outcome measures. This technique could be used in conjunction with other published algorithms to initially detect bone abnormalities and define the original healthy surface topology for further analyses of the diseased geometry.

Using HR-pQCT imaging, several groups have established metrics for quantifying cortical breaks [24, 25, 61], erosion depth [24, 76] and volume [60] for individual erosions in patients with RA [19, 21, 77] and PsA [10, 78]. Our discriminant analysis results support the relevance of these measures, since maximum erosion depth and maximum periosteal growth height were found to be discriminators between healthy and diseased surfaces. Defining erosions or periosteal bone growths covering large areas and that have complex geometries has been a consistent challenge to this research. The dashed ellipse in Figure 16 A illustrates this concept, where it may be difficult to define the outlined deformity. This highlights a limitation of using erosion site counts as a metric of bone destruction; it may be necessary to use the parameter in conjunction with other outcomes.

Here, we identified and assessed the usefulness of several candidate measures that would represent the overall deformity of a bone surface. However, the point-to-point distances that are calculated as a result of the present algorithm could be used to calculate additional measures (e.g. spatial locations of specific features), which may have greater clinical relevance or serve as useful research tools.

The current work builds upon that of others to quantify periosteal growth for the first time, and to increase objectivity in defining diseased bone surface. Previously reported techniques analyze
image data on a slice-by-slice basis (2D) and require human intervention to isolate an erosion site (e.g. [24]). These methods have limitations related to subjective identification of the erosion sites, the expertise required to use them, and difficulty in analyzing severely deformed bones. Semi-automated methods generally require a smooth cortical surface preceding and surrounding the erosion site to detect a sharp change in the gray scale gradient (e.g. [27]). These methods work well in cases where erosions are sparse, obvious, and the erosion cavity is smooth with minimal fenestration into the trabecular region. However, on joint surfaces where erosions are not well defined, are numerous or are adjacent to periosteal bone formation, as in PsA, it becomes very difficult to place seeding points for pseudo-automated algorithms to detect these bone abnormalities. Our algorithm fills this critical gap by automating the detection of abnormal sites.

This study has several important limitations. First, a relatively small sample of both healthy, PsA and RA subjects is used to establish and validate the algorithm. Although the outcome measures calculated here were different between diseased and healthy groups, these specific measures may not be appropriate for all types of inflammatory arthritis and additional validation may be necessary in other diseases. Second, the healthy control cohort was on average younger in age compared to the diseased cohort, and additional research is required to more robustly define appropriate healthy reference surfaces. Furthermore, it the healthy data showed an appreciable amount of variation and it is unknown to what extent this variation is typical. Extending the healthy cohort over a range of ages will provide insight into standardizing ideal healthy bone surfaces for comparison. The cut-off threshold worked well within our range of analyzed surfaces. However, it may be necessary to adjust this for a specific application or disease state. Unlike other work in this area, the present algorithm is limited to detecting surface features, and may not accurately quantify erosions that reside within the trabecular structure but have minimal cortical breaks.
However, the validation was quite robust and demonstrated accuracy that was comparable to our scan resolution. The sensitivity of the input parameters that control the CPD transformation to the output measures has not been fully investigated. An extensive analysis of the parameters to determine the ideal values for a specific bone size, cohort category or disease state may further increase the accuracy of the healthy surface prediction. A preliminary investigation was carried out to gain an understanding of the general settings required to produce a satisfactory predicted healthy surface, from which deformities could be identified and quantified. Finally, the data reported here are cross-sectional in nature, and the degree to which progression of surface deformity can be measured over time is not known. Despite these limitations, our algorithm was able to successfully facilitate visualization of, and report objective metrics related to, bone surface deformity in individuals with RA and PsA.

7 Conclusions

In conclusion, a means of objectively predicting healthy surfaces from the geometry of a diseased bone surfaces in patients with RA and PsA has been developed and validated. This algorithm can automatically detect and measure various clinically relevant bony features associated with the diseases, including features that previously could not be measured via human input or automated segmentation techniques. The new algorithm defined here detected significant differences between healthy and diseased groups, and was able to discriminate blindly between healthy and diseased bone surfaces. This may serve as a unique diagnostic tool for monitoring disease progression, or to detect small changes in joint surface in early disease. This algorithm will be useful by itself and in conjunction with current clinical techniques and research-based diagnostics for the evaluation of patients with RA and PsA.
Future work will be aimed at addressing some of the shortcomings of the current algorithm and enhance the relevancy of the algorithm to a clinical environment. Firstly, the efficiency of the current algorithm can be improved dramatically. A major bottleneck in the process occurred when it was required to process surfaces in one software, save the resultant surface in a useable format and run the algorithm code in a different software. The entire algorithm required this software interchange several times. The 3D surfaces could be processed, the various data transformations applied, and the outcome measures computed entirely in MATLAB. This would allow the user to input a few variables and produce outcomes from scans in a single step. To make the algorithm more user friendly, a user interface could be integrated once the algorithm is developed in a single software. This would allow a user to conveniently input the scans and obtain bone surface degradation diagnostics in a short time period. Secondly, the patient cohort should be increased in size, especially the healthy cohort. This may provide increased statistical power to analyze any additional significant results and identify more outcomes that may be useful for erosion and growth quantification. Although the input surfaces were shown to not be sensitive in this study, a larger sample number may produce greater accuracy and should be explored. It follows, that categorizing patients into similar groups such as age and sex may be helpful to increase accuracy. In this study, only the maximum bone growths and erosions were analyzed. Future development should include a convenient method to measure individual deformities and catalogue their relative location on the bone surface. This way further statistical analyses can be carried out on the relationship between deformity size and location as a result of disease severity. An extensive sensitivity analysis should be carried out on the CPD input parameters to determine the ideal values for various bone surfaces. It is suspected the geometry of the bone surfaces and respective deformity geometries will determine the ideal parameter
values. Lastly, it would be beneficial to run this algorithm in conjunction with clinical diagnoses of arthritic patient scans and compare the findings with clinical results. This would aid in understanding the limitations and benefits of this method in a clinical environment with feedback from a clinician in the field.
8 References


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9 Appendix I: Algorithm Work Flow and Code

9.1 Detailed work flow

Creating three-dimensional surface from patient scans

1. In Matlab, run code Align_dicoms. Set the target folder to that which contains the raw DICOM files from a specific patient scan. A new folder with the aligned DICOM files will be created within the original folder.

2. Open Mimics 18, start a new project and import aligned DICOMS. There are 330 individual DICOMS, make sure to select all. Allow import wizard to guide user through respective steps.

3. Mimics will request a definition of the orientation “Change orientation” screen will appear. It is important to get a consistent orientation throughout all the images. Orient the image such that:

   I. A (anterior) represents the palm of your hand.

   II. P (posterior) – back of your hand.

   III. T (top) - distal end of the phalanx.

   IV. B (bottom) - proximal end of the metacarpal.

   V. R (right) – side of your thumb if left hand, pinky if right hand. i.e hold right/left hand palm down in front of you. Right and left referenced by this orientation.

To change the orientation, click on the letters within the orientation window and select the respective side. Once orientation is correct, click an example of the correct orientation of a left hand below (Figure 17).
4. Apply Binomial blur filter for 3 iterations.

5. Segment bone from image slices by applying a threshold with minimum cut-off of 726. A color mask should appear over the pixels representing bone material.

6. Select bone of interest (MCP 2) by using the region growing tool and creating an isolated mask. Further segment the phalanx and metacarpal from one another. The two bones in the MCP joint may need to be manually separated by editing the resultant masks. See Figure 18.
7. Scroll through images slice by slice to assess and identify regions of motion artefact in the bone surface. Example (Figure 19): If there is motion, this needs to be removed before further editing. An easy first pass, is to edit the mask in 3D (Figure 20).
8. Only the bone surface is of interest in this study, therefore fill the bone cavity to get the outer bone surface. The purpose of this step is to close any gaps in the cortical surface. Make sure all cavities are filled within the trabecular region of the bone.

I. If there is extensive fenestration from the cortical surface to the trabecular region, use the wrapping tool to close these scan related gaps. Set the closing distance of the wrapping tool to 0.2 mm.

9. Produce a 3D model of the filled metacarpal mask and phalangeal mask, using the calculate 3D option.

I. Use a smoothing factor of 0.5 for 7 iterations when calculating a 3D model.

10. Remove the ‘bottom’ surface of the 3D model down the length of the bone where the region of interest is cut off. This artificial surface is not part of the analysis.

11. Export 3D models as .stl file.
Aligning, scaling and truncating 3D models

1. In Matlab, run code STL_convert to import the Mimics .stl file into Matlab, defined by faces, vertices and normals.

2. Pick one patient MCP (both phalanx and metacarpal) as a reference bone surface for size and position. Run code cpd_rigid_example4, whereby each scanned bone surface is rigidly aligned and scaled to the chosen reference bone.
   
   I. Use the reference bone’s vertices as the ‘X’ data set and the transforming surface vertices as the ‘Y’ data set.
   
   II. The code will output a .txt file with the scaled and aligned vertices of the respective 3D surface.

3. Import the .txt files to 3Matic where the transformed vertices will be imported as pointclouds for each surface. These pointclouds should be aligned and scaled in the same position.

4. Create 3D surfaces from the pointclouds using the mesh data tool, which will produce a mesh from triangulated surfaces between the vertices.
   
   I. Use a uniform point distribution with no smoothing.
   
   II. Identify any bad edges or flipped triangles and fix any irregular meshing areas
   
   III. Check to make sure the ‘bottom’ of the bone surface towards the length of the bone is open and not meshed. This surface is not part of the analysis.

5. Export the generated surfaces as .stl files and import the respective .stl’s to Matlab using the STL_convert function.

6. Run code define_study, which allows the user to truncate the bone surfaces at precisely the same location to create the same analysis area for each bone surface.
I. The user will be prompted to choose surfaces to be truncated. Identify the respective bone surfaces as imported from 3Matic, and run the code. The code will create a file name which contains the chosen surfaces.

7. Run code edit_surfaces_run using the filename as created in the above step. A GUI will be activated from which the user can select various options for surface truncation. The user can identify the orthogonal plane to the field of view from which the 3D bone surface can be truncated.

I. Identify that all surfaces are in the same orientation and if any rotation is applied, that the same rotation is applied to all surfaces. It is essential to maintain the same orientation for each surface, as per the rigid transformation with scaling.

II. There is an option to reduce the number of surface mesh triangles. For diseased bone surfaces, no triangle reduction is needed. However, for bone surfaces to be used as reference healthy surfaces to create a generic healthy surface, need the respective meshes to be reduced to 10 000 vertices. Further details for generating the healthy surface is described in the section following.

III. For the metacarpals, set the truncation plane 12 mm up the shaft starting from the furthest point of the metacarpal head (Figure 21).

IV. For the Phalanges, set the truncation plane 9 mm up the shaft from phalangeal base.

V. Review the truncated surfaces once generated and verify all surfaces areas are appropriately meshed

VI. Use the save option to save the resultant truncated surfaces in the format of .mat file with corresponding vertices, faces and normals.
Creating a generic healthy surface

1. The generic healthy surface is used as a base to transform to the shape of the diseased surfaces whilst maintaining healthy features. The generic healthy surface is made up of 12 healthy reference surfaces scanned from healthy individuals.

   I. Process all healthy surfaces through the edit_surfaces_run code and specify a surface vertices reduction to 10,000 points.

   II. Use a single healthy surface as a reference surface for further transformation steps.

2. Run code cpd_Nonrigid_same_points2all, which runs a non-rigid CPD algorithm with high ‘elasticity’. The premise of this code is to apply the same surface to each healthy surface to create an average generalized healthy surface.

   I. Use the single healthy reference surface as the ‘Y’ data set (transformed) and each healthy surface as the ‘X’ data set (stationary).
II. Verify CPD parameters $\beta = 1$ and $\lambda = 1$.

III. All transformed ‘Y’ data sets will be saved as a .txt file as a pointcloud representing surface vertices.

IV. All transformed ‘Y’ point sets will be in the shape of the respective healthy surface with inter surface points located at the same location on each bone surface.

3. Import the .txt files to 3Matic where the transformed vertices will be imported as pointclouds for each surface.

4. Create 3D surfaces from the pointclouds using the mesh data tool, which will produce a mesh from triangulated surfaces between the vertices.
   I. Use a uniform point distribution with no smoothing.
   II. Identify any bad edges or flipped triangles and fix any irregular meshing areas
   III. Check to make sure the ‘bottom’ of the bone surface towards the length of the bone is open and not meshed. This surface is not part of the analysis.

5. Export the generated surfaces in 3Matic as .stl files and import the respective .stl’s to Matlab using the STL_convert code.

6. Run code average_ref_surface, which averages the vertices of the imported .stl’s in XYZ cartesian space.
   I. Use the surface vertices with corresponding X, Y and Z coordinates to average all $N = 12$ surfaces corresponding points.
   II. The code will compute a final averaged point set and save the file as a .txt. See Figure 22 summarizing the progression.
Predicting healthy surface from diseased bone surface

1. Transform the averaged generic healthy surface to the shape of each diseased bone surface using the non-rigid CPD code, cpd_Nonrigid_example4_3D_registration.
   
   I. Use the generic healthy reference surface as the ‘Y’ data set (transformed) and each diseased surface as the ‘X’ data set (stationary).
   
   II. Verify CPD parameters $\beta = 11$ and $\lambda = 2$.
   
   III. All transformed ‘Y’ data sets will be saved as a .txt file as a pointcloud representing surface vertices.
   
   IV. All transformed ‘Y’ point sets will be in the shape of the respective diseased surface, but maintain healthy features from the original generic healthy surface. The transformed ‘Y’ point sets are the vertices for the predicted healthy surfaces.

2. Import the .txt files to 3Matic where the transformed vertices will be imported as pointclouds for each surface.

3. Create 3D surfaces from the pointclouds using the mesh data tool, which will produce a mesh from triangulated surfaces between the vertices.
I. Use a uniform point distribution with no smoothing.

II. Identify any bad edges or flipped triangles and fix any irregular meshing areas.

III. Check to make sure the ‘bottom’ of the bone surface towards the length of the bone is open and not meshed. This surface is not part of the analysis.

4. Export the generated surfaces in 3Matic as .stl files and import the respective .stl’s to Matlab using the STL_convert code.

Quantifying surface deformities

1. To quantify surface deformities, the distance between the predicted healthy surface and the original diseased surface is computed. Run code point2trimesh_run, which calculates the normal distances between faces of the predicted healthy surface and vertices of the diseased surface. The algorithm outputs distances for each diseased vertices and a 3D image of the diseased surface with an overlaid heat map indicating areas of erosion or periosteal bone growth (Figure 23).

   I. Set the respective diseased surface as the reference with faces and vertices defined.

   II. Set the corresponding predicted healthy surface as the ‘points’ data set.

2. The code outputs the distances for each vertices as a distance in mm, saved as a .txt file. A 3D image with heatmap, as described is saved as .fig.

3. From the distances the user can import the .txt file containing the distances to Excel or Matlab and compute outcomes such as: maximum erosion depth, maximum periosteal bone height, diseased-healthy surface variation and other outcomes as defined in this study.
9.2 Relevant Code for work Flow

1. Align_dicoms
   \%Code to register dicoms acquired from multiple stacks
   \%Adapted from Dicom_registration.m
   \%There may be an image shift each time the gantry moves between stacks
   \%Corrects for shift by registering slice n to slice n-1

   \%Monomodal registration method is default
   \%Use Multimodal if Monomodal does not work

   clear all
   clc
   tic
   l
   [dname dpath] = uigetfile('*.dcm','Select dicom file','Y:\'); \%get path
   files = dir(fullfile(dpath,'*.dcm')); \%read all dicom files

   \%registration method and parameters
   \%Monomodal – between same image modalities; Multimodal – between different modalities
   choice = questdlg('Method','Voxel Registration','Monomodal','Multimodal','Monomodal');
   switch choice
     case 'Multimodal'
       l = 1;
     case 'Monomodal'
1 = 2;
end

if l == 1
    [optimizer metric] = imregconfig('multimodal');
    optimizer.MaximumIterations=500;
    optimizer.InitialRadius=0.002;
    optimizer.GrowthFactor=1.03;
else
    [optimizer metric] = imregconfig('monomodal');
    % to change any default optimizer values
    optimizer.MaximumIterations=500;
    optimizer.GradientMagnitudeTolerance=1e-4;
    optimizer.MinimumStepLength=1e-6;
end

% create new directory to save registered dicoms
mkdir([dpath 'Registered']);

% first dicom file
DCM_fix = dicomread([dpath files(1,1).name]); % fixed image

for i = 2:length(files)
    % read files
    % DCM_fix = dicomread([dpath files(i-1,1).name]); % fixed image
    DCM_mov = dicomread([dpath files(i,1).name]); % moving image
    info_mov = dicominfo([dpath files(i,1).name]); % header info for moving image
    % registration
    DCM_reg = imregister(DCM_mov,DCM_fix,'rigid',optimizer,metric,'DisplayOptimization',true,'PyramidLevels',3);
    % write registered dicom
    dicomwrite(DCM_reg,[dpath 'Registered\' files(i,1).name],info_mov);

    % update fixed file with currently registered file
    DCM_fix = DCM_reg;
end

% register first image to itself to have the same HU interpolation as other registered images
DCM_fix = dicomread([dpath files(1,1).name]);
DCM_mov = dicomread([dpath files(1,1).name]);
info_mov = dicominfo([dpath files(1,1).name]);
figure, imshoipair(DCM_fix,DCM_mov,'Scaling','independent');
DCM_reg = imregister(DCM_mov,DCM_fix,'rigid',optimizer,metric,'DisplayOptimization',true,'PyramidLevels',3);
figure, imshoipair(DCM_fix,DCM_reg,'Scaling','independent');
dicomwrite(DCM_reg,[dpath 'Registered\' files(1,1).name],info_mov);
2. STL_convert

% Convert original STL's from MIMICS/3MATIC to faces, vertices and normals. Uses function 'trisurf'.
% change filename to desired stl in "Original STL folder".
% save: will save the .mat file in "STL import save files".
% Use the text files as point clouds or faces for truncation/CPD

clear all

[v,f,tnorm]=STL_Import('R:\RA project\RA project code\1 - convert STL to fv\STL import save files\validation 3\edited aligned for comp\RA909 healthy_edited_erosion.stl',1);

trisurf(f,v(:,1),v(:,2),v(:,3),Facecolor,'c'), axis equal

save('R:\RA project\RA project code\1 - convert STL to fv\STL import save files\validation 3\edited aligned for comp\RA909 healthy_edited_erosion.mat',f,'v', 'tnorm'),

3. cpd_rigid_example4

% CPD Rigid transformation
% Align and scale all surfaces to a reference surface.

clear all; close all; clc;
tic
% Reference surface
load('R:\RA project\RA project code\1 - convert STL to fv\STL import save files\validation\MC2 type 1_trunc.mat');
X=v;
% Transformation surface
load('R:\RA project\RA project code\1 - convert STL to fv\STL import save files\validation\healthy_reference_MC2.mat');
Y=v;

% Set the options
opt.method='rigid';

opt.viz=1; % show every iteration
opt.outliers=0; % use 0.6 noise weight to add robustness

opt.normalize=1; % normalize to unit variance and zero mean before registering (default)
opt.scale=1; % estimate global scaling too (default)
opt.rot=1; % estimate strictly rotational matrix (default)
opt.corresp=0; % do not compute the correspondence vector at the end of registration (default)

opt.max_it=100; % max number of iterations
opt.tol=1e-6; % tolerance

% registering Y to X
[Transform, Correspondence] = cpd_register(X, Y, opt);

% create registered figure
figure, cpd_plot_iter(X, Y); title('Before');

% X(Correspondence,:) corresponds to Y
figure, cpd_plot_iter(X, Transform.Y); title('After registering Y to X');
y_1 = Transform.Y;
save('R:\RA project\RA project code\3 - Coherent Point Drift code\validation\healthy_reference_MC2_align.mat', 'X', 'Y', 'y_1'), toc

% save transformed vertices as txt file for import into 3Matic
dlmwrite('R:\RA project\RA project code\3 - Coherent Point Drift code\validation\healthy_reference_MC2_align.txt', y_1, 'delimiter', '	');

4. define_study
%For truncation run this function first
%sets up files and folders for further steps to run gui
%main path needs to be "truncated surface saved files"
%Find the .mat surface files saved from STL import at R:\RA project\RA project code\1 - convert STL to fv\STL import save files

Next step once define study run: edit_surfaces_run

clearvars
clc

% define main_path for study and name of study
main_path = 'R:\RA project\RA project code\1 - convert STL to fv\STL import save files\validation 3';
study_name = 'validation all g';
study_file = [study_name, '_study.mat'];

% select surfaces for study
surf_path = 0;
surf_files = [];
while ~iscell(surf_files)
    [surf_files, surf_path] = uigetfile({'*.mat', 'Surface Files (*.mat)'; ... '.*', 'All Files (*.*)', 'Select surface files for SSD-FEM'; ... main_path, 'MultiSelect', 'on');
    if ~iscell(surf_files)
        uiwait(warndlg('Please select more than one surface.', 'Select surface files', 'modal'));
    end
end

orig_surf_path = fullfile(main_path, 'surfaces');
if ~exist(orig_surf_path)
    mkdir(orig_surf_path)
bound_dim_orig = 0;
orig_centroid_all = [];
n_orig_faces = [];

for ind=1:length(surf_files)
    fprintf('%s (%4i/%4i) : %s'
            'Reading surface',ind,length(surf_files),surf_files{ind})

    specimen_ids{ind} = surf_files{ind}(1:(find(surf_files{ind}=='.',1,'last')-1));

    switch surf_files{ind}((end-2):end)
        case 'mat'
            load(fullfile(surf_path,surf_files{ind}));
            if exist('fv')
                faces=fv.faces;
                vertices=fv.vertices;
            elseif exist('f')
                faces = f;
                vertices = v;
            else
                fprintf('neither fv or f variables exist in surface file
')
        end

    end

    disp(['  ',num2str(size(faces,1)),' faces
',num2str(size(vertices,1)),' vertices'])
    fprintf('(expecting units = mm)\n\n')

    n_orig_faces = [n_orig_faces; size(faces,1)];

    min_bound_dim = min(round(max(vertices)-min(vertices)));

    tmp_bound_dim = round(1.2*max(round(max(vertices)-min(vertices))));

    if tmp_bound_dim > bound_dim_orig
        bound_dim_orig = tmp_bound_dim;
    end

    orig_centroid = mean(vertices,1);

orig_centroid_all = [orig_centroid_all; orig_centroid];
orig_surface.faces = faces;
orig_surface.vertices = vertices;

save(fullfile(orig_surf_path,[specimen_ids{ind},'_surface.mat']),'orig_surface',
      'orig_centroid');
clear faces vertices orig_centroid;
end

save(fullfile(main_path,study_file),'specimen_ids','bound_dim_orig','n_orig_faces','orig_centroid_all')

fprintf(['FINISHED READING ALL SURFACES'n'n'])

5. cpd_Nonrigid_example4_3D_registration
% Nonrigid Coherent Point Drift (CPD).
% Full set options is explicitly defined. If you omit some options the
% default values are used, see help cpd_register.
clear all; close all; clc;
tic
load 'R:\RA project\RA project code\1 - convert STL to fv\STL import save files\validation 3\truncated surfaces\healthy_reference_RA910.mat';
Y=v;
load 'R:\RA project\RA project code\1 - convert STL to fv\STL import save files\validation 3\truncated surfaces\RA910 growth 3.mat';
X=v;

% Init full set of options %%%%%%%%%%%%%%%%%%%%
opt.method='nonrigid';  % use nonrigid registration
opt.beta=11;            % the width of Gaussian kernel (smoothness)
opt.lambda=2;           % regularization weight
opt.viz=1;              % show every iteration
opt.outliers=0.1;       % noise weight
opt.fgt=0;              % do not use FGT (default)
opt.normalize=0;        % normalize to unit variance and zero mean before
registration (default)
opt.corresp=0;          % compute correspondence vector at the end of
registration (not being estimated by default)
opt.max_it=100;         % max number of iterations
opt.tol=1e-8;           % tolerance
%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%%

[Transform, C]=cpd_register(X,Y, opt);

figure,cpd_plot_iter(X,Y); title('Before'); axis equal
figure,cpd_plot_iter(X, Transform.Y); title('After registering Y to X');axis equal

y_1=Transform.Y;

% save .mat file for outputs
save('R:\RA project\RA project code\3 - Coherent Point Drift code\validation 3\RA910 growth 3 healthy.mat', 'X', 'Y', 'y_1'),

% save transformed vertices as txt for 3Matic
save('R:\RA project\RA project code\3 - Coherent Point Drift code\validation 3\RA910 growth 3 healthy.txt', 'y_1', '-ASCII');
toc

6. average_ref_surface

% making an average reference surface
% Load all healthy rigid transformed surfaces
% calculates the euclidean distance between corresponding points. Must make
% sure the number of vertices between point sets is the same.
% Define variables x, y, z - appropriate for the number of files loading

clear all
tic
load('R:\RA project\RA project code\3 - Coherent Point Drift code\PsA run 1\MC2\MC2 healthy\RA901 MC2_points2all.mat', 'X', 'Y', 'y_1')
x1 = y_1(:,1); y1 = y_1(:,2); z1 = y_1(:,3);
% %
load('R:\RA project\RA project code\3 - Coherent Point Drift code\PsA run 1\MC2\MC2 healthy\RA902 MC2_points2all.mat')
x2 = y_1(:,1); y2 = y_1(:,2); z2 = y_1(:,3);
% %
load('R:\RA project\RA project code\3 - Coherent Point Drift code\PsA run 1\MC2\MC2 healthy\RA903 MC2_points2all.mat')
x3 = y_1(:,1); y3 = y_1(:,2); z3 = y_1(:,3);
% % %
load('R:\RA project\RA project code\3 - Coherent Point Drift code\PsA run 1\MC2\MC2 healthy\RA904 MC2_points2all.mat')
x4 = y_1(:,1); y4 = y_1(:,2); z4 = y_1(:,3);
% % %
load('R:\RA project\RA project code\3 - Coherent Point Drift code\PsA run 1\MC2\MC2 healthy\RA905 MC2_points2all.mat')
x5 = y_1(:,1); y5 = y_1(:,2); z5 = y_1(:,3);
% % % %
load('R:\RA project\RA project code\3 - Coherent Point Drift code\PsA run 1\MC2\MC2 healthy\RA906 MC2_points2all.mat')
x6 = y_1(:,1); y6 = y_1(:,2); z6 = y_1(:,3);
% % % %
load('R:\RA project\RA project code\3 - Coherent Point Drift code\PsA run 1\MC2\MC2 healthy\RA907 MC2_points2all.mat')
x7 = y_1(:,1); y7 = y_1(:,2); z7 = y_1(:,3);
load('R:\RA project\RA project code\3 - Coherent Point Drift code\PsA run 1\MC2\MC2 healthy\RA908 MC2_points2all.mat')
x8 = y_1(:,1); y8 = y_1(:,2); z8 = y_1(:,3);
% % %
% repeat load for n number of surfaces

x_sum=(x1+x2+x3+x4+x5+x6+x7+x8)/8;
y_sum=(y1+y2+y3+y4+y5+y6+y7+y8)/8;
z_sum=(z1+z2+z3+z4+z5+z6+z7+z8)/8;

ref_surf=[x_sum,y_sum,z_sum];
scatter3(x_sum,y_sum,z_sum);

% save reference surface file in 4 - Average healthy surfaces code\average surface saved files
save('R:\RA project\RA project code\1 - convert STL to fv\STL import save files\Healthy sensitivity\MC2 sensitivity\healthy_reference_MC2_n-8.mat','ref_surf');
toc
% will need to write a .txt file to produce surface in 3matic
dlmwrite('R:\RA project\RA project code\1 - convert STL to fv\STL import save files\Healthy sensitivity\MC2 sensitivity\healthy_reference_MC2_n-8.txt', ref_surf, 'delimiter', '\t');

% next step: go into 3matic and import text file. Produce .stl surface of % healthy reference bone

7. point2trimesh_run

% measuring distance between predicted healthy and diseased surface

clear all

tic
load('R:\RA project\RA project code\1 - convert STL to fv\STL import save files\validation 3\edited aligned for comp\RA903 multiple erosions healthyEdited.mat')

faces=f; vertices=v;
FV.faces    = faces;
FV.vertices = vertices;
load('R:\RA project\RA project code\1 - convert STL to fv\STL import save files\validation 3\edited aligned for comp\RA903 healthyEdited erosion.mat')

points = v;
[distances,surface_points] = point2trimesh(FV, 'QueryPoints', points);

max_distance=max(distances)
min_distance=min(distances)
hold on
figure
patch(FV,'Facecolor','c','FaceAlpha',.5); xlabel('x'); ylabel('y'); zlabel('z'); axis equal; hold on; grid on
plot3M = @(XYZ,varargin) plot3(XYZ(:,1),XYZ(:,2),XYZ(:,3),varargin{:});
plot3M(points,'*r')
plot3M(surface_points,'*k')
plot3M(reshape(shiftdim(points,-1);shiftdim(surface_points,-1);shiftdim(points,-1)*NaN,[],3),'k');
grid on

abs_distances = abs(distances);
max_abs_distances = max(abs_distances);
dir_dist=(1).*distances;

%create 3D figure with similar lighting to 3Matic
figure
trisurf(f,v(:,1),v(:,2),v(:,3),dir_dist(:,1), 'Edgecolor', 'none')
axis equal
material dull
lightangle(-45,30)
shading interp
FaceLighting = 'gouraud';
AmbientStrength = 0.9;
DiffuseStrength = 0.8;
SpecularStrength = 0.9;
SpecularExponent = 25;
BackFaceLighting = 'unlit';
caxis([-max_abs_distances max_abs_distances]);
colorbar('Ticks',-max_abs_distances:0.5:max_abs_distances)
colormap(jet)
colormapeditor
	save('R:\RA project\RA project code\5 - Measuring distance between pointcloud and mesh\point2trimesh saved files\validation 3\RA903 erosion - RMSE comparison b.mat');

toc