Left-Right Differences in Knee Cartilage Thickness Using Model-Based Correspondence

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Using MR imaging to quantify articular cartilage in the knee may be of value in assessing disease progression and response to therapy in arthritis. Population and longitudinal studies require cartilage thickness measurements to be aggregated and compared. Gross measures such as cartilage volume can be easily combined but are not, generally, sufficiently sensitive to be useful in Phase IIa clinical trials, because changes due to disease tend to be localised. The need is to aggregate detailed cartilage thickness maps of the knee. Non-rigid registration has been used previously to align cartilage surfaces [1], but this does not guarantee that anatomically equivalent points are corresponded. We propose to use the underlying bones of the knee joint to provide a more consistent inter-patient frame of reference for cartilage thickness measurements. We establish anatomically plausible correspondences between different subjects' bones by building a statistical shape model, using the minimum description length (MDL) principle [2]. Cartilage thickness is measured at corresponding points and aggregated to define the normal range in a population of healthy females. Linear Discriminant Analysis is used to characterise differences between groups of patients.

Image Acquisition
We conducted a trial to examine the cartilage of healthy female volunteers using MR Imaging [3]. 15 volunteers (one of whom had to be omitted from analysis because of a failure to apply the correct imaging protocol) were divided equally between three sites where they had one knee imaged. An additional 5 volunteers had both knees imaged at all three sites. Two MR volume images with 0.625 x 0.625 x 1.6mm resolution were taken during each visit: a fat-suppressed T1 sequence to visualise cartilage, and a T2 sequence to visualise the endosteal bone surface. Semi-automatic segmentations of the bone surfaces (femur, patella and tibia) were obtained, and each cartilage was segmented once each by each of two segmentors. Triangulated surface representations were constructed from the slice segmentations.

Establishing a Consistent Frame of Reference
We wished to define a set of anatomically equivalent points across a population of subjects. The underlying endosteal bone surface was chosen as a frame of reference for each cartilage compartment, and anatomically equivalent points were defined by building an MDL statistical shape model (SSM) of the bone surfaces. An SSM is constructed from a dense set of corresponding points on each of a training set of shapes, and describes how the relative locations of the points vary between examples. Correspondences that respect anatomical equivalence tend to result in simpler models. This can be formalised using an MDL objective function, which provides a measure of model complexity. An optimally simple model can be obtained by iteratively shifting the locations of the correspondences on each training shape, until the objective function is minimised. Separate MDL models were built for the Femoral Head, Patella and Tibial Head using all the patient data. There were a total of 9222 corresponding points with mean tangential separation of 2.16mm.

Aggregating Cartilage Thickness
Population trials require localised measurements of cartilage thickness to be combined for groups of subjects. By taking measurements at a dense set of corresponding points we can build detailed maps of cartilage thickness (one for each knee), which can be aggregated over the population. Cartilage thickness was measured along a 3D normal to the bone surface at each correspondence point. A cartilage coverage map was computed by counting, for each correspondence point, the fraction of subjects in which the normal intersected with cartilage. For points covered by cartilage, the thickness was measured as the distance between the intersection of the normal with the inner and outer surfaces of the cartilage. The normal range of cartilage thickness was summarised using maps of the mean and standard deviation of valid thickness readings for those points with at least 30% cartilage coverage.

Cartilage Coverage and Normal Range
The cartilage coverage map for the population of 19 healthy females is shown in Figure 1, displayed on the mean (right leg) bone shapes. As expected in healthy subjects, the main load bearing regions exhibit 100% coverage. The boundary of the aggregated readings is not well-defined, indicating that the position of the cartilage edge varies between subjects and is unreliable as an inter-patient frame of reference. Figure 2 shows the mean and standard deviation maps of cartilage thickness for 19 volunteers. The population exhibited mean(STD) cartilage thickness of 2.61(0.81), 1.88(0.39) and 1.85(0.56)mm for the patellar, femoral and tibial articular surfaces respectively. Cartilage is thickest on the load bearing regions and decreases towards the edges, with the centre of the patellar and medial tibial compartments exhibiting thickest coverage. The standard deviation map is relatively constant, indicating that segmentation uncertainty is not related to cartilage thickness.

Left-Right Knee Differences
Another important requirement in population trials is the ability to characterise differences in the results for two or more groups. To demonstrate the principle, we investigated Left-Right knee differences in the group of 5 subjects who had both knees imaged at all three sites. Principal Components Analysis was performed on the thickness maps to reduce the dimensionality of the data. The set of maps for each knee were labelled according to their class membership (Left or Right) and Linear Discriminant Analysis (LDA) was performed to determine the best axis of separation between the classes. Figure 3 shows the Left-Right differences, displayed as maps of the thickness variation corresponding to ± 1 SD variation of the linear discriminant function. The cartilage has a tendency to be thicker towards the lateral edge of the right knee, and medial edge of the left knee. These side differences may reflect unilateral leg dominance in the 5 volunteers. The Mahalanobis distance between the Left-Right classes was 5.78. The significance of this difference was tested using a permutation test. The same analysis was performed for 500 random labellings of the same data; in each case, the Mahalanobis distance between the classes was less than that observed for the correctly labelled data, implying $p \leq 0.002$ that the Left-Right differences observed were due to chance.
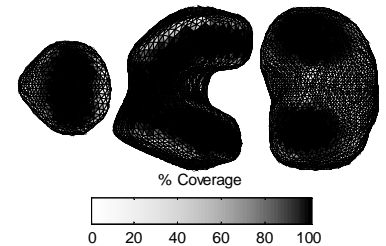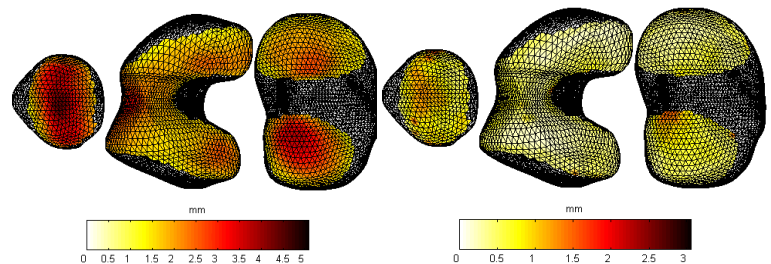

Fig. 1. Cartilage coverage

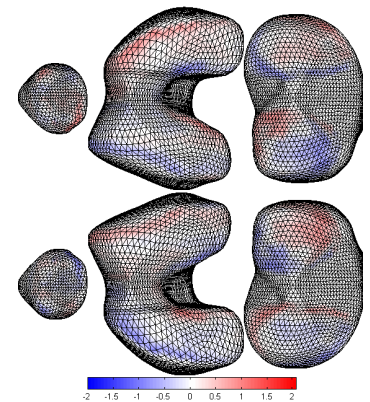**Fig. 2.** Mean and standard deviation of cartilage thickness

Fig. 3. Left(bottom)-Right(top) differences

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