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Automated image processing and analysis of cartilage MRI: enabling technology for data mining applied to osteoarthritis

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Abstract

Osteoarthritis (OA) is a heterogeneous and multi-factorial disease characterized by the progressive loss of articular cartilage. Magnetic Resonance Imaging has been established as an accurate technique to assess cartilage damage through both cartilage morphology (volume and thickness) and cartilage water mobility (Spin-lattice relaxation, T2). The Osteoarthritis Initiative, OAI, is a large scale serial assessment of subjects at different stages of OA including those with pre-clinical symptoms. The electronic availability of the comprehensive data collected as part of the initiative provides an unprecedented opportunity to discover new relationships in complex diseases such as OA. However, imaging data, which provides the most accurate non-invasive assessment of OA, is not directly amenable for data mining. Changes in morphometry and relaxivity with OA disease are both complex and subtle, making manual methods extremely difficult. This chapter focuses on the image analysis techniques to automatically localize the differences in morphometry and relaxivity changes in different population sub-groups (normal and OA subjects segregated by age, gender, and race). The image analysis infrastructure will enable automatic extraction of cartilage features at the voxel level; the ultimate goal is to integrate this infrastructure to discover relationships between the image findings and other clinical features.

Keywords

Atlas; Cartilage; Data Mining; Osteoarthritis

1. INTRODUCTION

Osteoarthritis (OA) is a type of arthritis that is caused by the breakdown and eventual loss of cartilage for one or more joints. OA is the most common form of arthritis and the major cause of activity limitation and physical disability in older people [1]. It is characterized clinically by pain, enlargement and deformity of the joints, and limitation of motion. The prevalence of OA in a population is difficult to assess because the degree of radiological change in symptomatic individuals varies greatly. Many individuals with radiographic evidence of OA have no symptoms [2]. Among the most commonly affected sites in OA, the knee is the major source of reported disability and loss of function [3, 4]. At present there is no medical treatment available for curing or halting the progress of osteoarthritis. An obstacle to assessing cartilage loss has been the absence of validated, non-invasive methods of quantifying articular cartilage degradation. Although substantial advances have been made through radiographic techniques the ability to assess cartilage loss has been

fundamentally limited due to the fact that they are an insensitive measure of OA pathology and reflect mainly on a more advanced disease. Moreover, radiography is a projection technique, which collapses three-dimensional (3D) anatomy into 2D images [5].

Significant advances in MRI and digital image analysis technology have revolutionized non-invasive assessment of cartilage macro-morphology such as volume and thickness. These techniques have enabled systematic assessment of the impact of various factors on normal knee cartilage morphology, including sex, maturity and age, body weight and height, body mass index (BMI), knee bone size, bone mineral density and level of physical exercise [6, 7]. Monitoring by serial MR imaging enables evaluation of potential effects of medical or surgical treatment on disease progression, in clinical research and eventually clinical practice. To derive quantitative morphological data from sequential, contiguous images, the articular cartilage must first be segmented from neighboring structures. Due to relatively low contrast in some regions of the joint's surface, fully automated segmentation of the joint cartilage from MR images has yet to be developed and requires different degrees of human interaction [8–11].

Data mining in medicine can be defined as a way to discover new knowledge from the existing data, and then applying the knowledge to aid in diagnosis and prognosis of new patient or data [12, 13]. There are many clinical trials in progress for evaluation of subjects with OA. For example, the Osteoarthritis Initiative (OAI), described in detail below, contains comprehensive information including extensive serial imaging data. Image data mining from such a comprehensive collection will certainly yield previously unknown and potentially useful information from the data. However, imaging data is not directly amenable to analysis and requires processing to extract characteristic image features that will serve as the signature for that image. Imaging features can then be integrated with other types of information stored in the database to perform comprehensive data mining.

The Osteoarthritis Initiative (OAI) is a multi-center, longitudinal, prospective observational study of knee osteoarthritis (OA). The overall aim of the OAI is to develop a public domain research resource to facilitate the scientific evaluation of biomarkers for osteoarthritis as potential surrogate endpoints for disease onset and progression. The OAI will establish and maintain a natural history database for osteoarthritis that will include clinical evaluation data, radiological (x-ray and magnetic resonance) images, and a bio-specimen repository from 4796 men and women ages 45–79. This seven-year project will recruit participants who have, and those who are at high risk for developing, symptomatic knee osteoarthritis. When complete, the OAI should provide an unparalleled state-of-the-art database documenting both the natural progression of the disease, information on imaging, biochemical biomarkers and, outcome measures. Valuable information can be obtained by data mining the OAI and our focus is on MR imaging data. In order to extract imaging features for data mining, automated robust image processing techniques are critical; these methods will be the focus of this chapter. Ultimately, image data mining will help establish one of the primary objectives of the OAI initiative: to help find biochemical, genetic and imaging biomarkers for development and progression of OA.

2. RELEVANT MR IMAGING FEATURES IN OSTEOARTHRITIS

2.1. Overview

Measurement of the dimensions of articular cartilage is believed to be important for assessing the progression of articular joint diseases; in particular, ability to quantify accurately small changes in cartilage thickness and volume may be useful not only in evaluation of disease progression but also for monitoring the efficacy of drug treatments or to monitor cartilage repair [14].

Magnetic resonance imaging (MRI), owing to its excellent soft tissue contrast, can visualize cartilage directly in three dimensions and distinguish it from the bone, other neighboring soft tissues, and synovial fluid. Comparisons of MR evaluation of the morphology of articular cartilage with data from histology have suggested good correlation across those two modalities. Cartilage thinning detected by MRI has been associated with arthritis in human subjects and, importantly, have been found to manifest earlier than that detected by conventional x-ray examinations. A number of studies have used MRI to quantify cartilage volume and thickness in human articular joints, particularly the knee.

In addition to morphological features, MR also provides additional information that has been shown to have potential in disease characterization of OA. These MR specific parameters include the spin-spin relaxation time, T2; Magnetization Transfer contrast, MTC; and Spin-lattice relaxation in the spin locked state, T1rho. Of these, the T2 relaxation time has been established more than the other parameters as relevant in OAI and is an image available in the OAI collection. Earlier studies have also demonstrated spatial dependency of cartilage T2 in both isolated cartilage explants and in vivo human patella. Studies have correlated changes in T2 with early symptomatic degeneration in patellar cartilage. T2, a time constant also known as the spin-spin relaxation time, characterizes the rate at which the M_{xy} component of the magnetization vector decays in the transverse magnetic field. T2 decay occurs 5 to 10 times more rapidly than T1 recovery, and different tissues have different T2s. For example, fluids have the longest T2s (700–1200 msec), and water based tissues are in the 40–200 msec range, while fat based tissues are in the 10–100 msec range. Immobilization of water protons in cartilage by the collagen-proteoglycan matrix promotes T2 decay, while mobile water protons in synovial fluid retain their high signal.

The cartilage is a very thin structure, and the variations in diseased state, especially at the early onset of disease, are small. It is important to be able to detect these subtle morphological and relaxivity changes. The ability to detect these imaging based changes automatically will enable researchers to determine correlation between imaging features with clinical outcomes in large data collections such as the OAI. Previous methods developed for measuring cartilage morphology and relaxivity measures were manual or semi-automatic and have primarily been validated on smaller datasets. Such methods would not be efficient in data mining tasks where a large corpus of images have to be examined.

Clearly, there is now an increasing need to establish fully automated and reproducible methods to quantify articular cartilage changes in morphology and relaxivity for diagnostic and prognostic purposes. In this chapter we emphasize the development of a fully automated image analysis technique which is designed to serve as an infra-structure for mining image information from a large database such as OAI.

2.2. Cartilage morphology

2.2.1. Volume—After segmentation, the cartilage volume can be readily derived as the number of voxels enclosed within the segmented structure. A number of studies have shown direct relation of volume reduction with cartilage degeneration in OA. However, the distribution of cartilage damage in articular joints tends to be uneven and can have higher statistical prevalence on load bearing sites than in the peripheral regions. Hence, the total cartilage volume may be less sensitive in identifying focal defects because small changes in some focal regions may be lost statistically against a background of the far larger volume of cartilage that remains unchanged across a series of measurements. To overcome this variability, the femoral and tibial cartilages of the knee are usually divided in their lateral and medial compartments and variations of thickness and volumes are studied for each compartment individually [15].

2.2.2. Cartilage thickness—The cartilage thickness is defined as the distance between the cartilage-bone and cartilage-synovium interface (articular surface of cartilage) and is determined from the 3D reconstruction of the cartilage by a 3D Euclidean distance algorithm. This algorithm calculates the cartilage thickness as the minimal distance between the bone-cartilage interface and the cartilage surface, taking into account deviations of the minimal distance vector out of the previous original section plane.

With the edges of the cartilage-bone and cartilage-synovium identified, the normal at each point on the bone surface is determined by a local surface-fitting technique. Each normal is extended to meet the cartilage-synovium interface, and the cartilage thickness then is calculated as the distance between the points of intersection of the normal to the two interfaces. The cartilage volume is calculated simply by voxel count for each femoral and tibial compartment. The values for mean and maximal thickness and volume for the cartilage are assessed separately for the medial and lateral tibial and femoral plateaus [11].

2.2.3. Cartilage relaxometry—As mentioned briefly above, MR provides information in addition to morphology. Cartilage transverse relaxation time (T2) mapping exploits the sensitivity of MRI to biophysical properties of tissue. These techniques have the potential to identify the earliest stages of matrix degeneration that precede visible cartilage damage. Cartilage T2 mapping uses intrinsic cartilage water as a probe to study the structural integrity of the extracellular matrix. The major component of cartilage is water, which is nonuniform in distribution, increasing from 67% near sub-chondral bone to 74% near the articular surface. The remaining 25 to 35% of the wet-weight of cartilage is solid matrix, primarily type II collagen and large aggregating proteoglycans [16]. The sequence of events leading to visible changes has been postulated in the following order. Collagen fatigue and breakdown are the earliest events in a destructive chain of events; the loss of the collagen framework integrity allows swelling of the proteoglycans, resulting in an increase in cartilage water, and a concurrent increase in cartilage permeability. Compressibility and permeability of cartilage are highly correlated with water content. As water content increases, the matrix of the tissue becomes more compressible, and a greater portion of the load is carried by the solid components of the extracellular matrix. This subsequently leads to increased stress, structural fatigue, fragmentation of cartilage, and ultimately, visible changes such as cartilage fibrillation and ulceration.

The spin lattice relaxation, T2, is a sensitive marker of free water content and mobility. T2 mapping methods have confirmed the non-uniform distribution of water in normal cartilage. E.g., T2 changes from the deep radial zone (32 ± 1 ms) to the outer transitional zone of cartilage (67 ± 2 ms) [17]. Further, T2 values also reflect the changes seen in OA: increased water mobility translates to increased T2 value. In osteoarthritis specimens, water content is increased by 9% compared to normal cartilage, suggesting an increase in T2 of 16 ms.

It is clear from the discussion on morphometry and relaxometry that complicated patterns are seen in normal cartilage and these patterns change with the disease state. The challenge is to extract these features (and their spatial variation) automatically and then reduce them to a compact set for future data mining applications. Image segmentation of the cartilage is a pre-requisite for feature extraction. In the next sections, we first review the status quo in cartilage segmentation from MR images. The review is then followed by a summary of our novel approach to cartilage segmentation and localized feature extraction that will address some of the limitations in the current approaches.

3. IMAGE PROCESSING

3.1. Segmentation

To derive quantitative data from sequential, contiguous images, the anatomical structure on interest (articular cartilage) must first be isolated from neighboring structures (segmented out). Due to relatively low contrast in some regions of the joints surface (e.g. articular contact areas, areas adjacent to the synovial folds, muscle, tendons, ligaments, Hoffa's fat pad, and repair tissue), fully automated segmentation of the joint cartilage from MR images has yet not been developed and the current algorithm require different degrees of human interaction. Verification (and some degree of correction) by an experienced user is generally required on a section by section basis.

There are number of algorithms which have been validated for articular cartilage segmentation and a brief overview follows: 1) Region Growing Method by Peterfly et.al. [18], Piplani et.al. [8], and Eckstein et. al. [19] In this method a connected component classification was performed, after which the object was manually edited to isolate segmented objects by inserting a line of null pixels to separate articular cartilage surfaces from neighboring surfaces. 2) Edge Detection by Kshirsagar et. al. [11]. Here, the binary image for the contour of the femoral bone-cartilage interface was derived from a 3-D edge-map obtained from each 3-D MRI data set using custom-written 3-D edge-detection. Additional manual refinements are made to eliminate any edges that are obviously artifactual. 3) Fitting B-Spline by Cohen et. al. [10]. In this approach, an initial set of points was digitized manually along each articular contour curve, with a coarse spacing of 1–2 cm. An interpolated cubic B-spline curve was fitted to the initial set of points. The B-spline curve, which followed the contour of the desired surface, was then sampled at 0.5 mm intervals. 4) Watershed Algorithm by Ghosh et. al. [9]. This segmentation procedure is initiated by sorting the pixels into a simple array according to intensity, and assigning a threshold pixel value. The cartilage contour is detected automatically by selecting contours with maximum perimeter and minimum cluster label. 5) Active Contours by Lynch et. al. and Kauffmann et. al. [20, 21]. The basic idea of active contour models or snakes is to evolve a curve which is subjected to constraints from the given image and hence is able to detect or segment the region of interest from the same image.

Most of the algorithms mentioned above are either semi-automated requiring some degree of human interaction or are not very accurate in segmenting the cartilage from the neighboring structures. Active contour models [20, 21] based on a 2D model and integrating edge information to stop the evolution of the curve work well but are limited by image noise, edge strength, and presence of iso-intense adjacent tissues, especially at the end of the cartilage volume. We address the limitations of 2D segmentation as well as the presence of fuzzy edges by implementing a 3D algorithm that does not depend on edge gradients as a stopping function for the curve evolution.

3.2. T and Z scores for cartilage abnormality detection

T and Z scores have been used in the diagnosis of osteoporosis providing a measure of deviation of bone density in patients versus normal subjects. Studies have shown these scores are applicable in quantifying the cartilage loss in osteoarthritis as well. T score is an indicator of the difference between patients and young healthy subjects whereas Z score is an indicator of difference between patients and age-matched healthy subjects. A relatively large inter-subject variability of normal cartilage volume has been reported; this variability is reduced by normalizing cartilage volume to joint surface area. In statistics, Z score also called standard score or normal score is a dimensionless quantity derived by subtracting the population mean from an individual raw score and then dividing the difference by the

population standard deviation. This conversion process is called standardizing or normalizing. The standard score indicates how many standard deviations an observation is above or below the mean. It allows comparison of observations from different normal distributions.

The patient data are compared with those from young healthy subjects and, if appropriate, also with those from age-matched (elderly) healthy subjects of the same sex. The absolute difference is then divided by the standard deviation of the mean value in the normal volunteers, to compute the T and Z score for each patient. Studies show T and Z scores calculated for imaging features such as cartilage mean and maximum thickness, and cartilage volume for better characterization of OA. Dunn et. al. [22] has calculated T and Z score in T2 mapping to improve the discriminatory power. Since significant differences in quantitative cartilage parameters have been reported between men and women, T score systems must be derived from sex-specific reference data; otherwise, cartilage loss is underestimated in men and overestimated in women. Studies show that physiologic changes of cartilage morphology occur with aging, even in the absence of joint disease. Therefore, T scores should be supplemented by Z scores, to express the difference between the patient and an age-matched (elderly) volunteer, if appropriate [23].

The spatial T and Z maps of relaxometry measurements are generated in the following way. Per-pixel and per-compartmental z scores are generated by using the mean and standard deviation of T2 values from healthy subjects in each compartment as given in Eq. 1:

$$z = \frac{(\text{voxel}_i - \text{mean}_{\text{healthy}})}{\text{sd}_{\text{healthy}}} \quad (1)$$

where voxel_i is the T2 value in the voxel of interest, $\text{mean}_{\text{healthy}}$ is the mean T2 value for all voxels of healthy knee in the same compartment, and $\text{sd}_{\text{healthy}}$ is the standard deviation of the same T2 distribution. The quantitative measure such as cartilage volume and thickness are global measures of the cartilage. The method we propose is a voxel based method which can characterize the cartilage changes taking place in the subject more comprehensively and enable one to identify even the most subtle changes.

4. NOVEL IMAGE ANALYSIS APPROACHES FOR CARTILAGE IMAGE DATA MINING

We build upon the extensive image analysis methods developed by other groups with focus on deriving features for data mining the OAI database. Our specific aims toward achieving this goal are: (1) to automate the image segmentation algorithm so that it works robustly for a wide variety of image quality including blurred cartilage edges and overlapping intensities of adjacent structures; (2) the creation of morphological and relaxivity atlases of the cartilage using normal subjects segregated by age, sex, and gender. These atlases capture the variation of shape/relaxivity patterns in normal subjects; (3) to identify regions of abnormality in cartilages of subjects with OA by comparison to the normal atlas; this will be based on the analysis of the 3D deformation field required to move voxels to their corresponding locations in the atlas. Deformations beyond $\pm 2\text{SD}$ of normal variations constitute regions with large morphological changes; (4) generating active shape models from the normal subject data and using the shape coefficients to classify cartilage morphology using a compact set of features; these features will be the basis for image data mining.

4.1. Segmentation

The first important task is to develop a fully automated segmentation technique to extract the cartilage from the surrounding structures in the MR images. Our segmentation model is an extension of the active contour without borders proposed by Chan and Vese [24]. The basic idea of active contour models or snakes is to evolve a curve which is subjected to constraints from the given image to segment a region of interest. In classical active contours and snakes models an edge detector is used which basically depends on gradient of the image to the stop the evolving curve. In practice, the discrete gradients are bounded and then the stopping function is never zero on the edges, and the evolving curve may pass through the boundary. The Chan-Vese model does not incorporate a stopping edge-function, and is ideal for segmenting cartilage from MR knee images (which often present with blurry edges).

The new model is described as follows: Let us define the evolving curve C in Ω , as the boundary of an open subset ω of Ω (i.e. $\omega \subset \Omega$, and $C = \partial\omega$). In what follows, $inside(C)$ denotes the region ω , and $outside(C)$ denotes the region $\Omega \setminus \omega$. The method is minimization of energy-based segmentation. Assume that an image u_0 is formed by two regions of approximately piece-wise constant intensities, of distinct values u_0^i and u_0^o . We now assume that the region u_0^i is the region of interest to be segmented. Then we have $u_0 \approx u_0^i$ inside the object [or $inside(C_o)$], and $u_0 \approx u_0^o$ outside the object [or $outside(C_o)$]. Now we define the following “fitting” term:

$$F_1(C) + F_2(C) = \int_{inside(C)} |u_0(x, y) - c_1|^2 dx dy + \int_{outside(C)} |u_0(x, y) - c_2|^2 dx dy \quad (2)$$

where C is any other variable curve, and the constraint c_1, c_2 , depending on C , are the averages of μ_0 inside C and respectively outside C . In this simple case it is obvious that C_0 , the boundary of the object will minimize the fitting term;

$$\inf_C \{F_1(C) + F_2(C)\} \approx 0 \approx F_1(C_0) + F_2(C_0) \quad (3)$$

Consider the following cases: 1) if the curve C is outside the object, then $F_1(C) > 0$ and $F_2(C) \approx 0$; 2) If the curve C is inside the object, then $F_2(C) > 0$ but $F_1(C) \approx 0$; 3) If the curve C is both inside and outside the object, then $F_1(C) > 0$ and $F_2(C) > 0$. Finally, the fitting energy is minimized if $C = C_o$, i.e., if the curve C is on the boundary of the object. The new active contour model minimizes the above mentioned fitting term and some new regularizing terms are added for example the length of the curve C , and (or) the area of the region inside C . Thus a new energy function is formed which is defined by Eq. 4

$$F(c_1, c_2, C) = \mu \cdot Length(C) + \nu \cdot Area(inside(C)) + \lambda_1 \int_{inside(C)} |u_0(x, y) - c_1|^2 dx dy + \lambda_2 \int_{outside(C)} |u_0(x, y) - c_2|^2 dx dy \quad (4)$$

where $\mu \geq 0$, $\nu \geq 0$, $\lambda_1, \lambda_2 > 0$ are fixed parameters. In all numerical calculations the values for $\lambda_1 = \lambda_2 = 1$ and $\nu = 0$. The minimization problem is solved by level sets. The final implementation integrates the active shape model to limit the evolution to known anatomical variability. The preliminary segmentation results based on the 2D algorithm is shown in Fig. 1.

4.2. Creation of morphological atlases

The methodology used to create the atlases includes both affine and non-linear transformations. The segmented cartilage obtained from the previous step is then interpolated to a pixel resolution of $0.365 \times 0.365 \times 0.365 \text{ mm}^3$. The atlas was created using the following steps:

Step I: One subject was randomly chosen from the pool of 20 to serve as a reference. Mutual information based affine transformation corrects for subject positioning and global size differences (with respect to reference).

Step II: An elastic registration based on demons algorithm [25] was employed to locally map all the images in the group of subjects to the reference image using the affine transformation parameters as an initial estimation. This provides 3D deformation fields that can map the spatial locations on an individual in the group to the coordinate system of the reference. The registration algorithm computes the transformation iteratively using Eq. 5.

$$v_{n+1} = G_{\sigma} \otimes \left(v_n + G_{\sigma} \otimes \frac{1}{2} \left[\frac{C(T - S \|\nabla S\| \|\nabla T\|)}{(\|\nabla T\|^2 + \|\nabla S\|^2 \langle \|\nabla S\|^2 + \|\nabla T\|^2 + 2(T - S)^2) } \nabla S \right] \right) \quad (5)$$

where v_{n+1} is the correction vector field at iteration $n+1$, G_{σ} is the Gaussian filter with variance σ_2 , $\otimes$ denotes the convolution, C is the scaling factor and T and S are the target and transformed images respectively. The algorithm estimates the displacement which maps a voxel at location $(x, y \text{ and } z)$ in T to the corresponding anatomical location in S . The algorithm is implemented hierarchically and to preserve the morphology, deformation vector fields were computed utilizing both the forward and backward transformation.

Step III: A mean intensity image with the shape of the reference image is created by averaging the globally and locally transformed images of the group.

Step IV: A mean deformation field that encodes the shape variation between the reference image and average shape of the elements in the subject group is created by averaging over 3D deformation vector fields of the individual subjects of the group.

Step V: Average deformation field is applied to the average intensity image to generate an average intensity and deformation image template for the group under study.

Step VI: Steps 1–5 are iterated until no significant change in the deformation field is observed relative to the previous computation. At the end of iteration the original reference image is replaced by the average template constructed at Step V generating both average shape (morphometric) and intensity atlases that represent the centroid of the population data set. Fig. 2 visualizes the atlas generated and also visually validates the accuracy of the non-linear registration algorithm.

The goal is to create atlases segregated by age, race and gender. The differences in average atlases from each sub-group can be used for data mining: e.g. to determine correlations in shape differences between sub-groups to body hiatus and/or life-style factors. The atlases will be further employed in detection of morphological abnormalities (based on the deformation maps) in patient with OA.

4.3. Deformation maps

Image registration aims to determine a correspondence between each pixel q in the reference image I_R to a pixel p in the test image I_T . When a reference image is warped to match a

subject image, some regions may get enlarged and some may be reduced. It is possible to determine the amount of scaling applied to an infinitesimal area around each point of the reference image, by computing the Jacobian determinant of the spatial transformation. In the case of three-dimensional images the displacement vector field from the reference image to the subject i , $\mathbf{u}_i$, can be decomposed into its components u_i , v_i and w_i . Similarly $\mathbf{q}$ can be expressed in terms of its co-ordinates (x , y , and z). The Jacobian's determinant $J_i(\mathbf{q})$ is defined as the determinant of the gradient of the mapping function $\mathbf{q} + \mathbf{u}_i(\mathbf{q})$ given in Eq. 6. The value of J is positive as the registration produces a continuous one to one mapping. As part of our preliminary work, deformation fields generated from warping a new subject to the 'normal' atlas were visually evaluated using a color encoding for the magnitude of the deformation.

$$J_i(\mathbf{q}) = |\nabla(\mathbf{q} + \mathbf{u}_i(\mathbf{q}))| = \left| \begin{pmatrix} \frac{\partial u_i(\mathbf{q})}{\partial x} & \frac{\partial u_i(\mathbf{q})}{\partial y} & \frac{\partial u_i(\mathbf{q})}{\partial z} \\ \frac{\partial v_i(\mathbf{q})}{\partial x} & \frac{\partial v_i(\mathbf{q})}{\partial y} & \frac{\partial v_i(\mathbf{q})}{\partial z} \\ \frac{\partial w_i(\mathbf{q})}{\partial x} & \frac{\partial w_i(\mathbf{q})}{\partial y} & \frac{\partial w_i(\mathbf{q})}{\partial z} \end{pmatrix} \right| \quad (6)$$

Deformation fields were evaluated for subjects used in the atlas creation, normal subjects from 2 different age groups not included in the atlas, and subjects in three different age groups from the progression cohort. The deformation fields are shown in Fig. 3. The top row shows deformation fields of 3 subjects from the incidence group and different ages. Similarly, the bottom row shows subject from the progression group of three different ages as shown. The region of maximum deformations is indicated by the color red. The image clearly shows that the oldest subject in the progression group with the maximum deformation indicating maximum difference in cartilage morphology with the 'normal subject' atlas. The first subject (denoted as (a) in Fig. 3) was one of the subjects used to create the atlas and as anticipated, shows the least deformations. Normal subjects who belonged to different age groups from those used in the atlas presumably show some morphological changes from 'normal' aging.

The 'progression' group subject in each abnormal image will be labeled by the location, extent and degree of morphological abnormality captured in the deformation maps. This feature set will be used to index the cartilage for data mining the OAI database.

4.4. T2 mapping

In addition to morphological atlases, relaxivity atlases capturing the variation in T2 in normal subjects are generated and then used to detect changes in subjects with OA. Cartilage T2 maps are generated from the multi-echo images obtained from the OAI database, by fitting the signal intensity (SI) for the i^{th} , j^{th} pixel as a function of time, t , as shown in the equation.

$$SI_{i,j}(t) = S0_{i,j} * \exp\left(\frac{-t}{T2_{i,j}}\right) \quad (7)$$

Here $S0_{i,j}$ is the pixel intensity at $t=0$, and $T2_{i,j}$ is the T2 relaxation time constant of pixel i and j . A T2 map is generated from the $T2_{i,j}$ data. Once the T2 maps are generated a color coded look-up table is generated to display the T2 maps as shown in Fig. 4.

Although it is rather simple to calculate a bulk cartilage T2 value, this method of analysis is insensitive to localized areas of cartilage damage and results in large standard deviations due

to the inherent spatial variation in T2 of normal cartilage. It is possible to account for the normal spatial variation by generating normalized cartilage T2 profiles, which describe the mean T2 value as a function of normalized distance from bone. With this method of analysis, it is possible to identify small regional differences in cartilage T2 between groups, for example, as a function of age.

5. SUMMARY

The novel segmentation strategy is robust to image noise and is less sensitive to fuzzy edges. The atlas based method allows one to model normal physiological variations and detection at the voxel level providing a detailed characterization not possible with current tools. The morphological and relaxivity features provide a compact signature for the images; these features can then be used for data mining the OAI database to uncover new correlations. The same methodology can be applied to the longitudinal studies in the database to infer knowledge on disease progression. In addition, the normal atlases will, in themselves provide a wealth of information on cartilage morphometry and relaxivity which can be used to construct age, gender, and ethnicity-specific models.

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References

1. Dunlop D, Manheim LM, Yelin EH, Song J, Chang RW. The cost of arthritis. *Arthritis & Rheumatism*. 2003;101–113. [PubMed: 12579600]
2. Bagge E, Bjelle A, Valkenburg HA, Svanborg A. Prevalence of radiographic osteoarthritis in two elderly European populations. *Rheumatology International*. 1992;33–38. [PubMed: 1598499]
3. Urwin M, Symmons DPM, Allison T, Brammah T, Busby H, Roxby M, Simmons A, Williams G. Estimating the burden of musculoskeletal disorders in the community: the comparative prevalence of symptoms at different anatomical sites and the relation to social deprivation. *Annals of Rheumatic Diseases*. 1998;649–655.
4. Peat G, McCarney R, Croft P. Knee pain and osteoarthritis in the older adults: a review of community burden and current use of primary health care. *Annals of Rheumatic Diseases*. 2001;91–97.
5. Eckstein F, Reiser M, Englmeier KH, Putz R. In vivo morphometry and functional analysis of human articular cartilage with quantitative magnetic resonance imaging – from image to data, from data to theory. *Anatomy & Embryology*. 2001;147–173. [PubMed: 11303902]
6. Cicuttini F, Forbes A, Morris K, Darling S, Bailey M, Stuckey S. Gender differences in knee cartilage volume as measured by magnetic resonance imaging. *Osteoarthritis and Cartilage*. 1999;265–271. [PubMed: 10329301]
7. Jones G, Glisson M, Hynes K, Cicuttini F. Sex and site difference in cartilage development: a possible explanation for variations in knee osteoarthritis in later life. *Arthritis and Rheumatism*. 2000;2543–9. [PubMed: 11083279]
8. Piplani M, Disler D, McCauley TR, Holmes TJ, Cousins JP. Articular cartilage volume in the knee: semi-automated determination from the three-dimensional reformations of MR images. *Radiology*. 1996;855–9. [PubMed: 8628883]
9. Ghosh S, Ries M, Lane N, Ghajar C, Majumdar S. Segmentation of the high resolution articular cartilage MR images. *Transaction of Orthopedic Research Society*. 2000;246.

10. Cohen Z, McCarthy D, Kwak S, Legrand P, Fogarasi F, Ciaccio E, Ateshian G. Knee cartilage topography, thickness, and contact areas from MRIL in-vitro calibration and in-vivo measurements. *Osteoarthritis and Cartilage*. 1999:95–109. [PubMed: 10367018]
11. Kshirsagar A, Watson P, Tyler J, Hall L. Measurement of localized cartilage volume and thickness of human knee joints by computer analysis of three-dimensional magnetic resonance images. *Investigative Radiology*. 1998:289–99. [PubMed: 9609488]
12. Lavrac, N. Machine Learning for Data Mining in Medicine. In: Horn, W., editor. *Artificial Intelligence in Medicine*. Berlin/Heidelberg: Springer; 2004. p. 47
13. Cios KJ, Moore GW. Uniqueness of Medical Data Mining. *Artificial Intelligence in Medicine*. 2002:1–24. [PubMed: 12234714]
14. Eckstein F, Cicuttini F, Raynauld JP, Waterton JC, Peterfly C. Magnetic Resonance Imaging of articular cartilage in knee osteoarthritis (OA): morphological assessment. *Osteoarthritis and Cartilage*. 2006:A46–A75. [PubMed: 16713720]
15. Burgkart R, Glaser C, Hyhlik-Dürr A, Englmeier K, Reiser M, Eckstein F. Magnetic Resonance Imaging-Based Assessment of Cartilage Loss in Sever Osteoarthritis. *Arthritis and Rheumatism*. 2001:2072–2077. [PubMed: 11592369]
16. Mosher T, Dardzinski B. Cartilage MRI T2 Relaxation Time Mapping: Overview and Applications. *Seminars in musculoskeletal radiology*. 2004:355–368. [PubMed: 15643574]
17. Dardzinski B, Mosher T, Li S, Van Slyke M, Smith M. Spatial variation of T2 in human articular cartilage. *Radiology*. 1999:546–550.
18. Peterfly C, Van Dijke C, Janzen D, Gluer C, Namba R, Majumdar S, Lang P, Genant H. Quantification of articular cartilage in the knee with pulsed saturation transfer subtraction and fat-suppressed MR imaging: optimization and validation. *Radiology*. 1994:485–491.
19. Eckstein F, Schneir M, Haubner M, Priebsch J, Glaser C, Englmeier K, Maximilian R. Accuracy of Cartilage Volume and Thickness Measurements With Magnetic Resonance Imaging. *Clinical Orthopedics and Related Research*. 1998:137–148.
20. Lynch, J.; Zaim, S.; Zhao, J.; Stork, A.; Peterfly, C.; Genant, H. Cartilage segmentation of 3D MRI scans of the osteoarthritic knee combining user knowledge and active contours. *Proceedings of SPIE. International Society for Optical Engineering*; 2000. p. 925-935.
21. Kauffman C, Gravel P, Godbout B, Gravel A, Beaudoin G, Raynauld J, Martel-Pelletier J, Pelleteir J, de Guise J. Computer aided method for quantification of cartilage thickness and volume changes using MRI: validation study using synthetic model. *IEEE transactions on Biomedical Engineering*. 2003:978–988. [PubMed: 12892325]
22. Dunn T, Lu Y, Jin H, Ries M, Majumdar S. T2 relaxation time of the cartilage at MR imaging: Comparison with severity of knee osteoarthritis. *Musculoskeletal Imaging*. 2004:592–598.
23. Burgkart R, Glaser C, Hinterwimmer S, Hudelmaier M, Englmeier K, Reiser M, Eckstein F. Feasibility of T and Z score from magnetic resonance imaging data for quantification of cartilage loss on osteoarthritis. *Arthritis and Rheumatism*. 2003:2829–2835. [PubMed: 14558088]
24. Chan T, Vese L. Active contours without edges. *IEEE Trans on Image Processing*. 2001:266–278.
25. Thirion J. Image matching as a diffusion process: an analogy with Maxwell's demons. *Medical Image Analysis*. 1998:243–260. [PubMed: 9873902]

FIGURE 1.

The bottom right image in the figure shows the final segmentation of the cartilage obtained on a test knee image shown in the top left corner.

FIGURE 2.

Image a is a 2D image showing sharp edges on the atlas created from 20 subjects. Image b is a 3D volume reconstruction of the cartilage from the atlas.

FIGURE 3.

Deformation fields of subjects in incidence and progression group. Maximum deformations are seen in subjects from the progression cohort.

FIGURE 4.

Color map showing increased T2 values on the subject from the progression group (right) as compared to the subject chosen from the incidence group (left). Unit in msec.