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Phase contrast imaging X-ray computed tomography: Quantitative characterization of human patellar cartilage matrix with topological and geometrical features

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Abstract

Current assessment of cartilage is primarily based on identification of indirect markers such as joint space narrowing and increased subchondral bone density on x-ray images. In this context, phase contrast CT imaging (PCI-CT) has recently emerged as a novel imaging technique that allows a direct examination of chondrocyte patterns and their correlation to osteoarthritis through visualization of cartilage soft tissue. This study investigates the use of topological and geometrical approaches for characterizing chondrocyte patterns in the radial zone of the knee cartilage matrix in the presence and absence of osteoarthritic damage. For this purpose, topological features derived from Minkowski Functionals and geometric features derived from the Scaling Index Method (SIM) were extracted from 842 regions of interest (ROI) annotated on PCI-CT images of healthy and osteoarthritic specimens of human patellar cartilage. The extracted features were then used in a machine learning task involving support vector regression to classify ROIs as healthy or osteoarthritic. Classification performance was evaluated using the area under the receiver operating characteristic (ROC) curve (AUC). The best classification performance was observed with high-dimensional geometrical feature vectors derived from SIM (0.95 ± 0.06) which outperformed all Minkowski Functionals ($p < 0.001$). These results suggest that such quantitative analysis of chondrocyte patterns in human patellar cartilage matrix involving SIM-derived geometrical features can distinguish between healthy and osteoarthritic tissue with high accuracy.

Keywords

phase contrast imaging; Minkowski functionals; scaling index method; texture analysis; support vector regression; osteoarthritis

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This work is not being and has not been submitted for publication or presentation elsewhere.

1. MOTIVATION/PURPOSE

Osteoarthritis is widely recognized as representing one of the leading causes of disability worldwide. This disease is characterized by progressive damage to the articular cartilage and subchondral bone. In this research context, phase-contrast computed tomography (PCI-CT) recently emerged as a novel imaging approach that provides soft-tissue discrimination in cartilage tissue at a micrometer scale resolution [1]. Previous work has shown the ability of PCI-CT to visualize differences between healthy and osteoarthritic patellar cartilage matrix specimens [1]. In this work, we explore the use of topological and geometrical approaches to quantify such differences.

We specifically investigate the use of topological features derived from Minkowski Functionals and geometric features derived from the Scaling Index Method (SIM) for purposes of characterizing chondrocyte patterns annotated in the radial zone of knee cartilage matrix, as visualized on PCI-CT images of both healthy and osteoarthritic specimens. In this work, Minkowski Functionals are used to capture global topological properties of the underlying gray-level patterns. SIM, on the other hand provides a detailed geometrical description of the underlying gray-level patterns within the ROI, specifically through estimation of local scaling properties. Both methods have been previously applied to other pattern recognition tasks in medical imaging, such classifying between healthy and pathological lung tissue on CT [2], estimating the bone strength through analysis of trabecular micro-architecture [3], classification of malignant and benign tumors on dynamic breast MRI [4] etc. We also note that these methods have been previously investigated in the context of classifying healthy and osteoarthritic cartilage on PCI-CT images [5–6].

The goal of this work is evaluate and compare the ability of such topological and geometrical descriptors to characterize chondrocyte patterns in the radial zone of the cartilage matrix and adequately discriminate between healthy and osteoarthritic cartilage. For this purpose, such features are extracted from regions of interest (ROI) placed on PCI-CT images and used in a machine learning task that attempts to predict the class of the ROI, as discussed in the following sections. Sample ROIs used in this study are shown in figure 1. This work is embedded in our group's endeavor to expedite 'big data' analysis in biomedical imaging by means of advanced pattern recognition and machine learning methods for computational radiology, e.g. [7–23].

2. DATA

Two osteochondral cylindrical samples of diameter 7 mm and height 12 mm were extracted from the lateral facet of the patella of 2 patients, one healthy and one osteoarthritic, within 48 hours post-mortem. These samples were subject to PCI-CT with an analyzer-based imaging (ABI) technique, where a parallel monochromatic beam of synchrotron radiation (X-rays of energy 26keV) was used to irradiate the sample. In an inversion of traditional computed tomography setup, each bone-cartilage sample was irradiated by the stationary source while rotating about an axis perpendicular to the incident beam, and a projection image was acquired at each angular step. Vertical displacement of the sample at the end of each rotation facilitated scanning of its entire volume. An analyzer crystal was positioned

between the sample and the detector to convert the tiny X-ray refraction angles into observable intensity differences. The images were acquired at the ID17 biomedical beamline of the European Synchrotron Radiation Facility (ESRF, France). Further details about the experimental setup used to acquire these images can be found in [1,24].

Axial images of dimensions 1124×1124 and in-plane resolution of $8\mu\text{m} \times 8\mu\text{m}$ were reconstructed by using a direct Hamming filtered-back projection algorithm. 805 such images were obtained from each specimen and reformatted to yield slices in the coronal plane. 404 regions of interest (ROI) of dimensions 51×51 pixels, capturing chondrocyte patterns, were annotated by an experienced radiologist in the radial zone of the cartilage matrix on these coronal slices. 233 of these ROIs were healthy while the remaining 171 were osteoarthritic. Examples of ROIs extracted from the radial zone of cartilage matrix and subsequently used for extraction of features are shown in Figure 1.

3. METHODS

3.1 Feature analysis

Minkowski Functionals (MF) are used to characterize morphological properties of binary images i.e. shape (geometry) and connectivity (topology) [25]. Three MF features i.e. area, perimeter and Euler characteristic can be calculated from binary images as follows -

$$\text{MF}_{\text{area}} = n_s$$

$$\text{MF}_{\text{perimeter}} = -4n_s + 2n_e$$

$$\text{MF}_{\text{Euler}} = n_s - n_e + n_v$$

where “ n_s ” is the total number of white pixels, “ n_e ” is the total number of edges and “ n_v ” is the number of vertices. The area feature records the number of white pixels in the binary image, the perimeter measure calculates the length of the boundary of white pixel areas and the Euler characteristic is a measure of connectivity between the white pixel regions. It has been shown that morphological properties of objects in an image can be fully specified in terms of Minkowski Functionals.

Binary images were generated from PCI-CT ROIs by subjecting them to a gray-level threshold; the three MF features specified above were subsequently extracted from these binary ROIs. In this study, ROIs were subjected to multiple thresholds, as illustrated in Figure 2, and the resulting MF features computed were stored in high-dimensional vectors. The behavior of MF features as a function of the gray-level threshold was then used to differentiate between healthy and osteoarthritic chondrocyte patterns observed in PCI-CT ROIs. Twenty such gray-level thresholds were used in this work, resulting in a 20-D feature vector for each MF.

Scaling Index Method (SIM) characterizes the structure observed in a ROI through geometric features that estimate the local dimension [26]. The 2D ROI is treated as a 3D volume where the gray-level intensity is treated as the third dimension. Now, for each pixel x_i in the ROI, the local dimension is calculated as –

$$\alpha(x_i, r) = \frac{\sum_{j=1}^N (d_{ij}/r)^2 \exp \left[-(d_{ij}/r)^2 \right]}{\sum_{j=1}^N \exp \left[-(d_{ij}/r)^2 \right]}$$

where d_{ij} is the distance between the i^{th} pixel (centre) and the j^{th} pixel (neighbor), r is the neighborhood radius and N is the number of pixels contained in the neighborhood. This transform essentially assigns each pixel a local scaling property $\alpha(x_i, r)$ in a neighborhood determined by the radius r .

The resulting distribution of α values, as seen in the SIM transformation and SIM histogram shown in Figure 3, characterizes the underlying gray-level structure and could be used to distinguish between healthy and osteoarthritic ROIs. We represent this distribution of α values with its 9 quantiles, stored in a 9-D feature vector which is subsequently processed in a classification task.

3.2 Classification

The extracted vectors were divided into training and testing datasets, and support vector regression [27] with a radial basis function kernel was used for the machine learning task. SVR is an extension of support vector machines (SVM) [28], which is a supervised learning model that is widely used in different machine learning tasks. SVM presents a computationally efficient approach for identifying a hyper-plane that imposes a maximum separation between two classes of data points in a high-dimension feature space.

The training phase employed a sub-sampling cross-validation strategy; the free parameters of the classifier (cost parameter and shape parameter of radial basis function) were optimized using the training set. Then, during the testing phase, the trained classifier was used to evaluate the character of the ROIs in the test set. An ROC curve was generated and used to compute the area under the curve (AUC). This process was repeated 50 times and a Wilcoxon signed rank was used to compare two AUC distributions. Significance thresholds were adjusted for multiple comparisons using the Holm-Bonferroni correction to achieve an overall type I error rate (significance level) less than α (where $\alpha = 0.05$) [29–30].

Texture feature extraction, classification and statistical analysis were implemented using Matlab 2010a (The MathWorks, Natick, MA).

4. RESULTS

Table 1 shows the classifier performance obtained when both Minkowski Functionals and SIM feature vectors are used to characterize chondrocyte patterns in ROIs placed on the radial zone of the knee cartilage matrix. The highest AUC was observed with the SIM feature vector (0.95 ± 0.06). Such geometric features significantly outperformed all topological

feature vectors derived from Minkowski Functionals ($p < 0.001$). Among the three Minkowski Functionals, the best performance was achieved by Euler Characteristic (0.88 ± 0.09) which outperformed the others. The worst performance was noted with Minkowski Functional Area (0.61 ± 0.07).

5. NEW AND BREAKTHROUGH WORK

PCI-CT has been demonstrated as a novel technique for visualizing the cartilage matrix in ex vivo specimens of human patellar cartilage at a micro-meter scale resolution [1]. However, this has also showcased the need quantitative measures to consistently capture differences observed in the chondrocyte patterns in the radial zone of the cartilage matrix in the presence or absence of osteoarthritis. This investigation compares the performance achieved by previously proposed topological [5] and geometrical [6] approaches in quantitatively discriminating between ROIs extracted from healthy and osteoarthritic cartilage matrix. As observed in this work, features that characterize these chondrocyte patterns through local geometry (SIM) outperform those that capture global topological properties (Minkowski Functionals). Such features have significant potential for serving as imaging markers in PCI-CT for diagnosing and monitoring disease progression of osteoarthritis in human patellar cartilage.

As shown in this work, quantitative features can be used in combination with machine learning algorithms to predict the label (healthy or osteoarthritic) of an ROI extracted from the radial zone of the cartilage matrix visualized on PCI-CT with high accuracy. The best classification performance was observed with the 9-D geometrical feature vector extracted using SIM. The effectiveness of SIM in distinguishing between healthy and osteoarthritic ROIs can be attributed to its capturing geometrical properties of local neighborhoods. As seen in Figure 3, the chondrocytes are more clustered in the radial zone of osteoarthritic cartilage leading smaller local dimensions being evaluated at most pixels. This is further reflected in the corresponding SIM histogram which represents the α value distribution in the ROI. However, since chondrocytes in healthy cartilage are less clustered and are instead aligned in a specific pattern radiating outward from the tidemark, a high local dimension is evaluated at a larger number of pixels corresponding to the extracellular matrix.

The poorer performance of topological texture features derived from Minkowski Functionals could indicate that global characterization of chondrocyte organization in these ROIs is not enough for accurate classification, specifically at small ROI sizes. Thus, local characterization of chondrocyte patterns in the radial zone of patellar cartilage matrix, such as that provided by SIM-derived geometrical features, could be more useful for the task of classifying healthy and osteoarthritic ROIs. Among the topological feature vectors derived from Minkowski Functionals, the best classification performance was achieved with Euler characteristic, which suggests that connectivity is the strongest distinguishing characteristic between healthy and osteoarthritic ROIs.

While our preliminary study suggests that quantitative features, such as those discussed here, can classify healthy and osteoarthritic cartilage patterns on PCI-CT images, future studies will need to address certain drawbacks. The current setup includes only two specimens, one

extracted from a healthy donor and the other one from an osteoarthritic donor (post-mortem). It is desirable to include more cartilage specimens in future studies as having ROIs from the same patient in the training and testing phase of the machine learning step could lead to some bias in the results. Further improvements to textural characterization of chondrocyte organization could include volumetric analysis as both SIM and Minkowski Functionals can be computed for 3D volumes of interest (VOI). Finally, the choice of ROI size in this study was arbitrary; the impact of ROI size on the classification performance achieved with these features should be investigated in future studies.

6. CONCLUSION

This study compared geometrical and topological approaches to characterizing chondrocyte patterns in the radial zone of cartilage matrix on PCI-CT images acquired from *ex vivo* human patellar cartilage specimens. Our results show that geometrical features derived from SIM outperform topological features derived from Minkowski Functionals at the task of classifying ROIs annotated on these PCI-CT images as healthy or osteoarthritic. We hypothesize that such features could offer significant potential as imaging markers in PCI-CT for diagnosing and monitoring disease progression of osteoarthritis in human patellar cartilage.

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Figure 1.

Regions of interest extracted from the radial zone of healthy and osteoarthritic knee cartilage matrix. The goal here is to classify these ROIs as belonging to either class based on quantitative analysis of the difference observed in chondrocyte patterns.

Figure 2.

A sample osteoarthritic ROI is shown on the extreme left. Images to the right are obtained by binarizing the ROI at 3 different gray-level thresholds. Each Minkowski Functional is computed at every binary image created and the resulting values are combined into a feature vector.

Figure 3.

LEFT: A sample osteoarthritic ROI. MIDDLE: ROIs after being processed with SIM ($r = 5$); color-coded based on local dimension estimates. RIGHT: SIM histogram of the ROI.

Table 1

Classification performance (mean $\pm$ std) achieved with features derived from Minkowski Functionals and SIM.

Features	AUC
Area	0.61 ± 0.07
Perimeter	0.85 ± 0.09
Euler Char.	0.88 ± 0.09
SIM	0.95 ± 0.06

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