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Volumetric quantitative characterization of human patellar cartilage with topological and geometrical features on phase contrast x-ray computed tomography

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Abstract

Phase contrast X-ray computed tomography (PCI-CT) has attracted significant interest in recent years for its ability to provide significantly improved image contrast in low absorbing materials such as soft biological tissue. In the research context of cartilage imaging, previous studies have demonstrated the ability of PCI-CT to visualize structural details of human patellar cartilage matrix and capture changes to chondrocyte organization induced by osteoarthritis. This study evaluates the use of geometrical and topological features for volumetric characterization of such chondrocyte patterns in the presence (or absence) of osteoarthritic damage. Geometrical features derived from the scaling index method (SIM) and topological features derived from Minkowski Functionals were extracted from 1392 volumes of interest (VOI) annotated on PCI-CT images of *ex vivo* human patellar cartilage specimens. These features were subsequently used in a machine learning task with support vector regression to classify VOIs as healthy or osteoarthritic; classification performance was evaluated using the area under the receiver-operating characteristic (ROC) curve (AUC). Our results show that the classification performance of SIM-derived geometrical features (AUC: 0.90 ± 0.09) significantly outperform Minkowski Functionals volume

(AUC: 0.54 ± 0.02), surface (AUC: 0.72 ± 0.06), mean breadth (AUC: 0.74 ± 0.06) and Euler characteristic (AUC: 0.78 ± 0.04) ($p < 10^{-4}$). These results suggest that such geometrical features can provide a detailed characterization of the chondrocyte organization in the cartilage matrix in an automated manner, while also enabling classification of cartilage as healthy or osteoarthritic with high accuracy. Such features could potentially serve as diagnostic imaging markers for evaluating osteoarthritis progression and its response to different therapeutic intervention strategies.

Keywords

osteoarthritis; phase contrast imaging; scaling index method; Minkowski functionals; volumetric features; support vector regression

1 Introduction

Osteoarthritis (OA) is widely recognized as one of the leading causes of disability worldwide [1–3]. This disorder is characterized by loss of articular cartilage, thickening of the underlying subchondral bone, and osteophyte formation [4]. Diagnostic markers currently used in clinical practice to monitor OA progression, such as joint pain or observation of joint space narrowing with conventional radiography, are only sensitive at advanced stages of the disease. Thus, imaging modalities that could provide early detection and allow visualization of any OA-induced degenerative modifications to the cartilage are currently of significant interest in the research field of cartilage imaging [5–9]. While several imaging techniques are currently being investigated for cartilage health assessment through evaluation of glycosaminoglycan (GAG) content, eg. delayed gadolinium-enhanced MR imaging of cartilage (dGEMRIC) [10], ^{23}Na MRI [11], T1 [12], GAG chemical exchange saturation transfer (gagCEST) [15] [13], none of these techniques currently possess the capability to visualize cartilage matrix structure at a cellular level.

In this context, phase contrast X-ray computed tomography (PCI-CT) stands out for its ability to visualize the internal architecture of the cartilage matrix at micrometer scale resolution in *ex vivo* samples of human patellae [14]. PCI exploits the fact that X-rays undergo a phase shift and are consequently refracted when passing through matter [15,16]. The contrast achieved by exploiting such phase/refraction effects can be much larger than conventional absorption-based contrast, specifically for the energy range of X-rays used in diagnostic modalities, and for soft tissue types encountered in clinical practice [17]. This allows PCI to be effective in imaging applications where conventional absorption-based contrast can be insufficient for soft tissue characterization, notably in breast [18,19] and cartilage [14,20,21]. Among the different PCI techniques, we specifically focus on the analyzer-based imaging (ABI) method [16,22,23], which has been applied in both *ex vivo* and *in vivo* cartilage studies and demonstrated greatly improved cartilage visualization [14,24, 25].

This study focuses on the cartilage of the retropatellar joint, which has significant potential for enabling early detection of treatable osteoarthritic changes to the cartilage matrix. Patellar cartilage represents the thickest cartilage tissue compartment in the human body

where any findings with PCI-CT could also be correlated with macroscopic differences in appearance between healthy and osteoarthritic states. Analysis of PCI-CT images acquired from normal and osteoarthritic cartilage of *ex vivo* human patellar specimens, as conducted previously in [14], captured specific differences in the internal organization of chondrocytes in the cartilage matrix. Chondrocytes in normal specimens maintained a zone-specific organization and exhibited specific alignment in the radial zone; a disorganized clustering of cells throughout the matrix was observed in osteoarthritic specimens [14]. This study aims to investigate different approaches to extract quantitative measures that could characterize such differences in chondrocyte organization, and to evaluate their ability to serve as diagnostic imaging markers for degenerative changes to the cartilage matrix induced by OA.

In this regard, texture features derived from gray-level co-occurrence matrices (GLCM) and gabor filters, fractal dimension estimators such as the Minkowski dimension, etc are commonly used to characterize patterns and quantify their properties in different medical imaging contexts [26–30]. Here, we investigate the use of two techniques, Minkowski Functionals [31] and the Scaling Index Method (SIM) [32] for characterizing chondrocyte organization in the radial zone. Minkowski Functionals provide a topological characterization of gray-level patterns being analyzed and have been previously investigated in fibrotic tissue classification on lung CT [33,34], dynamic characterization of tissue lesions on breast MRI [35,36] and hip-fracture prediction in post-menopausal women [37]. On the other hand, SIM enables computation of features indicative of local structure and geometry. This technique has been previously applied to pattern recognition tasks in medical imaging, specifically in bone strength estimation through analysis of trabecular bone micro-architecture on CT [38] and MRI [39]. We note that both of these analytic techniques have been previously investigated in the context of classifying healthy and osteoarthritic chondrocyte organization on PCI-CT images [40,41]. However, such studies only used 2D variants of these techniques to characterize chondrocyte organization in the radial zone of the cartilage matrix. Given the high spatial resolution achieved by PCI-CT (both in-plane and perpendicular-to-plane), we hypothesize that volumetric (3D) features could provide a richer characterization of such gray-level patterns, as shown in [42].

We evaluate the performance of volumetric feature sets derived from Minkowski Functionals and SIM in classifying volumes of interest (VOI) as being normal or osteoarthritic in an automated manner. This is achieved by extracting these features from VOIs annotated in the radial zone of the cartilage matrix on PCI-CT images, followed by processing in a machine learning task using support vector regression (SVR) [43], as discussed in the following sections.

2 Methods

2.1 Samples

The age of the donor, macroscopic visual inspection and cartilage surface examination at autopsy were taken into account for selection of patellar cartilage specimens. While no constraint in age was imposed on potential donors for osteoarthritic samples, normal samples were not extracted from donors older than 40 years. A smooth, white, and shiny surface present across the entire patellar cartilaginous surface and prompt resilience to

manually performed focal indentation probing were criteria that defined macroscopically normal cartilage. Lack of these criteria in addition to visually perceived defects in the joint surface were used to select osteoarthritic samples. IRB was waived by the institutional review board of the Ludwig Maximilians University, Munich, Germany. Based on these inclusion criteria, 2 healthy and 3 osteoarthritic cylinder-shaped osteochondral samples (diameter: 7 mm) were extracted within 48 hours postmortem from the lateral facet of 4 human patellae using a shell auger. Cylinders were trimmed to a total height of 12 mm including the complete cartilage tissue and the subchondral bone. The samples were continuously rinsed by 0.9% saline during extraction, trimming and removal of soiling from sawing. Samples were subsequently dipped into a 10% formalin solution for image acquisition.

2.2 PCI Experimental Setup

The ABI setup for the PCI technique involved irradiating the patellar specimen with a parallel monochromatic X-ray beam while a perfect crystal, which acted as the analyzer, was placed between the specimen and the detector [23]. The analyzer acted as an angular filter of radiation transmitted through the object; only those X-rays traveling in a narrow angle window close to the Bragg condition were diffracted onto the detector. Before being detected, the beam was modulated by the angle-dependent reflectivity of the crystal (rocking curve), which had a full width at half maximum (FWHM) typically of the order of a few micro-radians. All images were acquired at the half maximum position on one slope of the RC (50% position), which was chosen to achieve the best sensitivity. Further details of this ABI technique can be found in [14, 44].

Experiments were performed at the Biomedical Beamline (ID17) of the European Synchrotron Radiation Facility (ESRF, France). Quasi-monochromatic X-rays of 26 keV were selected from the highly collimated X-ray beam by means of a double Si (111) crystal system and an additional single Si (333) crystal [45]. The emerging refracted and scattered radiation from the sample was analyzed with a Si (333) analyzer crystal. The Fast Readout Low Noise (FReLoN) CCD camera, developed at the ESRF, was used as the imaging detector [46]. The X-rays were converted to visible light by a 60 μm thick Gadox fluorescent screen. This scintillation light was then guided onto a 2048 $\times$ 2048 pixel 14 $\times$ 14 μm^2 CCD (Atmel Corp, US) by a lens-based system. The effective pixel size at the object plane was 8 $\times$ 8 μm^2 .

2.3 Tomographic Image Reconstruction

Cartilage specimens were rotated about an axis perpendicular to the incident laminar beam to generate tomographic images with our PCI experimental setup. At the end of each rotation, the sample was displaced along the perpendicular axis to enable imaging of a different region. This presents an inversion of conventional CT imaging where the imaging subject is stationary. Each angular projection image was then subject to a flat field normalization to reduce the effects of any spatial and temporal X-ray beam inhomogeneities. A direct Hamming filter back projection (FBP) algorithm was used for reconstructing tomographic images [47]. For data analysis, coronal slices were reconstructed from the original data and subject to edge-preserving median filtering with a [5 5 5] sliding window

to smoothen noise artifacts. An example image acquired from one of the specimens is shown in Fig. 1.

2.4 Annotation

Chondrocyte patterns were annotated with 3D cubic VOIs in the radial zone of the cartilage matrix on coronally reconstructed PCI-CT images of all five specimens. 1392 VOIs were annotated in total, of which 824 were osteoarthritic and 568 were healthy. The annotations were made using cubes of $25 \times 25 \times 25$ voxels; VOIs of smaller size (21, 17, 13 and 9) were then extracted without any manual intervention using the same VOI center.

2.5 Texture Analysis

3D Minkowski Functionals were computed by first binarizing each VOI through the application of several thresholds between its minimum and maximum intensity limits, as previously implemented in [34,36,41] and illustrated in Fig. 2. The number of thresholds applied was a free parameter; a suitable choice for this parameter was investigated. On each binarized VOI, four Minkowski Functionals, i.e. volume, surface, mean breadth and Euler characteristic, were computed as follows -

$$MF_{volume} = n_c, \quad (1)$$

$$MF_{surface} = -6n_c + 2n_f, \quad (2)$$

$$MF_{meanbreadth} = (3n_c - 2n_f + n_e) / 2, \quad (3)$$

$$MF_{Eulerchar.} = -n_c + n_f - n_e + n_v, \quad (4)$$

where n_c is the total number of white voxels, n_f is the total number of faces, n_e is the total number of edges and n_v is the number of vertices [31]. Once computed for every binary image derived from a specific VOI, these values were stored in four high-dimensional vectors corresponding to each Minkowski Functional.

2D Minkowski Functionals were computed in a similar manner using the central slice of each VOI as the region of interest (ROI) for feature extraction. The three 2D Minkowski Functionals were

$$MF_{area} = n_s, \quad (5)$$

$$MF_{perimeter} = -4n_s - 2n_e, \quad (6)$$

$$MF_{Euler} = n_s - n_e + n_v, \quad (7)$$

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 [31]. Twenty thresholds were used for the computation of the topological texture feature vectors, as previously recommended in [40].

Scaling Index Method (SIM), while originally developed for analysis of multi-dimensional arbitrary point distributions [32], was extended for application to gray-level patterns in [48]. In a specific VOI, all N voxels are represented by a 4-D vector $x_i = (x_i, y_i, z_i, g_i)$, $i = 1, 2, \dots, N$, consisting of three spatial dimensions (x_i, y_i, z_i) and voxel gray-level intensity $g_i = g(x_i, y_i, z_i)$. A unit scaling constant is used to define the relationship between the spatial and intensity dimensions of each voxel. The application of SIM is treated as an image transformation; each voxel within the VOI is assigned a local scaling property $\alpha_i = \alpha(x_i, r)$ that reflects the geometrical properties of the surface formed in the voxel neighborhood defined by r . We use a previously proposed estimator for α that uses a Euclidean distance metric and Gaussian shaping functions, i.e.,

$$\alpha(x_i, r) = \frac{2 \sum_{j=1}^N (d_{ij}/r)^2 e^{-(d_{ij}/r)^2}}{\sum_{j=1}^N e^{-(d_{ij}/r)^2}}, \quad (8)$$

where d_{ij} is the Euclidean distance between pixel x_i and neighboring pixel x_j and r is the radius of the Gaussian neighborhood [48]. This is illustrated in Fig. 3. After the SIM transformation is computed, the resulting distribution of α -values reveals non-linear structural information of the gray-level patterns annotated in the VOI. Nine quantiles (10th, 20th...90th) of this distribution were computed and used to generate a 9-D geometrical feature vector. Different values for the neighborhood radius, i.e. $r = 1, 2, 3, 4, 5$ were investigated to evaluate its impact on achieved classification performance.

2D SIM-derived geometrical feature sets were also computed in a similar manner from the central slice of each VOI. For the computation of these feature sets, a radius of $r = 1$ was used, as previously recommended in [41].

2.6 Classification

The extraction of texture features was followed by a supervised learning step where the chondrocyte patterns were classified as healthy or osteoarthritic. In this work, support vector regression (SVR) with a radial basis function kernel was used for the machine learning task [43]. SVR extends the use of support vector machines to regression analysis and is used in this study as a function approximator that predicts the class label of texture feature vectors extracted from lesions of unknown character. While support vector machines can themselves be used in a classification task [49], they provide binary outputs for class predictions while SVR provides fuzzy class labels which can subsequently used to generate ROC curves, which is the accepted metric of classification performance in such studies. The SVR implementation was taken from the libSVM library [50].

To accommodate practical limitations imposed by the small size of the patient population used in this study, we specified the following patient constraints to the supervised learning step (1) VOIs from the same patient were not simultaneously used in both training and test sets, and (2) the same number of VOIs were used from every patient to ensure that the

classifier did not get over-trained on patterns from a specific patient. Based on these constraints, each iteration of the supervised learning step involved randomly sub-sampling 200 VOIs from each of the five patients and randomly designating one each of the healthy and osteoarthritic subjects as the test set (the other samples comprised the training set). Such a strategy, as previously proposed and implemented in [40,41], also ensured that training sets used in different iterations of supervised learning were not identical despite the patient constraint.

In the training phase, models were created from labeled data by employing a random sub-sampling cross-validation strategy where the training set was further split into 70% training samples and 30% validation samples. The purpose of the training was to determine the optimal parameters for the classifier that best captured the boundaries between the two classes of VOIs. The free parameters for the classifier used in this study were the cost parameter for SVR and the shape parameter of the radial basis function kernel. In the test phase that followed, the optimized classifier predicted the class of VOIs in the independent test set. A receiver operating characteristic (ROC) curve was generated and used to compute the area under the ROC curve (AUC), which served as a measure of classifier performance on the independent test set. This process was repeated 50 times resulting in an AUC distribution for each feature set.

2.7 Statistical Analysis

A Wilcoxon signed-rank test was used to compare AUC distributions corresponding to different texture feature sets. Significance thresholds were adjusted for multiple comparisons using the Holm-Bonferroni correction to achieve an overall type I error rate (significance level) less than 0.05 [51,52].

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

3 Results

3.1 Free parameter exploration

The classification performance of volumetric topological texture features derived from Minkowski Functionals, when extracted using different number of thresholds, is shown in Fig. 4. These texture features were computed from VOIs of size $25 \times 25 \times 25$ voxels. When 20 thresholds were used, the classification performance for different Minkowski Functionals were as follows volume (0.54 ± 0.02), surface (0.72 ± 0.06), mean breadth (0.74 ± 0.06) and Euler characteristic (0.78 ± 0.04). No significant improvements in performance were noted when the number of thresholds was increased further to 25.

Fig. 5 shows the classification performance achieved by volumetric SIM-derived feature sets computed with different neighborhood radii. The feature vectors were also computed from VOIs of size $25 \times 25 \times 25$ voxels. As seen here, the best classification performance is noted for smaller values for radii, i.e. $r = 1, 2$. The value $r = 1$ was used for further analysis presented in this study.

3.2 3D vs 2D features

Table 1 compares the classification performance achieved with topological texture feature vectors derived from Minkowski Functionals and geometrical feature vectors derived from SIM, when extracted from 3D VOIs and 2D ROIs. The best performance was observed with the 3D SIM-derived feature set (0.90 ± 0.09), which significantly outperformed its 2D counterpart ($p < 0.01$). Volumetric SIM features also outperformed both 3D and 2D feature sets derived from Minkowski Functionals ($p < 10^{-4}$).

3.3 Impact of ROI size

Fig. 6 shows the effect of ROI size on the classification performance of features extracted using Minkowski Functionals and SIM. All features exhibited their best results when extracted from VOIs of the largest size, i.e. $25 \times 25 \times 25$ voxels. Regardless of VOI size, SIM-derived features yielded significantly better performance than all Minkowski Functionals ($p < 10^{-4}$). SIM-derived features also exhibited least amount of deterioration in classification performance as the size of analyzed VOIs was reduced.

4 Discussion

In the context of cartilage imaging, PCI-CT has recently emerged as a novel imaging modality that can visualize structural details of human patellar cartilage matrix with high spatial resolution [14,20,21]. Analysis of patellar cartilage with PCI-CT imaging enabled the visualization of differences in chondrocyte organization between healthy and osteoarthritic specimens, specifically in the radial zone of cartilage matrix [14]. In this study, we investigated and compared the use of volumetric features derived from topological and geometrical approaches, i.e. Minkowski Functionals and SIM, in characterizing such differences, and evaluated their ability to potentially serve as imaging markers for OA. Our results show that geometrical descriptors outperform topological approaches at classifying chondrocyte patterns as normal or osteoarthritic.

The use of texture features for characterizing chondrocyte organization in patellar cartilage matrix, as visualized by PCI-CT, has been previously investigated in [40,41]. The current study expands on such work by using similar feature sets for purposes of volumetric characterization of chondrocyte patterns, rather than the 2D approach pursued in those studies. As shown in Table 1, such volumetric features are able to provide a richer characterization of chondrocyte patterns which results in improved classifier performance. Another important aspect that sets apart this study from previous work is the use of VOIs of small dimensions ($25 \times 25 \times 25$ voxels or less). While larger sized VOIs (or ROIs) are likely to yield better classification performance, as evidenced in previous work [40,41], smaller VOIs are advantageous for extending our work to texture feature-based segmentation for automated quantification of healthy and osteoarthritic cartilage. However, for this reason, we expect the classification performance results of our study to be poorer than those previously reported in [40,41].

As seen in Table 1, SIM-derived feature vectors significantly outperformed topological features derived from Minkowski Functionals ($p < 10^{-4}$). The superior performance of SIM-

derived feature sets at classifying between healthy and osteoarthritic VOIs can be attributed to the detailed characterization of local structure and geometry that they provide on a voxel-wise basis (captured as scaling indices α). This reveals specific differences in the distribution of α -values in both classes of VOIs, i.e. osteoarthritic VOIs have an increased content of lower α -values while healthy ROIs show more α -values of higher magnitude, as seen in Fig. 3, which correspond to differences in chondrocyte organization between the two classes of VOIs.

The poor performance of topological texture features derived from Minkowski Functionals suggests that global characterization of chondrocyte organization is insufficient for purposes of classification, especially at such small VOI sizes. This further supports the argument that a local characterization, such as that provided by SIM feature sets, is much more important in this context of classifying between healthy and osteoarthritic chondrocyte patterns. One possible approach to improving the characterization power of topological texture features is to extract them locally, using a kernel-based approach where Minkowski Functionals are computed at every voxel based on the surrounding neighborhood. This was proposed in [53] and will be explored with this dataset in future studies. We also note that the best classification performance was achieved with Euler characteristic, which suggests that connectivity is the strongest distinguishing topological factor between healthy and osteoarthritic ROIs.

The size of the VOI from which texture features are extracted from is also important when considering such approaches for characterizing patterns of interest. As seen in Fig. 6, while all features deteriorate in performance as the VOI size decreases, SIM-derived geometric features outperform topological feature vectors regardless of VOI size ($p < 10^{-4}$). The drastic deterioration in performance noted with Minkowski Functionals as the VOI size decreases lends further credence to the fact that the global characterization provided by such features may not be sufficient for small VOIs. On the other hand, SIM features do not exhibit such a drastic deterioration in performance, and still exhibit a high classification performance (0.90 ± 0.07) when extracted from VOIs as small as $13 \times 13 \times 13$ voxels. Such geometric features could potentially find use in SIM-based automated segmentation approaches for quantifying the percentage of the radial zone affected by OA, especially in cases where some portions of the cartilage remain healthy, thereby serving as an imaging marker for tracking osteoarthritic progression. This will be explored in further detail in future studies.

We acknowledge a limitation of this study concerning the small number of patients from whom cartilage specimens were extracted for image acquisition and processing. Thus, patient constraints imposed on the supervised learning step enabled classifier training on limited intra-class pattern variations only and could be over-trained on these patterns. Future studies should include more patients to ensure that the classifier is trained with a potentially larger variation of healthy and osteoarthritic patterns. We also note a practical limitation with the experimental setup used in this study where the imaging technique relies on synchrotron radiation. Thus, the current application of our imaging setup is restricted to *ex vivo* studies rather than *in vivo* exams of cartilage tissue. Given that several high-brilliance and high-energy compact X-ray sources are currently in development [54–56], future

research will be necessary to investigate the possibility of transferring PCI-CT imaging from synchrotron radiation facilities, which offer highly collimated, high fluence, and partially coherent X-rays, to a clinical environment.

5 Conclusion

This study evaluates the ability of volumetric topological and geometrical approaches to characterize chondrocyte organization in the radial zone of human patella cartilage matrix, as visualized by PCI-CT. The results of this work suggest that geometrical features derived from the Scaling Index Method (SIM) significantly outperform topological features derived from Minkowski Functionals at distinguishing between healthy and osteoarthritic VOIs ($p < 10^{-4}$). The automated and objective manner in which such cartilage matrix descriptors are extracted and the high classification performance they exhibit suggest tremendous potential in serving as imaging markers for OA progression and evaluating responses to therapeutic intervention. However, larger controlled trials need to be conducted in order to further validate the applicability of such features in a clinical setting.

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Fig. 1. Coronal reconstruction created from axial PCI-CT images of a single cartilage specimen. In this case, the cartilage specimen is healthy, as seen by chondrocyte alignment radiating outward from the tidemark.

Fig. 2.

Illustration of 3D Minkowski Functionals. Normal and osteoarthritic VOIs shown on the far left (top two rows) are binarized at five different thresholds. In the bottom row, the four Minkowski Functionals volume, surface, mean breadth, and Euler characteristic, are plotted as a function of the threshold for the healthy (gray) and osteoarthritic (black) VOIs; the subset of the five thresholds (of 20) used to create the binary images are marked as vertical-dotted lines. These curves depict the morphological properties of the binary VOIs and distinguish between healthy and osteoarthritic patterns.

Fig. 3.

The top two rows show examples of a normal and osteoarthritic VOIs (far left) and the corresponding SIM transformations for radius $r = 1, 2, 3, 4, 5$. In the SIM transformations, dark regions correspond to lower magnitudes of α while brighter regions reflect higher magnitudes of α . The third row shows the histogram of α -values from each SIM transformation; the fourth row shows the same distribution but represented by 9 quantiles (10^{th} 90^{th}). As seen here, such histograms can capture differences between healthy and osteoarthritic ROIs on PCI-CT.

Fig. 4.

Comparison of classification performance achieved with 3D Minkowski Functionals when different thresholds are used for computation of features. For each distribution, the central mark corresponds to the median and the edges are the 25th and 75th percentile. As seen here, the performance achieved is best for Euler characteristic when 20 thresholds are used.

Fig. 5. Comparison of classification performance achieved with volumetric SIM-derived features computed with different radii, $r = 1, 2, 3, 4, 5$. For each distribution, the central mark corresponds to the median and the edges are the 25th and 75th percentile. As seen here, the performance achieved is best for smaller radii, i.e. $r = 1, 2$.

Fig. 6.

Comparison of classification performance achieved with Minkowski Functionals (shown in the order volume, surface, mean breadth and Euler characteristic) and SIM when extracted from ROIs of different sizes. For each distribution, the central mark corresponds to the median and the edges are the 25th and 75th percentile. As seen here, SIM maintains significantly higher classification performance over Minkowski Functionals regardless of ROI size.

Table 1

Comparison of classification performance (mean AUC $\pm$ std) achieved with Minkowski Functionals and SIM extracted from 3D VOIs (size: 25 $\times$ 25 $\times$ 25 voxels) and 2D ROIs (size: 25 $\times$ 25 pixels). The best results (bold) are obtained with the 3D SIM feature vector.

Technique	Features	AUC
3D SIM	9-quantiles	0.90 $\pm$ 0.09
3D Minkowski Functionals	Volume	0.54 $\pm$ 0.02
	Surface	0.72 $\pm$ 0.06
	Mean Breadth	0.74 $\pm$ 0.06
	Euler Characteristic	0.78 $\pm$ 0.04
2D SIM	9-quantiles	0.85 $\pm$ 0.06
2D Minkowski Functionals	Area	0.56 $\pm$ 0.04
	Perimeter	0.62 $\pm$ 0.06
	Euler Characteristic	0.73 $\pm$ 0.03