K-means clustering of multi-parametric MRI data for improved classification of articular cartilage degeneration

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TARGET AUDIENCE: Researchers and clinicians aiming to apply quantitative MRI techniques in osteoarthritis research.
PURPOSE: To employ k-means clustering (KMC) of multiparametric MRI data for improved classification of articular cartilage degeneration.
METHODS: Bovine osteochondral samples were prepared from intact bovine patellae (d = 25 mm, N = 6), each samples was cut into three sections: one was used as control, one digested for 44 hours in collagenase (30 U/ml) and one in chondroitinase ABC (0.1 U/ml) to induce collagen or GAG depletion, respectively. Human tibial plateaus were harvested from total knee arthroplasty surgeries (d = 6 mm, N = 17) with permission from the local ethical committee. Multiparametric MR experiments were performed at 9.4 T (Oxford instruments Plc, Witney, UK), orienting the cartilage surface perpendicularly to the main magnetic field, and 11 different parameters were measured by modifying a preparation block followed by a fast spin echo readout (ETL = 4, TR = 5 s, TEeff = 5 ms, matrix = 256x128, slice thickness 1 mm, FOV = 16 x 16 mm^2): adiabatic $T_{1\rho}$ (γB_{1max} = 2.5 kHz), adiabatic $T_{2\rho}$ (γB_{1max} = 2.5 kHz), continuous waves (CW) $T_{1\rho}$ (γB_1 = 1 kHz), relaxation along a fictitious field (T_{RAFF}), T_1 during off resonance saturation (δ = +10 kHz, γB_1 = 250 Hz, $T_{1\,sat}$); T_2 was measured with FSE, CPMG sequences with train of hard and sinc pulses and adiabatic double echo (DE) preparation; T_1 relaxation time was measured by varying the TR saturation recovery with 7 TRs from 80 to 5120 ms; MTR was defined as 1-Msat/M0. Human samples were divided in two groups: early OA (OARSI grade ≤ 1.5, N = 5) and advanced OA (OARSI grade > 1.5, N = 12). For all samples, three ROI were considered: 5 % of thickness (superficial), 25 % (superficial and transitional cartilage) and 100 % (full thickness). With combinations of two and three MR parameters, K-means clustering (KMC) analysis was performed separately for human (k = 2) and bovine (k = 3) data set and repeated several times with different initial centroids and maximum grade of iteration allowed to avoid local optima, using all possible combinations of doublets and triplets of MR parameter z-scores. Specificity and sensitivity were defined taking the control samples for bovine and early OA samples for human cartilage as negative cases. Finally, Silhouette Index (SI) [1] and Within Cluster Sum of Square (WCSS) were computed for assessing the robustness of clustering analyses.
RESULTS: At best, high sensitivity and specificity were achieved with various doublets of MR parameters (Table 1). For the human data set, the best classification was achieved considering the whole cartilage thickness, and the best overall combination was (AD $T_{2\rho}$, DE T_2) once an adequate SI threshold of .75 was set. Several doublets were able to classify all the early OA samples in the same cluster in all ROIs and using the parameter combination ($CPMG_{(sinc)}$ T_2, T_1) in the superficial ROI only one advanced OA sample remained misclassified, however, a reduced SI indicated a scarce cluster separation. Enhanced SI and WCSS were obtained in the 25 % thickness ROI with decreased sensitivity. On the contrary, in bovine samples similar accuracies were attained in the three ROIs, although cluster separations were higher in the most superficial ROIs (Figure 1). The doublet (CW $T_{1\rho}$, T_{1sat}) was the best combination in both 5 % and 25 % thickness ROIs, whilst in the full thickness ROI (AD $T_{1\rho}$, AD $T_{2\rho}$) clustering showed limited ability to separate the two degenerated groups with significant overlapping. Similar results were obtained with combinations of 3 parameters with no improvements in terms of specificity and sensitivity and lower SI (data not shown).
DISCUSSION: Sensitivity and specificity in both human and bovine data sets were higher than those found in previous univariate studies and in a former investigation employing KMC with only four MR parameters [2]. Different results for the two data sets may be explained both by the classification method and sample characteristics. Enzymatic digestion is depth dependent and more efficient in the superficial layers, thus a better result for superficial ROI is expected. On the other hand, the classification of human samples was based on the OARSI grading, which evaluates the whole cartilage and thus offered the best result with the full thickness ROI. Moreover, collagen and GAG depletion models do not adequately mimic cartilage degeneration in osteoarthritis, therefore a complete correspondence of the two data sets is not to be expected. Interestingly, in both datasets rotating-frame techniques were frequently represented in the best clustering classifications. A combination of three parameters did not bring further improvements, and employing two parameters is also feasible in clinical perspective.
CONCLUSION: Best discrimination of cartilage status was obtained when employing k-means clustering of two MR parameters, particularly when rotating-frame techniques were used. Further in vitro and in vivo validation is yet required.

Table 1. Best clustering classifications for bovine and human data sets and for each ROI using combinations of 2 MR parameters, with Silhouette Indexes (SI), Within Cluster Sum of Squares (WCSS), Sensitivities and Specificities.

Data set	ROI (%)	Parameters	SI	WCSS	Specificity, Sensitivity
Human AC	5 %	$CPMG_{(sinc)}$ T_2, T_1	.56	15.88	100 %, 91.7 %
		T_{RAFF}, CW $T_{1\rho}$	.43	19.54	100 %, 83.3 %
		T_{RAFF}, AD $T_{2\rho}$	.61	13.76	100 %, 75.0 %
	25 %	$CPMG_{(sinc)}$ T_2, T_1	.62	14.43	100 %, 83.3 %
		AD $T_{2\rho}$, CPMG T_2	.75	9.30	100 %, 66.7 %
		$CPMG_{(sinc)}$ T_2, T_{1sat}	.75	9.18	100 %, 66.7 %
	100 %	AD $T_{2\rho}$, DE T_2	.78	8.32	100 %, 75.0 %
		AD $T_{1\rho}$, DE T_2	.69	11.32	100 %, 75.0 %
		DE T_2, T_{1sat}	.66	12.64	100 %, 75.0 %
Bovine AC	5 %	AD $T_{2\rho}$, T_{1sat}	.78	2.38	100 %, 75.0 %
		CW $T_{1\rho}$, T_{1sat}	.83	2.17	100 %, 75.0 %
		T_{RAFF}, T_1	.63	5.48	66.7 %, 100%
	25 %	CW $T_{1\rho}$, T_{1sat}	.81	2.92	100 %, 83.3 %
		AD $T_{2\rho}$, T_{1sat}	.74	3.18	100 %, 83.3 %
		T_2, T_1	.76	4.38	66.7 %, 100 %
	100 %	AD $T_{1\rho}$, T_2	.66	5.83	100 %, 83.3 %
		T_{RAFF}, DE T_2	.63	8.47	100 %, 83.3 %
		AD $T_{1\rho}$, AD $T_{2\rho}$	.77	4.04	100 %, 83.3 %

Sensitivities and Specificities defined as control vs. enzymatic degraded samples for bovine and early OA vs advanced OA for human samples.

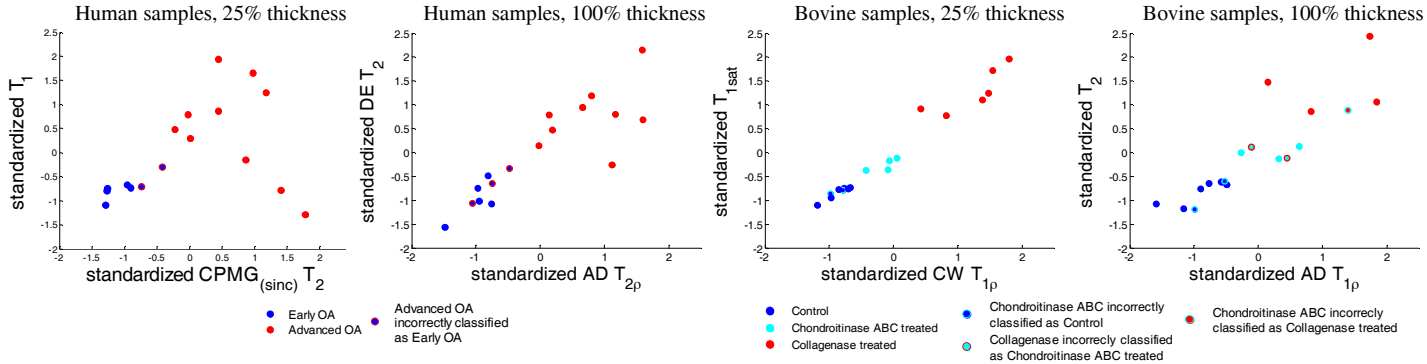

Figure 1. Two dimensional plots of the best classifications for human and bovine data set and for 25 % and full thickness ROIs.

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