Mean-Shift Clustering for Assessing Response Heterogeneity in Bone Metastases

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Introduction: Bone metastases are clinically categorized as unmeasurable by standard size criteria. Furthermore, the complex nature of the bone microenvironment makes it challenging to delineate regions of active disease, sclerosis, recovering/treated disease, and healthy bone. Currently, no single MR imaging modality can fully represent the underlying biology in bone metastases, which necessitates that clinicians employ complementary image data for disease diagnoses, response assessments, and treatment decisions. The sheer volume and richness of data can make image interpretation complex and overwhelming. In this work, we introduce a method for consolidating information by identifying like regions in the bone (e.g. active disease) based on a mean-shift analysis [1] of fat fraction (FF), apparent diffusion coefficient (ADC), and spatial location. This non-parametric method provides superb data visualization, makes no assumptions about the underlying data distributions or the number of components, and can track changes in the region of interest over time.

Methods: Two-point Dixon for fat/water identification, Diffusion-Weighted Imaging (DWI), and Computed Tomography (CT) studies were performed on two patients with metastatic prostate cancer in the pelvis at two time points, before/after conventional treatment on a 1.5T MRI scanner (MAGNETOM Avanto, Siemens AG, Healthcare Sector, Erlangen, Germany). The parameters for the coronally/axially acquired Dixon scans were: matrix = 192x192/256x256, TR = 7/7.63ms, pixel bandwidth = 491/400 Hz/px, flip angle = 3°/3°. The parameters for the DWI protocol (all axially acquired) were: matrix = 192x192, TE = 69ms, TR = 10.7s, b values = 50 and 900 s/mm^2. FF was calculated from the signal intensities on the resolved fat and water images (fat/(fat+water)*100%). Five standardized anatomical features in the pelvis (visible on both FF and ADC) were identified as registration points. For each time point, the FF and CT scans were registered to the DWI images using point-based rigid registration. In this way, we could analyze the pelvis across both time points and different modalities. The entire pelvis (on a few representative slices) was outlined on the registered CT series to create a mask. This mask was then transferred to the registered FF and ADC series. As the mean-shift analysis only requires a rough registration, these transferred masks were more than adequate in defining our regions of interest (ROIs). With each imaging modality (FF and ADC) and spatial positions along the x- and y-axes, we obtained a 4 dimensional probability density function (pdf), with clusters corresponding to like regions in bone. For the earliest time point, we used the scikit-learn library [2] to generate initial seed points for the mean-shift algorithm. The algorithm then iterates to find the local maxima corresponding to the modes of the non-parametric distribution of imaging data. The number of unique local maxima indicates the number of clusters in the pdf, and therefore, the like regions identified in the bone. These local maxima are then fed into the algorithm as the initial seed points for the next subsequent time point, which enables us to track the changes in each region over time. Additionally, the algorithm was tuned to place a higher or lower weight on a particular dimension depending on user discretion.

Results: For patient 1 (Figure 1), both ADC and FF were normalized and given a weighting factor of 1.0, and the x and y positions were both given a weighting of 0.5. Under these conditions, our algorithm identified 4 like regions in the pelvis. A senior radiologist confirmed that blue, cyan, and red are areas of likely disease infiltration, whereas the green regions correspond to fatty marrow. Of particular interest is the ~600 x10^{-6} mm^2/s increase in ADC from pre to post treatment in the iliac crests (represented by the blue and cyan regions) and a portion of the sacrum (represented by the red region). Though the ADC value alone has potential prognostic power, the clusters help identify where exactly the change is taking place, and provide confirmation that the region of disease is indeed the region responding to treatment. Furthermore, the change in area of each region can be assessed. Perhaps most striking example of this was shown in the second patient analyzed (Figure 2), where a decrease in the area of fatty tissue (green and blue regions) by 86% was observed.

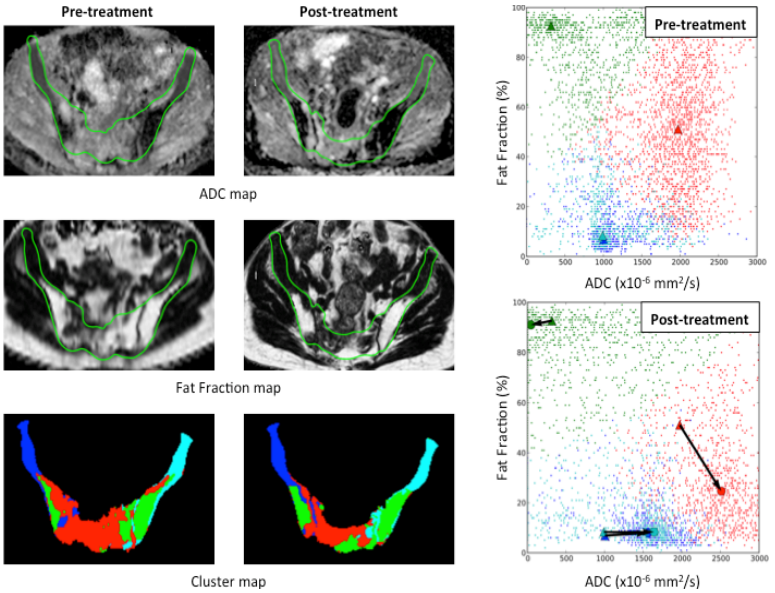

Figure 1: Pre and post treatment data for Patient 1 (3 months between time points). Top: Original ADC and FF images (columns are registered) with ROI outlined in green. Right column: scatter plots showing pre- and post- treatment clusters with the pre-treatment maxima super-imposed over the post-treatment clusters to highlight the magnitude of change of each cluster in response to treatment. Bottom: treatment clusters mapped back to ROI based on spatial coordinates. Note how the ADC values in the blue, cyan and red areas increase, and how the ADC decreases in areas of fatty marrow infiltration (green area) correlate with treatment response.

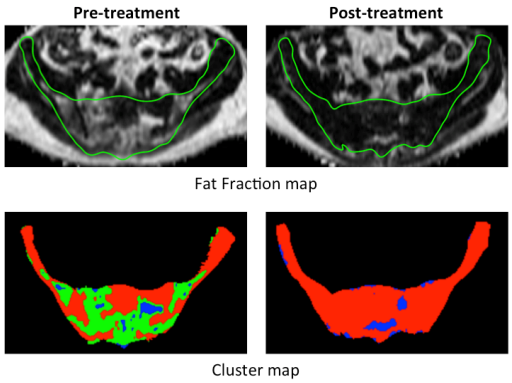

Figure 2: Top Row: Registered pre-post FF images (1 year between time points) with ROI outlined in green. Bottom row: Blue and green correspond to fatty marrow, and red corresponds to abnormal bone. Note the striking reduction in fat fraction, as indicated by the near disappearance of the blue and green regions in the post-treatment image. In this case a reduced weighting of 0.2 was used for x and y spatial components of the data modeling.

Discussion: This MR-data visualization technique successfully concatenates complicated and wide-ranging data into a single representative image. Furthermore, these results suggest that FF has an equal role to ADC in delineating like regions within the bone. This raises the question of the potential role of other contrasts in region classification. Additionally, we demonstrate the utility of maintaining the spatial component of the data because we can tell where ADC/FF is changing. This provides an advantage over traditional histogram techniques because we have a direct link between the image measurands and the lesion coordinates: This technique excels in tracking heterogeneous change over time. Exact pixel-to-pixel correspondence between time points is not required; a rough registration is sufficient for the mean-shift algorithm to pick out the relevant clusters and map them back to the image. By simplifying thousands of pixels into categories of clinical relevance, we can easily see how the imaging measurands and volume of each region changes in response to treatment. These early results motivate us to carry out further work in the role of multi-dimensional cluster analysis using a mean-shift algorithm in identifying biologically distinct regions in diseased bone, and tracking their changes over the course of treatment.

References: [1]: Comaniciu and Meer, IEEE Trans. Patt. Anal. Mach. Int. 2002; 24(5): 603-619. [2] Pedregosa *et al.*, JMLR 2011; 12: 2825-2830
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