How to analyse dynamic MRI in oncology; advanced histogram analysis gives better statistical power & insight than simple averagi

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Introduction

Parameter maps of tumours obtained from DCE-MRI indicate rich patterns of spatial and functional heterogeneity. Given this heterogeneity, it seems implausible that all regions of a tumour will respond in the same way to treatment. Typically, MRI studies of response to treatment base their significance tests on a single (or small number of) measures summarising the distribution of a parameter over the ROI, such as mean or median K^{trans}. This so-called '*histogram analysis'* discards all the spatial and heterogeneous information contained within the tumour. Registration of images before and after treatment is difficult, because the amount of remodelling between time points is uncertain. Here we present a novel way of analysing this type of data that characterises and assesses all of the changes in the distributions to provide additional insight and improved interpretation beyond the possibilities provided by crude histogram analysis in the situation where we cannot register images for a complete voxelwise "mapping" approach.

Methods

DCE-MRI using gadopentate dimeglumine, was used to monitor acute effects on tumour perfusion, following inhibition of signalling by VEGF and EGF. Mice bearing PC-3 human prostate adenocarcinoma xenografts, were treated with either a control vehicle or ZD6474 at 12.5, 25, 50 or 100 mg/kg/day and DCE-MRI was performed twice, immediately before and 24 hours after treatment with ZD6474. This is a VEGF receptor-2 (KDR) tyrosine kinase inhibitor that also has activity against the EGF receptor (Checkley et al, 2003). The pharmacokinetic parameter K^{trans} was obtained for each voxel within the tumour region of interest, which reflects vascular permeability and perfusion.

Statistical analysis focuses on the frequency distributions of the voxel values of K^{trans} in each ROI. Exploratory analyses use histograms and kernel density estimates (KDE) of the distributions. The main analysis is based upon the multivariate technique *functional principal component analysis* (FPCA), which determines the principal modes of variation of the distributions. Formal statistical assessment of the effects of treatment is based upon a randomization test involving the differences in PC scores between images before and after treatment. The results are compared to the familiar significance tests based on the change in mean K^{trans} averaged across the whole ROI.

Results

It is clear from visual inspection of histograms and kernel density estimates of the distributions that the treatment generally reduces the values of K^{trans}, a change that was picked up by a simple t-test of the mean K^{trans} pre and post treatment. However, other changes in distribution are apparent that are difficult to assess coherently since the observed changes are not merely ones of location and scale. This is addressed by the main analysis, FPCA, which reveals interesting structure in the variation between the observed distributions. The first PC is identified as reflecting differences between a diffuse distribution and a less variable and more peaked one. The second PC reflects the presence or absence of a secondary mode of higher values of K^{trans}. Scores for each probability density on the PCs can be calculated to give principle component score plots of the samples. The score plot for the controls reassuringly show that there is no consistent pattern pre to post treatment, however for each dose group the score plots reveal a pre to post shift to the bottom left corner, low PC1 and PC2. This corresponds to a post-treatment distribution with high primary peak and no secondary peak. These features indicate a distribution with overall lower values of K^{trans} and no secondary subset of high values post-treatment: a positive treatment effect. Randomisation tests are preformed using a test statistic based on the *city block difference* between PC1&2 and Figure 2 shows the histograms of simulated values for each group. The p-values indicate that all four dose groups (but not controls) show clear evidence of effect of treatment. These values are contained in Figure 1 (B) and correspond with those obtained from testing for a difference in mean K^{trans} before and after treatment (A). The results suggest that this statistic appears to be more sensitive for testing for a difference in the smaller groups. Furthermore, this statistic together with the score plots gives greater insight into where the changes are occurring.

Discussion

Images from DCE-MRI are clearly heterogeneous and assessment based on simple summary statistics will not capture all the available information. The analysis using FPCA detected the obvious changes in distribution corresponding to mean K^{trans} but has also provided additional insight, over and above the results obtained from commonly used 'histogram analysis'. This technique is currently being validated on different data sets where we need to assess heterogeneous voxel values on an ROI basis.

Reference: Checkley, D., et al., *Br J Cancer,* 2003. **89**(10):1889-95.

Group	Number of Observations N	(A) p-value (t-test based on mean)	(B) p-value (rand. test based on FPCA)
Control	11	0.77	>> 0.5
12.5mg	6	0.2	< 0.1
25mg	6	0.07	< 0.05
50mg	10	< 0.01	< 0.01
100mg	11	< 0.01	< 0.01

Figure 1: Results from the analysis of change in mean K^{trans} (A) and from FPCA (B)

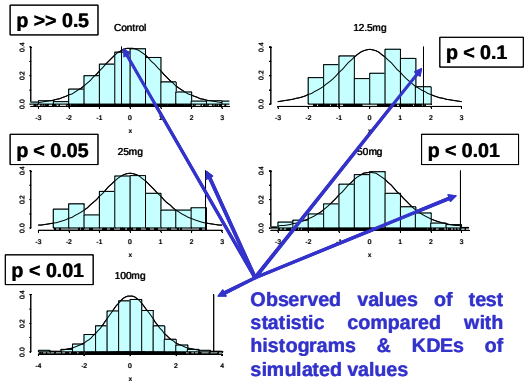

Figure 2: Histogram of simulated values