

Quantifying spatial heterogeneity in dynamic contrast-enhanced MRI parameter maps

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INTRODUCTION Dynamic contrast-enhanced (DCE) magnetic resonance imaging is often used in trials of cancer therapies¹. Current practice is to describe the contrast agent uptake curve using model-based (e.g. extended Tofts²) or model-free parameters (e.g. the initial area under the curve, IAUC) at each tumour voxel. The tumour may then be summarised as a whole by computing an average value of the chosen parameter. A change in such a summary statistic (such as mean or median values) after drug administration may be used as evidence of drug action. A problem with this approach is that these summary statistics do not consider that most solid tumours are spatially heterogeneous, or that drug-induced effects are also often spatially localised. Simple summary statistics neglect this potentially important spatial information. This abstract describes novel summary statistics that we have developed to capture this heterogeneity information using parameters' values and spatial locations, and applies them to two sets of clinical DCE-MRI data.

THEORY Heterogeneity in this work refers to the degree of spatial non-uniformity in a parameter map. Our statistics attempt to quantify this heterogeneity by accounting for both the distribution of parameter values and their spatial relationship. A 2-D grey-scale image can be thought of as being a surface in 3-D. By 'extruding' a 2-D image into a third dimension (representing grey-level intensity), heterogeneity can easily be visualised and methods of quantifying it developed. For example, an image with low heterogeneity will have a rather flat surface, while one with high heterogeneity will have a highly irregular surface. Surface characteristics can then be measured and used to assess heterogeneity. This idea can be extended to 3-D parameter maps: a 3-D K^{trans} map (for example) can be extruded into a fourth dimension, forming an object enclosed by a hyper-surface. We use 4-D binary arrays to represent the extruded objects and measure heterogeneity statistics on these.

We compute four heterogeneity statistics from the extruded 4-D parameter maps: surface area, volume, ratio of surface area to volume and box-counting fractal dimension^{3,4}. The box-counting dimension attempts to quantify object complexity and is computed by imposing regular grids of a range of scales on the object and investigating the relationship between scale and the number of grid elements (boxes) that are occupied by the object.

METHODS We applied our heterogeneity statistics to two sets of clinical DCE-MRI data. In the first experiment, four patients with a total of 25 liver metastases ($n_1=10, n_2=1, n_3=7, n_4=7$) underwent DCE-MR imaging at 1.5T on a Philips Intera System. The patients were scanned at two baseline visits in the week before dosing with an anti-angiogenic compound (though the first baseline scan was missing for patient 4), and then again after drug administration. Routine quality assurance identified 18 suitable tumours. DCE-MRI data were converted to signal intensities and the extended Tofts model was fitted to each tumour voxel, yielding maps of K^{trans} , v_p and v_e . 4-D Fractal and extrusion-based heterogeneity statistics were then computed for each parameter map. The tumours were assumed to be independent and non-parametric ANOVAs (Kruskal Wallis) were performed to investigate differences between the baselines and post-treatment scans for each parameter.

In the second experiment we investigated the ability of the heterogeneity statistics to identify meaningful heterogeneity in parameter maps computed for gliomas. Gliomas are histologically graded into four WHO grades⁵ on the basis of heterogeneity: high grade gliomas are characterised by areas of hypo- and hyper-cellularity corresponding to areas of necrosis and increased cell density, while low grades are less heterogeneous. Subjectively, such characteristics appear to be visible in DCE-MRI images. Nine glioma patients were recruited and, before surgery, underwent DCE-MR imaging on a 3T Philips Achieva

System. All tumours were histologically confirmed to be gliomas and were graded according to WHO criteria: there were 4 low grade (grade II) and 5 high grade (grades III and IV) gliomas. The extrusion-based heterogeneity statistics were computed for each tumour as described above. Differences between heterogeneity statistics for the two groups were investigated using Wilcoxon rank sum tests. Both studies were approved by local research ethics committees and all patients gave written informed consent.

RESULTS In the drug trial experiment, there were significant differences in surface area to volume ratio for extruded K^{trans} and v_e maps ($p=0.0013$ and $p=0.045$ respectively); see Fig. 1. Post hoc testing revealed significant differences between first baseline and post-treatment scans ($p=0.004$) and second baseline and post-treatment scans ($p=0.001$), without Bonferroni-like corrections. As anticipated, there were no significant differences in heterogeneity statistics between the baseline scans. The difference in spread between the first and second baselines (Fig. 1) is explained by the missing data for patient 4. In the glioma experiment there were significant differences between the heterogeneity statistics as grouped by grade for: box dimension computed for extruded v_e ; surface area computed for extruded K^{trans} and v_e ; and the volume of extruded v_e parameter maps (all $p<0.05$); see Fig. 2.

CONCLUSIONS This abstract has described approaches to quantifying heterogeneity in DCE-MRI parameter maps. Experiments using real data have shown that they are sensitive to the effects of an anti-angiogenic drug and glioma grade (which is related to heterogeneity). There was no combination of parameter and statistic that was sensitive in both experiments. However, it is interesting that heterogeneity statistics based upon v_e were able to achieve significant discrimination in both experiments because this parameter is often assumed to have little physiological importance compared to K^{trans} and v_p .

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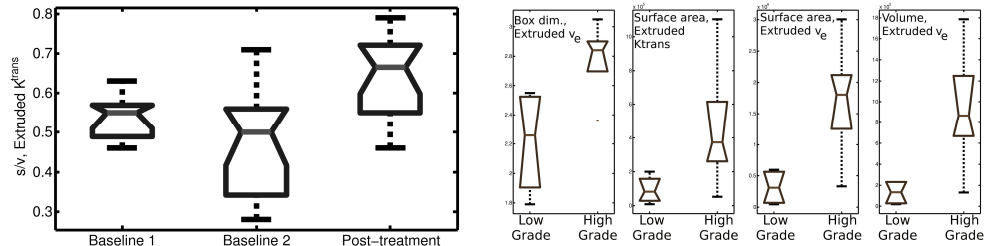


Figure 1 Box plots showing how one of the heterogeneity statistics is sensitive to drug action. **Figure 2** Box plots showing how heterogeneity statistics can distinguish between high and low grade gliomas.