Improving the reproducibility of DCE-MRI studies of treatment response

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Introduction

Dynamic contrast-enhanced (DCE) MRI using gadolinium-based contrast agents have widespread clinical use including lesion characterisation and monitoring response to treatment [1]. The distribution of parameters such as the volume transfer constant (K^{trans}) or the initial area under the gadolinium curve (IAUGC) are often characterised using histogram analysis [2]. However, the distributions of such parameters are often spatially heterogeneous due to local variations in tumour perfusion, vascular permeability and genotype, which hinders the robust characterisation of parameter histograms. For example, the validity of applying standard statistical measures such as sample mean, median, variance, etc. to non-normal distributions is questionable and, combined with other sources of variability such as differences in ROI definition, poor slice positioning, etc., results in poor reproducibility [3]. Fractal analysis can be used to characterise heterogeneous distributions [4] and provides metrics that have been shown to correlate with response to therapy [5]. The aim of this investigation was to apply two types of fractal analysis in conjunction with standard semi-quantitative analysis and to compare the reproducibility of each.

Methods and Materials

DCE-MRI data were acquired from 8 patients (5 gynaecological tumours, 3 breast tumours) with a FLASH sequence (TE/TR/α = 11ms/4.7ms/35º for dynamic T1w images and 350ms/4.7ms/6º for reference proton density-weighted images (required for conversion to Gd-DTPA concentration)). Images from four slices were reconstructed with a temporal resolution of 12.1s and total duration 607s; contrast agent (Gd-DTPA, 0.1 mMol/kg body weight) was injected at 4ml/s. Reproducibility data were acquired one day (for gynaecological tumours) or one week (for breast tumours) following the first measurement. Slice positions in reproducibility studies were registered using fixed internal landmarks derived from high-resolution T2w images. T1w time series curves were converted to Gd-DTPA concentration using a previously determined calibration. ROIs encompassing the whole tumour, in one central slice of each patient study, were defined by a radiologist using difference images (post-enhancement minus pre-enhancement T1w images). $IAUGC_{90}$ (i.e. IAUGC taken over the range contrast onset to 90s following onset) and $IAUGC_{180}$ maps were calculated for e ach ROI and the mean and median values were measured for each. The Hurst exponent (a fractal measure of the spatial correlation or 'roughness' of a parameter) was estimated for each $IAUGC_{90}$ and $IAUGC_{180}$ map, using the method of Bassingthwaighte [7]. Enhancement maps indicating pixels within each ROI that displayed significant contrast uptake above background noise were also calculated and the Hausdorf dimension (a fractal measure of how space-filling a shape is) for these were calculated, using a box-counting algorithm. The reproducibility of each parameter was assessed using the coefficient of reproducibility, CR (1.96 times the standard deviation of the difference between two measurements across the entire patient cohort). The CR indicates how large a percentage variation in a given parameter must be to indicate, with 95% certainty, that a significant change has been observed.

Results and Discussion

Maps of $IAUGC_{180}$ and enhancement for one patient are shown in Figure 1. CR for the mean and median $IAUGC_{180}$ were found to be 45.1% and 39.4%, respectively. Similar values were found for $IAUGC_{90}$. The CR for the Hurst exponent of $IAUGC_{180}$ was 98.8%, approximately twice that for the corresponding mean or median; however, as shown in Figure 2, the variation between reproducibility measurements is dependent on the number of pixels in the ROI. If all ROIs smaller than 1000 pixels are excluded, the CR for the Hurst exponent reduces to 6.6%; no similar effect was found for any of the other parameters. This suggests that the Hurst exponent algorithm requires a large sample size in order to ensure sufficient accuracy. CR for the Hausdorf dimension of the enhancement map was 4.5%, for the entire cohort. The implications of such a low CR for both the Hurst exponent of $IAUGC_{180}$ for ROIs of greater than 1000 pixels and the Hausdorf dimension of the enhancement map are striking. It suggests that the fractal measures are less susceptible to other sources of poor reproducibility such as outliers, poor ROI definition, poor slice alignment, etc. Figure 3 shows Bland-Altman plots for the median and Hurst exponent of $IAUGC_{180}$ and the Hausdorf dimension of the enhancement map. They display both the reproducibility and range evident in each parameter. The latter property is particularly important as it shows that the range of the Hausdorf dimension and the Hurst exponent found within a cohort is comparable with that of the median $IAUGC_{180}$, indicating that these parameters could be used for tumour classification or to effectively detect change due to therapy.

Conclusion

The Hausdorf dimension of the enhancement map and the Hurst coefficient of $IAUGC_{180}$ (for ROIs larger than 1000 pixels) are significantly more reproducible than either the mean or median $IAUGC_{180}$. These parameters could therefore be much more sensitive to small changes caused by therapy. Further work is required to establish precisely how these parameters could vary with therapy.

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References: [1] Padhani AR, Dzik-Jurasz A. Top Magn Reson Imaging 2004; 5:41-57. [2] Hayes C, et al. NMR Biomed 2002;15(2):154-63. [3] Leach MO. et al, Br J Radiol, 76 Suppl 1:S87-91 [4] Walker-Samuel S. et al, ISMRM 2004 #1971 [5] Walker-Samuel S. et al, ISMRM 2004 (e-poster) [6] Bassingthwaighte JB. et al, Fractal Physiology, 1994.

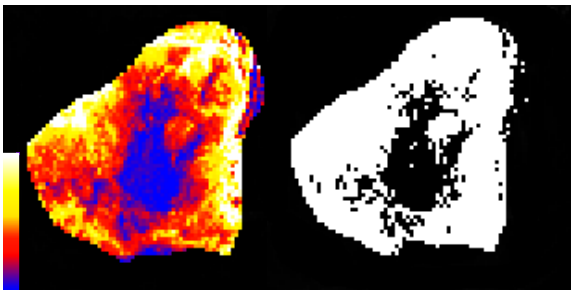

Figure 1: $IAUGC_{180}$ (left) and enhancement map (right) for one of the gynaecological tumours.

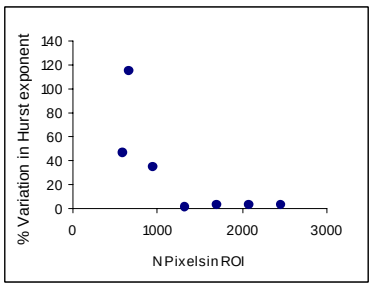

Figure 2: Percentage variation in the Hurst exponent of $IAUGC_{180}$ vs. the number of pixels in the ROI.

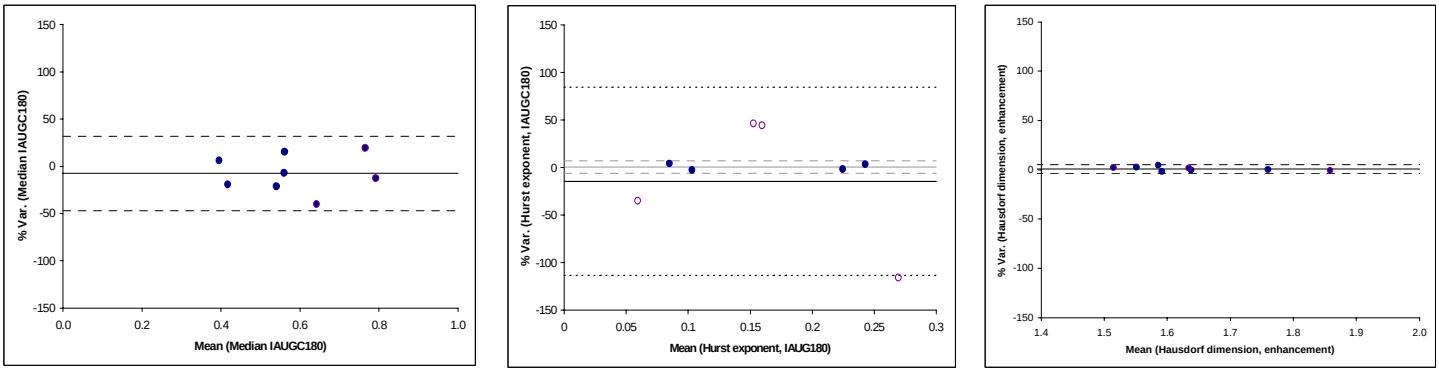

Figure 2: Bland-Altman plots for the median $IAUGC_{180}$ (left), the Hurst exponent of $IAUGC_{180}$ (centre) and the Hausdorf dimension (right) of the enhancement map. These show the percentage variation against the mean of a parameter between the reproducibility measurements. The solid horizontal line in each plot is the mean percentage variation and the dashed lines are this mean +/- the CR; the grey lines in the central plot (Hurst exponent) show the mean percentage variation for ROIs >1000 pixels (solid markers) and the black lines show the same for all the ROIs.