Fractal Properties of Tumours in Dynamic Contrast Enhanced Magnetic Resonance Imaging

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Introduction Dynamic contrast enhanced (DCE)-MRI parameter maps (of v_p, v_e , K^{trans} etc.) in tumours tend to be heterogeneous, with a mixture of regions displaying variable levels of perfusion and contrast agent leakage. Simple summary statistics of these parameter maps (e.g. the mean, median and standard deviation) neglect parameters' spatial organisation. A summary statistic sensitive to both the parameter values and their spatial organisation may be useful for investigating disease progression, the effects of treatment or candidate therapies. The fractal dimension of 2-D binary images, generated from DCE-MRI data, has been shown to correlate with regression in tumour size after treatment[1]. Fractal dimensions quantify how efficiently objects fill the space in which they are embedded; tortuous objects often fill space more efficiently than less tortuous objects. Fractal measures may therefore usefully characterise heterogeneity. This paper describes the novel application of a range of fractal measures to tumour DCE-MRI parameter maps; investigates the difference in fractal properties between v_p, v_e and K^{trans}; and characterises their sensitivity to inter-tumour differences.

Patients 23 patients with advanced solid tumours and ≥ 3cm residual masses within the abdomen and/or pelvis were enrolled in a phase I trial of a novel anti-vascular treatment. DCE-MRI was performed at two baseline visits and following treatment. In all, 38 tumours were suitable for evaluation. The study was approved by the local Research Ethics Committee.

DCE-MRI Protocol All data were acquired on a 1.5 T Philips Intera system using the whole body coil (Q body coil) for transmission and reception. The baseline T_1 measurement consisted of 3 axial spoiled Fast Field Echo volume acquisitions with flip angles 2, 10, 20 degrees respectively and 4 NSA. The dynamic series consisted of 75 consecutively-acquired axial volumes with a flip angle of 20 degrees, 1 NSA and a temporal resolution of 4.97 s covering the period of gadodiamide contrast agent administration (Omniscan, Nycomed). All studies maintained the same number of slices (25), field of view (375 mm × 375 mm), matrix size (128 × 128), TR (4.0 ms) and TE (0.82 ms). Elliptical *k*-space sampling, partial Fourier encoding, over-contiguous slice spacing and partial echo acquisition were used to improve temporal resolution. Slice thickness was 4 mm for small target lesions or 8 mm for larger lesions, giving volume coverage of 100 mm or 200 mm, respectively.

Fractal dimensions Three commonly-used fractal measures include the box-counting dimension, d_0; information dimension, d_1 and correlation dimension, d_2. Computing one of these measures for an object defined by DCE-MRI parameters involves quantifying how changing the number of voxels used to represent the object (its scale) affects some quantity (e.g. for d_0, the number of voxels occupied by the object). Let $P_i(s)$ be the probability of finding a piece of an object at a randomly-chosen point in its i^{th} voxel (of N) at scaling factor s. d_0, d_1 and d_2 can be computed as the 0th, 1st and 2nd order Renyi dimensions[2]:

$$d_q = \frac{1}{1-q}\lim_{s\to 0}\frac{\log\sum_{i=1}^{N} P_i^q(s)}{\log\frac{1}{s}} \quad \& \quad d_1 = \lim_{q\to 1} d_q$$

Box-counting, d_0, gives voxels equal weighting, irrespective of the values of those voxels, while d_1 and d_2 use voxels' values to weight their contribution. An object must satisfy $\sum_{i=1}^{N} P_i(s) = 1$ (i.e. the probability of finding the object at all is certainty). This constraint can be satisfied by dividing each voxel value by the sum of the values of all voxels belonging to the object (in the case of v_p and v_e, the link to the probabilistic definition of fractal dimension is preserved, but further exposition is beyond the scope of this paper).

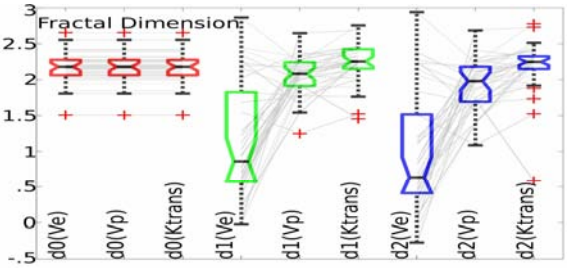

Figure 1. Box and whisker plot showing the distributions of $d_q(v_e)$, $d_q(v_p)$ and $d_q(K^{trans})$ for q=0 (red), q=1 (green) and q=2 (blue). The range and median of the fractal measures are shown by the horizontal bars. The 'notches' indicate the 95% confidence intervals on the true medians. The red dots indicate data points which are robustly considered to be outliers. Each connected line represents a tumour.

Method Each tumour was manually annotated by an expert radiographer. Enhancing voxels within the tumours were identified by comparing the pre- and post-contrast agent administration (defined over 60 s post-contrast) signal values using the Mann-Whitney-Wilcoxon hypothesis test (α=*0.05*). Parameter maps of v_p, v_e and K^{trans} were computed by fitting the extended Tofts model to the DCE-MRI time series for enhancing voxels[3]. Fractal dimensions (d_0, d_1 & d_2) were computed for the 3-D + grey level maps of v_p, v_e and K^{trans}. Three Kruskal-Wallis one-way analyses of variance were then performed (one for each measure). *Intra*class correlation coefficients (ICCs)[4] were computed to characterise sensitivity to *inter*-tumour differences using the repeated measurements at the two pre-treatment baselines.

Results There was no difference between median values of d_0 for the three parameter maps (*p=1*), which is to be expected as they all have the same shape and d_0 ignores voxel greylevel values. There were highly significant differences between median values of d_1 and d_2 for the three parameter maps (*p<<0.001*). Post-hoc testing (Tukey) revealed that for both d_1 and d_2, the median fractal dimensions were mutually significantly different (*p<0.05*)—see Figure 1. Figure 2 shows the ICCs.

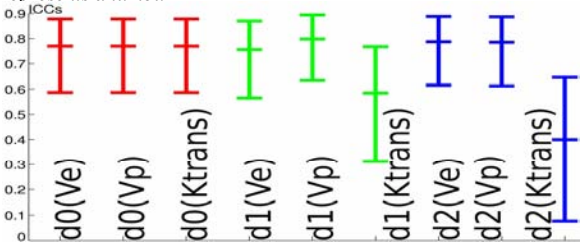

Figure 2. Intraclass correlation coefficients and their 95% confidence intervals for $d_q(v_e)$, $d_q(v_p)$ and $d_q(K^{trans})$ for q=0 (red), q=1 (green) and q=2 (blue).

Discussion Maps of v_e tend to be homogenous; they lack tortuosity and are simple. They therefore have low values of d_1 and d_2. Maps of v_p tend to be densely filled with low values and sparsely filled with high values; they do not fill space efficiently, but are not simple and so have higher d_1 and d_2 than v_e. Maps of K^{trans} tend to have a bright enhancing rim with lower values in the hypoperfused core; they fill space efficiently and are tortuous, having higher still d_1 and d_2. Stated formally, $d_q(v_e) \le d_q(v_p) \le d_q(K^{trans})$. Figure 1 shows that this inequality holds in general for *q={1, 2}*. It does not hold for *q=0*. Since box-counting does not consider voxel values, and the shapes of objects are identical, it is unsurprising that there is no difference between the distributions using d_0; however this does not mean that d_0 cannot contribute useful information, merely that the same result can be obtained irrespective of the DCE-MRI parameter chosen. The histograms of $d_q(v_e)$ for *q={1, 2}* exhibit bimodality; this may explain the high variability in this quantity (Figure 1). These modes may correspond to clinically interesting properties of the individuals, but further investigation is beyond the scope of this paper. The ICCs are generally high (>0.7), with the exception of $d_q(K^{trans})$ for *q={1, 2}*, which indicates that fractal dimension measured on this parameter may not be as sensitive to inter-tumour changes as the other parameters.

Conclusion Analysis of intraclass correlation coefficients indicate that fractal dimensions estimated from DCE-MRI parameters are generally repeatable and may be sensitive to inter-tumour changes. Low ICCs for K^{trans} (d_1 and $d2$), relative to v_p and v_e, suggests K^{trans} may be less useful in fractal analyses. There is a highly significant difference in median information and correlation dimension measured on objects defined by values of v_p, v_e and K^{trans}. These objects tend to exhibit different patterns of spatial organisation, so there is evidence to support the hypothesis that these measures might be useful summary statistics for describing heterogeneity.

References 1. A. Dzik-Jurasz et al. Fractal parameters derived from analysis of DCE-MRI data correlated with response to therapy in rectal carcinoma. *Proc. Int. Soc. Mag. Reson.* 11 (2004). **2.** H. O. Peitgen et al. Chaos and Fractals (2nd Ed.), ISBN 0-387-20229-3. Springer (2004). **3.** P. S. Tofts. Modelling tracer kinetics in dynamic Gd-DTPA MR imaging. J. Mag. Reson. Imag. 7:91-101, 1997. **4.** K. O. McGraw and S. P. Wong. Psychological Methods 1(1):30-46, 1996.

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