

# Simultaneous Quantification of Heterogeneity in Multiple DCE-MRI Parameters

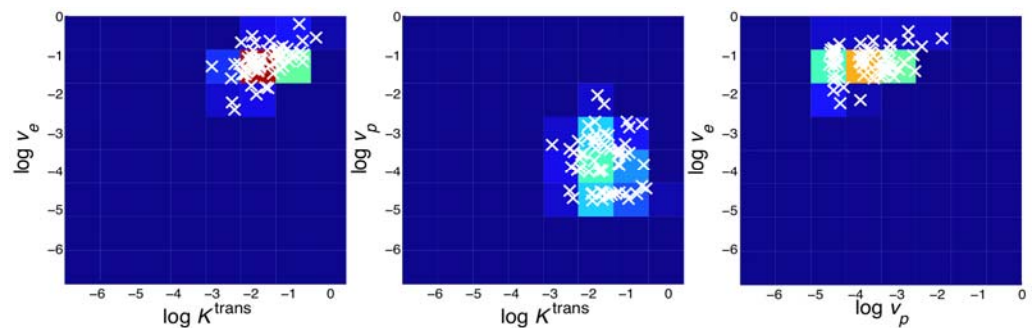
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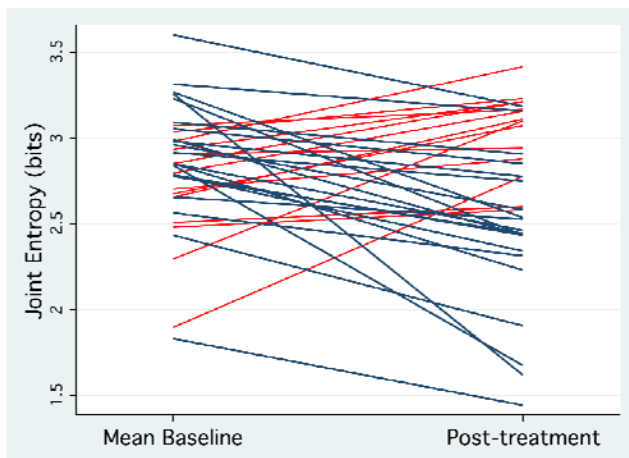
**INTRODUCTION** Dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) is increasingly being used in clinical trials of cancer therapies<sup>1</sup>. A dominant standard analysis technique is to describe the contrast agent concentration time series at each tumour voxel using a model (e.g. extended Tofts<sup>2</sup>). This usually results in a multivariate measurement at each tumour voxel—i.e. each voxel is described in terms of the model parameters  $K^{\text{trans}}$ ,  $v_e$  and  $v_p$ . Conventionally, these measurements are visualised as three parameter maps—one for each model parameter—and each map is summarised using an average; these averages are then used to represent the tumour within the trial. A post-treatment change in median  $K^{\text{trans}}$ , for example, may indicate drug action. There has recently been interest in describing the heterogeneity that is present in these parametric maps, given that solid tumours have structure that may be of diagnostic and prognostic value<sup>3</sup>. One approach is to analyse the histogram of each model parameter. A problem with this is that each parameter is treated separately; we propose to characterise the heterogeneity of all model parameters *simultaneously*.

**THEORY** Shannon's *entropy* is a measure of the uncertainty associated with a univariate discrete random variable<sup>4</sup>. Briefly, the entropy of a distribution is maximised when that distribution is flat—there is much uncertainty about an outcome when the distribution is sampled—and minimised when only a single outcome is possible. Entropy can therefore be considered to be a measure of the 'peakiness' and therefore the shape of the distribution. In the multivariate case, entropy can be generalised as *joint entropy*, which again is a measure of the shape of the distribution. If  $X$ ,  $Y$ , and  $Z$  are three random variables and  $P_{x,y,z}$  is the probability of event  $(x,y,z)$ , then the joint entropy of the joint distribution is given by  $H(X,Y,Z) = -\sum_{x,y,z} P_{x,y,z} \log_2 P_{x,y,z}$ . If the base of the logarithm is 2, as it is here, then joint entropy has units of bits. Given model parameter

values for each voxel in a given tumour, a joint histogram can be computed by binning those values within a three dimensional array. Given that DCE-MRI model parameters tend to be skewed, it is sensible to transform the model parameters into a logarithmic space. Fig. 1 shows marginal histograms for a single tumour. The shape of the full joint distribution can be summarised by computing the joint entropy,  $H(\log K^{\text{trans}}, \log v_e, \log v_p)$ . Drug-induced changes in the shape of the distribution can be assessed by computing joint entropy before and after treatment.



**Figure 1** Marginal histograms illustrating the distribution of the three model parameters, on logarithmic axes, for a single tumour at a single visit. The parameter value of each tumour voxel is also plotted. Note that the colour coding of the frequencies is not common across the three histograms.



**Figure 2** Each line represents a tumour. The plot illustrates the change in joint entropy between the pre- and post-treatment time points. Blue lines represent tumours whose joint entropy decreased and red lines represent tumours whose joint entropy increased. A borderline statistically significant decrease of 0.15 bits ( $p=0.0882$ ) was observed after chemo- and anti-VEGF therapy.

**METHOD** Ten patients with a total of 35 analysable liver metastases underwent DCE-MR imaging at 1.5T on a Philips Intera System. The patients were scanned at two baseline visits and following treatment with chemo- and anti-VEGF therapy. The extended Tofts model was fitted to contrast agent concentration data, yielding maps of  $K^{\text{trans}}$ ,  $v_e$  and  $v_p$ . For each visit, joint entropy was computed for each tumour using the method described above. The within-patient coefficient of variation was computed to assess repeatability<sup>5</sup>. A paired two-tailed  $t$ -test was used to assess the strength of evidence against the null hypothesis that there was no difference between mean baseline and post-treatment joint entropy. (Normality was confirmed by inspecting a QQ plot and by a Shapiro-Wilk normality test;  $p = 0.500$ .) Statistical analysis was performed using Stata IC/10.1.

**RESULTS** The within-patient coefficient of variation was 13%, which compares very favourably with conventional model-based DCE-MRI summary statistics. There was a borderline significant post-treatment decrease in joint entropy of 0.15 bits after treatment ( $p=0.0884$ ), which is illustrated in Fig. 2. Joint entropy is very quick to compute: this entire trial was analysed in less than 30s on a dual core 2.16GHz Apple MacBook Pro.

**CONCLUSIONS** The main contribution we make is to show how information from multiple DCE-MRI parameters can be analysed together to quantify heterogeneity, rather than having to treat each parameter independently. Joint entropy is quick and simple to compute, is highly repeatable, and sensitive to known drug effect. We used regularly spaced histogram cut points; future work should investigate an optimal approach to binning parameter values in order to maximise sensitivity to drug effect without sacrificing repeatability.

**REFERENCES** 1 O'Connor et al. Brit. J. Cancer, 2007;96:189–95. 2 Tofts. J. Mag. Reson. Imag. 1997;7:91–101. 3 Jackson et al. Clin. Cancer Res. 2007;13(12):3449–59. 4 Shannon. BLTJ, 1948;27:379–23 & 623–56. 5 Galbraith et al. NMR Biomed. 2002;15:132–42.