Assessing drug effects by comparing DCE-MRI parameter maps using the Earth Mover's Distance metric

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INTRODUCTION Tracer kinetic modelling of dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) data can be used to quantify drug effects in trials of cancer therapies[1]. Current practice involves computing parameters such as K^{trans} at each tumour voxel and then summarising the tumour by the mean or median K^{trans} value. The degree of drug action may then be determined by subjecting the average K^{trans} values of participants' tumours to statistical analysis. The difference between (change in) average values before and after treatment is therefore used as a dissimilarity measure. The effects of anti-vascular/angiogenic compounds are often observed in particular locations within the tumour (e.g. on the periphery, where angiogenic activity is usually greatest). Summary statistics such as the mean or median may be relatively insensitive to these heterogeneous local changes, they neglect the spatial location of parameters and are unable to pinpoint where changes in specific tumours occur. This abstract proposes an alternative dissimilarity measure that is sensitive to drug action, depends upon both parameter values and their locations, and allows one to localise changes in parameter maps generated using tracer kinetic modelling.

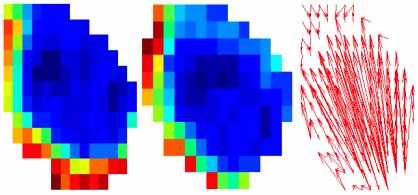

Figure 1 *Pre- and post-treatment K^{trans} maps (left and middle) and a vector field (right) which allows change in K^{trans} values to be localised.*

THEORY The Earth Mover's Distance (EMD) measure[2] originates in logistics and we use it to estimate the cost of transforming one parameter map into another. We shall explain the EMD problem in its original setting, and then show how dissimilarity between tracer kinetic parameter maps can be estimated using the EMD approach.

Imagine there are m warehouses and n stores. The i-th warehouse has a certain supply of goods, p_i, and the j-th store demands a certain amount of goods, q_j. Roads connect each warehouse to each store and there is an associated cost, $c_{i,j}$, of moving one unit of goods from warehouse i to store j. The EMD problem is to find the cheapest flow of goods from warehouses to stores, $\mathbf{F} = (f_{i,j})$, which satisfies the demands within the supply budget. This can be posed as a linear programming problem and the reader is directed to Ref. 2 for mathematical background. EMD problems can be balanced (when supply meets demand) or unbalanced (when there is a mismatch). The value of the EMD dissimilarity function, d, is the total cost of moving the goods according to the optimal solution, normalised to treat balanced and unbalanced problems fairly:

$$d(\mathbf{p},\mathbf{q}) = \frac{1}{F}\sum_{i=1}^{m}\sum_{j=1}^{n} c_{i,j} f_{i,j} \text{ where } F = \sum_{i=1}^{m}\sum_{j=1}^{n} f_{i,j}. \quad (1)$$

The dissimilarity between a pair of tracer kinetic parameter maps (e.g. before and after treatment) can be quantified as the EMD cost of rearranging one map (denoted **p**) to match the other (denoted **q**): **p** defines a supply of K^{trans} values and **q** defines a demand—voxels therefore replace the warehouses and stores. The voxel K^{trans} values themselves are used in the optimization and enter Eqn. 1 implicitly via the solution $\mathbf{F}=(f_{i,j})$. The distances between supply and demand voxels are defined by placing the parameter maps within the same frame of reference (e.g. by aligning their centres or by rigid body registration) and setting $c_{i,j}$ to be the Euclidean distance between the i-th voxel in the supply map and the j-th voxel in the demand map. The spatial locations of the K^{trans} values therefore enter Eqn. 1 implicitly via the cost matrix $\mathbf{C}=(c_{i,j})$. The sum of K^{trans} values in the supply map will typically not equal the sum of those in the demand map, due to therapy- or randomly-introduced parameter variation, creating an unbalanced problem. While an EMD cost could be computed, important differences would not be able to be explained and would be neglected in the resulting EMD cost. We therefore normalise the K^{trans} values in each map to sum to one, forcing problems to be balanced. In a typical study with tracer kinetic maps from two pre-treatment baseline visits, $\mathbf{b}_1$ and $\mathbf{b}_2$, and from a post-treatment visit, $\mathbf{t}$, drug action can be investigated by comparing $d(\mathbf{b}_1, \mathbf{b}_2)$ to $d(\mathbf{b}_1, \mathbf{t})$ for each tumour. Heterogeneous local changes in parameter maps can be localised by visualising the flow, **F**, as a vector field.

METHODS The space complexity of the implementation of the EMD algorithm we used was $O(N^2)$, where N is the number of voxels. This limitation prevented us from using full volumetric images, and in this initial work we manually selected single central slices of the tumours, chosen to be most similar to one another (note that this approach is likely to introduce noise into our results due to misregistration).

Four patients with 12 liver metastases were imaged using T_1-weighted DCE-MR at 1.5T on a Philips Intera; the study was approved by the local research ethics committee and all patients gave written informed consent. Two pre-treatment baseline scans were performed in the week preceding dosing with an anti-angiogenic compound. A post-treatment scan was then performed and voxel-wise estimates of K^{trans} were obtained using the extended Tofts model with a measured arterial input function[3].

The EMD costs between the first and second baseline K^{trans} maps—$d(\mathbf{b}_1, \mathbf{b}_2)$—and between the first baseline and post-treatment K^{trans} maps—$d(\mathbf{b}_1, \mathbf{t})$—were computed for each tumour according to the method above. Due to known drug action, we would expect that $d(\mathbf{b}_1, \mathbf{b}_2) < d(\mathbf{b}_1, \mathbf{t})$ and so a one-tailed paired t-test was performed. Vector fields were generated to visualise the flow for each paring.

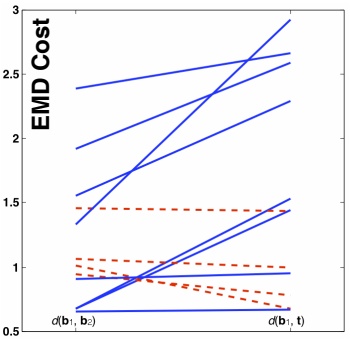

Figure 2 *Changes in EMD cost after dosing. Blue and red (dashed) lines show tumours for which EMD cost increases and decreases, respectively.*

RESULTS Figure 1 shows a pre- and post-treatment tumour and a flow vector field. There was a statistically significant increase in mean EMD cost (1.2 vs. 1.6, p = 0.02; see Figure 2), indicating that the values and spatial 'pattern' of K^{trans} changed due to treatment. We hypothesise that the drug disrupts the active blood vessels on the outer rim, causing K^{trans} values to decrease in this region, altering parameters' values and spatial arrangement. This is reflected by the EMD algorithm tending to move K^{trans} values towards the centre of the tumour to explain the observed spatial homogenisation of the K^{trans} values (see flow vector field in Fig. 1).

CONCLUSIONS We have developed a new dissimilarity measure between pairs of DCE-MRI parameter maps. EMD cost is sensitive to known drug action, considers both the value and spatial location of parameters and allows change to be localized within specific tumours. Future work will focus on using full 3-D volumetric data, improving pre-registration and developing a way to subject the flow vectors to statistical analysis.

REFERENCES 1. O'Connor et al. Brit. J. Cancer 96(2):189–195, 2007. **2.** Rubner et al. Int. J. Comp. Vision 40(2):99–121, 2000. **3.** Tofts. J. Mag. Reson. Imag. 7:91–101, 1997. **ACKNOWLEDGEMENTS** Financial support was provided by GlaxoSmithKline, Cancer Research UK and Apple.