Characterization of Image Heterogeneity using Minkowski Functionals

H. C. Canuto[1,2], M. I. Kettunen[1,2], C. I. McLachlan[3], A. S. Krishnan[1], A. A. Neves[1,2], D-E. Hu[1], M. P. Hobson[3,4], and K. M. Brindle[1,2]

[1]Biochemistry, The University of Cambridge, Cambridge, Cambridgeshire, United Kingdom, [2]Cancer Research UK, Cambridge, Cambridgeshire, United Kingdom, [3]Metropolis Data Consultants, Cambridge, Cambridgeshire, United Kingdom, [4]Astrophysics, Cavendish Laboratory, The University of Cambridge, Cambridge, Cambridgeshire, United Kingdom

Introduction

Measurements of cell death following drug-treatment are a good prognostic indicator for treatment outcome[1-4] and therefore we have been developing targeted MR contrast agents that bind to apoptotic cells and which can be used to image tumor cell death post-treatment [5-7]. More recently we have exploited the spatially heterogeneous nature of cell death in tumors to enhance the sensitivity of detection of one of these agents. We showed that by analyzing the heterogeneity of contrast agent binding that we could increase the sensitivity of detection of the agent and hence of tumor cell death[8]. Since tissue morphology is a very sensitive indicator of underlying tissue biology[9], we reasoned that we might also be able to apply this analysis to detect tumor response to treatment in the absence of any contrast agent. By simply parameterising, using 2D Minkowski Functionals (MFs), the morphological heterogeneity present in a T_2-weighted MR image of a tumor before and after drug-treatment, we have shown that we can detect a treatment response in the absence of contrast agent. 2D MFs have been widely used in cosmology as precise morphological and structural descriptors which have been used in the study of the evolution and morphology of galaxies and clusters of galaxies[10-13]. The recent observation that gadolinium-containing MRI contrast agents can cause the debilitating and sometimes fatal condition Nephrogenic Systemic Fibrosis (NSF) in patients with renal dysfunction[14] has cast some doubt on the further development of Gd^{3+}-based agents. Our approach could provide a viable alternative to contrast agent-based methods.

Materials and Methods

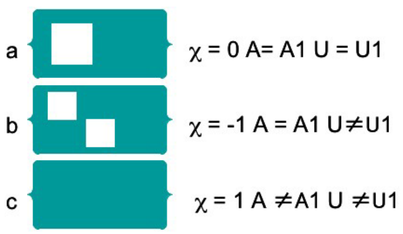

Fig. 1: The Minkowski Functionals: Area (A), Perimeter (U) and Genus (χ) used to describe simple shapes.

All MR imaging experiments were performed at 9.4T. Mice bearing EL4 murine lymphomas were either untreated or treated, by i.p. injection, with 67 mg/kg etoposide and then imaged 24 h later. T_2-weighted images (TR=1 s, TE=35 ms, FOV=35x35 mm, data matrix 256x128, slice thickness 1 mm) were acquired from the tumors. Tumors were manually segmented from multiple transverse slices from drug-treated (n=5, total number of slices = 53) and control animals (n=5, total number of slices = 47) with a contiguous non-square region extracted with standard image manipulation software. In the calculation of 2D MFs each tumor intensity value was linearly remapped onto the uniform interval 0 to 1. Tumor images were then converted to binary datasets by thresholding each image as a function of gray scale. Ten threshold steps were chosen to account for gray level variation, giving 11 thresholded images per slice. In each thresholded image the visible pixels were considered in the computation of the MFs.

MFs were calculated by software developed by Metropolis Data Consultants. The software calculates the three MFs area, perimeter and genus as a function of the image threshold. A schematic (Fig. 1) illustrates the MFs for simple objects. The MFs were also renormalized to remove any dependence on the total number of pixels in an image.

Results

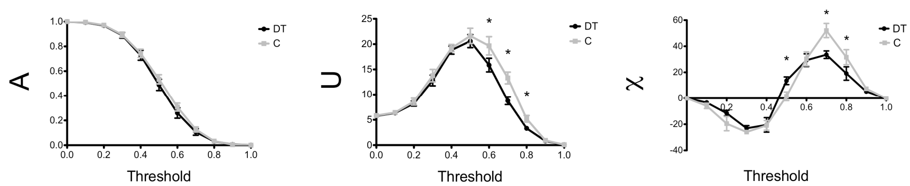

Fig. 2: 2D MFs are shown as a function of 11 gray-scale threshold levels from T_2-weighted images acquired without contrast agent.

The 2D MFs were computed for gray-scale threshold levels in the range 0 to 1.0 inclusive (Fig. 2) The area (A) calculated as a function of gray-scale threshold showed no significant differences between drug-treated and control animals. The perimeter (U) values in the threshold range from 0.6 – 0.8 and the genus (χ) values in the threshold range 0.5 and 0.7 - 0.8 were significantly different for control as compared to drug-treated animals. In particular, in the threshold range 0.7-0.8, the genus was significantly higher for control compared to drug-treated animals, in this case indicating a more statistically homogeneous morphology in the control tumors.

Conclusions

We are developing an automated image analysis tool to sensitively and quantitatively detect changes in tissue architecture that report changes in underlying tissue biology following chemotherapeutic treatment. Unlike other image analysis methods, 2D MFs provide an automated and reliable method of image analysis, which does not require prior assumptions about the number of regions or features in the image.

References

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