The trouble with apparent diffusion coefficient papers

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This issue of Journal of Medical Radiation Sciences includes a study (Rundle-Thiele et al.)¹ that investigates the correlation between magnetic resonance imaging (MRI)-based estimates of water mobility in glioblastoma tumours and expression of the prognostically important gene promoter methylguanine methyltransferase (MGMT). The authors address previous inconsistent reports regarding a correlation between apparent diffusion coefficient (ADC) and the presence of MGMT by consideration of the effect of tumour heterogeneity.

Since tissue water mobility is intimately and directly dependent on tissue microstructure, tumour heterogeneity will manifest as intervoxel differences of calculated ADC. The question then is how to correlate such heterogeneous measurements with tumour type markers. For the same clinical data set, different analyses may lead to different conclusions. One approach to this problem is to consider the histogram of intra-tumour voxel ADCs. If the tumour were homogeneous one would expect a normal distribution of voxel ADCs. This is clearly not the case for glioblastoma which shows a bimodal distribution in the measurements reported by Rundle-Thiele et al. The mean of the lower ADC component of the bimodal distribution correlated strongly with presence of MGMT while the minimum ADC in the tumour did not.

There are many potential methods of correlating measurements of heterogeneous tissue with properties such as pathologic status. For example, in the prostate the intervoxel ADC entropy in suspicious regions is reported to correlate more strongly with the presence of cancer than a simple mean.² This example, and the investigation reported by Rundle-Thiele et al. emphasise the importance of recognising and accounting for tissue heterogeneity when attempting to develop markers for pathology or pathologic type.

However, there is a dark undercurrent to the ADC story and the majority of publications describing clinical ADC-based analysis of diffusion-weighted MRI data. Quite separate from the inter-voxel ADC differences there are potential effects on calculated ADC from sub-voxel tissue heterogeneity, measurement technique and analysis method. This is rarely mentioned in the clinical diffusion MRI literature, and in many cases probably not recognised by authors or reviewers. To a significant extent it may be a confused usage of ADC that leads to inconsistent results when independent studies are compared. Unfortunately, the misuse of ADC is now deeply imbedded in the culture of radiology.

The Apparently Deceptive Coefficient

It is important to focus on the ‘apparent’ part of the ADC. Calculation of ADC is the crudest possible estimate of water mobility in tissue. The ADC method takes a model that is appropriate to the centre of a very still glass of water, namely a Gaussian displacement probability over a fixed time interval, and applies it to a system (biological tissue) in which water movement is very well known to be highly non-Gaussian. The deviation from Gaussian behaviour occurs because, in the time interval of a clinical diffusion-weighted MRI (DWI) measurement (typically 40–80 msec, but see below), each water molecule is likely to interact with multiple parts of the tissue microstructure (In a still glass of water at 37°C the average water molecule displacement over 40 msec would be around 27 µm – more than the average mammalian cell diameter). Some of the interactions of water with tissue structure will merely slow the ‘natural’ movement of the water molecules (hindered diffusion), while others may confine the water molecules to particular regions (restricted diffusion).

The time scale of the diffusion-weighted measurement is critical. It determines the spatial scale of the tissue structures that will most strongly affect image contrast. If the time scale is short the majority of water molecules will travel only a small distance and ‘probe’ only the smallest tissue structure details. If the time scale is long the majority of water molecules will interact with, and
average out, all the small structure detail and contrast differences will relate primarily to large-scale structure variations.

Separate from tissue microstructure effects, blood flow in perfused tissues leads to water displacements that are independent of true diffusion processes yet still manifest as DWI signal changes. It is not an exaggeration to state that in an environment as complex as biological tissue the concept of a single water diffusion coefficient is close to meaningless.

The highly non-Gaussian water movement behaviour in biological tissue means that the calculated ADC is dependent on both the way diffusion-weighted imaging is performed and the way the acquired images are analysed. MRI scanner displays (and, consequently, the majority of journal article authors) describe the diffusion weighting (sensitivity to molecular displacement) of a DWI scan in terms of a single parameter, the ‘$b$-factor’, which combines the strength, duration and timing of the diffusion-sensitising magnetic field gradients. A specific $b$-factor can be achieved in many different ways with different combinations of gradient strength and timing, and may be achieved in different ways on different scanners depending on both software and hardware. A scanner with low maximum gradient strength will achieve a selected high $b$-factor by using a longer diffusion time than a scanner with high-power gradients. Even on a specific scanner the diffusion time used to achieve a particular $b$-factor may depend on the chosen maximum $b$-factor in the scan. On most MRI scanners the actual diffusion time is not displayed or recorded and cannot be retrieved by the operator. As a consequence two apparently similar studies, using identical $b$-factors and ADC calculation methods, might arrive at contradictory conclusions because the scans were performed with non-identical diffusion times and thus measured different tissue properties.

Apart from the fuzziness of $b$-factors, non-Gaussian displacement probability also means the number of different $b$-factors used in the DWI scan, and their range, will affect the calculated ADC. Inclusion of data measured at $b$-factors less than ~100 sec/mm$^2$ may introduce perfusion effects, and data from $b$-factors greater than ~1000 sec/mm$^2$ will generally be very poorly fitted by the monoexponential ADC model. When only $b$-factors are reported ADC results will be unreliable – to the extent that one might compare pineapples by measuring their apple-ness but not mention which of a thousand different apple-o-metres was used.

But ADC Works!

Yes. There is ever-growing published evidence that ADC analysis works better (e.g. higher area under the curve (AUC) in a receiver operating characteristic (ROC) analysis) for MRI-based detection of cancer than either $T_2$ dynamic contrast or proton spectroscopy used alone. The combination of DWI with $T_2$ and dynamic contrast is the basis of the current gold standard for pre-treatment assessment of prostate cancer. So, given the untidiness of the ADC method, why does it work so well for cancer detection? We do not have to look long or far for the answer. The basis of solid tissue cancer diagnosis and grading is tissue microstructure – what a histopathologist sees looking down a light microscope at thin sections of stained tissue – and microstructure is what controls water diffusion in tissue. In comparison, the contrast mechanisms effective in $T_2$, dynamic contrast and spectroscopic imaging are much less closely related to the diagnostic features of cancer.

The microstructure-dependence of DWI also highlights the perversity of its common labelling as a ‘functional’ imaging technique that complements ‘structural’ $T_1$ and $T_2$ methods. No MRI contrast method relates more closely to tissue structure than diffusion-weighted imaging. It is very likely that diffusion-based cancer assessment can be improved a lot. Given the many weaknesses of the most popular ADC methods we can be confident that reduction in the measurement variance due to unreported method variations, together with more sophisticated signal modelling, will provide significant further enhancement of the clinical value of DWI.

The Details that Matter

Now is the time to confess that the title of this editorial was stolen and given a quick respray. In 1991, Paul Bottomley pleaded in a Radiology editorial, ‘The trouble with spectroscopy papers’, that one of the fundamental criteria for acceptance of a paper should be ‘that sufficient experimental detail is provided so that one skilled in the art could reproduce the study and its findings’. His complaint was that the translation of potentially valuable new imaging techniques to clinical practice was being inhibited by inconsistent and incomplete reporting of both data acquisition and data analysis methods. Fifteen years later, pointing to Bottomley’s editorial, Lin et al. described how a general failure of the spectroscopy community to respond to the imperative for detailed and appropriate description of methods was a major contributor to the failure of clinical spectroscopy to meet the assessment requirements of evidence-based medicine. In the US, this resulted in a decision to withdraw government reimbursements for clinical spectroscopy. Lin et al. argued that not only does this deny patients access to potential benefits of the technology but it also discourages manufacturers from
investing in development and compromises further research.

This history is relevant to everyone involved in development of clinical methods. In the specific case of diffusion-based techniques it is important for both authors and reviewers to ensure that critical parameters affecting ADC calculations are reported. To advance beyond the smokescreen of $b$-factors, we need to demand from MRI scanner vendors that critical parameters are not hidden from operators. This at least would enable a reliable meta-analysis of ADC-based studies from multiple sites. In the longer term, we need to dispense with ADC completely. The potential of diffusion-based cancer assessment will only be realised when our signal analysis methods account for the tissue structure heterogeneity to which the ADC method is blind. It is time – for diffusion glasnost!

**Conflict of Interest**

The author declares no conflict of interest.

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