

Uncertainty in Apparent Diffusion Coefficients Determined from Diffusion Weighted Magnetic Resonance Imaging

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Abstract

The experimental uncertainty in the Apparent Diffusion Coefficient (ADC) calculated from Diffusion Weighted Magnetic Resonance Images (DWMRI) has been estimated. Systematic uncertainty due to noise and transcription are combined with statistical uncertainties to arrive at a total.

Introduction

The use of diffusion weighted magnetic resonance imaging (DWMRI) has increased recently, as the application has spread from use mainly in ischemia diagnosis [1], to monitoring therapy efficacy in radiation oncology [2, 3]. Since diffusion weighting decreases the image intensity, there are number of additional challenges associated with it. Chief among these is to estimate the amount of uncertainty introduced when calculating ADCs for use in therapy evaluation.

Motivation

In preparation for treating brain tumors with radiotherapy, the lesion is generally contoured by a clinician on a non-diffusion weighted image, such as T2-weighted fluid attenuated inversion recovery (FLAIR). In order to calculate an apparent diffusion coefficient (ADC) for the lesion, used to monitor therapy efficacy [2], the contour must be transcribed to a diffusion weighted image. This transcription, along with other factors, contributes to uncertainty in the derived

ADC. Similar to previous work regarding the quantification of image uncertainty [4], a number of different factors need to be examined, among them: 1) Noise 2) Pixel intensity and 3) Pixel location.

Although therapy related changes in the ADC are what clinicians and others are looking for, it is possible that ADCs can undergo changes unrelated to radiation therapy. With this in mind, it is important to know how much uncertainty is involved in the calculation of ADCs, so that changes can be more easily deemed significant, regardless of the cause.

Methods and Materials

As part of an Internal Review Board (IRB) approved study, a number of patients have been enrolled in a research imaging protocol in which the brain was imaged using DWMRI [5]. Prior to this, the patients were clinically imaged using non-diffusion weighted MRI. These images were used to contour lesions, and to plan radiation therapy.

Geometric Transcription Algorithm

Since the clinical contour scan and the research protocol scan were in general different, a first order check to compare different axial slices involved the scan aspect ratio. This was calculated by dividing the width (left-right hyper-intense extent) by the height (anterior-posterior hyper-intense extent) for each scan and then comparing the two. If the ratios were within 3%, the following algorithm was applied [6]:

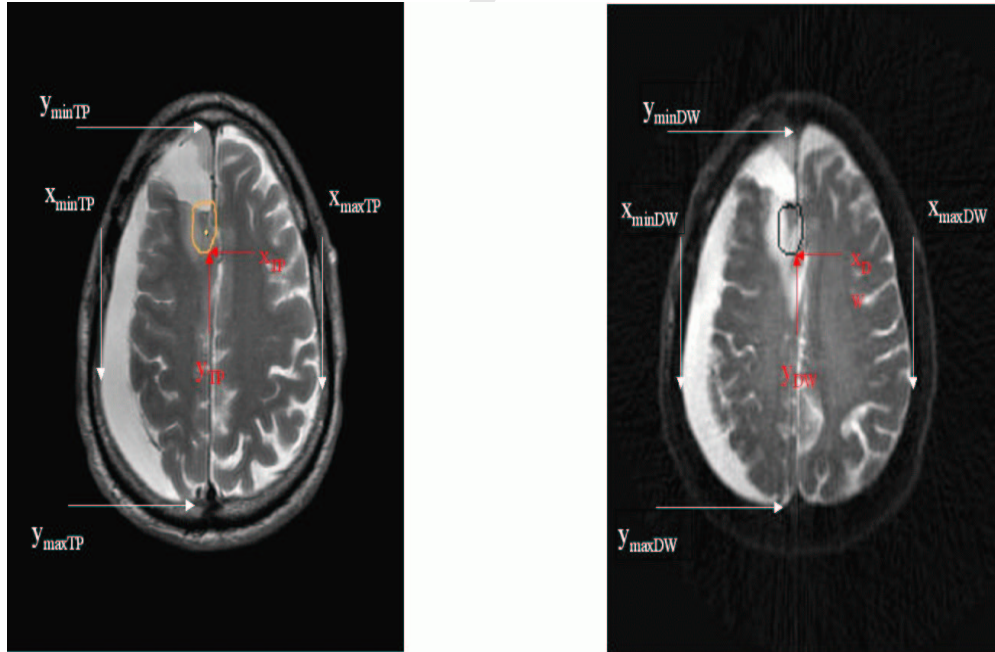
$$x_{DW} = (x_{TP} - x_{min,TP}) * \frac{\Delta x_{DW}}{\Delta x_{TP}} + x_{min,DW} \quad (1)$$

$$y_{DW} = (y_{TP} - y_{min,TP}) * \frac{\Delta y_{DW}}{\Delta y_{TP}} + y_{min,DW} \quad (2)$$

where, x,y are the voxel location, Δx and Δy are number of voxels between extreme points on tissue in the image, i.e. $\Delta x = x_{max} - x_{min}$, and the subscripts DW and TP indicate Diffusion Weighted or Treatment Plan, respectively, as depicted in Figure 1.

Slice Matching

While the protocol (DW) scans all had identical characteristics for all scan sets, the clinical (TP) scans, as indicated above, were in general, different. A typical comparison between the DW scan characteristics and those of the first scan set can be seen in Table 1. As can be seen in this table, the TP scans generally had lower slice spacing and slice thickness, so that it is necessary to match slices when transcribing lesions from TP scans to DW scans. Slice selection was based on comparison of anatomical landmarks within the image. Relative shape and structure of ventricles, sulci and other physical attributes were used for comparison. The DW image most closely matching the pertinent TP image was chosen based on the visual



Treatment Plan Scan

Diffusion Weighted Scan

Figure 1: Geometric Algorithm used for lesion transcription.

Table 1: Diffusion Weighted and Treatment Plan Comparison

Scan Type	Slice Thickness(mm)	Slice Spacing(mm)	Field Strength(T)
Diffusion Weighted	5.0	7.0	3.0
FLAIR	4.0	4.0	1.5

Table 2: Voxel Placement Uncertainties

Quantity	Location	Uncertainty
y_{minTP}	Treatment Plan Scan	$\sigma_{y_{minTP}} = 1\%$
x_{minTP}	Treatment Plan Scan	$\sigma_{x_{minTP}} = 1\%$
y_{maxTP}	Treatment Plan Scan	$\sigma_{y_{maxTP}} = 1\%$
x_{maxTP}	Treatment Plan Scan	$\sigma_{x_{maxTP}} = 1\%$
y_{TP}	Treatment Plan Scan	$\sigma_{y_{TP}} = 0^*$
x_{TP}	Treatment Plan Scan	$\sigma_{x_{TP}} = 0^*$
y_{minDW}	Diffusion Weighted Scan	$\sigma_{y_{minDW}} = 2\%$
x_{minDW}	Diffusion Weighted Scan	$\sigma_{x_{minDW}} = 2\%$
y_{maxDW}	Diffusion Weighted Scan	$\sigma_{y_{maxDW}} = 2\%$
x_{maxDW}	Diffusion Weighted Scan	$\sigma_{x_{maxDW}} = 2\%$

*Note: An assumption is made that the TP coordinates are known exactly. i.e., $\sigma_{x_{TP}} = \sigma_{y_{TP}} = 0$.

comparison. In general, there were fewer DW slices transecting the lesion than there were TP slices. In view of this fact, the closest matching TP image was paired with each DW image for analysis. TP images not matched with a corresponding DW image were not included to avoid redundancy in the ADC calculation.

Results

Systematic Uncertainty

The total uncertainty is divided into *systematic* uncertainty and *statistical* uncertainty [7]. A significant source of systematic uncertainty is associated with the transcription of the lesion coordinates from the non-DW image to the DW image. Although a significant amount of work has been devoted to how best to register (align) two different image sets [8], a non-zero transcription uncertainty is expected to remain. Normally, since the non-DW scan is brighter and has higher resolution, the uncertainty in voxel location is less than for DW scans. An estimate of the uncertainty in quantities involved in lesion transcription can be seen in Table 2. The uncertainty (error) in the DW coordinates is then calculated by propagating these uncertainties through equations (1) and (2) using standard error formulas[7]: i.e. if $x = au + bv$, then $\sigma_x^2 = a^2\sigma_u^2 + b^2\sigma_v^2$, if $x = auv$, then $\frac{\sigma_x^2}{x^2} = \frac{\sigma_u^2}{u^2} + \frac{\sigma_v^2}{v^2} + 2\frac{\sigma_{uv}^2}{uv}$ and finally, if $x = \frac{au}{v}$, then $\frac{\sigma_x^2}{x^2} = \frac{\sigma_u^2}{u^2} + \frac{\sigma_v^2}{v^2} - 2\frac{\sigma_{uv}^2}{uv}$ where σ_x is the uncertainty in x. We assume that u and v are uncorrelated so that $\sigma_{uv} = 0$.

$$\begin{aligned}
\sigma_{x_{DW}}^2 &= \sigma_{x_{TP}-x_{minTP}}^2 \left(\frac{\Delta x_{DW}}{\Delta x_{TP}} \right)^2 + (x_{TP} - x_{minTP})^2 \frac{\sigma_{\Delta x_{DW}}^2}{\Delta x_{TP}} + \sigma_{x_{minDW}}^2 \\
&= \left(\frac{\Delta x_{DW}}{\Delta x_{TP}} \right)^2 \left(\sigma_{x_{TP}-x_{minTP}}^2 + (x_{TP} - x_{minTP})^2 \left(\frac{\sigma_{\Delta x_{DW}}^2}{(\Delta x_{DW})^2} + \frac{\sigma_{\Delta x_{TP}}^2}{(\Delta x_{TP})^2} \right) \right) \\
&\quad + \sigma_{x_{minDW}}^2
\end{aligned} \tag{3}$$

and

$$\begin{aligned}
\sigma_{y_{DW}}^2 &= \left(\frac{\Delta y_{DW}}{\Delta y_{TP}} \right)^2 \left(\sigma_{y_{TP}-y_{minTP}}^2 + (y_{TP} - y_{minTP})^2 \left(\frac{\sigma_{\Delta y_{DW}}^2}{(\Delta y_{DW})^2} + \frac{\sigma_{\Delta y_{TP}}^2}{(\Delta y_{TP})^2} \right) \right) \\
&\quad + \sigma_{y_{minDW}}^2.
\end{aligned} \tag{4}$$

Since these coordinates, and their uncertainties, are not directly utilized in the calculation of an ADC, an assumption is necessary in order to estimate what effect these errors will have on the final result: It is assumed that the uncertainty in DW coordinates is equal in magnitude to the resulting uncertainty in pixel intensity. This assumption can be tested by moving the lesion, and observing the resulting change in the average lesion intensity. To this end, utilizing ImageJ¹, lesion boundaries in axial scans were translated in anterior-posterior, and left-right directions and resulting changes in lesion pixel intensity were observed. This can be seen in Figure 2. The resulting changes in pixel intensities from these translations can be seen in Table 3. As can be seen in this table, translation of the lesion by an amount associated with a typical transcription uncertainty (1-2%) results in a similar change in the average lesion intensity. Using (3) and (4) and the values in Table 2, the total systematic transcription uncertainty is arrived at: $\sigma_{tot-trans} \approx 3\%$. This is assumed to remain constant for different scan sets.

In addition to transcription, there is systematic uncertainty introduced by noise. Using a previously published method [9], the noise uncertainty has been estimated for the b=0, 520 and 850 s/mm^2 DWMRI scans. In Table 4, the results of these calculations are displayed. As can be seen in this table, the noise level is lowest for the b=0 scan, followed by the b= 520 s/mm^2 and finally is highest for the b= 850 s/mm^2 scan. This is consistent with the fact that the signal intensity is lowest for the highest (b= 850 s/mm^2) value of diffusion weighting.

The main components of the systematic uncertainty due to noise and transcription are added in quadrature to arrive at the total systematic uncertainty: i.e. $\sigma_{tot-sys} = \sqrt{\sigma_{noise}^2 + \sigma_{transc}^2}$. Once this quantity is known, the Apparent Diffusion Coefficient (ADC) can be determined graphically with an additional component of *statistical* uncertainty.

Statistical Uncertainty

In Figure 3 the b-value of the lesion contour is plotted vs. the log of the ratio of signal

¹see <http://rsb.info.nih.gov/ij/>

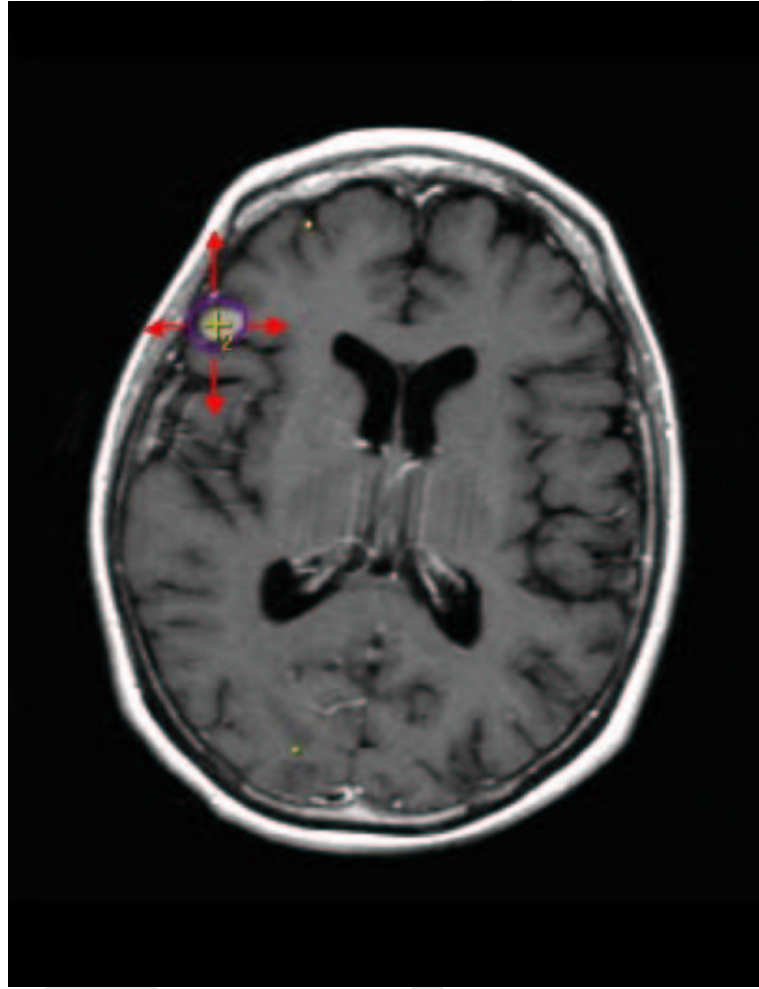


Figure 2: Lesion translation in the anterior-posterior and left-right direction.

Table 3: Lesion Pixel Intensity Variation with Translation

Area(px1 ²)	Mean Int.	Lf-Rt Dev(%)	Sup-Inf Dev (%)	Int Dev (%)
174.29	345.9	0	0	0
174.29	347.3	-2.8	0	0.4
174.29	345.7	-1.7	0	-0.07
174.29	350.6	0.6	0	1.3
174.29	363.5	1.7	0	5.1
174.29	329.0	0	-1.8	-4.9
174.29	350.7	0	-0.9	1.4
174.29	341.2	0	0.5	-1.4

Table 4: Average Noise Levels of Different Diffusion Weighted Scans

Scan Set	$b = 0$ (%)	$b = 520s/mm^2$ (%)	$b = 850s/mm^2$ (%)
1	4.9	8.0	10.7
2	8.2	16.7	24.0
Average	6.6	12.4	17.4

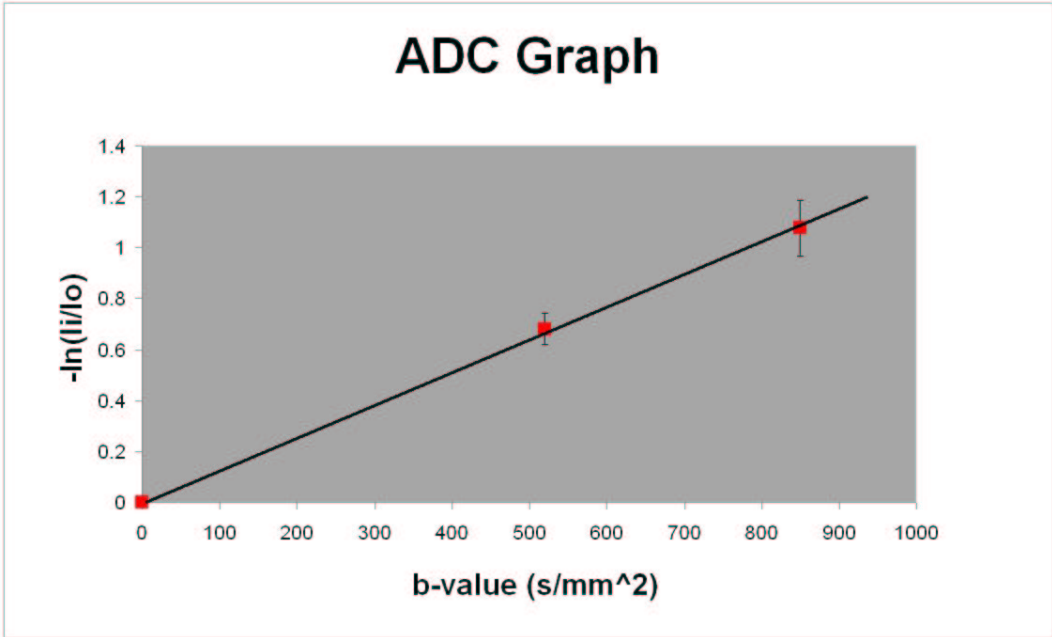


Figure 3: Plot used to determine ADC and Statistical Uncertainty.

Table 5: Uncertainty in ADC Values

Scan Set	ADC(mm ² /s)	σ_{ADC} (%)
1	1.45×10^{-3}	8.1
2	1.70×10^{-3}	25.9

intensity. The equation that is plotted can be written

$$\log \frac{I_i}{I_o} = -b_i * ADC \quad (5)$$

where $i=0, 520$ and 850 represents the different b-values of diffusion weighting, and I_i is the corresponding pixel intensities of the lesions in these scans. The error bars on this plot are the result of the total systematic uncertainty described above. As can be seen, the $b=0$ ($i=0$) point has no error bars since in the fraction, the numerator equals the denominator: I_o . Furthermore, since $\log(1) = 0$, there is no intercept. Previous work has demonstrated the importance of uncertainty in the highest b-value [10]. A weighted least squares fit to these data is then performed to determine the Apparent Diffusion Coefficient (ADC), as the slope of the resultant line[7]:

$$ADC = \frac{1}{\Delta} \left(\sum_{i=520}^{850} \frac{b_i}{\sigma_i^2} \log \frac{I_i}{I_o} \right) \quad (6)$$

with

$$\Delta = \sum_{i=520}^{850} \frac{b_i^2}{\sigma_i^2} \quad (7)$$

where σ_i are the total systematic uncertainties associated with the different log ratios determined above. Finally, the total (systematic + statistical) uncertainty in the ADC can be written

$$\sigma_{ADC}^2 = 1 / \left(\sum_{i=520}^{850} \frac{b_i^2}{\sigma_i^2} \right). \quad (8)$$

This uncertainty (8) now includes the *systematic* uncertainty, as represented by the error bars in Figure 3, and *statistical* uncertainty, due to the spread of the experimental data and the weighted least squares fit to these data. Using these formulas, the total uncertainty in the ADC is determined. The results of these calculations are seen in Table 5.

Discussion

Comparing the results of the noise uncertainty (see Table 3) with the transcription uncertainty ($\sigma_{tot-trans} \approx 3\%$), it becomes clear that the dominant systematic uncertainty in the ADC

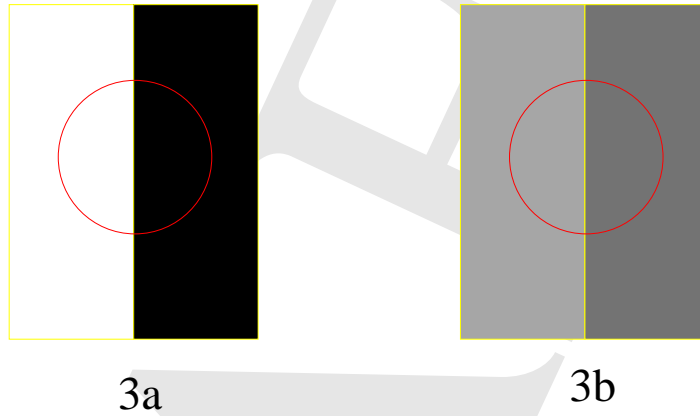


Figure 4: Comparison of correlation between lesion placement/coordinate uncertainty and lesion intensity uncertainty: 4a) High correlation. 4b) Low correlation.

calculation is due to noise. In particular, the noise associated with the highest value of diffusion weighting is, in general, the largest single contribution to the systematic uncertainty.

In addition to the variation with b-value, the lesion *location* also has substantial influence on the the amount of ADC uncertainty. Previous work has indicated the importance of sulci variation in ADC calculation [11]. The assumption (made above) that uncertainty in lesion location is proportional to uncertainty in lesion intensity can be examined further. In Figure 4 this relationship is compared. As can be seen in 4a, if the lesion straddles a bright and dark region, there may be high a correlation between these two different (location and intensity) systematic uncertainties. If the lesion straddles two regions of similar intensities as in 4b, there will be a lower correlation. Furthermore, in either of these two situations, a displacement along the boundary will result in less intensity variation, than a displacement transverse to the boundary so that this degree of freedom should also be considered when estimating uncertainty.

Conclusion

There are numerous challenges when attempting to estimate uncertainties associated with calculating an ADC. If a single source of uncertainty, e.g. noise in a heavily diffusion weighted image, is substantially larger than other sources, the process can be simplified by assuming that all uncertainty comes from this source. However, if this is not the case, then each source needs to be considered carefully so as to obtain the most accurate, clinically useful estimate.

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